European Journal of Internal Medicine 67 (2019) 65–69

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Increased risk of venous thromboembolism among patients with hyperthyroidism: a systematic review and meta-analysis of cohort studies

Sutat Srisawat[a], Tullaya Sitasuwan[b], Patompong Ungprasert[c,*]

[a] Pranangklao Hospital, Bangkok, Thailand
[b] Division of Ambulatory Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[c] Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

ARTICLE INFO

Keywords:
Venous thromboembolism
Graves's disease
Hyperthyroidism
Meta-analysis

ABSTRACT

Background: Studies have suggested that patients with hyperthyroidism may have a higher risk of venous thromboembolism (VTE) compared to individuals with normal thyroid function, although the data is quite limited. This systematic review and meta-analysis aims to comprehensively investigate this risk by summarizing all available studies.

Methods: A systematic review was performed using the MEDLINE and Embase databases from inception to February 2019 to identify all cohort studies that compared the risk of incident VTE in patients with hyperthyroidism versus individuals without hyperthyroidism. Pooled risk ratio and 95% confidence interval were calculated using random-effect, generic inverse-variance method.

Results: A total of 5 retrospective cohort studies with 237,667 cases with hyperthyroidism and 4,615,907 comparators without hyperthyroidism were included. The pooled analysis found a significantly increased risk of incident VTE among patients with hyperthyroidism, with a pooled risk ratio of 1.332 (95% CI, 1.275–1.391; I^2 14%). The funnel plot was asymmetric and may suggest the presence of publication bias in favor of studies that showed positive association.

Conclusion: A significantly increased risk of incident VTE among patients with hyperthyroidism compared to individuals without hyperthyroidism was demonstrated in this meta-analysis.

1. Introduction

Hyperthyroidism is one of the most common endocrinological disorders worldwide with the reported prevalence of up to 1.3% in iodine-sufficient areas [1]. It affects females more frequently than males with the female-to-male ratio of about 5–10:1 [2]. Graves' disease is by far the most common cause of hyperthyroidism followed by toxic multinodular goiter and toxic adenoma [1]. Excessive amount of triiodothyronine (T3) and thyroxine (T4) can cause myriad of signs and symptoms such as palpitation, tremor, insomnia, weight loss, heat intolerance and anxiety [3].

Recent studies have suggested that an elevated level of thyroid hormones may have a significant effect on the coagulation and fibrinolysis system. A systematic review and meta-analysis of 13 studies published in 2012 found that patients with hyperthyroidism had a higher level of factor VIII and IX, fibrinogen, von Willebrand factor and plasminogen activator inhibitor-1 than individuals with normal thyroid function [4]. Nonetheless, whether this altered coagulation system would result in clinically significant hypercoagulable state and increased incidence of venous thromboembolism (VTE) is not known with certainty. The current systematic review and meta-analysis was conducted to comprehensively identify all cohort studies that compared the risk of incident VTE in patients with hyperthyroidism versus individuals with normal thyroid function and summarize the results.

2. Methods

2.1. Search strategy

Two investigators (S.S. and P.U.) independently searched for published articles indexed in MEDLINE and EMBASE database from inception to February 2018 using the search strategy that included the terms for hyperthyroidism and venous thromboembolism as described in supplementary data 1. References of some retrieved articles were also manually reviewed to identify any potentially relevant studies that may be missed by the search terms.

* Corresponding author at: 2 Prannok Road, Bangkoknoi, Bangkok 10700, Thailand.
E-mail address: p.ungprasert@gmail.com (P. Ungprasert).

https://doi.org/10.1016/j.ejim.2019.06.012
Received 11 May 2019; Received in revised form 31 May 2019
Available online 19 June 2019

2.2. Inclusion criteria

The current meta-analysis included only cohort studies (either prospective or retrospective) that compared the incidence of VTE, either deep venous thrombosis (DVT) and/or pulmonary embolism (PE), after index date between cases with hyperthyroidism and comparators without hyperthyroidism. Individuals with prevalent VTE (i.e., history of VTE prior to index date) must be excluded from the analysis. Eligible studies reported relative risk (RR), hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence intervals (CI) of the risk of VTE between the groups. The decision not to include case-control studies and cross-sectional studies was made to maximize the validity of the pooled results, as a cohort study is the only design that can confirm the temporal relationship between the two conditions that the exposure of interest occurred prior to the outcome of interest.

