

## Incidence of Thromboembolism in Hospitalized Patients With Tuberculosis and Associated Risk Factors

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**Background:** Venous thromboembolism is a serious complication among hospitalized patients. Infectious diseases are known as a risk factor for thrombo-embolic events.

**Objectives:** The aim of the study is to evaluate incidence, characteristic pattern, and risk factors for thrombo-embolic events among patients hospitalized with pulmonary and extra-pulmonary tuberculosis.

**Patients and Methods:** This cohort study was performed among 1,153 new cases of tuberculosis. Suspected patients for DVT (deep venous thrombosis) or PTE (pulmonary thromboembolism) were investigated by Doppler sonography and pulmonary CT angiography. Another 100 tuberculosis patients without thromboembolism were also observed as control group.

**Results:** The incidence of diagnosed thrombo-embolic complication was 32 of 1,153 admitted patients (2.8%; 95% confidence interval: 1.9 to 3.9) with a median interval of 14 days after anti-TB treatment initiation. The incidence of DVT and PTE was 2% and 1%, respectively. Thrombo-embolic events and DVT were more common in men than in women: 4.2% versus 1.3% ( $P = 0.003$ ) and 3.5% versus 0.4%, respectively ( $P < 0.001$ ). Hypertension and opium addiction were significantly correlated with thromboembolism.

**Conclusions:** Incidence of DVT and PTE is noticeable among patients with tuberculosis.

**Keywords:** Thromboembolism; Tuberculosis; Venous Thrombosis; Pulmonary Embolism; Infection

### 1. Introduction

Venous thromboembolism is the major cause of morbidity and mortality especially in hospitalized patients. The most common presentations are deep vein thrombosis (DVT) of the lower extremity and pulmonary thromboembolism (PTE) (1, 2). Early diagnosis of these events may decrease associated mortality and morbidity (3). Tuberculosis (TB) is a disease with wide variety of clinical presentations. Like other infections, it can cause thrombosis (4-6) by various mechanisms such as local invasion, venous compression (7) or by producing a transitory hypercoagulable state (8). Hemostatic abnormalities can be normalized with adequate anti-tuberculosis therapy, although rifampin may result in higher risk of DVT by decreasing level of anticoagulants (4, 9).

### 2. Objectives

This study was performed to evaluate incidence, characteristic pattern and risk factors of thrombo-embolic events

among patients with TB in our center as a tertiary hospital and referral center for tuberculosis patients in Iran.

### 3. Patients and Methods

This prospective study was performed in National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran, Iran from August 2007 to November 2009. During this period, 1,153 new cases of pulmonary or extra-pulmonary TB were admitted. Doppler sonography with linear probe (6-12 MHz) was done for patients, suspected to have DVT (i.e. symptoms or signs such as calf pain, edema, erythema and warmth in the lower extremities or positive Homan's sign) (10). In addition, probable cases of PTE were evaluated by computerized tomography (CT) scan of the lung with intravenous contrast. The diagnosis of DVT was made by findings such as abnormal compressibility of the vein, abnormal Doppler color flow or the presence of an intra-luminal echogenic band.

On lung spiral CT scan with intravenous contrast, PTE

#### Implication for health policy/practice/research/medical education:

Deep venous thrombosis and pulmonary thromboembolism are common among TB cases, especially men, hypertensive patients and opium addicts. Accordingly, prophylactic measures have to be considered.

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was diagnosed with the presence of intraluminal filling defect and arterial flow cut-off. Prophylactic strategies for prevention of DVT and PTE were performed based on guidelines (11, 12). The incidence of thromboembolism was calculated in this period. A control group, consisting of 100 TB cases without thromboembolism was selected randomly. The risk factors of thrombosis between cases and control group were compared. These factors were sex, age, smoking status, opium and intravenous drug addiction, history of thrombo-embolic event, hypertension, diabetes mellitus, and other co-morbidities. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg or known history of hypertension under control with anti-hypertensive drugs (13). Human immune deficiency virus (HIV) test was performed for intravenous drug abusers and patients with history of high risk behaviors. History of anti-tuberculosis treatment and rifampin dose were considered.

