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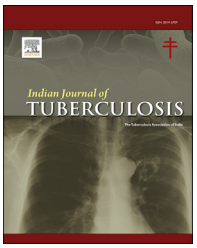

Editorial

Mycobacterium tuberculosis Next-Generation Whole Genome Sequencing

Tuberculosis (TB) is one of the leading infectious diseases and it continues to take a massive toll on human health globally. The emergence of Drug resistant TB (DR-TB) has further jeopardized global TB control achievements. Multi-drug resistant (MDR) (defined as resistance to isoniazid and rifampicin) and Rifampicin resistant (RR) (defined as resistance to rifampicin only) *Mycobacterium tuberculosis* complex strains are especially devastating (1, 2). Patients with MDR and RR TB require radical changes in treatment compared to those with drug-susceptible TB. Global roll-out of rapid molecular assays such as GeneXpert MTB/RIF Ultra and GenoType MTBDRplus assays has revolutionized the diagnosis of DR-TB yet the emergence of drug-resistant strains that escape detection by such assays reveals the importance of developing more comprehensive technologies that include a wider range of resistance determinants (3). Over the past decade, whole-genome sequencing (WGS) of *Mycobacterium tuberculosis* has proved to be an extraordinary tool in the study and control of TB. *Mycobacterium tuberculosis* WGS is an attractive method for both drug susceptibility testing (DST) to inform treatment decisions and surveillance of drug resistance in high burden settings where capacity for routine resistance testing for everyone with TB is inadequate.

Whole genome sequencing (WGS) refers to obtaining the complete genomic sequence of an organism in a single sequencing run which can be used for various applications. A small bacterial genome of *Mycobacterium tuberculosis* makes it the perfect candidate for this kind of technology. The opportunities on hand include prediction of Drug Resistance and understanding of mechanisms of Drug Resistance, investigation of transmission chains, identification of Mixed Infections and continuous Drug Resistance Surveillance.

a. Prediction of Drug Resistance and Understanding of Mechanisms of Drug Resistance

Unlike other molecular methods that typically target specific genes for determination of drug resistance, WGS allows for the interrogation of the entire *Mycobacterium tuberculosis* genome for mutations conferring drug resistance. Mutations occurring outside the genes known to be associated with drug resistance can be identified from TB whole genomes. The likelihood of finding novel drug resistance conferring mutations is thus increased. Although largely done retrospectively, WGS for determination of drug resistance has shown good concordance with conventional DST, with shorter turnaround times especially when done from early cultures (4, 5).

b. Investigation of Transmission Chain

The advent of next-generation sequencing (NGS) has made WGS a faster, more affordable, and increasingly accessible alternative for molecular epidemiologic studies. The data generated from WGS allows for an unparalleled ability to detect genetic variation in *Mycobacterium tuberculosis*. Analysis of WGS data has led to the reconstruction of *Mycobacterium tuberculosis* phylogeny and this has improved our understanding of the global distribution of *Mycobacterium tuberculosis*. WGS has been used to answer questions about TB transmission and will, in the near future, become the routine method for *Mycobacterium tuberculosis* typing because it has superior resolution to conventional typing methodologies.

c. Identification of Mixed Infections

Mycobacterium tuberculosis next-generation WGS analysis using heterozygous base calls can provide better resolution of mixed infections.

d. Continuous Drug Resistance Surveillance

In order to gauge the effectiveness of strategies to control *Mycobacterium tuberculosis* drug resistance globally, accurate data on the occurrence of drug resistance is critical. WHO recommends routine DST for all TB patients to provide continuous surveillance of drug resistance. WGS analysis for

routine drug resistance surveillance for all TB patients is an attractive avenue. However, this would have a prohibitive cost at the moment, given that most of the high burden countries struggle to even afford DST for suspected drug-resistant cases.

Limitations of the technology

Whole genome sequencing for resistance detection and surveillance is sure to become standard practice in the near future over other traditional techniques, but we must be aware of its limitations as of today. These include: (i) sequencing costs may be substantially higher than suggested by published estimates (ii) procurement and capacity building may take significantly longer than originally planned; (iii) the requirements for infrastructure need to be considered in an early project stage; (iv) quality assurance requires tailored solutions; (v) transitioning WGS to routine diagnostics demands careful planning; and (vi) ongoing support by experienced experts is required to ensure sustainable success.

Mycobacterium tuberculosis *Whole Genome Sequencing in India*

In India Central Tuberculosis Division (CTD), Ministry of Health and Family Welfare has taken an initiative and installed 5 WGS (MiSeq) platforms in various tuberculosis reference laboratories across the country. Although the exact utilization of these platforms is yet to be decided, at present, all the sites are preparing for India's first DR-TB surveillance using WGS technology.

Way forward

With the deployment of bench-top sequencers and rapid analytical software, WGS is poised to become a useful tool in the future for both diagnosis and surveillance of Tuberculosis. As ongoing WGS projects obtain more data, we will be able to accurately predict resistance for most antibiotics. India is a high TB burden country contributing around one fourth of the total global TB cases annually. Introduction of WGS for routine diagnosis would thus be a major challenge owing to the large number of patients requiring testing and associated costs. Hopefully with the development of resources in future, we will be able to incorporate WGS technology into our diagnostic algorithms.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Uplekar M, Weil D, et al. WHO's new end TB strategy. *Lancet*. 2015;385:1799–1801.
2. McBryde ES, Meehan MT, Doan TN, Ragonnet R, Marais BJ, Guernier V, et al. The risk of global epidemic replacement with drug resistant M. tuberculosis strains. *Int J Infect Dis*. 2017;56:14–20.
3. Makhado NA, Matabane E, Faccin M, Pinçon C, Jouet A, Boutachkourt F, et al. Outbreak of multidrug-resistant tuberculosis in South Africa undetected by WHO-endorsed commercial tests: an observational study. *Lancet Infect Dis*. 2018;18:1350–1359.
4. Köser CU, Bryant JM, Becq J, et al. Whole-genome sequencing for rapid susceptibility testing of *Mycobacterium tuberculosis*. *The New England Journal of Medicine*. 2013;369(3):290–291.
5. Dheda K, Limberis JD, Pietersen E, et al. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study. *The Lancet Respiratory Medicine*. 2017;5(4):269–281.

M. Hanif*
New Delhi Tuberculosis Centre, JLN Marg, New Delhi, India

Vijay Kumar Arora
Tuberculosis Association of India, Red Cross Road, Gokul Nagar, Sansad Marg Area, New Delhi, Delhi 110001

**Corresponding author*. New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, Delhi Gate New Delhi, India-110002
Phone: 9810979064.
E-mail address: irldlndc@rntcp.org (M. Hanif)

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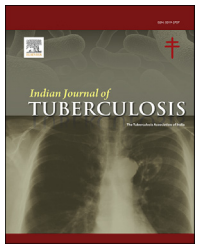

Editorial

Inhaled steroid – Long acting beta two agonist (ICS–LABA) combinations in asthma: Are all formulations the same?

Keywords:
Inhaled steroids
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Asthma
Formoterol-fluticasone

Asthma is one of the common health problem tackled by pulmonologists in their clinical practice. Asthma affects varying aged populations and its prevalence varies from 1% to 21% in adults.[1] Inhaled corticosteroids (ICS) are the fundamental agents used asthma treatment[2] with a short-acting b2-agonist (SABA) added as top up agents for acute symptom relief. However, many subjects treated in this fashion have inadequate asthma control.[3] Regular treatment with an ICS and a LABA, preferably as a fixed-dose combination, is advocated in subjects whose asthma is inappropriately controlled with moderate ICS doses alone; this may be supplemented by as and when needed doses of reliever inhaler. Usage of fixed dose ICS-LABA combination or single agent maintenance and reliever therapy (SMART) has proved to improve asthma control.[4] Therefore, ICS-LABA combination has been mentioned as a preferred option in asthma guidelines.[5,6] A fixed-dose combination (FDC) of ICS-LABA has beneficial impact on patient compliance to therapy. The combination inhaler minimises the potential to isolated SABA overuse for symptom relief as well as nullifies chances of ICS discontinuation. The additional need and expenses of separate inhalers is avoided.

Many formulations of ICS/LABA fixed-dose combinations (FDC) are available to treat asthma patients. These include budesonide/formoterol (Form-Bud) and salmeterol/fluticasone propionate (Sal-Flu) that have been available for many years with well established efficacy in multiple stringently designed RCTs. Other combinations have become available of late; these include beclometasone/formoterol, fluticasone/formoterol (FF) and vilanterol/fluticasone furoate. Mometasone/formoterol is also available in the USA. Thorough understanding of the relative merits and demerits of various ICS-LABA combinations will aid practitioners in their choice of asthma therapy.

The various ICS-LABA formulations available in Indian market include salmeterol–fluticasone, formoterol–budesonide, formoterol–mometasone and formoterol–fluticasone. Formoterol–beclomethasone combination is available in global market. Triple drug combinations (ILS–LABA with long acting antimuscarinic agent) are also commercially available, but predominantly cater to the need of COPD patients. Salmeterol–-fluticasone combination has been extensively studied in asthma and has been used in clinical practice for decades now. Although it affords excellent asthma control in clinical studies, the slow onset of bronchodilator action proves to be a stumbling block for usage as single inhaler maintenance and releiver therapy (SMART). Many studies have proved that the use of budesonide/formoterol as SMART improves both current asthma control as well as ameliorates risk of future exacerbations compared with fixed ICS/LABA use topped up by prn short-acting b2-agonist (SABA) administration. This improvement occurs despite a lower maintenance doses or cumulative ICS dose. A singleton study has shown that beclometasone/formoterol may be used as SMART with results similar to Form-Bud use. Formoterol–budesonide combination has excellent evidence and safety profile in pediatric population and pregnant ladies.

Among the various ICS–LABA combinations, FF deserves special mention. This combination has been freely available in India from the last decade. Both components of FF, fluticasone propionate (FP) and formoterol have peculiarities which makes this combination substantially advantageous in asthma therapy. FP has potent topical anti-inflammatory

activity,[7] and quick achievement of its peak action. Its systemic availability occurs solely via absorption from lungs, whereas for the other ICS oral bioavailability also needs to be considered. FP is more potent than budesonide, beclomethasone and flunisolide in the airways. Differences in the chemical structure account for varied clinical actions of inhaled beta 2 agonists.[8] Formoterol is a complete agonist at the beta 2 receptors and has fast onset of action than Salmeterol which is a partial agonist and exerts effect in a somewhat delayed manner. Although both drugs have prolonged action, Formoterol is intrinsically more active than Salmeterol. Rapid action onset is due to substantial solubility in aqueous solutions and adequate lipophilicity of Formoterol which promotes faster diffusion to the smooth muscle.

Direct comparision between the various ICS-LABA formulations is challenging because of the few head to head trials available. Comparisons between the newer formulations (Formoterol–mometasone, ultra LABAs etc) are scarce. Many of the studies have selected patient populations with moderate and reasonably controlled asthma; hence the superiority of an agent in severe asthmatics with frequent exacerbations is unclear.

A previous review[9] on single inhaler FF has critically appraised some of the less examined aspects of FF and concluded that FF inhaler has favorable efficacy and safety profile in real world. Change of therapy from other ICS-LABA to FF was well tolerated and health care costs were reduced in the studies evaluated in this review. The impact of these attributes on inhaler compliance has not been extensively studied. A recently published systematic review[10] analysed 16 studies comparing FF with other ICS–LABA with regard to clinical outcomes in asthma. FF therapy provided bronchodilatation with much less latency than SF. Improvement in pulmonary function was seen to a greater magnitude with FF inhaler use as compared with comparators. Asthma control and asthma related quality of life were comparable with FF as compared to Sal-Flu or Form-Bud. Lowest risk of pneumonia was seen with FF usage. The review concluded that FF provides faster onset of action, better improvement in lung function and equivalent asthma control than other ICS-LABA formulations. FF had better safety profile as noted by the lowest occurrence of pneumonia.

Increased risk of pneumonia has been reported with ICS use in asthma and COPD. However, RCTs conducted over 3–6 months may be too short to evaluate the real life pneumonia risk. A huge number of patients using ICS-LABA were evaluated for long length of time in a retrospective fashion in UK primary care.[11] The authors have critically gone through pneumonia events for up to 3 years after beginning ICS-LABA therapy. The occurrence of adverse events with FF were lower than SF or FB combinations. Specifically, the pneumonia risk per 100 person years was lowest for FF.

In addition to the administered drug, choice of inhaler delivery device is of paramount importance in asthma care. Poor inhaler technique and non-adherence effectively nullify the treatment benefit in asthma. A multitude of attributes like age, inspiratory capacity, beliefs, socio-cultural factors etc can influence the patient's capacity and intent to adhere to inhaled therapy. Treatment success is also determined by patient preferences and perceptions. Hence, consultants should ensure that they optimally match device prescriptions to respective patients' liking and abilities and empower patients by incorporating them into treatment decisions. Physicians have to be mandatorily aware of the characteristics and performance of each device in the patient population that they cater to.

Based on the above mentioned systematic review,[10] FF consistently demonstrates a faster onset of action that Sal-Flu. The asthma control, improvement in lung function and asthma related quality of life with FF has been shown to be superior in some studies and non-inferior in others. Healthcare budget allocation was lowest for FF in studies conducted in Europe. Incidence of pneumonia was lowest with FF in a long term real world study. In the light of these results, it may be concluded that the single inhaler FF formulation provides a therapeutic option in asthmatics requiring an ICS/LABA, with clinical outcomes that may position it as the agent of choice in this patient subset.

Novel aspects of the evidences on FF also deserve mention. FF achieves very good asthma control in real world settings, provides good results on switch over of therapy from other ICS-LABA and adequate drug deposition via HFA MDI and specialized devices.[9] Although the translation of these attributes on adherence to asthma drugs has not been formally evaluated, these unique features may prompt patients to better stick to their medications, a factor consistently improves real-world asthma control. Patients prefer drugs with rapid onset of bronchodilatation and have sustained action; hence, while choosing ICS/LABA combination, the potency of the ICS and the rapidity of action onset of LABA are given importance by the clinicians.[12,13] Hence a combination like FF containing components with the above-mentioned attributes has a definite edge in clinical practice.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Publ Health*. 2012;12(1):1–8.
2. Sin Don D, Man Jonathan, Sharpe Heather, Gan Wen Qi, Paul Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *JAMA*. 2004;292(3):367–376.
3. Global Initiative on Asthma (GINA). *Global Strategy for Asthma Management and Prevention*; 2020. Available from: http://ginasthma.org/.
4. Pedersen Søren, O'Byrne Paul. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy*. 1997;52:1–34.
5. Price David, Fromer Leonard, Kaplan Alan, Van Der Molen Thys, Román-Rodríguez Miguel. Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? *NPJ Prim Care Respr Med*. 2014;24(1):1–9.
6. (BTS). *B.T.S, BTS/SIGN British Guideline on the Management of Asthma*; 2016 [cited 2017 12 April]; Available from: https://

www.brit-thoracic.org.uk/standardsof-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/.
7. William KH. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43(3):519–527.
8. Lötvall J. Pharmacological similarities and differences between β2-agonists. *Respir Med*. 2001;95:7–11.
9. Rajesh V, Augustine J, Divya R, Cleetus M. Inhaled formoterol-fluticasone single inhaler therapy in asthma: real-world efficacy, budget impact, and potential to improve adherence. *Can Respir J J Can Thorac Soc*. 2020 Sep 14;2020.
10. Venkitakrishnan R, Thomas PK, Bansal A, et al. Fluticasone/Formoterol compared with other ICS/LABAs in asthma: a systematic review. *J Asthma*. 2021 Mar 9:1–3.
11. Price DB, Carter V, Martin J, et al. Comparative safety profile of the fixed-dose combination corticosteroid and long-acting β 2-agonist fluticasone propionate/formoterol fumarate: a 36-month longitudinal cohort study in UK primary care. *Drugs*. 2020 Jan;80(1):47–60.
12. Murphy KR, Bender BG. Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence. *J Asthma Allergy*. 2009;2:63.
13. Hauber AB, Mohamed AF, Johnson FR, Meddis D, Wagner S, O'Dowd L. Quantifying asthma patient preferences for onset of effect of combination inhaled corticosteroids and long-acting beta2-agonist maintenance medications. *Allergy Asthma Proc*. 2009 Mar 1;30(2):139–147.

Rajesh Venkitakrishnan*
Jolsana Augustine
Rajagiri Hospital, Kochi, India

**Corresponding author*. Tel.: +91 9745501976.
E-mail address: rajeshdhanya@rediffmail.com
(R. Venkitakrishnan)

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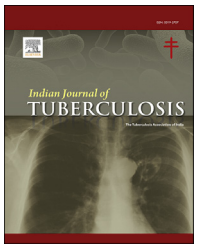

Viewpoint

Inhaled corticosteroids and risk of tuberculosis—How bad is the risk?

Rajesh Venkitakrishnan[*], *Divya Ramachandran*, *Jolsana Augustine*, *Melcy Cleetus*

Rajagiri Hospital, Kochi, Kerala, India

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ABSTRACT

Inhaled corticosteroids (ICS) have a central role in the management of obstructive airway diseases. Use of ICS in asthma and chronic obstructive pulmonary disease (COPD) is associated with a small but clear increase in incidence of pneumonia and tuberculosis. Since ICS use in obstructive airway diseases has beneficial effects with regard to symptoms, lung function, quality of life and exacerbations, denying the benefit of ICS solely based on this small elevated risk of pneumonias and tuberculosis is not justified. The present article attempts to elucidate mechanisms contributing to the increased risk, assesses the magnitude and risk factors of tuberculosis in patients using ICS and provides practical suggestions for practising clinicians.

1. Introduction

Inhaled corticosteroids (ICS) play a pivotal role in the management of obstructive airway diseases. They are the centre pillars of therapy in stable asthma.[1] Although COPD is being increasingly recognised and pictured as a steroid resistant disease, there are sub-categories within COPD where ICS therapy is encouraged. COPD patients with frequent exacerbations, those with significant peripheral blood eosinophilia and those who have overlap with an asthmatic phenotype are candidates for regular treatment with ICS.[2] Use of ICS in asthma and COPD is associated with a small but clear increase in incidence of pneumonia[3,4] which clinicians need to be aware and vigilant of. Given the synergistic benefits obtained with the combination of ICS with long acting beta 2 agonists (LABAs), a ICS-LABA combination has become the standard of care in asthma. Data have evolved with respect to risk of reactivation of latent tuberculosis infection (LTBI) also in asthma and COPD subjects using ICS.[5,6] On the other hand, ICS use in obstructive airway diseases has benefitial effects with regard to symptoms, lung function, quality of life and exacerbations. This benefit is specially worth mentioning in asthma and denying the benefit of ICS solely based on this small elevated risk of pneumonias and tuberculosis would be an injustice to asthma patients. The present manuscript attempts to analyse published evidences on the mechanisms, magnitude and risk factors of tuberculosis in patients using ICS and attempts to provide practical suggestions for practising clinicians.

2. Mechanisms of reactivation of LTBI

Inhaled corticosteroids are known to decrease local immunity in the lung. The known immunosuppressive effects of corticosteroids coupled with the high local concentrations

* *Corresponding author*. Tel.: +91-9745501976.
E-mail address: rajeshdhanya@rediffmail.com (R. Venkitakrishnan).
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achieved in the lung may contribute to a "localised immunosuppression" and increased risk of infections.[7] In fact, as mentioned previously, several studies and meta-analyses have found increased occurrence of pneumonia with ICS use. Corticosteroids act at multiple sites on the immune pathway resulting in a blunted immune response.[8] Steroid use leads to diminished monocytes in circulation which translates to impairment of monocyte functions like chemotaxis, killing of microbes and secretion of interleukin (IL)-1 and TNFα. In addition, T cell activation is inhibited resulting in inadequate cytokine production. Compartmentalisation of T lymphocytes to inactive sites and peripheral blood lymphocytopoenia results. Daily consumption of oral steroids at 7.5 mg of prednisolone[9] posed an elevated TB risk in one study. Realising that fluticasone at one tenth the dose of prednisolone produces similar adrenal suppression,[10] it may be reasonable to postulate that TB reactivation risk is elevated in patients using 750 mcg of fluticasone or equivalent per day.

3. Evidences for elevated risk

The risk associated with systemic corticosteroid therapy and reactivation of LTBI is clearcut and dose related.[9,11] A case–control study[9] revealed an adjusted odds ratio (OR) for TB of 4.9 in patients on OCS, which rose to 7.0 when prednisolone at mean daily dose of 7.5 mg or more was consumed. The risk association with ICS use is not as straight forward and GOLD guidelines 2019 acknowledge the uncertainty. Observational studies and some metaanalysis of randomized controlled trials tend to associate added risk, though.[10,12–14]

A nested case–control study[14] was undertaken in Canada on patients with obstructive airway diseases treated with ICS. The study population consisted of elderly citizens aged 66 years or more and was a mix of asthma, COPD and overlap syndrome. 4.1 lakh patients were identified in whom 2966 cases of NTM and 327 cases of TB occurred. ICS use was resulted in higher number of NTM infections (adjusted OR 1.86) and was statistically significant for fluticasone, but not for budesonide. The dose–event relationship between NTM disease and total ICS consumed was significant. The relation between ICS use and TB was not statistically significant (OR 1.43). This study concluded that ICS use is associated with an increased risk of NTM, but not TB. The study has the drawback that it was conducted at a setting with low population incidence of TB and hence has the inherent risk of underestimating the risk of progression of LTBI with ICS use.

A retrospective cohort study from Korea[15] looked at a 778 COPD patients who had COPD. 616 of them were followed them up for a period of 9 years. They were categorised based on their ICS use and radiological evidence of past TB in chest radiograph. 20 subjects from the study population developed pulmonary TB. Elevated risk was noted among the ICS those who had radiologic sequelae of TB (Hazard ratio of 9.079 in those with normal chest Xray versus hazard ratio of 24.946 in those with radiological sequelae). The radiological interpretation of healed TB can be subjective and overlapping radiological features can occur with non-mycobacterial disease. This factor seriously limits the extrapolation of this study into general practice.

A meta-analysis of RCTs that used ICS therapy for COPD for at least 6 months[11] (and reported occurrence of TB and influenza during the study or follow up period) was published in 2014. Twenty-five trials involving 22,898 subjects were analysed. ICS treatment led to a higher percentage of patients developing TB (OR, 2.29; 95% CI, 1.04–5.03). A higher number of ICS treated COPD patients developed TB in endemic areas when compared to non endemic areas. To be precise, the number of patients needed to be treated with ICS that results in one additional TB event was 909 in endemic areas versus 1667 in non-endemic areas. The study concluded that ICS use in COPD patients is associated with a higher risk of TB and this risk is higher in TB endemic areas. The results of this meta-analysis may be relevant to India.

RCTs badly replicate patient populations to whom the results need to be applied. Further, the quality of care ensured in RCTs is not extrapolatable in the real world. Hence, a meta-analysis of non randomised studies on ICS and TB risk was undertaken and published in 2019.[12] Nine studies published from 2010 to 2017 were analysed. A total of over 36,000 patients were reported. Use of inhaled corticosteroids resulted in an increased risk of TB (OR = 1.46; 95% CI 1.06 to 2.01). The risk was seen across all doses of ICS usage and a dose–response relationship was not demonstrated. Overuse of ICS by symptomatic patients in real world would have led to patients prescribed "low-to-medium ICS dose" ending up taking high doses. The population attributable fraction was very low (0.49%), thereby signifying the fact that the relative contribution of ICS usage to TB occurrence is very low.

4. Additional risk factors for TB in ICS users

From the preceeding studies,[11–15] it may be concluded that patients with radiological evidence of past TB, those with obstructive airway diseases and patients residing in high endemic areas are additional independent risk factors for TB among ICS users. Although not specifically looked for in trials or metaanalysis, it may be reasonable to assume that other immunosuppressing states like diabetes mellitus, TNF agent use and oral steroid use might have synergistic role. The immunosuppressive effects of ICS may be of much lesser magnitude as compared to oral corticosteroid (OCS) use and the additive risk may be insignificant, as concluded in one of the metaanalysis.[12] In this publication, the additional risk of TB with ICS use was not seen in current OCS users. A dose response effect with ICS usage is also postulated and association with high dose of ICS was seen in most studies except the metaanalysis by Castenella et al.[12]

5. Do all ICS-LABA combinations have similar risk?

Many formulations of ICS as well as ICS/LABA fixed-dose combinations (FDC) are available in the Indian market including budesonide/formoterol (Form-Bud), salmeterol/fluticasone propionate (Sal-Flu), beclometasone/formoterol, fluticasone/formoterol (FF) and mometasone/formoterol. Each formulation has unique pharmacological properties and the

risk of pneumonia and TB may be different for each. ICS use leads to a small increased risk of pneumonia.[16] In this context, the steroid with least pneumonia or TB risk has an obvious edge. The largest and longest real world study from UK database[17] to assess the pneumonia risk with various ICS-LABA formulations revealed that Formoterol-fluticasone (FF) is associated with the least pneumonia risk. Subsequent reviews and a systematic review[18,19] have echoed the findings of this study with regard to pneumonia risk associated with ICS-LABA.

Much less work has been done with the risk of TB with various ICS-LABA formulations. Fluticasone has been assessed in most studies involving TB risk of ICS usage and equipotent doses of other ICS have been extrapolated to have similar risk. A retrospective analysis of medical insurance records done in Taiwan[20] looked at 18,951 patients using ICS-LABA combinations, 11,515 of whom were using Sal – Flu and 7436 were using Form – Bud. During the follow up period, active TB occurred in 0.94% and 0.61% in the Sal - Flu and Form - Bud groups respectively. The Sal – Flu group had much more active TB cases (adjusted Hazard Ratio 1.41) even after competing risk analysis and matching of propensity score was done. This observation needs to be replicated in prospective studies before definite conclusions and practical recommendations can be made.

6. Recommendations for practitioners

As previously mentioned, inhaled steroids are valuable drugs in the treatment of obstructive airway diseases. A small elevated risk of TB should not preclude the astute clinician from using ICS or ICS-LABA in indicated cases, specifically those patients with asthma or asthma COPD overlap, where the benefits of ICS hugely outweigh the risks. As discussed, of 909 COPD patients treated with ICS in endemic areas, only one develops additional TB reactivation. The population attributable fraction of TB due to ICS usage is very low (0.49%), thereby signifying that 99% of TB reactivation occurring in endemic areas is not related to ICS usage. Special caution may be exercised in patients with past mycobacterial disease and vigilant watch out for new onset symptoms (fever, change in cough, weight loss etc) may be done. A low threshold should be kept for evaluation of tuberculosis in symptomatic patients and appropriate tests (sputum, chest radiograph etc) to confirm or reasonably rule out reactivation of TB should be carried out.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. *Global Strategy for Asthma Management and Prevention*; 2020. https://ginasthma.org/. Accessed May 6, 2021.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 Report*. GOLD; 2019. Available at: http://goldcopd.org/gold-reports/%20.
3. Calverley PM, Anderson JA, Celli B. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789.
4. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68(11):1029–1036.
5. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *Am J Respir Crit Care Med*. 2011;183(5):675–678.
6. Chung WS, Chen YF, Hsu JC, Yang WT, Chen SC, Chiang JY. Inhaled corticosteroids and the increased risk of pulmonary tuberculosis: a population-based case-control study. *Int J Clin Pract*. 2014;68(10):1193–1199.
7. Suissa S, McGhan R, Niewoehner D. Inhaled corticosteroids in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2007;4:535–542.
8. Lee C-H, Kim K, Hyun MK, et al. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax*. 2013;68:1105–1113.
9. Jick SS, Lieberman ES, Rahman MU. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum*. 2006;55:19–26.
10. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med*. 1999;159:941–955.
11. Dong YH, Chang CH, Wu FL, et al. Use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza: a systematic review and meta-analysis of randomized controlled trials. a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2014;145(6):1286–1297.
12. Castellana G, Castellana M, Castellana C, et al. Inhaled corticosteroids and risk of tuberculosis in patients with obstructive lung diseases: a systematic review and meta-analysis of non-randomized studies. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2219–2227.
13. Ni S, Fu Z, Zhao J, Liu H. Inhaled corticosteroids (ICS) and risk of mycobacterium in patients with chronic respiratory diseases: a meta-analysis. *J Thorac Dis*. 2014;6(7):971–978.
14. Brode SK, Campitelli MA, Kwong JC. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur Respir J*. 2017;50:1700037.
15. Kim JH, Park JS, Kim KH. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest*. 2013 Apr;143(4):1018–1024.
16. Singh S, Amin A, Loke Y. Longterm use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169(3):219–229.
17. Price DB, Carter V, Martin J. Comparative safety profile of the fixed-dose combination corticosteroid and long-acting b 2-agonist fluticasone propionate/formoterol fumarate: a 36- month longitudinal cohort study in UK primary care. *Drugs*. 2020 Jan;80(1):47–60.
18. Rajesh V, Augustine J, Divya R, Cleetus M. Inhaled formoterol fluticasone single inhaler therapy in asthma: real-world efficacy, budget impact, and potential to improve adherence. *Can Respir J J Can Thorac Soc*. 2020 Sep 14;2020.
19. Venkitakrishnan R, Thomas PK, Bansal A. Fluticasone/Formoterol compared with other ICS/LABAs in asthma: a systematic review. *J Asthma*. 2021 Mar 9:1–3.
20. Huang TM, Kuo KC, Wang YH. Risk of active tuberculosis among COPD patients treated with fixed combinations of long-acting beta2 agonists and inhaled corticosteroids. *BMC Infect Dis*. 2020;20:706.

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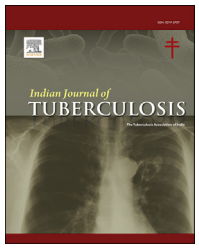

Viewpoint

Is pulmonary tuberculosis a true risk-factor for chronic obstructive pulmonary disease?

Surinder K. Jindal

Jindal Clinics, SCO 21, Sector 20 D, Chandigarh, 160020, India

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ABSTRACT

This viewpoint discusses the possible relationship of tuberculosis with chronic obstructive pulmonary disease. Pulmonary tuberculosis as a risk factor and/or complication of COPD is reported in several reports from African and Asian countries. History of TB seems to have an important role in the natural history of COPD. It is difficult to conclude whether this is a true causal relationship or merely an incidental observation due to the concurrent presence of the two commonly prevalent diseases and their risk factors. Many of these disease and treatment-related factors can promote and/or aggravate disease condition.

Chronic obstructive pulmonary disease (COPD), the third most common cause of death world-wide, poses a major burden on global health-care infrastructure.[1] Exposure to tobacco smoking, ambient air pollution and smoke from biomass fuels used for cooking and heating are some of the important risk factors of COPD.[2,3] Industrial exposures, childhood respiratory infections and tuberculosis (TB) are some of the other risk-factors which have been listed as possible causes of COPD, more so in case of non-smoker patients.[2,4] TB, the leading global cause of death from a single infectious agent, is a common disease which primarily affects the lungs. TB is one of the top 10 causes of death - an estimated 10 million people fell ill with TB and 1.4 million people died from TB in 2019 worldwide.[5]

Association of pulmonary tuberculosis (PTB) as a risk factor and/or complication of COPD is reported in several reports from African and Asian countries.[6–9] TB association has been reported in both non-smoker patients who are not exposed to the known risk factors as well as in the presence of tobacco smoking. This is however somewhat enigmatic to believe that a diffuse and progressive disease such as COPD could result from a healed and localized infection such as tuberculosis. Is it likely that any such association between the two diseases is a mere co-existence? It is important to analyze the reported sequelae of TB with particular reference to the presence of airways obstruction (AO) and chronic lung disease.

1. Sequelae of PTB

Treated in time, TB leaves nil or minor sequelae such as limited degree of scarring or calcification. It is not uncommon to find calcified granulomas or small linear scars on chest x-rays or computerized tomographic (CT) scans of otherwise healthy people in the third-world and developing countries. These findings are often attributed to old TB infection; healing of tubercular granulomas and cavities frequently results in

E-mail address: dr.skjindal@gmail.com.
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pulmonary scarring generally limited to the area of involvement with tuberculosis.

Significant anatomical and patho-physiological changes are seen even after completion of anti-tubercular treatment and complete bacteriological cure in patients with extensive disease especially in the presence of complications, delayed treatment and/or presence of additional factors or co-morbidities.[6] Chronic lung disease following complete treatment of TB is seen in the form of parenchymal lesions such as tuberculomas, thin walled cavities, broncholithiasis or cicatrization collapse. Other sequelae which are commonly described include the lesions of the airways (such as bronchiectasis or tracheobronchial stenosis), pleura and chest wall (empyema, fbrothorax, bronchopleural fistula and pneumothorax), pulmonary vasculature and mediastinum.[6,7]

Post TB patients are also more susceptible to future lung diseases and accelerated lung ageing. They are also predisposed to colonization and infection with non-tuberculous mycobacteria and fungi such as Aspergillus fumigatus. They may suffer from more frequent exacerbations of chronic obstructive pulmonary disease, bronchiectasis and pneumonias. Lung parenchymal damage due to post-TB fibrosis and bronchiectasis can lead to the development of pulmonary hypertension, chronic cor-pulmonale and chronic respiratory failure.

2. TB and chronic airways obstruction

It has always been a contentious issue whether long term sequelae of TB can progress to development of chronic airways obstruction or COPD. Historically, one can find reference to the association between TB and emphysema reported by Laennec over two hundred years earlier.[10] In the subsequent period, there had been mention of post-tuberculous "obstructive airways disease" in the medical literature in the 1950s and 1960s leading to comments by Hallet and Martin in 1961: "It is increasingly evident that a diffuse obstructive pulmonary syndrome is often associated with tuberculosis".[11] Ever thereafter, the association of COPD with TB in the developing countries continues to be widely recognised by clinicians in different clinical and/or epidemiological studies. Yet, it has remained a poorly understood subject in the absence of studies on pathogenesis and longitudinal relationship.

There are quite a few population studies which report TB as a risk factor for COPD. A nationwide survey in South Africa among 13,824 adults reported high Odds Ratios for this association (Men = 4.4; 95% CI = 2.6–9.2, Women = 6.6; 95% CI = 3.7–11.9)[12]. In a 5-city study from South America, the risk of COPD was more strongly associated with TB than with smoking or exposure to biomass smoke (Odds Ratio with history of TB = 2.9; 95% CI = 1.6–5.5; Odds Ratio with smoking = 2.6; 95% CI = 1.9–3.5)[13]. Similarly, in the Burden of Obstructive Lung Disease (BOLD) study of 14,050 patients from 18 countries, it was reported that there was a 2.5-fold increased risk of COPD with history of TB (independent of smoking and other factors).[14] It can be therefore safely surmised that long term lung-sequelae of pulmonary TB constitutes a significant contributor to COPD population attributable risk, esp. in TB endemic areas and in younger adults.

The association has been also reported in case–control and clinical studies. For example, among 5571 patients, there was a higher prevalence of COPD in those with a history of TB (30.7%) versus those without (13.9%).[15] In a recent study of 13,522 adults aged ⩾40 years in South Korea, there were 4.47 increased odds of airways obstruction (after adjusting for age, smoking, body mass index and other confounders) in patients detected to have history of TB and lesions on chest radiographs.[16] History of treated TB was an important risk factor for COPD (pooled OR = 3.05, 95% CI = 2.42–3.85) independent of smoking and age in a systematic review and meta-analysis of 9 eligible studies.[7] In the same report, it was also observed that increasing rates of smoking and worsening air pollution (indoor and outdoor) exacerbated the lung damage that results from TB.[7]

Besides the epidemiological link, there is adequate evidence to suggest an increased morbidity in COPD patients with associated TB. There were higher number of exacerbations associated with worsening of COPD and faster decline in lung function such as (FEV1); 93 of 598 patients (15%) hospitalized with COPD exacerbation, had a history of TB.[17] There was faster deterioration of health status as well as worsening survival in these patients. Patients with past TB were 4 years younger; these patients were diagnosed with COPD died 5 years earlier than others. The group of patients with past history of TB had higher arterial carbon dioxide tension and lower FEV1; higher hospitalization per year and lower median survival of 24 months compared to 36 months for those who did not have TB.[17] Some of the earlier studies, though small in nature and hospital based had also reported a significant association between the two diseases and/or presence of airways obstruction on lung function tests in patients with post-TB scarring.[18–21]

3. View point

There is enough published evidence to support an association and adverse relationship of TB with COPD. This has been particularly so in countries with high incidence of tuberculosis. There is also little doubt that history of TB has an important role in the natural course of COPD. It is however unclear whether this is a true' causal relationship or merely an incidental observation attributed to the co-presence of the two highly prevalent diseases. It is also possible that some of the related risk factors for poor lung function and airways obstruction after TB may include other associated co-variables which are widely prevalent in many developing countries. Some of these include the tobacco smoking, environmental factors like indoor smoke from biomass fuels, poverty, Human immunodeficiency virus (HIV) co-infection, childhood infections, other co-morbidities such as diabetes and industrial exposures (silicosis). HIV is increasingly being recognised as a cause of premature emphysema; emphysema occurs earlier, with fewer pack-yrs of smoking, and may be associated with colonisation by *P. jiroveci*.

Most of the epidemiological and clinical studies fail to find a causal relationship between the two diseases. TB heals by fibrosis which remains limited to the areas of infection. On the

other hand, COPD is a diffuse and progressive inflammatory disease of the airways and lung parenchyma. Post-tubercular fibrosis and/or parenchymal destruction of one or more lobes will result in some degree of airway distortion and loss of lung function. It is however a moot question whether the distortion and airway obstruction is also characterized by progression which one sees in COPD. Essentially speaking, post-TB airways obstruction does not fulfil both the important criteria of COPD as a diffuse and progressive disease.

On the other hand, if one considers COPD as any kind of airways obstruction, the spectrum will include a wide variety of illness causing lung destruction and fibrosis such as bronchiectasis, obstructive bronchiolitis, pneumoconioses and respiratory infections. This practice is likely to lump different diseases into a broad group of 'obstructive airway diseases' much like the approach to the 'interstitial lung disease'.

For routine clinical purpose, the lumping approach is reasonable as it helps in simplifying an otherwise complex disease syndrome. It is however antagonistic to the scientific way of thinking about the disease pathogenesis and management. Today, we understand COPD as a specific disease of chronic airway and systemic inflammation leading to progressive obstruction and consequences thereof. Association with TB, present or past is likely to be incidental. There are several disease and treatment-related factors which can promote and/or aggravate disease condition. But it is difficult to say whether TB leads to the development of COPD. As of today, one will need to revise the definition of COPD to link TB as its cause.

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Conflicts of interest

The author has none to declare.

REFERENCES

1. The Top 10 Causes of Death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. (Accessed on May 24, 2021).
2. Global Initiative for Chronic obstructive lung disease. Strategy for the diagnosis, management and prevention of chronic obstructive lung disease (2021 report). https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021 (Accessed on May 24, 2021).
3. Jindal SK, Jindal A. COPD in Biomass exposed non-smokers: a different phenotype. *Expet Rev Respir Med*. 2021;15(1):51–58.
4. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet*. 2009;374:733–743.
5. TB Statistics - 2019 Including Incidence. https://tbfacts.org/tb-statistics/(Accessed on May 24, 2021).
6. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. *Eur Respir Rev*. 2018;27:170077. https://doi.org/10.1183/16000617.0077- 2017.
7. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis*. 2015;32:138–146.
8. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration*. 2013;86:76–85.
9. Jung KH, Kim SJ, Shin C, Kim JH. The considerable, often neglected, impact of pulmonary tuberculosis on the prevalence of COPD. *Am J Respir Crit Care Med*. 2008;178:431.
10. Laënnec RTH. *In: A Treatise on the Diseases of the Chest (English Translation from the French) Forbes J*. London: T and G Underwood; 1821.
11. Hallett WY, Martin CJ. The diffuse obstructive pulmonary syndrome in a tuberculosis sanatorium. I. Etiologic factors. *Ann Intern Med*. 1961;54:1146–1155.
12. Ehrlich RI, White N, Norman R, et al. Predictors of chronic bronchitis in adults in South Africa. *Int J Tubercul Lung Dis*. 2004;8:369–376.
13. Caballero A, Torres-Duque CA, Jaramillo C, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest*. 2008;133:343–349.
14. Amaral AFS, Cotton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J*. 2015;46(4):1104–1112.
15. Menezes AM, Hallal PC, Perez-Padilla R, et al. Latin American project for the investigation of obstructive lung disease (PLATINO) team. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J*. 2007;30(6):1180–1185.
16. Choi CJ, Choi WS, Lee SY, Kim KS. The definition of past tuberculosis affects the magnitude of association between pulmonary tuberculosis and respiratory dysfunction: Korea National Health and Nutrition Examination Survey, 2008–2012. *J Kor Med Sci*. 2017;32:789–795.
17. Yakar HI, Gunen H, Pehlivan EP, Aydogan S. The role of tuberculosis in COPD. *Int J Chronic Obstr Pulm Dis*. 2017;12:323–329.
18. Hassan IS, Al-Jahdali HH. Obstructive airways disease in patients with significant post- tuberculous lung scarring. *Saudi Med J*. 2005;26(7):1155–1157.
19. Majumdar S, Sen S, Mandal SK. A hospital-based study on pulmonary function tests and exercise tolerance in patients of chronic obstructive pulmonary disease and other diseases. *J Indian Med Assoc*. 2007 Oct;105(10), 565-6, 568, 570.
20. Agarwal D, Gupta A, Janmeja AK, Bhardwaj M. Evaluation of tuberculosis associated chronic obstructive pulmonary disease at a tertiary care hospital: a case control study. *Lung India*. 2017;34:415–419.
21. Verma SK, Kumar S, Narayan K, Sodhi R. Post tubercular obstructive airway impairment. *Indian J Allergy Asthma Immunol*. 2009;23:95–99.

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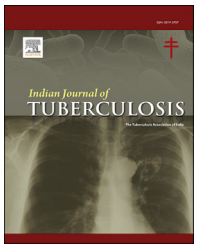

Original article

Challenges for tuberculosis control at selected primary healthcare centers in Bangladesh: A mixed-method study

Sarmin Sultana[*], *Marium Salwa*, *Muhammad Ibrahim Ibne Towhid*, *Syed Shariful Islam*, *M. Atiqul Haque*

Department of Public Health and Informatics, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, 1000, Bangladesh

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ABSTRACT

Background: The national tuberculosis control program in Bangladesh is progressing to end tuberculosis (TB) epidemic by 2035. Despite improved diagnostic and treatment facilities, the disease burden remains high. This mixed-method study aimed to identify existing challenges for successfully implementing the tuberculosis control program in primary healthcare centers (PHCs) of Bangladesh.

Methods: Qualitative data were collected by observing six PHCs and interviewing TB patients (n = 12) and healthcare providers (n = 12). Quantitative data were collected by interviewing 94 TB patients. Data were integrated through a narrative approach.

Results: Mean patient and health system delay were 99.0 (SD = 98.7) and 42.9 (SD = 79.9) days respectively. Patient delay was related to poor care-seeking behavior, unfamiliarity with tuberculosis symptoms, and unavailability of healthcare facilities. About 74 percent of patients sought initial treatment from village doctors or drug vendors. Health system delay was related to inadequate manpower, unskilled staff, and limited diagnostic facilities. Every second patient reported non-adherence to the directly observed treatment short-course (DOTS) guideline. DOTS provider's inaccessibility, inadequate incentive, and unreasonable patient demand lead to non-adherence. Insufficient administrative and structural facilities for infection control were observed at the selected facilities.

Conclusions: This study provides an insight into the recent challenges in TB control at PHCs in Bangladesh.

* *Corresponding author*. Department of Public Health and Informatics, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, 1000, Bangladesh. Tel.: +880 17357272623.
E-mail address: sarmindoc@gmail.com (S. Sultana).

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1. Introduction

Bangladesh is seventh among the 30 highest tuberculosis (TB) burden countries with 73,000 annual deaths.[1] The country adopted directly observed treatment, short-course (DOTS) strategy in 1993 through its National Tuberculosis Control Program (NTP), and since then, the government has been striving to strengthen NTP in collaboration with local and international partners.[2] An active case detection approach has been adopted by NTP to maximize case findings.

According to NTP, Bangladesh has achieved a treatment success rate of 95 percent for drug-susceptible TB and 73 percent for drug-resistant TB (DR-TB), while an estimated 39 percent drug-susceptible TB and 80 percent DR-TB cases still remain undetected.[3] Child TB detection rate in Bangladesh is only 3 percent,[4] which reflects under-reporting compared to global statistics of 11 percent.[5] NTP declared 100 percent DOTS coverage since 2003, but the quality remains largely unexplored.[2] Flora et al,[6] reported non-adherence to DOTS guidelines as a challenge in the Bangladeshi healthcare setting and an important factor for the development of DR-TB.

Empirical studies revealed several patient-level and system-level barriers related to patients' perception regarding illness, stigma, care-seeking behavior, knowledge about TB, poverty, accessibility of healthcare facilities, diagnostic capacity, health workforce for TB case finding, and treatment continuation.[7–10] Evidence suggests that undetected cases and inadequate infection control measures are accountable for a substantial disease burden.[11,12] It is important to identify context-specific barriers for effective TB control. This study was designed to identify recent challenges in controlling TB at primary healthcare centers (PHCs) in Bangladesh.

2. Methodology

2.1. Study design and settings

This mixed-method study was conducted from February to June 2019 in two administrative districts of Bangladesh. The study places were purposively selected from a district-wise list of low TB case notification rate.[3] Six Upazila (sub-district) Health Complexes (UHCs) based TB-DOTS facilities, three from each district, were selected randomly.

TB patients are monitored at specified time intervals for evaluation and documentation at UHCs. DOTS providers are assigned to all patients to ensure a regular intake of medicine. The providers are commonly community health volunteers (*Sasthya Shebika*), village doctors (informal healthcare providers), family members, cured TB patients, or government health staff.

2.2. Study population and sampling

A total of 94 TB patients aged above 18 years were interviewed while attending the DOTS corner for a follow-up visit.

Key informant interview (KII) was conducted with six government and six non-government organization (NGO) health officials who were responsible for the coordination of the TB program at the Upazila level. The government officials were Upazila Health and Family Planning Officers (UHFPO). NGO officials were three TB-Leprosy Control Officers (TLCO) and three Upazilla Managers (UM). In-depth interviews (IDI) were conducted with twelve purposively selected TB patients, two from each UHC, considering equal gender representation.

2.3. Research tool development

A semi-structured questionnaire was designed to obtain information about the patients' socio-demographic characteristics, healthcare-seeking behavior, patient delay, health system delay and treatment delay, DOTS supervision, and health education. Healthcare seeking behavior was evaluated by asking patients about whom they visited first with initial symptoms and the reason behind the delay in care-seeking. Patient delay was the duration from reported onset of symptoms to the first visit with a formal health provider (registered physician, e.g., MBBS or equivalent, and government or NGO healthcare staff). Health system delay was the duration between the first visit with a formal healthcare provider and diagnosis of TB, while treatment delay was the duration between confirmatory diagnosis and treatment initiation.

An observation checklist was designed to gather data about waiting room facilities, information education and communication (IEC) materials, logistics and human resources at UHCs.

The guidelines for IDI and KII were developed in consultative meetings with epidemiologists, anthropologists, and TB experts. Interview guidelines for IDI focused on patient's early symptoms, care-seeking behavior, treatment initiation and continuation, and hygiene practice to prevent infection transmission. Interview guideline for KII was comprised of questions regarding the challenges faced in case finding and ensuring proper treatment, logistic supply, healthcare provider's adequacy, and training.

2.4. Data collection

After explaining the study objectives to the respondents, IDI and KII were conducted in isolated places. All interviews were audio-taped and transcribed verbatim. The average duration of interviews was 30 minutes. Separate sets of patients were interviewed face to face for quantitative data. Observational data were collected on the initial day of data collection from each UHC.

2.5. Data analysis and integration

Descriptive statistics were used to present quantitative data as frequency, percentage, mean, and standard deviation (SD). Qualitative data were analyzed following the manual content analysis method. Initial key concepts (barriers in case finding, treatment initiation and continuation, and infection control measures) were derived from the literature review, which served as analytic categories or “master codes".[13] A line-by-line analysis of the interview transcripts and observations was done to generate codes under analytic categories. From these analytic categories, second and third level coding were conducted to generate themes and subthemes, respectively. Here, second and third level coding involved more detailed

Table 1 – Content analysis: Overview of category, themes, and subthemes.

Category	Themes and subthemes
1. Case finding	1.1 Patient delay
	Perception about the illness
	Care-seeking behavior
	Healthcare facility
	1.2 Health system delay
	Human resource
	Diagnostic facility
	1.3 Stigma related to TB
2. Treatment initiation and continuation	2.1 Treatment delay
	Ignorance of the patient
	Information about treatment
	2.2 Logistics supply
	2.3 Adherence to DOTS guideline
	Patients' inconvenience
	Negligence of DOTS provider
	Lack of incentive to DOTS provider
3. Infection control measures	3.1 Administrative measures
	3.2 Environmental control
	3.3 Personal respiratory protection

indexing of the interviews and observations. Finally, this coding scheme was applied to explore all the interview transcripts and observations by the research team, and a consensus was made on all codes to be grouped into particular categories, themes, and subthemes (Table 1).

Quantitative data were presented under the category of qualitative data using a weaving narrative approach.[14]

2.6. *Ethical consideration*

Ethical clearance was obtained from the institutional review board of Bangladesh Medical Research Council [BMRC/NREC/2016–2019/121]. Informed written consent was taken from each study participant after assuring the confidentiality of data.

3. Results

3.1. *Category 1: case finding*

3.1.1. *Quantitative finding*

Mean patient delay and health system delay were 99.0 (SD = 98.7) and 42.9 (SD = 79.9) days, respectively. Only 15 percent of patients visited a registered physician with their initial symptoms. Reliance on informal healthcare providers and negligence towards less severe symptoms were common reasons for the patient delay (Table 2).

3.1.2. *Qualitative finding*

3.1.2.1. *Patient delay*. Patients delayed in care-seeking due to their unawareness of TB symptoms like fever, cough or swelling in the neck. The majority of the patients thought they had a common cold, and it would be cured with medicine from a village doctor or drug vendor. Patients mostly visited a registered physician or government health facility when their condition deteriorated. A 60-year aged male patient said,

Table 2 – Patient's health care-seeking behavior (n = 94).

Care-seeking behavior	Frequency	Percentage
First medical consultation from		
Village doctor	41	43.6
Drug vendors	29	30.9
Registered physician	14	14.9
Govt. Field staff	10	10.6
Reason for patient delay[a]		
Reliance on informal health care provider	49	52.1
Negligence until severe symptoms	26	27.7
Waiting for natural cure	17	18.1
Lack of awareness about TB symptoms	16	17.0
Poverty	6	6.4
Distance	4	4.3

[a] Multiple responses.

> "I went to the pharmacy (drug vendor) for my fever. Even after one month, my condition did not improve. Then my neighbors suggested visiting a *Kabiraj* (informal practitioners who use wild plants for therapeutic purposes) in our village. After another month, I could not move out of bed. So, my son took me to the doctor and I am better now."

Another reason behind the patient delay was inadequate awareness-building campaigns by the government. One TLCO stated,

> "Patients don't consider visiting a health facility with a cough for two weeks. I don't blame patients, it's our fault. We failed to communicate the message and create awareness."

Service providers mentioned the distance of healthcare facilities while explaining the patient delay. Sometimes, patients start self-medication as it is difficult for them to travel from a remote area and seek appropriate healthcare. Occasional measures like announcements through loudspeakers were taken to encourage these patients to attend healthcare facilities. Although this measure is effective to some extent, it is inconvenient for regular practice.

3.1.2.2. *Health system delay*. Health system delay in TB control is largely related to the scarcity of registered medical doctors at UHCs. Only two of the selected UHCs had a registered physician assigned in TB control program. One UHFPO expressed,

> "If we don't have adequate doctors, there will be substandard performance. I'm suffering a lot to run a 50-bedded hospital with only three doctors where there should have been 21 doctors. Ultimately, clinical detection of tuberculosis has decreased drastically in this area."

Inadequate training of health staff in TB diagnosis was another reason for health system delay. Community-level government healthcare staff who follow the 'Integrated Management of Childhood Illness' strategy for treating under 5 children lack appropriate training on child TB. They often

fail to distinguish between pneumonia or other respiratory illness and TB.

Lack of laboratory facilities was also a cause of health system delay. Although all six UHCs had functioning sputum microscopy, only three facilities had operable X-ray machines. Two extra-pulmonary TB patients mentioned a year delay in diagnosis due to a lack of expert medical opinion and unavailability of diagnostic facilities. One TLCO addressed as,

> "We need diagnostic facilities nearby. We've to send patients to the capital for FNAC or biopsy. We only have three facilities for GeneXpert to cover an entire district."

Service providers complained about limited training programs on the latest diagnostic tools like GeneXpert for laboratory technologists.

3.1.2.3. Stigma related to TB. The active case finding approach was often interrupted due to patients' tendency to hide their disease owing to social stigma related to TB. Sometimes, they did not allow service providers to visit their household for screening the contacts. Service providers mentioned that educated and affluent patients are challenging to deal with. These patients demand privacy while they should have campaigned to remove the stigma and create awareness. One TLCO stated,

> "Generally, some educated patients, unmarried girls, and higher economic group request to hide the information. When we find a positive case, we usually conduct a screening investigation in the family and all nearby households. As they don't allow us to visit their home, it hampers the active case finding process."

3.2. *Category 2: treatment initiation and continuation*

3.2.1. *Quantitative finding*

The mean treatment delay was 1.1 (SD = 0.5) days. About 50 percent patient reported non-adherence to the DOTS guideline. The assigned DOTS providers were *Sasthya Shebika* (n = 24), village doctor (n = 17), family members (n = 35), and government health staff (n = 18). About 84 percent *Sasthya Shebika* and 69 percent of family members supervised intake of TB medicine regularly, while 90 percent of the village doctors and government health staff did not follow the guideline.

3.2.2. *Qualitative finding*

3.2.2.1. Treatment delay. Service providers mentioned that patients are usually compliant with TB treatment, and there is a minimum treatment delay. Few patients and their family members at times denied the disease and became rude with service providers. One UM mentioned,

> "When the patient's father was informed that his son has TB, he became angry and made slanderous remarks saying no one in their family ever suffered from TB, and it can't happen in their family."

Almost all patients start anti-TB medication without any delay after diagnosis. One female patient reported that she had to purchase drugs for two months after diagnosis as she did not know about free treatment. She suggested mass-media campaigning for detailed information on TB treatment.

3.2.2.2. Logistics supply. All selected UHCs had insufficient logistics supply like sputum mug, drug, TB card, etc. In one facility, patients were seen bringing sputum samples in small containers from home. Some patients from remote areas attended UHC to receive their daily dose of TB medication, whereas these drugs should be available to the nearest DOTS providers. One service provider mentioned,

> "We are facing some crisis with logistics like sputum mug and drugs for a few months. We aren't getting buffer stock for a year. We've to borrow from other centers to minimize the crisis."

Even after introducing Category-II TB with 4FDC and Levofloxacin, it was reported that there is no supply of Levofloxacin in some UHCs. So, TB patients had to purchase this drug from drug vendors.

3.2.2.3. Adherence to DOTS guideline. DOTS providers often failed to follow the NTP guideline. Some key informants reported negligence of DOTS providers and patients' demand for advanced medication supply as the possible reasons. One UM said,

> "Sometimes, patients ask for a medicine from providers on different excuses. Again, some providers think the patient will have to come every day. So, they hand over the medication to patients."

Distance between patient's and DOTS provider's residence often interrupts the proper implementation of the DOTS strategy. A patient said her son fetches medicine for 10 day as she lives far away from *Shebika*'s home, across the river.

Some patients refuse to receive DOTS service for fear of social isolation and losing dignity. Service providers often failed to monitor these patients whether they took the anti-TB drug regularly.

Lack of incentive was another limitation for discharging effective service. Service providers emphasized that regular supervision was relatively higher by *Shebikas* as they are paid a certain amount while, in most cases, village doctors are not given incentives for supervision. One TLCO mentioned,

> "When a village doctor gives symptomatic treatment to TB patients, they can sell medicines on an average of 1,000 BDT (12 USD). They also get monetary benefits from the diagnostic centers if they refer patients. However, when they refer the symptomatic patient to TB health facilities and perform DOTS for six months, they don't get a penny. Why would they be enthusiastic about DOTS?"

3.3. *Category 3: infection control measures*

3.3.1. *Quantitative finding*

Around 90 percent of TB patients were aware that they would transmit infection, while 80 percent did not know when they

would stop spreading infection. About 25 percent of TB patients were not informed about the side effects of anti-TB drugs and 70 percent did not know when to stop TB medication. Around 20 percent of patients did not know about any follow-up investigations.

3.3.2. *Qualitative finding*

3.3.2.1. *Administrative measures*. There were no observed measures for screening and prioritizing coughing patients to reduce waiting time at the facilities. Only one UHC had a separate waiting area for TB patients, while all patients had to share a common waiting space at other facilities. One UHFPO said,

> "DOTS corner shouldn't be in the hospital's main building. It should be anyhow isolated. Our DOTS corner is at the entrance of the hospital, next to the pathology room. TB patients wait at the corridor, putting other patients at risk."

None of the UHCs had displayed IEC materials on cough etiquette. Also, there were limited activities for patient education and counseling on TB disease and transmission. Patients emphasized using separate utensils, sleeping in separate rooms, and covering food to prevent contamination by flies when they were asked about how to stop spreading infection.

3.3.2.2. *Environmental control*. DOTS corners of all the UHCs had open windows and mechanical ventilation. However, at five facilities, the DOTS corner was a single room unit used to attend all suspected patients, registration, sample collection, follow-up examination, and sputum microscopy. DOTS corners were found crowded most of the time with patients. One NGO professional mentioned that they are always scared of getting infected because of an unsafe working environment.

3.3.2.3. *Personal respiratory protection*. A few patients were observed wearing masks during their visit at UHCs. Not every patient had a positive attitude towards using masks or covering mouth while coughing and sneezing. A 65 years old pulmonary TB patient who runs a tea stall explained that he needs not to wear a protective mask as he is on TB medication, and there is no chance of TB spread. Moreover, none of the service providers was found using masks while interacting with TB patients.

4. Discussion

This study elucidates that patient delay is commonly related to patients' practice of consulting village doctors or drug vendors with initial symptoms, negligence towards less severe symptoms, and the tendency to visit formal healthcare providers only when condition deteriorates. Shatil et al,[15] found a similar habitual approach of care-seeking from informal healthcare providers among Bangladeshi TB patients. However, such behavior has been described as a hindrance for early case detection and treatment in empirical studies.[16,17]

Patient's unawareness about TB symptoms, the distance of the nearest healthcare facility, shortage of manpower, inefficiency of service providers, and lack of diagnostic facilities are found to be the barriers of early case detection. Studies reported that greater knowledge on TB and nearby health facility is related to shorter patient delay, while efficient healthcare provider and diagnostic capacity is associated with shorter health system delay.[18–20] Moreover, findings of this study revealed that any interruption in logistic supply makes efficient TB service difficult for patients and service providers.

This study reflects how stigma compels patients to hide their disease, which interferes with the active case finding approach and DOTS activity. Paul et al,[21] also reported on the prevailing stigma around TB in Bangladesh, especially for females. A systemic review by Courtwright & Turner[22] showed that TB related stigma results in delayed care-seeking and poor treatment compliance.

Healthcare providers' adherence to DOTS guideline was found to be largely absent in the present study. DOTS providers' negligence to monitor patients regularly, long distance of patients' residence from DOTS provider's place, and lack of monetary incentive to DOTS providers are found as reasons for irregular DOTS. Gebreegziabher, Yimer, & Bjune[23] also reported DOTS provider's non-adherence to guidelines and health workers' dispense of TB drugs while describing poor monitoring system in Ethiopia.

This study showed inadequate administrative measures and the use of personal protective equipment for infection control at healthcare centers. Engelbrecht et al,[12] suggested that administrative measures like screening, separation, and health education programs are cost-effective and straightforward ways to protect staff and other patients from being exposed to TB. Bulage, Sekandi, Kigenyi, & Mupere[24] recommended adherence to a structured guideline and development of user-friendly IEC material might be helpful for effective TB control.

5. Limitation

The findings could not be generalized for other areas of the country as data were collected from only two administrative districts. A country representative sample and interviews with DOTS providers and treatment default patients might help better understand the challenges.

6. Conclusion

The study reflects patients' habitual approach of care-seeking from informal healthcare providers and lack of awareness about TB symptoms. Social stigma, unavailability of healthcare and diagnostic facilities, insufficient human resources, irregular logistic supply, and non-adherence to DOTS guidelines were identified as barriers in TB care. Measures are required to address infection control, like having an isolated waiting area for TB patients, well-displayed IEC materials, and regular health education sessions.

Data availability

Qualitative data: Data file is available from the Mendeley Data repository: https://data.mendeley.com/datasets/ztdxvpy2k3/1. Citation: Citation: Sultana, Sarmin (2020), "Challenges TB control program", Mendeley Data, V1, https://doi.org/10.17632/ztdxvpy2k3.1.

Quantitative data: Data file is available from the Mendeley Data repository: https://data.mendeley.com/datasets/7twpd239x6/1. Citation: Sultana, Sarmin (2020), "Challenges TB control program; from patient's experiences", Mendeley Data, V1, https://doi.org/10.17632/7twpd239x6.1.

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Islam MS, Sultana R, Hasan MA, Horaira MA, Islam MA. Prevalence of tuberculosis: present status and overview of its control system in Bangladesh. *Int J Life Sci Sci Res*. 2017;3(6):1471–1475. https://doi.org/10.21276/ijlssr.2017.3.6.8.
2. National Tuberculosis Control Programme. In: *National Guidelines and Operational Manual for Tuberculosis Control*. 5th ed. Dhaka, Bangladesh: National Tuberculosis Control Programme; 2013. https://www.ntp.gov.bd/ntp_dashboard/magazines_image/National%20Guide%20Lines-TB%205th%20Ed%20(1).pdf. Accessed April 21, 2021.
3. National Tuberculosis Control Programme. *Tuberculosis Control in Bangladesh Annual Report*; 2017. http://www.ntp.gov.bd/ntp_dashboard/magazines_image/NTP%20Annual%20Report-%202017.pdf. Accessed August 15, 2019.
4. Islam Z, Sanin KI, Ahmed T. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation. *BMC Publ Health*. 2017;17:131. https://doi.org/10.1186/s12889-017-4062-9.
5. World Health Organization. *Global Tuberculosis Report 2019*. Geneva, Switzerland: World Health Organization; 2019. https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1. Accessed November 21, 2019.
6. Flora MS, Amin MN, Karim MR, et al. Risk factors of multi-drug-resistant tuberculosis in Bangladeshi population: a case control study. *Bangladesh Med Res Counc Bull*. 2013;39(1):34–41. https://doi.org/10.3329/bmrcb.v39i1.15808.
7. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. *PLoS Med*. 2007;4(7):238. https://doi.org/10.1371/journal.pmed.0040238.
8. Cremers AL, Gerrets R, Kapata N, et al. Tuberculosis patients' pre-hospital delay and non-compliance with a longstanding DOT programme : a mixed methods study in urban Zambia. *BMC Publ Health*. 2016;16(1):1130. https://doi.org/10.1186/s12889-016-3771-9.
9. Sullivan BJ, Esmaili BE, Cunningham CK. Barriers to initiating tuberculosis treatment in sub-Saharan Africa : a systematic review focused on children and youth systematic review focused on children and youth. *Glob Health Action*. 2017;10(1). https://doi.org/10.1080/16549716.2017.1290317.
10. Huq KATME, Moriyama M, Zaman K, et al. Health seeking behaviour and delayed management of tuberculosis patients in rural Bangladesh. *BMC Infect Dis*. 2018;18(1):515. https://doi.org/10.1186/s12879-018-3430-0.
11. Nathavitharana RR, Daru P, Barrera AE, et al. FAST implementation in Bangladesh: high frequency of unsuspected tuberculosis justifies challenges of scale-up. *Int J Tubercul Lung Dis*. 2017;21(9):1020–1025. https://doi.org/10.5588/ijtld.16.0794.
12. Engelbrecht MC, Kigozi G, Janse van Rensburg AP, Van Rensburg DHCJ. Tuberculosis infection control practices in a high-burden metro in South Africa: a perpetual bane for efficient primary health care service delivery. *African J Prim Heal care Fam Med*. 2018;10(1). https://doi.org/10.4102/phcfm.v10il.1628.
13. Priest H, Roberts P, Woods L. Qualitative approaches. *Nurse Res*. 2017;10(1):30–42.
14. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs — principles and practices. *Health Serv Res*. 2013;48(6):2134–2156. https://doi.org/10.1111/1475-6773.12117.
15. Shatil T, Khan N, Yunus F, et al. What constitutes health care seeking pathway of tb patients : a qualitative study in rural Bangladesh. *J Epidemiol Glob Health*. 2019;9(4):300–308. https://doi.org/10.2991/jegh.k.190929.001.
16. Fluegge K, Malone LL, Nsereko M, et al. Impact of geographic distance on appraisal delay for active TB treatment seeking in Uganda: a network analysis of the Kawempe Community Health Cohort Study. *BMC Publ Health*. 2018;18(1):798. https://doi.org/10.1186/s12889-018-5648-6.
17. Sundaram N, James R, Sreynimol U, et al. A strong TB programme embedded in a developing primary healthcare system is a lose-lose situation: insights from patient and community perspectives in Cambodia. *Health Pol Plann*. 2017;32(2):32–42. https://doi.org/10.1093/heapol/czx079.
18. Bojovic O, Medenica M, Zivkovic D, et al. Factors associated with patient and health system delays in diagnosis and treatment of tuberculosis in Montenegro, 2015–2016. *PloS One*. 2018;13(3), e0193997. https://doi.org/10.1371/journal.pone.0193997.
19. Demissie M, Lindtjorn B, Berhane Y. Patient and health service delay in the diagnosis of pulmonary tuberculosis in Ethiopia. *BMC Publ Health*. 2002;2(1):23. https://doi.org/10.1186/1471-2458-2-23.
20. Awoke N, Dulo B, Wudneh F. Total delay in treatment of tuberculosis and associated factors among new pulmonary TB patients in selected health facilities of Gedeo Zone , Southern Ethiopia , 2017/18. *Interdiscip Perspect Infect Dis*. 2019;2019:1–14. https://doi.org/10.1155/2019/2154240.
21. Paul S, Akter R, Aftab A, et al. Knowledge and attitude of key community members towards tuberculosis: mixed method study from BRAC TB control areas in Bangladesh. *BMC Publ Health*. 2015;15(1):52. https://doi.org/10.1186/s12889-015-1390-5.
22. Courtwright A, Turner AN. Tuberculosis and stigmatization: pathways and interventions. *Publ Health Rep*.

2010;125(4):34–42. https://doi.org/10.1177/00333549101250S407.
23. Gebreegziabher SB, Yimer SA, Bjune GA. Qualitative assessment of challenges in tuberculosis control in West Gojjam Zone, Northwest Ethiopia: health workers' and tuberculosis control program coordinators' perspectives. *Tuberc Res Treat*. 2016:1–8. https://doi.org/10.1155/2016/2036234.
24. Bulage L, Sekandi J, Kigenyi O, Mupere E. The quality of tuberculosis services in health care centres in a rural district in Uganda: the providers' and clients' perspective. *Tuberc Res Treat*. 2014. https://doi.org/10.1155/2014/685982.

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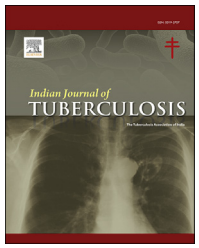

Original article

Trends and sub-national disparities in TB notifications in India: Insights from HMIS data

Javeed A. Golandaj[*], *Suvarna K. Naikar*, *Jyoti S. Hallad*

Population Research Centre, (Under Ministry of Health and Family Welfare, GOI), JSS Institute of Economic Research, Dharwad, Karnataka, 580004, India

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ABSTRACT

Background/objectives: Tuberculosis (TB) is a public health crisis across the globe, especially in the developing world including India. Around 27% of 10 million TB cases and 33% of 1.2 million TB deaths were contributed from India alone during 2018. Present study aims to estimate TB notification rates at national and sub-national levels up to District administrative blocks, which is very important with policy perspective.

Methods: The study mainly uses data from India's Health Management Information System (HMIS) for three consecutive years, 2017-18, 2018-19 and 2019-20. TB notification rates were calculated for India up to the lowest administrative level of health Districts. GIS maps were being used for mapping District-wise TB notification rates for 2017-18 and 2019-20.

