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Coexistent Pulmonary Tuberculosis and Lung Cancer: An Analysis of Incidence Trends, Financial Burdens and Influencing Factors

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Keywords: clinicopathological features | incidence | lung cancer | pulmonary tuberculosis | risk factors

ABSTRACT

Background: Tuberculosis (TB) and lung cancer (LC) are both major global health threats. However, coexistent pulmonary TB and LC (TBLC) is a unique condition for which incidence trends and risk factors have not been fully defined.

Methods: We retrospectively reviewed the medical records of patients with TBLC and LC alone between 2010 and 2022 at Beijing Chest Hospital, the standard authority for the diagnosis and treatment of TB and LC in China. The cumulative incidence rate (CIR) of TBLC was calculated as the number of new TBLC cases/number of LC cases at risk per 100,000 annually. The comparative incidence rate ratio (IRR) was estimated to be the TB incidence in LC patients/TB incidence in the general population. Logistic regression was used to explore risk factors for TBLC.

Results: The CIR of TBLC has rapidly increased each year since 2014 and reached 7027 per 100,000 LC patients in 2022. Patients with LC had a higher risk of developing active TB than the general population (IRR = 25.21, 95% confidence interval [CI]: 21.54–29.89). Medical expenditure per patient was 100.60 thousand yuan for those with TBLC and 105.60 thousand yuan for patients with LC ($p = 0.687$). Patients with TBLC were older (63.61 ± 10.46 vs. 61.08 ± 10.77, $p < 0.001$) and had a higher male-to-female ratio (2.82 vs. 1.59, $p = 0.044$) than those with LC alone. A tendency of earlier disease onset was observed in patients with LC rather than TBLC. A majority (44.92%) of TBLC lesions were located in the upper lobes of the lung and had a higher proportion of squamous cell carcinomas than LC alone (32.24% vs. 27.49%, $p = 0.002$). TBLC also presented more aggressively, with more lymph node involvement and distant metastases. Multivariate analysis revealed that older age, the male sex, mediastinal lymph node invasion, lung/bone metastases, anemia,

Abbreviations: ADC, adenocarcinoma; BALF, bronchoalveolar lavage fluid; CI, confidence interval; CIR, cumulative incidence rate; COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; IRR, incidence rate ratio; LC, lung cancer; LNM, lymph node metastases; PF, pulmonary fibrosis; RR, relative ratio; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; TB, tuberculosis.

Fei Qi, Hongjie Yang, and Yi Han contributed equally to this study and shared the first authorship.

hypoalbuminemia, malnutrition, pulmonary fibrosis, and chronic obstructive pulmonary disease were risk factors for active TBLC.

Conclusions: There has been a rise in the incidence of coexistent TBLC and a concomitant increase in its financial burden in China that deserves more awareness and attention.

1 | Introduction

Tuberculosis (TB) and lung cancer (LC) are both major global health threats. According to the World Health Organization global TB report in 2023, a total of 10.6 million people fall ill with TB, and 1.5 million die from TB every year [1–3]. The average annual incidence rate of TB was reported to be 59.17/100,000 on the Chinese mainland [4–6]. Meanwhile, LC is the most common malignancy and the leading cause of cancer death in China [7–9]. Coexistent TB and LC (TBLC) is a unique condition, and its diagnosis requires clinical, radiological, and microbiological evidence [10–13]. Although it accounts for only a small proportion of LC patients, there is a heavy financial burden associated with TBLC in China, given the large LC population base.

Trends in the incidence of TB and LC are in opposition to one another. Globally, TB has presented a downward incidence that has been sustained for many years [3]. In China, the incidence of TB decreased from 107 cases per 100,000 in 2000 to 52 cases per 100,000 in 2022, achieving a mortality reduction of 19% and a 29% reduction in morbidity [14]. In contrast, the incidence and death rates of LC have been continually increasing [8, 9]. Unfortunately, there is limited data on TBLC incidence globally or domestically. Therefore, an evaluation of TBLC prevalence may be helpful for public health control.

Numerous studies have identified an association between TB infection and LC development [13, 15–22]. A recent meta-analysis demonstrated that TB increased the risk of LC (relative risk [RR] = 2.170, 95% confidence interval [CI]: 1.83–2.57) including squamous cell carcinoma (SCC; RR = 3.57, 95% CI: 2.66–4.79), adenocarcinoma (ADC; RR = 2.61, 95% CI: 1.71–3.98), and small cell lung cancer (RR = 2.12, 95% CI: 1.54–2.91) [15]. The clinicopathological features of TBLC have not been fully investigated. In a small-sample study that included 48 patients with active TBLC, the TBLC patients were reported to have a more advanced T stage (T3–4, 70.9% vs. 50.6%, $p = 0.002$), lymph node metastasis (N2–3, 85.2% vs. 55.6%, $p < 0.001$) and distant metastasis (M1, 65.9% vs. 44.5%, $p = 0.007$) compared with patients with LC alone [23]. Patients with coexistent TBLC have also been reported to have lower survival rates than LC patients without TB infection [18, 24, 25]. However, because TB and LC mimic each other in radiology and clinical manifestations, misdiagnosis or diagnostic delay is unavoidable. Thus, identifying risk factors to help with the early and accurate diagnosis of TBLC is of vital clinical significance. Therefore, we conducted this large-sample, retrospective study to investigate the incidence trend of TBLC and explore the clinicopathological characteristics and risk factors for this condition.

2 | Methods

2.1 | The Aim, Design, and Setting of the Study

This was a real-world, single-center, retrospective analysis of patients with TBLC at Beijing Chest Hospital, the standard authority for the diagnosis and treatment of TB and LC in China.

2.2 | Study Population and Data Collection

Patients who were newly diagnosed with LC at Beijing Chest Hospital between 2010 and 2022 were enrolled in the study. Patients were divided into TBLC and LC alone (without TB) groups based on the existence of TB infection at the time of the LC diagnosis. Patients with other tumors suspected of TB, extrapulmonary TB, or non-tuberculosis mycobacteria were excluded from the study. Patient records were retrieved from the hospital's electronic medical records system. Patient data, including age, sex, occupation, marital status, diagnosis year, cancer type, tumor location, tumor stage, tuberculosis diagnosis, pathological type, anti-TB treatment, anticancer treatment, and complications, were collected.

