Risk Factors for extrapulmonary tuberculosis in Bangladesh

ABSTRACT

Tuberculosis (TB) is a major public health problem in Bangladesh. In this case-control retrospective study, a total of 348 patients, either with pulmonary or extrapulmonary TB, were surveyed from April 2020 to January 2023 from five different districts of Bangladesh, i.e. Rajshahi, Chapai Nawabganj, Sirajgonj, Moulvibazar and Chittagong to identify risk factors of tuberculosis in Bangladesh. The results revealed that most of the surveyed TB patients were infected with pulmonary TB (PTb) (225 patients) while 123 patients were infected with extrapulmonary TB (EPTb). Male was more susceptible to PTb while female was more prone to EPTb. EPTb was more prevalent in younger people than older people as compared with PTb. Likewise, married patients were more prone to PTb than EPTb while unmarried patients were equally susceptible to both PTb and EPTb. Brain, lymph node and intestine were major organs which were infected by EPTb, but the prevalence of EPTb of intestine, lymph node and breast were higher for female than for male. BCG vaccination showed more preventive role against EPTb than PTb. EPTb was prevalent in certain blood groups and occupations. Similarly, the people with black skin and underweight in childhood were more prone to EPTb. The data also revealed that black skin, underweight in childhood, family member with EPTb, regular medication including antibiotic use, less exposure to direct sunlight, and mental stress before active infection of Tb increased the prevalence of EPTb. Contrary, addiction to smoking, average sleeping hours, and use of mosquito coil were dispensable factors affecting the prevalence of EPTb. All these findings emphasize the necessity for targeted interventions, including expanded vaccination strategies and addressing specific risk factors, to decrease the burden of EPTb in Bangladesh.

Keywords: Tuberculosis, Extrapulmonary, Risk factor, Bangladesh

1. INTRODUCTION

Roughly one-third of the world's population has been infected with *M. tuberculosis*, and new infections occur at a rate of one per second [1]. Moreover, tuberculosis (TB) is a major public health problem in Bangladesh. Considering the estimated number among total population, Bangladesh is a high Tb burden and high drug resistant (DR) TB burden country and it ranks 7th among 22 high Tb burden countries [2]. People with TB can infect up to 10-15 other people

through close contact over the course of a year. Without proper treatment up to two thirds of people ill with TB will die [3]. Although, a considerable progress has been made to decrease the mortality rate of tuberculosis by DOTS but this success is undermined by very slow rate of decline as well as emergence of multidrug-resistant (MDR) and extremely drug-resistant (XDR) tuberculosis during the past decade. Moreover, Extra-pulmonary tuberculosis (EPTb) which can infect nearly every type of organs such as the lymph nodes, urinary tract, reproductive organs, meninges of the brain, bones and joints, pleural cavity, skin, and peritoneal cavity is becoming more notorious day by day because of lack of effective treatment and low recovery rate [4]. Thus, the threat of MDR-Tb and XDR-Tb are accompanied by an increasing trend of extra-pulmonary TB. Hence, even after the remarkable attempt to control TB worldwide, it remains a major global health threat because of the emergence of extra-pulmonary TB by drug-resistant mycobacteria. However, not all infections with *M. tuberculosis* cause TB disease and many infections are asymptomatic, called latent TB [5]. The risk of development to infection and disease is two different aspects and accurate understanding of these factors is critical for planning TB control policies. The risk of TB infection is principally governed by exogenous factors as well as is determined by an intrinsic blending of the infectiousness of the source case, closeness to contact and social and behavioral risk factors including smoking, aerosol, alcohol, and indoor air pollution etc. [6]. However, factors that increase the progression of infection to disease are primarily host related, called endogenous such as alteration of immune response due to HIV co-infection [7, 8]. Therefore, several studies have been undertaken addressing some socio-economic, cultural, and healthcare seeking related factors that influence TB [9-11]. It has been reported that the social and demographic factors such as, poor housing, low-income, overcrowding, lack of education, smoking habit, drug addiction etc. contribute to the incidence and transmission of TB [12, 13]. However, recent data on risk factors of extra-pulmonary TB in Bangladesh are inadequate. Hence, this study was designed to explore the risk factors of extra-pulmonary tuberculosis in Bangladesh.

2. MATERIALS AND METHODS

Patient population

A total of 348 patients, either with pulmonary or extrapulmonary TB, were surveyed from April, 2018 to January, 2020 from five different districts of Bangladesh, i.e. Rajshahi, Chapai Nawabganj, Sirajgonj, Moulvibazar and Chittagong. Rajshahi and Chapai Nawabganj are

northwestern districts of Bangladesh while Moulvibazar is a northeastern district of Bangladesh. Sirajgonj is located near the center of Bangladesh while Chittagong is located in southern side of Bangladesh.

Case and control definitions

The patients with pulmonary TB only who were confirmed by the *M. tuberculosis* infection limited to the intrathoracic region only, such as lungs, pleura, and intrathoracic lymph nodes, were classified as control patients (n=225). Conversely, the patients whose infection with *M. tuberculosis* was detected in organs or tissues outside the intrathoracic region, either with or without pulmonary TB, were classified as a case of extrapulmonary TB (n=123).

Data collection

A standardized survey tool which was developed for collection of data on demographic variable, lifestyle variables, physical and clinical characteristics of the patients was used for identification of risk factor of tuberculosis in Bangladesh. The address of the patients was collected from patient's records at different hospitals and NGOs who worked on TB in the surveyed districts. Then, data were obtained from detailed epidemiological interviews conducted by investigators at the hospitals or home of patients using the survey tool. Original clinical records were reviewed as needed.

Statistical analysis of data

Then, data entry was made from the survey tool into the SPSS program. Descriptive statistics were used to present role of different factors on prevalence of tuberculosis with an intention to identify the risk factors of extrapulmonary tuberculosis in Bangladesh.

3. RESULTS

In this study total 348 people were surveyed from 5 different districts (Rajshahi, Chapai Nawabganj, Sirajgonj, Moulvibazar and Chittagong) of Bangladesh. The results revealed that most of the surveyed TB patients were infected with pulmonary TB (PTb) (225 patients) while 123 patients were infected with extrapulmonary TB (EPTb) (Table 1 and Fig. 1). The highest percentage of EPTb was found in Rajshahi and Moulvibazar districts, while the lowest percentage of EPTb was observed in Chittagong district (Fig. 1).

Table 1 Number of surveyed PTb and EPTb patients from 5 different district of Bangladesh.

