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Venous thromboembolism risk in rheumatoid arthritis patients: a systematic review and updated meta-analysis

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Abstract. – OBJECTIVE: Rheumatoid arthritis (RA) patients are prone to develop thromboembolic complications due to the chronic inflammatory nature of RA. Only one systematic review and meta-analysis has attempted to evaluate venous thromboembolism risk in RA patients. However, this review has become outdated due to the recent publication of several high-quality retrospective cohort studies. The aim of the study was to evaluate the risks of deep vein thrombosis, pulmonary embolism, and overall venous thromboembolism event incidence in RA patients.

MATERIALS AND METHODS: Five databases (Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE) were systematically searched according to PRISMA guidelines for eligible studies. With the available literature, we conducted a random-effect meta-analysis to evaluate odds ratios of deep vein thrombosis, pulmonary embolism, and venous thromboembolism incidence in RA patients and healthy controls.

RESULTS: We found 12 eligible studies detailing 272,884 RA patients and 2,280,454 age and sex-matched healthy controls. Meta-analysis revealed elevated risks for deep vein thrombosis (Odd's ratio: 2.25), pulmonary embolism (2.15), and overall venous thromboembolism incidence (2.23) in RA patients.

CONCLUSIONS: This meta-analysis provides evidence concerning the elevated risks of deep vein thrombosis, pulmonary embolism, and venous thromboembolism in RA patients. The findings herein may aid in developing clinical awareness and assisting best practice guideline development for RA patients with thromboembolic complications.

Key Words:
Rheumatoid arthritis, Risk factor, Thromboembolism, Deep vein thrombosis.

Introduction

Rheumatoid arthritis (RA) is an autoimmune rheumatic disorder of the musculoskeletal structures affecting usually middle-aged men and women between 20 and 40 years of age[1]. Recent epidemiological studies[2,3] have reported high age-adjusted incidence rates for RA around the world, while the Global Burden of Disease study acknowledges that RA is a strong predictor of mortality, accounting for roughly 121,300 deaths worldwide in 2017[4,5].

RA patients present substantial joint damage, particularly to the synovial linings of articulatory surfaces, caused by autoimmune inflammatory changes induced by anti-citrullinated peptide/protein antibodies[6,7]. Furthermore, studies[8-10] have shown that peptidyl-arginine deiminase conversion of arginine to citrulline is an integral mechanism that promotes infiltration by CD4+ T cells, B cells, and other non-specific antibodies, such as immunoglobulins into the synovial joints.

In addition to affecting musculoskeletal structures, RA also activates global inflammatory pathways, resulting in systemic effects, such as impaired endothelial function, hypercoagulability, and stasis[11,12]. Hypercoagulability in particular promotes thromboembolic events, something that is further aggravated by the administration of antirheumatic drugs, which have been shown to potentially promote a hyper-coagulative phase[13-18].

Liang et al[19] mentioned that switching between synthetic and biological antirheumatic drugs could increase venous thromboembolic event risk. However, a consensus in the literature on this topic is currently absent. Several retrospective cohort studies[20-25], and case-con-

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trol studies[26,27], have attempted to evaluate venous thromboembolic event risk in RA patients. While some studies[20,21,27-29] reported increased pulmonary thromboembolism or deep vein thrombosis risk in RA patients, others found the opposite[20,22,24,24].

To the best of our knowledge, only one systematic review and meta-analysis to date has attempted to evaluate the overall risks of venous thromboembolism in RA patients[30]. However, this study was limited in two regards. First, the authors did not explore root causes of the severe heterogeneity that they observed, and second, several relevant high-quality retrospective cohort studies have been conducted since the original meta-analysis was published[21-24].

We, therefore, in this systematic review and meta-analysis, attempt to bridge the knowledge gap pertaining the overall risk of deep vein thrombosis, pulmonary embolism, and venous thromboembolism in RA patients. Our findings will hopefully elevate clinical awareness and understanding of the relationship between venous thromboembolism and rheumatoid arthritis.

Materials and Methods

This meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[31].

Data Search Strategy

Five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) were screened for relevant studies published prior to January 2020. A combination of MeSH keywords including "Rheumatoid arthritis", "deep vein thrombosis", "pulmonary thromboembolism", "venous thromboembolism", and "thromboembolism" were used. The reference sections for included studies were manually scanned to identify additional relevant studies.

