Outcomes among patients with cancer and incidental or symptomatic venous thromboembolism: A systematic review and meta-analysis

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ESSENTIALS

- Incidental venous thromboembolism (VTE) is frequent in patients with cancer.
- We conducted a systematic review and meta-analysis to evaluate the outcomes in these patients.
- Patients with incidental VTE have a lower risk of recurrent VTE than those with symptomatic VTE.
- A numerically increased risk of major bleeding events is found in patients with incidental VTE.

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SUMMARY

Background: Patients with cancer have an increased risk of venous thromboembolism (VTE) and it is commonly detected incidentally. The outcomes and optimal management for patients with cancer and incidental VTE remain debated.

Objectives: We conducted a systematic review and meta-analysis to evaluate the outcomes in patients with cancer and incidentally detected VTE compared to those with symptomatic events.

Patient/Methods: We searched the electronic database and included randomized controlled trials (RCTs) and observational studies reporting recurrent VTE, major bleeding events, and mortality in patients with cancer and incidental VTE comparing to symptomatic VTE.

Results: We included 23 studies for the systematic review: 3 RCTs and 20 observational studies. The meta-analysis of the 3 RCTs showed a significantly lower rate of VTE recurrence at 6 months in patients with incidental VTE compared to those with symptomatic VTE (RR 0.62, 95% CI 0.44-0.87). The risk of major bleeding events at 6 months was numerically higher with incidental VTE compared to symptomatic VTE (RR 1.47, 95% CI 0.99-2.20). There was no difference in overall mortality.

Conclusions: Among patients with cancer, incidental VTE was associated with a lower rate of VTE recurrence compared to symptomatic VTE, with a trend in increased major bleeding events. The risk-benefit ratio of anticoagulation may differ between incidental and symptomatic events and should be considered in the management.

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KEYWORDS

Systematic review; Venous thromboembolism; Incidental; Neoplasia; Hemorrhage.

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INTRODUCTION

Venous thromboembolism (VTE) is frequently related to cancer. Patients with malignancy have a high risk of VTE with an annual incidence of 1 case per 200 individuals [1] and it has been estimated that approximately 15% of patients with cancer will experience VTE [2] . The occurrence of VTE is commonly associated with an increased morbidity and mortality in cancer patients. The annual death rate of cancer-associated thrombosis is 448 per 100,000 patients which represents a 47-fold increase (95% CI, 6 to 89, p=0.03) compared to the general population [3].

Not uncommonly, VTE in cancer patients is detected incidentally on diagnostic imaging studies obtained for reasons other than a suspicion of VTE (e.g., staging computed tomography [CT] scan). With the improved image resolution and frequent use of multi-detector CT scanners [4], the prevalence of incidental VTE has increased. A recent large meta-analysis showed that the overall frequency of incidental pulmonary embolism (PE) was 3.36% in oncology patients [5]. Several studies have evaluated the prognosis and the clinical course of incidental VTE in the cancer population, but the optimal management of these patients is still debated. Current international guidelines recommend the same management for both clinically suspected and incidentally detected cancer-associated VTE [6, 7], but the supporting evidence is limited to mostly observational studies [8, 9]. More recent prospective studies showed a potentially lower rate of VTE recurrence [10, 11].

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Therefore, we conducted this systematic review and meta-analysis, aiming to evaluate the rates of recurrent VTE, bleeding complications, and overall mortality of incidental VTE in patients with cancer, compared to those with symptomatic VTE.

METHODS

The systematic review methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. We registered our protocol with the Open Science Framework (https://osf.io/yqmch).

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Search strategy

We searched Medline, Embase, and the Cochrane Database of Systematic Reviews databases, using the OVID interface, from inception through March 15th, 2021. The strategy used a combination of MeSH and clinical content terms (Supplemental Table 1).

Study selection

All studies (no language restrictions) including retrospective or prospective observational studies and randomized controlled trials (RCTs) fulfilling the eligibility criteria were incorporated in the systematic review. Eligibility criteria included: 1) enrolled adult patients (≥ 18 years of age) with cancer and VTE; and 2) reported the efficacy and safety of anticoagulation in patients with incidental and symptomatic index events. Incidental VTE refers to limb (upper or lower) deep vein thrombosis (DVT) or pulmonary embolism (PE) detected on diagnostic imaging studies obtained for reasons

other than suspicion of VTE [13]. Studies including only pediatric patients or only incidental VTE (without comparison to symptomatic VTE) were excluded. Similarly, studies not reporting on the outcomes of interest or without sufficient data to differentiate incidental *versus* symptomatic index events were not included. Additional data were sought from Select-D trial investigations to allow for meta-analysis of RCTs. Finally, studies including splanchnic vein thrombosis as index events (incidental or symptomatic) were excluded.

Studies were screened using Covidence software (Melbourne, Australia). Titles were directly imported into Covidence from the search databases and duplicates were removed. Three reviewers (LC, MC and T-F W) independently screened the titles and abstracts of all identified citations. The same reviewers subsequently independently assessed full texts of the selected articles following screening and determined the final list of included studies. All disagreements were resolved by consensus.

