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Pulmonary Embolism Does Not Have an Unusually High Incidence Among Hospitalized COVID19 Patients

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Abstract

Introduction: Acute respiratory illnesses from COVID19 infection are increasing globally. Reports from earlier in the pandemic suggested that patients hospitalized for COVID19 are at particularly high risk for pulmonary embolism (PE). To estimate the incidences of PE during hospitalization for COVID19, we performed a rigorous systematic review of published literature. **Methods:** We searched for case series, cohort studies and clinical trials from December 1, 2019 to July 13, 2020 that reported the incidence of PE among consecutive patients who were hospitalized for COVID19 in ICUs and in non-ICU hospital wards. To reflect the general population of hospitalized COVID19 patients, we excluded studies in which subject enrollment was linked to the clinical suspicion for venous thromboembolism (VTE). **Results:** Fifty-seven studies were included in the analysis. The combined random effects estimate of PE incidence among all hospitalized COVID19 patients was 7.1% (95% CI: 5.2%, 9.1%). Studies with larger sample sizes reported significantly lower PE incidences than smaller studies ($r^2 = 0.161$, $p = 0.036$). The PE incidence among studies that included 400 or more patients was 3.0% (95% CI: 1.7%, 4.6%). Among COVID19 patients admitted to ICUs, the combined estimated PE incidence was 13.7% (95% CI: 8.0%, 20.6%). The incidence of ICU-related PE also decreased as the study sample sizes increased. The single largest COVID19 ICU study ($n = 2215$) disclosed a PE incidence of 2.3% (95% CI: 1.7%, 3.0%). **Conclusion:** PE incidences among hospitalized COVID19 patients are much lower than has been previously postulated based on smaller, often biased study reports. The incidence of "microthrombosis," leading to occlusion of microscopic blood vessels, remains unknown.

Keywords

COVID-19, pulmonary embolism, SARS-COV-2, deep venous thrombosis, thromboembolism

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Introduction

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are common complications of illnesses that require hospitalization, especially in intensive care units (ICUs).[1] There are widely varying reports regarding whether hospitalization for respiratory illness from COVID19 entails an especially high risk of clinically significant PE, which in turn would further complicate the management of respiratory failure from COVID19. The perception that PE is a particularly common complication of COVID19 pneumonia has prompted some clinicians to lower the threshold for performing diagnostic studies, push for empiric treatment for acute PE and use higher than standard doses of pharmacological prophylaxis.

However, the fast pace of publications regarding the clinical properties and associated conditions specific to COVID19

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infection carries a risk of publication bias.[2] The risk may be increased particularly by the high number of observational studies published early in the pandemic, reporting outcomes of relatively small patient numbers.[3] Also, studies that include only hospitalized COVID19 patients for whom diagnostic tests for PE had already been performed for clinical reasons may overestimate the incidence of PE. In those studies, the indications for the tests may have been linked to clinical reasons to suspect PE other than the presence of COVID19.

In order to understand how the presence of COVID19 itself should guide clinical decisions regarding diagnostic thresholds, empiric treatment and prophylaxis for those in whom the diagnosis of PE has not been established, we performed a meta-analysis to estimate the incidence of PE during hospitalization for COVID19 within and outside ICUs. Our secondary aim was to estimate the incidence of DVT and of VTE (the combined incidence of PE and DVT) among those patients. We limited our analysis to groups in which study inclusion was not linked to a pre-existing suspicion for acute PE.

Methods

We followed the methodology of the Meta-analysis Of Observational Studies in Epidemiology group to evaluate the PE incidence among hospitalized COVID19 patients.[4] We performed a systematic search for case series, cohort studies and randomized control studies that reported the incidence of objectively measured PE, DVT, or both among consecutively hospitalized adult patients or consecutively hospitalized adult patients in which inclusion was not related to the suspicion for PE or DVT. Hospitalization for COVID19 would include admission to an intensive care unit (ICU) or to a non-ICU hospital ward.

