High Incidence of Venous Thromboembolism in Patients with Coronavirus Disease 2019: A Call for Improved Awareness and Prevention

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Keywords: Venous Thromboembolism, COVID-19, Incidence

Posted Date: August 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-60522/v1

Abstract

Background: An increased risk of venous thromboembolism (VTE) in patients with coronavirus disease 2019 (COVID-19) has been reported. We performed a meta-analysis to evaluate the prevalence of VTE in COVID-19 patients.

Methods: The PubMed and Embase databases were searched for studies reporting VTE in COVID-19 patients up to June 27, 2020. The selected studies were predefined into the "suspected screening group" and the "routine screening group." The VTE prevalence was calculated using random-effect models.

Results: We selected 20 studies including a total of 2763 COVID-19 patients. In 2203 COVID-19 patients from the suspected screening group, the pool VTE incidence was 15.2% (95% confidence interval [CI]: 10.5–21.6%). In 560 COVID-19 patients from the routine screening group, the VTE prevalence was 40.8% (95% CI: 20.6–64.7%). Furthermore, the VTE incidence of critically ill COVID-19 patients from the two groups was 19.6% and 61.4%, respectively, which indicates that critically ill COVID-19 patients were more susceptible to VTE.

Conclusions: A high incidence of VTE was observed in COVID-19 patients, especially in severe cases. The incidence of VTE in COVID-19 patients from the routine screening group was higher than that in patients from the suspected screening group. This indicates that a lower threshold of suspicion to perform VTE imaging tests may be reasonable and there is an urgent need to adapt a regular screening strategy for VTE.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to a global health crisis. Emerging evidence shows that patients with COVID-19, especially those who are severely ill, have a variety of risk factors for venous thromboembolism (VTE), including infection, immobilization, and mechanical ventilation [1]. The high mortality of COVID-19 patients has been presumed to be partly due to unrecognized pulmonary embolism (PE) and pulmonary in situ thrombosis[2]. Several studies have reported the incidence of VTE in COVID-19 patients [1, 3–6]. Accurate knowledge of the incidence of VTE in COVID-19 patients is important for decision making with respect to anticoagulation treatment. However, to our knowledge, no previous meta-analysis has estimated the global prevalence of VTE in COVID-19 patients. We therefore performed a meta-analysis and systematic review of studies investigating the prevalence of VTE in patients with COVID-19.

2. Methods

2.1. Search strategy

To find relevant studies, the international databases PubMed and Embase were searched for articles published until June 27, 2020. We performed our search with a search string focusing on "pulmonary embolism," "venous thromboembolism," "pulmonary thromboembolism," "deep venous thrombosis," "2019 novel coronavirus," "COVID 19," "COVID-19," "SARS-CoV-2," "2019 novel coronavirus," "novel coronavirus

pneumonia” or “2019-nCoV,” and “coronavirus disease-19.” These key words were translated specifically for each database. We additionally performed a manual search of references of the identified relevant original and review articles. The reporting of this meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [7].

2.2 Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) studies that included laboratory-proven COVID-19 patients or clinically confirmed COVID-19 patients screened by a multidisciplinary team, (2) cohort, case-control and cross-sectional studies reporting the incidence of image-proven VTE in COVID-19 patients, and (3) articles published in the English language. Conversely, the exclusion criteria were as follows: (1) abstracts, reviews, expert opinion articles, conference proceedings, and books; (2) studies with insufficient data for the calculation of incidence; (3) low-quality studies according to the Newcastle-Ottawa Scale (NOS) criteria or Agency for healthcare Research and Quality (AHRQ) criteria; and (4) studies that only chose the patients examined by computer tomography pulmonary angiography (CTPA) as the subjects.

2.3. Data extraction and quality assessment

Two reviewers independently screened and evaluated the literature. Any disagreements were resolved through a discussion. The quality of the included papers was assessed using the NOS, with the scores ranging from 0 to 9. Cohort studies or case-control studies with a score of≥5 were considered high-quality studies. Cohort studies or case-control studies with a score of <5 were considered low-quality studies and excluded from the meta-analysis. Cross-sectional studies with a score of ≥7 were considered high-quality studies. Studies with a score of <7 were considered low-quality studies and excluded from the meta-analysis. The following information was extracted: name of the first author, sample size, study type, diagnostic method for VTE, incidence of VTE in COVID-19 patients, and anticoagulant therapy.

2.4. Statistical analysis

Heterogeneity was evaluated using Cochran’s Q test and I^2 statistics. On the basis of the Q test, a random-effect model was used when the P value was < 0.1. I^2 statistics were utilized to measure the extent of the overall variation due to heterogeneity. I^2 statistics of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively. When substantial heterogeneity was observed ($I^2 > 50\%$), the sources of the heterogeneity was investigated using subgroup analyses. We investigated the possibility of publication bias using Egger and Begg tests for asymmetry. All statistical analyses were performed using the meta package in R software (3.3.2).