Type of TB	**District**					
	Chapai Nawabganj (CPN)	**Sirajganj (SRG)**	**Rajshahi (RJS)**	**Moulvibazar (MLB)**	**Chittagong (CTG)**	**Total**
Pulmonary (PTb)	47	69	39	33	37	**225**
Extra-pulmonary (EPTb)	22	30	31	25	15	**123**
Total	**69**	**99**	**70**	**58**	**52**	Grand Total = **348**

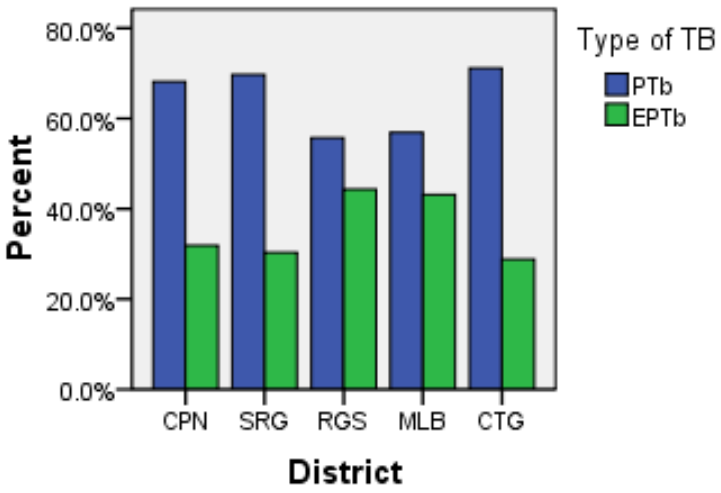

Fig. 1 Prevalence of different type of tuberculosis in different districts of Bangladesh. CPN=Chapai Nawabganj, SRG=Sirajganj (SRG), RJS=Rajshahi, MLB=Moulvibazar and CTG=Chittagong (CTG).

In this study, the mean age of patients for PTb was around 42 years while mean age for EPTb was around 35 years indicating that EPTb was more prevalent in younger people than older people as compared with PTb (Fig.2). It was also found that there was variation in prevalence of different types of tuberculosis for male and female patients in Bangladesh (Fig. 2). The results revealed that male was more prone to PTb than female. Conversely, female was more susceptible to EPTb than male (Fig. 2). This result has been supported by other studies reporting that female is more prone to EPTb than male [14-16].

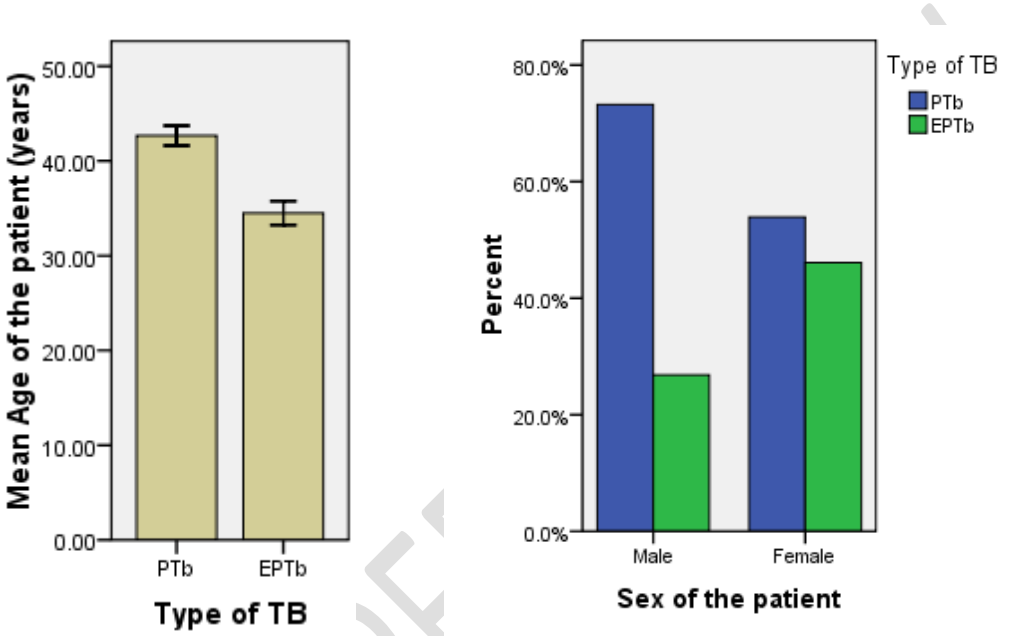

Figure 2. Role of age and gender of patients on prevalence of tuberculosis (Mean Age ± SE).

The results revealed that the lung was the most sensitive organ to TB infection in both male and female (Fig. 3 and 4). However, the brain, lymph node and intestine were major organs which were infected by EPTb (Fig. 3). The prevalence of EPTb of intestine, lymph node and breast were higher for female than for male (Fig. 4).

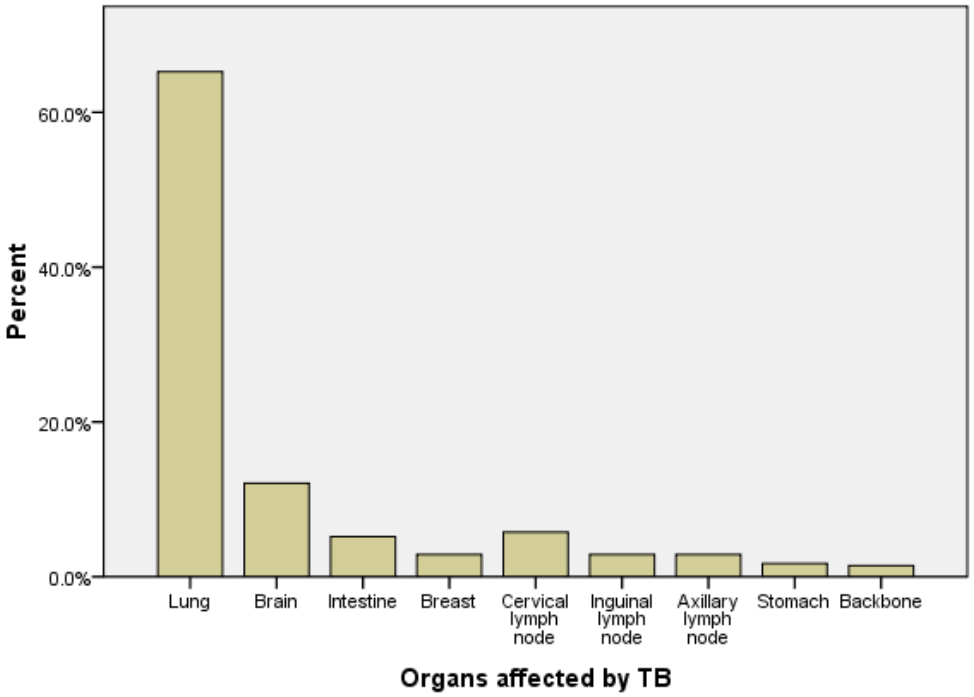

Figure 3. Percentage of different organs infected by tuberculosis in Bangladesh.