Results: Results show that TB notification rates have increased from 152/lakh population in 2017-18 to 197 in 2019-20, an increase of 30%. Similarly, the increasing trends in TB notification rates were also observed at State as well as District level. However, wide rural-urban and public-private differences were observed in TB notification rates. Further, results illustrated huge inter-State and inter-District variations; and half of the TB cases in India were contributed only by six larger States.

Conclusions: The findings of the study shows the increasing notification in India since 2017-18, which is a clear indication of the efforts put in the TB program to achieve targets and goals committed to end TB by 2025. In this regard present estimates based on HMIS data significantly contributes to the policy formulation even at the lowest administrative level of health Districts.

1. Introduction

Tuberculosis (TB) is a public health crisis across the globe, especially in the developing world including India. The Global Tuberculosis Report-2019 estimated 10 million new TB cases globally in 2018, of these; 2.7 million new cases were reported in India alone. Similarly, one-third of 1.2 million TB deaths were reported in India alone.[1] Moreover, India is ranked in the top of high TB burden countries; and top eight countries that contributes to two-thirds of TB

* *Corresponding author*. Tel.: +91 9886110749.
E-mail address: javeediips@gmail.com (J.A. Golandaj).

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disease burden are India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%).[1]

Furthermore, The TB case notification has witnessed a tremendous increase in recent years both globally,[1] and in India.[2] Moreover, the increase in the global TB notifications is mainly explained by the trends in India and Indonesia, the two countries that rank first and third worldwide in terms of estimated incidence cases per year. India has reported a record increase of 60% in new TB notifications, from 1.2 million cases in 2013 to 2.0 million cases in 2018.[1] Similarly, according to "India TB report-2020", India has reported a record high notification of 24 Lakh TB cases in 2019; an increase of over 12% as compared to 2018. This translates to an incidence rate of approximately 159 cases/lakh population. However, over half of the total notifications are contributed by five States namely Uttar Pradesh (20%), Maharashtra (9%), Madhya Pradesh (8%), Rajasthan (7%) and Bihar (7%).[2]

1.1. *Tuberculosis control program in India*

TB control activities have been implemented in the country for more than 50 years. The National Tuberculosis Programme (NTP) was launched by the Government of India in 1962. Further, a joint review of NTP by the Government of India, the World Health Organization (WHO) and the Swedish International Development Agency (SIDA) in 1992 found some shortcomings. Around the same time in 1993, the WHO declared TB as a global emergency, devised the Directly Observed Treatment Short-course (DOTS), and recommended it to be followed by all countries. Accordingly, the Government of India revitalized NTP as "Revised National Tuberculosis Control Programme (RNTCP)" in the same year. Moreover, DOTS was officially launched as the RNTCP strategy in 1997 and by the end of 2005 the entire country was covered under the programme.[3,4]

1.2. *Global and Indian commitments to end TB*

Sustainable Development Goals (SDGs) Target 3.3 includes ending the TB epidemic by 2030.[5] The End Tuberculosis Strategy, a WHO initiative, aims to achieve 20% reduction in TB incidence and 35% reduction in the absolute number of deaths by 2020 and a 90% reduction in TB incidence and 95% reduction in TB deaths by 2035, compared with 2015.[6] Following the targets of SDGs and the End TB Strategy, Government of India has committed to the SDG goal of eliminating TB in the country by 2025, five years ahead of the Global target. In the light of this, RNTCP, which was revitalized from NTP in 1993, was again renamed as "National Tuberculosis Elimination Program (NTEP)".[2,4] Moreover, "National Strategic Plan for Tuberculosis 2017–2025" (NSP) for control and elimination of TB in India by 2025 was released. In response to this, many States/Union Territories (UTs) have committed to end TB even before 2025.[2,4] Moreover, Government of India's 2018 gazette on behalf of the Ministry of Health and Family Welfare (MoHFW) gave strength to implement 'mandatory TB notification' for private practitioners, chemists and public health staff in the country.[2,7]

1.3. *Rationale*

Though, there are lots of studies which deal with TB, but again these are limited to regional and based on small samples. Moreover, India lacks a national TB prevalence survey, such prevalence surveys have provided rich insights in other Asian countries, is a major limitation[8]; and hence, there is dearth of studies which provide pan-India TB scenario, especially by lowest level of administrative control, such as Districts. Further, in the larger perspective it is a cause of concern as India contributes highest share in terms of absolute numbers of TB cases and deaths attributable to TB at the global level, and a study on TB care in India's public sector by Subbaraman, et al[9] found that around half of the TB cases went unregistered in India. In this perspective, the status of TB in India needs to be addressed through every possible source. In this regard, the Health Management Information System (HMIS), which provides vast information related to all healthcare service delivery including TB disease at national, sub-national, and even lower level up to Districts and sub-district level, may be a good source of data. But unfortunately it had not been explored till data to understand the TB situation in India. In this background the present study aims to estimate TB notification rates at national and sub-national levels up to District administrative blocks, which is very important with policy perspective.

2. Methods

2.1. *Ethical consideration*

Present study was approved by the Ministry of Health and Family Welfare (MoHFW), Government of India, under the Annual Work Plan (AWP) of Population Research Centres (PRCs). Further, the study utilized data obtained from Health Management Information System (HMIS), a web portal under digital initiative of MoHFW, which is an anonymous service delivery dataset, with no personal identifiable information on patients. Hence, no separate ethical approval was required as the HMIS collects the secondary data from the health-care facilities across India.

2.2. *Data source*

Present study mainly uses data from India's Health Management Information System (HMIS), a digital initiative launched in October 2008 under National Health Mission (NHM), a flagship healthcare programme under the MoHFW, Government of India.[10,11] HMIS data specifically designed to support planning, management, and decision making based on service delivery indicators at Block, District, State as well as National level. Universal data elements enable the HMIS to capture

similar information recorded across districts as well as at different healthcare facilities including Primary Health Centre (PHC), Community Health Centre (CHC), Sub-Divisional Hospital (SDH) and District Hospital (DH), and even as well as private hospitals.[10–12]

2.3. Data elements used

Following three HMIS data elements were being used for present analysis; 1) Number of on-going DOTS patients registered, 2) Number of DOTS cases completed successfully, and 3) Number of Adolescent/Adult deaths due to Tuberculosis. For all these data elements, the study uses HMIS data for three consecutive years 2017-18, 2018-19 and 2019-20.[13] The details of the number of TB cases by rural-urban and public-private healthcare facilities reported during three years, 2017-18, 2018-19 and 2019-20, was presented in Annexure 1.

In addition to HMIS data, projected population figures for India and States/UTs provided by the Office of the Registrar General of India,[14] as well as District level population projection for 640 census Districts provided by Chauhan, et al[15] were used to estimate TB notification rates to population.

2.4. Analysis plan

Furthermore, to estimate the TB notification rates, all three data elements of HMIS associated with TB have been clubbed to get total positive cases during the years. The TB notification rate is estimated based on per 100,000 population at National, States/UTs and District level using total TB positive cases reported during the year in the numerator and projected population[14,15] for the year in the denominator as follow:

$$\text{TB Notification Rate} = \frac{\textit{Total TB positive cases reported during the year}}{\textit{Projected population for the year}} * 100,000$$

Additionally, for spatial analysis, QGIS software[16] - an open source Geographic Information System (GIS) (available at: http://qgis.osgeo.org) - was being used to show the TB notification rates at District level. These estimates were done for all 640 census Districts according to the 2011 census using HMIS data for the year 2017-18 and 2019-20. It should be noted here that HMIS provides data for 704 Districts for the years considered for analysis, but for spatial analysis purposes, the authors have clubbed data according to 2011 census Districts, and the results are presented in GIS Maps.

The detailed descriptions of abbreviations used for Indian States and UTs in Figures are as follow: A&N = Andaman & Nicobar Islands; AP = Andhra Pradesh; AR = Arunachal Pradesh; AS = Assam; BR=Bihar; CH=Chandigarh; CT=Chhattisgarh; D&N = Dadra & Nagar Haveli; D&D = Daman & Diu; DL = Delhi; GA = Goa; GJ = Gujarat; HR=Haryana; HP=Himachal Pradesh; JK = Jammu & Kashmir; JH = Jharkhand; KA=Karnataka; KL=Kerala; LD = Lakshadweep; MP = Madhya Pradesh; MH = Maharashtra; MN = Manipur; ML = Meghalaya; MZ = Mizoram; NL=Nagaland; OR=Odisha; PY=Puducherry; PB=Punjab; RJ = Rajasthan; SK=Sikkim; TN = Tamil Nadu; TG = Telangana; TR = Tripura; UP=Uttar Pradesh; UT=Uttarakhand; WB=West Bengal.

3. Results

3.1. Tuberculosis case count and notification rates

Fig. 1 presents the absolute number of TB case count and notification rates at national level for three consecutive years. The HMIS data shows TB case count and notification rates at national level have increased every year since 2017-18. During 2019-20, India reported the highest number of TB cases (26.4 lakhs) compared to 2017-18 (19.8 lakhs) and 2018-19 (23.9 lakhs), respectively; and highest notification rates (197/lakh Population) compared to 2017-18 (152) and 2018-19 (180), respectively, on record (Fig. 1). However, this represents 33% increase in TB case count (Results not shown) and 30% increase in TB notification rate between 2017-18 and 2019-20 (Fig. 5).

3.1.1. Rural–Urban differences in TB notifications

Similarly, estimation of TB notification rates by rural-urban regions shows noticeable differences. The TB notification rate was higher in rural (224/lakh population) compared to urban (145/lakh population) during 2019-20 (Fig. 2). Moreover, the increasing trend of TB notifications in both the regions also shows substantial differences. The TB notification rate was 172 and 109 per/lakh population during 2017-18 in rural and urban areas, respectively; which increased to 207 and 127 during

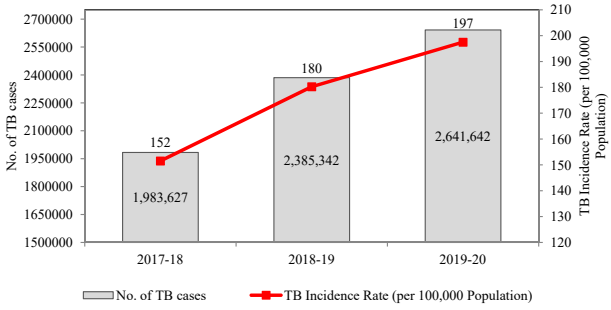


Fig. 1 – Tuberculosis Cases and Notification Rates (per 100,000 population), India, HMIS, 2017-18 to 2019-20.

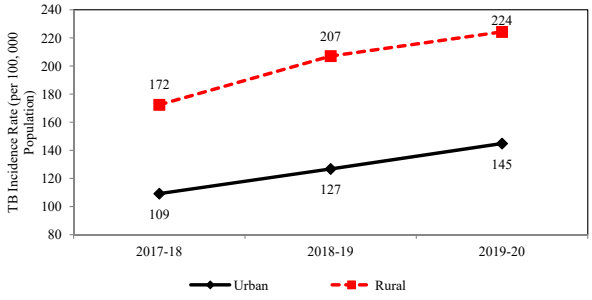


Fig. 2 – Tuberculosis Notification Rates (per 100,000 Population) by Rural-Urban sectors, India, HMIS, 2017-18 to 2019-20.

2018-19; and further increased to 224 and 145 during 2019-20 in rural and urban areas, respectively. This represents a rural-urban difference of 63, 80 and 79 TB cases per/lakh population during 2017-18, 2018-19 and 2019-20, respectively (Fig. 2). Indicating the rural-urban gap is substantially increased during 2017-18 to 2018-19 and stagnant in the next year. Moreover, a look on the trends of TB notification rates clearly shows that substantial increase was recorded during 2017-18 to 2018-19 compared to 2018-19 to 2019-20, in both rural (20% vs. 8%) and Urban (16% vs. 14%) regions, respectively.

3.1.2. *Half of TB cases were reported from six states*

Data is being reported by States and UTs, there are 29 State and 7 UTs in India which are reporting separately. The absolute number of TB case count and notification rates at States/UTs level for three consecutive years are presented in Annexure 2. In 2019-20, among Indian States, approximately half (51%) of the TB cases continued to be reported from six major States: Uttar Pradesh (411,531 cases; 15.6%), Maharashtra (216,438 cases; 8.2%), Madhya Pradesh (204,326 cases; 7.7%), Karnataka (192,839 cases; 7.3%), West Bengal (163,780 cases; 6.2%) and Andhra Pradesh (160,540 cases; 6.1%). Whereas, Lakshadweep (83 cases; 0.003%), Dadra & Nagar Haveli (232 cases; 0.009%) and Daman & Diu (1486 cases; 0.056%) have contributed lowest TB cases among UTs. Followed by smaller States like Sikkim (1679 cases; 0.064%), Mizoram (1845 cases; 0.070%) and Manipur (2151 cases; 0.081%) (Fig. 3 and Annexure 2).

3.2. *Inter-states/UTs variations in TB notification rates*

However, considering the notification rates of TB cases reported to the population by reporting States/UTs, Chandigarh (738/lakh population) has the highest TB notification rate, followed by Delhi (586), Andaman & Nicobar Island (569), Meghalaya (396), Puducherry (384) and Odisha (365) (Fig. 4). Further, Daman & Diu (351), Himachal Pradesh (351), Goa (345), Arunachal Pradesh (316), Andhra Pradesh (307), Karnataka (292), Nagaland (271), Sikkim (252), Madhya Pradesh (247), Uttarakhand (232) and Haryana (230) are showing the TB notification rates more than the national average of 197/lakh population. While, Dadra & Nagar Haveli (42), Manipur (69), Jammu & Kashmir (85) are having low TB notification rates, followed by Bihar (104), Tripura (108), Lakshadweep (122), Telangana (132), Tamil Nadu (144) and Kerala (149). Further, States like Mizoram (154), Rajasthan (167), Chhattisgarh (169), West Bengal (169), Gujarat (174), Maharashtra (177), Uttar Pradesh (182), Jharkhand (187) and Punjab (195) are also having TB notification rates of less than the national average (Fig. 4) (See Annexure 2 for TB cases and notification rates for all three years).

Further, one notable point in the aforementioned results is that five out of seven UTs in the list have recorded more than the national average of TB notification rate of 197/lakh population during 2019-20. Moreover, Chandigarh, Delhi and Andaman & Nicobar Island are in the top three places in the list. Whereas, Dadra & Nagar Haveli is showing lowest TB notifications, followed by Lakshadweep among UTs (Fig. 4).

3.3. *Percentage change in TB notification rates at States/UTs*

Fig. 5 presents the result of a percentage change in TB notification rates by States/UTs level. Overall, at the national level 30% increase was recorded in the TB notification rates during 2017-18 to 2019-20. While, a look on percentage change at States/UTs level demonstrates substantial variation between States/UTs. It shows that 11 (4 UTs and 7 States) out of 36 (7

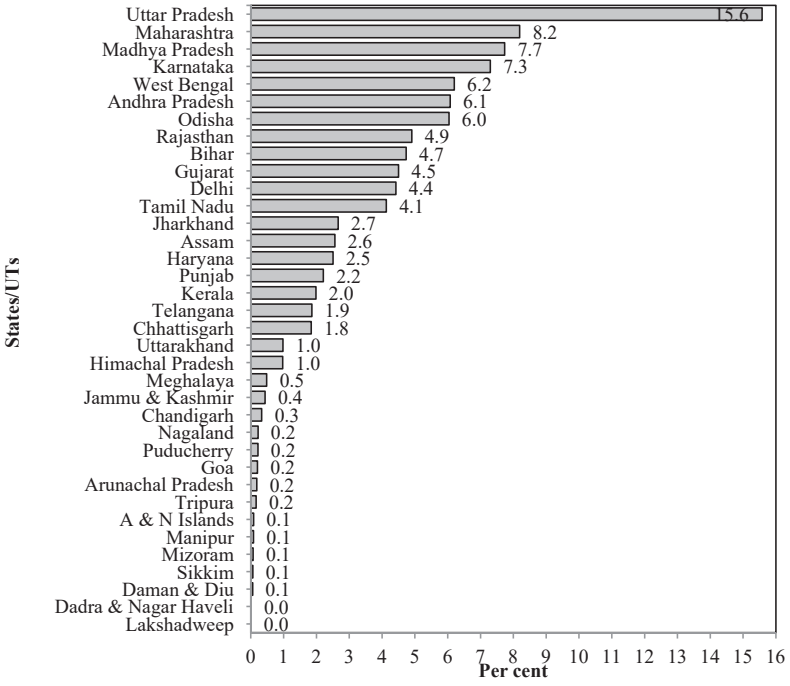
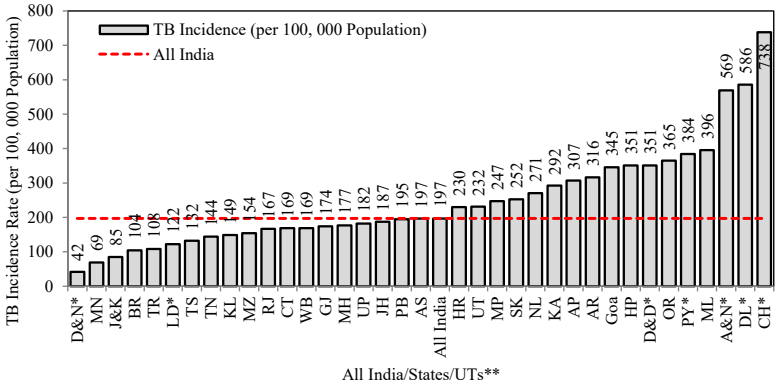


Fig. 3 – Percentage distribution of tuberculosis cases reported by States/UTs, India, HMIS, 2019-20.



Note: *Union Territories; **see text for full names of States/UTs.

Fig. 4 – Tuberculosis Notification Rates (per 100,000 Population) by India and States/UTs, HMIS, 2019-20. Note: *Union Territories; **see text for full names of States/UTs.

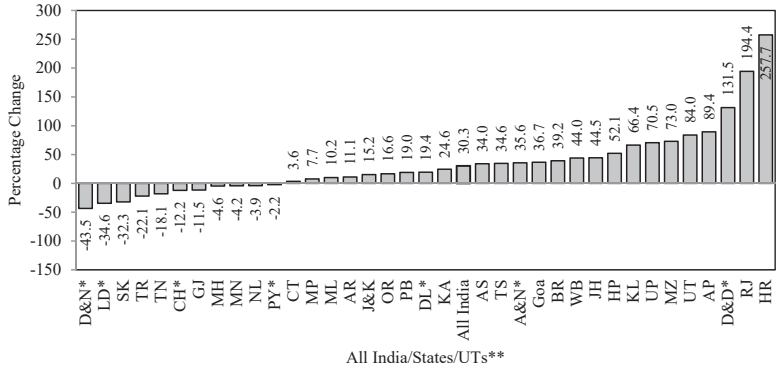
UTs and 29 States) States/UTs are having decreasing trends, and another 29 (7 UTs and 22 States) States/UTs are having increasing trends for TB notification rates during 2017-18 and 2019-20. Furthermore, 14 States and 2 UTs have recorded increasing percentage changes of more than the national average of 30%. Haryana has recorded the highest increase of 2.5 times more in TB notification rate compared to 2017-18, followed by Rajasthan (1.9 times) and Daman & Diu (1.3 times). Moreover, States like Andhra Pradesh (89%), Uttarakhand (84%), Mizoram (73%), Uttar Pradesh (71%), Kerala (66%) and Himachal Pradesh (52%) have recorded more than 50% increase during the same period. Whereas, Dadra & Nagar Haveli (–44%) has recorded highest decrease, followed by Lakshadweep (–34%), Sikkim (–32%), Tripura (–22%), Tamil Nadu (–18) and so on (Fig. 5).

3.4. *Inter-districts variations in TB notification rates*

To understand District level variations, we have estimated TB notification rates for 640 census Districts, and the results are presented using GIS Maps. For illustration purposes the districts have been categorized into four categories, such as Districts having TB notifications of less than 100 cases/lakh population, 100–199, 200–299 and 300 and above. This categorization is somewhat similar to the annual India TB report 2020.[2]

The results presented in Fig. 6 Maps A and B clearly depicts that, in line with the national and majority of States/UTs, TB notification rates at Districts level also recorded increasing trends in as many as 457 out of 640 census Districts. Many Districts which were falling in the lowest category in 2017-18 jumped to the next higher category in 2019-20. Similarly, Districts falling in second and third to lowest category were jumped to their next higher categories. Furthermore, the majority of Districts in Odisha and Chhattisgarh in East; Andhra Pradesh, Karnataka and Tamil Nadu in South; Madhya Pradesh in middle India, and many Districts of North-east States were consistently estimated to have higher TB notification rates during 2017-18 as well as 2019-20. However, majority of Districts from Uttar Pradesh, Bihar, Rajasthan, Punjab and Haryana were estimated TB notification rates of less than 100/lakh population during 2017-18, but many of them recorded increased TB notification rates during 2019-20.

Moreover, a look at TB notification rates according to categories presented in Maps shows that total 256 (40%) Districts have recorded TB notification rates of less than 100 during 2017-18, but this number decreased to 155 (24%) Districts during



Note: *Union Territories; **see text for full names of States/UTs.

Fig. 5 – Percentage Change in Tuberculosis Notification Rates during 2017-18 & 2019-20 by India and States/UTs, HMIS. Note: *Union Territories; **see text for full names of States/UTs.

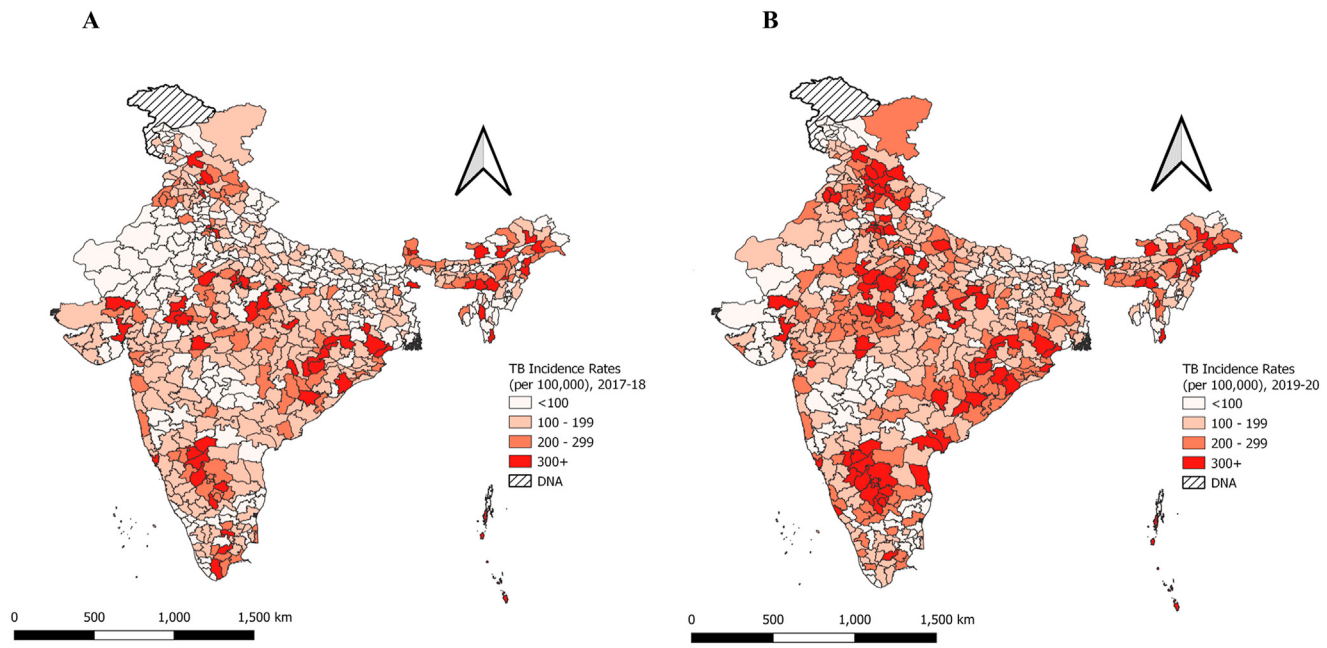


Fig. 6 – Tuberculosis Notification Rates/lakh population for 640 Districts according to the 2011 census is presented using GIS maps based on HMIS data for 2017-18 (A) and 2019-20 (B). Note: HMIS provides data for 704 Districts, but for analysis purposes we have clubbed in to 640 Districts according 2011 census; DNA = data not available.

2019-20. Further, more districts have been distributed in the higher categories during 2019-20 compared to 2017-18, indicating that the notifications have increased over the years (Table 1).

In addition, at the national level total 385 Districts have recorded TB notification rates of more than national average of 197/lakh population during 2019-20. Considering numbers of Districts, majority of Districts in Madhya Pradesh (31 Districts), Uttar Pradesh (26 Districts), Odisha (23 Districts), Karnataka (19 Districts) and Himachal Pradesh (11 Districts) have recorded TB notification rates of more than national average (Annexure 3). The total list of the Districts with TB notification rates higher than the national average is given in Annexure 3.

3.5. *Discussion and conclusions*

While the health-care facility TB notification data cannot substitute for national TB prevalence surveys, a more reliable source of information than case notification, the HMIS data, because of its pan-India coverage, do provide an opportunity to better understand the TB disease burden in India and at sub-national level to some extent. The results from the present analysis show that the annual TB notification is increasing year-by-year, both in terms of absolute numbers and notification rates. During 2019-20 a record high of 26.4 lakh TB cases were notified compared to 23.9 and 19.8 lakh during 2018-19 and 2017-18, respectively. This increasing trend in TB notification rates may be more reflected by the increasing trend in case notification, which is obviously due to improved case finding under DOTS and the NSP rather than the underlying trend in incidence.[2]

Further, TB notifications rate is higher among rural residents compared to urban counterparts, and it is also true during all three analysis years, 2017-18 (172 vs. 109), 2018-19 (207 vs. 127) and 2019-20 (224 vs. 145). A study based on pooled estimates of TB prevalence in India also shows high TB prevalence in rural strata (426 cases per 100,000 population) compared to 266 cases in urban counterparts.[17] Whereas, unlike this, Mazumdar, et al[18] after controlling for socio-economic factors found that the risk of TB appears to be about 20% less in rural residents than the urban counterpart.

Considerable differences in TB notification rates were observed between States/UTs. The TB notification rates relative to population is substantially high in Chandigarh (738/lakh population) and Delhi (586). These two UTs were also estimated highest according to "India TB report-2020".[2] Moreover, the vast variation in the TB disease burden within the country was well documented in India.[17–19]

Percentage change shows around 30% increase in TB notifications between 2017-18 & 2019-20 for India as a whole. Inter States/UTs level differences show that the majority of States/UTs have recorded an increase in the notifications in

Table 1 – Percentage Distribution of census Districts by categories of TB notification Rates, HMIS, 2017-18 and 2019-20.

TB notification rates	2017-18		2019-20	
	No. of Districts	%	No. of Districts	%
<100	256	40.0	155	24.2
100–199	229	35.8	234	36.6
200–299	90	14.1	139	21.7
≥300	65	10.2	112	17.5
Total	640	100.0	640	100.0

Note: HMIS provides data for 704 Districts, but for analysis purposes we have clubbed in to 640 Districts according 2011 census.
Source: HMIS, 2017-20.

line with the national average. Whereas, seven States and four UTs have recorded decreasing trends in TB notification rates.

Similarly, like inter States/UTs, District level TB notification rates also showed wide differences in-between, and many of them recorded an increase in TB notifications between 2017-18 and 2019-20. Total 256 (40%) Districts have recorded TB notification rates of less than 100 during 2017-18, but this number decreased to 155 (24%) Districts during 2019-20. Similarly, Districts which had fallen in lower categories of TB notification rates during 2017-18 have jumped into higher categories during 2019-20.

Hence, in conclusion the findings of the study shows the increasing trends of TB notifications in India since 2017-18, which is a clear indication of the efforts put in the TB program to achieve targets and goals committed to end TB by 2025. In this regard present estimates based on HMIS data significantly contributes to the policy formulation even at the lowest administrative level of health Districts.

Availability of data and materials

The data used for the study is obtained from the HMIS web-portal under union health ministry which is available in public domain. No separate ethics statement and consent for publication was required for this study.

Author's contributions

(1) Mr. Golandaj has conceptualized the study and design of the study. (2) Suvarna K. Naikar extracted and analysis the data (1) Mr. Golandaj drafted the article and revising it critically for important intellectual content. (3) Professor Hallad edited the article. Further, all authors finalized and approved the article version to be submitted.

Conflicts of interest

The authors have none to declare.

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Annexure 1. Number of TB cases reported for different data elements by rural-urban and public-private healthcare facilities, India, HMIS, 2017-18, 2018-19 and 2019-20.

HMIS TB Data Elements	Category	2017-18	2018-19	2019-20
Number of on-going DOTS patients registered	Rural	1,107,358	1,309,664	1,404,339
	Urban	352,073	423,344	462,009
	Public	1,445,296	1,712,978	1,851,458
	Private	14,135	20,030	14,890
	Combined	**1,459,431**	**1,733,008**	**1,866,348**
Number of DOTS cases completed successfully	Rural	381,272	493,572	562,767
	Urban	116,874	134,425	188,723
	Public	493,824	621,468	744,753
	Private	4322	6529	6737
	Combined	**498,146**	**627,997**	**751,490**
Number of Adolescent/Adult deaths due to Tuberculosis	Rural	22,457	21,875	21,053
	Urban	3593	2462	2751
	Public	25,532	23,864	23,379
	Private	518	473	425
	Combined	**26,050**	**24,337**	**23,804**
Total TB positive cases reported*	**Rural**	**1,511,087**	**1,825,111**	**1,988,159**
	Urban	**472,540**	**560,231**	**653,483**
	Public	**1,964,652**	**2,358,310**	**2,619,590**
	Private	**18,975**	**27,032**	**22,052**
	Combined	**1,983,627**	**2,385,342**	**2,641,642**

Note: *To get the total TB positive cases three data elements, 'Number of on-going DOTS patients registered', 'Number of DOTS cases completed successfully' and 'Number of Adolescent/Adult deaths due to Tuberculosis' have been clubbed; and this is done separately for rural, urban, public, private and combined.
Source: HMIS, 2017-20.

Annexure 2. Tuberculosis Cases count and notification rates/lakh population by States/UTs, HMIS, 2017-18 to 2019-20.

States/UTs	No. of reported TB cases			TB Notification Rates/lakh population		
	2017-18	2018-19	2019-20	2017-18	2018-19	2019-20
Andhra Pradesh	83,857	129,594	160,540	162	249	307
Arunachal Pradesh	4209	6278	4767	285	420	316
Assam	49,385	60,581	67,647	147	178	197
Bihar	87,156	94,084	125,060	75	80	104
Chhattisgarh	45,705	47,078	48,651	163	165	169
Goa	3849	4481	5329	253	292	345
Gujarat	130,703	110,904	118,938	197	165	174
Haryana	17,989	49,898	66,205	64	176	230
Himachal Pradesh	16,651	23,722	25,653	231	326	351
Jammu & Kashmir	9829	11,362	11,503	74	85	85
Jharkhand	47,324	63,960	70,365	130	173	187
Karnataka	152,318	187,703	192,839	235	287	292
Kerala	31,191	49,245	52,458	90	141	149
Madhya Pradesh	184,519	176,937	204,326	230	217	247
Maharashtra	222,537	216,066	216,438	185	178	177
Manipur	2202	2141	2151	72	70	69
Meghalaya	11,379	12,448	12,786	359	389	396
Mizoram	1046	2973	1845	89	251	154
Nagaland	5958	5225	5837	282	245	271
Odisha	135,640	152,038	159,509	313	349	365
Punjab	48,267	52,870	58,379	164	178	195
Rajasthan	42,871	110,723	129,561	57	145	167
Sikkim	2430	2417	1679	373	367	252
Tamil Nadu	131,915	157,231	109,081	176	208	144
Telangana	36,034	36,945	49,185	98	100	132
Tripura	5448	5814	4326	139	147	108
Uttar Pradesh	235,005	317,356	411,531	107	142	182
Uttarakhand	13,751	19,850	25,892	126	180	232
West Bengal	112,295	145,614	163,780	117	151	169
Union Territories						
Andaman & Nicobar Island	1654	1476	2266	420	373	569
Chandigarh	9704	10,685	8735	840	913	738
Dadra & Nagar Haveli	365	303	232	74	58	42
Daman & Diu	557	542	1486	152	137	351
Delhi	94,081	110,539	116,762	490	565	586
Lakshadweep	125	141	83	187	210	122
Puducherry	5678	6118	5817	392	413	384

Source: HMIS, 2017-20.

Annexure 3. List of districts having TB notification rates more than national average by States/UTs, India, 2019-20.

States/UTs	TB Incidence	List of Districts having TB incidence rates more than National average of 197/lakh population
Chandigarh	738	**1/1:** Chandigarh
Delhi	586	**9/9:** Central, East, New Delhi, North, North East, North West, South, South West & West
A & N Islands	569	**2/3:** Nicobar & South Andaman
Meghalaya	396	**7/7:** East Garo Hills, East Khasi Hills, Jaintia Hills, Ri Bhoi, South Garo Hills, West Garo Hills & West Khasi Hills
Puducherry	384	**2/4:** Karaikal & Puducherry
Odisha	365	**23/30:** Balangir, Baleshwar, Bargarh, Bhadrak, Cuttack, Debagarh, Dhenkanal, Gajapati, Ganjam, Jagatsinghapur, Jharsuguda, Kalahandi, Kandhamal, Kendrapara, Khordha, Koraput, Malkangiri, Mayurbhanj, Nabarangapur, Nayagarh, Nuapada, Rayagada & Sundargarh
Daman & Diu	351	**1/2:** Daman
Himachal Pradesh	351	**11/12:** Bilaspur, Chamba, Hamirpur, Kangra, Kinnaur, Kullu, Mandi, Shimla, Sirmaur, Solan & Una
Goa	345	**2/2:** North Goa & South Goa
Arunachal Pradesh	316	**10/16:** Anjaw, Changlang, East Siang, Lohit, Lower Subansiri, Papum Pare, Tawang, Tirap, West Kameng & West Siang
Andhra Pradesh	307	**12/23:** Adilabad, Anantapur, Chittoor, Guntur, Krishna, Kurnool, Medak, Sri Potti Sriramulu Nellore, Srikakulam, Visakhapatnam, Vizianagaram & West Godavari
Karnataka	292	**19/30:** Bangalore Urban, Bangalore Rural, Bellary, Bidar, Chamrajnagar, Chikkaballapur, Chitradurga, Dakshina Kannada, Davanagere, Dharwad, Gadag, Kolar, Koppal, Mandya, Mysore, Raichur, Ramanagara, Tumkur & Udupi
Nagaland	271	**6/11:** Dimapur, Kiphire, Longleng, Mon, Tuensang & Zunheboto
Sikkim	252	**2/4:** South & West
Madhya Pradesh	247	**31/50:** Anuppur, Ashoknagar, Balaghat, Bhind, Bhopal, Burhanpur, Damoh, Datia, Dewas, Dhar, East Nimar, Gwalior, Hoshangabad, Indore, Jabalpur, Jhabua, Mandsaur, Neemuch, Panna, Raisen, Rajgarh, Ratlam, Rewa, Sehore, Shajapur, Sheopur, Shivpuri, Sidhi, Ujjain, Umaria & Vidisha
Uttarakhand	232	**5/13:** Champawat, Dehradun, Garhwal, Rudraprayag & Tehri Garhwal
Haryana	230	**10/21:** Ambala, Faridabad, Fatehabad, Gurgaon, Hisar, Karnal, Kurukshetra, Palwal, Rewari & Yamunanagar
Assam	197	**8/27:** Barpeta, Cachar, Dhemaji, Dibrugarh, Golaghat, Karbi Anglong, Kokrajhar & Tinsukia
Punjab	195	**8/20:** Barnala, Bathinda, Faridkot, Ludhiana, Muktsar, Patiala, Sahibzada Ajit Singh Nagar & Sangrur
Jharkhand	187	**8/24:** Dumka, Godda, Khunti, Pakur, Palamu, Pashchimi Singhbhum, Purbi Singhbhum & Saraikela
Uttar Pradesh	182	**26/71:** Baghpat, Bara Banki, Bulandshahr, Chitrakoot, Etah, Faizabad, Gautam Buddha Nagar, Ghaziabad, Hardoi, Jalaun, Jhansi, Kanpur Dehat, Kaushambi, Kheri, Mahamaya Nagar, Mahoba, Mainpuri, Mathura, Meerut, Mirzapur, Moradabad, Rae Bareli, Saharanpur, Shrawasti, Sitapur & Sonbhadra
Maharashtra	177	**4/35:** Garhchiroli, Mumbai, Ratnagiri & Thane
Gujarat	174	**8/26:** Ahmadabad, Banas Kantha, Bharuch, Dohad, Porbandar, Sabar Kantha, Surat & The Dangs
West Bengal	169	**7/19:** Bankura, Barddhaman, Dakshin Dinajpur, Darjiling, Haora, Jalpaiguri & Kolkata
Chhattisgarh	169	**5/18:** Bastar, Bijapur, Dhamtari, Narayanpur & Raigarh
Rajasthan	167	**10/33:** Ajmer, Baran, Dhaulpur, Dungarpur, Ganganagar, Jaipur, Kota, Pali, Sawai Madhopur & Tonk
Mizoram	154	**3/8:** Aizawl, Kolasib & Saiha
Kerala	149	**4/14:** Ernakulam, Kasaragod, Palakkad & Pathanamthitta
Tamil Nadu	144	**6/32:** Krishnagiri, Madurai, Namakkal, Ramanathapuram, Sivaganga & Viluppuram
Bihar	104	**3/38:** Aurangabad, Jehanabad & Kaimur (bhabua)
Jammu & Kashmir	85	**2/22:** Leh (ladakh)& Samba

Source: HMIS, 2017-20.

REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2019*. Licence: CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization; 2019.
2. Ministry of Health & Family Welfare (MoHFW). *India TB Report-2020*. New Delhi: Central TB Division, Ministry of Health & Family Welfare, Government of India; 2020. Available at: https://tbcindia.gov.in/showfile.php?lid=3538. Accessed August 10, 2020.
3. Ministry of Health & Family Welfare (MoHFW) (internet). Revised national TB control programme (RNTCP). Available at: https://www.nhp.gov.in/revised-national-tuberculosis-control-programme_pg (accessed on August 17, 2020).
4. Ministry of Health & Family Welfare (MoHFW), (internet). National Strategic Plan for Tuberculosis Elimination 2017-2025, Central TB Division, MoHFW, New Delhi, available at: https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf, (accessed on August 10, 2020).
5. UN General Assembly. *Transforming our World: The 2030 Agenda for Sustainable Development*; 21 October 2015. A/RES/70/1, available at: https://www.refworld.org/docid/57b6e3e44.html. Accessed November 7, 2020.
6. World Health Organization. *The End TB Strategy*. Geneva, Switzerland: World Health Organization; 2015. Available at: https://www.who.int/tb/strategy/end-tb/en/. Accessed August 10, 2020.
7. Gazette. *Ministry of Health and Family Welfare, Government of India*. The Gazette of India: Extraordinary; 2018. Available at: http://egazette.nic.in/WriteReadData/2018/183924.pdf. Accessed August 17, 2020.
8. Onozaki I, Law I, Sismanidis C, et al. National tuberculosis prevalence surveys in Asia, 1990-2012: an overview of results and lessons learned. *Trop Med Int Health*. 2015;20:1128–1145.
9. Subbaraman R, Nathavitharana R, Satyanarayana S, et al. The tuberculosis cascade of care in India's public sector: recent estimates and gaps in knowledge. *PLoS Med*. 2016;13, e1002149.
10. Pandey A, Roy N, Bhawsar R, Mishra RM. Health information system in India: issues of data availability and quality. *Demogr India*. 2010;39(1):111–128. Available at: https://www.researchgate.net/publication/232084914. Accessed August 10, 2020.
11. Faujdar DS, Sahay S, Singh T, Jindal H, Kumar R. Public health information systems for primary health care in India: a situational analysis study. *J Fam Med Prim Care*. 2019;8(11):3640–3646. https://doi.org/10.4103/jfmpc.jfmpc_808_19.
12. Ministry of Health & Family Welfare (MoHFW). *Health Management Information System (HMIS), a Digital Initiative under National Health Mission*. New Delhi: MoHFW, Government of India; 2008a. available at: https://hmis.nhp.gov.in/#!/aboutus.
13. Ministry of Health & Family Welfare (MoHFW). Health management information system (HMIS). Available at: https://nrhm-mis.nic.in/hmisreports/frmstandard_reports.aspx; 2008. Accessed August 10, 2020.
14. Registrar General of India and Census Commissioner. *Population Projections for India and States 2011-2036, Report of the Technical Group on Population Projections Constituted by the National Commission on Population*. 2019 [New Delhi].
15. Chauhan RK, Mohanty SK, Mishra US. Population trends, distribution and prospects in the districts of India. In: Mohanty S, Mishra U, Chauhan R, eds. *The Demographic and Development Divide in India*. Singapore: Springer; 2019. https://doi.org/10.1007/978-981-13-5820-3_2.
16. QGIS Development Team. *QGIS Geographic Information System*. Open Source Geospatial Foundation Project; 2020. Available at: http://qgis.osgeo.org.
17. Chadha VK, Anjinappa SM, Dave P, et al. Sub-national TB prevalence surveys in India, 2006-2012: results of uniformly conducted data analysis. *PLoS ONE*. 2019;14(2), e0212264. https://doi.org/10.1371/journal.pone.0212264.
18. Mazumdar S, Satyanarayana S, Pai M. Self-reported tuberculosis in India: evidence from NFHS-4. *BMJ Global Health*. 2019;4, e001371. https://doi.org/10.1136/bmjgh-2018-001371.
19. International Institute for Population Sciences and ICF. *National Family Health Survey (NFHS-4), 2015-16. India*. Mumbai: IIPS; 2017.

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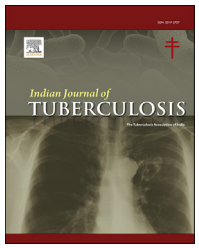

Original article

Genital footprints of extragenital tuberculosis in infertile women: Comparison of various diagnostic modalities

Swati Yadav [a,*], *Manju Puri* [a], *Swati Agrawal* [a], *Kamal Chopra* [b]

[a] *Department of Obstetrics and Gynaecology, Lady Hardinge Medical College, Smt. Sucheta Kriplani Hospital, New Delhi, 110001, India*

[b] *New Delhi Tuberculosis Centre, New Delhi, 110001, India*

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ABSTRACT

Background: Genital tuberculosis (TB) continues to remain an important cause of infertility in women, especially in developing countries. It is mostly consequent to a primary infection elsewhere in the body. The diagnosis is challenging, considering its paucibacillary nature. Although there are many studies on association of genital tuberculosis with infertility, there is paucity of literature on impact of extragenital tuberculosis on fertility of women through involvement of female reproductive organs. The various diagnostic modalities available have limitations and quest is ongoing for the best diagnostic test.

Method: This was a prospective observational study conducted at the infertility clinic of a tertiary care health facility where 60 infertile women with either tubal factor or unexplained infertility with or without past history of extragenital tuberculosis were enrolled as study subjects or controls respectively. Mantoux test was performed in all women and diagnostic laparo-hysteroscopy was performed in all women to look for any evidence of uterine and/or tubal damage. The peritoneal fluid was sent for GeneXpert and Liquid culture for mycobacterium tuberculosis. Results of Mantoux test, GeneXpert and liquid culture were compared with the laparohysteroscopic findings.

Result: Of the thirty infertile women in the study group, 27/30 (90%) had a history of pulmonary tuberculosis and 3/30 (10%) had history of tubercular cervical lymphadenopathy. It was observed that Mantoux test was positive (induration >10 mm) in 27/30 (90%) of women in the study group as compared to only 4/30 (13.3%) controls. Abnormal hysteroscopic findings were documented in 26.6% (8/30) study group women as compared to 6.6% (2/30) women in the control group. Similarly, 60% (18/30) of women in the study group had abnormal laparoscopic findings compared to 33% (10/30) in the control group. Seven out of thirty (23.3%) women were positive for GeneXpert in the study group compared to only 1/30 (3.3%) in the control group. Similarly, liquid culture was positive in 6/30 (20%) of women in the study group as compared to 1/30 (3.3%) in the control group. All the above differences were statistically significant. We observed that the sensitivity of Mantoux test (75.8%) stand alone was higher than the other tests combined (50%). However, specificity and positive predictive value (PPV) increases markedly (up to 100%) to when all the three tests are combined.

* *Corresponding author.*
E-mail address: swatilhmcgynae@gmail.com (S. Yadav).

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Conclusion: The authors conclude that all women presenting with infertility should be screened for a past history of tuberculosis and actively worked up for genital tuberculosis in case the history is positive. The various available tests (Mantoux test, GeneXpert and liquid culture) have their limitations for the diagnosis of genital tuberculosis. Thus an approach of early resort to laparohysteroscopy in suspected patients is desirable so that definitive management may be instituted timely and promptly.

1. Introduction

Genital tuberculosis (TB) is an important cause of infertility in women. The reported incidence of genital TB ranges from less than 1%–19% globally.[1–3] The actual incidence of genital TB cannot be determined accurately in any population because it is estimated that at least 11% of patients are asymptomatic and the disease is discovered incidentally. In cases of infertility, the incidence of genital TB is 17.4%. Autopsy studies by different authors reveal that 4–12% of women who have died of pulmonary TB had evidence of genital TB.[4]

Female genital tuberculosis is almost always secondary to a primary focus elsewhere in the body.[5] The mode of spread is usually hematogenous or lymphatic and occasionally occurs by way of direct contiguity with an intra-abdominal or peritoneal focus.[1,6] The focus in the lung often heals, and the lesion may lie dormant in the genital tract for years, only to reactivate at a late stage contributing towards infertility.

Considering high prevalence of pulmonary tuberculosis in India and female genital tuberculosis being almost always secondary to tuberculosis elsewhere, all women with infertility are screened for any past history or any evidence of TB.

The diagnosis of genital tuberculosis is often difficult and challenging due to its paucibacillary nature. The clinical diagnosis of genital TB requires a high index of suspicion. About 20% of patients with genital TB give history of TB in their immediate family.[1] About 30–50% of patients diagnosed with genital TB will give a history of prior diagnosis or treatment of extragenital TB.[1]

The Mantoux test or Mendel–Mantoux test (also known as the Mantoux screening test, tuberculin sensitivity test, Pirquet test, or PPD test for purified protein derivative) is a tool for screening for tuberculosis (TB) and for supporting the diagnosis of tuberculosis. It is one of the major tuberculin skin tests used around the world. The person's medical risk assessment determines the increment (5 mm, 10 mm, or 15 mm) of induration at which the result is considered positive. A positive result indicates TB exposure. In India a value of >10 mm is considered positive.

Conventional methods for the diagnosis of TB include microscopy and culture. Diagnostic uterine curettage during the week preceding menstruation can aid in diagnosis of endometrial tuberculosis by these methods. Ziehl-Neelsen (ZN) staining for acid fast bacilli (AFB) requires 10^4 -10^6 bacilli/ml of tissue or fluid specimens to give a positive result.[7,8] Although culture using Lowenstein Jensen (LJ) medium for mycobacterium is more sensitive, it still needs 10–100 bacilli/ml of sample for the diagnostic yield and requires 2–4 weeks for the growth of Mycobacterium. Liquid cultures require at least 9–10 days for positive results and six weeks for being considered negative. In LJ medium cultures, the minimum time-to-positivity is 4–8 weeks.[9]

A diagnostic method that is less time-consuming and has a high sensitivity and specificity is therefore desirable.[9] Nucleic acid amplification (NAA) tests represent a major advance in the diagnosis of TB.[10] With the use of amplification systems, nucleic acid sequences unique to MTB can be detected directly in clinical specimens, offering better accuracy than microscopy and greater speed than culture. GeneXpert (PCR), a type of NAA system has shown very promising results for early and rapid diagnosis of the disease due to its detection limit of one to ten bacilli in various clinical samples.[11]

Although there are many studies on association of genital tuberculosis with infertility, there is paucity of literature on impact of extragenital tuberculosis on fertility of women through involvement of female reproductive organs. India has a high prevalence of pulmonary tuberculosis, hence a need to study the impact of extragenital tuberculosis on female reproductive organs. Also, more research is warranted to compare various modalities to diagnose genital tuberculosis in infertile women.

Thus, this study was undertaken to find out whether the risk of uterine and tubal factor infertility increases in infertile women with extragenital tuberculosis compared to infertile women without extragenital tuberculosis so as to initiate early evaluation in such women presenting with infertility and timely treatment.

2. Materials and methods

An observational case control study was conducted in the Department of Obstetrics and Gynaecology at a tertiary care hospital in India from 1st November 2017 to 31st March 2019.

Study population comprised of all infertile women attending the infertility clinic and were subjected to routine work up for infertility as per local protocol. This included a detailed history and examination, blood investigations {Hemogram with peripheral smear and Erythrocyte Sedimentation Rate (ESR)}, Mantoux test, chest X-ray, husband semen analysis, pre-menstrual endometrial biopsy for histopathology, and Acid Fast Bacilli (AFB) smear and culture, ultrasound pelvis and Day 21 progesterone. All women were

especially screened for any evidence of extragenital TB through history, examination, and investigations.

The study enrolled sixty infertile women attending the infertility clinic at our hospital. Thirty infertile women with a history of extragenital tuberculosis in the past were enrolled as the study group and thirty age matched infertile women without any history of extragenital tuberculosis as controls after fulfilling the inclusion and exclusion criteria. Inclusion criteria included women with either tubal factor or unexplained infertility. Exclusion criteria included women diagnosed with genital TB (active or old) and those who are at predisposed to have pelvic adhesions such as those with history of abdominal TB; reproductive tract infection; puerperal sepsis; repeated dilatation and curettage; any surgery on reproductive organs like myomectomy, cystectomy, tubal surgery, oophorectomy, caesarean section etc; and known cases of endometriosis. Ethical clearance was obtained from the institutional ethical committee. A written informed consent was taken before enrolling the patients in the study. Diagnostic laparo-hysteroscopy with chromopertubation was performed in all patients to look for the cause of infertility with special emphasis on any evidence of uterine and/or tubal damage. The findings suggestive of tubal and/or uterine damage are listed in Table 1. The peritoneal fluid was collected for GeneXpert and liquid culture in Mycobacterial Growth Indicator Tube (MGIT). The primary outcomes were proportion of infertile women with laparohysteroscopic findings suggestive of uterine and/or tubal damage; or positive for tubercular bacillus on GeneXpert/liquid culture in both groups. Data was subjected to analysis using the Statistical Package for the Social Sciences (SPSS) latest version.

3. Results

The study enrolled women in the age group of 21–40 years. The mean age observed in the study group was 27.5 ± 3.9 years and 25.5 ± 3.5 years in the control group. Of the thirty infertile women in the study group, 27/30 (90%) had a history of pulmonary tuberculosis and 3/30 (10%) had history of tubercular cervical lymphadenopathy. It was observed that Mantoux test was positive (induration >10 mm) in 27/30 (90%) of women in the study group as compared to only 4/30 (13.3%) controls. The difference was statistically significant (p value = <0.001).

Table 1 – Findings suggestive of tubal and uterine damage.

Tubal damage	Uterine damage
Thick and edematous blocked tubes	Contracted and distorted uterine cavity
Tubo-ovarian masses	Intrauterine adhesions
Distortion of tubo-ovarian relationship	Intravasation of dye
Pelvic adhesions	Cornual adhesions/occlusions
Presence of tubercles on tubes	
Hydrosalpinx	
Beaded tubes	
Tobacco pouch appearance	
Damaged fimbriae.	

The women in both the study group and control group were subjected to diagnostic laparohysteroscopy. Abnormal hysteroscopic findings were documented in 26.6% (8/30) study group women as compared to 6.6% (2/30) women in the control group. Similarly, 60% (18/30) of women in the study group had abnormal laparoscopic findings compared to 33% (10/30) in the control group. The difference was statistically significant as regards to both hysteroscopic (p = 0.037) and laparoscopic findings (p = 0.038).

The spectrum of various abnormal hysteroscopic findings in both the groups was analysed and it was observed that contracted and distorted uterine cavity was present in 3.3% of women in the study group and none in the control group, whereas intrauterine adhesions were present in 16.6% of women in the study group and 3.3% of women in the control group. Cornual adhesions were present in 6.6% of women in both the groups.

The spectrum of tubal damage as evident on laparoscopy revealed thick and oedematous blocked tubes in 30% vs 3.33%, hydrosalpinx in 6.6% vs 6.6%, damaged fimbriae 10% vs 10%, distorted tubo-ovarian relationship in 23.3% vs 13.3% and pelvic adhesions in 33.3% vs 23.3% of women in the study group and the control group respectively. In addition, 16.6% of women in the study group had visible tubercles on tubes and surface of uterus.

Peritoneal fluid collected during laparoscopy was sent for GeneXpert and liquid culture to detect tubercular bacilli, 7/30 (23.3%) were positive for GeneXpert in the study group compared to only 1/30 (3.3%) in the control group. Similarly, liquid culture was positive in 6/30 (20%) of women in the study group as compared to 1/30 (3.3%) in the control group. The difference was statistically significant with regards to both GeneXpert (p value = 0.023) and liquid culture (p = 0.044).

On correlating the positive Mantoux test with the abnormal laparohysteroscopic findings in both cases and controls; 21/27 (70%) cases with positive Mantoux test had positive laparohysteroscopic findings compared to 4/4 (100%) amongst controls. The sensitivity and specificity of Mantoux test was 75.8% and 73.9% respectively and positive predictive value (PPV) and negative predictive value (NPV) for Mantoux test was 80.6% and 68.0% respectively with accuracy of 75.0%.

The results of GeneXpert test were correlated with the abnormal laparohysteroscopic findings in both cases and controls. It was observed that in 7/7 (100%) cases positive for GeneXpert had abnormal laparohysteroscopic findings compared to 1/1 (100%) in controls. Hence all women positive for GeneXpert had documented tubal/uterine damage on laparohysteroscopy. However, among cases who had positive laparohysteroscopic findings, 53.3% were found to have negative GeneXpert results compared to 15.0% in controls. The sensitivity and specificity of GeneXpert correlating with abnormal laparohysteroscopic findings was 24.2% and 100.0% respectively. Positive predictive value (PPV) of GeneXpert found was 100% and negative predictive value (NPV) was 47.9%. Accuracy was found to be 55.4%.

The results of peritoneal fluid samples were correlated with abnormal laparohysteroscopic findings. It was observed that the sensitivity and specificity of liquid culture was 21.2% and 100.0% respectively. The positive predictive value (PPV)

was 100.0% and negative predictive value (NPV) was 46.9%. The accuracy was 53.8%.

In the present study we compared Mantoux test, GeneXpert and liquid culture results with abnormal laparohysteroscopic findings (Table 2). Out of 60 infertile women including both cases and controls 33 women had evidence of tubal/or uterine damage, of these 23 were cases and 10 were controls.

Out of the 33 women with positive laparohysteroscopic findings 7 had all the three tests namely Mantoux test, GeneXpert and liquid culture positive, of these 6 were cases and 1 was control. Seven women had none of the tests positive. Among these, 6 were controls where the damage could have been due to a non -tubercular cause like chlamydia whereas the one case with all the tests was negative had a previous history of pulmonary TB and chest x –ray findings suggestive of old TB infection. This could be false negative as genital TB is paucibacillary and can be missed on GeneXpert and liquid culture.

In eighteen out of 33 infertile women with positive laparohysteroscopic findings only Mantoux test was positive, out of these 15 were cases and 3 were controls. These three controls could have had subclinical asymptomatic old TB and the abnormal laparohysteroscopic findings could be due to some other organism like Chlamydia as the GeneXpert and liquid culture results were negative with no significant chest x-ray finding.

There was one case with previous history of extragenital TB where only GeneXpert was positive with positive laparohysteroscopic findings. It could be a false positive case as the Mantoux test and liquid culture were both negative.

Among 7 cases with normal laparohysteroscopic findings 6 cases had only positive Mantoux test which can be explained based on an old tubercular infection with no genital involvement. Remaining one case with normal laparohysteroscopic findings and all three tests negative could be due to a false negative Mantoux test and no genital involvement.

4. Discussion

Genital tuberculosis can adversely affect the fertility in women of reproductive age group by not only causing tubal obstruction and dysfunction but also impairing implantation due to endometrial involvement and rarely, ovulatory failure due to ovarian involvement. The diagnosis is usually made by detection of acid-fast bacilli on microscopy or culture on endometrial biopsy or on histopathological detection of epithelioid granuloma on biopsy. However, it is not always possible to make a definitive diagnosis owing to the paucibacillary nature of the disease.

The present study infers that extragenital tuberculosis can affect the female genital tract without obvious manifestation of the involvement. This was evident by the high prevalence of abnormal laparohysteroscopic findings and cultures in infertile women with past history of extragenital tuberculosis, mostly pulmonary tuberculosis.

A study conducted by Hassan et al conducted on 200 women of childbearing age with pulmonary tuberculosis, menstrual abnormalities were seen in 66% of women, secondary amenorrhea in 26.5%, and peritubal and fine intrauterine adhesions were confirmed by laparoscopy and hysteroscopy in 0.7%. This study concluded that menstrual abnormalities and presence of infertility after completion of treatment need investigation for genital tract involvement in women with Pulmonary Tuberculosis. This study lacks the inclusion of Tuberculosis of other sites having primary foci such as spine, bones and joints.[12] Another retrospective observational study conducted on 290 infertile women with history of extragenital tuberculosis, 20.93% of women were found to have new onset menstrual problems, 4.65% had intravasation on hysterosalpingography and 35.29% demonstrated findings on laparoscopy. Incidence of genital tuberculosis with history of extragenital tuberculosis was 13.95%. This study showed that clinical evaluation combined with high level of accuracy tests are required to diagnose genital involvement in women with extragenital tuberculosis as there is a correlation between extragenital tuberculosis and infertility which is invariably irreversible.[13]

Mantoux is considered a non specific test for the diagnosis of tuberculosis but in the present study, we found a good correlation between abnormal Mantoux result and laparohysteroscopic findings. This is comparable to a similar case control study conducted on 200 women by Raut VS et al 2001 where the sensitivity and specificity of Mantoux test was found to be 55% and 80% respectively.[14] They inferred that in infertile women with positive Mantoux test, laparoscopy may be advocated early. We observed in the present study that the sensitivity for GeneXpert and liquid culture had increased combining all the three tests namely Mantoux test, GeneXpert and Liquid culture positive but the sensitivity of Mantoux test (75.8%) stand alone was higher than the other tests combined (50%). However, specificity and positive predictive value (PPV) had markedly increased to 100% with the three tests combined positive. The negative predictive value (NPV) was increased to 70.8% than each of the tests alone Mantoux 68%, GeneXpert 47.9% and liquid culture 46.9%. The accuracy also increased to 77.4% (Table 3).

Table 2 – Comparison of Mantoux test, GeneXpert and liquid culture results with abnormal laparohysteroscopic findings.

Cases (N = 30)	Controls (N = 30)	Mantoux test	GeneXpert	Liquid culture	Positive laparohysteroscopic findings
6	1	+	+	+	+
1	0	–	+	–	+
15	3	+	–	–	+
1	6	–	–	–	+
6	0	+	–	–	–
1	16	–	–	–	–

Table 3 – Comparison of various diagnostic modalities for genital tuberculosis.

Tests	Sensitivity	Specificity	PPV	NPV	Accuracy
Mantoux test	75.8%	73.9%	80.6%	68.0%	75%
GeneXpert	24.2%	100.0%	100.0%	47.9%	55.3%
Liquid culture	21.2%	100.0%	100.0%	46.9%	53.8%
Combined	50.0%	100.0%	100.0%	70.8%	77.4%

In the present study, peritoneal fluid testing for GeneXpert was found to be highly specific for the diagnosis of genital tuberculosis with a specificity and positive predictive value of 100%. However, it was not found to be very sensitive. Not many studies have been done with peritoneal fluid testing for GeneXpert but studies had been reported on endometrial samples. Vadwai V et al[15] in 2010 demonstrated GeneXpert sensitivity of 83% and specificity of 73% for 533 extrapulmonary TB (EPTB) patients assessed in comparison to a composite reference standard made up of smear and culture results and clinical, radiological, and histological findings. Their study had a higher proportion of biopsy and cold abscess samples than various body fluids, which might account for the higher sensitivity in their study compared to the present study (21.62%). In lymph nodes and its aspirates the bacteria are localised to the site of infection, whereas in body fluids, presence of PCR inhibitors and the paucibacillary nature of the specimens may result in lower sensitivity. The difference in the specificity of the present study and the study by Vadwai V et al could also be attributed to the inclusion criteria of patients and the sample size. In 2012, Sharma S.K et al[16] observed GeneXpert to have 33–50% sensitivity, 100% specificity in 1376 extrapulmonary TB samples (including body fluids and tissue biopsies) which was similar to our study. They also identified 68% of possible TB cases with GeneXpert where culture, histopathology and biochemistry were negative. They concluded that results of GeneXpert vary with the sample type but it is a promising diagnostic test for lymph nodes, cold abscesses and CSF specimens. In case of serosal fluids, which constitute a major challenge in extrapulmonary TB especially genital TB (GTB), the diagnostic utility of the assay is limited.

In a prospective study conducted by Shrivastava G et al[9] on 227 endometrial samples of infertile women suspected of GTB, 126 (86%) were positive only by PCR/GeneXpert. The results were compared with other diagnostic tests i.e., AFB smear and culture. The positive predictive value was found to be 86% which was comparable to the present study. Sharma J.B et al[17] in 2018 reported 35% sensitivity and 100% specificity in the detection of genital tuberculosis with GeneXpert. However, as the false-positive rate of PCR is high, many researchers have advised against PCR for the rapid detection of TB.

There are several limitations of the GeneXpert assay. GeneXpert is sensitive to high temperature and humid conditions, which are quite prevalent in countries with a high burden of tuberculosis like India. The presence of PCR inhibitors in peritoneal fluid and its contamination with blood can affect the results. GeneXpert cannot differentiate between live and dead bacilli. Approximately 30% of patients who are microbiologically cured after 6 months of treatment are still GeneXpert positive.[18] Detectable mycobacterium DNA, which can be extracellular or associated with nonintact cells (and hence is not culturable), is a possible cause of this false positivity, which may trigger unwarranted treatment delay in establishing the correct underlying diagnosis and its appropriate treatment and escalate healthcare costs.[18]

A literature review done by K.R. Munne et al[19] in 2020 suggests that though culture is an invaluable contributor in the diagnosis of FGTB(Female Genital Tuberculosis), the use of algorithm approach with combination of both rapid culture and newer molecular techniques like GeneXpert/PCR will facilitate the accurate and timely diagnosis of FGTB.

A study conducted by Oya Akkaya et al[20] among the clinical samples from 140 patients suspected of having TB, 12% (16/140), 15% (21/140), 16% (23/140), and 14% (20/140) were positive by AFB detection, LJ conventional culture, MGIT-960 liquid culture, and PCR methods, respectively. They concluded that molecular tests may be a complementary method for confirming a diagnosis of TB, considering that they yield same-day, high-sensitivity results. Due to the high specificity of PCR, positive results obtained by this test may be useful for early detection of TB. However, it would be appropriate to confirm negative results with culture and clinical findings.

5. Conclusion

The authors conclude that extragenital tuberculosis in women has the potential to spread to the genital region and the women may remain asymptomatic till they present with infertility. Thus all women presenting with infertility should be screened for a past history of tuberculosis and actively worked up for genital tuberculosis in case the history is positive. The authors recommend an approach of early resort to laparohysteroscopy in these patients so that definitive management may be instituted timely and promptly. In addition, the authors conclude all the three tests (Mantoux test, GeneXpert and liquid culture) have their limitations as regards their accuracy is concerned. Due to lack of sensitivity not a single test can be applied for the diagnosis. However it can be inferred that in women with positive Mantoux test laparohysteroscopy should be done early as it has high sensitivity. Endoscopic evaluation is an important diagnostic tool, but can neither confirm nor exclude genital TB. Hence the results should be analysed by GeneXpert and liquid culture as they had high specificity and can aid in a definite diagnosis of Genital TB in endemic areas like India.

Author contributions

Design, planning and conceptualisation: Manju Puri, Swati Agarwal.

Collection and assembly of data: Swati Yadav.

Data analysis and interpretation: Swati Yadav, Manju Puri.
Manuscript writing: Swati Yadav, Manju Puri.
Resources: Kamal Chopra.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Schaefer G. Female genital tuberculosis. *Clinical Obstet Gynaecol*. 1976;19(1):223–239.
2. Chattopadhyay SK, Sengupta BS, Edrees YB, Al-Meshari AA. The pattern of female genital tuberculosis in Riyadh, Saudi Arabia. *Br J Obstet Gynaecol*. 1986;93(4):367–371.
3. Bateman BG, Nunley Jr WC, Kitchin 3rd JD, Fechner RE. Genital tuberculosis in reproductive-age women. A report of two cases. *J Reproduct Med*. 1986;31(4):287.
4. Schaefer G. Tuberculosis of the female genital tract. *Clin Obstet Gynecol*. 1970;13(4):965–998.
5. Dutta DC. Pelvic infection. In: Konar H, ed. *Textbook of Gynecology*. 6 ed. New Delhi: Jaypee Brothers medical publishers; 2013:139.
6. Siegler AM, Kontopoulos V. Female genital tuberculosis and the role of hysterosalpingography. *Semin Roentgenol*. 1979;14(4):295–304.
7. Cheng VC, Yam WC, Hung IF, et al. Clinical evaluation of the polymerase chain reaction for the rapid diagnosis of tuberculosis. *J Clin Pathol*. 2004;57(3):281–285.
8. Grange JM. The biology of the genus Mycobacterium. *J Appl Bacteriol*. 1996;81, 1S-9S hers; 2013;13.
9. Shrivastava G, Bajpai T, Bhatambare GS, Patel KB. Genital tuberculosis: comparative study of the diagnostic modalities. *J Hum Reprod Sci*. 2014;7(1):30.
10. Singh UB, Seth P. PCR diagnosis of tuberculosis-experience in India. *Indian J Pediatr*. 2002 Nov;69:S20–S24.
11. Eisenach KD, Sifford MD, Cave MD, Bates JH, Crawford JT. Detection of Mycobacterium tuberculosis in sputum samples using a polymerase chain reaction. *Am Rev Respir Dis*. 1991;144:1160–1163.
12. Hassan W, Darwish A. Impact of pulmonary tuberculosis on menstrual pattern and fertility. *Clin Respir J*. 2010;4(3):157–161.
13. Sharma R, Puri M. Extragenital tuberculosis and female infertility - is there a correlation? A retrospective observational study. *IVF Lite*. 2016;3(1):7.
14. Raut VS, Mahashur AA, Sheth SS. The Mantoux test in the diagnosis of genital tuberculosis in women. *Int J Gynecol Obstet*. 2001;72(2):165–169.
15. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol*. 2011;49(7):2540–2545.
16. Sharma SK, Kohli M, Chaubey J, et al. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. *Eur Respir J*. 2014;44(4):1090–1093.
17. Sharma JB, Sharma E, Sharma S, Dharmendra S. Female genital tuberculosis: Revisited. *Indian J Med Res*. 2018;148(suppl 1):S71.
18. Theron G, Venter R, Calligaro G, et al. Xpert MTB/RIF results in patients with previous tuberculosis: can we distinguish true from false positive results? *Clin Infect Dis*. 2016;62(8):995–1001.
19. Munne KR, Tandon D, Chauhan SL, Patil AD. Female genital tuberculosis in light of newer laboratory tests: a narrative review. *Indian J Tubercul*. 2020;67(1):112–120.
20. Akkaya O, Kurtoglu MG. Comparison of conventional and molecular methods used for diagnosis of Mycobacterium tuberculosis in clinical samples. *Clin Lab*. 2019;65(10), 10.7754.