3. Results

3.1. Characteristics of the included studies

The initial search yielded 558 articles from the different databases. All papers were screened by reading the abstracts, and 173 articles were eliminated for being duplicates found in different databases. After evaluating the full texts, studies presenting data that were irrelevant to our aim were excluded. This left 20 original research articles for inclusion in the meta-analysis and systematic review (Fig. 1). The characteristics of the included studies are provided in Table 1.

Table 1
Characteristics of the included articles for the meta-analysis

Study	Sample Size and Characteristics	Study Type	Diagnostic Method	Incidence	Proportions of Patients Received Anticoagulant Therapy	Quality
Suspected screening						
Ioka et al. Netherlands	223 ICU patients	Cohort study	CTPA for PE, Ultrasonography for DVT	VTE (28, 15.2%) PE (25, 13.6%) DVT (3, 1.6%)	100%	6
Helms et al. France	150 ICU patients	Cohort study	CTPA for PE	VTE (25, 16.7%) PE (25, 16.7%) DVT (3, 2%)	100%	8
Lodigiani et al. Italy	388, (General ward 327, ICU 61)	Cohort study	CTPA for PE, Ultrasonography for DVT	VTE (16, 4.1%) PE (10, 2.6%) DVT (6, 1.5%)	100% for ICU patients, 75% for general ward patients	5
Cui et al. China	81 ICU patients	Cohort study	Ultrasonography for DVT	VTE (20, 24.7%) DVT (20, 24.7%)	0%	5
Middeldorp et al. Netherlands	198 (General ward 123, ICU 75)	Cohort study	CTPA for PE, Ultrasonography for DVT	VTE (39, 19.7%) PE (13, 6.6%) DVT (26, 13.1%)	93.9%	8

ICU: Intensive Care Unit; CTPA: Computer Tomography Pulmonary Angiography; VTE: Venous Thrombus Embolism; PE: Pulmonary Embolism;
DVT: Deep Venous Thrombosis.

Study	Sample Size and Characteristics	Study Type	Diagnostic Method	Incidence	Proportions of Patients Received Anticoagulant Therapy	Quality
Al-Samkari et al. America	400 (General ward 256, ICU 144)	Cohort study	Confirmed radiographically	VTE (19,4.8%) PE (10, 2.5%) DVT (10, 2.5%)	100%	6
Desborough et al. England	66 ICU patients	Case-control study	CTPA for PE, Ultrasonography for DVT	VTE (10, 15.2%) PE (5,7.6%) DVT (6, 9.1%)	100%	8
Fraissé et al. France	92 ICU patients	Case-control study	NO	VTE (31, 33.7%)	100%	8
Hippensteel et al. America	91 ICU patients	Cohort study	CTPA for PE, Ultrasonography for DVT	VTE (24, 26.4%) PE (5, 5.5%) DVT (19, 20.9%)	54.3%	8
Poissy et al. France	107 ICU patients	Cohort study	CTPA for PE	VTE (24, 22.4%) PE (22, 20.6%) DVT (5, 4.7%)	100%	7
Maatman et al. America	109 ICU patients	Case-control study	Contrast-enhanced CT for PE, ultrasonography for DVT	VTE (31, 28.4%) PE (5, 4.6%) DVT (30, 37.5%)	100%	7
ICU: Intensive Care Unit; CTPA: Computer Tomography Pulmonary Angiography; VTE: Venous Thrombus Embolism; PE: Pulmonary Embolism;						
DVT: Deep Venous Thrombosis.						

Study	Sample Size and Characteristics	Study Type	Diagnostic Method	Incidence	Proportions of Patients Received Anticoagulant Therapy	Quality
Stoneham et al. England	208 patients	Case-control study	Confirmed radiographically	VTE (21, 7.7%) PE (16, 5.8%) DVT (5, 1.8%)	100%	8
Thomas et al. England	63 ICU patients	Case-control study	CTPA for PE	VTE (5, 7.9%) PE (5, 7.9%)	100%	7
Routine screening						
Zhang et al. China	143 (General ward 128, ICU 15)	Cross-sectional study	Ultrasonography for DVT	VTE (66, 46.2%) DVT (66, 46.2%)	78.3%	9
Artifoni et al France	71 (General ward 58, ICU 13)	Case-control study	Ultrasonography for DVT	DVT (15, 21.1%)	99%	6
Demelo-Rodriguez et al Spain	156 general ward patients	Cross-sectional study	Ultrasonography for DVT	VTE (23, 14.7%) DVT (23, 14.7%)	98%	9
Criel et al Belgium	82 (General ward 52, ICU 30)	Cross-sectional study	Ultrasonography for DVT	VTE (6, 7.3%) DVT (6, 7.3%)	95.1%	8
Nahum et al France	34 ICU patients	Cross-sectional study	Ultrasonography for DVT	VTE (27, 79.4%) DVT (27, 79.4%)	100%	9

ICU: Intensive Care Unit; CTPA: Computer Tomography Pulmonary Angiography; VTE: Venous Thrombus Embolism; PE: Pulmonary Embolism;

DVT: Deep Venous Thrombosis.

