Association of Sarcoidosis With Increased Risk of VTE

A Population-Based Study, 1976 to 2013

Patompong Ungprasert, MD; Cynthia S. Crowson, MS; and Eric L. Matteson, MD, MPH

OBJECTIVE: The goal of this study was to investigate the risk of VTE among patients with sarcoidosis.

METHODS: A cohort of 345 incident cases of sarcoidosis and 345 sex- and age-matched comparator subjects in Olmsted County, Minnesota, from 1976 to 2013 were identified from the comprehensive medical record linkage system. Medical records were reviewed for DVT and pulmonary embolism (PE). The cumulative incidence was estimated, adjusted for the competing risk of death. Cox proportional hazards models were used to compare the rate of development of these events between patients with sarcoidosis and the nonsarcoidosis comparison cohort.

RESULTS: The prevalence of VTE, DVT, and PE prior to the index date was not significantly different between case and comparator subjects. The risk of incident VTE adjusted for age, sex, and calendar year was significantly higher among patients with sarcoidosis (hazard ratio [HR], 3.04 [95% CI, 1.47-6.29]). Significantly elevated risk was observed in both subtypes of VTE, with an HR of 3.14 (95% CI, 1.32-7.48) for DVT and an HR of 4.29 (95% CI, 1.21-15.23) for PE. A sensitivity analysis including only VTE events that occurred at least 6 months after the index date adjusted for age, sex, and calendar year revealed somewhat lower HRs: VTE, 2.73 (95% CI, 1.30-5.72); DVT, 3.00 (95% CI, 1.25-7.20); and PE, 3.58 (95% CI, 0.98-13.03).

CONCLUSIONS: An increased risk of VTE among patients with sarcoidosis was observed in this population-based cohort.

CHEST 2017; 151(2):425-430

KEY WORDS: DVT; epidemiology; pulmonary embolism; sarcoidosis; VTE

ABBREVIATIONS: HR = hazard ratio; IRB = institutional review board

AFFILIATIONS: From the Division of Rheumatology (Drs Ungprasert and Matteson and Ms Crowson), Department of Internal Medicine, Division of Biomedical Statistics and Informatics (Ms Crowson), Department of Health Science Research, and the Division of Epidemiology (Dr Matteson), Department of Health Science Research, Mayo Clinic, Rochester, MN.

FUNDING/SUPPORT: This study was made possible by using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health [R01AG034676], and a Clinical and Translational Science Award [UL1 TR000135] from the National Center for Advancing

Translational Sciences, a component of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CORRESPONDENCE TO: Patompong Ungprasert, MD, Division of Rheumatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: p.ungprasert@gmail.com or ungprasert.patompong@mayo.edu
Copyright © 2016 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: <http://dx.doi.org/10.1016/j.chest.2016.09.009>

VTE, which includes DVT and pulmonary embolism (PE), is a common medical condition associated with high morbidity and mortality. Studies from Europe and North America have estimated the incidence of VTE as 1 to 2 new cases per 1,000 population per year.¹⁻³ Recurrence is common. The estimated cumulative incidence of recurrence is 10% at 1 year and 30% at 5 years after withdrawal of anticoagulation therapy.⁴ Traditional risk factors of VTE include immobilization, hospitalization, surgery, malignancy, aging, thrombophilic state, and use of certain medications.³

More recently, chronic inflammation has been increasingly recognized as an independent risk factor for VTE. Chronic activation of coagulation cascade by inflammatory cytokines is believed to be the key pathogenesis behind this association.⁵ Epidemiologic studies have shown an increased incidence of VTE in several chronic immune-mediated inflammatory

disorders such as rheumatoid arthritis, vasculitis, and inflammatory bowel disease.⁶⁻⁸

Sarcoidosis is an immune-mediated disorder characterized by the presence of noncaseating granuloma. It is estimated that 70,000 incident cases of sarcoidosis are diagnosed in the United States annually.^{9,10} Patients with sarcoidosis may be at a higher risk of VTE. In fact, previous coding-based studies found a higher risk of VTE among patients with sarcoidosis, with relative risks ranging from 1.2 to 2.0. However, the accuracy of those studies was limited by the study design, which used an administrative registry to identify the sarcoidosis cohorts and the event of interest without medical record verification.^{8,11,12}

To further investigate this possible increased risk, the present population-based retrospective study was performed comparing the incidence of VTE between patients with sarcoidosis vs age- and sex-matched subjects without sarcoidosis. The risk of subtype of VTE (ie, DVT, PE) was also investigated.

