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TITLE OF MASTER THESIS

"The risk of venous thromboembolic events in patients with inflammatory bowel disease: A systematic review and meta-analysis"

ΤΙΤΛΟΣ ΜΕΤΑΠΤΥΧΙΑΚΗΣ ΕΡΓΑΣΙΑΣ

"Ο κίνδυνος φλεβικών θρομβοεμβολικών επεισοδίων σε ασθενείς με ιδιοπαθή φλεγμονώδη νόσο του εντέρου: Μία συστηματική ανασκόπηση και μέτα-ανάλυση"

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Year of submission of Master Thesis: 2020

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1. Summary

Background and Aims: Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract, that has been associated with increased risk of extrainstestinal manifestations, amongst which, is venous thromboembolism (VTE). We assessed the risk for VTE in patients with IBD through systematic review and meta-analysis.

Methodology: A systematic search for English language, observational studies was conducted in Medline, Scopus, and the Cochrane Library published from database inception till August 10, 2020 to identify relevant studies reporting the risk of VTE in patients with IBD. The population-intervention-comparison outcome (PICO) and statistically the random-effects and fixed-effect models were used to estimate relative risks (RRs) with their respective 95% confidence intervals (CIs). Quality of the included studies was assessed using the Newcastle–Ottawa scale.

Results: Eleven studies (1 case–control and 10 cohort studies) were included in this analysis, encompassing 3.175.012 patients with IBD and 920.144.253 controls without IBD. The overall RR for VTE in patients with IBD compared to non-IBD individuals was 2.03 (CI 95%, 1.72–2.39).

Conclusion: The present meta-analysis shows that IBD is linked to a 2-fold increase in the risk of VTE, whose primary prevention is of utmost importance.

1. Περίληψη

Εισαγωγή και στόχοι: Η ιδιοπαθής φλεγμονώδης νόσος του εντέρου (ΙΦΝΕ), η οποία περιλαμβάνει τη νόσο του Crohn και την ελκώδη κολίτιδα, χαρακτηρίζεται από χρόνια φλεγμονώδη διαταραχή του γαστρεντερικού σωλήνα και από αυξημένο κίνδυνο εξωεντερικών εκδηλώσεων, μεταξύ των οποίων, είναι η φλεβική θρομβοεμβολική νόσος (ΦΘΝ). Εκτιμήσαμε τον κίνδυνο φλεβικής θρομβοεμβολικής νόσου σε ασθενείς με ΙΦΝΕ μέσω των μεθόδων της συστηματικής ανασκόπησης και μετα-ανάλυσης.

Μεθοδολογία: Η συστηματική αναζητήση δημοσιευμένων μελετών παρατήρησης στην αγγλική γλώσσα, πραγματοποιήθηκε στο Medline, το Scopus και το Cochrane Library, από την έναρξη των βάσεων δεδομένων έως τις 10 Αυγούστου 2020 για τον εντοπισμό σχετικών μελετών που αναφέρουν τον κίνδυνο εμφάνισης ΦΘΝ σε ασθενείς με ΙΦΝΕ, σύμφωνα με την μεθοδολογία PICO για την απάντηση κλινικών ερωτημάτων. Στη στατιστική ανάλυση χρησιμοποιήθηκαν τα μοντέλα τυχαίων και σταθερών επιδράσεων για την εκτίμηση του σχετικού κινδύνου (RR) με τα αντίστοιχα διαστήματα εμπιστοσύνης 95% (CIs). Η ποιότητα των συμπεριλαμβανόμενων μελετών αξιολογήθηκε χρησιμοποιώντας την κλίμακα Newcastle-Ottawa.

Αποτελέσματα: Έντεκα μελέτες (1 μελέτη πασχόντων-μαρτύρων και 10 μελέτες κοόρτης) συμπεριλήφθηκαν σε αυτήν την ανάλυση, που περιελάμβαναν 3.175.012 ασθενείς με ΙΦΝΕ και 920.144.253 μάρτυρες χωρίς ΙΦΝΕ. Ο συνολικός σχετικός κίνδυνος για ΦΘΝ σε ασθενείς με ΙΦΝΕ σε σύγκριση με άτομα που δεν είχαν ΙΦΝΕ ήταν 2.03 (CI 95%, 1.72-2.39).

Συμπέρασμα: Η παρούσα μετα-ανάλυση δείχνει ότι οι ασθενείς με ΙΦΝΕ έχουν διπλάσιο σχετικό κίνδυνο εμφάνισης ΦΘΝ, η έγκαιρη πρόληψη της οποίας είναι μείζονος σημασίας.

