Risk factors associated with venous thromboembolism in tuberculosis: A case control study

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Abstract
Tuberculosis (TB) patients who develop venous thromboembolism (VTE) have poor clinical outcomes. This study aimed to explore the risk factors and the prognosis of TB patients with VTE. A total of 11 267 with TB patients from the Zhejiang University-affiliated Chest Hospital, China, were enrolled between January 2016 and January 2020. A total of 107 TB patients with VTE were selected as the VTE group. Patients in the control group were randomly screened in a 1:1 ratio between the VTE and control groups. Univariate and multivariate logistic regression analysis was used to evaluate the factors associated with VTE in TB patients. Of the 214 patients, 145 (60.17%) were male, 69 (32.2%) were female, with an average age of 62.21 ± 19.35. The incidence of VTE in TB patients was 0.95%. Using a univariate analysis, it was found that age, fever, dyspnea, lower limb edema, respiratory failure, malignant tumor, prothrombin time, activated partial thromboplastin time, D-dimer, and hemoglobin levels were different between the two groups (P < 0.05). Multivariate logistic regression analysis showed that higher D-dimer value, higher incidence of lower limb edema, and TB were risk factors for VTE; OR (95%CI) = 8.840 (2.383–32.794); OR (95%CI) = 4.957 (1.219–20.161); OR (95%CI) = 16.216 (4.779–55.025). However, the use of Rifamycin was found to be a protective factor against VTE [OR (95%CI) = 0.170(0.073–0.395)]. Receiver operating characteristic curve (ROC) curve of D-dimer (area under curve [AUC] = 0.831 ± 0.028 [95%CI: 0.776–0.886, P < 0.05]) and the cut-off value of 1855 μg/L was obtained according to the Youden index, with a sensitivity and a specificity rate of 82.2% and 74.3%, respectively. The risks of VTE seem higher in TB patients with fever, dyspnea, lower limb edema, and D-dimer levels of more than 1855 μg/L; therefore, it should be actively screened, and prophylactic anticoagulation given if necessary. Effective directly observed treatment plus short-course chemotherapy (DOTS) protocol anti-TB therapy helps reduce the probability of VTE in TB patients.

Keywords
correlation, risk factors, tuberculosis, venous thromboembolism
1 | INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disease associated with higher morbidity and mortality.1 Globally, tuberculosis (TB) is a serious infectious disease that mainly affects the lung and, if not treated well, is carried with high mortality, especially in developing countries. It is also one of the preventable infectious diseases that are common in China.2

Many studies have shown that TB patients are more likely to suffer from VTE, and the mortality is as high as 15%.3,4 So the key to reducing VTE incidence in TB patients is identifying high-risk patients and giving them timely prophylactic treatments. Consequently, this study aims to analyze the factors associated with the development of VTE in TB patients and its prognosis.

2 | METHODOLOGY

2.1 | Study population and design

This study was conducted at the Zhejiang University-affiliated Chest Hospital, China. We retrospectively analyzed all inpatient cases diagnosed with a clinically confirmed TB5 between January 2016 and January 2020. We excluded TB patients who stayed in the hospital for only 1 day and those with surgical treatments.

A total of 107 TB patients with VTE were identified.6 On the other hand, samples for the controls consisted of TB patients without VTE, in which one control was assigned for each case (107 cases). Controls were selected by random number table, totaling 214 patients (see supporting information Figure S1). We selected risk factors for TB patients with VTE based on previous studies from an accessible and reliable clinical database. Records were extracted from the patients’ electronic medical records database, including age, sex, clinical symptoms, physical exam findings, smoking and alcohol intake, comorbidities, clinical laboratory findings, the severity of TB, and treatment history (Rifamycin).

2.2 | Definitions

Active TB was defined as follows: (1) pulmonary TB: Mycobacterium tuberculosis complex was identified by Biochip assays using sputum specimens with acid-fast bacilli that were smear-positive or culture-positive. (2) Extrapulmonary TB (EPTB): patients with at least one specimen extracted from infected lesions other than the lung that was a confirmed M. tuberculosis infection using biochip assays. Rifamycin therapy was defined as the inpatient use of at least 3 days before or after hospitalization.

