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Post-thrombotic syndrome and recurrent thromboembolism in patients with upper extremity deep vein thrombosis: A systematic review and meta-analysis

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ABSTRACT

Introduction: There is limited data on the occurrence of complications in patients with upper extremity deep vein thrombosis (UEDVT).

Aims: We aimed to determine the frequency of post-thrombotic syndrome (PTS), thrombosis recurrence and major bleeding (MB) in patients with UEDVT.

Material and methods: We conducted a systematic review of the literature including studies from 1970 onwards. We included observational studies, randomized trials, or cases series including > 20 patients. We calculated pooled proportions using a random effects model. Subgroup analyses according to etiology and treatment modality were conducted.

Results: A total of 62 studies comprising 3550 patients were included. The pooled proportions for PTS and recurrence were 19.4% (95% CI 11.3–27.6) and 7.5% (95% CI 4.1–10.9), respectively. With a mean follow up of 6 months, the proportion of PTS was higher in patients with primary (unprovoked) UEDVT compared to secondary, whereas recurrence was higher in secondary UEDVT. PTS was more frequent in patients treated with anticoagulation alone compared to thrombolysis or surgical decompression. The pooled proportion for MB was 5.0% (95% CI 0.3–9.7) after anticoagulation alone and 3.8% (95% CI: 2.4–5.8%) after thrombolysis and/or surgery.

Conclusions: This study suggests that UEDVT is associated with significant rates of PTS and recurrence and its treatment has a relatively low risk of major bleeding. Differences exist depending on etiology and treatment modality.

1. Introduction

Upper extremity deep vein thrombosis (UEDVT) accounts for approximately 5% of all cases of DVT [1,2]. The majority of UEDVT cases can be attributed to secondary causes, such as central venous cannulation and malignancy [2,3], whereas the remaining cases are classified as primary or spontaneous. The latter refer to DVT that is unprovoked or occurs in the setting of venous thoracic outlet syndrome (vTOS). The thoracic outlet is defined anatomically by the bony structures of the spinal column, first ribs, and sternum. In vTOS, also known as Paget-Schroetter syndrome, the subclavian vein, which traverses the thoracic outlet, is compressed and venous thrombosis can occur [4]. Compared to secondary UEDVT, primary UEDVT is rarer. The overall UEDVT annual incidence is approximately 10 cases per 100,000 persons-year, whereas that of UEDVT is 2 cases per 100,000 persons-year [5,6].

UEDVT is associated with an increased risk of post-thrombotic syndrome (PTS), which can result in significant occupational disability and an overall reduced quality of life [7–9]. The frequency of PTS after both primary and secondary UEDVT has been reported from 6 to 37% [7–9]. Although less common, studies have shown that primary UEDVT is associated with a higher risk of PTS, compared to catheter-associated UEDVT [9,10]. In one prospective cohort study, which included 53 patients with UEDVT, the cumulative incidence of PTS at 5 years was 16.7% and 28.8% in patients with and without a venous catheter,

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respectively [9]. Furthermore, while the risk of recurrent thromboembolism has been well studied in patients with lower extremity DVT, the data on recurrence in patients with UEDVT is limited.

General management principles for patients with both primary and secondary UEDVT include symptomatic care (i.e. pain control and compression therapy) and anticoagulation however, many groups suggest the use of more aggressive and invasive therapies, which should only be considered if the benefit outweighs the risk [11]. For example, it has been suggested that, in patients with acute axillo-subclavian thrombosis associated with moderate-to-severe symptoms, successful catheter-directed thrombolysis may lower the frequency of PTS [12]. Also, some studies support surgical decompression of the thoracic outlet as a more aggressive, adjunctive therapy to reduce the risk of recurrent thromboembolism and PTS in patients with vTOS [13]. However, these recommendations are based on very limited evidence.

Some groups suggest that UEDVT, in particular primary events, are associated with high frequency of PTS [10]. However, the risk of PTS, recurrent thromboembolism or bleeding, is not well understood. To determine whether patients with UEDVT should be managed with anticoagulation alone or more aggressively, it is important to first establish the frequency of these complications. However, the information available regarding UEDVT is limited due to the fact that most studies include small numbers of patients. Therefore, we performed a systematic review of available studies aiming to evaluate the occurrence of PTS, recurrent thromboembolism and bleeding in patients with UEDVT, and to compare the frequency of these complications between patients with primary and secondary events.