2. Introduction

Inflammatory bowel disease (IBD), is an autoimmune systemic disorder that mainly affects the gastrointestinal tract and predominantly includes ulcerative colitis (UC) and Crohn's disease (CD). Its exact cause is not yet fully understood, with genetic susceptibility, environmental factors and alterations in host's innate as well as adaptive immunity being the principal etiological factors. Apart from the gastrointestinal involvement, IBD is also responsible for a multitude of extraintestinal manifestations, including thromboembolic events (TEs) that significantly increase morbidity and mortality. [1-3]

TEs in IBD are often missed, given the fact that the prevalence of thrombosis varies between 1.3% and 7.7% in patients with IBD, and the rate is increased up to 39% - 41% in autopsy series. [4-6] The pathologic process of TEs in IBD patients involves multiple factors and is not yet completely understood. Abnormalities in procoagulation, anticoagulation and fibrinolytic factors have been proven to contribute to the development of thrombus in IBD, although several studies have not reported any risk factors in about 50% of IBD patients with TEs. Acquired risk factors for venous thromboembolism (VTE) include oral contraceptive use, surgical operation, body mass index (BMI) >30kg/m^2, trauma, pregnancy, puerperium, lupus anticoagulants, malignancy, long-distance travel, myeloproliferative disorders and polycythemia vera. [7,8] Over half of the cases of VTE in IBD may be associated with factor V Leiden and prothrombin gene mutation, which may indicate that genetic factors play a role in TEE, however, this is inconsistent with other studies. [9-11] Venous thrombosis is commonly observed in deep veins of the lower extremities- deep venous thrombosis (DVT) and the pulmonary arterial circulation- pulmonary embolism (PE). Less frequently, cerebrovascular, portal, mesenteric, hepatic, and retinal vein thrombosis is observed. [12-14]

Even though several observational studies and a couple of meta analyses have been conducted investigating the relationship between VTE and IBD, [15-16] the exact risk estimate of VTE in IBD population remains ambiguous, as a result of methodological differences and heterogeneity across studies. The aim of this study was to evaluate the risk of VTE in patients with IBD compared to non-IBD population. As a result, we conducted a systematic review and meta-analysis of observational studies that investigated the incidence of VTE, including DVT and/or PE in patients with IBD.

3. Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [18] The present meta-analysis was performed based on previously published studies therefore no ethical approval and patient consent are required.

3.1. Search strategy

A systematic literature search of Medline, Cochrane Library and Scopus was conducted from inception till August 10, 2020 to identify studies that reported the risk of VTE in patients with IBD. Key questions were formulated according to the 'PICO' method: "Do adults diagnosed with IBD have increased risk for VTE compared to adults without IBD?" [70-71] Text words and, if applicable, database subject heading fields (e.g., Medical Subject Headings), were used to perform the searches: "Inflammatory bowel disease," "IBD," "ulcerative colitis," "Crohn's disease," "thromboembolism," "pulmonary embolism," "deep vein thrombosis," "thrombosis," "venous thromboembolism," "VTE," and "DVT". Furthermore, we examined the references of each of the retrieved studies to identify further articles that met our criteria. We did not utilize any search

software. Search filters of human and English language studies were used. The title and abstract of studies identified in the original search were reviewed by two independent authors (K.A. and A.A.) to eliminate studies that did not answer to our research question, based on predetermined inclusion and exclusion criteria. The full text of the remaining articles was evaluated to determine whether it contained pertinent information. The coefficient of agreement between the two reviewers for article selection (k ¼ 0.87; 95% CI, 0.77–0.96) was excellent. Conflicts in study selection were resolved by consensus, referring back to the original article and, if an agreement failed to be reached, a third author (C.K) was consulted.

3.2. Selection criteria

Studies in this meta-analysis were observational cohort or case-control studies that met the following inclusion criteria: 1) diagnosed IBD (CD and/or UC) according to well-defined criteria; 2) reported incident cases of first VTE/ DVT or PE event after the diagnosis of IBD; 3) included a non-IBD population for which VTE/ DVT or PE event rates were calculated (or could be inferred as expected event rates from a reference population); 4) reported relative risk (for cohort studies), rate or risk ratio (for cohort studies), odds ratios (for case-control studies), hazard ratio (for cohort studies) with 95% confidence intervals (CIs) or provided raw data for their calculation; and 5) assessed age and sex as confounding factors. We included peer-reviewed observational controlled data (case–control and cohort studies) deriving from hospital, referral center and population based-studies. Studies evaluating only pediatric patients (age < 18 years) were excluded. Cross-sectional studies, meta-analyses, review articles, short surveys, letters to the editor, notes, case reports, pilot studies and conference abstracts were excluded. In addition, studies including only pregnant or post-operative population as control groups, studies that evaluated only recurrent VTEs and studies that did not contain primary data were excluded. Selection was not restricted by the number of

participants of each study. If there were more than one published studies coming from the same population, only data from the most recent comprehensive report were included. VTE was defined as the presence of first episode of DVT and/or PE, confirmed by objective imaging techniques. IBD, which included UC and/or CD, was defined based on medical diagnostic codes and records of clinical, endoscopic, histological, and radiological findings.

