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Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis

Short title: Risk of thrombosis in COVID-19

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Essentials

- High rates of venous thromboembolism (VTE) have been reported in COVID-19
- We conducted a systematic review to estimate the VTE prevalence in COVID-19 patients
- 22.7% of COVID-19 patients treated at the intensive care unit (ICU) suffer from VTE
- Risk in non-ICU hospitalized patients is substantial and 8% develop VTE

Abstract

Background

Venous thromboembolism (VTE) is frequently observed in patients with coronavirus disease 2019 (COVID-19). However, reported VTE-rates differ substantially.

Objectives

We aimed at evaluating available data and estimating the prevalence of VTE in COVID-19 patients.

Methods

We conducted a systematic literature search (MEDLINE, EMBASE, WHO COVID-19 database) to identify studies reporting VTE-rates in COVID-19 patients. Studies with suspected high risk of bias were excluded from quantitative synthesis. Pooled outcome rates were obtained within a random effects meta-analysis. Subgroup analyses were performed for different settings (intensive care unit (ICU) vs. non-ICU hospitalization and screening vs. no screening) and the association of D-dimer levels and VTE-risk was explored.

Results

Eighty-six studies (33,970 patients) were identified and 66 (28,173 patients, mean age: 62.6 years, 60% men, 20% ICU-patients) were included in quantitative analysis. The overall VTE-prevalence estimate was 14.1% (95%CI 11.6-16.9), 40.3% (95%CI 27.0-54.3) with ultrasound-screening and 9.5% (95%CI 7.5-11.7) without screening. Subgroup analysis revealed high heterogeneity, with a VTE-prevalence of 7.9% (95%CI 5.1-11.2) in non-ICU and 22.7% (95%CI 18.1-27.6) in ICU patients. Prevalence of pulmonary embolism (PE) in non-ICU and ICU patients was 3.5% (95%CI 2.2-5.1) and 13.7% (95%CI 10.0-17.9). Patients developing VTE had higher D-dimer levels (weighted mean difference 3.26 µg/ml (95%CI 2.76-3.77) than non-VTE patients.

Conclusion

VTE occurs in 22.7% of patients with COVID-19 in the ICU, but VTE risk is also increased in non-ICU hospitalized patients. Patients developing VTE had higher D-dimer

levels. Studies evaluating thromboprophylaxis strategies in patients with COVID-19 are needed to improve prevention of VTE.

Keywords

COVID-19, Prevalence, Pulmonary Embolism, Severe Acute Respiratory Syndrome
Coronavirus 2, Venous Thromboembolism

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and formally declared a pandemic by the World Health Organization (WHO) in March 2020, is an infectious disease with a global impact on public health. It affects primarily the respiratory system, however, involvement of other organ systems may occur, especially with increasing severity of the disease. The high inflammatory burden associated with COVID-19 and inflammation in the vascular system can also result in cardiovascular complications with a variety of clinical presentations. [1-3] Early studies already reported on coagulation abnormalities and coagulopathy with a rather prothrombotic phenotype in patients with COVID-19. [4, 5]

With the better understanding of COVID-19 and its clinical course, venous thromboembolism (VTE), a disease entity covering pulmonary embolism (PE) and deep vein thrombosis (DVT), has been recognized as a particular complication of the disease. Initial studies have found alarmingly high rates of PE in patients with severe COVID-19 treated at intensive care units (ICU), reporting VTE incidences of up to 50%. [6] In response to the clinical challenges and the absence of high-quality evidence, experts groups and scientific societies have released guidance statements to address questions concerning diagnosis, prevention, and treatment of VTE in patients with COVID-19 which suggest the broad application of thromboprophylaxis in patients with severe COVID-19 in the absence of high bleeding risk. [7, 8]

In several studies of different design, size, and quality, rates of VTE in patients with COVID-19 have been reported. However, a definitive and robust estimate of the VTE risk in patients with COVID-19 is currently not available as of the high variability of reported rates. Therefore, the true underlying burden of VTE in COVID-19 patients is still not fully understood. In the light of the ever-growing infection rates worldwide and the clinical challenges in patient management, understanding of the true frequency of VTE in COVID-19 is important and may help to support clinical decision making.

We conducted a systematic review of the literature and meta-analysis of available data to determine the prevalence of VTE in patients with COVID-19. Our aim was to provide an overall estimate of VTE by aggregating reported rates and to thoroughly explore differences in the VTE prevalence according to study design and the health care setting, which may account for the high degree of heterogeneity in reported rates.

Methods

Register and protocol

We conducted a systematic review of the literature and meta-analysis of published data on the prevalence of VTE in patients with COVID-19. The study protocol was prepared prior to the initiation of the literature research according to the Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 [9] and submitted to PROSEPERO (International prospective register of systematic reviews) on June 11th, 2020 (protocol-ID: CRD42020191652). The study was conducted according to the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) and the guidance for reporting meta-analysis of observational studies in epidemiology (MOOSE). [10, 11]

Eligibility criteria

Full-text articles, letters, brief reports, editorials, and correspondences published in 2019 or 2020 with available title and abstract in English were eligible for inclusion. Inclusion criteria comprised studies reporting on patients with objectively confirmed COVID-19 in combination with reporting rates of VTE as outcome of the study (DVT and/or PE). Study designs eligible for inclusion were cohort studies (prospective and retrospective), cross-sectional studies, and interventional studies with VTE reported as an outcome or adverse event. Study designs that did not allow prevalence estimates such as case reports and case-series including autopsy studies were excluded.

Literature research

We systematically searched EMBASE, MEDLINE, and the WHO COVID-19 research database with distinct predefined search algorithms to identify relevant publications. The exact search protocol is available in the **Supplementary Methods**. Search for additional studies not identified by the search criteria (e.g. due to pre-print status) was conducted by inquiring databases of pre-print servers (medRxiv) and by manual research of relevant journals. Publications in pre-print status were only eligible if they had undergone full peer-review at the date of literature research. Duplicate search

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results were excluded prior to eligibility screening. Two researchers (SN, FM) screened title and abstract of the identified studies and potentially eligible studies underwent full-text evaluation. The inclusion of a study was based on the consensus of its suitability by the two researchers. Where consensus opinion could not be reached, a third reviewer was consulted to make the final decision (CA). All three literature researchers are medical doctors with a thorough research background in the field of thrombosis. The most recent literature research was conducted on August 26th, 2020. **Figure 1** displays the process of study identification following a PRISMA flow-diagram.

Data extraction

Studies that fulfilled the predefined inclusion criteria and did not meet any exclusion criteria were subjected to data extraction. In the case of multiple studies reporting on the same patient cohort, results were merged and considered only once. Data extraction of pre-defined baseline and outcome variables was performed. These included methodological specifics of the studies (study design, health care setting), clinical information of the study population (demographics, comorbidities, disease severity, use of pharmacological thromboprophylaxis, ultrasound screening, and D-dimer levels), and outcome specifics (definition, type, and rate of VTE). The full list of extracted variables is provided in the **Supplementary Methods**. All data were independently extracted from eligible studies by two authors (SN, FM) to ensure data reliability, with inconsistencies resolved by discussion with a third author (CA).

Risk of bias evaluation

Methodology of identified studies was assessed independently by two researchers (FM & SN). Risk of bias of included studies was independently rated with a validated tool for assessing studies reporting prevalence data (Joanna Briggs Institute Critical Appraisal Checklist; **Supplementary Appendix**). [12] This tool consists of 9 categories each classifying the study as low risk of bias, high risk of bias, or unclear. Subsequently, an overall evaluation based on these categories was derived. Studies with suspected high risk of bias were excluded from the subsequent quantitative data synthesis. Potential

publication bias was assessed graphically within a Funnel-plot, plotting the prevalence estimate of VTE against its' standard error (**Supplementary Figure S1A&B**).

Outcomes, definitions, and quantitative data synthesis

The primary outcome of the present meta-analysis is VTE, defined as DVT (including catheter-related thrombosis), PE, or the composite of both, as defined within the respective study. Thrombotic occlusions of mechanical components of extracorporeal devices such as dialysis machines or ECMO devices were not counted as outcome event. The prevalence estimate of the primary outcome is reported stratified by the use of systematic ultrasound screening for thrombosis in the respective studies.

Secondary outcomes included (i) the pooled prevalence of VTE (excluding studies only reporting isolated PE or isolated DVT rates), (ii) the pooled rate of PE, and (iii) the pooled rate of DVT. Outcomes of the secondary analyses were reported stratified for ICU patients and non-ICU hospitalized patients at study baseline and by the performance of DVT screening. The ICU cohort comprised patients admitted to the ICU, or alternatively those who were defined as being critically ill, or in need of mechanical ventilation at baseline. Further, an exploratory analysis of differences between baseline levels of D-dimer between patients experiencing VTE and those who did not was conducted.

Outcome definitions throughout the different studies were varying. Some studies reported pure incidence, while others reported prevalence, e.g. including patients who have been admitted due to VTE and COVID-19. In this systematic review, we have decided to aggregate the proportion of patients, who have been diagnosed with VTE as reported in the included studies.

