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Prevalence of extrapulmonary tuberculosis and factors influencing successful treatment outcomes among notified cases in South India

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Tuberculosis (TB) remains a significant public health issue globally, with extra pulmonary tuberculosis (epTB) accounting for a considerable number of TB cases. This study aims to improve our understanding of epTB epidemiology by evaluating treatment outcomes and identifying factors associated with positive and negative treatment results in epTB patients. A retrospective study was conducted from January 1, 2016, to December 31, 2019. EpTB and rifampicin-resistant epTB were identified using the GeneXpert MTB/RIF assay. Logistic regression analysis was performed to determine the associated risk factors. Among the 4,526 patients with extra pulmonary tuberculosis, the positivity rate of *Mycobacteriuum tuberculosis* among the epTB was 16.5%, and the rate of rifampicin-resistant epTB was 4.83%. Most of patients had lymphadenitis TB ($n = 348$, 38.79%), followed by those with pus ($n = 241$, 31.95%). Of 746 epTB cases, 679 patients (91.02%) achieved successful treatment outcomes. Of the 36 patients with rifampicin-resistant epTB, 30 (83.3%) exhibited successful treatment outcomes. Tuberculous peritonitis (OR: 1.58), aspirate (OR: 1.59), gastric lavage (OR: 1.45), biopsy (OR: 1.73), Tuberculosis meningitis (TBM) (OR: 1.46), and tissue samples (OR: 3.33) were all significantly associated with unfavourable treatment outcomes. Patients with extrapulmonary tuberculosis (epTB) aged between 35 and 44 had a significantly higher likelihood of experiencing unsuccessful outcomes (OR = 1.79; 95% CI: 0.74–4.31, $p = 0.0912$). Additionally, individuals with a history of alcohol use showed a higher likelihood of poor outcomes (OR = 1.90; 95% CI: 0.25–14.42). Moreover, tuberculosis patients who used tobacco also had an increased likelihood of unfavourable treatment outcomes (OR = 2.62; 95% CI: 0.35–19.68).The study indicated that the rate of favourable treatment outcomes among epTB patients surpassed the World Health Organization's target of ≥ 90%. However, a significant number of patients were lost to follow-up during treatment.

Keywords Mycobacterium tuberculosis, Rifampicin-resistant, Extrapulmonary, Cerebrospinal fluid, Lymphnode, Risk factors

Abbreviations

TB	Tuberculosis
epTB	extrapulmonary Tuberculosis
RR TB	Rifampicin-resistant tuberculosis

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OR	Odds ratio
TBM	Tuberculosis meningitis
WHO	World Health Organization
DRTB	Drug-resistant Tuberculosis
MDR TB	Multidrug-resistant tuberculosis
DRepTB	Drug resistant extrapulmonary Tuberculosis
NTEP	National TB Elimination Programme
MTB	Mycobacterium tuberculosis

Tuberculosis (TB) remains a serious global public health concern and is responsible for the highest number of deaths from any infectious disease worldwide. According to the World Health Organization, approximately two billion people, around 25% of the world's population, could be affected by TB. Despite being treatable, TB remains a fatal disease, causing over 1.25 million deaths annually, with about 3,500 people losing their lives to TB every day[1]. In 2024, globally, 10.8 million people were diagnosed and reported to have a new episode of TB. Of these cases, 81% had pulmonary TB, and 19% had extrapulmonary TB. While TB predominantly affects the lung parenchyma in more than 80% of people, extrapulmonary TB is also commonly encountered. Extrapulmonary tuberculosis (epTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB affecting organs other than the lungs[2].Extrapulmonary Tuberculosis (epTB) has been neglected in broad approaches to TB control partly because it is believed to be non-transmissible.

In 2024, the WHO reported around 10.8 million cases of Tuberculosis, with 16% being epTB[3]. While there has been progress in diagnosing pulmonary Tuberculosis, diagnosing epTB remains a challenge. In countries like India, 15 to 24% of Tuberculosis cases are extrapulmonary, and this percentage increases to over 50% in HIV co-infected patients. The host's immune status is a significant risk factor for epTB. Confirming the microbial diagnosis of epTB is often difficult[4]. Patients with this form of Tuberculosis face high mortality rates both during and after treatment. Drug-resistant epTB is a significant barrier to treatment success, affecting 16–20% of cases, with 8–14% showing isoniazid resistance, 2.4–3.9% showing rifampicin mono-resistance, and 2–10% having Multi-drug resistant Tuberculosis. The success rate for treating epTB in Pakistan was 71.1%, falling short of the WHO's 90% target in the End TB Strategy[5].

Among those who experienced unfavorable outcomes, most patients were lost to follow-up treatment. In contrast, a study conducted in Ethiopia reported treatment outcomes of 91.2%[6], which exceeded the international target of 90%. The success rate of treatment depends on the infrastructure of healthcare facilities responsible for the programmatic monitoring and treatment of tuberculosis patients. The treatment outcomes of patients can measure the success of the National TB Control program. Treatment outcomes for extrapulmonary tuberculosis (epTB) patients could be fall into one of six categories: cured, completed, died, failed, defaulted, or transferred out with an unknown outcome. A successful treatment outcome is defined as a patient being cured or completing their treatment. Any other outcome is considered unsuccessful. However, there is limited data on the clinical forms and treatment outcomes of extrapulmonary TB patients. It is important to clarify the common risk factors associated with unfavourable treatment outcomes for these patients. Therefore, this study aims to assess treatment outcomes and associated factors with unfavourable outcomes among extrapulmonary TB.

Materials and methods

Study setting, period, and design

A retrospective study was conducted at the Government Hospital for Chest Disease in Puducherry from January 2016 to December 2019. This 138-bed healthcare facility is equipped with advanced Intermediate Reference Laboratory (IRL) facilities for processing samples, which is one among the 36 IRLs across the country. The TB unit in the chest clinic operates under the National TB Elimination Programme and sees an average of 80 to 90 TB patients daily at the outpatient clinic. The study involved 4,526 suspects of extrapulmonary tuberculosis from the entire Puducherry region and eight adjoining districts in Tamil Nadu. The inclusion criteria for the studies were as follows: (1) studies that used Xpert to diagnose extrapulmonary tuberculosis (EPTB) in non-respiratory samples, such as lymph node aspirates, cerebrospinal fluid, and pleural fluid; (2) studies that evaluated the diagnostic performance of Xpert; and (3) studies that included paediatric patients aged 0 to 18 years. Additionally, immunocompromised patients, including those with HIV, were also included in the study. Patients with incomplete data and undocumented diagnostic methods were excluded from the study.