2.3 | Diagnosis of Coexistent TBLC

Owing to the high incidence of TB in China, TB surveillance is routinely conducted during bronchoscopies from bronchoalveolar lavage fluid (BALF) and sputum specimens, and from blood tests and chest computed tomography scans among LC patients. A diagnosis of active TB was confirmed by bacteriologic (smear-positive, acid-fast bacilli from sputum, bronchial washing or BALF, or positive culture for TB), pathologic (TB granuloma detected using biopsy or surgical resection), molecular (TB-PCR and TB-Xpert), radiographic, and/or clinical evidence. Patients with inactive or latent TB infection were confirmed using medical histories, blood testing, or radiologic evidence. Patients with TBLC were defined as cases with newly diagnosed LC combined with latent or active pulmonary TB. Patients with LC alone were defined as cases with no evidence of latent or active TB at the time of LC diagnosis. We rechecked the examinations of each patient to reduce the possibility of false positive and negative cases.

2.4 | Statistical Analysis

The cumulative incidence rate (CIR) of TBLC was calculated as the number of new, coexistent TB and LC cases/number of LC patients at risk per 100,000 annually between 2010 and

2022. We curve-fitted the incidence of TBLC from the entire cohort and different sexes. The comparative incidence rate ratio (IRR) was estimated to be the TB incidence in LC patients/TB incidence in the general population to adjust for the risk of prior tuberculosis exposure. China's annual TB incidence rate in the general population was obtained from the World Health Organization's estimates from 2000 to 2022 [14].

Means and standard deviations were calculated for normally distributed, continuous variables. Medians and interquartile ranges were used for non-normally distributed data. Comparisons of pathological and clinical characteristics between the TBLC and LC groups were performed using the Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Univariate and multivariate logistic regression analyses were used to investigate factors influencing TB infection among LC patients. All statistical analyses were performed using R software and SPSS 24.0. The R package included rms, rmda, and ggplot2 libraries. Statistical significance was set as a two-sided p-value < 0.05.

2.5 | Ethics Approval

This study was approved by the Ethics Committee of Beijing Chest Hospital (ID, JS-2023-10). Written, informed consent was exempt as no interventions were required in this study.

3 | Results

3.1 | An Increasing Trend in the Incidence of TBLC

From 2010 to 2022, there were 23,706 patients newly diagnosed with LC and admitted to Beijing Chest Hospital who were included in the study. There were 1427 cases diagnosed with coexistent TB (TBLC, 6.01%), including 387 cases with active TB (1.63%) and 1040 with latent TB (4.39%). The number of LC and TBLC cases steadily increased, with both diseases exhibiting similar trends from 2010 to 2022 (Figure 1A). The annual percentage change (APC) in the incidence was 8.84% for TBLC and 0.40% for LC ($p = 0.443$). The number of new TBLC cases had a similarly increasing rate in males and females (Figure 1B). However, for patients with LC, female cases showed a more rapidly increasing rate than males (Figure 1C).

We used the CIR of TBLC to assess the incidence of TB infection in LC patients. The CIR trend for all TBLC and active TBLC cases presented a short decrease during 2010–2014 but has rapidly increased since 2014 (Figure 1D,G). The CIR of all TBLC cases reached 7027 per 100,000 in 2022. The CIR of active TBLC was 2641 per 100,000 in 2022. In terms of the CIR of TBLC, male prevalence varied considerably over time (Figure 1E,H). Furthermore, our results found that patients with LC had a higher risk of TB (IRR = 92.30, 95% CI: 43.17–141.17), including active TB (IRR = 25.21, 95% CI: 21.54–29.89), compared with the general population. The IRRs of all TBLC and active TBLC cases also presented continually increasing trends over the study years (Figure 1F,I).

3.2 | Hospitalization and the Financial Burden of TBLC

We analyzed the hospitalization rate and financial cost of TBLC patients. From 2010 to 2022, a total of 90,131 and 5434 hospital admissions were documented for LC and TBLC patients at our institute, respectively, which presented increasing annual trends for the two diseases (Figure 2A). The number of hospital admissions per LC patient increased over time (Figure 2B). However, the average number of admissions per TBLC patient remained stable during the decade under study and was significantly smaller than that of LC patients (2.09 vs. 3.97 times per patient, $p < 0.001$; Figure 2C). Similar reduction trends in admission days per case during an entire treatment course and for each admission were observed in TBLC and LC patients (Figure 2D–F). In 2022, each TBLC patient spent an average of 21.29 total days in the hospital, with an average of 3.80 days per hospital admission—similar to that of LC patients (Figure 2G–I).

We calculated that 96.0 million and 5.9 million yuan were spent treating LC and TBLC patients annually, respectively. The medical expenditure per patient was 100.6 thousand yuan for TBLC and 105.6 thousand yuan for LC ($p = 0.687$, Figure 2G–I). With a reduction in the length of stay for LC and TBLC patients, the medical expenditure per case and per day gradually increased annually, with no significant difference between the two groups of patients (Figure 2J–M).

3.3 | Clinical and Pathological Features of TBLC

Patient baseline characteristics are summarized in Table 1. The male-to-female ratio (MFR) for TBLC and LC was 2.82:1 and 1.59:1, respectively (Figure 3A). Because of the relatively more rapid increase of LC incidence in females than males, the MFR has gradually decreased since 2015 (Figure 3B). However, for TBLC, the change in the MFR was more complicated, partly owing to the higher mobility of the male population (Figure 3B). The mean age of TBLC patients was 63.61 ± 10.46 years, which was higher than that of LC patients (61.08 ± 10.77 years, $p < 0.001$; Figure 3D–E). Rejuvenation of LC rather than TBLC was also observed because the mean age of LC patients has decreased in recent years (Figure 3C).

One-third of TBLC cases were first admitted to departments other than Oncology. Primary complaints were more complicated in TBLC patients than in LC patients, and TBLC patients showed lesions that were predominately located in the upper lobes of the lungs compared with LC patients (44.9% vs. 32.7%, $p < 0.001$), who showed lesions that primarily occurred in lower lung lobes. TBLC lesions were more prevalent in the right upper lobe, followed by the left upper lobe (Figure 4A). SCC was more commonly diagnosed in TBLC than in LC patients (32.2% vs.

