Coinfection of pulmonary tuberculosis with other lower respiratory tract infections: A retrospective cross-sectional study

Marwh G. Aldriwesh1,2,3, Raghad A. Alaqeel1,2,3, Aisha M. Mashraqi4,
Mutaib M. Mashraqi5, Bayan A. Albdah5,7, Azzah S. Alharbi5,8

Abstract:

BACKGROUND: Little attention has been given to the development of lower respiratory tract infections (LRTIs) in patients with pulmonary tuberculosis (PTB) during their anti-tuberculosis (anti-TB) treatment and how that might affect patients' health status. Here, the prevalence and etiologies of other LRTIs in a cohort of PTB patients were determined, and the clinical features and outcomes were described.

METHODS: Adult patients with PTB between 2015 and 2020 were recruited and monitored during their anti-TB treatment for the presence of LRTIs. Clinical data were retrospectively collected from patients' medical records.

RESULTS: Data from 76 PTB patients (57 [75%] males) were reviewed. The median age was 61.0 (interquartile range 83.5–35.5) years, and other LRTIs were detected in 45 (59.2%) PTB patients. Of the 126 episodes of LRTIs, 84 (66.7%) were due to bacterial infections, 37 (29.4%) were due to fungal infections, and 5 (3.9%) were due to viral infections. The development of LRTIs was significantly more common in older (P = 0.012) and hypertensive patients with PTB (P = 0.019). Patients with PTB and LRTIs experienced significantly more frequent extrapulmonary infections (P = 0.0004), bloodstream infections (P = 0.001), intensive care unit stays (P = 0.001), and invasive mechanical ventilation use (P = 0.03) than patients who did not develop LRTI.

CONCLUSIONS: The identification of host-related risk factors for LRTI development among patients with PTB could be used to develop a prediction model for LRTI development. Hence, initiating antimicrobials early, in parallel with appropriate anti-TB treatment, may mitigate PTB-related health and economic consequences.

Keywords:
Anti-tuberculosis, clinical outcomes, coinfection, machine learning, pulmonary infection, tuberculosis

Pulmonary tuberculosis (PTB) is an infectious disease caused by a group of acid-fast bacilli (AFB) bacteria that are known as the Mycobacterium tuberculosis (MTB) complex.1,2 According to the World Health Organization report, PTB is one of the top 10 etiological factors contributing to mortality worldwide.3 Millions of individuals are suffering from PTB annually. In 2017, approximately 10 million people (9.0–11.1 million) developed active PTB disease worldwide: approximately 5.8 million men, 3.2 million women, and 1 million children.4 Men had a higher risk of developing active PTB disease than women, and most PTB cases occurred in adults (≥15 years old).4 According to the 2019 Global tuberculosis report, the current PTB situation in the Kingdom of Saudi Arabia revealed that the...
The coinfection of PTB with other lower respiratory tract infection (LRTI) has been documented in the literature, particularly in areas where PTB is prevalent. The coinfection of PTB with other LRTIs may be facilitated by active PTB disease. The suppression of human immunity, which can occur due to T-lymphocyte deficiency during active PTB disease, could be the main explanation for the coinfection. Hormonal alterations, such as suppressed pituitary function, increased adrenal and pancreas functional activity, higher cortisol levels, and altered thyroid function, occur during the early stages of PTB disease and may lower immune competency. Failure to detect LRTI in patients with PTB may complicate PTB treatment and result in poorer health outcomes and higher mortality rates. Shimazaki et al. reported a high prevalence of bacterial coinfection among HIV-negative PTB cases, which contributed significantly to a higher death rate.

Although previous studies have investigated the epidemiology, anti-tuberculosis (anti-TB) drug resistance, prognosis, and outcomes of PTB, few have investigated the development of LRTIs in patients with PTB during their anti-TB treatment and how that might affect patients’ clinical outcomes. Therefore, the purpose of the current study was to estimate the prevalence and identify the etiologies of other LRTIs in a cohort of Saudi Arabian patients with PTB. In addition, we aimed to describe the clinical features and outcomes of patients with PTB who developed other LRTIs.

