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Predictive factors of clot propagation in patients with superficial venous thrombosis towards deep venous thrombosis and pulmonary embolism: a systematic review and meta-analysis

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ABSTRACT

Objective A subset of patients with superficial venous thrombosis (SVT) experiences clot propagation towards deep venous thrombosis (DVT) and/or pulmonary embolism (PE). The aim of this systematic review is to identify all clinically relevant cross-sectional and prognostic factors for predicting thrombotic complications in patients with SVT.

Design Systematic review.

Data sources PubMed/MEDLINE and Embase were systematically searched until 3 March 2023.

Eligibility criteria Original research studies with patients with SVT, DVT and/or PE as the outcome and presenting cross-sectional or prognostic predictive factors.

Data extraction and synthesis of results The CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling (CHARMS) checklist for prognostic factor studies was used for systematic extraction of study characteristics. Per identified predictive factor, relevant estimates of univariable and multivariable predictor—outcome associations were extracted, such as ORs and HRs. Estimates of association for the most frequently reported predictors were summarised in forest plots, and meta-analyses with heterogeneity were presented. The Quality in Prognosis Studies (QUIPS) tool was used for risk of bias assessment and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) for assessing the certainty of evidence.

Results Twenty-two studies were included (n=10 111 patients). The most reported predictive factors were high age, male sex, history of venous thromboembolism (VTE), absence of varicose veins and cancer. Pooled effect estimates were heterogenous and ranged from OR 3.12 (95% CI 1.75 to 5.59) for the cross-sectional predictor cancer to OR 0.92 (95% CI 0.56 to 1.53) for the prognostic predictor high age. The level of evidence was rated very low to low. Most studies were scored high or moderate risk of bias.

Conclusions Although the pooled estimates of the predictors high age, male sex, history of VTE, cancer and absence of varicose veins showed predictive potential in isolation, variability in study designs, lack of multivariable adjustment and high risk of bias prevent firm conclusions. High-quality, multivariable studies are necessary to be able to identify individual SVT risk profiles.

PROSPERO registration number CRD42021262819.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review systematically summarises all available evidence on prognostic and cross-sectional predictive factors of clot propagation in patients with superficial venous thrombosis towards deep venous thrombosis and pulmonary embolism.
⇒ This review is conducted based on guidance on systematic review of predictive factor studies.
⇒ We were able to perform meta-analysis if three or more effect estimates could be combined and in a sensitivity analysis, random-effects models and fixed-effects models were compared.
⇒ The results of this review should be interpreted with caution due to moderate to high risk of bias of most included studies, differences in study methods and some detected heterogeneity.

INTRODUCTION

Superficial venous thrombosis (SVT) is characterised by the combined presence of a blood clot and inflammation in a superficial vein. The condition can be visually diagnosed by clinicians as a red, swollen and painful cord running along the course of a superficial vein.[1 2] It is related to the more well-known thrombotic conditions deep venous thrombosis (DVT) and pulmonary embolism (PE) (together called venous thromboembolism (VTE)), although the disease course of SVT is considered more benign than the latter two conditions. SVT can often even be left untreated because in most cases the condition seems to resolve naturally without complications.[1]

However, a small, yet substantial subset of patients will develop propagation of the blood clot towards DVT and/or PE, conditions that require immediate anticoagulant treatment. The reported risk of developing DVT and/or PE in patients with SVT has a wide range between 3% and 19% in literature and is highly dependent on the setting where patients are first identified; in primary care a lower risk is being reported compared with (referred) patients in the hospital setting.[3–8] A systematic review on the effect of different treatment options to prevent progression in patients with SVT towards DVT and/or PE showed that treatment with fondaparinux seemed to perform best with the lowest VTE event rate in comparison with no treatment, surgery, non-steroidal anti-inflammatory drugs, and also compared with other anticoagulant treatments such as low molecular weight heparin and rivaroxaban. This finding, however, was highly influenced by a single large study while the authors concluded that there was insufficient data to draw definite conclusions on best treatment options to prevent clot propagation.[9 10]

However, as previously stated, in most patients SVT will resolve naturally and for that reason, most patients with SVT will not benefit from any anticoagulant or anti-inflammatory treatment. In order to make safe and effective treatment decisions to prevent clot propagation in the smaller SVT subgroup at higher risk of developing DVT and/or PE and at the same time to prevent unnecessary treatment burden and side effects such as bleeding complications in the larger group of lower risk patients with SVT, it is essential to identify clinical factors able to differentiate between individuals at higher or lower risk of ultimately developing DVT and/or PE. This is especially relevant in primary care as the majority of patients with SVT are managed in this setting. Yet, the clinical factors able to identify an individual patient at higher or lower risk are still ill-defined and differ between studies on SVT which hampers the individualised management of patients with SVT. Therefore, more knowledge on the clinical characteristics that are predictive of clot propagation in patients with SVT will contribute to identifying patients at higher risk and thus those benefitting from timely anticoagulant treatment initiation.

Because DVT and/or PE can develop concomitantly to SVT, and during follow-up of SVT, both the cross-sectional (DVT and/or PE present at baseline) and prognostic (DVT and/or PE development during follow-up) predictive factors are described in literature. Therefore, the aim of this systematic review is to identify both clinically relevant cross-sectional and prognostic predictive factors and explore their predictive value for clot progression towards DVT and/or PE in patients with SVT.

MATERIALS AND METHODS

This is a systematic review of predictive factor studies in a population of patients with SVT. The protocol of this systematic review is registered at the International Prospective Register of Systematic Reviews (PROSPERO) with protocol number CRD42021262819.[11] In the conduction of this research, the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were followed as well as currently available guidance on systematic review and meta-analysis of predictive factor studies.[12 13]

Box 1 PICOTS of the predictive factors systematic review

P: patients with superficial venous thrombosis (SVT)
I and C: all potential predictive factors
O: deep venous thrombosis and/or pulmonary embolism
T (timing): predictive factors measured at diagnosis of SVT. Outcome assessed at diagnosis (cross-sectional) or at follow-up (prognostic)
S (setting): both hospital and primary care

Search and study selection

Studies describing patients with SVT as the patient population and DVT and/or PE as the outcome and reporting on predictive factors were selected for this review. The PICOTS of this study is described in box 1. The inclusion criteria were studies (1) including patients with SVT based on clinical and/or ultrasonography diagnosis, (2) selected in primary and secondary care settings and (3) reporting on the outcome DVT and/or PE. Both cross-sectional—that is, assessing predictors for the outcome DVT and/or PE at baseline (ie, concomitant DVT/PE) and prognostic—that is, assessing the outcome DVT and/or PE at a follow-up time point after diagnosis of isolated SVT—studies were included. The exclusion criteria were (1) studies only describing therapeutic predictors, (2) study designs other than original research studies such as reviews, editorials and commentaries and (3) studies not written in the English language. PubMed/MEDLINE and Embase were systematically searched until 3 March 2023. Conference abstracts were omitted from the search. To identify predictive factor studies specifically, the Haynes broad filter for prognostic factor studies and its update were added to a general SVT search.[14] Together with a medical librarian trained in systematic review, the final search string was designed and is presented in online supplemental table 1. After removal of the duplicates, the studies meeting all the inclusion criteria and none of the exclusion criteria were independently selected based on title and abstract by two investigators (FS-AvR and G-JG). Cases of doubt were discussed until consensus was reached, if needed, a third investigator (SvD) was consulted for consensus. If deemed eligible, the study underwent full-text screening before final inclusion.