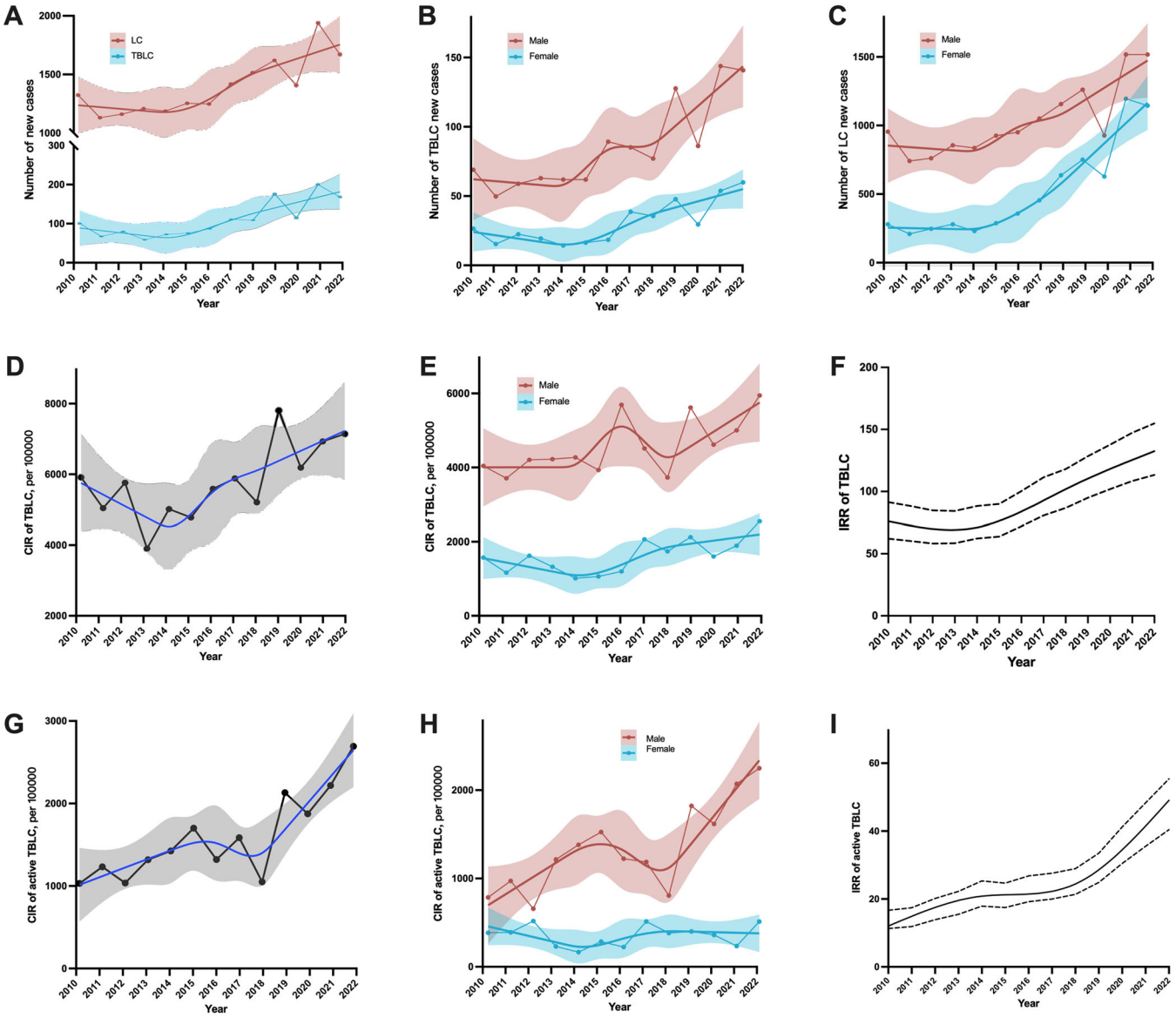

FIGURE 1 | The annual TBLC incident cases and rates from 2010 to 2022 in China. (A) The annual incidence of TBLC and LC cases from 2010 to 2022. (B and C) The annual incidence of TBLC (B) and LC (C) cases according to gender stratification. (D and E), The annual cumulative incidence rate (CIR) of TBLC in total (D) and in different gender groups (E). (F) The annual comparative incidence rate ratio (IRR) of TB in LC patients/general population. (G and H) The annual CIR of active TBLC in total (G) and in different gender groups (H). (I) The annual comparative IRR of active TB in LC patients/general population.

27.5%, $p = 0.002$; Figure 4B). Consistent with LC, ADC was the most common pathological subtype in TBLC patients, and the proportion of ADC has been gradually increasing each year (Figure 4C–D).

Compared with LC patients, TBLC patients presented a more aggressive illness, with higher proportions of the T2–4 disease (70.9% vs. 67.0%, $p < 0.001$), lymph node involvement (N+, 54.8% vs. 46.3%, $p < 0.001$) and distant metastasis (M1, 42.4% vs. 38.9%, $p < 0.001$; Figure 4E). Recently, with the application of LC screening techniques, an increasing number of early-stage and a decreasing number of advanced-stage LC and TBLC cases have been detected (Figure 3F–H). We subsequently explored the metastases features of TBLC (Table 2). Our results found that patients with TBLC were more vulnerable to metastases to the mediastinal lymph node ($p < 0.001$), supraclavicular lymph node ($p < 0.001$), bones ($p < 0.001$), lungs ($p < 0.001$), pleura ($p = 0.014$), pericardium ($p < 0.001$), and the celiac lymph node ($p = 0.007$).

3.4 | Sequence of TB and LC Occurences

The sequence of TB and LC occurrences may be difficult to discern, especially for those with inactive TB. To avoid uncertainty, we analyzed the diagnosis sequences of the two diseases among patients with active TB ($n = 387$). Patients were classified into two groups based on the diagnosis date of each disease: LC before TB ($n = 84$) and LC after TB or simultaneous with LC ($n = 303$). Patient characteristics were