Methods

Study design and settings

This research retrospectively reviewed the medical records of all accessible adult patients (>14 years of age) diagnosed with PTB between January 2015 and December 2020. The exclusion criteria consisted of patients with human immunodeficiency virus, patients with an unconfirmed PTB diagnosis, and patients with incomplete clinical and diagnostic data related to PTB. According to institution guidelines, a patient with suspected PTB needs to provide three sputum specimens taken at least 1 day apart during the 1st week of examination. In the first event of a positive sputum smear result, the Division of Infectious Diseases and the Department of Infection Prevention and Control at the institution begins the process of isolating the patient until PTB is confirmed. All patients with confirmed PTB are isolated at the hospital for a minimum of 3 weeks. A complete examination of the sputum specimen is performed once it is received at the Microbiology Laboratory. The quality of the sputum specimen is determined by a smear and culture on blood agar, chocolate agar, or MacConkey agar.

The treatment stages of active PTB disease are divided into two stages: an initial intensive stage of at least 2 months where a combination of four anti-TB treatment drugs are prescribed – Isoniazid (also known as isonicotinohydrazine), rifampin (RIF), ethambutol, and pyrazinamide – and a second stage (a continuation stage) of not <4 months where at least two anti-TB treatment drugs are used.

Data collection

The demographic and clinical data were extracted from patients’ medical records through the BestCare system and included age at PTB diagnosis, gender, nationality, place of residence, smoking status, and comorbidities. Signs, symptoms, and radiology findings at PTB presentation were also collected. The PTB-associated laboratory diagnostic data which were gathered include the AFB smear, sputum bacillary load, AFB culture, Xpert (MTB)/RIF assay, and QuantiFERON-TB results.

LRTI was detected in patients with active PTB disease during anti-TB treatment duration. In other words, the medical records of each patient with active PTB disease were reviewed to detect LRTI throughout the duration of anti-TB treatment of that patient. During that duration, the isolated bacterium from the patients’ sputum specimens was identified by either biochemical tests or VITEK II (bioMérieux) at the Microbiology Laboratory. Fungal isolates from patients’ sputum specimens were cultured on both Sabouraud agar and Sabouraud Dextrose slants and then examined by a potassium hydroxide smear. Biochemical tests, VITEK II (bioMérieux), or both were used to achieve full identification of fungal isolates from sputum specimens. The BioFire System multiplex polymerase chain reaction technology was employed to detect respiratory viruses in patients’ sputum specimens at the same laboratory.

The clinical outcomes of the patients with PTB were also collected. These outcomes consisted of mortality, intensive care unit (ICU) stays, the development of extrapulmonary infection and/or bloodstream infection, hemodialysis, invasive machinal ventilation, and extracorporeal membrane oxygenation.

Statistical analysis

For statistical analyses, the study population was grouped into two groups. The first was comprised of patients who were diagnosed with active PTB disease and did not develop LRTI during anti-TB treatment duration, while the second consisted of patients who...
were diagnosed with active PTB disease and developed LRTI during the same duration [Figure 1]. Data analysis was performed using the statistical program SAS (version 9.4) produced by SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. The patients’ data were expressed as a percentage for categorical variables and as a median with the interquartile range (IQR) for continuous variables. The association between categorical variables was assessed using Fisher’s exact test. The Wilcoxon two-sample test was applied to test the association between continuous variables. Statistical significance was defined as a $P < 0.05$.

**Ethics**

The procedures followed in the current study were in accordance with the Helsinki Declaration of 1975, as revised in 2000 and with the ethical standards of the Institutional Review Board at the institution in Riyadh, Saudi Arabia, where the study was conducted (protocol approval number RYD-21-417780-120649, August 25, 2021), with permission to access patients’ medical records. Since the current study is retrospective, the patient consent was waived.

