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Risk for Recurrent Venous Thromboembolism in Patients with Subsegmental Pulmonary Embolism Managed without Anticoagulation

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ABSTRACT

Venous thromboembolism (VTE) is a frequent complication in patients with cancer. Contemporary risk estimates indicate that a diagnosis of cancer increases the risk of VTE by the factor of 9 compared to individuals without cancer. The main objective of this meta-analysis is to find the risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation. For this study, Preferred Reporting Items guideline for conducting this systematic review analysis (PRISMA) was followed. Electronic articles from January 2014 to January 2023 were searched on PUB Med, online Willey library, and ScienceDirect site. For thromboembolism related studies we include articles from year 2014 to year 2023 for better comparison. We use keywords like thromboembolism, pulmonary, embolism, anticoagulants, risk factors, venous thromboembolism, subsegmental pulmonary embolism, and patients with thromboembolism to search relevant articles. At first sight, the initial symptoms of selected studies were noted. In patients with a VTE diagnosis in the absence of underlying cancer, the recurrence risk of VTE depends on the presence of risk factors and triggers, with the highest risk observed in patients with an unprovoked VTE (i.e. without a triggering event or identifiable risk factor). In contrast, VTE due to major transient provoking risk factors is associated with the lowest risk for recurrence. It is concluded that patients with subsegmental pulmonary embolism who did not have proximal deep venous thrombosis had a higher-than-expected rate of recurrent venous thromboembolism.

INTRODUCTION

Venous thromboembolism (VTE) is a frequent complication in patients with cancer. Contemporary risk estimates indicate that a diagnosis of cancer increases the risk of VTE by a factor of 9 compared to individuals without cancer [1]. VTE events adversely impact the clinical course of disease in cancer patients by contributing to morbidity, mortality, healthcare-costs, and adding to the psychological burden of patients as reviewed in Ref. [2]. Therefore, optimizing therapeutic approaches by personalizing primary prevention of cancer-associated VTE and secondary prevention of recurrent VTE is an unmet medical need, as the risk-benefit ratio of primary and secondary thromboprophylaxis in cancer patients needs to be carefully balanced based on the concurrent high risk of bleeding events. Various risk factors were identified for the first diagnosis of VTE in cancer patients [3].

Characterizing the risk of recurrent VTE in cancer patients requires the consideration and knowledge of underlying factors that influence risk of the first VTE event. Risk of VTE in cancer patients is highly heterogeneous and strongly depends on treatment-, tumor-and patient-related prothrombotic risk factors [3]. Among those, the underlying tumor type is among the most important factors that influence VTE risk, with the highest rates of up to 20% observed in patients with pancreatic and gastric cancer, and a low risk in patients with breast and prostate cancer. Further, advanced disease stage, certain anti-cancer treatments (e.g. surgery, radiotherapy, cisplatin-based chemotherapy, anti-angiogenic agents), and comorbidities including a prior history of VTE were identified as risk factors for VTE diagnosis [2,3]. Importantly, the increasingly utilized immune checkpoint inhibitors have lately been shown to be associated with an increased risk [4]. Based on the heterogeneity in VTE risk, in combination with an increased risk of bleeding events in cancer patients compared to the general population, primary thromboprophylaxis is not routinely recommended in the overall population of patients with cancer, necessitating the implementation of risk prediction strategies to identify high-risk subgroups. Different biomarkers were identified that can help predicting the future risk of VTE in patients with cancer beyond key clinical prothrombotic risk factors, including D-dimer [[5], [6]], soluble P-selectin (sP-selectin) [6,7], prothrombin fragment 1 + 2 (F1+2) [8] and citrullinated histone H3 [9] in the general population with cancer, and the expression of podoplanin on cancer cells in patients with glioblastoma.

In recent years, physicians have been increasingly confronted with unsuspected filling defects of the pulmonary artery - corresponding with pulmonary embolism (PE) identified on routine computed tomography (CT) scans of the chest, performed for indications other than suspected PE [10]. Although the available literature focusses mostly on this apparent diagnosis of incidental PE in cancer patients, this phenomenon is clearly relevant to other patients as well, including those referred for coronary artery imaging, evaluation of pulmonary infections, or those who have been subjected to major trauma. In general, unsuspected venous thrombosis accounts for an annual estimated 375 000 to 425 000 recognised incident cases in the US, at a total cost of $7 billion to $10 billion [11]. Despite this relatively high frequency, the optimal management of incidental PE has not been addressed in clinical trials and remains the subject of debate.