Data extraction

The modified CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) for Prognostic Factor studies (CHARMS-PF) was used for systematic extraction of study characteristics. CHARMS-PF focusses on nine domains: source of data, participants, outcomes to be predicted, prognostic factors, sample size, missing data, analysis,

results and interpretation and discussion.[13] Data were extracted per study and per prognostic factor by one investigator (FS-AvR, G-JG, MvS or SvD) in a systematic way using a single uniform data extraction sheet for all included studies.

Quality assessment

The methodological quality assessment of both the included cross-sectional and prognostic papers was done by estimating risk of bias using the Quality in Prognosis Studies (QUIPS) tool.[15] The QUIPS tool consists of six domains of which domain five was omitted. Domain five covers confounding, which is irrelevant in studies focusing on predictive factors. The remaining five domains are: study participation, study attrition, prognostic factor measurement, outcome measurement and statistical analysis and reporting. The second domain, study attrition, was not scored for cross-sectional studies as this domain contained only questions on follow-up of patients. Based on these five risk of bias domains, an overall risk of bias conclusion was drawn (low, moderate or high). If one or more of the domains were scored high risk of bias, the overall risk of bias of the study was assumed to be high. Similarly, if one of the domains was scored moderate risk of bias and none were scored high risk of bias, the overall risk of bias was deemed to be moderate. Per study, risk of bias was assessed by two investigators (FS-AvR, G-JG, MvS or SvD) independently using a single uniform data extraction sheet. Discrepancies between QUIPS scores were discussed and resolved and, if deemed necessary, a third investigator was consulted for consensus.

Data analyses

During CHARMS-PF data collection, estimates of the predictive effects were extracted per predictor. As we anticipated different reported effect measures between included studies, all possible effect measures were allowed, such as ORs, relative risks and HRs. We defined a predictor as any clinical characteristic that was presented as a univariable (unadjusted for other variables) or multivariable (adjusted for other variables) predictor—outcome association in the original publication, and both the univariable and multivariable effect estimates were collected. For further exploration of predictive value, estimates of predictive factors that were presented at least in 10 or more of the included studies were selected for further analysis and were explored in forest plots. This selection was necessary to prevent subgroups from becoming too small. Forest plots were separately presented for cross-sectional and prognostic predictors. Effect estimates that could be calculated based on reported data in studies that did not initially report effect measures of these predictors, were further added to the forest plots. No other transformations of data were done prior to analyses. If three or more effect estimates were included for a predictor, meta-analysis was performed. We only pooled effect measures that were the same (ie, univariable ORs and multivariable ORs were analysed separately). To account for uncertainty in estimated variances, the Hartung-Knapp method for random-effect models was used, yielding pooled estimates with 95% CI.[13 16] Heterogeneity was assessed by I^2 and tau^2 statistics. As a sensitivity analysis of the findings from meta-analyses, the Hartung-Knapp random-effects model estimates were compared with the estimates from a fixed-effects model. To assess the certainty of evidence, Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was rated per predictor by two investigators (FS-AvR and SvD).[17] As part of GRADE, publication bias was assessed by funnel plot inspection. All the analyses were performed in R (V.4.0.3) using the 'metafor' package.

Patient and public involvement

In the planning, design, conduction and reporting of this systematic review, patients and the public were not involved. For the interpretation of current literature, it was not deemed necessary to involve patients. Additionally, our study did not involve direct participation from patients or the public.

RESULTS

Search and study inclusion

The search yielded a total of 3192 records and after removal of 111 duplicates, 3081 records were screened for eligibility based on title and abstract. The full screening process is shown in figure 1. One hundred sixty-one eligible studies from the first screening were further discussed for inclusion and 25 underwent final full-text screening. Thirteen were included for the final analysis and nine studies were added via reference checking, yielding a total of 22 included studies for this systematic review.

Study characteristics

The characteristics of the included studies are presented in table 1 (summary table) and online supplemental table 2 (extended table). Ten studies had a cross-sectional design,[18–27] 10 studies had a prognostic design[4 6 7 28–34] and 2 studies[35 36] reported cross-sectional as well as prognostic outcomes. Follow-up time in six prognostic studies was 3 months. One study had a median follow-up time of 1026 days,[28] one study a follow-up of 1 year,[30] another study used a follow-up time of 120 days[34] and in one study it was unclear when the outcome was assessed.[36] In total, the studies included 10 111 patients with SVT with sample sizes ranging from 21 to 2008 patients per study, and clot progression was observed in 990 of these patients (9.8%). Some studies used the same datasets for their analyses: three studies used data from the POST (Prospective Observational Superficial

