Global epidemiology of venous thromboembolism in people with active tuberculosis: a systematic review and meta-analysis

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Abstract

Background: despite the wide range of studies supporting an association between exposure to active tuberculosis and risk of venous thromboembolism (VTE), the current systematic review and meta-analysis is the first study assessing the global epidemiology of VTE in patients having active tuberculosis.

Methods: In this systematic review and meta-analysis, EMBASE, PubMed, and Web of Science were searched to identify observational studies, published until December 15, 2019, and reporting on venous thromboembolism in patients with active tuberculosis. No language restriction was applied. Studies were synthetized using a random-effect model. This review is registered with PROSPERO, CRD42019130347.

Results: we included 9 studies with an overall total of 16,190 patients. The prevalence of VTE was 3.5 % (95%CI: 2.2-5.2) in patients with active tuberculosis. Furthermore, we found a prevalence of pulmonary embolism (PE) at 5.8% (95%CI: 2.2-10.7) and for deep vein thrombosis (DVT) at 1.3% (95%CI: 0.8-2.0) in patients with active tuberculosis. Patients with active tuberculosis had a higher risk for VTE (OR: 2.90; 95% CI: 2.30-3.67), DVT (OR: 1.56; 95% CI: 1.14-2.14), and PE (OR: 3.58; 95% CI: 2.54-5.05).

Conclusion: this study suggests that VTE is not rare among patients with active TB. Cost-effective preventive strategies and interventions to curb this dreadful burden of VTE among people with active TB are needed.

Keywords: Venous thromboembolism; tuberculosis; review; epidemiology; meta-analysis

INTRODUCTION

Tuberculosis (TB) is a contagious and life-threatening preventable infectious disease caused by a microorganism called *Mycobacterium tuberculosis* (1,2). It is one of the most common infectious diseases worldwide and affects almost 1/4 of the global population, 5-10% of whom will develop active TB (3). In 2017 South-East Asia, Western Pacific and Africa had the highest number of new diagnosed cases (4). Despite the availability of effective treatment, TB is still associated with a high mortality (2). It is estimated that 1.6 million people died because of tuberculosis, of whom 0.3 million were Human Immunodeficiency Virus (HIV) positive in 2017(4). This high mortality is partly due to the emergence of drug resistance (3.4% new cases of rifampin resistance reported in 2017, and 18 % among previously treated patients), and the presence of comorbidities that are often under-diagnosed in low-and-middle income countries, but that can be life-threatening such as venous thromboembolism (VTE) (3,5,6). Indeed, recent studies suggest an epidemiological and patho-physiologically plausible association between tuberculosis and VTE (7,8). Tuberculosis would act on the three components of the Virshow triad leading to an increased risk of venous thromboembolic event (7,9).

Despite the increasing number of studies reporting the association between TB and VTE, no study has to date summarised available evidence on the epidemiology of VTE in people with active TB (10,11). We herein propose the first systematic review and meta-analysis to determine the global prevalence of VTE in patients with active tuberculosis, and to investigate the risk of VTE for patients with active TB. Results would help to draw the attention of physicians and policymakers to the need for thorough monitoring of and preventive measures against VTE in patients having TB.

METHOD

The Meta-analyses and Systematic reviews of Observational Studies (MOOSE) guideline was used as template to report the current review (12). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019130347). This study was conducted according to the published protocol in a peer-review journal (13).

Search strategy and selection criteria

In brief, we searched EMBASE, Medline, and Web of Science (Web of Science Core Collection, Current Contents Connect, KCI-Korean Journal Database, SciELO Citation Index, Russian Science Citation Index) to identify observational studies, published until December 15, 2019, without language restriction, on VTE in patients having active TB. The initial search strategy was designed for EMBASE and was adapted to fit with other databases. The search strategy as illustrated in the study protocol was based on the combination of relevant text words and medical subject headings related to VTE and TB (13). Moreover, the references of all relevant articles found were scrutinized for potential additional data sources.