Objective

The main objective of this meta-analysis is to find the risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation.

Methodology of the study

Search Strategy:

For this study, Preferred Reporting Items guideline for conducting this systematic review analysis (PRISMA) was followed. Electronic articles from January 2014 to January 2023 were searched on PUB Med, online Willey library, and ScienceDirect site. For thromboembolism releted studies we include articles from year 2014 to year 2023 for better comparison. We use keywords like thromboembolism, pulmonary, embolism, anticoagulants, risk factors, venous thromboembolism, subsegmental pulmonary embolism and patients with thromboembolism to search relevant articles. We make assure that all the data have information such as thromboembolism and pulmonary embolism. With the help of keywords, we analyze the title, abstract aims, and objectives to extract the relevant data.

Inclusion criteria:

Articles and case studies with complete demographic information and complete medical symptoms of patients confirmed after diagnosis were included for this research.

Exclusion Criteria;

Articles which were written in other than English language were not included for this research. On the behalf of keywords seven hundred sixty two articles were found. Information in the form of posters, case studies without imaging, letters to editors, and articles with copied information were excluded from this study.

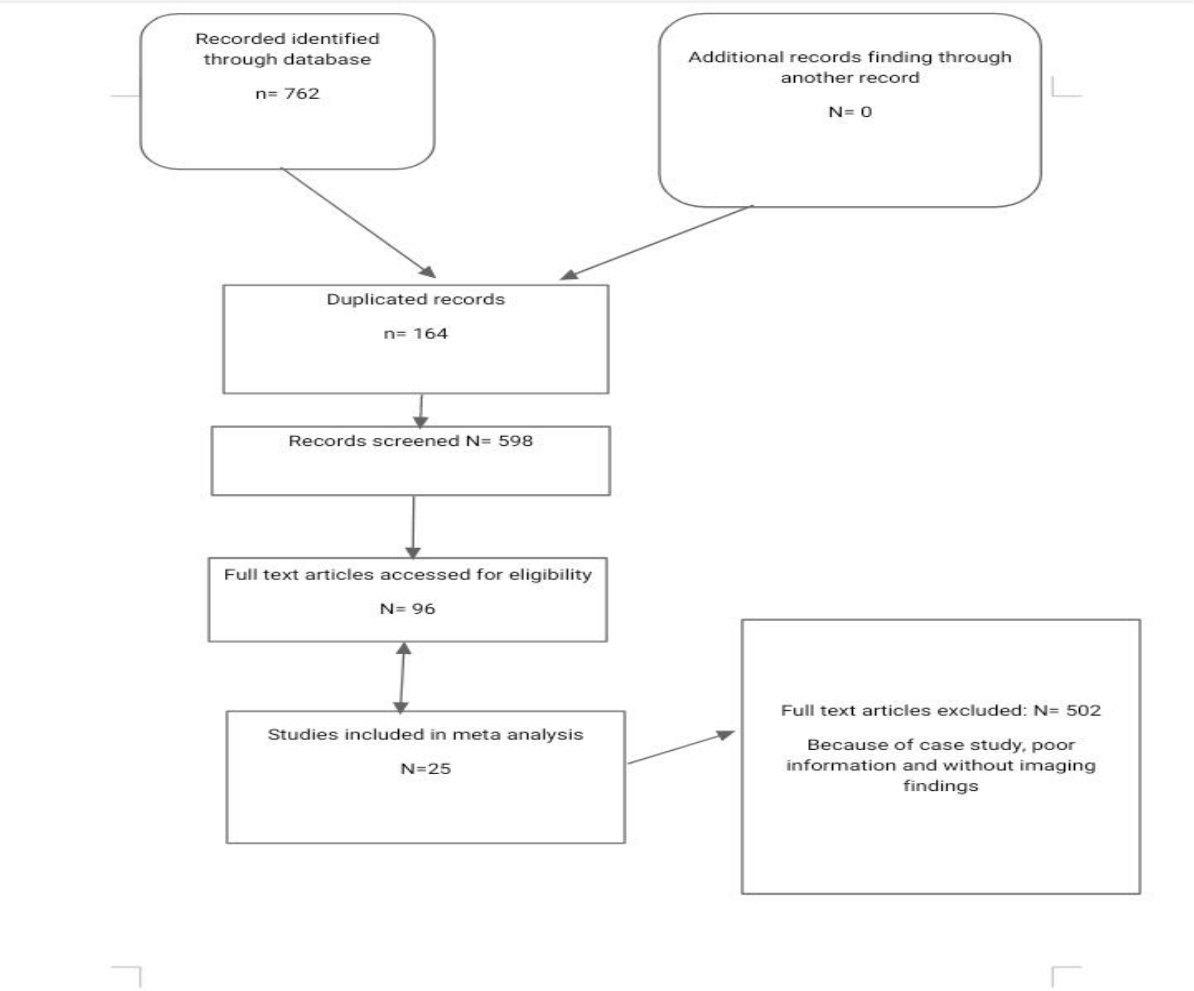

Fig 1: Inclusion Criteria of selected studies according to PRISMA follow up

The evaluation of selected data was further done into two phases first we select the data based on abstract and title. Secondly, the inner text of articles was examined and included if they were eligible to fill the inclusion criteria of our study. At the initial stage of collecting data, seven hundred and sixty-two articles were found with selected keywords. In the first screening, 164 duplicate articles were excluded and on further screening of the rest of 598 articles, we omitted 502 articles with poor information. Later on, remaining 96 articles were further gone through the screening process. At the last stage, 25 articles that fulfilled the