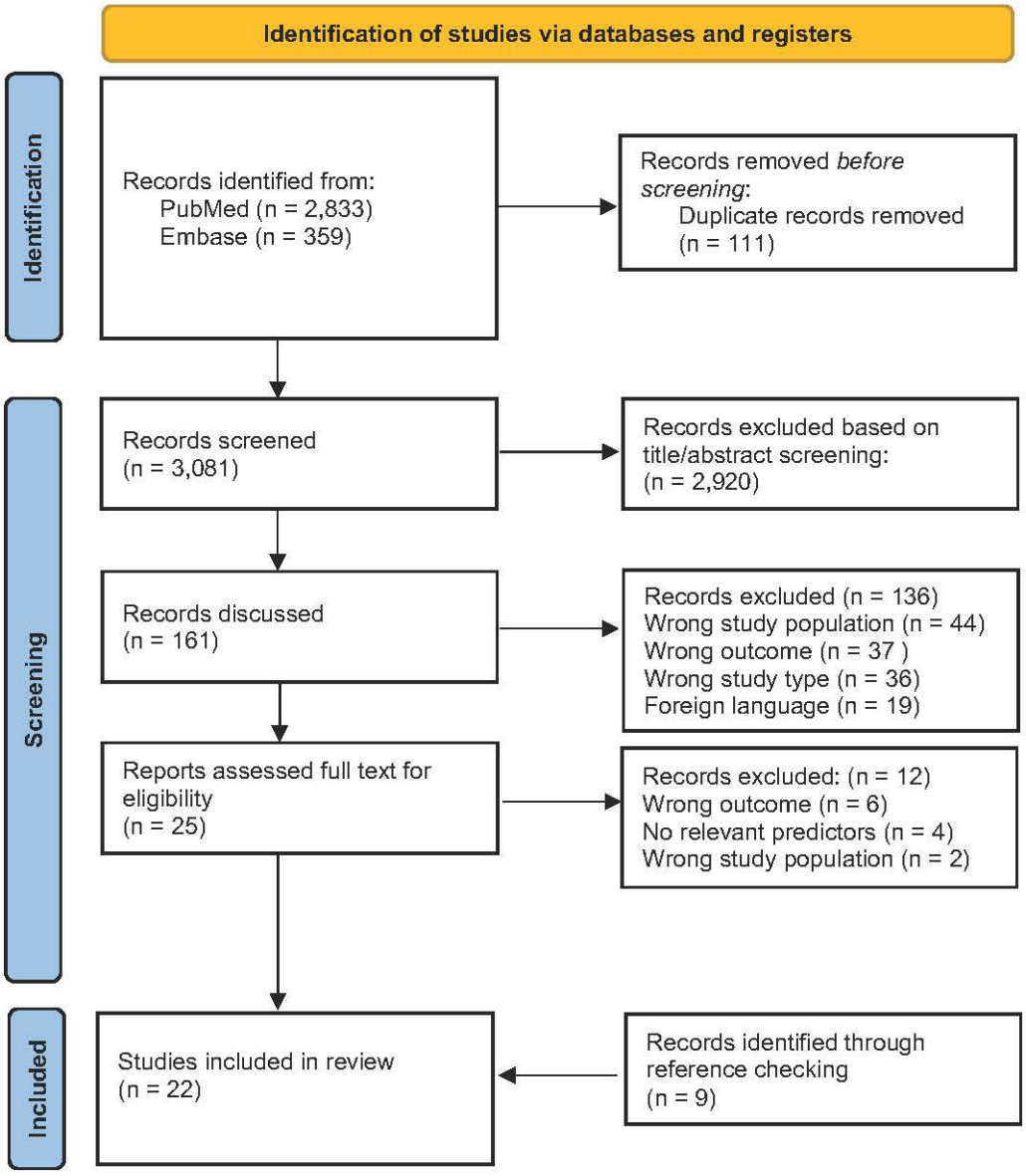

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Thrombophlebitis) dataset,[6 25 33] two studies used the OPTIMEV dataset (OPTimisation de l'Interrogatoire dans l'évalution du risque throMbo-Embolique Veineux),[33 35] two studies used the STEPH dataset[19 20] and two studies used the ICARO dataset.[24 28] Seven studies reported all VTE outcomes,[6 29 30 32–35] seven studies reported DVT and PE outcomes separately,[4 7 20 23 25 26 28] seven studies reported only DVT outcomes[18 19 21 22 24 31 36] and one study reported only PE outcome.[27]

Quality assessment

Risk of bias estimation by the QUIPS tool resulted in 11 studies that were considered 'high risk of bias', 10 studies were scored 'moderate risk of bias' and only 1 study was considered 'low risk of bias'. All risk of bias items for included studies are presented in table 2. Studies scored worst on the domains 3 (predictor measurement) and 6 (analysis and reporting). A lot of studies lacked clear description of the predictive factor and its measurement details (domain 3) and used inappropriate statistical methods (domain 6).

Predictive factors and meta-analysis

The 15 most reported predictors were: high age, male sex, idiopathic SVT, history of VTE, family history of VTE, absence of varicose veins, trauma, surgery, pregnancy, immobilisation, inpatient status, cancer, cardiovascular disease, respiratory disease and thrombophilia. More predictor details and their associations with the outcome are shown in online supplemental table 3. Based on this table, 5 predictors were identified that were presented in 10 or more studies and these predictors were selected for further analysis through forest plots and, if 3 or more of the same effect measures could be combined, meta-analysis: male sex, high age, history of VTE, absence of varicose veins and cancer. The definition of high age

Table 1 Study characteristics based on CHARMS-PF data extraction (summary table)

Study	Study type (prognostic, cross-sectional)	Country	Population	Setting	Outcome definition	Timing of outcome assessment	Patients (n)	Outcomes (n, %)
Barco *et al*[28]	Prognostic	Italy	Isolated SVT, ICARO dataset	Hospital	DVT, PE	1026 days median follow-up	411	52 (12.7%)
Bauersachs *et al*[29]	Prognostic	Germany	Isolated SVT, INSIGHT-SVT dataset	Hospital and office	DVT, PE, new SVT	90 days	1150	67 (5.8%)
Bell *et al*[30]	Prognostic	USA	First isolated SVT	Hospital outpatient clinic	Any VTE complication	1 year	381	49 (12.9%)
Binder *et al*[18]	Cross-sectional	Austria	SVT	Hospital outpatient clinic	Concurrent DVT	At inclusion	46	11 (23.9%)
Bounameaux and Reber-Wasem[31]	Prognostic	Switzerland	SVT	Hospital	DVT	3 months	551	31 (5.6%)
Cosmi *et al*[32]	Prognostic	Italy	SVT, STEFLUX dataset	Hospital	DVT, PE, SVT extension	93 days	627	45 (7.2%)
Decousus *et al*[6]	Prognostic	France	SVT, POST dataset	Hospital and office	DVT, PE, SVT extension, SVT recurrence	3 months	634	58 (9.1%)
Frappé *et al*[20]	Cross-sectional	France	SVT, STEPH dataset	Hospital and primary care	Concurrent DVT and/or PE	At inclusion	171	45 (24.0%)
Frappé *et al*[19]	Cross-sectional	France	SVT, STEPH dataset	Hospital and primary care	Concurrent DVT	At inclusion	150	28 (18.7%)
Galanaud *et al*[35]	Prognostic and cross-sectional	France	Symptomatic SVT or DVT, OPTIMEV dataset	Hospital and primary care	DVT, PE, SVT	3 months	499	15 (3.0%)
Galanaud *et al*[33]	Prognostic	France	Isolated SVT, POST and OPTIMEV datasets	Hospital and primary care	DVT, PE, new SVT	3 months	1074	42 (3.9%)
Geersing *et al*[4]	Prognostic	The Netherlands	SVT	Primary care	DVT, PE	3 months	2008	83 (4.1%)
Gorty *et al*[36]	Prognostic and cross-sectional	USA	SVT	Office	DVT	Unclear	60	7 (11.7%)
Hirmerova *et al*[21]	Cross-sectional	Czech Republic	SVT	Hospital	Concurrent DVT	At inclusion	138	42 (30.4%)
Jorgensen *et al*[22]	Cross-sectional	Australia	Symptomatic SVT	Hospital	Concurrent DVT	At inclusion	44	10 (22.7%)
Lutter and Kerr[23]	Cross-sectional	USA	SVT	Hospital	DVT, PE	Unclear	186	57 (30.6%)
Nikolakopoulos and Kakkos[34]	Prognostic	Greece	SVT >5 cm	Hospital	DVT, PE, SVT	120 days	147	15 (10.2%)
Pomero *et al*[24]	Cross-sectional	Italy	SVT, ICARO dataset	Hospital and outpatient clinic	Concurrent DVT	At inclusion	494	79 (16.0%)

Continued

Table 1 Continued

Study	Study type (prognostic, cross-sectional)	Country	Population	Setting	Outcome definition	Timing of outcome assessment	Patients (n)	Outcomes (n, %)
Quenet *et al*[7]	Prognostic	France	SVT >5 cm, STENOX dataset	Hospital	DVT, PE	3 months	427	19 (4.4%)
Quéré *et al*[25]	Cross-sectional	France	SVT >5 cm, POST dataset	Hospital	Concurrent DVT with or without PE	At inclusion	832	198 (23.8%)
Sobreira *et al*[26]	Cross-sectional	Brazil	Symptomatic SVT	Hospital	DVT, PE	Unclear	60	30 (50%)
Verlato *et al*[27]	Cross-sectional	Italy	Isolated SVT	Hospital	Concurrent PE	At inclusion	21	7 (33.3%)