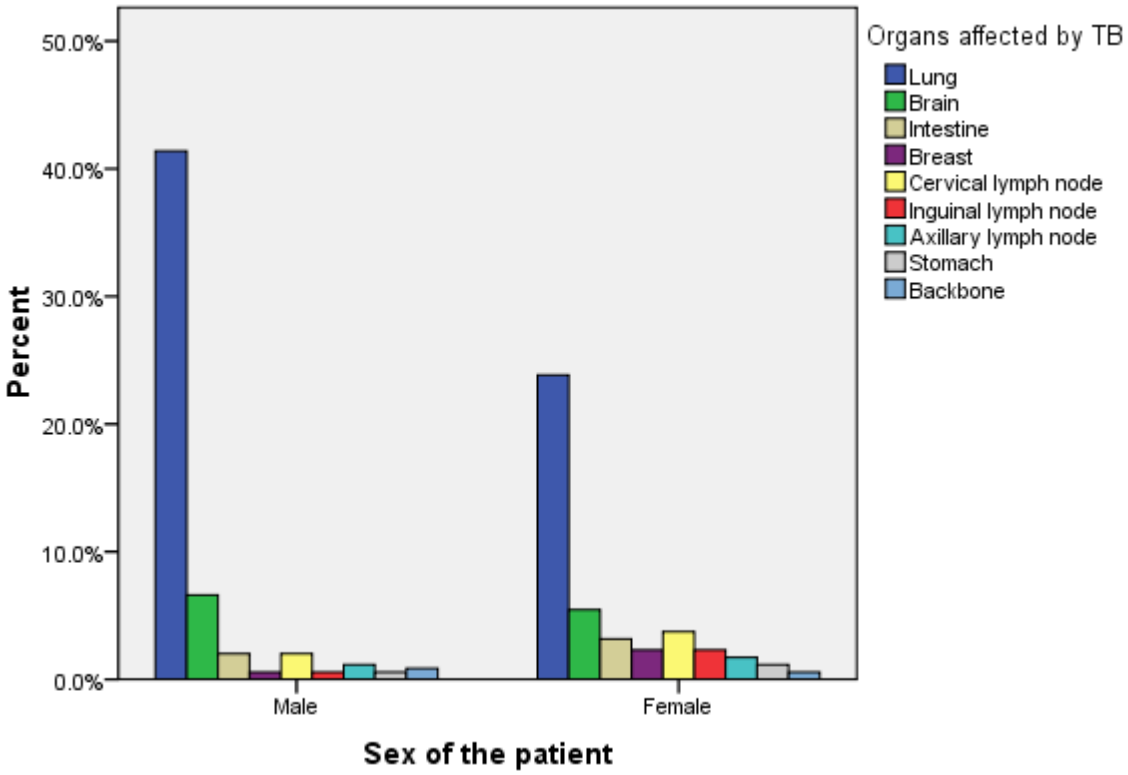

Figure 4. Role of gender of patients on types of organs infected by tuberculosis.

The results revealed that the prevalences of PTb and EPTb were different for married and unmarried patients (Fig. 5). However, married patients were more prone to PTb than EPTb while unmarried patients were equally susceptible to both PTb and EPTb (Fig. 5). It was also found that the number of siblings of patients was comparatively higher for PTb than EPTb indicating that higher number of siblings was not a risk factor for EPTb (Fig. 5).

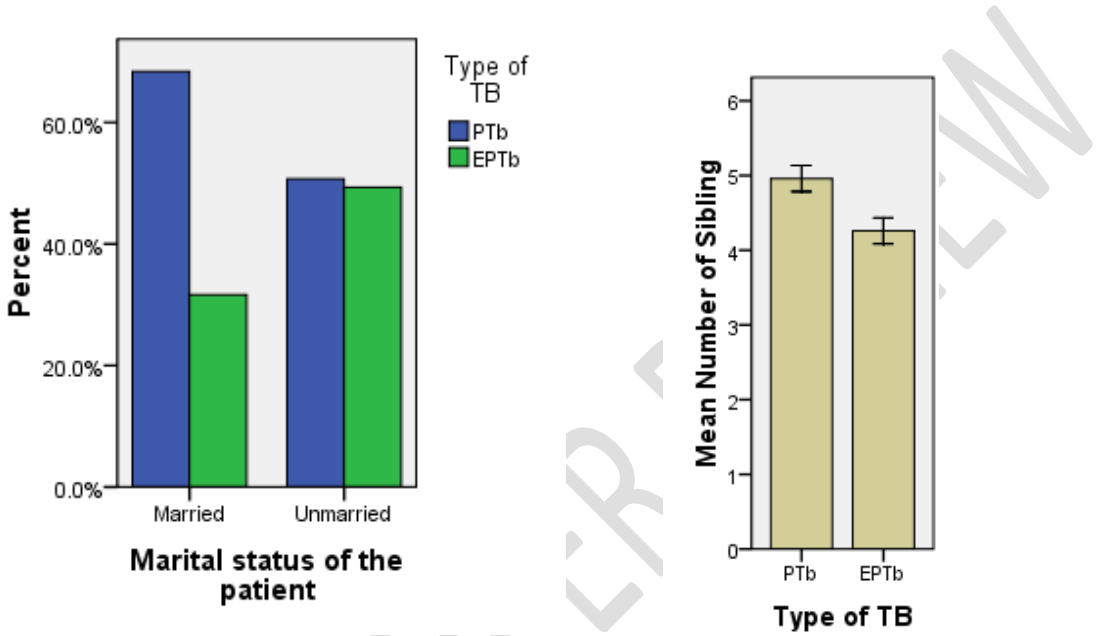

Figure 5. Role of marital status and number of siblings on prevalence of tuberculosis.

Surprisingly, this survey showed that incidence of EPTb was higher than that of PTb in patient with no BCG vaccination (Fig. 6). Thus, the results indicates that the BCG vaccination is more effective for prevention of EPTb than PTb (Fig. 6).

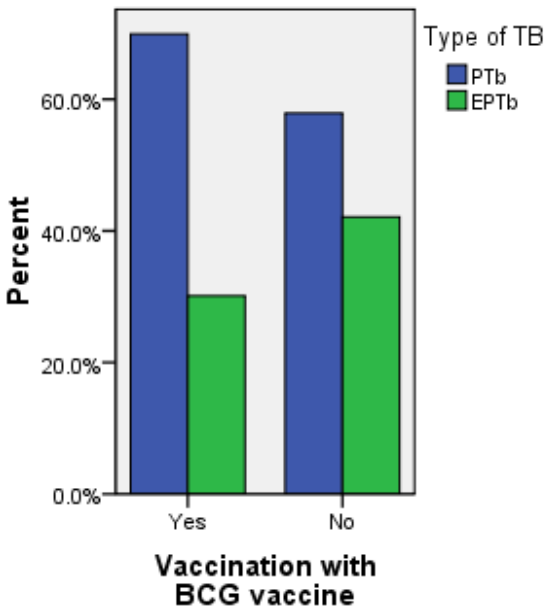

Figure 6. Role of BCG vaccination on prevalence of tuberculosis.

As shown in Fig. 7 the prevalence of different types of tuberculosis varied with the blood group of the patients. For PTb, the highest percentage of patients was observed to carry O-positive blood group followed by B-positive and A-positives blood group (Fig. 7). Conversely, the highest percentage of EPTb patients was found to carry B-positive blood group followed by O-positive and O-negative blood group (Fig. 7). Surprisingly, the prevalence of EPTb was higher in patients carrying O-negative and AB-negative blood groups as compared with that of PTb (Fig. 7).