Statistical methods

All statistical analyses were performed with the commercially available package STATA 15.0 (Stata Corp., Houston, TX, USA). Summary statistics were aggregated from included studies. Pooled prevalence of outcome variables was estimated by aggregating study results within a random-effects meta-analysis utilizing the STATA package

metaprop. [13] The Freeman-Tukey double arcsine transformation was utilized to normalize variance, and 95% confidence intervals (CI) were estimated by the score method. Heterogeneity of included studies is reported by I^2 as a measure of between-study variability beyond random variation. To explore differences in baseline D-dimer between VTE and non-VTE patients, mean D-dimer levels and corresponding standard deviation were calculated from reported median, interquartile range (IQR) and sample size according to Wan et al. [14] Weighted mean differences (WMD) in baseline D-dimer levels were calculated within a pooled-analysis weighted by corresponding sample sizes. Lastly, differences in VTE risk according to sex and comorbidities was explored within a random effects meta-analysis utilizing the Mantel–Haenszel procedure.

Results

Selection process and general study characteristics

We identified 2018 records upon literature research after the removal of duplicates. Title and abstract of these identified studies were screened for conformity with our predefined in- and exclusion criteria and 86 records were subsequently included in the full-text evaluation. From those, 66 studies were included in the qualitative data synthesis. **Figure 1** displays the screening and selection process, and the reasons for excluding studies.

Pooled summary characteristics of the 86 eligible studies reporting on VTE in COVID-19 patients are displayed in **Table 1**. Regarding geographic regions, 57 studies were performed in Europe, 17 in North America, 8 in Asia, 1 in Africa and 3 studies included patients from multiple continents. Fifty-eight cohort studies, 5 cross-sectional studies, and 2 case-control study were carried out to identify rate of VTE in the study populations, 15 cohort studies, and 2 case-control studies reported VTE as a secondary outcome, and 4 studies reported VTE as adverse events. VTE screening (ultrasound examination of deep veins of the upper and/or lower extremities) was performed in 19 studies, with one study conducting ultrasound screening in 28% of patients. [15] Twenty-four studies were conducted specifically in ICU cohorts only and 19 studies reported rates of VTE separately for ICU or critically ill patients, rendering 43 studies eligible for our ICU subgroup analysis.

A comprehensive summary of each study including the respective study design, demographics, thromboprophylaxis strategy, and outcome rates is presented in **Tables S1&2**.

Pooled patient characteristics and comorbidity data are displayed in **Table 2**. The overall weighted mean age of patients was 62.6 years (standard deviation [SD] 3.8) and 60% were male. Weighted mean age of patients in ICU-only studies was 62.6 years (SD 2.9) and 71.3% were male.

Risk of bias

Risk of publication bias was evaluated separately for studies on non-ICU hospitalized and ICU patients to enhance interpretability. Upon visual inspection of the Funnel plots, no indication for publication bias was detected, with outliers in the distribution being explained by differences in ultrasound screening strategies. (**Figures S1A&B**) Secondly, we conducted an exploration of potential time-dependencies in VTE rates of published studies suggesting a decrease of VTE rates over time upon visual inspection and fitting a regression line of the VTE rate and the last patient inclusion date of each respective study. (**Figure S2**)

Thirdly, a methodological assessment of included studies was conducted in order to evaluate the risk of underlying bias regarding the reported rate of VTE. Importantly, this evaluation is not to be regarded as a general evaluation of quality and goodness of included studies but rather an evaluation of the generalizability of reported VTE rates.

In our quality assessment, low risk of bias was attributed to our identified studies in median in 7 of 9 categories (range: 3-9, maximum: low risk of bias in all 9 categories). The results of our structured methodological assessment of all 86 studies are presented in **Table S3**. In consensus among the 3 reviewers, 20 studies were excluded from quantitative synthesis upon a strong suspicion of bias in the structured assessment. Reasons for exclusion include selection bias (19 studies), reporting/information bias (1 study), and lack of background information on setting and outcomes (1 study). Therefore, the 66 remaining studies (including 43 studies reporting on ICU patients and 43 studies

reporting on non-ICU hospitalized patients) were included in quantitative data synthesis. [6, 16-81]

Prevalence of venous thromboembolism

After excluding studies with a high risk of underlying bias, quantitative results from 66 studies were aggregated within a meta-analysis, including 28,173 patients (1,819 ambulatory, 20,886 non-ICU hospitalized, 5,468 ICU patients). In total, 1,824 VTE events were reported. The pooled prevalence estimate of all reported VTE events (outcomes: VTE, DVT, or PE) was 14.1% ([95%CI: 11.6-16.9], I^2 : 97.1%). In the 52 studies (n=27,130; 1492 VTE) in which no ultrasound screening was performed, the estimated rate of VTE was 9.5% ([95%CI: 7.5-11.7], I^2 : 96.5%). Conversely, in the 14 studies with ultrasound screening performed (n=1,043; 332 VTE), the estimated prevalence of VTE was 40.3% ([95%CI: 27.0-54.3], I^2 : 94.7%). **Figure 2** shows a Forrest plot of VTE rates, together with information on health care setting, the performance of screening and outcome definition of respective studies.

Prevalence of VTE in hospitalized and ICU patients

The rates of VTE within our primary analysis strongly differed between studies, depending on the specifics of the study setting, design, and outcome definition. Therefore, in order to further explore heterogeneity of the reported VTE rates, we conducted detailed subgroup analyses based on the health care setting (non-ICU hospitalized vs. ICU patients), and the performance of DVT screening (screening vs. no screening). In addition, within these subgroup analyses, we have separately estimated rates of VTE, PE, and DVT.

In 43 studies reporting on ICU-cohorts including 5,468 patients, the rate of VTE, PE, or DVT was available. The estimated prevalence of VTE, PE, and DVT was 22.7% ([95%CI: 18.1-27.6], I^2 : 87.3%), 13.7% ([95%CI: 10.0-17.9], I^2 : 87.6%), and 18.7% ([95%CI: 12.6-25.6], I^2 : 94.6%). Rates of VTE and DVT in studies with screening strategies in the ICU cohorts (9 studies, n=359) were 45.6% ([95%CI: 30.6-61.1], I^2 :

73.4%) and 48.5% ([95%CI: 31.0-66.2], I²: 91.0%), and in those without screening 18.7% ([95%CI: 14.9-22.9], I²: 83.1%) and 8.9% ([95%CI: 5.8-12.4], I²: 86.2%).

In the meta-analysis of studies reporting on non-ICU hospitalized patients at baseline, including 20,886 patients from 43 studies, prevalence estimates of VTE, PE, and DVT were 7.9% ([95%CI: 5.1-11.2], I²: 94.6%), 3.5% ([95%CI: 2.2-5.1], I²: 88.9%), and 4.1% ([95%CI: 2.3-6.4], I²: 94.6%). In studies with ultrasound screening performed (8 studies, n=684), rates of VTE and DVT were 23.0% ([95%CI: 3.2-52.5], I²: 96.5%) and 12.7% ([95%CI: 3.7-25.5], I²: 94.1%) compared to 5.5% ([95%CI: 3.6-7.9], I²: 91.0%) and 1.4% ([95%CI: 0.7-2.3], I²: 85.0%) in studies without screening. The results of these subgroup analyses are summarized in **Table 3** and corresponding Forrest plots are available in the **Figures S3A&B**.

Characteristics of patients with VTE vs. those without VTE

Available baseline characteristics of patients with VTE compared to those without VTE were aggregated and analyzed weighted by sample size of the respective study (**Table 4**). Mean weighted age of VTE and non-VTE patients was similar, with a mean age of 63.3 years (SD 3.9) and 63.4 years (SD 2.8), respectively. Men were 1.5 times more likely to develop VTE (95%CI: 1.22-1.72), while comorbidities did not differ between the two groups.

D-dimer and the risk of VTE

D-dimer levels at baseline were available in 21 studies, including 6,633 patients. Patients developing VTE had higher baseline D-dimer levels compared to those without VTE (weighted mean D-dimer levels: 5.18 µg/ml (SD 2.59) vs. 1.13 µg/ml (SD 0.95)) with a WMD of 3.26 µg/ml ([95%CI: 2.76-3.77], p < 0.001; I²: 87.3%). (**Figure 3**)

Discussion

In this systematic review and meta-analysis, data from studies reporting on rates of VTE in patients with COVID-19 were aggregated to estimate the prevalence of VTE. We found that the burden of VTE associated with COVID-19 is substantial, with an overall VTE prevalence estimate of 14.1% across all identified studies. However, rates of VTE varied across different health care settings (ICU vs. non-ICU hospitalized patients), depending on whether systematic screening was performed or not, and on outcome definitions in the selected studies. In subgroup analysis, rates of VTE ranged from 5.5% in non-ICU hospitalized patients without ultrasound screening to 45.6% in ICU patients undergoing screening strategies. Since no PE screening was performed, the PE prevalence of 3.5% in non-ICU hospitalized patients and 13.7% in ICU patients might provide a robust estimate and strongly highlights the high risk of VTE in patients with COVID-19, especially in those requiring intensive medical care.

