

RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT. *Background:* Recent studies have suggested that patients with idiopathic pulmonary fibrosis (IPF) may have a higher risk of venous thromboembolism (VTE) compared to general population even though the results were inconsistent. *Objective:* To investigate the risk of VTE among patients with IPF. *Methods:* Comprehensive literature review using MEDLINE and EMBASE database were performed to identify studies that compared the risk of VTE among patients with IPF to general population. Effect estimates from each study were combined together using random effect model, generic inverse variance method of DerSimonian and Laird. *Results:* Out of 510 retrieved articles, 5 studies met the inclusion criteria and were included in the meta-analysis. A significant risk of VTE in patients with IPF was observed with the pooled risk ratio of 2.11 (95% confidence interval, 1.28-3.48). The heterogeneity was moderate with I^2 of 64%. *Conclusion:* An approximately 2-fold increased risk of VTE among patients with IPF was observed in this meta-analysis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35: 109-114)

KEY WORDS: idiopathic pulmonary fibrosis, venous thromboembolism, thrombosis, deep vein thrombosis, pulmonary embolism

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a form of chronic progressive fibrosing interstitial lung disease characterized by the histopathologic pattern of usual interstitial pneumonia. Patients with IPF usually present with progressive respiratory symptoms with periods of acute exacerbations, resulting in significant morbidity and mortality. Prognosis of patients

with IPF is poor with median survival of only two to five years (1). The exact etiology is still unknown despite extensive research effort. There is no medication with proven efficacy for IPF and current standard treatment focuses mainly on symptom relief although lung transplantation could be an option for selected patients (2).

Venous thromboembolism (VTE), which consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is one of the common medical problems with approximately 900,000 new and recurrent cases diagnosed every year in the United States (3). Traditional risk factors of VTE include cancer, trauma, surgery, immobilization hospitalization and use of certain medications (4, 5). More recently, chronic inflammation has been recognized as an independent risk factor for VTE as increased in-

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cidence of VTE has been observed in several chronic inflammatory conditions, such as rheumatoid arthritis, psoriasis, systemic vasculitis and inflammatory myositis (6-9).

Patients with IPF may be at an elevated risk of VTE as well due to their increased systemic inflammatory burden. In addition, patients with advanced respiratory symptoms are also likely to have limited mobility, resulting in venous stasis that can predispose to thromboembolism. In fact, several epidemiologic studies have suggested an association between IPF and VTE although the results are inconsistent (10-14). To further investigate this possible association, we performed a systematic review and meta-analysis of studies that compared the VTE risk in patients with IPF to subjects without IPF.

METHOD

Search strategy

Both investigators independently searched published articles in MEDLINE and EMBASE database from inception to February 2017 using the search terms for idiopathic pulmonary fibrosis and venous thromboembolism as described in online supplementary data without any language restriction. References of selected articles were also manually searched for additional studies.

Inclusion criteria

Studies were eligible for this meta-analysis if they met these inclusion criteria: 1) Cohort (either prospective or retrospective), case-control study or cross sectional study published as original study to evaluate the association between IPF and VTE, 2) odds ratios (OR), relative risk (RR), hazard ratio (HR), and standardized incidence ratio (SIR) with 95% confidence intervals (CI) or sufficient raw data to calculate these ratios were provided, and 3) subjects without IPF were used as comparators in cohort and cross-sectional study while subjects without VTE were used as controls in case-control study.

Study eligibility was independently evaluated by the two investigators. Any disagreement was resolved by mutual consensus. The quality of each study was appraised using the Newcastle-Ottawa quality scale

(15). This scale assesses each study in three domains including 1) the representativeness of the subjects, 2) the comparability between the study groups, and 3) ascertainment of the exposure of interest for case-control study and the outcome of interest for cohort study. The modified version of Newcastle-Ottawa scale as described by Herzog et al. was used for cross-sectional study (16).

Review process and data extraction

The two study investigators independently reviewed the titles and abstracts of all retrieved articles. Articles that clearly did not fulfill the inclusion criteria were excluded. Only potentially relevant articles underwent full-text review to determine the eligibility. A standardized data collection form was used to extract the following information from the included studies: first author's name, year of publication, year of study, country where the study was conducted, study design, source of population, number of subjects, baseline characteristics of the subjects, methods used to identify IPF and VTE, and effect estimates. This data extraction process was also performed by both investigators to ensure the accuracy.