2.3 | Statistical analysis

The data were entered into SPSS for Windows, version 24 (SPSS Inc., USA). Continuous data were described as $\bar{X} \pm s$. Continuous variables were analyzed with the independent samples t-test. Categorical variables were compared with Pearson’s Chi-square test. We included variables with a p-value of <0.05 into a multivariate logistic regression model with stepwise forward selection to identify independent risk factors. Then, we used the receiver operating characteristic curve (ROC) to describe the continuous variables with statistical significance and derive the cut-off value per the Youden index. The criterion for statistical significance was $p < 0.05$.

2.4 | Ethics approval

This study was approved by the Hangzhou Red Cross Hospital Ethics Committee (2020) Quick review no. 187).

3 | RESULTS

A total of 11 267 patients were included in the study, with 7713 males (68.5%) and 3554 females (31.5%). Of this, 107 patients had confirmed concurrent TB with VTE. The incidence of VTE in TB patients was 0.95%. The median age of all patients included in the study was 62.21 ± 19.35 years; however, those with VTE were older (median age 65.78 ± 16.66; $p = 0.007$) as compared with those without VTE (median age 58.64 ± 21.19).

In total, 68 (31.78%) patients had a fever, of which 45 (66.18%) were confirmed with VTE. Analysis showed that patients with VTE were more likely to have fever ($p = 0.001$). Those with dyspnea were 67 (31.31), of which 41 (61.19%) were confirmed with VTE. Similarly, the analysis showed that patients with dyspnea were more likely to have VTE ($p = 0.027$). A total of 27 (12.62%) patients had lower limb edema, and 22 (81.48%) confirmed with VTE. Likewise, patients with lower limb edema were more likely to be diagnosed with VTE ($p = 0.000$). Lastly, respiratory failure ($p = 0.007$) and malignant tumor ($p = 0.017$) had a statistically significant association with VTE occurrence in TB patients (Figure 1).

Univariate analysis suggested that no significant differences were observed between the VTE group and the control group in the distribution of age, gender, cough,
smoking and alcohol status, hemoptysis, varicose veins of the lower limbs, and comorbidities such as diabetes, coronary heart disease, chronic obstructive pulmonary disease, nephrotic syndrome, heart failure, and ischemic stroke. The details of comparing the clinical characteristics of patients with and without VTE are summarized in Table 1.

Due to some unknown reason, the results of the routine blood test of one patient and the coagulation profile of another patient were both missing. The laboratory findings showed that the PT ($p = 0.001$), APTT ($p = 0.000$), and D-dimer ($p = 0.000$) were all significantly higher in the VTE group than in the control group. However, the hemoglobin level ($Hb$, $p = 0.000$) was significantly lower in the VTE group than in the control group. White blood cells and platelet count were not associated with the occurrence of VTE (Tables 2 and 3).

Active TB as a disease was associated with the occurrence of VTE ($p = 0.001$), while the use of Rifamycin reduced the risks of VTE occurrence ($p = 0.000$). The anatomical sites of TB were not associated with VTE risks (Table 4).

Multivariate logistic regression analysis revealed that high level of D-dimer (OR: 8.84; 95%CI: 2.383–32.794, $p = 0.001$), lower limb edema (OR: 4.957; 95%CI: 1.219–20.161, $p = 0.025$), and active TB (OR: 16.216; 95%CI: 4.779–55.025, $p = 0.000$) all contributed to occurrence of VTE in TB patients (Table 5).

D-dimer was analyzed using the ROC (Figure 2). The results showed that D-dimer levels differed significantly between the two groups (area under curve [AUC] = $0.831 \pm 0.028$ [95%CI: 0.776–0.886], $p < 0.05$). The cut-off value was 1855 μg/L, as calculated by the Youden index, with a sensitivity of 82.2% and a specificity of 74.3%.