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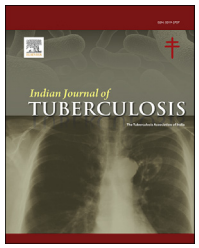

Original article

TB positive cases go up in ongoing COVID-19 pandemic despite lower testing of TB: An observational study from a hospital from Northern India

Shruti Srivastava, Research Scientist [a,*], *Namita Jaggi, Chairperson* [b,**]

[a] *Education & Research, Artemis Hospitals, Gurugram, Haryana, 122001, India*
[b] *Laboratory Services & Infection Control, Education & Research - Lab Medicine, Artemis Hospitals, Gurugram, Haryana, 122001, India*

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ABSTRACT

The whole world is wrestling against SARS-CoV-2 infection (COVID-19). COVID-19-TB co-infection is also reported but there are limited number of studies which analyze the impact of COVID-19 pandemic in TB diagnosis and management. In this retrospective study, we observed that the TB diagnosis was reduced in pandemic time. Before COVID-19 pandemic (March–December 2019), there were 644 TB tests out of which 127 were TB positive. In ongoing COVID-19 pandemic (January–October 2020), 484 TB tests were performed and 146 patients were TB positive. Male accounted for 64%/57% of TB cases in 2019/2020 whereas female patients were 35%/42% in 2019/2020. Increase in female TB positive cases was a noticeable feature. The newly diagnosed with TB cases in 2019/2020 were 112/130 respectively. Though, we have seen only 7 COVID-TB co-infection cases, we could not establish the causal relationship in COVID-TB co-infection. The increase in the number of TB positive cases during COVID-19 pandemic clearly showed how adversely COVID-19 has affected TB diagnosis and management. Anticipating the increase in TB cases in future, we emphasize the need to ensure continuous TB testing and treatment despite the pandemic burden. Further study on the COVID-TB co-infection in high TB-burden countries like India, is required to enable analyses of interactions, risk factors in COVID-19-TB co-infection.

Abbreviations: TB, Tuberculosis; AIDS, MERS, SARS, Chronic obstructive pulmonary disease, COPD; Human immunodeficiency virus, HIV; Diabetes mellitus, DM; Hypertension, HTN.

* *Corresponding author.*
** *Corresponding author.*
E-mail addresses: shruti.srivastava@artemishospitals.com, trivenishruti@gmail.com (S. Srivastava), namita@artemishospitals.com (N. Jaggi).

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic has attracted the interest due to its worldwide reach, clinical severity and higher mortality rate.[1] SARS-CoV-2 transmission is mainly through droplets, although aerosol transmission and surface contamination is still a subject of continuous debate. The initial symptoms of COVID-19 infection are similar to Middle east respiratory syndrome (MERS). Influenza, severe acute respiratory syndrome (SARS), tuberculosis (TB), though the immune response and disease manifestation are different.[2,3]

Most of the COVID-19 infected patients show mild or no symptoms. Elderly patients or, persons with underlying medical conditions are at higher risk of developing severe outcome. Thus it is important to study the associated factor along with COVID-19 infection to know more about this novel disease.[3]

TB-COVID-19 co-infections are not rare and both are associated with weaken protective immune responses.[4,5] TB care and management program has already suffered in the past during HIV/AIDS emergencies, outbreak of EBOLA, H1N1, MERS.[6] Currently, the unprecedented demand required by COVID-19 has hindered TB management in many countries[7] as lab personnal and laboratory facilities are re-assigned for COVID-19 testing, a major chunk of budget goes for the procurement of consumables.[8] The supply for scientific as well as general goods has suffered during worldwide lock-down.

Thus, the aim of the study was to analyze the effect of COVID-19 pandemic on TB diagnosis. The present study describes the first-ever comparative study of TB diagnosis in pre (10 months) vs ongoing COVID-19 pandemic (10 months). It is a purely observation study and no analysis for outcome assessment is performed.

2. Study setting and design

The study was performed in a 300-bed tertiary care private hospital in Gurgaon, Haryana (India). A retrospective observational analysis was undertaken of all patients with confirmed TB cases from GENE/Xpert test-a CBNAAT (cartridge based nucleic acid amplification test). For COVID-19 patients, patients with confirmed RT-PCR test were included in the study. The duration of time-period studied were, pre-COVID-19 time (From March–December 2019) and ongoing COVID-19 time (from January–October 2020).

Patient demographics gender, age, microbiology data, co-morbidities and death-record extracted from hospital information system (HIS) were de-identified as part of an ongoing outbreak investigation. Thus, institutional review board approval was deemed unnecessary. Also, due to the retrospective and purely observational nature of the study, the written informed consent from patients is not required.

The information available on patients details were as far as could be, is accurate, however, some details of patients were missing because either the patients did not continue the treatment at the hospital or left against medical advice.

3. Statistical analysis

Continuous variables are presented as medians (interquartile ranges, IQR), and categorical variables as counts (percentages). Fisher's exact test (two-tailed) was performed was performed was performed with GraphPad to compare data from pre-COVID-19 and ongoing COVID-19 period.

4. Results

4.1. *Ongoing COVID pandemic (from January–October 2020) sees lesser number of TB diagnostic tests*

From March 2019 to December 2019, 644 TB tests were performed and TB was detected in 127/644 (19.72%). In COVID time, total 484 TB tests were performed out of which 146/484 were TB positive (30.16%) (Table 1). TB positivity has gone up to 30% in 2020 from ~20% in 2019 despite decline in lesser tests in 2020 (484) as compared to 2019 (644).

In 2020, out of 146 confirmed TB cases, 134 were sensitive and 12 were resistant. Whereas in 2019, out of 127 confirmed TB cases, 101 were sensitive and 23 were resistant (Table 1).

Male (M) accounted for 64% of TB cases in 2019 and 57% in 2020 patients. Female (F) accounted 35% of TB cases in 2019 and 42% in 2020 patients (Table 1). One interesting feature is that female % in TB positive cases have increased from 2019.

The no. of patients newly diagnosed with TB in 2019/2020 was 112/130 respectively.

The median age was 46.5 years (IQR (2020): 36, M: 32, F: 37.5), and 53 years IQR (2019) = 38 M: 37 F: 39).

5. COVID-TB Co-infection

In 2020, approximately 71 COVID-19 tests (RT-PCR based) were conducted for confirmed TB cases and we observed 7 cases of COVID-TB co-infection (Table 2). All COVID-TB co-infection patients survived except one (Table 1). In COVID-TB co-infection (Table 2), 4/7 (57.14285714%) had TB (ongoing anti-TB treatment) before COVID-19, 2/7 (28.5%) had COVID-19 first and 1/7 (14.2%) had both diseases diagnosed within the same week. Signs and symptoms of COVID-19 infection were fever, cough and breathlessness (in different combinations). All the COVID-TB co-infection patients had at least one co-morbidity (Table 2) and were sensitive. The median age was 60 years, (IQR: 27, Coefficient of Variation (CV) = 0.23) in COVID-TB co-infection. Unfortunately, BCG vaccination status was not available; hence no significant correlation can be ascertained to BCG vaccination mediated protection from COVID-19 infection.

In patients, where COVID-19 was detected first, probably, an overlap of signs/symptoms of COVID-19 and TB have occurred and COVID-19 was diagnosed earlier because of a higher degree of suspicion. On a different note, suspicion of COVID-19 infection and overlapping symptoms with TB might have led to TB diagnosis before the onset of TB-related

Table 1 – Demographic and clinical characteristics of TB patients.

	Pre-COVID-19 period	Ongoing COVID-19 period	*p* value
No. of patients (n)	644	484	
Confirmed TB patients	127/644 (19.72%)	146/484 (30.16%)	p = 0.0001
Age (years)	53 (IQR: 38)	46.5 (IQR: 36)	–
Median (min–max)	53 (0–82)	46.5 (0–94)	–
Age (years)			
Sex			
Male	82/127 (64.5%)	84/146 (57.5%)	p = 0.26
Female	45/127 (35.4%)	62/146 (42.4%)	p = 0.26
Co-morbidities in TB patients			
Sepsis (all died)	3/127 (2.36%)	9/146 (6.16%)	p = 0.1489
Carcinoma	17/127 (13.38%)	21/146 (14.38%)	p = 0.8621
HIV	0	1/146 (0.68%)	p = 1
DM/HTN	21/127 (16.53%)	20/146 (13.69%)	p = 0.61
COPD	6/127 (4.72)	4/146 (2.73)	p = 0.52
Alcohol	2/127 (1.57%)	1/146 (0.68%)	p = 0.59
Smoker	3/127 (2.36%)	3/146 (2.05%)	p = 1
Candida/yeast infection	3/127 (2.36%)	3/146 (2.05%)	p = 1
Pneumonia	0	8	–
History of Tuberculosis			
Previous history of TB	15/127 (11.81%)	16/146 (10.95%)	p = 0.85
Newly Diagnosed TB	112/127 (88.18%)	130/146 (89.04%)	p = 0.85
Resistant	23/127 (18.11%)	12/146 (8.21%)	p = 0.01
Sensitive	101/127 (79.52%)	134/146 (91.78%)	p = 0.0047
Death	8/127 (6.29%)	13/146 (8.90%)	p = 0.49
COVID-19 infection in TB patients			
No. of COVID-19 test	–	71	–
Male	–	32	–
Female	–	39	–
Confirmed COVID-19 infection	–	7	–
Median age in years	–	60 (IQR: 27)	–
Asymptomatic	–	3/7 (42.85%)	–
Symptomatic	–	4/7 (57.14%)	–
Female	–	3/7 (42.85%)	–
Male	–	4/7 (57.14%)	–
Death	–	1/7 (14.28%)	–

*Pre-COVID-19 period (March–Dec 2019), ongoing COVID-19 period (Jan–Oct 2020), Chronic obstructive pulmonary disease (COPD), Human immunodeficiency virus (HIV), Diabetes mellitus (DM), Hypertension (HTN). Death is the number of patients who died during anti-TB treatment.

Table 2 – Characteristics of patients with COVID-TB co-infection.

Patient	Age/Sex	Co-morbities	TB Type	Sensitive/ Resistant TB	COVID Severity	Recovered/Death
Patient 1	60/F	CKD	EPTB	Sensitive	Severe, COVID pneumonia	Left hospital
Patient 2	65/M	Hypothyroidism, Cholelithisis	PTB	Sensitive	Mild	Delayed viral clearance
Patient 3	67/M	Metastatic NSCLC	PTB	Sensitive	Severe, COVID pneumonia	Death
Patient 4	39/F	Relapsed AML	PTB	Sensitive	Mild	Recovered
Patient 5	40/F	DM	EPTB	Sensitive	Severe	Recovered
Patient 6	68/M	DM	PTB	Sensitive	Mild	Delayed viral clearance
Patient 7	47/M	DM, CAP-PTCA	PTB	Sensitive	Moderate	No info

*Abbreviations: Chronic kidney disease(CKD),coronary artery perforation (CAP),Percutaneous transluminal coronary angioplasty (PTCA),Acute myeloid leukemia(AML), Nonsmall-cell lung carcinoma (NSCLC), Diabetes mellitus (DM), Multiple Organ Dysfunction Syndrome (MODS), Pulmonary tuberculosis (PTB), Extrapulmonary tuberculosis (EPTB).

symptoms.[4,10] This could be the reason behind higher percentage of confirmed TB cases in 2020 despite lower testing (Table 1).

In India where majority of the population is asymptomatic for COVID-19 infection (or who are missed in testing and contact tracing), it is pertinent to monitor the development of TB. We cannot either report or rule-out the potential contribution of COVID-19 towards development of TB based on this study. Although the diagnosis of TB preceded that of COVID-19 in 4/7 patients, any contribution of COVID-19 to TB pathogenesis or vice-versa can neither be excluded nor confirmed. We believe larger numbers of patient data are required to fully understand the impact of COVID-19 pandemic on TB diagnosis and treatment.

6. Discussion and conclusion

Due to the disruption in healthcare system caused by COVID-19 pandemic, TB reporting and diagnosis in 2020 sees a significant fall (Table 1). In 2020, we observed increase in confirmed TB cases as compared to 2019. It is possible that undiagnosed and untreated TB cases are contributing to TB transmission among household contacts. Longer indoor stay, failure to follow-up due to lock-down, discouraged-hospital visit, all these factors not only poses health hazard to the existing TB patient but also increases the chances of transmission within house-hold contacts or care-givers. Crowded live-in conditions, poor hygiene, are contributing factor for both COVID and TB infection, thus it is pertinent to identify and isolate TB patients at an earliest to reduce the severe outcome due to suppressed immunity.[9,10]

In high risk group or in TB-endemic areas like India, COVID-TB co-infection should be assessed critically.[10] Present study is an attempt to study COVID-TB co infection in a high burden country, India to fill the knowledge-gap in the concern area. The identification of COVID-TB co infection is important for proper disease management. This is, to our knowledge, the first comparison study of TB diagnosis/reporting in the pre and ongoing COVID-19. Our study represents a "snapshot" of TB diagnosis at different times. No attempt was made to represent the casual relationship on co-occurrence of both diseases. Given the small size of data and single-institutional study, we cannot directly correlate/or establish the relationship in COVID-TB co infection or its outcome, but such studies are important for prevention, treatment and management of TB, COVID-19 like infectious diseases in future. We believe that this observational research can motivate for larger studies to enable analyses of interactions, risk factors and determinants of outcomes in patients with COVID-TB co infection.

Author contribution statement

Shruti Srivastava: Conceptualization, Methodology, Investigation, Writing- Original draft preparation, reviewing, editing and manuscript submission.

Namita Jaggi: revised and approve the manuscript.

Both authors read and approved the final manuscript.

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Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Alagna R, Besozzi G, Codecasa LR, et al. Celebrating world tuberculosis day at the time of COVID-19. *Eur Respir J*. 2020;55:2000650. https://doi.org/10.1183/13993003.00650-2020.
2. Oei W, Nishiura H. The relationship between tuberculosis and influenza death during the influenza (H1N1) pandemic from 1918-19. *Comput Math Methods Med*. 2012;2012:124861. https://doi.org/10.1155/2012/124861.
3. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol*. 2020;11:1441. https://doi.org/10.3389/fimmu.2020.01441.
4. Tadolini M, Codecasa LR, García-García JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J*. 2020;56:2001398. https://doi.org/10.1183/13993003.01398-2020.
5. Crisan-Dabija R, Grigorescu C, Pavel CA, et al. Tuberculosis and COVID-19: lessons from the past viral outbreaks and possible future outcomes. *Canc Res J*. 2020;2020:1401053. https://doi.org/10.1155/2020/1401053.
6. Echeverría G, Espinoza W, de Waard JH. How TB and COVID-19 compare: an opportunity to integrate both control programmes. *Int J Tubercul Lung Dis*. 2020;24:971–974. https://doi.org/10.5588/ijtld.20.0417.
7. Bhatia V, Mandal PP, Satyanarayana S, Aditama TY, Sharma M. Mitigating the impact of the COVID-19 pandemic on progress towards ending tuberculosis in the WHO South-East Asia Region. *WHO South East Asia J Public Health*. 2020;9:95–99. https://doi.org/10.4103/2224-3151.294300.
8. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. *Inf Disp*. 2020;52:902–907. https://doi.org/10.1080/23744235.2020.1806353.
9. Gupta N, Ish P, Gupta A, et al. A profile of a retrospective cohort of 22 patients with COVID-19 and active/treated tuberculosis. *Eur Respir J*. 2020;56:2003408. https://doi.org/10.1183/13993003.03408-2020.
10. Tamuzi JL, Ayele BT, Shumba CS, et al. Implications of COVID-19 in high burden countries for HIV/TB: a systematic review of evidence. *BMC Infect Dis*. 2020;20:744. https://doi.org/10.1186/s12879-020-05450-4.

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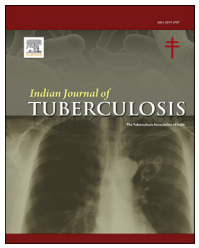

Original article

Utility of RNTCP (NTEP) guidelines in microbiological confirmation of pediatric tuberculosis

C.K. Indumathi[*], *Saurav Jain*, *Savita Krishnamurthy*, *Beninja Alexander*

Department of Pediatrics, St John's Medical College Hospital, Bengaluru, Karnataka, India

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ABSTRACT

Objective: To estimate the proportion of microbiologically confirmed disease among children diagnosed with tuberculosis using RNTCP guidelines.

Materials and methods: Retrospective chart review of a cohort of 151 children (aged between 1 month and 18 years) diagnosed with Tuberculosis between December 2016 and June 2020 at a pediatric department of a tertiary care hospital. We collected information on AFB (Acid Fast Bacillus) smear and Cartridge Based Nucleic Acid Amplification Test (CB NAAT) results.

Results: Out of 151 children with a diagnosis of Tuberculosis, 66 (44%) children were found to have microbiologically confirmed disease. Confirmatory rate was almost equal in children less than <5 and >5 years (48% vs 52%). Confirmatory rate did not differ between pulmonary and extra pulmonary samples (49% and 53%). Cartridge Based Nucleic Acid Amplification Test outperformed AFB by 10%, which was statistically significant ($p = .000$ by fisher exact test).

Conclusion: Although considered paucibacillary in nature, microbiological confirmation can be obtained in almost up to half of children with a diagnosis of TB by using RNTCP guidelines. Neither young age nor type of TB is a deterrent to bacteriologically confirm TB in children.

1. Introduction

Microbiological confirmation of Tuberculosis (TB) is rarely attempted/achieved in children and diagnosis is often based on clinical grounds.[1] Conventional teaching that pediatric pulmonary TB (PTB) is paucibacillary and children cannot bring out sputum often discourages attempts to microbiological confirmation. In fact, a study revealed that the number of cases where sputum examination was not done was higher in children (27.5% v/s 1%) than adults.[2] Studies so far have demonstrated an AFB smear positivity rate of 15%–20% in Indian children.[2,3] Bacteriological confirmation is an exception rather than the rule in Extra Pulmonary Tuberculosis (EPTB), which accounts for > 40% of pediatric TB.[4] The lack of microbiological confirmation results not only in under diagnosis of TB, but also adds to the danger of missing Multi Drug Resistant TB (MDRTB) in children, which is estimated to be around 8.5% in our country.[5,6]

* *Corresponding author*. Department of Pediatrics, St John's Medical College Hospital, Bengaluru, Karnataka, India.
E-mail address: ckindumathi@gmail.com (C.K. Indumathi).

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In the year 2016, Revised National Tuberculosis Control program (RNTCP) published guidelines which emphasized on microbiological confirmation of pediatric TB by using Acid Fast Bacilli (AFB) isolation enhancing techniques (Gastric aspiration in infants and induced sputum in young children) and upfront utilization of Cartridge Based Nucleic Acid Amplification Test (CB NAAT) in both pulmonary and extra pulmonary samples.[7]

In our department, we have been diligently practicing AFB isolation enhancing technics since 2016. In infants and young children up to 6 years with presumed PTB, gastric aspirations are done on two consecutive days after a fast of 3 hours. Children above 6 years with presumptive PTB are subjected to induced sputum nebulisations with 3% saline on 2 consecutive days. Gastric aspirate/induced sputum thus collected are sent for AFB smear on two consecutive days and CB NAAT once.

Several studies have reported higher confirmatory rate on gastric aspirate and induced sputum samples in children.[8,9] Apart from being a more sensitive test, CB NAAT has an additional advantage of simultaneously detecting rifampicin resistance.[10,11] With these improved measures, one can expect a rise in proportion of microbiologically confirmed cases. However, there is a paucity of published data on trend of proportion of confirmed cases among children with TB in India. We planned this study to fill this research gap and we hypothesized that bacteriological confirmatory rate would have improved over and above 20% since introduction of these measures.

Hence, objective of our study was to estimate the proportion of children with microbiologically proven TB among those diagnosed with active disease. We also tried to assess the relative performance of CB NAAT over AFB smear in microbiologically confirming the disease.

2. Methods

The present study is a retrospective analysis of records of children with a diagnosis of TB (PTB and EPTB), aged between 1 month and 18 years, at a tertiary care hospital during December 2016 and June 2020. Study was carried out after obtaining clearance from institutional ethics committee (204/2020). We excluded children with HIV co infection.

Demographic data was recorded in detail. Tuberculosis was categorized into 2 groups. Group 1: microbiologically confirmed TB and Group 2: clinically diagnosed TB as per RNTCP (NTEP) guidelines.[7] Children with either positive AFB smear or positive CB NAAT report were classified as having microbiologically confirmed TB. Children who were diagnosed based on the history of contact, positive Mantoux test, Chest X-ray findings highly suggestive of TB, histopathological features suggestive of granuloma, biochemical investigations on CSF/pleural/pericardial fluids, ultrasound/MRI findings were classified as having clinically diagnosed TB. Sputum, gastric aspirate and Broncho Alveolar Lavage (BAL) samples were recorded as pulmonary samples. Samples of Fine Needle Aspiration Cytology (FNAC), CSF/pleural/peritoneal/pericardial fluids/histopathology samples were classified as extrapulmonary samples. Reports of Line Probe Assay (LPA) and mycobacterial cultures were collected as per availability. A diagnosis of MDRTB was made when CB NAAT revealed rifampicin resistance. Data was analysed and proportion of children with microbiologically proven TB among those diagnosed with active disease was estimated.

2.1. *Statistical analyses*

Data was analysed with PSPP software. For the comparison of quantitative data, the Student's t test was applied. Values of $p < 0.05$ were regarded as significant. Fisher's exact probability was used for 2X2 contingency tables.

3. Results

During the study period, i.e., December 2016 and June 2020, 151 children were diagnosed with TB. Mean Age was 7.93 (±-4.79) years with a range of 4 months−17 years. Children less than 5 years (n = 54) accounted for 36% of study population. Male to female ratio was 1:1. Pulmonary TB accounted for 85 (56%) and EPTB 66 (44%) cases. Mean age of PTB/EPTB was 6.85 (±4.46) and 9.32 (±4.87) years respectively. Among 66 children with EPTB, neuro TB (TB meningitis + tuberculoma) accounted for 20, TB Lymphadenitis 16, abdominal TB 14, pleural effusion 6, genito urinary 4, osteoarticular 4, pericardial effusion and retinal vasculitis one each.

Among 151 cases, 130 children were microbiologically tested either by AFB or CB NAAT. Whereas AFB was done in all 130 children, CB NAAT could be done in 102 cases. In 21 cases (19 EPTB and 2 PTB), neither AFB nor CB NAAT could be done for the following reasons; inaccessible EPTB sites (intracranial tuberculoma, deep abdominal nodes, retina), insufficient biopsy samples where repeat biopsy was unethical, insufficient sputum and GA samples where parents refused to give repeat samples, unavailability of in house CB NAAT for the first 2 years of study period and inability to process for CB NAAT in blood tinged samples. Out of 85 PTB patients, pulmonary samples were obtained in 83 patients. Type of pulmonary samples was as follows; 48 sputum, 34 gastric aspirate and 1 BAL sample. Out of 66 extrapulmonary patients, samples could be obtained and tested in 47 patients.

Sixty six out of 151 children (44%) were found to have microbiologically confirmed TB either by AFB or by CB NAAT and 85 (56%) were clinically diagnosed. Confirmatory rate went up to 50% if the denominator were to be 130 tested samples (66/130). Mean age of microbiologically confirmed TB was 8.41 (±5.07) years and that of clinically diagnosed TB was 7.55 (±4.55) years. There were no statistically significant differences between two groups either in age distribution or in type of samples (pulmonary/non pulmonary). Table 1 provides basic data/comparison between two groups (Table 1).

In those where testing was done (n = 130), we analysed positivity rate in children < 5 years and >5 years. Twenty three out of 48 children who were <5 years, (23/48) were found to have confirmed disease giving a positivity rate of 48%. Out of 82 children who were > than 5 years old, 43 had confirmed disease, (43/82), giving a positivity rate of 52%. Positivity rate did not differ between two age groups.

Table 1 – Comparison between microbiologically confirmed and clinically diagnosed cases (N = 151).

Variable	Microbiologically Confirmed (n = 66)	Clinically diagnosed (n = 85)	P value
Age in years mean (SD)	8.41 (5.07)	7.55 (4.55)	0.3 (NS)
Age Less than 5 years	23 (35%)	31 (36.5%)	0.8 (NS)
Age More than 5 years	43 (65%)	54 (63.5%)	
Type of sample			
Pulmonary (n = 85)	41 (62%)	44 (52%)	0.2 (NS)
Extra Pulmonary (n = 66)	25 (38%)	41 (48%)	

Values in no (%).

Next, we analysed positivity rate on pulmonary/extrapulmonary samples. Out of 83 pulmonary samples that were tested, 41 were found to have microbiologically confirmed disease (41/83), giving a positivity rate of 49%. Out of 47 extrapulmonary samples tested, 25 were positive (25/47), yielding a rate of 53%. Like age, type of samples did not make a difference for confirming disease.

Out of 130 children, AFB was positive in 52 children (52/130), giving a AFB positivity rate of 40%. Out of 102 children where CB NAAT was done, it was positive in 43 children (43/102), giving a CB NAAT positivity of 42%. Individually, AFB smear and CB NAAT performed equally. When we analysed 102 children where both AFB smear and CB NAAT were done, AFB was positive in 33 (32%) and CB NAAT in 43 (42%), giving a p value of < 0.000 which was statistically significant in favor of CB NAAT ($p = .000$ fisher exact test). From the table (Table 2), it is clear that CB NAAT uniquely contributed to diagnosis in 14 cases whereas AFB contributed only in 4 cases. In other words CB NAAT outperformed AFB by 10% in cases where both tests were done.

Out of 14 cases where only CBNAAT was positive, the break of origin of the sample was as follows: pulmonary 5, CSF 4, FNAC 2, mesenteric 2 and urinary sample 1. In addition to unique contribution, CB NAAT picked up Rifampicin resistance in 4 children including a child with TB meningitis. Details of 4 cases where only AFB was positive are as follows: In 2 gastric aspirate samples, M.tb was confirmed by first line LPA though CB NAAT was negative. Third one was a FNAC sample from a child with Acute Lymphoblastic Leukemia, which later yielded growth of M. Chelonae, thereby explaining negative CB NAAT result.

In pulmonary samples, (n = 83) Individual performance of AFB smear ((35/83)and CB NAAT (30/72) were similar (42%). Comparative analysis where both were done did not show any superior performance of one over the other. In EP samples (n = 47), Individual performance of AFB and CB NAAT were (17/47) 36% and (13/30) 43% respectively. On comparative analysis where both were done (n = 30), only CB NAAT was positive in 8 cases (27%), where as in no case (0%) only AFB was positive. This difference was statistically significant ($p = .009$ by fisher's, exact test) in favor of CB NAAT.

Out of 66 children with microbiological confirmation, drug resistance was noted in 5 children (7.5%). Four were rifampicin resistant (6%) and 1 INH monoresistant (*Inh* A mutation-1.5%)

Table 2 – A relative performance of AFB smear and CB NAAT (N = 102).

AFB test result	CBNAAT test result		
	Positive	Negative	Total
Positive	29 (28)[a]	4 (4)	33 (32)
Negative	14 (14)	55 (54)	69 (68)
Total	43 (42)	59 (58)	102

Fisher's exact test: $p = 0.000$ (significant).
[a] Numbers in brackets are percentages of total (n = 102).

4. Discussion

By strictly adhering to AFB isolation enhancing technics and utilization of CB NAAT whenever feasible, the present study found that TB can be microbiologically confirmed in up to 44% of children who were diagnosed with TB. This finding was consistent with studies from South Africa, where proportion of bacteriologically confirmed tuberculosis was reported to be 40–48%.[12,13] Whereas these authors had employed both mycobacterial culture and/or AFB smear for diagnosis, we could confirm diagnosis in equal numbers by using AFB smear and CB NAAT.. This emphasizes the value of RNTCP/NTEP diagnostic algorithms that advocate upfront use of CBNAAT in pediatric TB. In contrast to our finding, studies from Uganda and Mozambique reported a lower proportion (13%–28%) of confirmation.[14,15] Recruiting only young children <3 years as the study population may explain the low figure in Mozambique study.

Our smear positivity rate of 42% on pulmonary samples was twice of that of average AFB positivity of 20% as reported in other Indian studies previously.[3] The possible explanation could be employment of AFB isolation enhancing technics in our study population. Performance of these special technics by well-trained nursing staff of our tertiary care centre may have contributed to the higher yield of smear positivity. As quoted studies were conducted from 1995 to 2008, researchers may not have employed these technics universally, there by reporting low smear positivity.

Chances of bacteriological confirmation are estimated to be at least 3 times higher in older children compared to younger children. Raizada et al, observed significantly higher TB positivity in 10–14 years age group (13.5%) compared to 0–4 years (4.8%).[5] A metaanalysis also showed a wide variation in positivity rate (0.5%–14%) between children < 5 years and >5 years.[3] However, in our study, microbiological positivity rate did not differ between young children <5 years compared to children >5 years (48% versus 52%). Young age was not a deterrent for attempts to confirm TB.

Diagnosis of EPTB is a major challenge and reported bacteriological confirmation of EPTB by different methods varies between 10 and 25%.[16–18] In our study, microbiological confirmation was obtained in at least half of samples

irrespective of origin of the sample (pulmonary 49%/extrapulmonary 53%). Like age, site of TB did not make a difference to confirmation of the disease.

Individually, AFB smear and CB NAAT performed equally in confirming TB though CB NAAT was expected to perform better.[5,6] However, on comparative analysis, not only CB NAAT performed better, it confirmed 9 EPTB including 4 TBM and 1 genito urinary TB where AFB had failed.

When we analyzed 4 AFB positive, but CB NAAT negative samples, CB NAAT was found to be falsely negative in 2 samples as first line LPA confirmed M.tb. Mycobacterial culture yielded *M. chelonae* in 3 rd sample. This emphasizes the value of further LPA testing and mycobacterial cultures in AFB positive but CB NAAT negative samples to detect M.tb/Non Tubercular Mycobacteria.[19,20]

When we further analysed the performance of CB NAAT and AFB smear in pulmonary and extrapulmonary samples, CB NAAT did better than AFB smear both individually (42% vs 36%) and as well as comparatively (*P* value 0.02) in EP samples. This potential of CB NAAT in significantly improving the diagnosis of EPTB has been demonstrated in other studies too.[16–18]

Four among 5 children with Drug Resistant TB (DRTB) were treatment naïve without having had contact with DRTB source and did not come under definition of "presumptive DRTB". This was in consistent with study by Rizada et al, where prior exposure to anti tubercular drugs was present only in 30% of confirmed DRTB[5] (We could have easily missed diagnosis of DRTB in these children if we had not employed CB NAAT as a routine.

5. Conclusion

Contrary to conventional belief, microbiological confirmation can be obtained in almost up to half of children with a diagnosis of TB. The challenge of paucibacillary nature of the disease can be partly overcome by employing AFB isolation enhancing technics to collect samples for AFB and CB NAAT as suggested by RNTCP guidelines. *The present study has shown that, neither young age nor type of TB is a deterrent to bacteriologically confirm TB in children*. Study also reiterates superiority of CB NAAT over AFB smear in confirming the disease, especially in EPTB. Hence it is imperative to send adequate and appropriate samples (saline) for the same. *The study challenges the traditional knowledge that children are minor contributors to community spread. Whether high positivity status means a high infectivity should be explored further*.

Strength of our study being strict application and reiterating the recommendations of RNTCP/NTEP in the diagnosis of pediatric TB. We hope that findings of our study would instil confidence in health care providers of the country in microbiologically confirming pediatric TB under national health program.

Our study is limited by the retrospective nature and small number. Further prospective studies with larger number are required to confirm our results. To the best of our knowledge, the present study is the first one to report proportion of microbiologically confirmed TB in children since the publication of RNTCP (NTEP) guidelines.

What this study adds?

Contrary to conventional belief, microbiological confirmation can be obtained in almost up to half of children with a diagnosis of TB.

Author's contributions

IK: study concept, study design and writing the paper. SJ, SK and AS were involved in clinical care and data interpretation. BA: data collection. All authors approved the study.

Ethical approval

Status of ethical clearance: IEC approval number -204/2020.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Swaminathan S, Datta M, Radhamani M, et al. A profile of bacteriologically confirmed pulmonary tuberculosis in children. *Indian Pediatr*. 2008;45(9):737–739.
2. Mukherjee A, Chowdhury R, Singla R, Saha I, Dutta R, Das T. Comparison between childhood and adult tuberculosis in a rural tuberculosis unit of West Bengal: a retrospective study. *Lung India*. 2014;31(2):116. Official Organ of Indian Chest Society.
3. Kunkel A, zur Wiesch PA, Nathavitharana RR, Marx FM, Jenkins HE, Cohen T. Smear positivity in paediatric and adult tuberculosis: systematic review and meta-analysis. *BMC Infect Dis*. 2016;16(1):282.
4. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis*. 2010;50(supplment_3):S184–S194.
5. Raizada N, Khaparde SD, Salhotra VS, et al. Accelerating access to quality TB care for pediatric TB cases through better diagnostic strategy in four major cities of India. *PloS One*. 2018 Feb 28;13(2), e0193194. Hasnain SE.
6. Yadav R, Vaidya P, Mathew JL, et al. Utility of Xpert MTB/RIF assay for diagnosis of pediatric tuberculosis under programmatic conditions in India. *J Epidemiol Global Health*. 2020;10(2):153–156.
7. Revised National Tuberculosis Control Programme (RNTCP). *Technical and Operational Guidelines for Tuberculosis Control in India*. 2016.
8. Marais BJ, Pai M. New approaches and emerging technologies in the diagnosis of childhood tuberculosis. *Paediatr Respir Rev*. 2007;8(2):124–133.
9. Coulter J. Diagnosis of pulmonary tuberculosis in young children. *Ann Trop Paediatr*. 2008;28(1):3–12.
10. Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2012;54(10):1388–1396.
11. Singh S, Singh A, Prajapati S, et al. Xpert MTB/RIF assay can be used on archived gastric aspirate and induced sputum

samples for sensitive diagnosis of paediatric tuberculosis. *BMC Microbiol*. 2015;15(1):1–10.
12. Marais B, Hesseling A, Gie R, Schaaf H, Enarson D, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. *Clin Infect Dis*. 2006;42(8):e69–71.
13. Marais BJ, Gie RP, Hesseling AC, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics*. 2006;118(5):e1350–e1359.
14. Bonnet M, Nansumba M, Bastard M, et al. Outcome of children with presumptive tuberculosis in Mbarara, Rural Uganda. *Pediatr Infect Dis J*. 2018;37(2):147–152.
15. López-Varela E, Augusto OJ, Gondo K, et al. Incidence of tuberculosis among young children in rural Mozambique. *Pediatr Infect Dis J*. 2015;34(7):686–692.
16. Chakravorty S, Sen MK, Tyagi JS. Diagnosis of extrapulmonary tuberculosis by smear, culture, and PCR using universal sample processing technology. *J Clin Microbiol*. 2005;43(9):4357–4362.
17. Zenebe Y, Anagaw B, Tesfay W, Debebe T, Gelaw B. Smear positive extra pulmonary tuberculosis disease at University of Gondar Hospital, Northwest Ethiopia. *BMC Res Notes*. 2013;6(1):21.
18. Agrawal R, Agarwal R, Gupta U. *Utility of Xpert® MTB/RIF Assay for Extrapulmonary Tuberculosis, a Two Year Study*. 2019.
19. Aricha S, Kingwara L, Mwirigi N, et al. Comparison of GeneXpert and line probe assay for detection of Mycobacterium tuberculosis and rifampicin-mono resistance at the National Tuberculosis Reference Laboratory, Kenya. *BMC Infect Dis*. 2019;19(1):852.
20. Aubry A, Veziris N. Smear microscopy complements Xpert MTB/RIF when considering nontuberculous mycobacterial infections. *Am J Respir Crit Care Med*. 2019;200(8):1072–1073.

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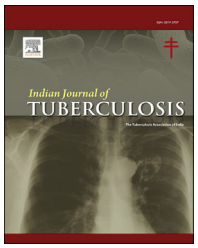

Original article

Predictors of outcomes in children with Central Nervous System tuberculosis

Sushant S. Mane, Jyothi Janardhanan, Sharanya Ramakrishnan, Aniruddh Shah, Manas Pustake, Anindita R. Mandal*

Department of Paediatrics, Grant Government Medical College and Sir JJ Group of Hospitals, Byculla, Mumbai, 400008, India

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ABSTRACT

Background: Central Nervous system tuberculosis (CNS–Tb) is the most lethal form of extrapulmonary tuberculosis in children. The lack of markers of outcome provides little information on the efficacy of the current treatment protocols for CNS–Tb and thus results in a higher mortality rate than other extrapulmonary manifestations of tuberculosis. This study aims to identify significant factors that will reliably predict the outcomes at discharge in children admitted with CNS–Tb.

Methods and material: This is a prospective observational study in children with neurotuberculosis admitted at a tertiary care hospital. Clinical presentations at the time of admission were studied. Outcomes at the end of in-patient care (completely cured, survival with some/severe disability or death) were correlated with clinical, laboratory, microbiological, and radiological parameters. Univariate and multivariate analyses were applied to study the parameters and a p-value $\leq$ 0.05 with a confidence interval (CI) of 95% was considered as statistically significant.

Findings: The study included 100 children between 4 months and 12 years of age with a mean of 5.84 (±3.5) years. At discharge, 55% of children recovered completely, 20% had some or severe disability and 25% died. On multivariate analysis, high CSF protein ($p = 0.050$) and drug resistance ($p = 0.034$) were highly associated with fatality. Meningeal enhancements with basal exudates ($p = 0.021$) and CSF lymphocyte count >90% were highly associated with survival with disability. Stage I disease at presentation ($p < 0.0001$) was the only variable associated with complete recovery.

Interpretation: Reliable prognostic markers for CNS–Tb can aid in predicting the efficacy of the current treatment and the anticipated outcome in the children with this disease.

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* *Corresponding author*. Apna Boys' Hostel, JJ Hospital Campus, Byculla, Mumbai, 400 008, India. Tel.: +919420420431.
E-mail address: pustakemanas@gmail.com (M. Pustake).

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1. Introduction

Tuberculosis is a socially, economically, financially, and medically devastating disease that affects most human populations in the world, to different degrees.[1]This disease is endemic to most developing nations[2] and often causes extensive involvement of most organ systems especially in infants, younger children, and patients in immunocompromised states.[3]

Of the 10 million people who develop tuberculosis every year,[4] 1.1 million are below 15 years of age. Of the 1.1 million children, 210,000 children die from complications of the disease.[5] CNS–Tb constitutes approximately 1% of all cases of active tuberculosis and is the most lethal form of the disease. While several studies have shown that the efficacy of the Bacillus Calmette Guerin (BCG) vaccine against neurotuberculosis is around 55–60%,[6–8] some studies have raised concerns that BCG simply delays the onset of CNS–Tb.[9]

A child presenting with symptoms suggestive of CNS–Tb should be promptly evaluated and treated to get better outcomes. There are very few studies focusing on the factors which predict the outcome in CNS–Tb. Our research aims to study the clinical presentations, laboratory findings and imaging findings as determinants of outcomes in children with CNS–Tb. Additionally, we aim to study the effect of bacterial resistance and prior BCG vaccination on the prognosis of the patient.

2. Materials and methods

2.1. Participants

A prospective observational study was done in 100 (the total number of patients who presented with CNS–Tb in the duration of the study) patients aged 4 months to 12 years admitted at a tertiary health center in western India between January 2018 to August 2019, who were diagnosed as a case of CNS–Tb using microbiological and/or pathological and/or radiological methods. Patients with other co-morbid neurological conditions like cerebral palsy, epilepsy, metabolic brain disorders, etc. or co-existing CNS infections due to bacterial, viral, parasitic, fungal agents were excluded from the study.

2.2. Data collection

After getting the required approval from the Institutional Ethics Committee (Letter number: IEC/PG/16/JAN/2018), informed and written consent was taken from all parents willing to participate. The demographics, anthropometry, history, symptomatology, clinical features, vaccination status and investigations were recorded using a pre-designed proforma. Glasgow coma scale (GCS)[10] was used to assess the level of consciousness. Cases were diagnosed based on the Indian Academy of Pediatrics (IAP) – RNTCP Consensus Guidelines for Pediatric Tuberculosis.[11] Staging for patients with TBM was carried out according to the British Medical Research Council clinical criteria for the severity of TBM.[12] Complete blood counts, liver and renal profiles, mantoux testing, chest x-ray, computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the brain, cerebrospinal fluid (CSF) and other appropriate specimens (sputum/gastric aspirate) for routine microscopy, biochemical analysis, cartridge-based nucleic acid amplification test (CBNAAT) was done for all patients. Drug sensitivity testing (DST) on MGIT was done for both first and second-line anti-tuberculous drugs, wherever applicable.

2.3. Data analysis

Patient's outcome was graded as per the following criteria.[13] Complete recovery- No residual neurological deficits and unaided day to day activities, some disability- Mild neurological deficits, needing aids for day to day activities, severe disability- Bedridden, requires assistance in all activities of daily living, and Death.

The stage of disease in patients with TBM was categorized as per BMRC (British Medical Research Council grading)[14] as follows- Stage 1 corresponds to a Glasgow coma score of 15 with no neurological signs, Stage 2 a score of 11–14 or a score of 15 with focal neurological signs, and Stage 3 a score of $\leq$10.

2.4. Statistical analysis

We used the IBM SPSS Statistics software to analyze our data. A Chi-square ($\chi 2$) or Fisher test was used to study the association between categorical variables and to compare categorical prognostic factors between recovered, recovered with a disability and deceased patients. A Student's t-test (t) was used to compare the mean values of the continuous variables. Continuous variables were expressed in mean ± standard deviation (SD). Statistical analysis was evaluated with univariate analysis. All variables that proved statistically significant in the univariate analysis were subjected to a multivariate analysis using the stepwise multiple logistic regression model with the forward likelihood ratio method. In all subjects, the missing data were excluded, but outliers were not removed from the model. Odds Ratio (OR) with a 95% Confidence Interval (CI) was reported. A p-value $\leq$ 0.05 was considered as statistically significant.

3. Results

This study included 100 patients, aged 4 months to 12 years, with a mean age of 5.84 ± 3.5 years. 9 children (9%) were below 1 year of age, 36 (36%) were between 1 and 5 years of age, 35 (35%) were between 5 and 10 years of age, and 20 children (20%) were 10 years and older. The male to female ratio was 1.08:1.

3.1. CSF analysis

The CSF analysis of these patients were studied under four categories- CSF cells, CSF lymphocytes, CSF sugar and CSF proteins. A univariate analysis revealed that the effect of CSF protein level on the outcome of the patient was significant ($p = 0.012$). Further, we studied the level at which CSF protein

proved to influence the outcome of the patient. A CSF protein value of 100mg/dl was chosen in accordance to the findings of Thilothammal et al.[15] 74 children were found to have a CSF value of >100mg/dl, of which 25 children died, 12 had a severe disability, 3 had some disabilities while the rest recovered completely. It was concluded that a CSF protein value of >100mg/dl was strongly associated with death ($p = 0.050$), while there was no significant correlation between CSF protein level >100mg/dl and severe disability ($p = 0.101$) or some disability ($p = 0.602$). CSF lymphocytes level of 90% was arbitrarily chosen. It was found that 77 children had a CSF lymphocyte value > 90%. 18 children with CSF lymphocytes >90% died, 10 children with CSF lymphocytes had severe disability and 3 had some disabilities. On analyzing the above data using univariate analysis, we concluded that there was a strong association between a CSF lymphocyte count >90% and severe disability ($p = 0.024$), while there was no association with mortality ($p = 0.642$) and some disability ($p = 0.23$).

3.2. *Radiological findings*

Of the 92 patients in whom Contrast-enhanced Computerized Tomography (CECT) Brain was done, 59 (64.1%) had meningeal enhancement with basal exudates, 50 (54.3%) had tuberculoma, 46 (50%) had hydrocephalus and 18 (19.5%) had infarcts. MRI brain was done in 26 children, which showed tuberculoma in all, hydrocephalus in 11, and infarcts in 5 children. A higher proportion of children in stage III TBM showed meningeal enhancement ($p = 0.001$), hydrocephalus ($p < 0.0001$), and infarct ($p = 0.012$) on CT brain. For stage I disease, Tuberculoma on CT brain ($p = 0.038$) was found to be statistically significant. An infarct on MRI brain was highly associated with stage III of the disease ($p = 0.028$). On univariate analysis, only meningeal enhancement with basal exudates were associated with a severe disability ($p = 0.046$). A multivariate analysis confirmed that meningeal enhancements was a significantly associated with severe disability ($p = 0.021$), but was not associated with death ($p = 0.426$) or some disability ($p = 0.206$).

3.3. *Clinical signs*

Out of the 100 children included in the study, 77 developed seizures. Of these 77 children, 39 (50.6%) had a full recovery while 38 (49.39%) did not. On univariate analysis, we concluded that seizures were associated with disability on discharge ($p = 0.048$). However, multivariate analysis, revealed no association with death ($p = 0.929$), severe disability ($p = 0.168$) or some disability ($p = 0.348$).

3.4. *Drug resistance*

Our data revealed that 15 children had *Mycobacterium tuberculosis* growth on culture, which were drug resistant strains. One child had CB-NAAT negative on CSF but culture showed a mono-resistance pattern to isoniazid. Hence, 16 children were treated as drug-resistant tubercular meningitis, of which 9 were MDR TB, 6 were MDR with fluoroquinolone resistance and 1 child had mono-resistance to isoniazid. The remaining 84 children were treated as drug-sensitive TB. Our study revealed an association between drug resistance and death ($p = 0.034$). However, there was no association between the drug resistance and severe disability ($p = 0.283$) or some disability ($p = 0.106$).

3.5. *BCG scar*

In our study, 89 children had BCG scar and 11 didn't have scar. Of the 89 children with the scar, 20 children died, 14 developed severe disability and 4 were left with some disability. Further analysis revealed that BCG vaccine did not influence the outcome of the patient viz. death ($p = 0.267$), severe disability ($p = 0.997$) and some disability ($p = 0.463$).

3.6. *Determinants of outcomes*

A depiction of the patients' outcome at discharge is illustrated in the pie-chart (Fig. 1). On univariate analysis, seizures, drug resistance, high protein levels in CSF, and meningeal enhancements were highly associated with poor outcomes. Stage I at presentation was the only variable associated with complete recovery ($p < 0.0001$). Multivariate analyses were performed with these variables as covariates (independent variables) and the outcome as a dependent variable. The results of which are demonstrated in Table 1. High CSF protein, drug resistance, were significant in predicting mortality; whereas, predictors of survival with disability included CSF lymphocytes >90% and meningeal exudates.

4. Discussion

The main objective of this study was to identify the determinants of outcome at discharge in patients with CNS–Tb.

Our study concluded that high CSF protein (>100mg/dl) was associated with mortality. Thilothammal et al[15] in their study concluded that 11 and 15 per cent of the children with Stage 2 and 3 disease, respectively, had CSF protein value > 100 mg/dl. We studied this association further and found that a CSF protein level >100mg/dl was associated with higher mortality.

We also found that CSF Lymphocytes accounting for more than 90% of the total CSF cell count, was associated with disability. However, we found no literature to support this finding.

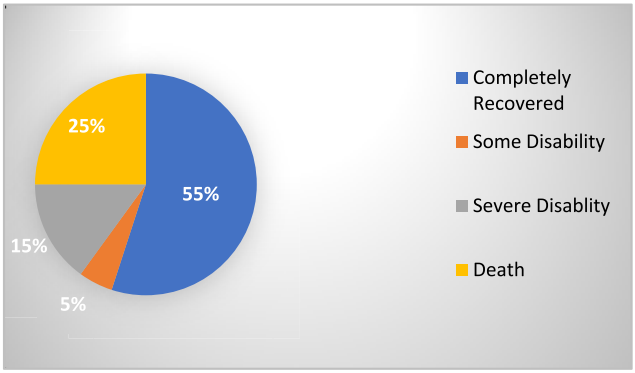

Fig. 1 – Outcomes at Discharge (include colour).

Table 1 – Association of outcome at discharge based on results from the multiple logistic regression analysis using determinants as independent variables.

Outcome	Determinants	B	SE	Wald χ2	P-value	OR	95% Confidence Interval for OR	
							Lower Bound	Upper Bound
Death	High CSF Protein	0.005	0.003	3.808	**0.050***	1.005	1.000	1.011
	BCG scar	0.983	0.886	1.231	0.267	2.672	0.471	15.163
	HIV Status	−0.351	1.517	0.054	0.817	0.704	0.036	13.758
	Drug resistance	−1.867	0.878	4.520	**0.034**	0.155	0.028	0.864
	Meningeal enhancements with basal exudates	0.536	0.673	0.634	0.426	1.709	0.457	6.390
	seizures	−0.069	0.769	0.008	0.929	0.933	0.207	4.212
Severe Disability	CSF protein >100	−0.011	0.007	2.685	0.101	.989	.977	1.002
	BCG scar	−17.590	4609.238	0.000	0.997	2.296E−8	0.000	.c
	HIV Status	−17.858	6905.210	0.000	0.998	1.756E−8	0.000	.c
	Drug resistance	−1.179	1.098	1.152	0.283	0.308	0.036	2.649
	Meningeal enhancements with basal exudates	2.216	0.964	5.288	**0.021**	9.171	1.387	60.632
	seizures	−1.562	1.134	1.896	0.168	0.210	0.023	1.937
Some Disability	CSF protein >100	−0.005	0.009	0.272	0.602	0.995	0.977	1.013
	BCG scar	0.995	1.356	0.539	0.463	2.705	0.190	38.568
	HIV Status	−18.392	0.000	.	.	1.030E−8	1.030E-8	1.030E−8
	Drug resistance	−2.384	1.476	2.609	.106	.092	.005	1.663
	Meningeal enhancements with basal exudates	1.639	1.296	1.598	.206	5.148	.406	65.326
	seizures	1.049	1.119	.880	.348	2.856	.319	25.578

*Significant, SE=Standard Error, OR=Odds Ratio

On CECT, 64.1% of children had meningeal enhancement, 50% of children had hydrocephalus and 19.5% of children had infarcts. Our study concluded that meningeal exudate was associated with severe disability on discharge ($p = 0.054$). Faella et al[18] in their study showed similar findings, with basilar enhancement in 81%, hydrocephalus in 47%, and cerebral infarcts in 16% of the patients. Rashmi Alva et al[19] conducted a study in which CT findings were abnormal in 91.11% of patients with TBM.

These residual disabilities can be explained by the dense meningeal exudates consisting of erythrocytes, lymphocytes, neutrophils and macrophages which get deposited on the brain stem, sylvian fissure and basal cisterns. This causes both the obstruction of the CSF flow, through the foramen of Luschka and Foramen of Magendie, and periarteritis of cerebral arteries leading to microinfarcts in the both the basal ganglia and the internal capsule.[20]

We found that drug resistance to one or more antituberculous drug significantly affected mortality in patients with neurotuberculosis. Murilo Gimenes Rodrigues et al[22] found that drug resistance was a prognostic marker for neurotuberculosis. Bella Daniel et al[23] in their study suggested that rifampicin resistant TB, had a positive correlation with poor outcome.

Karande et al[16] found that nine variables affected survival with disability viz. presence of tonic motor posturing, cranial nerve palsy, focal neurological deficits, hypertonia, cerebral infarction on cranial CT, requirement of shunt surgery, moderate to severe hydrocephalus, absence of extracranial tuberculosis and no hepatotoxicity to drugs. In our study, two variables were associated with survival with disability which included CT findings viz. meningeal enhancements with basal exudates and a CSF lymphocyte count greater than or equal to 90% of the total CSF cell count.

Only one variable was strongly associated with complete recovery, stage I of presentation ($p < 0.0001$); Lee et al,[24] Karande et al[16] and Mohan J et al[17] in their study had similar conclusions.

Malnutrition, infections such as measles, pertussis, HIV, varicella along with other viral illnesses, corticosteroids and other immunosuppressive therapies are some known factors that predispose to TB. Our study showed malnutrition in all patients and 3% of the children tested positive for HIV. However, no significant association was found with HIV status and mortality ($p = 0.817$), impairing our conclusions because of the limited number of HIV positive children in our test population. Karande S et al[16] in their study had one-third of patients with malnutrition, 27% with marasmus, 2.4% with kwashiorkor and 0.8% with marasmic-kwashiorkor. In the study by Bang et al,[25] 4% of patients were co-infected with HIV and Karande et al[26] found that 6.5% of their test population tested positive for HIV. None of them could establish a statistically significant association between HIV positivity and the outcome of the disease. However, literature suggests that mortality in HIV patients with TBM is as high as 50%.[27]

BCG scar was seen in 89 children. A statistical significance could not be obtained between the presence of a BCG scar and neurotuberculosis ($p = 1.000$) in our study. Several studies have shown that BCG protects against TBM,[6–8] while other studies have shown that it delays the onset of TBM.[9] Ahmet Yaramis et al.[28] reported that only 12% of children with TBM had a history of BCG vaccination. Although the BCG vaccine has been in use since 1921, the efficacy of the vaccine continues to be debated mainly because there are very few studies

in developing countries[29,30] where the immune parameters of cell-mediated immunity have been estimated to assess the level of its efficacy.

5. Limitations

As the study was conducted in a government hospital, most of the enrolled patients were from lower to lower-middle income families. This may have possibly led to sampling bias in our study. As our hospital is a tertiary care center, most of the referred patients, at the time of admission had an advanced stage of presentation.

6. Conclusions

Our study found that a higher CSF protein value, especially >100mg/dL was associated with higher mortality rates. A high CSF lymphocyte count (90% of the total cells in CSF) and meningeal enhancement with basilar exudates were associated with severe disability on discharge. While the exact cause of raised CNS protein >100mg/dL and its association with mortality, and the raised CSF lymphocytes (90% of total cells) and its association with disability cannot be explained, we hope to contribute these findings in order to undertake a study with larger sample size. We believe that the criteria listed above can help to establish a standard scoring system that can help predict the prognosis of these children with CNS-Tb. Determining the indicators of prognosis can effectively allow a physician to predict the probability of disability or mortality in the child, better equipping the physician to understand the effectiveness of the ongoing treatment.

Consent

Written informed consent was obtained from the patient for publication of this original article.

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low-and middle-income countries: a systematic review. *Eur Respir J*. 2014 Jun 1;43(6):1763–1775.
2. Castañeda-Hernández DM, Rodriguez-Morales AJ. Epidemiological burden of tuberculosis in developing countries, Current Topics in Public Health, Alfonso J. Rodriguez-Morales. *IntechOpen*; May 15th 2013. Available from https://www.intechopen.com/books/current-topics-in-public-health/epidemiological-burden-of-tuberculosis-in-developing-countries.
3. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. *Lancet Neurol*. 2013 Oct 1;12(10):999–1010.
4. World Health Organization (WHO). *Global Tuberculosis Report 2019*. Geneva: WHO; 2019. Available from: https://www.who.int/tb/publications/global_report/en/.
5. World Health Organization. . *Global Tuberculosis Report 2016*. World Health Organization; 2016. Available from: https://apps.who.int/iris/handle/10665/250441.
6. Awasthi S, Moin S. Effectiveness of BCG vaccination against tuberculous meningitis. *Indian Pediatr*. 1999 May;36(5):455–460.
7. Bhattacharjee J, Sharma RS, Singh JA, Datta KK, Verghese T. Case series evaluation of BCG vaccine efficacy against tubercular meningitis in children in Delhi. *J Comm Dis*. 1993 Jun;25(2):71–74.
8. Camargos PA, Guimaraes MD, Antunes CM. Risk assessment for acquiring meningitis tuberculosis among children not vaccinated with BCG: a case-control study. *Int J Epidemiol*. 1988;17:193–197.
9. Mittal SK, Aggarwal V, Rastogi A, Saini N. Does B.C.G. vaccination prevent or postpone the occurrence of tuberculous meningitis. *Indian J Pediatr*. 1996;63:659–664.
10. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974 Jul 13;304(7872):81–84.
11. Amdekar YK. Consensus statement on childhood tuberculosis. *Indian Pediatr*. 2010 Jan 1;47(1):41–55.
12. Marais BJ, Heemskerk AD, Marais SS, et al. Standardized methods for enhanced quality and comparability of tuberculous meningitis studies. *Clin Infect Dis*. 2017;64(4):501–509. https://doi.org/10.1093/cid/ciw757.
13. Mohan J, Rakesh PS, Moses PD, Varkki S. Outcome of children with tuberculous meningitis: a prospective study from a tertiary care centre in Southern India. *Int J Commun Med Public Health*. 2016;4:220–223.
14. Alarcón F, Moreira J, Rivera J, Salinas R, Dueñas G, Van den Ende J. Tuberculous meningitis: do modern diagnostic tools offer better prognosis prediction. *Indian J Tubercul*. 2013 Jan;60(1):5–14.
15. Thilothammal N, Krishnamurthy PV, Banu K, Ratnam SR. Tuberculous meningitis in children–clinical profile, mortality and morbidity of bacteriologically confirmed cases. *Indian Pediatr*. 1995 Jun;32(6):641–647.
16. Karande S, Gupta V, Kulkarni M, Joshi A. Prognostic clinical variables in childhood tuberculous meningitis: an experience from Mumbai, India. *Neurol India*. 2005 Apr 1;53(2):191.
17. Mohan J, Rakesh PS, Moses PD, Varkki S. Outcome of children with tuberculous meningitis: a prospective study from a tertiary care centre in Southern India. *Int J Commun Med Public Health*. 2016;4:220–223.
18. Faella FS, Pagliano P, Attanasio V, et al. Factors influencing the presentation and outcome of tuberculous meningitis in childhood. *in vivo*. 2006 Jan 1;20(1):187–191.
19. Alva R, Alva P. A Study of CT Findings in children with neurotuberculosis. *Int J Biomed Res [Internet]*. 2014 Nov. 30 [cited 2021 Jun. 21];5(11):685–687. Available from https://ssjournals.com/index.php/ijbr/article/view/1108.
20. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: clinical management & outcome. *Indian J Med Res*. 2019 Aug;150(2):117.

22. Misra UK, Kalita J, Roy AK, Mandal SK, Srivastava M. Role of clinical, radiological, and neurophysiological changes in predicting the outcome of tuberculous meningitis: a multivariable analysis. *J Neurol Neurosurg Psychiatr*. 2000 Mar 1;68(3):300–303.
23. Gimenes Rodrigues M, Jose da Rocha A, Rodrigues Masruha M, Soares Cianciarullo Minett T. Neurotuberculosis: an overview. Central nervous system Agents in medicinal chemistry (formerly current medicinal chemistry-central nervous system Agents). 2011 Dec 1;11(4):246–260.
24. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: clinical management & outcome. *Indian J Med Res*. 2019 Aug;150(2):117.
25. Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the philippine children's medical center. *Brain Dev*. 2000 Dec 1;22(8):469–474.
26. Bang ND, Caws M, Truc TT, et al. Clinical presentations, diagnosis, mortality and prognostic markers of tuberculous meningitis in Vietnamese children: a prospective descriptive study. *BMC Infect Dis*. 2016 Dec 1;16(1):573.
27. Karande S, Gupta V, Kulkarni M, Joshi A, Rele M. Tuberculous meningitis and HIV. *Indian J Pediatr*. 2005 Sep 1;72(9):755–760.
28. Wilkinson RJ, Rohlwink U, Misra UK, et al. Tuberculous meningitis. *Nat Rev Neurol*. 2017;13(10):581–598. https://doi.org/10.1038/nrneurol.2017.120.
29. Yaramiş A, Gurkan F, Elevli M, et al. Central nervous system tuberculosis in children: a review of 214 cases. *Pediatrics*. 1998 Nov 1;102(5):e49.
30. Kumar P, Kumar R, Srivastava KL, Kumar M. Protective role of BCG vaccination against tuberculous meningitis in Indian children: a reappraisal. *Natl Med J India*. 2005 Jan-Feb;18(1):7–11. PMID: 15835483.

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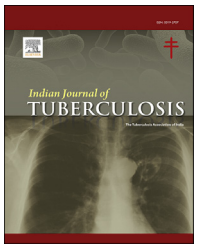

Original article

Assessment of prevalence of depression and its associated factors among tuberculosis patients in Ernakulam district, Kerala

*Charutha Retnakumar, Leyanna Susan George**

Department of Community Medicine & Public Health, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, India

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ABSTRACT

Background: India is one of the few countries where Tuberculosis is still widely prevalent. People with TB, often suffers from depression. It is estimated that more than 300 million people suffer from depression at the global level, accounting to 4.4 percent of the world's population.

Objectives: **Primary objective**—To assess the prevalence of depression among tuberculosis patients in Ernakulam district using PHQ9. **Secondary objective**—To assess the factors associated with depression among tuberculosis patients in Ernakulam district.

Methodology: A cross sectional study was carried out among the tuberculosis patients who were currently under treatment from December 2019 to March 2020 in Ernakulam district of Kerala. From the 8 TUs of Ernakulam, 8 clusters were selected using PPS. 485 adult TB patients from these clusters were interviewed using PHQ9 questionnaire to assess prevalence of depression.

Results: The prevalence of depression among the TB patients in Ernakulam district was found to be 16.1%. The proportion of TB patients with depression were significantly higher among the age group of 18–40 years (36.3%), unmarried (54%) and from urban area of residence (19%). It was also significantly higher among previously treated patients (45.7%) & MDR TB patients (43.8%).

Conclusion: It was observed that one-sixth of TB patients suffered from depression. Hence it is crucial that TB patients need to be regularly assessed for depression and managed appropriately. Since depression has affects adherence to TB treatment & thereby result in delay of TB elimination in the state.

* *Corresponoding author*. Department of Community Medicine & Public Health, Amrita Institute of Medical Sciences, Ponekkara, Kochi, Kerala, 682041, India.
E-mail address: leyanna.george@gmail.com (L.S. George).

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1. Introduction

TB is one of the top 10 causes of death and the leading cause of the single most infectious agent, ranked above HIV/AIDS.[1] Every year about 10 million people worldwide suffer from tuberculosis (TB). The WHO 2019 global TB report, estimated that 10 million people worldwide suffered from TB in 2018. India, was identified to be the seventh-largest country in terms of TB burden in the world.[2]

Depression is a common disease throughout the world, affecting over 264 million people.[3] Depression or major depressive disorder is a common and serious medical condition that has a negative effect on ones feelings, thoughts and actions.[4] Depression can become a serious health condition, particularly if it is long-lasting and with moderate to extreme severity. It can affect a person severely and result in their poor performance at their workplace, school or in their homes. Depression at its worst may lead to suicide.[5]

Patients with tuberculosis (TB) are often suffering from depression.[6] A person with TB may develop depression over time due to several factors, including the long duration of TB treatment, stigma due to the disease, lack of family support etc. Different studies across the world have reported prevalence of depression among TB patients to range from 41.1% in Nigeria to 56% in Pakistan.[7,8]

Therefore, the aim of the study was to assess the prevalence of depression among TB patients and to study the factors associated with it.

2. Materials and methods

After obtaining institutional ethical committee clearance and relevant permissions from the State TB officer, a cross sectional study was conducted among adult TB patients undergoing treatment in Ernakulam district of Kerala, from December 2019 to March 2020. Informed consent was obtained from the participants prior to the start of the study. All tuberculosis patients registered under NTEP previously known as RNTCP and who were undertaking anti-tuberculosis treatment from the 8 TUs of Ernakulam district formed the sampling frame. Patients who had a known history of any psychiatric disorder (other than depression), were excluded from the study. Patients who could not be contacted despite 3 attempts were also excluded.

The prevalence of depression among TB patients in a study done in Delhi[8] was found to be 23.6% and with 95% of confidence interval and 20% of allowable error, minimum sample size was calculated to be 323.[8] Since cluster sampling was done, it was multiplied by design effect 1.5 to get a sample size of 485.

According to 2019 RNTCP data, 1276 patients with TB were under treatment in Ernakulam district. The sample size calculated to be was 485 by using cluster sampling technique. There are 8 tuberculosis units in Ernakulam. Population proportion to size sampling was used to identify the clusters. A total of 8 clusters were selected with a cluster size of 61. The total population under the units was found to be 1276. So, the sampling interval was calculated as 160. A random number was selected in the range of 0–160, which was 60. Thus 8 clusters were identified for the conduct of the study. The entire list of patients was collected. Patients to all categories of TB treatment were included. All selected patients were contacted either personally or by phone and an appointment was fixed. Patients who were not responding despite contacting them three times were excluded. Data was collected till 61 patients from each TU were obtained. The details of which are depicted in Fig. 1.

Information was collected using questionnaire consisting of two parts. First part gathered information regarding basic socio-demographic data and the second part assessed depression using the PHQ 9 questionnaire in Malayalam/English/Hindi since the study included migrants as well.

The collected data was entered into Microsoft excel sheet and was analysed using IBM Statistical Package for Social Science (SPSS) version 20. Study participant who scored 10 or more than 10 in PHQ 9 scale was considered to be depressed. To test the statistical significance of the factors related to depression, chi square test and multiple logistic regression were applied.

3. Result

A total of 485 patients participated in the study. Mean age of the patients was 49.55 ± 15.01 years and 46.2% were of the age group between 41 and 60 years. Majority of the patients (70.9%) were males and were residents of an urban area (45%). The religion followed by 58.8% of the population was Hinduism. Patients who were currently married constituted 87% of the study group. The educational qualification of 33.4% of the patients was Higher secondary level and 33.3% of the patients were currently employed in skilled work. Majority of the

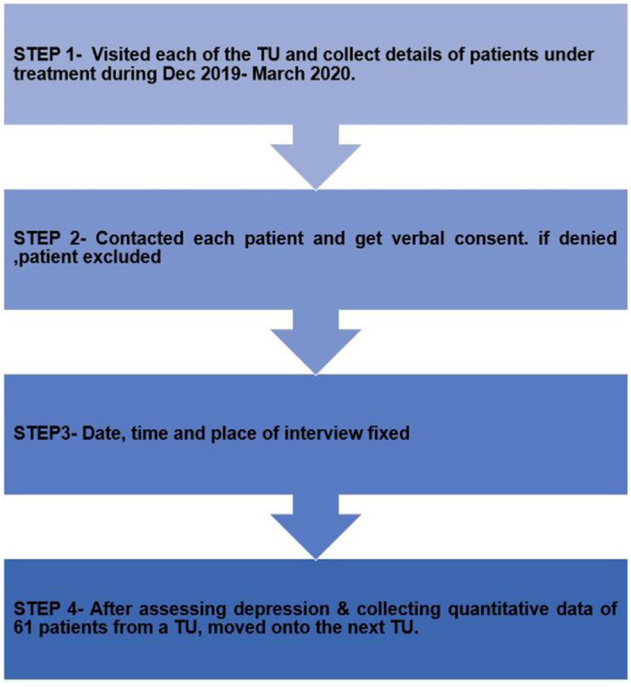

Fig. 1 – Selection of study participants.

patients (58.6%) belonged to the BPL category. The details of which are provided in Table 1.

It was observed that 14.6% of patients had history of contact with TB patients. While 4.2% were migrants and only 1% were health care workers. The largest proportion of patients were suffering from pulmonary TB (67.4%), followed by extra pulmonary (26%) and MDR TB (6.6%). Most of the patients (92.8%) were newly diagnosed and had no family history of TB (86.4%). It was observed that 61% of patients were in the continuous phase of treatment and had no history of adverse events (95.7%). It was observed that, 40.2% of the study participants suffered from co-morbidities, out of which the most common comorbidity was found to be diabetics mellitus (31.1%) followed by hypertension (14%) and COPD (5.6%). Majority of them, i.e. 38.5% of the patients suffered from multiple co-morbidities. With regard to addictions, 30.1% of the patients stated that, they had history of tobacco use at any point of their life. 22.1% of the TB patients were smokers and 2.7% of the patients were currently using tobacco. 17.9% of the patients gave a history of alcohol intake. After initiation of treatment, it was found that none of them were taking alcohol but they were continuing with tobacco. Details are provided in Table 2.

It was observed that 14.6% of the patients did not have any depression. Rest of them had minimal to severe depression. As per the reference study done by Salodia et al in Delhi,[9] a scoring of 10 and above was considered to be having depression. At score 10 and above, the sensitivity and specificity of PHQ9 tool is 88.8%. Therefore, we considered score 10 and above as having depression. Details are provided in Table 3.

PHQ9 Score above and equal to 10 was considered to have depression. Thus, the prevalence of depression among TB patients in Ernakulam district was found to be 16.1%.

On univariate analysis (Table 4), it was observed that the proportion of TB patients with depression were significantly higher among the age group of 18–40 years (36.3%), unmarried (54%) and from urban area of residence (19%). It was also significantly higher among previously treated patients (45.7%) & MDR TB patients (43.8%). The proportion of TB patients with depression was found to be significantly lower among patients with no history of adverse events (15.1%).

All factors with p value <0.2 in univariate analysis were included in binary logistic regression model; to find the independent predictors of depression. Final model had 6 variables of which age group 18–40 years (aOR = 6.656, 95% CI 2.573–17.216), Unmarried patients (aOR = 4.781, 95% CI 2.389–9.571) and newly diagnosed patients (aOR = 0.147, 95% CI 0.051–0.423) were the statistically significant predictors for depression. Details of which are provided in Table 4.