Statistical analysis

All statistical analyses were performed using Review Manager 5.3 software from the Cochrane Collaboration (London, UK). The pooled RR of VTE in IPF patients in comparison to subjects without IPF was calculated using generic inverse method of DerSimonian and Laird (17). Random effect model was used given the high likelihood of between-study variance due to the difference in underlying population and methodology. As the outcome of interest was relatively uncommon, the ORs of cross-sectional study and case-control study were used as an estimate to pool with the RR from cohort study. Cochran's Q-test, which is supplemented by I^2 statistic, was used to evaluate the statistical heterogeneity. This I^2 statistic quantifies the proportion of the total variation across studies, that is, due to true heterogeneity rather than chance. A value of I^2 of 0% to 25% represents insignificant heterogeneity, more than 25% but $\leq 50\%$ represents low heterogeneity, more than 50% but $\leq 75\%$ represents moderate heterogeneity, and more than 75% represents high heterogeneity(18).

RESULTS

The initial search yielded 510 articles, all of which underwent title and abstract review. The majority of them were excluded at this step as they were case report, letter to editor, review article or interventional study which clearly did not fulfill our inclusion criteria. A total of 15 studies underwent full-

length article review and 10 of them were excluded at they did not include patients with IPF or did not report the outcome of interest. Therefore, a total of five studies met our inclusion criteria (four cohort studies and one cross-sectional study (10-14)) and were included in the meta-analysis. Baseline characteristics of the included studies are summarized in table 1.

Table 1. Main characteristics of the studies included in the meta-analysis. USA indicates United States of America; UK, United Kingdom; N/A, Not available; IPF, idiopathic pulmonary fibrosis

	Hubbard et al. [10]	Collard et al. [11]	Sprunger et al. [12]	Dalleywater et al. [13]	Navaratnam et al [14]
Country	UK	USA	USA	UK	UK
Study design	Retrospective cohort	Retrospective cohort	Cross-sectional study	Retrospective cohort	Prospective cohort
Year of publication	2008	2012	2012	2014	2014
Participants	Cases were identified from The Health Improvement Network database from general practitioners across the UK from 1991 to 2003. Comparators were sex and age-matched randomly selected from the same database.	Cases were identified from two US insurance databases from January 1, 2001 to September 30, 2008. Comparators were sex and age-matched randomly selected from the same database.	Cases were identified from the US cause-of-death mortality database of the National Centre for Health Statistics from 1988 to 2007. Comparators were the rest of subjects in the database.	Cases were identified from The Health Improvement Network database from general practitioners across the UK from 2000 to 2013. Comparators were sex and age-matched randomly selected from the same database.	Cases were recruited from five teaching hospitals and eight district general hospitals in the Greater Trent region and Wales between January 2010 and February 2012. Comparators were sex and age-matched recruited from the same hospitals.
Diagnosis of IPF	Diagnostic code from the registry	Diagnostic code from the registry	Diagnostic code from the registry	Diagnostic code from the registry	Diagnosis of IPF was made by clinicians who saw the patients based on clinical presentation and imaging study
Diagnosis of VTE	Diagnostic code from the registry	Diagnostic code from the registry	Diagnostic code from the registry	Diagnostic code from the registry	Self-reported by participants
Number of participants	Case 920 Comparator 3,593	Case 9,286 Comparator 9,286	Case 218,991 Comparator 46,450,489	Case 3,211 Comparator 12,307	Case 211 Comparator 256
Mean age (years)	Case 71 Comparator 71	Case 74 Comparator 74	N/A	Case 76 Comparator 76	Case 74 Comparator 71
Percentage of male	Case 62 Comparator 62	Case 55 Comparator 55	N/A	Case 64 Comparator 64	Case 75 Comparator 74
Confounder adjusted	Age, sex, smoking habit and medications	None	Age, sex, and year of death	Age, sex, smoking and use of warfarin	Age and sex
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 stars Comparability: 2 stars Outcome: 2 stars	Selection: 4 stars Comparability: 1 star Outcome: 2 stars	Selection: 4 stars Comparability: 1 star Outcome: 2 stars	Selection: 4 stars Comparability: 1 star Outcome: 2 stars	Selection: 4 stars Comparability: 2 stars Outcome: 2 stars