**FIGURE 1** Flowchart of study recruitment and screening process of the cases and controls

4 | DISCUSSION

Epidemiological studies estimate the incidence of VTE to be around 0.1% to 0.2% in the general population and 0.7% to 3.9% in patients with active pulmonary TB.\(^7\)\(^–\)\(^9\) In this study, the incidence of VTE was 0.95%, which is consistent with previously reported studies. These data show that TB patients have a higher risk of VTE than the general population, and physicians should be educated on the prevention and treatment of VTE in TB patients.

In our analysis, patients in the VTE group were older than those in the control group, which indicates that older age could be at a higher risk of developing VTE. However, older patients generally have other comorbidities, and sometimes their symptoms could overlap with VTE. Other studies also show that the clinical manifestations of VTE are usually diverse and sometimes nonspecific; hence, misdiagnosis and treatment delay are common.\(^10\) We also found that VTE easily complicated clinical symptoms such as fever, dyspnea, and lower limb edema.

Hypercoagulability is one component of the Virchow triad. There is evidence that TB patients are in a hypercoagulable state with a higher D-dimer level than the general population.\(^11\) In clinical practice, if the plasma D-dimer is negative, VTE can be largely excluded; however, D-dimer has a poor positive predictive value, mainly because it can also be higher in patients with active inflammation, malignancy, or infectious processes.\(^12\) Nonetheless, some studies show that elevated D-dimer levels, despite being nonspecific, still guide clinical evaluation in patients with suspected VTE.\(^13\) D-dimer was found to be a risk factor for VTE in TB patients (OR 8.84, 95%CI: 2.383–32.794, $p < 0.05$), with an AUC value of 0.78–0.89 and a cut-off value of

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**Table 1** General information in two groups

| Characteristics                  | VTE group (n = 107) | Control group (n = 107) | Statistic | P-value |
|----------------------------------|---------------------|-------------------------|-----------|---------|
| Age (X ± s)                      | 65.78 ± 16.66       | 58.64 ± 21.19           | −2.736    | 0.007   |
| **Gender (n, %)**                |                     |                         |           |         |
| Male                             | 78 (72.9%)          | 67 (62.6%)              | 2.588     | 0.108   |
| Female                           | 29 (27.1%)          | 40 (37.4%)              |           |         |
| **Smoking**                      |                     |                         |           |         |
| Yes                              | 52 (48.6%)          | 41 (38.3%)              | 2.301     | 0.129   |
| No                               | 55 (51.4%)          | 65 (61.7%)              |           |         |
| **Alcohol**                      |                     |                         |           |         |
| Yes                              | 32 (29.9%)          | 27 (25.2%)              | 0.585     | 0.444   |
| No                               | 75 (70.1%)          | 83 (74.8%)              |           |         |
| **Clinical symptoms**            |                     |                         |           |         |
| **Cough**                        | 70 (65.4%)          | 57 (53.3%)              | 3.273     | 0.07    |
| **Hemoptysis**                   | 6 (5.6%)            | 11 (10.3%)              | 1.597     | 0.206   |
| **Fever**                        | 45 (42.1%)          | 23 (21.5%)              | 10.433    | 0.001   |
| **Chest pain**                   | 6 (5.6%)            | 13 (12.1%)              | 2.83      | 0.093   |
| **Dyspnea**                      | 41 (38.3%)          | 26 (24.3%)              | 4.889     | 0.027   |
| **Physical exam findings**       |                     |                         |           |         |
| Lower limb edema                 | 22 (20.6%)          | 5 (4.7%)                | 12.249    | 0.000   |
| **Comorbidities**                |                     |                         |           |         |
| Varicose veins of lower limb     | 2 (1.9%)            | 0 (0%)                  | 0.505     | 0.477*  |
| Diabetes                         | 15 (14.0%)          | 17 (15.9%)              | 0.147     | 0.701   |
| Hypertension                     | 34 (31.8%)          | 36 (33.6%)              | 0.085     | 0.771   |
| Coronary heart disease           | 13 (12.1%)          | 10 (9.3%)               | 0.438     | 0.508   |
| COPD                             | 13 (12.1%)          | 14 (13.1%)              | 0.042     | 0.837   |
| Nephrotic syndrome               | 2 (1.9%)            | 2 (1.9%)                | 0         | 1.000   |
| Respiratory failure              | 17 (15.9%)          | 5 (4.9%)                | 7.298     | 0.007   |
| Heart failure                    | 6 (5.6%)            | 1 (0.9%)                | 3.692     | 0.055   |
| Ischemia stroke                  | 5 (4.7%)            | 0 (0%)                  | 3.277     | 0.07    |
| Myocardial infarction            | 0 (0%)              | 0 (0%)                  |           | 1.0     |
| Acute infectious diseases        | 1 (0.9%)            | 0 (0%)                  | 0         | 1.0     |
| Malignant tumor                  | 10 (9.3%)           | 2 (1.9%)                | 5.65      | 0.017   |