### 3.1. Statistical Analysis

All data was entered into the SPSS software (Version 15.0) for statistical analysis. The Chi-Square test was used for nominal variables, and the Fisher's exact test as necessary. To analyze for risk factors, we also used logistic regression for risk factors of thromboembolism. A P value

$< 0.05$  was considered statistically significant. To determine the independent risk factors, a multivariate logistic regression analysis was performed for the factors which had P values of  $< 0.2$  in univariate analysis. The Scientific and Ethics Committee of the NRITLD approved the study protocol.

## 4. Results

Study was performed on 1,153 hospitalized TB patients with mean (SD) age of  $52 \pm 22$  years. Of them 51.8% was man. Thirty two patients were found to have thromboembolism (2.8%; 95% CI: 1.9 - 3.9). Median interval from beginning of anti-TB medications to diagnosis of thromboembolism was 14 days, all of them occurred before the 60th day of treatment. Sixteen (50%) of these patients with thromboembolism had received anti-coagulation prophylaxis. The incidence of DVT was 2% (23 cases) and it was 1% for PTE (11 cases), three patients had both complications. Also, one patient suffered from arterial thrombosis. Thrombo-embolic events and DVT were more common among men than in women; 4.2% versus 1.3% ( $P = 0.003$ ) and 3.5% versus 0.4% ( $P < 0.001$ ), respectively. There was no significant difference in incidence of PTE between men and women (1.2% vs. 0.7%,  $P > 0.05$ ). Comparing cases and control groups, there was not any significant difference in incidence of TEE given the age of the subjects ( $P > 0.05$ ).

**Table 1.** Comparison of Risk Factors Between Case and Control Groups

	Case Group, No. (%)	Control Group, No. (%)	OR <sup>a</sup>	95% CI <sup>a</sup>	P value
<b>Gender male</b>	26 (81.2)	48 (48)	4.69	1.78 - 12.40	0.001 <sup>b</sup>
<b>Age</b>					
Mean, y	55 $\pm$ 20	50 $\pm$ 22			0.236
$\geq 65$ years	13 (40.6)	35 (35)	1.27	0.56 - 2.88	0.565
<b>Types of habit</b>					
Active smoker	13 (40.6)	24 (24)	2.17	0.93 - 5.03	0.068
<b>Types of addiction</b>					
Opium	15 (46.9)	22 (22)	3.13	1.36 - 7.25	0.006 <sup>b</sup>
IDUs <sup>a</sup>	7 (21.9)	12 (12)	2.05	0.73 - 5.77	0.166
<b>Types of disease</b>					
Diabetes mellitus	3 (9.4)	12 (12)	0.76	0.20 - 2.88	1.000
HIV <sup>a</sup>	4 (12.5)	8 (8)	1.64	0.46 - 5.87	0.484
Hypertension	9 (28.1)	13 (13)	2.62	1.00 - 6.88	0.046 <sup>b</sup>
Total	32	100			

<sup>a</sup> Abbreviations: OR, odds ratio; CI, confidence interval; IDU, intravenous drug user; HIV, human immunodeficiency virus

<sup>b</sup> significant

Hypertension was more common among patients with thromboembolism than in control group: 28.1% versus 13% ( $P = 0.046$ ). Furthermore, opium addiction was

more common among cases with thromboembolism than in control group: 46.9% versus 22% ( $P = 0.006$ ). Although, there was not any significant relation

between history of thromboembolism and its recent occurrence, both persons with positive history, had recurrent episodes concomitant with TB. One of them was a known case of Behcet's disease and another was a known case of hypercoagulable disorder due to factor V Leiden complicated by TB and concomitant lung adenocarcinoma. There was no relation between TEE and prescription of medical prophylaxis for DVT and other risk factors such as smoking, diabetes mellitus and dose of rifampin between cases and control group. After adjusting with logistic regression, sex, hypertension and opium addiction retained their statistical significance. Results are summarized in Table 1.

