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ORIGINAL ARTICLE

Exploring heterogeneity in reported venous thromboembolism risk in COVID-19 and comparison to other viral pneumonias: a systematic review and meta-regression

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Abstract

Background: Sources of heterogeneity in venous thromboembolism (VTE) risk in COVID-19 are unclear and comparisons to other viruses are lacking.

Objectives: To describe VTE risk in patients with COVID-19, explore sources of heterogeneity, and make comparisons with other viral pneumonia.

Methods: PubMed and Embase data were searched on March 14, 2021, for studies on VTE in adults hospitalized with viral pneumonia. VTE risk estimates were pooled in a random effects meta-analysis stratified by virus type. Heterogeneity in COVID-19 was explored in multivariable meta-regression.

Results: Seventy studies in COVID-19 (intensive care [ICU] [47] vs ward [23]), 4 studies in seasonal influenza (ICU [3] vs ward [1]), 2 ICU studies in H1N1 and 1 ICU study in SARS-CoV-1 were included. For COVID-19 ICU, pooled VTE risk was 19.6% (95% confidence interval [CI], 16.2%–23.5; I^2 = 92.8%) for nonscreening studies and 30.0% (95% CI, 17.9%–45.7%; I^2 = 81.9%) for screening studies. For COVID-19 ward, pooled VTE risk was 3.4% (95% CI, 2.4%–4.7%; I^2 = 91.3%) and 22.5% (95% CI, 10.2%–42.7%; I^2 = 91.6%) for nonscreening and screening studies, respectively. Higher sample size was associated with lower VTE risk. Pooled VTE risk in seasonal influenza and H1N1 at ICU were 9.0% (95% CI, 5.6%–14.2%; I^2 = 39.7%) and 29.2% (95% CI, 8.7%–64.2%; I^2 = 77.9%), respectively. At ward, VTE risk of seasonal influenza was 2.4% (95% CI, 2.1%–2.7%). In SARS-CoV-1, VTE risk was 47.8% (95% CI, 34.0–62.0).

Conclusion: Pooled risk estimates in COVID-19 should be interpreted cautiously as a high degree of heterogeneity is present, which hinders comparison to other viral pneumonia. The association of VTE risk in COVID-19 to sample size suggests publication bias.

KEYWORDS
COVID-19, pneumonia, pulmonary embolism, venous thromboembolism, thrombosis

Essentials

- Reported venous thromboembolism risk estimates in COVID-19 are highly heterogeneous.
- Furthermore, comparisons to other types of viral pneumonia are lacking.
- In COVID-19, higher sample size was associated with lower venous thromboembolism risk, suggesting publication bias.
- Heterogeneity in pooled risk estimates in COVID-19 hinders comparison to other viral pneumonia.

1 | INTRODUCTION

In recent years, infections have been recognized as a risk factor for venous thromboembolism (VTE). This has become a pressing issue because of the COVID-19 pandemic [1,2]. Early in the pandemic, Tang et al. [3] reported coagulation abnormalities at admission among nonsurvivors compared with survivors of COVID-19. This was rapidly followed by reports showing an increased risk of thrombotic complications in patients hospitalized with COVID-19 with incidences up to 30% in intensive care unit (ICU) patients [4–6].

Whether this coagulopathy is a distinct pathologic feature of COVID-19, or a manifestation of "thrombo-inflammation" found in other viral infections, is not clear. Severe COVID-19 infection has been associated with a "cytokine storm," a maladaptive and excessive immune response, with high mortality rates [7]. However, the specificity of this "cytokine storm" to the pathophysiology of COVID-19 has been debated, as the circulating cytokine levels in critically ill patients with COVID-19 were low or similar compared with other patients with acute respiratory distress syndrome [8,9]. Furthermore, hyperproduction of inflammatory cytokines has not only been described for emerging acute respiratory infections, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, pandemic H1N1, and avian H5N7 influenza, but also to a lesser extent for seasonal influenza [10]. Indeed, high rates of thrombotic complications have been observed in patients hospitalized with SARS [11,12] and H1N1 [13,14].

Since the first notion of a high rate of VTE among hospitalized patients with COVID-19, numerous articles have been published describing this risk in different cohorts. Multiple systematic reviews and meta-analyses were undertaken in an effort to summarize this data [15–18]. In these meta-analyses, it became clear that the reported risks vary widely among studies. However, until now minimal efforts have been made to specify the sources of heterogeneity.

Heterogeneity in its broadest sense may refer to clinical diversity (eg, patient characteristics), methodological diversity (ie, study design) and statistical heterogeneity [19]. The latter is present if observed outcomes differ more than could expected by chance alone, and is likely a consequence of clinical and/or methodological diversity. Understanding the sources of heterogeneity among studies on VTE risk in COVID-19 is pivotal, as therapeutic consequences have been imposed on these findings. Any unrecognized between-study heterogeneity due to methodological shortcomings is problematic. Furthermore, one should be cautious of publications bias as centers observing spuriously high rates of VTE are more likely to publish their findings than the centers which do not. Available data would then not be representative of the "true" VTE risk.

Considering the above, we will focus on 2 aims in this systematic review. First, we will describe the risk for VTE in patients hospitalized with COVID-19 and explore the sources of heterogeneity in reported risk estimates. Second, we will compare the risk of VTE in hospitalized patients with COVID-19 to patients hospitalized with other types of viral pneumonia.

2 | METHODS

In accordance with the *Preferred Items for Systematic Reviews and Meta-Analyses* guidelines, the study protocol was registered with the *International Prospective Register of Systematic Reviews* (PROSPERO) (CRD42020192597). This systematic review and meta-analysis is reported according to the *Preferred Items for Systematic Reviews and Meta-Analyses* guidelines [20].

2.1 | Eligibility criteria

We conducted a systematic review of studies reporting on the risk of VTE in adult inpatients hospitalized with a diagnosis of any viral pneumonia identified from medical records or diagnostic codes. Diagnosis of viral pneumonia needed to be confirmed by virologic diagnostics (ie, polymerase chain reaction, antigen tests, viral culture, serologic tests) or suspected by a clinician. Peer-reviewed cohort studies were considered for inclusion. The outcome of interest was VTE, namely deep vein thrombosis (DVT), pulmonary embolism (PE) and other, as provided by medical report data or registration codes (eg, *International Classification of Diseases* codes).