4. Discussion

The prevalence of depression among TB patients in the present study was found to be 16.1%. This was found to be lower than that reported by Basu et al, which was 44% among tuberculosis patients, who were taking treatment from a DOTS clinic in a sub divisional hospital of West Bengal.[10] The prevalence of depression reported by many authors varies according to the research setting rural and urban areas. It also depends on the screening tool that was used. According to the study done by Umang P. Salia et al, at DOTS center in Rural Delhi, using PHQ 9, the prevalence of depression was found to be 23.6% which was slightly higher than the current study. (45) While a study done in a tertiary care hospital of South India, had reported a prevalence of 41.5%.[11] In the global level using PHQ9 tool, a study conducted by Dasa et al at Ethiopia reported 51.9% depression among TB patients and higher rates of depression have been reported in Pakistan (72%), South Africa (81%) (51), (52), (53). All these values were found to be higher than our value. When compared to other countries, the prevalence in the current study was found to be lower. The lower depression level among TB patients in Ernakulam district, could probably due to the various health care support provided such as counselling sections and patient provider interaction sessions.

In this study, depression was found to be more prevalent among those who belong to the age group of 18–40 years of age. 62.8% of patients in this age group were found to be depressed and this finding was found to be significant. This could probably be due to the fact that people belonging to this age group are the ones who are responsible for earning for

Table 1 – Distribution of study participants according to their sociodemographic characteristics.

Sl. No	Sociodemographic characteristics	Frequency	Percentage (%)
1.	**Age** (in years)		
	18–40	135	27.8%
	41–60	224	46.2%
	>60	126	26%
2.	**Gender**		
	Male	344	70.9%
	Female	141	29.1%
3.	**Area of residence**		
	Urban slum	56	11.5%
	Urban	218	45%
	Rural	211	43.5%
4.	**Marital status**		
	Married	422	87.0%
	Unmarried	57	11.8%
	Widow/widower	6	1.2%
5.	**Religion**		
	Hindu	285	58.8%
	Christian	145	29.9%
	Muslim	55	11.3%
6.	**Education**		
	Primary school	43	8.9%
	Middle school	56	11.5%
	High school	161	33.2%
	Higher secondary	162	33.4%
	University	63	13%
7.	**Occupation**		
	Professional	29	6%
	Skilled	162	33.4%
	Unskilled	92	19%
	Unemployed	89	18.4%
	Retired	11	2.3%
	Homemaker	89	18.4%
	Student	13	2.7%
8.	**Socio-economic class**		
	APL	201	41.4
	BPL	284	58.6

their families. Suffering from TB may affect their productivity and hence result in depression. It may also occur as a result of fear of stigma and discrimination by their colleagues and family members. The fear of social isolation and loss of job may also result in depression among the TB patients.[12] Similar results were observed in the study done by Sulehri et al in Faisalabad, Javaid et al in Pakistan, and a study done by Kehbila et al in Cameroon, showed that about 75% and 63.8% of patients respectively had depression belong to age group of 18–40 years of age.[12–15] Whereas a study done by Kunal Kumar et al among TB patients in Respiratory department only 10% of TB patients belonged to age group 18–40 years of age had depression.[16]

In current study, depression is significantly associated with patients residing in Urban area. 66.6% of patients residing in Urban area were depressed and it was found to be significant.

Table 2 – Distribution of TB associated factors.

Sl. No	Associated factors	Frequency	Percentage (%)
1.	**Key population**		
	Contact with TB patients	71	14.6%
	Migrants	20	4.2%
	Health care workers	5	1.0%
	Others	389	80.2%
2.	**Type of TB**		
	Pulmonary TB	327	67.4%
	Extrapulmonary TB	126	26.0%
	MDR TB	32	6.6%
3.	**Type of patient**		
	New	450	92.8%
	Previously treated	35	7.2%
4.	**Family history of TB**		
	Yes	66	13.6%
	No	419	86.4%
5.	**Current treatment phase**		
	Intensive phase	189	39%
	Continuation phase	296	61%
6.	**H/o adverse events**		
	Present	21	4.3%
	Absent	464	95.7%
7.	**Comorbidities**		
	Present	195	40.2%
	Absent	290	59.8%
8.	**Type of comorbidities**		
	Diabetics mellitus	151	31.1%
	Hypertension	68	14%
	COPD	27	5.6%
	Other	22	4.4%
9.	**Number of comorbidities**		
	Single co-morbidity	120	61.5%
	Multiple co-morbidities	75	38.5%
10.	**History of tobacco use**		
	Yes	146	30.1%
	No	339	69.9%
11.	**History of smoking**		
	Yes	107	22.1%
	No	378	77.9%
12.	**Current status of tobacco use/smoking**		
	Yes	13	2.7%
	No	472	97.3%
13.	**H/o alcohol intake**		
	Yes	87	17.9%
	No	398	82.1%

Table 3 – Distribution of study participants based on their serenity of depression.

Depression Severity	Frequency	Percentage (%)
No depression (0)	71	14.6%
Minimal Depression (1–4)	209	43.1%
Mild depression (5–9)	127	26.2%
Moderate depression (10–14)	70	14.4%
Moderately severe depression (15–19)	7	1.4%
Severe depression (20–27)	1	0.2%
Total	485	100%

Results observed in the study done by Dasa et al in Ethiopia also substantiated this, where 65% of the TB patients with depression belonged to Urban area.[17] Similar results were found in a study done by AT Islam et al in Bangladesh, where higher depression was found among patients residing in Urban area (51%).[18] This may be because most of them had a nuclear type of family and stayed away from their relatives. The lack of a proper social support and social isolation would have worsened the depression.

The study found no association of depression with gender, religion, education, occupation or socioeconomic status. In most of the studies, it was found that depression is more prevalent in women and among those with lower educational status.[9] Our findings suggest that male and female patients of TB suffered from depression alike. This may be due to the fact that gender equality is prevalent in Kerala. Whereas in the study done in BRICS countries, it was found that females with TB were found to be more vulnerable to depression.[19]

In the present study, it was observed that marital status and depression were significantly associated. 54% of unmarried/widowed TB patients were suffering from depression. It was similar to the study conducted by Islam et al in Bangladesh and study done by Basu et al reported that, 51% and 64% of the patients with depression were unmarried.[10,18] Similarly, 55.5% of unmarried patients with TB were depressed in a study conducted by Ige et al.[7] Lack of a partner to provide emotional support, the loneliness faced, stigma associated with fertility and marriage would be the reason that led to the depression in such patients.[20]

In our study, it's found that depression is significantly higher among MDR TB patients (43.8%), when compared to pulmonary TB and extrapulmonary TB. Similar results were found in a study done by Walker et al in Punjab where 42.8% of MDR TB patients were depressed.[21] However, it is similar to the study done by Umang et al in Delhi, where a higher prevalence of depression was reported among drug resistant TB patients (33.3%).[9] MDR-TB treatment takes apparently longer duration to complete, and may produce physical and psychiatric side effects. This may lead to poor treatment adherence and is a considerable challenge.[22] Research by Vega et al stated that 52% of all patients with MDR TB were depressed, which was slightly greater when compared to the current study.[23]

In this study, 45.7% of previously treated TB patients developed depression. Similar results were observed in studies done by Ige et al[7] in Nigeria and Bender et al in Canada

Table 4 – Univariate & Multivariate logistic regression analysis for independent predictors of depression.

Sl. No	Variable	Univariate regression		Multivariate regression					
		X^2	P value	Depression n (%)	Crude OR	95% CI	Adjusted OR	95%CI	P value
1.	**Age**								
	18–40	57.724	**<0.001***	49 (36.3%)	9.686	4.185–22.417	6.656	2.573–17.216	**<0.001**
	41–60			22 (9.8%)	1.851	0.768–4.464	1.723	0.686–4.331	
	>60			7 (5.6%)	1		1		
2.	**Marital status**	77.005	**<0.001***						
	Married			44 (10.4%)	1		1		
	Unmarried			34 (54%)	10.072	5.608–18.090	**4.781**	2.389–9.571	**<0.001**
3.	**Area of residence**								
	Rural			26 (12.3%)	1		1		
	Urban	10.666	**0.048***	35 (16.1%)	0.49	0.36–0.99	1.149	0.621–2.124	0.659
4.	**Type of patient**	24.542	**<0.001***						
	New			62 (13.8%)	0.190	0.093–0.389	0.147	0.051–0.423	**<0.001**
	Previously treated			16 (45.7%)	1		1		
5.	**Type of TB**	19.697	**<0.001***						
	MDR TB			14 (56.3%)	1		1		
	TB other than MDR TB			64 (14.1%)	4.727	2.240–9.976	0.833	0.278–2.494	0.744
6.	**H/O Adverse events**	7.881	**0.012***						
	Present			8 (38.1%)	1		1		
	Absent			70 (15.1%)	0.289	0.115–0.722	1.312	0.381–4.519	0.667

where depression was found to be more among previously treated patients.[24] The fear of treatment failure, recurrence of the disease and the longer duration of treatment may be the reasons for depression among these previously treated patients.

4.1. *Limitations*

The study was done among patients utilizing health services of government sector only and vast majority of patients utilizing private health care facilities were not captured.

5. Conclusion

One-sixth of TB patients suffered from depression. It was found that unmarried, younger age group and those living in urban were especially prone to depression. It's also found that, MDR TB patients, who were on longer duration of treatment and those who had history of adverse events are more likely to develop depression. Thus, it is recommended that screening of depression or psychiatric evaluation at the beginning of treatment, in the continuation phase and end of continuous phase of treatment. Compulsory screening form for depression should be included along with the treatment card. Those patients with depression should be given proper treatment & management, and further follow up. All health care providers and caregivers to be briefed about signs of depression and, they should be trained to diagnose and take appropriate measures. Create a linkage between NTEP and Psychology department. Need based counselling support for depressed patients.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. WHO | World Health Day 2017 Let's Talk about Depression and TB [Internet]. WHO. World Health Organization; [cited 2020 May 28]. Available from: http://www.who.int/tb/features_archive/whd2017_TB/en/.
2. reportWHO | Global Tuberculosis Report 2019 [Internet]. [cited 2020 May 28]. Available from: https://www.who.int/tb/publications/global_report/en/.
3. Depression [Internet]. [cited 2020 May 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression.
4. Major Depressive Disorder: Symptoms, Causes, and Treatment [Internet]. Healthline. [cited 2020 May 28]. Available from: https://www.healthline.com/health/clinical-depression.
5. Depression [Internet]. [cited 2020 Mar 22]. Available from: https://www.who.int/westernpacific/health-topics/depression.
6. Pachi A, Bratis D, Moussas G, Tselebis A. *Psychiatric Morbidity and Other Factors Affecting Treatment Adherence in Pulmonary Tuberculosis Patients. Tuberc Res Treat* [Internet]; 2013 [cited 2020 Mar 22];2013. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3649695/.
7. Ige OM, Lasebikan VO. Prevalence of depression in tuberculosis patients in comparison with non-tuberculosis family contacts visiting the DOTS clinic in a Nigerian tertiary care hospital and its correlation with disease pattern. *Ment Health Fam Med*. 2011 Dec;8(4):235–241.

8. Salodia UP, Sethi S, Khokhar A. Depression among tuberculosis patients attending a DOTS centre in a rural area of Delhi: a cross-sectional study. *Indian J Public Health*. 2019 Jan 1;63(1):39.
9. Depression among Tuberculosis Patients Attending a DOTS Centre in a Rural Area of Delhi: A Cross-Sectional Study Salodia up, Sethi S, Khokhar A - Indian J Public Health [Internet]. [cited 2020 Mar 22]. Available from: http://www.ijph.in/article.asp?issn=0019-557X;year=2019;volume=63;issue=1;spage=39;epage=43;aulast=Salodia.
10. Basu G, Chatterjee C, Singh R, Biswas S. Depression and its correlates among Tuberculosis patients: experience from a DOTS clinic of a sub divisional hospital of West Bengal. *Indian J Res Rep Med Sci*. 2012 Dec 1;2:14.
11. Mandaknalli DR, Giriraj DB. Research Article Prevalence of Depression in Tuberculosis Patients in a Tertiary Care Hospital.:4.
12. Javaid A, Mehreen S, Khan MA, Ashiq N, Ihtesham M. Depression and its associated factors with multidrug-resistant tuberculosis at baseline [Internet] *J Depress Anxiety*. 2017;6(1) [cited 2021 Mar 31]. Available from: https://www.omicsgroup.org/journals/depression-and-its-associated-factors-with-multidrugresistant-tuberculosis-at-baseline-2167-1044-1000253.php?aid=80831.
13. Sulehri MA, Dogar IA, Sohail H, et al. Prevalence of depression among tuberculosis patients. *Ann Punjab Med Coll APMC*. 2010 Dec 14;4(2):133–137.
14. Ann_Punjab_Med_Coll_2010_4_2_133_137.pdf [Internet]. [cited 2020 Mar 24]. Available from: http://applications.emro.who.int/imemrf/Ann_Punjab_Med_Coll/Ann_Punjab_Med_Coll_2010_4_2_133_137.pdf.
15. Kehbila J, Ekabe CJ, Aminde LN, Noubiap JJN, Fon PN, Monekosso GL. Prevalence and correlates of depressive symptoms in adult patients with pulmonary tuberculosis in the Southwest Region of Cameroon [Internet] *Infect Dis Poverty*. 2016 Jun 2;5 [cited 2020 Mar 12]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4895984/.
16. A Study of Prevalence of Depression and Anxiety in Patients Suffering from Tuberculosis [Internet]. [cited 2020 Mar 24]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4943123/.
17. Dasa TT, Roba AA, Weldegebreal F, et al. Prevalence and associated factors of depression among tuberculosis patients in Eastern Ethiopia. *BMC Psychiatr*. 2019 Dec;19(1):1–7.
18. Islam A. Pattern of psychiatric illness among tuberculosis Patients an analysis in a tertiary care hospital of Bangladesh. *Int J Appl Res*. 2016 Nov 3;1:763–766.
19. Janse Van Rensburg A, Dube A, Curran R, et al. Comorbidities between tuberculosis and common mental disorders: a scoping review of epidemiological patterns and person-centred care interventions from low-to-middle income and BRICS countries. *Infect Dis Poverty*. 2020 Jan 15;9(1):4.
20. Hatherall B, Newell JN, Emmel N, Baral SC, Khan MA. "Who will marry a diseased girl?" Marriage, gender, and tuberculosis stigma in asia. *Qual Health Res*. 2019 Jul 1;29(8):1109–1119.
21. Walker IF, Khan AM, Khan AM, et al. Depression among multidrug-resistant tuberculosis patients in Punjab, Pakistan: a large cross-sectional study. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2018 01;22(7):773–778.
22. Kumar K, Kumar A, Chandra P, Kansal HM. A study of prevalence of depression and anxiety in patients suffering from tuberculosis. *J Fam Med Prim Care*. 2016 Jan 1;5(1):150.
23. Vega P, Sweetland A, Acha J, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2004 Jun;8(6):749–759.
24. Bender A, Guruge S, Hyman I, Janjua M. La tuberculose et les troubles mentaux courants: des leçons d'autres pays applicables à la santé des immigrants au Canada. 2012;44(4):20.

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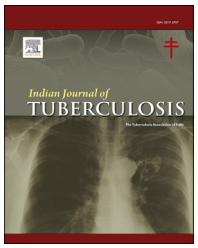

Original article

Utility of stool CBNAAT in the diagnosis of pediatric pulmonary tuberculosis in India

Anurag Agarwal [a], *Dhrithi Kodethoor* [a,*], *Ashwani Khanna* [b], *Mahmud Hanif* [c]

[a] *Department of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi, India*
[b] *Chest Clinic(TB), Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi, India*
[c] *New Delhi Tuberculosis Centre, New Delhi, India*

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ABSTRACT

Background: India houses 27% of the tuberculosis cases worldwide. Pediatric tuberculosis accounts for 11% cases worldwide. Microbiological confirmation of diagnosis is difficult in children. We aimed to study the proportion of Stool CBNAAT (Cartridge Based Nucleic Acid Amplification Test) and GA CBNAAT positive cases among the presumptive cases of tuberculosis in children and assess diagnostic utility of the Stool CBNAAT in comparison to GA CBNAAT and culture.

Methods: Ours was a cross sectional study. 75 children, aged 6 months to 12 years who were presumptive cases of pulmonary tuberculosis and who were unable to expectorate, were enrolled. Gastric aspirate and stool samples were obtained and CBNAAT and culture was done. Results of stool CBNAAT were compared with GA CBNAAT and culture.

Results: Of the 75 children enrolled, 28 were started on antitubercular therapy, 12 of whom were microbiologically confirmed and 16 were started on clinical grounds. Overall, 10 (13.3%) and 11 (14.6%) were positive by Stool CBNAAT and GA CBNAAT respectively. GA CBNAAT and Stool CBNAAT were found to have near perfect agreement (Cohen's kappa 0.834). Stool CBNAAT had sensitivity and specificity of 73% and 97% as compared to culture.

Conclusions: Stool CBNAAT may be used for bacteriological confirmation of pediatric pulmonary tuberculosis. It was found to have a high degree of concordance with the conventionally used GA CBNAAT. This test would be helpful in endemic countries where there is a dearth of trained staff, especially in the periphery, to obtain gastric aspirate. Discomfort associated with sampling would be avoided.

* *Corresponding author*. Department of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, 2, Bahadur Shah Zafar Marg, Maulana Azad Medical College Campus, Balmiki Basti, New Delhi, 110002, India.
E-mail address: dhrithi.kodethoor@gmail.com (D. Kodethoor).

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1. Introduction

Childhood tuberculosis is a major cause of mortality and morbidity in children. According to WHO estimates, 1.1 million children developed TB in the year 2019.[1]

The diagnosis of pulmonary tuberculosis in young children is challenging as they seldom expectorate spontaneously and obtaining an appropriate specimen from the lower respiratory tract is difficult.[2] In addition, pulmonary TB in children is often paucibacillary and children rarely form cavitary lesions which contain the bacilli.[3]

In view of the lower sensitivity of sputum smear and culture in children, WHO in 2014, made a conditional recommendation for the use of rapid molecular testing, that is, Cartridge Based Nucleic Acid Amplification Test (CBNAAT), as an initial test for accurate diagnosis with microbiological confirmation.[4]

Studies have shown CBNAAT on gastric aspirate (GA) and induced sputum to be 44% and 36% more sensitive than smear microscopy, respectively.[5] Other samples such as bronchoalveolar lavage and nasopharyngeal aspirates have also been used. However, obtaining these samples requires skilled staff and invasive procedures which cause discomfort to the child.

Children tend to swallow sputum rather than expectorate and mycobacterial DNA survives the harsh digestive environment of the gastrointestinal tract.[6] Hence, stool could be a potential specimen for diagnosis of pulmonary TB in children as it can be collected non-invasively.

With the current focus on elimination of tuberculosis in India, CBNAAT has been made available at the district level. However, dearth of skilled manpower to obtain GA samples in periphery and in outpatients continues to be a problem. Stool specimen could prove to be a probable alternative in order to overcome this problem.

Thus, we decided to do this study to explore the possibility of using stool in the diagnosis of TB in children.

2. Methods

The study was conducted in the Department of Pediatrics and Chest Clinic of a tertiary care hospital in India between May 2019 to February 2020.

Children between 6 months and 12 years were considered for enrolment. Those who had ≥1 of the following: 1)unexplained fever for two weeks or more, 2) unexplained cough for 2 weeks or more, 3) history of weight loss or those unable to gain weight (loss of >5% body weight as compared to highest record in the last 3 months or no weight gain in 3 months; reliable history of weight loss was considered in the absence of weight records; assessment of reliability was subjective; weight loss was suggested by change in appearance and loosening of clothes) and 4) contact history of tuberculosis (contact in the past 2 years) were defined as a suspected case pulmonary tuberculosis in accordance with the RNTCP definition.[7] Children who had received antitubercular therapy (ATT) for more than 3 days, those who could expectorate spontaneously and those with pain abdomen for more than 2 weeks with ultrasonographic features suggestive of gastrointestinal tuberculosis were excluded.

2.1. Study design and sample size

Ours was an observational cross sectional study. As per published studies, the proportion of stool samples positive by CBNAAT among the suspected cases of pulmonary tuberculosis was 8.3% (M.Chipinduro et al).[3]

Calculations were made using the following formula

$$\text{Sample size} = Z^2 1\text{-}\alpha/2 * p(1\text{-}p)/d^2$$

Z1-α/2–1.96 for confidence level of 95%

d-allowable error/desired precision (taken as 5%)

The estimated sample size based on this formula is 117. A sample size of 75 was chosen owing to the change of circumstances in our hospital due to COVID-19 outbreak.

2.2. Study procedure and sample collection

The study was approved by the Institutional Ethics Committee. It was also registered with CTRI with registration no. CTRI/2019/05/019261. Written informed consent and assent if child was above 7 years was taken from parents and children respectively. The procedure of the test and nature of the study was explained to the children following which their assent was obtained. Detailed history was taken and clinical examination was done.

All enrolled patients were subjected to a chest radiograph (CXR) and Tuberculin Skin Test (TST). TST was performed using 0.1ml of 5 tuberculin unit (TU) purified protein derivative (PPD) injected intradermally on the volar aspect of the left forearm, raising a wheal of around 6mm. The results were read after 48–72 hours. Induration of more than 10mm, measured horizontally, was considered positive. Other investigations were done as appropriate.

Inpatients were asked to remain fasting overnight whereas the outpatients were asked to present to the hospital in the morning following a fast of at least 4–6 hours. Parents were advised to ensure minimal ambulation prior to sample collection. To obtain gastric aspirate (GA), a nasogastric tube of suitable size was passed into the stomach. Aspiration was attempted after confirming the position of the tube. If direct aspiration failed, 10ml of normal saline was instilled and re-aspiration was done. Around 5–10 ml of sample was collected. Enrolled children were asked to collect a small amount of stool sample, approximately 5 g, in a plastic specimen container.

The gastric aspirate and stool samples were transported to laboratory within 2 hours. Samples were stored at −20 °C in case of delay. Samples were processed as soon as possible, preferably on the same day. CBNAAT testing and Mycobacterial Growth Indicator Tube (MGIT, culture) was done on all samples.

2.3. Laboratory methods

2.3.1. Gastric Aspirate Processing[8]

The GA sample was centrifuged at 10,000×*g* for 10 minutes at 4° C. The supernatant was decanted and the pellet was

then re-suspended in an equal volume of 0.5% NALC(N acetyl L cysteine)- 4% NaOH(sodium hydroxide) mixture. The suspension was vortexed and incubated at 37° C for 10 minutes. After incubation, the alkaline pH was neutralised with phosphate buffer saline (PBS) followed by a final centrifugation at 10,000×*g* for 10 min at 4° C. The supernatant was decanted and the pellet was re-suspended in 2ml of PBS and 0.5 ml volume was aliquoted into two sterile tubes. One aliquot was used culture (MGIT) and another was used for CBNAAT.

2.3.2. *Stool Processing*[2]

0.15g of the stool sample was measured into a centrifuge tube using a sterile disposable plastic loop which was left inside the tube. 2.4 ml of PBS was then added, and mixture was vortexed to remove stool particles from the loop. The loop was removed and the mixture was left undisturbed at room temperature for 20 minutes. The processed stool sample was then centrifuged at 3200×*g* for 15 mins. The sediment was resuspended in 1ml of PBS, mixed with 2ml of CBNAAT reagent and tested.

2.3.3. *Culture*[9]

The gastric aspirate was decontaminated according to standard protocol. The stool sample was processed in a similar manner as mentioned for CBNAAT testing but decontamination was carried out prior to centrifugation. Using a sterile pipette, 0.5 ml of the specimen concentrate was introduced into an MGIT tube containing 0.8ml of PANTA supplement (Polymyxin B, Amphotericin B, Nalidixic acid, Trimethoprim, Azlocillin). The tube was then placed in the MGIT 960 system. Positive culture was indicated by a red light on the front of the of the MGIT 960 drawer where the tube is located. Cultures were considered positive after they were confirmed to show AFB by ZN stained smear. Culture were considered negative if there was no growth at the end of 42 days.

2.4. *Diagnosis and management*

The decision to start ATT was made by the treating physician based on the clinical picture and investigations. Suspected cases of pulmonary tuberculosis were categorised for the purpose of our study as: 1) Confirmed: gastric aspirate culture confirmed case, 2) Clinically Diagnosed: those started on ATT on clinical grounds and those who were CBNAAT positive but culture negative, 3) Not Started on ATT. Culture was considered gold standard.

2.5. *Statistical analysis*

Data was collected by interviewing the parents/caregiver, examining the patient and conducting relevant clinical tests. Data was analysed using SPSS software 25.0. Fisher's exact test and Chi square test were used to compare qualitative variables. Sensitivity, specificity, positive predictive values (PPV) and negative predictive value (NPV) of GA CBNAAT, Stool CBNAAT and stool MGIT were calculated taking GA MGIT as gold standard. GA and Stool CBNAAT were compared using Cohen's kappa. P value of ≤0.05 was taken as significant.

3. Results

The median age of the study population of 75 children was 6.58 (Inter Quartile Range IQR 5.92) years with majority of children above the age of 5 years. Most of the children were inpatients. Fever was the most prominent symptom followed by cough. A history of contact with a case of tuberculosis was found in 24 patients (32%). Many patients in our study were underweight. TST was positive in approximately half of the study participants (47.3%). Baseline characteristics are listed in Table 1.

Of the 75 study participants, 11 were confirmed cases, 17 were started on ATT on clinical basis and 47 were not started on ATT. There was no significant difference in age and sex distribution in the three groups.

Majority of those started on ATT were malnourished in our study (p value < 0.001) Also, the duration of symptoms had been longer in those who were eventually started on ATT. Majority of patients in the confirmed and clinically diagnosed group had persistent, unremitting cough (p < 0.001). History of contact and TST positivity were not significantly different in the three groups. Miliary shadowing was significantly more common among those with confirmed tuberculosis and non specific findings were present only in those who did not have culture confirmed TB (Table 2).

Results of Stool CBNAAT, GA CBNAAT and Stool MGIT are presented in Table 3. Stool CBNAAT was positive in 10 of the 75 (13.3%) children who participated in the study. It was positive in 8/11 culture confirmed cases (72.7%) and additionally 2 patients who were culture negative were identified. In our

Table 1 – Baseline characteristics.

Characteristics	n (%)
Age (median, inter quartile range)	6.58 years (5.92 years) 6 months to 1 year - 4 (5.3) 1 to 2 years- 6 (8) 2 to 5 years- 12 (16) 5–10 years –29 (38.7) 10 to 12 years-24 (32)
Sex	Males- 43 (57.3) Females-32 (42.7)
Weight for height	−2 to +2 SD -43 (57.3) −2 to −3 SD-16 (21.3) <-3 SD-16 (21.3)
Symptoms	
Cough	50 (66.6)
Fever	74 (98.6)
Weight loss	23 (30.67)
Not gaining weight	6 (8)
Night Sweats	19 (25.3)
History of contact	24 (32)
TST positivity	35 of 74 (47.3)
HIV Status	Neg- 32 (42.7) Unknown-43 (57.3)
CXR findings	Mediastinal/Hilar Lymph nodes-17 (22.7) Consolidation-14 (18.7) Effusion-15 (20) Miliary Lesions-6 (8) Fibro cavitary Lesion-1 (1.3) Collapse-4 (5.3) Non-Specific Infiltrates-24 (32)

Table 2 – Characteristics of the three groups.

	Tuberculosis			p Value
	Confirmed (11) n (%)	Clinically Diagnosed (17) n (%)	Not started on ATT (47) n (%)	
Cough	10 (90.9)	8 (47.1)	32 (68.1)	0.053[a]
Fever	11 (100)	17 (100)	46 (97.9)	1.000[b]
Duration of cough				0.022[c]
<2 weeks	0 (0.0)	0 (0.0)	7 (14.9)	
2–4 weeks	4 (36.4)	1 (5.9)	16 (34.0)	
>4 weeks	6 (54.5)	7 (41.2)	9 (19.1)	
History of contact	6 (54.5)	4 (23.5)	14 (29.8)	0.198[a]
Mtx positivity	5 (50.0)	12 (70.6)	18 (38.3)	0.072[a]
Weight for height/BMI for age				
+2 to −2 SD	2 (18.2)	6 (35.3)	35 (74.5)	
−2 to −3 SD	4 (36.4)	8 (47.1)	4 (8.5)	<0.001[a]
<-3 SD	5 (45.5)	3 (17.6)	8 (17.0)	

[a] Chi Square Test
[b] Fisher Exact test
[c] Kruskal Wallis Test.

study, twelve cases were bacteriologically confirmed, that is, positive gastric aspirate culture or CBNAAT. Nine of these 12 were positive stool CBNAAT.

The sensitivity and specificity of Stool CBNAAT was 73% (95% CI 0.39–0.94) and 97% (95% CI 0.89–1.00). The PPV and NPV of Stool CBNAAT were 80% and 95% respectively. The sensitivity and specificity of GA CBNAAT with culture as gold standard was 91% (95%CI 0.59–1.00) and 98% (95% CI 0.92–1.00). The PPV and NPV were 91% and 98% respectively. Stool MGIT had a sensitivity of 36.3% (95% CI 0.11–0.69) and specificity- 100% (95% CI 0.42–1.00).

The two tests, namely Stool CBNAAT and GA CBNAAT, were compared. Stool CBNAAT was positive in 9 of the 11 GA CBNAAT positive cases (Table 4). The two tests were found to agree in 96% of the cases. There was Near Perfect agreement between the two methods, and this agreement was statistically significant (Weighted Kappa = 0.834, p = <0.001). This implies that stool CBNAAT is comparable to the widely accepted test, GA CBNAAT.

The diagnostic performance of Stool CBNAAT in comparison to GA CBNAAT was as follows: Sensitivity: 82%, Specificity: 98%, PPV: 90%, NPV: 97%, Diagnostic Accuracy: 96%.

4. Discussion

This tertiary hospital based cross-sectional study done to evaluate the utility of Stool CBNAAT in the diagnosis of paediatric pulmonary tuberculosis found near perfect agreement between stool CBNAAT and GA CBNAAT with MGIT on GA as gold standard.

Studies evaluating stool CBNAAT have had varied results. The proportion of Stool CBNAAT positives among confirmed cases in our study was slightly less (73%) than that reported by Hasan et al and Moussa et al- 88.9% and 83.33% respectively, both of which utilised stool sample processing techniques which were similar to that used in our study.[10,11] This could be because 2 of the children with culture confirmed TB in our study had GA CBNAAT result: Mtb detected Very Low which indicates low bacillary load. Stool has potential inhibitors of polymerase chain reaction (PCR) which, when coupled with a low bacillary load, may make detection of bacilli on CBNAAT less likely. Also, Hasan et al included a significant number of immunocompromised children in their study population. Moussa et al used LJ media, instead of MGIT, as a reference standard which by itself has a lower yield. The proportion reported in our study was higher than that reported by Nicol et al (47%) and Chipunduro et al (66.7%) using the same stool processing technique.[2,3]

In a systematic review and meta analysis done by McLean et al, the sensitivity and specificity of Stool CBNAAT to diagnose microbiologically confirmed pediatric pulmonary tuberculosis was found to be 67% (95%CI 52–79%) and 99% (95%CI 98–99%).[12] Studies included in this analysis differed in their stool specimen storage and processing techniques.

The poor results of stool CBNAAT in some studies such as Memon et al (sensitivity and specificity of 11.54% and 98.65%

Table 3 – Diagnostic performance of GA and Stool CBNAAT in the three groups.

Test	Tuberculosis		
	Confirmed (11) n (%)	Clinically Diagnosed (17) n (%)	Not Started on ATT (47) n (%)
GA CBNAAT Positive	10 (90.9)	1 (5.9)	0 (0.0)
Stool CBNAATPositive	8 (72.7)	1 (5.9)	1 (2.1)
Stool MGITPositive	4 (36.3)	0 (0.0)	0 (0.0)

Table 4 – Comparison of stool and GA CBNAAT.

CBNAAT		CBNAAT (GA)			Weighted Kappa	
		Positive	Negative	Total	K	P Value
CBNAAT (Stool)	Positive	9 (12.0%)	1 (1.3%)	10 (13.3%)	0.834	<0.001
	Negative	2 (2.7%)	63 (84.0%)	65 (86.7%)		
	Total	11 (14.7%)	64 (85.3%)	75 (100.0%)		

respectively against culture) might be due to the difference in processing methodology, such as lack of centrifugation of stool samples.[13]

Using GA CBNAAT as a reference standard, the sensitivity and specificity of stool CBNAAT in our study was 82%, and 98% respectively which is similar to that reported by Hasan et al (sensitivity of 81.8% (95% CI 47.8–96.8) and specificity of 94.7% (95% CI 80.9–99.1%)) [10]; Banada et al (sensitivity of 85% and 84% respectively using 0.6g and 1.2 g of stool).[14]

Stool MGIT was found to have poor diagnostic yield. This is in comparison with other studies and may be owing to the lack of live bacteria in the stool specimen.[15]

Of the 75 children enrolled in our study, the diagnosis of tuberculosis was confirmed by culture in 11 children, i.e. 14.6%. Culture was positive in 39.2% of those started on ATT. This is lower than the culture positivity noted in a study done by Singh et al (46.9%).[8] The high positivity of Singh et al could be explained by more stringent criteria for enrolment with adherence to Xray findings and the increased diagnostic yield achieved by obtaining both gastric aspirate and induced sputum sample in every patient. Our findings are similar to those of T.Cruz et al and Gupta et al.[16,17] The widely variable yield of cultures across studies, from 25% to 55.7% may be due to age, disease severity, type and quality of specimen.[18,19,5] This limits the role of culture as gold standard in the diagnosis of pediatric tuberculosis.

To the best of our knowledge, this is one of the few studies evaluating stool CBNAAT in pediatric pulmonary TB in India, a country with high burden of disease. It is the first study in India to have incorporated centrifugation as a part of stool processing procedure. Immunocompetent children were enrolled in our study. Additionally, GA MGIT was used as reference standard.

Our study is limited by the small sample size. The number of children aged <5 years is small which is a limitation. In our centre, however, we have observed that a significant number of children aged ≥5 years have difficulty in expectorating sputum, often even after inducing sputum, thereby necessitating GA collection. Multicentric studies with larger sample sizes, a mix of inpatients and outpatients and more children ≤5 years are required to further validate the utility of stool CBNAAT.

We conclude that stool sample can be used for point-of-care testing for pulmonary tuberculosis in children to overcome the shortage of trained staff to obtain GA samples in periphery and from OPD patients. Besides, it will be less traumatic for the paediatric patients.

Author contributions

Dr. Anurag Agarwal: Conceptualization, Methodology, Writing- Review & editing, Supervision.

Dr. Dhrithi Kodethoor: Investigation, Data curation, Writing- original draft, Writing- Review and editing.

Dr. Ashwani Khanna: Conceptualization, Methodology, Supervision.

Dr. Mahmud Hanif: Methodology, Supervision, Project administration.

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Conflicts of interest

The authors have none to declare.

REFERENCES

1. *Global Tuberculosis Report 2020*. Geneva: World Health Organisation; 2020. Available from: https://www.who.int/publications.
2. Nicol MP, Spiers K, Workman L, et al. Xpert MTB/RIF testing of stool samples for the diagnosis of pulmonary tuberculosis in children. *Clin Infect Dis*. 2013;57(3):e18–21.
3. Chipinduro M, Mateveke K, Makamre B, Ferrand RA, Gomo E. Stool Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis at primary clinic in Zimbabwe. *Int J Tubercul Lung Dis*. 2017;21(2):161–166.
4. World Health Organization. *Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF Assay for the Diagnosis of Pulmonary an Extrapulmonary TB in Adults and Children: Policy Update*. World Health Organization; 2013. Available from: https://apps.who.int/iris/handle/10665/112472.
5. Detjen AK, DiNardo AR, Leyden J, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(6):451–461.
6. Cordova J, Shiloh R, Gilman RH, et al. Evaluation of molecular tools for detection and drug susceptibility testing of Mycobacterium tuberculosis in stool specimens from patients with pulmonary tuberculosis. *J Clin Microbiol*. 2010;48:1820–1826.
7. Kumar A, Gupta D, Nagaraja SB, Singh V, Sethi GR, Prasad J. Updated national guidelines for pediatric tuberculosis in India,2012. *Indian Pediatr*. 2013;50:301–306.
8. Singh S, Singh A, Prajapati S, et al. Xpert MTB/RIF assay can be used on archived gastric aspirate and induced sputum sample for sensitive diagnosis of paediatric tuberculosis. *BMC Microbiol*. 2015;15:191.
9. Eisenach K. *Mycobacteriology Laboratory Manual.Geneva: Global Laboratory Initiative a Working Group of the Stop TB Partnership*;

2014. Available from: http://www.stoptb.org/wg/gli/assets/documents/gli_mycobacteriology_lab_manual_web.pdf.
10. Hasan Z, Shakoor S, Arif F, et al. Evaluation of Xpert MTB/RIF testing for rapid diagnosis of childhood pulmonary tuberculosis in children by Xpert MTB/RIF testing of stool samples in a low resource setting. *BMC Res Notes*. 2017;10:473.
11. Moussa HS, Bayoumi FS, Mohamed AMA. Gene xpert for direct detection of Mycobacterium tuberculosis in stool specimens from children with presumptive pulmonary tuberculosis. *Ann Clin Lab Sci*. 2016;46(2):198–203.
12. MacLean E, Sulis G, Denkinger CM, Johnston JC, Pai M, Khan FA. Diagnostic accuracy of stool xpert MTB/RIF for detection of pulmonary tuberculosis in children: a systematic review and meta-analysis. *J Clin Microbiol*. 2019;57(6). e02057-18.
13. Memon SS, Sinha S, Sharma SK, Kabra SK, Lodha R, Soneja M. Diagnostic accuracy of xpert mtb/Rif assay in stool samples in intrathoracic childhood tuberculosis. *J Tuberc Ther*. 2018;3(2):115.
14. Banada PP, Naidoo U, Deshpande S, et al. A novel sample processing method for rapid detection of tuberculosis in the stool of pediatric patients using the Xpert MTB/RIF Assay. *PLos One*. 2016;11(3), e0151980.
15. Walters E, Demers AM, Van der Zalm MM, et al. Stool culture for diagnosis of pulmonary Tuberculosis in children. *J Clin Microbiol*. 2017;55(12):3355–3365.
16. Cruz AT, Revell PA, Starke JR. Gastric aspirate yield for children with suspected pulmonary Tuberculosis. *J Pediatric Infect Dis Soc*. 2013;2(2):171–174.
17. Gupta N, Kashyap B, Dewan P, Hyanki P, Singh NP. Clinical spectrum of pediatric tuberculosis: a microbiological correlation from a tertiary care center. *J Trop Pediatr*. 2019;65(2):130–138.
18. Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D, Hussey G. Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Arch Dis Child*. 2000;82(4):305–308.
19. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. *Clin Infect Dis*. 2006;42(8):e69–e71.

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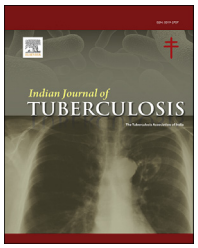

Original article

Clinical, laboratory and evolutionary features of abdominal tuberculosis in comparison with other forms of extrapulmonary tuberculosis

Fatma Hammami [a,*], *Houda Ben Ayed* [b], *Makram Koubaa* [a,**], *Amal Chakroun* [a], *Manel Hsairi* [c], *Fatma Smaoui* [a], *Lamia Gargouri* [c], *Khaoula Rekik* [a], *Mounir Ben Jemaa* [a]

[a] *Infectious Diseases Department and Extra-pulmonary Research Unity UR17SP12, Hedi Chaker University Hospital, University of Sfax, Tunisia*

[b] *Preventive Medicine and Hygiene Department, Hedi Chaker University Hospital, University of Sfax, Tunisia*

[c] *Pediatric Emergency and Reanimation Department, Hedi Chaker University Hospital, University of Sfax, Tunisia*

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ABSTRACT

Background/objectives: Tuberculosis is a multisystem disease that might affect any organ. Abdominal tuberculosis (ABT) represents 5–17% from all extrapulmonary tuberculosis (EPT) sites. We aimed to study the clinical, laboratory and evolutionary features of ABT cases and to identify predictive factors associated with ABT.

Methods: We conducted a retrospective study including all patients hospitalized in the infectious diseases department for EPT between 1991 and 2019. We studied the characteristics of ABT cases, and we compared them with other EPT cases.

Results: We identified 519 patients with EPT, among whom 86 (16.6%) patients had ABT. There were 58 females (67.4%). Peritoneal tuberculosis was the most common clinical form of ABT (68.6%), followed by intestinal tuberculosis (18.6%). Patients aged 60 years and above were significantly less affected with ABT (odds ratio (OR) = 0.2; p = 0.001). The revealing systemic symptoms including fever (OR = 2.04; p = 0.006), weight loss (OR = 2.5; p < 0.001) and anorexia (OR = 1.7; p = 0.021) were significantly more frequent among ABT patients. Inflammatory markers including C-reactive protein levels (37 [10–89] mg/l vs 10 [4–57] mg/l; p < 0.001) and erythrocyte sedimentation rates (43 [15–95] mm/h vs 27 [15–60] mm/h; p = 0.044) were significantly higher among ABT cases. Multivariate logistic regression analysis showed that anorexia (adjusted OR (AOR) = 1.9; p = 0.015) and pulmonary involvement (AOR = 3.3; p = 0.002) were independent predictors of higher rate of ABT. Concomitant involvement of neuro-meningeal (AOR = 0.18; p = 0.001) and osteo-articular (AOR = 0.2; p = 0.01) sites, 40–59 (AOR = 0.2; p < 0.001) and ≥60 (AOR = 0.2; p < 0.001) age groups as well as hemoglobin rate (AOR = 0.7; p < 0.001) were independently associated with lower rate of ABT.

* *Corresponding author*. Infectious Diseases Department, Hedi Chaker University Hospital, University of Sfax, Tunisia. Tel.: +216 20 755 665, fax: +216 74246906.

** *Corresponding author*. Infectious Diseases Department, Hedi Chaker University Hospital, University of Sfax, Tunisia. Tel.: +216 21 880 402; fax: +216 74246906.

E-mail addresses: fatma.hammami@medecinesfax.org (F. Hammami), koubaa_makram@medecinesfax.org (M. Koubaa).

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Conclusions: Anorexia and pulmonary involvement were independent predictors of higher rate of ABT. Concomitant involvement of neuro-meningeal and osteo-articular sites, 40–59 and ≥60 age groups and hemoglobin rate were independently associated with lower rate of ABT.

1. Introduction

Although its incidence has been relatively stable in recent years, tuberculosis (TB) epidemic remains a public health issue. Its burden varies among countries with an estimated 10 million new cases globally in 2018.[1] It's a multisystem disease that might affect any organ. TB typically affects the lungs.[2] However, extrapulmonary tuberculosis (EPT) is becoming relatively more common.[3] The rate of abdominal TB (ABT) is ranging from 5 to 17% of EPT sites.[4,5] When *Mycobacterium* reaches the abdomen, it may infect different, usually combined, sites. Four forms of the disease are reported, represented by abdominal tuberculous lymphadenopathy, peritoneal TB, intestinal TB and visceral TB involving the solid organs.[6] While abdominal distension and ascites are suggestive of peritoneal TB, abdominal pain and diarrhea are suggestive of intestinal TB.[7] Due to its non-specific clinical features and various presentations, the diagnosis of ABT might be challenging and confusing, especially in the absence of lung involvement. In this perspective, we aimed to study the clinical, laboratory and evolutionary features of ABT cases and to identify predictive factors associated with ABT.

2. Methods

2.1. Study design

We conducted a retrospective study including all patients hospitalized in the infectious diseases department for EPT between 1991 and 2019. We studied the characteristics of ABT cases, and we compared them with other EPT cases.

2.2. Data collection and case definitions

We collected data from the patient's medical records. We specified socio-demographic characteristics including age, gender, residency and previous medical history. We specified systemic symptoms, laboratory investigations and anatomical sites. Clinical presentation, diagnostic methods, treatment prescribed and its duration, and disease outcome were reviewed.

The diagnosis of ABT cases was based on microbiological evidence represented by a positive acid-fast bacilli (AFB) smear or culture from ascites or biopsy specimen, and/or histological evidence represented by isolation of caseating granulomas on biopsy specimen from the abdomen. Microbiological or histological evidence of TB elsewhere in the body associated with strong clinical and radiological signs of ABT confirmed the diagnosis. In default, it was clinically confirmed: When typical presentation of ABT was associated with a positive tuberculin skin test (TST) and negative diagnostic workup, adequate response to antitubercular therapy confirmed the diagnosis of ABT. An adequate response to therapy was based on the disappearance of abdominal and systemic revealing symptoms associated with normalization of laboratory investigations. Control abdominal imaging or control colonoscopy were not systematically indicated, unless in case of the absence of improvement with antitubercular therapy.

According to the involved organs, we identified 5 forms of the disease: intestinal, peritoneal, nodal, visceral and mixed TB. Intestinal TB included TB from the oral cavity to the rectum.[8] In order to avoid confusion, we identified two types of peritoneal TB: the wet and the dry type.[9,10] The traditional classification includes the wet ascitic type, the fixed fibrotic type and the dry plastic type. There was no distinctive feature differentiating fixed-fibrotic type and dry plastic type,[9] that's why we classified peritoneal TB in two type. While the wet ascitic type was associated with the formation of ascites without any peritoneal or omental thickening, fixed-fibrotic and dry plastic types were considered as the dry type.[9,10]

Visceral TB was defined as the involvement of solid organs including the spleen, the liver and the adrenal glands.[10]

2.3. Statistical analysis

We used the SPSS 20 software for statistical analysis. Categorical variables were expressed as numbers and percentages. When they were normally distributed, continuous variables were expressed by means and standard deviations. Otherwise, median and interquartile ranges were used. Chi square and Fisher exact test were used to compare two frequencies when applicable. Mann–Whitney test was used to compare two means in independent samples when the variables were non-normally distributed.

Variables associated with ABT in the univariate analysis ($p < 0.20$) were included in a logistic regression model, and a backward stepwise approach was used to identify independent predictors of ABT (adjusted odds ratio [AOR], 95% CI, p). Any variable with a p value of ≤ 0.05 was retained in the final model. Calibration was assessed using the Hosmer–Lemeshow test for goodness of fit, which evaluated expected and observed probabilities in population deciles. The discriminatory power of the prediction model was expressed as the area under the receiver operating characteristic curve (AUROC). The sensitivity and specificity of the prediction model were calculated. The difference between two groups was considered significant when $p < 0.05$.

3. Results

3.1. Characteristics of abdominal tuberculosis cases

During the study period, we encountered 86 patients with ABT, among whom 58 were females (67.4%). The mean age was 31 ± 16 years. Patients aged between 19 and 39 years were the most affected age group (52.3%). According to residency, 60 patients came from rural areas (69.8%). Five patients were previously treated for TB (5.8%) and 10 patients had a family history of TB (11.6%). Twenty-three patients consumed unpasteurized milk and products (26.7%) and 12 patients had a close contact with animals (14%). Systemic symptoms included fever in 63 cases (73.3%), asthenia in 52 cases (60.5%) and weight loss in 49 cases (57%) (Table 1).

Peritoneal TB was the most common clinical form of ABT in 59 cases (68.6%) and followed by intestinal TB in 16 cases (18.6%). Multifocal TB was noted in 32 cases (37.2%). ABT was associated with other TB sites represented by extra-abdominal lymph node TB in 22 cases (25.6%), pulmonary TB in 19 cases (22.1%) and urogenital TB in 12 cases (14%) (Table 2).

TST was positive in 37 cases (43%). The diagnosis of ABT was microbiologically confirmed in 14 cases (16.2%) and histologically confirmed in 62 cases (72.1%). Both microbiological and histological evidence were obtained for 8 cases (9.3%). The remaining 18 cases were clinically confirmed (20.9%) (Table 2).

Laboratory investigations revealed elevated C-reactive protein (CPR) levels in 53 cases (61.6%) with a median of 37 mg/l [10–89 mg/l] and accelerated erythrocyte sedimentation rates (ESR) in 28 cases (32.5%) with a median of 43 [15–95 mm/h]. Anemia was noted in 54 cases (62.7%) (Table 3).

Patients received antitubercular therapy based on fixed-dose combinations in 37 cases (43%). The median duration of antitubercular therapy was 12 months [10–15 months]. Adverse effects were noted in 32 cases (37.2%) represented by increase in hepatic enzyme levels in 13 cases (15.1%) and neurological symptoms in 12 cases (14%) (Table 1). Corticosteroid therapy was prescribed in 19 cases (22.1%) for a median duration of 21 days [12–30 days]. The disease evolution was favorable in 78 cases (90.7%). Complications occurred in 16 cases (18.6%) and relapse in 4 cases (4.7%). Four patients were dead (4.7%) (Table 1). The median duration of hospitalization was 12 days [4–24 days].

3.2. Specificities of abdominal tuberculosis in comparison with other forms of extrapulmonary tuberculosis

During the study period, we identified 519 patients with EPT, among whom 86 (16.6%) patients had ABT and 433 patients

Table 1 – Socio-demographic, clinical and evolutionary characteristics of patients with abdominal tuberculosis.

Variables		Number	Percentage (%)
Total		86	100
Age groups (years)	≤18	21	24.4
	19–39	45	52.3
	40–59	11	12.8
	≥60	9	10.5
Previous medical history	Family TB	10	11.6
	TB	5	5.8
	Diabetes mellitus	5	5.8
	Immunosuppressive or corticosteroid therapy	5	5.8
	Malignancy	4	4.7
	Chronic hepatitis B or C	3	3.5
	HIV infection	2	2.3
Systemic symptoms	Fever	63	73.3
	Asthenia	52	60.5
	Loss of appetite	51	59.3
	Weight loss	49	57
	Night sweats	37	43
Adverse effects of ATT	**Total**	**32**	**37.2**
	Increase in hepatic enzyme levels	13	15.1
	Neurological symptoms	12	14
	Paresthesia	10	11.6
	Optic neuropathy	7	8.1
	Gastrointestinal symptoms	6	7
	Abdominal pain	5	5.8
	Nausea and vomiting	4	4.7
	Leukopenia	5	5.8
	Skin reactions	3	3.5
Disease evolution	Recovery	78	90.7
	Complications	16	18.6
	Sequelae	9	10.5
	Relapse	4	4.7
	Death	4	4.7

TB: Tuberculosis, HIV: Human immunodeficiency virus, ATT: antitubercular therapy.

Table 2 – Clinical presentation and diagnostic methods of abdominal tuberculosis.

Variables	Number	Percentage (%)
Total	86	100
Associated sites		
Multifocal (≥2 sites)	32	37.2
Extra-abdominal lymph node	22	25.6
Pulmonary	19	22.1
Urogenital	12	14
Osteoarticular	6	7
Neuro-meningeal	5	5.8
Involvement sites		
Peritoneal	**59**	**68.6**
Wet ascitic type	52	60.5
Dry ascitic type	7	8.1
Intestinal	**16**	**18.6**
Ileocecal	9	10.5
Jejunal	4	4.7
Appendicular	3	3.5
Visceral	**12**	**14**
Hepatic	6	7
Splenic	5	5.8
Adrenal	1	1.1
Nodal	**12**	**14**
Mixed	**13**	**15.1**
Peritoneal and gastrointestinal	3	3.5
Peritoneal and visceral	3	3.5
Peritoneal and nodal	2	2.3
Gastrointestinal and nodal	3	3.5
Gastrointestinal and visceral	1	1.1
Visceral and nodal	1	1.1
Diagnostic methods		
Microbiological diagnosis	14	16.2
Histological diagnosis	62	72.1
Clinical diagnosis	18	20.9

When the difference between the groups was significant (p<0.05), we used bold p-value.

Table 3 – Laboratory investigations of abdominal tuberculosis cases.

Variables	Number	Percentage (%)
Total	86	100
Anemia	54	62.7
Elevated CRP	53	61.6
Lymphopenia	45	52.3
Accelerated ESR	28	32.5
Hyponatremia	19	22.1
Leukocytosis	11	12.8

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

had other forms of EPT (83.4%). Patients aged 60 years and above were significantly less affected with ABT (odds ratio (OR) = 0.2; p = 0.001). Comparison of previous medical history revealed that patients with ABT received immunosuppressive or corticosteroid therapy more frequently (OR = 3.2; p = 0.048). The revealing systemic symptoms including fever (OR = 2.04; p = 0.006), weight loss (OR = 2.5; p < 0.001) and anorexia (OR = 1.7; p = 0.021) were significantly more frequent among ABT patients. Pulmonary TB (OR = 3.2; p < 0.001) was significantly associated with ABT cases (Table 4).

Comparison of laboratory investigations revealed that CRP levels (37 [10–89] mg/l vs 10 [4–57] mg/l; p < 0.001) and ESR (43 [15–95] mm/h vs 27 [15–60] mm/h; p = 0.044) were significantly higher among ABT cases. Hemoglobin level was significantly lower among ABT cases in comparison with other EPT cases (10 [8–12] g/dl vs 12 [10.5–13] g/dl; p < 0.001) (Table 5).

ABT patients required a longer duration of hospitalization (12 [4–24] days) in comparison with other EPT cases (9 [3–17] days), with a significant difference (p = 0.048). As to the median duration of antitubercular therapy, no significant difference was noted (p = 0.068) (Table 5). Comparison of the disease evolution revealed no significant difference between patients with ABT and other forms of EPT (Table 4).

Multivariate logistic regression analysis showed that 40–59 (AOR = 0.2; p < 0.001) and ≥60 (AOR = 0.2; p < 0.001) age groups, concomitant involvement of neuro-meningeal (AOR = 0.18; p = 0.001) and osteo-articular (AOR = 0.2; p = 0.01) sites as well as hemoglobin rate (AOR = 0.7; p < 0.001) were independently associated with lower rate of ABT. On the other hand, anorexia (AOR = 1.9; p = 0.015) and pulmonary involvement (AOR = 3.3; p = 0.002) were independent predictors of higher rate of ABT (Table 6).

3.3. *Validity of the model*

The results of Hosmer-Lemshow chi-square testing ($\chi^2 = 10.22$; $p = 0.25$) were indicative of good calibration. The AUROC of the predictive logistic regression model was 0.82, indicating good predictive power in discriminating, with a sensitivity of 80% and a specificity of 70%.

4. Discussion

Our study highlighted the clinical, laboratory and evolutionary characteristics of ABT cases in comparison with other forms of EPT. ABT ranked at an alarming rate in our region and affected younger age group. A recent study reported that ABT affects most commonly patients between 35 and 45 years.[11] The routes of the abdomen infection are through hematogenous spread from a distant focus, or through direct spread from adjacent organs, or through ingestion of infected milk or sputum,[5] which has become an uncommon etiology among adults in the post pasteurization era. However, it remains an important cause of ABT in the pediatric population. Four forms of the disease were reported, among which, peritoneal TB was the most common form,[12] which was concordant with our results. Cho et al studied 139 cases of ABT, among which almost half of the cases were intestinal TB, followed by peritoneal TB in 20% of the cases.[10] Differences between studies might be related to the inclusion criteria since Cho et al included adults only,[10] while our study included both children and adults. In fact, a previous study reported that intestinal TB was predominant in adults, while peritoneal and nodal TB was predominant in children.[13] Other studies also found that intestinal TB was more frequent than peritoneal TB,[14,15] which might be related to a referral bias since the diagnosis of intestinal TB is more difficult to obtain and therefore, such cases

Table 4 – Socio-demographic, clinical, therapeutic and evolutionary factors associated with abdominal tuberculosis in comparison with other extrapulmonary tuberculosis forms.

			Odds ratio [95% CI]	p-value
Gender	Male		1	0.351
	Female		0.9 [0.7–1.08]	
Age groups	≤18		1	**<0.001**
	19–39		0.7 [0.4–1.3]	0.31
	40–59		0.2 [0.1–0.6]	**0.001**
	≥60		0.2 [0.1–0.5]	**0.001**
Place of residence	Urban		1	0.513
	Rural		0.8 [0.5–1.3]	
Previous medical history	Diabetes mellitus	No	1	0.789
		Yes	1.1 [0.4–3.1]	
	Immunosuppressive or corticosteroid therapy	No	1	**0.048**
		Yes	3.2 [1.04–10.2]	
	Malignancy	No	1	1
		Yes	0.9 [0.3–2.8]	
	HIV infection	No	1	0.194
		Yes	3.4 [0.5–20.7]	
Systemic symptoms	Fever	No	1	**0.006**
		Yes	2.04 [1.2–3.4]	
	Asthenia	No	1	0.481
		Yes	1.1 [0.7–1.9]	
	Anorexia	No	1	**0.021**
		Yes	1.7 [1.08–2.7]	
	Weight loss	No	1	**<0.001**
		Yes	2.5 [1.5–4]	
	Night sweats	No	1	**0.010**
		Yes	1.8 [1.1–2.9]	
Associated sites	Pulmonary	No	1	**<0.001**
		Yes	3.2 [1.7–5.9]	
	Neuro-meningeal	No	1	**0.013**
		Yes	0.3 [0.1–0.7]	
	Osteo-articular	No	1	**0.04**
		Yes	0.4 [0.2–0.9]	
Fixed dose combinations of ATT		No	1	0.499
		Yes	1.1 [0.7–1.8]	
Disease evolution	Recovery	No	1	0.836
		Yes	0.9 [0.4–2.05]	
	Complications	No	1	0.531
		Yes	0.8 [0.4–1.4]	
	Sequelae	No	1	0.267
		Yes	0.6 [0.3–1.3]	
	Relapse	No	1	1
		Yes	1.06 [0.3–3.2]	
	Death	No	1	0.096
		Yes	2.9 [0.8–10.1]	

Values are presented as number (%), mean ± standard deviation, ABT: abdominal tuberculosis, EPT: extrapulmonary tuberculosis, ATT: anti-tubercular therapy, CI: Confidence interval.
When the difference between the groups was significant ($p<0.05$), we used bold p-value.

usually present to a tertiary center.[14] The revealing symptoms varied according to the clinical presentation. Systemic symptoms including fever, weight loss, fatigue and anorexia were more prominent with peritoneal TB than with other forms.[16] They were reported in about one-third to more than 80% of ABT patients.[17,18] The frequent presence of systemic symptoms might be explained by the concomitant pulmonary TB, which was significantly more frequent in ABT cases in comparison with other forms of EPT cases. We found that both anorexia and pulmonary involvement were independent predictors of higher rate of ABT. The rate of pulmonary involvement ranged from 5% to 50% in ABT cases.[19] Previous studies reported that patients with ABT with concomitant pulmonary TB presented higher prevalence of fever and anorexia, with significant weight loss compared to those without pulmonary TB.[18] Clinicians should be aware of the frequent association between pulmonary and ABT and should guide laboratory investigations in order to diagnose even asymptomatic cases of ABT associated with pulmonary TB, especially in the presence of anorexia.

Similar to our results, the most common laboratory investigations included elevated CRP, elevated ESR, hypoalbuminemia and anemia.[20] Lymphomonocytosis was not uncommonly reported, although the white blood cell (WBC) count was usually normal.[11] Along with routine tests, specific investigations are required in order to confirm the diagnosis,

Table 5 – Laboratory investigations and treatment duration of abdominal tuberculosis cases in comparison with other extrapulmonary tuberculosis forms.

	ABT group	Other forms of EPT group	p-value
Total	86 (16.6)	433 (83.4)	–
WBC/mm^3	5420 (4300–6770)	6420 (5330–8355)	**0.012**
Lymphocyte count/mm^3	1400 (780–2000)	1600 (1182–2100)	0.066
Neutrophil count/mm^3	3510 (2820–4320)	4070 (3200–5575)	**0.039**
Hemoglobin level (g/dl)	10 (8–12)	12 (10.5–13)	**<0.001**
ESR (mm/h)	43 (15–95)	27 (15–60)	**0.044**
CRP (mg/l)	37 (10–89)	10 (4–57)	**<0.001**
Blood sodium level (mEq/L)	136 (134–140)	138 (135–140)	0.348
Duration of hospitalization (days)	12 (4–24)	9 (3–17)	**0.048**
Duration of ATT (months)	12 (10–15)	12 (9–15)	0.068

Values are presented as number (%), median (interquartile range), WBC: White blood cells, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ATT: antitubercular therapy, ABT: abdominal tuberculosis, EPT: extrapulmonary tuberculosis.
When the difference between the groups was significant ($p<0.05$), we used bold p-value.

Table 6 – Independent predictive factors of abdominal tuberculosis: results of multivariate logistic regression analysis.

Variables		Adjusted odds ratios (95% CI)	p-value
Age groups	<18	1	**<0.001**
	19–39	0.7 [0.4–1.5]	0.49
	40–59	0.2 [0.1–0.5]	**<0.001**
	≥60	0.2 [0.07–0.5]	**<0.001**
Anorexia	No	1	**0.015**
	Yes	1.9 [1.4–3.3]	
Associated sites			
Osteo-articular	No	1	**0.01**
	Yes	0.2 [0.09–0.7]	
Neuro-meningeal	No	1	**0.001**
	Yes	0.18 [0.06–0.5]	
Pulmonary	No	1	**0.002**
	Yes	3.3 [1.5–7.3]	
Hemoglobin rate		0.7 [0.6–0.8]	**<0.001**

CI: Confidence interval.
When the difference between the groups was significant ($p<0.05$), we used bold p-value.

which are guided according to the clinical presentation. For intestinal TB, endoscopic biopsies should be obtained for culture, Ziehl-Neelsen stain and histology.[21] When peritoneal TB is suspected, ascitic fluid analysis should be performed including acid-fast bacilli stain/smear and culture, WBC count, lactate dehydrogenase (LDH) and serum-ascites albumin gradient (SAAG) score.[22] Lymphocyte-predominant ascitic fluid, raised LDH level, protein levels >25 g/L and a low SAAG score (<11g/L) were suggestive of the tuberculous etiology of ascites.[11]

Management of ABT is based mainly on medical treatment represented by isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampicin for the rest of the period. However, the treatment duration remains a controversial issue.[23] A recent study revealed that 7 months was associated with the lowest mortality and extended therapy was associated with worse survival.[24] Another study compared the outcome of ABT patients with six-month regimens versus nine-month regimens and found no additional benefits of nine-month regimens regarding relapse or clinical cure at the end of the treatment.[25] However, clinicians tend to extend the treatment duration up to 12 months and beyond, in order to prevent complications and relapse. The treatment duration might be extended until the occurrence of subjective and objective parameters. Previous studies suggested the benefit of CRP measurement during the follow-up. The CRP decline was associated with objective response to antitubercular therapy.[26] In fact, the resolution of clinical symptoms, normalization of laboratory tests and disappearance of ascites are useful in monitoring response to therapy, which usually occur within 3 months of antitubercular therapy.[11] Repeating colonoscopy and biopsy for histopathology and culture at the end of treatment is not done routinely among ABT cases.[25]

As for the treatment regimen, the World Health Organization continues to recommend the use of fixed dose combinations since they prevent acquisition of drug resistance due to monotherapy, which may occur with separate drugs.[27] Along with antitubercular therapy, corticosteroids might reduce fibrotic consequences, stricture formation and post tubercular sequelae.[28] Similar to our results, Calin et al included 80 patients with ABT, among whom corticosteroid therapy was indicated in 18.7% of the cases, either for paradoxical reaction or to prevent complications.[29] Comparison of the outcome between EPT cases showed that neuromeningeal TB had the highest mortality rate and among 262 cases of ABT, 9 patients (3.5%) died,[30] which is concordant with the results found in our study.

In comparison with other forms of EPT, anorexia and pulmonary involvement were independent predictors of higher rate of ABT. Concomitant involvement of neuro-meningeal and osteo-articular sites, 40–59 and ≥60 age groups and hemoglobin rate were independently associated with lower rate of ABT. Inflammatory markers including ESR and CRP were higher among ABT cases, while the outcome was similar in comparison with other forms of EPT cases.

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Conflicts of interest

The authors have none to declare.

REFERENCES

1. WHO. *Global Tuberculosis Report 2019*; 2019. Available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports.
2. Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ. Extrapulmonary tuberculosis: pathophysiology and imaging findings. *Radiographics*. 2019;39(7):2023–2037. https://doi.org/10.1148/rg.2019190109.
3. Banta JE, Ani C, Bvute KM, Lloren JIC, Darnell TA. Pulmonary vs. extra-pulmonary tuberculosis hospitalizations in the US [1998–2014]. *J Infect Public Health*. 2020;13(1):131–139. https://doi.org/10.1016/j.jiph.2019.07.001.
4. Sheer TA, Coyle WJ. Gastrointestinal tuberculosis. *Curr Gastroenterol Rep*. 2003;5(4):273–278. https://doi.org/10.1007/s11894-003-0063-1.
5. Abu-Zidan FM, Sheek-Hussein M. Diagnosis of abdominal tuberculosis: lessons learned over 30 years: pectoral assay. *World J Emerg Surg*. 2019;14:33. https://doi.org/10.1186/s13017-019-0252-3.
6. Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: revisited. *World J Gastroenterol*. 2014;20(40):14831–14840. https://doi.org/10.3748/wjg.v20.i40.14831.
7. Mamo JP, Brij SO, Enoch DA. Abdominal tuberculosis: a retrospective review of cases presenting to a UK district hospital. *QJM*. 2013;106(4):347–354. https://doi.org/10.1093/qjmed/hct003.
8. Malikowski T, Mahmood M, Smyrk T, Raffals L, Nehra V. Tuberculosis of the gastrointestinal tract and associated viscera. *J Clin Tuberc Other Mycobact Dis*. 2018;12:1–8. https://doi.org/10.1016/j.jctube.2018.04.003.
9. Ahamed ZR, Shah J, Agarwala R, et al. Controversies in classification of peritoneal tuberculosis and a proposal for clinico-radiological classification. *Expert Rev Anti Infect Ther*. 2019;17(8):547–555. https://doi.org/10.1080/14787210.2019.1642746.
10. Cho JK, Choi YM, Lee SS, et al. Clinical features and outcomes of abdominal tuberculosis in southeastern Korea: 12 years of experience. *BMC Infect Dis*. 2018;18(1). https://doi.org/10.1186/s12879-018-3635-2.
11. Sanai FM, Bzeizi KI. Systematic review: tuberculous peritonitis–presenting features, diagnostic strategies and treatment. *Aliment Pharmacol Ther*. 2005;22(8):685–700. https://doi.org/10.1111/j.1365-2036.2005.02645.x.
12. Gupta P, Kumar S, Sharma V, et al. Common and uncommon imaging features of abdominal tuberculosis. *J Med Imaging Radiat Oncol*. 2019;63(3):329–339. https://doi.org/10.1111/1754-9485.12874.
13. Sartoris G, Seddon JA, Rabie H, Nel ED, Schaaf HS. Abdominal tuberculosis in children: challenges, uncertainty, and confusion. *J Pediatric Infect Dis Soc*. 2020;9(2):218–227. https://doi.org/10.1093/jpids/piz093.
14. Mandavdhare HS, Singh H, Dutta U, Sharma V. A real-world experience with 6 months of antitubercular therapy in abdominal tuberculosis. *JGH Open*. 2019;3(3):201–205. https://doi.org/10.1002/jgh3.12136.
15. Tan KK, Chen K, Sim R. The spectrum of abdominal tuberculosis in a developed country: a single institution's experience over 7 years. *J Gastrointest Surg*. 2009;13(1):142–147. https://doi.org/10.1007/s11605-008-0669-6.
16. Vaid U, Kane GC. Tuberculous peritonitis. *Microbiol Spectr*. 2017;5(1). https://doi.org/10.1128/microbiolspec.TNMI7-0006-2016.
17. Kapoor VK. Abdominal tuberculosis. *Postgrad Med J*. 1998;74(874):459–467. https://doi.org/10.1136/pgmj.74.874.459.
18. Chong VH. Differences in patient profiles of abdominal and pulmonary tuberculosis: a comparative study. *Med J Malaysia*. 2011;66(4):318–321.
19. Fillion A, Ortega-Deballon P, Al-Samman S, et al. Abdominal tuberculosis in a low prevalence country. *Med Mal Infect*. 2016;46(3):140–145. https://doi.org/10.1016/j.medmal.2016.02.003.
20. Shi XC, Zhang LF, Zhang YQ, Liu XQ, Fei GJ. Clinical and laboratory diagnosis of intestinal tuberculosis. *Chin Med J (Engl)*. 2016;129(11):1330–1333. https://doi.org/10.4103/0366-6999.182840.
21. Roberts S, Newsholme W, Gibson T. Diagnosis and management of intra-abdominal tuberculosis. *Br J Hosp Med (Lond)*. 2018;79(6):C86–C89. https://doi.org/10.12968/hmed.2018.79.6.C86.
22. Wu DC, Averbukh LD, Wu GY. Diagnostic and therapeutic strategies for peritoneal tuberculosis: a review. *J Clin Transl Hepatol*. 2019;7(2):140–148. https://doi.org/10.14218/JCTH.2018.00062.
23. Evans RPT, Mourad MM, Dvorkin L, Bramhall SR. Hepatic and intra-abdominal tuberculosis: 2016 update. *Curr Infect Dis Rep*. 2016;18(12):45. https://doi.org/10.1007/s11908-016-0546-5.
24. Pusch T, Pasipanodya JG, Hall RG, Gumbo T. Therapy duration and long-term outcomes in extra-pulmonary tuberculosis. *BMC Infect Dis*. 2014;14(1). https://doi.org/10.1186/1471-2334-14-115.
25. Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. *Cochrane Database Syst Rev*. 2016;11:CD012163. https://doi.org/10.1002/14651858.CD012163.pub2.
26. Sharma V, Mandavdhare HS, Lamoria S, Singh H, Kumar A. Serial C-reactive protein measurements in patients treated for suspected abdominal tuberculosis. *Dig Liver Dis*. 2018;50(6):559–562. https://doi.org/10.1016/j.dld.2017.12.008.
27. WHO. *TreatmenT of Tuberculosis Guidelines*. 4th ed. 2010.
28. Soni H, Bellam BL, Rao RK, et al. Use of steroids for abdominal tuberculosis: a systematic review and meta-analysis. *Infection*. 2019;47(3):387–394. https://doi.org/10.1007/s15010-018-1235-0.
29. Calin R, Belkacem A, Caraux-Paz P, et al. Abdominal tuberculosis: experience from two tertiary-care hospitals in the Paris region. *Am J Trop Med Hyg*. 2020;104(1):223–228. https://doi.org/10.4269/ajtmh.20-0023.
30. Cherian JJ, Lobo I, Sukhlecha A, et al. Treatment outcome of extrapulmonary tuberculosis under revised National Tuberculosis Control Programme. *Indian J Tuberc*. 2017;64(2):104–108. https://doi.org/10.1016/j.ijtb.2016.11.028.