Procedure and Preparation of samples for GeneXpert MTB/RIF assay

Extrapulmonary tuberculosis (epTB) is classified based on the site of infection. The main forms include: lymphatic tuberculosis (lymph nodes), pleural tuberculosis (pleural effusion), and meningeal tuberculosis (tuberculous meningitis). It also includes genitourinary (affecting the kidneys and bladder), gastrointestinal (affecting the digestive tract), and bone and joint (e.g., spinal) tuberculosis. Peritoneal tuberculosis involves the peritoneum, while skin tuberculosis may present as scrofuloderma, and breast tuberculosis affects breast tissue. Each type of epTB requires specific diagnostic methods and treatment approaches tailored to the area affected.

The extrapulmonary samples were categorized into two main groups based on their level of contamination: aseptically collected tissues and contaminated specimens. Liquids were first concentrated for 15 min at 3000 g, while sediments were suspended in 2–5 ml of sterile phosphate buffer saline, except for CSF samples, which were processed directly. Biopsy materials were cut into small pieces using a sterile scalpel or scissors and homogenized in a sterile porcelain mortar or sonicated with 2–5 ml sterile PBS. The sample reagent was added to the unprocessed specimen in a 2:1 ratio in a 50 ml falcon tube, which was manually agitated twice during a 10-minute incubation period at room temperature. The processed sample was then incubated at room temperature for 5 min, and 2 mL of it was transferred to the cartridge using a fresh sterile transfer pipette. After pre-labelling the barcode, it was

scanned into the cartridges once the system connected to the GeneXpert instrument was powered on. Finally, the cartridge was loaded into the GeneXpert instrument following the manufacturer's instructions[7].

Clinical diagnosis of EpTB and EP rifampicin-resistant tuberculosis and their treatment

EpTB is diagnosed based on clinical and microbiological evidence. If a patient is diagnosed with drug-sensitive tuberculosis, they are given a standard regimen of HRZE (isoniazid, rifampicin, pyrazinamide, and ethambutol) for 2 months, followed by HR (isoniazid and rifampicin) for 4 months (2HRZE/4HR). For patients with meningeal TB, treatment may last up to 20 months. If patients miss more than four weeks of treatment, they are contacted by a TB coordinator and traced. Patients with epTB and Rifampicin resistance receive either a shorter injectable-containing regimen for 9–11 months or an all-oral longer regimen for 18–20 months as per the guidelines of the National Tuberculosis Elimination Programme, Ministry of Health and Family Welfare Services, India[8,9].

Reporting of treatment outcomes

The outcome of TB treatment was assessed using standard criteria. If a patient's treatment failed based on the physician's clinical judgment, including factors like the size of lymph nodes, radiographic findings, and colonoscopy, it was considered treatment failure. Conversely, successful completion of the treatment was classified as a favorable outcome. If the patient experienced unfavorable outcomes such as treatment failure, death, or loss of follow-up, it was classified as unfavorable. The definitions of the outcome measures for this study were based on the WHO's TB framework[10]. Table 1 presents the standard definitions of treatment outcomes clearly and concisely.

Ethical consideration

The Ethics and Scientific Review Committee at the General Hospital Institute, part of the Directorate of Health and Family Welfare Services in Puducherry, approved this study (No/GHIEC/2016/22; March 2016) and granted a waiver for informed consent. All methods were conducted in accordance with the guidelines and regulations established by the World Health Organization (WHO) and the National Tuberculosis Elimination Program.

Statistical analysis

The data analysis was performed using the MedCalc Software Ltd., Odds Ratio Calculator (Version 23.1.6)[11], and the meta-analysis was conducted using online tools[12]. Categorical variables were presented as percentages (%) and counts. A simple logistic regression analysis was used to investigate the relationship between the dependent variable (unfavorable treatment outcome) and the selected independent variables. Independent factors associated with unfavorable treatment outcomes were identified by analyzing statistically significant variables from the univariate analysis using multivariate binary logistic regression analysis. The Odds ratio (OR) and 95% confidence intervals (CI) were recorded for each variable. Statistical tests were considered significant at a p-value of less than 0.05.

Results

Study participants

During the study period, 4,526 epTB samples were processed. The GeneXpert assay provided valid results for 4,524 cases, which account for 99.96% of all processed samples. Only two cases (0.04%) had invalid results attributed to improper sample processing, causing sample processing control failure. Among the 4,524 valid results, *M.tuberculosis* was detected in 746 samples, equal to 16.5% of all valid results, and not in 3,778 samples, making up 83.5% (Fig. 1). The distribution of 16.5% epTB and 4.83% extrapulmonary rifampicin-resistant tuberculosis among the 746 epTB cases is presented in Fig. 2. The GeneXpert assay provides semi-quantitative detection of rifampicin-resistant *M. tuberculosis* based on the PCR cycle threshold (Ct) of the probes required to amplify *M. tuberculosis* DNA to detectable levels. Among the 36 rifampicin-resistant detected results, 12 (33.3%) were reported as "dropout" (no hybridization), and 24 (66.7%) cases were reported as "delayed" ($\Delta Ct > 4$). The most common probes used for rifampicin resistance detection were D ($n = 4$, 11.23%), E ($n = 3$, 8.3%), A

Outcome	Definition
Unfavourable treatment outcome	
Died	Patient with tuberculosis who passes away due to any cause either before initiating or during the treatment.
Treatment failure	Patients who were initially diagnosed with EPTB, with or without bacteriological confirmation, and those who were started on treatment based on clinical and radiological findings. It also includes patients who have not shown any clinical improvement or have become smear or culture positive, or whose condition has deteriorated during treatment. However, this definition does not include patients who are diagnosed with RR-TB or MDR-TB during their treatment.
Loss to follow-up	TB patient who has not started or has interrupted treatment for two consecutive months or more.
Favourable treatment outcome	
Cured	A patient with bacteriologically confirmed pulmonary TB, who was smear or culture-negative in the last month of treatment and at least once before.
Treatment completed	A patient with tuberculosis who successfully completed the treatment, but without any documentation to confirm that sputum smear or culture tests were negative during the last month of treatment and at least once before that. This could be due to the tests not being conducted or the results being unavailable.
Treatment success	The sum of cured and treatment completed.