Search Strategy

Two trained investigators (NGC and JYZ) performed a search of the U.S. National Library of Medicine MEDLINE database using the PubMed search engine with the search terms [(SARS-CoV2 OR COVID-19 OR COVID19) AND (trial OR series OR cohort OR incidence)] from December 1, 2019 to July 13, 2020. They manually searched the reference lists of relevant review articles and meta-analyses for additional reports of primary data. Since the rapid publication of COVID19 studies had precluded timely categorization of article type in the PubMed search engine at the time of the search, the authors manually screened all study titles and abstracts and discarded those that did not refer to clinical data on hospitalized adult patients with COVID19.

Study Selection

All authors reviewed the full text of the remaining published papers for inclusion and exclusion criteria. Studies were included if (1) the published paper described original primary clinical data from COVID19 patients; (2) the study population was 18 years of age or older; and (3) the published paper was written in English. Studies were excluded on the basis of quality if they (1) had not been peer-reviewed; (2) were not performed within a specified time interval; (3) did not report the results of a set of hospitalized patients with confirmed diagnosis of COVID19. In addition, studies were excluded on the basis of imprecision if (4) they did not describe a method whereby clinically detected VTE was tabulated; or (5) they did not report the VTE incidence (PE, DVT, or both) among the specified study population. Finally, studies were excluded on the basis of enrichment of the sample population if (6) they did not describe a consecutive case series or consecutive cohort studies or controlled trials with consecutive enrollment of subjects that met specific inclusion criteria (e.g., cross-sectional studies of patients already in hospital); or (7) inclusion on the sample population was related to the clinical suspicion for PE, DVT or both.

Factors that were considered to raise the risk of bias but did not require exclusion were (1) the published paper did not specify the proportions of non-ICU hospitalized patients and ICU patients; (2) the indication to initiate diagnostic testing for VTE (clinical suspicion for VTE, specified algorithm for work-up of VTE, universal testing for DVT or PE, etc.) was not specified; (3) the diagnostic methods to confirm PE, DVT or both were not specified; (4) thromboprophylaxis regimens were not specified; (5) thromboprophylaxis regimens were heterogeneous within the study population (5% or more of the population were treated with different protocols); and (6) thromboprophylaxis regimens were not standard for hospitalized or ICU patients. The investigators contacted the authors if the publications were unclear regarding the study procedures.

Data Extraction

All authors individually extracted data from the remaining publications. Results were compared among the authors in an unblinded fashion and disagreements were settled by consensus. Extracted data included the type of study (prospective or retrospective; interventional trial or observational study); sites (single or multiple); geographic location (Europe, Asia, USA, or other); study population (ward or ICU); reason for DVT imaging (screening vs symptom-based); reason for PE imaging; prophylactic anticoagulation; number of COVID19 patients in each setting (ICU vs non-ICU ward); numbers of PE in each setting; numbers of segmental and larger PE (when specified); numbers of DVT and VTE in each setting; and numbers of proximal vein DVT (when specified). Arterial events were not included in this analysis.

Potentially confounding variables were discussed among all authors and decisions regarding data extraction were made by consensus.

Statistical Analysis

The incidence of PE was the primary outcome. The incidence of DVT and VTE were secondary outcomes that were treated separately. The incidence ($\hat{p}$) for each study was estimated as