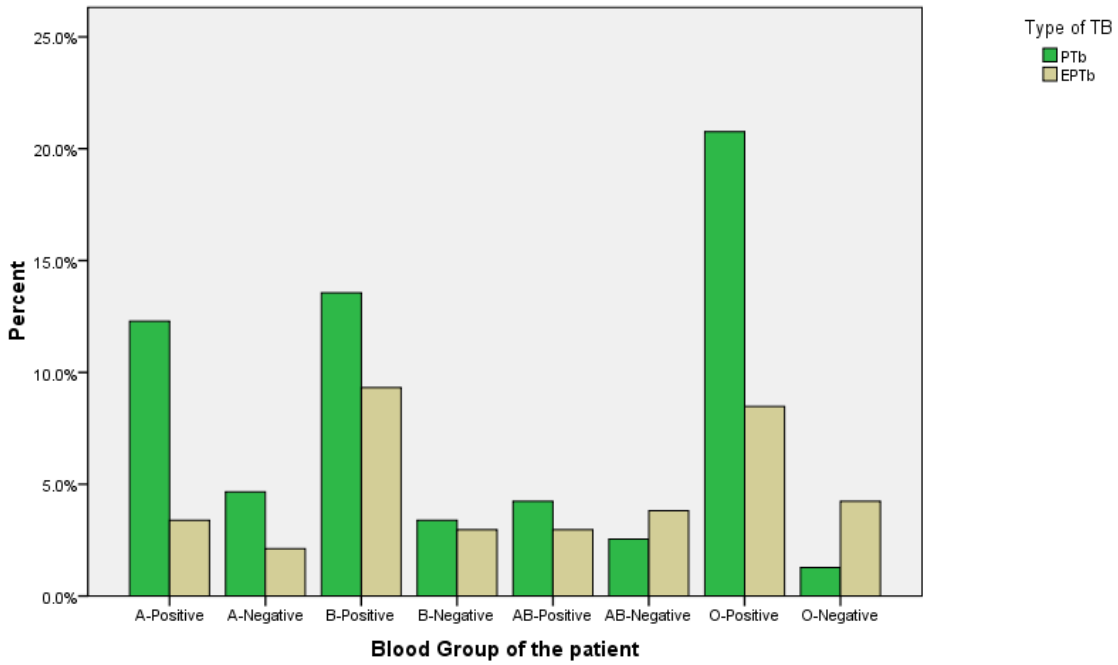

Figure 7. Role of blood groups of patients on prevalence of tuberculosis.

The results of this survey revealed that the prevalence of different types of tuberculosis varied with the occupation of the patients. The highest percentage of TB patients was student followed by housewife and farmer (Fig. 8). However, incidence of EPTb was higher in the case of bankers, advocates and government servants as compared with that of PTb (Fig. 8).

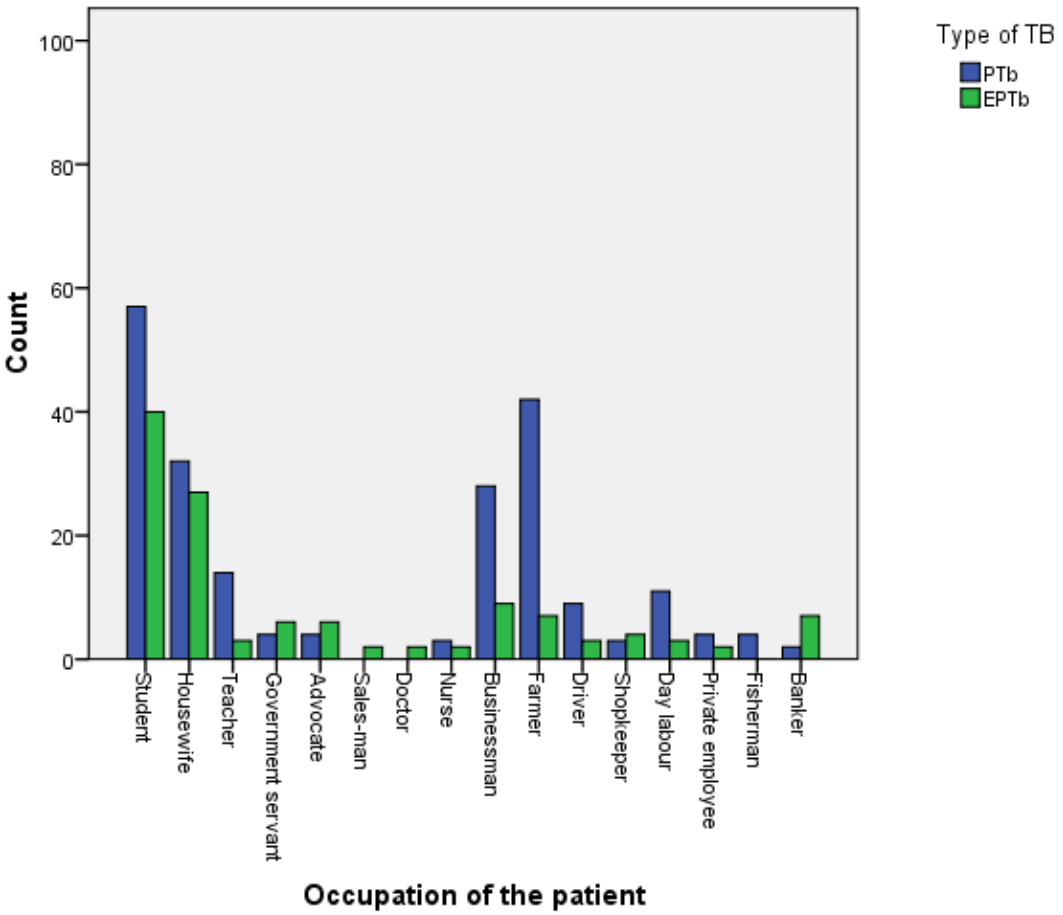

Figure 8. Role of occupation of patients on prevalence of tuberculosis.

The results showed that prevalence of EPTb was higher in black people as compared with the percentage of EPTb for other skin colour indicating that black skin may be a risk factor of EPTb (Fig. 9).