inclusion criteria and had adequate data on required topic were included. Demographic information of patients like mean age and rang, the sample size was kept in tabular form.

RESULTS:

At first sight, the initial symptoms of selected studies were noted. In patients with a VTE diagnosis in the absence of underlying cancer, the recurrence risk of VTE depends on the presence of risk factors and triggers, with the highest risk observed in patients with an unprovoked VTE (i.e. without an triggering event or identifiable risk factor). In contrast, VTE due to major transient provoking risk factors is associated with the lowest risk for recurrence.

Table 1. Risk factors and predictors for recurrent VTE in cancer patients.

Study	Study type	Treatment	n	Finding	Risk estimate	Setting
Chee CE et al. 2014	Cohort study	Long term treatment: 74% heparin followed by warfarin, 9% inferior vena cava filter	477	Metastasis Stage IV pancreatic cancer Brain cancer Myeloproliferative or myelodysplastic disorders Ovarian cancer Stage IV cancer (non-pancreatic) Lung cancer Neurological disease with leg paresis Cancer stage progression	HR 1.5 [95% CI: 1.03–2.17] HR 6.38 [95% CI: 2.69–15.13] HR 4.57 [95% CI: 2.07–10.09] HR 3.49 [95% CI: 1.59–7.68] HR 3.22 [95% CI: 1.57–6.59] HR 2.85 [95% CI: 1.74–4.67] HR 2.73 [95% CI: 1.63–4.55] HR 2.38 [95% CI: 1.14–4.97] HR 2.14 [95% CI: 1.30–3.63]	Recurrence during and after stopping anticoagulation
Khorana AA et al. 2017	Posthoc analysis of RCT	Tinzaparin or warfarin for 6 months	900	Venous compression Hepatobiliary cancer	SHR 3.0 [95% CI: 1.8–4.9] SHR 2.9 [95% CI: 1.2–7.0]	Recurrence during anticoagulation
Young AM et al. 2018	RCT	Dalteparin or rivaroxaban for 6 months	406	Stomach or pancreas versus other malignancies Lung, lymphoma, gynecologic, or bladder versus other malignancies Symptomatic VTE versus incidental	HR 5.55 [95% CI: 1.97–15.66] HR 2.69 [95% CI: 1.11–6.53] HR 2.78 [95% CI: 1.2–6.41]	Recurrence during anticoagulation