Studies with a cross-sectional design, including populations restricted to specific diseases or baseline characteristics (eg, patients with cancer, liver disease, or obesity), that did not report on VTE risk throughout complete hospital stay (eg, VTE risk within certain days of admission) and autopsy studies were excluded. Furthermore, studies with <20 participants were excluded because we assumed that these studies were likely to be of insufficient data quality. Inclusion of these studies would be problematic when pooling risk estimates in a random-effects model (see *Data analysis*), as weighting is less driven by sample size [21].

2.2 | Information sources and search strategy

A comprehensive systematic search was conducted in PubMed and Embase with consultation of a medical librarian from the medical faculty of the *University of Groningen*. A first search was performed from inception to August 18, 2020. Because of the rapid publication of new reports at the end of the first wave of COVID-19, we performed an updated search on March 14, 2021. A filter for the English language was used. Data-management and de-duplication was executed using software tools Rayyan [22] and Mendeley (version v1.19.6).

MeSH terms and synonyms for "viral pneumonia," including search terms for viruses causing lower respiratory tract infections, and VTE were combined. A detailed description of the search strategy is provided in the Supplementary Methods. Gray literature was not included.

2.3 | Selection strategy

Two authors (S.B. and C.C.) independently screened titles, abstracts, and full-text publications. In case of any discrepancies in title and abstract evaluation, a record was included in full-text evaluation. Any discrepancies in full-text evaluation were solved with a third author (K.M.). All full-text articles were checked for overlap in included populations. In case of a complete overlap, the study with the largest number of participants was included. In case of partial overlap, all studies were kept in the data synthesis and analysis. Thereafter, we performed a sensitivity analyses by including the largest studies of the partially overlapping ones, as described more in detail later (see Data synthesis and analysis).

2.4 | Data collection process

Data were independently extracted by 2 reviewers (S.B. and C.C.) by a standardized case report form. Again, in case of any discrepancies, a third author (K.M.) was consulted to resolve this. We extracted the following data: study design (retrospective vs prospective), sample size, number of patient admitted to the ICU and/or ward, average age, sex, number of deceased patients, number of patients on mechanical ventilation, follow-up duration, date of publication, journal impact factor, region, whether screening was performed, the type of outcome presented (DVT, PE, or other), number of VTE events, and the number of patients at risk (ie, sample size). Any missing data in the aforementioned variables were requested from the authors and were used in data synthesis and analysis if provided.

2.5 | Risk of bias assessment

Risk of bias was independently assessed by 2 reviewers (S.B. and C.C.) using a modified version of the Newcastle Ottawa Scale [23]. We assessed the following items: 1) representativeness of the cohort, 2) ascertainment of exposure, 3) demonstration that the outcome of interest was not present at study initiation, 4) assessment of the outcome, 5) duration of follow-up and 6) adequacy of follow-up. In the end, each article was marked on a scale from 0 to 6. An example of the score form is provided in the Supplementary Methods.

2.6 | Data synthesis

A difficulty arose from the pooling of risk measures by different methods that were used to estimate the risk of VTE in the original studies. There were studies that provided the sample size, ie, the number of VTE divided by the number of patients at risk and studies that performed survival analysis to determine the cumulative incidence of VTE.

These 2 methods were applied erroneously in a few studies. The following was considered problematic: a) >10% incomplete observations regarding the outcome in-hospital VTE in a number of events divided by patients at risk analysis and b) >10% discharged or deceased patients in survival analysis, that were not handled as competing risks, resulting in incorrectly inflated cumulative incidence estimates [24]. The latter is problematic, as discharge or death result in incomplete observation regarding the outcome in-hospital VTE. This concerned 5 [25–29] and 3 studies [4,6,30], respectively. These studies were excluded from the primary analysis.

To harmonize outcome estimates, we pooled number of events divided by number of patients at risk for all studies. We tested sensitivity of our findings by including the aforementioned 8 studies with number of events divided by the number of patients at risk approach. Subsequently, outcomes for still admitted patients were imputed as following: 1) assuming that still admitted patients had a similar VTE risk as discharged and deceased patients and 2) assuming that still admitted patients have a VTE risk twice as high as discharged and deceased patients.

2.7 | Data analysis

2.7.1 | Meta-analysis

Risk estimates for VTE were pooled in a random-effects model stratified by virus type and setting. Parameter estimation was done by restricted maximum-likelihood estimation. To meet the assumption of a normal distribution of the outcome data, the incidences were logit-transformed.

Setting was categorized as ICU or ward. According to the *World Health Organization* (WHO) COVID-19 guidance, study cohorts with patients admitted to the ICU or referred to as critically ill were categorized as ICU studies. Studies comprising patients admitted to either the general ward or referred to as noncritically ill were categorized as ward studies [31]. If risk estimates were not stratified by setting and <5% of the cohort consisted of either patients admitted to the ICU or ward, a cohort was categorized as ICU or ward, respectively. Cohorts in which risk estimates were not stratified by ICU and ward patients were categorized as "mixed." Mixed cohorts were not analyzed. Analysis of these studies was considered futile, as distribution of ICU and ward patients was not reported in most instances.