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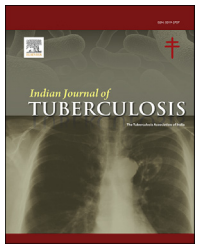

Original article

Interleukin-37 gene polymorphism and susceptibility to pulmonary tuberculosis among Iraqi patients

Zainab A. Ali [a], *Ahmed A. Mankhi* [b], *Ali H. Ad'hiah* [c,*]

[a] *Biotechnology Department, College of Science, University of Baghdad, Baghdad, Iraq*
[b] *National Specialized Center for Chest and Respiratory Diseases, Ministry of Health and Environment, Baghdad, Iraq*
[c] *Tropical-Biological Research Unit, College of Science, University of Baghdad, Baghdad, Iraq*

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ABSTRACT

Background: Control of tuberculosis (TB) depends on a balance between host's immune factors and bacterial evasion strategies. Interleukin-37 (IL-37) is among the immunomodulatory factors that have been proposed to influence susceptibility to tuberculosis.
Methods: A case–control study was conducted on 105 patients with pulmonary TB (37 active, 41 multi-drug resistant and 27 relapse) and 79 healthy controls to determine serum levels and single nucleotide polymorphisms (SNPs) of IL-37. The IL-37 level was assessed with an enzyme-linked immunosorbent kit, while DNA-sequencing was used to detect SNPs in the promoter region of *IL37* gene.
Results: Median level of IL-37 was markedly increased in serum of TB patients compared to controls (325.0 *vs.* 169.1 pg/mL; $p < 0.001$). This increase was universally determined in subgroups of patients distributed according to gender, age groups, and clinical type of disease, while no significant differences were found between the subgroups in patients or controls. Analysis of receiver operating characteristic curve confirmed these findings and IL-37 occupied a very good area under the curve, which was 0.816 (95% CI = 0.744–0.888; $p < 0.001$). At a cut-off value of 185.6 pg/mL, the sensitivity and specificity of IL-37 were 81.0 and 82.3%, respectively. Of the nine detected SNPs (rs2466449 G/A, rs2466450 A/G, rs2723168 G/A, rs3811042 G/A, rs3811045 T/C, rs3811046 G/T, rs3811047 A/G, rs3811048 G/A and rs200782323 G/A), only rs3811048 showed a significant association with TB; the *G* allele showed a significantly decreased frequency in TB patients compared to controls (25.2 *vs.* 44.9%; OR = 0.41; $p < 0.001$). It was possible to assign five haplotypes, and three showed significant differences between patients and controls. Frequency of haplotype A-A-G-A-C-T-G-A-G (0.331 *vs.* 0.213; OR = 2.10; $p = 0.015$) was significantly increased in TB patients compared to controls. On the contrary, frequencies of haplotypes A-A-G-A-C-T-G-G-G (0.029 *vs.* 0.116; OR = 0.24; $p = 0.01$) and A-A-G-G-T-G-A-G-G (0.140 *vs.* 0.275; OR = 0.45; $p = 0.015$) were significantly decreased in patients.

Abbreviations: CI, Confidence interval; D', Linkage disequilibrium coefficient; HWE, Hardy–Weinberg equilibrium; IFN, Interferon; IL, Interleukin; LD, Linkage disequilibrium; MDR, Multi-drug resistant; OR, Odds ratio; *p*, Probability; ROC, Receiver operating characteristic; SNP, Single nucleotide polymorphism; TB, Tuberculosis; Th, T helper; TNF, Tumor necrosis factor.

* *Corresponding author*. Tropical-Biological Research Unit, College of Science, University of Baghdad, Al-Jadriya, Baghdad, Iraq.
Tel.: +964 770 422 6884.
E-mail addresses: dr.ahadhiah@sc.uobaghdad.edu.iq, dr.a.h.adhiah@gmail.com (A.H. Ad'hiah).

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Conclusions: IL-37 was up-regulated in the serum of TB patients irrespective of their gender, age or clinical type of disease. SNPs in the promoter region of *IL37* gene were proposed to be associated with susceptibility to TB.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*; one of the pathogenic bacterial species belongs to the *Mycobacteriaceae* family.[1] The disease is associated with increasing morbidity and mortality rates worldwide, particularly in developing and least developed countries.[2] In Iraq, TB is also a health problem and recent data indicate that the disease remains out of control, although low infection rates have been reported. Moreover, the emergence of multidrug-resistant (MDR) cases and relapses is a major threat to TB control.[3]

Control of *M. tuberculosis* infection depends on a balance between host's immune factors and bacterial evasion strategies. Both innate and adaptive immunity are critical factors in eliminating this infectious pathogen.[4] *M. tuberculosis* is primarily engulfed by macrophages, where the bacteria is able to survive; however infected cells produce tumor necrosis factor-alpha (TNF-α) to recruit T lymphocytes (CD4+ and CD8+ cells) to site of infection where these cells mount effector functions including production of interferon-gamma (IFN-γ).[5] Accordingly, the killing of *M. tuberculosis* is made by activated macrophages, as well as, by cytotoxic actions of activated T cells or through TNF-α pathway, which induces apoptosis in infected macrophages.[6]

T lymphocyte is the principal cell in cell-mediated immunity against *M. tuberculosis*, but the reasons behind impaired function of these cells in active TB have not been disclosed. It has been found that patients having mutations in the signaling pathways of T helper (h) 1 cytokines (IFN-γ and IL-12 [interleukin-12]) are more susceptible to TB infection.[7] Impaired response of Th1 cells during HIV infection has also been associated with ineffective immunity against *M. tuberculosis*.[8] On the contrary, in latent TB infection or reactivated and advanced TB, Th2 cytokines (IL-4 and IL-10) were up-regulated. Actually, overexpression of Th2 cytokines was associated with increased severity of disease, and virulent *M. tuberculosis* strains were found to preferentially induce the expression of Th2 cytokines, whereas Th1 cytokines (IFN-γ and TNF-α) were associated with less virulent strains.[9] Accordingly, the outcome of *M. tuberculosis* infection is regulated by a complex network of cytokines.[10] Cytokines are soluble, low molecular weight glycoproteins produced by different cells and act in autocrine, paracrine or endocrine manner to influence the activity of cells that secrete them, nearby cells or distant cells, respectively. Through these actions, they coordinate innate immunity and initiate, amplify, direct, mediate, and regulate adaptive immunity.[11] Several cytokines have been linked with susceptibility or resistance to TB infection; for instance, IFN-γ, TNF-α and members of IL-1, IL-12 and IL-17 families.[12] It has been highlighted that mutations in the IL-1, IL-12 and IFN-γ pathways are risk factors associated with increased susceptibility to *M. tuberculosis* infection.[10] Therefore, this study focused on a member of IL-1 family, which was IL-37.

IL-37 (originally known as IL-1F7) is a new member of the IL-1 family, which includes eleven members of cytokines and cytokine receptors (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-1Ra, IL-36Ra, IL-37 and IL-38).[13] IL-37 is 17–26 KDa protein encoded by a gene of six exons (molecular size: 3.617 kb) on the long arm of chromosome 2 (2q14.1).[14] The expression of IL-37 is linked to inflammation, and some inflammatory stimuli have been described to up-regulate the expression of IL-37; for instance, IL-1β, IL-18, IFN-γ and TNF-α, while a down-regulated expression is associated with IL-4 and GM-CSF (granulocyte-macrophage colony-stimulating factor).[15] The expression of IL-37 is regulated by two signaling pathways; mitogen activated protein kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K).[16] Functionally, IL-37 is considered a cytokine with anti-inflammatory and inhibitory potentials that influence inflammatory responses and innate and adaptive immune responses. These effects of IL-37 are mediated through down-regulating production of pro-inflammatory cytokines from macrophages and dendritic cells.[16] It has also been demonstrated that epithelial cell-derived IL-37 can inhibit the activation of T cells and dendritic cells by reducing the surface expression of CD86 and MHC (major histocompatibility complex)-class II molecules.[17] Due these functions, IL-37 is proposed to have role in pathogenesis of infectious diseases.[18]

In TB patients, elevated serum levels of IL-37 have been found, and its role in pathogenesis of the infection has been proposed. The mRNA expression of *IL37* gene in peripheral blood mononuclear cells (PBMCs) was also increased in patients with active TB compared to controls.[19–22] These findings indicate the potential role of IL-37 in the development of TB. Moreover, two studies have reported that single nucleotide polymorphisms (SNPs) of *IL37* gene may influence susceptibility to TB,[21,22] but the available evidence has not been conclusive.

In line with these findings, the current study sought to investigate serum level of IL-37 in TB of Iraqi patients. Three types of disease were included; active TB, MDR TB and relapse TB. Further, a region of the *IL37* gene promoter was sequenced to determine some SNPs that may impact susceptibility to TB. To the best knowledge of investigators, these evaluations have not been conducted on Iraqi TB patients.

2. Materials and methods

2.1. Populations studied

A case–control study was conducted at the National Specialized Center for Chest and Respiratory Diseases (NSCCRD) in Baghdad during March–September, 2019. The study populations consisted of 105 patients with pulmonary TB (mean age ± standard deviation [SD] = 39.6 ± 15.6 years; 58.1% males and 41.9% females) and 79 healthy controls (mean age ± SD = 35.2 ± 11.3 years; 57.0% males and 43.0% females). The patients were classified to three age groups (years); 16–24 (19.0%), 25–40 (32.4%) and >40 (48.6%). The corresponding figures among controls were 15.2, 62.0 and 22.8%, respectively. The patients were classified to three clinical types of TB; 37 active TB, 41 MDR TB and 27 relapse TB. The standard guidelines established by the World Health Organization (WHO) were followed in the laboratory diagnosis of TB. These guidelines recommended examining the sputum by three main methods; direct microscopy (acid-fast Ziehl-Neelsen stain method), culturing in Löwenstein–Jensen medium and nucleic acid amplification (GeneXpert DX [Cepheid AB, Sweden] and TB-loop-mediated isothermal amplification [TB-LAMP, Eiken Chemical Co., Ltd.]). These methods were previously described.[23] Patients with MDR TB were those who showed resistance to standard anti-TB drugs (isoniazid and rifampicin) after six months of treatment. MDR was diagnosed by drug susceptibility testing and GeneXpert MTB/RIF Assay. Patients with relapse TB were those who completed the six month anti-TB drug treatment and then returned with TB diagnosis again within two years of their last treatment (i.e. the sputum smear and culture were again positive or the patient had clinical and radiological features compatible with active TB). Pregnant women and patients who had respiratory allergic reactions or infectious diseases other than TB were excluded. The controls were blood donors and the serum profile for anti-pathogen antibodies at the Central Blood Bank (Baghdad) was tested negative. Further, they reported no clinical complaints, and had no history of TB and/or respiratory infectious diseases within the past 12 months. Written-informed consent was obtained from participants, and the study protocol was approved by the Ethic Committee at the Iraqi Ministry of Health and Environment (Approval number: D.S.A./11/4 on March 3, 2019).

2.2. Serum level of IL-37

The level of IL-37 was assessed in serum of participants using sandwich enzyme-linked immunosorbent assay (ELISA) kit, and instructions of the manufacturer were followed (MyBioSource, Inc., USA). The detection range of kit was 31.2–2000 pg/mL.

2.3. Gene polymorphism of IL37

The available DNA sequence of *IL37* gene in the National Center for Biotechnology Information (NCBI) website was downloaded before designing primers (https://www.ncbi.nlm.nih.gov/gene/27178). The study was interested in SNPs in the promoter region of the gene. The included SNPs were those with a minor allele frequency greater than 5%. Besides, a review of the literature revealed that this region includes SNPs that have been suggested to be associated with susceptibility to TB.[21,22] Based on these criteria, two primers were designed (Forward: 5′- GCACAGACCCAGTTGTTT-3′ and Reverse: 5′-GCTCATCTTTCCCAGAGTTATC-3′) to amplify a DNA region of 877 bp using Geneious software version 11.1.5.[24] The primers were online-tested to ensure their specificity using *in silico* PCR analysis (https://genome.ucsc.edu).[25] The analysis revealed that the target region had a molecular size of 877 bp (chr2:112913166+112914042).

The thermocycling was performed with PCR Express (Thermal Cycler, BioRad, USA). A reaction mix of 25 μL was prepared to include 12.5 μL GoTaq Green Master Mix (2X: Promega, U.S.A), 1 μL of each primer (10 pmol); 8.5 μL nuclease free water and 2 μL of template DNA. The PCR machine was programmed for the following optimized conditions: initial denaturation at 95 °C for 5 min (one cycle), followed by 30 cycles of denaturation at 95 °C (30 sec), annealing at 60 °C (30 sec) and extension at 72 °C (60 sec). A final extension cycle was accomplished at 72 °C (7 min), followed by 10 min hold at 4 °C.

Table 1 – Median levels of IL-37 in serum of tuberculosis patients and controls.

Group		IL-37 median (IQR: 25–75%); pg/ml		*p*
		TB patients (N = 105)	HC (N = 79)	
TB patients *vs.* HC		325.0 (39.3–680.2)	169.1 (134.4–252.9)	**<0.001**
Gender	Male	329.5 (39.3–680.2)	169.1 (135.1–252.9)	**<0.001**
	Female	315.9 (40.6–544.9)	169.4 (134.4–252.2)	**<0.001**
	p	0.659	0.866	
Age group; year	16–24	419.7 (172.5–680.2)	168.2 (147.5–252.9)	**<0.001**
	25–40	316.0 (39.3–563.7)	172.9 (134.4–252.9)	**<0.001**
	>40	297.2 (45.0–534.1)	165.8 (135.1–194.4)	**<0.001**
	p	(0.144)	0.399	
PTB type	Active	294.7 (51.2–680.2)	169.1 (134.4–252.9)	**<0.001**
	MDR	329.5 (40.6–514.8)		**<0.001**
	Relapse	350.0 (39.3–482.8)		**<0.001**
	p	0.683		

TB: Tuberculosis; HC: Healthy controls; MDR: Multi-drug resistance; IQR: Interquartile range; *vs.*: Versus; *p*: Mann–Whitney *U* or Kruskal–Wallis test probability (significant *p*-value indicated in bold).

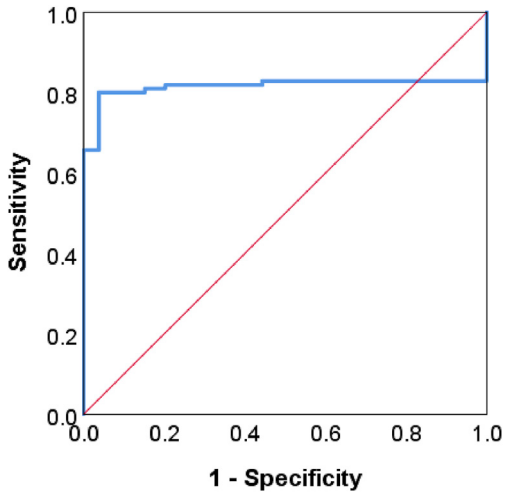

Fig. 1 – ROC curve analysis of IL-37 in tuberculosis. The increased serum level of IL-37 occupied an area under curve of 0.816 (95% CI: 0.744–0.888; $p < 0.001$). At a cut-off value of 185.6 pg/mL, the sensitivity and specificity of IL-37 were 81.0 and 82.3%, respectively.

The PCR products were sent for forward DNA sequencing (Sanger sequencing, Macrogen Corporation, South Korea). The received DNA sequences were subjected to alignments with reference DNA sequences of *IL37* gene SNPs available in the NCBI. The Geneious software version 11.1.5 was used to reveal genotypes of *IL37* gene SNPs.[24]

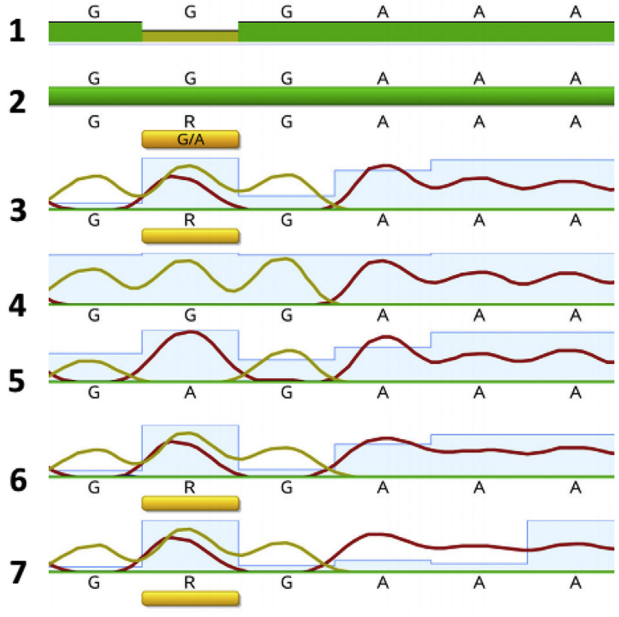

Fig. 2 – A representative DNA sequence chromatogram of *IL37* gene showing rs3811042 G/A SNP. 1: *IL37* gene reference sequence; 2: rs3811042 SNP reference sequence; 3, 6 and 7: Heterozygous genotype (GA); 4: Wild homozygous genotype (GG); 5: Mutant homozygous genotype (AA).

2.4. Statistical analysis

Serum level of IL-37 was tested for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests. The level was not normally distributed, and thus the parameter was expressed as median and interquartile range (IQR: 25–75%). Significance of difference between medians was assessed by Mann–Whitney U (to compare two groups) or Kruskal–Wallis (to compare more than two groups) test. Receiver operating characteristic (ROC) curve analysis was performed to determine area under curve (AUC) and the optimum cut-off value of IL-37 best predicting TB. Alleles and genotypes of IL37 gene SNPs were given as number and percentage frequency. Hardy–Weinberg equilibrium (HWE) analysis of genotype frequencies was performed using Pearson Chi-square test. Direct-gene counting method was used to estimate allele frequencies of SNPs. Significant differences between patients and controls regarding allele and genotype frequencies were assessed by two-tailed Fisher exact probability (p). Logistic regression analysis was used to estimate odds ratio (OR) and confidence interval (CI) for each SNP. A p-value $\leq$0.05 was considered significant after applying Bonferroni correction. The statistical package IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.) was used to perform these analyses. Haplotypes between IL37 gene SNPs were constructed using SHEsis software, which was also used to determine linkage disequilibrium (LD) between SNPs. The LD coefficient (D′) was estimated to define LD. The D' value has a range between 0 (no LD) and 1.0 (complete LD).[26]

3. Results

3.1. Serum level of IL-37

Median level of IL-37 was markedly increased in serum of TB patients compared to healthy controls (325.0 *vs.* 169.1 pg/mL; $p < 0.001$). This increase was universally determined in subgroups of patients distributed according to gender, age groups, and clinical type of disease, while no significant differences were found between the subgroups in patients or controls (Table 1). Analysis of ROC curve confirmed these findings and IL-37 occupied a very good AUC, which was 0.816 (95% CI = 0.744–0.888; $p < 0.001$). At a cut-off value of 185.6 pg/mL, the sensitivity and specificity of IL-37 were 81.0 and 82.3%, respectively (Fig. 1).

3.2. SNPs of IL37 gene

A region of 877 bp of *IL37* gene promoter was DNA-sequenced in order to determine some SNPs in the region. It was found that the region harbored many SNPs, but SNPs that had minor allele frequency greater than 5% in TB patients or controls were only nine. They were rs2466449 G/A, rs2466450 A/G, rs2723168 G/A, rs3811042 G/A, rs3811045 T/C, rs3811046 G/T, rs3811047 A/G, rs3811048 G/A and rs200782323 G/A. A representative chromatogram of SNP rs3811042 sequences is given in Fig. 2. Analyses of HWE revealed that genotype frequencies of most SNPs in TB patients and controls were in a good agreement with HWE. Two SNPs were exceptions. Genotype

frequencies of SNP rs2466449 were significantly deviated from HWE in TB patients (p < 0.001). The second SNP was rs3811048, and the significant deviation of genotype frequencies involved patients and controls ($p < 0.001$) (Table 2).

Genotype frequencies of the nine *IL37* gene SNPs were compared between TB patients and controls. Only two SNPs showed a significant association with TB. The GA genotype of rs2723168 SNP showed a significantly increased frequency in patients compared to controls (12.4 *vs.* 0.0%; OR = 23.21; $p = 0.009$). The second SNP was rs3811048, and frequency of GG genotype was significantly decreased in patients compared to controls (17.1 *vs.* 31.6%; OR = 0.34; $p = 0.036$). However, when the Bonferroni correction was applied, both *p*-values did not attend any significant level ($pc = 0.135$ and 0.54, respectively) (Table 2).

At the allele level, two significant associations were encountered. Frequency of A allele (rs2723168) was significantly increased in TB patients compared to controls (6.2 *vs.* 0.0%; OR = 21.67; $p = 0.009$). On the contrary, the allele G (rs3811048) showed a significantly decreased frequency in TB patients (25.2 *vs.* 44.9%; OR = 0.41; $p < 0.001$). When the *p*-value was corrected, only the rs3811048 G allele maintained a significant level ($pc = 0.001$) (Table 3).

To determine whether the alleles of *IL37* gene SNPs had an influence on TB clinical type, allele frequencies of the nine SNPs were explored in the three groups of PTB (active, MDR and relapse). Statistical analyses revealed no significant differences between these frequencies (Table 4).

3.3. *Haplotypes and LD*

SHEsis software was used to estimate haplotype frequencies between alleles of *IL37* gene SNPs in TB patients and controls (in the order: rs2466449, rs2466450, rs2723168, rs3811042, rs3811045, rs3811046, rs3811047, rs3811048 and rs200782323). Only haplotypes having a frequency greater than 3% were recorded. Based on this criterion, it was possible to assign five haplotypes, and three showed significant differences between patients and controls. Frequency of haplotype A-A-G-A-C-T-G-A-G (0.331 *vs.* 0.213; OR = 2.10; $p = 0.015$) was significantly increased in TB patients compared to controls. On the contrary, frequencies of haplotypes A-A-G-A-C-T-G-G-G (0.029 *vs.*

Table 2 – Logistic regression and Hardy–Weinberg equilibrium analyses of *IL37* gene SNP genotypes in tuberculosis patients and controls.

SNP	Genotype	TB (N = 105)		HC (N = 79)		OR	95% CI	*p* (*pc*)
		N	%	N	%			
rs2466449 G/A	AA	92	87.6	76	96.2	Reference		
	AG	10	9.5	3	3.8	2.67	0.71–9.95	0.157 (1.0)
	GG	3	2.9	ND	ND	5.43	0.28–104.73	0.261 (1.0)
	HWE-*p*	**< 0.001**		0.863				
rs2466450 A/G	AA	93	88.6	78	98.7	Reference		
	AG	12	11.4	1	1.3	10.06	1.30–78.12	0.072 (1.0)
	HWE-*p*	0.534		0.954				
rs2723168 G/A	GG	92	87.6	79	100.0	Reference		
	GA	13	12.4	ND	ND	23.21	1.38–389.67	**0.009** (0.135)
	HWE-*p*	0.498		1.000				
rs3811042 G/A	GG	41	39.0	31	39.2	Reference		
	GA	49	46.7	39	49.4	0.95	0.51–1.78	0.873 (1.0)
	AA	15	14.3	9	11.4	1.26	0.49–3.26	0.633 (1.0)
	HWE-*p*	0.953		0.531				
rs3811045 T/C	CC	42	40.0	27	34.2	Reference		
	CT	52	49.5	38	48.1	0.88	0.46–1.67	0.694 (1.0)
	TT	11	10.5	14	17.7	0.51	0.20–1.28	0.148 (1.0)
	HWE-*p*	0.383		0.920				
rs3811046 G/T	TT	42	40.0	23	29.1	Reference		
	TG	51	48.6	41	51.9	0.68	0.35–1.31	0.250 (1.0)
	GG	12	11.4	15	19.0	0.44	0.18–1.09	0.077 (1.0)
	HWE-*p*	0.553		0.664				
rs3811047 A/G	GG	42	40.0	25	31.6	Reference		
	GA	53	50.5	40	50.6	0.79	0.42–1.50	0.469 (1.0)
	AA	10	9.5	14	17.7	0.43	0.16–1.10	0.078 (1.0)
	HWE-*p*	0.247		0.771				
rs3811048 G/A	AA	70	66.7	33	41.8	Reference		
	AG	17	16.2	21	26.6	0.38	0.18–0.82	0.117 (1.0)
	GG	18	17.1	25	31.6	0.34	0.16–0.71	**0.036** (0.54)
	HWE-*p*	**< 0.001**		**< 0.001**				
rs200782323 G/A	GG	98	93.3	69	87.3	Reference		
	GA	7	6.7	10	12.7	0.49	0.18–1.36	0.171 (1.0)
	HWE-*p*	0.723		0.548				

SNP: Single nucleotide polymorphism; TB: Tuberculosis; HC: Healthy controls; HWE: Hardy–Weinberg equilibrium; OR: Odds ratio; CI: Confidence interval; ND: Not detected; *p*: Two-tailed Fisher exact probability (significant *p*-value is indicated in bold); *pc*: Bonferroni correction probability.

Table 3 – Logistic regression analysis of *IL37* gene SNP alleles in tuberculosis patients and controls.

SNP	Allele	TB (N = 105)		HC (N = 79)		OR	95% CI	*p* (*pc*)
		N	%	N	%			
rs2466449 G/A	A	194	92.4	155	98.1	Reference		
	G	16	7.6	3	1.9	4.26	1.22–14.83	0.144 (1.0)
rs2466450 A/G	A	198	94.3	157	99.4	Reference		
	G	12	5.7	1	0.6	9.52	1.23–73.50	0.081 (0.729)
rs2723168 G/A	G	197	93.8	158	100.0	Reference		
	A	13	6.2	ND	ND	21.67	1.29–364.10	**0.009** (0.081)
rs3811042 G/A	G	131	62.4	101	63.9	Reference		
	A	79	37.6	57	36.1	1.07	0.70–1.64	0.827 (1.0)
rs3811045 T/C	C	136	64.8	92	58.2	Reference		
	T	74	35.2	66	41.8	0.76	0.50–1.16	0.233 (1.0)
rs3811046 G/T	T	135	64.3	87	55.1	Reference		
	G	75	35.7	71	44.9	0.68	0.45–1.04	0.085 (0.765)
rs3811047 A/G	G	137	65.2	90	57.0	Reference		
	A	73	34.8	68	43.0	0.71	0.46–1.08	0.129 (1.0)
rs3811048 G/A	A	157	74.8	87	55.1	Reference		
	G	53	25.2	71	44.9	0.41	0.27–0.64	**< 0.001 (0.001)**
rs200782323 G/A	G	203	96.7	148	93.7	Reference		
	A	7	3.3	10	6.3	0.51	0.19–1.37	0.213 (1.0)

SNP: Single nucleotide polymorphism; TB: Tuberculosis; HC: Healthy controls; OR: Odds ratio; CI: Confidence interval; ND: Not detected; *p*: Two-tailed Fisher exact probability (significant *p*-value is indicated in bold); *pc*: Bonferroni correction probability.

0.116; OR = 0.24; $p = 0.01$) and A-A-G-G-T-G-A-G-G (0.140 *vs.* 0.275; OR = 0.45; $p = 0.015$) were significantly decreased in patients (Table 5). The pairwise analysis of LD revealed different values of D' (the LD coefficient) among the nine SNPs. Some SNPs were in a strong LD, while others showed weak or no LD. This profile was different in TB patients and controls. Among patients; for instance, the SNPs rs2723168, rs3811042, rs3811045 and rs3811046 were in a strong LD (D' = 0.99). In contrast these SNPs showed no LD in controls (D' = 0) (Fig. 3).

3.4. *Impact of* IL37 *gene SNP genotypes on IL-37 level*

The final part of these results dealt with the influence of *IL37* gene SNP genotypes on serum level of IL-37 in TB patients and controls. Among the patients, some variations were observed, but no significant level was attended. Among the controls, four SNPs were significantly associated with variations in serum level of IL-37; rs3811042, rs3811045, rs3811046 and rs3811047 (Table 6).

Table 4 – Allele frequencies of *IL37* gene SNP in tuberculosis patients (active, MDR and relapse).

SNP	Allele	TB patients (N = 105)						*p*
		Active (N = 37)		MDR (N = 41)		Relapse (N = 27)		
		N	%	N	%	N	%	
rs2466449 G/A	A	65	87.8	77	93.9	52	96.3	0.164
	G	9	12.2	5	6.1	2	3.7	
rs2466450 A/G	A	70	94.6	78	95.1	50	92.6	0.816
	G	4	5.4	4	4.9	4	7.4	
rs2723168 G/A	G	69	93.2	78	95.1	50	92.6	0.810
	A	5	6.8	4	4.9	4	7.4	
rs3811042 G/A	G	46	62.2	48	58.5	37	68.5	0.500
	A	28	37.8	34	41.5	17	31.5	
rs3811045 T/C	C	45	60.8	58	70.7	33	61.1	0.350
	T	29	39.2	24	29.3	21	38.9	
rs3811046 G/T	T	43	58.1	58	70.7	34	63.0	0.252
	G	31	41.9	24	29.3	20	37.0	
rs3811047 A/G	G	45	60.8	58	70.7	34	63.0	0.396
	A	29	39.2	24	29.3	20	37.0	
rs3811048 G/A	A	53	71.6	67	81.7	37	68.5	0.165
	G	21	28.4	15	18.3	17	31.5	
rs200782323 G/A	G	73	98.6	78	95.1	52	96.3	0.465
	A	1	1.4	4	4.9	2	3.7	

SNP: Single nucleotide polymorphism; TB: Tuberculosis; MDR: Multi-drug resistance; *p*: Pearson Chi-square probability.

Table 5 – Estimated haplotype frequencies of *IL37* gene SNPs (in order: rs2466449, rs2466450, rs2723168, rs3811042, rs3811045, rs3811046, rs3811047, rs3811048 and rs200782323) in tuberculosis patients and controls.

Haplotype	TB patients (N = 105)		HC (N = 79)		OR	95% CI	*p*
	N	Frequency	N	Frequency			
A-A-G-A-C-T-G-A-G	69.46	0.331	33.63	0.213	2.10	1.28–3.43	**0.015**
A-A-G-A-C-T-G-G-G	6.18	0.029	18.40	0.116	0.24	0.01–0.62	**0.010**
A-A-G-G-C-T-G-A-G	49.38	0.235	23.66	0.150	1.94	1.12–3.37	0.085
A-A-G-G-T-G-A-A-G	18.59	0.089	19.62	0.124	0.73	0.37–1.44	0.363
A-A-G-G-T-G-A-G-G	29.39	0.140	43.37	0.275	0.45	0.26–0.77	**0.015**

TB: Tuberculosis; HC: Healthy controls; OR: Odds ratio; CI: Confidence interval; *p*: Two-tailed Fisher exact probability (significant *p*-value is indicated in bold).

4. Discussion

IL-37 showed up-regulated levels in serum of TB patients irrespective of their gender, age or type of disease. Consistent with these findings, it has been demonstrated for the first time in 2015 that IL-37 serum level was significantly elevated in 25 Chinese patients with active TB compared to 25 healthy donors or to the same patients after six months of anti-TB therapy (rifampicin, isoniazid, pyrazinamide and ethambutol). After therapy, the level of IL-35 was restored to the level of healthy donors. These findings were confirmed, when mRNA expression of *IL37* gene in PBMCs was determined. The *IL37* mRNA expression was significantly higher in active TB patients than in patients after therapy or in healthy donors.[19] In the same year, Zhang and colleagues reported that plasma level of IL-37 was significantly increased in Chinese TB patients compared to healthy controls, and the level was reduced after anti-TB therapy.[20] A further Chinese study reported similar findings, and IL-37 level and its mRNA expression were increased in TB patients compared to controls.[21] In Saudi patients with active TB, IL-37 serum level was significantly higher than in controls.[22] However, a recent Indian study reported that IL-37 level was significantly increased in patients with latent TB compared to patients with active TB, and the latter patients showed a reduced level of IL-37 compared to healthy controls.[27] These findings suggest a role for IL-37 in evolution of TB, and it might be considered as an indicator of recovery, as well as, a new molecular therapeutic target in the therapy of disease.[19–21]

In addition to the elevated serum level of IL-37, two investigations have demonstrated that SNPs of *IL37* gene may influence susceptibility to TB or the IL-37 level.[21,22] These findings motivated us to explore the promoter region of *IL37* gene in order to gain a further understanding of this cytokine in TB. In this study, certain promoter variants (SNPs) of *IL37* gene were proposed to be associated with susceptibility to or protection against this infectious disease. The heterozygous genotype of SNP rs2723168 (GA) was indicated to increase the risk of TB by 23.21-fold. The minor allele of the SNP (allele *A*) was similarly associated with susceptibility to TB (OR = 21.67). On the contrary, the protective effect against TB development of the allele *G* (or the homozygous genotype GG) of the SNP rs3811048 was indicated. Although the *pc*-values of these associations were not significant (with the exception of rs3811048 *G* allele), the results suggest a role for the promoter region of

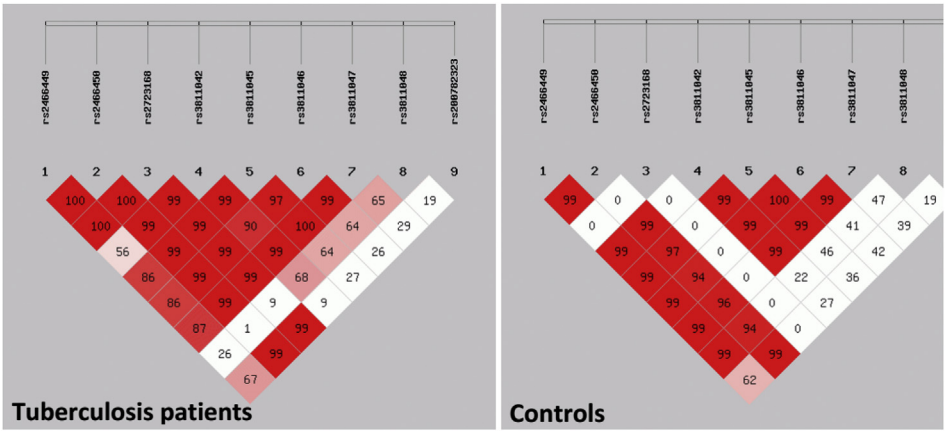

Fig. 3 – Pairwise linkage disequilibrium (LD) map of nine *IL37* gene SNPs (rs2466449, rs2466450, rs2723168, rs3811042, rs3811045, rs3811046, rs3811047, rs3811048 and rs200782323) genotyped using SHEsis software in tuberculosis patients (left) and healthy controls (right). The LD between any pair of SNPs is expressed as D′ values (normalized LD measure or D) multiplied by 100; D′ is calculated as D divided by the theoretical maximum for the observed allele frequencies. Values approaching zero indicate no LD, and those approaching 100 indicate complete LD. The square colored red represent varying degrees of LD and darker shades indicate stronger LD.

Table 6 – Median levels of IL-37 in tuberculosis patients and controls stratified according to genotypes of *IL37* gene SNPs.

SNP	Genotype	IL-37 median (IQR: 25–75%); pg/ml	
		TB (N = 105)	HC (N = 79)
rs2466449 G/A	AA	322.6 (219.5–433.4)	169.4 (158.5–180.1)
	AG	446.8 (311.6–480.3)	164.4 (162.8–177.0)
	GG	116.8 (114.3–680.2)	ND
	p	0.086	0.875
rs2466450 A/G	AA	311.6 (215.7–434.1)	169.1 (158.5–178.6)
	AG	429.8 (336.3–454.8)	192.7
	p	0.222	NA
rs2723168 G/A	GG	315.9 (214.5–439.6)	169.1 (158.5–179.8)
	GA	428.6 (325.0–446.1)	ND
	p	0.072	NA
rs3811042 G/A	GG	325.0 (186.1–432.7)	177.6 (168.8–186.9)^{A}
	GA	322.6 (241.3–446.1)	163.5 (147.8–176.9)^{B}
	AA	327.0 (213.2–476.3)	158.5 (146.9–172.3)^{B}
	p	0.903	**0.006**
rs3811045 T/C	CC	291.9 (215.7–410.8)	160.5 (147.1–169.1)^{A}
	CT	381.7 (240.1–467.1)	176.2 (161.1–185.9)^{B}
	TT	325.0 (239.4–424.5)	177.3 (168.8–180.4)^{B}
	p	0.255	**0.006**
rs3811046 G/T	TT	291.9 (215.7–410.8)	158.5 (146.9–167.3)^{A}
	TG	375.0 (238.8–448.0)	176.2 (161.1–185.9)^{B}
	GG	363.1 (274.3–504.0)	177.6 (168.8–185.3)^{B}
	p	0.178	**0.006**
rs3811047 A/G	GG	291.9 (215.7–410.8)	159.5 (147.1–167.3)^{A}
	GA	388.4 (241.3–463.5)	176.6 (161.1–185.9)^{B}
	AA	323.9 (239.4–424.5)	177.3 (168.8–180.4)^{B}
	p	0.271	**0.006**
rs3811048 G/A	AA	305.7 (209.4–445.2)	169.1 (159.5–181.4)
	AG	322.6 (248.9–428.6)	172.9 (161.1–177.9)
	GG	407.9 (309.3–476.4)	164.4 (158.5–177.6)
	p	0.244	0.642
rs200782323 G/A	GG	322.6 (223.3–445.2)	169.7 (158.5–180.4)
	GA	363.7 (289.0–480.3)	167.3 (162.8–175.2)
	p	0.248	0.338

SNP: Single nucleotide polymorphism; TB: Tuberculosis; HC: Healthy controls; IQR: Interquartile range; NA: Not applicable; ND: Not detected; *p*: Mann–Whitney *U* or Kruskal–Wallis test probability (significant *p*-value is indicated in bold). Similar superscript letters indicate no significant difference between medians in columns of each SNP, while different superscript letters indicate significant difference.

IL37 gene in TB etiology. This suggestion was enhanced when nine-locus haplotype analysis of the region was performed (in the order: rs2466449, rs2466450, rs2723168, rs3811042, rs3811045, rs3811046, rs3811047, rs3811048 and rs200782323). The haplotype A-A-G-A-C-T-G-A-G was associated with a high risk of developing TB, while two other haplotypes showed significantly decreased frequencies in TB patients (A-A-G-A-C-T-G-G-G and A-A-G-G-T-G-A-G-G). In addition, some *IL37* gene SNPs influenced the serum level of IL-37. To the best knowledge of investigators, only two previous studies investigated *IL37* gene SNPs in TB. In the first, five SNPs were assessed in Saudi TB patients (rs3811046, rs3811047, rs2723176, rs2723186 and rs2723187). Only SNP rs2723176 was significantly associated with susceptibility to disease. The C allele (80 *vs.* 52%; OR = 3.67; 95% CI = 1.89–7.31); $p < 0.001$) and CC genotype (68 vs. 42%; OR = 3.54; 95% = 1.40–8.98); $p = 0.008$) frequencies were significantly increased in patients compared to controls. Further, the C allele of the SNP was associated with a high serum level of IL-37.[22] The second study investigated three SNPs of *IL37* gene in Chinese TB patients (rs3811047, rs2723176 and rs6717710), and only rs3811047 SNP was associated with susceptibility to TB.[21] In fact, neither allele nor genotype frequencies of the SNP rs3811047 showed significant differences between patients and controls of the current study. However, although the findings of both studies were inconsistent with ours, the data indicated that *IL37* gene variants are involved in TB development. However, three studies are not sufficient to understand the precise role of *IL37* gene SNPs in the development of TB, and further studies are warranted.

As presented earlier in this discussion, two SNPs of *IL37* gene may be of importance in etiology of PTB (rs2723168 and rs3811048). The SNP rs2723168 appeared in two publications. In the first, the association with systemic juvenile idiopathic arthritis was investigated in English patients,[28] while in the second publication, it was investigated in Saudi patients with hepatitis B virus infection.[29] In both publications, no significant associations were found. The SNP rs3811048 has not been investigated, but a SNP having LD with it (rs3811047) has been considered a marker of disease activity in Egyptian patients with rheumatoid arthritis.[30]

Together, these data suggest a role of IL-37 in etiopathogenesis of TB. This role may involve the circulating IL-37 and SNPs in the promoter region of *IL37* gene. The first role may be mediated through immunological functions of IL-37,

particularly those related to inhibiting innate and adaptive immune responses as well as inflammatory reactions. In this context, IL-37 has been proposed to exert pivotal effects in antibacterial responses including *M. tuberculosis*.[14] These effects may be influenced by SNPs in *IL37* gene through their impact on IL-37 production or may be associated with genetic susceptibility to TB.[20–22] Regarding the SNPs of the *IL37* gene in this study, the results should be interpreted with caution. The sample size of TB patients and controls may limit the significance of the observed associations. Further, the rs3811048 SNP genotype frequencies were incompatible with HWE, and this bias might be due to the effect of sample size. Therefore, the current evidence is not well elaborated to understand the role of IL-37 in etiopathogenesis of TB, and further studies are required, especially those based on larger samples of patients and controls.

5. Conclusions

IL-37 was up-regulated in the serum of TB patients irrespective of their gender, age or clinical type of disease. SNPs in the promoter region of *IL37* gene were proposed to be associated with susceptibility to TB.

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Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Venketaraman V, Kaushal D, Saviola B. Mycobacterium tuberculosis. *J Immunol Res*. 2015;2015:857598. https://doi.org/10.1155/2015/857598.
2. MacNeil A, Glaziou P, Sismanidis C, Date A, Maloney S, Floyd K. Global epidemiology of tuberculosis and progress toward meeting global targets — worldwide, 2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(11):281–285. https://doi.org/10.15585/mmwr.mm6911a2.
3. Ali ZA, Al-Obaidi MJ, Sameer FO, et al. Epidemiological profile of tuberculosis in Iraq during 2011–2018. *Indian J Tuberc*. January 2021. https://doi.org/10.1016/j.ijtb.2021.01.003.
4. Barber-Mayer KD, Barber DL. Innate and adaptive cellular immune responses to Mycobacterium tuberculosis infection. *Cold Spring Harb Perspect Med*. 2015;5(12), a018424. https://doi.org/10.1101/cshperspect.a018424.
5. Zuiga J, Torres-García D, Santos-Mendoza T, Rodriguez-Reyna TS, Granados J, Yunis EJ. Cellular and humoral mechanisms involved in the control of tuberculosis. *Clin Dev Immunol*. 2012;2012. https://doi.org/10.1155/2012/193923.
6. Romero-Adrian TB, Leal-Montiel J, Fernández G, Valecillo A. Role of cytokines and other factors involved in the Mycobacterium tuberculosis infection. *World J Immunol*. 2015;5(1):16. https://doi.org/10.5411/wji.v5.i1.16.
7. Amelio P, Portevin D, Reither K, et al. Mixed Th1 and Th2 Mycobacterium tuberculosis-specific CD4 T cell responses in patients with active pulmonary tuberculosis from Tanzania. *PLoS Negl Trop Dis*. 2017;11(7), e0005817. https://doi.org/10.1371/journal.pntd.0005817.
8. Zeng G, Zhang G, Chen X. Th1 cytokines, true functional signatures for protective immunity against TB? *Cell Mol Immunol*. 2018;15(3):206–215. https://doi.org/10.1038/cmi.2017.113.
9. Arrigucci R, Lakehal K, Vir P, et al. Active tuberculosis is characterized by highly differentiated effector memory Th1 cells. *Front Immunol*. 2018;9(SEP):2127. https://doi.org/10.3389/fimmu.2018.02127.
10. Kumar NP, Moideen K, Banurekha VV, Nair D, Babu S. Plasma proinflammatory cytokines are markers of disease severity and bacterial burden in pulmonary tuberculosis. *Open Forum Infect Dis*. 2019;6(7). https://doi.org/10.1093/ofid/ofz257.
11. Holdsworth SR, Can PY. Cytokines: names and numbers you should care about. *Clin J Am Soc Nephrol*. 2015;10(12):2243–2254. https://doi.org/10.2215/CJN.07590714.
12. Domingo-Gonzalez R, Prince O, Cooper A, Khader SA. Cytokines and chemokines in Mycobacterium tuberculosis infection. *Microbiol Spectr*. 2016;4(5). https://doi.org/10.1128/microbiolspec.tbtb2-0018-2016.
13. Quirk S, Agrawal DK. Immunobiology of IL-37: mechanism of action and clinical perspectives. *Expet Rev Clin Immunol*. 2014;10(12):1703–1709. https://doi.org/10.1586/1744666X.2014.971014.
14. Wang L, Quan Y, Yue Y, Heng X, Che F. Interleukin-37: a crucial cytokine with multiple roles in disease and potentially clinical therapy (Review). *Oncol Lett*. 2018;15(4):4711–4719. https://doi.org/10.3892/ol.2018.7982.
15. Nold MF, Nold-Petry CA, Zepp JA, Palmer BE, Bufler P, Dinarello CA. IL-37 is a fundamental inhibitor of innate immunity. *Nat Immunol*. 2010;11(11):1014–1022. https://doi.org/10.1038/ni.1944.
16. Jia H, Liu J, Han B. Reviews of interleukin-37: functions, receptors, and roles in diseases. *BioMed Res Int*. 2018;2018. https://doi.org/10.1155/2018/3058640.
17. Liu M, Guo S, Hibbert JM, et al. CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications. *Cytokine Growth Factor Rev*. 2011;22(3):121–130. https://doi.org/10.1016/j.cytogfr.2011.06.001.
18. Allam G, Gaber AM, Othman SI, Abdel-Moneim A. The potential role of interleukin-37 in infectious diseases: role of IL-37 in HIV-1, viral myocarditis, HCV, HBV, tuberculosis, leprosy, pneumonia, listeria, aspergillosis, candidiasis, and eumycetoma infection. *Int Rev Immunol*. 2020;39(1):3–10. https://doi.org/10.1080/08830185.2019.1677644.
19. Huang Z, Gao C, Chi X, et al. IL-37 expression is upregulated in patients with tuberculosis and induces macrophages towards an M2-like phenotype. *Scand J Immunol*. 2015;82(4):370–379. https://doi.org/10.1111/sji.12326.
20. Zhang J, Liu G, Zeng J, et al. Clinical detection and significance of plasma IL-37 in patients with active pulmonary tuberculosis. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi*. 2015;31(4):520–523. https://pubmed.ncbi.nlm.nih.gov/25854573/. Accessed October 30, 2020.
21. Liu H, Zheng R, Wang P, et al. IL-37 confers protection against mycobacterial infection involving suppressing inflammation

and modulating t cell activation. *PLos One*. 2017;12(1), e0169922. https://doi.org/10.1371/journal.pone.0169922.
22. Allam G, Mohamed IAA, Alswat KA, et al. Association of IL-37 gene polymorphisms with susceptibility to tuberculosis in Saudi subjects. *Microbiol Immunol*. 2016;60(11):778–786. https://doi.org/10.1111/1348-0421.12444.
23. Ryu YJ. Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms. *Tuberc Respir Dis (Seoul)*. 2015;78(2):64–71. https://doi.org/10.4046/trd.2015.78.2.64.
24. Kearse M, Moir R, Wilson A, et al. Geneious Basic: an integrated and extendable desktop software platform for the organization and analysis of sequence data. *Bioinformatics*. 2012;28(12):1647–1649. https://doi.org/10.1093/bioinformatics/bts199.
25. Yu B, Zhang C. In silico PCR analysis. In: *Methods in Molecular Biology (Clifton, N.J.)*. vol. 760. 2011:91–107. https://doi.org/10.1007/978-1-61779-176-5_6.
26. Yong Y, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res*. 2005;15(2):97–98. https://doi.org/10.1038/sj.cr.7290272.
27. Moideen K, Kumar NP, Bethunaickan R, Banurekha VV, Nair D, Babu S. Heightened systemic levels of anti-inflammatory cytokines in pulmonary tuberculosis and alterations following anti-tuberculosis treatment. *Cytokine*. 2020;127:154929. https://doi.org/10.1016/j.cyto.2019.154929.
28. Stock C. *The Interleukin 1 Gene Family in Systemic Juvenile Idiopathic Arthritis*. 2011.
29. Al-Anazi MR, Matou-Nasri S, Al-Qahtani AA, et al. Association between IL-37 gene polymorphisms and risk of HBV-related liver disease in a Saudi Arabian population. *Sci Rep*. 2019;9(1):1–14. https://doi.org/10.1038/s41598-019-42808-4.
30. El-Sayed EH, Saleh MH, Al-Shahaly MH, Toraih EA, Fathy A. IL-37 gene variant (rs3811047): a marker of disease activity in rheumatoid arthritis: a pilot study. *Autoimmunity*. 2018;51(8):378–385. https://doi.org/10.1080/08916934.2018.1551373.

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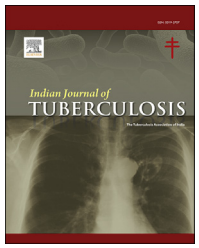

Original article

Impact of dietary counselling on the nutritional status and quality of life among pulmonary tuberculosis patients - A randomized control trial

V.G. Sharan kumar [a,*], R. Pajanivel [a], Abhijit V. Boratne [b], R. Vimal Raj [a]

[a] Department of Pulmonary Medicine, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth – Deemed to Be University, Pillayarkuppam, Puducherry, 607402, India

[b] Department of Community Medicine, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth – Deemed to Be University, Pillayarkuppam, Puducherry, 607402, India

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ABSTRACT

Background & aim: Undernutrition and TB have a bidirectional relationship, which is especially relevant in the Indian context. Undernutrition is an established risk factor for the progression of latent TB infection to active TB. Undernutrition at the population level contributes to an estimated 55% of annual TB incidence in India. TB leads to weight loss, wasting, and worsening of nutritional status. Hence, the present study aimed to determine the impact of dietary counselling on the nutritional status and the health-related quality of life of PTB patients.

Materials & method: This was an interventional study (randomized controlled trial) that involved patients with PTB. 46 patients (23 patients as experimental and 23 patients as a control group) were enrolled in the study from June 2019 to February 2020 and they were divided into 2 categories based on BMI (underweight and normal weight). The special dietary counselling was given to the experimental group patients and the normal protocol was followed with the control group. The patients were followed up, till completion of treatment i.e., 6 months from enrolment.

Results: In our study, nearly half of the patients were underweight and DM was the predominant comorbidity. The BMI increased after dietary counselling in the experimental group than the control group ($P = 0.0053$) in underweight individuals. Total protein ($P = 0.0025$), and serum albumin ($P = 0.0048$) levels were found to be significantly improved in the experimental group. SGRQ symptom score ($P = 0.0036$) has significantly reduced in the experimental group in underweight individuals than the control group.

Conclusion: Personalized dietary counselling was found to have a positive impact on BMI, total protein, and albumin levels in the experimental group, especially in underweight individuals. Besides, the quality of life measured using SGRQ showed that symptom score were also significantly reduced in the experimental group than the control group.

* *Corresponding author.*
E-mail address: drsharankumar92@gmail.com (V.G. Sharan kumar).

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1. Introduction

Tuberculosis (TB) is a chronic multi-systemic disease that results from infection with *Mycobacterium tuberculosis*.[1] Tuberculosis is usually typified by the pulmonary disease—Pulmonary Tuberculosis (PTB) which accounts for about 90% of cases of TB.[2] Extra-pulmonary sites of infection are common in the lymph node; spine (Potts disease); central nervous system, where it can cause meningitis, tuberculoma; gastro-intestinal system, with ileocecal involvement in 80–90% of such cases. The World Health Organization (WHO) declared TB as a global public health emergency in 1993.[3] In 2018, an estimated 10 million people developed TB and out of whom, about 1.2 million were Human Immunodeficiency Virus (HIV) positive. In the same year, 1.4 million died from TB, including 400,000 deaths among those with HIV co-infection.

Patients with active TB are more likely to be emaciated[4] and have a low body mass index (BMI), with a value less than 18.5 kg/m^2 being considered as an index of undernutrition,[5] An Indian study reports that TB patients are 11 times more likely to have a BMI <18.5 kg/m^2 than the control group.[6] Undernutrition is a risk factor for the increased severity of TB and unfavourable treatment outcomes, including delayed TB recovery/TB relapse and mortality.[7–9] Previous studies have shown that TB patients who have received treatment, adequate diet and supplementary nutritional care have significant early nutritional changes in their BMI recovery, which is related to the obvious immune system improvement and treatment success outcomes.[10–12] Quality of life (QOL) is a vital measure in the assessment of population well-being and health status which is measured using Saint George Respiratory Questionnaire (SGRQ).[13] Health is one of the domains in quality of life and the concept of health-related quality of life (HRQOL) is a multidimensional construct that broadly describes how well individuals function in their daily lives and their perception of well-being in physical, psychological, and social aspects, thus encompassing those aspects of overall quality of life that directly affect health.[14] It has been employed both in cross-sectional and analytic studies and is increasingly being used as an endpoint in clinical trials, particularly as it relates to chronic health-related conditions.[15–17] However, beyond the diagnosis of the physical disease, the impact of a chronic illness like TB on an individual patient is often far-reaching, affecting not only his/her physical health but also psychological, economic and social components of health.[18–20]

2. Materials & method

The present study was an interventional study (randomized controlled trial). The study has been registered in CTRI (clinical trials registry India). Registration number for the trial is CTRI/2019/06/019511. This study was conducted in the Department of Pulmonary Medicine, from a tertiary care hospital in Pondicherry from June 2019 to August 2020, after getting clearance from the Institutional Human Ethics Committee. The minimum sample size for the study was 46 patients, with 23 patients as control group and 23 patients in the experimental group. Patients were enrolled after fulfilling the inclusion criteria (Patients diagnosed as a case of PTB according to RNTCP (Revised national tuberculosis control programme guidelines). All willing consecutive patients satisfying inclusion criteria were enrolled. Patients not willing for the study, Age <18 years, Patients with Extrapulmonary Tuberculosis, Patients with chronic kidney disease, Patients with HIV were excluded from the study. Eligible patients were allocated randomly to either Personalized dietary counselling (PDC) group or Standard dietary counselling (SDC) group by computer generated simple random sequence method.

For all the enrolled patients, baseline demographic variables like age, sex, socio-economic status were recorded. Body mass index (BMI), serum total protein and albumin levels, dietary intake by 24 h recall method was done. SGRQ questionnaire comprising of symptom, activity, impact domains & total score was used for assessing the quality of life.

Personalized dietary counselling group was provided dietary counselling with the help of locally available, culturally acceptable foods according to their socio-economic status with the help of diet chart by the nutritionist. The **Standard dietary counselling group** patients were advised to take high protein diet, where the diet was not charted by the nutritionist.

Counselling was given to patients at the initiation of treatment, and at the end of IP phase and the patients were followed up till the completion of treatment over phone/in-person and all the baseline parameters were recorded. Patient's dietary intake was noted by 24 h recall method during each visit.

All patients were given the same anti-tuberculosis treatment according to RNTCP guidelines.

The data was entered in Microsoft excel sheet. Data was exported to Medcalc 19.2.6 for further processing. Continuous variables were expressed as mean ± standard deviation and the statistical significance of mean differences was compared using paired t-test across cohorts. All values were considered statistically significant if the *P*-value was <0.05.

3. Results

The present study enrolled 46 TB patients with a mean age of 49.16 ± 15 years (Ranged from 18 to 81 years). The study had predominantly male subjects (67.34%). The socioeconomic status of the study participants were almost similar, however, the lower socioeconomic class was slightly higher (51.11%). While more than half of the patients did not have any co-morbidities, 24.44% had diabetes mellitus (DM) and 11.11% had DM with systemic hypertension (SHTN) (Table 1).

BMI was increased in the experimental group (21.91 ± 3.93) compared to the control group (20.85 ± 2.90). However, the increment was not statistically significant. Similar kinds of

Table 1 – Baseline characteristics of the study participants.

Baseline characteristics	Overall N = 46	Control N = 23	Experimental N = 23
Age in years	49.16 ± 15.10	51.57 ± 16.30	46.43 ± 13.44
M:F	31:15	18:5	13:10
Height in cm	158.18 ± 8.84	157.80 ± 8.03	158.60 ± 9.83
Weight in kg	48.48 ± 9.33	47.07 ± 6.46	50.08 ± 11.73
Smoking	20 (40.81)	11 (47.82)	9 (39.11)
Socio-economic Status			
Lower socioeconomic class	24 (51.11)	15 (65.21)	8 (34.78)
Middle socioeconomic class	22 (48.88)	08 (34.78)	15 (65.21)
Co-morbidities			
DM	11 (24.44)	7 (30.43)	4 (17.39)
DM with SHTN	5 (11.11)	3 (13.04)	2 (8.69)
Coronary artery disease (CAD)	1 (2.22)	1 (4.34)	–
Hypothyroidism	1 (2.22)	–	1 (4.34)
Nil	28 (60)	12 (52.17)	16 (69.56)

results were obtained with protein, albumin, dietary intake of carbohydrates, proteins and fats. The percentage of improvement was higher in the experimental group than in the control group. The SGRQ profile was also significantly decreased in both the control and experimental groups. However, the percentage of decrease in the symptom domain, activity domain, impact domain, and total score was higher in the experimental group than the control group (Table 2).

The study population was further divided into two groups based on their BMI. The BMI <18.5 was considered as underweight and >18.5–24.9 considered as normal weight (Table 3).

In the underweight category, the BMI improved to normal in the experimental group than the control group after dietary counselling. The total protein and albumin concentration also increased significantly in the experimental group than the control group. The dietary intake of carbohydrates and protein was increased after dietary counselling in both the control and experimental group. However, there was a difference that in the experimental group after counselling the percentage of intake of carbohydrates and proteins was higher, but it was not statistically significant. Whereas in the intake of fat, the experimental group had significantly higher intake than the control group. After dietary counselling, the intake of fat was increased significantly in the experimental group which could be the reason for the increased BMI. In this study, the health-related quality of life of Pulmonary Tuberculosis patients was assessed using the St. George questionnaire. The symptom and activity domain were significantly reduced in the experimental group than the control group. The impact and total domains have equally differed significantly between the experimental and control groups.

In the Normal weight category, the dietary intake of carbohydrates and fat was increased after dietary counselling in both the control and experimental group. However, there was a difference that in the experimental group after counselling the percentage of intake of carbohydrates and fat was higher, but it was not statistically significant. Whereas in the intake of protein, the experimental group had significantly higher than the control group.

The health-related quality of life of Pulmonary Tuberculosis patients was assessed using the St. George questionnaire. The four domains such as symptoms, activity, impact and total were shown a significant reduction in both the control and experimental group. The four domains have equally differed significantly between the experimental and control groups.

Table 2 – The study variables categorised based on experimental and control groups.

Variables	Control (N = 23)		*P* value	Experimental (N = 23)		*P* value
	Pre	Post		Pre	Post	
Age (years)	51.57 ± 16			46.43 ± 13		0.2381
BMI (kg/m^2)	19.07 ± 2.67	20.85 ± 2.90	**<0.0001**	19.72 ± 4.04	21.91 ± 3.93	**<0.0001**
Total Protein (g/l)	6.72 ± 0.73	7.16 ± 0.55	**<0.0001**	6.59 ± 0.70	7.23 ± 0.67	**<0.0001**
Albumin (g/l)	3.40 ± 0.39	3.67 ± 0.35	**<0.0001**	3.46 ± 0.40	3.78 ± 0.41	**<0.0001**
Dietary Intake						
Carbohydrates (Kcal)	1451.92 ± 171.16	1655.76 ± 194.07	**<0.0001**	1521.73 ± 138.02	1766.08 ± 162.50	**<0.0001**
Proteins (gms)	38.30 ± 7.93	42.03 ± 6.93	**<0.0001**	39.89 ± 6.99	45.52 ± 7.65	**<0.0001**
Fat(gms)	42.23 ± 5.96	46.69 ± 4.73	**<0.0001**	41.17 ± 7.49	47.43 ± 5.75	**<0.0001**
SGRQ						
Symptom	35.53 ± 15.10	22.25 ± 14.29	**<0.0001**	33.90 ± 20.37	22.17 ± 18.64	**<0.0001**
Activity	39.96 ± 28.63	26.65 ± 21.20	**0.0001**	37.63 ± 28.22	25.29 ± 22.38	**0.0003**
Impact	39.04 ± 23.72	20.05 ± 20.32	**<0.0001**	31.67 ± 26.31	16.12 ± 24.80	**0.0001**
Total	39.08 ± 21.66	22.43 ± 18.27	**<0.0001**	33.70 ± 23.37	19.95 ± 21.98	**<0.0001**

P value <0.001 is considered as significant.

Table 3 – Study variable: Analysis based on BMI Categories.

Variables	Underweight						Normal weight					
	Control (N = 9)			Experimental (N = 10)			Control (N = 14)			Experimental (N = 13)		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
Age (years)	42.75 ± 20.16			42.22 ± 18.21			55.23 ± 13.40			48.69 ± 9.24		
BMI (kg/m^2)	15.84 ± 0.90	17.64 ± 1.02	**<0.0001**	16.06 ± 1.11	18.96 ± 2.70	**0.0053**	20.42 ± 1.76	22.50 ± 2.07	**<0.0001**	22.30 ± 3.45	24.03 ± 3.45	**<0.0001**
Total Protein (g/dl)	6.55 ± 0.49	7 ± 0.46	**0.0155**	6.87 ± 0.70	7.37 ± 0.58	**0.0025**	6.4 ± 0.68	6.96 ± 0.7	**<0.0001**	6.81 ± 0.84	7.25 ± 0.60	**0.0006**
Albumin (g/dl)	3.4 ± 0.42	3.63 ± 0.26	**0.0209**	3.41 ± 0.55	3.72 ± 0.45	**0.0048**	3.40 ± 0.39	3.69 ± 0.40	**0.0008**	3.5 ± 0.30	3.77 ± 0.35	**0.0029**
Dietary Intake												
Carbohydrate (Kcal)	1375 ± 138.87	1556.25 ± 163.52	**0.0001**	1522.22 ± 139.44	1766.66 ± 173.20	**0.0006**	1491.17 ± 180.48	1700 ± 200	**<0.0001**	1538.46 ± 132.52	1770.76 ± 167.40	**<0.0001**
Protein (gms)	31.12 ± 2.90	35.5 ± 2.97	**<0.0001**	36.22 ± 5.86	41.11 ± 7.28	**0.0037**	42.05 ± 7.18	45.35 ± 6.09	**0.0012**	43.19 ± 6.04	48.84 ± 6.65	**<0.0001**
Fat (gms)	40.5 ± 4.50	44.25 ± 2.71	**0.0112**	40.22 ± 5.51	46.77 ± 6.15	**<0.0001**	43.76 ± 5.78	48.11 ± 5.03	**0.0001**	43.07 ± 7.51	48.61 ± 5.10	**0.0032**
SGRQ												
Symptom	32.49 ± 15.22	27.10 ± 16.80	**0.0074**	33.89 ± 16.57	21.28 ± 11.98	**0.0036**	37.28 ± 15.66	20.08 ± 13.37	**<0.0001**	33.13 ± 23.85	25.50 ± 23.23	**0.0010**
Activity	37.22 ± 22.35	26.52 ± 21.37	**0.0275**	36.24 ± 28.63	22.12 ± 19.33	**0.0163**	43.17 ± 31.32	27.86 ± 21.84	**0.0017**	39.20 ± 30.06	27.13 ± 25.62	**0.0106**
Impact	43.12 ± 24.71	24.51 ± 20.07	**0.0026**	32.06 ± 26.30	17.77 ± 26.88	**0.0434**	37.26 ± 24.49	18.26 ± 21.31	**0.0002**	31.93 ± 28.35	14.88 ± 25.34	**0.0014**
Total	40.83 ± 22.08	25.62 ± 18.57	**0.0007**	33.21 ± 23.14	19.67 ± 20.68	**0.0118**	39 ± 22.55	21.46 ± 18.96	**<0.0001**	34.34 ± 25.35	19.93 ± 24.50	**0.0004**

P value <0.001 is considered as significant.

4. Discussion

TB is a major worldwide infectious disease. Under-nutrition is highly prevalent among TB patients with the relationship between TB and nutrition has long been recognized. TB causes weight loss and in turn being underweight acts as the risk factor for developing active TB.[4,7,21] WHO indicated that undernutrition at the time of diagnosis of active TB is a predictor of increased risk of death and TB relapse.[22] Therefore, nutritional counselling and support have played a prominent role in the prevention and treatment of TB.

Our study shows that, according to the required dietary allowance (RDA), nearly half of TB patients do not consume enough calories, the proportion of underweight during the registration period being 42.33%. In a study conducted in central India,[9] it was observed that >85% of TB patients were underweight at baseline. In contrast, studies conducted in other countries/regions like Ghana,[23] Malawi[24] & Tanzania[25] showed 51%,57% and 58% of the study population to be underweight during initiation of treatment respectively, while 70.6% were underweight in a Brazilian study.[26] This may be due to differences in sample size and research settings.

The prevalence of comorbidities was 40%, among which DM was the most common followed by both DM & SHTN, which was similar to studies conducted in other parts of India, the annual number of TB cases among diabetic patients increases to 46%.[27]

Different studies in Indonesia,[28] Britain,[29] and Japan,[30] found that the nutritional status of patients with active TB was significantly lower than that of healthy controls. TB may be associated with more severe malnutrition than other chronic diseases. A study in Uganda showed that malnutrition was a common disease in adults with TB.[31] In studies conducted in other parts of India, patients with TB had a BMI <18.5 kg/m^2, mid-arm circumference was<24 cms and serum albumin levels were also low at baseline[6,32] The present study results corresponded with the above-mentioned study results in which serum total protein and albumin were lower in both control and experimental group before dietary counselling. After personalized dietary counselling, the experimental group had significant improvement especially in underweight category ($P < 0.005$).

Paton et al[33] conducted a nutritional support study in Singapore that randomized 36 patients who recently started anti-TB drug treatment and a high energy-protein supplement (600 900 kcal/d, 25–37.5 gm protein/d) for six weeks compared with a control TB group not receiving the supplement. All participants were given nutrition counselling to correct imbalances noted in reported dietary intake. Food intake was assessed via recall and was reported to not differ between groups at baseline. At six weeks, the subjects in the nutrition supplement group had a significant increase in body weight and lean mass compared to the control group (2.6 ± 1.8 kgs vs. 0.8 ± 0.9 kg, $p = 0.001$) & (1.2 ± 0.9 vs. 0.04 ± 1.3 kg, $p = 0.006$). Fat mass increased in both groups. Besides, there was a significant increase in hand grip strength in the supplement group. In our study, both underweight and normal-weight group showed significant improvements in BMI ($P < 0.05$). However, the underweight group after PDC significantly

improved their fat intake (P < 0.0001), which was similar with the above study findings.