It is known from large clinical trials in critically ill patients with various underlying diseases that the rate of VTE in the ICU setting is elevated, with VTE rates ranging from 5 to 15%. [82-86] Higher VTE rates in COVID-19 patients in the ICU and also non-ICU setting might not only be explained by hospitalization and complications occurring during the course of the disease such as systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), shock and organ failure but support the hypothesis of direct involvement of the viral infection with effects on the vascular and haemostatic system leading to a prothrombotic state and high risk of VTE. Interestingly, a small study of critically ill patients with severe acute respiratory syndrome coronavirus (SARS-CoV) from the early 2000s reported similarly high VTE rates (14 of 46 patients suffered from VTE). [87] VTE events were observed less frequently in other respiratory viruses such as the Middle East respiratory syndrome coronavirus (MERS-CoV; coagulopathy was reported in 2 of 161 hospitalized patients) [88] and influenza viruses (4 of 119 hospitalized patients developed VTE). [89] Taken together, the increased risk of VTE in patients with COVID-19 appears to be substantial and while the mechanisms are not yet understood, similar rates in SARS and COVID-19 in contrast to MERS and influenza might speculatively suggest a common underlying pathophysiology.

Interestingly, autopsy studies in COVID-19 patients revealed severe endothelial injury, endotheliitis, increased angiogenesis, and widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries. [1, 2, 90-92] Based on such findings, the aetiology of the increased PE rates reported in COVID-19 patients has been discussed and two not mutually exclusive pathomechanisms have been proposed. On the one hand, it has been suggested that in-situ pulmonary thrombi, which develop on the basis of diffuse alveolar and local vascular damage, microangiopathy, and inflammation in the pulmonary circulation triggered by the virus, rather than “classical” PE itself may contribute to the high prevalence of PE observed in patients with COVID-19. [93-97] On the other hand, DVT rates of up to 90% in studies, where ultrasound screening was performed in ICU patients, support the hypothesis of embolism originating from peripheral thrombosis rather than pulmonary in-situ thrombosis largely contributes to the substantial burden of pulmonary artery occlusion observed in patients with COVID-19. However, the exact role, data on frequency, and clinical consequences of in-situ pulmonary thrombosis in COVID-19 need further investigations.

We believe that our meta-analysis is representative of COVID-19 patients requiring hospitalization, as our systematic review confirmed the previously reported sex differences in COVID-19 patients (higher proportion of men among more severe disease). [98] The sex differences further increased among patients admitted to the ICU suggesting that men were more likely to suffer from greater disease severity than women. [99] Correspondingly, men were at higher risk to develop VTE, but we observed no association between comorbidities and risk of VTE. Interestingly, age did not differ between the groups. This suggests that in contrast to the general population, age did not contribute to the VTE risk in COVID-19 patients. [100] Similar results have been reported for VTE risk in patients with cancer suggesting that the high VTE baseline risk of the underlying disease overwhelms general risk factors such as age. [101] Furthermore, explorative analysis has revealed that D-dimer levels were higher in patients developing VTE compared to those who remained free from a VTE event.

Our findings support guidance statements from experts and scientific societies which suggest that thromboprophylaxis is a key element in the medical care of patients with COVID-19, especially in those with severe illness. [7, 8, 102-104] However, VTE

occurred in many patients despite the use of thromboprophylaxis, and even patients with therapeutic anticoagulation developed VTE. Therefore, the ideal anticoagulation approach to reduce the high risk of VTE in patients with COVID-19 needs to be established. Further, the observed higher baseline D-dimer levels in patients who had VTE strengthens the idea that D-dimer-guided thromboprophylaxis strategies should be evaluated in prospective randomized-controlled trials.

The main limitation of our meta-analysis is the high heterogeneity of included studies with regard to design, clinical setting, local practice (e.g. with respect to thromboprophylaxis strategies), and consequently highly variable event rates. Additionally, the disproportionate number of ICU studies with higher VTE rates than the general ward population may confound the overall estimation of VTE prevalence in patients with COVID-19. To address this issue, we aimed at thoroughly describing the respective clinical settings and provide subgroup analysis, e.g. ICU vs. non-ICU hospitalized patients or according to diagnostic approaches (studies with screening vs. no screening for DVT) to provide a more precise estimate of VTE rates. Further, early reports of high VTE rates in patients with COVID-19 might have led to the implementation of more specific and intensive thromboprophylaxis approaches over time, which might have confounded the outcomes in subsequently conducted studies. We have analyzed studies according to the date of the last patient recruitment and visual inspection reveals a decrease of VTE rates of reported studies over time (**Figure S2**). We also provided data on thromboprophylaxis modalities for the respective studies to allow a better interpretation of differences observed in the studies. However, the generalizability of the results of our systematic review and meta-analysis still needs to be interpreted with caution, because only data from patients in North America, Europe, and Asia were available and included in the meta-analysis. Upon visual inspection, VTE rates across continents and countries seem to be mainly related to between-study heterogeneity with respect to study design, clinical setting, and local clinical practice with regard to thromboprophylaxis (**Figure S4**).

Given the high mortality especially in ICU patients with COVID-19, competing risk of death might lead to an underdiagnosis of VTE. Further, the concern of restricting the use of imaging to avoid disease exposure to healthcare worker might further lead to

false-low rates of VTE in patients with COVID-19. These uncontrollable factors in a study level analysis should be considered upon interpreting and generalizing our findings. Also, the practice of avoiding imaging due to concerns about healthcare worker exposure should be critically reviewed given the risk of underdiagnosis and consequently undertreatment of patients.

Furthermore, exploratory analysis of D-dimer levels between patients developing VTE and those who did not is limited by the lack of patient-level data and the inability to adjust for between assay variability. Therefore, this exploration should be interpreted with appropriate caution and regarded as hypothesis generating.

Lastly, there is some evidence that non-hospitalized COVID-19 patients are at increased risk of developing VTE as well. [105] As of the unavailability of sufficient data within our meta-analysis, we were unable to provide prevalence estimates for this population of patients and our findings are therefore not representative for the outpatient setting of COVID-19.

In summary, we found a high prevalence of VTE in patients with COVID-19 in hospitalized non-ICU patients, and especially high VTE rates in those being critically ill and requiring intensive medical care. There is a clinical need for further research to better understand the risk and prevent VTE in patients with COVID-19. These findings support the broad use of thromboprophylaxis, specifically in ICU patients. Future randomized clinical trials are needed to assess whether patients with COVID-19 may benefit from an intensified anticoagulation approach compared to standard thromboprophylaxis or whether a biomarker-based personalized thromboprophylaxis regimen reduces the high prevalence of VTE in patients with COVID-19.

Addendum

Author contributions: S. Nopp and F. Moik contributed to study design, data collection, data interpretation, statistical analysis, and drafting of the manuscript. C. Ay contributed to study design, data interpretation, and critical review of the manuscript. I. Pabinger contributed to data interpretation and critical review of the manuscript. S. Nopp, F. Moik, C. Ay are the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read the manuscript and approved its submission.

Disclosure of Conflicts of Interest

S. Nopp and F. Moik report no potential conflict of interest. B. Jilma has received reimbursement for scientific advice from Bayer, Octapharma and Sanofi. The ongoing ACOVACT trial randomizing COVID patients to different anticoagulants is financially supported by the Austrian Federal Ministry of Education, Science and Research. I. Pabinger received honoraria for occasional lectures and advisory board meetings from Bayer, Daiichi-Sanchyo, Pfizer and Sanofi. C. Ay received honoraria for lectures and participation in advisory board meetings from Bayer, Daiichi-Sanchyo, Pfizer/BMS, Sanofi, Shire/Takeda, Sobi, CSL Behring.

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References

- 1 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *New England Journal of Medicine*. 2020. 10.1056/NEJMoa2015432.
- 2 Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*. 2020; **395**: 1417-8. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5).
- 3 BMJBestPractice. Coronavirus disease 2019 (COVID-19), Complications. July, 2020.
- 4 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis*. 2020; **18**: 1094-9. 10.1111/jth.14817.
- 5 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020; **18**: 844-7. 10.1111/jth.14768.
- 6 Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis research*. 2020; **191**: 148-50. <https://doi.org/10.1016/j.thromres.2020.04.041>.
- 7 Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020; **18**: 1023-6. 10.1111/jth.14810.
- 8 Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD, The Subcommittee on Perioperative CCT, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis, Haemostasis+. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of

Venous Thromboembolism in Hospitalized Patients with COVID-19. *Journal of Thrombosis and Haemostasis*. n/a. 10.1111/jth.14929.

9 Shamseer L, Moher D, Clarke M, Gherzi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal*. 2015; **349**: g7647. 10.1136/bmj.g7647.

10 Moher D, Liberati A, Tetzlaff J, Altman DG, Group atP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Annals of Internal Medicine*. 2009; **151**: 264-9. 10.7326/0003-4819-151-4-200908180-00135.

11 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB, Group ftM-aOOSiE. Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting. *Jama*. 2000; **283**: 2008-12. 10.1001/jama.283.15.2008.