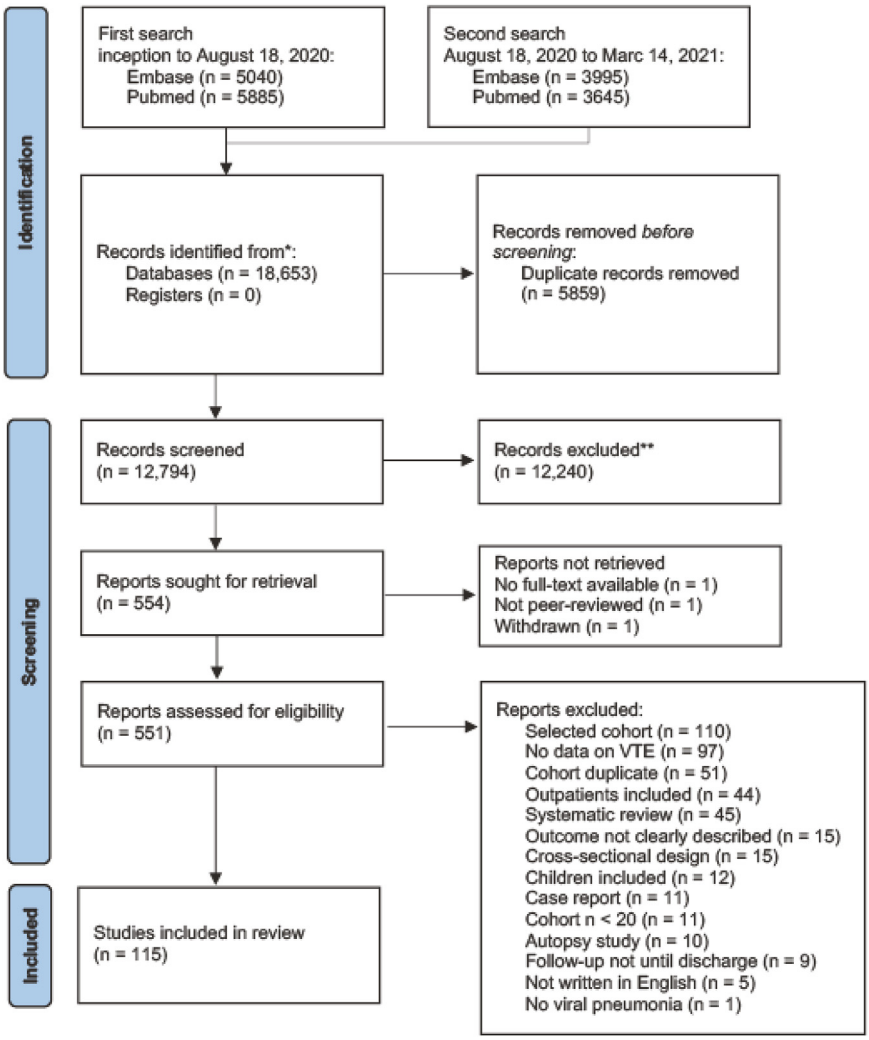

FIGURE 1 Flow chart of study selection.

Study design was categorized as retrospective and prospective. Prospective was defined as data collection on VTE was prospectively collected upon study enrolment. Retrospective was defined as data collection on VTE after study enrolment (eg, data collection from medical reports).

Some studies did not present an overall risk of VTE, but risk stratified by a certain baseline characteristic. Risk of VTE in these studies was aggregated by calculating weighted averages for continuous variables and the sum of categorized variables. Studies stratifying results by thromboprophylaxis regimen were aggregated accordingly, as most studies did not present results stratified based on this characteristic.

2.7.2 | Meta-regression

We performed *post-hoc* meta-regression with logit-transformed risk estimates in studies reporting COVID-19 to explain the observed heterogeneity. During the conduct of this study, quite a large number of systematic reviews had been published on the VTE risk in patients with COVID-19. These reviews also reported high heterogeneity, but thorough analyses explaining this heterogeneity were mostly lacking.

The used predictor variables were the clinical and methodological variables described in the section *Data collection process*, and square-rooted sample size of the original studies. Sample size was square-rooted to approach a normal distribution. The variable region was divided into Asian and non-Asian, as VTE incidence is lower in Asia [32]. The type of VTE reported in each study was categorized as PE only, DVT only, PE and DVT only and including other VTE (eg, portal vein thrombosis or cerebral vein thrombosis). The date of publication was transformed into a numerical value by subtracting 1-1-2020 from the date of publication.

First, we analyzed all pre-specified predictors univariably. Subsequently, a multivariable model was constructed in a stepwise fashion, because of the limited degrees of freedom. For the final models, we aimed to construct models on a foundation of >80% of the included studies per stratum. Variables were entered into the model based on a pre-specified hierarchy on plausibility to influence the outcome, effect size of the regression coefficient, and amount of missing data. The outcome measure was the regression coefficient with a 95% CI. The remaining I^2 is presented, as a measure of remaining variability in the data, which is attributed to between-study heterogeneity that cannot be explained by the predictor variables.

