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Risk factors and prognosis of tuberculous pleural effusion in TB patients

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Abstract

The objective of this study was to examine the epidemiological characteristics of Tuberculous pleural effusion (TPE) and to evaluate the risk factors and prognostic outcomes of TPE in patients diagnosed with tuberculosis (TB). The study included all TB patients admitted to Shanghai Pulmonary Hospital from January 2014 to December 2020. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for TPE, while univariate and multivariate Cox proportional hazards models were employed to assess prognostic factors. A total of 18,258 TB patients were enrolled in the study, of whom 1,665 had TPE. Univariate logistic regression analysis revealed that male gender (OR = 1.276; 95% CI: 1.146–1.420, p < 0.001), age ≥ 70 years (OR = 1.275; 95% CI: 1.100-1.479, p = 0.001), and a history of psychosis (OR = 2.565; 95% CI: 1.278–5.147, p = 0.008) were risk factors for TPE. Multivariate logistic regression analysis confirmed that male gender (OR = 1.284; 95% CI: 1.153–1.429, p < 0.001), age ≥ 70 years (OR = 1.280; 95% CI: 1.102–1.485, p = 0.001), and a history of psychosis (OR = 2.450; 95% CI: 1.217–4.903, p = 0.012) remained independent risk factors for TPE. Univariate Cox regression analysis indicated that age ≥ 70 years (HR = 6.114; 95% CI: 2.425–15.415, p < 0.001) and diabetes (HR = 5.072; 95% CI: 1.468–17.528, p = 0.010) were correlated with an increased risk of mortality in TPE patients. Conversely, Whole-course management reduced the risk of death (HR = 0.291; 95% CI: 0.109–0.776, p = 0.014). Multivariate Cox regression analysis further confirmed that age ≥ 70 years (HR = 5.207; 95% CI: 2.043–13.267, p < 0.001) and diabetes (HR = 3.530; 95% CI: 1.007–12.377, p = 0.049) were independent predictors of mortality, while Whole-course management remained protective (HR = 0.319; 95% CI: 0.119–0.853, p = 0.023). The study elucidated the epidemiological characteristics correlated with the risk and prognosis of TPE among TB patients in China.

Introduction

Tuberculous pleurisy (TP) is an inflammatory condition resulting from a delayed-type hypersensitivity reaction secondary to Mycobacterium tuberculosis (MTB) infection of the pleura [1].The most common clinical manifestation is Tuberculous pleural effusion (TPE). TPE may occur in conjunction with other forms of tuberculosis (TB), such as pulmonary TB, lymphatic TB, or bone TB, or it may present independently[2, 3].Given the low positivity rate of bacteriological detection in pleural fluid, including liquid culture systems (e.g., Bactec 960), the diagnosis of TPE often relies on bacteriological and pathological findings from other affected organs. Adenosine deaminase (ADA) levels in pleural fluid have diagnostic utility, although their specificity is limited, and the clinical feasibility of invasive pleural biopsy remains challenging. In recent years, technological advancements have significantly expanded rapid diagnostic methods, such as Xpert MTB/RIF and line probe assays[4].

The pathogenesis of TPE is a complex immunological process that encompasses cellular immunity, humoral immunity, and the intricate interactions among cytokines. [5].An in-depth investigation into the predisposing factors will facilitate the development of more effective diagnostic methods and therapeutic strategies, ultimately improving patient outcomes. As the designated clinical research center for infectious diseases (specifically TB) in Shanghai, Shanghai Pulmonary Hospital is the leading

medical institution for the diagnosis, treatment, and management of TB in the region. We conducted a retrospective analysis of all TPE cases admitted to our hospital from December 2014 to December 2020, evaluating the risk factors and prognosis correlated with TPE in TB patients. This study aims to provide valuable insights into the pathogenesis and prognosis of TPE.