Table 1. Definition of treatment outcomes for patients with extrapulmonary tuberculosis.

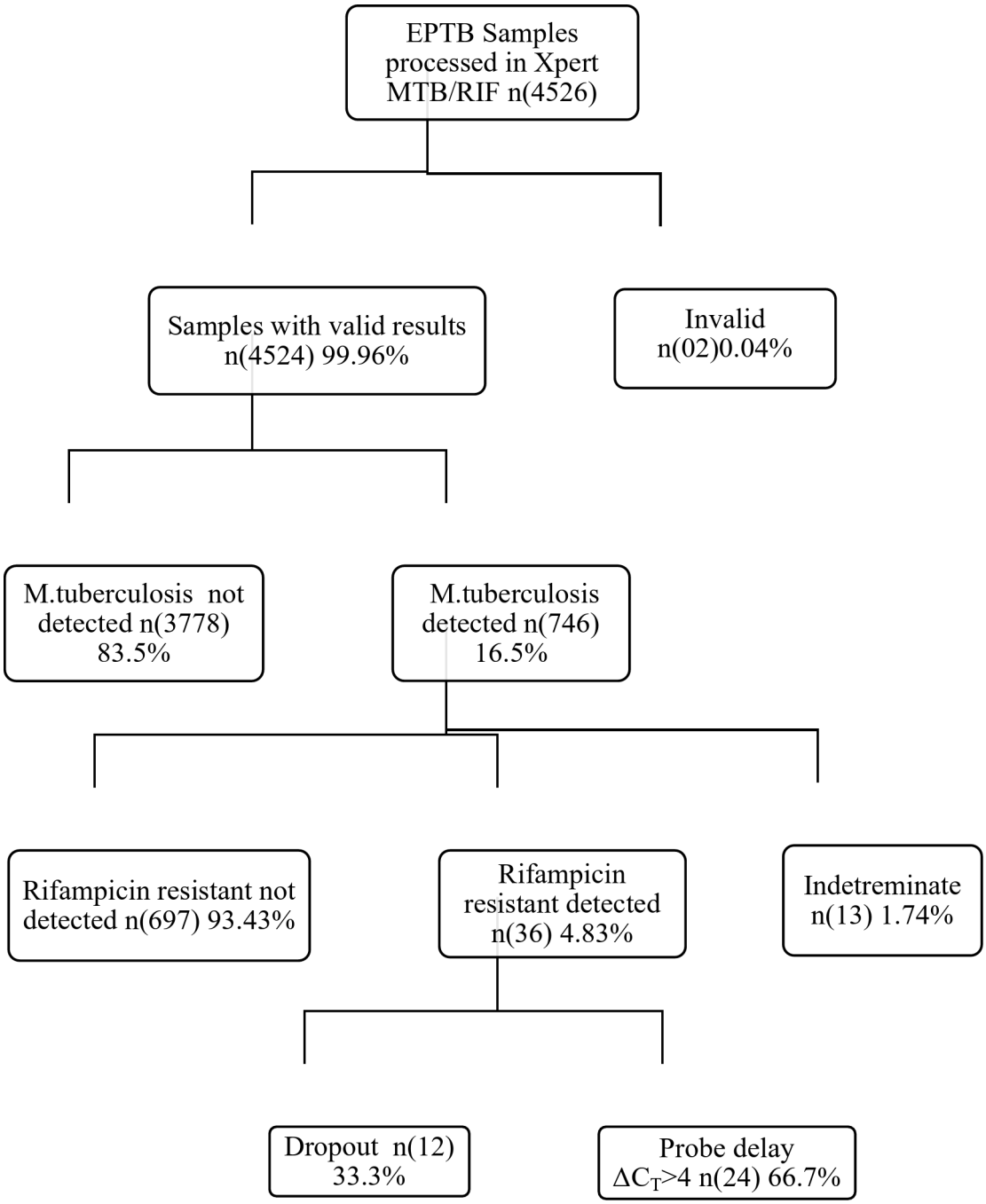

Fig. 1. Flowchart for analyzing extrapulmonary samples to detect EPTB using GeneXpert MTB/RIF.

($n=3$, 8.3%), and B ($n=2$, 5.6%), as shown in Table 2. A strong positive correlation was observed between rifampicin-resistant epTB and the semi-quantification value, with a Spearman correlation coefficient of 0.92 (P-value = 0.078). This indicates a significant relationship between the two variables. However, the P-value of 0.078 suggests that this correlation is not statistically significant at the conventional threshold of 0.05.

Of the 4526 TB cases registered, the majority of patients were found to have pleural fluids ($n=1052$, 23.2%), followed by gastric lavage ($n=923$, 20.4%), cerebrospinal fluid ($n=552$, 12.2%), aspirate ($n=395$, 8.7%), lymph node ($n=516$, 11.4), pus ($n=241$, 5.3%), and ascetic fluid ($n=193$, 4.3%). Out of the 746 cases of epTB, 6.84% of patients ($n=51$) had various affected sites, including pericardial, genitourinary, peritoneal, bone, skin, and breast, which were categorized as "others." The overall *M.tuberculosis* positivity rate among epTB samples was 16.5%. Table 3 shows that the highest positivity rates of extrapulmonary tuberculosis (epTB) were found in abscesses (47.06%), lymph nodes (38.37%), pus (31.95%), tissues (18.06%), gastric lavage (15.82%), pleural fluid (12.45%), other fluids (10.39%), and tuberculosis meningitis (8.88%).Table 4 presents treatment outcomes for patients with epTB. Among 710 patients with rifampicin-sensitive TB, 649 (91.41%) had successful treatment,