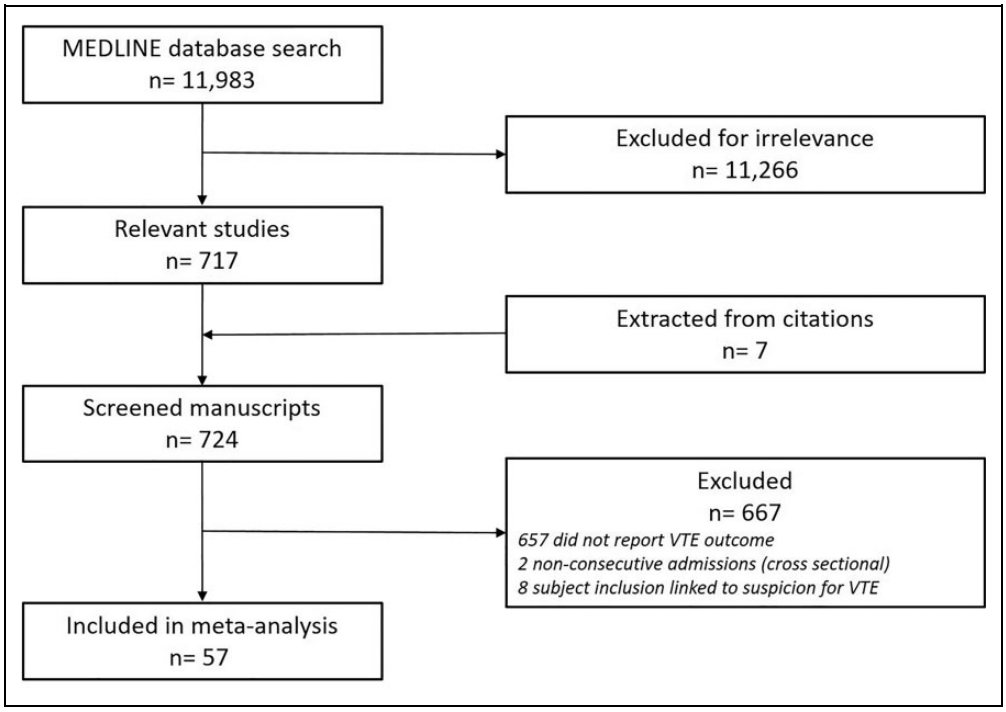

Figure 1. Study selection. Flow diagram of search and selection of published papers.

$$\hat{p} = x/N$$

where x was the number of cases and N was the number of patients at risk. Ninety-five per cent confidence intervals were estimated by the method of Clopper & Pearson for display in forest plots.[5] There were a few studies where a zero event was recorded. In those cases, we added 0.1 to both x and N to avoid division by zero. An arcsine transformation (arcsine $[\sqrt{\hat{p}}]$) was applied in order to stabilize the variance because the values of $\hat{p}$ were strongly skewed. The variance of the transformed variable was 1/4 N and the weight for each study was the inverse of the variance.

A few estimates of $\hat{p}$ were much higher than the others. If (arcsine $[\sqrt{\hat{p}}]$) was more than 3 standard deviations from the mean of the transformed distribution, then we assumed that the study was drawn from a different population of patients and it was excluded from subsequent analysis.

Estimates were combined using random-effects method that accounts for heterogeneity between studies.[6] We used the meta-analysis macro *MA_summary*.[7] The estimate and its 95% confidence interval were back-transformed to give the overall estimate of incidence and displayed in the forest plot.[8] Heterogeneity was assessed by the I^2 index.[9]

There were 5 categorical variables: region (Europe, Asia, USA, Middle East, multinational, design (retrospective, prospective, mixed), observational (observational, interventional), site (single center, multicenter), setting (ward, ICU, or both ward and ICU). The median (IQR) incidence for each category was tabulated. Categories were compared by the Wilcoxon or Kruskal-Wallis tests as appropriate. We fitted meta-regression models to examine the effect of covariates on incidence. For each model, the outcome was (arcsine $[\sqrt{\hat{p}}]$). The independent variables were a polynomial function of logN and one categorical covariate. The results were displayed as bubble plots where the size of the bubbles reflected the precision of each study.

Results

Search Results

The search of MEDLINE database from December 1, 2019 to July 13, 2020 generated 11,983 published papers, 11,266 of which were excluded for irrelevance (Figure 1). Among the remaining papers, 657 were excluded because they did not report VTE incidences. Two studies were cross-sectional that did not include consecutively admitted patients, while 8 studies included patients based in part on the clinical suspicion of PE, DVT or both (Appendix 1). Data from the remaining 57 papers were extracted for analysis (described in Appendix 1). The extracted data described 18,110 patients hospitalized for COVID19. Observation studies accounted for 51 of the papers, while 7 came from interventional trials.