Methods

Study design

A retrospective study was conducted on all outpatients and inpatients diagnosed with TB and TPE at Shanghai Pulmonary Hospital from January 2014 to December 2020. This study received approval from the Ethics Committee of Shanghai Pulmonary Hospital, and written informed consent was obtained from each participant prior to their involvement.

The risk factors for TPE in TB patients were analyzed based on gender, age ≥ 70 years, nationality, Time interval from symptom onset to hospital presentation(Time from S to H) >30 days, comorbidities (including diabetes, psychosis and other comorbidities), severe case, drug resistance, and Relapse. Additionally, the prognosis of TPE was evaluated considering gender, age ≥ 70 years, nationality, Time from S to H > 30 days, comorbidities, severe case, drug resistance, Relapse, and Whole course management of treatment.

The diagnosis of Psychosis is based on a documented past medical history that includes the following disorders (schizophrenia, depression, anxiety, etc.)

Diagnostic Criteria for TPE

The diagnosis of TPE is based on the following criteria[6–10]:1) characteristic clinical manifestations of TB, including low-grade fever in the afternoon, night sweats, fatigue, and weight loss; 2) positive blood interferon-γ release assays (IGRAs); 3) evidence of TB in the lungs or other organs; 4) imaging findings indicative of pleural effusion; 5) specific gravity of pleural effusion ≥ 1.018, a positive Rivalta test, total protein concentration > 30 g/L, and a pleural effusion protein-to-serum protein ratio > 0.5; 6) elevated adenosine deaminase (ADA) levels in pleural effusion; 7) positive acid-fast bacilli smear, Xpert MTB/RIF test, or culture (Bectec960) results from pleural effusion samples; 8) histopathological findings from pleural biopsy showing epithelioid cells, Langerhans giant cells, and caseous necrosis; 9) systemic and local anti-TB chemotherapy demonstrating efficacy.

The diagnosis of tuberculous pleurisy must satisfy 1) to 6) and at least one of (7), (8) or (9)

Statistical Analysis

Statistical analyses were conducted using SPSS (IBM, Armonk, New York, version 22.0). Quantitative data are presented as mean ± standard deviation (SD) and were compared between groups using the student’s t-test. Qualitative data are reported as n (%) and were analyzed using Pearson's chi-square test

or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were employed to identify risk factors for TPE in patients with TB. Additionally, univariate and multivariate Cox proportional hazards regression models were utilized to determine significant prognostic factors for TPE. Variables with p-values < 0.1 in univariate analysis were included in the multivariate Cox regression model, with significance determined by the log Rank test. Forest plots and Kaplan-Meier survival curves were generated using GraphPad Prism version 8.4 (GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 18,258 TB patients were included in this study, comprising 1,665 (9.1%) patients with TPE and 16,593 (90.9%) patients without TPE. Detailed comparisons of the clinical characteristics between the two groups are presented in Table 1. Statistically significant differences were observed between the two groups in age (P = 0.037), age ≥ 70 years (P = 0.001), gender (P < 0.001), Time from S to H>30 days (P = 0.007), diabetes (P = 0.003), psychosis (P = 0.006), severe case (P = 0.019), drug resistance (P < 0.001), whole course management (P < 0.001), and mortality (P = 0.023). No significant differences were found in nationality (P = 0.399), other comorbidities (P = 0.165), or relapse (P = 0.529).