Determination of the eligibility of retrieved articles was independently conducted by the two investigators. In the case of different determinations, the studies in question were jointly reviewed again by both investigators to make the final decision. The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of the included studies. This scale assessed the quality of each study in three areas including (1) the representativeness of cases and comparators (2) the comparability between the groups and (3) the ascertainment of the outcomes of interest [5].

2.3. Data extraction

A standardized data collection form was used to extract the following information: title of the study, first author's name, year of publication, year(s) when the study was conducted, country or countries of origin, background population, methods used to recruit cases and comparators, methods used to diagnose hyperthyroidism and VTE, total number and baseline demographic data of cases and comparators, average duration of follow up, confounders that were adjusted in multivariate analysis and adjusted effect estimates with 95% CI.

To ensure the accuracy of the data extraction, this process was independently performed by the two investigators. The data collection forms filled by each investigator were cross-checked to identify any discrepancies, which would trigger a joint re-review of that study by both investigators.

2.4. Statistical analysis

All data analyses were performed using the Comprehensive Meta-Analysis program, version 2.2 (Biostat, Englewood, New Jersey, USA). Point estimates were extracted from the included cohort studies and were combined together to calculate pooled effect estimates using the generic inverse-variance method as described by DerSimonian and Laird [6]. The random-effect model was chosen over the fixed-effect model as the assumption of the fixed-effect model, that all studies should yield the exactly same result, is not true in most circumstances, particularly for meta-analysis of studies with different background populations. The between-study statistical heterogeneity was assessed using Cochran's Q test and I^2 statistic. The I^2 statistic 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, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and more than or equal to 76% high heterogeneity [7]. Funnel plot and Egger regression test were used for assessment of publication bias [8]. If the tests were suggestive of the presence of publication bias, trim-and-fill sensitivity analysis would be performed [9]. This technique is used to find hypothetical missing studies based on symmetry of the funnel plot. Imputed values from these studies are added to the meta-analysis to investigate if the pooled result would be significantly altered. If not, this would suggest that the effect of publication bias is not substantial.

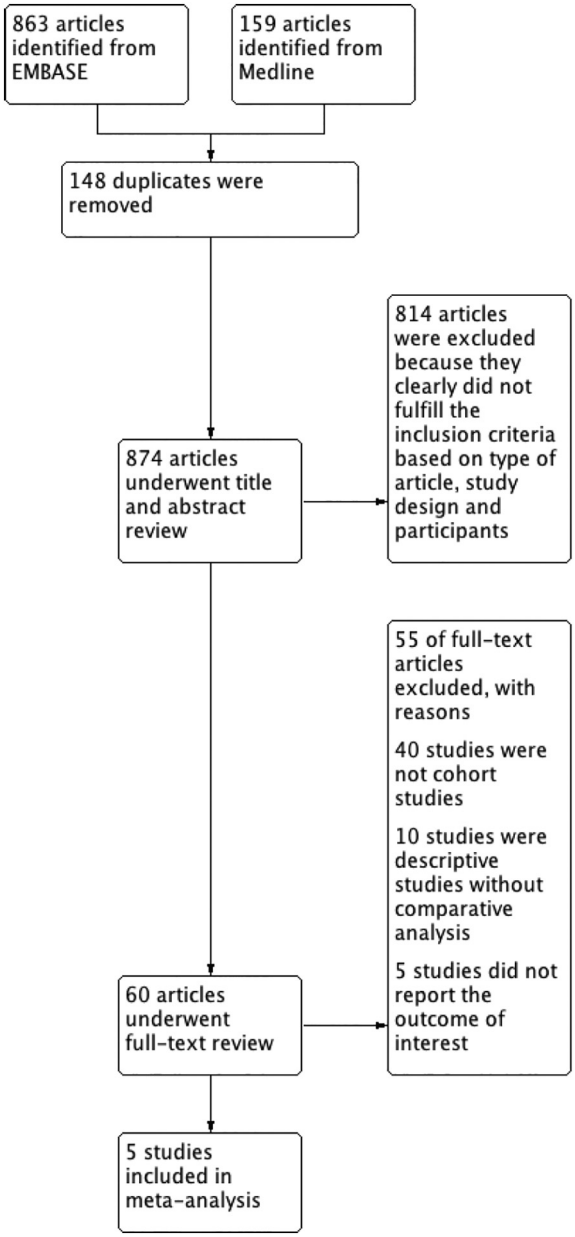

Fig. 1. Literature identification and selection process.