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Data extraction, outcome measures and quality assessment

Two investigators (LC, T-F W) abstracted the following variables: author information, year of publication, study design, patient baseline characteristics [i.e., age, sex, types and stage of cancers, chemotherapy use, type of anticoagulants, and location (i.e., PE or DVT) of index events] and the outcomes measures. The primary efficacy outcome measure was recurrent VTE objectively confirmed by contrast venography, ultrasound doppler, CT scan, magnetic resonance imaging, ventilation/perfusion scan, pulmonary angiography or autopsy. The primary safety outcome measure was major bleeding episodes. Major bleeding was defined as per the

International Society on Thrombosis and Haemostasis (ISTH) [14] or as per the individual study definitions. Secondary outcome measures included clinically relevant non-major bleeding (CRNMB) as per the ISTH definition (or individual study definitions) [15] and overall mortality. In the event of overlapping patient cohorts, we preferentially included data from the most recent report.

Two reviewers (LC, T-F W) independently assessed the study methodological quality by using Cochrane risk-of-bias tool for randomized trials (RoB2) for RCTs [16] and the Newcastle-Ottawa Scale (NOS) for observational studies [17]. Disagreement was resolved by consensus. For RCTs, five domains were assessed, and each was assigned as low risk, some concerns, or high risk of bias. The overall risk of the study was determined as low if all domains were judged as low risk and high if at least one domain was judged as high risk of bias [16]. For observational cohort studies, the risk of bias was determined in three categories: selection, comparability, and outcome, while for observational case-control studies, similar three categories – selection, comparability, and exposure – were assessed [17].

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Data synthesis

Aggregate participant data were used for the quantitative meta-analysis. The primary and secondary outcomes were reported by narrative synthesis and pooled rate estimates with a random effects model using the R software (version 4.0.3). Risk ratio (RR), risk difference (RD), and 95% confidence interval (CI) were estimated using the inverse-variance random effects model by DerSimonian and Laird [18]. The I^2 statistic was used to assess for heterogeneity between studies. An I^2 below 30% was

determined as non-significant heterogeneity, an I² between 30-70% as moderate heterogeneity and an I² greater than 70% as considerable heterogeneity. The meta-analysis was performed using Review Manager 5.4.1 (Copenhagen) and R software (version 4.0.3). Forest plots were generated using Review Manager 5.4.1.

RESULTS

Study selection and characteristics

Our literature search identified 3378 citations, and after removing duplicates and screening for abstracts and titles, 97 studies were assessed for eligibility by full text and 3 additional studies were identified from references of included studies (Figure 1, PRISMA diagram). Twenty-three studies were eventually included in the systematic review (3 RCTs and 20 observational studies), with a total of 12,977 patients with cancer and VTE, 4200 (32.4%) of which were incidental [8, 11, 19-39]. Among the observational studies, there were one case-control study [31], 4 prospective cohort [24-26, 39], and 15 retrospective cohort studies [8, 21-23, 27-30, 32-38]. Meta-analysis was performed for the 3 RCTs [11, 19, 20]. Table 1 summarizes the characteristics of all included studies in the systematic review. The percentages of incidental VTE varied significantly among studies from 3.8% to 80.8%. The percentage of incidental VTE was capped at 20% in one RCT (Caravaggio trial). Among the 19 observational studies reporting the type of VTE, the majority (89%, n=17) reported 100% PE (with or without DVT).

Quality assessment

The risk of bias assessment is summarized in Supplemental Tables 2-4. All 3 RCTs were deemed to have low risk of bias. Although they were all open label (without blinding), the outcomes were independently adjudicated by a committee that was unaware of the treatment assignment. The quality of observational cohort studies (N=20) were heterogenous, with studies in abstracts only generally judged to have a lower quality given the lack of study details. Nine studies (45%) did not adjust outcomes by different variables (lack of comparability), 6 studies (30%) did not report on assessment of outcomes, while 8 studies (40%) did not report adequate follow-up.

No formal funnel plots were illustrated to assess publication bias because fewer than 10 studies were available to include in the meta-analysis.

Outcome analysis

Outcomes of recurrent VTE, major bleeding events, and mortality for each study are summarized in Table 2 (RCTs) and Table 3 (observational studies). CRNMB events were rarely reported in observational studies and therefore were not included in the final analysis. Most studies reported that therapeutic anticoagulation was given in >90% of both patient groups (incidental or symptomatic) (Table 3).

Three RCTs (Select-D, Hokusai VTE Cancer, and Caravaggio trials) were included in the meta-analysis [11, 19, 20]. The risk of recurrent VTE at 6 months was significantly lower in patients with incidental VTE compared to symptomatic VTE as the index event (RR 0.62, 95% CI 0.44-0.87, I^2: 0%, Figure 2A). With a baseline risk of recurrent VTE in symptomatic group of 8.0%, the RD compared to incidental VTE was -3.2% (95% CI -5.4% to -1.0%). The risk of major bleeding events at 6 months was

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higher with incidental VTE compared to symptomatic VTE, although not statistically significant (RR 1.47, 95% CI 0.99-2.20, I^2: 0%, Figure 2B). With a baseline risk of major bleeding events in patients with symptomatic VTE of 3.5%, the RD compared to incidental VTE was +1.8% (95% CI -0.1 to +3.6%), There was no difference in overall mortality by incidental vs symptomatic VTE when available data from Hokusai VTE Cancer and Select-D trials were combined (incidental vs. symptomatic, RR 1.03, 95% CI 0.85-1.25, RD: +1.4% (95% CI -4.8% to +7.6%) [11, 19].