Primary Outcomes

There were 41 estimates of PE incidence ranging from 0% to 53% (Figure 2A). The combined random effects estimate of PE incidence was 7.1% (95% CI: 5.2%, 9.1%). There was a very high degree of between-study heterogeneity ($I^2 = 94\%$). This variation is illustrated by the forest plot (Figure 3A).

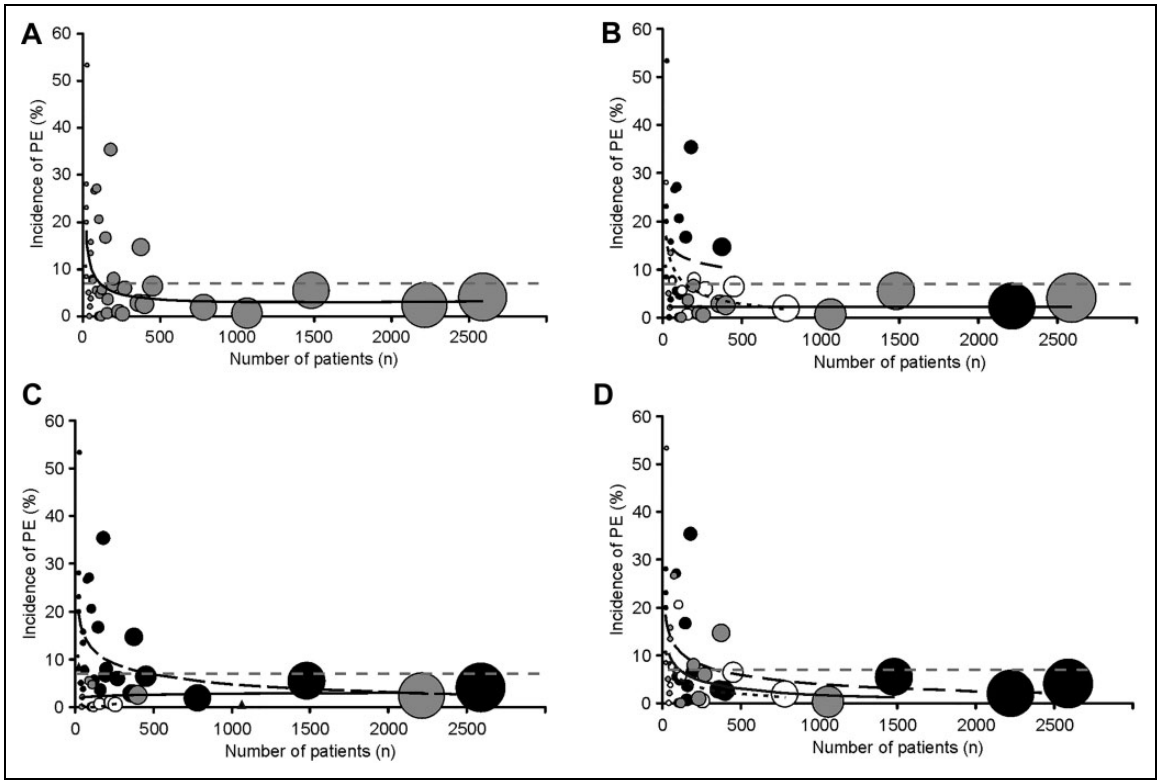

Figure 2. The incidence of PE against the number of hospitalized COVID19 patients at risk. The size of each bubble is proportional to the study weight (1/variance), which reflects the precision of the study. Panel A. Estimated incidence of PE incidence decreases with study sample size. r2 = 0.161, p = 0.036. Panel B. PE incidence decreases with study sample size and varies with clinical location (white circles and dotted line—non-ICU wards, black circles and dashed line—ICU, grey circles and solid line—combination of ICU and non-ICU wards). r2 = 0.351, p = 0.001. Panel C. PE incidence decreases with study sample size and varies with geographic location (white circles and dotted line—Asia, black circles and dashed line—Europe, grey circles and solid line—USA). Middle East and multinational were too few to be included in the regression model. r2 = 0.550, p < 0.001. Panel D. PE incidence plotted against study size but does not vary with anticoagulation regimen (white circles and dotted line—at least 95% of patients were on standard prophylaxis regimens, black circles and dashed line—mixed prophylaxis regimens, grey circles and solid line—not specified). r2 = 0.198, p = 0.040.

