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Original Article

Clinical outcomes of patients with coronavirus disease 2019 and active tuberculosis co-infection in Beijing China: A retrospective single-center descriptive study

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A R T I C L E I N F O

Keywords:
Tuberculosis
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A B S T R A C T

Background: Coronavirus disease 2019 (COVID-19) and tuberculosis (TB) co-infection (COVID-19-TB) has the potential to exacerbate lung damage; however, information about the clinical features of COVID-19-TB is limited. This study aims to clarify the clinical characteristics and outcomes of patients with COVID-19-TB.

Methods: In this single-center retrospective study, the clinical features and outcomes of patients with COVID-19 with active TB who were admitted to Beijing Chest Hospital, Beijing, China, from 1 December 2022 to 18 January 2023 were collected. The severity of COVID-19 and TB was graded according to guidelines from the World Health Organization. The relationships of demographic and clinical variables with intensive care unit (ICU) admission were evaluated using univariable and multivariable logistic regression models.

Results: Overall, 102 patients with COVID-19-TB were enrolled. The mean age was 54.5 years (range 36.5–70 years). The most common clinical manifestations were cough (68.63%), sputum production (53.92%), fever (51.96%), and ground-glass opacities (35.29%). Complications included acute respiratory distress syndrome (11.76%), sepsis (9.8%), and respiratory failure (7.84%). Patients with COVID-19-TB had high concentrations of various proinflammatory cytokines, including interferon-γ, interleukin-1β, interferon-γ-inducible protein 10 kD, and monocyte chemoattractant protein-1. Sixteen of the 102 patients with COVID-19-TB (15.69%) were admitted to the ICU, and 10 (9.80%) died during hospitalization. The significant risk factors for ICU admission were respiratory failure, pulmonary fungal infection, and ventilation and oxygen therapy.

Conclusions: The mortality rate of COVID-19-TB was 9.80%. Several demographic and clinical characteristics were associated with adverse outcomes, indicating the importance of early recognition and treatment.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis; COVID-19-TB, COVID-19 and tuberculosis (TB) co-infection; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been ongoing for more than three years, and its high incidence and mortality rates pose a serious challenge to public health worldwide.[1] As of 21 February 2023, there had been 757 264 511 confirmed cases of COVID-19 globally, and 6 850 594 deaths had been reported to the World Health Organization. Recent studies have shown that the Omicron variant is less virulent and more contagious than the other variants.[2] From 30 November 2022 to 10 December 2022, the daily number of confirmed COVID-19 cases doubled in Beijing, China.[3] Advanced age, comorbidities, male sex, and bacterial co-infection have been identified as risk factors for COVID-19 severity and mortality.[4,5]

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (M. *tuberculosis*), remains a major global public health threat. TB causes 1.4 million deaths annually, and it currently ranks as the second leading cause of death after COVID-19. The rapid spread of SARS-CoV-2 throughout the population resulted in a high likelihood of COVID co-infection in patients with TB, further exacerbating the challenges to public health and healthcare systems. Importantly, around one quarter of the world's population harbors latent TB, and suppression of cell-mediated immunity caused by COVID-19 can induce the activation of latent TB.[6] The primary target of both M. *tuberculosis* and SARS-CoV-2 is the lungs. As a result, the lung damage and functional impairment caused by active TB may be further exacerbated by SARS-CoV-2 infection. Thus, COVID-19-TB co-infection can be potentially devastating, with severe public health consequences. Given that an estimated 15.0 million people are infected with TB annually and more than 2 billion people have latent TB worldwide, it is of vital importance to identify the relationship between COVID-19 and TB to prevent the development of serious disease.

Few studies have reported cases of COVID-19-TB, and case reports of active TB and COVID-19 co-infection are limited,[7,8] with most case reports describing only a small number of cases. This limited information precludes systematic summaries of the clinical features of COVID-19-TB.[9-13] Additionally, it remains unclear whether patients with COVID-19-TB have a worse prognosis or are more likely to progress to severe disease, thus necessitating further studies. Considering the large population and uneven distribution of health services in China, accurately predicting the future incidence and severity of COVID-19-TB poses a significant challenge. From the perspectives of public health and clinical care, the burden imposed by a single COVID-19 outbreak has already placed substantial strain on healthcare systems; therefore, the burden of overlapping epidemics is likely to be huge. Therefore, a greater understanding and effective management of COVID-19-TB co-infection are of paramount importance and would help to control this complex public health challenge.

Here, we aim to describe the clinical, laboratory, and radiological features, as well as the outcomes, of patients confirmed to have COVID-19 and TB co-infection. We also aim to highlight the clinical characteristics of both intensive care unit (ICU) and non-ICU patients. The findings of this study may assist in the development of public health guidelines for the treatment and prevention of COVID-19-TB.

2. Materials and methods

2.1. Ethical approval

This study was approved by the ethics committee of Beijing Chest Hospital (ethics approval No. BJXK-KY-2023-01). The requirement for written informed consent was waived due to the retrospective nature of the study.

2.2. Study design

Beijing, the capital of China, is located in northern China. If a patient is diagnosed with TB in Beijing, they are transferred to Beijing Chest Hospital, which is a TB-designated hospital. This retrospective study was conducted at Beijing Chest Hospital (Beijing, China). All patients with COVID-19 between 1 December, 2022 and 18 January, 2023 were screened. Patients diagnosed with active TB were identified, regardless of the location of the disease (pulmonary or extra-pulmonary). For healthy controls, the inclusion criteria were a negative result for the interferon-γ release assay and normal X-ray findings.

2.3. Data collection

Patients' information was collected by two well-trained medical practitioners using a data collection table including the following items: (1) demographic data, (2) underlying conditions, (3) complications, (4) signs and symptoms, (5) vital signs (blood pressure, oxygen saturation), (6) laboratory investigations (white blood cell count, hemoglobin, platelet count, lymphocyte count, albumin, lactate dehydrogenase, procalcitonin, C-reactive protein, creatinine, and D-dimer), (7) chest radiological findings, and (8) in-hospital outcomes.

2.4. Participants and definitions

All patients were screened for COVID-19 before admission to the TB treatment unit at Beijing Chest Hos-

pital during the SARS-CoV-2 Omicron subvariant surge (November 2022 to January 2023). COVID-19 was diagnosed by nasopharyngeal or throat swab using reverse transcription polymerase chain reaction for SARS-CoV-2. The severity of COVID-19 was graded according to the guideline from the World Health Organization.[14] Critical COVID-19 was defined according to the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy. Severe COVID-19 was defined by any of (1) oxygen saturation < 90% on room air; (2) in adults, signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute); or (3) in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia. Non-severe COVID-19 was defined as the absence of the criteria for severe or critical COVID-19.

