SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 182-187

Sarcoidosis and risk of venous thromboembolism: A systematic review and meta-analysis

Patompong Ungprasert[1, 2], Narat Srivali[3], Karn Wijarnpreecha[4], Charat Thongprayoon[5]

[1] Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [2] Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3] Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [4] Cardiac Electrophysiology Unit, Department of Physiology, and Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [5] Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Abstract. *Background*: Several chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory myositis and systemic lupus erythematosus, have been linked to an increased risk of venous thromboembolism (VTE). However, the data on sarcoidosis is unclear. *Objectives:* To evaluate the risk of VTE among patients with sarcoidosis. *Methods*: We conducted a systematic review and meta-analysis of observational studies that reported odds ratio, relative risk, hazard ratio or standardized incidence ratio comparing risk of VTE in patients with sarcoidosis versus non-sarcoidosis participants. Estimated effects were extracted from each study and were pooled together using the random-effect, generic inverse variance method of DerSimonian and Laird. *Result*: Out of 772 potentially relevant articles, three eligible studies were identified and included in the data analysis. The pooled risk ratio of VTE in patients with sarcoidosis was 1.42 (95% CI, 1.12-1.79). The statistical heterogeneity of this study was moderate with an I^2 of 72%. *Conclusion*: Our study demonstrated a statistically significant increased VTE risk among patients with sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 205; 32: 182-187)*

Key words: meta-analysis; sarcoidosis; venous thromboembolism; epidemiology

Introduction

Venous thromboembolism (VTE) is one of the major medical problems with a reported incidence of 1-2 cases per 1,000 person-years (1, 2). Deep venous thrombosis (DVT) of the lower extremity and pulmonary embolism (PE) are the most common subtype. VTE is associated with a significant morbidity and mortality as one study showed that patients with PE had a 90-day mortality rate as high as 15% (3). Several medical conditions, such as hospitalization, trauma, surgery, malignancy, thrombophilic state and use of certain medications are well recognized as its risk factors (4, 5).

Several auto-immune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathy, psoriasis and inflammatory bowel disease have been increasingly recognized as predisposing factors for VTE (6-10). Several in vivo and in vitro studies have suggested that chronic inflamma-

Received: 3 April 2015
Accepted after revision: 18 June 2015
Corresponce: Patompong Ungprasert, MD
200 First street SW, Rochester, MN, USA 55905
E-mail: P.Ungprasert@gmail.com

Authors' contributions: All authors had access to the data and a role in writing the manuscript.

tion might serve as the cornerstone of the relationship between these two conditions (11-12).

Sarcoidosis is a chronic inflammatory disorder of unclear etiology that typically affects the lungs but can virtually affect any organs. Presence of non-caseating granuloma is the histopathological hallmark of the disease. The clinical course of sarcoidosis can range from an acute self-limiting process to a chronic progressive process with significant morbidity and mortality. The disease is generally categorized into two subgroups, pulmonary and extra-pulmonary sarcoidosis, based on the site of involvement (13, 14).

The incidence of sarcoidosis varies from 6.1 to 71 per 100,000 person-years with a peak incidence in males 30 to 39 years old and in females 40 to 49 years old. This disease has no sex predilection. Survival, compared with that of the general population, appears to be unimpaired (15-17). Racial differences are observed (16).

As observed in other autoimmune diseases, patients with sarcoidosis have a higher inflammatory burden compared with the general population and, thus, might have a higher likelihood of developing VTE. Nonetheless, epidemiological data is limited and inconclusive. Therefore, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the VTE risk in patients with sarcoidosis versus non-sarcoidosis participants.

Methods

Search strategy

A literature search of published studies indexed in MEDLINE and EMBASE database from inception to February 2015 was independently performed by two investigators (P.U. and N.S.) using the search strategy described in Supplementary data 1, without any language restriction. Manual search of references of selected retrieved articles was also performed.