3. Results

3.1. Identification of eligible studies

The search strategy resulted in 1022 potentially relevant articles (863 articles from EMBASE and 159 articles from MEDLINE). After exclusion of 148 duplicated articles, 874 articles underwent title and abstract review. After title and abstract review, 814 articles were excluded because they clearly did not fulfill the inclusion criteria based on type of article, study design and participants, leaving 60 articles for full-length article review. A total of 55 studies were excluded after the full-length review for the following reasons: 40 studies were not cohort studies, 10 studies were descriptive cohort studies without comparative analysis, and 5 studies did not report the outcome of interest (incident VTE). Finally, 5 retrospective cohort studies with 237,667 cases with hyperthyroidism and 4,615,907 comparators without hyperthyroidism were included in the meta-analysis [10–14]. All studies were administrative database-based studies that used International Classification of Disease (ICD) codes to diagnose hyperthyroidism and VTE. All but one

Table 1
Characteristics and quality assessment of studies included in the meta-analysis.

	Lin et al. [10]	Ramagopalan et al. [11]	Zoller et al. [12]	Lerstad et al. [13]	Dekkers et al. [14]
Country of origin	Taiwan	England	Sweden	Norway	Denmark
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Year of publication	2010	2011	2012	2015	2017
Cases	All patients who were diagnosed with thyrotoxicosis between 2001 and 2003. Cases were identified from the Taiwan Longitudinal Health Insurance Database which covered one million Taiwan populations.	All patients who were diagnosed with thyrotoxicosis between 1999 and 2008. Cases were identified from the database of English National Hospital Episode Statistics (which is an inpatient database).	All patients who were diagnosed with Graves' disease between 1964 and 2008. Cases were identified by using the Swedish national hospital admission database (which is an inpatient database).	All patients who were diagnosed with thyrotoxicosis during the population-based survey of Tromso study. This study surveyed the population of the municipality of Tromso, Norway in the year 1994–1995, 2001–2002 and 2007–2008. The response rates were between 66% - 78%.	All patients who were diagnosed with thyrotoxicosis between 1980 and 2012. Cases were identified from the Danish National Patient Registry which covered the entire population of Denmark.
	Patients with history of VTE prior to first diagnosis of thyrotoxicosis were not included.	Patients with history of VTE prior to first diagnosis of thyrotoxicosis were not included.	Patients with history of VTE prior to first diagnosis of Graves' disease were not included.	Patients with history of VTE prior to the survey date were not included.	Patients with history of VTE prior to first diagnosis of thyrotoxicosis were not included.
Comparators	Sex and age-matched comparators without thyrotoxicosis were randomly selected from remaining patients in the database.	Hospitalized patient without thyrotoxicosis 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.	Individuals with normal TSH level in the survey served as comparators	Sex and age-matched comparators without thyrotoxicosis were randomly selected from the same database.
	Patients with history of VTE prior to the index date were not included.	Patients with history of VTE prior to the index date were not included.			
Diagnosis of thyrotoxicosis	Presence of ICD-9 codes for thyrotoxicosis (242) in medical records	Presence of ICD-9 codes for thyrotoxicosis (242) or equivalent codes of ICD-7, 8 and 10 in medical records	Diagnostic code from the database	TSH level that was obtained during the survey was less than 0.05 mU/I	Presence of ICD-8 codes (242) or ICD-10 codes (E05.00, E05.01, E05.02 or E05.09) for thyrotoxicosis in medical records
Diagnosis of VTE	Presence of ICD-9 codes (415.1, 415.11 and 415.9) for PE in medical records.	Presence of ICD-7 code (465), ICD-8 code (450), ICD-9 codes (415.1, 451.1 and 453.9) or ICD-10 codes (I26 and I80.2) for DVT and/or PE in medical records.	Presence of ICD-7 code (465 and 684), ICD-8 code (450 and 673.9), ICD-9 codes (415B, 416 W, 673C and 639G) or ICD-10 codes (I26, o882 and o082) for PE in medical records.	Presence of ICD-9 codes (325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9) or ICD-10 codes (I26, I97.6, I80, I81, I82, O22.3, O22.5, O87.1 and O87.3) for DVT and/or PE in medical records.	Presence of ICD-8 codes or ICD-10 codes for DVT and/or PE in medical records.
	These medical records were retrieved from the Taiwan Longitudinal Health Insurance Database.	These medical records were retrieved from the database of English National Hospital Episode Statistics.	These medical records were retrieved from the Swedish national hospital admission database.	These medical records were retrieved from the database of the University Hospital of North Norway which is the only hospital in the region.	These medical records were retrieved from the Danish National Patient Registry.
Follow up	Until death, first record of PE, emigration or 5 years after index date	Until death, first record of DVT and/or PE or March 31, 2008	Until death, first record of PE, emigration or December 31, 2008	Until death, emigration, first record of DVT and/or PE or December 31, 2010	Until death, emigration, first record of DVT and/or PE or December 31, 2012
Number of cases	8903	91,913	50,954	41	85, 856
Number of Comparators	44,515	3,707,315	N.A.	17,020	847,057
Mean duration of follow-up in years	5.0	N.A.	N.A.	6.0	9.2
Woman, %	Cases: 77.0 Comparators: 77.0	Cases: 79.0 Comparators: 41.0	Cases: 82.2 Comparators: N.A.	Cases: 75.6 Comparators: 56.3	Cases: 82.1 Comparators: 82.1
Mean age in years	Cases: 40.7 Comparators: 40.5	Cases: N.A. Comparators: N.A.	Cases: N.A. Comparators: N.A.	Cases: 62.0 Comparators: 61.0	Cases: N.A. Comparators: N.A.
Confounder adjusted in multi-variates analysis	Age, sex, region of residence, income and several co-morbidities	Age, sex and region of residence	Age, sex, calendar years and several co-morbidities	Sex, body mass index and smoking	Age, sex, calendar years and several co-morbidities
Quality assessment (Newcastle– Ottawa scale)	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 2 stars Comparability: 1 star Outcome: 3 stars	Selection: 2 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars

VTE indicates venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; N.A., not available; ICD, International Classification of Disease; TSH, thyroid-stimulating hormone.

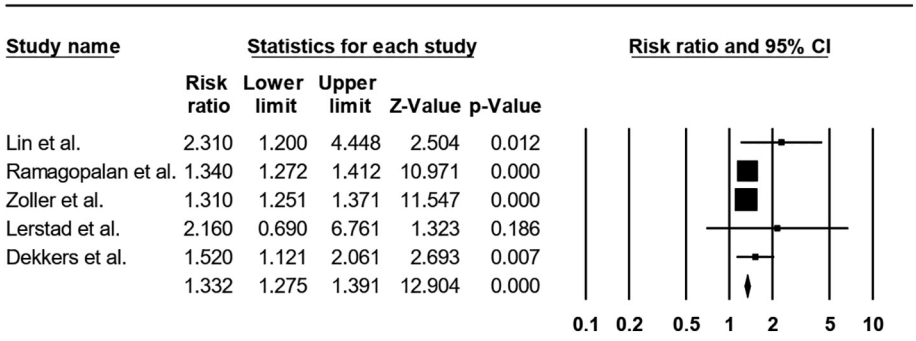

Fig. 2. Forest plot of the meta-analysis of risk of venous thromboembolism among patients with hyperthyroidism.