CHARMS- PF, CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies for Prognostic Factor studies; DVT, deep venous thrombosis; PE, pulmonary embolism; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

ranged from age >50 years to age >75 years between the included studies. Figures 2–11 show the forest plots and pooled estimates of these five factors for prognostic and cross-sectional studies separately. Further details of the meta-analyses including prediction intervals, between-study heterogeneity and comparison with a fixed-effect modelling approach are provided in online supplemental table 4. In total, the manuscript included 21 meta-analyses, in most of these (n=12), I^2 was calculated at 0% and in five meta-analyses, some heterogeneity was detected (<50%). In four meta-analyses more substantial heterogeneity (>50%) was detected: absence of varicose veins multivariable ORs in cross-sectional studies (55%), male sex univariable HRs in prognostic studies (63%), male sex univariable ORs in cross-sectional studies (51%) and history of VTE univariable HRs in prognostic studies (66%). Furthermore, in sensitivity analyses, the random-effects models and the fixed-effects models showed similar results and as expected, the CIs of the estimates from the random-effects model were wider, especially when within-study or between-study heterogeneity was detected (online supplemental table 4). The highest pooled estimate was observed for the predictor cancer (pooled estimated univariable OR 3.12 (95% CI 1.75 to 5.59) from the cross-sectional studies) and the lowest pooled estimate was observed for the predictor high age (pooled estimated univariable OR 0.92 (95% CI 0.56 to 1.53) from the prognostic studies). Pooled estimates per predictor were overall similar for both cross-sectional and prognostic studies. The certainty of evidence as assessed through GRADE per predictor was rated low to very low, except for the predictor high age from cross-sectional studies, which was rated moderate. Online supplemental table 5 shows GRADE scores per predictor and per domain, and below the table the rationale for the scores is provided. Funnel plot inspection did not raise any concern for publication bias (data not shown). Clinical SVT characteristics from physical examination, such as length or location of the clot, were generally insufficiently reported and could therefore not be further analysed.

DISCUSSION

This systematic review discusses the clinical predictive factors described in literature for clot propagation towards DVT and/or PE in patients with SVT. It describes both the most reported cross-sectional factors as well as the most reported prognostic factors in literature. The cross-sectional and prognostic factors were difficult to separate in the available literature and were sometimes used interchangeably and for that reason, we chose to report all available predictive factors regardless of timing of outcome measurement. The most reported predictive factors for DVT and/or PE progression in patients with SVT were high age, male sex, history of VTE, cancer and absence of varicose veins. Although the pooled estimates showed predictive potential in isolation, we observed some heterogeneity in the estimates, many included

Table 2 Risk of bias assessment using QUIPS

Study	Domain 1: participation	Domain 2: attrition	Domain 3: predictor measurement	Domain 4: outcome measurement	Domain 6: analysis and reporting	Overall
Barco *et al*[28]	L	M	M	M	L	M
Bauersachs *et al*[29]	L	M	M	L	L	M
Bell *et al*[30]	M	H	M	M	M	H
Binder *et al*[18]	M	NA	M	L	M	M
Bounameaux and Reber-Wasem[31]	M	H	M	L	M	H
Cosmi *et al*[32]	L	M	M	L	M	M
Decousus *et al*[6]	M	M	L	L	M	M
Frappé *et al*[20]	M	NA	L	L	L	M
Frappé *et al*[19]	M	NA	M	M	M	M
Galanaud *et al*[35]	L	H	M	L	H	H
Galanaud *et al*[33]	L	M	M	L	M	M
Geersing *et al*[4]	L	L	L	L	L	L
Gorty *et al*[36]	H	H	H	H	L	H
Hirmerova *et al*[21]	L	NA	M	L	H	H
Jorgensen *et al*[22]	L	NA	H	L	H	H
Lutter *et al*[23]	L	NA	H	L	M	H
Nikolakopoulos *et al*[34]	M	H	M	M	H	H
Pomero *et al*[24]	M	NA	H	L	H	H
Quenet *et al*[7]	M	H	M	L	M	H
Quéré *et al*[25]	M	NA	M	L	M	M
Sobreira *et al*[26]	L	NA	M	L	L	M
Verlato *et al*[27]	L	NA	M	H	L	H

H, high risk of bias; L, low risk of bias; M, moderate risk of bias; NA, not applicable; QUIPS, Quality in Prognosis Studies.

studies were scored high risk of bias and the certainty of evidence through GRADE was rated low to very low. Furthermore, while multivariable estimates are preferred when analysing the predictive potential of individual predictors, they were often not reported and if reported, the analyses did not include the same set of predictors. This is one of the reasons that heterogeneity is unavoidable in a systematic review of predictive factor studies. To provide an overview of predictive factors as complete as possible, therefore, both multivariable and univariable estimates were presented in this study. Our results should be interpreted with caution and further multivariable exploration is necessary to be able to identify an individual patient risk profile (based on the combination of different variables) to be able to select patients with SVT at higher risk and at lower risk of DVT and/or PE clot propagation.

Strengths and limitations

The main strength of this review is the systematic approach of the search, study selection, data collection, risk of bias assessment and analysis.[13] Consequently, it was possible to obtain an impression of the most important predictors of clot propagation in patients with SVT. Nevertheless, a few challenges and limitations of this review need to be addressed. First, predictive factors studies are often not well-indexed and are difficult to identify. The Haynes broad filter and its update were applied to enhance findability of studies on predictive factors, however, still, 9 out of 22 included studies were identified through reference checking, again emphasising the challenge of identifying these type of studies.[14] Second, studies were included that presented predictive factors for clot propagation somewhere in their results where this was not the primary focus of that particular study (thus not a true predictive factor study by design, eg, the study by Lutter *et al*[23]), adding to the heterogeneity of included studies. Because of including a wide range of study designs, the data extraction with CHARMS-PF and quality assessment through QUIPS did not suit some of the included studies, such as studies with a cross-sectional approach. However, it was deemed desirable to assess all studies uniformly instead of implementing multiple tools and both CHARMS-PF and QUIPS include many general domains that are important to all study types. Third, there are some deviations from

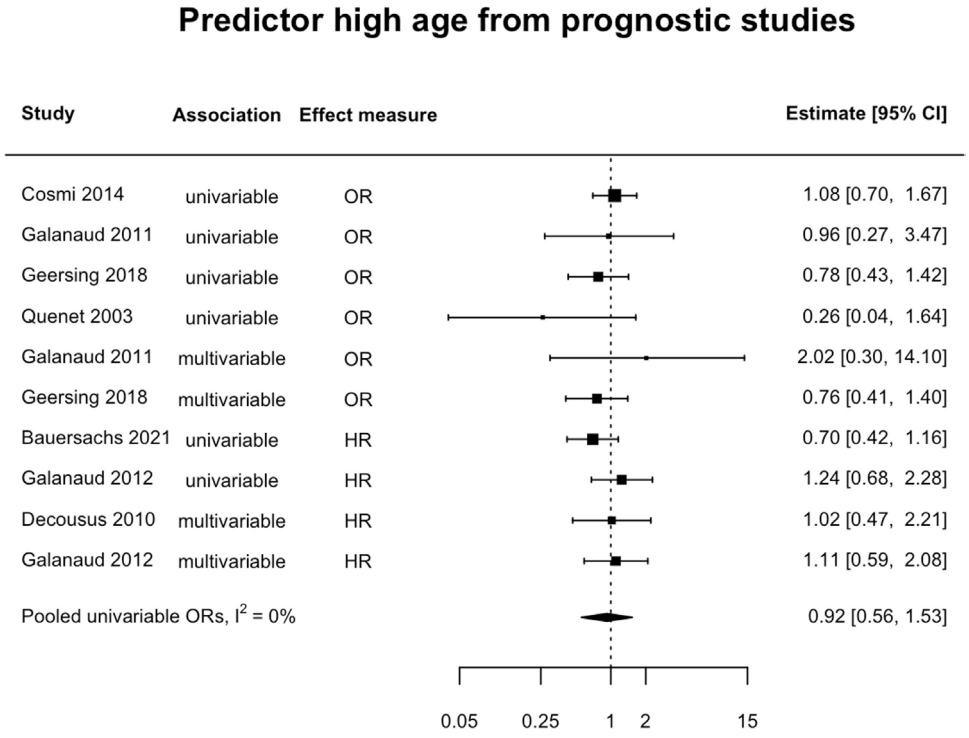

Figure 2 Forest plot of predictor high age from prognostic studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