Selection of studies for inclusion in the review

We included cross-sectional, cohort studies, case–control, and case series with at least 30 participants. Letters, reviews, commentaries and editorials, studies lacking key data and/or explicit method description as well as studies in which relevant data on VTE was impossible to extract even after contacting the corresponding author were excluded. We considered studies conducted among adults (> 15 years) with enough data to compute the prevalence of VTE, PE, and DVT in people with active pulmonary TB or extrapulmonary drug-susceptible or drug-resistant TB. We also considered studies conducted among adults (> 15years) with enough data to compute the association between exposure to active TB and the occurrence of VTE, PE, and DVT.

Data extraction and management

Two authors (CD and JJB) independently screened the title and abstract of articles for eligibility. Full text of potentially eligible articles was retrieved and screened for final inclusion. Disagreements between the two authors were solved by discussion.

A data extraction sheet was used by two reviewers (CD and JJB) to independently extract data from individual studies. The surname of the first author, year of publication, country where the study was conducted, study design, sampling method, timing of data collection, mean or median age, proportion of males, specific characteristics of the study population, sample size, number of cases of VTE, ascertainment of active TB, DVT and VTE were retrieved.

To evaluated the methodological quality of each study, two reviewers (CD and JJB) used an adapted version of the tool of bias assessment for prevalence studies developed by Hoy and colleagues (14).

Data analysis

In the current study, prevalence was defined as the number of cases (VTE or PE or DVT) occurring divided by the total number of patients with active TB.

In order to measure the association between exposure to active tuberculosis and risk for VTE, a DerSimonian and Laird random-effect meta-analysis was performed to obtain an overall summary estimate (odds ratio) with 95% confidence intervals (95%CI). (15). For prevalence meta-analysis, unadjusted prevalence with their standard errors in each study were recalculated based on the information of crude numerators and denominators provided by individual studies. The variance of the study-specific prevalence were stabilized with the Freeman-Tukey double arc-sine transformation (16), before computing a common value (summary effect) using a random-effect meta-analysis model. All summaries effects were reported with 95% confidence interval. The presence of heterogeneity was determined using the χ^2 test on Cochran's Q statistic (17) and the I^2 values (18).

Inter-rater agreement for study inclusion was assessed using Cohen's κ coefficient (19). Egger's test ($p < 0.10$) were performed to detect the presence of publication bias (20). A *p* value <0.05 was considered as statistically significant. Meta-analysis was conducted with R, version 3.6.1.

RESULTS

Study selection

After database searches, 1459 citations were identified. Duplicates were removed and 65 potentially eligible full texts were scrutinized for final inclusion after screening of title and abstract of retrieved citations. Finally, nine study met the inclusion criteria and were included in the narrative and quantitative synthesis (21–29). Supplementary Figure 1 displays the process of study selection. The Cohen's coefficient for the selection of studies based on title and abstract was 0.71.

Characteristics of included studies

Studies included in this review were from South Africa (26,29), Egypt (24), France (21), Israel (28), Iran (24), South Korea (25), Netherlands (22). Studies were conducted between 1981, and 2018. Two studies prospectively collected data while all the others were retrospective. Two studies were clinical series while others were cross-sectional. The male proportion varied from 29.9% to 81.2 %, and the mean/median age varied from 35 to 70 years (Table 1). Three studies had a low risk, five a moderate, and one a high risk of bias (Table 1).

Prevalence of venous thromboembolism in people with active tuberculosis

Figure 1 depicts details on the prevalence analysis. Overall, the prevalence of VTE in people with active tuberculosis was 3.5 % (95%CI: 2.2-5.2; 9 studies; 16,190 participants) (Figure 1). For the components of VTE, the prevalence of PE and DVT in people with active tuberculosis was 5.8% (95%CI: 2.2-10.7; 6 studies; 5,512 participants) and 1.3% (95%CI: 0.0-4.1; 5 studies;

12,928 participants) (Figure 1). There was substantial heterogeneity for all prevalence analyses (Figure 1). There was no publication bias except for the PE outcome (Table 1). The leave-one-out analysis demonstrated that excluding each study yielded a prevalence in the range of the crude analysis (Supplementary Figures 2, 3, and 4). In subgroup analysis, the prevalence of VTE in patients with TB diagnosed with newest method namely MALDI-TOF and PCR (8.1%; 95%CI: 0.0-40.7) was not significantly different from the one in the subgroup where diagnosis was made with other diagnostic tools (3.4%; 95%CI: 2.0-5.1), p =0.60 (Figure 1).