Table 1
Demographic and clinical characteristics of two groups

Variable	No TPE group (n = 16593)	TPE group (n = 1665)	t/χ^2	*P* value
Age, mean ± SD	43.98 ± 18.987	44.70 ± 19.861	-0.169	= 0.037
Age, n (%)			10.429	= 0.001
<70 years	14757 (88.9)	1437 (86.3)		
≥ 70 years	1836 (11.1)	228 (13.7)		
Gender, n (%)			20.006	< 0.001
Male	10216(61.6)	1118(67.1)		
Female	6377(38.4)	547 (32.9)		
Nationality, n (%)			0.711	0.399
Han	16570(99.9)	1664(99.9)		
Others	23 (0.1)	1 (0.1)		
Time from S to H, n (%)			7.328	0.007
>30days	1528(9.2)	120(7.2)		
≤ 30days	15065(90.8)	1545(92.8)		
Co-morbidities, n (%)				
Diabetes mellitus	946 (5.7)	66 (4.0)	8.722	0.003
psychosis	39(0.2)	10 (0.6)	7.555	0.006
Others	255(1.5)	33(2.0)	1.932	0.165
severe case, n (%)			5.482	0.019
Yes	696 (4.2)	50 (3.0)		
No	15897 (95.8)	1615 (97.0)		
Resistance to drugs, n (%)			42.305	<0.001
Yes	1143(6.9)	46(2.8)		
No	15450(93.1)	1619(97.2)		
Relapse, n (%)			0.397	0.529
Yes	237(1.4)	27(1.6)		

Variable	No TPE group (n = 16593)	TPE group (n = 1665)	t/χ^2	*P* value
No	16356(98.6)	1638(98.4)		
Whole¯course management, n (%)			42.070	<0.001
Yes	13380 (80.6)	1451 (87.1)		
No	3213 (19.4)	214 (12.9)		
Death, n (%)			5.184	0.023
Yes	308 (1.9)	18(1.1)		
No	16285 (98.1)	1647 (98.9)		

Time from S to H: Time interval from symptom onset to hospital presentation

Univariate logistic regression analysis revealed that male gender (OR = 1.276; 95% CI = 1.146–1.420, P < 0.001), age ≥ 70 years (OR = 1.275, 95% CI = 1.100-1.479, p = 0.001), and psychosis (OR = 2.565, 95% CI = 1.278–5.147, p = 0.008) were positively correlated with an increased likelihood of TPE. Conversely, Time from S to H >30 days (OR = 0.766, 95% CI = 0.631–0.929, P = 0.007), diabetes (OR = 0.683, 95% CI = 0.529–0.881, p = 0.003), severe case (OR = 0.707, 95% CI = 0.528–0.946, P = 0.020), and drug resistance (OR = 0.384, 95% CI = 0.285–0.518, P < 0.001) negatively correlated with TPE. Factors such as Han nationality (OR = 2.310, 95% CI = 0.312–17.114, P = 0.413), other comorbidities (OR = 1.296, 95% CI = 0.898–1.868, P = 0.166), and relapse (OR = 1.138, 95% CI = 0.762–1.699, P = 0.529) did not show significant correlation with TPE (Fig. 1A).

Multivariate logistic regression analysis further confirmed that male gender (OR = 1.284; 95% CI = 1.153–1.429, P < 0.001), age ≥ 70 years (OR = 1.280, 95% CI = 1.102–1.485, p = 0.001), and comorbid psychosis (OR = 2.450, 95% CI = 1.217–4.034, p = 0.012) remained positively correlated with TPE. Meanwhile, Time from S to H>30 days (OR = 0.771, 95% CI = 0.636–0.936, p = 0.009), diabetes mellitus (OR = 0.652, 95% CI = 0.504–0.843, p = 0.001), severe disease (OR = 0.710, 95% CI = 0.530–0.951, P = 0.022), and drug resistance (OR = 0.387, 95% CI = 0.287–0.523, P < 0.001) continued to exhibit negative correlations with TPE. Additionally, Han nationality (OR = 2.250, 95% CI = 0.303–16.686, P = 0.428), other comorbidities (OR = 1.314, 95% CI = 0.910–1.900, P = 0.146), and relapse (OR = 1.202, 95% CI = 0.803–1.801, P = 0.371) did not demonstrate correlation with TPE (Fig. 1B).