**Results**

**Clinical characteristics of patients with pulmonary tuberculosis**

During the study period (January 2015–December 2020), 76 patients had a confirmed diagnosis of active PTB disease (75% of males and 25% of females). The patients with active PTB disease were divided into two groups based on the detection of LRTI during anti-TB treatment duration (9 months, IQR 12–6) [Figure 1]. Of the 76 patients with active PTB disease, 45 (59.2%) had at least one episode of LRTI (bacterial, fungal, or viral). The development of LRTI was significantly associated with older ($P = 0.012$) and hypertensive patients with PTB ($P = 0.019$). The frequency of patients with active PTB disease who developed LRTI and underwent antimicrobial therapy 3 months before PTB diagnosis was significantly higher (62.2%) than patients who did not develop LRTI (38.7%), at $P = 0.036$. Moreover, the development of LRTI was significantly associated with hospitalized patients with PTB ($P = 0.01$). Patients with PTB who developed LRTI were noted at PTB presentation to have significantly lower night sweats ($P = 0.046$), haemoglobin ($P = 0.043$) and albumin ($P = 0.03$), but higher blood urea nitrogen ($P = 0.03$), than patients who did not develop LRTI [Table 1].

**Identification of lower respiratory tract infections in patients with pulmonary tuberculosis**

As shown in Table 2, 126 episodes of LRTI were detected in 45 patients with PTB during their anti-TB treatment duration (9.0 months, IQR 12.0–6.0). Of the 126 episodes, 84 (66.6%) were due to bacterial infections, 37 (29.4%) were due to fungal infections, and 5 (3.9%) were due to viral infections. Gram-negative *Pseudomonas aeruginosa* was the most frequently isolated bacterium and identified in 31 episodes (24.6%) of LRTI. At least four of these episodes were due to drug-resistant...
### Table 1: Clinical characteristics of patients with pulmonary tuberculosis