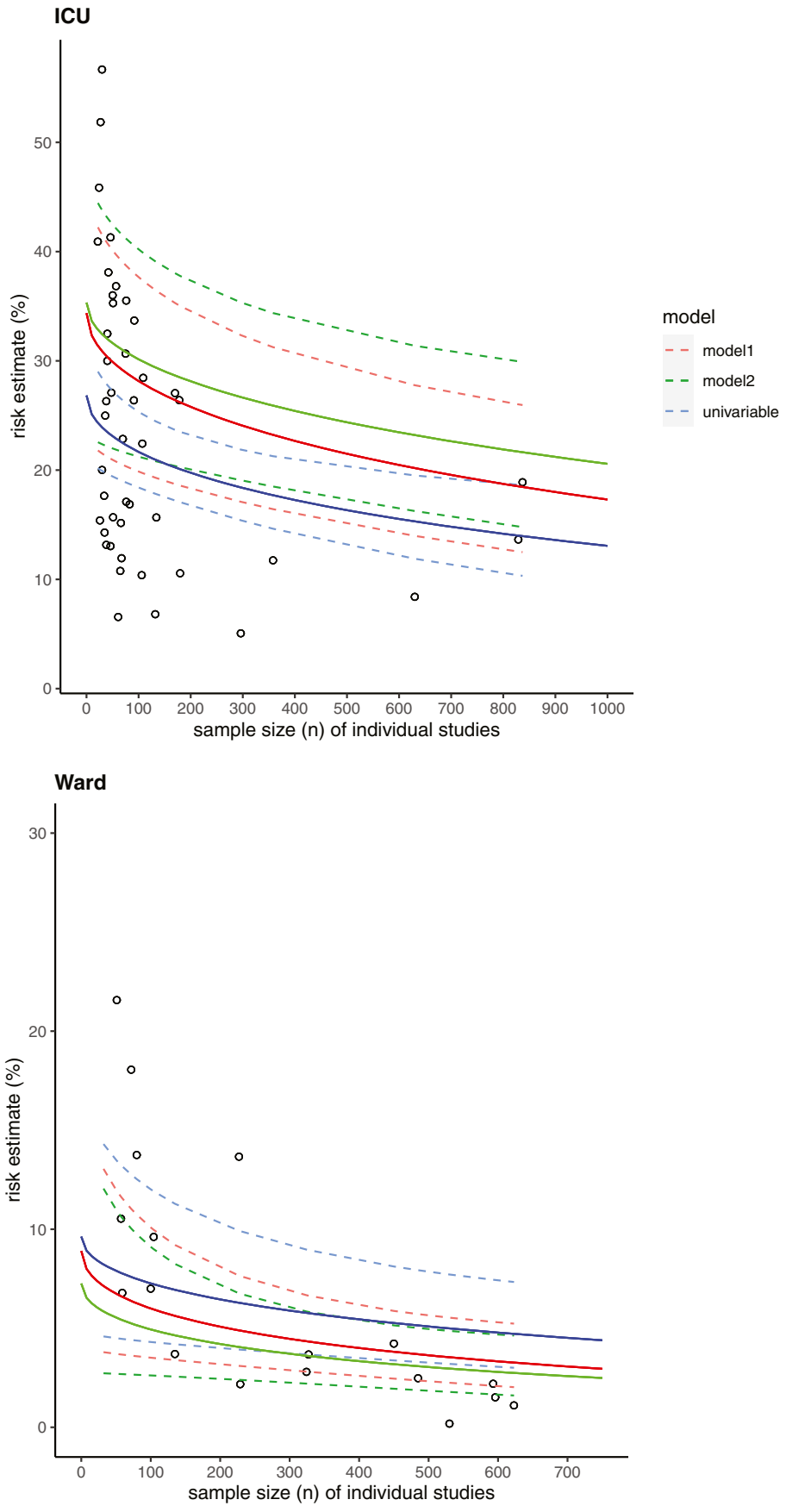

FIGURE 2 Association between sample size and venous thromboembolism risk estimated stratified by setting (ICU vs ward)Dots depict the reported risk estimates. Solid lines represent the regression lines of the univariable (blue), multivariable – model 1 (red), multivariable model 2 (green) analyses. Dashed lines are the corresponding upper and lower bounds of the 95% CI. A lower sample size was associated with a higher risk estimate.The regression line was defined as: logit(y) = β*square-rooted (sample size) + intercept. For the multivariable analysis, continuous variables were set at the mean. Categorical variables were set at prospective studies, without screening and from non-Asian countries, if included in the model.

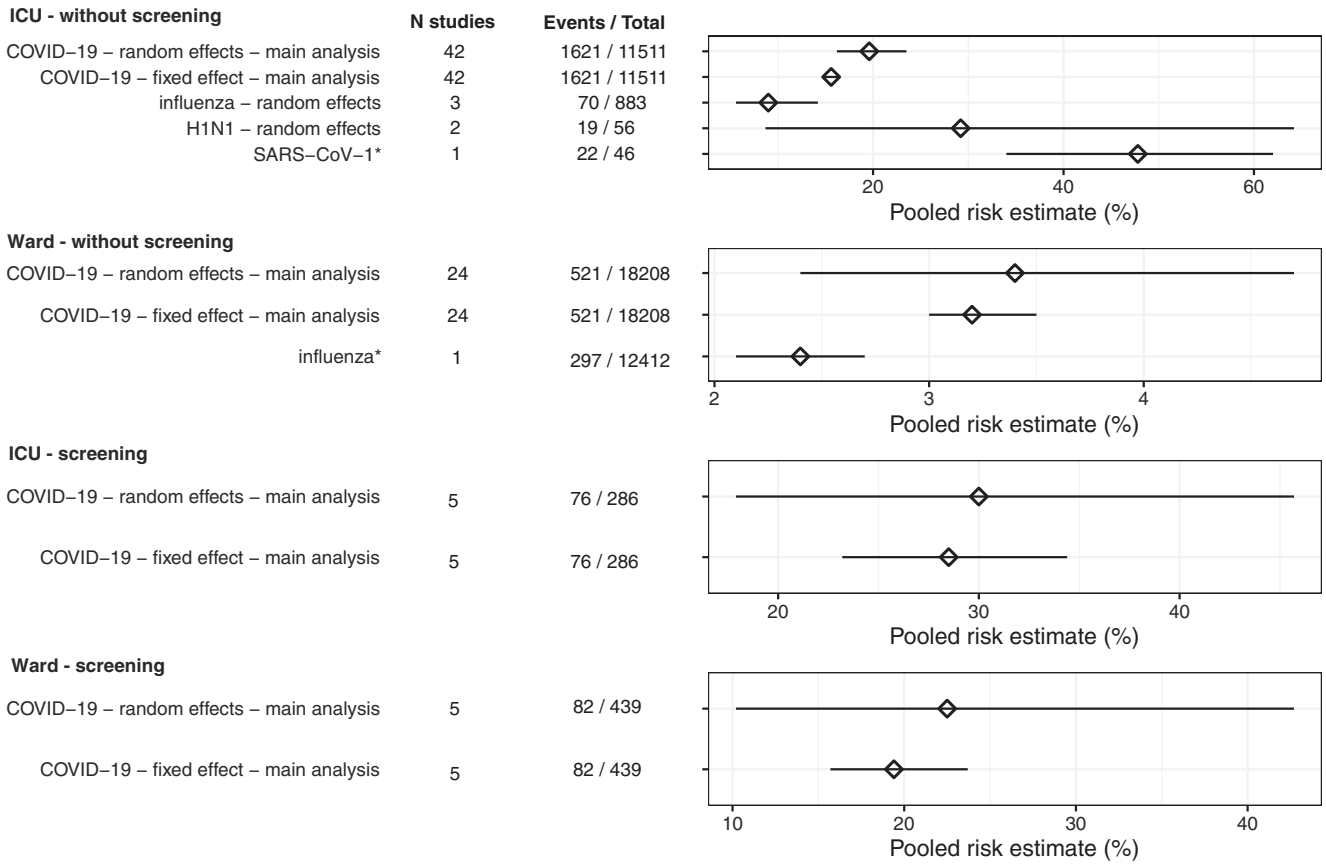

FIGURE 3 Overview of pooled venous thromboembolism risk estimates for each virus stratified by setting and implementation of screening. *only 1 study was included.

Two additional sensitivity analyses were performed. In the main analysis, studies reporting zero events were excluded. Therefore, the main analysis was repeated with continuity correction of 1 event to all studies. Second, we repeated the main analysis by excluding studies with partially overlapping study populations. Studies with the largest sample size were kept in this analysis.