During the treatment and follow-up period, 18 (5.5%) deaths were reported in the TPE group, while 308 (94.5%) deaths occurred in the non-TPE group. Univariate Cox regression analysis indicated that for patients with TPE, age ≥ 70 years (HR = 6.114, 95% CI = 2.425–15.415, p < 0.001) and diabetes (HR = 5.072, 95% CI = 1.468–17.528, p = 0.010) were correlate with an increased risk of mortality. Conversely, Whole course management of treatment was correlate with a reduced risk of death (HR = 0.291, 95% CI = 0.109–0.776, p = 0.014). Multivariate Cox regression analysis further revealed that the HR for patients

age ≥ 70 years was 5.207 (95% CI = 2.043 to 13.267, p < 0.001), and the HR for patients with diabetes was 3.530 (95% CI = 1.007 to 12.377, p = 0.049). Whole course management of treatment was correlate with a lower risk of death, with an HR of 0.319 (95% CI = 0.119–0.853, p = 0.023).

The Kaplan-Meier survival curve demonstrated that patients receiving TPE had a significantly lower risk of death and better prognosis compared to those not receiving TPE (Fig. 2C). Additionally, patients with diabetes exhibited a higher risk of death and worse prognosis than those without diabetes (Fig. 2D). Patients aged 70 years or older also faced a higher risk of death and worse prognosis (Fig. 2F). In contrast, patients who received Whole course management of treatment had a lower risk of death and better prognosis (Fig. 2E).

Discussion

Approximately 15–25% of TB infections manifest as extrapulmonary TB, affecting various sites through hematogenous or lymphatic dissemination of MTB[11].The most frequently affected extrapulmonary sites include the pleura, lymph nodes, and musculoskeletal system[12, 13].According to R. W. Light [14] 3–25% of patients with TB develop TPE. The cellular immune response, particularly that mediated by T lymphocytes, especially $CD4^+$ T cells, plays a crucial role in both TB infection and pathogenesis [15], and is essential for the development of TPE [[16].

This study identified male sex as a risk factor for the development of TPE in TB patients, consistent with findings from a Spanish report[7].This may be attributed to differences in immune cell function between males and females [17], particularly variations in T cell responses [18].Additionally, the average age of patients with TPE was marginally higher compared to those without TPE, and an age ≥ 70 years emerged as a notable risk factor for TPE in TB patients. A study by M. Goto et al[19] revealed a unique subset of CXCR3 (intermediate) $CD4^+$ effector memory T cells that expands with age. Consequently, further investigation into $CD4^+$T cells could provide deeper insights into the pathogenesis of TPE.

Numerous studies have demonstrated a significant association between TB and mental health, with TB and depression being widely recognized as a "comorbid condition" due to their bidirectional synergistic effects[20].When the body experiences various physiological insults or psychological stressors, numerous inflammatory mediators reach the affected areas, triggering immune responses that can lead to psychiatric disorders. Conversely, an excessive release of inflammatory factors and immune dysregulation can exacerbate TB[21], This study identified comorbid psychosis as a risk factor for TPE in TB patients. Further investigation is required to determine whether this relationship is mediated by inflammatory factors and immune imbalance. However, owing to societal stigma and potential side effects of anti-TB medications, TB patients often experience a high prevalence of psychological disorders[22], Therefore, it is imperative to provide enhanced support and care during the treatment process for these patients[23].

An intriguing finding in this study was the negative correlation between the Time from S to H>30 days and the occurrence of TPE. Specifically, patients with TPE tended to seek medical attention earlier compared to those without TPE, likely due to the discomfort caused by pleural effusion compressing the adjacent lung tissue. Additionally, diabetes and severe case were identified as protective factors against TPE. In diabetic patients, hyperglycemia has been shown to inhibit the absolute counts of T lymphocytes, $CD8^+$ T lymphocytes, and NK cells in TB patients through the downregulation of both innate and adaptive immune responses[24, 25].Severe cases often exhibit rapid disease progression, extensive lesions, respiratory failure, hypoproteinemia, and diminished host immune function[26], all of which contribute to a reduced immune response and a lower likelihood of pleural inflammation resulting from highly allergic reactions. The study also identified a negative correlation between drug resistance and the incidence of TPE. Despite reports[27]indicating that TPE and pulmonary TB exhibit similar patterns of drug resistance, data on drug resistance of TPE remain limited due to the relatively low detection rate of MTB in pleural fluid [28].