Inclusion criteria

The inclusion criteria were: 1. Cohort studies (either prospective or retrospective) or case-control studies published as original study comparing risk of VTE between sarcoidosis and non-sarcoidosis participants 2. Odds ratio (OR), relative risk (RR), hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) were provided, and 3. Non-sarcoidosis participants were used as a reference group for cohort study while participants without VTE were used as a control group in case-control study.

Study eligibility was independently determined by the two investigator noted above. The senior investigator (C.T.) supervised the review process and settled disagreements on the study eligibility. Newcastle-Ottawa quality assessment scale was used to appraise the quality of the included studies. This scale assessed each study in three areas including 1.The selection process of the cohorts 2.The comparability between the cohorts and 3. The ascertainment of the exposure for case-control study and the outcome of interest for cohort study (18).

Data extraction

A standardized data collection form was used to extract the following information: title of the article, name of the first author, year of publication, study location, study size, characteristic of study population, method used to diagnose sarcoidosis and VTE, duration of follow up (for cohort study), adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariable analysis. If additional data was considered to be necessary, the authors of the original studies would be contacted.

To ensure the accuracy of data extraction, this process was independently performed by three investigators (P.U., N.S. and K.W.). Any data discrepancy was also resolved by consensus.

Our study was not directly involved with human subjects and, thus, was exempted from ethics approval.

Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration. Adjusted point estimates and standard errors were extracted from each study and were combined by the generic inverse variance method of DerSimonian and Laird (19). As the outcome of the studies was relatively uncommon, we used the OR of case-control study as the estimate of RR to pool this data

with RR or HR of cohort study. In light of the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0% to 25% represents insignificant heterogeneity, more than 25% but less than or equal to 50% represents low heterogeneity, more than 50% but less than or equal to 75% represents moderate heterogeneity, and more than 75% represents high heterogeneity (20).

Result

Our search strategy yielded 772 potentially relevant articles (152 articles from Medline and 620 articles from EMBASE). After exclusion of 146 duplicated articles, 626 of them underwent title and abstract review. Six hundred and fourteen articles were excluded as they were clearly not observational studies, were review article or were not conducted in patients with sarcoidosis, leaving 12 articles for full-length article review. Seven of them were excluded since they did not report the outcome of interest (VTE) while one of them were excluded since it was descriptive study without a control group (21). Another article was excluded as the authors used death certificates to identify cases of sarcoidosis and VTE, leading to a serious concern of incompleteness of diagnosis. This study was also at a substantial risk of selection bias as it recruited only patients who passed away (22).

Therefore, a total of three studies (two retrospective cohort studies and one case-control study) met our eligibility criteria and were included in the data analysis (23-25). Figure 1 outlines our literature search and review process. The main characteristics and the Newcastle-Ottawa scale of the included studies are illustrated in Tables 1.

The pooled risk ratio of VTE of subjects with sarcoidosis versus controls was 1.42 (95% CI, 1.12-1.79). The risk ratios from individual study were fairly consistent, ranging from 1.18 to 1.92. The statistical heterogeneity was moderate with an I^2 of 72%. Figure 2 demonstrates the forest plot of this meta-analysis.

To further explore the statistical heterogeneity, we performed a sensitivity analysis by excluding the study by Johannesdottir et al. (24) as it was the only study with case-control design. Exclusion of this study did not significantly alter the pooled risk ratio (RR 1.55; 95% CI, 1.41-1.70) but did dramatically reduce the I^2 to 0%.