The inclusion criteria were as follows:

- Studies evaluating the incidence of pulmonary thromboembolism, deep vein thrombosis, and venous thromboembolism in RA patients.
- Studies with human participants.
- Case-control studies, prospective trials, or retrospective cohort trials.
- Studies published in peer-reviewed scientific journals.
- Studies published in English.

Screening was performed by two reviewers independent of each other. Disagreements were resolved through discussion with a third reviewer.

Quality Assessment

Bias risk for each included study was assessed using Cochrane's risk of bias assessment tool for non-randomized controlled trials[32]. This tool evaluates study outcomes for selective reporting, confounding bias, measurement of outcomes, and incomplete data availability. Methodological quality was appraised, again, by two reviewers working independently of each other. Again, a third reviewer arbitrated in case of dispute.

Data Analysis

We performed a within-group meta-analysis using Comprehensive Meta-analysis (CMA) software version 2.0[33] based on a random-effects model[34]. We calculated odds ratios to determine overall incidence of deep vein thrombosis, pulmonary embolism, and venous thromboembolism in RA patients. We also assessed study heterogeneity using I^2 statistics (0-25%: negligible heterogeneity, 25-75%: moderate heterogeneity, ≥75%: substantial heterogeneity)[35]. Publication bias was evaluated using Duval and Tweedie's trim and fill procedure[36]. The significance level for this study was set at 5%.

Results

Initial database scanning yielded 980 studies. A further 13 studies have been added to this total when screening reference sections from included studies. From this, 12 studies remained after applying inclusion criteria (Figure 1). Nine of these were retrospective cohort studies[20-25,28,29,37], two were case-control studies[26,27], and one was a prospective cohort study[38] (Table I).

Participant Information

The 12 included studies[20-29,37,38] contained data on 2,553,338 patients (1,226,984 female, 941,868 male). Among these, 272,884 suffered from RA (126,179 females, 107,474 males) while the remainder were healthy controls. Two studies[25,26] did not report the gender distribution of their study cohort. Average patient age was 56.3 ± 3.8 years, with average RA patient age being 57.2 ± 3.2 years and average healthy control individual age being 55.2 ± 3.8 years. Three studies[25-27] did not report patient age information.

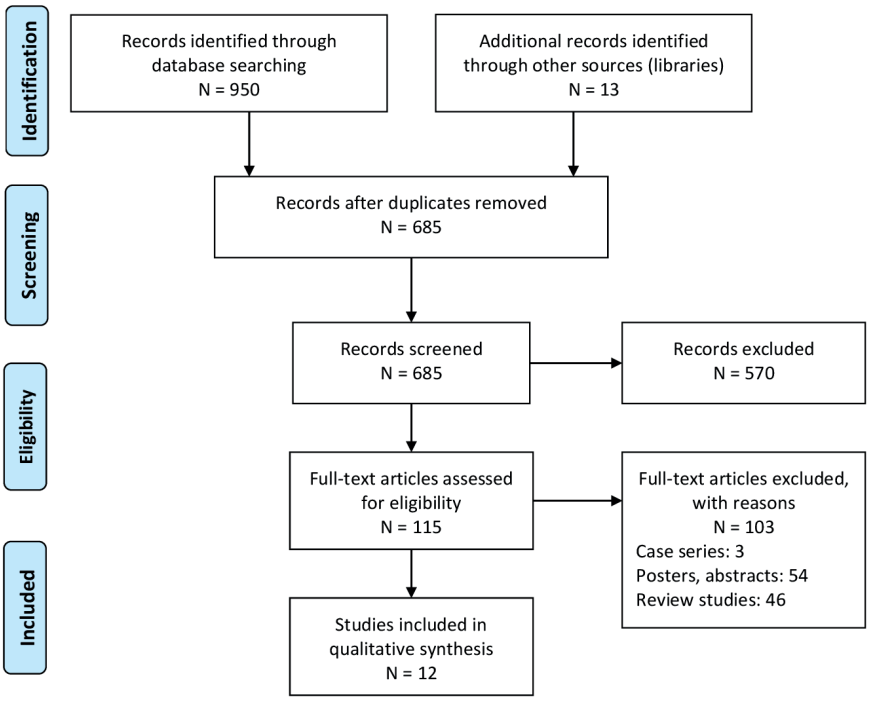

Figure 1. PRISMA flowchart for identification of eligible studies.