|                         | All patients (n=76), n (%) | Patients with PTB only (n=31), n (%) | Patients with PTB and other LRTI (n=45), n (%) | P    |
|-------------------------|----------------------------|-------------------------------------|-----------------------------------------------|------|
| Age (years)             | 61.0 (83.5-35.5)           | 39.0 (67.0-33.0)                    | 71.0 (85.0-44.0)                               | 0.012|
| Gender                  |                            |                                     |                                               |      |
| Male                    | 57 (75.0)                  | 23 (74.1)                           | 34 (75.5)                                     | 1.00 |
| Female                  | 19 (25.0)                  | 8 (25.8)                            | 11 (24.4)                                     |      |
| BMI (18.5-24.9 kg/m)    | 23.1 (26.9-18.6)           | 23.1 (26.6-18.5)                    | 21.1 (26.9-18.7)                              | 0.75 |
| Diabetes                | 35 (46.0)                  | 12 (38.7)                           | 23 (51.1)                                     | 0.352|
| Hypertension            | 38 (50.0)                  | 10 (32.2)                           | 28 (62.2)                                     | 0.019|
| Nationality             |                            |                                     |                                               |      |
| Saudi                   | 74 (97.3)                  | 30 (96.7)                           | 44 (97.7)                                     | 1.00 |
| Non-Saudi               | 2 (2.6)                    | 1 (3.2)                             | 1 (2.2)                                       |      |
| Place of residence      |                            |                                     |                                               |      |
| Central                 | 62 (81.5)                  | 27 (87.1)                           | 35 (77.7)                                     | 0.702|
| Northern                | 4 (5.2)                    | 2 (6.4)                             | 2 (4.4)                                       |      |
| Eastern                 | 4 (5.2)                    | 1 (3.2)                             | 3 (6.6)                                       |      |
| Southern                | 3 (3.9)                    | 0 (0.0)                             | 3 (6.6)                                       |      |
| Western                 | 1 (1.3)                    | 0 (0.0)                             | 1 (2.2)                                       |      |
| Outside Saudi Arabia    | 2 (2.6)                    | 1 (3.2)                             | 1 (2.2)                                       |      |
| Smoking status          |                            |                                     |                                               |      |
| Former                  | 9 (11.8)                   | 4 (12.9)                            | 5 (11.1)                                      | 0.39 |
| Current                 | 19 (25.0)                  | 10 (32.2)                           | 9 (20.0)                                      |      |
| Nonsmoker               | 48 (63.1)                  | 17 (54.8)                           | 31 (68.8)                                     |      |
| PTB category            |                            |                                     |                                               |      |
| New                     | 69 (90.7)                  | 28 (90.3)                           | 41 (91.1)                                     | 1.00 |
| Retreatment             | 7 (9.2)                    | 3 (9.6)                             | 4 (8.8)                                       |      |
| Source of PTB           |                            |                                     |                                               |      |
| Family                  | 17 (22.3)                  | 5 (16.1)                            | 12 (26.6)                                     | 0.405|
| Hospital                | 5 (6.5)                    | 3 (9.6)                             | 2 (4.4)                                       |      |
| Unknown                 | 54 (71.0)                  | 23 (74.1)                           | 31 (68.8)                                     |      |
| Number of times PTB treated |                       |                                     |                                               |      |
| 1                       | 65 (85.5)                  | 28 (90.3)                           | 37 (82.2)                                     | 0.51 |
| 2+                      | 11 (14.4)                  | 3 (9.6)                             | 8 (17.7)                                      |      |
| Referrals               | 17 (22.3)                  | 6 (19.3)                            | 11 (24.4)                                     | 0.78 |
| Prior antimicrobial use within last 3 months of PTB diagnosis | 40 (52.6) | 12 (38.7) | 28 (62.2) | 0.036 |
| Direct sputum smear for AFB |                       |                                     |                                               |      |
| Positive                | 45 (59.2)                  | 21 (67.7)                           | 24 (53.3)                                     | 0.242|
| Negative                | 31 (40.7)                  | 10 (32.2)                           | 21 (46.6)                                     |      |
| Sputum bacillary load   |                            |                                     |                                               |      |
| 1+                      | 14 (18.4)                  | 5 (16.1)                            | 9 (20.0)                                      | 0.47 |
| 2+                      | 8 (10.5)                   | 4 (12.9)                            | 4 (8.8)                                       |      |
| 3+                      | 4 (5.2)                    | 3 (9.6)                             | 1 (2.2)                                       |      |
| 4+                      | 19 (25.0)                  | 9 (29.0)                            | 10 (22.2)                                     |      |
| No bacillary load       | 31 (40.7)                  | 10 (32.2)                           | 21 (46.6)                                     |      |
| AFB culture             |                            |                                     |                                               |      |
| Positive                | 67 (88.1)                  | 29 (93.5)                           | 38 (84.4)                                     | 0.29 |
| Negative                | 9 (11.8)                   | 2 (6.4)                             | 7 (15.5)                                      |      |
| Xpert MTB/RIF assay     |                            |                                     |                                               |      |
| Positive                | 68 (89.4)                  | 29 (93.5)                           | 39 (86.6)                                     | 0.82 |
| Negative                | 7 (9.2)                    | 2 (6.4)                             | 5 (11.1)                                      |      |
| Unperformed             | 1 (1.3)                    | 0 (0.0)                             | 1 (2.2)                                       |      |
| QuantiFERON-TB          |                            |                                     |                                               |      |
| Positive                | 24 (31.5)                  | 15 (48.3)                           | 9 (20.0)                                      | 0.07 |
| Negative                | 6 (7.8)                    | 2 (6.4)                             | 4 (8.8)                                       |      |
| Indeterminate           | 10 (13.1)                  | 3 (9.6)                             | 7 (15.5)                                      |      |
| Unperformed             | 36 (47.3)                  | 11 (35.4)                           | 25 (55.5)                                     |      |

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Table 1: Contd...