12 Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015; **13**: 147-53. 10.1097/xeb.0000000000000054.

13 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Archives of Public Health*. 2014; **72**: 39. 10.1186/2049-3258-72-39.

14 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*. 2014; **14**: 135. 10.1186/1471-2288-14-135.

15 Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020. 10.1111/jth.14888.

16 Maatman TK, Jalali F, Feizpour C, Douglas A, 2nd, McGuire SP, Kinnaman G, Hartwell JL, Maatman BT, Kreutz RP, Kapoor R, Rahman O, Zyromski NJ, Meagher AD. Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019. *Critical care medicine*. 2020: 10.1097/CCM.0000000000004466. 10.1097/CCM.0000000000004466.

- 17 Desborough MJR, Doyle AJ, Griffiths A, Retter A, Breen KA, Hunt BJ. Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. *Thrombosis research*. 2020; **193**: 1-4. 10.1016/j.thromres.2020.05.049.
- 18 Galeano-Valle F, Oblitas CM, Ferreiro-Mazón MM, Alonso-Muñoz J, Del Toro-Cervera J, di Natale M, Demelo-Rodríguez P. Antiphospholipid antibodies are not elevated in patients with severe COVID-19 pneumonia and venous thromboembolism. *Thrombosis research*. 2020; **192**: 113-5. 10.1016/j.thromres.2020.05.017.
- 19 Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *European Heart Journal*. 2020; **41**: 1821-9. 10.1093/eurheartj/ehaa388.
- 20 Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020; **395**: 1569-78. 10.1016/S0140-6736(20)31022-9.
- 21 Ren B, Yan F, Deng Z, Zhang S, Xiao L, Wu M, Cai L. Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan. *Circulation*. **0**. doi:10.1161/CIRCULATIONAHA.120.047407.
- 22 Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes P-M, Meziani F, Group CT. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Medicine*. 2020; **46**: 1089-98. 10.1007/s00134-020-06062-x.
- 23 Llitjos J-F, Leclerc M, Chochois C, Monsallier J-M, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of Thrombosis and Haemostasis*. **n/a**. 10.1111/jth.14869.

- 24 Stoneham SM, Milne KM, Nuttal E, Frew GH, Sturrock BR, Sivaloganathan H, Ladikou EE, Drage S, Phillips B, Chevassut TJ, Eziefula AC. Thrombotic risk in COVID-19: a case series and case-control study. *Clinical Medicine*. 2020: clinmed.2020-0228. 10.7861/clinmed.2020-0228.
- 25 Wright FL, Vogler TO, Moore EE, Moore HB, Wohlaer MV, Urban S, Nydam TL, Moore PK, McIntyre RC, Jr. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. *Journal of the American College of Surgeons*. 10.1016/j.jamcollsurg.2020.05.007.
- 26 Thomas W, Varley J, Johnston A, Symington E, Robinson M, Sheares K, Lavinio A, Besser M. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. *Thrombosis research*. 2020; **191**: 76-7. 10.1016/j.thromres.2020.04.028.
- 27 Faggiano P, Bonelli A, Paris S, Milesi G, Bisegna S, Bernardi N, Curnis A, Agricola E, Maroldi R. Acute pulmonary embolism in COVID-19 disease: Preliminary report on seven patients. *International Journal of Cardiology*. 2020; **313**: 129-31. <https://doi.org/10.1016/j.ijcard.2020.04.028>.
- 28 Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research*. 2020; **191**: 145-7. 10.1016/j.thromres.2020.04.013.
- 29 Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of Thrombosis and Haemostasis*. **n/a**. 10.1111/jth.14888.
- 30 Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Medicine*. 2020; **46**: 1121-3. 10.1007/s00134-020-06040-3.
- 31 Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *International Journal of Laboratory Hematology*. 2020; **42**: 19-20. 10.1111/ijlh.13230.

- 32 Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020; **18**: 1421-4. 10.1111/jth.14830.
- 33 Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thrombosis and haemostasis*. 2020; **120**: 998-1000. 10.1055/s-0040-1710018.
- 34 Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, Goodarzi K, Bendapudi P, Bornikova L, Gupta S, Leaf D, Kuter DJ, Rosovsky RP. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. *Blood*. 2020. 10.1182/blood.2020006520.
- 35 Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. *Critical Care*. 2020; **24**: 275. 10.1186/s13054-020-03025-y.
- 36 Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. *British Journal of Haematology*. **n/a**. 10.1111/bjh.16908.
- 37 Voicu S, Bonnin P, Stépanian A, Chousterman BG, Le Gall A, Malissin I, Deye N, Siguret V, Mebazaa A, Mégarbane B. High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients. *Journal of the American College of Cardiology*. 2020: 27399. 10.1016/j.jacc.2020.05.053.
- 38 Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, Tomelleri A, Baldissera E, Rovere-Querini P, Ruggeri A, Monti G, De Cobelli F, Zangrillo A, Tresoldi M, Castagna A, Dagna L, Group T-RS. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *European journal of internal medicine*. 2020; **76**: 43-9. 10.1016/j.ejim.2020.05.021.
- 39 Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*. **0**. doi:10.1161/CIRCULATIONAHA.120.046702.

- 40 Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. *Circulation*. **0**. doi:10.1161/CIRCULATIONAHA.120.047430.
- 41 Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt J-D, Sacco C, Alexia B, Sandri MT, Barco S. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research*. 2020; **191**: 9-14.
<https://doi.org/10.1016/j.thromres.2020.04.024>.
- 42 Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography. *Radiology*. **0**: 201544. 10.1148/radiol.2020201544.
- 43 Longchamp A, Longchamp J, Manzocchi-Besson S, Whiting L, Haller C, Jeanneret S, Godio M, Garcia Martinez JJ, Bonjour T, Caillat M, Maitre G, Thaler JM, Pantet R, Donner V, Dumoulin A, Emonet S, Greub G, Friolet R, Robert-Ebadi H, Righini M, Sanchez B, Delaloye J. Venous Thromboembolism in Critically Ill Patients with Covid-19: Results of a Screening Study for Deep Vein Thrombosis. *Research and Practice in Thrombosis and Haemostasis*. **n/a**. 10.1002/rth2.12376.
- 44 Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR, Nahid M, Ringel JB, Hoffman KL, Alshak MN, Li HA, Wehmeyer GT, Rajan M, Reshetnyak E, Hupert N, Horn EM, Martinez FJ, Gulick RM, Safford MM. Clinical Characteristics of Covid-19 in New York City. *New England Journal of Medicine*. 2020; **382**: 2372-4. 10.1056/NEJMc2010419.
- 45 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapsen V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh M-d, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine*. 2020. 10.1056/NEJMoa2007764.
- 46 Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler AJ, Venugopal S, Makki I, Qin Q, Dharmapuri S, Jun T, Bhalla S, Berwick S, Feld J, Mascarenhas J, Troy K,

Cromwell C, Dunn A, Oh WK, Naymagon L. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. *Blood*. 2020.

10.1182/blood.2020006941.

47 Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache J-M, Bézie Y, Laplanche S, Le Berre A, Le Pavec J, Salmeron S, Emmerich J, Mourad J-J, Chatellier G, Hayem G. Anakinra for severe forms of COVID-19: a cohort study. *The Lancet Rheumatology*. 2020; **2**: e393-e400. 10.1016/S2665-9913(20)30164-8.

48 Nahum J, Morichau-Beauchant T, Daviaud F, Echegut P, Fichet J, Maillet J-M, Thierry S. Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Network Open*. 2020; **3**: e2010478-e.

10.1001/jamanetworkopen.2020.10478.

49 Zerwes S, Hernandez Cancino F, Liebetrau D, Gosslau Y, Warm T, Märkl B, Hyhlik-Dürr A. [Increased risk of deep vein thrombosis in intensive care unit patients with CoViD-19 infections?-Preliminary data]. *Chirurg*. 2020: 1-7. 10.1007/s00104-020-01222-7.

50 Betoule A, Martinet C, Gasperini G, Muller P, Foucher S, Benner P, Renard A. Diagnosis of venous and arterial thromboembolic events in COVID-19 virus-infected patients. *Journal of thrombosis and thrombolysis*. 2020: 1-3. 10.1007/s11239-020-02163-y.

51 Grandmaison G, Andrey A, Périard D, Engelberger RP, Carrel G, Doll S, Dexpert J-B, Krieger C, Ksouri H, Hayoz D, Sridharan G. Systematic Screening for Venous Thromboembolic Events in COVID-19 Pneumonia. *TH open : companion journal to thrombosis and haemostasis*. 2020; **4**: e113-e5. 10.1055/s-0040-1713167.

52 Le Jeune S, Suhl J, Benainous R, Minvielle F, Purser C, Foudi F, Warzocha U, Dhote R. High prevalence of early asymptomatic venous thromboembolism in anticoagulated COVID-19 patients hospitalized in general wards. *Journal of thrombosis and thrombolysis*. 2020: 1-5. 10.1007/s11239-020-02246-w.