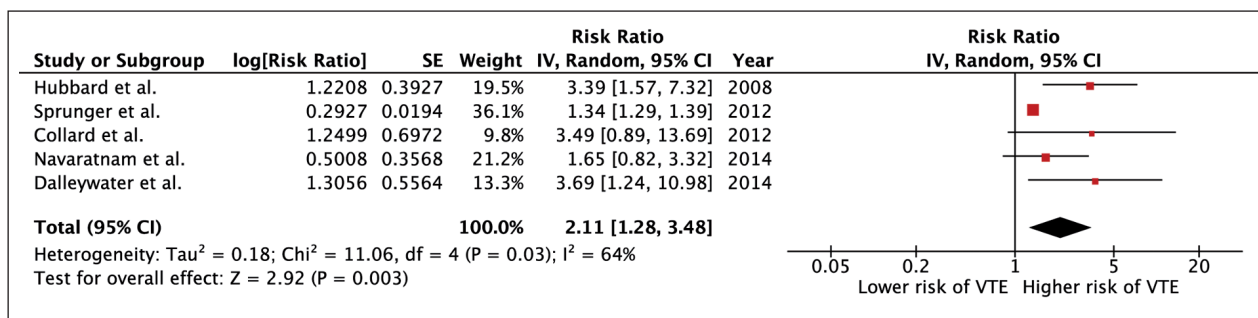


Fig. 1.

Our meta-analysis revealed a significantly increased risk of VTE among patients with IPF with the pooled RR of 2.11 (95% CI, 1.28-3.48). The heterogeneity was moderate with I^2 of 64%. Figure 1 demonstrates the forest plot of this study

Evaluation for publication bias

The funnel plot is shown in figure 2. It is symmetric and does not suggest the presence of publication bias in favor of positive study.

Sensitivity analysis

Since the statistical heterogeneity was not low in this meta-analysis, a sensitivity analysis was performed by excluding one study at a time to investigate the effect of each study on the overall heterogeneity. Interestingly, exclusion of the study by Sprunger et al. (12), the only cross-sectional study,

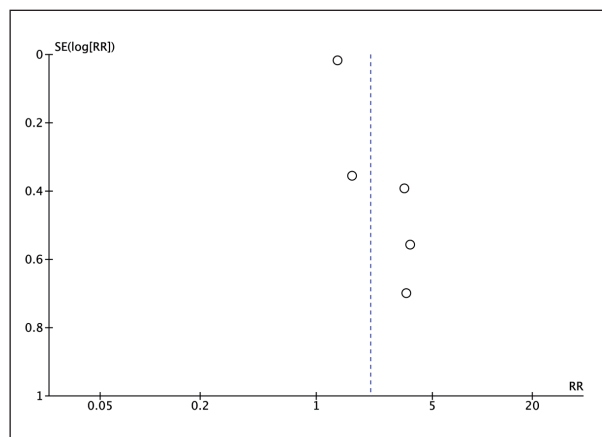


Fig. 2.

dramatically reduced I^2 to 0%. The pooled effect estimate from this sensitivity analysis remained essentially unchanged (RR 2.58; 95% CI, 1.66-4.02).

DISCUSSION

This is the first meta-analysis to demonstrate a significantly increased risk of VTE among patients with IPF. The risk is increased by approximately 2-fold. The exact mechanism behind the increased risk is not known but several possible explanations have been proposed.

First, the higher inflammatory burden in patients with IPF could be responsible for the increased tendency for blood clot. The underlying mechanisms of inflammation-induced thrombosis include up-regulation of coagulation factors and down-regulation of anticoagulants/fibrinolysis by inflammatory cytokines as well as injury to endothelial cells by free radicals and oxidative stress. Further evidence to support that inflammation plays an important role in the development of VTE is that VTE is observed more frequently when the inflammatory disease is active (19, 20).

Second, VTE and IPF may share a common origin. Thrombin, a key enzyme in coagulation cascade, could be the link as it is also an inducer of fibrogenic cytokines (21) and has been found in increased concentration in bronchoalveolar lavage from patients with fibrotic lung disease (22). In fact, a recent study has suggested that recombinant human thrombomodulin, which could form a reversible complex with thrombin to inactivate coagulation cascade, is effective for treatment of acute exacerbation of IPF (23).

Third, it is also possible that the increased risk is simply due to immobility as most patients with IPF have respiratory symptoms and reduced exercise capacity (24).