2. Methods

2.1. Search strategy

We conducted a systematic literature search in Ovid MEDLINE® and Embase® electronic databases with restrictions to adults older than 18 years of age and studies published in English. The search queries were developed using combinations of subject headings and free text words including *upper extremity deep vein thrombosis*, *thoracic outlet syndrome*, *upper extremity*, *axillary vein*, *subclavian vein*, *axillosubclavian vein*, *venous thromboembolism*, *postthrombotic syndrome*, *prevalence*, and *recurrence*. The complete search strategy is shown in the Appendix. We used optimized methodological search "filters" and text words to focus search results on research from observational studies to complement data from randomized controlled trials (RCTs) published on the topic. The search strategies were adapted for each database to include database-specific thesaurus terms and field names. To identify additional relevant studies that met our inclusion criteria, we also examined bibliographies of the relevant retrieved articles. Conference publications presented at major national and international hematology meetings were also reviewed for relevance.

2.2. Criteria for including studies

We included observational studies (cohort studies and case-control studies), RCTs, and case series (if they included > 20 patients). We excluded letters to the editor, review articles, editorials, and commentaries. Eligible studies must have been published in 1970 or after and include only patients age 18 or older. Studies must have objectively diagnosed UEDVT by means of venography or ultrasound. UEDVT was defined as DVT involving the axillary and/or more proximal veins.

2.3. Outcome measures

The primary outcome measures were PTS and an objectively documented recurrence of UEDVT in patients with previously documented UEDVT. PTS was defined by the authors of the individual studies based on clinical assessment and ideally using the modified Villalta scale (score ≥ 5). The secondary outcome measure was major bleeding (MB), using a standard definition and ideally as defined by the International Society on Thrombosis and Haemostasis (ISTH), following the initiation of treatment for UEDVT.

2.4. Study selection

Five reviewers independently examined retrieved studies for possible inclusion by assessing the study title and abstract. Potentially relevant studies were marked for full-text review. The studies selected for further review were evaluated in detail according to the inclusion criteria and outcome measures. All studies selected for final inclusion in the systematic review were also evaluated by the lead author and any disagreements regarding data were resolved by discussion and consensus.

2.5. Assessment of study quality and data extraction

Using a standardized data extraction form, five reviewers (KT, LE, KE, AH, JR) independently collected data on the number of included patients with UEDVT, association of DVT with venous thoracic outlet syndrome or secondary causes (central venous catheter, malignancy), choice of treatment (anticoagulation, thrombolytic therapy, and/or thoracic outlet decompression), and the occurrence of PTS, recurrent UEDVT, and MB. Study quality data, including enrolment of patients (retrospective versus prospective, consecutive versus non-consecutive), duration of follow-up and losses to follow-up, for each study were also noted.

2.6. Statistical analysis

We calculated a pooled proportion and its 95% confidence interval (CI) for each outcome using a random effects model and heterogeneity was assessed using χ^2 tests, as previously described [14]. Given that there is no general consensus regarding the best statistical model to obtaine pooled proportion estimates, we also calculated pooled proportions using a fixed effects model and determined the median proportions of patients with outcomes and the interquartile ranges (IQR) of single proportions from individual studies. These results are shown in the appendix. Pre-specified subgroup analyses according to etiology (primary versus secondary UEDVT) were also conducted. All statistical analyses were performed using Microsoft Excel.

2.7. Registration

The protocol for this systematic review was registered in the PROSPERO international prospective register of systematic reviews with the number CRD42017063833.

3. Results

3.1. Study selection & characteristics

We identified 3026 citations published between 1970 and June 2017 through our initial literature search and included 311 studies in our full text review. There were 62 studies that met our inclusion criteria and presented relevant data on our primary and/or secondary outcomes and were included in the final meta-analysis (Fig. 1). Of these 62 studies, 22 reported data on the occurrence of PTS in patients with UEDVT [15–36], 37 on recurrent UEDVT [16,19–21,23–25,31,32,37–64], and 29 on MB [15,16,18–20,22,27,32,34,44,46,52,56–58,60,62,65–76]. There were 59 full-text articles and 3 conference publications (abstract only) included. The 62 studies comprised a total of 3550 patients diagnosed with UEDVT. The studies were primarily single-arm cohort studies (n = 49). There were 5 sequential cohort studies, 2 case-control studies, 4 case series studies, and 2 RCTs (one