3.3. Data extraction

Two investigators (K.A. and A.A.) reviewed and abstracted the data independently onto a standardized form. The following data were collected from the studies: author and year of publication, study design, time period of study conduction, origin of the study population, type of exposure (IBD [CD and/or UC] and control population), primary outcome (VTE, DVT, and/or PE) and definition of outcome, total number of participants in each group (IBD vs. non-IBD controls), frequency of VTE, DVT and PE adjusted for potential confounders, as well as confounding factors reported in each study. When frequencies of IBD patients and associated VTE events were not reported in the studies, we merged data on UC and CD to evaluate the VTE risk estimate of IBD population as a whole. Risk estimates of outcomes were extracted as relative risks (RRs) and their 95% confidence intervals (CI). Data on the following covariates for DVT or PE were extracted from each study, wherever available: age, sex, history of cancer, history of major surgery, body mass index (BMI), history of pregnancy, history of PE or DVT, and smoking habits.

3.4 Outcome measures

The primary analysis focused on assessing the relative risk of VTE defined as DVT and/or PE in patients diagnosed with IBD (CD and/or UC) according to well-defined criteria, compared with non-IBD subjects originating from the general population, hospital or a referral center.

Furthermore, based on information available from individual studies, we performed subgroup analysis evaluating the risk estimates for DVT and PE separately in patients diagnosed with IBD compared to controls and additionally compared the risk for DVT vs. PE in IBD individuals. Moreover, CD and UC risk estimates for VTE, DVT and PE compared to controls were calculated individually. In addition, risk estimates for VTE, DVT and PE events were separately estimated in patients with UC vs. CD. Risk estimates for VTE in IBD individuals were also calculated for the included studies by separating them in two groups, according to their size. Finally, we assessed the risk for VTE in IBD patients vs. controls adjusted for BMI and smoking based on available data.

3.5. Data presentation

The PRISMA flow chart was used to report the selection process of the studies and includes an overall summary of the number and types of articles incorporated into the review (Figure 1).

3.6. Quality assessment of the studies

The quality of case-control and cohort studies included in our meta-analysis was independently assessed by two investigators (K.A. and A.A.), using the Newcastle-Ottawa scale (NOS). [19] The scale is based on a "star system" that ranges from 0 to 9, with 0 being the lowest possible quality, and judges study quality according to three perspectives: selection of the study groups (4 questions), comparability of the groups (2 questions) and ascertainment of the outcome of interest (3 questions). Each question was rated with maximum one star except for "comparability of the groups", for which separate stars were awarded for controlling age and/or sex (maximum 2 stars). Any differences between the two investigators were addressed via a re-evaluation of the original article.

3.7. Data synthesis and statistical analysis

All information was reported according to the PRISMA guidelines for meta-analyses. The Cochrane Collaboration's Review Manager Software (version 5.4) was used to perform the data analysis. [19] The generic inverse variance method was used to combine the studies with different scales of outcome estimates for random-effect meta-analysis, calculating ln (RRs) and the SE (ln(RR)). [21] When relative risks (RRs) and their respective confidence intervals (CIs) were not reported in the studies, they were calculated using the original data. Because the evaluated outcomes are relatively rare and the effects estimated are generally small, ORs in case–control studies were considered reasonable approximations of the corresponding RRs in cohort studies. [49-51] We assessed heterogeneity between study specific estimates using 2 methods. First, the Cochran Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was measured. Because this test is underpowered to detect moderate degrees of heterogeneity, the presence of statistically significant heterogeneity across the studies was evaluated by utilizing a P value < .10. Second, to estimate what proportion of total variation across studies was caused by study-related factors (clinical setting, methodological or statistical differences) rather than chance, the I2 statistic was calculated, where $I^2 = 100\% \times (Q-df)/Q$ representing the magnitude of the heterogeneity [moderate: 30–60%, substantial: 50–90%, considerable: 75–100%].[21-25] Dichotomous outcomes were pooled using the Mantel–Haenszel random-effects model (when more than moderate heterogeneity was detected among studies), which was used to calculate the RRs and corresponding 95% CIs. Mantel–Haenszel fixed effects model was used to calculate the RRs and corresponding 95% CIs in case of homogenous studies. For all tests (except for heterogeneity), a probability level < .05 was considered statistically significant.

