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SHORT COMMUNICATION

Risk of venous thromboembolism in patients with idiopathic inflammatory myositis: a systematic review and meta-analysis

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Abstract We performed this meta-analysis to assess venous thromboembolism risk in patients with idiopathic inflammatory myositis (IIM). A comprehensive search was performed in MEDLINE, EMBASE and the Cochrane database. Three observational studies met our inclusion criteria and were included in the data analysis. The pooled risk ratio of venous thromboembolism in patients with IIM compared with non-IIM participants was 2.85 (95 % CI 2.12–3.84). Our result indicates a significant increased risk of venous thromboembolism among patients with IIM.

Keywords Venous thromboembolism · Deep venous thrombosis · Pulmonary embolism · Dermatomyositis · Polymyositis · Idiopathic inflammatory myositis · Meta-analysis

Introduction

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common medical problem with a significant morbidity and mortality. Its reported 30-day case-fatality rate is as high as 30 % [1, 2]. Several conditions, such as malignancy, hypercoagulable state, immobilization, surgery and hospitalization are well recognized as risk factors for VTE.

Chronic inflammatory disorders, though not generally regarded as traditional risk factors for VTE, might increase the risk of developing VTE as inflammatory cytokines have been shown to be associated with hypercoagulable state by up-regulating procoagulants and down-regulating anticoagulant and fibrinolytic systems [3]. Moreover, several chronic inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), have been shown to increase VTE risk in large epidemiologic studies [4–6].

Dermatomyositis (DM) and polymyositis (PM), collectively known as idiopathic inflammatory myositis (IIM), are uncommon chronic inflammatory disorders that primarily affect the skeletal muscle. Anecdotal evidence has suggested an increased VTE risk among these patients [7, 8]. Nevertheless, epidemiological data on VTE risk in this population are still limited and conflicting. Thus, to obtain a more accurate and precise estimated effect, we conducted a systematic review and meta-analysis of observational studies that compared the risk of VTE in patients with IIM versus non-IIM participants.

Methods

Search strategy

The two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to January 2014 using the terms “pulmonary embolism,” “deep venous thrombosis” and “venous thromboembolism” in conjunction

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with the terms "dermatomyositis," "polymyositis," "idiopathic inflammatory myopathy" and "idiopathic inflammatory myositis." A manual search of references of selected retrieved studies was also performed. The inclusion criteria were as follows: (1) observational studies (case–control, cross-sectional or cohort studies) published as original studies to evaluate the association between IIM and risk of VTE, DVT or PE, (2) odds ratios (OR's), relative risks (RR's), hazard ratios (HR's) or standardized incidence ratios (SIR's) with 95 % confidence intervals (CI's) or survival curves were provided and (3) random non-IIM participants were the reference group. Study eligibility was independently determined by each investigator noted above. Differing decisions were resolved by consensus. Figure 1 demonstrates our search methodology.

Statistical analysis

Data analysis was performed using the Review Manager 5.2 software from the Cochrane collaboration. We reported the pooled effect estimate of VTE risk using the combination of the data from case–control and cohort analyses to increase the precision of our estimates. We used the OR of case–control studies as an estimate of the RR to pool this data with the RR or HR of cohort studies as the outcome of interest was relatively uncommon. Point estimates and standard error were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird [9]. Given the high likelihood of between-study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic

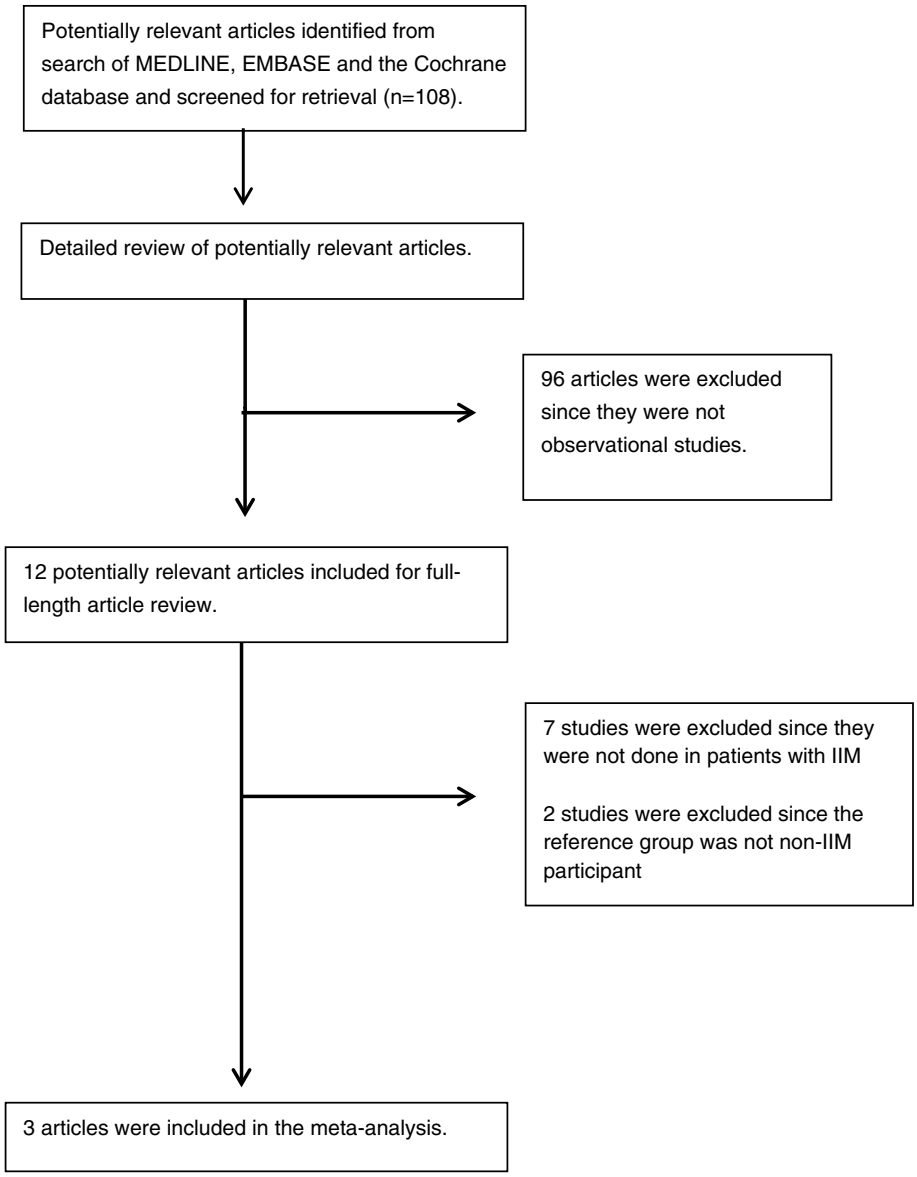

Fig. 1 Search methodology

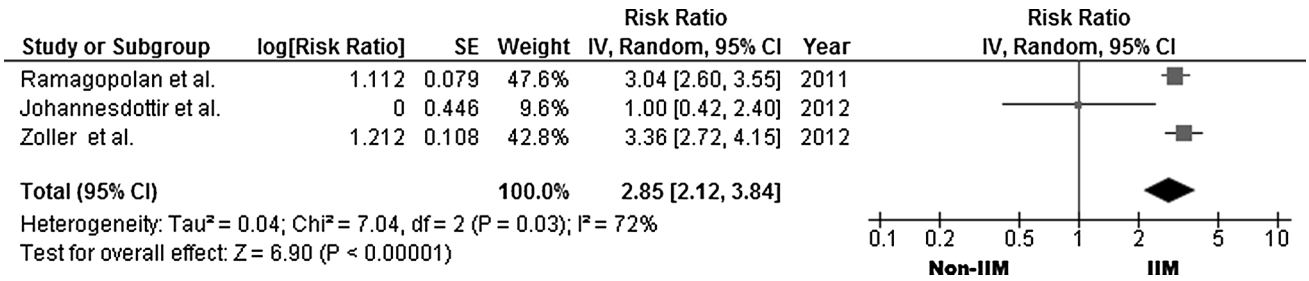

Fig. 2 Forest plot of included studies. Study by Ramagopolan et al., Johannesdottir et al. and Zoller et al. included 6,022, 47 and 2,122 patients with IIM, respectively. The sizes of the *boxes* used for each study represent the weight of that study used for calculation of the pooled effect. The *diamond* at the bottom of this forest plot represents the pooled risk ratio with 95 % CI (the *center of the diamond* represents the pooled risk ratio, and the *lateral lips of diamond* represent the associated 95 % CI)

is complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0–25 % represents insignificant heterogeneity, 25–50 % low heterogeneity, 50–75 % moderate heterogeneity and 75–100 % high heterogeneity [10].

Results

Our search strategy yielded 108 potentially relevant articles. Ninety-six articles were excluded as they were not observational studies. Twelve articles underwent full-length article review; seven of them were excluded since the studies were not done in patients with IIM while two of them were excluded since the reference group was not non-IIM participant. Three studies (two retrospective cohort studies and one case–control study) with 8,191 subjects with IIM met our inclusion criteria and were included in the analysis [11–13]. The pooled risk ratio of VTE of subjects with IIM versus control subjects was 2.85 (95 % CI 2.12–3.84). The statistical heterogeneity was moderate with an I^2 of 72 %. Since only three studies were included in this meta-analysis, an evaluation for publication bias was not performed. Figure 2 demonstrates the forest plot of the included studies.

Discussion

Our meta-analysis demonstrated a significant association between IIM and VTE with an overall 2.85-fold (95 % CI 2.12–3.84) increased risk compared with non-IIM participants. One of the included three studies [13] found no association between IIM and VTE, but this study is relatively small compared with the other two. The mechanism behind this association remains unclear but is believed to be related to the chronic inflammatory state. As mentioned earlier, chronic inflammation with autoimmune diseases has been demonstrated to promote the coagulation cascade, impair the anticoagulation pathway and inhibit the fibrinolytic process [3, 4]. Also, the deleterious effect of inflammatory cytokine and oxidative stress on endothelial function, another determinative factor in the development of VTE, is extensively documented [14, 15].