Highly effective drugs such as isoniazid and rifampicin have significantly improved patient prognosis and survival rates. The pharmacotherapy regimen for TPE mirrors that of TB [27]. Interventions like pleural aspiration and closed thoracic drainage can alleviate symptoms and prevent pleural thickening and adhesion. Surgical treatment has proven beneficial for encapsulated pleural effusion and tuberculous empyema with significant pleural thickening [29].

During the treatment and follow-up of patients with TPE, we observed that age ≥ 70 years and diabetes mellitus significantly increased the risk of mortality (by 5–6 times), consistent with findings from a study by Liu, S.F.[30].Therefore, it is imperative to pay closer attention to TPE patients aged ≥ 70 years with comorbid diabetes. A more proactive evaluation of these high-risk patients is essential to improve their prognosis. Additionally, comprehensive management throughout the entire course of treatment was found to reduce the risk of mortality to nearly one-quarter. This whole-course management involves establishing and maintaining a consistent and uninterrupted supply of anti-TB drugs to ensure continuous treatment. Simultaneously, healthcare providers monitor, guide, and evaluate patients throughout the treatment process, aligning with the Directly Observed Treatment, Short-course (DOTS) strategy recommended by the World Health Organization (WHO)[31, 32], This approach ensures regular medication adherence and improves cure rates [33].In this study, 87.1% of TPE patients received whole-course management, resulting in better outcomes compared to those without such management, thereby validating the efficacy and promoting the broader application of this strategy.

Despite the substantial number of cases collected in this study, the analysis of comorbidities was limited due to (1) Single-center retrospective design, which may have selection bias and information bias; (2) As a first-tier city in China, the patient characteristics and medical level of Shanghai may not be completely representative of other regions in China. (3) the lack of detailed records for conditions other than diabetes and psychosis in the original data. Future multi-center studies with larger sample sizes are necessary to validate and extend our findings concerning Chinese patients with TPE.

Conclusion

This study systematically analyzed the epidemiological characteristics of TPE cases in a hospital in China. The findings indicate that male gender, age ≥ 70 years, and comorbid psychosis are independent risk factors for TPE among TB patients. Additionally, age ≥ 70 years and diabetes were identified as factors that increase the mortality risk in TPE patients. Conversely, Whole course management of treatment was correlate with a reduced risk of mortality. This research contributes to enhancing clinical understanding of TPE and provides valuable insights for further studies on its pathogenesis and prognosis.

Declarations

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Author Contribution

Yong Fang and Wei Sha designed the study protocol. Yi-Wei Wang, Li-Ping Yan, Qin-qi Zhou, Xiao-fang You and Li Liang collected, recorded, and collated the data. Yong Fang prepared all the figures and tables and wrote the main manuscript text. All authors reviewed the manuscript. Wei Sha and Zhong-Hua Liu put forward suggestions for revision.

Acknowledgement

Yong Fang and Wei Sha designed the study protocol. Yi-Wei Wang, Li-Ping Yan, Qin-qi Zhou, Xiao-fang You and Li Liang collected, recorded, and collated the data. Yong Fang prepared all the figures and tables and wrote the main manuscript text. All authors reviewed the manuscript. Wei Sha and Zhong-Hua Liu put forward suggestions for revision.