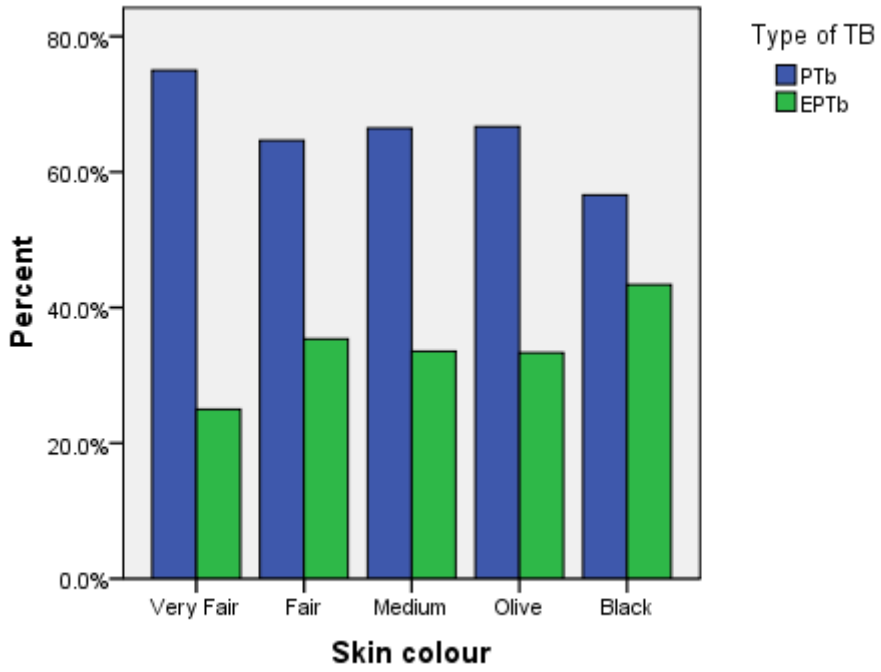

Figure 9. Role of skin colour of patients on prevalence of different types of tuberculosis.

As shown in Fig. 10 the prevalence of tuberculosis varied with childhood body weight of the patients. The highest percentage of EPTb was recorded in patients who were underweight from childhood. However, prevalence of EPTb in overweight patients was little bit higher than normal weight patients but the pattern of incidence was similar (Fig. 10).

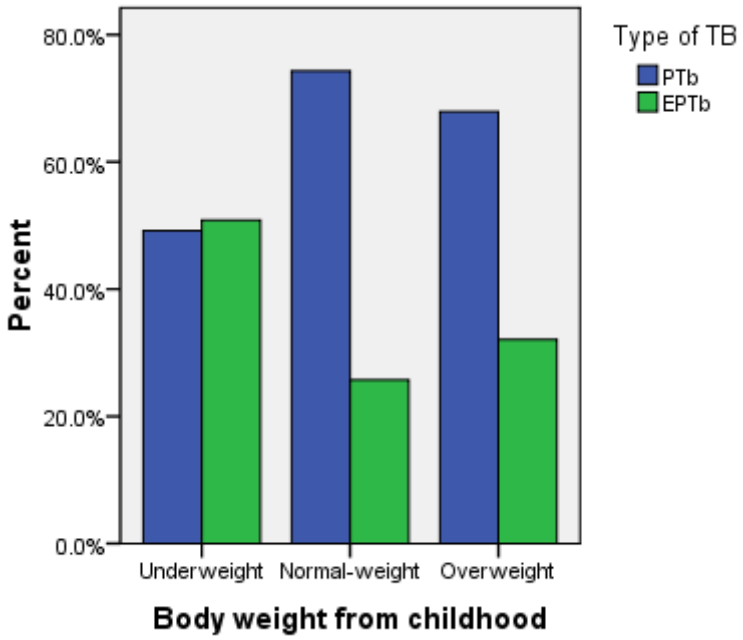

Figure 10. Role of childhood body weight of patients on prevalence of tuberculosis.

The results showed that the regular medication and antibiotic use for any other disease before active infection of tuberculosis had a remarkable role in the increase of prevalence of EPTb (Fig. 11).

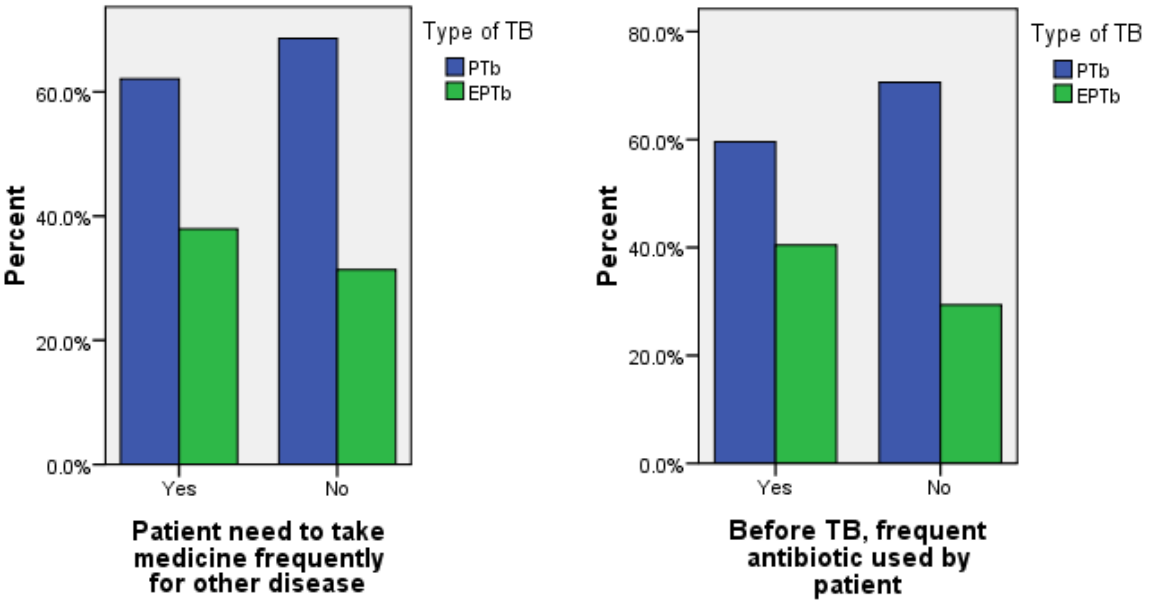

Figure 11. Role of regular medication and antibiotic use on prevalence of tuberculosis.

As shown in Figure 12, higher percentages of PTb and EPTb were observed for the patients who had family members with tuberculosis. However, this increase of incident of EPTb was more prominent when family members having EPTb indicating that the infection of EPTb might be related to the availability of those strains of TB pathogens which can cause EPTb (Fig 12).