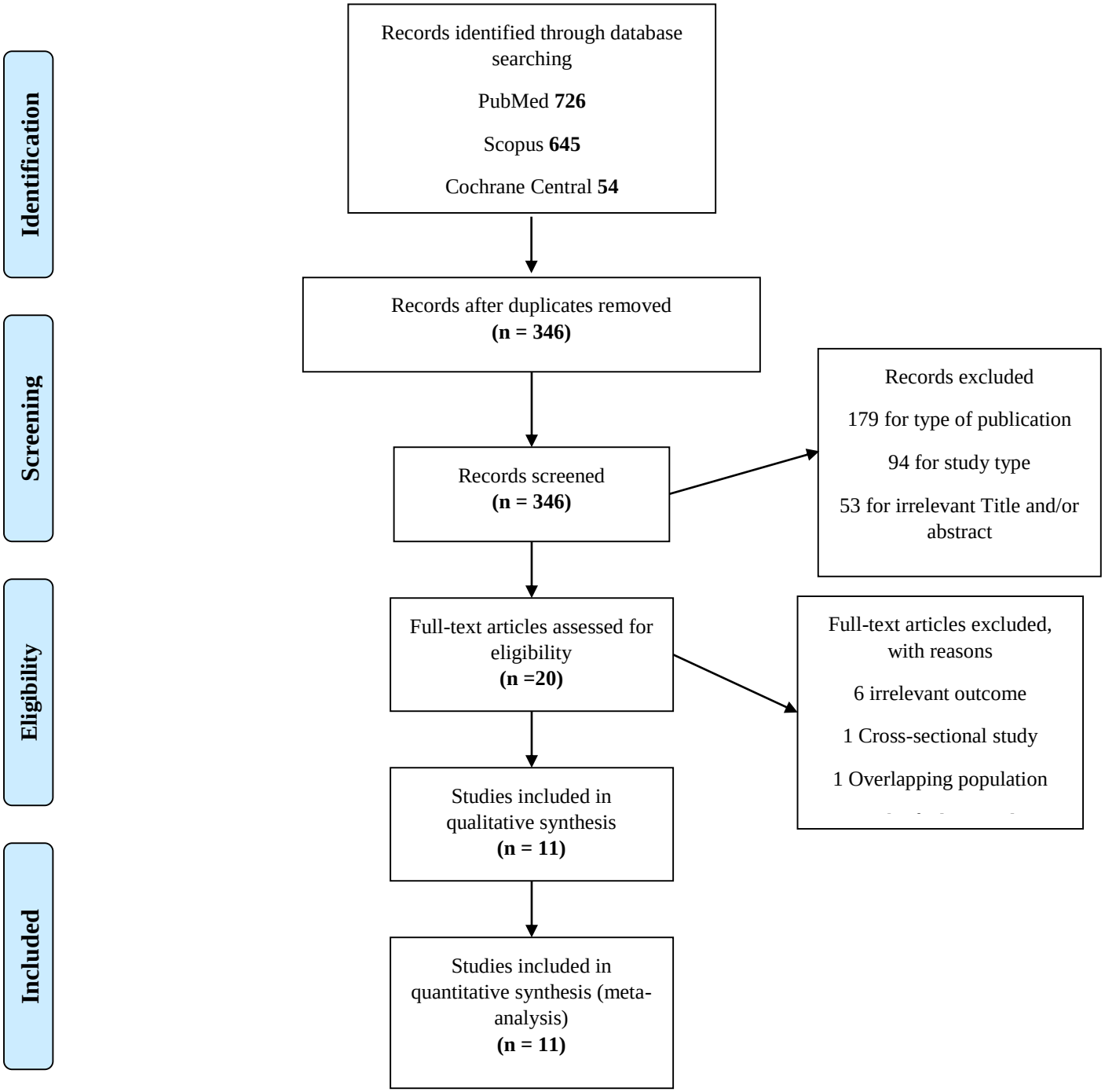
Visual inspection of the funnel plot demonstrated the asymmetry typically associated with publication bias. [26] That is, smaller, less precise studies [those with the larger standard errors (S.E.)] appear to have higher RRs than the large, more precise studies. Evidence of publication bias was also confirmed by the Egger's test, [27] which was performed using linear regression analysis on the IBM SPSS statistics 26.0 software, since the number of the included studies was n>10. [28]

4. Results

4.1. Eligible studies

The search strategy identified 1425 articles (Figure 1). After removal of duplicates and screening of titles, abstracts and keywords, 20 papers underwent full-text review. During this process, 6 articles [29-34] were excluded due to irrelevant outcomes, while 1 study was excluded due to a cross-sectional design. [35] Moreover, 2 studies [36-37] reported outcomes that originated from the same database, and as a result, the study with the shorter follow up period was excluded. [36] Additionally, 1 study [38] was excluded because neither did it provide an overall risk estimate for VTE, nor did it offer available data for calculating it. The remaining 11 studies, [37, 39-48] published between 2001 and 2018, fulfilled the selection criteria.

Figure 1. Study selection flow diagram presented according to the PRISMA Statement.



4.2. Quality assessment of the included studies

We used the Newcastle–Ottawa scale to evaluate the quality of the studies included in our meta-analysis. 2 studies were rated as 9-star, 5 studies as 8-star and 4 studies as 7-star. [12] The included studies averaged a quality score of 7.8. All studies provided a clear definition of the diagnosis of VTE, including the details of the confirmation based on imaging techniques. Some studies used the international disease codes for VTE diagnosis. (Table 1)

Table 1.

The Newcastle-Ottawa Scale for assessing risk of bias of the included studies. [37,39-48]

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Exposure/Outcome (max 3 stars)	Overall Quality Score (max 9 stars)
Ha 2009	****	*	**	7
Kappelman 2011	****	*	***	8
Bernstein 2001	****	*	***	8
Chung 2015	****	*	***	8
Grainge 2010	****	**	***	9
Miehsler 2004	***	**	**	7
Nguyen 2008	****	*	**	7
Rothberg 2011	****	*	**	7
Saleh 2010	****	*	**	8
Weng 2018	****	*	***	8
Chu 2018	****	**	***	9

A 'star' symbol identifies ‘high’ quality choices. The score allows maximum of one ‘star’ for each item within the ‘Selection’ and ‘Outcome’ categories and maximum of two ‘stars’ for ‘Comparability’. Highest quality choice allows 4 stars for ‘Selection’, 2 stars for 'Comparability' and 3 stars for ‘Outcome’. In comparability, 1 star was allocated in studies that adjusted for the confounder “age” and 2 stars in studies that also adjusted for the confounder “smoking”.