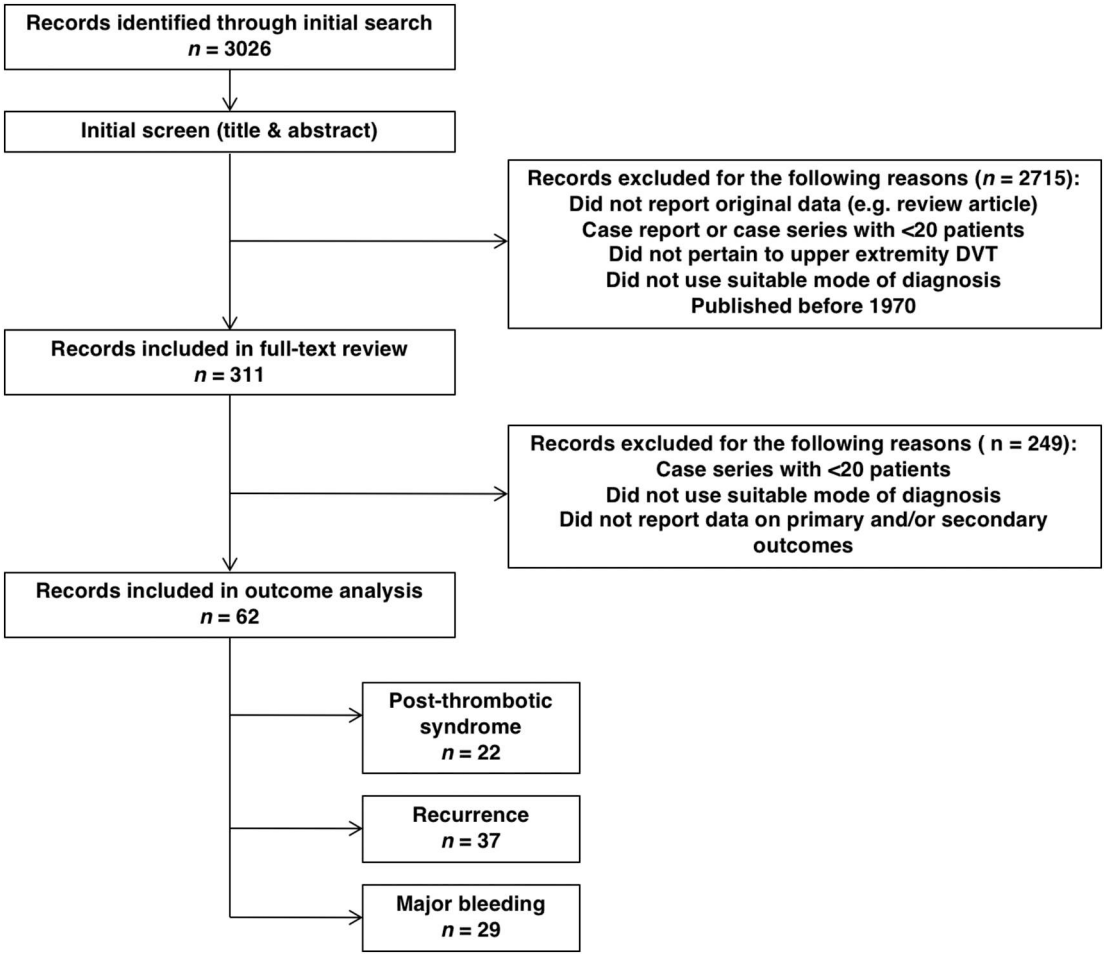

Fig. 1. Flow diagram displaying the number of studies screened, assessed in-depth for eligibility, and included in review and specific outcome analyses.

evaluating primary prophylaxis with dalteparin and one comparing central versus peripherally inserted lines). The characteristics of included studies are found in Supplementary Table 1.

3.2. Study quality

Key quality features and quality assessment of each study are shown in Supplementary Tables 2 and 3. Of the 62 included studies, 17 were prospective studies. The mean duration of follow-up was 6 or more months in 32 (51.6%) of the 62 studies, and 3 or more months in 37 studies (59.7%). Of the 17 prospective studies, the number of patients lost to follow-up was < 5% in 8 studies that reported this (47.1%).