Patients and Methods

This study used the Rochester Epidemiology Project medical record linkage system. Through the resources of this project, comprehensive medical records, both inpatient and outpatient, from all health-care providers for the local population (including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes, and the few private practitioners for all residents of Olmsted County, Minnesota, seeking medical care for > 6 decades) are available. The potential of this data system for use in epidemiologic studies has been described previously.¹³ This medical record linkage system allows identification of virtually all clinically recognized cases of sarcoidosis among the residents of Olmsted County as well as complete ascertainment of the event of interest.

Using this medical record linkage system, a cohort of 345 incident cases of sarcoidosis in Olmsted County from 1976 to 2013 were identified.¹⁴ All patients with diagnosis codes related to sarcoid, sarcoidosis, and contextual noncaseating granuloma were identified from the database. Medical records of all potential cases were individually reviewed. Inclusion required physician diagnosis supported by histopathologic evidence of noncaseating granuloma without evidence of acid-fast bacilli or fungi, radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. The only exception to the requirement of histopathologic confirmation was stage I pulmonary sarcoidosis, which required only symmetric bilateral hilar adenopathy on thoracic imaging in the absence of other identifiable causes. Isolated granulomatous disease of a specific organ except for the skin was also included given that there was no better alternative diagnosis.¹⁵ Case subjects with a diagnosis of sarcoidosis prior to residency in Olmsted County were excluded.

For each patient with sarcoidosis, 1 subject without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly selected from the same population to serve as a comparator. Matching criteria were similar age (± 3 years) and same sex. The sarcoidosis incidence date of the case subjects was assigned to be the index

date of the matched comparator. The medical records of case and comparator subjects were then reviewed for DVT and PE. Event verification was based on physician diagnosis supported by venography, angiography, ultrasonography, computerized angiography, and scintigraphy or autopsy findings. Data on baseline cardiovascular risk factors, including smoking status, BMI, diabetes mellitus, hypertension, and dyslipidemia, were also collected. Follow-up was continued until death, migration, or January 1, 2015.

Approval for this study was obtained from the Mayo Clinic and Olmsted Medical Center institutional review boards (IRBs), and the need for informed consent was waived (Mayo Clinic IRB: 14-008651; Olmsted Medical Center IRB: 012-OMC-15).

Descriptive statistics (eg, percentages, mean) were used to summarize the characteristics of each cohort. Comparisons between cohorts were performed by using χ^2 and rank sum tests. Comparisons of prior VTE, DVT, and PE between cohorts were conducted by using the Fisher exact test to examine whether there were any increases in prevalence of VTE and its subtypes prior to the onset of sarcoidosis. The cumulative incidence of VTE, DVT, and PE adjusted for the competing risk of death was estimated.¹⁶ These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who die before experiencing VTE events are appropriately accounted for to avoid overestimation of the rate of occurrence of the events of interest, which can occur if such subjects are simply censored at death. Patients whose first occurrence was prior to the date of diagnosis for patients with sarcoidosis, or prior to the index date for subjects in the nonsarcoidosis comparison cohort, were excluded from the analysis of cumulative incidence. For the estimation of the cumulative incidence of VTE overall, the date of occurrence was the earliest date of occurrence of DVT or PE.

Cox proportional hazards models were used to compare the rate of development of VTE, DVT, and PE between patients with sarcoidosis and the nonsarcoidosis comparison cohort. In addition, Cox proportional hazards models were used to assess the

association of risk factors on the development of VTE events among patients with sarcoidosis. Risk factors of interest included those described earlier. A *P* value < .05 was considered statistically

significant for all analyses. Analyses were performed by using SAS version 9.4 (SAS Institute, Inc) and R 3.1.1 (R Foundation for Statistical Computing).