TB was diagnosed based on clinical symptoms, radiological findings, bacteriological evidence, or histopathological examination results. The diagnosis of TB was then confirmed using acid fast bacilli smear microscopy, *Mycobacterium* culture, or Xpert MTB/RIF or MeltPro TB assays of respiratory specimens. Drug susceptibility testing was performed using phenotypic and/or genotypic methods.[15]

New cases were defined as patients with TB who had never been treated with anti-TB drugs or those who had received anti-TB treatment for < 1 month. Previously treated cases were defined as patients who had been treated for TB for ≥ 1 month. Extensive (or advanced) pulmonary TB was defined based on the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. Non-severe pulmonary TB was defined as intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion; or paucibacillary non-cavitary disease confined to one lobe of the lung and without a miliary pattern.[16]

2.5. Data analysis

Normally distributed continuous variables are expressed as the mean ± standard deviation, while non-normally distributed continuous variables are expressed as the median (interquartile range). Comparisons were made using the Mann–Whitney *U* test.[17] Categorical variables are summarized as frequencies and proportions. Frequencies were compared using the chi-square test or Fisher's exact test. The effect of prognostic factors was evaluated by univariable and multivariable logistic regression models, with 5–10 events per variable used in the multivariable logistic regression analysis. Missing data were assumed to be missing at random, and missing data were not imputed. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS, version 25.0, and GraphPad Prism, version 9.4.1.

3. Results

3.1. Demographic characteristics of patients with COVID-19-TB

From 1 December 2022 to 18 January 2023, 2 362 patients had laboratory-confirmed COVID-19 infection at Beijing Chest Hospital. Among these, 102 (4.32%) were diagnosed with active TB (Fig. S1). Three patients with COVID-19-TB (2.94%) were aged < 18 years, 57 (55.88%) were aged 18–60 years, and 42 (41.18%) were aged > 60 years (Table 1, Fig. 1). The median age of the patients was 54.5 (37–70) years (Table 1). Seventy-nine (77.45%) of the patients were male and 23 (22.55%) were female (Table 1). More than half of the patients had underlying diseases (64 [62.75%]), including diabetes mellitus (28 [27.45%]), hypertension (22 [19.61%]), cardiovascular disease (16 [15.69%]), anemia (13 [12.75%]), and cerebrovascular disease (7 [6.86%]), amongst others. None of the 102 patients with COVID-19-TB were infected with human immunodeficiency virus.

3.2. Clinical features and complications of patients with COVID-19-TB

The most common symptoms at the onset of illness among the patients with COVID-19-TB were cough (70 [68.63%]), sputum production (55 [53.92%]), and fever (53 [51.96%]). Less common symptoms included hemoptysis (10 [9.8%]), headache (4 [3.92%]), and abdominal pain (1 [0.98%]). Diarrhea was not observed in patients with COVID-19-TB. Six patients (5.88%) presented with cerebral infarction. Around one third of the patients (33 [32.35%]) developed dyspnea. ARDS (12 [11.76%]), sepsis (10 [9.8%]), and respiratory failure (8 [7.84%]) were the most common complications of patients with COVID-19-TB (Table 2). On admission, 90 patients (88.24%) presented with mild-to-moderate symptoms, while five patients (4.9%) had severe symptoms. Seven patients (6.86%) required ICU admission (Table 2). The median time from symptom onset to dyspnea was 5 (1–30) days, to ARDS was 6.5 (3–30) days, to ICU admission was 10 (3–33) days, and to death was 14.5 (10–33) days (Fig. S2).

Forty-nine of the 102 patients with COVID-19-TB (48.04%) required oxygen support. Of these, 45 required a nasal cannula/oxygen mask and four underwent in-

Table 1
Demographic and baseline characteristics of the 102 patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023.

	All patients (n = 102)	ICU care (n = 16)	Non-ICU care (n = 86)	p
Characteristics				
Age, year	54.5 (36.5, 70)	64 (48.25, 78.75)	50.5(34.75, 67.25)	0.047
Sex				
Male	79 (77.45)	11 (68.75)	68 (79.07)	0.349
Female	23 (22.55)	5 (31.25)	18 (20.93)	
Comorbidity				
Diabetes	28 (27.45)	5 (31.25)	23 (26.74)	0.763
Hypertension	20 (19.61)	3 (18.75)	17 (19.77)	1.000
Anemia	13 (12.75)	5 (31.25)	8 (9.30)	0.030
Cardiovascular disease	16 (15.69)	4 (25.00)	12 (13.95)	0.272
Cerebrovascular disease	7 (6.86)	3 (18.75)	4 (4.65)	0.075
COPD	1 (0.98)	1 (6.25)	0 (0.00)	0.157
Malignancy	11 (10.78)	2 (12.50)	9 (10.47)	0.682
Chronic liver disease	12 (11.76)	5 (31.25)	7 (8.14)	0.020
Nervous system diseases	3 (2.94)	1 (6.25)	2 (2.33)	0.404
Chronic renal disease	9 (8.82)	4 (25.00)	5 (5.81)	0.032
Autoimmune diseases	5 (4.90)	1 (6.25)	4 (4.65)	0.582
Pulmonary fungal infections	4 (3.92)	3 (18.75)	1 (1.16)	0.012
Signs and symptoms				
Fever	53 (51.96)	12 (75.00)	41 (47.67)	0.045
Cough	70 (68.63)	9 (56.25)	61 (70.93)	0.245
Sputum production	55 (53.92)	7 (43.75)	48 (55.81)	0.374
Headache	4 (3.92)	1 (6.25)	3 (3.49)	0.500
Hemoptysis	10 (9.80)	1 (6.25)	9 (10.47)	1.000
Dyspnea	33 (32.35)	11 (68.75)	22 (25.58)	0.001
Abdominal pain	1 (0.98)	0 (0.00)	1 (1.16)	1.000
Complications				
ARDS	12 (11.76)	9 (56.25)	3 (3.49)	<0.001
Respiratory failure	8 (7.84)	5 (31.25)	3 (3.49)	0.002
Sepsis	10 (9.80)	8 (50.00)	2 (2.33)	<0.001
Ventilation and oxygen therapy				
No ventilation	53 (51.96)	1 (6.25)	52 (60.47)	<0.001
Nasal cannula/ Oxygen mask	45 (44.12)	12 (75.00)	33 (38.37)	
Respirator	4 (3.92)	3 (18.75)	1 (1.16)	
Severity of COVID-19				
Mild	64 (62.75)	6 (37.50)	58 (67.44)	<0.001
Moderate	26 (25.49)	2 (12.50)	24 (27.91)	
Severe	5 (4.90)	1 (6.25)	4 (4.65)	
Critical	7 (6.86)	7 (43.75)	0 (0.00)	
Severity of TB				
Non-severe	73 (71.57)	9 (56.25)	64 (74.42)	0.225
Extensive/Advanced	29 (28.43)	7 (43.75)	22 (25.58)	
Number of comorbidity				
1	21 (20.59)	2 (12.50)	19 (22.09)	0.001
2	24 (23.53)	2 (12.50)	22 (25.58)	
≥ 3	19 (18.63)	10 (62.50)	9 (10.47)	
Outcome (death/ hospital discharge)	10 (9.80)/92 (90.20)	7 (43.75)/9 (56.25)	3 (3.49)/83 (96.51)	<0.001

Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; TB, tuberculosis.

Table 2
Descriptive analysis of TB in patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023.

	Tuberculosis	All patients (n = 102)	ICU care (n = 16)	Non-ICU care (n = 86)	p
History of previous TB treatment	New case	56/102 (54.90)	7/16 (43.75)	49/86 (56.98)	0.329
	Previously treated	46/102 (45.10)	9/16 (56.25)	37/86 (43.02)	
Anatomical site of the disease	PTB	92/102 (90.20)	15/16 (93.75)	77/86 (89.53)	–
	EPTB	10/102 (9.80)	1/16 (6.25)	9/86 (10.47)	
TB laboratory confirmation		95/102 (93.14)	14/16 (87.5)	81/86 (94.19)	0.302
Microbiology	Sputum smear	38/96 (39.58)	3/14 (21.43)	35/82 (42.68)	0.133
	Liquid culture	49/64 (76.56)	4/7 (57.14)	45/57 (78.95)	0.340
	Gene Xpert	88/98 (89.80)	13/15 (86.67)	75/83 (90.36)	0.648
	MeltPro TB	30/79 (37.97)	4/11 (36.36)	26/68 (38.24)	1.000
Drug resistant pattern at TB diagnosis	Pan-susceptible TB	41/76 (53.95)	6/11 (54.55)	35/65 (53.85)	0.966
	Mono-drug resistant TB	16/76 (21.05)	4/11 (36.36)	12/65 (18.46)	0.229
	Multi-drug resistant TB	19/76 (25.00)	1/11 (9.09)	18/65 (27.69)	0.273

Abbreviations: TB, tuberculosis; ICU, intensive care unit; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.

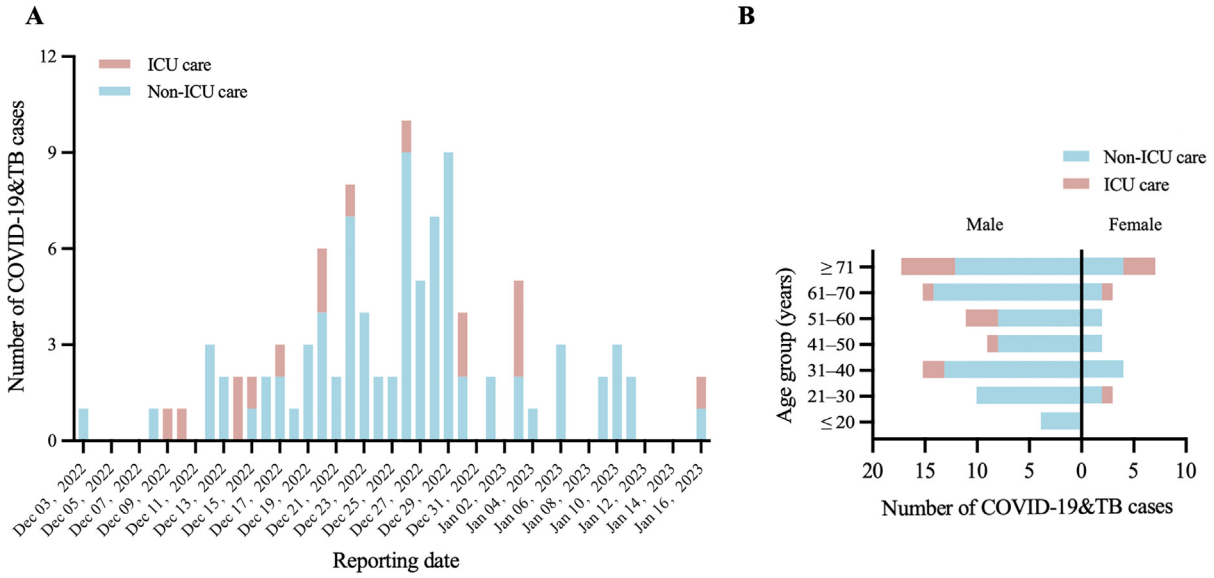

Fig. 1. Date of illness onset, and age and sex distribution, of patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023. (A) Daily cases of COVID-19 and TB co-infection at Beijing Chest Hospital from 1 December 2022 to 18 January 2023. (B) Number of hospital admissions by age and sex group.

vasive mechanical ventilation (Table 1). Of the 102 patients with COVID-19-TB, 95.10% reported being vaccinated against COVID-19. Owing to delayed or limited access to antiviral drugs, Paxlovid was used in 19 patients (18.63%), among whom five died (26.32%). Additionally, 38 patients (37.25%) were given systemic corticosteroids, of whom 10 died (26.32%) during hospitalization.

3.3. TB-associated characteristics of patients with COVID-19-TB

Of the 102 patients with COVID-19-TB, 56 (54.90%) were new TB cases and 46 (45.10%) were previously treated TB cases (Table 2). Of the 56 new TB cases, 47 had both TB and COVID-19 diagnosed within the same week (Fig. 1), while nine were confirmed to have TB 7–30 days before their COVID-19 diagnosis. Ninety-two patients (90.20%) had pulmonary TB, while 10 (9.80%) had extra-pulmonary TB. The majority of the patients were bacteriologically confirmed (95/102 [93.14%]) and had pan-susceptible TB (41/76 [53.95%]) (Table 2). Seventy-three patients (71.57%) presented with a minimal or moderate radiographic extent, while 29 patients (28.43%) exhibited an advanced radiographic extent of TB (Table 1).