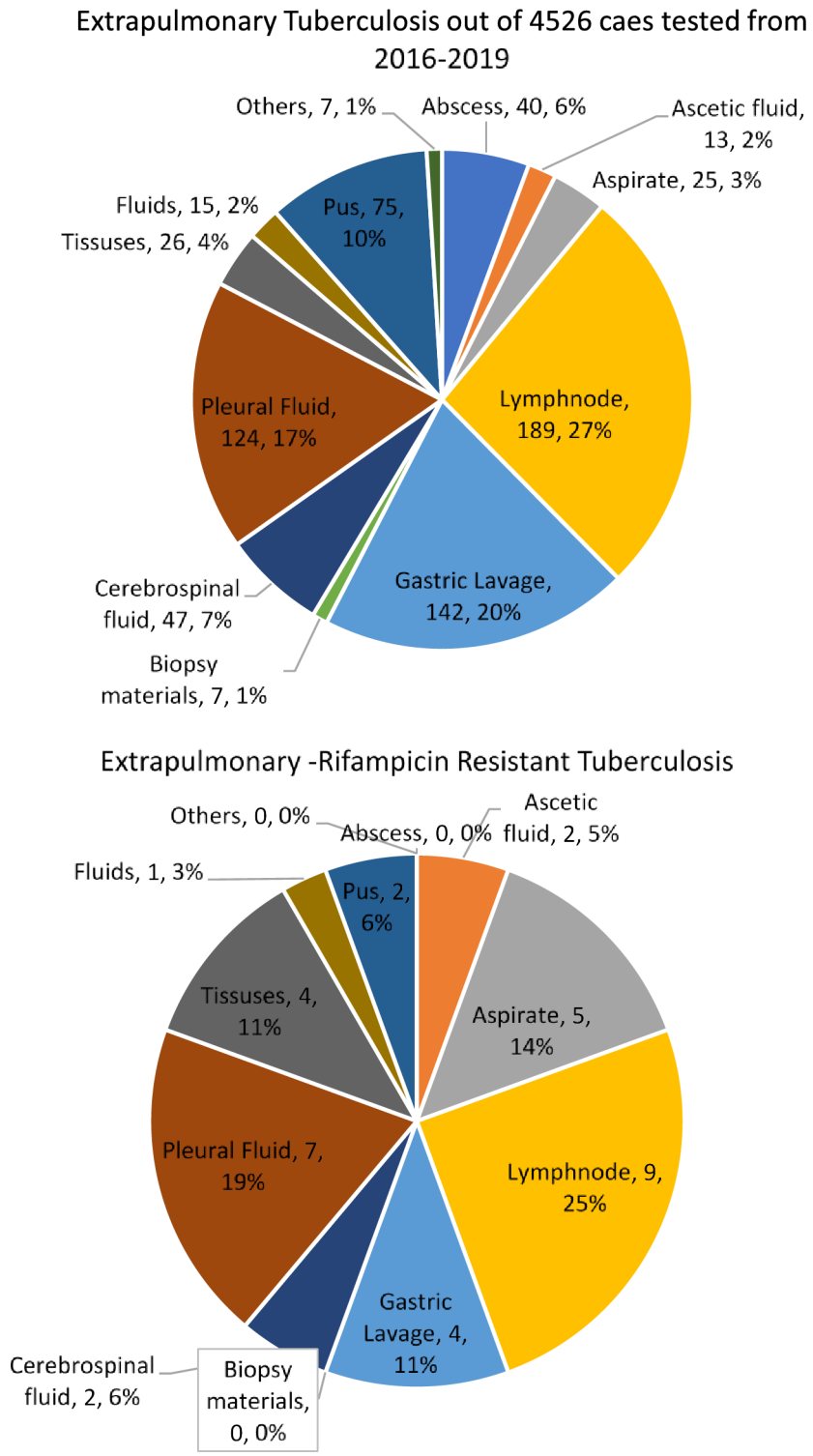

Fig. 2. Distribution of Rifampicin-sensitive and Rifampicin-resistant extrapulmonary Tuberculosis in southern India from 2016–2019.

while 61 (8.59%) faced unfavourable outcomes, including 10 deaths (1.41%) and 46 lost to follow-up (6.48%). For the 36 patients with rifampicin-resistant TB, 30 (83.33%) completed treatment successfully, but 6 (16.67%) had unfavourable outcomes, including 2 deaths (5.56%) and 4 lost to follow-up (11.18%).

Determinants of unfavourable treatment outcomes

This study found that the overall success rate for tuberculosis treatment was 91.02%. Figure 3 presents a forest plot analysis of twelve variables associated with outcomes in patients with extra pulmonary tuberculosis, using

GeneXpert results	Rif- Resistant Detected	Resistant Probes					Probe Delay- ΔC_T value > 4	No of Drop out
		A	B	C	D	E		
Very low	14(38.9%)	1	1	0	0	0	12	
Low	11(30.6%)	0	0	0	2	2	07	12*
Medium	08(22.2%)	2	1	0	2	0	03	
High	03(08.3%)	0	0	0	0	1	02	
Total	36 (100%)	**3(8.3%)**	2(5.6%)	0	**4(11.2%)**	**3(8.3%)**	24 (66.6%)	12 (33.3%)

Table 2. Rifampicin resistance patterns in patients with extrapulmonary tuberculosis registered from 2016 to 2019. * Number of dropout cases in which one or more molecular probes failed to produce an amplification signal. Significant values are in bold.

Variables	MTB detected		MTB detected	Positive percentage	Positive not detected	Total cases tested	*p* - Value
	Sensitive	Resistant					
Abscess	40	0	40	47.06	45	85	0.5876
Ascetic fluid	13	2	15	7.77	178	193	0.0001
Aspirate	25	5	30	7.59	365	395	0.0001
Lymph node	189	9	198	38.37	318	516	0.0001
Gastric Lavage	142	4	146	15.82	777	923	0.0001
Biopsy	7	0	7	8.75	73	80	0.0001
Cerebrospinal fluid	47	2	49	8.88	503	552	0.0001
Pleural Fluid	124	7	131	12.45	921	1052	0.0001
Tissues	26	4	30	18.06	119	147	0.0001
Fluids	15	1	16	10.39	138	154	0.0001
Pus	75	2	77	31.95	164	241	0.0001
Others	7	0	7	13.73	44	51	0.0001
Total	710	36	746	16.48	3780	4526	0.0001

Table 3. Attributes and sites of infection for extrapulmonary tuberculosis patients registered from 2016 to 2019.