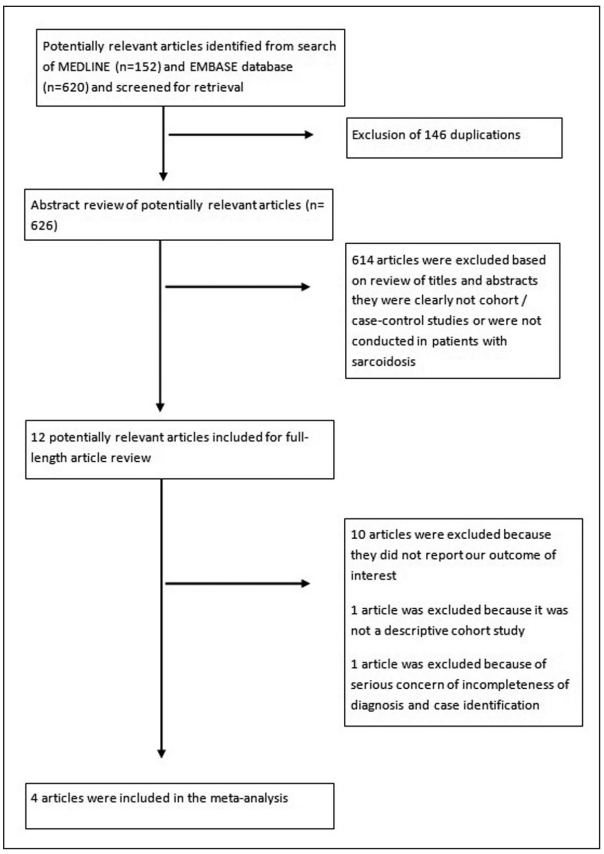

Fig. 1. Study identification and review process

Evaluation for publication bias

We did not conduct an evaluation for publication bias as the number of primary studies included in this meta-analysis was too small.

Discussion

The association between sarcoidosis and unusual blood clot has long been described in medical literature (26-28). In fact, a descriptive cohort study has demonstrated a higher than expected number of pulmonary embolism among patients with sar-

Table 1. Main characteristics of included studies

	Crawshaw et al. (23)	Johannesdottir et al. (24)	Zoller et al. (25)
Country of origin	England	Denmark	Sweden
Study design	Retrospective cohort	Case–control	Retrospective cohort
Year of publication	2011	2012	2012
Cases	All patients who were diagnosed with sarcoidosis between 1963 and 1998. Cases were identified by using the admission database of the National Health Service of Oxfordshire region.	All northern Denmark residences who were diagnosed with DVT and/or PE between 1999 and 2009. Cases were identified from Danish national registry database.	All patients who were diagnosed with sarcoidosis between 1964 and 2008. Cases were identified by using the Swedish national hospital admission database.
Controls	Hospitalized patient randomly selected from the same database.	Sex and age-matched subjects randomly selected from the same database.	General Swedish population was used as reference to calculate age, sex, period and socioeconomic status-specific standardized incidence ratio.
Diagnosis of sarcoidosis	Diagnostic code from the database.	Diagnostic code from the database.	Diagnostic code from the database.
Diagnosis of VTE	Diagnostic code of PE from the database.	Diagnostic code of PE and/or DVT from the database.	Diagnostic code of PE from the database, confirmed by peer review.
Follow up	Until death, first record of PE or end of 1998.	N.A.	Until death, first record of PE, emigration or 31 December 2008.
Mean age of cases, Y	N.A.	67.0	N.A.
Percentage of female in cases	N.A.	52.9	49.8
Number of cases	1,002	14,721	13,547
Number of controls	526,107	147,210	N.A.
Confounder adjusted	None	Hospitalization, co-morbidity and medications used	Age, sex, hospitalization and co-morbidity.
Quality assessment (Newcastle– Ottawa scale)	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Exposure: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars

VTE indicated venous thromboembolism; N.A., not available; DVT, deep vein thrombosis; PE, pulmonary embolism

coidosis (21). Our study is the first meta-analysis that combined all the available data. We were able to demonstrate a statistically significant association between sarcoidosis and VTE with an approximately 1.4-folds increased risk compared with non-sarcoidosis participants.