3.4. Laboratory and radiological characteristics of patients with COVID-19-TB

Of the 102 patients with COVID-19-TB, 16 (15.69%) showed leucopenia on admission (white blood cell count $< 3.5 \times 10^9$/L) and 55 (53.92%) showed lymphopenia (lymphocyte count $< 1.1 \times 10^9$/L). Patients in the ICU were characterized by increased white blood cell (8.83×10^9/L vs. 5.51×10^9/L, $p = 0.002$) and neutrophil (7.33×10^9/L vs. 3.96×10^9/L, $p < 0.001$) counts, increased neutrophil-to-lymphocyte ratio (13.22 vs. 3.83, $p = 0.001$), and a lower lymphocyte count (0.93×10^9/L vs. 1.13×10^9/L, $p = 0.019$) than non-ICU patients. Furthermore, the serum concentrations of lactate dehydrogenase (223 U/L vs. 174.5 U/L, $p = 0.001$), C-reactive protein (70.34 mg/L vs. 25.55 mg/L, $p = 0.001$), and D-dimer (1.62 mg/L vs. 0.93 mg/L, $p = 0.016$) were significantly higher in ICU patients than in non-ICU patients on admission (Table 3). Both ICU patients and non-ICU patients had normal serum procalcitonin.

The plasma concentrations of interferon-γ, interleukin-5, interleukin-17A, interleukin-21, interleukin-13, interleukin-1β, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, interleukin-22, interleukin-27, interleukin-4, interleukin-18, interleukin-9, interferon-α, interleukin-15, interleukin-1α, interleukin-8, RANTES, interleukin-1RA, interleukin-7, macrophage inflammatory protein (MIP)−1α, eotaxin, growth-regulated gene α, MIP-1β, and stromal cell-derived factor1α were similar between ICU patients and non-ICU patients (Fig. S3). In contrast, the plasma concentrations of interleukin-6, interleukin-12p70, interleukin-2, interleukin-10, interferon-γ-inducible protein 10 kD, and monocyte chemoattractant protein (MCP)−1 were significantly higher in ICU patients than in non-ICU patients (Fig. 2).

X-ray or plain chest radiographs were obtained for all recruited patients. The representative chest CT findings of ICU patients with COVID-19-TB more frequently showed bilateral multiple lobular and subsegmental areas of consolidation with more peripheral nodules than those of non-ICU patients (Fig. 3). Among the 102 patients

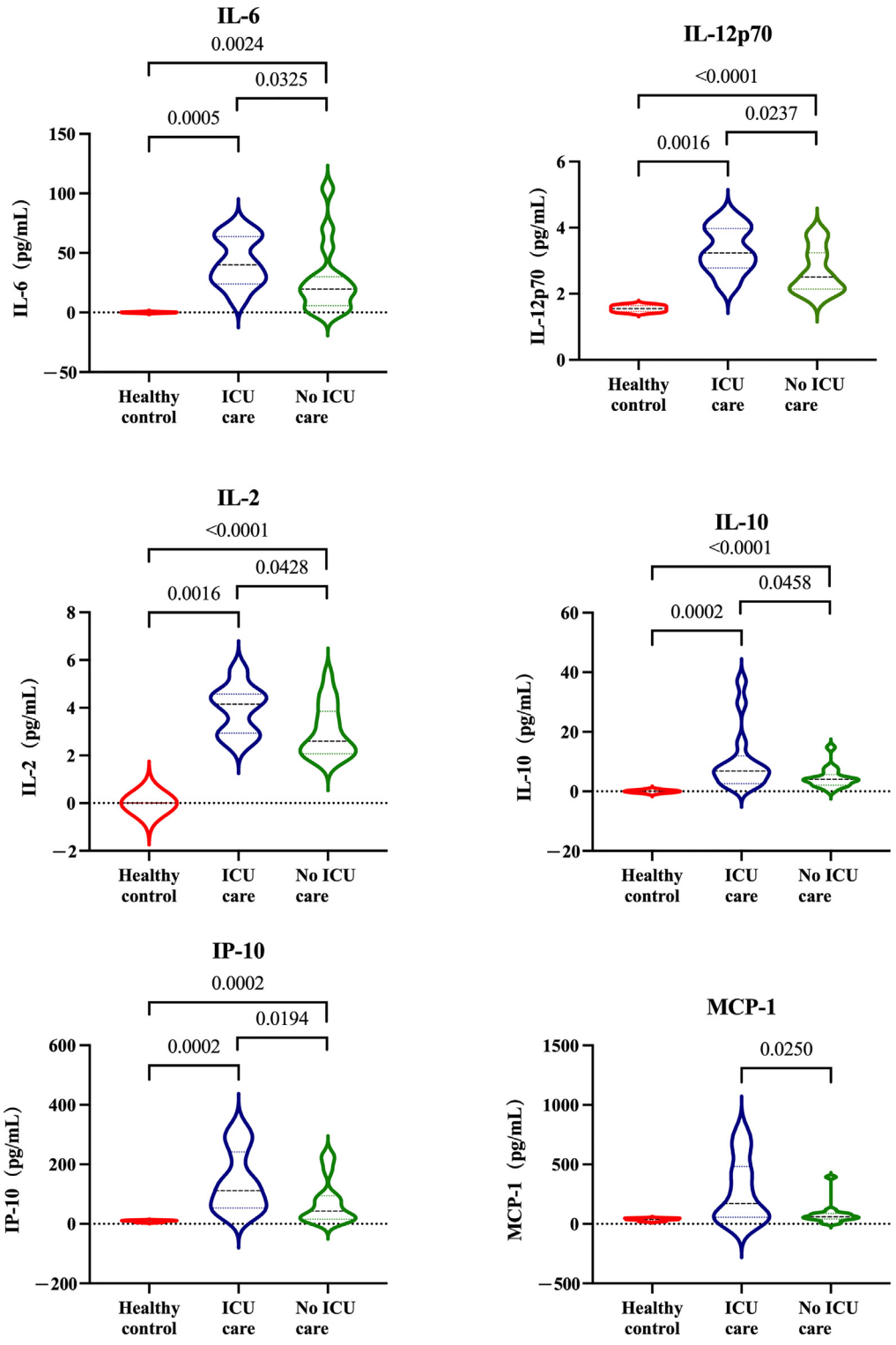

Fig. 2. Plasma concentrations of cytokines and chemokines among healthy controls, ICU patients, and non-ICU patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023. Interleukin-6, interleukin-12p70, interleukin-2, IP-10, and MCP-1 are proinflammatory cytokines, while interleukin-10 is an anti-inflammatory cytokine.
Abbreviation: IL, interleukin.

