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Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis

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ABSTRACT

Background: Studies have suggested that there is increased risk of thromboembolism (TE) associated with coronavirus disease 2019 (COVID-19). However, overall arterial and venous TE rates of COVID-19 and effect of TE on COVID-19 mortality is unknown.

Methods: We did a systematic review and meta-analysis of studies evaluating TE in COVID-19. We searched PubMed, Cochrane, and Embase for studies published up to June 12, 2020. Random effects models were used to produce summary TE rates and odds ratios (OR) of mortality in COVID-19 patients with TE compared to those without TE. Heterogeneity was quantified with I^2.

Findings: Of 425 studies identified, 42 studies enrolling 8271 patients were included in the meta-analysis. Overall venous TE rate was 21% (95% CI:17–26%): ICU, 31% (95% CI: 23–39%). Overall deep vein thrombosis rate was 20% (95% CI: 13–28%): ICU, 28% (95% CI: 16–41%); postmortem, 35% (95% CI:15–57%). Overall pulmonary embolism rate was 13% (95% CI: 11–16%): ICU, 19% (95% CI:14–25%); postmortem, 22% (95% CI:16–28%). Overall arterial TE rate was 2% (95% CI: 1–4%): ICU, 5% (95%CI: 3–7%). Pooled mortality rate among patients with TE was 23% (95%CI:14–32%) and 13% (95% CI:6–22%) among patients without TE. The pooled odds of mortality were 74% higher among patients who developed TE compared to those who did not (OR, 1.74; 95%CI, 1.01–2.98; $P = 0.04$).

Interpretation: TE rates of COVID-19 are high and associated with higher risk of death. Robust evidence from ongoing clinical trials is needed to determine the impact of thromboprophylaxis on TE and mortality risk of COVID-19.

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1. Introduction

In December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was described and by March 2020, the World Health Organization had declared the disease (Coronavirus disease 2019, COVID-19) a pandemic [1,2]. There is much that remains to be known about the virus and the disease it causes. However, in terms of disease manifestation, it is clear that while some infected people experience a life-threatening severe acute respiratory syndrome, others experience a mild respiratory illness and some others are completely asymptomatic [1]. Whereas respiratory symptoms are the fundamental feature of the disease, evidence is emerging which indicates that the disease is associated with coagulation dysfunction which predisposes patients to an increased risk of both venous and arterial thromboembolism (TE) and potentially increased mortality risk as a consequence [3].

The rate of TE reported in the literature is varied. Some studies have reported TE rates in the range of 20–30% [4–6] while others have reported rates as high as 40–70% [7–9]. The presence of hypercoagulation and thromboembolic complications been noted to correlate with a more severe course of the disease involving the need for admission into intensive care units and potentially, death. The association of the increased thrombotic risk of COVID-19 with mortality is however not well characterized. While some studies found a higher risk of mortality in COVID-19 patients with TE [10], others did not find any association [5].

With studies reporting varying rates of TE among patients with COVID-19, the overall rate of venous and arterial TE and the extent to which TE in COVID-19 may increase mortality remains unknown. Therefore, the objective of this systematic review and meta-analysis is to estimate the overall rates of TE of COVID-19 and further determine the association of TE with mortality among patients with COVID-19.

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Research in context

Evidence before this study

Early reports indicated that in COVID-19 may be associated with coagulation dysfunction. Studies have reported varying rates of thromboembolism. We searched PubMed, Cochrane and Embase for systematic reviews and meta-analyses evaluating thromboembolism rates in COVID-19 published until June 12, 2020. The search terms were "COVID-19", "SARS-CoV-2" or "novel coronavirus" and "venous thromboembolism", "arterial thromboembolism", "deep vein thrombosis" or "pulmonary embolism". There were varying rates of venous and arterial thromboembolism rates reported by several articles. Some studies noted TE rates in the range of 20–30% while others reported rates as high as 40–70%. However, there were no published systematic reviews and meta-analyses evaluating thromboembolism in COVID-19. We assessed and provided summary estimates of the overall thromboembolism rates of COVID-19 and further evaluated the impact of thromboembolism on COVID-19 mortality risk.

Added value of this study

This is the first systematic review and meta-analysis to provide pooled estimates of both the venous and arterial thromboembolism rates of COVID19 and the associated mortality risk. We evaluated the evidence of 42 studies. We found that the overall arterial and venous and thromboembolism rates of COVID-19 were significantly high. COVID-19 patients who developed thromboembolism were at a significantly higher odds of mortality compared to those who did not.