Pasipanodya et al[34] used the Saint George Respiratory Questionnaire (SGRQ) in 100 patients with PTB, and showed a mean total SGRQ score of 23.5. In all the available literature, the average SGRQ total score beyond which quality of life was considered impaired was not clear. Maguire et al[35] described the change in health status of 115 Indonesian smear positive TB subjects by using a revised version of SGRQ, with an average of 41.9 (symptom score), 50.8 (activity score), 43.4 (impact score) and a total score of 45.4 points. After 2 months of treatment, improvement by a minimum of 4 points was recorded. Similarly in our study, when TB was diagnosed, it showed an average SGRQ score of 33.90 (symptom domain), 37.63 (activity domain), 31.67 (impact domain) and the total score was 33.70 respectively and the same decreased PDC group.

The limitations of the study include 1) Information regarding health conditions was collected by self-reported questionnaires, which may not be accurate for the items measuring subjective feelings, such as anxiety. 2) The present study did not collect information on smoking index and the duration of alcohol consumption, which may have been the confounding factors for undernutrition. 3) As it is a single centre study, the study results could not be extrapolated to various ethnic groups.

5. Conclusion

In our study, 42.33% of the patients were underweight. DM was the most common comorbidity. Dietary counselling had a commendable impact on the improvement of BMI, total protein, and albumin levels. Besides, the dietary intake improved towards attaining the RDA levels after personalized dietary counselling. The SGRQ showed significant decrease in both the PDC & SDC group. However, SGRQ symptom score of the three domains showed a significant decrease (p < 0.005) in the experimental group after completion of treatment, especially in the underweight individuals.

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Conflicts of interest

The authors have none to declare.

REFERENCES

1. Reddington K, Zumla A, Bates M, et al. SeekTB, a two-stage multiplex real-time-PCR-based method for differentiation of the Mycobacterium tuberculosis complex. *J Clin Microbiol*. 2012 Jul;50(7):2203–2206.
2. Global Tuberculosis Report 2019 [Internet]. [cited 2020 Nov 16]. Available from: https://www.who.int/publications-detail-redirect/global-tuberculosis-report-2019.
3. Nakajima H. Editorial: tuberculosis: a global emergency. *World Health*. 1993 Jul;46(4):3.
4. Gupta KB, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and nutrition. *Lung India*. 2009 Jan 1;26(1):9.
5. World Health Organization. *Global Database on Body Mass Index: BMI Classification*. 2006 [Internet] [cited 2020 Nov 16].
6. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. *Int J Tuberc Lung Dis*. 2006 Jan;10(1):80–86.
7. Semba RD, Darnton-Hill I, de Pee S. Addressing tuberculosis in the context of malnutrition and HIV coinfection. *Food Nutr Bull*. 2010 Dec;31(4):S345–S364.
8. Koethe JR, von Reyn CF. Protein-calorie malnutrition, macronutrient supplements, and tuberculosis. *Int J Tuberc Lung Dis*. 2016;20(7):857–863.
9. Bhargava A, Chatterjee M, Jain Y, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLos One*. 2013;8(10):77979.
10. Mupere E, Malone L, Zalwango S, et al. Wasting among Uganda men with pulmonary tuberculosis is associated with linear regain in lean tissue mass during and after treatment in contrast to women with wasting who regain fat tissue mass: prospective cohort study. *BMC Infect Dis*. 2014;14(1):24.
11. Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev*. 2016;6:CD006086.
12. Martins N, Morris P, Kelly P. Food incentives to improve completion of tuberculosis treatment: randomised controlled trial in Dili, Timor-Leste. *Br Med J*. 2009;339(7730):1–8.
13. Akinyemi O, Owoaje E, Popoola O, Ilesanmi O. Quality of life and associated factors among adults in a community in South West Nigeria. *Ann Ib Postgrad Med*. 2012;10(2):34–39.
14. Kuyken W, Orley J, Power M, Herrman H, Schofield H, Murphy B. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1982;41(10):1403–1409, 1995 Nov.
15. Cote J, Delmas P, Delpierre C, Sylvain H, Delon S, Rouleau G. Factors related to quality of life in treatment-adherent, successfully treated HIV patients in France. *Open Nurs J*. 2009 Apr 30;3:10–17.
16. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol*. 2003 May;56(5):395–407.
17. Michalos CA. *Connecting the Quality of Life Theory to Health, Well-Being and Education*. Springer; 2017 Jun 26 (1).
18. Rieder HL, Chiang C-Y, Gie R, Enarson D, Crofton J. *International Union against Tuberculosis and Lung Disease, et al. Crofton's Clinical Tuberculosis*. 2009.
19. Babikako HM, Neuhauser D, Katamba A, Mupere E. Feasibility, reliability and validity of health-related quality of life questionnaire among adult pulmonary tuberculosis patients in urban Uganda: cross-sectional study. *Health Qual Life Outcome*. 2010;8(1):93.
20. Li C-T, Chu K-H, Reiher B, Kienene T, Chien L-Y. Evaluation of health-related quality of life in patients with tuberculosis who completed treatment in Kiribati. *J Int Med Res*. 2017;45(2):610–620.
21. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in

humans and experimental animals. *Int J Tuberc Lung Dis*. 2004 Mar;8(3):286–298.
22. World Health Organization | Fact sheets on tuberculosis [Internet]. World Health Organization. World Health Organization; [cited 2020 Nov 17]. Available from: http://www.who.int/tb/publications/factsheets/en/.
23. Dodor E. Evaluation of nutritional status of new tuberculosis patients at the Effia-Nkwanta regional hospital. *Ghana Med J*. 2008 Apr 1;42:22–28.
24. Zachariah R, Spielmann MP, Harries A, et al. Moderate to severe malnutrition in patients with tuberculosis is a risk factor with early death. *Trans R Soc Trop Med Hyg*. 2002 May 1;96:291–294. Transactions of the Royal Society of Tropical Medicine and Hygiene. 96:291–294.
25. Kennedy N, Ramsay A, Uiso L, Gutmann J, Ngowi FI, Gillespie SH. Nutritional status and weight gain in patients with pulmonary tuberculosis in Tanzania. *Trans R Soc Trop Med Hyg*. 1996 Apr;90(2):162–166.
26. Bacelo AC, Ramalho A, Brasil PE, et al. Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients. *PLos One*. 2015 Aug 27;10(8), e0134785.
27. Dye C, Trunz BB, Lönnroth K, Roglic G, Williams BG. Nutrition, diabetes and tuberculosis in the epidemiological transition. *PLos One*. 2011 Jun 21;6(6):e21161.
28. Karyadi E, Schultink W, Nelwan RH, et al. Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. *J Nutr*. 2000 Dec;130(12):2953–2958.
29. Onwubalili JK. Malnutrition among tuberculosis patients in Harrow, England. *Eur J Clin Nutr*. 1988 Apr;42(4):363–366.
30. Tsukaguchi K, Yoneda T, Yoshikawa M, et al. [Interaction between interleukin-1 and tumor necrosis factor productions by peripheral blood monocytes and nutritional disturbance in active pulmonary tuberculosis]. *Kekkaku*. 1991 Jul;66(7):477–484.
31. Shah S, Whalen C, Kotler DP, et al. Severity of human immunodeficiency virus infection is associated with decreased phase angle, fat mass and body cell mass in adults with pulmonary tuberculosis infection in Uganda. *J Nutr*. 2001 Nov;131(11):2843–2847.
32. Saha K, Rao KN. Undernutrition in lepromatous leprosy. V. Severe nutritional deficit in lepromatous patients co-infected with pulmonary tuberculosis. *Eur J Clin Nutr*. 1989 Feb;43(2):117–128.
33. Paton NI, Chua Y-K, Earnest A, Chee CB. Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting. *Am J Clin Nutr*. 2004;80(2):460–465.
34. Pasipanodya JG, Miller TL, Vecino M, et al. Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. *Chest*. 2007 Nov;132(5):1591–1598.
35. Maguire GP, Anstey NM, Ardian M, et al. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. *Int J Tuberc Lung Dis*. 2009 Dec;13(12):1500–1506.

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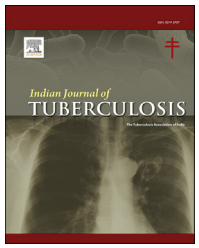

Original article

Efficacy of smoking cessation intervention delivered through mobile tele-counseling among smokers with tuberculosis in a Revised National Tuberculosis Control Program

Lalita Fernandes[*], *Abhilash Narvekar*, *Durga Lawande*

Department of Pulmonary Medicine, Goa Medical College, Goa, India

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ABSTRACT

Background: India has high burden of tuberculosis and smokers. Prevalence of tuberculosis is three times higher in smokers than non-smokers. Active smoking causes severe disease, delay in seeking treatment, lost to treatment follow up, delayed sputum conversion and drug resistance. WHO advocates mobile phone technology to improve health outcomes (mHealth). We used mobile tele-counseling as a smoking cessation intervention in smokers with tuberculosis (TB) receiving treatment under tuberculosis control program.

Aim: To determine smoking quit rate at six months of TB treatment among smokers receiving mobile tele-counseling versus brief advice and to estimate smoking quit rates and relapse rates during the tele-counseling period.

Methods: Open label randomized controlled trial. Newly detected pulmonary tuberculosis or pleural effusion patients received brief advice on smoking cessation as per The UNION's guiding framework. Subjects were then randomly allocated to intervention or control group. Intervention group was contacted telephonically at 2,3,4,5 and 6 months to assess smoking quit rates and provide continued smoking cessation advice.

Results: Intervention group had 80 and 82 in the control group, mean (SD) age was 40.6(12.6), 43.5(12.7) $p = 0.53$. Quit rate at six months was 54 (67.5%) in intervention group versus 34 (42%) in control group; RR 1.60 (95% CI 1.19, 2.16) $p = 0.001$. Trend in smoking quit rates in intervention group was 81.3%, 61.3%, 55%, 73.8% at 2,3,4 and 5 months respectively. Smoking relapse rate was 43.1%, 53.1%, 20.5%,15.3% at 3,4,5 and 6 months respectively. 27.5%, 43.8% were abstinent for last three, two months.

Conclusions: Mobile tele-counseling is an effective strategy for smoking cessation among TB patients.

* *Corresponding author*. CA 3/8, Sapana Gardens, Porvorim, Bardez, Goa, 403521, India. Tel.: +919822102177 (mobile).
E-mail address: drlalitafernandes@gmail.com (L. Fernandes).

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1. Introduction

Tuberculosis (TB) and smoking are two major public health concerns having epidemic proportions and together are considered syndemics.[1,2] As per the Global TB report 2020, an estimated 10.0 million people developed TB in 2019 and India contributed to highest number of global burden (26%).[1] In high TB burden countries 17.6% of TB cases and 15.2% of TB mortality is attributed to smoking.[3]The Global adult tobacco survey (GATS 2 India 2016–17) revealed that 19% men and 2% women are smokers in India.[4]

Smoking increases susceptibility to pulmonary TB because of altered cellular and humoral immune responses.[5] There is suppressed alveolar macrophage function and decreased phagocyte activity of the monocyte[6,7,8] Smoking is a significant risk factor for TB infection (LTBI),[9] disease,[10] recurrence[11,12] and mortality.[13] Smokers have delayed health care seeking behavior,[14] delayed sputum conversion[15,16] and lost to treatment follow up.[17] Smoking cessation reduces the risk of TB and mortality by one third.[18]

In India, TB patients are three times likely to be smokers and 50% of deaths from TB among Indian men were attributed to smoking.[19] WHO reported that TB rates could decline by 20% if smoking was eliminated and recommends incorporating tobacco cessation intervention in TB control program with an aim of controlling both the epidemics. WHO and The UNION (International Union Against Tuberculosis and Lung Disease) released monograph on TB and tobacco control in 2007.[20] However smoking cessation interventions are not fully implemented in the TB Control Program. Patients are more receptive to health education messages and willing to modify their health behavior when they are ill.[21] Therefore it makes sense to provide for smoking cessation intervention (SCI) in smokers with TB during anti – TB treatment.

Modalities of SCI include brief counseling and medicinal support. WHO advocates mobile phone technology to improve health outcomes (mHealth). 'mHealth' or 'Mobile health' is healthcare supported by mobile technology such as mobile phone or personal digital assistants.[22] Smoking cessation programs delivered through mobile phone text messaging have shown increase in self-reported quitting.[23,24] India has large coverage of mobile phones, however the rural population may not be able to read the text messages or decline to read the messages. A study based around Bangalore, India found that 14% of respondents preferred text messages, 89% preferred voice calls alone and 98% preferred receiving reminders for drug adherence.[25]

Our hospital initiates TB treatment for patients with tuberculosis and then refers them to their respective health centers to continue treatment under the Revised National Tuberculosis Control Program (RNTCP). There is no active smoking cessation intervention program offered under RNTCP. As the smokers with TB were from far off locations from our hospital, we planned to use voice calls on mobile phones (mobile tele-counseling) as a smoking cessation intervention.

The aim of our study was to determine the smoking quit rate at six months of TB treatment among those receiving monthly mobile tele-counseling on smoking cessation versus brief advice received at the start of anti-TB treatment. Secondary aim was to estimate the smoking quit rates and smoking relapse rates during the tele-counseling period.

2. Methods

2.1. Study Design

Open label randomized controlled trial.

2.2. Study setting

The Tuberculosis and Chest Diseases hospital of Goa Medical College, Goa, India, a tertiary care hospital for diagnosis and treatment of tuberculosis.

2.3. Study population

All consecutive newly detected TB patients registered from November 2017–October 2019 were invited to be part of the study. Inclusion criteria were newly detected pulmonary TB with sputum smear AFB positive and sputum GeneXpert MTB detected, Rifampicin sensitive or new TB pleural effusion with ADA ≥40 IU/L, age ≥18 years, current smoker and having a personal mobile phone. We excluded patients with TB recurrence, MDR-TB, HIV, psychiatric disease and migrant population. Anti-TB treatment was provided under the Revised National Tuberculosis Control Program. All study participants gave informed consent and the study was approved by the Institutional Ethics Committee of Goa Medical College.

2.4. Smoking status

Smoking status was defined as per The UNION's 2010 guiding framework.[26]At enrollment a current smoker was defined as one who has smoked even one puff in last three months (self-reported smoking) while a non-smoker was one who has never smoked or who used to smoke but not smoked in the last three months. After randomization, in the follow up period at 2,3,4,5,6th month a current smoker was defined as one who has smoked even one puff in the last two weeks of telephonic contact and a quitter was defined as a smoker who has quit and not smoked at all in the last two weeks. If any quitter in the previous telephonic visit gave history of smoking within the two weeks of telephonic call visit, he/she was considered current smoker and a relapsed smoker. The quit status was based on patient's self-reporting. All smokers completed the Fagerstrom test[27] for nicotine dependence at the beginning of the study.

2.5. Sampling and randomization

Non probability sampling of patients reporting to the tertiary care hospital and randomization was done using random permuted block numbers. The subjects were randomly assigned to intervention group and control group.

2.6. Intervention arm

Smoking cessation intervention was based on The Union's ABC (A = ask if they smoke, B = brief advise about stopping

tobacco use, C = cessation support with regular monitoring) and WHO's guiding framework. All patients diagnosed with TB were asked about their smoking status by the question "do you smoke tobacco"? If yes then, "have you smoked at all - even a puff-in the last three months"? If yes then they were defined as current smokers and were given general advice that smoking is harmful for health and smoking can cause cancer of mouth and lung, myocardial infarction, stroke, peptic ulcer, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease (COPD) and that passive smoking is harmful to the family. Then the patients were given personalized advice on the harmful effects of smoking on TB like "you need to quit smoking so that you can recover properly from TB, as soon as you quit smoking your coughing and sputum will decrease and your breathing will become easier", "quitting smoking will reduce your risk of getting TB again". "By making your home smoke free, you will reduce the risk of your family getting TB". The patients were asked to set a quit date, tell family members and ask for support, remove triggers like ash trays and avoid those who smoke. After giving brief advice, they were randomized to either the control group who were contacted at six months of TB treatment while the intervention group was contacted telephonically on their mobile phones at 2,3,4,5,6 months of anti- TB treatment to assess for smoking status of either quit or current smoker. At every telephonic contact the intervention group was again provided with general advice on smoking cessation and personalized advice on effect of smoking on TB. The entire tele-counseling would last for 5–10 minutes which was conducted by a trained physician.

Control arm received smoking cessation advice prior to randomization. They were contacted at the end of six months for smoking status. Both groups were assessed for TB outcome from the TB register through the RNTCP personnel.

Assuming efficacy of monthly tele-counseling to be 65%, sample size was estimated to be 69 per group in order to have a difference of 0.25 with power of 80% and $\alpha = 0.05$. Accounting for approximate 20% drop out, a sample size of 82 per group was calculated.

2.7. *Statistical analysis*

Statistical analysis was performed using IBM statistical package for social sciences (SPSS) version 24 (IBM Corp, SPSS Inc, Chicago, IL). Continuous variables are presented either as mean (SD) or median and interquartile range (IQR). Categorical variables are presented as percentages. Independent student's t test, Mann Whitney U tests, Pearson's chi square test and Fisher's exact test were applied to study differences between two groups. All statistical tests were 2 tailed and a p value of <0.05 was considered statistically significant.

3. Results

166 subjects were screened and 162 enrolled; 80 in intervention and 82 in control group. There were 160 (98.7%) males, 80 (100%) in the intervention group and 80 (97.6%) in the control group. The mean (SD) age was 40.6(12.6), 43.5(12.7) p = 0.53, the mean age of the smoking initiation was 22.9(2.7), 23.7(4.3) p = 0.05 and the Fagerstrom score of nicotine addiction was 6.65(0.9), 6.61(1.0) p = 0.30 in the intervention and control group respectively. Both groups were well matched for the baseline characteristics which are described in Table 1.

All 80 patients in the intervention group completed the study while 1 patient was lost to follow up in the control group. At the end of 6 months of anti-TB treatment 54 (67.5%) quit smoking in the intervention group compared to 34 (42%) in the control group; p = 0.001, RR = 1.60 (95% CI = 1.19, 2.16).

The trend in smoking quit rates was 81.3%, 61.3%, 55%, 73.8%, 67.5% at 2,3,4,5 and 6 months respectively while smoking relapse rate were 43.1%, 53.1%, 20.5%,15.3% at 3,4,5 and 6 months respectively. 27.5% were abstinent for last three months of TB treatment while 43.8% remained abstinent for last two months. We also assessed TB outcomes in both groups. In the intervention group 79 (98.8%) were cured/completed treatment, and 1 (1.25%) was a treatment failure while in the control group 78 (95.1%) were cured/completed treatment, 3 (3.7%) were treatment failure and 1 (1.2%) was lost to follow, p = 0.37. A consort diagram showing the flow of enrollment and follow up of study subjects is shown in Fig. 1.

Table 1 – Baseline characteristics of subjects enrolled in the intervention and control groups.

Variable	Intervention n = 80	Control n = 82	P Value
Age			
Mean (SD)	40.6 (12.6)	43.5 (12.7)	0.53
Gender n (%)			
Male	80 (100)	80 (97.6)	0.50
Female	0	2 (2.4)	
Alcohol Use n (%)	28 (35)	27 (32.9)	0.78
Marital Status n (%)	58 (72.5)	60 (73.2)	0.92
Education Status n (%)			
Illiterate	14 (17.5)	19 (23.2)	0.10
Secondary	15 (18.6)	18 (21.9)	
SSC	37 (46.3)	29 (35.4)	
HSSC	8 (10)	15 (18.3)	
Graduate	6 (7.5)	1 (1.2)	
Smoking initiation age			
Mean (SD)	22.9 (2.7)	23.7 (4.3)	0.05
Pack years			
Median (IQR)	6.75 (2.18,12.38)	8.5 (3.5,12.7)	0.35
Fagerstrom Score			
Mean (SD)	6.65 (0.9)	6.61 (1.0)	0.30
Previous Quit Attempt n (%)	3 (3.8)	9 (11)	0.08
No. of cigarettes per day	8.96 (3.4)	8.6 (2.4)	0.08
Nicotine Dependence n (%)			
Low – Moderate	1 (1.3)	2 (2.4)	0.85
Moderate	65 (81.3)	66 (80.5)	
High	14 (17.5)	14 (17.1)	
Weight (Kg)			
Mean (SD)	51.4 (8.7)	51.1 (8.7)	0.91
Alcohol Use n (%)	28 (35)	27 (32.9)	0.78

SSC (Secondary School Certificate), HSSC (Higher Secondary School) Certificate).

4. Discussion

Our study has shown that 67.5% of smokers with TB receiving mobile tele-counseling on smoking cessation quit smoking at six months of TB treatment compared to 42% in the control group. To the best of our knowledge this is the first randomized controlled study assessing the efficacy of smoking cessation intervention using mobile phone tele-counseling among smokers with TB taking treatment under the RNTCP. There are studies assessing the efficacy of using mobile phone text messaging in smoking cessation among general population but these are done in high-income countries with good tobacco control policies.[28]

Of the randomized controlled trials (RCT) evaluating smoking cessation interventions in smokers with TB; the definition of smoking and quit smoking and type of interventions vary making comparison between studies difficult. There is a need to have a standard definition for smoking and quitter in order to compare studies. We used standard definitions of The UNION.

In a RCT by Louwagie et al done in South Africa, the control group received brief advice by the TB nurse while the intervention group had added motivational interviewing by community health care worker. They observed six months of self-reported sustained abstinence of 21.5% in interventional group and 9.3% in the control group (RR = 2.29, 95% CI 1.4, 3.92).[29] Self-reported three months sustained abstinence was 25.4% in the intervention group compared to 12.8% in the control group. We also observed a continuous abstinence for three months of 27.5% in the intervention group.

In another RCT by Nichter et al done in Indonesia, one group of smokers with TB received brief advice from physician at every visit while the other group received added family support in smoking cessation for the total TB treatment period of six months and reported smoking cessation rates of 73% versus 71%, $p > 0.05$.[30] Aryanpur et al reported a RCT in Iran comparing standard of care to behavioral counseling and

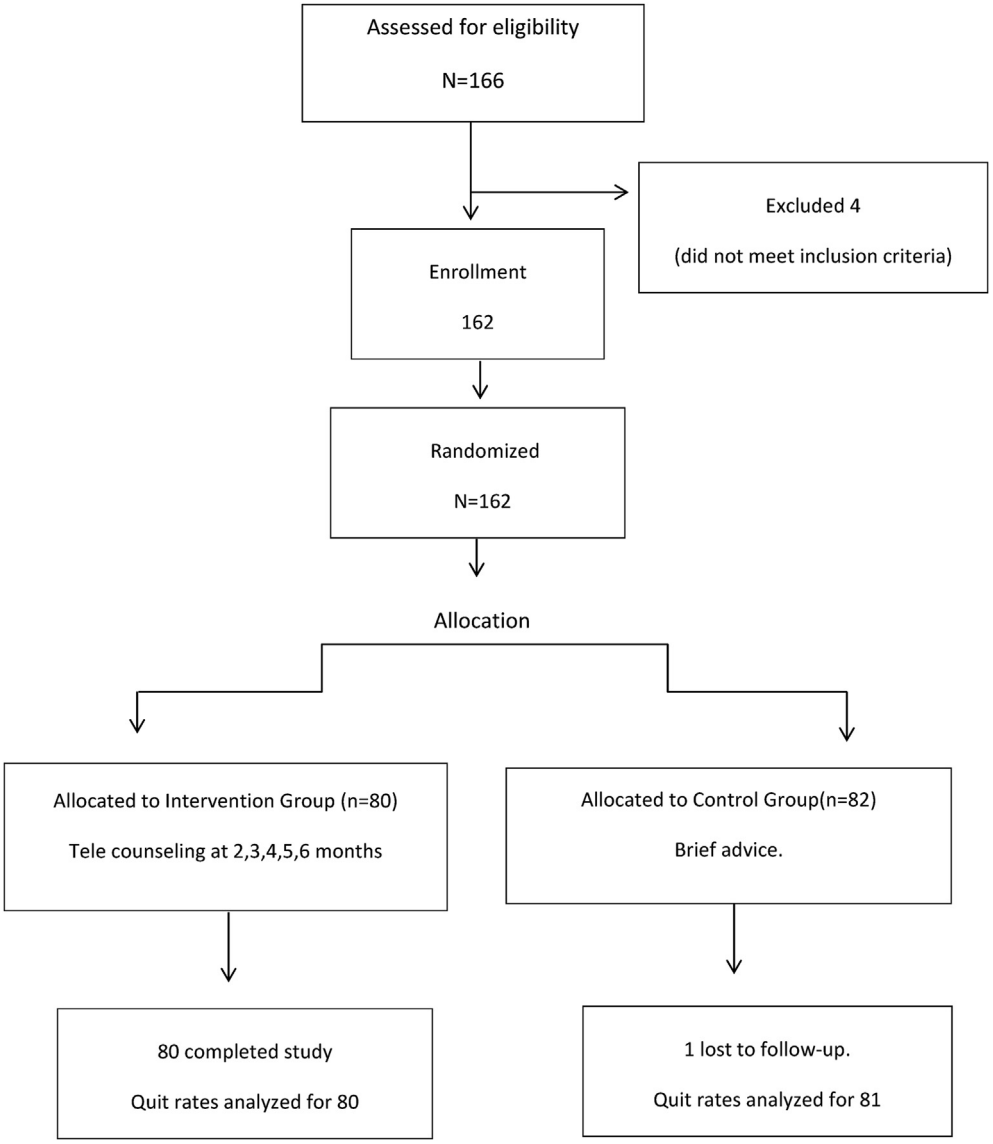

Fig. 1 – Consort diagram showing enrollment and follow up of the study subjects.

behavioral counseling with added medication and reported smoking abstinence at six months of 9.8%, 33.9% and 71.7% respectively.[31]

There are other cluster randomized studies and non-randomized control studies on smoking cessation in TB patients with success of intervention ranging from 39% to 82.5%.[32]

We observed a high quit rate of 81.3% at two months of follow up which can be attributed to Hawthorne bias wherein the individual modifies an aspect of their behavior in response to their awareness of being observed. The smoking quit rate gradually dropped over six months. During our study period we observed smoking relapse rates which ranged from 43.1% at three months, 53.1% at four months, 20.5% at five months and 15.3% at six months. Relapse during smoking cessation program is known but it is advisable to continue counseling as smoking related immunological abnormalities are reversible within six weeks of smoking cessation.[17] We also compared response to TB treatment in the intervention and control group and found no statistical difference in the TB outcomes, $p = 0.37$.

The strength of our study was that we had low attrition among the study participants and it was a pragmatic study in the existing TB control program. The limitation was the self-reported smoking status as well as quit status from the patient. However a study using plasma cotinine showed that self-reporting is reliable to measure smoking status.[33]

5. Conclusion

The ABC framework of The UNION on smoking cessation delivered through mobile tele counseling is an effective strategy for smoking cessation in smokers with TB. Our study results are encouraging and implementation of this strategy in the TB program may go a long way in achieving the goals of End TB strategy.

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Nil.

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2020: Executive Summary*. Geneva: World Health Organization; 2020.
2. World Health Organization. *WHO Global Report on Trends in Prevalence of Tobacco Smoking 2000-2025*. 2nd ed. Geneva: World Health Organisation; 2018.
3. Amere GA, Nayak P, Salindri AD, Narayan KMV, Magee MJ. Contribution of smoking to tuberculosis incidence and mortality in high-tuberculosis-burden countries. *Am J Epidemiol*. 2018;187:1846–1855.
4. Global Adult Tobacco Survey. FACT SHEET INDIA 2016-17. Accessed at https://ntcp.nhp.gov.in/assets/document/surveys-reports-publications/GATS-2-FactSheet.pdf.
5. Shang S, Ordway D, Henao-Tamayo M, et al. Cigarette smoke increases susceptibility to tuberculosis–evidence from in vivo and in vitro models. *J Infect Dis*. 2011;203:1240–1248.
6. O'Leary SM, Coleman MM, Chew WM, et al. Cigarette smoking impairs human pulmonary immunity to Mycobacterium tuberculosis. *Am J Respir Crit Care Med*. 2014;190:1430–1436.
7. Aryanpur M, Mortaz E, Masjedi MR, et al. Reduced phagocytic capacity of blood monocyte/macrophages in tuberculosis patients is further reduced by smoking. *Iran J Allergy, Asthma Immunol*. 2016;15:174–182.
8. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2:372–377.
9. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:335–342.
10. Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. *Am J Respir Crit Care Med*. 2009;180:475–480.
11. Thomas A, Gopi PG, Santha T, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *Int J Tubercul Lung Dis*. 2005;9:556–561.
12. d'Arc Lyra Batista J, de Fátima Pessoa Militão de Albuquerque M, de Alencar Ximenes RA, Rodrigues LC. Smoking increases the risk of relapse after successful tuberculosis treatment. *Int J Epidemiol*. 2008;37:841–851.
13. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007;4, e20.
14. Bam TS, Enarson DA, Hinderaker SG, Bam DS. Longer delay in accessing treatment among current smokers with new sputum smear-positive tuberculosis in Nepal. *Int J Tubercul Lung Dis*. 2012;16:822–827.
15. Maciel EL, Brioschi AP, Peres RL, et al. Smoking and 2-month culture conversion during anti-tuberculosis treatment. *Int J Tubercul Lung Dis*. 2013;17:225–228.
16. Nijenbandring de Boer R, Oliveira e Souza Filho JB, Cobelens F, et al. A delayed culture conversion due to cigarette smoking in active pulmonary tuberculosis patients. *Tuberculosis*. 2014;94:87–91.
17. Schneider NK, Novotny TE. Addressing smoking cessation in tuberculosis control. *Bull World Health Organ*. 2007;85(10):820–821.
18. Wen C-P, Chan T-C, Chan H-T, Tsai M-K, Cheng T-Y, Tsai S-P. The reduction of tuberculosis risks by smoking cessation. *BMC Infect Dis*. 2010;10:1–9.
19. Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. *Lancet*. 2003;362:507–515.
20. World Health Organization and International Union Against Tuberculosis and Lung Disease. *A WHO/The Union Monograph on TB and Tobacco Control: Joining Efforts to Control Two Related Global Epidemics*. Geneva: World Health Organization; 2007. Accessed at https://www.who.int/tobacco/resources/publications/tb_tobac_monograph.pdf.

21. Slama K, Chiang CY, Enarson DA. Introducing brief advice in tuberculosis services. *Int J Tubercul Lung Dis*. 2007;11:496–499.
22. World Health Organisation. *mHealth: New Horizons for Health through Mobile Technologies: Second Global Survey on eHealth*, 20 Avenue Appia, 1211 Geneva 27. Switzerland: Global Observatory for eHealth series; 2011. Accessed at: http://www.who.int/goe/publications/goe_mhealth_web.pdf.
23. Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet*. 2011;378:49–55.
24. Bock B, Heron K, Jennings E, et al. A text message delivered smoking cessation intervention: the initial trial of TXT-2-quit: randomized controlled trial. *JMIR Mhealth Uhealth*. 2013;1(2):e17.
25. DeSouza SI, Rashmi MR, Vasanthi AP, Joseph SM, Rodrigues R. Mobile phones: the next step towards healthcare delivery in rural India? *PloS One*. 2017;9, e104895.
26. Bissell K, Fraser T, Chiang C-Y, Rnarson DA. *Smoking Cessation and Smokefree Environments for Tuberculosis Patients*. Paris, France: International Union Against Tuberculosis and Lung Diseases; 2010.
27. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrome Tolerance Questionnaire. *Br J Addict*. 1991;86:1119–1127.
28. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016;4:CD006611.
29. Louwagie GM, Okuyemi KS, Ayo-Yusuf OA. Efficacy of brief motivational interviewing on smoking cessation at tuberculosis clinics in Tshwane, South Africa: a randomized controlled trial. *Addiction*. 2014;109:1942–1952.
30. Nichter M, Padmawati S, Ng N. Introducing smoking cessation to Indonesian males treated for tuberculosis: the challenges of low-moderate level smoking. *Soc Sci Med*. 2016;152:70–79.
31. Aryanpur M, Hosseini M, Masjedi MR, et al. A randomized controlled trial of smoking cessation methods in patients newly-diagnosed with pulmonary tuberculosis. *BMC Infect Dis*. 2016;16:369.
32. Whitehouse E, Lai J, Golub JE, Farley JE. A systematic review of the effectiveness of smoking cessation interventions among patients with tuberculosis. *Public Health Action*. 2018;8:37–49.
33. Brunet L, Pai M, Davids V, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. *Eur Respir J*. 2011;38:139–146.

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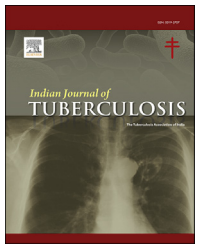

Original article

Active case finding of pulmonary tuberculosis and HIV infection among prisoners of South Gujarat: A cross sectional study

J.K. Kosambiya [a,*], *Parul Vadgama* [b], *U.C. Samudyatha* [a], *Dhaval Rathod* [c], *Rutu Buch* [a], *Rahul Damor* [a]

[a] *Department of Community Medicine, Government Medical College, Surat, India*
[b] *Department of Pulmonary Medicine, Government Medical College, Surat, India*
[c] *District TB Centre, Surat District (Rural), India*

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ABSTRACT

Background: In a close knit congregation such as prison, Tuberculosis (TB) and HIV can be major health problems. However, their prevalence in Indian prisons is under reported. This study aimed at adopting a camp based, active case finding approach to identify cases of TB, HIV and at risk prisoners in a central prison of South Gujarat.

Methods: A multidisciplinary team of public health experts, pulmonologists, social workers and lab technicians conducted a week-long camp to screen 1665 prisoners for TB using clinical examination, sputum smear for AFB, CBNAAT and Chest X-Ray and for HIV through Rapid Antigen Testing.

Results: Majority of participants (1392, 84%) were under trail prisoners, having spent an average of 1.4 years in prison. About 2.9% of participants had previous history of TB, of whom only 59% had completed treatment. About 14% of participants were underweight. Weight reduction was found to be significant in first five years of imprisonment. Of all participants, 3.6% were found to have diabetic range of blood sugar. Seven new active, drug sensitive pulmonary TB cases and three new cases of HIV infection were identified. All new cases of TB, HIV and increased blood sugar levels were linked to treatment.

Conclusion: Camp based approach is effective in active case finding of pulmonary TB and predisposing factors such as malnourishment, Diabetes and HIV among prisoners. Routine screening of all prisoners at the time of entry and monthly thereafter in a camp based approach should be adopted to identify TB and at risk prisoners.

* *Corresponding author.*
E-mail address: jkkosambiya@gmail.com (J.K. Kosambiya).

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1. Introduction

Tuberculosis in prisons is a major public health problem in many countries, with a 11 to 81 times higher notification rate of TB among prisoners than from general population.[1] The prisons are places of concern for TB control and elimination because prisons act as reservoirs of TB by receiving, concentrating, disseminating, worsening and exporting TB.[2]

However, only very few countries have data regarding the prevalence TB in prisons. Even fewer countries have data on provision of TB preventive treatment for prisoners.[3] In India, the National Strategic Plan for Tuberculosis Elimination (2017–2025) strongly advocates for Active Case Finding activity (ACF) among vulnerable groups, including prison inmates.[4]

This study aimed at taking the active case finding strategy one step further, by estimating the prevalence of risk factors for TB (long term prison stay, presence of undernourishment, Diabetes, HIV, history of exposure to TB and substance use) along with active case finding for TB, among prisoners of a Central Jail in South Gujarat. The goals of this study were detection of Rifampicin sensitive and resistant TB, to ensure early initiation of Anti Tuberculosis Treatment (ATT), inform the authorities regarding presence of risk factors and document the operational issues of a campaign mode, camp based approach for active case finding for Tuberculosis in prisons.

2. Methodology

The study was approved by Institutional Review Board, State Operational Research Committee, and Jail Authority. In the preparatory phase, jail authorities were briefed about the study and feasibility was assessed. Inmates who were voluntarily working in the medical wing of the prison were explained regarding the study and involved in the study as peers, to motivate other inmates for the study. A fifteen member research team, consisting of public health experts, pulmonologists, lab technicians, Integrated Counseling and Testing Centre (ICTC) counselor and medico social workers visited the prison for seven consecutive days for active case finding in September 2019. All available prisoners (convicted and under trail) were screened using a semi structured questionnaire detailing the sociodemographic characteristics, medical history and general physical examination. On site laboratory was set up to screen for Diabetes (using Glucometer) and RPR for Syphilis. Venous blood sample was collected after pre test counseling and separated serum was transported to the nearest ICTC for HIV testing with three different antigen test kits. The reports were provided to the participants after post test counseling in the prison itself by the ICTC counselor. All participants with HIV infection were linked and started on ART at the nearest ART centre.

All participants were screened for presumptive pulmonary TB using the case definition as presence of any one of the following symptoms: cough more than 2 weeks, fever more than 2 weeks, significant weight loss or hemoptysis. Participants with presumptive pulmonary TB and all the participants with the predisposing risk factors such as previous history of pulmonary TB, contact with known cases of pulmonary TB, Diabetes or HIV were investigated for the presence of active TB through sputum examination and Chest X-rays. On site chest X-ray was made available through a mobile X-ray van in the prison. Sputum samples were transported District TB Centre for sputum microscopy and CBNAAT. All the participants with microbiologically confirmed and clinically detected TB were re evaluated at tertiary care hospital by a team of pulmonologists and radiologists before starting ATT. Upon return to the prison, they were provided accommodation in separate TB isolation barrack in the prison. The prison authorities were also informed of the other study findings, including the presence of risk factors of acquiring TB among the prison inmates.

3. Results

In the seven days of the study, 2100 inmates were present each day, on an average. However during the restricted time allowed in the prison, 1665 participants could be motivated and enrolled in the study. The reasons for non participation of the remaining 435 prisoners included pre-scheduled legal proceedings, hospital appointments, release from prison and lack of interest in the study.

Among 1665 participants who participated in the study, 1579 (94.8%) were men and 86 (5.2%) were women. Most of them belonged to the economically productive age group of 18–30 years (915, 54%), median being 30 years.

3.1. *Prison stay*

Majority of the participants (1392, 84%) were under trail prisoners, constituting the floating population, having spent an average of 1.4 years in prison. The convicted prisoners (273) had spent an average of 3 years in prison. About 16% (253) of all male participants and 17.5% (15) of all female participants had spent more than 3 years in prison.

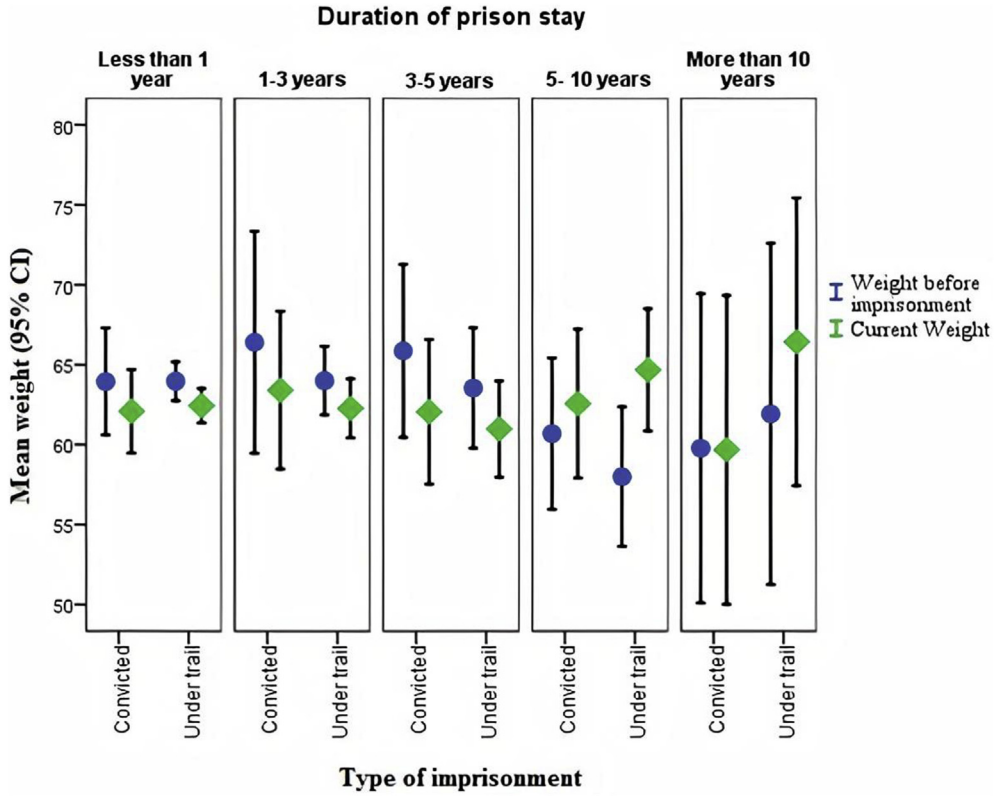
3.2. *Presence of malnutrition*

About 14% (233) of all participants were underweight. The mean BMI of convicted (22.6 ± 3.9) and under trail (22.5 ± 4) participants was statistically similar ($p = 0.802$). The records of body weights at the time of imprisonment were available for 899 participants and could be compared with the current body weight. In participants imprisoned for less than 5 years, the current body weight was less than that at the time of imprisonment. Among those imprisoned for more than 5 years, the body weight was slightly higher than when they were imprisoned, though not significantly (Graph 1).

About 56.2% (77) of previously underweight (137) participants remained underweight during the imprisonment. It was also found that, 11% (36) of participants with normal BMI before imprisonment (320), 2% (3) of previously overweight (147) and 3% (9) of previously obese (295) participants became underweight during imprisonment (Graph 2).

3.3. *Presence of co-morbid conditions*

A total of 1652 blood samples were screened for Diabetes and HIV and 13 participants refused to provide samples for blood



Graph 1 – Comparison of current body weight and body weight at the time of imprisonment, among participants with varying periods of imprisonment (n = 899).

test. It was found that 60 participants (3.6%) were found to have diabetic range of blood sugar. Using JNC-8 classification,[5] 16.9% of participants (281) were pre hypertensive, 9.2% had Stage 1 hypertension (153) and 2.5% had Stage 2 hypertension (42).

As per prison records, there were 9 known cases of HIV, on ART. In this study, three new infections were identified and linked to ART (Table 1). The prevalence of HIV infection in the prison was estimated as 0.7%, including both existing and new cases.

3.4. *Clinical examination and medical history of participants*

A total of 121 participants were classified as having presumptive pulmonary TB or symptoms (Graph 3) and screened for active TB. Majority of the participants (61%, 1016) had lived in overcrowded dwellings before imprisonment and 3.7% (62) had at least one family member with TB. Though 49 participants had past history of TB, only 34 (69%) had received AKT. Unavailability of medicines following imprisonment in a different city, unwillingness to take medicines daily, temporary relief from symptoms and migration were the major reasons for lack of adherence or non initiation of treatment. In only 7 cases, the participants had disclosed their previous history of TB to jail authorities. Only 17 had a follow up after treatment completion.

3.5. *Detection of new TB cases*

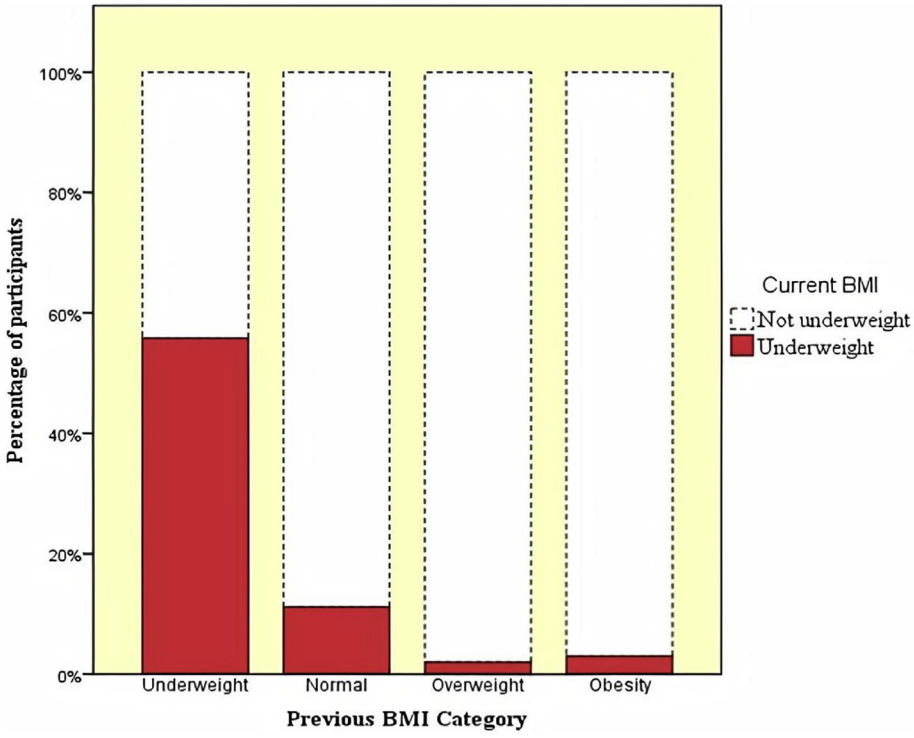
A total of seven new active pulmonary TB cases were detected, among the 121 presumptive cases. The screening algorithm had a yield of 0.4%. Among them, two cases were microbiologically confirmed, Rifampicin sensitive pulmonary TB, while five cases were clinically diagnosed cases of pulmonary TB, using chest X-ray. The profile of the newly detected TB cases is given below (Table 2).

4. Discussion

The three main characteristics of the prison were: presence of active, untreated pulmonary TB, high turnover rate and presence of predisposing factors such as malnourishment, Diabetes and HIV among the other participants studied, making them vulnerable to TB infection and disease.

In this study, the prevalence of HIV was estimated as 0.7% among the participants screened, which was less than the national HIV prevalence of 2.1% (95% CI: 1.9%–2.3%) and state HIV prevalence of 1.5%, reported in HIV Sentinel Surveillance Plus report 2019.[6]

Systematic review of studies on TB in prison noted that high levels of TB among prison inmates is likely to be attributable to the fact that a disproportionate number of prisoners are from



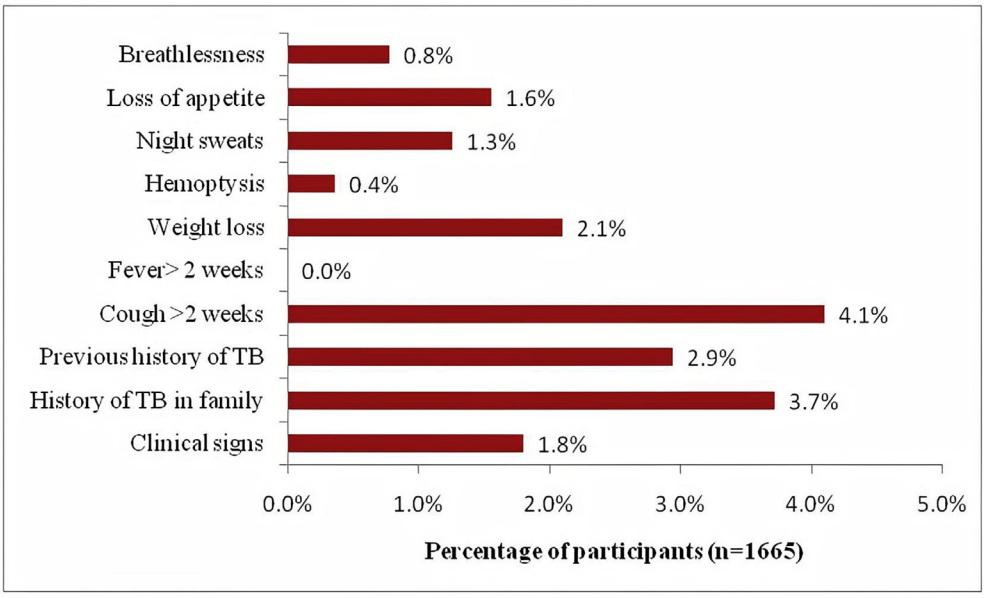
Graph 2 – Comparison of BMI before and after imprisonment (n = 899).

population groups that are already at high risk of TB infection and TB disease, like alcohol or drug users, homeless people, mentally ill individuals, former prisoners and immigrants from regions with high TB prevalence.[7] In this study, three of the seven newly detected TB cases had lived in overcrowded dwellings before imprisonment and one of the seven reported history of TB in the family. One of the newly detected case in this study had past history of defaulting on TB treatment. It can be noted here at least 2.9% of participants had previous history of TB, of whom only 59% had completed treatment. Imprisonment in different prisons, in different cities and durations, was one of the reasons for discontinuation of treatment. The prisoners had not informed jail authorities regarding ongoing or past TB treatment in most cases. The untreated or default cases of TB are routes by which prisons "receive TB" and "disseminate TB". This is similar to other studies, where the researchers

Table 1 – Socio demographic and clinical profile of newly detected cases of HIV infection.

	Patient ID of Newly detected cases of HIV infection		
	1	2	3
Age (years)	36	25	26
Gender (Female- F, Male-M)	F	M	M
Imprisonment (Under trail – U, Convicted - C)	U	U	U
Duration of imprisonment[a]	2 m	3 m	2 m
Under nutrition before imprisonment [b]	N	N	Y
History of smoking [b]	N	Y	N
History of Alcohol consumption [b]	N	Y	Y
IV drug use[b]	N	Y	N
Duration of IV drug use	NA	3 y	NA
Marital status	Married	Unmarried	Unmarried
Duration of active sexual life[b]	12y	N	5y
Diabetes[b]	N	N	N
Past history of TB[b]	N	N	N
Active TB[b]	N	N	N
Were they aware of their HIV status?	N	N	N

[a] d = days, wk = weeks, m = months, yr = years.
[b] Y = Yes, N = No, NA= Not applicable.



Graph 3 – Clinical examination and medical history of participants.

Table 2 – Sociodemographic and clinical profile of newly detected cases of pulmonary TB.

	Patient ID of Newly detected cases of TB						
	1	2	3	4	5	6	7
Age (years)	60	39	28	29	30	19	22
Gender (Female- F, Male-M)	F	M	M	M	M	M	M
Imprisonment (Under trail – U, Convicted - C)	U	U	U	U	U	U	C
Duration of imprisonment[a]	6 m	1 yr	9 m	10 d	3 yr	15 d	5 yr
Previous history of TB[b]	N	N	N	N	Y	N	N
History of defaulting on AKT[b]	NA	NA	NA	NA	Y	NA	NA
History of TB in family[b]	N	N	Y	N	N	N	N
Overcrowding at home[b]	N	Y	Y	N	N	N	Y
History of smoking[b]	N	Y	Y	Y	N	Y	Y
History of Alcohol consumption [b]	N	Y	Y	Y	N	N	N
Other substance abuse[b]	N	N	Tobacco chewing	Tobacco chewing	N	Tobacco chewing	N
Duration of cough [a]	2 wk	–	>2 mo	2 wk	8 wk	3 wk	>2 mo
Weight loss[b]	Y	N	N	N	Y	N	Y
Fever> 2 weeks[b]	N	N	N	N	N	N	N
Night sweats[b]	Y	N	N	N	N	N	Y
Breathlessness[b]	N	Y	N	Y	N	N	N
BMI (kg/m^2)	24.2	23.1	19.3	19	13	16	21
General physical examination	–	–	Clubbing	Pallor	–	–	–
Respiratory system examination	Normal	Normal	Wheeze	Normal	Normal	Normal	Rhonchi
Diabetes[b]	N	N	N	N	N	N	N
HIV[c]	NR	NR	NR	NR	NR	NR	NR
Sputum microscopy	0	0	0	0	1+	0	0
CBNAAT[d]	ND	ND	ND	ND	RS	RS	ND
Chest X-Ray suggestive of TB[b]	Y	Y	Y	Y	N	N	Y

[a] d = days, wk = weeks, m = months, yr = years.
[b] Y = Yes, N = No, NA = Not applicable.
[c] NR = Non reactive.
[d] ND = Not detected, RS = Rifampicin sensitive.

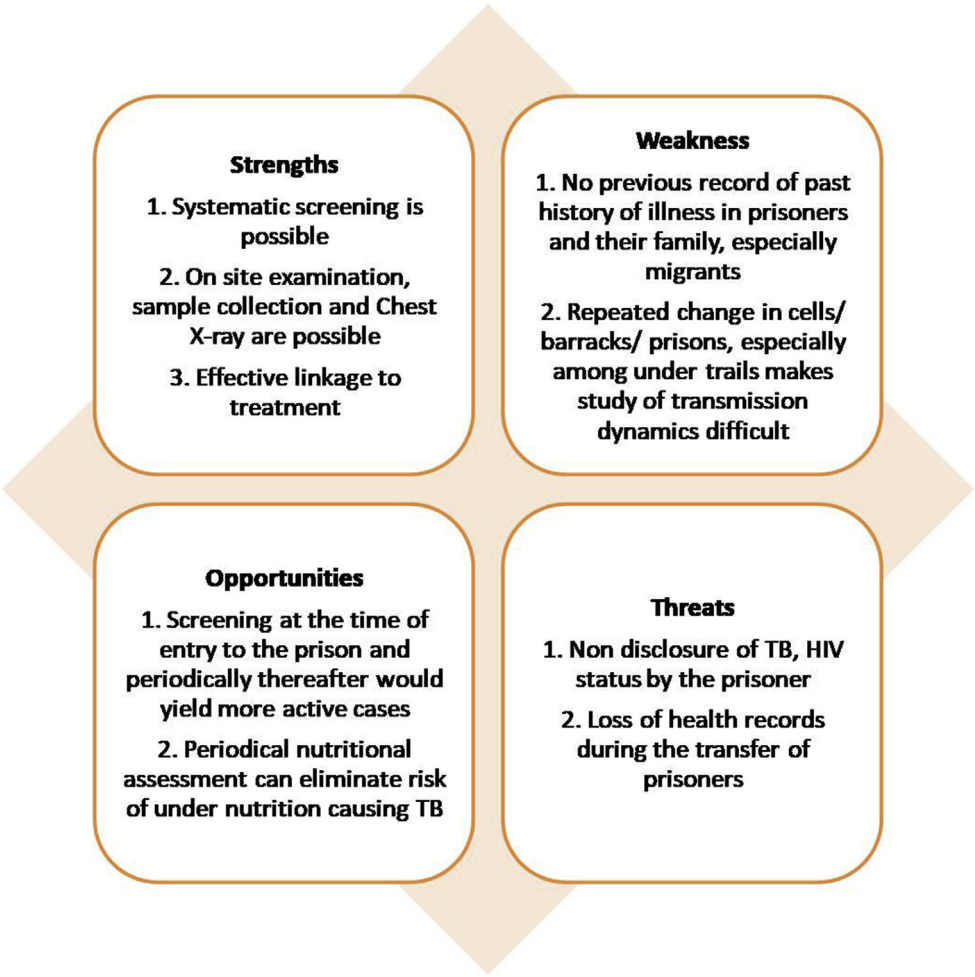


Fig. 1 – Strengths, weaknesses, opportunities and threats of a camp based active case finding strategy in prisons.

have identified a breech in the continuum of care due to delayed diagnosis[8] and repeated imprisonment, transfers and release into community before treatment completion.[9]

While BMI less than 18.5 kg/m^2 was found in only two of the seven new TB cases, 14% of total participants were underweight. About 3.6% were diabetic and had most had irregular treatment. Smoking (41.4%), alcohol consumption (34.7%) and IV drug abuse (1.8%) in the past were reported by prisoners. These could be additional risk factors for acquiring TB and HIV.

In this context, active case finding for TB, HIV and their risk factors in the prison inmates is important. The SWOT analysis of a such a camp based, active screening activity, as undertaken in this study was prepared after a discussion with the study team (Fig. 1).

5. Conclusion

The prison under study receives active cases of TB and HIV into a setting where there are people vulnerable to acquire infection. Routine screening of all prisoners at the time of entry and monthly thereafter in a camp based approach should be adopted by the District TB team, not only to diagnose active TB but also to detect other prisoners at risk for acquiring TB. The screening should emphasize on the past history and treatment history for TB, HIV and Diabetes, to help maintain the continuum of care. A group of volunteer peers should be identified and trained in recognizing the symptoms of TB. The study team also felt the need of strengthening the health education provided to the inmates, both in terms of content and frequency, and establishing a strong peer support system for the same. Upon transfer or release of the prisoners receiving TB treatment or ART, they should be linked to the nearest public health facility for further follow up.

Source of support

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Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Dara M, Chorgoliani D, De Colombani P. TB prevention and control care in prisons. In: *Prisons and Health*. Geneva: World Health Organization; 2014:56–72.
2. Tuberculosis Coalition for Technical Assistance and International Committee of the Red Cross. *Guidelines for Control of Tuberculosis in Prisons*. 2009.
3. World Health Organization. *Global Tuberculosis Report 2017* [Internet]. France; 2017. Available from: https://creativecommons.org/licenses/by-nc-sa/3.0/igo.
4. Revised National Tuberculosis Control Programme. *National Strategic Plan for Tuberculosis Elimination 2017-2025*. 2017. New Delhi, India.
5. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8) [Internet] *J Am Med Assoc*. 2014;311:507–520. https://doi.org/10.1001/jama.2013.284427. Available from:.
6. National AIDS Control Organisation. *HSS Plus 2019: Central Prison Sites*. 2020. New Delhi, India.
7. Baussano I, Williams BG, Nunn P, Beggiato M, Fedeli U, Scano F. Tuberculosis incidence in Prisons: a systematic review. *PLoS Med*. 2010;7:1–10.
8. Niveau G. Prevention of infectious disease transmission in correctional settings: a review [Internet] *Public Health*. 2006;120:33–41. Available from: https://www.sciencedirect.com/science/article/pii/S003335060500154X.
9. Shin G, Khoshnood K. The impact of prison amnesties on tuberculosis control in Russia. *Harvard Health Pol Rev*. 2004;5:20–35.

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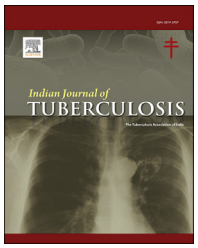
journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original article

Demographic, clinical and etiological profile of pericardial effusion in India: A single centre experience

Akshyaya Pradhan [a], *Pravesh Vishwakarma* [a], *Monika Bhandari* [a,*], *Rishi Sethi* [a], *B. Snigdha* [a], *V.S. Narain* [a], *Sharad Chandra* [a], *S.K. Dwivedi* [a], *Jyoti Bajpai* [b], *Suryakant Tripathi* [b], *Vikas Singh* [c]

[a] *Department of Cardiology, King George's Medical University, Uttar Pradesh, India*
[b] *Department of Respiratory Medicine, King George's Medical University, Uttar Pradesh, India*
[c] *Department of Cardiothoracic Vascular Surgery, King George's Medical University, Uttar Pradesh, India*

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ABSTRACT

Introduction: Pericardial effusion (PE) is a life-threatening condition. However, there are very few Indian studies which determined etiological distribution. The current retrospective observational study was carried out to assess etiological factors responsible for PE in a tertiary care centre in India.

Methods: The study enrolled consecutive 55 patients with the diagnosis of moderate to large PE as established by echocardiography between January 2018 and December 2018. The echocardiography guided percutaneous pericardiocentesis was performed by the standard procedure.

Results: Amongst the enrolled PE patients in the study, 30 (54.55%) were males and 25 (45.45%) were females, with the average age of 43.00 ± 15.54 years. In clinical assessment, tamponade was found in 52 (94.54%) patients. Tuberculosis was the most common etiology for PE (n=35, 63.64%) followed by hypothyroidism (n = 6, 10.9%), and malignancies (n = 4, 7.27%). Among 12.72% patients, the PE was of recurrent type. Additionally, no death or any complication was encountered during pericardiocentesis.

Conclusion: Pericardial disease and effusion is a major cause of morbidity in India. Despite developments in the healthcare facilities, tuberculosis was the most common etiology for PE. Additionally, the raised number of hypothyroid and malignant PE cases demonstrates the changing etiological trends, similar to western countries.

* *Corresponding author*. Tel.: +8800208247 (mobile).
E-mail address: drmonikab@gmail.com (M. Bhandari).

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1. Introduction

Pericardial effusion (PE) manifested as asymptomatic effusions to cardiac tamponade, is mostly detected trivially. Despite being a common finding in a variety of disease presentation, the data on prevalence and incidence of PE and also on its formation and removal is scarce.[1] The common etiology of PE may be a systemic or a cardiac disease, which, may produce effusions at varying rates in the pericardial space. The most common causes of PE include infections (viral, bacterial especially tuberculosis), malignancies, connective tissue disorders, pericardial injury syndromes like post myocardial infarction, post pericardiotomy or post −traumatic. The other common causes include metabolic (renal failure, hypoparathyroidism, myopericarditis, aortic dissection, drugs example minoxidil. The relative frequency of particular etiology varies according to the local epidemiology, like tuberculosis (>60%) is more common in developing nations and in areas where HIV is more prevalent. Whereas, malignancies (10–25%) and idiopatic (up to 50%) etiologies are more common in developed nations.[1,2] Moreover, the disease etiology also depends on the demographic characteristics of patients such as age, geography, and comorbidities.[2]

The clinical presentation of pericardial effusion varies according to the speed of pericardial fluid accumulation which itself depends upon the etiology. Even a small amount of rapid fluid collection can cause tamponade as in post myocardial infarction and traumatic cases. On the other hand, a slowly accumulating fluid causes symptom in days and weeks when a significant amount of fluid is accumulated.[1] As PE is life-threatening, it must be diagnosed as soon as possible for expedited treatment and management. However, the establishment of diagnosis using only the physical and clinical examinations is difficult and requires imaging diagnostic techniques such as ultrasound, cardiovascular magnetic resonance (CMR), computed tomography (CT) and echocardiography. Additionally, virology is not useful as because of the high cost involved, and negligible impact on the disease management.[3] Earlier, ultrasound was the gold standard, however, echocardiography is also feasible due to its ease of use, and availability, cost-effectiveness and comprehensive appraisal of the heart and its hemodynamics.[3] However, these days use of integrated multimodality imaging using various techniques is a fundamental of modern management of such conditions.[4]

There are very few studies carried out in India determining the prevalence and etiologies of PE. The current prospective observational study was conducted to assess the etiological factors responsible for PE in a tertiary care centre in India.

2. Materials and methods

2.1. Study design

This prospective, observational study was conducted in a tertiary care center, in India. The study enrolled consecutive 55 patients with the diagnosis of moderate to large PE with or without tamponade as established by echocardiography between January 2018 and December 2018. The diagnosis of PE and tamponade was made according to the standard criteria. In this study, PE considered as moderate when echo-free space in diastole was between 10 and 20 mm and large when echo-free space in diastole was ≥20 mm.[5] The written informed consent was obtained from all the enrolled patients.

2.1.1. *Inclusion criteria*

Any patient with moderate to large pericardial effusion who was able to give consent was included in study.

2.1.2. *Exclusion criteria*

Patients with life expectancy less than 1 year, or patients who failed to give written informed consent were excluded from the study.

2.2. *Data collection*

Patients' demographics and past medical history was recorded. Evaluation tests done find out the etiologies associated with the PE are enlisted below: Clinical Examinations, echocardiography, computed tomography (CT), chest X-ray examinations, pericardial fluid characteristics, complete blood profile, tuberculosis PCR/CB NAAT (Cartridge based nucleic acid amplification test), adenosine deaminase (ADA), ultrasound of abdomen, thyroid profile, viral markers, and anti-nuclear antibody (ANA). The echocardiography guided pericardiocentesis pericardiocentesis was performed by the standard procedure.[6] Data was collected at the baseline only and no follow-up was planned in the study. Patients received the treatment according to the etiology of pericardial effusion. The study protocol was approved by the Institutional ethics committee and conducted in accordance with the Declaration of Helsinki. The diagnosis of tubercular pericardial effusion was based on presence of lymphocytic predominant pericardial fluid along with positive ADA(cut off value > 30UL with 94% sensitivity and 68% specificity), or by TB PCR/CB NAAT, presence of active tuberculosis elsewhere in the body.[7]

2.3. *Statistical analysis*

The statistical package for social sciences (SPSS Statistics; Chicago, IL, USA) program, version 15 was used for statistical analysis. Continuous variables are presented as mean and standard deviation. Total numbers and proportions are used for categorical outcomes.

3. Results

3.1. *Baseline and demographic profile*

Baseline and demographic profile of the enrolled patients is shown in Table 1. Out of 6140 patients admitted to the emergency department, fifty five cases of large PE with or without tamponade were detected giving a annual prevalence of 0.92% (Fig. 1). Among 55 patients included in the study, 30 (54.55%) were male and 25 (45.45%) were female, with an average age of 43.00 ± 15.54 years. In the past history, dyspnea on exertion

was present in 51 (92.73%) patients followed by fever in 39 (70.91%) patients, cough in 32 (58.18%), and 16 (29.09%) patients with pedal edema.

3.2. *Clinical and radiological profile*

Among the enrolled patients, 52 (94.55%), had raised jugular venous pressure. Muffled heart sound was witnessed in 34 (61.82%) patients, tachycardia in 28 (50.91%) patients, and 29 (52.73%) patients had hypotension. Among the 55 PE patients included in the study, 52 (94.54%) patients had tamponade. The presenting symptoms of the enrolled patients are shown in Fig. 2. The average amount of pericardial fluid was 1130.36 ± 1529.80 ml. Straw colored pericardial fluid was found in 31 (56.36%) patients, and hemorrhagic in 22 (40.00%) patients. Only 1 (1.82%) patient had malignant cells present. Approximately ¼th (14 (25.45%) patients) of the population was tuberculosis positive. The majority of the patients showed normal ultrasound investigations. Among 55 patients, 53 (96.36%) patients showed no viral markers. Among the remaining 2 patients, 1 was hepatitis B virus surface antigen (HBSAg) positive and other was human immunodeficiency virus (HIV) positive. Majority of the patients, 49 (89.09%), were ANA negative (Table 2).

3.3. *Etiological profile*

The etiological profile of PE is shown in Fig. 3. Among 55 patients included in the study, in 35 (63.64%) patients the etiology for PE was tuberculosis and was the most common etiology. It was followed by hypothyroidism (10.9%), and malignancy (7.27%). Among 12.72% of patients, the PE was recurrent type. Additionally, 3 (5.45%) patients having tuberculous etiology showed constrictive pericarditis.

Table 1 – Baseline demographic characteristics of the study population.

Variable, n (%)	n = 55
Age, Mean ± SD	43.00 ± 15.54 years
Gender, n (%)	
Male	30 (54.55%)
Female	25 (45.45%)
Past History, n(%)	
Dyspnea on exertion	51 (92.73%)
Fever	39 (70.91%)
Cough	32 (58.18%)
Pedal Edema	16 (29.09%)
Systemic illness	
1. anemia, bleeding per vagina	1 (1.82%)
2. Ascites	1 (1.82%)
3. Carcinoma Lung	1 (1.82%)
4. Chronic kidney disease	1 (1.82%)
5. Dengue	3 (5.45%)
6. Hypothyroid	3 (5.45%)
7. Intracranial hemorrhage, Chronic kidney disease	1 (1.82%)
8. Non-Hodgkin's Lymphoma with pleural effusion	1 (1.82%)
9. Pulmonary Tuberculosis	1 (1.82%)
10. Tuberculosis	6 (10.91%)
11. Tuberculus Pleural effusion	2 (3.64%)

Table 2 – Clinical and radiological profile of the study population.