Results

Baseline characteristics of patients with sarcoidosis and the nonsarcoidosis comparison cohort are described in Table 1. Demographic characteristics were similar between the two cohorts except that there more non-white subjects in the sarcoidosis cohort and more current smokers in the nonsarcoidosis comparison cohort. There was no difference in prevalence of baseline cardiovascular risk factors except for higher BMI among case subjects.

The prevalence of VTE prior to diagnosis of sarcoidosis/index date was not significantly different between patients with sarcoidosis and the nonsarcoidosis comparison cohort (1.4% and 1.4%, respectively; *P* = 1.0). The cumulative incidence of VTE after diagnosis/index date for case and comparator subjects

is shown in Figure 1. The risk of incident VTE adjusted for age, sex, and calendar year was significantly higher among patients with sarcoidosis with a hazard ratio (HR) of 3.04 (95% CI, 1.47-6.29). Significantly elevated risk was observed in both subtypes of VTE, with an HR of 3.14 (95% CI, 1.32-7.48) for DVT and an HR of 4.29 (95% CI, 1.21-15.23) for PE. Further adjustment for baseline cardiovascular risk factors (current smoker, obesity, diabetes mellitus, hypertension, and dyslipidemia) did not significantly alter the risk estimates as shown in Table 2.

Because surveillance bias (due to more frequent thoracic imaging among patients with sarcoidosis) could play an important role in this association, a sensitivity analysis including only VTE events that occurred at least 6 months after the index date was performed. The HR

TABLE 1] Characteristics of Case and Comparator Subjects at Sarcoidosis Incidence/Index Date

Characteristic	Case Subjects (n = 345)	Comparator Subjects (n = 345)	<i>P</i> Value
Age, mean ± SD, y	45.6 ± 13.6	45.4 ± 13.7	.87
Female sex	174 (50%)	174 (50%)	1.0
Ethnicity			< .001
White	301 (90%)	327 (95%)	
African-American	18 (5%)	2 (1%)	
Asian	6 (2%)	0 (0%)	
Native American	2 (1%)	0 (0%)	
Other	7 (2%)	14 (4%)	
Unknown	11	2	
Length of follow-up, mean ± SD, y	15.1 ± 10.5	16.8 ± 10.8	...
Smoking status			< .001
Never	198 (60%)	132 (42%)	
Ex-smoker	71 (21%)	70 (22%)	
Current smoker	63 (19%)	115 (36%)	
Unknown	13	28	
BMI, mean ± SD, kg/m ²	29.8 ± 7.3	27.5 ± 5.6	< .001
Cholesterol, mean ± SD, mg/dL			
Total cholesterol	201.1 ± 38.2	201.7 ± 42.1	.65
LDL	115.6 ± 32.0	120.0 ± 36.6	.20
HDL	48.9 ± 15.8	50.6 ± 15.5	.26
TG	150.6 ± 101.4	137.5 ± 85.5	.21
Hypertension	75 (22%)	75 (22%)	1.0
Diabetes mellitus	31 (9%)	26 (8%)	.49

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TG = triglyceride.

Figure 1 – Cumulative incidence of VTE among patients with sarcoidosis (solid line) and comparators without sarcoidosis (dashed line).

for VTE from this sensitivity analysis adjusted for age, sex, and calendar year was slightly lower at 2.73 (95% CI, 1.30-5.72). The adjusted HRs were also slightly lower for DVT (HR, 3.00 [95% CI, 1.25-7.20]) and PE (HR, 3.58 [95% CI, 0.98-13.03]). The number of events and HRs of VTE, DVT, and PE comparing patients with sarcoidosis vs subjects without sarcoidosis, adjusted for demographic features and demographic features plus baseline cardiovascular risk factors and from the sensitivity analysis, are given in Table 2.