Table 3
Laboratory findings of patients with COVID-19-TB on admission to hospital in Beijing, China, from 1 December 2022 to 18 January 2023.

	All patients (n = 102)	ICU care (n = 16)	Non-ICU care (n = 86)	p
White blood cell count, × 10^9/L	6.26 (4.22, 8.92)	8.83 (7.59, 22.84)	5.51 (4.04, 8.18)	0.002
< 3.5	16 (15.69)	0 (0.00)	16 (18.60)	0.048
3.5–9.5	66 (64.71)	10 (62.50)	56 (65.12)	
> 9.5	20 (19.61)	6 (37.50)	14 (16.28)	
Neutrophil count, × 10^9/L	4.37 (2.51, 7.18)	7.33 (5.88, 18.04)	3.96 (2.33, 6.58)	<0.001
< 1.8	12 (11.76)	0 (0.00)	12 (13.95)	0.002
1.8–6.3	57 (55.88)	5 (31.25)	52 (60.47)	
> 6.3	33 (32.35)	11 (68.75)	22 (25.58)	
Monocyte, × 10^9/L	0.47 (0.34, 0.66)	0.46 (0.25, 0.66)	0.48 (0.35, 0.67)	0.716
Lymphocyte count, × 10^9/L	1.04 (0.71, 1.34)	0.93 (0.47, 1.00)	1.13 (0.74, 1.36)	0.019
< 1.1	55 (53.92)	13 (81.25)	42 (48.84)	0.013
1.1–3.2	45 (44.12)	2 (13.00)	43 (50.00)	
> 3.2	2 (1.96)	1 (6.25)	1 (1.16)	
Neutrophil lymphocyte ratio	4.05 (2.41, 8.24)	13.22 (6.10, 37.85)	3.83 (2.27, 7.11)	0.001
Hemoglobin, g/L	113 (99.75, 136)	104.5 (89, 125.25)	119 (100, 136)	0.092
Platelet count, × 10^9/L	231.5 (169, 306.75)	186.5 (143, 245.5)	238 (169.75, 311.25)	0.061
< 125	12 (11.76)	3 (18.75)	9 (10.47)	0.396
≥ 125	90 (88.24)	13 (81.25)	77 (89.53)	
Albumin, g/L	35.8 (29.33, 40.53)	29.55 (26.53, 38.83)	36.35 (30.3, 40.9)	0.009
< 35	48 (47.06)	12 (75.00)	36 (41.86)	0.015
≥ 35	54 (52.94)	4 (25.00)	50 (58.14)	
Total bilirubin, mmol/L	10.3 (8.58, 12.85)	11.5 (8.95, 15.58)	10 (8.5, 12.43)	0.147
Potassium, mmol/L	4.1 (3.78, 4.45)	4.18 (3.92, 4.63)	4.08 (3.71, 4.43)	0.170
Sodium, mmol/L	137.3 (132.85, 140.2)	134.05 (127.95, 138.05)	137.7 (134.50, 140.30)	0.036
Chlorine, mmol/L	103 (98.35, 105.7)	99.30 (95.18, 105.03)	103.4 (99.70, 105.75)	0.098
Urea nitrogen, mmol/L	4.76 (3.67, 6.95)	6.97 (5.49, 11.13)	4.48 (3.46, 6.26)	<0.001
Choline esterase, U/L	5748 (3979.5, 7013.25)	3440 (1613.25, 5205.25)	5921.5 (4361.25, 7383)	0.001
Creatinine, μmol/L	65.8 (55, 80.53)	63.55 (47.05, 80.35)	66.75 (55.58, 80.98)	0.587
D-dimer, mg/L	1.00 (0.42, 2.47)	1.62 (0.93, 6.55)	0.93 (0.39, 2.08)	0.016
≤ 0.55	34 (36.96)	2 (13.33)	32 (41.56)	0.038
> 0.55	58 (63.04)	13 (86.67)	45 (58.44)	
Lactate dehydrogenase, U/L	176.5 (147, 217.75)	223 (168.25, 386.25)	174.5 (145, 209.25)	0.008
< 109	1 (0.98)	0 (0.00)	1 (1.16)	0.042
109–245	80 (78.43)	9 (56.25)	71 (82.56)	
> 245	21 (20.59)	7 (43.75)	14 (16.28)	
Procalcitonin, ng/mL	0.07 (0.04, 0.13)	0.05 (0.05, 0.23)	0.07 (0.04, 0.11)	0.355
Hypersensitive C-reactive protein, mg/L	32.28 (6.63, 67.67)	70.34 (45.88, 121.62)	25.55 (4.73, 60.34)	0.001
N-terminal pro-B-type natriuretic peptide, ng/L	817 (307, 1872)	1666 (351.25, 3252.15)	801 (298, 1443.6)	0.201
CT scan findings				
Typical ground-glass opacities, bilateral	10/99 (10.10)	3/16 (18.75)	7/83 (8.43)	0.014
Typical ground-glass opacities, unilateral	13/99 (13.13)	0/16 (0.00)	13/83 (15.66)	
Atypical ground-glass opacities, bilateral	12/99 (12.12)	6/16 (37.5)	6/83 (7.23)	
Atypical ground-glass opacities, unilateral	1/99 (1.01)	1/16 (6.25)	0/83 (0.00)	

Abbreviations: CT, computed tomography; ICU, intensive care unit.

with COVID-19-TB, 23 (22.55%) had typical ground-glass opacities, while 13 (12.75%) had atypical ground-glass opacities. Overall, 22 of these 36 patients (61.11%) had bilateral ground-glass opacities (Table 3).

3.5. In-hospital outcomes of patients with COVID-19-TB

During hospitalization, 10 of 102 patients (9.90%) died and 16 (15.79%) were admitted to the ICU. Five patients died due to respiratory failure, and another five died due to multiple organ dysfunction syndrome or sepsis. All of the patients that died were aged > 60 years and had one or more comorbidities. Twelve of 16 (75.00%) ICU patients were aged > 50 years, and 13 (81.25%) had underlying diseases. Patients with more comorbidities in the older age groups were more likely to experience ICU admission and death (Fig. 4A). Four of 7 patients (57.14%) in the critical COVID-19 group died, while two of five patients (40%) in the severe COVID-19 group died. By comparison, only four of 90 patients (4.44%) with mild/moderate disease died (Fig. 4B). The severity of TB, drug resistance, or whether they were new TB cases did not appear to be major determinants of the outcome (Fig. S4A–C).