Quality assessment for Non-Randomized Controlled Trials

Cochrane's risk of bias assessment tool for non-randomized controlled trials showed that overall bias risk was low in all of the included studies (Table II, Figure 2). We observed that missing data, selection of reported results, measurement in outcome, and selection bias were the most predominant aspects of concern.

Publication Bias

We used Duval and Tweedie's trim and fill method to identify whether studies are missing from this meta-analysis on either side of the mean effect. This method found that no studies were missing. The overall random effects model determined the point estimate and 95% confidence interval for all studies combined to be 2.21 (1.91 to 2.56) (Figure 3).

Deep Vein Thrombosis

Deep vein thrombosis incidence was reported by seven studies[20-22,24,27-29]. We noted increased odds for deep vein thrombosis in RA patients relative to healthy controls (Figure 4) (2.25, 95% CI: 1.70 to 2.98, $p<0.001$) with no heterogeneity (I^2: 0%).

Pulmonary Embolism

Pulmonary embolism incidence was reported by six studies[20-22,24,25,28]. We noted increased odds for pulmonary embolism in RA patients relative to healthy controls (Figure 5) (2.15, 95% CI: 1.39 to 3.49, $p=0.001$) with moderate heterogeneity (I^2: 44.8%).

Venous Thromboembolism

Venous thromboembolism incidence was reported by ten studies[21-27,29,38]. We noted increased odds for venous thromboembolism events in RA patients relative to healthy controls (Figure 6) (2.23, 95% CI: 1.79 to 2.77, $p<0.001$) with no heterogeneity (I^2: 0%).

Discussion

This systematic review and meta-analysis provide comprehensive evidence showing elevated risk for deep vein thrombosis, pulmonary embolism, and overall venous thromboembolism in RA patients, confirming and updating previous findings[30]. An elevated predisposition to thromboembolic events has been associated with poor prognostic outcome for RA patients in terms of short- and long-term morbidity and mortality[39,40]. The onset of thromboembolic events in RA patients is multifactorial – caused by inflammation-induced endothelial dysfunction, inflammatory monocyte vascular infiltration, and thrombogenic factor upregulation[41,42]. One study included in this meta-analysis (Choi et al[28]

Table I. Key details for included studies.

Study	Country	Type of study	Sample descriptive	Age M ± S.D (years)	Events of deep vein thrombosis	Events of venous thromboembolism	Events of pulmonary embolism
Li et al (2021)[22]	Canada	Retrospective cohort study	RA: 39,142 (25,732F, 13,410M) Control: 78,078 (51,343F, 26,735M)	RA: 59.5 ± 15.7 Control: 59.5 ± 15.7	RA: 1,068 Control: 1,484	RA: 1,432 Control: 2,069	RA: 543 Control: 791
Galloway et al (2020)[21]	UK	Retrospective cohort study	RA: 23,410 (16,634F, 6,776M) Control: 13,512 (128,129F, 85,383M)	RA: 59.0 ± 15.5 Control: 51.7 ± 17.8	RA: 542 Control: 1,242	RA: 845 Control: 2,020	RA: 373 Control: 916
Mansour et al (2019)[23]	Israel	Retrospective cohort study	RA: 11,782 (9,103F, 2,679M) Control: 57,973 (44,589F, 13,384M)	RA: 61.1 ± 17.0 Control: 60.8 ± 17.0	–	RA: 815 Control: 1,841	–
Ogdie et al (2018)[24]	USA	Retrospective cohort study	RA: 51,762 (36,021F, 15,741M) Control: 1,225,571 (679,354F, 546,217M)	RA: 60.5 ± 15.5 Control: 50.3 ± 17.8	RA: 1,864 Control: 25,490	RA: 2,330 Control: 30,356	RA: 579 Control: 6,066
Yusuf et al (2015)[25]	USA	Retrospective cohort study	RA: 70,768 Control: 198,044	–	–	RA: 909 Control: 981	–
Chung et al (2014)[20]	Taiwan	Retrospective cohort study	RA: 29,238 (6,735F, 22,503M) Control: 116,952 (26,940F, 90,012M)	RA: 52.4 ± 15.6 Control: 52 ± 15.9	RA: 623 Control: 921	–	RA: 233 Control: 469
Choi et al (2013)[28]	UK	Retrospective cohort study	RA: 9,589 (6,651F, 2,938M) Control: 95,776 (66,449F, 29,327M)	RA: 58.3 ± 14.1 Control: 58.3 ± 14.1	RA: 110 Control: 512	–	RA: 82 Control: 358
Kim et al (2013)[29]	USA	Retrospective cohort study	RA: 22,143 (16,513F, 38,656M) Control: 88,752 (66,052F, 22,700M)	RA: 52.2 ± 12 Control: 52.2 ± 12	RA: 197 Control: 364	RA: 265 Control: 448	RA: 111 Control: 164