Implications of all the available evidence

The available evidence indicates that COVID-19 poses a significant risk of thromboembolism and that strategies that succeed in preventing the development of thromboembolism could reduce COVID-19 mortality. This underscores the need for clinicians to implement thromboprophylaxis protocols in order to reduce the thromboembolism risk among COVID-19 patients and to potentially reduce the mortality risk of thromboembolism. Further research is however needed to determine the optimal dosing of anticoagulation and its mortality benefit among COVID-19 patients.

2. Methods

2.1. Search strategy and selection criteria

The systematic review was conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [11]. A systematic search was conducted in PubMed, Cochrane and Embase database for studies evaluating vascular events in COVID-19. "COVID-19", "SARS-CoV-2" or "novel coronavirus" and "venous thromboembolism", "arterial thromboembolism", "deep vein thrombosis" or "pulmonary embolism" were the key words used in all searches to identify studies. No language filters were applied in the search. Forward reference searching was used to identify additional studies. The literature search was conducted on June 12, 2020 and all studies published in English or with an English translated version available up to that date of search were eligible for screening.

Title/abstract screening was done independently by two investigators (IN and NE) to identify studies which evaluated thromboembolic events in COVID-19. Studies screened in full text were eligible for inclusion in the meta-analysis if the rate of a thromboembolic event could be calculated based on the number of vascular events and the number of patients in the overall cohort [12]. All disagreements between the two independent investigators after title/abstract and full-text screening were resolved by consensus and/or discussion with a third investigator (MM).

2.2. Data extraction

Data were extracted from eligible studies by 2 independent investigators (IN, NE). Discrepancies were resolved by discussions to reach a consensus. Data collected included study specific information (first author name, year of publication, country in which study was conducted, setting of study, number of patients), demographic information (mean/median age and gender of study participants), comorbidities [hypertension, diabetes mellitus (DM), coronary artery disease (CAD) and cardiovascular disease (CVD) when reported as a composite], and outcomes (venous and arterial TE), deep vein thrombosis (DVT) and pulmonary embolism (PE) as individual endpoints.

2.3. Methodological quality assessment

The methodological quality of the non-comparative studies was assessed with a tool for evaluating the methodological quality of case reports and case series [13], whereas that of comparative studies was assessed using the Newcastle Ottawa tool [14].

2.4. Outcomes

Primary outcomes were venous and arterial TE as well as DVT and PE as individual endpoints and mortality in patients who develop TE compared to those who do not. Secondary outcomes were myocardial infarction (MI), cerebrovascular accident (CVA) and acute limb ischemia (ALI). Venous TE was defined as a composite of DVT or PE or as defined by the individual studies. Arterial TE was defined as a

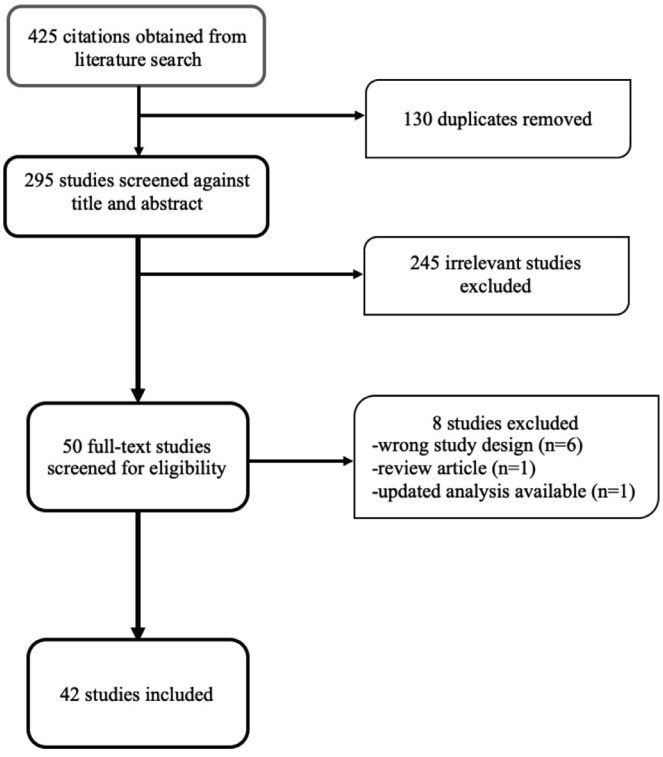

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of study selection.

composite of MI, CVA, ALI or mesenteric ischemia, or as defined by the individual studies. All individual endpoints were captured as per the definitions in the individual studies. Outcomes were reported stratified by the setting of the study/disease (ICU vs. non-ICU vs. post-mortem).