There was high heterogeneity of outcome reporting in observational studies and data were frequently insufficient for a formal meta-analysis. Most studies except for four [8, 25, 31, 36] reported lower mortality or better survival in patients with incidental VTE.

DISCUSSION

Our meta-analysis of data from RCTs comparing direct oral anticoagulants (DOACs) to low molecular weight heparin (LMWH) which included patients with incidental VTE (20-52% of index events), showed that the rates of recurrent VTE are significantly lower among patients with cancer and incidental VTE compared to those with symptomatic events (RR 0.62, 95% CI: 0.44 to 0.87). The rates of major bleeding complications from anticoagulant therapy are higher (not statistically significant) in patients with incidental VTE (RR 1.47, 95% CI 0.99-2.20). The systematic review including 20 additional observational studies revealed that most studies also reported a lower rate of overall mortality in patients with incidental events. These findings suggest that the risk-benefit ratio of anticoagulation may differ between incidental and

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symptomatic events and should be considered in the management of patients with cancer and VTE.

Understanding the clinical relevance of incidental VTE is crucial for practicing clinicians since approximately 50% of all cancer-related PE are detected on diagnostic imaging obtained for reasons other than suspicion of VTE [40]. International guidelines suggest the same management strategies for both clinically suspected and incidental VTE in patients with cancer [6, 7, 13]. However, these recommendations are based on observational studies, where a various proportion (5-50%) of patients were untreated (Table 3), and some results were conflicting. Whereas some studies have reported a lower rate of recurrent VTE among patients with cancer and incidental VTE compared to symptomatic events, others have not [8-10]. Heterogeneity in patient and cancer characteristics, as well as anticoagulation type, intensity, and duration may account for these different findings. For example, only approximately 50% of patients in the study of den Exter et al. were anticoagulated with LMWH (vitamin K antagonists for the other 50%) [8], compared to over 80-90% in later studies, which reported a lower rate of recurrent VTE [9, 10]. Although our study revealed a lower risk of recurrent VTE associated with incidental VTE, the risk remained significant and justified for anticoagulation. Additionally, the majority (>90%) of patients with incidental VTE in observational studies received therapeutic anticoagulation (Table 3), so outcomes without anticoagulation remained limited. Nonetheless, our results highlighted the importance of understanding the different characteristics and outcomes of incidental vs symptomatic VTE which could have important implications in future study design and interpretation when incidental VTE is included.

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Cases of incidental VTE diagnosed on imaging studies obtained for reasons other than suspicion of VTE may not be homogenous, as symptoms that could be related to VTE are often missed or attributed to cancer and anticancer treatments. A retrospective case-control study showed that 44% of patients had typical VTE symptoms (shortness of breath, chest pain, limb pain or swelling) 2 weeks prior to the diagnosis of an incidental PE, up to 75% when fatigue was included in the symptomology, significantly higher than controls without VTE [41]. Among the studies included in our systematic review, the EPIPHANY study was the only one investigating outcomes stratified by the presence of symptoms in patients with incidental VTE [26]. Interestingly, 45.6% of the patients with incidental PE had signs and symptoms of PE and their mortality rates were similar to those with suspected VTE, and both were significantly increased compared to those with truly asymptomatic incidental PE (30-day mortality: 20% vs 21% vs 3%, respectively, $p<0.001$) [26]. The VTE recurrence rates were not different among all three groups [26]. Similarly, O'Connell et al. reported that survival was significantly reduced in patients with symptomatic unsuspected VTE compared to those with truly asymptomatic events [42]. These indicate the importance of careful assessment of symptoms in patients diagnosed with incidental VTE, and the presence of symptoms could be important for risk stratification.

It is of interest that in our meta-analysis of RCT data, the risk of recurrent VTE was lower and the risk of major bleeding events was higher in those with incidental VTE compared to symptomatic VTE. Reasons for these findings were unclear but could be postulated. Incidental VTE may not be thrombotic in nature as a recent large Dutch study showed a noticeable portion of PE (14.1%) observed at autopsy in cancer

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patients were tumor embolism, along with other types (septic, fat tissue, bone marrow) [43]. In addition, incidental VTE might already be subacute or chronic at the time of diagnosis. Both factors could result in a lower rate of VTE recurrence. Differences in baseline characteristics can also play a key role. For example, type of malignancy differentially found in incidental compared to symptomatic VTE can be an important contributor to the risk of bleeding. In the Hokusai VTE Cancer trial, a larger percentage of gastrointestinal (GI) cancer and lower percentage of hematological cancer, as well as more metastatic disease were found in the incidental group [11]. This is not surprising from the routine use of staging CT scans in GI cancer but not hematological cancers. GI malignancies and metastatic disease are associated with an increased risk of bleeding events, which could explain the increased bleeding in the incidental group [44]. This finding is hypothesis generating and could challenge the current practice of same management strategies for both incidental and symptomatic VTE. Whether a limited duration or reduced dose of anticoagulation can be considered in at least some patients (such as those who are truly asymptomatic or with high risks of bleeding) could be an area of future research.