Variables (outcome)	Rifampicin resistant 36 (%)	Rifampicin sensitive 710 (%)	Total *N*(746)	*p*-value
Successful outcome N(679)	**30(83.33)**	**649(91.41)**	**679(91.02%)**	0.0759
Cured	16(44.44)	324(45.63)	340(45.58%)	0.0001
Treatment completed	14(38.89)	325(45.78)	339(45.44%)	0.0001
Unfavourable outcome N(67)	**6(16.67)**	**61(8.59)**	**67(8.98%)**	0.0001
Died	2(5.56)	10(1.41)	12(1.61%)	0.0001
Lost to Follow-up	4(11.11)	46(6.48)	50(6.70%)	0.116
Defaulter	-	3(0.42)	3(0.40%)	0.0001
Treatment failure	-	2(0.28)	2(0.27%)	0.0001

Table 4. Treatment outcomes for patients with extrapulmonary tuberculosis who were registered from 2016 to 2019. Significant values are in bold.

multivariate regression and a random effects model with the inverse variance method to compare the odds ratio (OR). An analysis conducted with a random effects model using the inverse variance method to compare the odds ratio (OR) found no statistically significant difference. The summarized odds ratio was 0.82, with a 95% confidence interval ranging from 0.63 to 1.09. The overall effect test also did not show a significant impact. Furthermore, Heterogeneity was not significant, suggesting that the effect sizes across the cohorts were consistent in magnitude and direction. We employed multivariable logistic regression to analyse factors affecting treatment outcomes, finding that age between 35 and 44, alcohol use, and tobacco use were linked to unfavourable outcomes. Patients with a history of alcohol use had greater odds of unsuccessful treatment outcomes (OR, 1.90; 95% CI [0.25–14.42]) than non-alcoholic patients. Similarly, tobacco users displayed even higher odds of unsuccessful treatment (OR, 2.62; 95% CI [0.35–19.68]) than non-users. This suggests that both alcohol and tobacco use are associated with a greater chance of negative outcomes. The study included all clinically relevant variables that showed marginal association at $p < 0.5$ following univariate analysis in the logistic regression analysis to assess associated factors affecting treatment outcomes.

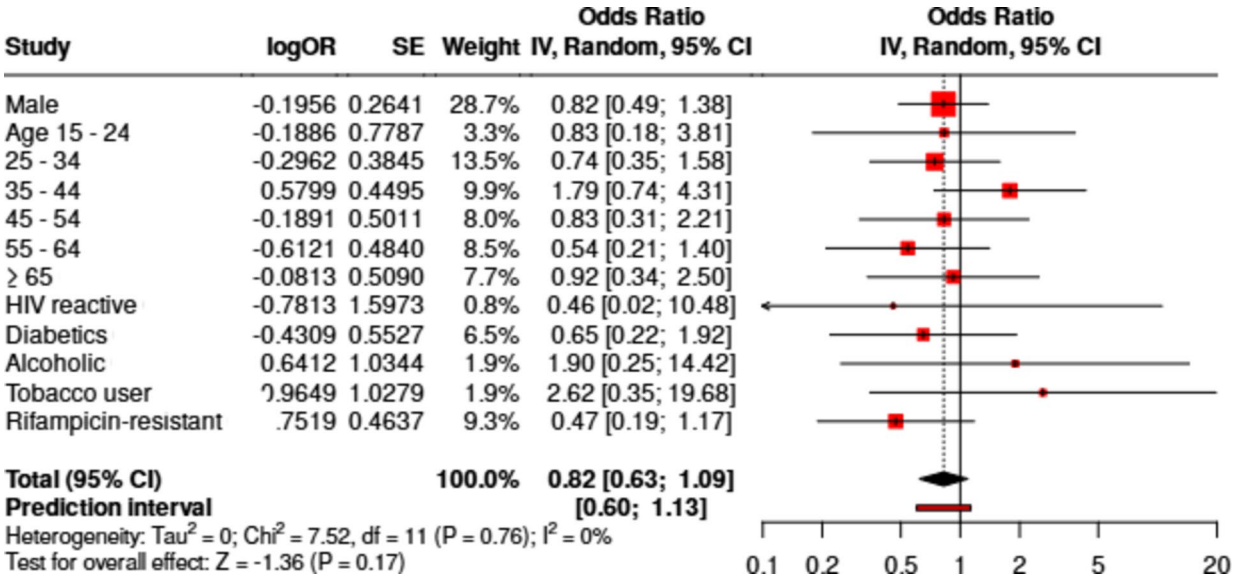

Fig. 3. Association between potential socio-demographic predictors and unsuccessful treatment outcomes in extrapulmonary tuberculosis.

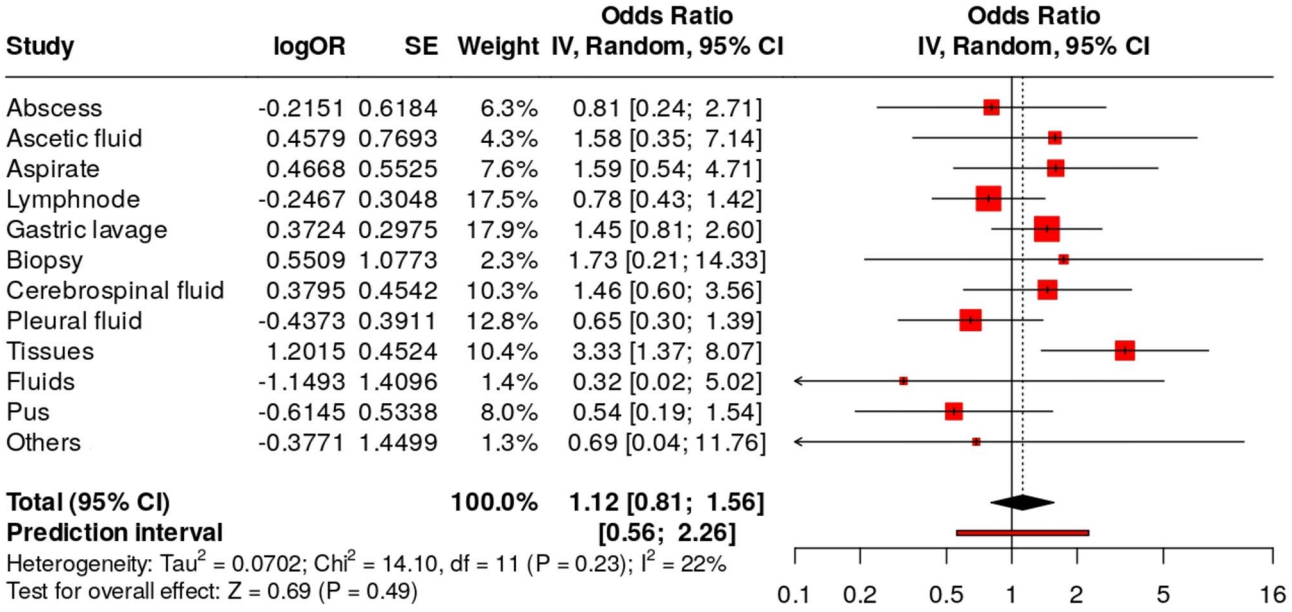

Fig. 4. Association between sample predictors and unsuccessful treatment outcomes in extrapulmonary tuberculosis.