2.5. Statistical methods

We reported the outcomes from the individual studies as cumulative event rates with corresponding 95% confidence intervals estimated using the binominal distribution. The pooled log transformed rates of events and Wald 95% confidence intervals were estimated using DerSimonian and Laird random effects model [15]. Freeman–Tukey double arcsine transformation or logistic-normal random-effects model was used as needed for continuity correction in order to ensure that studies with zero events were not excluded from the meta-analysis. To evaluate whether TE increases the risk of mortality among patients with COVID-19, we estimated pooled Mantel–Haenszel odds ratios (OR) for mortality using a random effects model. In this comparative analysis, patients with COVID-19 who developed TE were compared with those who did not develop TE using studies that reported mortality in the two groups of interest. Heterogeneity among studies was quantified with the I^2 statistic, with $I^2 > 50\%$ (P value < 0.05) considered to indicate significant heterogeneity among studies. Given the significant heterogeneity between the included studies, random effects models were used throughout.

Table 1
Baseline characteristics of study participants.

Study	Country	Setting	*N*	Fem, %	Mean age	BMI, %	DM, %	HTN, %	CAD, %	CVD, %
Al-Samkari, 2020	USA	Non-ICU	256	47.3	60.0	–	25.4	–	–	32.0
		ICU	144	35.4	65.0	–	40.3	–	–	29.9
Artifoni, 2020	France	Non-ICU	71	39.4	64.0[a]	27.3	20.0	41.0	–	–
Benzakoun, 2020	France	PM	64	23.4	65.0[a]	–	–	–	–	–
Betoule, 2020	France	Non-ICU	76	50.0	62.0	–	13.1	32.9	–	–
Bompard, 2020	France	Non-ICU	111	–	–	–	–	–	–	–
		ICU	24	–	–	–	–	–	–	–
Cantador, 2020	Spain	Non-ICU	1419	–	–	–	–	–	–	–
Criel, 2020	Belgium	Non-ICU	52	44.0	64.0	–	17.0	38.0	–	–
		ICU	30	33.0	65.0	–	17.0	33.0	–	–
Cui, 2020	China	ICU	81	54.0	60.0	–	10.0	25.0	12.0	–
D-Rodríguez, 2020	Spain	Non-ICU	156	34.6	68.0	26.9	–	–	–	–
Desborough, 2020	UK	ICU	66	27.0	59.0[a]	28	41.0	45.0	–	–
Edler, 2020	Germany	PM	80	38.0	79.0	25.9	21.0	–	–	–
Faggiano, 2020	Italy	Non-ICU	25	16.0	71.0	–	8.0	32.0	52.0	–
Fraissé, 2020	France	ICU	92	21.0	61.0[a]	–	38.0	64.0	10.0	–
Galeano-Valle, 2020	Spain	Non-ICU	785	–	–	–	–	–	–	–
Gervaise, 2020	France	Non-ICU	72	25.0	62.0	26.7	–	–	–	–
Grandmaison, 2020	Switzerland	Non-ICU	29	–	–	–	–	–	–	–
		ICU	29	–	–	–	–	–	–	–
Grillet, 2020	France	Non-ICU	61	–	–	–	–	–	–	–
Hekimian, 2020	France	ICU	39	–	–	–	–	–	–	–
Helms, 2020	France	ICU	150	18.7	63.0[a]	–	20.0	–	–	48.0
Hippensteel, 2020	USA	ICU	91	41.8	56.0	32.3	30.8	–	–	22.0
Klok, 2020	Netherlands	ICU	184	24.0	64.0	–	–	–	–	–
Leonard-Lorant, 2020	France	Non-ICU	58	–	–	–	–	–	–	–
		ICU	48	–	–	–	–	–	–	–
Llitjos, 2020	France	ICU	26	23.1	68.0[a]	–	–	85.0	–	–
Lodigiani, 2020	Italy	Non-ICU	314	34.3	68.0[a]	–	23.5	47.7	14.4	–
		ICU	48	19.7	61.0[a]	–	18.0	44.3	11.5	–
Longchamp, 2020	Switzerland	ICU	25	36	68.0	27.5	4.0	40.0	–	12.0
Louhaichi, 2020	Tunisia	Non-ICU	20	55.0	61.0[a]	–	30.0	55.0	–	–
Maatman, 2020	USA	ICU	109	43	61.0	34.8	39.0	68.0	–	15.0
Menter, 2020	Switzerland	PM	21	19.0	76.0	–	35.0	100.0	–	71.0
Middeldorp, 2020	Netherlands	Non-ICU	123	41.0	60.0	28.0	–	–	–	–
		ICU	75	23.0	62.0	27.0	–	–	–	–
Nahum, 2020	France	ICU	34	22.0	62.2	31.4	44.0	38.0	–	–
Pavoni, 2020	France	Non-ICU	40	40.0	61.0	28.4	40	40	–	–
Poissy, 2020	France	ICU	107	–	–	–	–	–	–	–
Poyiadji, 2020	USA	Non-ICU	246	–	–	–	–	–	–	–
		ICU	82	–	–	–	–	–	–	–
Ren, 2020	China	ICU	48	45.8	70.0[a]	–	27.1	39.6	–	22.9
Rey, 2020	Spain	Non-ICU	2021	–	–	–	–	–	–	–
Stoneham, 2020	UK	Non-ICU	274	–	–	–	–	–	–	–
Thomas, 2020	UK	ICU	63	31.0	–	–	–	–	–	–
Voicu, 2020	France	ICU	56	25.0	–	–	45	46	20	–
Wichmann, 2020	Germany	PM	12	25.0	73.0[a]	28.7	33.3	25.0	50.0	–
Xing, 2020	China	Non-ICU	9	–	–	–	–	–	–	–
		ICU	11	–	–	–	–	–	–	–
Zerwes, 2020	Germany	ICU	20	30.0	62.0	28.1	10.0	65.0	–	–
Zhang, 2020	China	Non-ICU	128	–	–	–	–	–	–	–
		ICU	15	–	–	–	–	–	–	–