Interestingly, the relative risk of VTE in patients with IIM is considerably higher than the relative risk of patients RA and IBD, the other two common chronic inflammatory autoimmune disorders, as recent meta-analyses show the relative risk of 1.90 and 1.96 for patients with RA and IBD, respectively [5, 16]. This higher relative risk might be due to the fact that patients with IIM have several other predisposing factors for VTE (apart from chronic inflammation) such as concurrent malignancy and immobilization from the muscle weakness.

Even though the included studies in this meta-analysis were of high quality, there are some limitations, and thus, the result should be interpreted with caution. First, all of the included studies were conducted using data from medical registry, implying the possibility of coding inaccuracy. Second, statistical heterogeneity is not low in this study. Third, this is a meta-analysis of observational studies, which, at the best, can only demonstrate an association, not the causality. Hence, we cannot be certain that IIM itself versus other potential confounders, such as use of corticosteroid or the coexistence of malignancy, which is found in about 12–15 % of these patients [17], causes the increased VTE risk. Furthermore, the higher detection rate of VTE in patients with IIM might be, in part, due to the fact that they have chronic illness and, thus, exposed more to medical community.

In conclusion, our meta-analysis demonstrates a statistically significant increased VTE risk among patients with IIM. As the morbidity and mortality of VTE are very high, physicians should carefully monitor patients with IIM for VTE, particularly those with other conventional risk factors, though the role of VTE prophylaxis remains unclear and merits further investigations.

Conflict of interest The authors have no financial or nonfinancial conflict of interest to declare.

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