## 5. Discussion

Thromboembolism, as a frequent cause of morbidity and mortality in hospitalized patients, may be asymptomatic in over 70% of patients; so many cases are not diagnosed (11). In admitted patients, the prevalence of thromboembolism is approximately 100 times higher than in general population (10). Incidence of thromboembolism was 2.8% (2% for DVT and 1% for PTE) in our admitted TB cases in spite of prophylaxis for high risk patients. There are many studies about the incidence of thromboembolism especially DVT in admitted patients. In a large study, among 612,000,000 hospital admissions over 21 years, average incidence of thromboembolism, DVT and PTE were 1.24%, 0.93% and 0.4%, respectively (14). Stein and colleagues reported prevalence of proximal DVT as 0.78% in a general hospital (15). These were reported as 0.1% and 0.18% in other studies (16, 17). Studies about incidence of thromboembolism among TB patients are scarce. In a retrospective study, White reported DVT in 46 (3.4%) of 1,366 adult cases of TB, who were admitted in 1986. In addition, he found a relative risk of 4.74 for DVT in patients treated with regimens including rifampin compared with other regimens among 7,542 admissions during 1978-86 (18). El Fekih and colleagues reported 14 cases of DVT associated with TB in a period of 7 years, all of them were men and DVT occurred within a mean of 20 days after the diagnosis of TB was made (19). In Italy, among 1,237 cases of TB, seven patients were complicated by thromboembolism (0.6%) and incidence of DVT was 0.4% (20).

The estimation of thromboembolism in non-TB patients in our center has not stated yet but we found significantly higher incidence among our TB patients in comparison to the above mentioned studies ( $P < 0.001$ ). To our knowledge, mentioned Italian study is the only report about the incidence of PTE in TB patients. They found four cases among 1,237 TB patients (0.3%), two of them concomitant with DVT (20). Stein reported incidence of PTE in a general hospital as 0.23% but he showed that it is higher in a tertiary care hospital (21). Higher incidence of PTE (1%) in our patients is remarkable. It is reported that

60% of patients with symptomatic PTE may have lower-limb DVT, mostly asymptomatic, but the presence of DVT had no detectable prognostic impact and no result in additional treatment (22). We found symptomatic DVT in three cases among eight TB patients with PTE.

Our study showed a relation between sex, hypertension and opium addiction with thromboembolism but the number of cases was limited and a larger study is necessary for evaluating other risk factors. Stein and colleagues also found higher incidence of DVT among men aged 20 to 49 years (15). In a study from Iran, the crude odds ratio of opioid addiction for DVT was 4.25 (95% CI = 2.6 - 6.9) but multivariate logistic regression analysis revealed that opioid addiction was not an independent risk factor for DVT (23). It may be due to lower physical activity of these patients and other comorbidities. Acute infectious disease is a known risk factor for thrombo-embolic events (11, 24). Among cases of active TB, hypercoagulable state may be related to hemostatic changes consisting of elevated plasma fibrinogen with impaired fibrinolysis, a decrease in antithrombin III, a decrease in protein C, and reactive thrombocytosis (8, 25, 26). The hypercoagulable state also has been reported in childhood TB (27). Additional studies required to determine clinical aspects of thromboembolism among TB patients. This study was performed in a tertiary hospital and this may cause selection bias, because many of our patients were complicated. However, it deemed necessary to pay special attention to thromboembolism in admitted (and probably non-admitted) TB patients. In conclusion, incidence of DVT and PTE is noticeable among TB patients and it may be more frequent among male, hypertensive and opium addicts.

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## Authors' Contribution

Study concept and design: Marjani, Tabarsi and Velayati. Data collection: Baghaei and Gorgi Biani. Analysis and data interpretation: Baghaei and Marjani. Drafting of the manuscript: Marjani and Shamaei. Critical revision of the manuscript: Marjani, Masjedi and Mansouri.