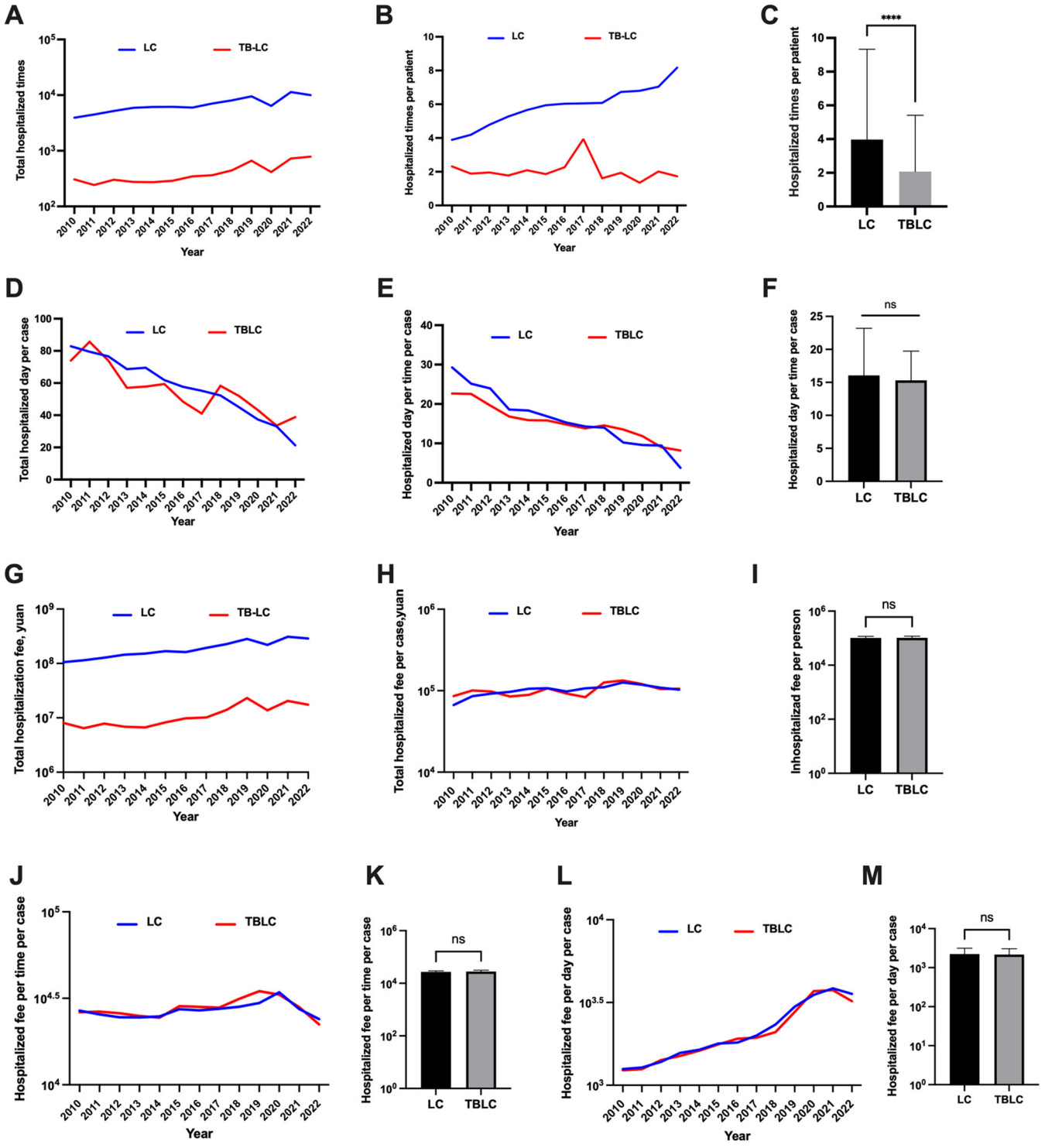

FIGURE 2 | Hospitalization and financial burden of TBLC and LC patients from 2010 to 2022. (A–C) Hospitalization times for patients with TBLC and LC. The annual total hospitalization times (A), mean hospitalization times per case (B), and a comparison between patients with TBLC and LC (C). (D–F) Number of hospitalized days for patients with TBLC and LC. Total hospitalized days per case (D), mean number of hospitalized days per case per admission (E), and a comparison of the number of hospitalized days per case per admission between patients with TBLC and LC. (G–M) Hospitalization cost of patients with TBLC and LC. Total hospitalization fees (G), mean hospitalization fee per case (H), mean hospitalization fee per case per hospitalization (J), a comparison between patients with TBLC and LC (K), daily hospitalization fee per case (L), and a comparison between patients with TBLC and LC (M). ns, not significant; ****$p < 0.0001$.

similar between the two groups (Table S1). However, compared with those with simultaneous TBLC or TB before LC, patients who developed TB after LC received more varied anticancer treatments, including chemotherapy (63.10% vs. 41.25%, $p < 0.001$), radiation (14.29% vs. 6.13%, $p = 0.033$), and targeted therapies (17.86% vs. 7.26%, $p = 0.033$). This may have been due to the therapeutic constraints between anti-TB and anticancer agents.

TABLE 1 | Baseline patient characteristics.

Variables	Total, *n* (%) (*N* = 23,706)	LC, *n* (%) (*N* = 22,279)	TBLC, *n* (%) (*N* = 1427)	*p*
Age, Mean ± SD	61.23 ± 10.77	61.08 ± 10.77	63.61 ± 10.46	< 0.001
Gender				< 0.001
Male	14,738 (62.17)	13,685 (61.43)	1053 (73.79)	
Female	8968 (37.83)	8594 (38.57)	374 (26.21)	
Marital status				0.479
Unmarried	342 (1.44)	315 (1.41)	27 (1.89)	
Married	21,540 (90.86)	20,244 (90.87)	1296 (90.82)	
Widowed	1391 (5.87)	1311 (5.88)	80 (5.61)	
NA	433 (1.83)	409 (1.84)	24 (1.68)	
Ethnic group				0.752
Han	22,484 (94.85)	21,128 (94.83)	1356 (95.02)	
Others	1222 (5.15)	1151 (5.17)	71 (4.98)	
First visiting department				< 0.001
Surgical	11,163 (47.09)	10,850 (48.70)	313 (21.93)	
Medical	8620 (36.36)	7966 (35.76)	654 (45.83)	
Others	3923 (16.55)	3463 (15.54)	460 (32.24)	
Primary imaging manifestation				< 0.001
Pulmonary shadow/mass	21,619 (91.20)	20,850 (93.58)	769 (53.89)	
Pleural effusion	977 (4.12)	532 (2.39)	445 (31.18)	
Atelectasis	60 (0.25)	57 (0.26)	3 (0.21)	
Pleural lesion	27 (0.11)	24 (0.11)	3 (0.21)	
Mediastinal neoplasm	92 (0.39)	89 (0.40)	3 (0.21)	
Others	931 (3.93)	727 (3.26)	204 (14.30)	
Primary site				0.237
Right lung	13,224 (55.78)	12,403 (55.67)	821 (57.53)	
Left lung	9851 (41.55)	9273 (41.62)	578 (40.50)	
Bilateral lungs	51 (0.22)	48 (0.22)	3 (0.21)	
NA	580 (2.45)	555 (2.49)	25 (1.75)	
Lesion location				< 0.001
Upper lobe	7934 (33.47)	7293 (32.73)	641 (44.92)	
Middle lobe	893 (3.77)	826 (3.71)	67 (4.70)	
Lower lobe	11,257 (47.49)	10,778 (48.38)	479 (33.57)	
Trans-lobe	297 (1.26)	235 (1.05)	64 (4.34)	
NA	3325 (14.03)	3147 (14.13)	178 (12.47)	
Pathology				0.002
SCC	6585 (27.78)	6125 (27.49)	460 (32.24)	
ADC	12,422 (52.40)	11723 (52.62)	699 (48.98)	
SCLC	2648 (11.17)	2497 (11.21)	151 (10.58)	
Others	2051 (8.65)	1934 (8.68)	117 (8.20)	
T-stage				< 0.001
1	5348 (29.81)	5057 (30.62)	291 (20.39)	
2	5382 (29.99)	4928 (29.84)	454 (31.81)	
3	2319 (12.92)	2117 (12.82)	202 (14.16)	