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Figures

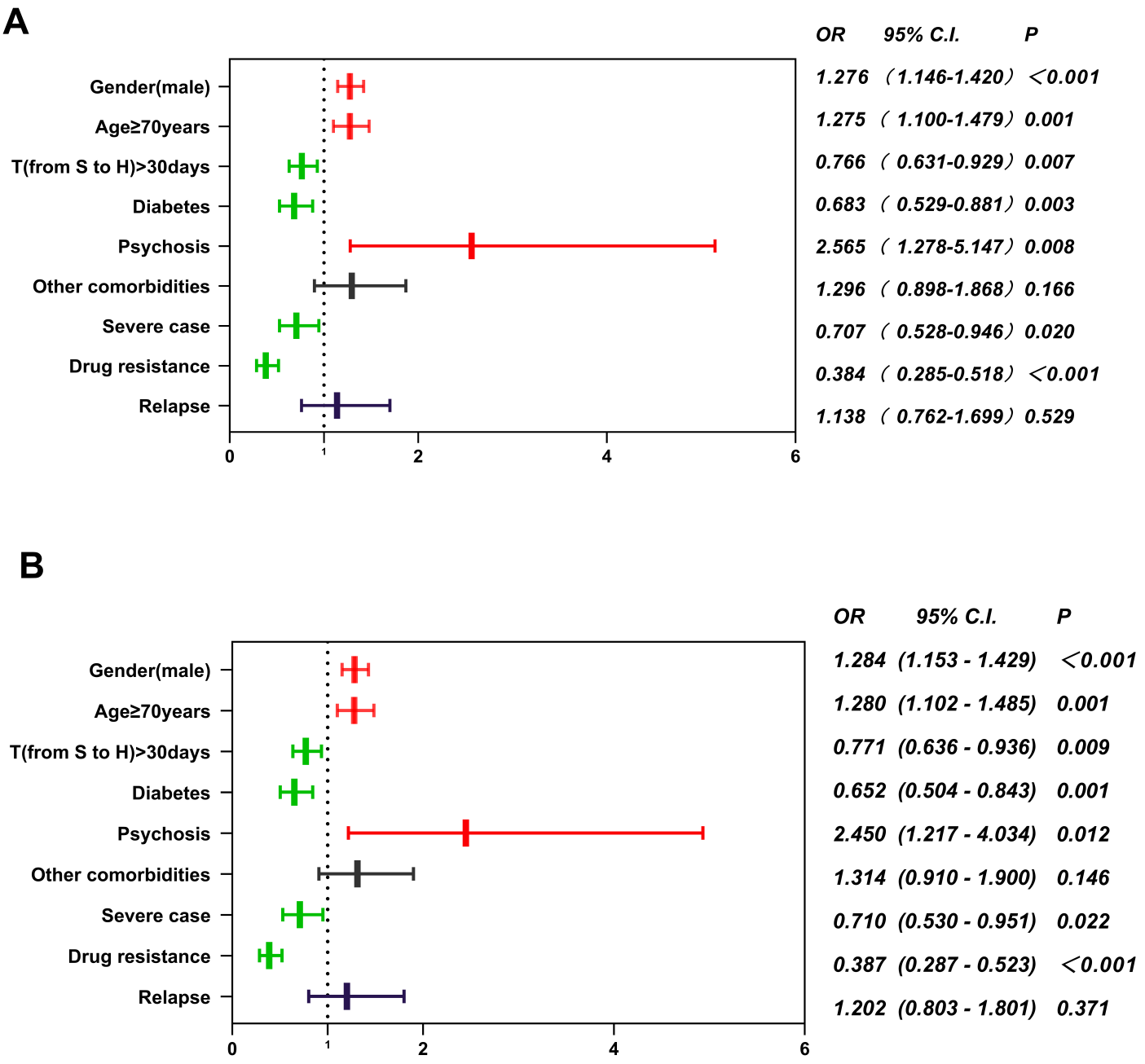


Figure 1

A: Forest plot of univariate binary logistic regression analysis of the risk of TPE in TB patients; B: Forest plot of multivariable binary logistic regression analysis of TPE risk in TB patients. T(from S to H): Time interval from symptom onset to hospital presentation.