Fourth, the increased risk could be due to exposure to glucocorticoids, the medication often used to treat acute exacerbation of IPF. In vitro studies have demonstrated that glucocorticoids increase levels of coagulation factors and fibrinogen (25, 26). In addition, a dose-response relationship between exposure to glucocorticoids and incidence of VTE has been demonstrated by a recent population-based study (27).

Although the literature review process was rigorous and the included studies were of high quality, this meta-analysis has some limitations. Therefore, the interpretation of the results needs to be performed with caution. First, most of the included studies were medical registry-based studies, with the exception for the study by Navaratnam et al. (14), which were inherently at risk of inaccurate coding for both IPF and VTE. As a result, the completeness of case/event identification and the accuracy of diagnosis were limited. Second, statistical heterogeneity was not low in this study. Interestingly, the I^2 dropped dramatically to 0% with the sensitivity analysis that excluded the study by Sprunger et al. (12). We suspect that the difference in study design was responsible for the between-study heterogeneity as the study by Sprunger et al. was the only cross-sectional study. Third, this is a meta-analysis of observational studies that can only demonstrate an association but cannot confirm causality. It is possible that confounders that were not adjusted in the primary studies, rather than IPF itself, are accountable for the increased risk of VTE. Last, surveillance bias may also play a role. It is possible that patients with IPF may have more medical examinations because of their chronic illness. Also, they may have more imaging studies of the thorax due to their respiratory symptoms.

CONCLUSION

An approximately 2-fold increased risk of VTE among patients with IPF was observed in this meta-analysis.

REFERENCE

- Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine* 2011; 183(4): 431-40. Epub 2010/10/12. doi: 10.1164/rccm.201006-0894CI. PubMed PMID: 20935110.
- Raghu G, Rochwert B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *American journal of respiratory and critical care medicine* 2015; 192(2): e3-19. Epub 2015/07/16. doi: 10.1164/rccm.201506-1063ST. PubMed PMID: 26177183.
- Heit JA. The epidemiology of venous thromboembolism in the community. *Arteriosclerosis, thrombosis, and vascular biology* 2008; 28(3): 370-2. Epub 2008/02/26. doi: 10.1161/atvbaha.108.162545. PubMed PMID: 18296591; PubMed Central PMCID: PMC2873781.
- Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007; 92(2): 199-205. Epub 2007/02/14. PubMed PMID: 17296569.
- Ungrasert P, Srivali N, Wijarnpreecha K, Charoenpong P, Knight EL. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology (Oxford, England)* 2015; 54(4): 736-42. Epub 2014/09/26. doi: 10.1093/rheumatology/keu408. PubMed PMID: 25252703.
- Ungrasert P, Sanguankeo A. Risk of venous thromboembolism in patients with idiopathic inflammatory myositis: a systematic review and meta-analysis. *Rheumatology international* 2014; 34(10): 1455-8. Epub 2014/04/22. doi: 10.1007/s00296-014-3023-1. PubMed PMID: 24748492.
- Ungrasert P, Sanguankeo A, Upala S, Suksaranjit P. Psoriasis and risk of venous thromboembolism: a systematic review and meta-analysis. *QJM : monthly journal of the Association of Physicians* 2014; 107(10): 793-7. Epub 2014/04/10. doi: 10.1093/qjmed/hcu073. PubMed PMID: 24713224.
- Ungrasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Clinical rheumatology* 2014; 33(3): 297-304. Epub 2014/01/16. doi: 10.1007/s10067-014-2492-7. PubMed PMID: 24424839.
- Tomasson G, Monach PA, Merkel PA. Thromboembolic disease in vasculitis. *Current opinion in rheumatology* 2009; 21(1): 41-6. Epub 2008/12/17. doi: 10.1097/BOR.0b013e32831de4e7. PubMed PMID: 19077717; PubMed Central PMCID: PMCPCMC3204384.
- Hubbard RB, Smith C, Le Jeune I, Gribbin J, Fogarty AW. The association between idiopathic pulmonary fibrosis and vascular disease: a population-based study. *American journal of respiratory and critical care medicine* 2008; 178(12): 1257-61. Epub 2008/08/30. doi: 10.1164/rccm.200805-725OC. PubMed PMID: 18755924.
- Collard HR, Ward AJ, Lanes S, Courtney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. *Journal of medical economics* 2012; 15(5): 829-35. Epub 2012/03/30. doi: 10.3111/13696998.2012.680553. PubMed PMID: 22455577.
- Sprunger DB, Olson AL, Huie TJ, Fernandez-Perez ER, Fischer A, Solomon JJ, et al. Pulmonary fibrosis is associated with an elevated risk of thromboembolic disease. *The European respiratory journal* 2012; 39(1): 125-32. Epub 2011/07/09. doi: 10.1183/09031936.00041411. PubMed PMID: 21737559; PubMed Central PMCID: PMCPCMC3757572.
- Dalleywater W, Powell HA, Fogarty AW, Hubbard RB, Navaratnam V. Venous thromboembolism in people with idiopathic pulmonary fibrosis: a population-based study. *The European respiratory journal* 2014;