				PE		
Bosch FTM et al. 2021	Posthoc analysis of RCT	Edoxaban or LMWH for 6 months (up to 12 months)	1050	Age <50 years Body weight >110 kg DVT only as index event Upper GI tumor	SHR 2.0 [95% CI: 1.12–3.58] SHR 2.3 [95% CI: 1.14–4.62] SHR 1.93 [95% CI: 1.25–2.99] SHR 3.35 [95% CI: 1.07–10.57]	Recurrence during and after stopping anticoagulation
Louzada ML et al. 2021	Retrospective cohort	37% Vitamin K antagonist, 63% LMWH	543	Sex Primary tumor		Recurrence during anticoagulation
Trujillo-Santos J et al. 2008	Prospective registry	49% long term LMWH, 43% long term vitamin K antagonists, 3.8% inferior vena cava filter	3805	Patients aged <65 years Clinically overt PE at entry Cancer detected <3 months earlier	OR 1.6 [95% CI: 1.0–2.4] for DVT; OR 3.0 [95% CI: 1.9–4.9] for PE OR 1.9 [95% CI: 1.2–3.1] for PE OR 2.4 [95% CI: 1.5–3.6] for DVT; OR 2.0 [95% CI: 1.2–3.2] for PE	Recurrence during anticoagulation
Napolitano M et al. 2014	Prospective study	LMWH 6 months, if RVT then randomization: LMWH 6 more months or stop, no RVT anticoagulation stop	347 (242 patients with RVT)	RVT after 6 months of LMWH or PE as index event	HR 9.56 [95% CI: 2.8–28.5]	Recurrence during and after stopping anticoagulation
Marshall A et al. 2020	RCT	Dalteparin or rivaroxaban for 6 months, then second randomization rivaroxaban or placebo for 6 more months	92	RVT after 5.5 months or PE as index event		Recurrence during and after stopping anticoagulation
Bauersachs R et al. 2018	Posthoc analysis of RCT	Tinzaparin or warfarin for 6 months	900	Renal impairment	RR 1.74 [95% CI: 1.06–2.85]	Recurrence during anticoagulation
Van Es N et al. 2018	Prospective observational study	Full dose heparin for 1 month, followed by 75% dose for 5 months	117	Baseline P-selectin levels	SHR 4.0 [95% CI: 1.1–14]	Recurrence during anticoagulation
Lapébie	Prospective	Full dose	3414	Age		Recurrence

FX et al. 2021	registry	anticoagulation for at least 3 months, then stop of anticoagulation and follow-up of 1 year		Obesity Renal insufficiency Previous VTE Type of cancer (pancreas, lung, kidney, carcinoma of unknown origin, metastasis) Association of pulmonary embolism and deep vein thrombosis Inferior vena cava filter Direct oral anticoagulant (compared to low molecular weight heparin) in the first 7 days Post-thrombotic syndrome and residual venous or pulmonary artery obstruction after 3 months No recent surgery Not catheter-related thrombosis		after stopping anticoagulation
Sakamoto J et al. 2019	Retrospective cohort study	Long term treatment: warfarin 83%, DOAC 2.9%, LMWH 2.6%	695	Metastasis		Recurrence during and after stopping anticoagulation
Mulder FI et al. 2020	Post hoc analysis of RCT	Edoxaban or LMWH for 6–12 months	331	ECOG 2 versus 0 for recurrent incidental VTE	HR 5.24 [95% CI: 1.81–15.18]	Recurrence during anticoagulation
Louzada ML et al. 2011	Systematic review (6 prospective studies)	Vitamin K antagonist or LMWH	4573	Metastatic versus localized disease	RR 1.36 [95% CI: 1.06–1.74]	Recurrence during and after stopping anticoagulation
Otero Candelera R et al. 2021	Prospective study	More than 3 months of anticoagulation than stop and blood draw, 21 days later blood draw	166	Male sex Ratio basal D-dimer to 21 days D-dimer >2 Increasing hs-CRP (day 21) Increasing P-	SHR 4.32 [95% CI: 1.10–16.96] SHR 7.53 [95% CI: 1.97–28.71] SHR 5.15 [95% CI: 1.37–19.34] SHR 5.60 [95%	Recurrence after stopping anticoagulation

		again		selectin (day 21)	CI: 1.48–21.08]	
Mahé I et al. 2017	Prospective registry	Long-term treatment: 67% LMWH, 20% Vitamin K antagonists, 1.1% rivaroxaban, 1.6% fondaparinux	3947	Lung cancer versus breast cancer	HR 3.8 [95% CI: 2.6–5.6]	Recurrence during anticoagulation
Jara-Palomares L et al. 2018	Prospective study	At least 3 months of LMWH, then anticoagulation stop and blood draw, 21 days later blood draw again	114	hs-CRP >4.5 mg/L D-dimer >600 ng/mL	SHR 9.82 [95% CI: 1.86–51.7] SHR 5.81 [95% CI: 1.06–31.72]	Recurrence after stopping anticoagulation
Gal Le et al. 2023	Cohort Study	Patients with isolated subsegmental pulmonary embolism.	266	Patients with subsegmental pulmonary embolism who did not have proximal deep venous thrombosis had a higher-than-expected rate of recurrent venous thromboembolism.	Of the 266 patients included in the primary analysis, the primary outcome occurred in 8 patients, for a cumulative incidence of 3.1% (95% CI, 1.6% to 6.1%) over the 90-day follow-up. The incidence of recurrent venous thromboembolism was 2.1% (CI, 0.8% to 5.5%) and 5.7% (CI, 2.2% to 14.4%) over the 90-day follow-up in patients with single and multiple isolated subsegmental pulmonary embolism, respectively. No patients had a fatal recurrent pulmonary embolism.	Recurrence during anticoagulation