Study	Sample Size and Characteristics	Study Type	Diagnostic Method	Incidence	Proportions of Patients Received Anticoagulant Therapy	Quality
Llitjos et al France	26 ICU patients	Cohort study	Ultrasonography for DVT	DVT (14, 53.8%)	100%	7
Ren et al China	48 ICU patients	Cross-sectional	Ultrasonography for DVT	VTE (41, 85.4%) DVT (41, 85.4%)	97.9%	9
ICU: Intensive Care Unit; CTPA: Computer Tomography Pulmonary Angiography; VTE: Venous Thrombus Embolism; PE: Pulmonary Embolism;						
DVT: Deep Venous Thrombosis.						

Thirteen studies used lower-extremity venous ultrasound scanning or CTPA to confirm the diagnosis of VTE only in the presence of a clinical suspicion, and we predefined this study group as the “suspected screening group.”[1, 3–6, 8–15] Seven studies routinely screened VTE in every patient using lower-extremity venous ultrasound scanning, and this study group was predefined as the “routine screening group.”[16–22] Our primary aim was to determine the incidence of VTE in COVID-19 patients in two predefined cohort subtypes: (1) suspected screening group and (2) routine screening group.

3.2. Prevalence of VTE in COVID-19 patients from the suspected screening group

Figure 2 shows the incidence of VTE in COVID-19 patients when screening for VTE was performed only in the presence of a clinical suspicion. The incidence ranged from 4.1–33.7%, with a pooled incidence of 15.2% (95% confidence interval [CI]: 10.5–21.6%) (Fig. 2). The highest pooled incidence was observed in France (33.7%), and the lowest incidence was seen in Italy (4.1%). A substantial amount of heterogeneity was found among the studies (I^2 = 91.0%, $P < 0.01$) (Fig. 2). However, there was no indication of publication bias, as evidenced by nonsignificant results in Egger and Begg tests (P = 0.388 and 0.329, respectively).

Similarly, Fig. 3A shows that the pooled incidence rate of deep venous thrombosis (DVT) in COVID-19 patients from the suspected screening group was 7.2% (95% CI: 4.5–111.3%), using random-effect models. Figure 3B shows that the pooled incidence rate of PE in COVID-19 patients from the suspected screening group was 7.2% (95% CI: 4.5–11.3%), with rates in individual studies varying from 2.5–20.6%, using random-effect models.

We performed subgroup analyses to investigate the sources of heterogeneity. The subgroup analyses were conducted across various clinically relevant subgroups and methodological factors, including population source, geographic location, study quality, and number of cases. Statistically significant heterogeneity was observed in all subgroups (I^2 > 50%, $P < 0.001$). Although we did not find clear sources of heterogeneity, the

subgroup analyses provided additional insights. The intensive care unit (ICU) subgroup tended to yield a higher incidence (21.1%, 95% CI: 16.5–26.5%) than the ICU plus general ward subgroup (7.6%, 95% CI: 3.4–16.1%) (Online Figure I).

To further clarify the incidence of VTE in ICU-admitted COVID-19 patients from the suspected screening group, we extracted detailed information on the study population and recalculated the pooled incidence. Of the 2203 admitted COVID-19 patients, 1223 were admitted to the ICU. The recalculated incidence of VTE was 19.6% (95% CI: 14.3–26.4%) (Fig. 4), which indicates that ICU-admitted COVID-19 patients were more susceptible to VTE.

3.3. Prevalence of VTE in COVID-19 patients from the routine screening group

Figure 5 shows the incidence of VTE in COVID-19 patients when routine screening of VTE was performed in all patients. The incidence ranged from 7.3–85.4%, with a pooled incidence of 40.8% (95% CI: 20.6–64.7%). A substantial amount of heterogeneity was found among the studies ($I^2 = 95.0\%$, $P < 0.01$) (Fig. 5).

We performed subgroup analyses using a number of moderators (population source, geographic location, study quality, and number of cases) to assess whether they can explain some of the heterogeneity. These factors did not explain the heterogeneity. In addition, consistent with the prevalence in the routine screening group, our subgroup analyses indicated that patients in the ICU subgroup had a higher incidence of DVT (74.7%, 95% CI: 52.9–88.6%) than those in the ICU plus general ward subgroup (21.6%, 95% CI: 6.9–50.3%) and those in the general ward subgroup (14.7%, 95% CI: 10.0–21.2%) (Online Figure II).

A total of 216 ICU-admitted patients from six studies in the routine screening group were evaluated to prospectively determine the incidence of VTE among ICU patients. The incidence of VTE in ICU-admitted COVID-19 patients was 61.4% (95% CI: 40.3–78.9%) (Fig. 6), which demonstrates a high incidence rate of VTE in ICU patients from the routine screening group. This finding supports considering routine screening for VTE in ICU-admitted COVID-19 patients in the pandemic context.

4. Discussion

This timely rapid meta-analysis provides a comprehensive synthesis of the existing evidence highlighting the high prevalence rates of VTE in COVID-19 patients. Our main findings were the VTE incidences of 15.2% and 40.8% in two predefined groups: suspected screening group and routine screening group, respectively. Furthermore, our analysis revealed that COVID-19 patients admitted to the ICU ward had a higher VTE prevalence.