3.6. Predictors of the outcomes of patients with COVID-19-TB

The relationships of demographic and clinical variables with ICU admission were assessed by logistic regression analysis. In the univariate analysis, the statistically significant risk factors for ICU admission were older age, one or more comorbidities, pulmonary fungal infection, chronic liver disease, chronic renal disease, dyspnea, raised lactate dehydrogenase, raised D-dimer, and anemia (Table 4). In the multivariate analysis, the significant independent variables included respiratory failure, pulmonary fungal infection, and ventilation and oxygen therapy (Table 4).

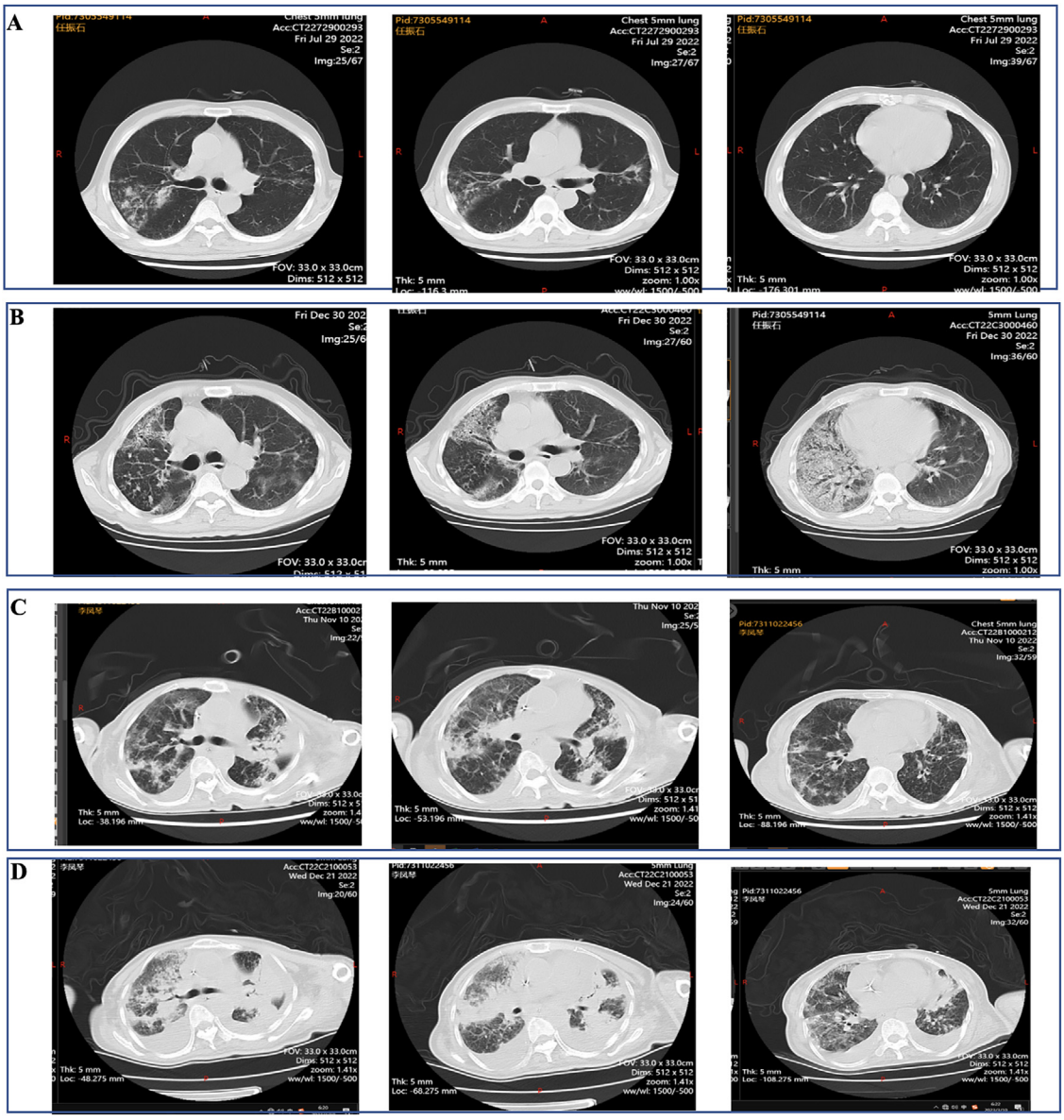

Fig. 3. (A) Chest CT images of two patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023. Transverse chest CT images from a 68-year-old male with TB showing the tree-in-bud sign and small cavitations before COVID-19 infection. (B) On day 14 after COVID-19 infection, the CT images show bilateral multiple lobular and subsegmental areas of consolidation. (C) Transverse chest CT images from a 63-year-old female with TB showing extensive segmental consolidation and centrilobular nodules before COVID-19 infection. (D) On day 14 after COVID-19 infection, the CT images show bilateral multiple lobular and subsegmental areas of consolidation and pleural effusion.

4. Discussion

COVID-19 is a major global public health concern, and accurate diagnosis is crucial because it leads to appropriate and timely infection control and prevention. Co-infection with other pathogenic species in patients with COVID-19 is also of crucial concern as it can complicate the diagnosis, treatment, and prognosis of patients with COVID-19. Therefore, concomitant infections must be carefully identified.[18] Investigating the course of COVID-19 in patients with active TB is crucial for the management of these diseases. Here, we report the results of a cohort of 102 patients with laboratory-confirmed COVID-19 and TB co-infection. Generally, the clinical presentation of co-infected patients resembled that of patients with either COVID-19 or TB infection; however, co-infected patients had an increased neutrophil-to-lymphocyte ratio and higher serum concentrations of lactate dehydrogenase, C-reactive protein, D-dimer, and various proinflammatory cytokines. Patients with more comorbidities and advanced age were more likely to experience ICU admission and death. Active TB appears to increase the risk of COVID-19 mortality. In this cohort, the mortality rate of co-infected patients (9.80%) was higher than that of patients with only COVID-19 infection (0.0339%).[19]