Continued

Table I *(Continued)*. Key details for included studies.

Study	Country	Type of study	Sample descriptive	Age M ± S.D (years)	Events of deep vein thrombosis	Events of venous thromboembolism	Events of pulmonary embolism
Holmqvist et al (2012)[38]	Sweden	Prospective cohort study	RA: 7,904 (5,420F, 2,484M) Control: 37,350 (25,436F, 11,914M)	RA: 57 ± 15 Control: 57 ± 15	–	RA: 223 Control: 648	–
Bacani et al (2012)[37]	USA	Retrospecti cohort study Control: 464 (320F, 144M)	RA: 464 (320F, 144M)	RA: 55.6 ± 15.5 Control: 55.5 ± 15.5	–	RA: 15 Control: 7	–
Johannesdottir et al (2012)[26]	Denmark	Case control study	RA: 1489 Control: 147,210	–	–	RA: 319 Control: 13,806	–
Kang et al (2012)27	Taiwan	Case control study	RA: 5,193 (3,050F, 2143M) Control: 20,772 (12,193F, 8,578M)	–	RA: 87 Control: 158	–	–

Legends: M: Mean: S.D: Standard deviation, F: Female, M: Male.

2013) noted pulmonary embolism and deep vein thrombosis incidence increased with prolonged follow-up, something that the authors hypothesized was due to continued systemic changes caused by RA including the development of Virchow's triad[43,44].

Furthermore, the use of disease modifying anti-RA medications can precipitate a transient vascular hyper-coagulative phase, inhibit selective COX inhibitors, and disbalance prostacyclin-thromboxane levels[16-18,45], thereby further elevating venous thromboembolism risk[15,45]. One study[24] included in this meta-analysis also examined deep vein thrombosis and pulmonary embolism incidence in RA patients either receiving or not receiving disease modifying anti-rheumatoid

Table II. Bias risk as assessed using Cochrane's risk of bias assessment tool for non-randomized controlled trials.

Study	Confounding bias	Selection bias	Deviation from intended intervention	Missing data	Measurement in outcome	Selection of reported result	Classification of intervention
Li et al (2021)	+	+	+	+	+	+	+
Galloway et al (2020)	+	+	+	+	+	+	+
Mansour et al (2019)	+	?	+	-	?	?	+
Ogdie et al (2018)	+	+	+	+	+	+	?
Yusuf et al (2015)	+	?	+	?	?	?	+
Chung et al (2014)	+	+	+	+	+	+	+
Choi et al (2013)	+	?	+	-	?	?	+
Kim et al (2013)	+	+	+	+	+	+	+
Holmqvist et al (2012)	+	?	+	?	?	?	+
Bacani et al (2012)	+	?	+	?	-	-	+
Johannesdottir et al (2012)	+	?	+	?	-	-	+
Kang et al (2012)	+	?	+	?	-	-	+

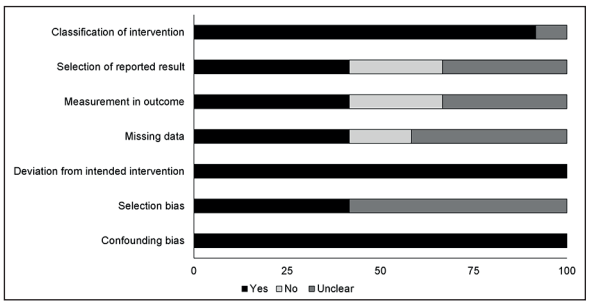

Figure 2. Bias risk in included studies according to Cochrane risk of bias assessment for the randomized controlled trials.