To our knowledge, this is the first meta-analysis study to assess the incidence of VTE in patients with COVID-19. Our meta-analysis reported that the incidence of VTE in COVID-19 patients from the suspected screening group was 15.2% (95% CI: 10.5–21.6%) and that in COVID-19 patients from the routine screening group was 40.8% (95% CI: 20.6–64.7%). Our findings indicate a high prevalence of VTE in COVID-19

patients, which is consistent with previous clinical and post-mortem reports. Histologic analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were nine times as prevalent in patients with COVID-19 as in patients with influenza ($P < 0.001$) [23]. This confirms that VTE is an important complication in COVID-19 patients. Physicians need to recognize the significant possibility of VTE in COVID-19 patients and should maintain a low threshold for investigating this complication in all patients. The concrete mechanisms underlying the increased risk of VTE in COVID-19 patients are not yet identified. Several mechanisms may explain the hypercoagulability in COVID-19 patients, which may involve multiple pathogenetic mechanisms. Endothelial cells are known to play an important role in regulating hemostasis, fibrinolysis, and vessel wall integrity. Profound hypoxemia in the pulmonary capillaries may induce endothelial dysfunction and platelet dysfunction [24]. Endothelial cell injury activates a large number of pro-inflammatory cytokines, contributing to microvascular thrombosis including plugging of the pulmonary microvasculature and the occurrence of VTE [25, 26]. A better knowledge of the pathogenesis of abnormal coagulation in COVID-19 patients is urgently needed to provide the potential basis of targeted treatments.

VTE is a common complication in the ICU. Critically ill patients are prone to developing VTE as they are susceptible to both general risk factors of VTE and risk factors specific to ICU patients, such as sedation, immobilization, and vasopressor use [27]. As mentioned in Sect. 3, COVID-19 patients in the ICU were more susceptible to VTE than non-ICU patients, which is in agreement with the previous study. However, the prevalence of VTE in COVID-19 patients in the ICU seemed to be in the higher range than that in published reports on ICU patients admitted for other disease conditions [28–30]. In a meta-analysis of seven studies including 1783 ICU patients, the mean rate of VTE diagnosis was 12.7% (95% CI: 8.7–17.5%) [31]. In our meta-analysis, the incidence of VTE in ICU-admitted COVID-19 patients was 19.6% (95% CI: 14.3–26.4%). A previous study identified that abnormal coagulation in critically ill COVID-19 patients is associated with a poorer outcome, indicating that VTE may influence the outcome of critically ill patients with COVID-19[32]. However, the relationship between VTE and the prognosis of COVID-19 patients needs further studies.

The clinical value of ultrasound screening of the lower extremities in ICU patients with COVID-19 is a matter of debate. Our meta-analysis revealed that the VTE incidence was 40.8% (95% CI: 20.6–64.7%) in the routine screening group, which was much higher than that in the suspected screening group. In addition, the incidence of VTE in ICU-admitted COVID-19 patients routinely screened for VTE was as high as 61.4% (95% CI: 40.3–78.9%). A recent autopsy study found DVT in 7 of 12 patients (58%) in whom VTE was not suspected before death, and PE was the direct cause of death in 4 patients [33]. This suggests that the incidence may have been highly overlooked owing to the low number of specific imaging tests performed. From the above, when hemodynamic deterioration occurs in a patient with COVID-19, VTE, especially PE, should always be suspected. It is important to routinely screen for VTE in COVID-19 patients, particularly in severe cases.

Almost all patients from 19 of the 20 included studies underwent thromboprophylaxis. However, the patients, especially those who were seriously ill, had a high incidence of VTE despite the application of thromboprophylaxis. Thus, physicians should maintain a high suspicion for VTE in COVID-19 patients, even when VTE prophylaxis had been performed. A previous meta-analysis has been conducted to determine

whether antithrombotic therapies improve the outcomes of COVID-19. Overall, the meta-analysis identified a small number of studies, each with serious methodological limitations or inadequate reporting. It indicated that new evidence on thromboembolism in COVID-19 does not warrant a change in the current guidelines on thromboprophylaxis among COVID-19 patients [34]. The results implied that prospective studies on thromboprophylaxis for hospitalized patients with COVID-19 are urgently needed. Additional studies investigating whether higher doses of heparinoids or combination prophylaxis with both heparinoids and mechanical devices may be more effective in patients with COVID-19 are also required.

Our study had several limitations. First, most of the included studies had a small sample size. Second, the heterogeneity among the studies was high in the analysis of the VTE incidence. We failed to find clear sources of heterogeneity through subgroup analyses. Several sources of heterogeneity should be considered in the design and conduct of the individual studies. We postulated that the potential sources of heterogeneity may be related to the different population sources, thromboprophylaxis use, and VTE screening strategies among the included studies. Accordingly, the results need to be interpreted with caution.

5. Conclusions

In conclusion, our meta-analysis and systematic review found a high incidence of VTE in COVID-19 patients, especially in severe cases. A lower threshold of suspicion to perform VTE imaging tests may be reasonable, and there is an urgent need to adapt a regular screening strategy for VTE.