(Continues)

TABLE 1 | (Continued)

Variables	Total, *n* (%) (*N* = 23,706)	LC, *n* (%) (*N* = 22,279)	TBLC, *n* (%) (*N* = 1427)	*p*
4	4376 (24.39)	4013 (24.30)	363 (25.44)	
NA	518 (2.89)	401 (2.43)	117 (8.20)	
N-stage				< 0.001
0	7999 (44.58)	7451 (45.11)	548 (38.40)	
1	1120 (6.24)	1009 (6.11)	111 (7.78)	
2	5325 (29.68)	4917 (29.77)	408 (28.59)	
3	3404 (18.97)	3139 (19.01)	265 (18.57)	
NA	95 (0.53)	0 (0.00)	95 (6.66)	
M-stage				0.001
0	10,404 (57.98)	9635 (58.34)	769 (53.89)	
1	7019 (39.12)	6416 (38.85)	603 (42.26)	
NA	520 (2.90)	465 (2.82)	55 (3.85)	
TNM stage				< 0.001
1	5150 (29.66)	4844 (30.39)	306 (21.44)	
2	1220 (7.03)	1083 (6.79)	137 (9.60)	
3	3898 (22.45)	3581 (22.47)	317 (22.21)	
4	7020 (40.42)	6416 (40.25)	604 (42.33)	
NA	78 (0.45)	15 (0.09)	63 (4.41)	
Firstline antitumor treatment				
Surgery	8588 (36.23)	8067 (36.21)	521 (36.51)	0.819
Chemotherapy	5979 (25.22)	5338 (23.96)	641 (44.92)	< 0.001
Radiation	514 (2.17)	434 (1.95)	80 (5.61)	< 0.001
Immunotherapy	1823 (7.69)	1737 (7.80)	86 (6.03)	0.015
Targeted therapy	2036 (8.59)	1904 (8.55)	132 (9.25)	0.358
Comorbidity				
Diabetes	3276 (13.82)	3055 (13.71)	221 (15.49)	0.060
Hypertension	6114 (25.79)	5734 (25.74)	380 (26.63)	0.455
COPD	300 (1.27)	258 (1.16)	42 (2.94)	< 0.001
Obstructive pneumonia	2158 (9.10)	2005 (9.00)	153 (10.72)	0.028
Heart disease	1618 (6.83)	1512 (6.79)	106 (7.43)	0.352
Anemia	1933 (8.15)	1738 (7.80)	195 (13.67)	< 0.001
Hypoalbuminemia	2810 (11.85)	2548 (11.44)	262 (18.36)	< 0.001
Malnutrition	248 (1.05)	212 (0.95)	36 (2.52)	< 0.001
PF	415 (1.75)	368 (1.65)	47 (3.29)	< 0.001

Abbreviations: ADC = adenocarcinoma, COPD = chronic obstructive pulmonary disease, LNM = lymph node metastases, met = metastases, NA = not available, PF = pulmonary fibrosis, SCC = squamous cell carcinoma, SCLC = small cell lung cancer.

3.5 | Logistic Regression Analysis of Factors Influencing TBLC Among LC Patients

TB infections in LC patients make treatment more difficult and lead to a worse prognosis. Additionally, TBLC mimics LC in terms of clinical, pathological, and radiological manifestations, making it challenging to distinguish between coexisting TBLC and LC patients. Therefore, we explored the risk of TB infection among LC patients using univariate and multivariate logistic regression models (Table 3). No significant multicollinearity of factors was demonstrated, with collinearity tolerances of 0.674–0.998, variance inflation factors of 1.002–1.794, and a condition index of 14.336. In the logistic regression analysis, a median age of 63 years was used as the cut-off value. Our analysis found that older age, male gender, upper lung lobes, more advanced cancer stage, distant metastasis, anemia, malnutrition, chronic obstructive pulmonary disease (COPD), hepatitis, hypoalbuminemia, and pulmonary fibrosis were risk factors for TBLC. Relevant examinations for TB are recommended for patients with these risk factors.