53 Taccone FS, Gevenois PA, Peluso L, Pletchette Z, Lheureux O, Brasseur A, Garufi A, Talamonti M, Motte S, Nobile L, Grimaldi D, Creteur J, Vincent J-L. Higher Intensity Thromboprophylaxis Regimens and Pulmonary Embolism in Critically Ill Coronavirus Disease 2019 Patients. *Critical care medicine*. 2020:

10.1097/CCM.0000000000004548. 10.1097/CCM.0000000000004548.

- 54 Violi F, Ceccarelli G, Cangemi R, Alessandri F, D'Ettorre G, Oliva A, Pastori D, Loffredo L, Pignatelli P, Ruberto F, Venditti M, Pugliese F, Mastroianni CM. Hypoalbuminemia, Coagulopathy, and Vascular Disease in COVID-19. *Circulation Research*. 2020; **127**: 400-1. doi:10.1161/CIRCRESAHA.120.317173.
- 55 Santoliquido A, Porfidia A, Nesci A, De Matteis G, Marrone G, Porceddu E, Cammà G, Giarretta I, Fantoni M, Landi F, Gasbarrini A, Pola R, Group tGAC-, D'Alfonso ME, Lo Monaco MR. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *Journal of Thrombosis and Haemostasis*. **n/a**. 10.1111/jth.14992.
- 56 Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, Saez-Vaquero T, Torres-Macho J, Abad-Motos A, Cortina-Camarero C, Such-Diaz A, Ruiz-Velasco E, Churruca-Sarasqueta J, Muñoz-Rivas N, Infanta Leonor Thrombosis Research G. Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. *Journal of thrombosis and thrombolysis*. 2020: 1-7. 10.1007/s11239-020-02190-9.
- 57 Patell R, Bogue T, Bindal P, Koshy A, Merrill M, Aird WC, Bauer KA, Zwicker JI. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. *Journal of Thrombosis and Haemostasis*. **n/a**. 10.1111/jth.15018.
- 58 Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyaphongs Y, Cao M, Goldenberg R, Hindenburg A, Horowitz J, Parnia S, Petrilli C, Reynolds H, Simon E, Slater J, Yaghi S, Yuriditzky E, Hochman J, Horwitz LI. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. *Arteriosclerosis, Thrombosis, and Vascular Biology*. **0**: ATVBAHA.120.314872. doi:10.1161/ATVBAHA.120.314872.
- 59 Dubois-Silva Á, Barbagelata-López C, Mena Á, Piñeiro-Parga P, Llinares-García D, Freire-Castro S. Pulmonary embolism and screening for concomitant proximal deep vein thrombosis in noncritically ill hospitalized patients with coronavirus disease 2019. *Internal and Emergency Medicine*. 2020; **15**: 865-70. 10.1007/s11739-020-02416-x.
- 60 Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, Douair A, Barbin E, Fraix A, Bouchot O, Benmansour O, Godeau G, Mecheri Y, Lebourdon R, Yvorel C, Massin M, Leblon T, Chabbi C, Cugney E, Benabou L, Aubry M, Chan C, Boufoula I, Barnaud C, Bothorel L, Duceau B, Sutter W, Waldmann V, Bonnet G, Cohen A, Pezel T,

Investigators ftCC-F. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *European Heart Journal*. 2020. 10.1093/eurheartj/ehaa500.

61 Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. *Thrombosis research*. 2020; **195**: 95-9. 10.1016/j.thromres.2020.07.025.

62 Rieder M, Goller I, Jeserich M, Baldus N, Pollmeier L, Wirth L, Supady A, Bode C, Busch H-J, Schmid B, Duerschmied D, Gauchel N, Lothar A. Rate of venous thromboembolism in a prospective all-comers cohort with COVID-19. *Journal of Thrombosis and Thrombolysis*. 2020. 10.1007/s11239-020-02202-8.

63 Mattioli M, Benfaremo D, Mancini M, Mucci L, Mainquà P, Polenta A, Baldini PM, Fulgenzi F, Denetta D, Bedetta S, Gasperoni L, Caraffa A, Frausini G. Safety of intermediate dose of low molecular weight heparin in COVID-19 patients. *Journal of Thrombosis and Thrombolysis*. 2020. 10.1007/s11239-020-02243-z.

64 Pesavento R, Ceccato D, Paschetto G, Monticelli J, Leone L, Frigo A, Gorgi D, Postal A, Marchese GM, Cipriani A, Saller A, Sarais C, Criveller P, Gemelli M, Capone F, Fioretto P, Pagano C, Rossato M, Avogaro A, Simioni P, Prandoni P, Vettor R. The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. *Journal of Thrombosis and Haemostasis*. **n/a**. 10.1111/jth.15022.

65 Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA*. 2020; **324**: 799-801. 10.1001/jama.2020.13372.

66 Hanif A, Khan S, Mantri N, Hanif S, Saleh M, Alla Y, Chinta S, Shrestha N, Ji W, Attwood K, Adrish M, Jain KR. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. *Ann Hematol*. 2020. 10.1007/s00277-020-04216-x.

67 Zermatten MG, Pantet O, Gomez F, Schneider A, Méan M, Mazzolai L, Hugli O, Bart P-A, Papadimitriou-Olivgeris M, Alberio L. Utility of D-dimers and intermediate-dose prophylaxis for venous thromboembolism in critically ill patients with COVID-19. *Thrombosis research*. 10.1016/j.thromres.2020.08.027.

- 68 Moll M, Zon RL, Sylvester KW, Chen EC, Cheng V, Connell NT, Fredenburgh LE, Baron RM, Cho MH, Woolley AE, Connors JM. VTE in ICU Patients With COVID-19. *Chest*. 2020. <https://doi.org/10.1016/j.chest.2020.07.031>.
- 69 Trimaille A, Curtiaud A, Marchandot B, Matsushita K, Sato C, Leonard-Lorant I, Sattler L, Grunebaum L, Ohana M, Von Hunolstein J-J, Andres E, Goichot B, Danion F, Kaeuffer C, Poindron V, Ohlmann P, Jesel L, Morel O. Venous thromboembolism in non-critically ill patients with COVID-19 infection. *Thrombosis research*. 2020; **193**: 166-9. [10.1016/j.thromres.2020.07.033](https://doi.org/10.1016/j.thromres.2020.07.033).
- 70 Lendorf ME, Boisen MK, Kristensen PL, Løkkegaard ECL, Krog SM, Brandt L, Brinth LS, Nolsøe RLM, Rysø C, Eiken P, Bestle MH, Jørgensen IM, Pedersen-Bjergaard U, Lindegaard B, Christensen TB, Fischer TK. Characteristics and early outcomes of patients hospitalised for COVID-19 in North Zealand, Denmark. *Dan Med J*. 2020; **67**.
- 71 Koleilat I, Galen B, Choinski K, Hatch AN, Jones DB, Billett H, Indes J, Lipsitz E. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*. [10.1016/j.jvsv.2020.06.012](https://doi.org/10.1016/j.jvsv.2020.06.012).
- 72 Mei F, Fan J, Yuan J, Liang Z, Wang K, Sun J, Guan W, Huang M, Li Y, Zhang WW. Comparison of Venous Thromboembolism Risks Between COVID-19 Pneumonia and Community-Acquired Pneumonia Patients. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2020; **40**: 2332-7. doi:10.1161/ATVBAHA.120.314779.
- 73 Aleva FE, van Mourik L, Broeders MEAC, Paling AJ, de Jager CPC. COVID-19 in critically ill patients in North Brabant, the Netherlands: Patient characteristics and outcomes. *Journal of Critical Care*. 2020; **60**: 111-5. <https://doi.org/10.1016/j.jcrc.2020.08.001>.
- 74 Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F, Airò P, Bazzani C, Crisafulli F, Filippini M, Frassi M, Gerardi MC, Gorla R, Lazzaroni MG, Lini D, Nalli C, Panaro S, Piantoni S, Regola F, Taglietti M, Tincani A, Toniati P, Vojinovic T, Zingarelli S. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. *The Lancet Rheumatology*. 2020; **2**: e549-e56. [10.1016/S2665-9913\(20\)30169-7](https://doi.org/10.1016/S2665-9913(20)30169-7).