Abbreviations

VTE: venous thromboembolism; COVID-19: coronavirus disease 2019; CI: confidence interval; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; PE: pulmonary embolism; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; NOS: the Newcastle-Ottawa Scale criteria; AHRQ: Agency for healthcare Research and Quality; CTPA: computer tomography pulmonary angiography; ICU: Intensive care unit; DVT: deep venous thrombosis;

Declarations

Acknowledgements

Not applicable

Authors’ contributions

Zhenguo Zhai conceived and designed the study. Meng Zhang and Yunxia Zhang analyzed the data and wrote the manuscript. Wei Qin, Yimin Wang, Zhu Zhang and Chenghong Li were involved in the revision of the manuscript. All the authors approved the final version to be published.

Funding

This study was funded by the Chinese Academy of Engineering emergency research and cultivation project for COVID-19 (2020-KYGG-01-05), the National Key Research and Development Program of China (nos. 2016YFC0905600 and 2016YFC0901104), and the CAMS Innovation Fund for Medical Sciences (no. 2018-I2M-1-003).

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

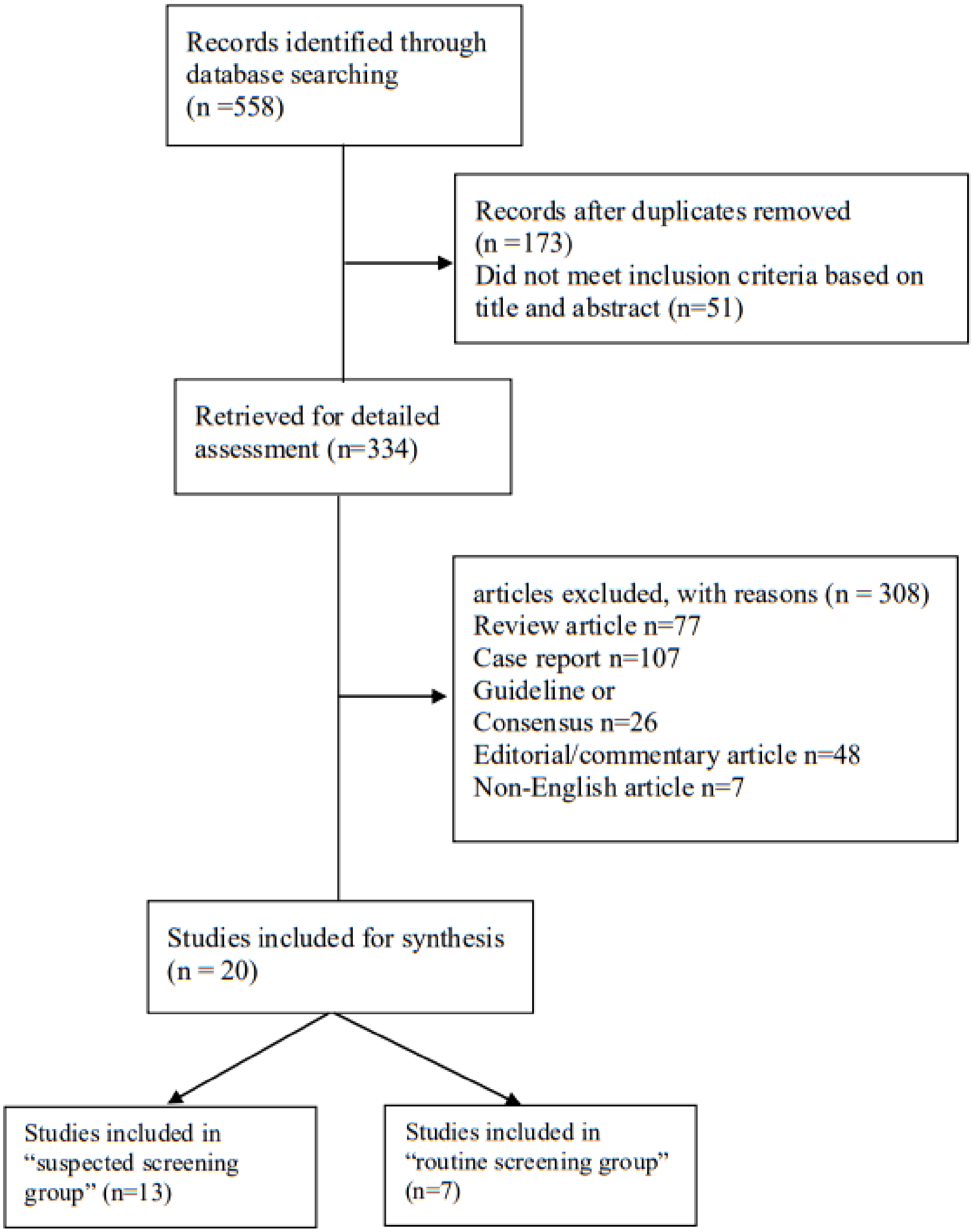

Figure 1

Flowchart for selection of included studies

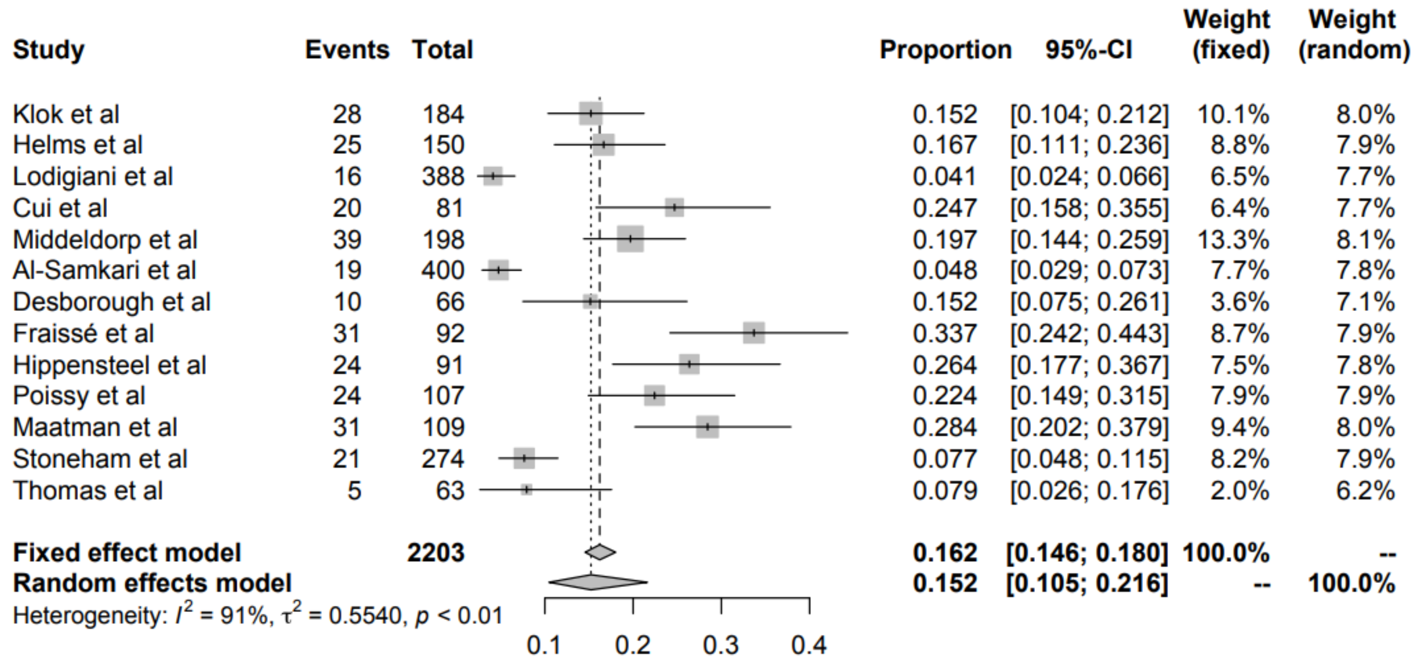

Figure 2

Prevalence of VTE in COVID-19 patients from the suspected screening group. VTE, venous thromboembolism; COVID-19, coronavirus disease 2019.