The mortality outcome in association with incidental or symptomatic VTE is also variable among studies. Eighty percent (16/20) of the included observational studies reported lower mortality rate associated with incidental VTE, but other studies have shown otherwise [23]. Both Hokusai VTE Cancer and select-D trials showed comparable overall mortality in patients with incidental vs. symptomatic VTE [11, 19]. Therefore, although incidental VTE may be associated with a lower rate of recurrent

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events, its prognostic role on overall mortality may be related to advanced or aggressive underlying malignancy [23] or poor performance status [31].

This study has limitations that are important to consider. This is a study-level meta-analysis, and some of the included observational studies did not report rates of recurrent VTE or major bleeding and may have generated selection bias. In addition, patient selection bias could occur in RCTs as well given the strict inclusion and exclusion criteria employed in RCTs. The large variation in proportion of incidental VTE in observational studies and limiting percentage of incidental VTE in one RCT highlighted the heterogeneity in study design and difficulties in combined analysis from all studies. As one cannot randomize between incidental vs symptomatic VTE, baseline characteristics (such as type of malignancy, ECOG, etc) could be different between the two groups which may impact outcomes, although the type of anticoagulant assigned to incidental vs symptomatic groups was balanced in all 3 RCTs [11, 19, 20]. Furthermore, due to the limitation of available data, outcomes as related to type of VTE (PE vs DVT) or the extent of VTE burden (subsegmental vs. centrally located PE) could not be directly evaluated. We excluded incidental splanchnic vein thrombosis and 89% of the observational studies included patients with PE only (+/- DVT) as index events, so our results are mostly applicable to PE patients, but this is the most common type of incidental VTE. Given the availability of data, we were not able to perform all analyses originally planned in the registered protocol, such as rates per patient-month follow up. Finally, none of the studies included data on fatal recurrent VTE and only one study reported the rate of fatal major bleeding events [37].

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Despite these limitations, our meta-analysis of pivotal RCTs showed that the rate of recurrent VTE was significantly lower in patients with incidental VTE compared to symptomatic events, with a trend of increased major bleeding events, which has not been reported previously. Although the quality and outcome reporting in observational studies are more variable, we provided a comprehensive review of the current literature and revealed limitations and future directions.

In conclusion, cancer patients with incidental VTE have a lower risk of VTE recurrence compared to those with symptomatic events and seem to have a higher risk of major bleeding complications on anticoagulant therapy. A more individualized approach, based on the risk of bleeding, life expectancy, and patient preference, among other factors, may be needed in the treatment of patients with cancer and incidental VTE. Future studies are needed to identify risk factors and potentially a lower-risk group of cancer patients with incidental VTE in whom limited duration or reduced dose of anticoagulation could be considered.

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AUTHORSHIP CONTRIBUTIONS

L Caiano and T-F Wang contributed to study design, data analysis, and wrote the manuscript. M Carrier was responsible for study conception and planning, and provided key revisions to the manuscript. A Young, A Marshall, W Ageno, and A Delluc contributed to the interpretation of data, and provided key revisions to the manuscript.

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CONFLICTS OF INTEREST

L Caiano has no relevant conflicts of interest to disclose.

M Carrier has received research funding from BMS, Pfizer, and Leo Pharma. He has also received honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma.

A Marshall has no conflicts of interest to disclose.

AM Young has received honoraria from Leo Pharma, BMS/Pfizer Alliance, Chugai, Bayer, and educational grant from Bayer.

W Ageno has received research grant from Bayer Healthcare; and participation in advisory boards for Bayer, Portola, Janssen, Norgine, Aspen, Sanofi.

A Delluc has received research grants from Leo Pharma and Pfizer, personal fees from BMS, Leo Pharma, Pfizer, Servier.

T-F Wang received research funding from Leo Pharma and participated in advisory boards for Servier.

REFERENCES

1 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000; **160**: 809-15. 10.1001/archinte.160.6.809.

2 Eichinger S. Cancer associated thrombosis: risk factors and outcomes. *Thromb Res*. 2016; **140 Suppl 1**: S12-7. 10.1016/S0049-3848(16)30092-5.

3 Khorana AA. Venous thromboembolism and prognosis in cancer. *Thromb Res*. 2010; **125**: 490-3. 10.1016/j.thromres.2009.12.023.

4 Patel S, Kazerooni EA, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. *Radiology*. 2003; **227**: 455-60. 10.1148/radiol.2272011139.

5 Meyer HJ, Wienke A, Surov A. Incidental pulmonary embolism in oncologic patients-a systematic review and meta-analysis. *Support Care Cancer*. 2021; **29**: 1293-302. 10.1007/s00520-020-05601-y.

6 Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, Leavitt AD, Lee AYY, Macbeth F, Morgan RL, Noble S, Sexton EA, Stenehjem D, Wiercioch W, Kahale LA, Alonso-Coello P. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021; **5**: 927-74. 10.1182/bloodadvances.2020003442.

7 Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020; **38**: 496-520. 10.1200/JCO.19.01461.

8 den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol*. 2011; **29**: 2405-9. 10.1200/JCO.2010.34.0984.