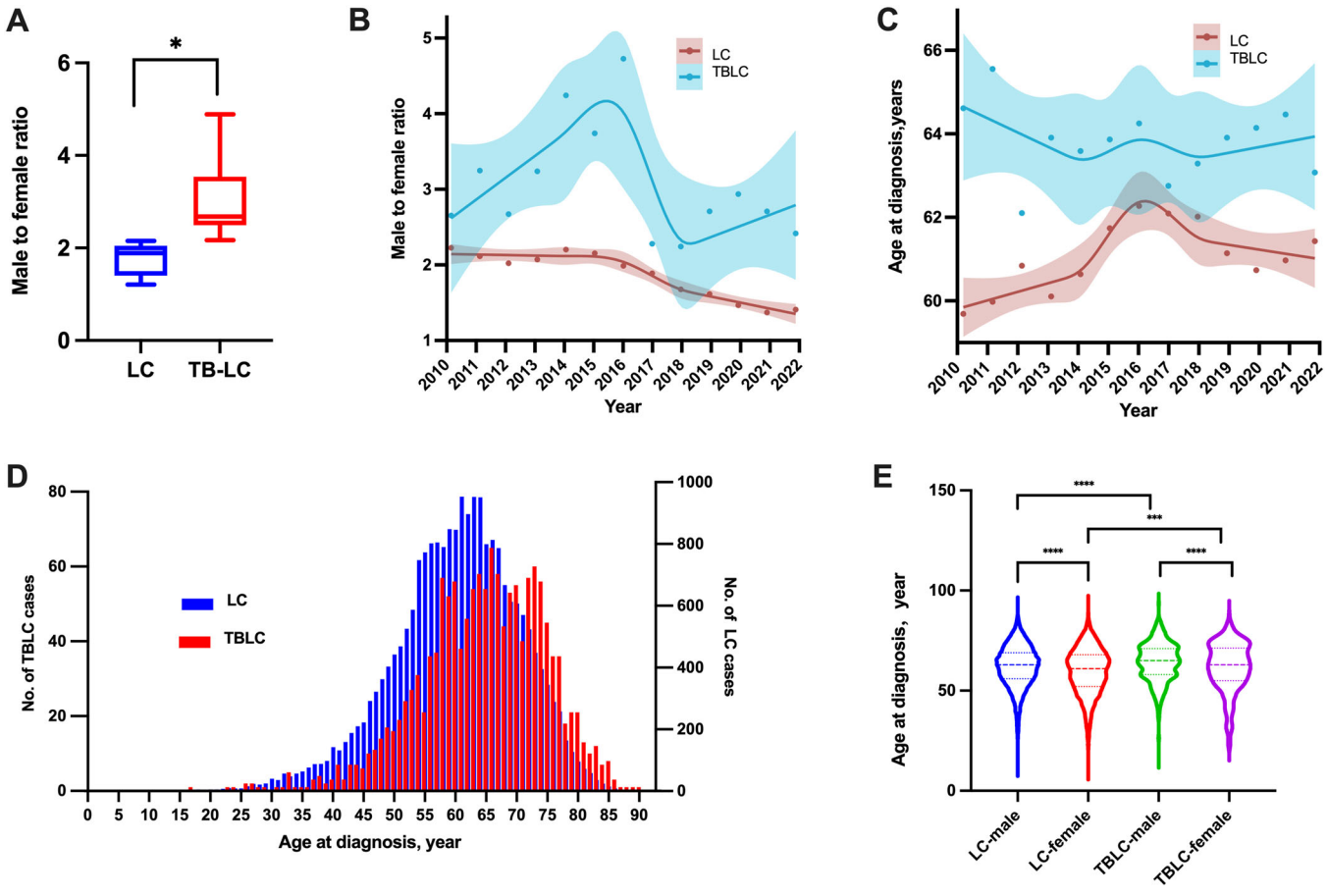

FIGURE 3 | Comparison and dynamics of gender and age between patients with TBLC and LC from 2010 to 2022. (A) Comparison of the male-to-female ratio (MFR) between patients with TBLC and LC. (B) MFR dynamics of patients with TBLC and LC from 2010 to 2022. (C) Age dynamics of patients with TBLC and LC from 2010 to 2022. (D) Age distribution of patients with TBLC and LC. (E) Comparison of age at diagnosis between TBLC and LC patients according to gender stratification. *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$.

4 | Discussion

The coexistence of TB and LC has been investigated in Lithuania, China, Serbia, Japan, and the Netherlands [26–30]. Pulmonary TB has been reported in 0.9%–13.7% of LC cases globally [31]. The prevalence of TBLC varies depending on spatial and regional factors, and older, male, Asian, and Caucasian LC patients are more prone to developing TB [31, 32]. Cheon et al. conducted an 18-year, retrospective cohort study in Korea, and a total of 116 out of 3454 LC patients developed TB during the study period, yielding an incidence rate of 3.4% and an IRR of 2804/100,000 person-years [33]. A cohort study from Japan reported that the cumulative incidence of TB among LC patients after one and 2 years of treatment was 1.15% and 1.38%, respectively [30]. In addition, a high frequency and an upward trend have been reported in the presence of TB in LC patients [34].

This was a large-sample, retrospective study on coexistent TBLC over a 12-year period in China. Our results revealed an increasing CIR of TBLC. LC patients had a higher risk of developing TB infection than the general population, especially among older males with anemia, malnutrition, pulmonary fibrosis, or COPD. Furthermore, patients with TBLC were more vulnerable to lymph node metastasis and distant dissemination than LC alone. This study provides insights into the epidemiological and clinicopathological characteristics of TBLC and places a strong emphasis on prevention and control strategies for the condition.

Coexistent TBLC is recognized as the combined presence of pulmonary TB and LC within an individual. Its incidence is considered to be influenced by the prevalence and disease control of both TB and LC. In the present study (though it accounted for only a small proportion of LC), both the number of new cases and the CIR of TBLC significantly increased per year, similar to LC. Male TBLC prevalence varied considerably over time, partly because of the high mobility of the male population. Furthermore, an increasing number of TBLC patients with Stage I disease have been identified in recent years. Apart from demographic, medical and health resources, and economic factors, other variables such as widely applied low radiation dose chest computed tomography scans, improvement in TB detection techniques, environmental pollution, and smoking may contribute to the increasing incidence of TBLC and its early diagnosis [16, 17, 24, 35–37].

In the present study, patients with LC had a higher risk of developing an active TB infection, with an IRR of 25.21 (95% CI:

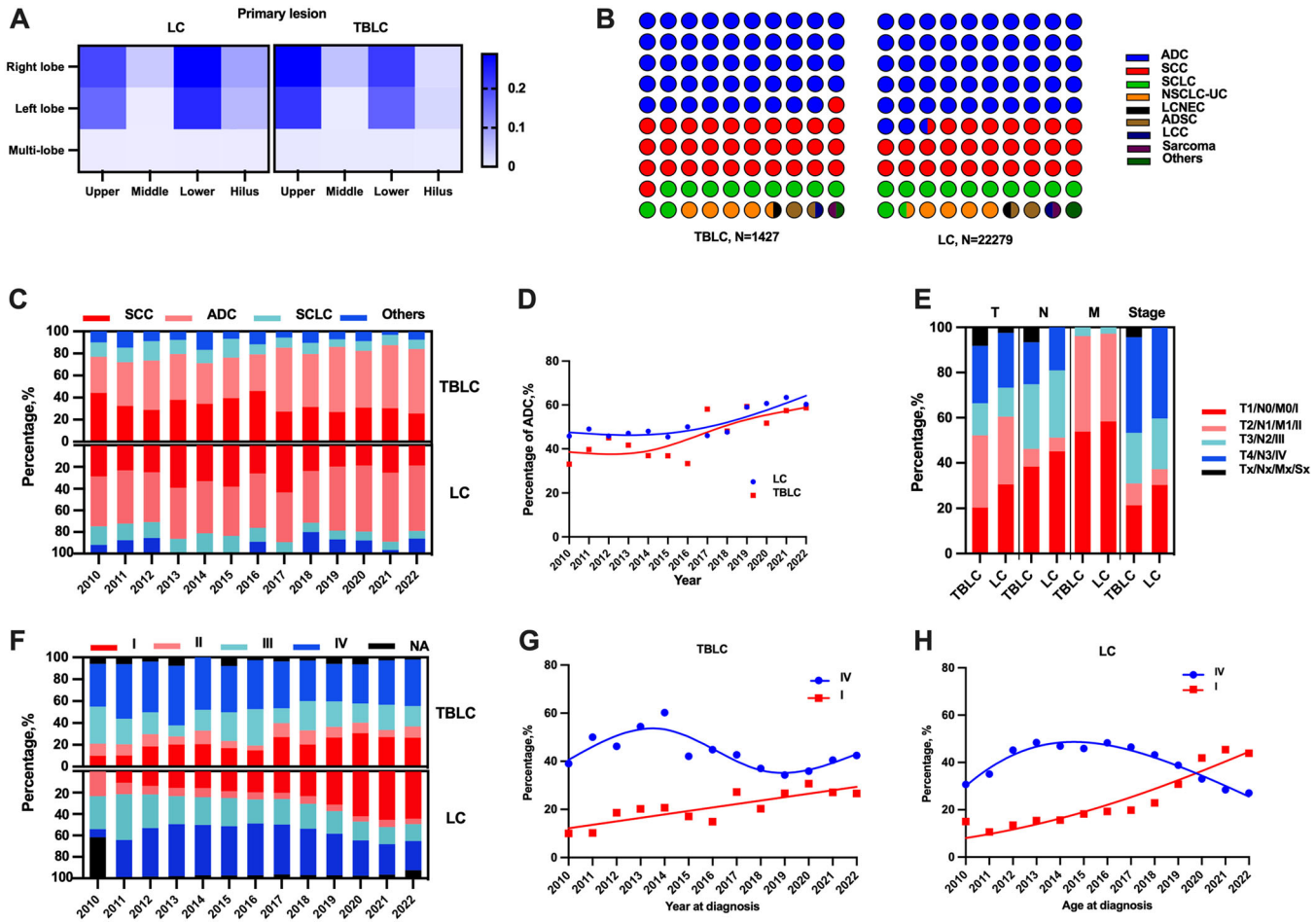

FIGURE 4 | Clinicopathological characteristics and dynamics of patients with TBLC vs. LC. (A) Heatmap of the proportions of the primary lesion locations of TBLC and LC. (B) Pathological subtypes of TBLC and LC. (C and D) Dynamics of pathological types of TBLC and LC from 2010 to 2022. (E–H) Tumor stage distributions and dynamics of TBLC and LC from 2010 to 2022.

TABLE 2 | Metastasis of patients with TBLC and LC.

Metastasis	Total, *N* (%)	LC, *N* (%)	TBLC, *N* (%)	*p*
Pilar lymph node	3961 (16.71)	3620 (16.25)	341 (23.90)	< 0.001
Mediastinal lymph node	7298 (30.79)	6636 (29.79)	662 (46.39)	< 0.001
Bone	2829 (11.93)	2552 (11.45)	277 (19.41)	< 0.001
Lung	2921 (12.32)	2650 (11.89)	271 (18.99)	< 0.001
Pleura	3099 (13.07)	2882 (12.94)	217 (15.21)	0.014
Liver	1064 (4.49)	994 (4.46)	70 (4.91)	0.432
Brain	1918 (8.09)	1803 (8.09)	115 (8.06)	0.964
Adrenal gland	851 (3.59)	788 (3.54)	63 (4.41)	0.084
Pericardium	376 (1.59)	311 (1.40)	65 (4.56)	< 0.001
Celiac lymph node	455 (1.92)	414 (1.86)	41 (2.87)	0.007

21.54–29.89). Consistent with this, a meta-analysis of six studies from the United States found that patients with LC had a ninefold higher rate of developing active TB compared with those without LC [37]. Intrinsic immunosuppression of LC itself (the immunosuppressive effects of anticancer treatment) and other host factors may increase the susceptibility of TB in LC patients [22, 23, 38, 39]. Interestingly, the IRR of TB infection among LC patients exhibited a continuously increasing trend over the past decade (Figure 1F,I), suggesting an increase in TBLC that is independent of LC incidence. The application of multiple, enhanced treatment strategies, especially immune checkpoint inhibitors (ICIs), reactivate TB infections among LC patients [40–42]. In addition, the prolonged survival of LC patients may be another factor responsible for this observation.

TABLE 3 | Logistic regression of risk factors of TBLC.