3.3. Post-thrombotic syndrome

The occurrence of PTS was described in 22 studies including a total of 944 patients with UEDVT. The pooled proportion of PTS using a random effects model was 19.4% (95% CI 11.3–27.6). Details are shown in Table 1. Median and pooled proportion using a fixed effects model are shown in Supplementary Table 4. We calculated proportions for PTS in all patients with UEDVT, patients with primary UEDVT (in the setting of venous thoracic outlet syndrome), and patients with secondary upper extremity (catheter-associated and/or malignancy-associated). The pooled proportions of patients with PTS were higher in patients with primary UEDVT than in patients with secondary UEDVT by both fixed and random effects models.

3.4. Recurrent thromboembolism

Table 1 also shows the pooled proportions of patients with recurrent UEDVT during the follow up periods reported in studies (mean 6 months) using data from 37 studies and a total of 2552 patients. The overall proportion of recurrent DVT was 7.5% (95% CI 4.1–10.9) and it was higher in patients with secondary UEDVT than in patients with primary UEDVT (15.9% vs 6.4%). This was consistent with the pooled proportions calculated by median and fixed effects models (Supplementary Table 4).

3.5. Outcomes by treatment modality

3.5.1. Post-thrombotic syndrome and recurrent thromboembolism

Although not included in the original study protocol, we examined the proportions of patients with PTS and recurrent thromboembolism in patients who were treated conservatively with anticoagulation alone compared to patients treated more aggressively with thrombolysis and/or thoracic outlet decompression (in the setting of primary UEDVT). We found that the rates of PTS in patients with both primary and secondary UEDVT treated with anticoagulation alone seemed to be higher compared to patients treated by an invasive procedure. Across all patients with UEDVT, the rate of recurrent thromboembolism was similar in patients treated invasively compared to patients treated conservatively (Table 2). In general, the estimates were consistent when assessed using medians and fixed effects models (Supplementary Tables 5 and 6).

3.5.2. Major bleeding

Table 2 shows the proportions of patients with MB after initiation of

Table 1
Overall proportion of post-thrombotic syndrome and recurrent thrombosis in patients with upper extremity deep vein thrombosis, using a random effects model[a].

	Post-thrombotic syndrome			Recurrent thrombosis		
	Patients, *n*	Pooled proportion (%)	(95% CI)	Patients, *n*	Pooled proportion (%)	(95% CI)
All UEDVT	944	19.4	(11.3–27.6)	2552	7.5	(4.1–10.9)
Primary	656	20.3	(11.0–29.5)	1011	6.4	(3.7–9.1)
Secondary	187	14.0	(0.0–30.0)	335	15.9	(0.6–31.2)

Abbreviation: UEDVT Upper extremity deep vein thrombosis.
[a] Primary UEDVT indicates an event that is unprovoked or occurs spontaneously in the setting of venous thoracic outlet syndrome; Secondary UEDVT indicates an event that occurs in the presence of a transient risk factor (e.g. central catheters, tumors, etc.)

treatment (during active treatment) using data from 29 studies and a total of 2000 patients. Overall, MB was similar amongst patients treated with anticoagulation alone, compared to patients treated more aggressively with thrombolysis and/or surgery (i.e. thoracic outlet decompression). Limited data according to primary or secondary UEDVT precluded drawing any further conclusions. However, when evaluating median proportions and fixed effects models MB was higher in patients treated more agressively (Supplementary Table 7).

4. Discussion

To the best of our knowledge the present study is the largest systematic review on complications of UEDVT. Our study's main findings are: 1) primary and secondary UEDVT are associated with high proportion of PTS (19.4%); 2) the risk of thrombotic recurrence is significant (7.5%); and 3) there seem to be differences in outcomes depending on the etiology and the treatment modality. Regarding the frequency of PTS, which was found to be higher in patients with primary UEDVT, it has been postulated that in contrast with primary UEDVT, in patients with secondary UEDVT, removal of the catheter (the most frequent cause) reduces the ongoing vessel injury and minimizes the risk of developing chronic venous insufficiency. Still, despite removal of venous catheters, thrombosis in this setting can cause significant vessel injury and subsequent PTS. With regard to recurrent thromboembolism, this was higher in patients with secondary UEDVT. We speculate that this could be due to the fact that the studies which included patients with secondary UEDVT and examined risk of recurrence did so both in the setting of ongoing catheterization and removal of the venous catheter. While removal of a venous catheter reduces the risk of recurrent thromboembolism, the vessel injury sustained from catheter-associated thrombosis may still predispose patients to recurrence. Furthermore, active malignancy or reinsertion of the catheters may present an ongoing risk for recurrent thromboembolism. Finally, the rate of MB in all patients with UEDVT was similar between treatment groups when assessed by a random effects model. However, when assessing MB using medians or a fixed effects model, the proportion was higher in patients treated more aggressively with thrombolysis, thoracic outlet decompression, or both, compared to patients treated non-invasively with anticoagulation alone. We speculate that his difference may be due to differences in reporting events and the availability of data from studies.