the initially published protocol: while screening the literature for predictive factor studies, we decided to include prognostic (follow-up) studies and cross-sectional predictor studies because including both would provide a completer and more granular picture of potential predictors. Fourth, although often recommended as such in guidelines, we were unable to confirm—nor refute—that clinical SVT characteristics

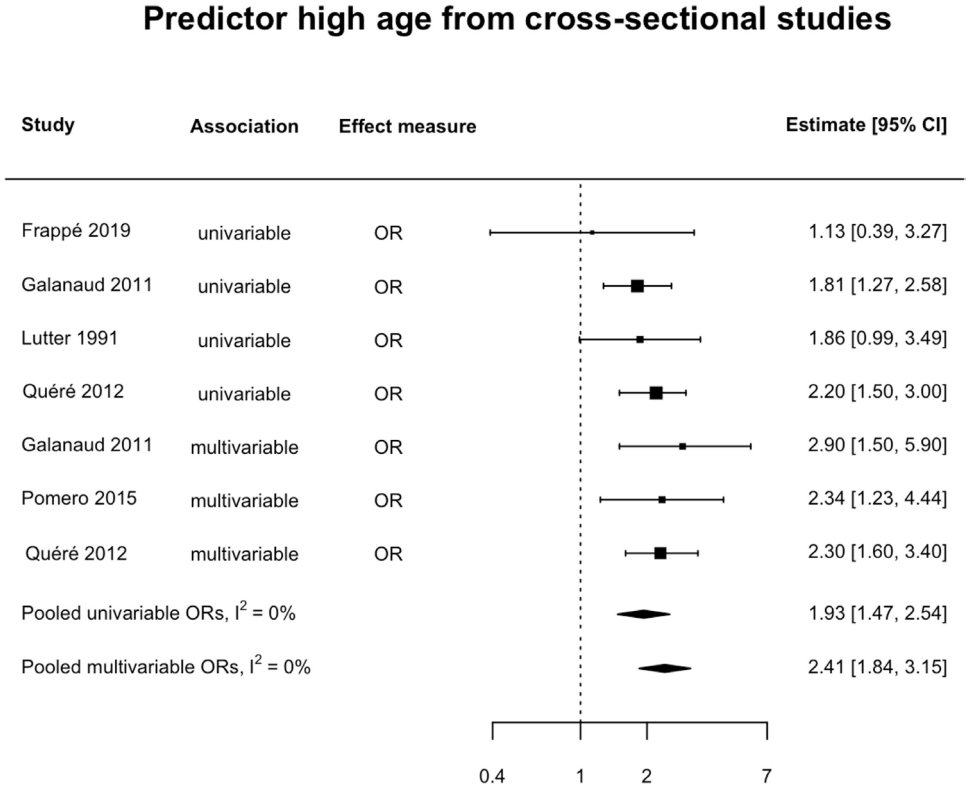

Figure 3 Forest plot of predictor high age from cross-sectional studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

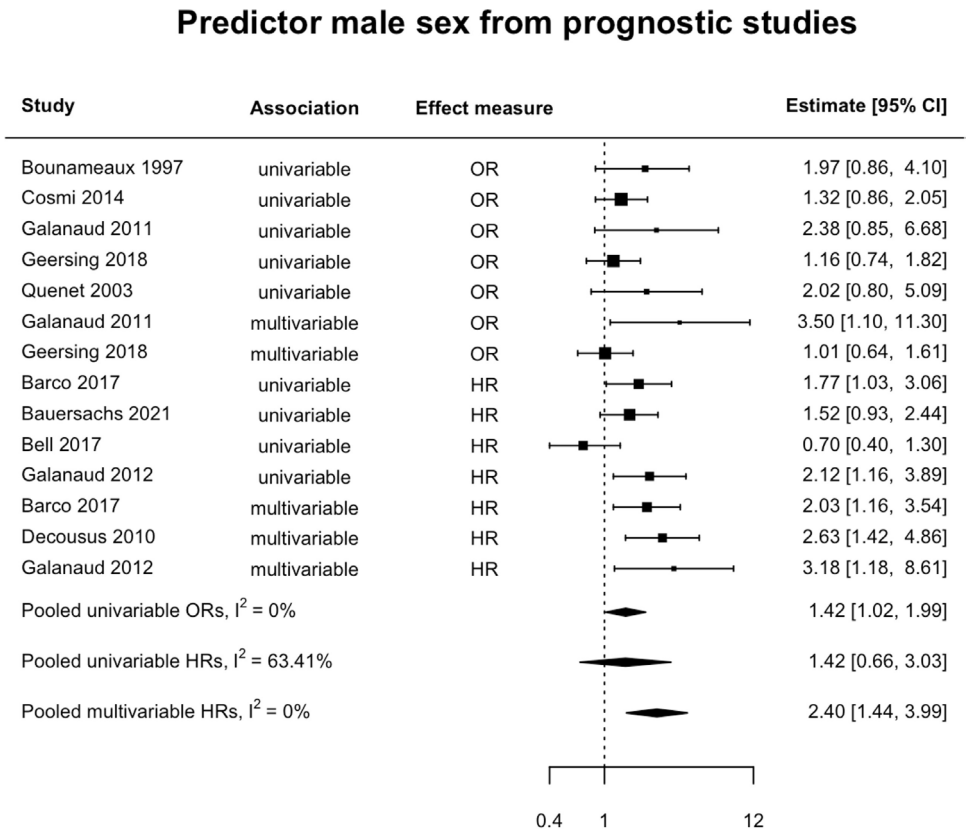

Figure 4 Forest plot of predictor male sex from prognostic studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

(such as SVT location close to the saphenofemoral junction, or length) are predictive for clot propagation in patients with SVT. These items were simply not extensively studied and reported enough to reliable estimate their predictive power for clot progression in patients with SVT, highlighting an important