The highest estimates of PE incidence were associated with smallest sample sizes, (Figure 2A) and PE incidences decreased as the sample sizes grew larger ($r^2 = 0.161$, $p = 0.036$). Although the rate of change of incidence declined rapidly with increasing N, the rate became constant in studies containing 400 or more patients. The combined estimate for the 7 studies with 400 or more patients at risk was 3.0% (95% CI: 1.7%, 4.6%).

The PE incidences trended higher among studies of ICU patients than among studies of patients on non-ICU wards ($p = 0.087$) and was higher than in studies that included patients in both wards and ICUs ($p = 0.001$), after adjusting for the log of the study population size (Figure 2B). The combined estimate for 19 ICU studies was 13.7% (95% CI: 8.0%, 20.6%). However, similar to the incidence estimates for all hospitalized COVID19 patients, the incidence of PE among those on the ICU also decreased as the study sample sizes increased (Figures 2B, 3B). All but one study included less than 400 patients, but in the single large study (n = 2215), the incidence of PE among COVID19 patients in 65 ICUs was 2.3% (95% CI: 1.7%, 3.0%).[10]

There were marked differences among geographic regions, with higher values in Europe compared to USA and Asia (Table 1, Figure 2C). After adjusting for the log of the study population size, the incidences of PE among hospitalized COVID19 patients were significantly lower in the USA ($p = 0.006$) and Asia ($p < 0.001$) than in Europe.

None of the included studies reported the PE incidence among groups in which 95% or more patients received no anticoagulant prophylaxis. Conversely, none reported the PE incidence among studies in which 95% or more patients received a prophylactic anticoagulant dose higher than the standard does used by the hospital for similar patients without COVID19. There was no significant difference in PE incidences among studies in which at least 95% of COVID19 patients were treated with standard prophylactic anticoagulant doses, those in whom 5% or more patients were given higher prophylactic anticoagulant doses and those in whom the doses were not specified ($p = 0.269$), after adjusting for the log of the study population size (Table 1, Figure 2D).

Most studies did not specify the size distribution or the ranges of clinical significance for the PEs that were observed.