Baseline characteristics are reported as numbers and percentages, mean and SD, or median and IQR. All analyses were performed in R version 4.1.2 (R Core Team, Vienna, Austria) with packages "dmetar," "metafor," and "ggplot2."

2.8 | Role of the funding source

None.

3 | RESULTS

3.1 | Search results

After deduplication, 7,914 and 4,880 records were identified by the first and updated literature search, respectively (Figure 1). Combined, 12,240 records were excluded during title and abstract screening, leaving 554 full-text articles for eligibility assessment. A further 436 articles were excluded, mainly because of the inclusion of a selected patient population (eg, population confined to patients with cancer or liver disease), not having VTE as outcome, duplicates of cohorts and inclusion of outpatients. Eventually, 115 articles were included in this review (Figure 1) [4,6,12–14,25–28,33–136].

3.2 | Characteristics of the included studies

Of the included 115 articles, 105 reported on COVID-19 [4,6,25–30,38–66,69–136], 5 reported on seasonal influenza (type A and B) [35,37,50,59,119], 4 reported on H1N1 influenza (ie, "swine" flu) [13,14,33,34]. One reported on SARS-CoV-1 [12] and 3 on viral pneumonia not specified [36–38]. Within COVID-19 studies, the majority concerned retrospective cohort studies (n = 85) [3,4,6,15,24,26–30,38–40,42–46,48,49,50–53,55–57,59,60,63–65,67–70,72–87,92,94,96,97,99–113,115,116,119–128,131,132,134,135], followed by prospective cohort studies (n = 20) [41,47,58,61,62,66,88,89,93,95,98,114,117,118,129,130,133,136]. Studies concerning the other viruses were all retrospective cohort studies [13,14,33–38,50,59,119].

TABLE 1 Study-level baseline characteristics.

Variables	COVID-19				Seasonal influenza				H1N1		SARS-CoV-1	
	ICU	*N*	Ward	*N*	ICU	*N*	Ward	*N*	ICU	*N*	ICU	*N*
Articles, (*n*)	47		23		3		1		2		1	
Total patients	11,797		17,838		883		12,412		56		46	
Patients, (*n*)	66 (40 – 132)		277 (78 – 594)		40 (39 – 423)		12,412 (NA)		28 (24 – 32)		46 (NA)	
Average age (y), median (IQR)	62.8 (60.7 – 64.1)	39	67.5 (65.5 – 71.2)	18	61 (NA)	1	NA	0	37.8 (36.9 – 38.6)	2	51 (NA)	1
Females (%), median (IQR)	27.0 (25.1 – 38.0)	38	42.3 (37.2 – 46.5)	19	47.4 (NA)	1	NA	0	46.4 (37.1 – 55.7)	2	47.8 (NA)	1
Region, *n* (%)												
Asian	3 (6.4)	47	1 (4.4)	23	0	3	0	1	0 (0)	2	0 (0)	1
Non-Asian	44 (93.6)		22 (95.7)		3 (100)		1 (100)		2 (100)		1 (100)	
Mortality (%), median (IQR)	28.1 (20.5 – 41.9)	34	9.7 (5.2 – 14.8)	18	26.4 (23.8 – 29.0)	2	6.2 (NA)	1	33.1 (31.5 – 34.5)	2	52.2 (NA)	1
Mechanical ventilation (%), median (IQR)	81.4 (62.6 – 92.6)	27	-	-	42.5 (NA)	1	-	-	85.0 (77.5 – 92.5)	2	87.0 (NA)	
Outcome reported, *n* (%)												
PE and DVT	15 (31.9)	47	11 (47.9)	23	2 (66.7)	3	0	1	1 (50)	2	1 (100)	1
PE	8 (17.0)		1 (4.4)		0		0		0		0	
DVT	0 (0.0)		2 (8.7)		0		0		0		0	
Other included	17 (36.2)		5 (21.7)		0		0		1 (50)		0	
Not defined	7 (14.9)		4 (17.4)		1 (33.3)		1 (100)		0		0	
Screening, *n* (%)												
No	42 (89.4)	47	18 (78.3)	23	3 (100)	3	1 (100)	1	2 (100)	2	1 (100)	1
Yes	5 (10.6)		5 (21.7)		0 (0)		0 (0)		0 (0)		0	
Design, *n* (%)												
Retrospective	35 (74.5)	47	19 (82.6)	23	3 (100)	3	1 (100)	1	2 (100)	2	1 (100)	1
Prospective	12 (25.5)		4 (17.4)		0 (0)		0 (0)		0 (0)		0	
Duration of admission (d), median (IQR)	21 (17.3 – 28.3)	28	11 (6.5 – 17.3)	15	NA	0	NA	0	15 (NA)	1	91 (NA)	1

Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; *N*, number of studies in which variable is reported; PE, pulmonary embolism.

Pooled baseline characteristics of studies included in the main analysis with continuous variables presented as median with an IQR and discrete variables as numbers with a proportion.

TABLE 2 Univariable and multivariable meta-regression in patients with COVID-19 at the ICU with sample size as predictor variable.

	Univariable			Multivariable			
				Model 1[b]		Model 2[c]	
Variable	ß (95% CI)	*P* value	K[a]	β (95% CI)	*P* value	β (95% CI)	*P* value
Average age, (y)	-0.0092 (-0.068; 0.050)	.76	39	-0.0047 (-0.058; 0.049)	.86		
Date of publication, (d)[d]	-0.0018 (-0.0034; -0.0002)	.030	47	-0.0014 (-0.0030; 0.0001)	.074	-0.0011 (-0.0026; 0.0004)	.14
Impact factor	-0.0034 (-0.043; 0.036)	.87	47				
ROB[e]	0.13 (-0.039; 0.31)	.13	47				
Region							
Asian	ref			ref		ref	
Non-Asian	0.52 (-0.42; 1.47)	.27	47	0.41 (-0.41; 1.23)	.33	0.36 (-0.47; 1.20)	.40
Female (%)	-1.20 (-3.27; 0.87)	.26	38				
Mortality (%)	-0.97 (-2.67; 0.73)	.26	34				
Mechanical ventilation (%)	0.71 (-0.57; 1.99)	.28	27				
Screening							
No	ref	.13		ref		ref	
Yes	0.56 (-0.16; 1.28)		47	-0.019 (-0.70; 0.66)	.96	0.077 (-0.62; 0.77)	.83
Median duration of admission (days)	0.017 (-0.0011; 0.035)	.066	28				
Outcome reported							
PE and DVT	ref						
PE	0.15 (-0.52; 0.81)	.67	47				
DVT	-	-					
Other included	0.36 (-0.17; 0.90)	.18					
Not defined	0.024 (-0.68; 0.73)	.95					
Sample size, n[f]	-0.28 (-0.45; -0.11)	.0012	47	-0.24 (-0.42; -0.050)	.013	-0.29 (-0.45; -0.13)	.0006
Design							
Retrospective	ref			ref		ref	
Prospective	0.39 (-0.11; 0.89)	.12	47	0.42 (-0.087; 0.94)	.10	0.43 (-0.053; 0.91)	.081

Abbreviations: DVT, deep vein thrombosis; FU, follow-up; PE, pulmonary embolism; ROB, risk of bias.