Abbreviations: COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism.

*Method of successive corrections.

**Table 2** Coagulation profile of the two groups

| Laboratory findings | VTE group (n = 107) | Control group (n = 106) | Statistic | P-value |
|--------------------|---------------------|-------------------------|-----------|---------|
| **PT (s)**         |                     |                         |           |         |
| >14.3              | 22 (20.6%)          | 6 (5.7%)                | 10.355    | 0.001   |
| ≤14.3              | 85 (79.4%)          | 100 (94.3%)             |           |         |
| **APTT (s)**       |                     |                         |           |         |
| >34                | 33 (30.8%)          | 12 (11.3%)              | 12.177    | 0.000   |
| ≤34                | 74 (69.2%)          | 94 (88.7%)              |           |         |
| **D-dimer (μg/L)** |                     |                         |           |         |
| >550               | 104 (97.2%)         | 64 (60.4%)              | 42.327    | 0.000   |
| ≤550               | 3 (2.8%)            | 41 (39.6%)              |           |         |

Abbreviations: APTT, activated partial thromboplastin time; PT, prothrombin time; VTE, venous thromboembolism.
### TABLE 3  Routine blood test results of the two groups

| Laboratory findings | VTE group (n = 106) | Control group (n = 107) | Statistic | P-value |
|---------------------|---------------------|-------------------------|-----------|---------|
| **WBC ($^{10^9}$)** |                     |                         |           |         |
| >9.5                | 21 (19.8%)          | 15 (14.1%)              | 1.457     | 0.483   |
| 3.5–9.5             | 77 (72.7%)          | 85 (79.4%)              |           |         |
| <3.5                | 8 (7.5%)            | 7 (6.5%)                |           |         |
| **Hemoglobin (gL)** |                     |                         |           |         |
| >170                | 2 (1.9%)            | 10 (9.3%)               | 23.442    | 0.000   |
| 120–170             | 42 (39.6%)          | 68 (63.6%)              |           |         |
| <120                | 62 (58.5%)          | 29 (27.1%)              |           |         |
| **Platelet**        |                     |                         |           |         |
| >300                | 24 (22.6%)          | 12 (11.2%)              | 5.267     | 0.072   |
| 100–300             | 76 (71.7%)          | 90 (84.1%)              |           |         |
| <100                | 6 (5.7%)            | 5 (4.7%)                |           |         |

Abbreviations: VTE, venous thromboembolism. WBC, white blood cells.

### TABLE 4  Active tuberculosis as use of Rifamycin between the two groups

| Characteristics | VTE group (n = 107) | Control group (n = 107) | Statistic | P-value |
|-----------------|---------------------|-------------------------|-----------|---------|
| Active TB       | 99 (92.5%)          | 81 (75.7%)              | 11.329    | 0.001   |
| **Anatomical site of TB** |             |                         |           |         |
| PTB             | 75 (70.1%)          | 77 (72.0%)              | 0.226     | 0.893   |
| EPTB            | 21 (19.6%)          | 21 (19.6%)              |           |         |
| Both            | 11 (10.3%)          | 9 (8.4%)                |           |         |
| Use of Rifamycin| 39 (36.4%)          | 70 (65.4%)              | 17.969    | 0.000   |

Abbreviations: EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; VTE, venous thromboembolism.

