

Study on D-Dimer Levels in Microbiologically Confirmed Patients of Pulmonary Tuberculosis to Anticipate the Risk of Hypercoagulable State

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ABSTRACT

Background: Pulmonary tuberculosis (PTB) is a major global health burden with systemic implications beyond the lungs. Recent studies suggest that TB may induce a hypercoagulable state, increasing the risk of thromboembolic complications. D-dimer, a fibrin degradation product, is a reliable biomarker for assessing coagulation activity. Elevated D-dimer levels in PTB patients may reflect subclinical thrombosis and help predict thrombotic risk.

Methods: This was a 24-month case-control study conducted at the Department of Respiratory Medicine and General Medicine, Era's Lucknow Medical College and Hospital. A total of 94 microbiologically confirmed PTB patients and 47 bronchial asthma patients were enrolled. Inclusion criteria included adults ≥ 18 years with microbiologically confirmed PTB. Controls included bronchial asthma patients.

Results: Among PTB patients, 89.4% had elevated D-dimer levels (>0.50 $\mu\text{g/mL}$), which were significantly higher than those in controls (38.3%; $p < 0.001$). Most PTB patients had intermediate Well's scores, suggesting elevated thrombotic risk with thrombus detection (4.3%) in USG Doppler and two had confirmed pulmonary embolism on CTPA.

Conclusion: Elevated D-dimer levels in microbiologically confirmed PTB patients signify a hypercoagulable state and a potentially increased risk of thromboembolic events, warranting closer evaluation of thrombotic risk during TB management.

Key-words: Pulmonary tuberculosis, D-dimer, hypercoagulable state, thromboembolism, venous Doppler, Well's score

INTRODUCTION

Pulmonary tuberculosis (PTB) continues to pose a significant global health challenge, especially in resource-constrained regions.

According to the Global TB Report 2024, the estimated incidence of TB is approximately 10.6 million cases worldwide ^[1]. The World Health Organisation (WHO) has outlined ambitious goals through its END TB strategy, aiming to reduce TB-related deaths by 95% and new TB cases by 90% by 2035 ^[2]. Achieving these global TB targets necessitates robust improvements in diagnostic, preventive, and treatment services. ^[3,4] Tuberculosis infection (TBI) acts as a precursor to the development of active TB, particularly in individuals with compromised immunity ^[5].

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Although tuberculosis is primarily a pulmonary condition, it is increasingly acknowledged as a systemic illness with noteworthy hematologic consequences [6]. One area of growing interest is the development of a hypercoagulable state in TB patients, leading to potential thromboembolic complications. Inflammatory processes associated with TB have been shown to provoke a cascade of coagulation disturbances, with elevated D-dimer levels emerging as a key indicator [7]. D-dimer, a product of fibrin degradation, reflects both thrombin generation and fibrinolysis and is widely used to evaluate thrombotic risk in diverse clinical scenarios [8-11]. These cytokines enhance tissue factor expression on endothelial cells and monocytes, thereby activating the coagulation cascade. The overall effect is subclinical or overt coagulation activation, with D-dimer levels serving as a practical biomarker for this process [12].

Studies report significantly higher D-dimer concentrations in newly diagnosed TB patients compared to healthy controls, supporting its role in identifying patients at increased thrombotic risk [13]. Additional research has shown raised levels of D-dimer and fibrinogen, along with reduced levels of natural anticoagulants, in TB patients [14]. Notably, up to 40% of microbiologically confirmed PTB patients exhibit D-dimer levels above the conventional threshold for excluding venous thromboembolism (VTE), even in the absence of overt symptoms [15]. This suggests the possibility of undetected or subclinical thrombosis in TB cases. More recent findings indicate that persistently high D-dimer levels during TB treatment are linked to adverse clinical outcomes and a heightened risk of thromboembolic events [16, 17].

MATERIALS AND METHODS

Study Design and Setting- This case-control study was conducted in the Department of Respiratory Medicine and Department of Medicine at Era's Lucknow Medical College and Hospital. The study was conducted over 24 months following Institutional Ethics Committee approval.

Study Population- Microbiologically confirmed cases of pulmonary tuberculosis (PTB) were included as cases (Group A), and bronchial asthma patients were included as controls (Group B).

Inclusion Criteria- Patients of either sex aged ≥ 18 years with microbiologically confirmed pulmonary tuberculosis attending OPD and IPD services of the Departments of Respiratory Medicine and General Medicine were included in the study.