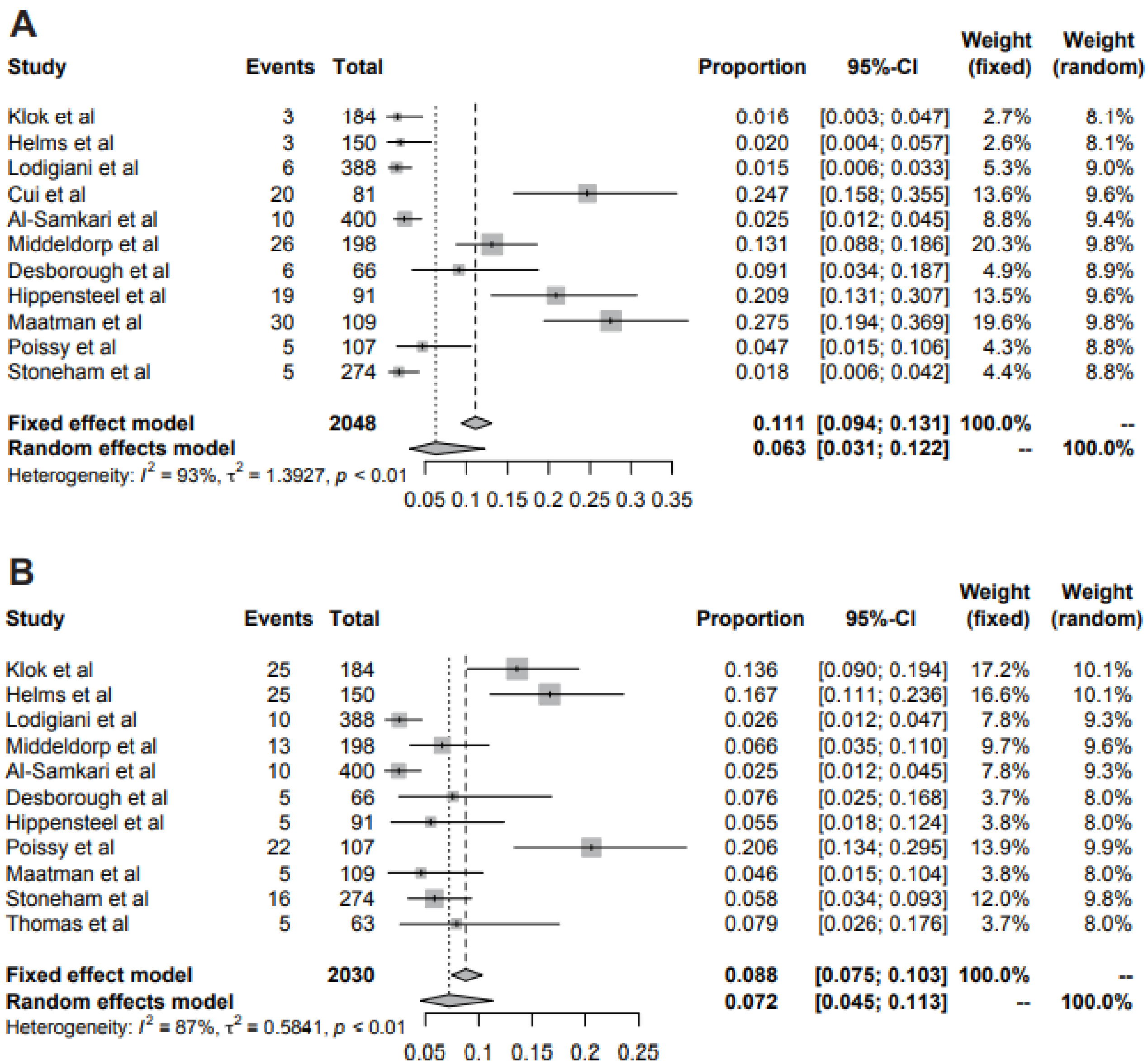

Figure 3

Prevalence of PE and DVT in COVID-19 patients from the suspected screening Prevalence of PE and DVT in COVID-19 patients from the suspected screening group. A. Prevalence of PE in COVID-19 patients from the suspected screening group. B. Prevalence of DVT in COVID-19 patients from the suspected screening group. PE, pulmonary embolism; DVT, deep venous thromboembolism; COVID-19, coronavirus disease 2019.

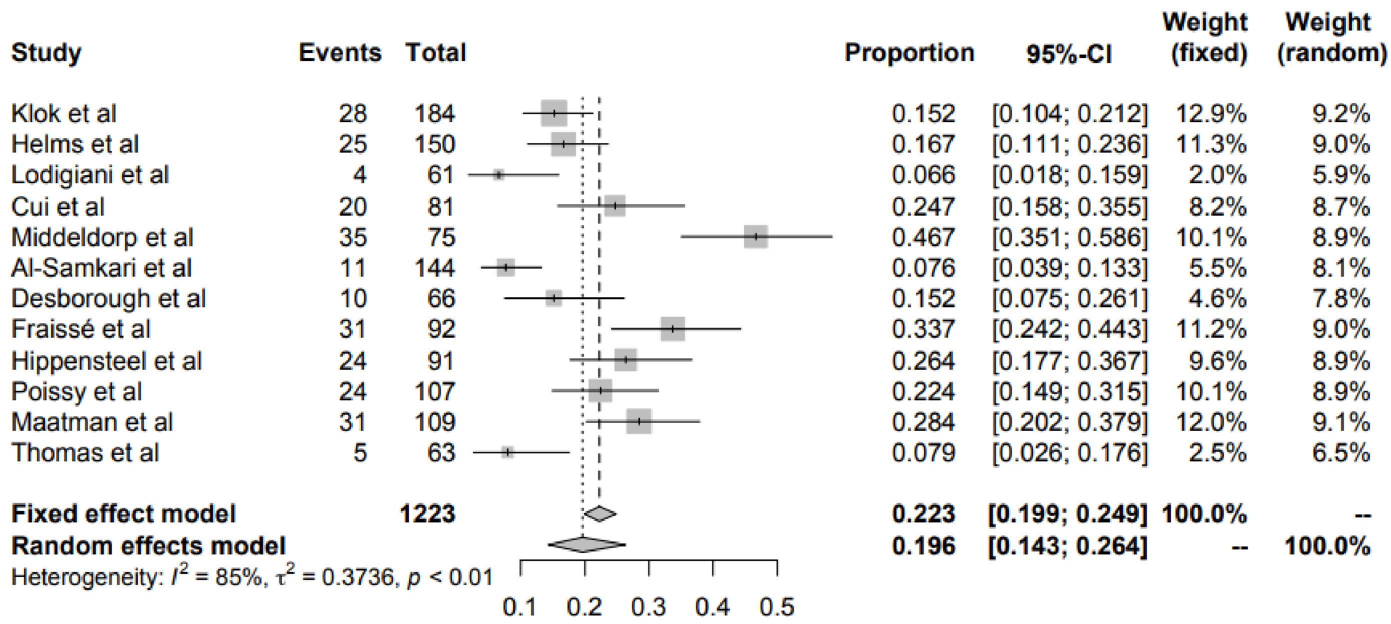

Figure 4

Prevalence of VTE in ICU-admitted COVID-19 patients from the suspected screening group. VTE, venous thromboembolism; COVID-19, coronavirus disease 2019.