- 44(6): 1714-5. Epub 2014/10/18. doi: 10.1183/09031936.00099614. PubMed PMID: 25323238.
14. Navaratnam V, Fogarty AW, McKeever T, Thompson N, Jenkins G, Johnson SR, et al. Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case-control study. *Thorax* 2014; 69(3): 207-15. Epub 2013/09/05. doi: 10.1136/thoraxjnl-2013-203740. PubMed PMID: 24002055.
 15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010; 25(9): 603-5. Epub 2010/07/24. doi: 10.1007/s10654-010-9491-z. PubMed PMID: 20652370.
 16. Herzog R, Alvarez-Pasquin MJ, Diaz C, Del Barrio JL, Estrada JM, Gil A. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC public health* 2013; 13: 154. Epub 2013/02/21. doi: 10.1186/1471-2458-13-154. PubMed PMID: 23421987; PubMed Central PMCID: PMC3602084.
 17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986; 7(3): 177-88. Epub 1986/09/01. PubMed PMID: 3802833.
 18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003; 327(7414): 557-60. Epub 2003/09/06. doi: 10.1136/bmj.327.7414.557. PubMed PMID: 12958120; PubMed Central PMCID: PMC3602084.
 19. Stassen PM, Derks RP, Kallenberg CG, Stegeman CA. Venous thromboembolism in ANCA-associated vasculitis--incidence and risk factors. *Rheumatology (Oxford, England)* 2008; 47(4): 530-4. Epub 2008/03/22. doi: 10.1093/rheumatology/ken035. PubMed PMID: 18356178.
 20. Weidner S, Hafezi-Rachti S, Rupprecht HD. Thromboembolic events as a complication of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis and rheumatism* 2006; 55(1): 146-9. Epub 2006/02/08. doi: 10.1002/art.21704. PubMed PMID: 16463427.
 21. King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. *The Lancet Respiratory medicine* 2017; 5(1): 72-84. Epub 2016/09/08. doi: 10.1016/s2213-2600(16)30222-3. PubMed PMID: 27599614.
 22. Hernandez-Rodriguez NA, Cambrey AD, Harrison NK, Chambers RC, Gray AJ, Southcott AM, et al. Role of thrombin in pulmonary fibrosis. *Lancet (London, England)* 1995; 346(8982): 1071-3. Epub 1995/10/21. PubMed PMID: 7564789.
 23. Isshiki T, Sakamoto S, Kinoshita A, Sugino K, Kurosaki A, Homma S. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. *Respiration; international review of thoracic diseases* 2015; 89(3): 201-7. Epub 2015/02/11. doi: 10.1159/000369828. PubMed PMID: 25659984.
 24. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 2005; 127(6): 2028-33. Epub 2005/06/11. doi: 10.1378/chest.127.6.2028. PubMed PMID: 15947316.
 25. Squizzato A, Gerdes VE, Ageno W, Buller HR. The coagulation system in endocrine disorders: a narrative review. *Internal and emergency medicine* 2007; 2(2): 76-83. Epub 2007/07/28. doi: 10.1007/s11739-007-0026-X. PubMed PMID: 17657422.
 26. van Zaane B, Nur E, Squizzato A, Gerdes VE, Buller HR, Dekkers OM, et al. Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors. *Journal of thrombosis and haemostasis: JTH.* 2010; 8(11): 2483-93. Epub 2010/08/26. doi: 10.1111/j.1538-7836.2010.04034.x. PubMed PMID: 20735729.
 27. Johannesdottir SA, Horvath-Puho E, Dekkers OM, Cannegieter SC, Jorgensen JO, Ehrenstein V, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA internal medicine* 2013; 173(9): 743-52. Epub 2013/04/03. doi: 10.1001/jamainternmed.2013.122. PubMed PMID: 23546607.