Risk estimates for venous thromboembolism were logit-transformed to meet the assumption of linearity.

[a]number of studies included.

[b]39 studies included.

[c]47 studies included.

[d]transformed to numeric variable by subtracting 1-1-2020 from date of publication.

[e]per unit increase.

[f]per square-rooted(sample size increase) of 10 patients.

TABLE 3 Univariable and multivariable meta-regression in patients with COVID-19 at the ward with sample size as predictor variable.

	Univariable			Multivariable			
				Model 1[b]		Model 2[c]	
Variable	β (95% CI)	*P* value	K[a]	β (95% CI)	*P* value	β (95% CI)	*P* value
Average age, (y)	0.075 (0.015; 0.14)	.014	18	0.11 (0.029; 0.20)	.0085	0.088 (0.013; 0.16)	.022
Date of publication, (d)[d]	-0.0029 (-0.0084; 0.0026)	.31	23				
Impact factor	-0.064 (-0.17; 0.047)	.26	23				
ROB[e]	-0.27 (-0.84; 0.31)	.37	23				
Region							
Asian	ref			ref		ref	
Non-Asian	0.92 (-1.60; 3.43)	.48	23	-2.32 (-4.51; -0.13)	.038	-1.84 (-4.40; 0.71)	.16
Female (%)	-1.83 (-7.87; 4.20)	.55	19	-10.99 (-18.32; -3.65)	.0033	-3.36 (-8.28; 1.56)	.18
Mortality (%)	7.00 (-3.44; 17.43)	.19	18	4.077 (-8.40; 16.55)	.52		
Screening							
No	ref			ref		ref	
Yes	2.13 (1.30; 2.96)	<.0001	23	1.10 (0.054; 2.15)	.039	1.36 (0.30; 2.42)	.012
Median duration of admission (d)	0.020 (-0.045; 0.086)	.54	15				
Outcome reported			23				
PE and DVT	ref						
PE	-1.51 (-3.80; 0.79)	.20					
DVT	0.77 (-0.99; 2.53)	.39					
Other included	-1.17 (-2.41; 0.077)	.066					
Not defined	-1.20 (-2.54; 0.15)	.081					
Sample size, *n*[f]	-0.31 (-0.56; -0.054)	.017	23	-0.43 (-0.79; -0.067)	.020	-0.41 (-0.84; 0.024)	.064
Design							
Retrospective	ref						
Prospective	0.44 (-0.93; 1.80)	.53	23				

Abbreviations: DVT, deep vein thrombosis; FU, follow-up; PE, pulmonary embolism; ROB, risk of bias.

Risk estimates for venous thromboembolism were logit-transformed to meet the assumption of linearity.

[a]number of studies included.

[b]14 studies included.

[c]17 studies included.

[d]transformed to numeric variable by subtracting 1-1-2020 from date of publication.

[e]per unit increase.

[f]per square-rooted (sample size) increase of 10 patients.

Regarding study setting, most COVID-19 articles concerned ICU patients (*n* = 53) [4,6,25,26,27,29,30,40,42,43,46,48–50,52,54,55,57–59,62–66,68,69,73,76,79,83,86,88,93,94,97,98,104,106,108,113,114,116,119,121,123,124,126,130,132,133,135,136] followed by a mix of ICU and ward patients (*n* = 38) [3,38,41,44,45,47,56,61,67,70,75,77,78,80,84,85,90,92,95,96,99,101–103,105,107,109–112,120,122,125,127–129,131,134], and ward patients only (*n* = 27) [6,25–27,40,43,49,51–53,57,59,64,65,69,71–74,86,89,93,94,100,115–117]. In 6 COVID-19 articles, study setting was unclear [39,59,60,81,87,118] In articles reporting on seasonal influenza, 3 concerned ICU patients [35,50,119], 1 related to ward patients [35]. In 2 seasonal influenza articles setting was unclear, as these concerned population-based registry studies [37,59]. Regarding articles on H1N1 influenza, 2 included ICU patients [14,33] and in 2 a mix of ICU and ward patients [13,34]. The sole study on SARS-CoV-1 included ICU patients [12]. Articles concerning viral pneumonia not specified reported either on a mix of ward and ICU patients [36,38] or were in an unclear setting [37].

In 14 COVID-19 articles, a screening strategy for DVT was implemented [27,54,62,71,72,74,88,92,95,100,113,114,117,130], Definitions used for VTE varied from articles reporting on PE only [34,39,44,60,61,66,70,76,81,83,93,103,104,107,109,118,123,126,127,129,133,134] or DVT only [54,56,72,90] to a combination of both [6,12–14,27,28,37,46–51,53,55,57–59,67–69,71,73,74,77,80,82,85,87,89,99,100,106,108,116,117,119,124,128,25,131,132] or other VTE included [6,29,30,38,98,105,113–116,120–122,125,136] (eg, mesenteric or cerebral vein thrombosis). In 15 articles, the definition of VTE was unclear [35–37,41,43,52,59,65,75,78,86,91,92,101,102,110–112,130,135]. An overview of individual study characteristics is provided in Supplementary Table S1.