- 75 Pizzolo F, Rigoni AM, De Marchi S, Friso S, Tinazzi E, Sartori G, Stefanoni F, Nalin F, Montagnana M, Pilotto S, Milella M, Azzini AM, Tacconelli E, Marchi G, Girelli D, Olivieri O, Martinelli N. Deep vein thrombosis in SARS-CoV-2 pneumonia-affected patients within standard care units: Exploring a submerged portion of the iceberg. *Thrombosis research*. 2020; **194**: 216-9. 10.1016/j.thromres.2020.08.008.
- 76 Larsen K, Coolen-Allou N, Masse L, Angelino A, Allyn J, Bruneau L, Maillot A, Lagrange-Xelot M, Vitry T, André M, Travers JY, Foch E, Allou N. Detection of Pulmonary Embolism in Returning Travelers with Hypoxemic Pneumonia due to COVID-19 in Reunion Island. *The American Journal of Tropical Medicine and Hygiene*. 2020; **103**: 844-6. <https://doi.org/10.4269/ajtmh.20-0597>.
- 77 Ierardi AM, Coppola A, Fusco S, Stellato E, Aliberti S, Andrisani MC, Vespro V, Arrichiello A, Panigada M, Monzani V, Grasselli G, Venturini M, Rehani B, Peyvandi F, Pesenti A, Blasi F, Carrafiello G. Early detection of deep vein thrombosis in patients with coronavirus disease 2019: who to screen and who not to with Doppler ultrasound? *Journal of Ultrasound*. 2020. 10.1007/s40477-020-00515-1.
- 78 Soumagne T, Lascarrou J-B, Hraiech S, Horlait G, Higny J, d'Hondt A, Grimaldi D, Gaudry S, Courcelle R, Carbutti G, Blonz G, Aissaoui N, Vinsonneau C, Vandebunder B, Textoris J, Szychowiak P, Serck N, Sauneuf B, Piagnerelli M, Ly A, Lejeune F, Lefebvre L, Piton G. Factors Associated With Pulmonary Embolism Among Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: A Multicenter Study Among 375 Patients. *Critical Care Explorations*. 2020; **2**: e0166. 10.1097/cce.000000000000166.
- 79 Gatto M, Perricone C, Tonello M, Bistoni O, Cattelan AM, Bursi R, Cafaro G, De Robertis E, Mencacci A, Bozza S, Vianello A, Iaccarino L, Gerli R, Doria A, Bartoloni E. Frequency and clinical correlates of antiphospholipid antibodies arising in patients with SARS-CoV-2 infection: findings from a multicentre study on 122 cases. *Clin Exp Rheumatol*. 2020; **38**: 754-9.
- 80 Mazzaccaro D, Giacomazzi F, Giannetta M, Varriale A, Scaramuzzo R, Modafferi A, Malacrida G, Righini P, Marrocco-Trischitta MM, Nano G. Non-Overt Coagulopathy in Non-ICU Patients with Mild to Moderate COVID-19 Pneumonia. *Journal of clinical medicine*. 2020; **9**: 1781. 10.3390/jcm9061781.
- 81 Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19?

Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?

Thrombosis and haemostasis. 2020; **120**: 1230-2. 10.1055/s-0040-1712097.

82 Lim W, Meade M, Lauzier F, Zarychanski R, Mehta S, Lamontagne F, Dodek P, McIntyre L, Hall R, Heels-Ansdell D, Fowler R, Pai M, Guyatt G, Crowther MA, Warkentin TE, Devereaux PJ, Walter SD, Muscedere J, Herridge M, Turgeon AF, Geerts W, Finfer S, Jacka M, Berwanger O, Ostermann M, Qushmaq I, Friedrich JO, Cook DJ. Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients*. *Crit Care Med*. 2015; **43**: 401-10. 10.1097/ccm.0000000000000713.

83 Patel R, Cook DJ, Meade MO, Griffith LE, Mehta G, Rocker GM, Marshall JC, Hodder R, Martin CM, Heyland DK, Peters S, Muscedere J, Soth M, Campbell N, Guyatt GH. Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *J Crit Care*. 2005; **20**: 341-7. 10.1016/j.jcrc.2005.09.014.

84 Samama MM, Cohen AT, Darmon J-Y, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson C-G, Turpie AG, Weisslinger N. A Comparison of Enoxaparin with Placebo for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients. *New England Journal of Medicine*. 1999; **341**: 793-800. 10.1056/nejm199909093411103.

85 Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, Turpie AG, Egberts JF, Lensing AW. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *Bmj*. 2006; **332**: 325-9. 10.1136/bmj.38733.466748.7C.

86 Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004; **110**: 874-9. 10.1161/01.Cir.0000138928.83266.24.

87 Lew TWK, Kwek T-K, Tai D, Earnest A, Loo S, Singh K, Kwan KM, Chan Y, Yim CF, Bek SL, Kor AC, Yap WS, Chelliah YR, Lai YC, Goh S-K. Acute Respiratory Distress Syndrome in Critically Ill Patients With Severe Acute Respiratory Syndrome. *JAMA*. 2003; **290**: 374-80. 10.1001/jama.290.3.374.

88 Who Mers-Cov Research G. State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. *PLoS Curr*. 2013; **5**:

ecurrents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8.

10.1371/currents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8.

89 Bunce PE, High SM, Nadjafi M, Stanley K, Liles WC, Christian MD. Pandemic H1N1 Influenza Infection and Vascular Thrombosis. *Clinical Infectious Diseases*. 2011; **52**: e14-e7. 10.1093/cid/ciq125.

90 Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, Dela Cruz CS, Dumont A, Halene S, Hwa J, Koff J, Menninger H, Neparidze N, Price C, Siner JM, Tormey C, Rinder HM, Chun HJ, Lee AI.

Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *The Lancet Haematology*. 2020; **7**: e575-e82. 10.1016/s2352-3026(20)30216-7.

91 Morici N, Bottiroli M, Fumagalli R, Marini C, Cattaneo M. Role of von Willebrand Factor and ADAMTS-13 in the Pathogenesis of Thrombi in SARS-CoV-2 Infection: Time to Rethink. *Thrombosis and haemostasis*. 2020. 10.1055/s-0040-1713400.

92 Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *Journal of Thrombosis and Haemostasis*. 2020; **18**: 1738-42. 10.1111/jth.14850.

93 Gabrielli M, Lamendola P, Esperide A, Valletta F, Franceschi F. COVID-19 and thrombotic complications: Pulmonary thrombosis rather than embolism? *Thrombosis research*. 2020; **193**: 98. 10.1016/j.thromres.2020.06.014.

94 van Nieuwkoop C. COVID-19 associated pulmonary thrombosis. *Thrombosis research*. 2020; **191**: 151. 10.1016/j.thromres.2020.04.042.

95 Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Critical Care*. 2020; **24**: 353. 10.1186/s13054-020-03062-7.

96 McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology*. 2020; **2**: e437-e45. 10.1016/S2665-9913(20)30121-1.

97 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020; **135**: 2033-40. 10.1182/blood.2020006000.

- 98 Li L-q, Huang T, Wang Y-q, Wang Z-p, Liang Y, Huang T-b, Zhang H-y, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of Medical Virology*. 2020; **92**: 577-83. 10.1002/jmv.25757.
- 99 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A, Network ftC-LI. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020; **323**: 1574-81. 10.1001/jama.2020.5394.
- 100 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016; **41**: 3-14. 10.1007/s11239-015-1311-6.
- 101 Ay C, Dunkler D, Marosi C, Chiriac A-L, Vormittag R, Simanek R, Quehenberger P, Zielinski C, Pabinger I. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010; **116**: 5377-82. 10.1182/blood-2010-02-270116.
- 102 Langer F, Kluge S, Klamroth R, Oldenburg J. Coagulopathy in COVID-19 and Its Implication for Safe and Efficacious Thromboprophylaxis. *Hamostaseologie*. 10.1055/a-1178-3551.
- 103 Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian CD, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *Journal of the American College of Cardiology*. 2020: 27284. 10.1016/j.jacc.2020.04.031.
- 104 Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Jimenez D, LeGal G, Rali P, Wells P. Prevention, Diagnosis, and Treatment of VTE in Patients With COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 10.1016/j.chest.2020.05.559.
- 105 Overstad S, Tjonnfjord E, Garabet L, Fronas S, Bergan J, Aballi S, Ghanima W. Venous thromboembolism and coronavirus disease 2019 in an ambulatory care setting -

A report of 4 cases. *Thrombosis research*. 2020; **194**: 116-8.

10.1016/j.thromres.2020.06.032.

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Tables

Table 1. Characteristics of identified studies

	No. of studies	No. of patients
Study location		
Europe	57	11,709
North America	17	17,127
Asia	8	1,962
Multinational and other	4	3,172
Study design		
Randomized controlled trial	2	1,296
Cohort study	75	28,536
Cross sectional study	5	502
Case-control study	4	3,636
Institutional setting		
Single center	64	20,729
Multicenter	22	13,241
Health care setting		
Ambulatory & hospitalized	9	4,773
Hospitalized (+/- ICU)	53	27,155
ICU	24	2,042
Reported outcomes		
Overall VTE	50	20,961
PE	61	22,618
DVT	54	20,773
VTE screening		
Yes	19	1,440
No	59	27,106
Not reported	8	5,424
Use of anticoagulation (either prophylactic or therapeutic)		
100% of patients	34	3,312
>90% of patients	7	1,762
<90% of patients	10	4,681

not reported	35	24,215
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Abb.: DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 2. Patient characteristics

	No./Total (%) of patients	No./Total (%) of ICU/critical care patients
Mean age (\pm SD) <i>in years</i>	62.6 (\pm3.8)	62.6 (\pm4.2)
Sex		
- Male	11,817/19,671 (60.1%)	1,632/2,321 (71.3%)
- Female	7,854/19,671 (39.9%)	689/2,321 (29.7%)
Hypertension	6,446/12,583 (51.2%)	779/1,509 (51.6%)
Dyslipidaemia	2,993/8,330 (35.9%)	177/436 (40.6%)
Diabetes mellitus type 2	4,088/13,361 (30.6%)	533/1,748 (30.5%)
Current or former smoker	985/7,421 (13.3%)	214/899 (23.8%)
Cancer	805/7,979 (10.1%)	90/965 (9.3%)
- Active cancer	55/1,509 (3.6%)	20/587 (3.4%)
Chronic kidney disease	1,024/8,101 (12.6%)	136/1,328 (10.2%)
Coronary artery disease	1,693/10,622 (15.9%)	132/979 (13.5%)
Congestive heart failure	865/9,612 (9.0%)	49/786 (6.2%)
Chronic liver disease	85/3,011 (2.8%)	42/839 (5.0%)
Chronic lung disease	1,214/9,728 (12.5%)	162/1,233 (13.1%)
Prior VTE	321/7,392 (4.3%)	40/699 (5.7%)
Cardiovascular disease	412/1,198 (34.4%)	249/706 (35.2%)
Cerebrovascular disease	182/2,282 (8.0%)	42/411 (10.2%)
Immune disease or immunosuppression	175/2,456 (7.1%)	49/629 (7.8%)
Asthma	208/2,120 (9.9%)	58/480 (12.1%)

Abb.: ICU, intensive care unit; SD, standard deviation; VTE, venous thromboembolism.