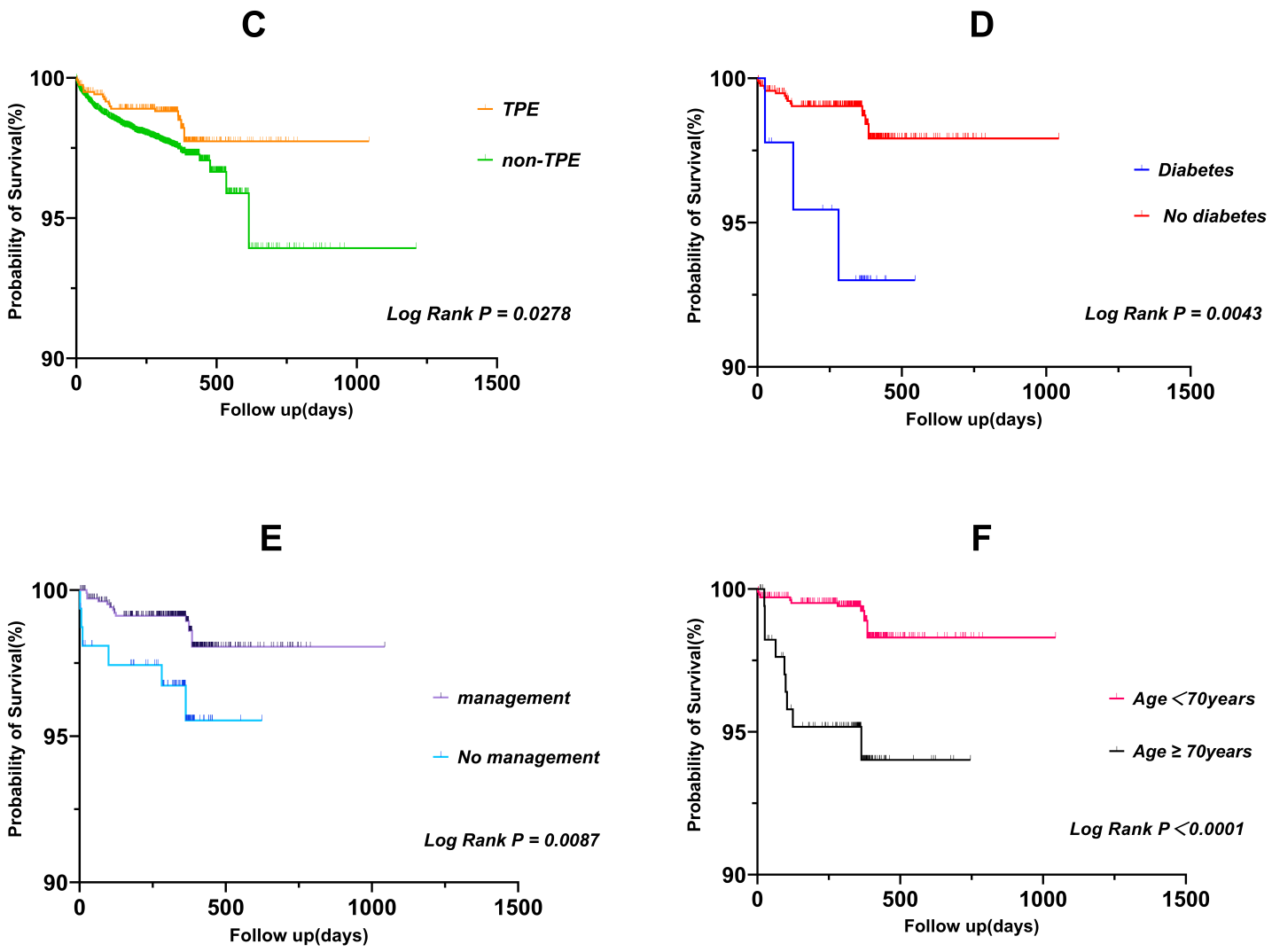


Figure 2

Kaplan-Meier curves. C: comparison between TPE and non-TPE groups; D: comparison of TPE with and without diabetes; E: comparison of Whole course management versus no management of TPE; F: comparison of TPE between patients aged ≥70 years and those aged < 70 years.