Exclusion Criteria- Patients with other non-infectious lung diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or emphysema were excluded, except those with bronchial asthma. Additional exclusions included patients receiving anticoagulant therapy, those with clinical evidence of sepsis, and non-ambulatory patients, as these conditions could independently alter coagulation parameters.

Study Procedure, Testing and Monitoring- After obtaining written informed consent, D-dimer levels were measured in patients with microbiologically confirmed pulmonary tuberculosis (cases) and bronchial asthma (controls).

Patients with D-dimer levels >0.5 $\mu\text{g/mL}$ were further evaluated for signs and symptoms of venous thromboembolism using the Wells score. This scoring system was used to stratify patients and assess baseline thrombotic risk in both groups, particularly in relation to elevated D-dimer levels among PTB patients.

This was followed by venous Doppler ultrasonography (USG) of the bilateral lower limbs. In cases where thrombus was detected, computed tomography pulmonary angiography (CTPA) was performed to evaluate for pulmonary embolism.

Statistical Analysis- All statistical analyses were performed using SPSS version 26.0 (IBM, USA). Continuous variables were expressed as mean \pm standard deviation (SD) and analyzed using Student's t-test. Categorical variables were analyzed using the chi-square test. Ranked data were analyzed using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

Ethical Approval- Ethical approval for this study was obtained from the Institutional Ethics Committee in accordance with international and institutional guidelines. Written informed consent was obtained from all participants before enrollment.

RESULTS

The present study examined occupational and demographic patterns among microbiologically confirmed PTB patients (group A: cases, n=94) and Bronchial Asthma patients (group B: controls, n=47), with a particular focus on D-dimer levels. In Group A, the

majority were ≥ 51 years old (36.2%), primarily semi-skilled workers (17.0%). In contrast, in Group B, the majority were 18-20 years (29.80%) and 21–30 years (36.17%), primarily consisting of skilled workers (61.7%) (Table 1). Statistically, a higher proportion of Cases were in the older age group (median age: 42 ± 18.37) than in the Controls (median age: 35 ± 16.17).

Table 1: Demographic profile of the cases VS control

Demographical Profile	CASE- Group A (n = 94)		Control-Group B (n=47)	
	Age-Distribution			
18-20 yrs	10	10.60%	14	29.80%
21- 30 yrs	14	14.89%	17	36.17%
31- 40 yrs	20	21.27%	7	14.90%
41 – 50 yrs	16	17%	5	10.6%
≥ 51 yrs	34	36.20%	4	8.50%

$\chi^2 = 23.62$; $p < 0.001$

D-dimer levels $> 0.55 \mu\text{g/mL}$ were observed in 38 of 40 (3+), 19 of 22 (2+), 26 of 27 (1+), and 1 of 4 (scanty). Only 10 individuals had D-dimer $\leq 0.55 \mu\text{g/mL}$, confirming that

D-dimer levels increase with increasing bacterial load in sputum (Table 2).

Table 2: AFB Grading and D-Dimer Levels for Cases (*n=94)

AFB Grade	D-Dimer ≤ 0.50	D-Dimer > 0.50	Total
Scanty	4	1	1
1+	3	19	22
2+	1	26	27
3+	2	38	40

In this study, the majority of PTB cases (89.4%) had elevated D-dimer levels ($> 0.50 \mu\text{g/mL}$). However, in the control group, the majority (61.7%) had D-dimer levels $\leq 0.50 \mu\text{g/mL}$, while the remaining (38.3%) had D-dimer levels $> 0.50 \mu\text{g/mL}$. The difference in D-dimer

distribution between cases and controls was statistically significant ($\chi^2 = 50.2$; $p < 0.001$), highlighting a clear association between TB infection and a hypercoagulable state (Table 3).

Table 3: D-dimer Comparison: Cases vs. Controls

Group	D-Dimer ≤ 0.55	D-Dimer > 0.55	Total
Cases	10 (10.6%)	84 (89.4%)	94
Controls	29 (61.7%)	18 (38.3%)	47

$*(\chi^2 = 50.2$; $p < 0.001)$ *

Fig. 1 shows the distribution of D-dimer levels among cases and controls. A significantly higher proportion of PTB cases had elevated D-dimer levels (>0.55 µg/mL) compared to controls, where most individuals had

normal levels. The difference was statistically significant ($\chi^2 = 50.2$; $p < 0.001$), indicating a strong association between PTB and elevated D-dimer levels.