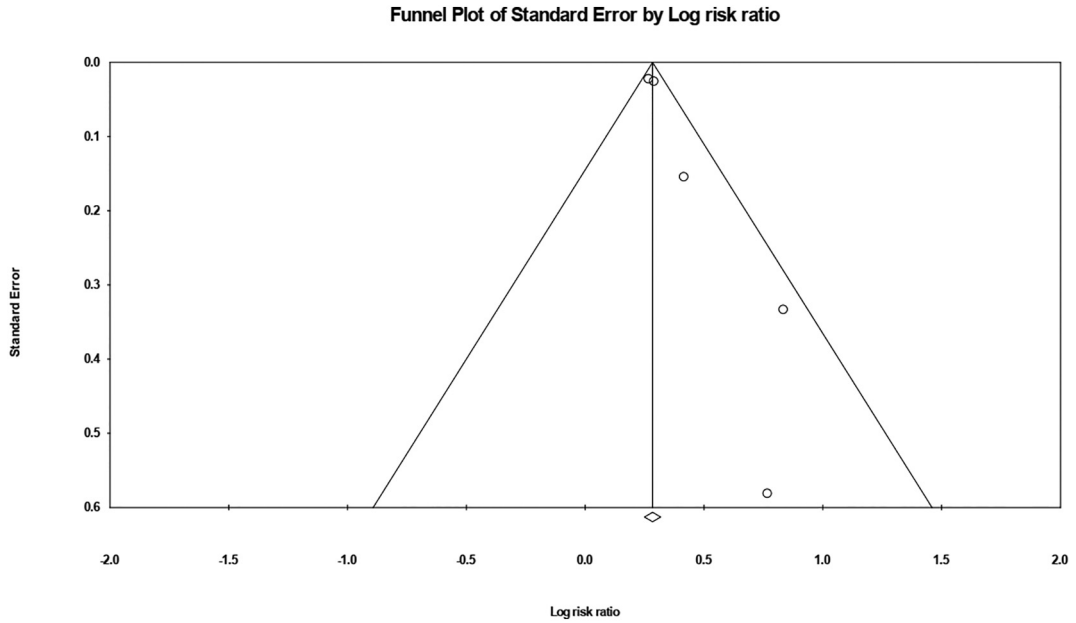

Fig. 3. Funnel plot of the meta-analysis of risk of venous thromboembolism among patients with hyperthyroidism (white dots represent included studies).

study was from Europe. The average duration of follow-up ranged from 5.0 to 9.2 years. The study identification and review process are outlined in Fig. 1. The characteristics of included studies and their participants are described in Table 1.

3.2. Risk of venous thromboembolism among patients with hyperthyroidism

The pooled analysis of the five included studies demonstrated a significantly increased risk of incident VTE in patients with hyperthyroidism compared to individuals without hyperthyroidism, with the pooled risk ratio of 1.332 (95% CI, 1.275–1.391). The statistical heterogeneity was negligible with an I^2 of 14%. The forest plot of this meta-analysis is shown in Fig. 2.

Subgroup analysis was performed on risk of pulmonary embolism. A total of three studies [10,12,13] reported data on this subgroup and the meta-analysis of these studies revealed a pooled risk ratio of 1.489 (95% CI, 1.037–2.138) (supplementary Fig. 1). The statistical heterogeneity was low with an I^2 of 31%. A similar subgroup analysis on risk of deep venous thrombosis could not be performed as only one study provided data for this subgroup [13].

3.3. Evaluation for publication bias

The funnel plot (Fig. 3) was asymmetric, suggesting the presence of publication bias in favor of studies that showed positive association. This was confirmed by Egger's regression test that showed a significant result with a *p*-value of 0.03.

3.4. Trim-and-fill sensitivity analysis.\

As the presence of publication bias was suggested by both visualization of funnel plot and Egger's regression test, trim-and-fill sensitivity analysis as described by Duval et al. [9] was conducted to evaluate if publication bias had severely skewed the pooled result. Using this technique, two hypothetical missing studies were identified (supplementary Fig. 2). Inclusion of these two hypothetical missing studies into the meta-analysis only slightly decreased the pooled risk ratio down to 1.331 (95% CI, 1.255–1.411).

4. Discussion

The current study is the first systematic review and meta-analysis to summarize all available data on the risk of VTE among patients with hyperthyroidism. We found that the risk of developing VTE was significantly higher among patients with hyperthyroidism compared to individuals with normal thyroid function, with approximately 30% excess risk. The exact mechanisms leading to the increased risk remain unknown and further investigations are still needed. A few possible explanations are discussed below.

First, studies have demonstrated a higher level of coagulation factors, fibrinogen, von Willebrand factor and plasminogen activator inhibitor-1 among patients with hyperthyroidism [4,15–17], possibly due

to thyroid-receptor mediated up-regulation of gene transcription in hepatic and endothelial cells [4,18,19]. This alteration of factors related to hemostasis could tip the normal balance toward hypercoagulability and could eventually lead to the formation of a venous blood clot.

The second explanation is related to anti-phospholipid antibodies. Several case series have demonstrated a higher-than-expected prevalence of sero-positivity for anti-phospholipid antibodies among patients with Graves' disease, with the prevalence of as high as 43% [20–22]. These antibodies are known to induce clot formation in vivo and may explain the observed higher risk. The pathogenic mechanism behind the association between Graves' disease and anti-phospholipid antibodies is still unknown. The authors of one of the aforementioned case series postulated that it could be an epiphenomenon that synthesis of anti-thyroid stimulating hormone receptor antibodies by autoreactive B cell clones is accompanied by production of anti-phospholipid antibodies [20].