Interestingly, 56 new TB cases (54.90%) were diagnosed in this cohort. During the study period, most

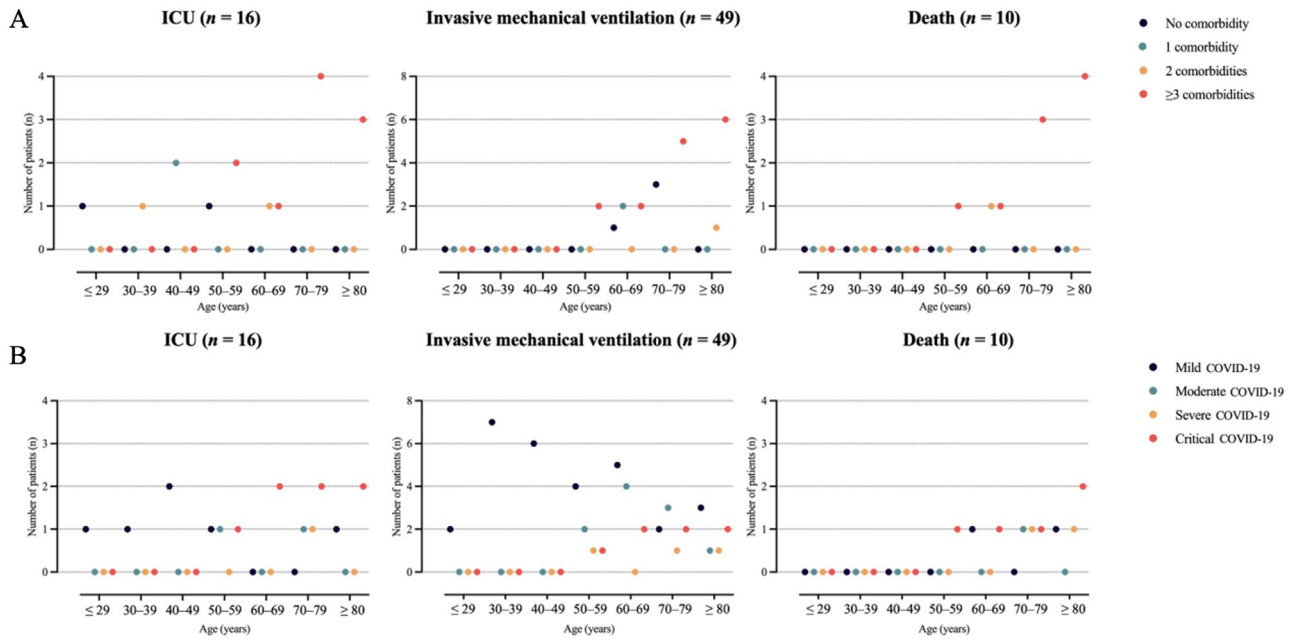

Fig. 4. ICU admission, invasive mechanical ventilation, and death of hospitalized patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023. (A) Number of patients according to age and presence of comorbidities. (B) Number of patients according to age and COVID-19 severity.

Table 4
Logistic regression analysis to assess the relationships of demographic and clinical variables with ICU admission among patients with COVID-19-TB in Beijing, China, from 1 December 2022 to 18 January 2023.

Parameter	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age, year (one-year increase)	1.029 (1.001, 1.059)	0.046		
Male (yes vs. no)	0.582 (0.179, 1.891)	0.368		
Dyspnea (yes vs. no)	6.400 (2.001, 20.473)	0.002		
Respiratory failure (yes vs. no)	12.576 (2.634, 60.051)	0.002	9.805 (1.745, 55.093)	0.010
Anemia (yes vs. no)	4.432 (1.228, 15.993)	0.023		
lymphopenia (yes vs. no)	7.000 (1.500, 32.675)	0.013		
Neutrophil raise (yes vs. no)	3.365 (1.074, 10.543)	0.037		
LDH raise (yes vs. no)	3.681 (1.185, 11.442)	0.024		
Chronic liver disease (yes vs. no)	5.130 (1.385, 19.004)	0.014		
Cerebrovascular disease (yes vs. no)	4.731 (0.948, 23.602)	0.058		
Chronic renal disease (yes vs. no)	5.400 (1.269, 22.971)	0.022		
Pulmonary fungal infections (yes vs. no)	19.615 (1.895, 203.068)	0.013	12.963 (1.173, 143.292)	0.037
Comorbidity (yes vs. no)	5.040 (1.078, 23.563)	0.040		
Previous TB treatment (yes vs. no)	1.703 (0.581, 4.994)	0.332		
Rifampicin resistant (yes vs. no)	0.337 (0.071, 1.604)	0.172		
Ventilation and oxygen therapy (yes vs. no)	22.941 (2.895, 181.783)	0.003	13.783 (1.643, 115.604)	0.016
TB diagnosis (clinical diagnosis versus bacteriological confirmed)	0.267 (0.057, 1.256)	0.095		

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; TB, tuberculosis.

patients attended hospital due to COVID-19. As a TB-designated hospital, we were able to test the admitted patients for TB, which led to many new TB cases being diagnosed in patients with COVID-19, although during the COVID-19 pandemic, there was a substantial drop in TB testing and diagnosis.[20] Our findings support that TB testing in the COVID-19 era should not be neglected as it is important to prevent the spread of both TB and COVID-19.[21,22]

In our cohort, the mortality rate of patients with COVID-19-TB was 9.80% (10 of 102 patients), which is similar to previous observations. In the first pilot study of the Global Tuberculosis Network (2020), the mortality rate was 12.24% (6/49) among patients infected with both diseases[11]. Moreover, in a global study by the TB/COVID-19 Global Study Group (2021), 11.08% (85/767) of patients with COVID-19-TB died.[12] The long-term outcomes of another global cohort of patients with COVID-19-TB showed that death was the outcome in 10.8% (85/788) of patients.[23] A study in Russia reported a mortality rate of 9.33% (7/75) from October 2020 to August 2021 in patients with COVID-19-TB.[9] Furthermore, a review conducted by Sereda et al.[24] in 2022 reported that 13.0% of patients with COVID-19-TB

died. In contrast, the overall mortality was 0.70%–5.00% from sole COVID-19 infection during the Omicron outbreak,[4,25,26] while the global prevalence of COVID-19-related death was around 7.00%.[27] In the present study, the mortality rate of patients with COVID-19-TB (9.80%) was also higher than the mortality rate of patients with COVID-19 infection only (0.0339%) over the same period.[19] These results imply that when patients with active TB acquire COVID-19, there is a greater risk of COVID-19 mortality. Several meta-analyses have also suggested that patients with TB have an increased mortality risk when co-infected with COVID-19,[27–30] although other studies have observed no association between TB and COVID-19 disease severity or mortality.[31–34] Our study suggests that active TB should be prioritized as part of the effort to prevent COVID-19, and older patients with comorbidities should be considered for closer monitoring upon a positive COVID-19 diagnosis.