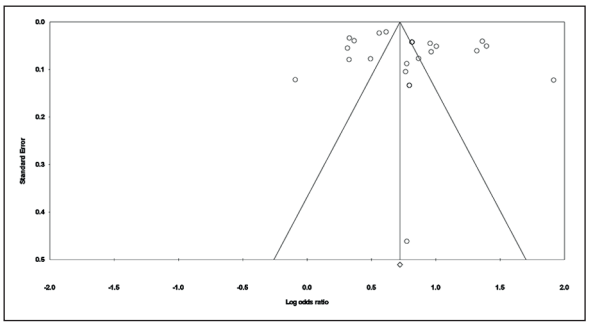

Figure 3. Publication bias as assessed using Duval & Tweedy's trim and fill method.

drugs. Ogdie et al (2018)[24] reported a slightly increased event rate for both deep vein thrombosis and pulmonary embolism for patients taking anti-rheumatoid drugs.

Although this study is novel, it faces several challenges. First, it has not been registered in a systematic review repository, such as PROSPERO York or Joanna Briggs Institute due to

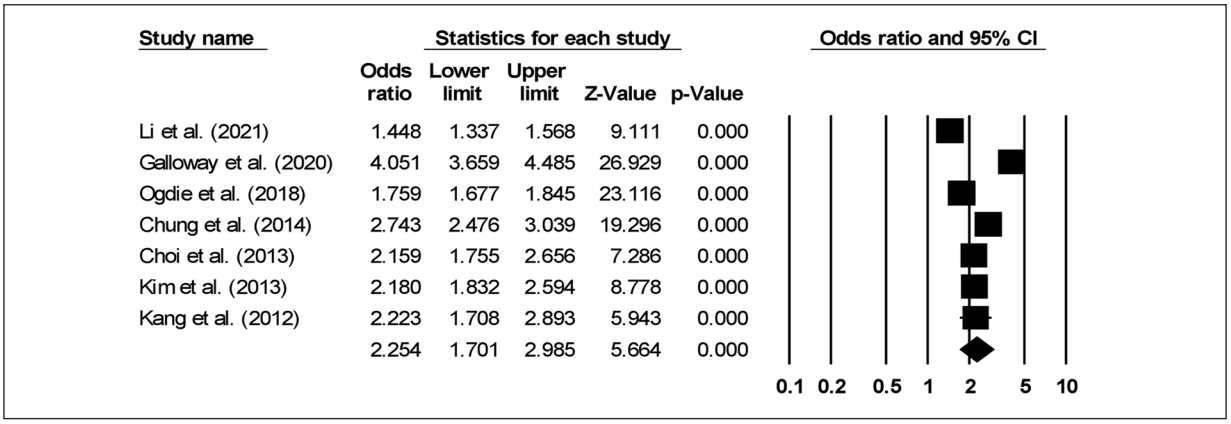

Figure 4. Forest plot for studies evaluating deep vein thrombosis incidence in RA patients and healthy controls. The odds ratios (ORs) are presented as black boxes while 95% confidence intervals are presented as whiskers. Smaller OR values represent lower odds of deep vein thrombosis in RA patients, while larger OR values represent the opposite.