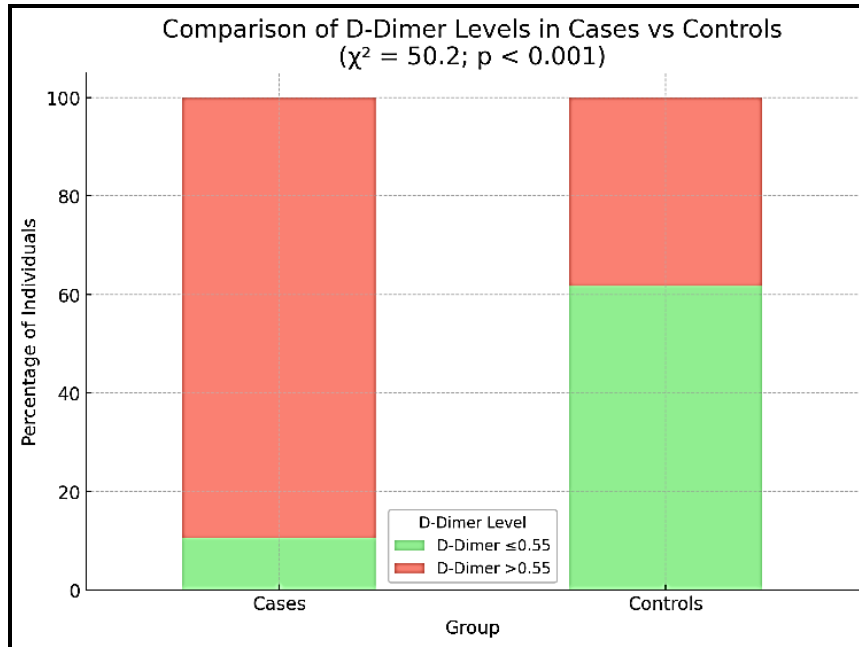


Fig. 1: Comparison between D.dimer levels in Cases and Controls

Table 4 shows that the majority of PTB cases (95.2%) had an intermediate Wells score, while 4.8% had a high score. In contrast, all controls (100%) were in the low-

risk category. This indicates a significantly higher thrombotic risk among PTB patients compared to controls.

Table 4: Well's Score among 84 Cases and 18 Control with D-dimer levels >0.50 µg/mL

Well's Score	CASE- Group A (n = 94)		Controls (n=47)	
	No.	%	No.	%
Low	0	0	18	100
Intermediate	80	95.2%	0	0
High	4	4.8%	0	0

$\chi^2 = 102.0$; $p < 0.001$

Table 5 demonstrates that most PTB cases had normal Doppler findings (88.1%), while a small proportion showed abnormalities such as venous thrombus, sluggish

flow, and atherosclerotic changes. No abnormalities were observed in controls, indicating a higher occurrence of thrombotic changes in PTB patients.

Table 5: USG results among 84 Cases with D-dimer levels >0.50 µg/mL

USG Doppler B/L Lower LIMB	Case- Group A (n = 94)		Controls (n=47)	
	No.	%	No.	%
Normal	74	88.1	18	100

RT Popliteal Vein Venous Thrombus	1	1.2	0	0
Sluggish Flow B/L Lower Limb	3	3.6	0	0
Atherosclerotic Changes in B/L Lower Limb	3	3.6	0	0
Left Proximal Femoral Vein Thrombus	2	2.4	0	0
Venous Thrombosis Left Sup.Femoral Vein, Left Popliteal Vein, and Both Deep Post.Tibial Vein S/O Partial Thrombus	1	1.2	0	0

$$\chi^2 = 2.37; p = 0.79$$

Table 6 shows the final findings in PTB patients with elevated D-dimer levels. High and intermediate Wells score patients demonstrated abnormalities on USG Doppler, including venous thrombus and sluggish flow,

with CTPA confirming pulmonary embolism. These findings indicate a significant association between elevated D-dimer levels and thromboembolic complications in PTB cases.

Table 6: Final result findings in PTB Cases

D-dimer	Wells score	USG Doppler	CTPA
2.25	High	Thrombus in right popliteal vein extending into anterior tibial vein, tibio-peroneal trunk, peroneal vein, and posterior tibial vein as described.	RT main pulmonary artery 70% occlusion of lumen extending into the segmental division along the RT upper, middle and lower lobes, suggestive of pulmonary embolism.
>8.10	Intermediate	Sluggish Flow B/L Lower Limb	Acute pulmonary thromboembolism involving B/L distal main Pulmonary arteries extending into lobar and segmental arteries with dilated RT-sided chamber of heart.

DISCUSSION

Pulmonary tuberculosis (PTB) has been recognized as a condition associated with a hypercoagulable state, predisposing patients to venous thromboembolism (VTE). D-dimer is a sensitive marker, but it lacks specificity [18].