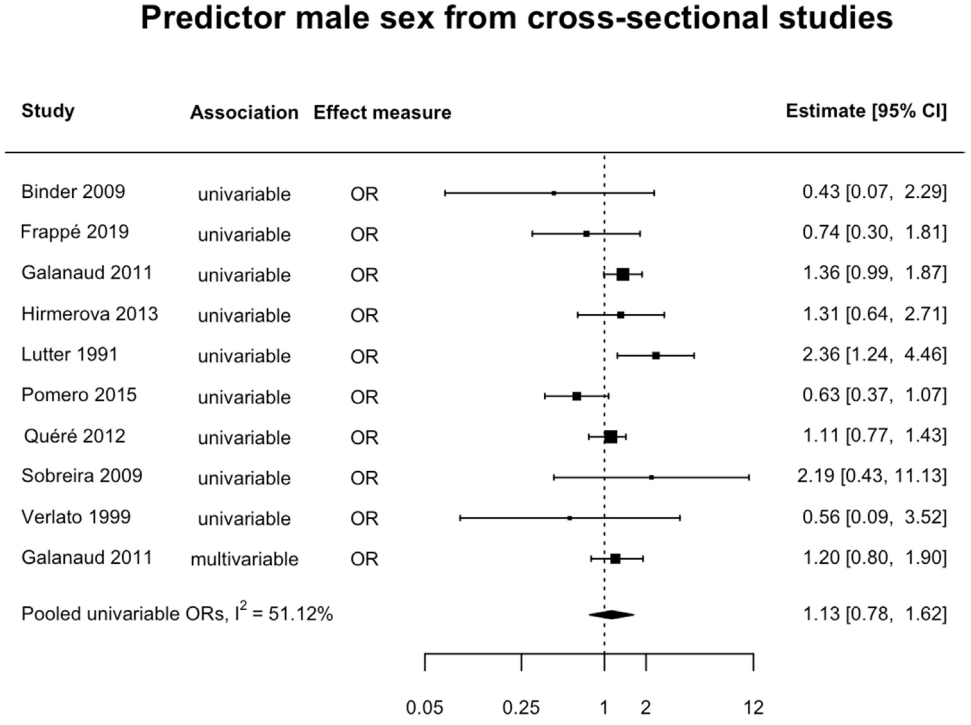

Figure 5 Forest plot of predictor male sex from cross-sectional studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

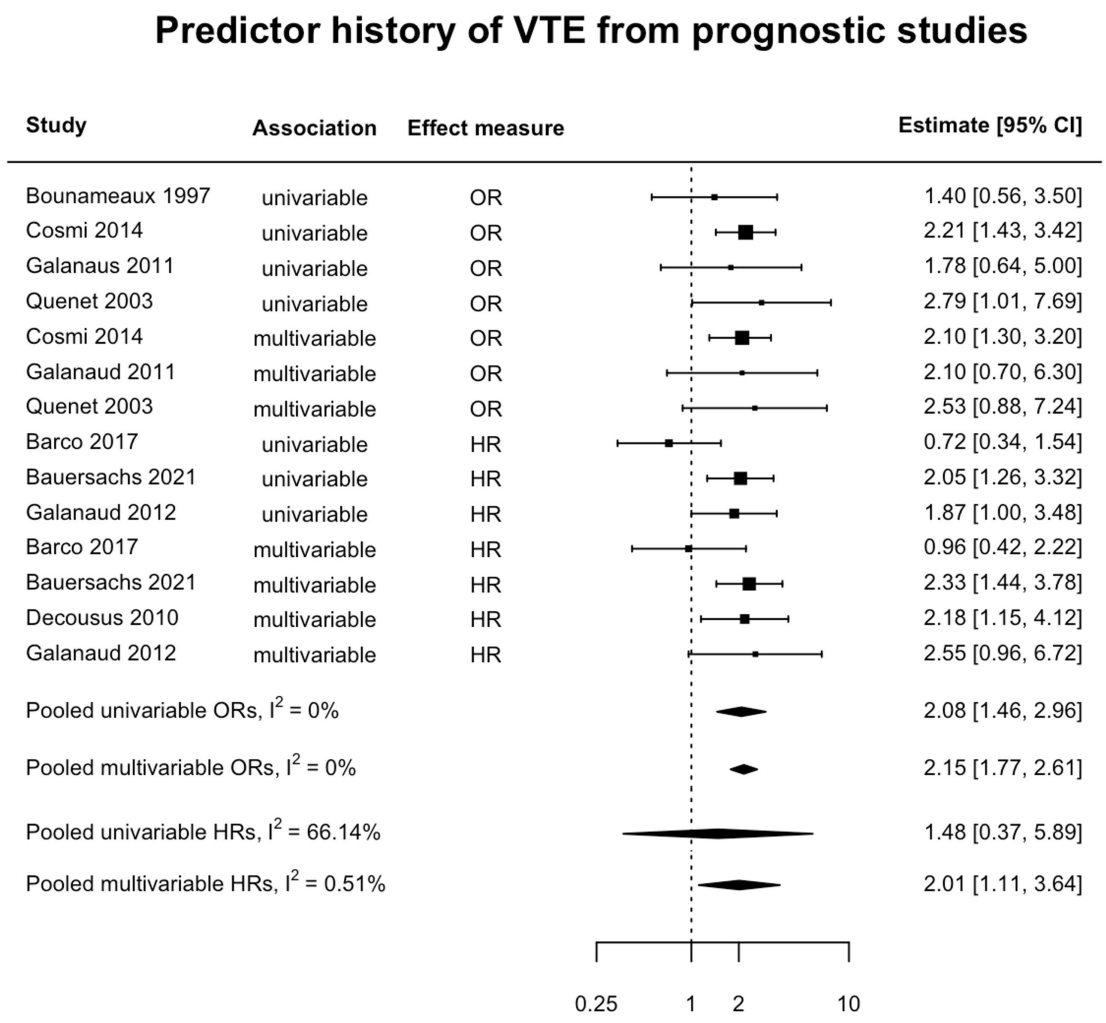

Figure 6 Forest plot of predictor history of venous thromboembolism (VTE) from prognostic studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

knowledge gap that needs to be addressed in future research, and limiting their current 'evidence-based' status in guidelines. Lastly, there was great variability in included studies in terms of study design, for instance, in setting (primary care vs referred patients), patient population, treatment received, outcome definition (VTE, DVT and/or PE, or DVT/PE only) and in definitions of predictors. Moreover, the included prognostic studies showed a wide range in follow-up time (from 3 months up to >1 year), raising the question whether DVT/PE outcome can be considered a true thrombotic complication of the initial SVT event, further clinical information about this is lacking in these prognostic studies. Additional sensitivity analyses would further aid in the assessment of the robustness of findings and in increasing the level of evidence (which was now rated as low or very low using GRADE), however, the limited number of studies prevented such analyses. Furthermore, almost all studies were rated moderate to high risk of bias mainly due to lack of predictive factor definition and to poor analysis techniques and reporting issues. Despite these limitations though, our results provide a good impression of the current available evidence on clinical predictors and the predictive potential of the predictors male sex, high age, history of VTE, cancer and absence of varicose veins.