3.3 | Quality assessment

Overall, study quality was mediocre with median 3 (IQR, 3–4) stars awarded (Supplementary Table S2) according to a modified version of the Newcastle Ottowa Scale. In 66 out of 115 papers 3 or less stars were awarded [12–14,29,30,33,36,38,39,43,45,46,48–51,53–55,59–62,65–67,72,74–76,78–81,85,86,92,93,96,100,101,103,105–109,111,113,119–121,124,126–128,130,131,34,133–135]. Main concerns were that it could not be assured that all participants were free of the outcome of interest at study entry (111[97%]), assessment of the outcome was not clear (56(49%)) and follow-up was poorly described (71[62%]). A detailed overview of risk of bias assessment is provided in Supplementary Table S2.

3.4 | Study characteristics

Study characteristics are provided in Table 1. As explained in the methods, only studies presenting VTE risk stratified by setting (ICU vs ward) are included in the analysis. Various baseline characteristics were missing in a notable number of studies. Patients with COVID-19 and seasonal influenza were roughly of similar age, whereas patients with SARS-CoV-1 and H1N1 were younger. Other characteristics (including mechanical ventilation and sex distribution) were difficult to compare, because of missing data in up to 20% of studies.

3.5 | Analysis within COVID-19 studies

Forest plots summarizing found VTE risks are presented in Supplementary Figures S1–S4.

3.6 | Meta-analysis VTE risk estimates

For ICU patients, random-effects pooled VTE risk was 19.6% (95% CI, 16.2%–23.5%; I^2 = 92.8%) for nonscreening studies and 30.0% (95% CI, 17.9%–45.7%; I^2 = 81.9%) for screening studies (Supplementary Figures S1 and S2). Pooled estimates were similar in sensitivity analyses (Supplementary Table S3). The point estimates for VTE risk varied from 19.2% to 20.1% for nonscreening studies and from 24.9% to 30.0% for screening studies.

For the ward patients, pooled VTE risk was 3.4% (95% CI, 2.4%–4.7%; I^2 = 91.3%) and 22.5% (95% CI, 10.2%–42.7%; I^2 = 91.6%) for nonscreening and screening studies, respectively (Supplementary Figures S3 and S4). In these sensitivity analyses, the VTE risk was consistent with the risk found in the main analysis. This pooled estimate was similar in sensitivity analyses too (Supplementary Table S4). The point estimates for VTE risk varied from 3.4% to 3.5% for nonscreening studies and from 17.7% to 24.4% in screening studies.

3.7 | Meta-regression VTE risk in COVID-19

Results of the analyses exploring heterogeneity are presented in Tables 2 and 3 stratified by hospital setting (ward and ICU). Again, meta-regression was performed with logit-transformed risk estimates.

3.7.1 | ICU studies

In univariable analyses, studies with an earlier date of publication (β= -0.0018 [95% CI, -0.0034; -0.002] per day later), longer hospital admission (β = 0.017 [95% CI, -0.0011; -0.035] per day longer) and smaller sample sizes (β = -0.28 [95% CI, -0.45; -0.11] per square-rooted sample size of 10 patients more) were associated with a higher VTE risk. In multivariable analyses mechanical ventilation, mortality, sex, median duration of admission, risk of bias, impact factor, and outcome definition were not included, because of either missing data or assumed limited effect based on the univariable analysis. Multivariable analyses showed that smaller sample size (model 1: β = -0.24 [95% CI, -0.42; -0.050] and model 2: β = -0.29 [95%

CI, -0.45; -0.13] per square-rooted sample size of 10 patients more) was independently associated with a higher VTE risk. Final models are presented in Table 2. Remaining I^2 was 85.2% and 80.0% in multivariable model 1 and 2, respectively.

3.7.2 | Ward studies

In univariable analyses, a higher average age (β = 0.075 [95% CI, 0.015; 0.14] per year), presence of VTE screening strategies (β = 2.13 [95% CI, 1.30; 2.96]), and smaller sample size (ß = -0.31 [95% CI −0.56; -0.054] per square-rooted sample size of 10 patients more), were associated with a higher VTE risk. Again, median duration of admission, sex, risk of bias, date of publication, impact factor, design, and outcome definition were left out of the multivariable analysis, because of missing data and assumed limited effect based on the univariable analysis. Similar to ICU studies, multivariable models showed that smaller sample size (model 1: β= -0.43 [95% CI, -0.79; -0.067] and model 2: β = -0.41 [95% CI, -0.84; -0.024] per square-rooted sample size of 10 patients more) was independently associated with a higher VTE risk. Final models are presented in Table 3. Remaining I^2 was 87.3% and 77.3% in multivariable model 1 and 2, respectively.

A summary of the association between sample size and VTE risk is presented in Figure 2 for univariable and multivariable analyses. A lower sample size was associated with a higher VTE risk estimate.

3.8 | Sensitivity analyses

3.8.1 | ICU studies

Findings of the sensitivity analyses correcting for incorrect censoring showed similar results as described above (Supplementary Tables S5 and S7). The same was the case when a continuity correction of +1 was applied to the main analysis (Supplementary Table S9) and to the analysis correcting for incorrect censoring (Supplementary Tables S11 and S13). When we repeated the main analysis with exclusion of overlapping cohorts, the effect of sample size on VTE risk was higher (model 1: -0.94 [95% CI, -1.60; -0.26], model 2: -0.54 [95% CI, -0.54; -0.28]) (Supplementary Table S15).

3.8.2 | Ward studies

In this stratum, sensitivity analysis for incorrect censoring (Supplementary Tables S6 and S8) and continuity correction (Supplementary Tables S10, S12 and S14) showed similar correction compared to the main analysis too. Estimates for sample size were somewhat different when excluding overlapping cohorts (model 1: -0.23 [95% CI -0.88; 0.42], model 2: -0.58 [95% CI -1.30; 0.19]).

3.9 | Comparison of VTE risk estimates in COVID-19 to other viruses

As the meta-regression exploring heterogeneity in VTE risk estimates within COVID-19 revealed an association between sample size and VTE risk, we also determined pooled risk estimates in a fixed-effects model. By doing so, the contribution of small studies reporting spuriously high VTE risks to the pooled risk estimate is less prominent than in a random-effects model. Furthermore, pooled VTE risk for ICU patients with seasonal influenza (9.0% [95% CI, 5.6%–14.2%], I^2=39.7%) and H1N1 (29.1% [95% CI, 3.7%–81.4%], I^2=77.9%) were determined. Only one study provided a VTE risk for influenza patients admitted to the ward, 2.4% (95% CI, 2.1%–2.7%) and for SARS-CoV-1 patients at the ICU, 47.8% (95% CI, 34.0%–62.0%), Pooled estimates are shown in Figure 3. Forest plots of the meta-analyses per virus type are shown in Supplementary Figures S1–S6.