Discussion

Over the past few decades, with the better understanding of disease pathogenesis and advances in therapy, morbidity and mortality from direct organ damage from disease pathology has been declining in several autoimmune diseases.¹⁷ As a result, these patients live longer, and attention has turned to their comorbidities.

The present study is the first population-based study, to our knowledge, using comprehensive individual medical record review to illustrate the increased risk of VTE after diagnosis of sarcoidosis, adjusting for baseline

cardiovascular risk factors. The risk remains elevated even after excluding events that occurred within 6 months after diagnosis/index date to reduce the likelihood of surveillance bias. These observations are consistent with previous coding-based studies, although the magnitude of risk was higher in the present study. The differences in magnitude of risk reported in other studies may be due to the methods used to identify the cohorts and events of interest. All previous studies were based on diagnostic codes to identify sarcoidosis and VTE in the respective databases, without verification by use of medical record review. Coding inaccuracy may then result in false-positive and false-negative results. In the present study, the diagnosis of sarcoidosis and VTE was confirmed by using individual medical review. Other possible explanations include differences in populations, disease features, and treatments.

Elevated risk of VTE has been observed in several autoimmune disorders. A recent record linkage study from the United Kingdom reported a significantly increased risk of VTE in all 23 studied autoimmune disorders, with the relative risk ranging from 1.30 to 3.83.¹⁸ The threefold increased risk of VTE in the present study falls within this range.

The three main precursors of VTE, known as Virchow's triad, are venous stasis, endothelial injury, and increased blood coagulability. Chronic inflammation is known to provoke a hypercoagulable state through several mechanisms, including upregulation of tissue factor by inflammatory cytokines, mobilization of clot-promoting membrane phospholipids by complement complexes, suppression of fibrinolysis, and downregulation of natural anticoagulants such as thrombomodulin by tumor necrosis factor- α .¹⁹ Endothelial injury associated with chronic inflammation as a result of the detrimental effect of inflammatory cytokines and oxidative stress on endothelial cells is also well recognized.²⁰ These factors

TABLE 2] Number of Events and HRs of VTE, DVT, and Pulmonary Embolism Comparing Patients With Sarcoidosis vs Subjects Without Sarcoidosis

Variable	No. of Events After Index Date for Case/Comparator	HR (95% CI) for All Events After Index Date, Adjusting for Age, Sex, and Calendar Year	HR (95% CI) for All Events After Index Date, Adjusting for Age, Sex, Calendar Year, Current Smoking, DM, HTN, DLP, and Obesity	No. of Events That Occurred at Least 6 Months After Index Date for Case/Comparator	HR (95% CI) for Events That Occurred at Least 6 Months After Index Date, Adjusting for Age, Sex, and Calendar Year
VTE	27/10	3.04 (1.47-6.29)	3.09 (1.27-7.53)	24/10	2.73 (1.30-5.72)
DVT	19/7	3.14 (1.32-7.48)	3.04 (1.06-8.71)	18/7	3.00 (1.25-7.20)
Pulmonary embolism	12/3	4.29 (1.21-15.23)	4.38 (1.15-16.74)	10/3	3.58 (0.98-13.03)

DLP = dyslipidemia; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension.

could predispose patients with sarcoidosis to the development of VTE. Other possible risk factors include the presence of antiphospholipid antibodies and use of glucocorticoids.^{21,22} A population-based study showed a dose-response relationship between glucocorticoids and the risk of VTE even after adjusting for underlying inflammatory conditions.²³ Conversely, use of glucocorticoids in autoimmune diseases to reduce the systemic inflammatory burden of the disease may contribute to a reduction of likelihood of developing VTE.

The major strength of this research is that it was a population-based study using a comprehensive database that allowed capture of nearly all the clinically recognized cases of sarcoidosis in the population. This approach captured the complete spectrum of the disease and minimized referral bias. The diagnoses of sarcoidosis and VTE were verified by medical record review, which minimized the likelihood of misclassification, a common concern in coding-based studies. The study also had a long length of follow-up (mean duration of follow-up, > 15 years).