Association between VTE and active tuberculosis

Only one study with 3,485 participants with active TB and 27,656,462 without was eligible for the quantitative synthesis (23). Participants with active TB were more likely to have VTE (OR: 2.90; 95% CI: 2.30-3.67), DVT (OR: 2.47; 95% CI: 1.80-3.39) and PE (OR: 3.58; 95% CI: 2.54-5.05) (Figure 2).

DISCUSSION

In the current systematic review with meta-analysis, we found that 35 out of 1000 patients having active TB may experience VTE. Although the evidence was from one high sample size study, we found that patients with active TB had an increased risk to present VTE, PE and DVT. The burden of VTE in people with active tuberculosis is high, compared to the general population (30–33). The global prevalence we found in this review was 4 to 8 times higher compared to the one estimate in the general population (1.2% to 2.7%) (30,31). This suggests that patients with active TB are at a higher risk to develop VTE compared to the general population as confirmed in this study. Indeed, evidence from the sole study we found, demonstrated that the risk was three times higher in people with active TB compared to those without. The increased risk may be due by TB itself or may be induced by rifampicin used for the treatment of TB (29). Indeed, three elements represent the cornerstones of VTE

pathophysiology: stasis, endothelial lesions, and hypercoagulability (34,35). Active TB induces enlargement of lymph nodes which can lead to compression of venous system and stasis (23). Moreover, having active TB favors bed rest, limiting peripheral muscles contractions for blood circulation, one of the most important mechanism of venous blood circulation (36). Concerning hypercoagulability, TB induces chronic inflammation and thus disturbs the blood clothing pathways by increasing the plasma level of factor VIII, fibrinogen, and plasminogen activator inhibitor 1, while reducing the plasma level of protein C and antithrombin III (7,8). Furthermore, chronic inflammation linked to the presence of *Mycobacterium tuberculosis*, and the use of rifampicin as an anti-tuberculosis drug are thought to be the cause of endothelial lesions (9). White *et al.*, in a study done on a sample of 7542 patients, found that the risk of having DVT in patients treated with rifampicin was five times higher compared to patients treated without (29). Active TB may therefore favour the occurrence of the component of Virchow's triad and induce a state prone to VTE especially during the first month of treatment (8).

In the general population, the estimated global incidence of VTE and PE is about 45-117 per 100,000 person-year and 29-78 per 100,000 person-year, respectively (32,37,38). We found a high prevalence of PE and DVT in patients with active TB. As per VTE, the mechanism underlining this high prevalence is probably the same. Moreover, we found a higher prevalence of PE compared to DVT. Because clinicians tend to request chest CT scans in any patient with persistent pulmonary symptomatology, particularly in patients with tuberculosis, this usually leads to over-diagnosis of pulmonary embolism. On the other hand, Doppler ultrasonography of the lower limbs has much more limited indications, thus limiting the incidental discovery of venous thrombosis of the limbs. Moreover, the new and more performant imaging technics used to diagnose pulmonary embolism make it easy to rule-out the presence of this condition even by a non-qualified team. On the contrary, the diagnosis of DVT is very sensitive to the

experience and qualification of the team involved, given that it is done with ultrasonography which are known to be operator-dependant (39,40).

The findings of this study call clinicians, policy makers and researchers for efficient interventions to reduce the burden of VTE among people with active tuberculosis. This would help to reduce mortality in people with active TB. Cost-effective interventional studies are needed to inform policy makers on how to implement strategies to prevent and reduce the burden VTE in patients with active TB. Tuberculosis treatment centres should have trained personnel able to diagnose and treat VTE.

The results of the current review should be considered in the context of some limitations. Firstly, we included only one study that investigated the association between active TB and VTE. Secondly, in the estimation of the prevalence of VTE in patients with active TB, we did not identify studies from South-East Asia WHO region. This can hinder the generalisability of the findings. Thirdly, VTE and its components (PE and DVT) were not systematically searched in all patients with active TB. Only patients with clinical presentation of VTE were screened. Therefore, the prevalence of VTE in active TB patients may be higher than the estimates we found since some patients may have clinically silent VTE. Despite these limitations, this is the first systematic review and meta-analysis summarizing the current evidence on the burden of VTE in people with active tuberculosis. A protocol has been published before, and we used rigorous methodological and statistical procedures to obtain and pool data.