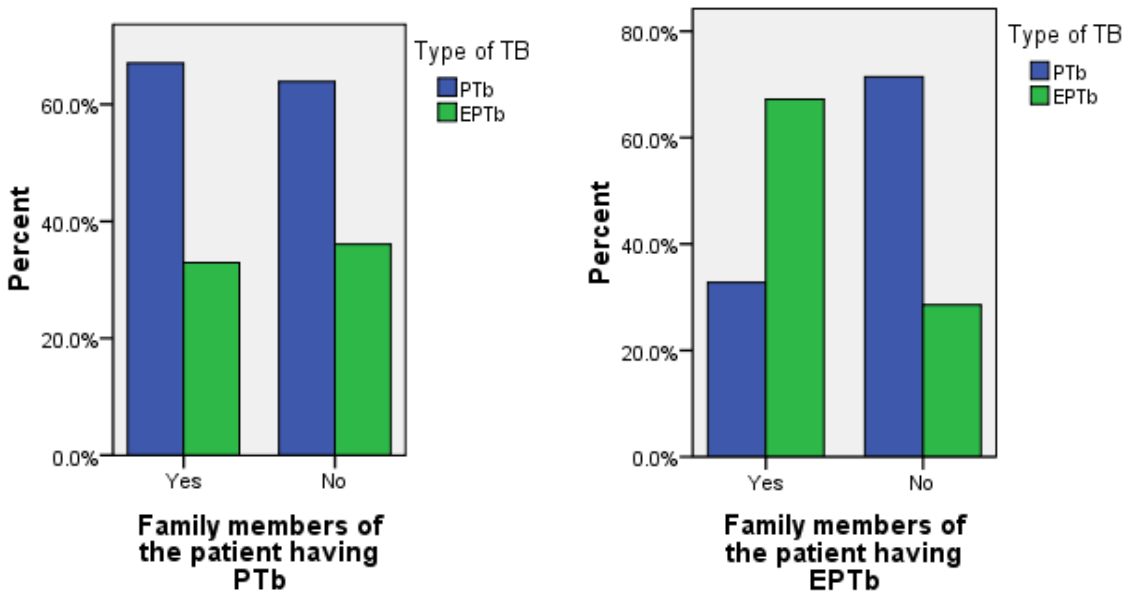

Figure 12. Role of active TB infection of family members of patients on prevalence of different types of tuberculosis.

The results showed that addiction of patients to smoking had a remarkable role in high prevalence of PTb but not for enhancing the prevalence of EPTb (Fig. 13). Moreover, the results showed that higher number of EPTb patients were addicted to other drugs as compared to smoking indicating the relation of prevalence of EPTb to other drugs rather than smoking (Fig. 13).

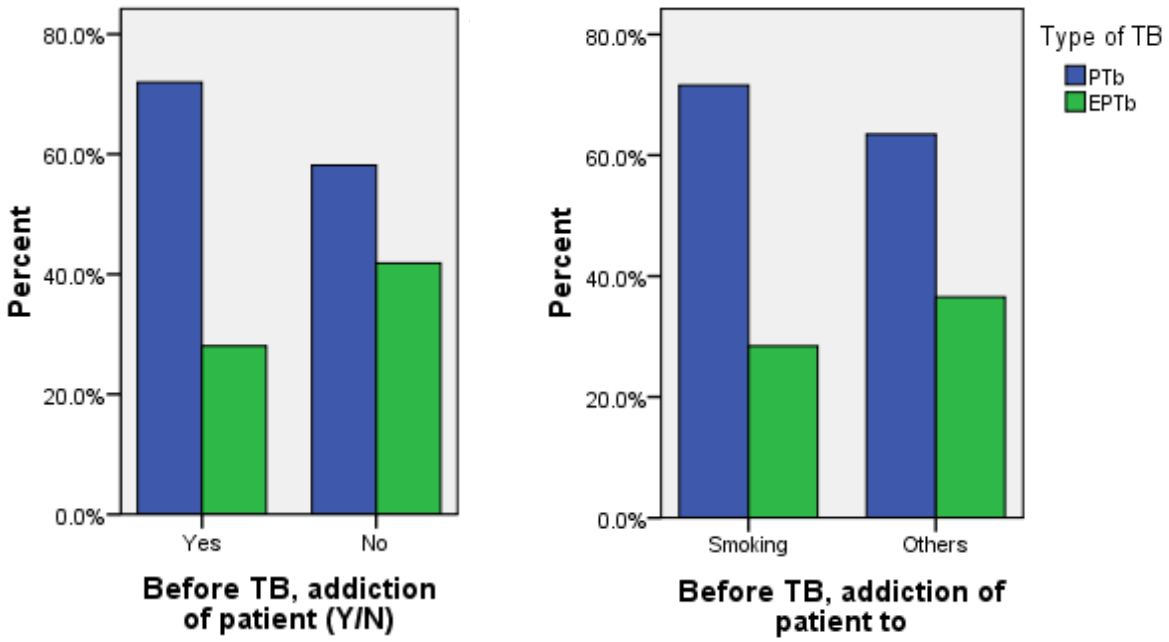

Figure 13. Role of addiction on prevalence of different types of tuberculosis.

As shown in Fig. 14, parentage of EPTb was increased for the patients who were suffering from mental stress before his/her infection of tuberculosis as compared with patient who did not suffer from mental stress. Thus, the results indicate that mental stress is a risk factor of EPTb.

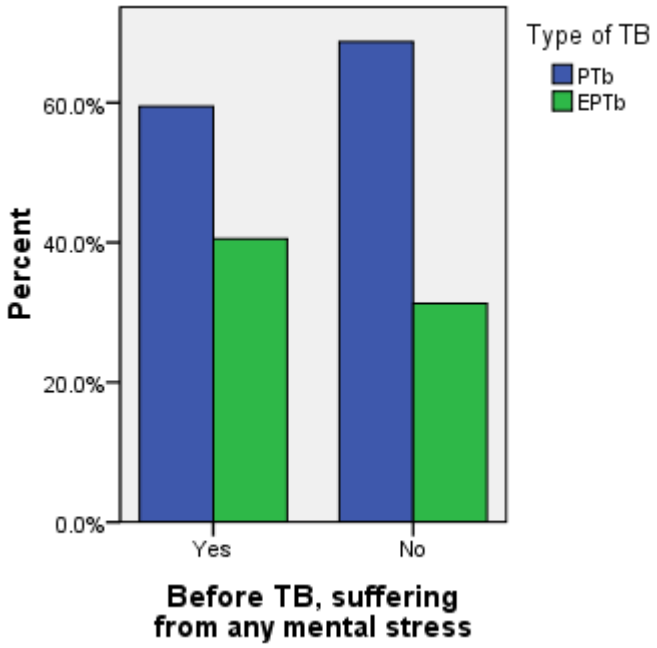

Figure 14. Role of mental stress on prevalence of tuberculosis.

As shown in Fig. 15, before Tb infection, the average sleeping hours per day for PTb and EPTb patients was comparable indicating that the role of sleeping hours on prevalence of EPTb was obscure. But there was prominent difference between PTb and EPTb in case of average exposure of the surveyed patients to direct sunlight before their Tb infection (Fig. 15). Before Tb infection, the average exposure to sunlight (hours per day) was lower for EPTb than PTb patients indicating that lack of sufficient sunlight exposure to human body is a risk factor for EPTb (Fig. 15).