The major limitations are those inherent in the retrospective nature of the study. Clinical information

and laboratory data were not systematically obtained and, thus, all pertinent data might not be recorded. Surveillance bias might play a role because patients with sarcoidosis could undergo more medical examinations and thoracic imaging simply because of their pulmonary disease. However, the effect estimates from the sensitivity analysis which included only VTE that occurred at least 6 months after diagnosis/index date remained significantly elevated. Generalizability of the results to other populations could be limited because clinical phenotype and epidemiology of sarcoidosis varied among different racial groups,^{9,10} but the population of Olmsted County is predominantly of Northern European ancestry. Moreover, there is a higher proportion of health-care workers in this population that could affect the pattern of health-care utilization and disease detection.

Conclusions

An increased risk of VTE among patients with sarcoidosis was observed in this population. How this risk should be addressed in clinical practice requires further investigation.

Acknowledgments

Author contributions: P. U. and C. S. C. serve as guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. P. U. was responsible for: conception and design, acquisition and interpretation of data, drafting of the manuscript, and statistical analysis. C. S. C. was responsible for: conception and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis. E. L. M. was responsible for: conception and design, acquisition and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis, and supervision.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost.* 2007;5(4):692-699.
2. Anderson FA, Zazaruzny M, Heit JA, et al. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. *Am J Hematol.* 2007;82(9):777-782.
3. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis.* 2016;41(1):3-14.
4. Prandoni P, Noventa F, Ghirarduzzi A, 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.
5. Silvarino R, Danza A, Merola V, et al. Venous thromboembolic disease is systemic autoimmune diseases: an association to keep in mind. *Autoimmun Rev.* 2012;12(2):289-294.
6. Ungprasert P, Srivali N, Spanuchart I, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol.* 2014;33(5):297-304.
7. Tomasson G, Monach PA, Merkel PA. Thromboembolic disease in vasculitis. *Curr Opin Rheumatol.* 2009;21(1):41-46.
8. Zoller B, Li X, Sunquist J, et al. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. *Lancet.* 2012;379(9812):244-249.
9. Rybicki BA, Major M, Popovich J Jr, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol.* 1997;145(3):234-241.
10. Cozier YC, Berman JS, Palmer JR, et al. Sarcoidosis in black women in the United States: data from the Black Women's Health Study. *Chest.* 2011;139(1):144-150.
11. Crawshaw AP, Wotton CJ, Yeates DG, et al. Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study. *Thorax.* 2011;66(5):447-448.
12. Johannesdottir SA, Schmidt M, Horvath-Puho E, et al. Autoimmune skin and connective tissue diseases and risk of venous thromboembolism: a population-based case-control study. *J Thromb Haemost.* 2012;10(5):815-821.
13. Rocca WA, Yawn BP, St Sauver JL, et al. History of the Rochester Epidemiology Project: half a century of medical records linkage in a U.S. population. *Mayo Clin Proc.* 2012;87(12):1202-1213.
14. Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946-2013: a

- population-based study. *Mayo Clin Proc.* 2016;91(2):183-188.
15. Costabel U, Hunninghake GW. ATS/ERS/ WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *Eur Respir J.* 1999;14(4):735-737.
 16. Gooley TA, Leisenring W, Crowley J, et al. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18(6):695-706.
 17. Lee YH, Choi SJ, Ji JD, et al. Overall and cause-specific mortality in systemic lupus erythematosus: an update meta-analysis. *Lupus.* 2016;25(7):727-734.
 18. Ramagopalan SV, Wotton CJ, Handel AE, et al. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. *BMC Medicine.* 2011;9:1.
 19. Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. *Hamostaseologie.* 2010;30(1):5-6, 8-9.
 20. 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.* 2011; 63(2):178-183.
 21. Ina Y, Takada K, Yamamoto M, et al. Antiphospholipid antibodies. A prognostic factor in sarcoidosis? *Chest.* 1994;105(4):1179-1183.
 22. Brotman DJ, Girod JP, Posch A, et al. Effect of short-term glucocorticoids on hemostatic factors in healthy volunteers. *Thromb Res.* 2006;118(2):247-252.
 23. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med.* 2013;173(9): 743-752.