4.3. General characteristics

Our meta-analysis included 11 observational studies (10 cohort studies [39-48] and 1 case-control study [37]), the general characteristics of which are described in Table 2. Four studies were conducted in the USA, 2 in the UK, 1 in Denmark, 1 in Canada, 1 in Austria, and 1 in Taiwan. Six studies were population-based, 4 were hospital-based and 1 study had a referral center as a population source. The primary analysis was conducted in 3.175.012 patients with IBD and 920.144.253 controls without IBD. In the analysis of secondary outcomes regarding the evaluation of risk estimates for DVT and PE respectively, in IBD patients compared to controls without IBD, 5 studies were included. [37,41,43-44,48] In addition, four studies [37,43,47-48] were included in the analysis regarding the risk of VTE in patients with UC compared to patients with CD, while 3 studies [37,43,48] were used to evaluate the risk of DVT and PE respectively, in the same subgroups. Articles had large differences in their selection of covariates for adjusted analyses. Covariates included demographics like age and sex, past medical history like history of surgery, history of pregnancy, history of cancer, history of PE or DVT and other risk factors like body mass index (BMI) and smoking habits. A subgroup analysis was performed including 3 studies that evaluated smoking and BMI as confounding factors. [40,42,44]

Table 2. Characteristics of the studies included in the meta-analysis of venous thromboembolic events in patients with inflammatory bowel disease..

Study (Year)	Location	Study Period	Study Design	Data source (Setting)	Definition of Outcome	IBD		Controls		Confounders adjusted for*	Quality of Study 0-9 Stars
						VTE (n)	Total (n)	VTE (n)	Total (n)		
Ha[43] 2009	USA	2001-2006	Cohort	Thomson Reuters MarketScan Research claims database Population based	CVA (TIA, cerebrovascular occlusion);IHD (including acute MI, atherosclerosis), peripheral vascular disease	446	17487	830	7480	1,2	7
Kappelman [37] 2011	Denmark	1980-2007	Case-Control	Danish Civil Registration System Danish National Patient Registry Population based	Occurrence of DVT and PE	1181	49799	6646	477504	1,2,4,6,7	8
Bernstein[39] 2001	Canada	1984-1997	Cohort	Manitoba Health administrative Population based	Deep venous thrombosis (DVT) and pulmonary embolism (PE) occurrence in hospitalized patients	187	6027	N/A	55290	1,2	8
Chung[41] 2015	Taiwan	2000-2010	Cohort	National Health Insurance (NHI) database Population based	DVT and PE diagnosis	90	11445	195	45780	1,2,4,6,7	8
Grainge [42] 2010	UK	1987-2001	Cohort	General Practice Research Database(GPRD) Population based	Changes in the state of IBD and venous thromboembolism after hospitalization	139	13756	165	71672	1,2,3,5,7,8	9
Miehsler[44] 2004	Austria	N/A	Cohort	Three out-patient clinics of Division of Gastroenterology and Hepatology Referral center	History of TE, any cases of which had to be confirmed radiologically	38	618	10	618	1,2,3,4,5,6	7

Nguyen[45] 2008	USA	1998-2004	Cohort	Nationwide Inpatients Sample (NIS) Hospital based	VTE and in-hospital mortality	1933	116842	7213	522703	1,2,4	7
Rothberg[46] 2011	USA	2004-2005	Cohort	Patients discharged from 374 acute care facilities in the United States that participated in Premier's Perspective Hospital based	VTE during hospitalization and within 30 days after discharge	11	814	1041	241924	1,2,7	7
Saleh[47] 2010	USA	1979-2005	Cohort	The National Hospital Discharge Survey Hospital based	Pulmonary embolism (PE), deep venous thrombosis (DVT), or VTE, defined as PE and/or DVT	43000	2932000	10421000	918570000	1,2	8
Weng[48] 2018	Taiwan	2001-2013	Cohort	Taiwan National Health Insurance Research Database (NHIRD) Population based	Patients with VTE diagnosis	21	3178	96	31780	1,2,3,4	8
Chu[40] 2018	UK	1987-2011	Cohort	Clinical Practice Research Datalink linked with Hospital Episode Statistics Hospital based	Thromboembolism in hospital and within 6 weeks after leaving hospital, with or without undergoing major surgery, and while ambulant	430	23046	1065	106795	1,2,3,4,5,7,8	9