| Management | All patients (n=76), n (%) | Patients with PTB only (n=31), n (%) | Patients with PTB and other LRTI (n=45), n (%) | P |
|------------|---------------------------|-------------------------------------|-----------------------------------------------|---|
| Hospitalization | 71 (93.4) | 26 (83.8) | 45 (100.0) | 0.01 |
| Outpatient | 5 (6.5) | 5 (16.1) | 0 | |
| Duration of anti-TB treatment, months | 9.0 (12.0-6.0) | 9.0 (10.0-6.0) | 9.0 (12.0-6.0) | 0.362 |
| Diagnostic delay: Symptoms duration ≥3 weeks | 54 (71.0) | 20 (64.5) | 34 (75.5) | 0.356 |
| Presence of lung disease at PTB diagnosis | | | |
| None | 55 (72.3) | 24 (77.4) | 31 (68.8) | 0.18 |
| COPD | 1 (1.3) | 0 (0.0) | 1 (2.2) | |
| ARDS | 2 (2.6) | 0 (0.0) | 2 (4.4) | |
| Pneumonitis | 4 (5.2) | 0 (0.0) | 4 (8.8) | |
| Bronchiectasis | 2 (2.6) | 0 (0.0) | 2 (4.4) | |
| Bronchial asthma | 5 (6.5) | 4 (12.9) | 1 (2.2) | |
| Respiratory failure | 1 (1.3) | 0 (0.0) | 1 (2.2) | |
| Interstitial lung fibrosis | 3 (3.9) | 2 (6.4) | 1 (2.2) | |
| Presence of two lung diseases | 3 (3.9) | 1 (3.2) | 2 (4.4) | |
| Signs and symptoms at PTB diagnosis | | | |
| Cough | 67 (88.1) | 28 (90.3) | 39 (86.6) | 0.73 |
| Weight loss | 37 (48.6) | 17 (54.8) | 20 (44.4) | 0.48 |
| Night sweats | 24 (31.5) | 14 (45.1) | 10 (22.2) | 0.046 |
| Dyspnea | 44 (57.8) | 16 (51.6) | 28 (62.2) | 0.479 |
| Sputum | 41 (53.9) | 17 (54.8) | 24 (53.3) | 1.00 |
| Fever | 53 (69.7) | 22 (70.9) | 31 (68.8) | 1.00 |
| Anorexia | 34 (44.7) | 14 (45.1) | 20 (44.4) | 1.00 |
| Malaise | 2 (2.6) | 1 (3.2) | 1 (2.2) | 1.00 |
| Hemoptyis | 13 (17.1) | 6 (19.3) | 7 (15.5) | 0.76 |
| Systolic BP, <120.0 mmHg | 116.0 (133.0-106.0) | 120.0 (131.0-109.0) | 113.0 (133.5-102.0) | 0.275 |
| Diastolic BP, <80.0 mmHg | 66.0 (74.0-61.0) | 67.0 (75.0-63.0) | 65.5 (73.5-61.0) | 0.67 |
| Pulse rate | 94.0 (100.0-84.0) | 95.0 (105.0-90.0) | 90.5 (98.5-81.0) | 0.07 |
| Respiratory rate, 12.0-118.0/min | 20.0 (23.0-19.0) | 20.0 (22.0-19.0) | 20.0 (23.0-19.5) | 0.51 |
| Clinical chest x-ray interpretations | | | |
| Lung cavitation | 44 (57.8) | 20 (64.5) | 24 (53.3) | 0.35 |
| Lung infiltration | 12 (15.7) | 3 (9.6) | 9 (20.0) | 0.34 |
| Lung consolidation | 39 (51.3) | 20 (64.5) | 19 (42.2) | 0.06 |
| Lung opacities | 54 (71.0) | 22 (70.9) | 32 (71.1) | 1.00 |
| Centrilobular nodules | 45 (59.2) | 20 (64.5) | 25 (55.5) | 0.48 |
| Pleural effusion | 39 (51.3) | 14 (45.1) | 25 (55.5) | 0.48 |
| Lymph nodes | 43 (56.5) | 15 (48.3) | 28 (62.2) | 0.25 |
| Laboratory values at PTB diagnosis | | | |
| White blood cell, 4.0-11.0×10^9/L | 7.7 (10.1-5.4) | 7.7 (10.0-6.4) | 7.7 (10.2-4.5) | 0.241 |
| Hemoglobin | 112.5 (129.5-99.0) | 121.0 (133.0-108.0) | 107.0 (121.0-97.0) | 0.043 |
| Albumin, 34.0-150.0 mg/L | 31.0 (36.0-26.0) | 35.0 (37.0-28.0) | 29.0 (34.5-24.5) | 0.03 |
| AST, 5.0-134.0 U/L | 25.0 (43.5-17.0) | 26.0 (42.0-18.0) | 25.0 (54.0-16.0) | 0.95 |
| ALT, 5.0-155.0 U/L | 19.0 (36.0-12.0) | 26.0 (40.0-14.0) | 16.0 (27.0-11.0) | 0.16 |
| Blood urea nitrogen | 5.0 (7.7-3.3) | 4.7 (5.2-3.0) | 5.4 (8.9-3.5) | 0.03 |
| Creatinine, 64.0-110.0 μmol/L | 64.0 (82.0-53.5) | 64.0 (74.0-57.0) | 65.0 (107.0-52.0) | 0.49 |