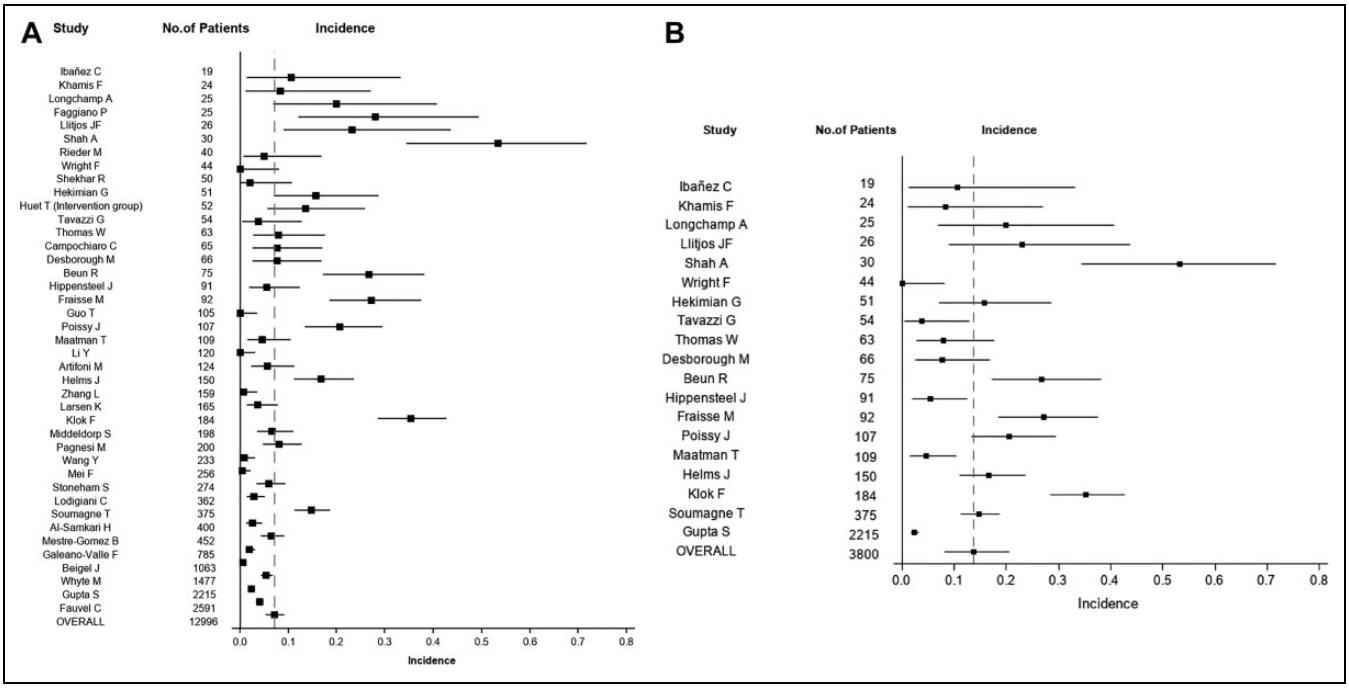

Figure 3. Incidence of PE among patients hospitalized for COVID19. The reported incidences of PE among the included studies are represented by Forest plots. Panel A. The reported incidences of PE among all patients hospitalized for COVID19. Panel B. PE incidences among patients admitted to ICUs for COVID19.

Table 1. Comparison of PE incidence estimates by potential categorical predictors. Significant differences in PE incidence were associated with differences in clinical location and in geographic region. Categories with only 1 or 2 studies (e.g. 'Middle East' or 'multinational' are not included.

	p̂ Median	IQR	n	p
Category:				
Retrospective	0.04	0.01, 0.14	8	0.447
Prospective	0.06	0.03, 0.15	32	
Design:				
Interventional	0.01		3	0.305
Observational	0.06	0.03, 0.16	38	
Site:				
Multi-site	0.05	0.02, 0.15	13	0.604
Single-site	0.06	0.03, 0.15	28	
Clinical location:				
ICU	0.15	0.05, 0.23	19	0.001
Wards	0.06	0.04, 0.08	8	
Wards and ICU	0.03	0.01, 0.05	14	
Geographic region:				
Asia	0.00	0.00, 0.01	5	<0.001
Europe	0.08	0.06, 0.20	28	
USA	0.02	0.02, 0.05	6	
Anticoagulation prophylaxis:				
≥95% on standard prophylaxis	0.06	0.02, 0.08	10	0.665
Mixed prophylaxis regimens	0.05	0.04, 0.20	17	
Not specified	0.07	0.01, 0.15	14	

Abbreviations: p Median, median incidence of PE; IQR, interquartile range; n, number of studies; p, p-value for Wilcoxon or Kruskal-Wallis.

Among the studies that did specify their sizes, about one quarter of PEs were subsegmental.[11-21] No studies performed imaging of all hospitalized COVID19 patients for PE. Universal testing for DVT was limited to small studies that disclosed mostly asymptomatic and distal DVTs, which are of uncertain clinical significance.[20,22-27]

Secondary Outcomes

There were 43 estimates of DVT incidence ranging from 0% to 79% (on-line supplement Figures S1, S2). The combined random effects estimate of DVT incidence was 8.3% (95% CI: 6.1%, 10.9%). There was a very high degree of between-study heterogeneity (I2 = 96%). Thirty-two studies reported the incidence of VTE (PE, DVT or both), with estimates ranging from 0% to 42% (on-line supplement Figures S1, S2) of patients hospitalized with COVID19. The combined random effects estimate of VTE incidence was 14.2% (95% CI: 10.7%, 18.1%), with a very high degree of between-study heterogeneity (I^2 = 95%). Among patients hospitalized with COVID19 to ICUs or non-ICU wards, the incidence of DVT and VTE followed the same patterns as was observed for PEs (Figures S1B, S3B). Similarly to what was described for PE, the plots of VTE and DVT incidences vs study size disclosed inflections in slopes reflecting consistently lower incidences among studies with at least 400 subjects. Including only the studies with at least 400 subjects, the estimated incidence of