The studies we included encompassed a large number of patients diagnosed with both primary and secondary UEDVT ($n = 3550$), however the study is limited by number of issues. First, there was a large number of small, observational and retrospective studies which may lead to unaccounted sources of bias. Only two randomized-controlled trials were included, one comparing line insertion techniques and the other evaluating anticoagulant prophylaxis, and the majority of the included studies were single-arm cohort studies. Second, while the majority of studies had at least 3 months of follow-up of patients, several studies did not specify the duration of follow-up and/or losses to follow-up, thus, limiting their validity. Third, a common definition for PTS was not used uniformly across studies. We however evaluated PTS as defined by the authors and in virtually all studies this was done using a standard approach. Fourth, the overall estimates for the outcomes showed the presence of statistical heterogeneity. We ran a number of pre-determined subgroup analyses and found that at least part of the heterogeneity was due to the treatment modality and to the type of UEDVT (primary vs. secondary). However, unknown bias could be accounting also for the observed heterogeneity. A meta-regression analysis was not planned a priori and we believe that given the aforementioned considerations, it is unlikely that all sources of heterogeneity will be properly accounted for using such analysis. Finally, it is conceivable that the occurrence of outcomes may be influenced by treatment duration. Unfortunately, this information was either not available in many studies, or reported using different statistical approaches not

Table 2
Proportion of post-thrombotic syndrome, recurrent thrombosis and major bleeding by treatment modality in patients with upper extremity deep vein thrombosis, using a random effects model.

	Anticoagulation alone			Thrombolysis and/or surgical decompression		
	Patients, *n*	Pooled proportion (%)	(95% CI)	Patients, *n*	Pooled proportion (%)	(95% CI)
Post-thrombotic syndrome						
All UEDVT	284	24.2	(7.8–40.5)	507	11.8	(3.8–19.8)
Primary	115	24.7	(2.2–47.3)	504	12.1	(4.0–20.0)
Secondary	69	36.9	(0.0–79.5)	3	NC	NC
Thrombosis recurrence						
All UEDVT	383	8.7	(1.4–16.0)	772	12.5	(3.4–21.7)
Primary	69	6.6	(0.0–20.3)	731	11.6	(2.4–20.9)
Secondary	214	10.2	(0.5–19.9)	41	32.8	(0.0–78.7)
Major bleeding						
All UEDVT	1498	5.0	(0.3–9.7)	502	4.0	(1.7–6.3)
Primary	12	NC	NC	399	4.9	(2.0–7.9)
Secondary	268	6.7	(0.0–13.5)	84	NC	NC

Abbreviation: NC, not calculable; UEDVT Upper extremity deep vein thrombosis.

appropriate for meta-analysis. It is important to note that most studies do report that the duration of anticoagulation used was at least 3 months. Finally, we must caution that given the lack of randomized studies in this area, the difference in the outcomes between different treatment modalities cannot be directly compared as it can be due to bias and caution should be had when interpreting this data. This is particularly important considering the results of the ATTRACT study in patients with lower extremity deep vein thrombosis which showed no benefit of thrombolysis in terms of PTS, but did report a higher risk of bleeding [77]. Given the differences in anatomy between lower and upper extremities, the benefit-risk profile of thrombolysis or other invasive approaches may be different but this is yet to be determined.

In conclusion, both primary and secondary UEDVT are associated with significant rates of PTS and recurrent thromboembolism of about 19% and 7%, respectively. The frequency of treatment-associated MB may be higher following an invasive treatment approach. Further prospective studies including all relevant outcomes and clinical information are needed to better investigate the association of PTS and recurrent thromboembolism with anticoagulation alone versus thrombolysis and thoracic outlet decompression, as the morbidity associated with UEDVT in some cases may warrant consideration of a more aggressive management approach. However, in the absence of properly conducted and adequately powered RCTs, even with the present data, no recommendation can be made favouring either treatment strategy. Finally, this review highlights the need for developing and using standard definitions and data collection tools for studies assessing clinical outcomes in this population using a cooperative approach.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.12.012.

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