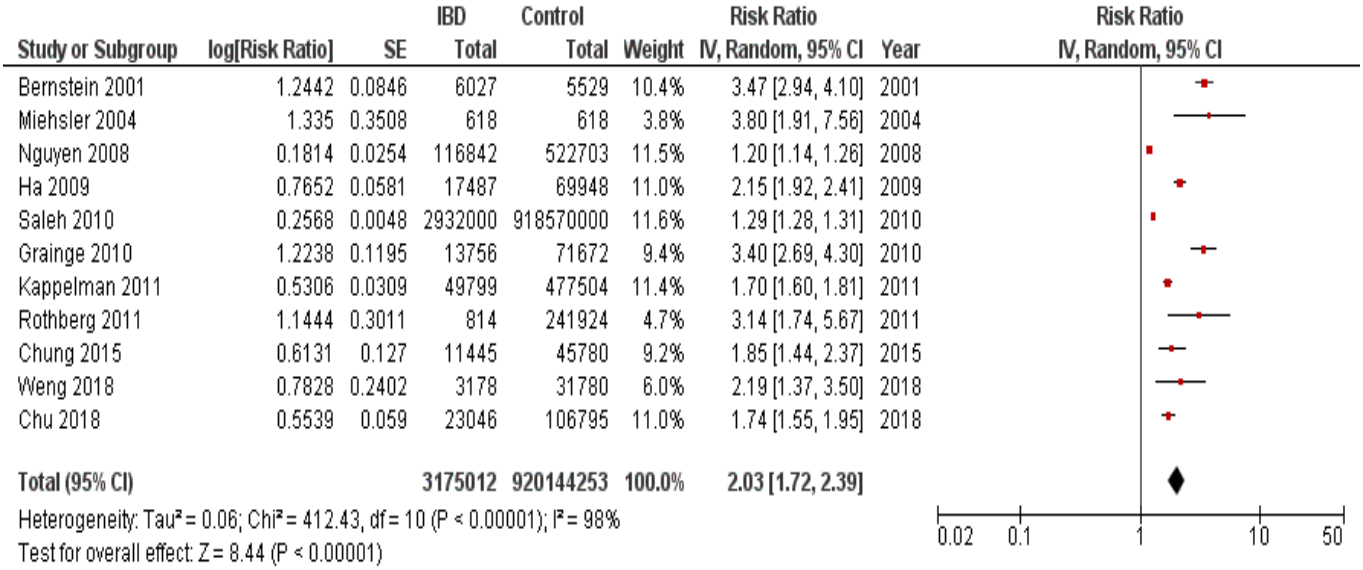
IBD, inflammatory bowel disease; VTE, venous thromboembolism; N/A, not available;

* Variables adjusted for 1. age, 2.sex, 3. smoking, 4. history of surgery, 5. body mass index (BMI), 6. history of pregnancy , 7. history of cancer, 8. history of pulmonary embolism or deep vein thrombosis

4.4. Quantitative analysis and evaluation of heterogeneity

The overall RR for VTE in patients with IBD compared to non-IBD individuals was 2.03 (CI 95%, 1.72–2.39). All individual studies had RR estimates above 1.0 with statistical significance. Significant heterogeneity was observed among studies (Q statistic=412.43, P < .10 I^2= 98%). (Figure 2).

Figure 2. Meta-analysis of 11 studies on venous thromboembolic events in patients with inflammatory bowel disease.



IBD: inflammatory bowel disease, CI: confidence intervals

In order to identify possible sources of heterogeneity, several subgroup analyses according to study size, IBD type, thrombosis location and adjustment for confounders were performed (Table 3). Analysis of studies with larger population size demonstrated a lower risk for VTE (RR 1.77, 95% CI 1.48–2.13) among patients with IBD, whereas studies with a smaller population size provided a greater risk for VTE (RR 2.67, 95% CI 1.97-2.93). The risk for VTE was increased among patients with UC (RR 1.8, 95% 1.15-2.82) and CD (RR 1.72, 95% CI 1.58-1.88) respectively with

no difference between the two groups (RR=1.03, 95% CI, 0.72–1.46). Similarly, an increased risk for DVT and PE was detected in patients with UC and CD respectively, with no difference between the two IBD clinical entities (Table 3). Additionally, patients with IBD presented an increased risk for DVT (RR 1.95, 95% CI, 1.59–2.39) and PE (RR 1.91, 95% CI 1.75–2.08) compared to controls. The risk for DVT was almost two-fold higher than that for PE in IBD population (RR 1.96, 95% CI 1.34 - 2.86). After adjusting for smoking and BMI the RR for VTE was moderately increased (RR 2.65, 95% CI, 1.51–4.65). The remaining 8 studies that did not adjust for these confounders demonstrated a lower but increased risk for VTE in patients with IBD compared to controls (RR 1.88, 95% CI, 1.57–2.24).

All studies included in the aforementioned subgroup analyses presented significant heterogeneity among them (Table 3). Only studies evaluating the risk for PE in patients with IBD compared to non-IBD subjects demonstrated no evidence of heterogeneity (Chi-Squared =2.06, P=0.72, I^2=0%). Finally, a secondary analysis was performed using the most recent published studies, [40,41,48] which demonstrated that the risk of VTE in patients with IBD was increased (RR 1.88, 95% CI, 1.70–2.07), without evidence of heterogeneity among them (Q statistic=0.43, P = 0.81 I^2 = 0%). (Table 3)

Table 3. Results of subgroup analyses.