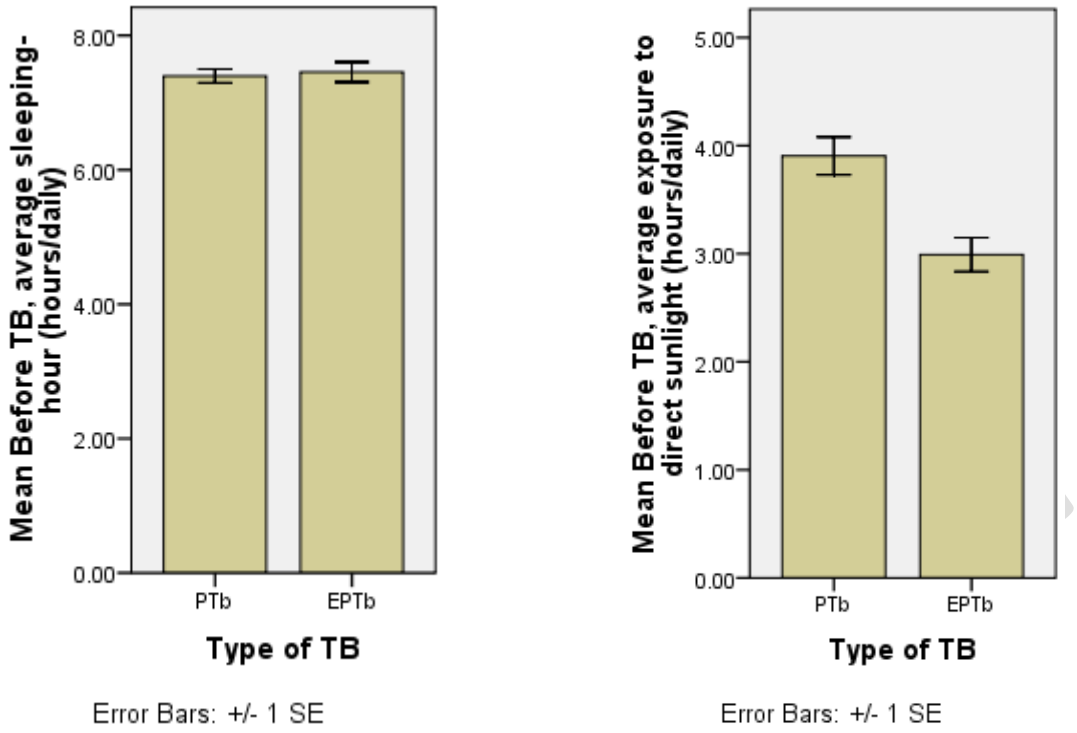

Figure 15. Role of sleeping hours and direct sunlight exposure hours on prevalence of tuberculosis.

The results showed that the frequent use of mosquito coil by the people had a remarkable role in enhancement of prevalence of PTb, but no similar effect was observed for EPTb (Fig. 16). Thus, it indicated that the frequent use of mosquito coil might be a risk factor for PTb but not for EPTb.

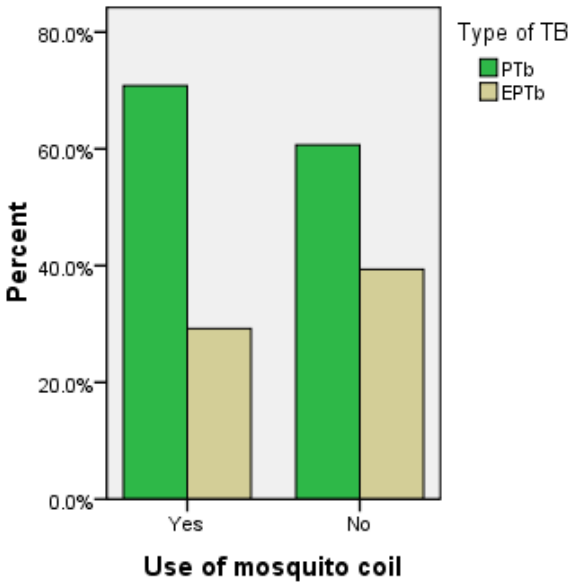

Figure 16. Role of frequent use of mosquito coil on prevalence of tuberculosis.

4. DISCUSSION

In this study it was found that there was variation in prevalence of different types of tuberculosis for male and female patients in Rajshahi city. Female was more susceptible to EPTb than male. It was supported by other studies reporting that females were more prone to EPTb than male [17, 18]. Another study conducted in Rajshahi city with a view to analyze the socio-demographic and epidemiological factors among registered DR TB cases at two chest disease hospitals of northern part of Bangladesh. Among the study subjects, male was more prevalent to PTb and the age group from 16-45 were mostly vulnerable [19]. In the present study, EPTb was more prevalent in younger people than older people. Similar results were also reported by other studies showing that young patients were more likely to be affected by EPTb than elderly ones [18, 20]. We found that BCG vaccination has no remarkable role on prevention of PTb, but its preventive role was observed against EPTb. It has been reported by others that BCG vaccination protects against EPTb for up to 10 years [21]. We also found that the prevalence of different types of tuberculosis varied with the blood group of the patients. The highest percentage of PTb patients was observed to carry O-positive blood group followed by B-positive while the highest percentage of EPTb patients was found to carry B-positive blood group. A study on distribution of ABO and Rh blood groups in patients with tuberculosis in Rohilkhand region of Uttar Pradesh, India showed that the most TB patients were of B-positive group, followed by O-positive [22]. In the present study, the highest percentage of TB patients was student followed by housewife and farmer. However, a study on latent tuberculosis infection in family members in household contact with active tuberculosis patients in Semarang City, Central Java, Indonesia reported that the occupation of laborers/farmers/fishers was the most dominant risk factor associated with latent TB infection [23]. We found that prevalence of EPTb was higher in black people indicating that black skin may be a risk factor of EPTb. Likewise, a study on extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis in USA concluded that African American ethnicity (people with black skin) was an independent risk factor for EPTb [24]. The present study revealed that the highest percentage of EPTb was recorded in patients who were underweight from childhood. Similar results are reported in other studies indicating that children underweight is risk factors of TB, especially of EPTb [25-27]. We found that the regular medication and antibiotic use for any other disease before active infection of tuberculosis was a risk factor of EPTb which was

supported by another study on outcome of EPTb in India [28]. The present study showed that people were more frequently infected with EPTb when family members were EPTb patients. It has been reported by others that high prevalence of EPTb disease was resulted from the close contacts of adults with EPTb [29]. We found that smoking had a remarkable role on high prevalence of PTb but not for enhancing the prevalence of EPTb. However, few study reported that smoking is a risk factor for both PTb and EPTb [30].

.

5. CONCLUSION

This study highlights notable differences in the susceptibility and risk factors for PTb and EPTb. Males were more prone to PTb, while females and younger individuals were more susceptible to EPTb, particularly affecting organs like the brain, lymph nodes, and intestines. Certain demographic and lifestyle factors, such as underweight status in childhood, family history of EPTb, reduced sunlight exposure, and mental stress, were identified as key contributors to EPTb prevalence. In contrast, factors like smoking, sleep patterns, and mosquito coil use were found to have minimal impact. Importantly, BCG vaccination demonstrated a more protective role against EPTb. These findings underscore the need for targeted interventions, including improved vaccination strategies and addressing specific risk factors, to reduce the burden of EPTb in Bangladesh.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

For our study, we received research authorization from the Department of Zoology, Faculty of Biological Sciences, University of Rajshahi, Bangladesh.