	Univariate		Multivariate	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age, ≥ 63 vs. 63 years	1.42 (1.26–1.40)	< 0.001	1.44 (1.25–1.66)	< 0.001
Gender, female vs. male	0.54 (0.48–0.61)	< 0.001	0.63 (0.54–0.73)	< 0.001
Marital, married vs. Unmarried	0.71 (0.47–1.06)	0.095	0.73 (0.46–1.17)	0.195
Pathology (vs. SCC)				
ADC	0.70 (0.62–0.79)	< 0.001	0.94 (0.80–1.09)	0.408
SCLC	0.79 (0.65–0.96)	0.016	0.82 (0.65–1.03)	0.087
Others	1.00 (0.81–1.23)	0.977	0.92 (0.71–1.19)	0.525
TNM stage (vs. Stage 1)				
Stage 2	2.00 (1.62–2.48)	< 0.001	1.58 (1.20–2.09)	0.001
Stage 3	1.40 (1.19–1.65)	< 0.001	1.49 (1.13–1.97)	0.005
Stage 4	1.49 (1.29–1.72)	< 0.001	1.52 (1.12–2.10)	0.001
Location, left vs. right lobe	0.95 (0.84–1.07)	0.387		
Lesion of location (vs. upper lobe)				
Middle lobe	0.90 (0.69–1.18)	0.454	1.00 (0.75–1.32)	0.972
Lower lobe	0.51 (0.45–0.58)	< 0.001	0.52 (0.45–0.59)	< 0.001
Pilar LNM, yes vs. no	1.23 (1.09–1.40)	0.001	0.94 (0.78–1.14)	0.535
Mediastinal LNM, yes vs. no	1.73 (1.55–1.93)	< 0.001	4.63 (3.72–5.76)	< 0.001
Bone met, yes vs. no	1.44 (1.25–1.65)	< 0.001	1.71 (1.42–2.06)	< 0.001
Lung met, yes vs. no	1.43 (1.24–1.64)	< 0.001	1.80 (1.48–2.19)	< 0.001
Plural met, yes vs. no	1.15 (0.99–1.33)	0.077		
Liver met, yes vs. no	1.01 (0.79–1.30)	0.917		
Brain met, yes vs. no	0.91 (0.75–1.11)	0.371		
Adrenal gland met, yes vs no	1.09 (0.84–1.42)	0.519		
Pericardium met, yes vs. no	3.13 (2.37–4.14)	< 0.001	3.25 (2.38–4.45)	< 0.001
Diabetes, yes vs. no	1.12 (0.96–1.30)	0.136		
Hypertension, yes vs. no	0.98 (0.87–1.11)	0.801		
COPD, yes vs. no	2.46 (1.76–3.45)	< 0.001	1.85 (1.23–2.76)	0.003
Hyperlipemia, yes vs. no	0.81 (0.68–0.96)	0.014	0.91 (0.75–1.09)	0.304
Hepatitis, yes vs. no	2.31 (1.71–3.13)	< 0.001	2.52 (1.81–3.51)	< 0.001
Anemia, yes vs. no	1.66 (1.42–1.95)	< 0.001	1.36 (1.11–1.66)	0.003
Hypoalbuminemia, yes vs. no	1.52 (1.32–1.75)	< 0.001	1.30 (1.09–1.56)	0.004
Malnutrition, yes vs. no	2.24 (1.56–3.21)	< 0.001	1.76 (1.15–2.69)	0.010
PF, yes vs. no	1.89 (1.38–2.58)	< 0.001	1.60 (1.13–2.26)	0.008

Abbreviations: ADC = adenocarcinoma, COPD = chronic obstructive pulmonary disease, LNM = lymph node metastases, met = metastases, PF = pulmonary fibrosis, SCC = squamous cell carcinoma, SCLC = small cell lung cancer.

With an increase in the incidence and economic burden of coexistent TBLC, early diagnosis, and appropriate management are important concerns. Because TB and LC mimic each other in regard to clinical symptoms and radiological evidence, delayed diagnosis or misdiagnosis is unavoidable. Older age, male sex, a previous history of TB, and LC treatment were shown to be risk factors for developing an active TB infection [38, 43, 44]. Our results also found that LC patients with malnutrition, preexisting COPD, pulmonary fibrosis, and a more advanced cancer stage were more vulnerable to TB infection. We, therefore, recommend routine TB-related testing for LC patients with risk factors in TB-epidemic regions.

TBLC presents unique clinicopathological features in comparison to LC alone. The present study found that there was a higher proportion of SCC among patients with TBLC than LC alone (32.24% vs. 27.49%, $p = 0.002$), indicating differences in both diseases' pathogenesis and pathological processes. TB infection is a chronic inflammatory reaction of the

pulmonary parenchyma that causes irreversible fibrosis and scarring, accompanied by an impaired immune response. It causes the accumulation of genomic changes, and exposure to growth factors can cause multistep, cellular transformations, leading to dysplasia and malignant SCC.

In the present study, TBLC was presented as an aggressive disease with lymph node involvement and distant metastasis. However, based on current studies, the effect of TB infection on the survival of LC patients remains controversial [25, 45–47]. TB coinfection was an independent predictor of LC mortality (hazard ratio [HR] = 2.01, 95% CI: 1.40–2.90; $p < 0.001$) after adjustment for multiple potential confounders [48]. Several studies have also demonstrated an elevated risk of mortality in LC patients with comorbid TB [25, 45, 49]. Additionally, patients with TBLC were found to respond poorly to EGFR-tyrosine kinase inhibitors [18, 50]. However, in a matching study, Ye reported no differences in the median overall survival (OS, 14.0 vs. 17.0 months, $p = 0.312$) in patients with TBLC ($n = 33$) and LC alone ($n = 66$) [46]. Some studies have shown that active TB is an independent predictor of better survival; effective T-cell immunity near tumors possibly underlies the mechanism [23, 47].

This study has several limitations. First, patient recall and selection bias were inevitable owing to the retrospective nature of the study. To reduce these biases, we rechecked the diagnoses of TB and LC for each patient to minimize false positive and negative cases; hence, the diagnosis of inactive/previous TB not only depended on past medical history but was also confirmed by TB-relevant tests and examinations. Moreover, structured interviews were used to collect the past medical history of each patient. Second, this single-center study may not be representative of the entire Chinese population. Third, possible risk factors, such as lifestyle, smoking status, and combined medications, were not available from the electronic system and were not assessed.

5 | Conclusion

This study showed that TBLC is a rare condition with increasing incidence in Chinese populations. Older age, male sex, anemia, malnutrition, pulmonary fibrosis, COPD, and more advanced stages are risk factors for developing a TB infection among LC patients. Given the increasing incidence and aggressive nature of TBLC, we recommend routine screening for TB infection in LC patients and more attention be paid to health control and the multidisciplinary treatment of this disease.

Author Contributions

Fei Qi: conceptualization (equal), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), writing – original draft (lead), writing – review and editing (lead). **Hongjie Yang:** data curation (equal), investigation (equal), resources (equal). **Yi Han:** data curation (equal), formal analysis (lead), writing – original draft (equal). **Yujie Dong:** data curation (equal), resources (equal), software (equal), supervision (equal). **Fan Zhang:** formal analysis (equal), software (equal), validation (equal). **Yishuo Wang:** data curation (equal), formal analysis (equal). **Juan Du:** data curation (equal), resources (equal), software (equal), validation (equal), visualization (equal). **Yuan Gao:** resources (equal), visualization (equal), writing – review and editing (equal). **Xuegang Hu:** methodology (equal), software (supporting). **Liqun Zhang:** validation (equal), visualization (equal). **Tongmei Zhang:** conceptualization (lead), funding acquisition (lead), project administration (equal), supervision (lead), writing – review and editing (equal).

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Ethics Statement

This study was approved by the Ethics Committee of Beijing Chest Hospital (approval ID: JS-2023-10).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The study data can be accessed by contacting the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.