Clinical implications

This review contributes to the clinical knowledge on the natural prognosis of SVT, a prevalent but still understudied thrombotic condition. It provides guidance for clinicians as well as clinical researchers in interpreting the current evidence on predictors of clot propagation in patients with SVT. Based on the evidence provided by this review, some clinical predictors might be considered predictive (preferably in combination with each other) to select patients at higher risk of thrombotic complications and thus consider them for referral for ultrasonography or immediately starting anticoagulant treatment. Additionally, the absence of these predictors might be used to identify the majority of the patients with SVT at lower risk of thrombotic complications for whom anticoagulant treatment (and thereby exposure to undesirable bleeding risk) is unwarranted. Predictors that might be useful in

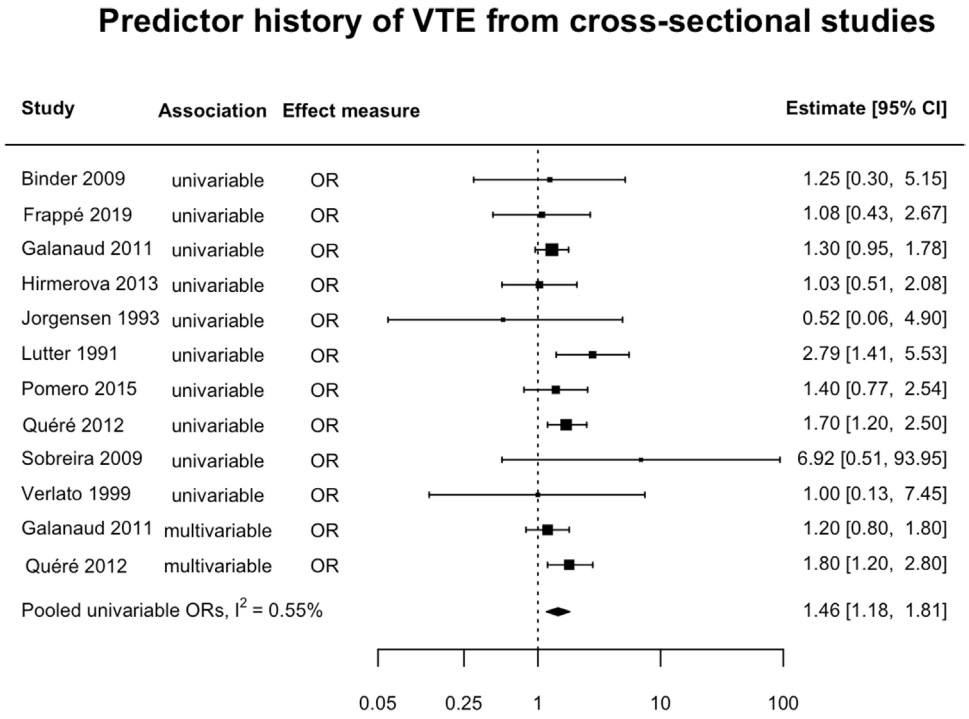

Figure 7 Forest plot of predictor history of venous thromboembolism (VTE) from cross-sectional studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

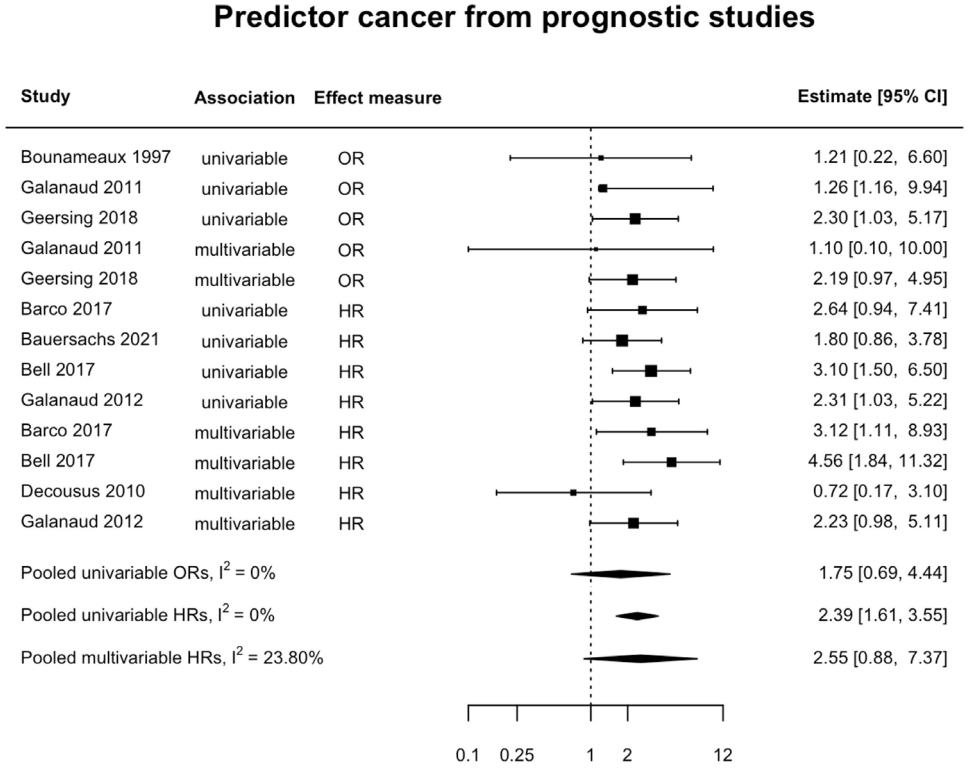

Figure 8 Forest plot of predictor cancer from prognostic studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

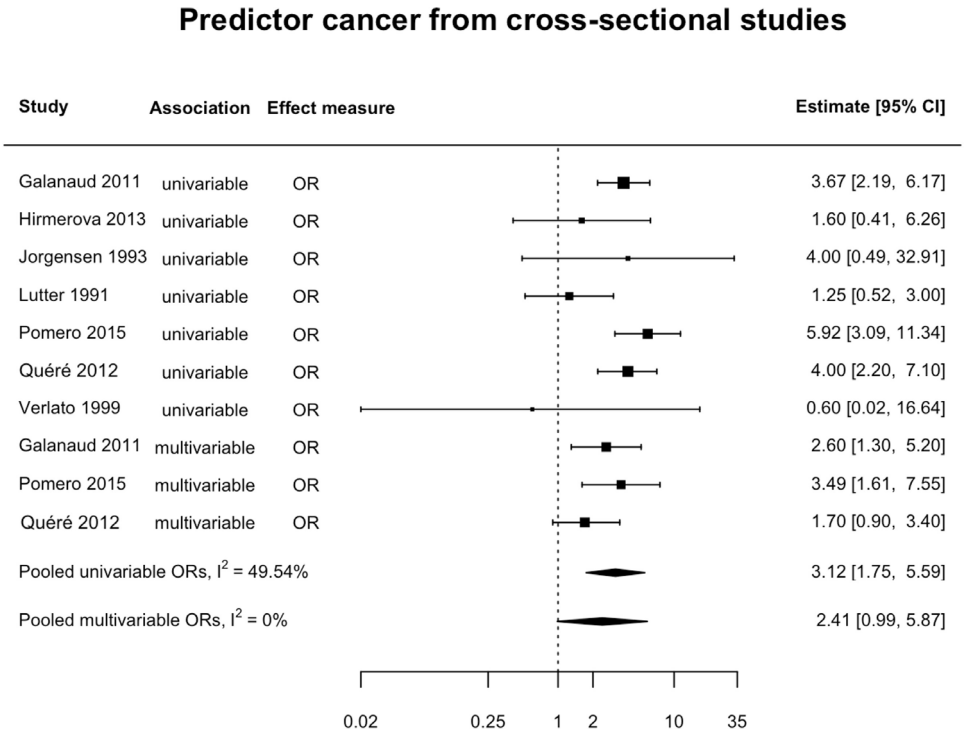

Figure 9 Forest plot of predictor cancer from cross-sectional studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