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## References

1. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Manage-

- ment of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med.* 2007;**146**(3):211-22.
2. Lawall H, Hoffmanns W, Hoffmanns P, Rapp U, Ames M, Pira A, et al. Prevalence of deep vein thrombosis (DVT) in non-surgical patients at hospital admission. *Thromb Haemost.* 2007;**98**(4):765-70.
  3. Elliott CG, Goldhaber SZ, Jensen RL. Delays in diagnosis of deep vein thrombosis and pulmonary embolism. *Chest.* 2005;**128**(5):3372-6.
  4. Goncalves IM, Alves DC, Carvalho A, do Ceu Brito M, Calvario F, Duarte R. Tuberculosis and Venous Thromboembolism: a case series. *Cases J.* 2009;**2**:9333.
  5. Fiorot Junior JA, Felicio AC, Fukujima MM, Rodrigues CA, Morelli VM, Lourenco DM, et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? *Arq Neuropsiquiatr.* 2005;**63**(3B):852-4.
  6. Fullerton DG, Shrivastava A, Munavvar M, Jain S, Howells J, Macdowall P. Pulmonary tuberculosis presenting with central retinal vein occlusion. *Br J Ophthalmol.* 2007;**91**(12):1714-5.
  7. Gogna A, Pradhan GR, Sinha RS, Gupta B. Tuberculosis presenting as deep vein thrombosis. *Postgrad Med J.* 1999;**75**(880):104-5.
  8. Robson SC, White NW, Aronson I, Woolgar R, Goodman H, Jacobs P. Acute-phase response and the hypercoagulable state in pulmonary tuberculosis. *Br J Haematol.* 1996;**93**(4):943-9.
  9. Naithani R, Agrawal N, Choudhary VP. Deep venous thrombosis associated with tuberculosis. *Blood Coagul Fibrinolysis.* 2007;**18**(4):377-80.
  10. Minichiello T, Fogarty PF. Diagnosis and management of venous thromboembolism. *Med Clin North Am.* 2008;**92**(2):443-65.
  11. Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med.* 2007;**356**(14):1438-44.
  12. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;**126**(3 Suppl):338S-400S.
  13. Mansia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press.* 2007;**16**(3):135-232.
  14. Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. *Am J Cardiol.* 2005;**95**(12):1525-6.
  15. Stein PD, Patel KC, Kalra NK, El Baage TY, Savarapu P, Silbergleit A, et al. Deep venous thrombosis in a general hospital. *Chest.* 2002;**122**(3):960-2.
  16. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol.* 2000;**85**(11):1334-1337.
  17. Igbini A, Malik GM, Grillo IA, Seidi OA, Egere JU, Hachem MM, et al. Deep venous thrombosis in Assir region of Saudi Arabia. Case-control study. *Angiology.* 1995;**46**(12):1107-13.
  18. White NW. Venous thrombosis and rifampicin. *Lancet.* 1989;**2**(8660):434-5.
  19. El Fekih L, Oueslati I, Hassene H, Fenniche S, Belhabib D, Megdiche ML. Association deep venous thrombosis with pulmonary tuberculosis. *Tunis Med.* 2009;**87**(5):328-9.
  20. Ambrosetti M, Ferrarese M, Codecasa LR, Besozzi G, Sarassi A, Viggiani P, et al. Incidence of venous thromboembolism in tuberculosis patients. *Respiration.* 2006;**73**(3):396.
  21. Stein PD, Huang HL, Afzal A, Noor HA. Incidence of acute pulmonary embolism in a general hospital: relation to age, sex, and race. *Chest.* 1999;**116**(4):909-13.
  22. Girard P, Sanchez O, Leroyer C, Musset D, Meyer G, Stern JB, et al. Deep venous thrombosis in patients with acute pulmonary embolism: prevalence, risk factors, and clinical significance. *Chest.* 2005;**128**(3):1593-600.
  23. Masoomi M, Ramezani MA, Shahriari S, Shahesmaeeli A, Mirzaeepour F. Is opium addiction a risk factor for deep vein thrombosis? A case-control study. *Blood Coagul Fibrinolysis.* 2010;**21**(2):109-12.
  24. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med.* 2004;**164**(9):963-8.
  25. Turken O, Kunter E, Sezer M, Solmazgul E, Cerrahoglu K, Bozkanat E, et al. Hemostatic changes in active pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2002;**6**(10):927-32.
  26. Baynes RD, Bothwell TH, Flax H, McDonald TP, Atkinson P, Chetty N, et al. Reactive thrombocytosis in pulmonary tuberculosis. *J Clin Pathol.* 1987;**40**(6):676-9.
  27. Schoeman J, Mansvelt E, Springer P, van Rensburg AJ, Carlini S, Fourie E. Coagulant and fibrinolytic status in tuberculous meningitis. *Pediatr Infect Dis J.* 2007;**26**(5):428-31.