9 van der Hulle T, den Exter PL, Planquette B, Meyer G, Soler S, Monreal M, Jimenez D, Portillo AK, O'Connell C, Liebman HA, Shteinberg M, Adir Y, Tiseo M, Bersanelli M, Abdel-Razeq HN, Mansour AH, Donnelly OG, Radhakrishna G, Ramasamy S, Bozas G, Maraveyas A, Shinagare AB, Hatabu H, Nishino M, Huisman MV, Klok FA. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost*. 2016; **14**: 105-13. 10.1111/jth.13172.

10 Kraaijpoel N, Bleker SM, Meyer G, Mahe I, Munoz A, Bertoletti L, Bartels-Rutten A, Beyer-Westendorf J, Porreca E, Boulon C, van Es N, Iosub DI, Couturaud F, Biosca M, Lerede T, Lacroix P, Maraveyas A, Aggarwal A, Girard P, Buller HR, Di Nisio M, investigators UPE. Treatment and Long-Term Clinical Outcomes of Incidental Pulmonary Embolism in Patients With Cancer: An International Prospective Cohort Study. *J Clin Oncol*. 2019; **37**: 1713-20. 10.1200/JCO.18.01977.

11 Mulder FI, Di Nisio M, Ay C, Carrier M, Bosch FTM, Segers A, Kraaijpoel N, Grosso MA, Zhang G, Verhamme P, Wang TF, Weitz JI, Middeldorp S, Raskob G, Beenen LFM, Buller HR, van Es N. Clinical implications of incidental venous thromboembolism in cancer patients. *Eur Respir J*. 2020; **55**. 10.1183/13993003.01697-2019.

For Peer Review

12 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; **151**: 264-9, W64. 10.7326/0003-4819-151-4-200908180-00135.
13 Di Nisio M, Lee AY, Carrier M, Liebman HA, Khorana AA, Subcommittee on H, Malignancy. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2015; **13**: 880-3. 10.1111/jth.12883.
14 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005; **3**: 692-4. 10.1111/j.1538-7836.2005.01204.x.
15 Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of A. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015; **13**: 2119-26. 10.1111/jth.13140.
16 Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; **366**: l4898. 10.1136/bmj.l4898.
17 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**: 177-88. 10.1016/0197-2456(86)90046-2.
19 Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018; **36**: 2017-23. 10.1200/JCO.2018.78.8034.
20 Agnelli G, Becattini C, Meyer G, Munoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M, Caravaggio I. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020; **382**: 1599-607. 10.1056/NEJMoa1915103.
21 Chang H, Kim MS, Lee SY, Shin SH, Park HY, Chang SA, Park TK, Kim DK, Kim EK. Does anticoagulation needed for distally located incidental pulmonary thromboembolism in patients with active cancer? *PLoS One*. 2019; **14**: e0222149. 10.1371/journal.pone.0222149.
22 Deng K, Parameswaran R, Soff BP, Soff GA. Incidental versus symptomatic pulmonary embolism in cancer patients: A multivariate analysis of recurrent vte and mortality. *Blood*. 2012; **120**: 70962518.
23 Dentali F, Ageno W, Giorgi Pierfranceschi M, Imberti D, Malato A, Nitti C, Salvi A, Siragusa S, Squizzato A, Vitale J, Agnelli G. Prognostic relevance of an asymptomatic venous thromboembolism in patients with cancer. *J Thromb Haemost*. 2011; **9**: 1081-3. 10.1111/j.1538-7836.2011.04259.x.
24 Fernandez-Martinez A, Selvi M, Vargas A, Carmona-Bayona sA, Aibar J, Beato C, C. F. Short and longterm outcomes of cancer patients with incidental and symptomatic pulmonary

For Peer Review

embolism (PE): Data on a prospective cohort of 138 consecutive patients. *Supportive Care in Cancer* 2013; **21(SUPPL. 1)**: S221-S2.
25 Font C, Farrus B, Vidal L, Caralt TM, Visa L, Mellado B, Tassies D, Monteagudo J, Reverter JC, Gascon P. Incidental versus symptomatic venous thrombosis in cancer: a prospective observational study of 340 consecutive patients. *Ann Oncol*. 2011; **22**: 2101-6. 10.1093/annonc/mdq720.
26 Font C, Carmona-Bayonas A, Beato C, Reig O, Saez A, Jimenez-Fonseca P, Plasencia JM, Calvo-Temprano D, Sanchez M, Benegas M, Biosca M, Varona D, Vicente MA, Faez L, Solis MD, de la Haba I, Antonio M, Madridano O, Castanon E, Martinez MJ, Marchena P, Ramchandani A, Dominguez A, Puerta A, Martinez de la Haza D, Pueyo J, Hernandez S, Fernandez-Plaza A, Martinez-Encarnacion L, Martin M, Marin G, Ayala F, Vicente V, Otero R, Asociacion para la Investigacion de la Enfermedad Tromboembolica de la region de M. Clinical features and short-term outcomes of cancer patients with suspected and unsuspected pulmonary embolism: the EPIPHANY study. *Eur Respir J*. 2017; **49**. 10.1183/13993003.00282-2016.
27 Li G, Li Y, Ma S. Lung Cancer Complicated With Asymptomatic Pulmonary Embolism: Clinical Analysis of 84 Patients. *Technol Cancer Res Treat*. 2017; **16**: 1130-5. 10.1177/1533034617735930.
28 Machida H, Hom MS, Maeda M, Yeo JJ, Ghattas CS, Grubbs BH, Matsuo K. Signs and Symptoms of Venous Thromboembolism and Survival Outcome of Endometrial Cancer. *Int J Gynecol Cancer*. 2016; **26**: 924-32. 10.1097/IGC.0000000000000684.
29 Peris M, Lopez-Nunez JJ, Maestre A, Jimenez D, Muriel A, Bikdeli B, Weinberg I, Ay C, Mazzolai L, Lorenzo A, Monreal M, Investigators R. Clinical characteristics and 3-month outcomes in cancer patients with incidental versus clinically-suspected and confirmed pulmonary embolism. *Eur Respir J*. 2020. 10.1183/13993003.02723-2020.
30 Piacentini G, Fregoni V, Gervaso L, Sansi C, Cefali M, Pavesi L, Riccardi A. Asymptomatic versus symptomatic pulmonary embolism in oncologic patients: Does clinical presentation influence outcome? *European Journal of Cancer*. 2017; **72 (Supplement 1)**: S140.
31 Sahut D'Izarn M, Caumont Prim A, Planquette B, Revel MP, Avillach P, Chatellier G, Sanchez O, Meyer G. Risk factors and clinical outcome of unsuspected pulmonary embolism in cancer patients: a case-control study. *J Thromb Haemost*. 2012; **10**: 2032-8. 10.1111/j.1538-7836.2012.04868.x.
32 Savla GV, Gladish G, Zhou X, Vadhan-Raj S. Differences in the clinical presentation, severity, and treatment outcome for symptomatic versus asymptomatic pulmonary embolism in cancer patients. *J Clin Oncology* 2008; **26**: 20688