Figure 4 presents a forest plot analysis of twelve variables associated with outcomes in patients with extrapulmonary tuberculosis. This analysis utilized multivariate regression and a random effects model using the inverse variance method to compare the odds ratios (OR). The results showed no statistically significant differences, with a summarized odds ratio of 0.82 and a 95% confidence interval ranging from 0.63 to 1.09. The overall effect test did not indicate a significant impact. Additionally, there was no notable variability observed, suggesting that the effect sizes in the study were consistent in both scale and direction. We also employed multivariable logistic regression to analyze factors influencing unfavourable treatment outcomes, including ascetic fluid, aspirates, gastric lavage, cerebrospinal fluid, biopsy, and tissue samples. Tuberculous peritonitis, specifically involving ascetic fluid, was associated with greater odds of unsuccessful treatment outcomes (odds ratio [OR], 1.58; 95% confidence interval [CI] [0.35–7.14]). Additionally, aspirates from extrapulmonary tuberculosis (epTB) patients showed even higher odds of unsuccessful treatment (OR, 1.59; 95% CI [0.54-2-4.71]). Biopsy samples and gastric lavage also indicated higher odds of unsuccessful treatment, with ORs of 1.73 (95% CI [0.21–14.33]) and 1.45 (95% CI [0.81–2.60]), respectively. Furthermore, TB meningitis and tissue

Variables	MTB detected	Successful outcome		Successful outcome (%)	*p*-value	Unfavourable outcome				Unfavourable outcome (%)	*p* < value
		Cured	Rx Completed			Died	LTFU	Defaulter	Rx failure		
Abscess	40	16	21	37(92.50)	0.7324	1	2	-	-	3(7.50)	0.0001
Ascetic fluid	15	11	2	13(86.67)	0.7055	1	1	-	-	2(13.33)	0.0016
Aspirate	30	12	14	26(86.67)	0.593	1	3	-	-	4(13.33)	0.0001
Lymph node	198	80	103	183(92.42)	0.666	-	14	-	1	15(7.58)	0.0001
Gastric Lavage	146	76	53	129(88.36)	0.3053	2	12	2	1	17(11.64)	0.0001
Biopsy	7	1	5	6(85.71)	0.7815	-	1	-	-	1(14.29)	0.0339
Cerebrospinal fluid	49	21	22	43(87.76)	0.5316	2	4	-	-	6(12.24)	0.0001
Pleural Fluid	131	60	63	123(93.89)	0.6157	2	6	-	-	8(6.11)	0.0001
Tissues	30	15	8	23(76.67)	0.2967	1	5	1	-	7(26.92)	0.0009
Fluids	16	8	8	16(100.00)	-	-		-	-	-	-
Pus	75	35	36	71(94.67)	0.7406	2	2	-	-	4(5.33)	0.0001
Others	7	3	4	7(100.00)	-	-		-	-	-	-
Total	746	340	339	679(91.02)	0.0759	12	50	3	2	67(8.98)	0.0001

Table 5. Predictors and successful treatment outcome among tuberculosis patients on samples wise ($n = 746$).

samples from epTB patients had greater odds of unsuccessful treatment outcomes, with ORs of 1.46 (95% CI [0.60–3.56]) and 3.33 (95% CI [1.37–8.07]), respectively.

Table 5 presents the results of a simple logistic regression analysis aimed at identifying predictors of successful treatment outcomes among tuberculosis patients, categorized by sample type. Positive treatment outcomes were observed for various sample types, including lymph nodes (92.42%), ascetic fluid (86.67%), aspirate (86.67%), abscess (92.5%), gastric lavage (88.36%), biopsy materials (85.71%), cerebrospinal fluid (87.76%), pleural fluid (93.89%), tissues (76.67%), other fluids (100%), and pus (96.67%). In contrast, the highest rates of unfavourable treatment outcomes were found in certain samples: Tissues (26.92%), biopsy (14.29), Ascetic fluid (13.33%), aspirate (13.33%), Cerebrospinal fluid (12.24%), and gastric lavage (11.64%). Of 746 patients with extrapulmonary tuberculosis (epTB), the overall mortality rate was 1.61%, representing 12 patients, and the overall unfavourable outcome rate was 8.98%.The highest mortality rates were noted among patients with cerebrospinal fluid (16.67%) and pleural fluid (16.67%). Although the mortality rate among patients with pus-related epTB was also elevated, the actual number of cases was relatively small (2 out of 71 patients).

Discussion

Extrapulmonary Tuberculosis is a significant contributor to the global Tuberculosis burden, particularly in developing countries. Globally, epTB accounts for approximately 15 to 20% of all TB cases[13]. Our study found that 16.5% of all TB cases were epTB, which is lower to rates found in other developed countries like the Netherlands (38%), the United States (27%), and Germany (21.6%), as reported by Rolo et al.[14]. Of all DR-TB patients registered, the study found that the rate of rifampicin resistance among epTB cases was 4.83%, which is lower than the rate reported by previous studies conducted in India by Kant et al.,2018 (13.4%)[15], Lohiya et al. 2020 (16%)[16], and Misra et al. in 2021[17]. This study revealed that lymphatic TB (25%; 9/36) and pleural TB (19.4%; 7/36) were the most common sites of rifampicin-resistant-epTB, accounting for almost half of the cases. A similar pattern rifampicin-resistant epTB was seen in the previous literature from India (16%), the Netherlands (39%), the United States (40%), and the United Kingdom (37%) as reported by Khan et al. (13.4%)[15], Lohiya et al. (16%)[16].The prevalence of drug resistance among epTB patients highlights the need for drug susceptibility testing and the development of more effective regimens for epTB treatment.