DVT was 1.8% (95% CI: 0.6%, 4.5%) and the estimated incidence of VTE was 5.5% (95% CI: 3.2%, 8.3%).

Discussion

Our analysis disclosed rates of PE and DVT among hospitalized COVID19 patients within non-ICU wards and within ICUs that are comparable to the rates observed among similarly ill patients without COVID19.[1,28-30] Notably, the incidence of PE among studies with 400 or more subjects was substantially lower than the incidence among smaller studies, suggesting a publication bias towards positive results in those studies that could lead to an overestimation of the true incidence of PE.[3] The same pattern was observed across the studies that reported incidences of DVT and of VTE.

Most importantly, our incidence estimates are much lower than those from other analyses[31,32] because we specifically excluded studies in which the inclusion criteria for entry was related to the clinical suspicion that the patients had PE, DVT or both. For example, we excluded studies that included only patients in whom contrast-enhanced chest CT scans or compression ultrasound examinations had already been performed for clinical indications. We excluded eight such studies (on-line supplement Table S2) because they do not represent in an unbiased manner the clinical population of hospitalized COVID-19 patients.[33-40] The incidence of PE among those excluded studies ranged between 22% and 66%. However, similar rates are reported in the non-COVID19 population when PE is clinically suspected and then searched for by imaging. For example, PE was confirmed objectively in 27%-28% of patients in whom there was a moderate suspicion for PE and in 74%-78% of patients with a high clinical suspicion.[41-43] Therefore, depending on the degree of suspicion, the COVID19 incidence among the excluded studies appears comparable to what would be expected in patients without COVID19.

Prior to the COVID19 pandemic, PE was estimated to occur in approximately 3.9% of hospitalized medical patients, while DVT occurred at a rate of about 6.7%.[1] In general, the incidence of VTE in critically ill patients rises with illness severity.[44] Towards that it was shown previously that PE was present in 11.3% of mechanically ventilated non-COVID19 patients who required chest CT scans for reasons other than the clinical suspicion of PE, while 19.9% were diagnosed with DVT.[28] VTE was reported among 20.9% of non-COVID19 patients with sepsis who developed Acute Respiratory Distress Syndrome (ARDS), a condition that also underlies COVID19-related lung disease.[29] Furthermore, VTE occurred in 9% of patients infected with H1N1, an infectious disease with pulmonary manifestation, who were admitted to ICUs.[30] Taken together, these studies demonstrate high rates of VTE in (critically) ill patients, especially when associated with viral infections and pulmonary manifestations such as ARDS, comparable to the results from this meta-analysis. Therefore, it does not appear that COVID19 portends a higher than usual risk for VTE in hospitalized and critically ill patients.

It is noteworthy that studies performed in Asia reported lower incidences of acute PE than studies from Europe or North America. The observed geographic differences in VTE risk are congruent with previously observed genetic/ethnic differences in the baseline risk for VTE. While African Americans have a higher risk for developing COVID19 infection, they also have a higher risk of VTE unrelated to COVID19.[45] African American patients have 5 times higher VTE incidence compared to Asian populations while those of European or Hispanic descent have an intermediate risk.[46] Similar differences in VTE incidence have been observed among the ethnically diverse populations of California.[47]

Additional studies published after our final literature search reported results that are aligned with our findings.[48-60] Among ten additional studies that reported the numbers of PE among hospitalized COVID19 patients, the combined incidence was 3.8% (268 cases among 7015 subjects).[48-57] Also similar to our findings, the incidence of PE among studies with at least 400 subjects decreased to 3.0% (174 cases among 5711 subjects).[49,57] Finally, the PE incidence among COVID19 patients admitted to ICUs in the newer studies was 8.0% (87 cases among 1081 COVID19 patients admitted to ICUs), similar to the incidence among the studies we had included.[48-51] The newer studies, which also described relatively low incidences of VTE, further support that COVID19 is a condition associated with a risk of VTE, but not beyond what would be expected in other critical illnesses.