Table 3. Prevalence of venous thromboembolism, pulmonary embolism and deep vein thrombosis in ICU and non-ICU hospitalized COVID-19 patients

Outcome	Studies	Number of patients	Number of outcomes	Estimate of prevalence [95%CI]	Heterogeneity (I ²)
ICU-patients only					
VTE (studies reporting both outcomes)	25	2966	617	22.7% [18.1-27.6]	87.3%
---No Screening	20	2791	535	18.7% [14.9-22.9]	83.1%
---Screening*	5	175	82	45.6% [30.6-61.1]	73.4%
PE (±DVT)†	27	3085	410	13.7% [10.0-17.9]	87.6%
DVT (±PE)	30	3001	423	18.7% [12.6-25.6]	94.6%
---No Screening	19	2642	251		
---Screening*	9	359	172	48.5% [31.0-66.2]	91.0%
Non-ICU hospitalized patients‡					
VTE (studies reporting both outcomes)	23	7390	411	7.9% [5.1-11.2]	94.6%
---No Screening	19	7053	321	5.5% [3.6-7.9]	91.0%
---Screening*	4	337	90	23.0% [3.2-52.5]	96.5%
PE (±DVT)†	23	8698	263	3.5%	88.9%

				[2.2-5.1]	
DVT (\pm PE)	22	10519	256	4.1% [2.3-6.4]	94.6%
---No Screening	14	9835	144	1.4% [0.7-2.3]	85.0%
---Screening*	8	684	112	12.7% [3.7-25.5]	94.1%

The meta-analysis of VTE comprises all studies reporting rates of PE and DVT, the analysis of PE comprises all studies reporting PE as a separate outcome and the analysis of DVT comprises studies reporting DVT rates separately. Studies with a suspected high risk of bias have been excluded from these analyses.

Abb.: DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.

* In one study screening was performed in 28% of total patients (ICU 51%, non-ICU hospitalized 14%) [15]

† No screening for pulmonary embolism was performed.

‡ All patients who were hospitalized at study baseline, excluding ICU patients. ICU admission during later hospital course was possible.

Table 4. Characteristics of COVID-19 patients with vs. those without venous thromboembolism

	No./Total (%) of VTE patients	No./Total (%) of non-VTE patients	Pooled OR for VTE [95%CI]	p-value
Mean age (\pm SD) <i>in years</i>	63.3 (\pm 3.9)	63.4 (\pm 2.8)	/	/
Sex				
- Male	627/940 (66.7%)	2,315/3,803 (60.9%)	1.45 [1.22-1.72]	<.001
- Female	313/940 (33.3%)	1,488/3,803 (39.1%)	Ref.	Ref.
Hypertension	278/584 (47.6%)	1,115/2,359 (47.3%)	0.88 [0.51-1.51]	0.650
Diabetes mellitus type 2	189/652 (29.0%)	618/2,725 (22.7%)	0.97 [0.58-1.63]	0.918
Current or former smoker	75/446 (16.8%)	296/1,913 (15.5%)	0.83 [0.42-1.64]	0.590
Cancer	58/676 (8.6%)	306/2,852 (10.7%)	1.17 [0.72-1.88]	0.421
Chronic kidney disease	32/444 (7.2%)	202/1,914 (10.6%)	0.76 [0.49-1.19]	0.230
Coronary artery disease	32/285 (11.2%)	190/1,731 (11.0%)	1.04 [0.67-1.60]	0.866
Congestive heart failure	25/389 (6.4%)	161/2,025 (8.0%)	0.86 [0.51-1.46]	0.576
Chronic lung disease	49/424 (11.6%)	179/2,101 (8.5%)	0.92 [0.49-1.70]	0.783
Prior VTE	38/524 (7.3%)	132/2128 (6.2%)	1.61 [0.97-2.67]	0.068
Cardiovascular disease	42/121 (34.7%)	72/404 (17.8%)	1.52 [0.51-4.56]	0.456
Immune disease or immunosuppression	11/252 (4.4%)	98/1310 (7.5%)	1.24 [0.60-2.59]	0.563
Cerebrovascular disease	18/161 (11.2%)	67/1273 (5.3%)	0.54 [0.22-1.33]	0.177

Abb.: CI, confidence interval; OR, odds ratio; SD, standard deviation; VTE, venous thromboembolism.