Conclusion

This study suggests a high prevalence of VTE in patients with active tuberculosis. We estimated that 35 out of 1000 people living with active TB may experience VTE, a life-threatening disease. Cost-effective prevention strategies and innovative interventions to curb this dreadful

burden of VTE among people with active TB are needed. High quality observational studies are needed to better investigate the association between active TB and the risk for VTE.

List of abbreviations

DVT: deep venous thrombosis

HIV: Human Immunodeficiency Virus

MOOSE: Meta-analyses and Systematic reviews of Observational Studies

PE: pulmonary embolism

PROSPERO: Prospective Register of Systematic Reviews

TB: tuberculosis

VTE: venous thromboembolism

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

CD and APA conceived the study and with JJB, designed the protocol. CD and JJB did the literature search. CD and JJB selected the studies. CD and JJB extracted the relevant information. CD and JJB synthesized the data. CD wrote the first draft of the paper. CD, PAA, RNN, JJB, and AR critically revised successive drafts of the paper and approved the final version. AR supervised the overall work. CD is the guarantor of the review.

Acknowledgements

None.

REFERENCES

1. Corbett EL, Marston B, Churchyard GJ, Cock KMD. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. The Lancet. 2006 Mar 18;367(9514):926–37.

2. Dheda K, Barry CE, Maartens G. Tuberculosis. The Lancet. 2016 Mar 19;387(10024):1211–26.

3. WHO | Global tuberculosis report 2019 [Internet]. WHO. [cited 2019 Nov 2]. Available from: http://www.who.int/tb/publications/global_report/en/

4. WHO | 10 facts on tuberculosis [Internet]. WHO. [cited 2019 Sep 2]. Available from: http://www.who.int/features/factfiles/tuberculosis/en/

5. Khan PY, Yates TA, Osman M, Warren RM, Heijden Y van der, Padayatchi N, et al. Transmission of drug-resistant tuberculosis in HIV-endemic settings. Lancet Infect Dis. 2019 Mar 1;19(3):e77–88.

6. Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med. 2017 Apr 1;5(4):291–360.

7. Robson SC, White NW, Aronson I, Woollgar R, Goodman H, Jacobs P. Acute-phase response and the hypercoagulable state in pulmonary tuberculosis. Br J Haematol. 1996 Jun;93(4):943–9.

8. 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 Off J Int Union Tuberc Lung Dis. 2002 Oct;6(10):927–32.

9. Lang IM, Mackman N, Kriett JM, Moser KM, Schleef RR. Prothrombotic activation of pulmonary arterial endothelial cells in a patient with tuberculosis. Hum Pathol. 1996 Apr;27(4):423–7.

10. Ben Amar J, Dahri B, Aouina H, Bouacha H. [Venous thromboembolism in patients with acute tuberculosis]. Rev Pneumol Clin. 2015 Dec;71(6):327–34.

11. Kouismi H, Laine M, Bourkadi J-E, Iraqi G. Association of deep venous thrombosis with pulmonary tuberculosis. Egypt J Chest Dis Tuberc. 2013 Jul 1;62(3):541–3.

12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008–12.

13. Awana PA, Danwang C, Tochie JN, Bigna JJ. Epidemiology of venous thromboembolism in people with active tuberculosis: a systematic review and meta-analysis protocol. BMJ Open. 2019 Nov 12;9(11):e031402.

14. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep;65(9):934–9.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015 Nov;45(Pt A):139–45.

16. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. Am Stat. 1978 Nov;32(4):138–138.

17. Cochran: The combination of estimates from different... - Google Scholar [Internet]. [cited 2018 Aug 23]. Available from: https://scholar.google.com/scholar_lookup?hl=en&volume=10&publication_year=1954&pages=101-129&journal=Biometrics&author=GW+Cochran.&title=The+combination+of+estimates+from+different+experiments

18. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006 Jun;11(2):193–206.

19. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005 May;37(5):360–3.

20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.