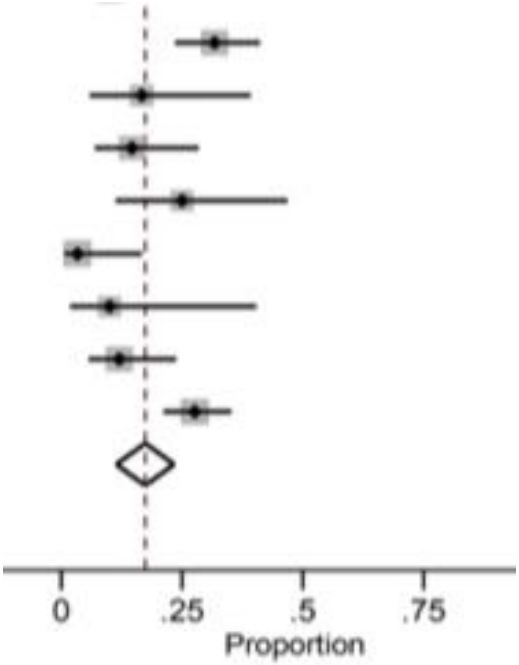

Figure 2: Forest plot for pooled estimated values

Discussion

There are several angles from which the relevance of incidental PE could be considered, i.e. comparison of the prognosis of 1) incidental PE in cancer patients versus cancer patients without VTE; 2) incidental PE with a large versus a smaller embolic load; and 3) incidental PE versus symptomatic PE [11]. Most studies in incidental PE have been performed in cancer patients, because they comprise the overall majority of incidental PE diagnoses detected by CT scanning performed for cancer staging [12]. The relevance of incidental PE could best be demonstrated by showing its natural history without anticoagulant treatment. Unfortunately, there are very few studies to demonstrate this phenomenon [13]. The landmark trial of Barritt and Jordan showed that untreated symptomatic PE is followed by high recurrent PE, and even fatal PE. In fact, of the 19 patients who were not administered anticoagulant treatment, almost 25% died of fatal PE, and five showed progression of PE at 3 months, whereas none of the treated patients suffered PE-related death or progression. One study in patients with incidental PE evaluated the safety of withholding anticoagulant treatment [14]. Patients with confirmed distal or proximal DVT, but without symptoms of PE randomly received i.v. heparin, followed by vitamin-K antagonists, or a non-steroidal agent, phenylbutazone. A total of 42 out of 90 study patients (47%) were found to have silent PE. Perfusion-ventilation lung scans showed no significant changes at 10 and 60 days, between the two groups [15].

Moreover, within 12 months, six patients died in the anticoagulant group, with one death being attributed to PE. Furthermore, seven patients died in the non-anticoagulant group, none of which was reportedly related to PE, suggesting that anticoagulant therapy could have been withheld. The small sample size however, does not permit a strong conclusion. Notably, a recent patient level meta-analysis indicated that patients with incidental PE who remained untreated – presumably due to a high risk of bleeding or other relevant prognostic factors– have a very high 6-month risk of recurrent VTE (12%) and mortality (47%) [16]. Moreover, data from a retrospective observational study that was not included in the aforementioned meta-analysis confirmed that patients with incidental PE who did not receive anticoagulant treatment showed poorer survival [17]. Several retrospective studies in patients with cancer indicate that incidental PE can have important effects on survival, as well as on recurrent VTE [18-20]. In one study that included a control group of patients without PE, matched for age, cancer histology and severity, the median survival in patients with incidental PE was 8 months, compared to 12 months for the matched controls. In two studies of heterogeneous groups of cancer patients, incidental PE had a similar influence on survival, compared to cancer patients with symptomatic PE. In the first study, 6-month mortality rates were around 50% in both groups, which was significantly worse than the 27% mortality rate in the 60 patients with symptoms suggestive of PE, but for whom the diagnosis of PE was excluded [21]. In the second study, 12-month mortality rates were ~53% in both groups. In addition, a similar incidence of recurrent VTE between patients with symptomatic VTE and patients with incidental PE (16.9% versus 13.3%; p=0.77) was observed. In contrast, a very recent observational study of a relatively small number of 66 patients reported that malignancy-associated incidental PE was not associated with a higher risk of mortality, compared to matched control patients without incidental PE [22].

Conclusion

It is concluded that patients with subsegmental pulmonary embolism who did not have proximal deep venous thrombosis had a higher than expected rate of recurrent venous thromboembolism.

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