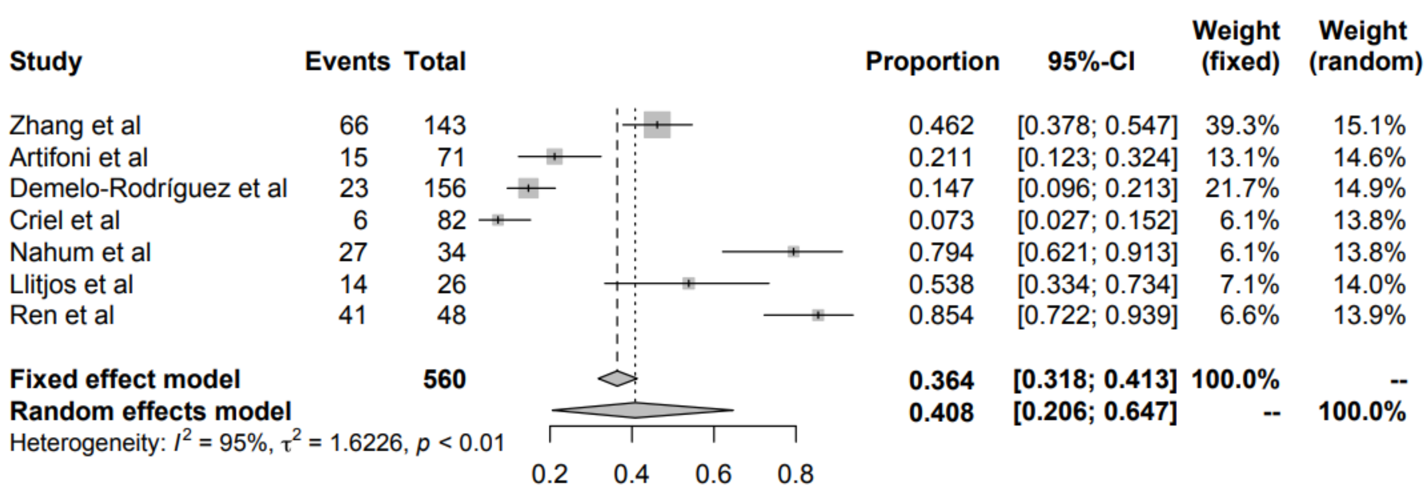

Figure 5

Prevalence of VTE in COVID-19 patients from the routine screening group. VTE, venous thromboembolism; COVID-19, coronavirus disease 2019.

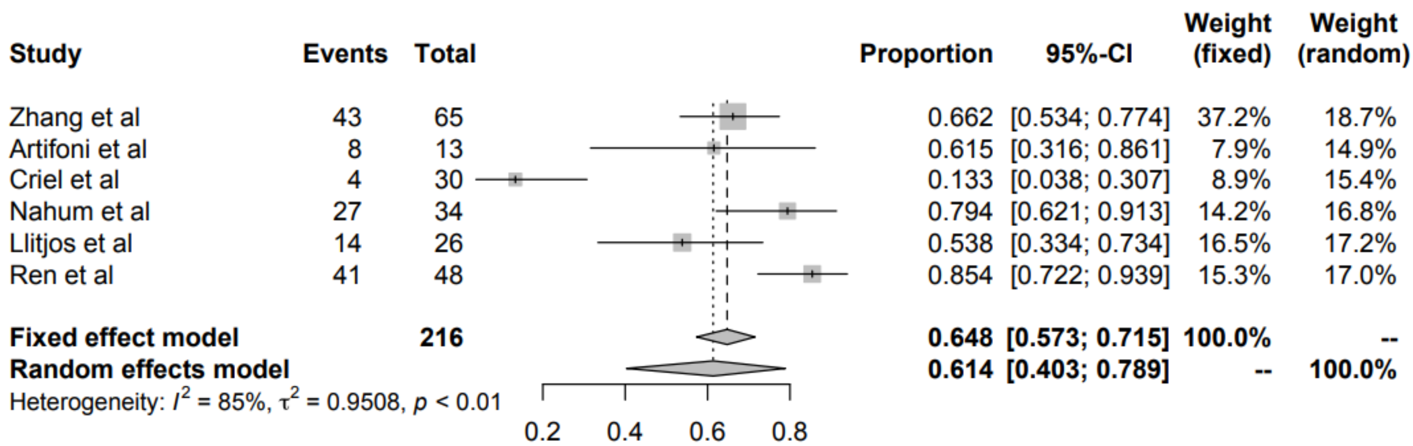

Figure 6

Prevalence of VTE in ICU-admitted COVID-19 patients from the routine screening group. VTE, venous thromboembolism; COVID-19, coronavirus disease 2019.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- OnlineFigureII.pdf
- OnlineFigureI.pdf