33 Shinagare AB, Okajima Y, Oxnard GR, Dipiro PJ, Johnson BE, Hatabu H, Nishino M. Unsuspected pulmonary embolism in lung cancer patients: comparison of clinical characteristics and outcome with suspected pulmonary embolism. *Lung Cancer*. 2012; **78**: 161-6. 10.1016/j.lungcan.2012.08.007.
34 Silva P, Rosales M, Milheiro MJ, Santos LL. Pulmonary Embolism in Ambulatory Oncologic Patients. *Acta Med Port*. 2015; **28**: 463-8.
35 Soler S, Delgado C, Ballaz A, Cisneros E, Maly R, Babalis D, Monreal M, Investigators R. Unsuspected pulmonary embolism in patients with cancer. *Thromb Res*. 2012; **129 Suppl 1**: S16-9. 10.1016/S0049-3848(12)70010-5.
36 Spirk D, Sebastian T, Barco S, Banyai M, Beer JH, Mazzolai L, Baldi T, Aujesky D, Hayoz D, Engelberger RP, Kaeslin T, Korte W, Escher R, Husmann M, Blondon M, Kucher N. Clinical Outcomes of Incidental Venous Thromboembolism in Cancer and Noncancer Patients:

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The SWIss Venous ThromboEmbolism Registry (SWIVTER). *Thromb Haemost*. 2021; **121**: 641-9. 10.1055/s-0040-1720977.

37 Sun JM, Kim TS, Lee J, Park YH, Ahn JS, Kim H, Kwon OJ, Lee KS, Park K, Ahn MJ. Unsuspected pulmonary emboli in lung cancer patients: the impact on survival and the significance of anticoagulation therapy. *Lung Cancer*. 2010; **69**: 330-6. 10.1016/j.lungcan.2009.11.015.

38 Tiseo M, Bersanelli M, Pesenti Barili M, Bartolotti M, De Luca G, Gelsomino F, Camisa R, Cademartiri F, Ardizzoni A. Asymptomatic pulmonary embolism in lung cancer: prevalence and analysis of clinical and radiological characteristics in 141 outpatients. *Tumori*. 2012; **98**: 594-600. 10.1700/1190.13200.

39 Wysokinska E, Houghton DE, Vlazny D, Ashrani AA, Froehling DA, Hodge DO, Peterson L, McBane RD, Wysokinski WE, Casanegra AI. Incidental pulmonary embolism. Analysis of Mayo Clinic venous thromboembolism database. *Blood*. 2019; **134(Supplement 1)**.

40 van Es N, Bleker SM, Di Nisio M. Cancer-associated unsuspected pulmonary embolism. *Thromb Res*. 2014; **133 Suppl 2**: S172-8. 10.1016/S0049-3848(14)50028-X.

41 O'Connell CL, Boswell WD, Duddalwar V, Caton A, Mark LS, Vigen C, Liebman HA. Unsuspected pulmonary emboli in cancer patients: clinical correlates and relevance. *J Clin Oncol*. 2006; **24**: 4928-32. 10.1200/JCO.2006.06.5870.

42 O'Connell CL, Razavi PA, Liebman HA. Symptoms Adversely Impact Survival Among Patients With Cancer andUnsuspected Pulmonary Embolism. *J Clin Oncology* 2011; **29**: 4208-9. DOI: 10.1200/JCO.2011.37.2730;.

43 Gimbel IA, Mulder FI, Bosch FTM, Freund JE, Guman N, van Es N, Kamphuisen PW, Buller HR, Middeldorp S. Pulmonary embolism at autopsy in cancer patients. *J Thromb Haemost*. 2021; **19**: 1228-35. 10.1111/jth.15250.