Clinical profile, n (%)	n = 55
Hypotension	29 (52.73%)
Tachycardia	28 (50.91%)
Muffled Heart Sounds	34 (61.82%)
Raised Jugular venous pressure	52 (94.55%)
Tamponade	52 (94.54%)
Total Lung capacity, Mean ± SD	2628 ± 5150.60 ml
Pericardial fluid volume, Mean ± SD	1130.36 ± 1529.80 ml
Pericardial fluid analysis, n (%)	
Hemorrhagic	22 (40.00%)
Purulent	02 (3.64%)
Straw	31 (56.36%)
Malignant Cells	1 (1.82%)
Gram Stain	0
Acid fast bacilli Stain	0
TB PCR/CB NAAT (Cartridge based nucleic acid amplification test) positive, **n (%)**	14 (25.45%)
Thyroid	
T3, Mean ± SD (n = 15)	22.80 ± 37.18 ng/dL
T4, Mean ± SD (n = 15)	5.30 ± 4.53 ng/dL
TSH, Mean ± SD (n = 47)	9.86 ± 36.72 μU/mL
Viral Markers, n (%)	
Hepatitis B virus surface antigen positive	1 (1.82%)
Human immunodeficiency virus positive	1 (1.82%)
Anti-nuclear antibody positive	6 (10.92%)
Blood Tests	
Hemoglobin	11.18 ± 1.78g/dL
Serum Creatinine	1.37 ± 2.40mg/dL
Blood urea	37.96 ± 38.76mg/dL
Random blood sugar	117.44 ± 25.98 mg/dL
Serum sodium	136.11 ± 4.41 mmol/L
Serum potassium	4.30 ± 0.65 mmol/L
Mean cell volume	83.91 ± 8.76
Mean cell hemoglobin concentration	33.11 ± 3.19 g/dL

The etiological comparison between de novo and recurrent PE showed that tuberculosis is the key etiological factor. It is followed by hypothyroidism and malignancy for de novo and dengue and bacterial infection as the major etiologies for recurrent PE (Table 3 & 4). The presenting symptoms like raised jugular venous pressure, dyspnea on exertion, pedal edema, and muffled heart sounds are strongly associated with PE. However, none of the PE patient with pedal edema had hypothyroidism. However, 94.54% of PE patients were diagnosed with tamponade. Additionally, muffled heart sounds are associated mostly with tuberculosis, and malignant PE. In the current study, among patients aged ≤65 years, the incidence of infective etiology is large. While, no gender influence on the incidence of PE was observed (Table 5).

4. Discussion

The present study demonstrated tuberculosis as the most common etiology of PE in about 61.81% of patients, followed by hypothyroidism and malignancy. The cardiac tamponade was present in almost all patients except 3 cases. Additionally, no death or any complication was encountered during

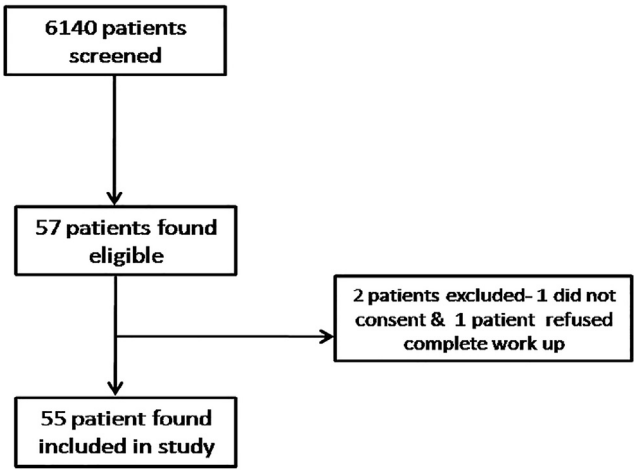

Fig. 1 – Number of participants in the study.

pericardiocentesis. Overall, the outcomes encountered in PE patients were favorable. The classical symptoms of PE are dyspnea on exertion progressing to orthopnea, chest pain and or fullness.[1] In our study dyspnea on exertion was found in 92.73% of patients.

The hemodynamic significance of PE mainly depends upon the speed of pericardial fluid accumulation. The rapid accumulation of pericardial fluid measuring only 200ml may cause tamponade, on the contrary, the large amount accumulated slowly may not have haemodynamic effect.[5,8] The cardiac tamponade is clinically featured by hypotension, pulsus paradoxux, jugular venous distension, and muffled or absent heart sounds.[9] In the current study majority of the patients presented with hypotension (52.73%), muffled heart sound (61.82%) and raised jugular pressure (94.55%) while pedal edema was found in 29.09% of the patients. In the current study 94.54% of patients had cardiac tamponade. Thus, compared to the previous studies the rate of cardiac tamponade was relatively high.[10,11] It is largely attributable to the inclusion criteria of our study, which have specifically enrolled only moderate to large PE patients requiring hospitalization. Various studies have also shown that the development of cardiac tamponade is more common with bacterial (eg, tuberculosis), post radiation pericardial diseases and pericardial injury syndromes. Also the size is also correlated to prognosis as the moderate to large effusion are more prone to progress into tamponade.[1]

The presenting symptoms in the current study were dyspnea, fever and cough. The proportion of presenting symptoms in our study was similar with the study conducted by Himalayan Institute of Medical Sciences in Uttarkhand. They found dyspnea in 75%; cough in 30%; and fever in 30% patients.[12] In the study conducted by Jain et al tuberculosis is the most common cause of tamponade followed by malignancy.[13] The finding is in line with the finding of our study. We observed that muffled heart sound, hence, tamponade is strongly associated with both tuberculosis and malignancy in PE patients. Manjusha et al observed that, adult male (40–59 years) patients are more associated with PE.[10] In the current study, we also noted that the higher incidence of PE in adults aged less than 65.

In the diagnosis of PE, echocardiography is the major diagnostic tool, and is also useful in the pericardiocentesis.[3] In the current study we used echocardiography, chest X-ray, and CT scan to confirm the diagnosis along with clinical and pathological tests. In the current study all patients showed cardiomegaly on chest X-ray. The CT scan which is highly sensitive in the detection of tuberculous PE,[14] study it has helped in identifying PE and malignancy. All patients in the current study underwent echocardiography guided pericardiocentesis, and no in-hospital death was recorded. The pericardiectomy is preferred in conditions like recurrent pericarditis, effusive constrictive or constrictive disease.[8] In our study study, 7 (12.72%) patients had recurrent pericarditis,

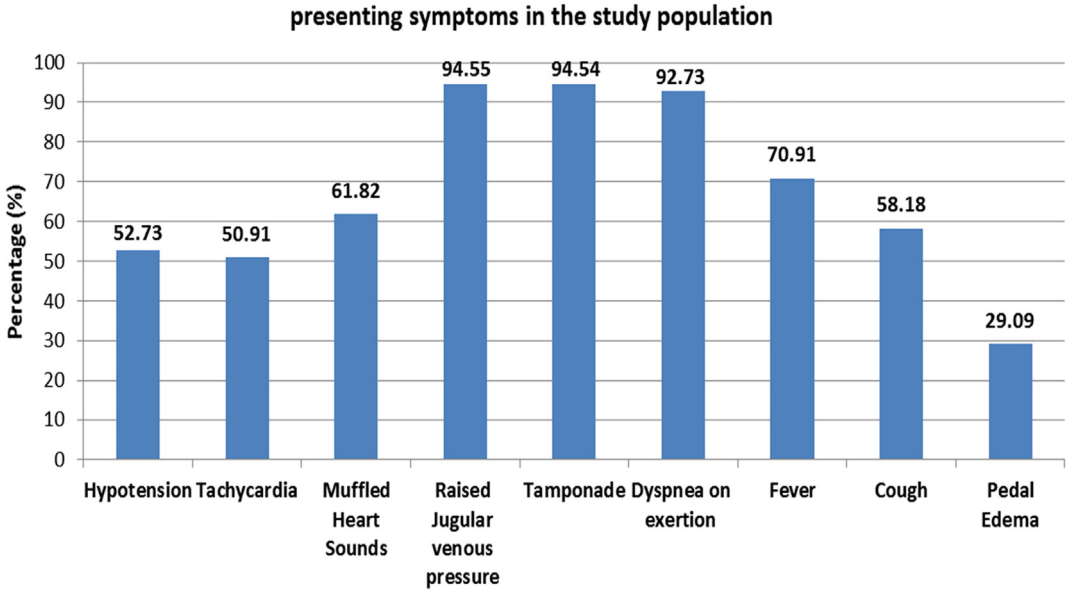

Fig. 2 – Presenting symptoms in the study population.

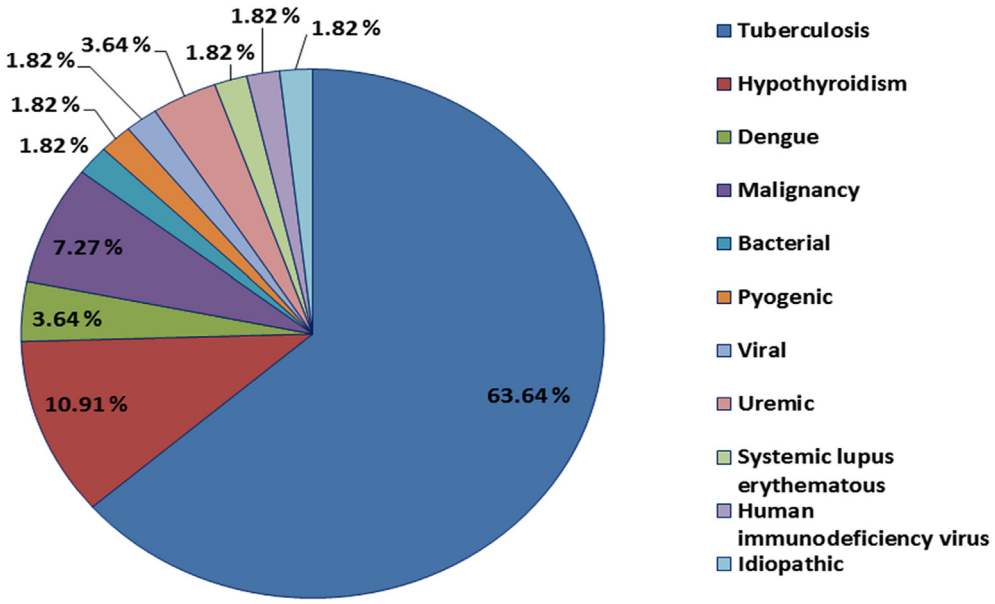

Fig. 3 – Etiological distribution of pericardial effusion in the study population.

and 3 (5.45%) patients had constrictive pericarditis. However, we haven't discussed further treatments of the patients in this study except pericardiocentesis, as it is out of the scope of this article.

Tuberculosis is a leading cause of pericarditis in developing Asian-Africa countries, as opposed to developed countries where tuberculous pericarditis accounts rarely up to 4%.[15,16] In tuberculosis the fluid in pericardium is accumulates slowly and it can only be incidentally and is asymptomatic. So the early detection of effusions is difficult and this can cause tamponade at a late stage.[17] In spite of advancing medical treatment in the developing countries, the tuberculosis is still endemic. Additionally, the high prevalence of TB has also been attributed to the increasing number of HIV positive cases in such countries.[18] The estimated burden of TB in India was approximately 2.790 million, among them 87,000 were HIV positive in 2016.[19] In the current study, 61.81% patients had tuberculosis and is a number one etiology for PE. Although, in the current study there was only one (1.81%) HIV positive patient.

Hypothyroidism, a disease with a multi systemic character that may present clinically in various forms, one being unusual pericardial effusion, is a cardiovascular complication that, according to the literature, is associated with hypothyroidism in 30%–80% of cases.[20,21] However, the occurrence of hypothyroidism and pericardial tamponade is a rare event. Pericardial effusion has a high concentration of protein and, like other serous effusions of hypothyroidism, its pathogenesis is not fully understood.[22] The slow accumulation of liquid observed in the pericardial space causes frequent rarity of hemodynamic premonitory signs, even in the presence of large effusions. Hypothyroidism is closely associated with PE, also, in our study hypothyroidism is the second commonest cause of PE. With increase in the severity of hypothyroidism, severity of PE increases and it is frequently associated with the myxedema.[23] In the study by Gunasekaran et al the rate of PE in hypothyroid patients was 17%.[24] Another study conducted by Rachid, et al demonstrated 15 patients with PE among 20 patients with hypothyroid cardiomyopathy.[25]

In the first world countries malignant pericarditis is comparatively more common. The study conducted in Mayo clinic, in 2003, on 1127 patients showed that the major etiology of pericardial effusion was malignancy, whereas tuberculosis etiology was rare.[8] Some other studies from developed countries also demonstrated malignancy as the prime cause of PE.[13,26,27] Additionally, in the current study it is the third most common cause of pericarditis and PE. The findings in our study are in line with an Indian study where one third patients

Table 3 – Etiological distribution of *De novo* pericardial effusion patients.

Etiological factor	N, %
Tuberculosis	35 (63.64%)
Hypothyroidism	6 (10.9%)
Dengue	2 (3.64%)
Malignancy	4 (7.27%)
Pyogenic	1 (1.81%)
Viral	1 (1.81%)
Uremic	2 (3.63%)
Systemic lupus erythematous	1 (1.81%)
Human immunodeficiency virus	1 (1.81%)
Idiopathic	1 (1.81%)

Table 4 – Etiological distribution of recurrent pericardial effusion patients.

Etiological factor	N, %
Tuberculosis	5 (71.42%)
Dengue	1 (14.28%)
Bacterial	1 (14.28%)

Table 5 – Correlation between the demographic and etiological profile of patients.

Etiological Factors	Tuberculosis	Hypothyroidism	Dengue	Malignancy
Age (<65 years)	33 (94.28%)	6 (100%)	2 (100%)	3(75%)
Gender:				
Male	14 (40%)	4 (66.66%)	0 (0%)	2 (50%)
Female	21 (60%)	2 (33.33%)	2 (100%)	2 (50%)
Muffled Heart Sounds	25 (71.42%)	1 (16.66%)		3 (75%)
Raised JVP	32 (91.42%)	6 (100%)	2 (100%)	4 (100%)
Dyspnea on exertion	33 (94.28%)	5 (83.33%)	1 (50%)	4 (100%)
Tamponade	33 (94.28%)	6 (100%)	1 (50%)	4 (100%)
Pedal Edema	9 (25.71%)			3 (75%)

had malignant pericarditis.[28] The changing trend in the etiology of PE and pericarditis is mainly attributed either to the increased incidence and diagnosis of malignancies, or better control measures and management of tuberculosis with a comparatively low incidence of HIV in this region.

Overall, the etiological distribution found in our study is quite similar with previous other studies conducted in India. In the study conducted by Manjusha et al, the etiological profile of PE patients showed following distribution: tuberculosis (33.33%), uremia (20%), viral/idiopathic (16.67%), bacterial (10%), malignancy (10%), hypothyroidism (3.33%), and post MI with ischemic cardiomyopathy (3.33%), systemic lupus erythematous (SLE) (3.33%) and HIV (10%).[10] Another prospective study conducted by Agarwal et al, in Rohilkhand, in 322 consecutive PE patients. They showed 80% were TB+/HIV-; 10% TB+/HIV+, 4% septic pericarditis and 1% uraemic pericarditis, 4% Neoplastic, 1% miscellaneous etiologies for PE.[29] These studies highlight the fact that the etiological distribution in various regions is different with the difference in the demographic and clinical profile of the patients.

4.1. *Study limitations*

The study is limited by its small sample size. The current study only included the patients with moderate to severe effusion requiring hospitalization, hence, the patients with clinically insignificant or mild effusion treated on ambulatory basis were excluded. Additionally, the study is limited by lacking the data related to treatment and, follow-up, and the observational study design.

5. Conclusion

Despite of developments in the healthcare facilities, PE is a major cause of morbidity in India. Tuberculosis is the most common etiology of PE which is followed by hypothyroid and malignant etiologies. Additionally, increased cases of hypothyroid and malignant etiologies demonstrate the changing etiological trends of PE.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Imazio M, Adler Y. Management of pericardial effusion. *Eur Heart J*. 2012;34(16):1186–1197.
2. Willner DA, Kiel J. *Pericardial Effusion. Treasure Island (FL)*. StatPearls Publishing; 2019.
3. Perez-Casares A, Cesar S, Brunet-Garcia L, Sanchez-de-Toledo J. Echocardiographic evaluation of pericardial effusion and cardiac tamponade. *Frontiers in pediatrics*. 2017;5:79.
4. Klein AL, Abbara S, Agler DA, et al. American society of echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the society for cardiovascular magnetic resonance and society of cardiovascular computed tomography. *J Am Soc Echocardiogr*. 2013;26(9):965–1012. official publication of the American Society of Echocardiography e15.
5. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; the Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. *Eur Heart J*. 2004;25(7):587–610.
6. Özer OH, Davutoglu V, Çakýcý M, et al. Echocardiography-guided pericardiocentesis with the apical approach. *Turk Kardiyol Dernegi Arsivi*. 2009;37(3):177–181.
7. Burgess IJ, Reuter H, Carsytens ME, et al. The use of adenosine deaminase and interferon gamma as diagnostic tools for tuberculous pericarditis. *Chest*. 2002;122:900–905.
8. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Outcomes of clinically significant idiopathic pericardial effusion requiring intervention. *Am J Cardiol*. 2003;91(6):704–707.
9. Pannu AK, Sandal R, Singh H, Suri V, Bhalla A, Kumari S. Tuberculous pericarditis: a review. *Cell Cellular Lif Sci J*. 2018;3(3), 000130.
10. Manjusha M, Manoj Kumar B, Venkat Rajaiah N, Narayana P. Study of characteristic of pericardial effusion and to analyze pericardial fluid in various etiologies. *IAIM*. 2017;4(10):221–229.
11. Yaqoob I, Khan K, Beig J, et al. Etiological profile of pericardial effusion in kashmir: a study from northern India. *IIJMMS*. 2016;3:2408–7246.
12. Singh Y, Ahmed S, Srivastava S, Verma SK, Shirazi N, Surya AD. Trends in aetiology and outcome of patients with pericardial effusion: a five-year experience. *Jiacm*. 2008;9(2):96–99.
13. Jain S, Sharma N, Varma S, Rajwanshi A, Verma JS, Sharma BK. Profile of cardiac tamponade in the medical emergency ward of a North Indian hospital. *Can J Cardiol*. 1999;15(6):671–675.

14. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart*. 2000;84(2):183–188.
15. Fowler NO. Tuberculous pericarditis. *Jama*. 1991;266(1):99–103.
16. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tuber Lung Dis*. 1992;73(6):311–321. the official journal of the International Union against Tuberculosis and Lung Disease.
17. Ivens EL, Munt BI, Moss RR. Pericardial disease: what the general cardiologist needs to know. *Heart*. 2007 Aug;93(8):993–1000.
18. Kanabus A. *Information about Tuberculosis*. GHE.; 2018. Available from: www.tbfacts.org.
19. Hardisty CA, Naik DR, Munro DS. Pericardial effusion in hypothyroidism. *Clin Endocrinol*. 1980;13(4):349–354.
20. Hardisty CA, Naik DR, Munro DS. Pericardial effusion in hypothyroidism. *Clin Endocrinol*. 1980;13:349–354 [Links].
21. Kerber RE, Sheman B. Echocardiographic evaluation of pericardial effusion in myxedema. Incidence and biochemical and clinical correlations. *Circulation*. 1975;52:823–827.
22. Parving HH, Hansen JM, Nielson SL, Rossing N, Munck O, Lassen NA. Mechanisms of edema formation in myxedema: increased protein extravasation and relatively slow lymphatic drainage. *N Engl J Med*. 1979;301:460–465.
23. Gunasekaran A, Karunanidhi K, Ramasamy J. A study on prevalence of pericardial effusion in newly diagnosed adult hypothyroid patients. *IAIM*. 2018;5(5):83–86.
24. Rachid A, Caum LC, Trentini AP, Fischer CA, Antonelli DAJ, Hagemann RP. Pericardial effusion with cardiac tamponade as a form of presentation of primary hypothyroidism. *Arq Bras Cardiol*. 2002;78(6):583–585.
25. Sagrista-Sauleda J, Merce J, Permanyer-Miralda G, Soler-Soler J. Clinical clues to the causes of large pericardial effusions. *Am J Med*. 2000;109(2):95–101.
26. Corey GR, Campbell PT, Van Trigt P, et al. Etiology of large pericardial effusions. *Am J Med*. 1993;95(2):209–213.
27. Levy PY, Corey R, Berger P, et al. Etiologic diagnosis of 204 pericardial effusions. *Medicine*. 2003;82(6):385–391.
28. Cherian G, Uthaman B, Salama A, Habashy AG, Khan NA, Cherian JM. Tuberculous pericardial effusion: features, tamponade, and computed tomography. *Angiology*. 2004;55(4):431–440.
29. Agarwal N, Chaturvedi A, Agarwal S, Mehra D, Kumar A, Statiction MS. Prevalence of tubercular pericardial effusion in Rohilkhand region, a prospective study. *International Journal of Applied Research*. 2017;3(9):298–301.

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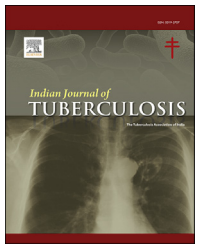

Review article

Drug resistant tuberculosis: Current scenario and impending challenges

*Shivendra Singh Dewhare**

School of Studies in Life Science, Pt. RavishankarShukla University, Raipur, 492010, Chhattisgarh, India

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ABSTRACT

Tuberculosis is still one of the ten leading causes for death worldwide. In spite of the latest medical and health advance gained over a period of time, tuberculosis effectively evades the successful targeting by drugs. The persistence abilities demonstrated by the mycobacteria had surprised the global community, since its discovery and pathogenesis in humans. Emergence and detection of drug resistant mycobacteria (MDR-TB, XDR-TB) had further complicated the treatment regime. Under the aegis of WHO, there is a concerted understanding and effort by the global community to eradicate TB. Towards this goal, novel drug molecules, new vaccine and treatment regime are being developed. Here, our current understanding pertaining to mode of action, molecular mechanisms of novel as well as traditional drug molecules and possible drug resistance mechanism in *M. Tuberculosis* is reviewed. Recent advances on new vaccination regime are also reviewed as it demonstrated huge potential in containing TB. This knowledge is essential for the development of more effective drug molecules, vaccines and may help in devising new strategy for containing and eradicating TB.

1. Introduction

Tuberculosis has become an epidemic in the world amounting to approximately one fourth of the world's population being infected with the latent form of tuberculosis.[1] According to World Health Organization (WHO), a total of 1.4 million people died from TB in 2019 (including 2, 08,000 people with HIV). Epidemiologically, TB is still one of the top 10 causes of death from a single infectious agent (above HIV/AIDS). *Mycobacterium tuberculosis* (MTB), the causative agent, primarily affects human lungs (pulmonary tuberculosis, PTB), but can affect other tissues and organs such as brain, bone and liver.[2,3] TB is predominant in developing countries due to poor heath regime and lack of awareness. Majority of the people who developed tuberculosis in 2019 were localized in South East Asian countries (44%), followed by Africa (25%), Western Pacific (18%), Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%). Eight countries, namely India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%), accounted for almost two thirds of the total patients.[4] Emergence of drug-resistant TB had further complicated the treatment regime and poses a grave threat to public health. Globally in 2019, close to half a million people developed rifampicin-resistant TB (RR-

* *Corresponding author.*
E-mail address: shivendraprsu@gmail.com.
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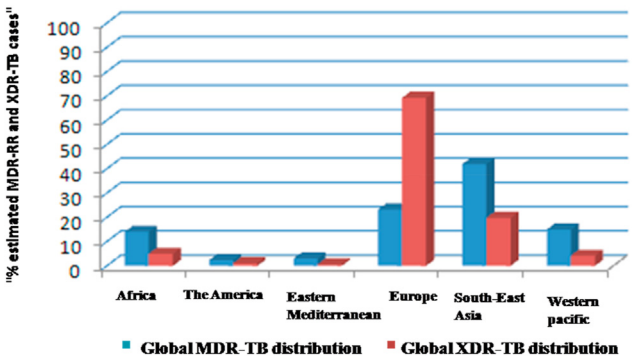

Fig. 1 – Global percentage burden of MDR-TB and XDR-TB cases.[4]

TB) of which 78% had multidrug-resistant TB (MDR-TB). Globally, of all the TB cases documented, 3.3% new and 17.7% of previously treated cases were found to contain MDR/RR-TB strains. Worldwide, 2,06,030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected in 2019 which amounts to a net10% increase from the cases reported in 2018. Currently, about half of the global burden of MDR-TB is in 3 countries – India, China and the Russian Federation. Furthermore, a global total of 12,350 people with XDR- TB were detected in 2019, with majority of cases reported from Europe (Fig. 1). Now, MDR-TB strains which demonstrate additional resistance to any fluoroquinolone along with at least one of three injectable drugs (Amikacin, kanamycin, or capreomycin) are classified as XDR-TB.[5]

M. tuberculosis, the causative agent for TB, is able to evade the host defence mechanism as well effectively circumvent the effects of TB drugs. Some of the possible reasons which are attributed for its survival are its slow generation time, ability to stay dormant and the presence of complex cell wall structure, amongst other mechanisms. Moreover, incomplete drug regime followed by patients is giving rise to drug resistant tuberculosis bacteria (MDR, XDR strains), which are slowly becoming difficult to treat using first and second line TB drugs.[6] Although there are upcoming new generation drug molecules which are showing promising results, but most of them are in clinical trials and it will take considerable time before it reaches masses.

2. Advancements in testing and tuberculosis diagnostic

Traditionally, diagnosis of TB including the MDR/XDR-TB strains has relied on phenotypic drug susceptibility testing, such as sputum smear microscopy and culture-based methods. While considered as gold standard for identification, it demands significant skill, resource and time, which occasionally hampers the rapid treatment and judicious management of TB.

However, with the advent and approval by WHO, the rapid molecular testing of TB had managed to significantly reduce the detection time (within 2 h) and considerably improved the accuracy of detecting MDR/XDR-TB. The molecular testing performed are nucleic acid amplification test (NAAT), example being are Gene-Xpert/RIF MTB assay, Amplified Mycobacterium Tuberculosis Direct (MTD) Test and Amplicor *Mycobacterium tuberculosis* Test. Apart from NAAT tests other detection tests include, line probe assay, lateral flow lipoarabiomannan assay (LAM) and whole genome sequencing (WGS) technique is also being used to accurately predict the drug resistant TB strains.[7] In 2020, a rapid communication by WHO had endorsed the use of India-made Truenat MTB assay, which has high accuracy for molecular diagnostic test of pulmonary and extra-pulmonary TB and rifampicin-resistant TB. The Overall sensitivity of the Truenat MTB assay was found to be 83% and that of the MTBPlus assay 89%. Specificity was found to be 99% for the MTB and 98% for the MTBPlus assay. The sensitivity and specificity was found to be comparable to Xpert and Xpert Ultra, but had significant cost benefit well suited for low cost operation required in developing countries.[8]

3. Treatment regime and resistance mechanism

Streptomycin, the first antibiotic, was used for the treatment of TB, however it was soon realized that, the mycobacteria had rapidly developed drug resistance, which ultimately leads to high treatment failure rate.[9] To overcome this problem, combination therapy involving at least two active drugs was used to prevent tuberculosis resistance.[10] One of the major concerns was the relapse of tuberculosis, which often happens due to incomplete medication regime. Combination therapy involving isoniazid for 18–24 months, demonstrated a remarkable success rate.[11] The course of treatment was further reduced to 6–9 months, with the addition of rifampicin using the combination therapy.[12] Use of Ethambutol demonstrated additional protective function, wherein isoniazid and rifampicin resistance was present. Inclusion of pyrazinamide in the combination therapy significantly shortened the treatment course to 6 months.[13]

Early on, the drug resistance phenomenon in tuberculosis was recognized and documented, but the molecular mechanism responsible is still being worked out. This had led to the switching of morphological or phenotypic study towards chromosome mutation study, thereby assisting in the study of molecular mechanism towards drug resistance. Interestingly, all the drug resistance mutations can be attributed to spontaneous chromosomal alterations. These mutations are confined to restricted gene loci. Rifampicin and fluoroquinolones resistance are mapped to *rpoB* and *gyrA* genes and can be rapidly diagnosed (within 2 h) by a fully-automated platform i.e. Xpert MTB/RIF (Cepheid).[14]

4. Standard therapy for drug-susceptible tuberculosis: mode of action, mechanisms and resistance

4.1. *Isoniazid*

Introduced in 1952, the isoniazid (INH) is probably the most effective and specific drug to act against tuberculosis and

exhibited excellent early bactericidal activity resulting in inhibition of colony forming units.[15] INH enters the mycobacterial cell wall by passive diffusion and exhibits actively towards fast growing tubercle bacilli, whereas it does not show activity against non-replicating bacilli.[16] INH, which is a prodrug, is activated by the mycobacterial catalase peroxidase enzyme KatG.[15] Activated INH further inactivates the NADH-dependent enoyl-acyl carrier protein reductase, which is encoded by *inhA*, thus inhibiting the synthesis of essential mycolic acids.[17] The minimal inhibitory concentration of INH for tuberculosis is 0.2 μg ml^{-1}. Isoniazid resistance are associated with mutations in genes *katG* and *inhA*. Single base mutation S315T in *katG* gene causes deficient complex formation between INH and NAD.[18] Also, mutation in the promoter region of *inhA* causing an overexpression of InhA, which resulted in the low level INH resistance along with cross resistance to ethionamide.[15,17]

4.2. *Rifampicin*

Introduced in 1972, rifampicin exhibited excellent sterilizing activity against tubercle bacilli.[19] Rifampicin binds to the β-subunit of RNA polymerase (*rpoB*) and interferes with RNA synthesis.[20] Rifampicin is also effective against actively growing and slowly metabolizing (non-growing) bacilli.[21] The minimal inhibitory concentration of RIF for tuberculosis is 0.8 μg ml^{-1}. Rifampicin resistance-determining region also called as "hot-spot region" is an 81-bp spanning codon of the *rpoB* gene which is responsible for resistant to rifampicin.[20]

4.3. *Pyrazinamide*

Introduced in early 1950s, Pyrazinamide is an important first-line antituberculosis drug. Pyrazinamide is a pro-drug and is acted upon by the enzyme pyrazinamidase/nicotinamidase (coded by the *pncA* gene) and is converted to its active form i.e. pyrazinoic acid[22] which in turn inhibit the fatty acid synthase type I in growing *M. tuberculosis* bacilli.[23] Pyrazinamide also has the ability to inhibit semidormant bacilli.[24] The minimal inhibitory concentration of pyrazinamide for tuberculosis is 20 μg ml^{-1}. Resistance to Pyrazinamide is attribute to mutation in *pncA* gene, which causes reduction in PZase activity.[25]

4.4. *Ethambutol*

Introduced in 1966, ethambutol is also an important first line tuberculosis drug. Ethambutol is bacteriostatic against rapidly dividing bacilli. It interfere with the biosynthesis of arabinogalactan by inhibiting the gene product of the *embCAB* cluster (codes for arabinosyl transferase), thus effectively inhibiting the biosynthesis of cell wall.[26] The minimal inhibitory concentration of EMB for tuberculosis is 1–5 μg ml^{-1}. Resistance to ethambutol is attributed to mutation in the *embCAB* operon.[27]

5. Current recommended WHO treatment regimen for MDR-TB

Patients diagnosed with MDR-TB faces multiple hurdles in their treatment, as it incorporate drugs which display reduced efficacy and increased toxicity. According to the WHO 2019 guidelines, all three Group A agents, which includes bedaquiline and linezolid and one of the fluoroquinolones such as levofloxacin or moxifloxacin and at least one Group B agent (clofazimine and cycloserine or terizidone) should be included for the treatment of MDR-TB.

However, if one or two Group A agents are used for the treatment, then both Group B agents must be included. Further, if the treatment schedule is devoid of Groups A and B agents, then Group C agents must be included to complement the medication course.[28] Consequently, the drugs have been grouped accordingly to WHO guidelines and their proposed mechanism along with mode of resistance is discussed below.[29]

5.1. *Group A drugs*

5.1.1. *Moxifloxacin and Levofloxacin*

Moxifloxacin and levofloxacin belongs to class fluoroquinolones and exhibits excellent antimicrobial activities. These drugs binds and target bacterial topoisomerases (DNA gyrase) enzyme which are encoded by genes i.e. *gyrA* and *gyrB*. These drugs interfere with DNA replication, repair, and transcription eventually resulting in death of the bacteria. . Moxifloxacin and Levofloxacin had demonstrated activity against MDR as well as XDR-TB with an MIC value in the range of 0.032–0.5 and 0.125–0.5 μg ml^{-1}respectively.Presence of single or double missense mutations in quinolone-resistance-determining region (QRDR) have been attributed to the fluoroquinolones resistance in tuberculosis.[30]

5.1.2. *Linezolid*

Linezolid is one of the first oxazolidinone approved for clinical use and it is recently re-classified as a Group A drug by the World Health Organization (WHO). Linezolid acts by inhibiting protein synthesis at an early stage of translation by binding to the 70S initiation complex of bacterial ribosomes.[31] Linezolid had demonstrated activity against MDR as well as XDR-TB with an MIC value in the range of 0.125–0.5 μg ml^{-1}. Mutation in *rrl* and *rplC* genes are implicated in the resistance to Linezolid in mycobacteria.[32,33]

5.1.3. *Bedaquiline*

Bedaquiline belongs to group of drugs known as diarrylquinolines. It has been recently included in group A drugs for the treatment of MDR-TB. Bedaquiline targets *atpE* gene coding for the subunit c of the ATP synthase complex. It binds specifically and inhibit mycobacterial ATP synthase.[34] Bedaquiline had demonstrated activity against MDR TB with an MIC value in the range of 0.0039–0.25 μg ml^{-1}. Mutations in *atpE* and *Rv0678* genes are associated with Bedaquiline resistance.[34–36]

5.2. *Group B drugs*

5.2.1. *Clofazimine*

It belongs to a member of class riminophenazine drugs and is used for the treatment of TB.[37] This drug has also been used for the treatment of leprosy.[38] Clofazimine might acts as a prodrug, which is reduced by the enzyme NADH dehydrogenase. Possible mode of bacterial inhibition is attributed to the

interference in the electron transport and ATP synthesis. Clofazimine had demonstrated activity against MDR as well as XDR-TB with an MIC value in the range of 0.12–0.25 μg ml^{-1} Mutations in *Rv0678* genes is thought to be associated with Clofazimin resistance.

5.2.2. *Cycloserine or terizidone*

Cycloserine is a broad-spectrum bacteriostatic. It is a cyclic derivative of serinehydroxamic acid and its structural analog, terizidone is a condensation product containing two cycloserine molecules. They inhibit cell wall synthesis by blocking enzyme such as alanine racemase and D-alanine:D-alanine ligase.[39] Cycloserine had demonstrated activity against TB with an MIC value in the range of 25–75 μg ml^{-1}. Mutations in *alr* gene is thought to be associated with cycloserine resistance.[40]

5.3. *Group C drugs*

5.3.1. *Delamanid*

Delamanid is a novel anti-TB agent belonging to nitroimidazole class. It is also referred as OPC-67683, and is a prodrug which gets activated by the enzyme deazaflavin dependent nitroreductase. Delamanid have been shown to have activity against both replicating and non-replicating, as well as drug-resistant TB, Delamanid acts by inhibiting the synthesis of cell wall components (methoxy mycolic acid and ketomycolic acid).[41] Delamanid had demonstrated activity against MDR as well as XDR-TB with an MIC value in the range of 0.006–0.024 μg ml^{-1}. Mutations in *fbiA*, *fbiB*, *fbiC*, *ddn* and *fgd1* genes are thought to be associated with delamanid resistance.[42]

5.3.2. *Imipenem-cilastatin or meropenem*

Imipenem and meropenem belong to class of antibiotics known as carbapenems. Equal concentrations of cilastatin. is always included along with imipenem while administering the drug. Presence of methyl group in the carbapenem moiety of meropenem is the distinguishing feature from imipenem.[43] Both drugs bind to high molecular weight penicillin-binding proteins (PBPs) with very high affinity and causes inhibition of cell wall. Meropenem has an MIC value of 2.5 μg ml^{-1} against MDR TB.

5.3.3. *Amikacin or streptomycin*

Amikacin is a bactericidal and is the most widely used semisynthetic aminoglycoside antibiotics. Amikacin inhibits protein synthesis by binding to 16S rRNA in the 30S small ribosomal subunit.[44] The minimal inhibitory concentration of amikacin for tuberculosis is 4–8 μg ml^{-1}. Mutations were found in the *rrs*, *tlyA*, *eis* promoter and *gidB* genes which were associated with amikacin resistance.[45]

Streptomycin is highly bactericidal against replicating tubercle bacilli and belongs to aminoglycoside class of antibiotic. It exerts its action by inhibiting the initiation of the translation in the protein synthesis by binding to 16S rRNA in the 30S small ribosomal subunit.[46] Streptomycin has an MIC value of 5.0 μg ml^{-1} against TB. Streptomycin resistance in mycobacteria is associated with mutations in *rpsL*, *rrs* and *gidB* genes.[47,48]

5.3.4. *Ethionamide or prothionamide*

Ethionamide and prothionamide are bacteriocidal and are thioamide drugs. Both being pro drugs are activated by independent enzymes EthA and KatG. Ethionamide and prothionamide inhibit mycobacterial fatty acid synthesis by targeting InhA. Ethionamide has an MIC value of 2.5 μg ml^{-1} against MDR TB. Mutations in the *inhA* promoter region confer ethionamide resistance.[17] Also, a mutation in the *ethA* gene is responsible for the resistance conferred to mycobacterium.[49]

5.3.5. *Para-aminosalicylic acid*

Para-aminosalicylic acid is a prodrug and is a structural analog of p-aminobenzoic acid. It inhibits the growth of bacteria by binding with dihydrofolate reductase, thus effectively inhibiting folate metabolism.[50] PAS has an MIC value of 0.063 μg ml^{-1} against MDR TB Mutation in the *thyA* gene is thought to confer resistance to p-aminosalicylic acid.

Pyrazinamide and ethambutol mode of action and mechanism of resistance is discussed in section 4.3 and 4.4.

6. Clinical trial of new candidate drugs and their potential target

Recently, WHO has approved the use of two drugs namely, bedaquiline and delamanid for the treatment of MDR and XDR-TB strain. This development has positively fuelled the desire to discover new drug molecules capable of targeting TB. With the advent of information in understanding the TB pathogenesis and novel scientific breakthrough pertaining to mycobacteria, can help in devising new drug molecules. Globally, there is a general consensus that discovery of new potential drug compounds is the need of hour to contain and eradicate TB. According to WHO, as of August 2020, there are 22 drugs in Phase I, II or III trials, which includes 13 new compounds namely BTZ-043, delpazolid, GSK-3036656, macozinone, OPC-167832, Q203, SQ109, SPR720, sutezolid, TBAJ-876, TBA-7371, TBI-166 and TBI-223(Table 1).

7. Clinical development of new TB vaccine: current status

TB vaccination is probably one of the safest methods to fight against tuberculosis amongst all the other strategy available. Proper vaccination successfully prevents the risk of infection and also helps in containing the spread of mycobacteria. One of the top priorities is to achieve “Herd immunity” in general population as it will greatly reduce the spread of TB. Now, BCG vaccination is probably one of the most preferred methods of protection against TB in early childhood. However, after BCG, which was introduced in 1920, no other vaccine had been approved till now for general public, despite being the prime focus for containing TB. According to WHO, as of August 2020, there are 14 candidate new generation vaccines in Phase I, II or III trials (Table 2).

Table 1 – TB drugs under various stages of phase trials.[4]

Name of the Compound	Class of Compound	Target	Status	Place of Study
BTZ-043	Benzothiazinone	DprE1 enzyme	Phase Ib/IIa	South Africa.
Delpazolid (LCB01–0371)	Oxazolidinone	Protein Synthesis (23S rRNA)	Phase II	Republic of Korea.
GSK-3036656	Oxaborole	Leucyl-tRNA Synthetase	Phase IIa	South Africa.
Macozinone (PBTZ169)	Benzothiazinone	DprE1 enzyme	Phase I	Switzerland
OPC-167832	Carbostyril	DprE1 enzyme	Phase I/II	South Africa
Telacebec (Q203)	Imidazopyridine amide	Cytochrome bc1 complex	Phase I/IIa	South Africa
SQ109	Ethylenediamine	MmpL3	Phase IIb/III	Russian Federation
SPR720	Aminobenzimidazole	DNA gyrase GyrB	Phase I	United Kingdom (Great Britain and Northern Ireland)
Sutezolid (PNU-100480)	Oxazolidinone	Protein Synthesis (23S rRNA)	Phase IIb	South Africa and the United Republic of Tanzania.
TBAJ-876	Diarylquinoline	ATPase	Phase I	
TBA-7371	Azaindole	DprE1 enzyme	Phase II	South Africa
TBI-166	Clofazimine	cytochrome bc1 complex	Phase I	China
TBI-223	Oxazolidinone	Protein synthesis (23S rRNA)	Phase I	USA

Abbreviations: DprE1 enzyme: Decaprenylphosphoryl-D-ribose oxidase, MmpL3: Mycobacterial membrane protein Large 3.

Table 2 – TB Vaccines under various stages of phase trails.[4]

Current status	Name of Vaccine	Type	Antigen	Developers
Phase I	Ad5 Ag85A	Viral vectored vaccines	Adenovirus serotype 5 vector expressing Ag85A	McMaster University, CanSino
	AEC/BC02	Protein/Adjuvant	Ag85b and fusion protein ESAT6-CFP10 were combined with BCG CpG	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.
	ChAdOx185A – MVA85A (ID/IM/Aerosol)	Viral vectored vaccines	Simian adenovirus and recombinant pox virus – both express antigen 85A	Oxford University, Aeras
Phase IIa	MTBVAC	Whole cell vaccines — live	Live, attenuated Mtb vaccine with PhoP and Fad26 deletions.	Universidad de Zaragoza, BIOFABRI, TBVI
	ID93 + GLA-SE	Adjuvanted protein subunit vaccine	Recombinant fusion protein (ID93) of four antigens associated with virulence and latency	Infectious Disease Research Institute, Quratis, Wellcome Trust
	TB/FLU-04L	Viral vectored vaccines	Attenuated influenza viral vector expressing Mtb Ag85A and ESAT-6	Research Institute for Biological Safety Problems MoH Russia
	GamTBvac	Adjuvanted protein subunit vaccine	fusion protein of antigens Ag85A, ESAT6 and CFP10 with a dextran-based adjuvant	
Phase IIb	DAR-901 booster	Whole cell vaccines — inactivated	Heat Killed *M. obuense*	Dartmouth, Geisel School of Medicine, Global Health Innovative Technology Fund
	H56:IC31	Adjuvanted protein subunit vaccine	Recombinant fusion protein of three antigens (Ag85B, Rv2660c,ESAT-6)	Statens Serum Institut; Valneva; Aeras
	M72/AS01$_E$	Adjuvanted protein subunit vaccine	Two *M. tuberculosis* antigens (32A and 39A) with an adjuvant (AS01E).	GlaxoSmithKline, Aeras
	MRI-TBV01-201	Whole cell vaccines — live	Live *M. Bovis* BCG vaccine	Gates MRI
	RUTI	Whole cell vaccines — inactivated	Detoxified, fragmented Mtb cells	Archivel Farma
Phase III	MIP/Immuvac	Whole cell vaccines — live	Live, attenuated Mtb vaccine	Universidad de Zaragoza, BIOFABRI, TBVI
	VPM1002	Whole cell vaccines — live	Recombinant BCG	Max Planck Institute, Vakzine Projekt Management, TBVI, Serum Institute of India

Abbreviations: ESAT6: Early secretory antigenic target-6, CFP10: culture filtrate protein 10, BCG: bacille Calmette-Guerin.

8. Concluding remarks

Antimicrobial resistance by mycobacteria hinder the global efforts to curb and eradicate the disease. The sustained evolution of mycobacteria conferring antimicrobial resistance and continued spreading of drug resistant TB strains in the form of MDR-and XDR-TB, poses a grave challenges for the global community. Poor sanitization practice, lack of awareness, inadequate medical status and financial constrains had further aggravated the emergence of drug resistant tuberculosis. However, there is an ever-increasing understanding amongst international community, that a collective effort is required to contain, treat and eradicate the TB disease. Towards this effort, new rapid diagnostics methods, novel drug molecules, development of new TB vaccine and new treatment regimens are being developed and tested. Some of the recent advances had already shown promising results. There is a hope that this contagious disease can be eradicated permanently. This can be achieved by the collective effort of global community, by pooling together scientific, financial and technological advancement.

Author contributions

Shivendra Singh Dewhare has solely conceived and drafted the manuscript. The author also confirms and approves the final manuscript.

Conflicts of interest

None.

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REFERENCES

1. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. *Lancet Infect Dis*. 2019;19(8):903–912. https://doi.org/10.1016/S1473-3099(19)30307-X.
2. Zhan Y, Li B, Huo Y, Lin A, Wu H. A case of multiple organ tuberculosis. *Radiol Infect Dis*. 2018;5(1):50–54. https://doi.org/10.1016/j.jrid.2018.02.003.
3. Smith I. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. *Clin Microbiol Rev*. 2003;16(3):463–496. https://doi.org/10.1128/CMR.16.3.463-496.2003.
4. Global tuberculosis report 2020. https://www.who.int/publications/i/item/9789240013131. Accessed February 20, 2021.
5. World Health Organization. *Global Tuberculosis Report*. Geneva: World Health Organization; 2014. https://apps.who.int/iris/handle/10665/137094.
6. Mabhula A, Singh V. Drug-resistance in: Mycobacterium tuberculosis: where we stand. *Medchemcomm*. 2019;10(8):1342–1360. https://doi.org/10.1039/c9md00057g.
7. Nurwidya F, Handayani D, Burhan E, Yunus F. Molecular diagnosis of tuberculosis. *Chonnam Med J*. 2018;54(1):1. https://doi.org/10.4068/cmj.2018.54.1.1.
8. Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children: rapid communication - PAHO/WHO | Pan American Health Organization. https://www.paho.org/en/documents/molecular-assays-intended-initial-tests-diagnosis-pulmonary-and-extrapulmonary-tb-and. Accessed February 20, 2021.
9. Streptomycin treatment of pulmonary tuberculosis. *Br Med J*. 1948;2(4582):769–782. https://doi.org/10.1136/bmj.2.4582.769.
10. The prevention of streptomycin resistance by combined chemotherapy. *Br Med J*. 1952;1(4769):1157–1162. https://doi.org/10.1136/bmj.1.4769.1157.
11. Long-term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavitation: a report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee. *Tubercle*. 1962;43(3):201–267. https://doi.org/10.1016/S0041-3879(62)80066-X.
12. Short-course Chemotherapy in Pulmonary Tuberculosis. A controlled trial by the British thoracic and tuberculosis association. *Lancet*. 1975;305(7899):119–124. https://doi.org/10.1016/S0140-6736(75)91426-9.
13. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. *Int J Tubercul Lung Dis*. 1999;3(10 suppl 2):S231–S279. https://europepmc.org/article/med/10529902.
14. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005–1015. https://doi.org/10.1056/nejmoa0907847.
15. Zhang Y, Heym B, Allen B, Young D, Cole S. The catalase - peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. *Nature*. 1992;358(6387):591–593. https://doi.org/10.1038/358591a0.
16. Bardou F, Raynaud C, Ramos C, Lanéelle MA, Lanéelle G. Mechanism of isoniazid uptake in Mycobacterium tuberculosis. *Microbiology*. 1998;144(9):2539–2544. https://doi.org/10.1099/00221287-144-9-2539.
17. Banerjee A, Dubnau E, Quemard A, et al. inhA, a gene encoding a target for isoniazid and ethionamide in Mycobacterium tuberculosis. *Science*. 1994;263(5144):227–230. https://doi.org/10.1126/science.8284673 (80-).
18. Vilchèze C, Jacobs WR. The mechanism of isoniazid killing: clarity through the scope of genetics. *Annu Rev Microbiol*. 2007;61:35–50. https://doi.org/10.1146/annurev.micro.61.111606.122346.
19. Girling DJ, Chan SL. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide: results at 30 months. *Am Rev Respir Dis*. 1991;143(4 I):700–706. https://doi.org/10.1164/ajrccm/143.4_pt_1.700.
20. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. *Tuber Lung Dis*. 1998;79(1):3–29. https://doi.org/10.1054/tuld.1998.0002.

21. Mitchison DA. Basic mechanisms of chemotherapy. *Chest*. 1979;76(6 suppl l):771–781. https://doi.org/10.1378/chest.76.6_supplement.771.
22. Scorpio A, Zhang Y. Mutations in pncA, a gene encoding pyrazinamidase/nicotinamidase, cause resistance to the antituberculous drug pyrazinamide in tubercle bacillus. *Nat Med*. 1996;2(6):662–667. https://doi.org/10.1038/nm0696-662.
23. Zimhony O, Vilchèze C, Arai M, Welch JT, Jacobs WR. Pyrazinoic acid and its n-Propyl ester inhibit fatty acid synthase type I in replicating tubercle bacilli. *Antimicrob Agents Chemother*. 2007;51(2).
24. Mitchison DA. The action of antituberculosis drugs in short-course chemotherapy. *Tubercle*. 1985;66(3):219–225. https://doi.org/10.1016/0041-3879(85)90040-6.
25. Cheng SJ, Thibert L, Sanchez T, Heifets L, Zhang Y. pncA mutations as a major mechanism of pyrazinamide resistance in Mycobacterium tuberculosis: spread of a monoresistant strain in Quebec, Canada. *Antimicrob Agents Chemother*. 2000;44(3):528–532. https://doi.org/10.1128/AAC.44.3.528-532.2000.
26. Belanger AE, Besra GS, Ford ME, et al. The embAB genes of Mycobacterium avium encode an arabinosyl transferase involved in cell wall arabinan biosynthesis that is the target for the antimycobacterial drug ethambutol. *Proc Natl Acad Sci U S A*. 1996;93(21):11919–11924. https://doi.org/10.1073/pnas.93.21.11919.
27. Telenti A, Philipp WJ, Sreevatsan S, et al. The emb operon, a gene cluster of Mycobacterium tuberculosis involved in resistance to ethambutol. *Nat Med*. 1997;3(5):567–570. https://doi.org/10.1038/nm0597-567.
28. *WHO | WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*. WHO; 2019. Published online http://www.who.int/tb/areas-of-work/drug-resistant-tb/guideline-update2018/en/. Accessed February 20, 2021.
29. *WHO | WHO consolidated guidelines on drug-resistant tuberculosis treatment*. WHO; 2019. Published online http://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/. Accessed February 20, 2021.
30. Alangaden GJ, Manavathu EK, Vakulenko SB, Zvonok NM, Lerner SA. Characterization of fluoroquinolone-resistant mutant strains of Mycobacterium tuberculosis selected in the laboratory and isolated from patients. *Antimicrob Agents Chemother*. 1995;39(8):1700–1703. https://doi.org/10.1128/AAC.39.8.1700.
31. Ford CW, Hamel JC, Stapert D, et al. Oxazolidinones: new antibacterial agents. *Trends Microbiol*. 1997;5(5):196–200. https://doi.org/10.1016/S0966-842X(97)01032-9.
32. Zhang S, Chen J, Cui P, et al. Mycobacterium tuberculosis mutations associated with reduced susceptibility to Linezolid. *Antimicrob Agents Chemother*. 2016;60(4):2542–2544. https://doi.org/10.1128/AAC.02941-15.
33. Wasserman S, Louw G, Ramangoaela L, et al. Linezolid resistance in patients with drug-resistant TB and treatment failure in South Africa. *J Antimicrob Chemother*. 2019;74(8):2377–2384. https://doi.org/10.1093/jac/dkz206.
34. Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. *Nat Chem Biol*. 2007;3(6):323–324. https://doi.org/10.1038/nchembio884.
35. Ismail NA, Omar SV, Joseph L, et al. Defining bedaquiline susceptibility, resistance, cross-resistance and associated genetic determinants: a retrospective cohort study. *EBioMedicine*. 2018;28:136–142. https://doi.org/10.1016/j.ebiom.2018.01.005.
36. Degiacomi G, Sammartino JC, Sinigiani V, Marra P, Urbani A, Pasca MR. In vitro study of bedaquiline resistance in Mycobacterium tuberculosis multi-drug resistant clinical isolates. *Front Microbiol*. 2020;11. https://doi.org/10.3389/fmicb.2020.559469.
37. Dey T, Brigden G, Cox H, Shubber Z, Cooke G, Ford N. Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2013;68(2):284–293. https://doi.org/10.1093/jac/dks389.
38. Shepard CC. Spaced clofazimine therapy of lepromatous leprosy. *Am J Trop Med Hyg*. 1976;25(3):437–444. https://doi.org/10.4269/ajtmh.1976.25.437.
39. Bruning JB, Murillo AC, Chacon O, Barletta RG, Sacchettini JC. Structure of the Mycobacterium tuberculosis D-alanine:D-alanine ligase, a target of the antituberculosis drug D-cycloserine. *Antimicrob Agents Chemother*. 2011;55(1):291–301. https://doi.org/10.1128/AAC.00558-10.
40. Nakatani Y, Opel-Reading HK, Merker M, et al. Role of alanine racemase mutations in Mycobacterium tuberculosis D-cycloserine resistance. *Antimicrob Agents Chemother*. 2017;61(12). https://doi.org/10.1128/AAC.01575-17.
41. Xavier AS, Lakshmanan M. Delamanid: a new armor in combating drug-resistant tuberculosis. *J Pharmacol Pharmacother*. 2014;5(3):222–224. https://doi.org/10.4103/0976-500X.136121.
42. Nguyen TVA, Anthony RM, Cao TTH, et al. Delamanid resistance: update and clinical management. *Clin Infect Dis*. 2020;71(12). https://doi.org/10.1093/cid/ciaa755.
43. Pryka RD, Haig GM. Meropenem: a new carbapenem antimicrobial. *Ann Pharmacother*. 1994;28(9):1045–1054. https://doi.org/10.1177/106002809402800910.
44. Recht MI, Douthwaite S, Puglisi JD. Basis for prokaryotic specificity of action of aminoglycoside antibiotics. *EMBO J*. 1999;18(11):3133–3138. https://doi.org/10.1093/emboj/18.11.3133.
45. Georghiou SB, Magana M, Garfein RS, Catanzaro DG, Catanzaro A, Rodwell TC. Evaluation of genetic mutations associated with mycobacterium tuberculosis resistance to amikacin, kanamycin and capreomycin: a systematic review. *PloS One*. 2012;7(3), e33275. https://doi.org/10.1371/journal.pone.0033275.
46. Moazed D, Noller HF. Interaction of antibiotics with functional sites in 16S ribosomal RNA. *Nature*. 1987;327(6121):389–394. https://doi.org/10.1038/327389a0.
47. Gillespie SH. Evolution of drug resistance in Mycobacterium tuberculosis: clinical and molecular perspective. *Antimicrob Agents Chemother*. 2002;46(2):267–274. https://doi.org/10.1128/AAC.46.2.267-274.2002.
48. Okamoto S, Tamaru A, Nakajima C, et al. Loss of a conserved 7-methylguanosine modification in 16S rRNA confers low-level streptomycin resistance in bacteria. *Mol Microbiol*. 2007;63(4):1096–1106. https://doi.org/10.1111/j.1365-2958.2006.05585.x.
49. Rueda J, Realpe T, Mejia GI, et al. Genotypic analysis of genes associated with independent resistance and cross-resistance to isoniazid and ethionamide in Mycobacterium tuberculosis clinical isolates. *Antimicrob Agents Chemother*. 2015;59(12):7805–7810. https://doi.org/10.1128/AAC.01028-15.
50. Minato Y, Thiede JM, Kordus SL, McKlveen EJ, Turman BJ, Baughn AD. Mycobacterium tuberculosis folate metabolism and the mechanistic basis for para-aminosalicylic acid susceptibility and resistance. *Antimicrob Agents Chemother*. 2015;59(9):5097–5106. https://doi.org/10.1128/AAC.00647-15.

Available online at www.sciencedirect.com

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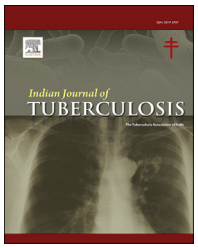

Review article

Interventions to respond to COVID 19 pandemic in Mumbai and way forward

Sunil Khaparde [a,*], *Khyati Aroskar* [a], *Radha Taralekar* [b], *Mangala Gomare* [c]

[a] *Public Health Specialist, Mumbai, India*
[b] *NTEP, Mumbai, India*
[c] *Municipal Corporation of Greater Mumbai, India*

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ABSTRACT

With the emergence of COVID 19 pandemic, the approach used by Municipal Corporation of Greater Mumbai (MCGM) was based on all guidelines of COVID 19 prepared by Ministry of Health and Family Welfare (MoHFW). However, Mumbai undertook a special innovate model used in the mission Mumbai – Dharavi for COVID 19. Additionally, MCGM undertook a proactive approach of "chasing the virus" with its 4Ts: 1. Tracing 2. Tracking 3. Testing 4. Treating in high-risk slum clusters and it reflects the result of declining the incidence and case fatality due to COVID 19. Establishing public health surge capacities which include active surveillance, contact-tracing and follow-up besides early detection, isolation and management of cases are important steps for fighting the COVID 19 pandemic. Collaborating with all partners and setting up a Task force for establishing clinical management protocols was unmissable.

1. Introduction

Pneumonia of unknown aetiology was detected in Wuhan, China and first reported to the WHO Country Office in China on 31 December 2019. The outbreak was declared a Public Health Emergency of International Concern (PHEIC) on 30 January 2020. The emergence of the novel coronavirus in China followed by its rapid spread to other countries, was a cause of great concern. This prompted the World Health Organization (WHO) to declare the Coronavirus Disease (COVID 19), a pandemic on 11 March 2020[1]

In India the number of active cases are 289,240, Cured/Discharged 9,663,382 and 146,444 deaths. Maharashtra recorded 1,794,080 total confirmed cases, 59,502 active cases and 48,876 COVID 19 deaths higher than any other state in the country.[2] The capital of Maharashtra, Mumbai which has the highest population density, contributed hugely to the overall positive cases and deaths recorded in the state. As of 22 December 2020, Mumbai alone recorded 287,816 total positive cases and 11,019 deaths - a fatality rate of 3.82 which is slightly higher than India's overall fatality as reported.[3]

The intervention and approach used by Municipal Corporation of Greater Mumbai (MCGM) were based on containment

* Corresponding author. Public Health Specialist, Port Health Organization, Ministry of Health and Family Welfare, Govt. Of India Pattan Swashthya Bhavan, 7 Mandlik Road, Behind Hotel Taj palace, Colaba, Mumbai, Maharashtra, 400001, India. Tel.: 9958097015.
E-mail address: sdkhaparde.naco@gmail.com (S. Khaparde).

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strategy and guidelines on COVID 19 prepared by Ministry of Health and Family Welfare (MoHFW). Central teams constituted by MoHFW have time to time visited and monitored the COVID 19 pandemic situation in Mumbai and provided the advice, suggestions and recommendations. These are reflected in the MCGM approach and model used in the mission Mumbai – Dharavi for COVID 19.

MCGM took a proactive approach of "chasing the virus" with its 4Ts: 1. Tracing 2. Tracking 3. Testing 4. Treating in high-risk slum clusters, rather than waiting for cases to happen is a very timely response for containment of COVID 19 and it shows the result of declining the incidence and case fatality due to COVID 19.[4]

Director General of WHO complemented Dharavi for focusing on community engagement and the basics of testing, tracing, isolating, and treating all those that are sick as key to breaking the chains of transmission and suppressing the virus.

The MCGM established teams consisting of a doctor, a community health worker, and a local volunteer; since April, these teams have knocked on doors of 47,500 Dharavi homes and screened 360,000 individuals, including measuring temperature and oxygen saturation levels. Those having oxygen concentration of less than 95% are taken to a quarantine center, where they are provided comprehensive care. In addition, about 2000 older people have been taken into protective quarantine. This active case search has helped to identify suspects much faster and to move them to local clubs and schools, which serve as quarantine facilities are very relevant approach to curb the COVID 19.

A multi-sectorial micro planning process in the slums was undertaken to - consider engaging with people's representatives, policy makers, civil society and other stakeholders to facilitate and ensure the community participation civil society and private sector engagement:

Challenges in Mumbai slum, Dharavi is a slum area spread over 2.5 Sq Kms with approximately official population of 8–9 Lakh, while police and MCGM stated that actually double that number reside there. These people use community toilets, making them vulnerable to any communicable infections. A comprehensive response and containment strategy for COVID 19 in slums to be designed and validated through a consultative process with MCGM, Government, Development Partners, Non-Governmental Organizations and community block officers.

Dharavi COVID 19 Intervention Model: With 8 to 10 people living in 10 ft × 10 ft spaces and 80% population dependent on community toilets, home isolation was not really an option in Dharavi. It needed institutional quarantine facilities on scale. These were set up in schools, community halls in timely fashion. The Government responded fast to chase the virus. The first fever clinic was in fact set up three days after the first case. Oximeters, mobile vans and private clinics were roped in alongside MCGM health workers for early screening, which helped in both prompt separation of suspected cases from the community and lowering the mortality rate. Aggressive and accessible testing was part of the arsenal.

2. Interventions to combat COVID 19 pandemic response in Mumbai

- **Precautionary measures and alert undertaken**

The government take strict vigilance with response to COVID 19 at individual and community level to take precautions and avoid getting infected with the virus. The Government officials and the leadership is bold and must be congratulated for strong action–From hourly live updates, unleashing the avalanche of information/advisories/notifications, awareness through social media, teaching cough etiquette, physical distancing, tracking of cases, contact tracing, quarantine/isolation (even forcible in few cases), to high level meetings, lockdowns, unprecedented mobilization of resources and manpower, infection control measures in health centers.

- **Port-of-entry-based entry screening of travellers**

The Government had initiated several measures for the early detection of imported cases with universal fever screening initiated at 21 airports, 12 major seaports, 65 minor seaports and land crossings, particularly those bordering Nepal. By May 9, 2020, nearly 1524266 incoming airline passengers and 12,500 passengers coming through seaports have been screened.[2]

As per Ministry of Home Affairs orders, under the 'Vande Bharat' evacuation was carried out for Indians stranded abroad through the embassy under standard operating procedures. Port-of-entry-based entry screening of travellers with suggestive clinical features and from COVID 19 affected countries, would achieve modest delays in the introduction of the virus into the community.

- **Public health experts and community medicine**

They played an important role right from the beginning of the pandemic by initiating planning at micro, meso (mid) and tertiary levels. At primary level, apart from the healthcare workers, the community itself is a major stakeholder. Enhanced involvement of Public Health Specialists, Epidemic Intelligence service Officers, Community Medicine/Clinical Department and other pre- and para-clinical departments of the medical colleges and government institutes within Mumbai for analysis, projections, preparing the containment plan, cluster and hot spots surveillance, close monitoring of activities, and also estimated preparedness for further management of COVID-19 and further research.

- **Private healthcare providers and other partners**:

The MCGM involved private healthcare providers through capacity building into delivering healthcare during pandemics from the beginning itself to ensure a continuity of care. From the beginning of the pandemic, multiple partners were involved from Central Government, State Government and

Medical Colleges, WHO, UNICEF, IAPSM, Epidemic Intelligence Services, Non-Governmental organizations. Fire Brigade of MCGM is relentlessly carrying out sanitization work. The sanitization of hospitals, containment areas, quarantine areas, markets, bus stations, railway stations, Government buildings, slum areas, housing societies, roads, lanes are being carried out by fire brigade officers and staff.

- **Comprehensive risk communication strategy** (CRCS)

Human behavior is critical to manage this disease; there is a need to strengthen the risk communication strategies through community engagement. There have been instances where people living in containment zones are not disclosing illness due to fear of discrimination. To avoid such situations, we need to work towards reducing discrimination based on COVID 19.

There is a need for strengthening the psycho-social support to as COVID 19 patients and their families as well as frontline workers. Mumbai established jumbo quarantine facilities where Yoga/Breathing exercises were facilitated for improving physical and mental health.

Mental health is another major issue that is becoming critical in managing COVID-19 pandemic due to extended lockdowns. Efforts must be made to address these and reassure public through a systematic approach led by social and mental health experts at a larger scale.

- **Community preparedness**

Institutional quarantine was advocated with special care for the community level disinfection of toilets and common spaces of grocery and essential supplies for the large-scale slum and semi slum scenario in the Mumbai. Sero-surveillance was carried out in high risk clusters of Mumbai supported by ICMR in collaboration with MCGM to know the community spread of COVID 19.

Enhanced involvement of public health specialist. Community medicine/Clinical Department and other pre- and para-clinical departments of the medical colleges and central government institutes within Mumbai for analysis, projections, preparing the containment plan, cluster and hot spots surveillance, close monitoring of activities, and also estimated preparedness for further management of COVID 19 and further research. Surveillance activities and door to door survey for identifying the symptomatic patients within the high-risk areas were strengthened to identify high risk at earliest.

Two phases of 'My family, my responsibility' campaign were conducted with house to house survey for all of Mumbai households. Oxygen saturation and temperature monitoring of the vulnerable groups was done.

- **Testing strategy for COVID19**

Rapid involvement of private laboratories by the administrators supported scaling up testing of COVID 19.[5,6] RTPCR and antigen testing were the main modalities of testing and 2225190 tests have been conducted till 22 December 2020. The government capped the prices for the testing and ensured turnaround time for COVID 19 reporting was within 24 hours.

- **Preparedness of Hospitals**

ICU beds were augmented (15% admissions within the designated hospital for COVID-19 patients were recommended for ICU bed strengthening). There was requirement of additional medical staff for ventilator management. The specialist doctors/nurse and other paramedical staff were outsourced and trained on ventilator management. Necessary steps were taken to procure adequate ventilators and critical care equipment based on the local projection of cases.

All isolation centers and the hospitals acquired by districts authority developed the oxygen line beds/oxygen provision in their facilities. New facilities were identified as to provide COVID 19 services. Central team guided based on modelling for state level needs for bed capacity, oxygen flow masks and tanks and ventilators. In addition, the health personnel need to be trained and the availability of guidelines and an adequate amount of supplies, such as personal protection equipment, gloves, masks, medicines, test kits for diagnosis and ventilators and oxygen flow shall be ensured in health facilities.

- **Clinical Management of cases**

On lines of central guidelines, MCGM set up a three-tier care system, beginning with dedicated COVID 19 hospitals at the top of the pyramid, followed by DCHCs and with COVID 19 care centres (CCC) at the bottom.[7] Ambulance Service Expansion from initial 100 ambulances, now scaled up the number to more than 700. Fever clinics that are flu clinics have been started with the aid of Medical Colleges for testing and segregation of patients in the community. The oxygen saturation criteria for categorization of COVID 19 patients was added in Mumbai way ahead than rest of India.

Best practices noticed were Artificial Intelligence and private practitioners involved fully with the 500 bedded facility at the National Sports Complex Institute dome, Mahalaxmi Race course, MMRDA grounds and Goregaon open grounds facility in Mumbai. Taskforce was created for the clinical management of cases.

Bed arrangements for all COVID 19 diagnosed patients were made immediately in a decentralized manner through a War Room in each Ward of Mumbai to allocate beds through designated helpline numbers for the 24 wards. Online dashboard was established for real time monitoring.

- **Integrated surveillance approach**

Surveillance under the Integrated Disease Surveillance Programme should be strengthened with regular outbreak investigations and reporting. Surveillance system for Acute Respiratory Infections/Influenza like Illness (ARI/ILI) and screening at community level, as well as health facility level to identify and respond to clustering of cases for early detection of impending SARI outbreaks is important.

COVID 19 response Dashboard document elaborates various measures and initiatives taken up by MCGM in

response to crisis. The document covers key statistics for Mumbai like testing results, Contact tracing & home quarantine, Status of COVID 19 positive cases, facilities update, Bed capacity & other initiatives. The data for these fields keep getting updated in near real-time and the report.

3. Way forward future action

Establishing public health surge capacities which include active surveillance, contact-tracing and follow-up besides early detection, isolation and management of cases are important. Strengthening healthcare budgeting allocated to preventive health services, surveillance, outbreak investigations, trained epidemiological workforce and inter sectoral coordination will remain important. Involvement of Professional organizations, Self-help groups and Non-Governmental organizations to map out services effectively. Early testing and healthcare in this population could help significantly reduce the mortality toll of the epidemic. Routine hospital services remain key and the crux for priority action today. For tuberculosis and other communicable/non communicable diseases, Antenatal Care, Immunization, Blood Transfusion, Dialysis services should not be hampered. Earmarking and public awareness of facilities and timings should be given wide propagation and it should be ensured that these services should not suffer. Equity should be maintained at all times particularly for the vulnerable of the society. The challenges of the crisis should be encountered through scientific evidence available.

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SK contributed in study Conceptualization. SK, KA, RT contributed in data collection, data analysis, data interpretation, manuscript writing, literature review and revising; SK, MG contributed in data acquisition. All authors read and approved the final version of manuscript.

Declaration of competing interest

All authors have none to declare.