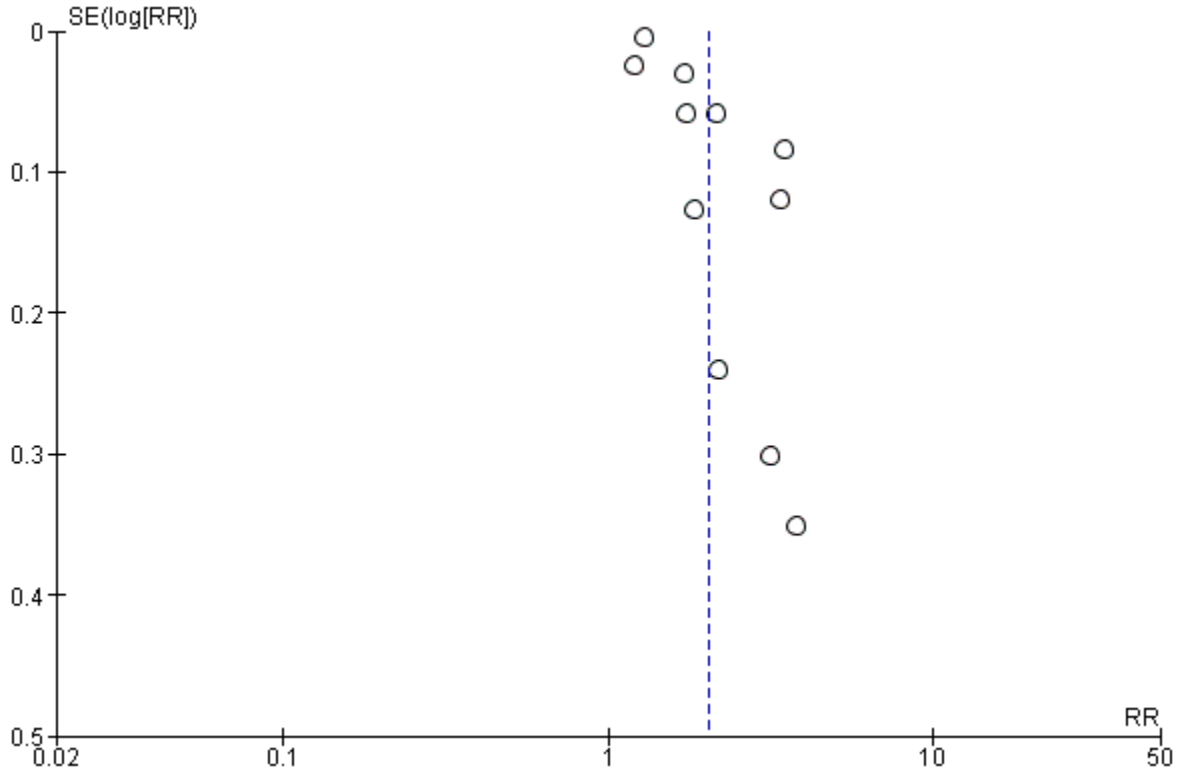
Outcome of interest	Number of studies	RR (95% CI)	Effect Model	Heterogeneity		
				I^{2} (%)	P-value	Q-statistic
VTE in IBD	11	2.03 (1.72–2.39)	Random	98 %	<0.01	412.43
DVT in IBD	5	1.95 (1.59–2.39)	Random	75 %	<0.01	16.07
PE in IBD	5	1.91 (1.75–2.08)	Fixed	0 %	=0.72	2.06
DVT vs. PE in IBD	5	1.96 (1.34–2.86)	Random	86 %	<0.01	29.23
VTE in UC	4	1.72 (1.58–1.88)	Random	74 %	<0.01	11.54
VTE in CD	4	1.80 (1.15–2.82)	Random	98 %	<0.01	181.37
DVT in CD vs. UC	3	1.06 (0.78–1.42)	Random	67 %	=0.05	6.13
PE in CD vs. UC	3	1.15 (0.89–1.49)	Random	30 %	=0.24	2.88
VTE in larger size studies	6	1.77 (1.48–2.13)	Random	98 %	<0.01	319.15
VTE in smaller size studies	5	2.67 (1.93–3.71)	Random	72 %	<0.01	14.39
Adjusted VTE risk*	3	2.65 (1.51–4.65)	Random	93 %	<0.01	28.27
Unadjusted VTE risk*	8	1.88 (1.57–2.24)	Random	98 %	<0.01	316.11

IBD: inflammatory bowel disease, CD: Crohn's disease, DVT: deep vein thrombosis, PE: pulmonary embolism, UC: ulcerative colitis, VTE: venous thromboembolism, RR: relative risk, CI: confidence intervals. * Variables adjusted for were smoking and body mass index

4.5. Publication bias

Upon inspection, the funnel plot of studies included in the primary analysis showed evidence of asymmetry suggestive of publication bias which was statistically confirmed (Egger P= 0.017) (Figure 3). After removing 6 studies [39,42-45,47] that appeared to be the cause of the asymmetry, little to no evidence of underlying bias could be found. Similarly, visual inspection of the funnel plots of studies included in most of the subgroup analyses presented asymmetry that was indicative of possible publication bias.