Our study has several limitations. Approximately a quarter of the included published papers did not specify the proportions of PE and DVT among non-ICU hospitalized patients versus ICU patients, which limited the precision of our estimates for each group (on-line supplement Table S1). The screening methods to initiate diagnostic testing for PE and DVT were heterogeneous, and over a third of the studies did not specify which methods were used. Thus, it is possible that VTE diagnoses were missed in some studies because they were not as vigorously investigated. On the other hand, the methods used to confirm PE and DVT were not well described in over a third of the studies, which may have led to an overestimation of the true incidence. Finally, almost half of the studies did not specify the pharmacological thromboprophylaxis regimens administered to the populations at risk of PE and DVT. Among those that did, the majority described a heterogeneous mix of no anticoagulation, standard doses of anticoagulation and anticoagulation doses that were increased solely based on COVID19 infection.

The data presented here demonstrate that the rates of PE, DVT and VTE among hospitalized patients with COVID19 are on par with the rates seen in other medical illnesses. There is emerging evidence demonstrating that COVID19 may lead to microthrombi in the pulmonary capillaries due to pulmonary endothelialitis.[61] It is important to emphasize that diagnosis and management of microthrombotic disease is distinct from VTE and not part of this review.

In conclusion, there is no clear evidence that PE rates in COVID19 patients exceed PE rates in medically or critically

ill patients without COVID19. These findings appear valuable to inform medical decision-making processes pertaining to diagnostic thresholds and empiric treatment of COVID19 patients. Overall, the results of the analyses presented here are generalizable to patients within ICUs and those in non-ICU wards.

Summary

This systematic review reveals that the incidence of PE among hospitalized COVID19 patients appears comparable to the incidence typically seen among patients without COVID19. The impression that COVID19 is associated with a disproportionally high risk for VTE has been largely driven by publication bias inherent to smaller, often single institution studies, and should be discarded. Prospective trials are needed to better delineate risks and benefits of specific diagnostic, prophylctic and treatment strategies in hospitalized COVID19 patients.

Authors' Note

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Coronaviruses, Adult, SARS-CoV-2/COVID-19, Study Population. Date: Monday, December 7, 2020.

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Author contributions

Drs Gallastegui, Zhou and Morris collected the study data, assisted with the analysis and drafted the manuscript. Dr. von Drygalski and Fernandes assisted with data analysis and drafted the manuscript. Dr Barnes performed the statistical analysis, created the figures and drafted the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Fernandes reports no disclosures related to submitted works but has received consulting fees from Bayer Pharmaceuticals, Arena Pharmaceuticals, Bristol-Myers-Squibb and research funds from Janssen and United Therapeutics. Dr Morris reports no disclosures related to submitted works but has received grants from Bayer, grants from CHEST Foundation, personal fees from Bayer, personal fees from Pfizer, personal fees from Faegre, personal fees from Inari, outside the submitted work. Dr von Drygalski reports no disclosures related to submitted works but received fees from Biomarin, Bioverativ/Sanofi-Genzyme, Novo Nordisk, Pfizer, Takeda and Uniqure for participation in Industry sponsored Education events and Advisory Boards, and research support from Pfizer and Bioverativ/Sanofi. She is Co-Founder and a member of the Board of Directors of Hematherix Inc and holds a patent for a superFVa. She is the inventor of the Joint Activity and Damage Examination (JADE) Ultrasound measurement tool, which is copyrighted and is commercialized by the University of California San Diego. Drs Barnes, Zhou and Gallastegui Crestani report no potential conflicts of interest.

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Supplemental Material

Supplemental material for this article is available online.

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