The clinical implications of hyperthyroidism as a predisposing factor for VTE are enormous. For instance, physicians may need to routinely check thyroid function for patients newly diagnosed with VTE. It will also dictate the duration of anticoagulation therapy if VTE associated with hyperthyroidism is considered provoked. Nevertheless, this study had some major limitations, and such a conclusion cannot be made until additional studies with better design are available. The limitations arise from the relatively low quality of the primary studies included in this meta-analysis, as they were all administrative database-based studies that relied solely on diagnostic codes to identify and diagnose hyperthyroidism and VTE, resulting in limited accuracy and concerns for misclassification. Most of them also did not provide data on the subtype of VTE (pulmonary embolism or deep venous thrombosis) and were unable to classify whether the episodes were provoked or unprovoked. Since the studies were retrospective in nature, surveillance bias could also play a role, as patients with hyperthyroidism may undergo more medical examinations simply because of their thyroid illness, and thus a higher likelihood of detection of any other medical conditions. Data on other potential risk factors for VTE were not systemically collected that may limit the accuracy of adjustment for confounders in the multivariate analysis. Prospective studies with predefined follow-up and data collection protocol would reduce these biases. Last, publication bias is also suggested by funnel plot and Egger's regression test, although trim-and-fill analysis suggests that the effect of missing studies is minimal.

5. Conclusion

In conclusion, this systematic review and meta-analysis demonstrated a significantly increased risk of VTE among patients with hyperthyroidism compared with individuals without hyperthyroidism. However, several limitations are noted and studies with better design are still needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.06.012.

Acknowledgement

We would like to thank Mr. Matthew Roslund, medical librarian at Bassett Medical Center, Cooperstown, New York, for his assistance with language review and editing.

Disclosure

None.

Funding

None.

Conflict of interests statement for all authors

We do not have any financial or non-financial potential conflicts of interest.

Authors' contributions

All authors had access to the data and a role in writing the manuscript.

References

[1] Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018;14:301–16.
[2] Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99:39–51.
[3] Ehlers M, Schott M, Allelein S. Graves' disease in clinical perspective. Front Biosci (Landmark Ed) 2019;24:35–47.
[4] Stuijver DJ, van Zaane B, Romualdi E, et al. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors. Thromb Haemost 2012;108:1077–88.
[5] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[6] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[7] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[8] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[9] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[10] Lin HC, Yang LY, Kang JH. Increased risk of pulmonary embolism among patients with hyperthyroidism: a 5-year follow-up study. J Thromb Haemost 2010;8:2176–81.
[11] Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldcare MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med 2011;9(1).
[12] Zoller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012;379:244–9.
[13] Lerstad G, Enga KF, Jorde R, et al. Thyroid function, as assessed by TSH, and future risk of venous thromboembolism: the Tromso study. Eur J Endocrinol 2015;173:83–90.
[14] Dekkers OM, Horvath-Puho E, Cannegieter SC, et al. Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: a population-based cohort study. Eur J Endocrinol 2017;176:1–9.
[15] Erem C, Ersoz HO, Karti SS, et al. Blood coagulation and fibrinolysis in patients with hyperthyroidism. J Endocrinol Invest 2002;25:345–50.
[16] Roger 2nd JS, Shane SR, Jencks FS. Factor VIII activity and thyroid function. Ann Intern Med 1982;97:713–6.
[17] Lippi G, Franchini M, Tagher G, Montagnana M, Salvagno GL, Guidi GC, et al. Hyperthyroidism is associated with shortened APTT and increased fibrinogen values in a general population of unselected out patients. J Thromb Thrombolysis 2009;28(3):362–5.
[18] Niessen RW, Pfaffendorf BA, Sturk A, Lamping RJ, Schapp MC, Hack CE, et al. The influence of insulin, beta-estradiol, dexamethasone and thyroid hormone on the secretion of coagulant and anticoagulant proteins by HepG2 cells. Thromb Haemost 1995;74(2):686–92.
[19] Shih CH, Chen SL, Yen CC, et al. Thyroid hormone receptor-dependent transcriptional regulation of fibrinogen and coagulation proteins. Endocrinology 2004;145:2804–14.
[20] Nabriski D, Ellis M, Ness-Abramof R, Shapiro M, Shenkman L. Autoimmune thyroid disease and antiphospholipid antibodies. Am J Hematol 2000;64:73–5.
[21] Paggi A, Caccavo D, Ferri GM, et al. Anti-cardiolipin antibodies in autoimmune thyroid diseases. Clin Endocrinol (Oxf) 1994;40:329–33.
[22] Marongiu F, Conti M, Murtas ML, et al. Anticardiolipin antibodies in Grave's diseases: relationship with thrombin activity in vivo. Thromb Res 1991;64:745–9.