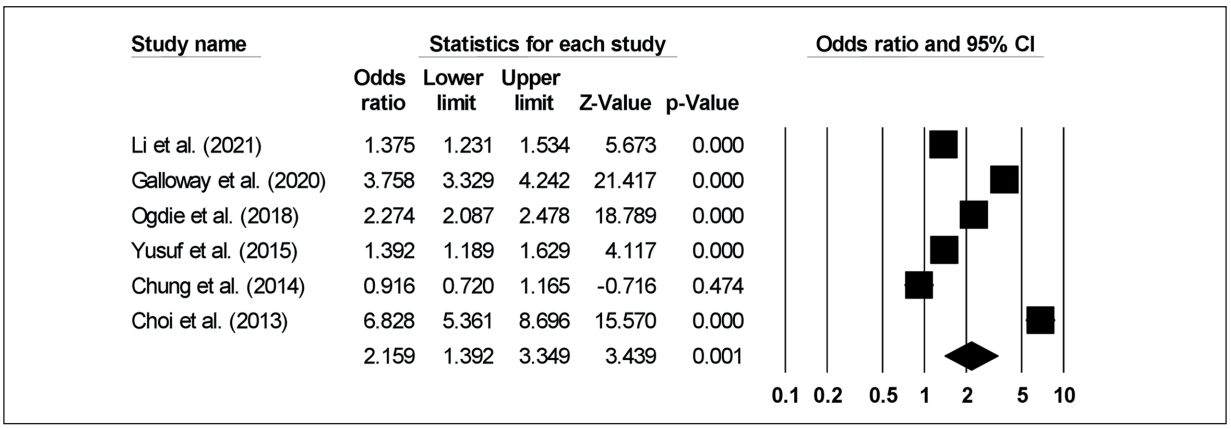

Figure 5. Forest plot for studies evaluating pulmonary thromboembolism incidence in RA patients and healthy controls. The odds ratios (ORs) are presented as black boxes while 95% confidence intervals are presented as whiskers. Smaller OR values represent lower odds of pulmonary thromboembolism in RA patients, while larger OR values represent the opposite.

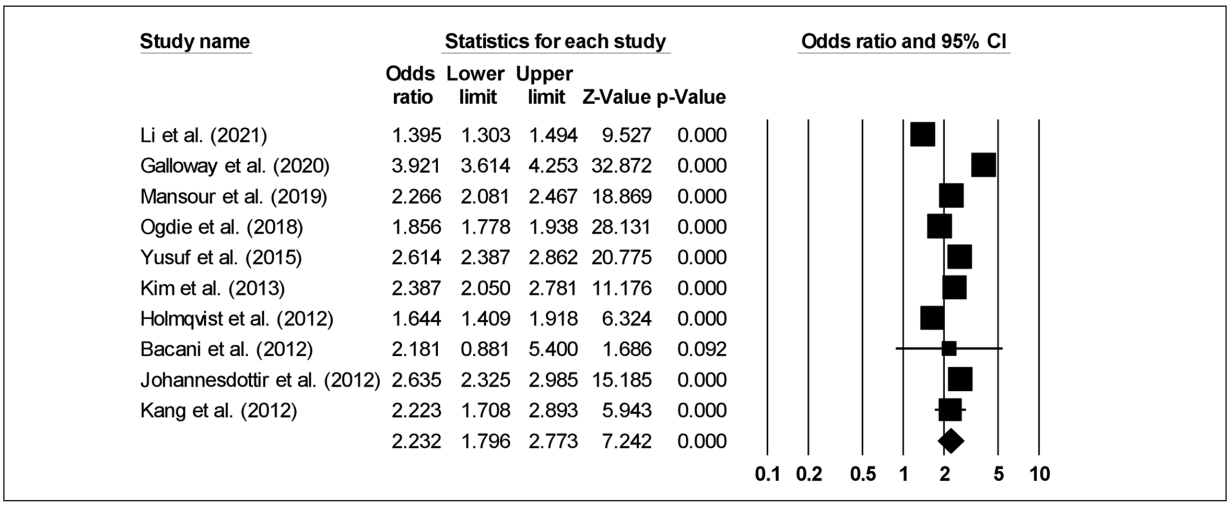

Figure 6. Forest plot for studies evaluating venous thromboembolism incidence in RA patients and healthy controls. The odds ratios (ORs) are presented as black boxes while 95% confidence intervals are presented as whiskers. Smaller OR values represent lower odds of venous thromboembolism in RA patients, while larger OR values represent the opposite.

conditions imposed by the ongoing COVID-19 pandemic that have caused registration wait times to exceed one year. Second, we acknowledge that the relative paucity of data within eligible studies may limit our understanding of the individual incidence risk for deep vein thrombosis and pulmonary embolism in RA patients. While 10 included studies analyzed the overall risks of combined venous thromboembolism, only six studies a piece evaluated risk levels for pulmonary embolism or deep vein thrombosis. Therefore, a type II error cannot be ruled out[46]. Future cohort, case-control studies to evaluate pulmonary embolism and deep vein thrombosis risk in RA patients would help strengthen the data available in this area.

Conclusions

We herein provide preliminary evidence regarding the overall risk levels of deep vein thrombosis, pulmonary embolism, and venous thromboembolism in RA patients. Our meta-analysis shows elevated risk in RA patients compared to healthy controls. These findings can potentially aid in developing best practice guidelines for managing co-existing thromboembolic conditions in RA patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

LH designed the project; LH and BJ were involved in data collection and data analysis; LH prepared the manuscript; HF edited the manuscript; all authors read and approved the final manuscript.

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