21. Thromboses in tuberculosis are linked to antiphosphatidylethanolamine antibodies levels: A cross-sectional study - ScienceDirect [Internet]. [cited 2019 Oct 2]. Available from: https://www.sciencedirect.com/science/article/pii/S2405579418300913

22. Borjas-Howard JF, Bierman WFW, Meijer K, van der Werf TS, Tichelaar YIGV. Venous thrombotic events in patients admitted to a tuberculosis centre. QJM Mon J Assoc Physicians. 2017 Apr 1;110(4):215–8.

23. Dentan C, Epaulard O, Seynaeve D, Genty C, Bosson J-L. Active tuberculosis and venous thromboembolism: association according to international classification of diseases, ninth revision hospital discharge diagnosis codes. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Feb;58(4):495–501.

24. Marjani M, Tabarsi P, Baghaei P, Shamaei M, Biani PG, Mansouri D, et al. Incidence of Thromboembolism in Hospitalized Patients With Tuberculosis and Associated Risk Factors. Arch Clin Infect Dis [Internet]. 2012 Apr 28 [cited 2019 Oct 3];7(2). Available from: http://archcid.com/en/articles/20867.html

25. Park SY, Lee SM, Shin JW, Choi BW, Kim H, Lee JS, et al. Epidemiology of chronic thromboembolic pulmonary hypertension in Korea: results from the Korean registry. Korean J Intern Med. 2016 Mar;31(2):305–12.

26. Ramlakhan R, Andronikou S, Rajkumar A. The prevalence and radiological findings of pulmonary embolism in HIV-positive patients referred for computed tomography pulmonary angiography in the Western Cape of South Africa. Cardiovasc J Afr. 2017 Aug 23;28(4):221–8.

27. Shaarawy H, Mohamed EE-S. Assessment of the prevalence of pulmonary embolism in patients with severe pulmonary tuberculosis. Egypt J Chest Dis Tuberc. 2018 Jan 1;67(1):62.

28. Shitrit D, Fox L, Preiss R, Raz M, Mtvitzuk A. [Incidence of venous thromboembolism in 700 patients with acute tuberculosis]. Harefuah. 2012 Apr;151(4):208–10, 254.

29. White N. VENOUS THROMBOSIS AND RIFAMPICIN. The Lancet. 1989 Aug 19;334(8660):434–5.

30. Wendelboe Aaron M., Raskob Gary E. Global Burden of Thrombosis. Circ Res. 2016 Apr 29;118(9):1340–7.

31. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014;12(10):1580–90.

32. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015 Aug;12(8):464–74.

33. Danwang C, Temgoua MN, Agbor VN, Tankeu AT, Noubiap JJ. Epidemiology of venous thromboembolism in Africa: a systematic review. J Thromb Haemost JTH. 2017 Sep;15(9):1770–81.

34. Kyrle PA, Eichinger S. Deep vein thrombosis. Lancet Lond Engl. 2005 Apr 26;365(9465):1163–74.

35. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008 Oct;143(2):180–90.

36. CV Physiology | Factors Promoting Venous Return [Internet]. [cited 2019 Nov 6]. Available from: https://www.cvphysiology.com/Cardiac%20Function/CF018

37. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998 Mar 23;158(6):585–93.

38. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000 May;83(5):657–60.

39. Sarolo L, Milan M, Turatti G, Bilora F, Prandoni P. Inter-observer variability of compression ultrasound for the assessment of residual vein thrombosis. Thromb Res. 2016 Sep;145:1–2.

40. Stamm M, Zavodni A, Mitchell L, Bonanni JR, Noga M. Evaluation of the interpretation of serial ultrasound examinations in the diagnosis of deep venous thrombosis in children: a retrospective cohort study. Can Assoc Radiol J J Assoc Can Radiol. 2014 Aug;65(3):218–24.

Figures Legend

Figure 1. Meta-analysis prevalence of venous thromboembolism, pulmonary embolism, and deep venous thrombosis in the global population with active tuberculosis

Figure 2. Association between venous thromboembolism and tuberculosis

Tables Legend

Table 1: Characteristics of studies included in the estimate of the prevalence of venous thromboembolism, pulmonary embolism, and deep venous thrombosis in patients with active tuberculosis