Data reported as median (IQR) or n (%). Normal ranges: Normal pulse rate range is 50.0-90.0 and 55.0-90.0 beats/min for males and females, respectively; normal range of hemoglobin is 135.0-180.0 and 120.0-160.0 mg/L for males and females, respectively; normal range of blood urea nitrogen is 3.0-9.2 and 3.5-7.2 mmol/L for males and females, respectively. LRTI: Lower respiratory tract infection, BMI: Body mass index, AFB: Acid-fast bacilli, TB: Tuberculosis, MTB/RIF: Mycobacterium TB/Rifampin, COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, BP: Blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IQR: Interquartile range, PTB: Pulmonary TB

P. aeruginosa. A pattern of drug resistance was also detected in Klebsiella pneumonia, Staphylococcus aureus, and Acinetobacter baumannii at 16.6%, 3.9%, and 3.2%, respectively. Candida albicans (an opportunistic yeast that is part of human microbiota) was the most isolated fungus in the sputum specimens of patients with PTB, and it was detected in nine episodes (7.1%) of LRTI. However, viral agents were the least frequent causes of
LRTI in patients with PTB and were identified in only five episodes (3.9%).

**Clinical outcomes of patients with pulmonary tuberculosis during anti-tuberculosis treatment duration**

Patients with active PTB who developed LRTI during their anti-TB treatment duration were associated with worse clinical outcomes than patients who did not develop LRTI during the same duration [Table 3]. For instance, patients with active PTB and LRTI showed significantly more frequent extrapulmonary infections ($P = 0.0004$) and bloodstream infections ($P = 0.001$) than patients who did not develop LRTI. Furthermore, ICU stays ($P = 0.001$) and invasive mechanical ventilation use ($P = 0.03$) were significantly associated with PTB patients who developed LRTI. However, no significant differences in hemodialysis, extracorporeal membrane oxygenation use, and mortality rate were observed between the two groups [Table 3].

**Discussion**

PTB in Saudi Arabia is likely to rise due to the substantial influx of religious visitors who travel to the holy cities of Makkah and Madinah for Hajj and Umrah every year and due to the country’s current robust economic expansion, which is expected to attract large numbers of the immigrant laborer.[10-12] Most of these visitors and workers come from areas where PTB is highly endemic, such as India, Pakistan, Bangladesh, and Yemen.[10-12] The available literature comprises a substantial number of PTB studies on the epidemiology, anti-TB drug resistance, prognosis, and outcomes of the disease. However, little attention has been given to the development of LRTIs in patients with PTB during their anti-TB treatment duration and how that might affect patient outcomes.