44 Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Buller HR, Hokusai VTECI. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018; **378**: 615-24. 10.1056/NEJMoa1711948.

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Figure 1. PRISMA flow diagram

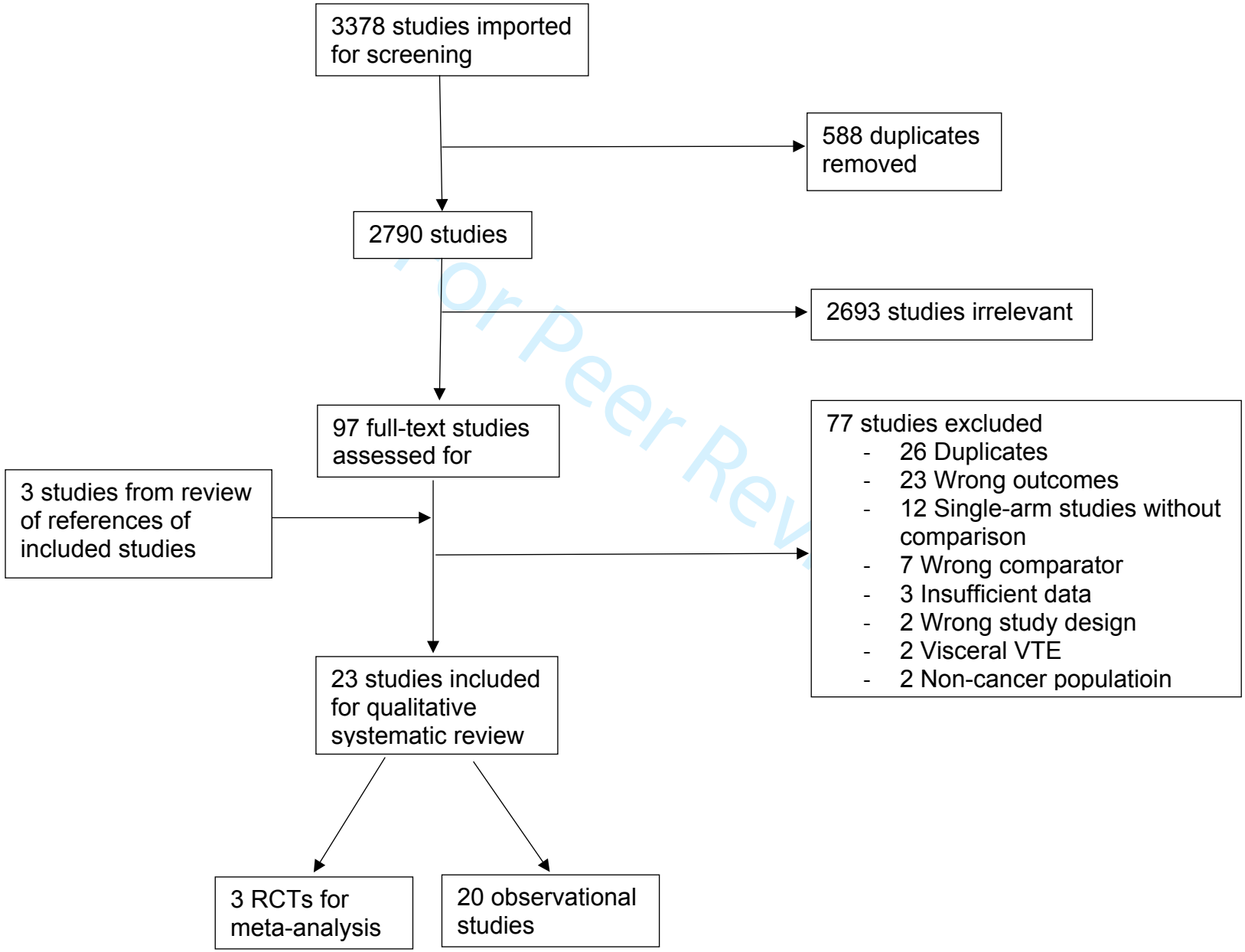

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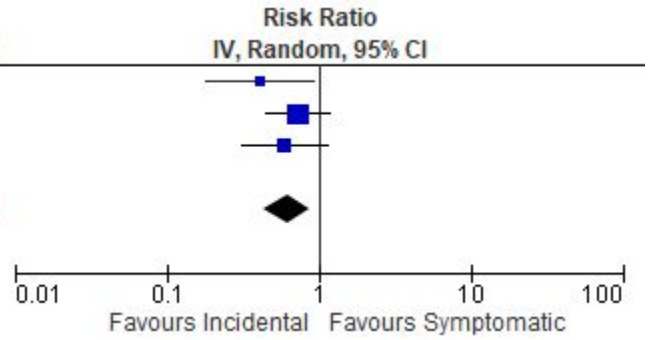
Figure 2. Meta-analysis of 6-month outcomes from randomized controlled trials