According to our research, there is limited published data in India on the success rate of treatment among epTB patients. However, we found that the overall treatment success rate for epTB patients was 91.02%, which is slightly higher than the target of at least 90% set by the WHO and also higher than study conducted in Bhutan (90.0%) and previous study in India (90.5%)[5]. This might be associated with better healthcare facilities, social support and family support and improved adherence to Tuberculosis treatment. The success rates for rifampicin-resistant epTB was 83.33% and 6.7% of patients were lost to follow-up, while 1.6% died during treatment. These findings were comparable with state, national, and previous Indian studies[18]. However, the percentage of TB-related deaths in this study (1.6%) was lower than in national (4%) and other studies in India, Bhutan, and Ethiopia[19,20].The loss to follow-up rate among epTB patients were 6.7% in this study, which is lower than the other studies conducted in the Cameroon (20%), South Africa (17.2%), Thailand (11%) and Pakistan (15.7%)[21]. In a recent study, the overall treatment success rate among epTB was 91.02%. This treatment success rate is higher than the findings of a previous study in India and a Pakistani study, which reported 83.8% and 71.1% treatment success rates among epTB patients, respectively[20]. Other studies conducted in high TB burden countries such as Malaysia (67.6%), Brunei (79.7%), and China (98.24%) also reported suboptimal treatment success rates among epTB patients[22,23]. There could be several reasons for the lower treatment success rates, including non-adherence to anti-TB drugs, potential side effects associated with these drugs, lack of patient knowledge about the consequences of loss to follow-up, and distance from the treatment centre[24]. In contrast to these findings, studies conducted in Ethiopia (89.2%) and Bhutan (90%) showed relatively better treatment

success rates[25,26]. This could be attributed to better quality healthcare facilities, political commitment, support from family, friends, and healthcare workers, social support, better patient knowledge, and improved adherence to TB treatment. The reason for the better treatment comes might be consequences of lower the loss to follow-up, which could be also the reason for lower the treatment failure, relapse, transmission of disease to high risk patients, development of drug resistance, and mortality. Understanding and minimizing the impact of these factors is important to improve treatment completion rate. Improved patient counselling and awareness of disease, better healthcare facilities and social support to the patients can reduce loss to follow-up treatment.

Our study found that epTB patients with 35–44 age group face a higher risk of unsuccessful treatment outcomes compared to other age group patients, with a risk ratio of 1.61. Berihe Hiluf et al.[27] reported that older patients (> 35 years) were more likely to experience unsuccessful treatment outcomes than younger patients. As people age, they often face concurrent diseases like malnutrition, diabetes, and cancer, which can lead to treatment failures. Aging also causes biological deterioration that weakens the immune system, increasing death rates among older adults. Additionally, frailty and reliance on family for medical care can result in more treatment interruptions.

Our study found that individuals who consumed alcohol had 1.90 times greater odds of experiencing unsuccessful treatment outcomes. Likewise, Song et al.[28] reported that alcohol abuse increased the odds of poor treatment outcomes in patients with tuberculosis, ranging from 1.3 to 1.8 times. Ragan et al.[29] discovered that alcohol use was associated with 1.5 to 2.0 time's higher odds of poor treatment outcomes for both drug-sensitive and drug-resistant tuberculosis compared to those without alcohol exposure. Additionally, Karthickeyan et al.[30] identified alcohol consumption during the treatment of multidrug-resistant tuberculosis as the most significant risk factor for unsuccessful treatment outcomes. The relationship between alcohol consumption and treatment results is complex. Studies indicate that both tobacco chewing and alcohol consumption negatively impact successful treatment outcomes by suppressing immune mechanisms through nicotine and altering drug metabolism (Johnson et al.[31] 5. Overall, individuals who consumed alcohol during treatment were more likely to miss doses in both the intensive and continuation phases of tuberculosis treatment compared to those who did not. This suggests that missed doses may significantly contribute to unsuccessful outcomes. Alcohol consumption can also detract from general health and impair the immune response against *M.tuberculosis*, potentially leading to treatment failure or delayed response. Numerous studies have shown that alcohol can enhance the ability of mycobacteria to survive within human macrophages by reducing mobilization, adherence, phagocytosis, and superoxide production. Furthermore, alcohol can inhibit antigen-specific T-cell activation by interfering with the presentation of mycobacterial antigens to lymphocytes. Chronic alcohol exposure may also suppress cytokine production, which is essential for cellular communication, activation, proliferation, migration, and regulating inflammation and other healing processes[30]. In summary, alcohol use significantly alters the immune response, increasing susceptibility to tuberculosis. Moreover, alcohol abuse affects not only the incidence of tuberculosis but also its clinical course and outcomes, leading to higher rates of treatment noncompliance and relapse. This is particularly true in precarious living conditions and with an increased risk of hepatotoxicity. Overall, alcohol use significantly increases the risk of poor treatment outcomes in patients with extrapulmonary tuberculosis.

Personal habits, such as chewing tobacco, can weaken the immune system. Research indicates that tobacco use is linked to less successful treatment outcomes for multidrug-resistant tuberculosis (MDR-TB). India is the second-largest producer and consumer of tobacco, with approximately 266.8 million adults about 28.6% of the adult population using tobacco in various forms[32]. The study revealed that tobacco users have 2.63 times higher odds of experiencing unsuccessful treatment outcomes among patients with extrapulmonary tuberculosis. This is because tobacco weakens the lung's defence mechanisms, making individuals more susceptible to infections. Tobacco use reduces the activity of Natural Killer (NK) cells and impairs mucociliary clearance. Additionally, it may have an irreversible inhibitory effect on nitric oxide synthase, an enzyme that alveolar macrophages need to produce nitric oxide, which is essential for inhibiting the multiplication of *M.tuberculosis*. In the lower respiratory tract, tobacco increases the availability of iron, which binds with nitric oxide to create toxic radicals that can disrupt macrophage function. This disruption affects the production of critical defenders against TB, such as cytokines TNF-α and IL-12. Furthermore, older smokers tend to experience a decline in the antioxidant defences of their alveolar macrophages. This imbalance between oxidants and antioxidants can lead to tissue damage in the lungs of smokers.