Figure 3. Funnel plot of the 11 studies included in the meta-analysis



5. Discussion

Our meta-analysis, which evaluated pooled data from all currently available observational studies assessing the risk of VTE in patients with IBD, indicated that the overall risk of VTE was found to be twofold higher in the IBD group, compared to the non-IBD control group. Due to both a qualitative as well as a quantitative confirmation of funnel plot's asymmetry, publication bias was suspected of being the main culprit for the resultant relationship between VTE and IBD. As the pooled RR for VTE, derived from the six studies with the larger sample size, was substantially higher than the pooled RR from the "smaller" ones, the aforementioned assumption seemed quite plausible. However, the pooled RR for VTE derived from the "larger" studies did not differ to a great extent from the pooled RR of the primary analysis, indicating that publication bias on its own, could not have been the causal factor for our results.

Subgroup analysis revealed that the risk of VTE in IBD was moderately increased after adjusting for smoking and BMI indicating that when considered together, these factors could act as confounders in the relationship between IBD and VTE. In addition, patients with IBD demonstrated an almost 2-fold higher risk for DVT compared to the risk for PE. Finally, an increased risk for VTE, as well as for DVT and PE was found in patients with UC and CD that was similar to that of the total IBD population.

In total, two meta-analyses were previously published, regarding the risk of VTE in patients with IBD. [15-16] Fumery et al. described an increased risk of VTE in patients with IBD (RR, 1.96; CI 95%, 1.67–2.30). Yuhara et al., on the other hand, described an even greater risk of VTE in IBD-patients (RR, 2.20; CI 95%, 1.83–2.65). The slight discrepancy in the size estimates, between the previous meta-analyses and this study, lies in the fact that different inclusion and exclusion criteria were utilized. In contrast to the previous published studies, we specifically excluded articles

including solely post-operative patients or pregnant women with IBD in order to avoid selection bias. In general, pregnant women develop 4 to 5 times more frequently VTE than non-pregnant women, [52-53] while a recent meta-analysis estimated the VTE risk in pregnant women with IBD to be 10-fold higher compared to that of non-pregnant ones without IBD. [17] Furthermore, major surgery has been proven to be a strong risk factor for VTE. [54-57] Another difference is that 3 new studies [40-41,48] were included in our meta-analysis that had no evidence of statistical heterogeneity among them. Furthermore, we excluded the study by Bernstein et al. [38] that was instead included in the other meta-analyses, because it did not satisfy our inclusion criteria; in particular, frequencies of VTE events developed both in the population with IBD as well as the controls were not reported in the original study, while there was no overall risk estimate of VTE in patients with IBD; only age- and sex-specific comorbidity rates were reported.

There is a long-standing debate about the prevention methods and treatment options of VTE in patients with IBD. According to recent consensus statements for the prevention and treatment of VTE in patients with IBD published by Nguyen et al. [58], moderate to severe disease activity increases the risk of VTE and thus should be considered as a provoking factor. In fact, 60% to 80% of IBD patients have active disease when they develop VTE [5,10,44,66-67]. Moreover, anticoagulant thromboprophylaxis is strongly recommended for hospitalized patients with moderate to severe IBD flares without severe bleeding[68] and for inpatients with IBD who have undergone major abdominal-pelvic or general surgery.[69] It is alarming that up to date, inadequate use of anticoagulants for VTE prophylaxis in IBD has been reported, [62] that is mainly attributed to: (1) gastroenterologists' lack of awareness of both the increased risk of VTE in IBD patients and the recommended use of pharmacological prophylaxis in hospitalized IBD patients; [63] and (2) concerns about the safety of anticoagulant drugs in patients with active IBD. [64-65]

Several limitations of this study must be acknowledged. First of all, since no RCTs have been performed to explore the association of VTE and IBD, our meta-analysis included only observational studies, which are often susceptible to selection bias and have a tendency of not taking into account several potential confounders for the investigated risk factor. [59] Second, significant heterogeneity (>90%) was observed among studies, that could be attributed to a variety of factors, such as different population characteristics of the included studies; 1. some studies were population-based cohorts, while in others data were abstracted from hospitalized patients or referral centers, 2. different follow-up period and variability in the disease phenotype of IBD among patients. Although colonic involvement as well as the extension of the disease have been proven to correlate with VTE risk, [44-45] not all of the studies provided sufficient information on disease location or disease characteristics, so we were not able to further analyze this factor. Third, in most of the included studies there were no quantitative activity indices for both UC and CD available, and as a result we could not estimate the effect of the exact severity of the disease on VTE risk. Fourth, since VTE is frequently diagnosed post-mortem, [60-61] some degree of differential misclassification of outcome is to be expected in the studies of this meta-analysis. Finally, we cannot rule out that we omitted relevant articles by having imposed English language, as a filter, on the search.

6. Conclusion

To conclude, patients with IBD carry a 2-fold risk of VTE compared to non-IBD subjects and therefore it is of utmost importance to increase gastroenterologists' awareness on the primary prevention of VTE in this group of patients. Further, adequately conducted prospective cohort studies as well as randomized trials are warranted to provide more robust data regarding the relationship of all forms of VTE with UC and CD, repsectively.

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