REFERENCES

1. Houben RM and Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS medicine. 2016; 13(10):e1002152.
2. Kundu S, Marzan M, Gan SH and Islam MA. Prevalence of antibiotic-resistant pulmonary tuberculosis in bangladesh: A systematic review and meta-analysis. Antibiotics. 2020; 9(10):710.
3. Bhatt G, Vyas S and Trivedil K. An epidemiological study of multi drug resistant tuberculosis cases registered under Revised National Tuberculosis Control Programme of Ahmedabad City. The Indian journal of tuberculosis. 2012; 59(1):18-27.
4. Haque MF, Boonhok R, Prammananan T, Chaiprasert A, Utaisincharoen P, Sattabongkot J, Palittapongarnpim P and Ponpuak M. Resistance to cellular autophagy by Mycobacterium tuberculosis Beijing strains. Innate immunity. 2015; 21(7):746-758.
5. Khabibullina NF, Kutuzova DM, Burmistrova IA and Lyadova IV. The biological and clinical aspects of a latent tuberculosis infection. Tropical medicine and infectious disease. 2022; 7(3):48.
6. Narasimhan P, Wood J, MacIntyre CR and Mathai D. Risk factors for tuberculosis. Pulmonary medicine. 2013; 2013(
7. Gautam K, Negi S and Saini V. Targeting endogenous gaseous signaling molecules as novel host-directed therapies against tuberculosis infection. Free Radical Research. 2021; 55(8):903-918.
8. Anes E, Azevedo-Pereira JM and Pires D. Cathepsins and their endogenous inhibitors in host defense during mycobacterium tuberculosis and HIV infection. Frontiers in Immunology. 2021; 12(726984.
9. Nidoi J, Muttamba W, Walusimbi S, Imoko JF, Lochoro P, Ictho J, Mugenyi L, Sekibira R, Turyahabwe S and Byaruhanga R. Impact of socio-economic factors on Tuberculosis treatment outcomes in north-eastern Uganda: a mixed methods study. BMC Public Health. 2021; 21(1-16.
10. Hussain T, Tripathy SS, Das S, Satapathy P, Das D, Thomas B and Pati S. Prevalence, risk factors and health seeking behaviour of pulmonary tuberculosis in four tribal dominated districts of Odisha: Comparison with studies in other regions of India. PLoS One. 2020; 15(4):e0227083.
11. Onyango PA, Ter Goon D and Rala NMD. Knowledge, attitudes and health-seeking behaviour among patients with tuberculosis: a cross-sectional study. The Open Public Health Journal. 2020; 13(1):
12. Etim NG, Mirabeau Y, Olorode A and Nwodo U. Risk Factors of Tuberculosis and Strategies for Prevention and Control. 2024;
13. Zarakpege NG, *Examination of the Association Between Poverty, Income, and Education Levels on Tuberculosis Prevalence in Nigeria: Rural Niger Delta Case Study*. 2023, Walden University.
14. Pervin R, Haque MA, Bushra T, Afroz S, Das S, Talukder R, Asha SS, Sultana S, Fatema K and Khan MMH. Risk factors of childhood extrapulmonary tuberculosis compared to pulmonary tuberculosis in Bangladesh: A hospital-based study. Preventive Medicine: Research & Reviews. 2024; 1(1):29-32.
15. Lin C-Y, Chen T-C, Lu P-L, Lai C-C, Yang Y-H, Lin W-R, Huang P-M and Chen Y-H. Effects of gender and age on development of concurrent extrapulmonary tuberculosis in patients with pulmonary tuberculosis: a population based study. PLoS One. 2013; 8(5):e63936.
16. Fang Y, Zhou Q, Li L, Zhou Y and Sha W. Epidemiological characteristics of extrapulmonary tuberculosis patients with or without pulmonary tuberculosis. Epidemiology & Infection. 2022; 150(e158.
17. Thakur S, Chauhan V, Kumar R and Beri G. Adolescent females are more susceptible than males for tuberculosis. Journal of Global Infectious Diseases. 2021; 13(1):3-6.

18. Rolo M, González-Blanco B, Reyes C, Rosillo N and López-Roa P. Epidemiology and factors associated with extra-pulmonary tuberculosis in a low-prevalence area. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2023; 32(100377.
19. Karmaker H, Basar MA, Karim MR, Rana MM, Hossain MG, Wadood MA and Islam MR. An epidemiological study of drug resistant tuberculosis cases: survey in the northern part of Bangladesh. Public Health Res. 2016; 6(2):52-8.
20. Arega B, Mersha A, Minda A, Getachew Y, Sitotaw A, Gebeyehu T and Agunie A. Epidemiology and the diagnostic challenge of extra-pulmonary tuberculosis in a teaching hospital in Ethiopia. PLoS One. 2020; 15(12):e0243945.
21. Ben Ayed H, Koubaa M, Marrakchi C, Rekik K, Hammami F, Smaoui F, Ben H, Sourour Y, Imed M and Damak J. Extrapulmonary tuberculosis: update on the epidemiology, risk factors and prevention strategies. Int J Trop Dis. 2018; 1(006):
22. Tiwari VK, Kumar A, Mohan N, Kumar A, Agarwal R and Khurana A. Distribution of ABO and Rh blood groups in patients with tuberculosis in Rohilkhand region of Uttar Pradesh. International Journal of Medical Science and Public Health. 2015; 4(6):760.
23. Karbito K, Susanto H, Adi MS, Sulistiyani S, Handayani OWK and Sofro MAU. Latent tuberculosis infection in family members in household contact with active tuberculosis patients in Semarang City, Central Java, Indonesia. Journal of public health in Africa. 2022; 13(2):
24. Gonzalez O, Adams G, Teeter L, Bui T, Musser JM and Graviss EA. Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2003; 7(12):1178-1185.
25. Laghari M, Sulaiman SAS, Khan AH and Memon N. Epidemiology of tuberculosis and treatment outcomes among children in Pakistan: a 5 year retrospective study. PeerJ. 2018; 6(e5253.
26. Mushtaq A, Lodhi AM, Rizwan W, Ruth C, Muzaffar M and Mir A. Clinical spectrum and outcome of extra-pulmonary tuberculosis in children. The Professional Medical Journal. 2021; 28(09):1336-1340.
27. Laghari M, Sulaiman SAS, Khan AH and Memon N. A prospective study of socio-demographic, clinical characteristics and treatment outcomes of children with tuberculosis in Sindh, Pakistan. BMC infectious diseases. 2019; 19(1-11.
28. Anaghashree U, *Outcome of Patients with Extrapulmonary Tuberculosis on Treatment with Anti Tubercular Therapy*. 2019, Rajiv Gandhi University of Health Sciences (India).
29. Wingfield T, MacPherson P, Cleary P and Ormerod LP. High prevalence of TB disease in contacts of adults with extrapulmonary TB. Thorax. 2018; 73(8):785-787.
30. Gambhir HS, Kaushik RM, Kaushik R and Sindhwani G. Tobacco smoking-associated risk for tuberculosis: a case-control study. International health. 2010; 2(3):216-222.