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REFERENCES

1. World Health Organization (WHO) Rolling updates https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (as accessed on 9 May 2020).
2. MoHFW. Ministry of Health and Family Welfare website https://www.mohfw.gov.in/(as accessed on 14 May 2020).
3. MCGM COVID 19 dashboard https://stopcoronavirus.mcgm.gov.in/key-updates-trends (Accessed December 23, 2020).
4. Mapping Mumbai's slum challenge in coronavirus battle https://www.livemint.com/news/india/mapping-mumbai-s-slum-challenge-in-coronavirus-battle-11586334352966.html.
5. MoHFW Laboratory testing advisory https://www.mohfw.gov.in/pdf/LabTestingAdvisory.pdf (as accessed on 9 May 2020).
6. ICMR guidelines private laboratory https://www.mohfw.gov.in/pdf/NotificationofICMguidelinesforCOVID19testinginprivatelaboratoriesiIndia.pdf (as accessed on 9 May 2020).
7. National Centre for Disease Control website https://ncdc.gov.in/(as accessed on 9 May 2020).

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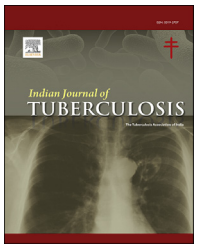
journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Review article

Post COVID fatigue: Can we really ignore it?

Priya Sharma, Senior Resident [a,*], *Sumit Bharti, Senior Resident* [b], *Isha Garg, Assistant Professor* [c]

[a] *AIIMS PATNA, EDAR, DNB TB and Respiratory Diseases, Kalpana Chawla Govt Medical College, Karnal, Haryana, 132001, India*

[b] *IDCCM Fellow at Max Mohali, MD Respiratory Diseases, Kalpana Chawla Govt Medical College, Karnal, Haryana, 132001, India*

[c] *Kalpana Chawla Govt Medical College, Karnal, Haryana, 132001, India*

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ABSTRACT

Long-COVID, also referred to as post-acute COVID-19, chronic COVID-19, post-COVID syndrome, or post-acute sequelae of SARS-CoV-2 infection (PASC), generally refers to symptoms that develop during or after acute COVID-19 illness, continue for ≥12 weeks, and are not explained by an alternative diagnosis. It is not yet known whether "long-COVID" represents a new syndrome unique to COVID-19 or overlaps with recovery from similar illnesses. It's difficult for physicians to predict when symptoms will improve as it varies differently in different people. Patient's recovery depends on various factors including age, associated comorbidities, severity of COVID-19 infection. Some symptoms, like fatigue, might continue even while others improve or go away. This review addresses the pathogenesis, presentation of post covid fatigue, its severity and its management.

1. Introduction

Although COVID-19 is a short term, self-limited illness in majority of people, still a large proportion of patient enters into an entity called long COVID haulers[1,2] and present to the physician with most common symptom i.e., fatigue. The British Medical Journal defines 'long COVID' as illness in people who have either recovered from COVID-19 but are still reporting lasting effects of the infection or have had the usual symptoms for far longer than would be expected".[3] Even World Health Organization has classified post-viral fatigue syndrome under the section of "diseases of the nervous system".[4] It is defined as a complex medical condition characterized by long-term fatigue and other symptoms which vary to such a degree that they limit a person's ability to carry out ordinary daily activities. Simply it is a long-term state of chronic fatigue characterized by post-exertional neuroimmune exhaustion.[5] Rio and Malani highlighted that fatigue is commonly seen in COVID-19 epidemic, and also, the patients still have high levels of fatigue and anhedonia after recovery from infection.[6]

* *Corresponding author.*
E-mail address: priyasharma25292@gmail.com (P. Sharma).

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2. Prevalence

Data from UK's COVID-19 symptom app[7] found that around 300,000 UK people have reported symptoms lasting for more than a month. Over 60,000 were still experiencing symptoms after three months. A team of researchers from Italy reported that nearly nine in 10 patients (87%) discharged from hospital after recovering from covid-19 were still experiencing at least one symptom 60 days after onset. They found that 13% of the 143 people were completely free of any symptoms, while 32% had one or two symptoms, and 55% had three or more. Although none of the patients had fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). Worsening of quality of life was reported in around 2/5th of patients.[8] One study of 143 people with COVID-19 discharged from a hospital in Rome found that 53% had reported fatigue an average of 2 months after their symptoms started.[9] A study of patients in China showed that 16% were still fatigued.[10]

In a multistate telephone survey of symptomatic adults who had a positive outpatient test result for SARS-CoV-2 infection, 35% had not returned to their usual state of health when interviewed 2–3 weeks after testing. One in five had not returned to their usual state of health among persons aged 18–34 years with no chronic medical conditions.[11]

In a study, fatigue was assessed using the Chronic fatigue score (CFQ-11 questionnaire in 128 patients 52.3% (67/128) met the criteria for fatigue, with the mean (±SD) CFQ-11 score in this group being 20 ± 4.4.[12]

Post-COVID fatigue is a different entity and cannot be just defined as normal tiredness. Along with total exhaustion, people with post-COVID fatigue feel generally unwell which can also be seen in patients recovering from other viruses (flu or mumps). It is generally associated with unexplained muscle and joint pain, poor concentration, sore throat, headaches and rarely it can be extremely debilitating.

Unfortunately, any patient can be affected by this entity irrespective of the severity of initial infection.

3. Pathogenesis

Some are of the view that it is the effect of quarantine in COVID-19 infection leading to development of psychological and cognitive manifestations of post-COVID-19 depressive symptoms, stress, anxiety, chronic fatigue, and anhedonic state.[13] Like chronic fatigue syndrome, pro-inflammatory components like cytokines such as IFN gamma, and IL-7 are supposed to compromise the neurological regulation of the "Glymphatic System".[14] Many cases of COVID-19 lands up in "post-COVID-19 Syndrome" which is a persistent condition of chronic fatigue, disturbed sleep/wake cycle, neuro-cognitive implications, and progressive anhedonia.[15]

The exact mechanism behind post-viral fatigue is not clearly understood. One of the likely explanations can be neuro-inflammation in brain due to infection caused by COVID-19 or any systemic inflammation that which activate the innate immune system in the brain via both humoral and retrograde neural signals (largely involving the vagus nerve).[16–18] While our body is fighting off a virus, the immune system releases chemicals called cytokines, which promote inflammation and cause many of the classic symptoms of post COVID fatigue (tiredness, aches and pains, malaise).[19]

4. Chronic fatiue syndrome/myalgic encephalomyelitis

The persistence of long-term symptoms in some COVID-19 patients has opened up a new line of research into the mechanisms underlying myalgic encephalomyelitis/Chronic fatigue Syndrome (ME/CFS).[20–22]

This is part of its frontline attack on the invading virus which normally stops once the virus itself has been dealt with, but in some cases cytokines levels fails to return to normal, causing on going symptoms. The buildup of cytokines in the Central Nervous System (CNS) may lead to post viral symptoms due to pro-inflammatory cytokines passing through the blood brain barrier in circumventricular organs such as the hypothalamus, leading to autonomic dysfunction manifesting acutely as a high fever and in the longer term to dysregulation of the sleep/wake cycle, cognitive dysfunction and profound unremitting anergia, all characteristic of CFS/ME.[23]

The symptoms are essentially the same as those of chronic fatigue syndrome, also called myalgic encephalomyelitis or ME, which is why the WHO places them under the same category of neurological disorders.[24] A key feature of the condition is the sudden worsening of symptoms following only minimal physical or mental activity. Sleep is non-restorative and the tiredness can intensify after very minor mental or physical exertion.

5. COVID-19 brain fog

It is a condition described as fatigue and forgetfulness/puzzled, in patients who recovered from COVID-19 irrespective of severity. Many people who have recovered from COVID-19 have reported feeling not like themselves: experiencing short-term memory loss, confusion, an inability to concentrate, and just feeling differently than they did before contracting the infection. This brain fog has different spectrum varying from mild reversible forgetfulness to drowsiness and totally withdrawn. Actual mechanism is not clearly understood yet but as per the clinicians dealing with these cases frequently, one of the proposed mechanisms can be[25] COVID-19 virus enters the body through an ACE-2 receptor. And these receptors are widely distributed all over the body. That is why the virus can gain access to every system.

It is known that it gains access to the nervous system also, and that is the reason for the loss of sense of taste and smell. Probably that is the reason for the brain fog. One reason could be actual damage by the virus to these organ systems, and the second could be also a byproduct of the stress a person undergoes during the whole COVID episode. However, the long-term neurological and cognitive consequence of SARS-CoV-2 infection will remain conjectural for some time and will likely require the creation of cohort studies that include uninfected individuals. Recent studies shows that the occlusion

of brain capillaries by large megakaryocyte cells, a new report suggests.[26]

6. Management

Sadly, there is no specific medication or speedy treatment for post-viral fatigue or chronic fatigue syndrome. The most effective current treatment is total rest. This means relaxing as much as possible, with no mental stimulation. People who have experienced the condition talk about lying in a darkened room for long periods to promote mental and physical rest. These are the steps which can be taken to manage post COVID Fatigue [xxiv]:

1. REST: One of the most important intervention implying no TV, phones or internet, instead use relaxation, breathing and meditation apps, reduce any sensory input that makes you feel tense or is demanding (noise and bright lights), use sensory input to help you rest and relax – (favorite relaxing music, blanket, fragrance, or a hot water bottle). If all this does not work, try something else until you find something that gives you relaxation physically and mentally. It will support your recovery.
2. ACTIVITY: Keep activity levels low – both physical and cognitive (thinking) activities as they both use energy.
3. NOURISH: Keep eating and drinking, with as normal a routine as possible and maintain a balanced diet, specially increase your fluid intake.
4. MOVE: Get up and move around slowly and gently a few times each day to keep your body moving and to aid circulation. If you are too unwell for this, then you can try and move around in bed a little (stretching out, moving all of your joints, and tensing and relaxing your muscles).
5. ALLOW TIME: COVID can affect people to varying degrees, so give yourself the time you need for recovery. Avoid pressure to get back to your usual activities as soon as possible.
6. HAVE FUN: Do some low energy enjoyable activities every day. Balance activity with regular rests.
7. STOP STUDIES/WORK: Unless you feel fully well, you should stop studies or work to allow your body to focus on fighting the infection and recovering.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/?utm_source=share&utm_campaign=share.
2. Callard F, Perego E. How and why patients made Long Covid. *Soc Sci Med*. 2020:113426. https://doi.org/10.1016/j.socscimed.2020.113426.
3. Covid-19. What do we know about "long covid"? *BMJ*. 2020;370, m2815. https://doi.org/10.1136/bmj.m2815.
4. https://icd.who.int/browse10/2019/en#/G93.3.
5. Carruthers BM, van de Sande MI, De Meirleir KL. Myalgic encephalomyelitis: international consensus criteria. *J Intern Med*. 2011;270:327–338 [PMC free article] [PubMed] [Google Scholar] [Ref list].
6. del Rio C, Malani PN. New insights on a rapidly changing epidemic. *J Am Med Assoc*. 2020;323(24):1339–1340.
7. https://covid.joinzoe.com/data.
8. Carfì A, Bernabei R, Landi F, Gemelli, Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute covid-19. *J Am Med Assoc*. 2020;9. https://doi.org/10.1001/jama.2020.12603. pmid:32644129.
9. Carfì A, Bernabei R, Landi F. For the gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19. *J Am Med Assoc*. 2020;324(6):603–605. https://doi.org/10.1001/jama.2020.12603.
10. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClin Med*. 2020;25:100463.
11. Tenforde MW, Kim SS, Lindsell CJ, et al, IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR. Morbid Mortal Weekly Rept*. 2020;69(30):993–998. https://doi.org/10.15585/mmwr.mm6930e1.
12. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PloS One*. 2020;15(11), e0240784. https://doi.org/10.1371/journal.pone.0240784.
13. Brooks K, Webster K, Smith E, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*. 2020;395:912–920.
14. Hives L, Bradley A, Richards J. Can physical assessment techniques aid in diagnosing people with chronic fatigue syndrome/myalgic encephalomyelitis? A diagnostic accuracy study. *BMJ Open*. 2017;7, e017521.
15. Perrin R, Riste L, Hann M. Into the looking glass: post-viral syndrome post COVID-19. *Med Hypotheses*. 2020;144:14–21.
16. Komaroff AL. Advances in understanding the pathophysiology of chronic fatigue syndrome. *J Am Med Assoc*. 2019;322:499–500. https://doi.org/10.1001/jama.2019.8312.
17. Mueller C, Lin JC, Sheriff S, Maudsley AA, Younger JW. Evidence of widespread metabolite abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. *Brain Imag Behav*. 2019;14:562–572. https://doi.org/10.1007/s11682-018-0029-4.
18. Poon DC, Ho YS, Chiu K, Wong HL, Chang RC. Sickness: from the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons. *Neurosci Biobehav Rev*. 2015;57:30–45. https://doi.org/10.1016/j.neubiorev.2015.07.015.
19. VanElzakker MB. Chronic fatigue syndrome from vagus nerve infection: a psychoneuroimmunological hypothesis. *Med Hypotheses*. 2013;81:414–423. https://doi.org/10.1016/j.mehy.2013.05.034.
20. Shepherd CB. *Post-covid 19 fatigue, post/long covid-19 syndromes and post-covid ME/CFS*. ME Association; November 2019.
21. Topol E, Verghese A, Fauci A. *Fauci to medscape: 'we're all in it together and we're gonna get through it'*. Medscape; 2020. Available online at: https://www.medscape.com/viewarticle/933619#vp_2.
22. Pan R, Zhang Q, Anthony SM, et al. Oligodendrocytes that survive acute coronavirus infection induce prolonged inflammatory responses in the CNS. *Proc Natl Acad Sci USA*. 2020;117:15902–15910. https://doi.org/10.1073/pnas.2003432117.

23. Holmes TH, Anderson JN. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. *Proc Natl Acad Sci Unit States Am*. 2017;114:E7150–E7158 [PMC free article] [PubMed] [Google Scholar] [Ref list].
24. British Association for Cfs/ME (BACME). Post-viral fatigue: a guide to management: https://www.nbt.nhs.uk/our-services/a-z-services/bristol-chronic-fatigue-syndromeme-service/post-viral-fatigue-a-guide-management.
25. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020.
26. Nauen DW, Hooper JE, Stewart CM, Solomon IH. Assessing brain capillaries in coronavirus disease 2019. *JAMA Neurol*. 2021 Jun 1;78(6):760–762. https://doi.org/10.1001/jamaneurol.2021.0225. PMID: 33576767; PMCID: PMC7881367.

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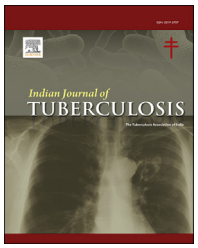

Short communication

'Personalizing' shorter regimens: Need of the hour

Kranti Garg[*], *Komaldeep Kaur*, *Aditi Gupta*, *Vishal Chopra*, *Sudesh Kumari*

Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India

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ABSTRACT

Introduction: The launch of injectable shorter regimens under Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines 2017 under Revised National Tuberculosis Control Program (RNTCP) was a welcome step as it decreased the duration of treatment significantly in Drug Resistant Tuberculosis (DRTB) patients.

The objective of the present study was to evaluate the treatment outcomes of patients started on injectable shorter regimens from March 2018 to May, 2019.

Methods: Retrospective study which scrutinized medical records of 85 patients started on injectable shorter regimen was conducted. Necessary information on possible patient and disease related predicting factors like age, gender, weight, HIV status, presence of diabetes mellitus (DM), anemia, gap between diagnosis and initiation of treatment, duration of intensive phase (IP) and time of sputum conversion was retrieved, and analyzed for possible association with treatment outcomes.

Results: 56.5% had successful treatment outcomes. Age, gender, BMI, diabetic/anemic status and gap between diagnosis and initiation of treatment had no statistically significant relationship with the final outcomes. Duration of IP, sputum conversion and time of outcome during the course of illness emerged as significant factors in successful outcomes.

Conclusion: The injectable shorter regimens were suitable for a variety of population irrespective of demographic disparities. Patients need to be followed closely as microbiological parameters serve as early indicators of unsuccessful outcomes. These regimens can serve as an alternate choice in patients not tolerating the all oral shorter Bedaquiline containing shorter regimen. Similar such options with combinations of different drugs for individualizing treatment regimens is the need of the hour.

1. Introduction

TB is a global health problem and endemic in India.[1] In a resource-limited country like India, drug-resistance undermines the continuous anti TB efforts and its burden.[1] Its increasing magnitude over years has strained our efforts for TB elimination dramatically. Treatment regimens have undergone rapid changes during the last few years with the generation of evidence on the benefits of different drug combinations.[2,3] There has been a special focus on decreasing the duration of treatment, pill burden, early detection of

* *Corresponding author*. Tel.: +91 9646121601, +91 9914433515.
E-mail address: drkrantigarg@yahoo.com (K. Garg).

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resistance, and improving tolerance to various medications.[4] One of such efforts was the launch of shorter regimens for Drug Resistant Tuberculosis (DRTB) under Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines 2017 and 2021.[2,3]

However, the drugs in the shorter regimen could not be modified/replaced/substituted, they have to be stringently administered only as prescribed combinations. If not possible, patient had to be shifted to alternative regimens.[2,3] The Department of Pulmonary Medicine, Government Medical College, Patiala is having the nodal DRTB centre and is providing services to 8 districts in the state of Punjab. Shorter regimen was incorporated for the patients at our centre in the month of March, 2018.The study aimed to analyse the treatment outcomes of patients started on shorter regimen, and factors affecting the same, from March 2018 to May, 2019.

2. Materials and methods

It was a retrospective study which scrutinized the medical records of 89 patients suffering from rifampicin-resistant (RR)/multidrug-resistant (MDR) tuberculosis and enrolled under RNCTP at DRTB centre from March 2018 to May 2019, and started on shorter regimen.[3] Necessary information on possible predicting factors like age, gender, weight band (16–29kg, 30–45 kg, 46–70 kg),[2] hemoglobin levels, HIV status, presence of diabetes mellitus (DM) and duration of intensive phase (IP) as determined by sputum conversion, was retrieved. Gap between diagnosis and treatment initiation was also noted. These factors were analyzed with relation to the treatment outcomes.

Anemia was defined as a Hb < 13 g/dl in males and <12 g/dl in females.[5] Diabetes mellitus was defined as fasting plasma glucose (FPG) > 126 mg/dl or glycated hemoglobin >6.5%.[6] The RR/MDR patients were started on shorter regimen as per inclusion and exclusion criteria propsed under PMDT 2017.[2] Intensive phase was given for 4–6 months with kanamycin, high dose moxifloxacin, ethionamide, clofazamine, pyrazinamide, ethambutol and high dose isoniazid. Continuation phase (CP) had a fixed duration of 5 months with high dose moxifloxacin, clofazamine, pyrazinamide and ethambutol.[2] It was ensured that sample for second line line probe assay (SL-LPA) was sent. If additional resistance was detected, regimen was changed accordingly.[2]

Treatment outcomes were defined as per PMDT guidelines and categorized into cured/treatment completed/died/failed/lost to follow-up/regimen changed/not evaluated.[2]

The patients who were declared as cured/treatment completed were considered in successful outcomes. Those who died/failed/lost to follow-up/regimen changed were labeled as having unsuccessful outcomes. Out of a total 89 patients enrolled at baseline, 4 patients were not evaluated as they were transferred out to other districts, and hence were excluded. Final analysis thus consisted of 85 patients.

The study was approved by the institute's ethics committee.

2.1. Statistical analysis

Categorical variables were reported as counts and percentages. Group (outcome) comparisons were made with the Chi–Sq test or Fisher's exact test whichever was applicable. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of Normality. Continuous data were given as mean ± SD and range or median and interquartile range, as appropriate. For non normally distributed (skewed) data, comparison based on the basis of groups was made by Mann–Whitney test. For normally distributed data, Student t-test was applied to compare the 2 groups. A P value < 0.05 was considered significant. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

3. Results

The characteristics of the study population and relationship of final outcomes with various parameters are depicted in Table 1. There was no gender predilection. The majority (n = 33) of the patients were in the age group of 21–30 years. 38.9% patients were started on treatment within 1 week of diagnosis, and rest within 2 weeks.

Outcomes of the studied patient population is depicted in Fig. 1. Of 85 patients whose outcome was analyzed, 48 (56.5%) (n = 36 cured, n = 12 treatment completed) had a successful outcome and 37 (43.5%) were declared as having unsuccessful outcomes as 9 patients died, 14 patients were lost to follow up during the study period and regimen was changed in the same number (n = 14) of patients due to intolerance to the given regimen (3/14) or due to additional drug resistance found later (11/14), after the start of shorter regimen. It was found that age, gender, diabetic status, anemic status and the gap between diagnosis and initiation of the treatment, all had no statistically significant relationship with the final outcomes. 35.2% patients had IP duration of <4 months and all had an unsuccessful outcome. In the remaining patients with IP duration between 4 and 6 months, majority had successful outcomes (p < 0.001). Follow up smears of only 57 patients were available and the results are depicted in Table 1. Follow up sputum reports (smear and culture) of 28 patients could not be traced as their outcome was already declared as unsuccessful (died/lost to follow up/regimen changed). 35 patients were sputum culture-negative at 4 months, 13 at 6 months and had a final successful outcome (p = 0.004). All these 48 patients who had culture conversion were also found to have successful outcomes at the end of treatment (cured and treatment completed). In rest of the patients, the regimen was changed as per their resistance patterns or because of intolerance to drugs before start of CP.

4. Discussion

Programmatically, shorter regimen was successful in 56.5% (48/85) of the patients. 75% (36/48) of these patients were

Table 1 – Characteristics of the study population and their relationship with the final outcomes.

Parameter		Treatment outcome		P value
		Successful (n = 48)	Unsuccessful (n = 37)	
Gender	Male (n = 42)	23 (47.9%)	19 (51.4%)	0.754
	Female (n = 43)	25 (52.1%)	18 (48.6%)	
Age (in years)	<20 (n = 21)	12 (25%)	9 (24.3%)	0.091
	21–30 (n = 33)	21 (43.75%)	12 (32.5%)	
	31–40 (n = 13)	9 (18.75%)	4 (10.8%)	
	41–50 (n = 10)	5 (10.4%)	5 (13.5%)	
	>50 (n = 8)	1 (2.1%)	7 (18.9%)	
Diabetes Mellitus	Yes (n = 12)	6 (12.5%)	6 (16.2%)	0.626
	No (n = 73)	42 (87.5%)	31 (83.8%)	
Anaemia	Yes (n = 23)	33 (68.75%)	29 (78.4%)	0.322
	No (n = 62)	15 (31.25%)	8 (21.6%)	
Gap between diagnosis & treatment initiation	<7 (n = 33)	16 (33.3%)	17 (45.9%)	0.268
	8–14 (n = 52)	32 (66.7%)	20 (54.1%)	
Weight (in kg)	16–29 (n = 3)	1 (2.1%)	2 (5.4%)	0.702
	30–45 (n = 53)	30 (62.5%)	23 (62.2%)	
	46–70 (n = 29)	17 (35.4%)	12 (32.4%)	
IP duration (in months)	<4 (n = 30)	0 (0%)	30 (81.1%)	<0.001
	4 (n = 36)	33 (68.75%)	3 (8.1%)	
	5 (n = 10)	9 (18.75%)	1 (2.7%)	
	6 (n = 9)	6 (12.5%)	3 (8.1%)	
Follow-up sputum smear conversion (n = 57)	Negative (n = 53)	48/57	5/57	<0.001
	Positive (n = 4)	0/57	4/57	
Follow-up culture (n = 57)	At 4 months (n = 44)	35/57	9/57	0.004
	At 6 months (n = 13)	13/57	0	
Outcome in IP/CP	IP (n = 35)	00	35	<0.001
	CP (n = 50)	48 (100%)	02	

IP: Intensive Phase, CP: Continuation Phase.

declared cured and had bacteriological success. 25% (12/48) of these patients were labeled as 'treatment completed' as they improved clinically and radiologically, however, since they were non sputum producing, sputum culture could not be done at end CP. In 16.5% of the patients, the regimen was changed because of intolerance to drugs or additional drug resistance (flouroquinoles/second line injectables) which was detected late during the course of treatment, only after initiation of shorter regimen, due to resource limited settings. The outcomes of the treatment were unaffected by age, gender, diabetic status, anemic status and the gap between diagnosis and initiation of the treatment. These findings give an indication that the shorter regimen is otherwise well tailored and can be administered to the population at large.[2,7]

However, our results highlight the fact that detection of additional drug resistance early in the course of the disease can improve the numbers and percentages of successful outcomes, as patients rather than being labeled as 'regimen changed' at a later date, will be started on appropriate regimens from the time of initiation of treatment itself and will cease to be a part of the denominator in calculation of success of the regimen.[2,3] In addition, intolerance to drugs in shorter regimen need to be dealt with on priority.[8,9] Since the duration of treatment is much lesser than the conventional regimens, shorter regimen is highly acceptable at the patient level.[4,10] However, modification of a few drugs in the fixed regimen, if possible, may deal with the issue of intolerance. Hence, there is an urgent need to test combination of different drugs in the cocktail, so as to give the physician the choice of drug replacement if required. The duration of intensive phase, sputum smear and culture conversion and the time of outcome during the course of illness emerged as significant factors in successful outcomes. It is expected that the patients who default in IP, or are not smear/culture converted early are deemed to have unsuccessful outcomes, and this was further strengthened from our study. These findings reinforce the fact that these indicators should be carefully monitored at individual level and appropriate actions taken without delay to prevent unsuccessful outcomes later. In addition, there is an urgent need for focused community outreach activities regarding management of tuberculosis and record updation for benefit of one and all. Simultaneously, the patients and their relatives should also be made well aware of the direct bank transfer schemes of the Government at regular follow-ups and on completion of their treatment. This will assist in reducing the number of patients lost to follow-up.

PMDT 2021 has changed the shorter injectable containing regimen to an all oral shorter bedaquiline containing regimen.[3] Preliminary clinical experience with this new combination shows the issue of intolerance of even higher degree. The strength of the shorter injectable containing regimen under the programme (PMDT 2017) we studied is its treatment success and the fact that it can be used as an efficient alternative to all oral shorter bedaquiline containing regimen in patients with intolerance. 'Individualizing' the shorter regimen, or atleast allowing some choices in drug combinations if required, is the need of the hour to address drug resistance, improve tolerance and increase patient

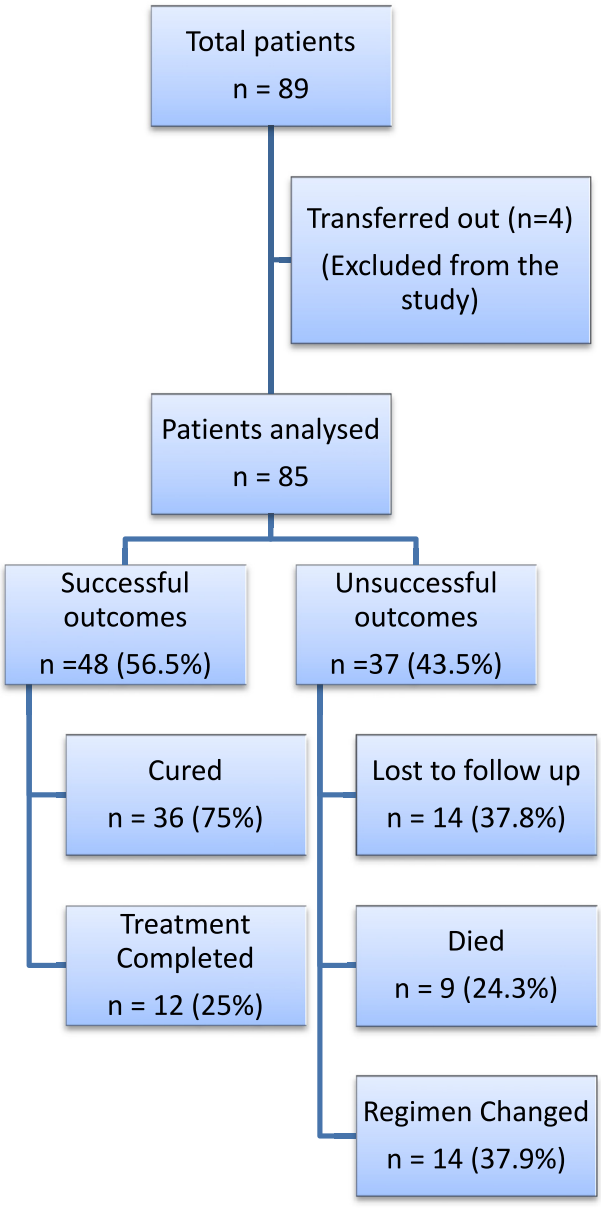

Fig. 1 – Flowchart showing enrollment of the patients and their final outcomes.

acceptance. There is an urgent need for research in this area. The short duration of treatment, as the name itself says, is very encouraging for the patient, and the full potential of various drugs which can be used in such shorter regimen in different combinations needs to be exploited to the full capacity, before switching over to the longer regimens.

5. Conclusion

Flexibility in the drug constituents is required in patients with intolerance to the tailored shorter regimens, so as to increase acceptability and decrease switch overs to longer regimens. Experiences of our past with injectable shorter regimen, should be applied in clinical practice in the present, and for tailoring the research for future.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. (Internet). *Global Tuberculosis Report 2020*; 2020 [cited 2021 May 20]. Available from: http://apps.who.int/bookorders.
2. [Internet]. *Guideline for PMDT in India 2017*; 2017. Available from: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=4781&lid=3306.
3. [Internet]. *Guidelines for Programmatic Management of Drug Resistant Tuberculosis India*; 2021. Available from: https://tbcindia.gov.in/showfile.php?lid=3590.
4. WHO treatment guidelines for drug-resistant tuberculosis 2016 update [Internet]. [cited 2021 May 18]. Available from: https://www.who.int/publications/i/item/9789241549639.
5. World Health Organization. *Iron Status of Populations Assessing the Second Edition Including Literature Reviews Centers for Disease Control and Prevention Division of Nutrition and Physical Activity International Micronutrient Malnutrition Prevention and Control Program Department* [Internet]; 2007 [cited 2021 May 18]. Available from: https://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9789241596107/en/.
6. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. *Int J Diabetes Dev Ctries*. 2018 Mar 1;38(suppl 1):1.
7. Trebucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tubercul Lung Dis*. 2018 Jan 1;22(1):17–25.
8. Buziashvili M, Mirtskhulava V, Kipiani M, et al. Rates and risk factors for nephrotoxicity and ototoxicity among tuberculosis patients in Tbilisi, Georgia. *Int J Tubercul Lung Dis*. 2019 Sep 1;23(9):1005–1011.
9. Sturdy A, Goodman A, Joś RJ, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. *J Antimicrob Chemother*. 2011;66(8):1815–1820.
10. Prasad R, Gupta N, Banka A. Shorter & cheaper regimen to treat multidrug-resistant tuberculosis: a new hope. *Indian J Med Res*. 2017 Sep 1;146(3):301–303.

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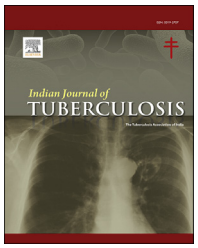

Case report

Incidental encounter of intraperitoneal tuberculosis during renal surgeries: A surgeon's dilemma

Harkirat Singh Talwar, Senior Resident, Sunil Kumar, Assistant Professor, Ankur Mittal, Associate Professor, Tushar Aditya Narain, Assistant Professor, Vikas Kumar Panwar, Assistant Professor*

Department of Urology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, 249203 India

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ABSTRACT

Tuberculosis is a major healthcare burden in India, which accounts for the maximum number of cases worldwide. Due to its non-specific features, peritoneal tuberculosis has been dubbed as the great mimicker of various other abdominal pathologies. This case series highlights the importance of incidental intra operative detection of peritoneal tuberculosis in cases being operated for renal pathologies. Diagnostic and therapeutic dilemma is bound to occur when surgeon is faced with such an unexpected finding. Incidental peritoneal tuberculosis was defined as peritoneal tubercular lesions (ascites or tubercles) detected intraoperatively in patients being operated for non-tuberculosis related indications and no prior preoperative suspicion of abdominal tuberculosis. We here review 3 cases with different renal pathologies and no prior history or exposure to tuberculosis in which intraperitoneal tuberculosis was encountered incidentally at the time of surgery. Case 1 was a suspected case of right renal cell carcinoma and underwent right robotic nephron sparing surgery. Case 2 underwent robotic assisted lap simple nephrectomy for a right nonfunctioning kidney due to obstructive ureteric calculus. Case 3 was a suspected case of left upper tract urothelial carcinoma who underwent robotic nephroureterectomy with bladder cuff excision. In all 3 cases, on encountering the peritoneal lesions, an intraoperative decision to continue with the proposed surgery was made after frozen section biopsies from the multiple peritoneal and omental deposits revealed no malignant cells. Histopathology of these lesions in all 3 cases revealed caseating granulomas consistent with a diagnosis of disseminated peritoneal tuberculosis. None of the resected specimen had features suggestive of tuberculosis. ATT was started and on follow up the patients are doing well. Peritoneal tuberculosis although uncommon is not a rare presentation of active tuberculosis. Surgeons on encountering such lesions during non-related surgeries should always have a high suspicion of tuberculosis. Despite the existing literature favoring abandoning the procedure in such situations, we successfully completed the proposed surgeries.

* *Corresponding author*. Tel.: +91 9639657019.
E-mail address: drmittal.ankur@gmail.com (A. Mittal).

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1. Introduction

Incidental detection of peritoneal tuberculosis during surgical exploration for unrelated pathologies is uncommon. Prompt diagnosis and further management of this rare entity in such situations is not well elucidated. Moreover, if encountered during surgical management of a malignant tumor, it is bound to add to the dilemma of continuing with the proposed surgery or not.

The natural course of abdominal tuberculosis is varied and might range from chronic asymptomatic states to acute surgical abdomen.[1] Incidental intraoperative detection of such lesions may be confused with disseminated intraabdominal malignancy. Thus, it is rightly dubbed as the "great mimicker" of various abdominal pathologies due to its non-specific features.

We herein present three cases of incidentally detected peritoneal tuberculosis during robot assisted laparoscopic surgeries being performed for unrelated renal pathologies with no prior history or exposure to tuberculosis. With a diagnostic and therapeutic dilemma in mind, we went ahead with the proposed surgeries with good post-operative outcome.

2. Case report

We retrospectively reviewed all the cases operated in our department by robot assisted laparoscopic means during the period from January 2019 to February 2020. Of the 221 surgeries performed by robotic means, three had incidental detection of intraabdominal tuberculosis (1%).

Suspected diagnosis of peritoneal tuberculosis was defined as the endoscopic visualization of intraabdominal tubercles, military nodules, bands, ascites, membranes and/or calcification.

Definitive diagnosis of peritoneal tuberculosis was defined as the histopathological confirmation of caseating granulomatous lesions either with or without the presence of acid-fast bacilli in the aforementioned manifestations of tuberculosis.

Definition of "incidental" peritoneal tuberculosis had the following strict criteria.

1) Suspected/Definitive diagnosis of peritoneal tuberculosis
2) No pre-operative history of exposure to tuberculosis or any radiological investigation suggestive of tuberculosis.
3) No lesion of tuberculosis elsewhere in the body

3. Case 1

A sixty-year-old lady presented with right flank pain for 3 months. Ultrasonography revealed a 5 cm mass arising from the lower pole of right kidney. CECT scan characterized it as an enhancing exophytic mass 5.7 × 5 cm in size with no evidence of tumor thrombus and away from the collecting system. She underwent a robot assisted (*daVinci Xi platform*) nephron sparing surgery. Intraoperatively, multiple tubercles were found spread across the surface of liver, omentum and peritoneum (Fig. 1a). Frozen section biopsies from these lesions revealed caseous granuloma suggestive of tuberculosis. Post-operative histopathology of the renal specimen was suggestive of renal cell carcinoma and histopathology of deposits showed granulomatous inflammation with caseous necrosis and presence of acid-fast bacilli confirming a diagnosis of peritoneal tuberculosis.

4. Case 2

A 26-year-old lady presented with right lower abdominal pain for six months. She had history of nephrostomy insertion elsewhere 3 months back followed by endoscopic insertion of ureteral stent. Serum creatinine was normal. CT urography revealed an obstructive ureteric calculus of size 1cm in the upper ureter with stent in situ and small shrunken right kidney with no contrast excretion. Left kidney was normal with no features suggestive of GUTB. DTPA scan showed differential function of 8% and she underwent robot assisted right simple nephrectomy. Intraoperatively, multiple tubercles were found spread across the surface of solid organs, bowel, omentum and peritoneum (Fig. 1b). Frozen section biopsies from these lesions revealed caseous granuloma suggestive of tuberculosis. Post-operative histopathology of the renal specimen was suggestive of chronic pyelonephritis and histopathology of deposits showed granulomatous inflammation with caseous necrosis and presence of acid-fast bacilli confirming a diagnosis of peritoneal tuberculosis.

5. Case 3

A 60-year-old lady presented with left flank pain for 7 months with intermittent hematuria. CT urography revealed a centrally located hypoenhancing lesion in the left kidney 4.9 × 5.6 cm in size suggestive of upper tract urothelial carcinoma. Metastatic work up was negative. Urine cytology and cystoscopy revealed no positive findings. She underwent a robot assisted left nephroureterectomy with bladder cuff excision. Intraoperatively, multiple tubercles were found spread across the surface of liver, omentum and parietal peritoneum (Fig. 1c). Frozen section biopsies were suggestive of tubercular lesions. Post-operative histopathology of the renal specimen was suggestive of upper tract TCC and histopathology of deposits showed granulomatous inflammation with caseous necrosis and presence of acid-fast bacilli confirming a diagnosis of peritoneal tuberculosis.

Pre-operatively, in all the three cases, a thorough past history and family history had been taken which was not significant for tuberculosis. Also, a pre-operative chest x-ray as well as the abdominal imaging had no features to suggest tuberculosis. A post-operative search found no evidence of pulmonary tuberculosis on chest imaging and none of the patients were immunocompromised. All the cases completed a 9-month course of ATT and on follow-up, are asymptomatic.

6. Discussion

Peritoneal tuberculosis accounts for 25–50% of abdominal tuberculosis cases and 0.1–0.7% of total cases of tuberculosis

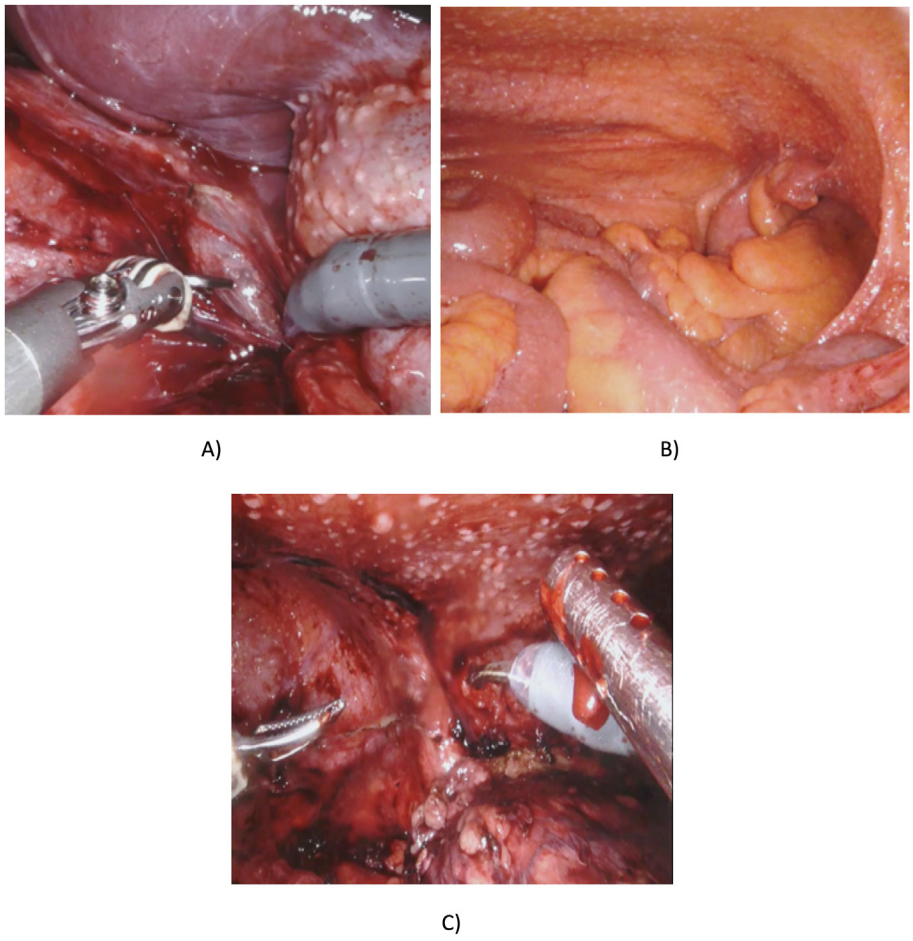

Fig. 1 – Intraoperative laparoscopic findings of a) peritoneal deposits, adhesions and ascites in case 1; b) parietal and visceral peritoneal deposits in case 2; c) deposits over the liver and bowel with multiple adhesions in case 3.

worldwide.[2] It is most commonly seen in females <40 years of age. Majority are asymptomatic, although abdominal pain, fever, bowel disturbances, weight loss, anorexia and malaise may be present.[3] Pathogenesis includes hematogenous spread, transmural spread, lymphatic spread or reactivation of latent foci in abdomen.[4] Peritoneal tuberculosis can be classified as wet ascitic type, dry type with dense adhesions and the fibrotic type with loculations and omental thickening.[1] Laparoscopic features of the disease includes whitish granulations, free fluid, adhesions, mesenteric and omental thickening and the characteristic stalactic band.[5]

There is a lack of literature on what actually constitutes "incidental" peritoneal tuberculosis. *It can be defined as an unexpected finding of lesions characteristic of tuberculosis (tubercles/ascites/adhesions) intraoperatively in patients who undergo laparotomy/laparoscopy for unrelated pathologies with no prior history of exposure and no preoperative clinical or radiological suspicion of active or latent tuberculosis.* Diagnostic and therapeutic dilemma is bound to occur when surgeon is faced with such an unexpected finding with the lesions mimicking peritoneal carcinomatosis. Even if carcinomatosis has been ruled out, there always exists a theoretical risk of port/incision site tuberculosis or tubercular dissemination.

In our series, the decision to continue with the surgery was relatively simpler in case 2 considering she was a young female with a benign lesion coming from an endemic area. However in the other two cases, the decision of completing the proposed surgery in spite of etiology being malignant was taken as both renal cell carcinoma and upper tract urothelial carcinoma very rarely present with disseminated peritoneal carcinomatosis and the laparoscopic findings were consistent with the characteristic tubercular lesions. Also, the frozen section taken from the deposits revealed caseating granulomas with no malignant cells seen.

This is a situation where both continuing and abandoning the surgery both have their own proponents.[6] Several factors which should be taken into consideration include:

a) Age of the patient
b) Endemicity of tuberculosis
c) Reconfirming the clinical history and the radiological findings
d) If being operated for a malignancy, consider the clinical stage of the disease and whether metastasis could be expected

e) Always rethink whether laparoscopic findings are consistent with those of tuberculosis.

If even after careful deliberation, dilemma persists, frozen section is recommended as also suggested by Koc and colleagues.[7] Another important consideration with continuing the surgery is the risk of dissemination of tuberculosis. Although rare, but miliary tuberculosis has been reported post-surgical intervention in cases of tubercular epididymitis, intraocular tuberculosis and even after splenectomy. Two very important factors which reduced the probability of this rare event even further was the use of minimally invasive surgical technique and the inevitable anti tubercular therapy in the post-operative period.

Follow up poses certain challenges as most of the patients are asymptomatic and response assessment is difficult. Also lack of a proper imaging modality for peritoneal tuberculosis compounds the existing difficulty. Weight gain and general well-being are important considerations for an effective response to anti tubercular therapy. ATT in the immediate post-operative period is inevitable when peritoneal tuberculosis is diagnosed incidentally.[8] It also decreases the theoretical risk of developing port site/incision site recurrences. More studies are warranted in future to evidently support our hypothesis.

Conflicts of interest

The authors have none to declare.

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The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work. The manuscript has not been published in part or whole or is not under consideration for publication elsewhere in any language.

REFERENCES

1. Safarpor F, Aghajanzade M, Kohsari MR, Hoda S, Sarshad A, Safarpor D. Role of laparoscopy in the diagnosis of abdominal tuberculosis. *Saudi J Gastroenterol*. 2007;13:133–135.
2. Chow KM, Chow VC, Szeto CC. Indication for peritoneal biopsy in tuberculous peritonitis. *Am J Surg*. 2003;185:567–573.
3. Shi XC, Zhang LF, Zhang YQ, Liu XQ, Fei GJ. Clinical and laboratory diagnosis of intestinal tuberculosis. *Chin Med J Engl*. 2016;129:1330–1333.
4. Singh MM, Bhargava AN, Jain KP. Tuberculous peritonitis. An evaluation of pathogenetic mechanisms, diagnostic procedures and therapeutic measures. *N Engl J Med*. 1969;281:1091–1094.
5. Vaid U, Kane GC. Tuberculous peritonitis. *Microbiol Spectr*. 2017;5. https://doi.org/10.1128/microbiolspec.TNMI7-0006-2016.
6. Krishnamurthy G, Singh H, Rajendran J, et al. Gallbladder tuberculosis camouflaging as gallbladder cancer – case series and review focusing on treatment. *Ther Adv Infect Dis*. 2016;3:152–157.
7. Koc S, Beydilli G, Tulunay G, et al. Peritoneal tuberculosis mimicking advanced ovarian cancer: a retrospective review of 22 cases. *Gynecol Oncol*. 2006;103:565–569.
8. Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. *Cochrane Database Syst Rev*. 2016;11, CD012163.

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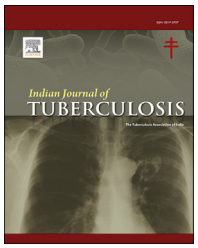

Case report

Mycobacterium W. - An unusual side effect

Rakesh K. Chawla, Senior Consultant [a,*], *Aditya K. Chawla, Consultant* [b], *Gaurav Chaudhary, DNB(Final year)* [a], *Kamal Chopra, Director* [c], *Madhav K. Chawla, Junior Resident* [d]

[a] *Jaipur Golden Hospital, Delhi, India*
[b] *Saroj Superspeciality Hospital, Delhi, India*
[c] *New Delhi TB Centre, Delhi, India*
[d] *Dr. Baba Saheb Ambedkar Medical College & Hospital, Delhi, India*

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ABSTRACT

Objective: To present an interesting case of unusual side effect of Mycobacterium W. in an adult COVID 19 positive male and discuss its assessment and management.
Methods: -
Design: Case Report.
Setting: Tertiary care hospital.
Patient: One.
Results: 70 years male was admitted with complaints of fever, persistent dry cough since 10–12 days and progressive breathlessness since 3–4 days. Patient was found COVID-19 RTPCR positive and is known case of Type-II Diabetes with CAD (Post PTCA). Patient was managed conservatively with Oxygen support, I/V antibiotics, I/V Steroids, oral Favipiravir and other supportive treatment.

Patient was also given injection Mycobacterium W. in dose of 0.3 ml per day intradermally at 3 different sites (both deltoids) consecutively for three days. 7–8 days after administration, patient developed bright red pustules which later got converted into small punched out ulcerations on all nine local sites of administration, which were managed conservatively with oral analgesics and local steroids for 8–10 days which healed without any scar formation.
Conclusion: Injection Mycobacterium W. is used in COVID 19 patients as an immunomodulator agent and has been proved to be safe in most of the cases but we encountered this unusual side effect of bright red pustules formation at all nine local sites of injection in our case most likely because of being administered subcutaneously instead of intradermally, making this an interesting case which is being reported to scientific fraternity.

* *Corresponding author*. Department of Pulmonary Medicine, Critical Care and Sleep disorders, Jaipur Golden Hospital, Saroj Super Speciality Hospital 36, Pocket: E-3, Sector-3, Rohini, New Delhi, 110085, India.
E-mail address: rakeshchawla8888@gmail.com (R.K. Chawla).
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1. Introduction

Coronaviruses are enveloped non segmented positive-sense RNA viruses belonging to the family coronaviridae and the order Nidovales and broadly distributed in humans and other mammals. Although most human coronavirus infections are mild, the epidemics of the two betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS- CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have caused more than 10,000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV. The coronaviruses already identified might only be the tip of the iceberg, with potentially more novel and severe zoonotic events to be revealed.

2. Case history

A 70 years male was admitted with complaints of fever, persistent dry cough since 10–12 days and progressive breathlessness since 3–4 days. Patient was found COVID-19 RTPCR positive and is known case of Type-II Diabetes with CAD (Post PTCA). On examination, vitals were stable, maintaining SpO2 94% on room air, on chest examination bilateral crepts present, rest systemic examination was within normal limits. Patient was managed conservatively with Oxygen support, I/V antibiotics, I/V Steroids, oral Favipiravir and other supportive treatment.

Patient was also given injection Mycobacterium W. 0.3 ml per day intradermally at 3 different sites (both deltoids) consecutively for three days. 7–8 days after administration, patient developed bright red pustules which later got converted into small punched out ulcerations on all nine local sites of administration (Figs. 1–2). Lesions were painful, tender on touch, non-discharging in nature, local erythema present, with no signs of systemic inflammation, managed conservatively with oral analgesics and local steroids for 8–10 days which healed without any scar formation.

3. Discussion

Patients with COVID requiring intensive care unit (ICU) admission have higher

cytokine levels compared to those who do not need ICU care.[1] Even among patients admitted to ICU, those discharged from hospital had lower cytokine levels compared to those who died.[2] An immunomodulator may thus be of potential benefit in managing these critically ill COVID patients. The

Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R) and the World Health Organization have identified adjuvant therapy as one of the key areas of research to save lives of patients infected with COVID-19.[3] A heat-killed *Mycobacterium* w (Mw), originally developed as an

immunomodulator for leprosy, which acts through the toll-like receptors (TLRs) pathway and enhances the host-T cell responses.[4] Sehgal IS et al showed the benefit of Mw in patients with severe sepsis.[5] Use of Mw in COVID-19 patients was observed to be safe and well tolerated, without any major safety

concerns in patients with COVID-19.[6]

Herein our case report, we are discussing the issue arising due to use of Injection Mycobacterium W. in COVID 19 patients. Patient developed bright red pustules which later got converted into small punched out ulcerations on all nine local sites of administration which were painful, tender on touch, non-discharging in nature, local erythema present, with no signs of systemic inflammation, managed conservatively.

Local site reactions were observed at the site of injection of Mw in 85.47% of the patients. Out of which majority of the patients had mild reaction (54%). Patients developed erythema at the site of injection which was followed by development of induration and pustule formation. This was converted in to a small punched out ulceration which healed by a formation of healthy scar without the need of any specific treatment.[6]

Injections site immunological reaction to Mw is a known phenomenon.[7] Sharma SK et al reported injection site reaction in 82.4% of the patients. 68% of the patients experienced

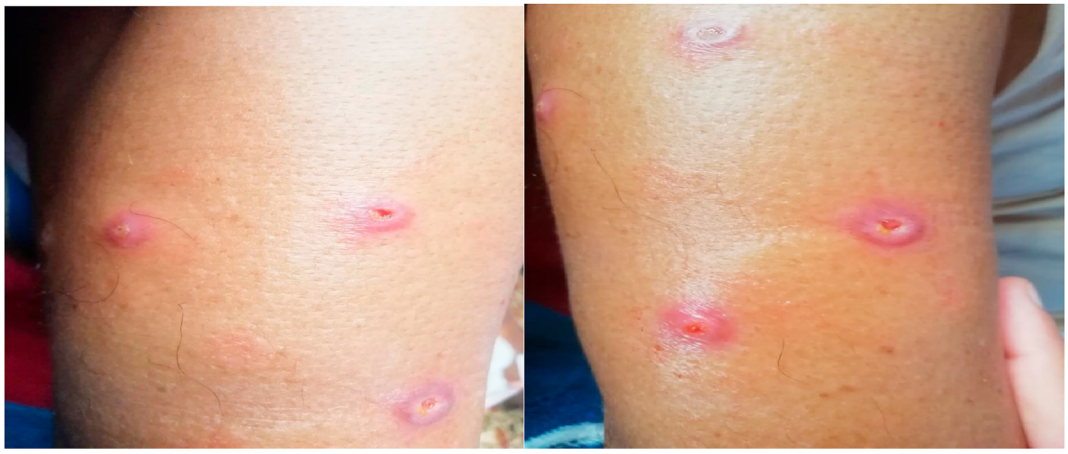

Fig. 1 – Bright red pustules formation at six local sites of administration (right deltoid).

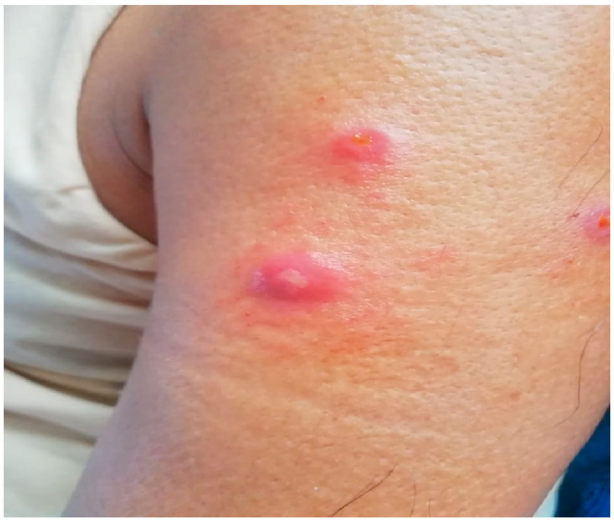

Fig. 2 – Bright red pustules formation at three local sites of administration (left deltoid).

mild intensity of the reaction whereas 12.91% had moderate to severe reaction at local site.[8] d'Aleo F reported exaggerated response at the injection when BCG was administered into the subcutaneous space instead of intradermal inoculation which resulted in development of local abscess.[9] Looking in to the skills required for the intradermal injection and paramedical staff working with PPE kits on, we believe there are chances of erroneous injection of Mw in to the subcutaneous space, instead of intradermal space, in some of the patients. We are reporting this case to make clinicians aware that this can also occur as adverse site reaction which resolved with oral anti-inflammatory drugs and local steroids for 8–10 days.

We used Injection Mycobacterium W. in COVID 19 patients as per protocol developed in our hospital, but patient developed this adverse site reaction most likely because of being administered subcutaneously instead of intradermally making this an interesting case, hence it is being reported to the scientific community.

4. Conclusion

Injection Mycobacterium W. is used in COVID 19 patients as an immunomodulator agent and proved to be safe in most of the cases, in our case patient had this unusual side effect most likely because of being administered subcutaneously instead of intradermally making this an interesting case to be reported to the scientific community and make clinicians aware of this possible unusual side effect of the forementioned injection.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506 [PMCID: PMC7159299] [PubMed: 31986264].
2. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020. doi:101007/s00134-020-05991-x. [PMCID: PMC7080116] [PubMed: 32125452].
3. *COVID 19 public health emergency of international concern global research and innovation forum: towards a research roadmap*; 2020 [Last accessed on 2020 Mar 23]. Available from: https://wwwwhoint/blueprint/priority-diseases/keyaction/Global_Research_Forum_FINAL_VERSION_for_web_14_feb_2020pdfua=1.
4. Desai NM, Khamar BM. Immunotherapy for tuberculous pericarditis. *N Engl J Med*. 2014;371:2533–2534 [PubMed: 25539119].
5. Sehgal IS, Agarwal R, Aggarwal AN, Jindal SK. A randomized trial of *Mycobacterium* w in severe sepsis. *J Crit Care*. 2015;30:85–89 [PubMed: 25241089].
6. Ingale A, Ingale F, Kunwar B, et al. Role of Mycobacterium w for the treatment of COVID-19: an observational study. *Japi*. 2021 Jan;69(2747444):1.
7. Walia R, Sarathchandra KG, Pandey RM, et al. Field trials on the use of Mycobacterium w vaccine in conjunction with multidrug therapy in leprosy patients for immunotherapeutic and immunoprophylactic purposes. *Lepr Rev*. 1993;64:302–311.
8. Sharma SK, Katoch K, Sarin R, et al. Efficacy and Safety of Mycobacterium indicus pranii as an adjunct therapy in Category II pulmonary tuberculosis in a randomized trial. *Sci Rep*. 2017;7:3354. https://doi.org/10.1038/s41598-017-03514-1. PMID: 28611374; PMCID: PMC5469738.
9. d'Aleo F, Bonanno R, Constatino ALP, et al. A case of abscess after BCG vaccine in an immunocompetent child without other clinical signs. *JMM Case Rep*. 2015;2:1–3. https://doi.org/10.1099/jmmcr.0.000103.

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Case report

Beware of spurious tracheo-bronchial stents

Rakesh K. Chawla [a,*], *Kamal Chopra* [b], *Aditya K. Chawla* [a], *Gaurav Chaudhary* [a], *Ashish Sinha* [a], *Madhav K. Chawla* [a]

[a] *Jaipur Golden Hospital, Rohini, New Delhi, India*
[b] *NDTB Centre, Rohini, New Delhi, India*

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ABSTRACT

Objective: To present a case of accidental sheath removal of tracheo-bronchial self-expandable metallic airway stent in a patient with endotracheal tumour.
Methods: **Design:** Case Report; **Setting:** Tertiary care hospital; **Patient:** One.
Results: A 65 years male, follow up case of endotracheal tumor with tracheo-bronchial self-expandable metallic stenting done presented with dry cough and difficulty in breathing since 8–10 days and suddenly coughed out thin whitish paper-like material 2 days back (which later proved as sheath of metallic stent). Direct laryngoscopy with flexible video-bronchoscopy was done which showed tracheal stent well placed and intact, coughed out sheath couldn't be replaced back. Procedure was uneventful and patient was discharged in satisfactory condition and is doing well on regular follow up.
Conclusion: Self-expandable metallic airway stents (SEMAS) represents a standard method of airways stenting especially when employed for the management of malignant central airway obstruction. Despite the obvious stenting advantages, it may be complicated with stent migration and accidental removal or coughing out of stent especially in high tracheal stenosis. In our case, as a peculiar complication there was accidental removal of the tracheal stent sheath which couldn't be replaced back whereas stent was well in place and intact. We need to be beware of such spurious tracheo-bronchial stents.

1. Introduction

Bronchoscopic stent insertion represents a chosen treatment for patients presented with malignant central airways stenosis with a palliative purpose to re-establish airway patency and provide an immediate and significant relief of the patient's symptoms.[1] Self-expandable metallic airway stents (SEMAS) represents a standard method of airways stenting especially when employed for the management of malignant central airway obstruction.[2] Covered self expandable metallic airway stents (SEMAS) have been used for benign tracheal stenosis, post intubation tracheal stenosis, tracheal burn or trauma, tracheo-bronchomalacia, and extrinsic compression of trachea.[3] Despite the obvious stenting advantages, it may be complicated with stent migration and accidental stent

* *Corresponding author*. Department of Pulmonary Medicine, Critical Care and Sleep disorders, Jaipur Golden Hospital, Saroj Super Speciality Hospital, 36, Pocket: E-3, Sector-3, Rohini, New Delhi, 110085, India. Tel.: 9810072860 (mobile).
E-mail address: rakeshchawla8888@gmail.com (R.K. Chawla).
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0019-5707/

removal especially in high tracheal stenosis. The incidence of stent migration is estimated as 5–17% and is more common in tracheal than bronchial lesions.[4]

In this report we are describing a case in which there was accidental removal (coughing out) of thin whitish paper-like material which later proved to be as stent sheath. When the stent manufacturer was confronted, he agreed to the fact that the pasting of sheath around the stent metallic mesh must not had been proper and was of sub-standard quality, this resulted in accidental removal of the stent sheath in a forceful bout of cough and the sheath couldn't be replaced back over the stent.

2. Case history

65 years male, follow up case of endotracheal tumor with tracheal self-expandable metallic stenting done, known case of COPD and chronic smoker, controlled with regular medications was admitted with complaints of dry cough and difficulty in breathing since 8–10 days and suddenly coughed out thin whitish paper-like material 2 days back (Fig. 1). On examination, vitals were stable, maintaining SpO2- 97% on room air, chest examination-bilateral air entry present, rest systemic examination also within normal limits. Routine investigations done showed nothing much significant and patient was started on conservative management. Under conscious sedation, flexible videobronchoscopy was done which showed tracheal stent well embedded in tracheal mucosa (Fig. 2). The accidently coughed out stent sheath could not be placed back, so stent was left as such. Procedure was uneventful, patient was convinced and discharged with advice to come to hospital if he experiences symptoms like stridor or difficulty in breathing, etc. Patient was discharged in satisfactory condition and is doing well on regular follow up.

3. Discussion

The management of malignant tracheal stenosis is a highly challenging which warrant a multidisciplinary approach in every individual case.[5] Bronchoscopic stent insertion represents a palliative therapeutic option in symptomatic patients with proximal tracheal stenosis,[5] in whom the radical surgical

Fig. 1 – Coughed out sheath of tracheo-bronchial SEMAS.

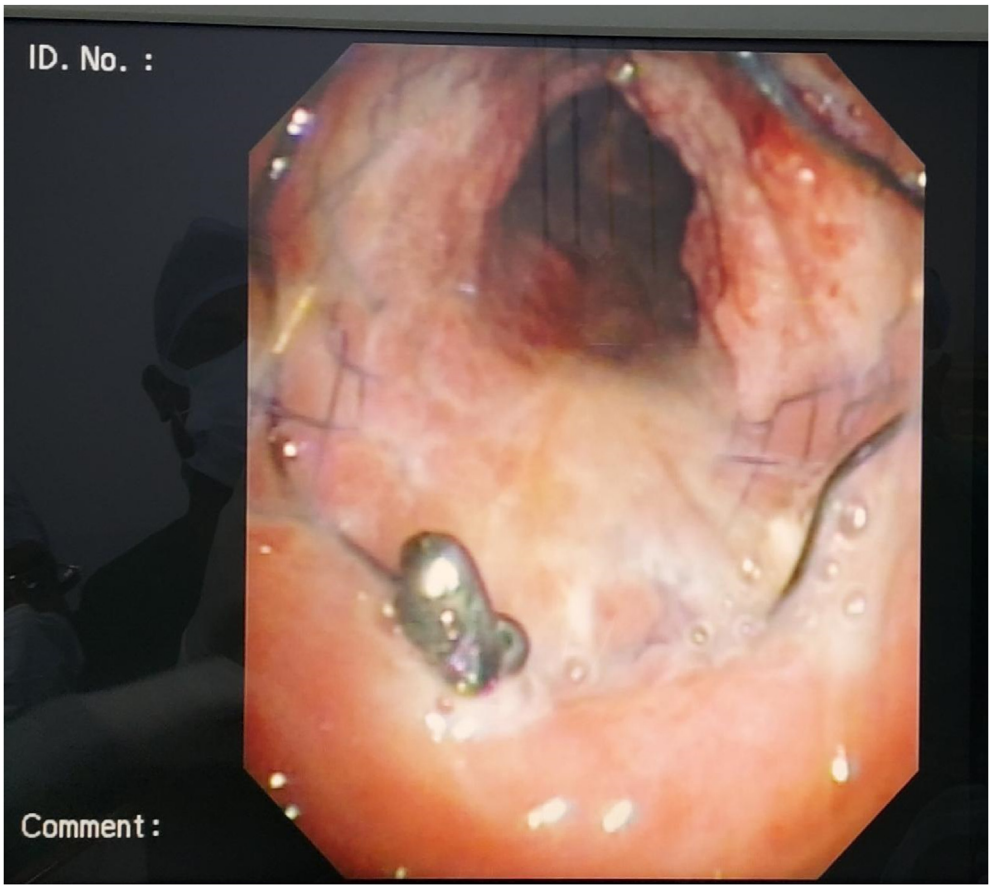

Fig. 2 – Tracheo-bronchial SEMAS well in place, embedded into mucosa.

resection is not possible or contraindicated due to medical unfitness or unresectable lesion depending upon the location and the length of the stenosis.[6,7] Tracheal stent provides not only an immediate significant symptomatic and functional improvement but also a preservation of the phonation function and improvement of the quality of life, as well as increases the survival rate of those patients.[1,8–11]

SEMAS have the following advantages over the silicon stents: firstly, they can be successfully inserted using a flexible bronchoscopy.[12] Secondly, low complication rate; including stent migration, low incidence of mucus plug formation or tumor ingrowth.[13,14] Thirdly, SEMAS have morphologically a thinner wall which provide a larger cross sectional diameter and therefore fits the airways better, making them preferable choice in complex stenosis with irregular airways. Additionally, their adaptation in the airways is improved by their intrinsic radial force which keeps them in position by embedding their ends into the bronchial mucosa.[2,12] The disadvantages of the SEMAS include: removal difficulties, high price,[12] and high rates of granulation tissues formation leading to stent's obstruction.[15] Finally, stent migration was also reported.[15]

In our case, there was peculiar complication that the patient expectorated whitish thin paper-like material (covering sheath of the stent) which could not be replaced back as stent was intact and well embedded in tracheal mucosa. Upon confrontation, stent manufacturer apologized and agreed that the pasting of sheath around the stent mesh must not had been proper and was of sub-standard quality. That accidently coughed out stent sheath could not be replaced back, so stent was left as such.

4. Conclusion

Despite the obvious stenting advantages, SEMAS placement may be complicated with stent migration and accidental removal or coughing out of stent especially in high tracheal stenosis. Also there could be accidental removal of the tracheal stent sheath as seen in this case, so also we need to be beware of such spurious tracheo-bronchial airway stents.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Lin X, Ye M, Li Y, et al. A novel simple external fixation for securing silicone stent in patients with upper tracheal stenosis. *J Thorac Dis*. 2018;10:E194–E198.
2. Saad CP, Murthy S, Krizmanich G, et al. Self-expandable metallic airway stents and flexible bronchoscopy: long-term outcomes analysis. *Chest*. 2003;124:1993–1999.

3. Chawla RK, Madan A, Singh I, et al. Removal of self expandable metallic airway stent: a rare case report. *Lung India*. 2013 Jan;30(1):64. Official Organ of Indian Chest Society.
4. Kim JH, Shin JH, Song HY, et al. Benign tracheobronchial strictures: long-term results and factors affecting airway patency after temporary stent placement. *AJR Am J Roentgenol*. 2007;188:1033–1038.
5. Colt HG, Harrell J, Neuman TR, et al. External fixation of subglottic tracheal stents. *Chest*. 1994;105:1653–1657.
6. Temes RT, Wernly JA, Cooper JD, et al. Internal fixation of high tracheal stents. *Ann Thorac Surg*. 1995;59:1023–1024.
7. Musani AI, Jensen K, Mitchell JD, et al. Novel use of a percutaneous endoscopic gastrostomy tube fastener for securing silicone tracheal stents in patients with benign proximal airway obstruction. *J Bronchology Interv Pulmonol*. 2012;19:121–125.
8. Ranu H, Madden BP. Endobronchial stenting in the management of large airway pathology. *Postgrad Med J*. 2009;85:682–687.
9. Marchese R, Poidomani G, Paglino G, et al. Fully covered self-expandable metal stent in tracheobronchial disorders: clinical experience. *Respiration*. 2015;89:49–56.
10. Amjadi K, Voduc N, Cruysberghs Y, et al. Impact of interventional bronchoscopy on quality of life in malignant airway obstruction. *Respiration*. 2008;76:421–428.
11. Murgu S, Langer S, Colt H. Bronchoscopic intervention obviates the need for continued mechanical ventilation in patients with airway obstruction and respiratory failure from inoperable non-small-cell lung cancer. *Respiration*. 2012;84:55–61.
12. Kim YH, Shin JH, Song HY, et al. Tracheal stricture and fistula: management with a barbed silicone-covered retrievable expandable nitinol stent. *AJR Am J Roentgenol*. 2010;194:W232–W237.
13. Carré P, Rousseau H, Lombart L, et al. Balloon dilatation and self-expanding metal wallstent insertion: for management of bronchostenosis following lung transplantation. *Chest*. 1994;105:343–348.
14. Brichon PY, Blanc-Jouvan F, Rousseau H, et al. Endovascular stents for bronchial stenosis after lung transplantation. *Transplant Proc*. 1992;24:2656–2659.
15. Cho SB, Cha SA, Choi JY, et al. Serious complications after self-expandable metallic stent insertion in a patient with malignant lymphoma. *Tuberc Respir Dis (Seoul)*. 2015;78:31–35.