4 | DISCUSSION

In the current systematic review and meta-analysis, we found a higher risk of VTE in patients admitted to critical care with COVID than among those admitted to the ward in studies that did not perform screening. On the other hand, VTE risk seemed to be similar between patients admitted to the ICU or ward when screening was applied. Meta-regression showed evidence of publication bias, as sample size was strongly associated with VTE risk. Our findings suggest that spurious reports of a high VTE risk, originating from small studies, were more likely to be published than small studies with a low VTE risk. However, a considerable amount of unexplained heterogeneity was still present after fitting multivariable meta-regression models. Clinical diversity, resulting from different patient selection, could not be explored properly as the source of heterogeneity, because report of variables reflecting this (eg, age, mortality, thromboprophylaxis regime, and duration of hospital admission) were insufficiently reported. Pooled estimates for COVID-19 seemed to be higher than for seasonal influenza. H1N1 influenza and SARS-CoV-1 might be associated with a risk of VTE comparable to COVID-19. However, these comparisons should be interpreted very cautiously, as risk estimates varied widely, available data on other viruses than COVID-19 were sparse, and profound differences in patient selection and methodology, including definition of VTE, were present.

Our findings regarding the risks dependent on disease severity and statistical heterogeneity were generally in line with other meta-analyses. Indeed, other literature has also suggested study quality and sample size explaining heterogeneity. Longchamp et al. [137] found in subgroup analyses that a lower VTE risk was present in high quality studies. In addition, Mansory et al. [138] and Tan et al. [17] showed in their meta-regression that a larger sample size was associated with a lower VTE risk. In the current analysis, we attempted to explain heterogeneity more broadly by not only performing multivariable meta-regression but also by harmonizing VTE risk estimates

by excluding studies with insufficiently complete data and inflated VTE risk estimates due to incorrect use of survival analysis. Specifically, in the latter, we would expect to trim spuriously high VTE risk estimates, thus lowering heterogeneity.

Several limitations in our analysis should be considered. We found substantial missing data about clinical characteristics, therefore, we cannot be confident about whether we captured heterogeneity due to patient characteristics. For instance, data regarding age, sex, and mortality rates were missing in up to 30% of studies. There is also inherent between-study heterogeneity of what constitutes admission to ward and/or critical care. We attempted to define ICU and ward studies in accordance with the WHO COVID-19 guidance in which studies including critically ill patients were considered ICU studies. All other studies were included in stratum ward, which could potentially vary from mild to severe disease, as long as it did not entail ICU admission. We cannot exclude misclassification, as some patients might have been admitted to wards for quarantine purposes early in the pandemic, and some patients with severe COVID might only have been admitted to the ICU for close monitoring. Furthermore, definitions of VTE and use of thromboprophylaxis varied between studies. Again, we could not account for this as specifics on this were not reported consistently.

Although our finding that estimated VTE risk was associated with study sample size strongly suggests publication bias, it is important to consider confounding or alternative explanations for these findings. The predominance of small studies to report high estimates may compound studies executed during surges of the pandemic. Indeed, there is some evidence that COVID-19 mortality was low outside of hospital surges, reflecting quality of care, which might impact VTE risk. What's more, evolving awareness of VTE risk may have not only led to a shift in thromboprophylaxis, but also diagnostic practice and thus lead to a shift in the detection of VTE before patients are admitted to receive high levels of care (ie, diagnosis of VTE in the emergency department will lower the proportion of COVID related VTE diagnosed in the ward), shifting the relative timing of VTE detection to less intensive levels of care. It is possible that practice in larger studies reflects this evolution in practices more than small studies from single centers. Finally, we cannot exclude that larger studies include a hospital population that is inherently less susceptible to VTE.

This issue of shifting susceptibility profile in the population extends also to any comparison of SARS-COV2 VTE risk with seasonal influenza, including the comparisons among populations with different host-pathogen relationship with regards to susceptibility of the populations under study. Further research should evaluate whether increasing population immunity, either vaccine or infection-acquired, will modulate overall, in-hospital and ICU VTE risks.

The results of our systematic review provide some important lessons for clinicians and policymakers. In a rapidly evolving pandemic of an unknown virus, it is comprehensible and some instances necessary, that new treatment modalities are included in preliminary data. However, eventually good-quality data in unselected patients with COVID-19 with clear methodological definitions are still necessary to gain more precise insight into the VTE risk. In the first place, to guide therapeutic actions, but also to put VTE risk in COVID-19 in perspective of other viral pneumonia. Overall, it should be considered to re-evaluate the VTE risk in COVID-19 in a changed landscape with evolving virulence with new virus-strains, host-pathogen relationship and thromboprophylaxis measures, compared with the data presented in this meta-analysis. Joint efforts in multicenter studies are needed for this.

5 | CONCLUSION

Despite numerous reports on VTE risk in COVID-19, pooled reported risk estimates should be interpreted with caution as a high degree of heterogeneity is presented among studies. Heterogeneity may arise from differences in patient selection and methodology. This hinders comparison to VTE risk in other viral pneumonia. More importantly, analyses exploring the sources of heterogeneity indicated that sample size was strongly correlated to reported VTE risk estimates in COVID-19, indicating the presence of publication bias.

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AUTHOR CONTRIBUTIONS

S.B. conceptualized the study, performed the search, risk of bias assessment, the analysis and wrote the manuscript. C.C. performed the search, risk of bias assessment and reviewed the manuscript. V.T. reviewed the manuscript. J.B.H. conceptualized the study, participated in the analysis and reviewed the manuscript. K.M. conceptualized and supervised the study, was third reviewer in case of disagreements in study selection and data extraction and reviewed the manuscript.

RELATIONSHIP DISCLOSURE

S.B., C.C., J.B.H., and V.T. have nothing to disclose. K.M. reports consulting fees from Uniqure, honoraria from Alexion, Bayer and CSL Behring, participation on a data safety monitoring board or advisory board from Octapharma and Bayer and an unpaid chair position at the Dutch Society of Haematology. All payments were made to the institution.

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SUPPLEMENTARY MATERIAL

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