A) Recurrent venous thromboembolism

Study or Subgroup	Incidental Events	Incidental Total	Symptomatic Events	Symptomatic Total	Weight	Risk Ratio IV, Random, 95% CI
Select-D 2018	8	211	18	195	18.5%	0.41 [0.18, 0.92]
Hokusai VTE Cancer 2018	21	331	59	679	52.6%	0.73 [0.45, 1.18]
Caravaggio 2020	10	230	68	925	28.9%	0.59 [0.31, 1.13]
Total (95% CI)		**772**		**1799**	**100.0%**	**0.62 [0.44, 0.87]**
Total events	39		145			

Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 2 (P = 0.48); I² = 0%

Test for overall effect: Z = 2.71 (P = 0.007)

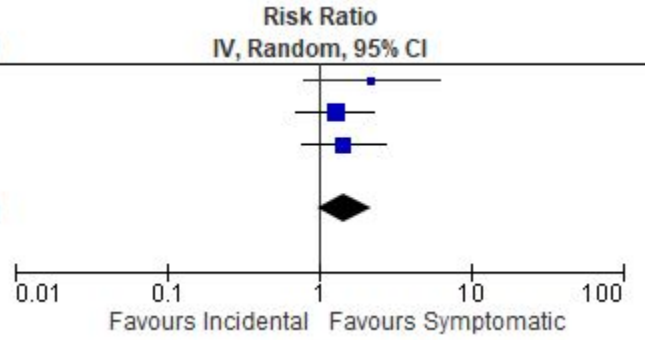


B) Major bleeding events

Study or Subgroup	Incidental Events	Incidental Total	Symptomatic Events	Symptomatic Total	Weight	Risk Ratio IV, Random, 95% CI
Select-D 2018	12	211	5	195	15.3%	2.22 [0.80, 6.18]
Hokusai VTE Cancer 2018	17	331	27	679	45.9%	1.29 [0.71, 2.34]
Caravaggio 2020	12	230	33	925	38.8%	1.46 [0.77, 2.79]
Total (95% CI)		**772**		**1799**	**100.0%**	**1.47 [0.99, 2.20]**
Total events	41		65			

Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.89 (P = 0.06)



Supplemental Table 1. Search strategy

1.	exp Neoplasms/
2.	Cancer.mp.
3.	Tumor.mp.
4.	Malignancy.mp.
5.	1 or 2 or 3 or 4
6.	exp Incidental Findings/
7.	Incidental.mp.
8.	Unsuspected.mp.
9.	Asymptomatic.mp
10.	6 or 7 or 8 or 9
11.	exp Venous Thromboembolism/
12.	exp Venous Thrombosis/
13.	Deep vein thrombosis.mp.
14.	exp Pulmonary Embolism/
15.	Pulmonary thromboembolism.mp.
16.	11 or 12 or 13 or 14 or 15
17.	5 and 10 and 16

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Supplemental Table 2. Risk of bias assessment for randomized controlled trials (Rob2)

Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Young 2018	+	+	+	+	+	+
Mulder 2020	+	+	+	+	+	+
Agnelli 2020	+	+	+	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
+ Low

Supplemental Table 3. Risk of bias assessment for observational cohort studies (Newcastle Ottawa Scale)

Study	Selection				Comparability	Outcome			
Categories	Representativeness of exposed cohort	Representativeness of non exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Comparability of cohorts	Assessment of Outcome	Was follow-up long enough?	Adequacy of follow-up	Total
Chang 2019 [21]	★	★	★	N/A	★	★	-	-	5/8
den Exter 2011 [8]	★	★	★	N/A	★★	★	★	★	8/8
Deng 2012 Abstract [22]	★	★	★	N/A	★	-	★	-	5/8
Dentali 2011 [23]	★	★	★	N/A	★★	★	★	★	8/8
Fernandez-Martinez 2013 Abstract [24]	★	★	-	N/A	-	-	★	-	3/8
Font 2011 [25]	★	★	★	N/A	★★	★	★	★	8/8
Font 2017 Epiphany [26]	★	★	★	N/A	★★	★	★	★	8/8
Li 2017 [27]	★	★	-	N/A	-	★	★	★	5/8
Machida 2016 [28]	★	★	★	N/A	★	★	★	★	7/8
Peris 2020 RIETE [29]	★	★	★	N/A	★★	★	★	★	8/8
Piacentini 2017 Abstract [30]	★	★	-	N/A	-	-	-	-	2/8
Savla 2008 Abstract [32]	★	★	-	N/A	-	-	★	-	3/8
Shinagare 2012 [33]	★	★	★	N/A	★	★	★	-	6/8
Silva 2015 [34]	★	★	-	N/A	-	-	-	-	2/8
Soler 2012 RIETE [35]	★	★	-	N/A	-	★	★	★	5/8
Spirk 2020 SWIVTER [36]	★	★	★	N/A	-	★	★	★	6/8

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Sun 2010 [37]	★	★	★	N/A	★	★	-	★	6/8
Tiseo 2012 [38]	★	-	-	N/A	-	★	-	★	3/8
Wysokinska 2019 Abstract [39]	★	★	-	N/A	-	-	★	-	3/8

Abbreviations: N/A – not applicable

Supplemental Table 4. Risk of bias assessment for case-control observational study (Newcastle Ottawa Scale)

Study	Selection				Comparability	Exposure			
Categories	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and control	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
Sahut d'Izarn 2012 [31]	★	★	★	★	★★	★	★	N/A	8/8

Abbreviations: N/A – not applicable

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