Why patients with sarcoidosis have a higher risk of VTE is not clear but chronic inflammation is thought to be the pathogenic link of this association. The propensity of development of VTE is associated with three provocative factors, known as Virchow triad, including hyper-coagulability, endothelial dysfunction/injury and flow disturbance. Chronic inflammation appears to increase the propensity of clotting by stimulating the coagulation cascade while inhibiting the anticoagulation pathway, resulting in a thrombophilic state (29-31). Endothelial dysfunction is also observed in chronic inflammatory state

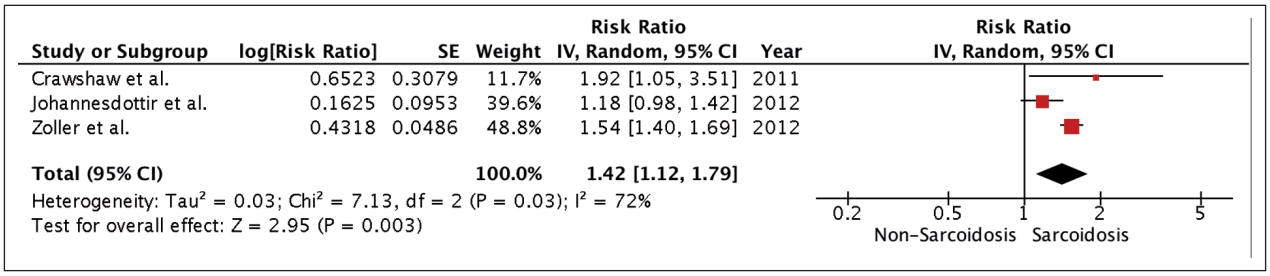

Fig. 2. Forest plot of risk of VTE in patients with sarcoidosis

as a result of detrimental effect of inflammatory cytokines and oxidative stress on endothelial cells (32-33). Moreover, patients with sarcoidosis may be less physically active compared with general population because of their pulmonary symptoms (13, 14), rendering them at higher risk of venous stasis.

Even though the primary studies included in this analysis were of high quality, we acknowledged that our study had some limitations and, thus, our results should be interpreted with caution. First, all of the studies included in this meta-analysis used medical register to identify cases of sarcoidosis and VTE. As a result, these studies were at potential risk of coding inaccuracy and incompleteness of case identification. In fact, the study by Zoller et al. (25) was the only study that conducted chart review to verify the diagnosis of VTE while other studies relied entirely on the diagnostic codes. Second, the definition of VTE was not consistent as the study by Johannesdottir et al. (24) included both PE and DVT while the rest included only PE. Third, we cannot perform an evaluation for publication bias. Thus, publication bias in favor of positive studies might be present. Fourth, this is a meta-analysis of observational studies that can establish an association but cannot demonstrate causality. Therefore, we cannot conclude that sarcoidosis itself versus other potential confounders were accountable for the increased VTE risk. Furthermore, the increased incidence VTE incidence might merely be a result of detection bias as patients with sarcoidosis, because of their chronic illness, are exposed more to medical examinations (34).

In conclusion, our meta-analysis demonstrated that sarcoidosis was associated with a statistically significant increased VTE risk. Physicians who take care of these patients should be aware of this association and should carefully monitor them for VTE, particularly those with other traditional risk factors.

Reference

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: A population-based study. J Thromb Haemost 2007; 5: 692-9.
2. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep venous thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004; 117: 19-25.
3. Goldhaber SZ. DVT Prevention: what is happening in the "real world"? Semin Thromb Hemost 2003; 29 (Suppl 1): 23–31.
4. Hawbaker S. Venous thromboembolism in the cancer population: pathology, risk, and prevention. J Adv Pract Oncol 2012; 3: 23-33.
5. Ungprasert 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) 2015; 54: 736-42.
6. Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. World J Gastroenterol 2014; 20: 13863-78.
7. Ungprasert P, Sanguankeo A. Risk of venous thromboembolism in patients with idiopathic inflammatory myositis: a systematic review and meta-analysis. Rheumatol Int 2014; 34: 1455-8.
8. Ungprasert P, Sanguankeo A, Upala S, et al. Psoriasis and risk of venous thromboembolism: a systematic review and meta-analysis. QJM 2014; 107: 793-7.
9. Tomasson G, Monach PA, Merkel PA. Thromboembolic disease in vasculitis. Curr Opin Rheumatol 2009; 21: 41-6.
10. Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol 2014; 33: 297-304.
11. Nagareddy P, Smyth SS. Inflammation and thrombosis in cardiovascular disease. Curr Opin hematol 2013; 20: 457-63.
12. Silvarino R, Danza A, Merola V, Bérez A, Méndez E, Espinosa G, et al. Venous thromboembolic disease in systemic autoimmune diseases: An association to keep in mind. Autoimmune Rev 2012; 12: 289-94.
13. Thomas WK, Hunninghake GW. Sarcoidosis. JAMA 2003; 289: 3300-3.
14. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA 2011; 305: 391-9.
15. Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester Minnesota: A population-based study of incidence and survival. Am J Epidemiol 1986; 123: 840-5.
16. Rybicki BA, Major M, Popovich J, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol 1997; 145: 234-41.
17. Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg

L. Sarcoidosis in black women in the United States: Data from the black women's health study. Chest 2011; 139: 144-50.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trial 1986; 7: 177-88.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
21. Vorselaars AD, Snijder RJ, Grutters JC. Increased number of pulmonary embolisms in sarcoidosis patients. Chest 2012; 141: 826-7.
22. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon JJ, Sprunger D, et al. Increased risk of pulmonary embolism among US decedents with sarcoidosis from 1988 to 2007. Chest 2011; 140: 1261-6.
23. Crawshaw AP, Wotton CJ, Yeates DG, Goldacre MJ, Ho LP. Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study. Thorax 2011; 66: 447-8.
24. Johannesdottir Sa, Schmidt m, Horvath-Puho E, Sorensen HT. Autoimmune skin and connective tissue diseases and risk of venous thromboembolism: a population-based case–control study. J Thromb Haemost 2012; 10: 815-21.
25. Zoller B, Li X, Sunquist J, Sunquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012; 379: 244-9.
26. Ungprasert P, Srivali N. Is sarcoidosis a thrombophilic disorder? Ann Hematol 2013; 92: 1721-2.
27. McLaughlin AM, McNicholas WT. Sarcoidosis presenting as upper extremity venous thrombosis. Thorax 2003; 58: 552-4.
28. Vahid B, Wildemore B, Marik PE. Multiple venous thromboses in a young man with sarcoidosis: is there a relation between sarcoidosis and venous thrombosis? South Med J 2006; 998-9.
29. Montecucco F, Mach F. Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. Rheumatology (Oxford) 2009; 48: 11-22.
30. Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. Hamostaseologie 2010; 30: 5-6, 8-9.
31. Bartoloni E, Shoenfeld Y, Gerli R. Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. Arthritis Care Res (Hoboken) 2011; 63: 178-83.
32. Biasillio G, Leo m, Della Bona R, et al. Inflammatory bio-marker and coronary artery disease: from bench to bedside and back. Intern Emerg Med 2010; 5: 225-33.
33. Jezovnik mK, Poredos P. Idiopathic venous thrombosis is related to systemic inflammatory response and to increased levels of circulating markers of endothelial dysfunction. Int Angiol 2010; 29: 226-31.
34. Ungprasert P, Sanguankeo A, Upala S, et al. Risk of malignancy in patients with giant cell arteritis and polymyalgia rheumatica: A systematic review and meta-analysis. Semin Arthritis Rheum 2014; 44: 366-70.

Supplementary data 1

Search strategy

Database: Medline
1. exp Sarcoidosis, Pulmonary/ or exp Sarcoidosis/ or sarcoidosis.mp.
2. exp Thromboembolism/
3. Thromboembolism.mp.
4. exp Venous Thrombosis/
5. venous thrombosis.mp.
6. exp Pulmonary Embolism/
7. pulmonary embolism.mp.
8. or/2-7
9. 1 and 8

Database: EMBASE
1. exp sarcoidosis/ or exp lung sarcoidosis/
2. sarcoidosis.mp.
3. 1 or 2
4. pulmonary embolism.mp. or exp lung embolism/
5. deep vein thrombosis.mp. or exp deep vein thrombosis/
6. venous thromboembolism.mp. or exp venous thromboembolism/
7. exp thromboembolism/ or thromboembolism.mp.
8. or/4-7
9. 3 and 8