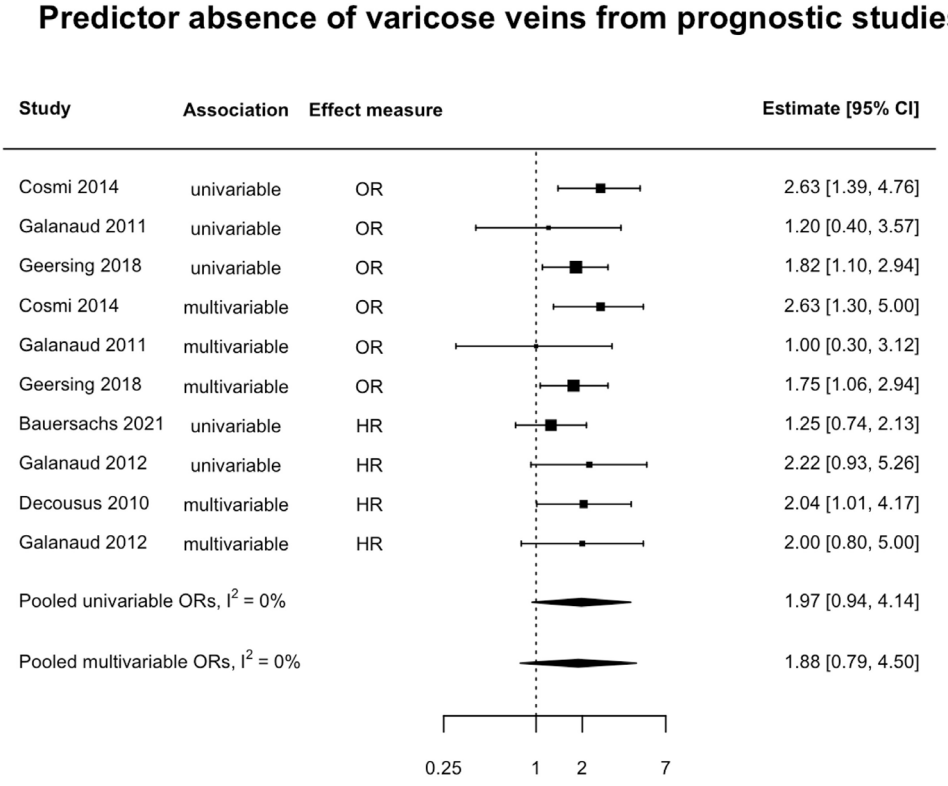

Figure 10 Forest plot of predictor absence of varicose veins from prognostic studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

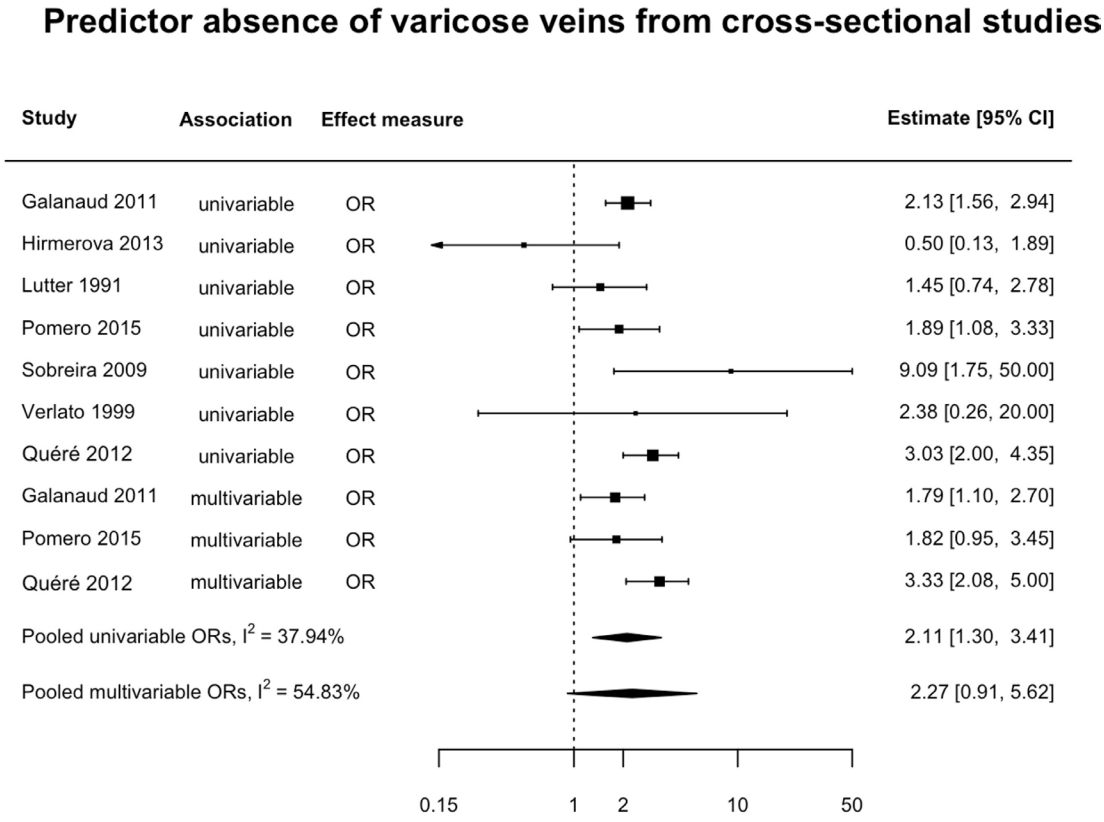

Figure 11 Forest plot of predictor absence of varicose veins from cross-sectional studies. Forest plot with meta-analysis estimates (when three or more effect measures could be combined). The forest plot is presented on the logarithmic scale.

this setting include high age, male sex, history of VTE, cancer and absence of varicose veins, that all appear to increase the risk of clot propagation or progression to DVT or PE. The predictive potential of the predictor cancer was also confirmed in a recent study performed in a study population of patients with cancer with SVT.[37] For several reasons and as mentioned previously, our results should be interpreted with caution and further research is needed to confirm predictors in clinical practice.

Research implications

This review emphasises the need for further research and ultimately, multivariable analysis is needed to assess the combined prognostic information of these variables on clot propagation in patients with SVT, followed by (internal and external) validation techniques. Subsequently, this information can be translated into a set or prediction tool on clinically useful predictors that may help to estimate individual probabilities for adverse thrombotic outcomes in SVT. Such a clinical prediction tool for clot propagation is currently being developed by our team and this review contributes to the evidence-based selection of predictors for this tool.[38]

CONCLUSION

This is a systematic summary of 22 papers describing prognostic and cross-sectional clinical predictors in patients with SVT of clot propagation towards DVT and/or PE up to 3 March 2023. The most reported clinical predictors were high age, male sex, history of VTE, cancer and absence of varicose veins and these predictors show potential for further multivariable exploration.

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Contributors All authors contributed to the design of the study. Screening of the literature was done by FS-AvR and G-JG, SvD was consulted if needed to reach consensus. Data extraction and risk of bias scoring was done by FS-AvR, G-JG, SvD and MvS. The analyses were performed by FS-AvR. FS-AvR was responsible for the first draft and all authors contributed to writing the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: the lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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