In the current study, it was found that 45 patients with PTB (59.2%) developed other LRTI during anti-TB treatment duration [Table 1]. The present study’s findings are in line with those of Ibadin et al., who found that 50.0% (13 out of 26) of confirmed PTB cases found that 50.0% (13 out of 26) of confirmed PTB cases and Attia et al., who found that 33.0% of patients with active PTB disease have other LRTI.[14] Similarly, 55.4% (56 out of 101) of suspected PTB cases in Cameroon showed microbiological growth of *M. tuberculosis* and other bacteria implicated in LRTI.[15] The significantly high LRTI detection rate among older patients with PTB (71.0 years, IQR 85.0–44.0) in the present study is consistent with previous studies, where age was found to significantly affect LRTI development.[16,17] This trend can be attributed to the progressive deterioration of immunity due to aging and age-associated comorbidities.[18-20]

As depicted in Table 2, 66.6% of the isolated microorganisms were bacteria, and *P. aeruginosa* was the most frequently isolated bacterium. Similar findings have been reported in Nepal,[21] Cambodia,[14] and Pakistan.[22] The ability of *P. aeruginosa* to colonize a wide range of ecological niches, such as air polluting agents, animal hosts, and people, may explain the high
prevalence of *P. aeruginosa* in the sputum of patients with PTB. The finding that 29.4% of all isolated microorganisms were fungi with predominating isolates of *C. albicans* is in agreement with a previous report that showed that 15.0%–32.0% of all PTB co-infected cases were related to fungal infections where *C. albicans* was commonly recovered. The detection of *C. albicans* in the respiratory tract may be due to their distribution as an opportunistic pathogen that can infect the immunocompromised individuals. However, there is a paucity of data on viral respiratory coinfection in adults with PTB. Comparable research on adults with PTB has been conducted in Tanzania and Indonesia. The authors of these studies detected respiratory viruses at rates of 20.4% and 46.0%, more than in the present study. Although seasonal fluctuation is unlikely to explain these differences, since both studies were carried out over an entire year, these differences could partially be clarified by changes between the years when the investigations took place. Major distinctions between these studies included the age of the studies’ populations, the geographic locations from which these populations were recruited and the sampling procedures. As shown in Table 3, PTB with LRTI was significantly associated with worse clinical outcomes related to the development of bloodstream and extrapulmonary infections, as well as the need for assisted ventilation and ICU admission. The current study’s results are in agreement with previous studies which reported that patients with PTB and co-infected with other respiratory pathogens were at higher risk of severe forms of PTB, clinical deterioration, and death.

In our view, these results represent an initial step toward conducting further comprehensive studies on patients with PTB who are at an elevated risk of acquiring other LRTIs. The identification of host-related risk factors for LRTI development among patients with PTB could be used to develop a prediction model for LRTI development in these patients. Machine learning (ML) prediction models have been shown to be promising infection management tools. With a larger sample size, different ML algorithms can be tested and evaluated in terms of specificity, sensitivity, precision, and accuracy. Hence, initiating antimicrobials early, in parallel with appropriate anti-TB treatment, may mitigate PTB-related health and economic consequences.

This study was limited by its retrospective scope and small sample size; it was conducted at a single center serving a population with distinctive demographic features. Thus, the present results cannot be generalized globally. Nonetheless, studies from several areas with high PTB prevalence have reported similar rates of LRTI. The main strength of the current study is our access to advanced, high-quality PTB and microbiologic diagnostic data from well-established, CAP-accredited laboratories.

**Conclusions**

Patients with active PTB who developed an LRTI during their anti-TB treatment tended to experience worse clinical outcomes than patients who did not develop an LRTI during the same duration. The high rate of LRTIs in a sizeable number of patients with PTB during their anti-TB treatment is concerning and points to a need for conducting large-scale prospective studies to elaborate on the role of LRTIs in the clinical presentation of patients for better PTB management. Moreover, the findings of the current study represent an initial step toward conducting further comprehensive studies of patients with PTB who are at an elevated risk of acquiring other LRTIs at the time of PTB diagnosis. Thus, initiating antimicrobials early, in parallel with appropriate anti-TB treatment, may mitigate PTB-related health and economic consequences.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.
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