In this study, D-dimer levels (>0.50 µg/mL) were significantly higher (89.4%) in PTB patients than in controls (38.29%). Similarly, Alhassan and Gaufri [19] reported significantly higher D-dimer levels in PTB patients than in healthy controls (0.82 vs 0.33 µg/mL), suggesting that higher thresholds may better predict thrombosis in TB. Nan *et al.* [16] study reported that a D-dimer >1855 µg/L (apx. 1.855 µg/mL) was strongly associated with VTE.

In this particular study, the majority of PTB cases had sputum AFB grading of 3+ (42.7%) [20], similar to the Di Bari *et al.* [21] study, which had a higher proportion of advanced TB cases (65.5% with extensive disease). D-dimer levels >0.55 µg/mL [22,23] were predominantly observed in sputum AFB-positive patients, with 38 as (3+), 19 as (2+), 26 as (1+), and 1 as (scanty), confirming the correlation between elevated D-dimer levels and the severity of bacterial load in sputum. Similarly, in the Suryakusumah *et al.* [24] study, 30 new cases of PTB showed elevated Prothrombin time, aPTT, and D-dimer levels in far-advanced lesions and in the smear-positive sputum group (p<0.001), findings similar to those in the present study.

The present study used Well's Score for evaluation of DVT risk, followed by usg doppler b/l lower limb for

thrombus detection and CTPA to detect pulmonary embolism. Similarly to Jia *et al.* [24], who enrolled 43 patients diagnosed with PTB and employed D-dimer followed by Padua score and CTPA. Higher levels of Padua score, D-dimer, and CTPA in cases of PTB, compared with controls, emphasise that D-dimer is a marker of a hypercoagulable state in PTB patients and that CTPA is important for detecting pulmonary embolism.

A few studies have reported remarkable evidence of coagulation abnormalities in PTB patients. The present study found that out of the 89.4% microbiologically confirmed PTB cases (who had elevated D-dimer levels), only 4.3% reported thrombus detection. These findings closely align with the Di Bari *et al.* [21] study, which reported a 1.61% prevalence of pulmonary thromboembolism (PTE) in a large TB cohort, and the Nan *et al.* [16] study, which found a 0.95% incidence of VTE in PTB.

In this study, CTPA findings were acute pulmonary thromboembolism (PTE) involving b/l distal main pulmonary arteries, extending into lobar and segmental arteries, with a dilated right-sided heart chamber; a similar finding was observed in Hyeyoung *et al.* [20], who reported right ventricular dilation on CTPA. The study highlights the importance of considering tuberculosis as a potential comorbidity in patients with PTE, particularly in regions with intermediate tuberculosis burden. Hence, providing compelling evidence that pulmonary tuberculosis (PTB) induces a hypercoagulable state leading to an increase in the risk of venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE).

A critical question arising from these findings is whether PTB patients should routinely receive thromboprophylaxis. Studies of Nan *et al.* [16] and Di Bari *et al.* [21] advocated for active screening and prophylaxis in high-risk patients with D-dimer levels $>1.0 \mu\text{g/mL}$. The rationale for prophylaxis is supported by showing that anti-TB therapy (ATT) reverses hypercoagulability. Suryakusumah *et al.* [24] documented a remarkable decrease in PT, aPTT, fibrinogen, and D-dimer after intensive-phase treatment of PTB patients ($p < 0.001$), suggesting that thrombotic risk is highest during active disease.

Hence, the present study reinforces contemporary evidence that PTB induces a hypercoagulable state, with

D-dimer serving as a useful screening tool. Key recommendations include:

- Routine D-dimer testing in PTB patients
- Imaging (Doppler/CTPA) for high-risk cases (immobile, high D-dimer, extensive TB).
- Individualized thromboprophylaxis in VTE patients

Addressing these gaps will enhance VTE prevention in TB patients, ultimately reducing morbidity and mortality in this vulnerable population.

CONCLUSIONS

In the present study, elevated D-dimer levels ($>0.55 \mu\text{g/mL}$) were observed in 89.4% of cases, and most patients had an intermediate risk according to the Wells score, while a few had a high risk. 11.9% showed venous abnormalities on Doppler ultrasound, including sluggish flow, atherosclerotic changes, and thrombus detection in the lower limb veins. CT pulmonary angiography was performed in thrombus-detected cases of group A, revealing pulmonary embolism and acute thromboembolism in two individuals.

CONTRIBUTION OF AUTHORS

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