Figures

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection

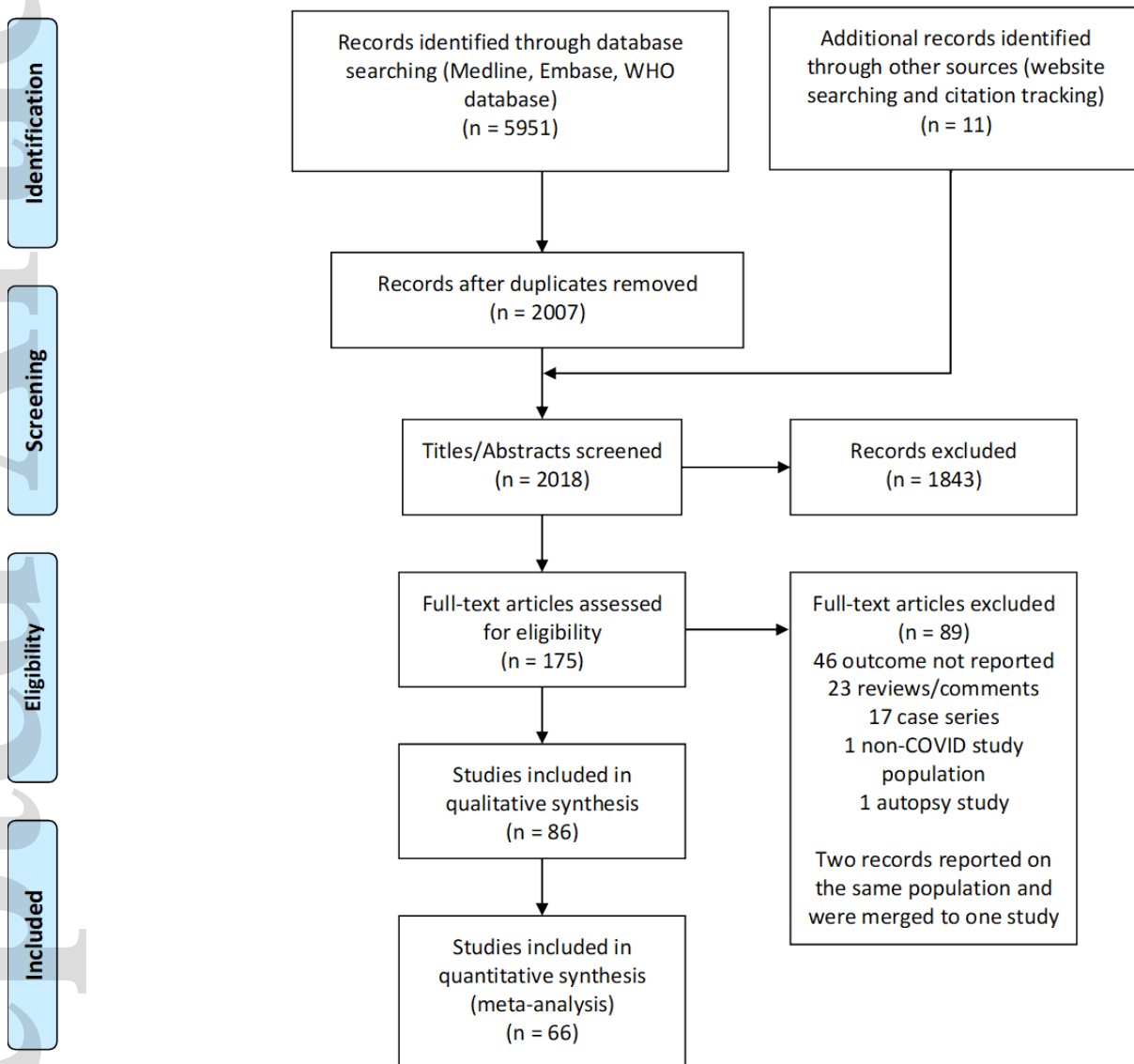
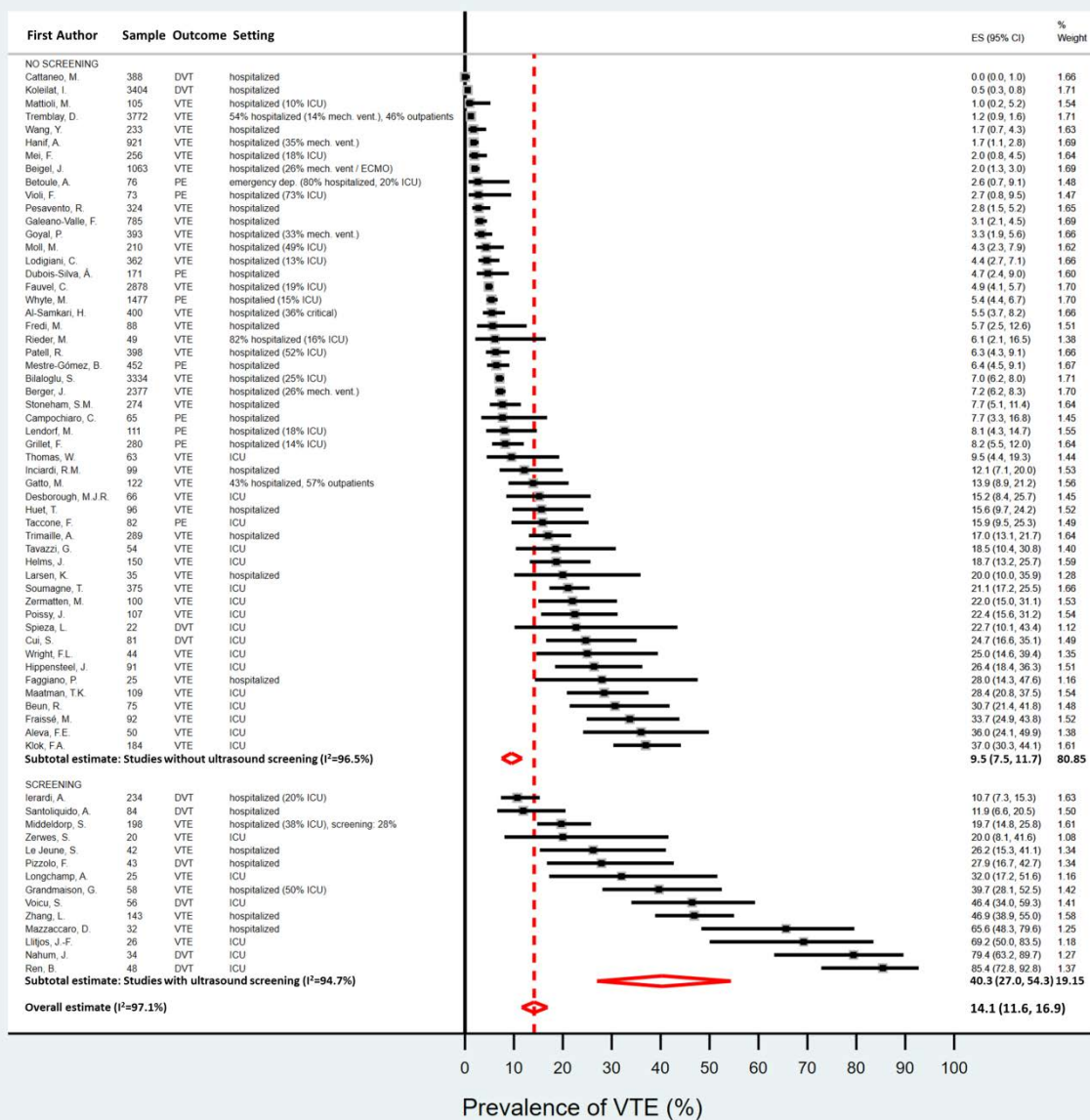


Figure 2. Prevalence of venous thromboembolism in patients with COVID-19

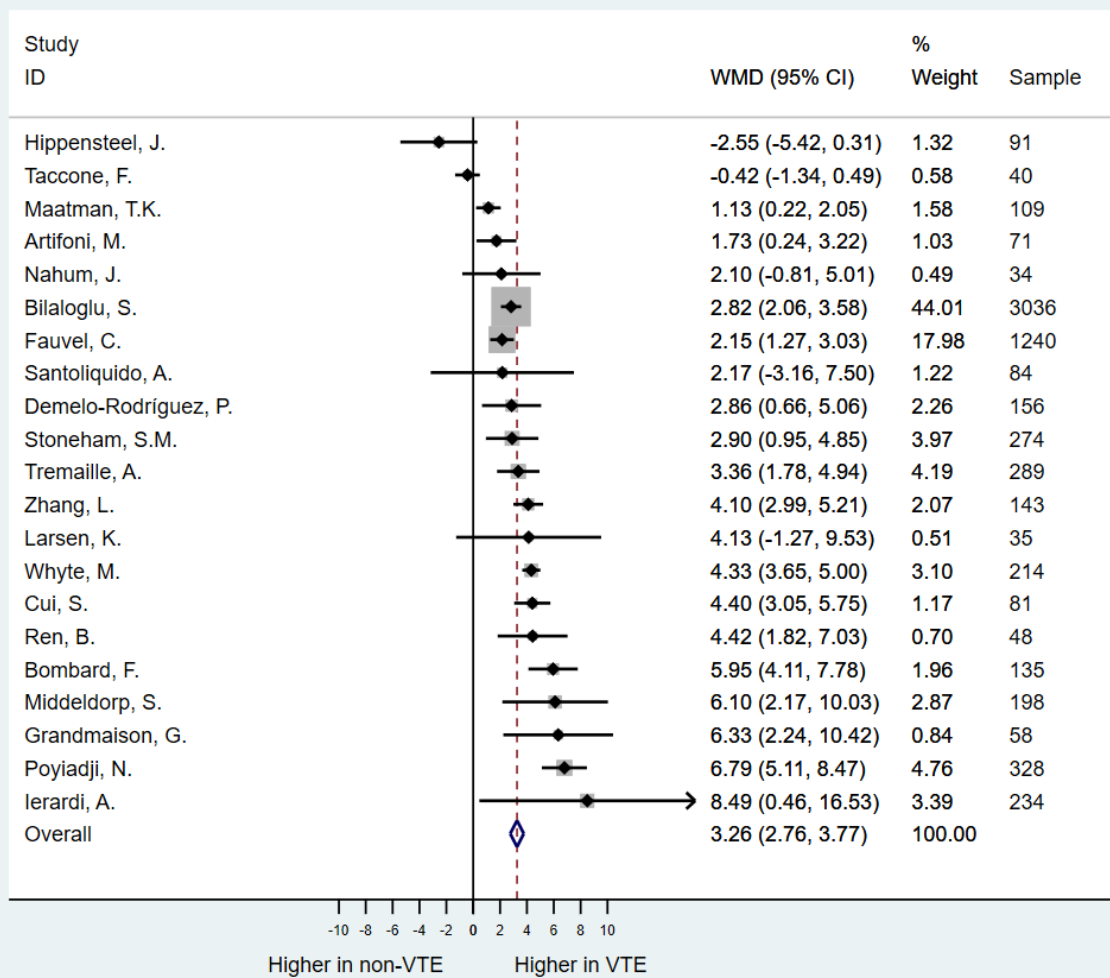


Legend: Prevalence of venous thromboembolism (VTE) is estimated based on 66 studies and stratified by the performance of ultrasound screening for VTE. The overall VTE prevalence was 14.1% ([95%CI: 11.6-16.9] and 40.3% ([95%CI: 27.0-54.3] in those screened and 9.5% ([95%CI: 7.5-11.7] in those not screened. Red rhombuses represent subtotal (screening studies vs non-screening studies) and overall prevalence estimates and corresponding 95% CI of VTE outcomes. VTE comprises the specific outcome as reported by the respective study (PE and/or DVT). Details on each study are listed in **Tables S1&2**.

Abb.: CI, confidence interval; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ES, estimates; mech. vent., mechanically ventilated; ICU, intensive care unit; PE, pulmonary embolism.

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Figure 3: Differences in baseline D-dimer between VTE and non-VTE patients



Legend: Patients developing VTE had higher baseline D-dimer levels compared to those without VTE. D-dimer levels at baseline were available in 21 studies, including 6,633 patients. In the pooled analysis, levels of D-dimer were substantially higher at baseline in patients experiencing VTE (WMD: 3.26 µg/ml ([95%CI: 2.76-3.77], $p < 0.001$; $I^2: 87.3\%$).

Abb.: CI, confidence interval; VTE, venous thromboembolism; WMD, weighted mean difference.