In the present study, COVID-19-TB was associated with unfavorable outcomes, which may have been related to the immune response.[35–37] Early studies in patients with COVID-19 or TB have indicated that elevated concentrations of proinflammatory cytokines in the serum (e.g., interleukin-6, interleukin-1β, IP-10, and MCP-1) are related to extensive lung damage and pulmonary.[38] We found that patients with COVID-19-TB also had high concentrations of various proinflammatory cytokines (e.g., interferon-γ, interleukin-1β, IP-10, and MCP-1), probably resulting in activated T helper 1 cell responses. In addition, co-infected patients also demonstrated elevated secretion of T helper 2 cytokines, such as interleukin-4 and interleukin-10, which suppress inflammation. Hence, we recommend further research to characterize the proinflammatory and anti-inflammatory cytokines, as well as the T helper 1 and 2 responses, in COVID-19-TB and to clarify their role in its pathogenesis. Corticosteroids have been frequently used for the treatment of patients with severe disease owing to the possible benefit of reducing inflammation-associated lung injury. However, current evidence indicates that corticosteroids are not beneficial in patients with COVID-19.[39] In contrast, corticosteroids have a beneficial effect in patients with TB by inhibiting *M. tuberculosis*-induced cell death.[40] In our cohort of 102 laboratory-confirmed patients with COVID-19-TB, corticosteroids were not administered to non-ICU patients, and low-to-moderate doses of corticosteroids were given to only some ICU patients. In addition to corticosteroids, treatments blocking cytokines and their receptors have been approved for TB and COVID-19.[41] Previous evidence has suggested that treatment with tocilizumab is beneficial for severe COVID-19 and TB.[42–44] However, further studies are needed to evaluate whether treatments blocking proinflammatory cytokines (e.g., interleukin-6) and their receptors are beneficial in patients with both conditions.

In addition to the increased concentrations of proinflammatory cytokines in the serum, an elevated neutrophil-to-lymphocyte ratio also reflects enhanced inflammation, with a ratio of > 3.63 correlating with higher mortality in patients with COVID-19.[45] In our study, the median neutrophil-to-lymphocyte ratio was 4.05 among the 102 patients with COVID-19-TB. Furthermore, the median concentration of the inflammatory marker C-reactive protein (32.28 mg/L) was elevated. Our results further confirm that patients with COVID-19-TB are in a hyper-inflammatory state. Hence, these patients may require close monitoring.

We also identified some demographic and clinical features that were associated with ICU admission, including respiratory failure, pulmonary fungal infection, and ventilation and oxygen therapy, some of which have been described previously.[23,46] Therefore, early recognition of these features and appropriate treatment are important for preventing ICU admission among patients with COVID-19-TB.

Although data on patients with COVID-19-TB are still limited, some studies have reported the clinical characteristics of this population through case reports and case series; however, previous studies have only included small numbers of co-infected patients.[9,13,47,48] The small number of cases and limited deaths weaken the robustness of the results. The present study utilized a large sample size, adding to the body of literature on this topic.

Nevertheless, this study also has some limitations that should be noted. First, changes in the characteristics of the infected population are possible. For instance, during the initial phase of policy relaxation, high-risk groups, such as the elderly or those with underlying conditions, might have been infected first. Their clinical manifestations and outcomes might have differed from those of the general population infected later. Second, in the early stages of policy relaxation, the healthcare system would likely have been under huge pressure, with limited resources, which could have influenced the patient management and treatment outcomes. Therefore, the data from the initial phase may reflect the outcomes under resource-constrained conditions rather than reflecting the general outcomes. Third, the short study period could not capture the long-term trends of COVID-19 and TB co-infection, especially post-peak follow-up data. Fourth, the data were sourced exclusively from Beijing Chest Hospital, and these single-center results may not be generalizable to other hospitals. In addition, regional differences in healthcare systems may limit the generalizability of the results. Fifth, this study lacked a control group (e.g., those with COVID-19 or TB only) for comparison with the COVID-19-TB group, which limits the external validity of the study's conclusions. We recommend for future research to include such comparisons to enhance the external validity. Finally, only in-hospital outcomes were reported; long-

term follow-up data were lacking. Therefore, future studies should consider long-term outcomes to more comprehensively evaluate the impact of COVID-19-TB.

5. Conclusion

This study demonstrated that active TB augmented the risk of COVID-19 mortality. Several demographic and clinical characteristics were associated with adverse outcomes and indicated the importance of early recognition and treatment. The results highlight the need for continuous testing of TB in the COVID-19 era to prevent the spread of both TB and COVID-19.

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CRediT authorship contribution statement

Xinting Yang: Writing – review & editing, Supervision, Methodology, Conceptualization. **Chaohong Wang:** Visualization, Software, Formal analysis, Data curation. **Yu Xue:** Formal analysis, Data curation. **Yun Zhang:** Formal analysis, Data curation. **Maike Zheng:** Formal analysis, Data curation. **Qing Sun:** Formal analysis, Data curation. **Sibo Long:** Formal analysis, Data curation. **Da Wang:** Formal analysis, Data curation. **Jun Yan:** Formal analysis, Data curation. **Xinlei Liao:** Formal analysis, Data curation. **Tiantian Zhang:** Formal analysis, Data curation. **Lei Cao:** Formal analysis, Data curation. **Yan Chen:** Formal analysis, Data curation. **Wenfu Ju:** Formal analysis, Data curation. **Jing Zhang:** Software, Resources. **Mengqiu Gao:** Software, Resources. **Yan Zhao:** Software, Resources. **Laurence Don Wai Luu:** Writing – review & editing, Methodology. **Junhua Pan:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Yi Wang:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Guirong Wang:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

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None.

Declaration of competing interest

The authors declare no conflict of interest.

Data available statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical statement

This study was approved by the ethics committee of Beijing Chest Hospital (ethics approval No. BJXK-KY-2023-01).

Informed consent

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.imj.2025.100169.

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