The current study found that the prevalence of tuberculous peritonitis among patients with extrapulmonary tuberculosis was 7.77%. This rate is higher than the 2.07% reported by Garcia et al.[33]. Our findings showed that the presence of tuberculous peritonitis significantly increased the likelihood of poor treatment outcomes in patients with extrapulmonary tuberculosis, with odds ratios ranging from 1.2 to 7.14. This increase may be due to chronic inflammation, elevated protein content, and malabsorption of peritoneal fluid caused by tuberculous peritonitis. Patients with extrapulmonary tuberculosis (epTB) may experience malabsorption due to malnutrition. As a result, decreased absorption of anti-TB medications is likely to lead to insufficient drug exposure. This situation may result in unfavourable outcomes, including treatment failure and the development of drug resistance[34]. The current study revealed that the prevalence of definite tuberculosis meningitis (TBM) among patients with extrapulmonary tuberculosis was 8.88%. This percentage is higher than the 3.3% reported by Huang et al.[35] in China, but lower than the 20% reported by Evans et al.[36] in Georgia. Our findings indicated that the presence of definite TBM significantly increased the odds of poor treatment outcomes in patients with extrapulmonary tuberculosis, with odds ratios ranging from 1.2 to 3.56. This increase may be attributed to malnutrition. Huang et al.[35] also noted that malnutrition heightened the risk of developing definite TBM. Cellular immunity is crucial for the immune response against M. tuberculosis infection. Malnutrition can impair T-cell function, particularly affecting the production of T-helper-1 cytokines and the antimicrobial activity of macrophages. Improving living conditions and addressing malnutrition could reduce the incidence of both tuberculosis and TBM, ultimately

leading to better patient outcomes. Our study found that the prevalence of tuberculosis (TB) in biopsy materials was 8.75%, which is consistent with the 8.93% reported by Fu et al.[37]. Our findings indicated that the presence of TB in biopsy samples increased the likelihood of poor treatment outcomes in patients with extrapulmonary tuberculosis, with odds ratios ranging from 1.5 to 14.33. This may be due to the difficulty in accurately targeting the exact lesion site during the biopsy procedure. Additionally, aspirates, gastric lavage, and tissue samples also significantly increased the odds of poor treatment outcomes in these patients.

Only microbiologically confirmed cases of extra pulmonary tuberculosis (epTB) were included in this study, which introduces a selection bias and represents a significant limitation. The exclusion of microbiologically negative cases may affect the generalizability of our findings, especially concerning treatment success rates. Clinically diagnosed epTB cases, which often rely on imaging, histopathology, and clinical judgment rather than microbiological confirmation, may exhibit different treatment responses and outcomes. As a result, our study may overestimate treatment success rates since the confirmed cases are more likely to have received early and targeted therapy. Future research that includes both microbiologically confirmed and clinically diagnosed cases is essential for a more comprehensive evaluation of treatment outcomes. Despite this limitation, our findings provide valuable insights into the burden of microbiologically confirmed epTB and highlight the importance of accurate diagnosis and adherence to treatment.

The study also found that the most common forms of epTB were lymphatic, abscess, pus, and pleural TB. Patients with meningeal, tissue, ascetic fluid, aspirate, biopsy and gastric lavage were more likely to have unfavorable outcomes, while patients with lymphatic TB, abscess, pus and pleural fluid were relatively more likely to achieve favourable treatment outcomes. These findings are consistent with other published studies[5,38]. Furthermore, the study revealed that patients with lymph node TB had a lower probability of unfavorable treatment outcomes. This could be due to the relatively lower loss to follow-up (7.1%) patients. The results of multivariate logistic regression analysis indicated that patients diagnosed with meningeal TB had unfavorable treatment outcomes in 12.24% of cases. This could be attributed to the longer treatment duration required for meningeal TB caused by the reduced penetration of anti-TB drugs, such as ethambutol and rifampicin, to cerebrospinal fluid, as suggested by Atif et al.[5]. Our data also support this notion, as 8.16% of the meningeal TB patients were lost to follow-up, and 4.1% died during the treatment[39].

The study's findings reported that the rate of successful treatment outcomes among patients with epTB was higher than the target of at least 90% set by the WHO in the End TB Strategy. A significant proportion of patients with epTB, specifically 6.7%, were lost to follow-up, raising concerns for policymakers. Our study's loss to follow-up rate aligns with findings from other research conducted in various countries: Cameroon (20%), South Africa (17.2%), Thailand (11%), and Pakistan (15.7%)[5]. This 6.7% rate is notably high and demands urgent attention. Of 746 individuals diagnosed with confirmed extrapulmonary cases, fifty were lost to follow-up, and twelve died during treatment. The concerning death rate among epTB patients receiving treatment for drug-resistant disease aligns with the limited reports available, highlighting the ineffectiveness of current treatments[36].LTFU can increase the risk of clinical deterioration, treatment failure, and further complications in tuberculosis patients. Patients who discontinue treatment too early are one of the leading causes of treatment failure[40]. The dropout rate is critical because low LTFU as a result of improved TB management will reduce re-treatment case by 10–20% in the coming years.Additionly, one of the reasons for the development of acquired Drug Resistance Tuberculosis (DR-TB) is LTFU. The potential consequences of losing patients to follow-up include treatment failure, relapse, the transmission of the disease to high-risk individuals, the development of drug resistance, and increased mortality. Therefore, interventions should be developed and implemented to minimize treatment interruptions. Furthermore, future studies should be conducted to determine the reasons for the loss to follow-up. The study also provides clinicians with an opportunity to identify patients who are at higher risk of unfavourable treatment outcomes.

Conclusion

The study investigates the distribution and burden of extrapulmonary tuberculosis among registered TB cases in South India. The most common samples included in the study were pleural fluid, lymph nodes, pus and gastric lavage. Pleural TB and lymph node TB were the most prevalent forms, while tuberculosis meningitis had the lowest positivity rate. The treatment success rate for epTB was 91.02%, surpassing the WHO target of 90%, though it was 83.33% for extrapulmonary rifampicin-resistant TB. Tuberculous peritonitis, aspirate, gastric lavage, biopsy, Tuberculosis meningitis (TBM), and tissue samples were all significantly associated with unfavourable treatment outcomes. Unfavourable outcomes were primarily due to patients lost to follow-up, especially among those with gastric, lymphatic, pleural fluid, tissues and meningeal TB, while lymph node, abscess, pus and pleural TB patients had better outcomes. The findings highlight the need for improved diagnostic strategies for epTB, which has a lower positivity rate (16.5%) than pulmonary TB. Enhancing clinical awareness, targeted screening in high-risk groups, and better follow-up and counselling could improve treatment success rates. Further research is necessary to identify risk factors and optimize management approaches for epTB.

Data availability

All primary and secondary data are available with the corresponding author and in the Nikshay portal, Government of India. Permission is granted to the corresponding author to access the data through login credentials. The datasets generated and analyzed during the current study are not publicly available. The datasets are available from the corresponding author upon reasonable request. Contact no: +91 9944737597 Email.ID: drmuthurajm@gmail.com.

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Author contributions
CKV, MM and BRM--prepared manuscriptMJA, MA and BU--prepared figuresRV, SSR, SP and GP--prepared tablesVK, SS, SG and MM--statistical analysis.All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
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