### TABLE 5  Risk factors of VTE in TB patients

| Risk factors       | SE   | Wald | OR (95%CI)          | P-value |
|--------------------|------|------|---------------------|---------|
| Age                | 0.011| 0.003| 1.001 (0.980–1.022) | 0.956   |
| Fever              | 0.431| 3.44 | 2.224 (0.956–5.176) | 0.064   |
| Dyspnea            | 0.457| 2.435| 2.045 (0.835–5.007) | 0.117   |
| Lower limb edema   | 0.716| 5.002| 4.957 (1.219–20.161)| 0.025   |
| Respiratory failure| 0.696| 0.162| 1.323 (0.338–5.176) | 0.687   |
| Malignant tumor    | 1.266| 2.987| 8.919 (0.746–106.640)| 0.084   |
| PT                 | 0.674| 0.174| 1.324 (0.354–4.959) | 0.677   |
| APTT               | 0.576| 0.447| 1.470 (0.475–4.548) | 0.888   |
| D-dimer            | 0.669| 10.617| 8.840 (2.383–32.794)| 0.001   |
| Hemoglobin         | 0.975| 2.748| 5.032 (0.745–33.995)| 0.097   |
| Active TB          | 0.623| 19.974| 16.216 (4.779–55.025)| 0.000   |
| use of Rifamycin   | 0.431| 16.897| 0.170 (0.073–0.395) | 0.000   |

Abbreviations: APTT, activated partial thromboplastin time; PT, prothrombin time; TB, tuberculosis; VTE, venous thromboembolism.
1855 μg/L. Therefore, clinicians should pay more attention to patients with a high D-dimer level, especially if higher than 1855 μg/L.

Currently, the mechanisms underlying the increased risk of VTE in TB patients remain unknown. Some researchers\textsuperscript{14,15} proposed that the chronicity of TB infection might cause vascular endothelial cell remodeling and subsequent release of numerous inflammatory mediators and cytokines such as IL-6 and TNFα. These cytokines further cause the production of various proteins of acute inflammation and coagulation factors, while simultaneously inhibiting fibrinolysis by downgrading antithrombin III, free protein C, protein S, and protein C.

White et al.\textsuperscript{16} found that, compared with other anti-TB regimens, the risk of DVT was higher in Rifamycin containing regimen (OR 4.74). Conversely, we found rifamycin use as a protective factor in which it reduced the occurrence of VTE. The reason may be that Rifamycin has a strong anti-TB effect.

Moreover, the data by White and colleagues are from the period between 1978 and 1986, an era in which short-course therapy with isoniazid and rifampicin was the standard of care, as compared with modern-day directly observed treatment plus short-course chemotherapy (DOTS); therefore, absolute causation of Rifamycin with VTE cannot be concluded. Similarly, our study is a retrospective study with a small sample size, and therefore, larger studies are needed to confirm the effect of Rifamycin in TB patients with VTE.

5 | CONCLUSION

VTE risks seem higher in TB patients, and therefore, there is a need for active prevention and treatment. Patients with fever, dyspnea, lower limb edema, and D-dimer levels of more than 1855 μg/L should be actively screened for VTE and prophylactic anticoagulation given if necessary. Effective DOTS protocol anti-TB therapy helps reduce the probability of VTE in TB patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The manuscript has been read and approved by all the authors and that each author believes that the manuscript represents honest work.

ETHICS STATEMENT

The permission was obtained for the study from the Local Ethics Committee of Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine. This study was exempted from signing patient consent statement, because this study only uses patient data with identifiable information and the research project does not involve personal privacy and commercial interests.

AUTHOR CONTRIBUTIONS

Guo Yi Nan collected patients’ data and carried out statistical analysis and article writing. He Fei wrote the original manuscript; Wang Zhen offered guidelines for the research design; Duan Tian Yun: research design idea, proofreading, and offered guidance on statistical analysis.

DATA AVAILABILITY STATEMENT

The data set used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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