– Data not reported/applicable.
[a] Median age rather than mean age reported.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVD, cardiovascular disease; ICU, intensive care unit; PM, postmortem.

Publication bias and small study effects was assessed with visual inspection of funnel plots and formally testing with Egger test. All analyses were performed using Stata/SE version 16.1 statistical software (StataCorp LLC, College Station, Tex). The *meta, metaprop and metaprop_one* commands of Stata were used as appropriate.

2.5.1. Ethics review

This study was exempt from Institutional Review Board review since no individual level data were used.

Role of funding source: No funding was received to support this study.

3. Results

3.1. Study identification, and characteristics of included studies

The literature search yielded 425 studies, of which 295 remained after duplicates were removed and therefore were screened. Fifty (50) studies were reviewed in full text and 42 studies [4–7,9,10,16–51] enrolling 8271 patients were eventually included in the meta-analysis. No studies were excluded from the meta-analysis on the basis of the language in which they were originally published. The study design of 6 of the 8 studies excluded after full-text screening did not allow an event rate to be estimated. These were small case series in which all patients had the event of interest but the sample size of the overall cohort was not available to enable a rate to be calculated. Also, one study was a review article and an updated analysis was available for the other. Fig. 1 depicts the process of study selection. Four (4) of the 42 included studies evaluated thromboembolic events at autopsy while the rest studied antemortem outcomes. The characteristics of the included studies are shown in Table 1. The methodological quality of included studies was accessed to be adequate. In the 4 postmortem studies, autopsies were performed on consecutive deaths and not on a selective basis. In 18 of the 38 antemortem studies, systematic screening was done to look for TE. Diagnosis of TE was based on symptom driven diagnostics in the remaining studies.

3.2. Outcomes

3.2.1. Venous thromboembolism (VTE)

The composite outcome of VTE was reported by 16 studies (Fig. 2A). The overall VTE rate was 21% (95% CI:17–26%); 5% (95% CI: 3–8%) among non-ICU patients but as high as 31% (95% CI: 23–39%) among ICU patients. DVT events were reported by 28 studies, 3 of which studied postmortem outcomes (Fig. 2B). The overall DVT rate was 20% (95% CI: 16–23%). The pooled DVT rate was 8% (95% CI:3–14%) among 12 non-ICU studies, 28% (95% CI: 16–41%) among

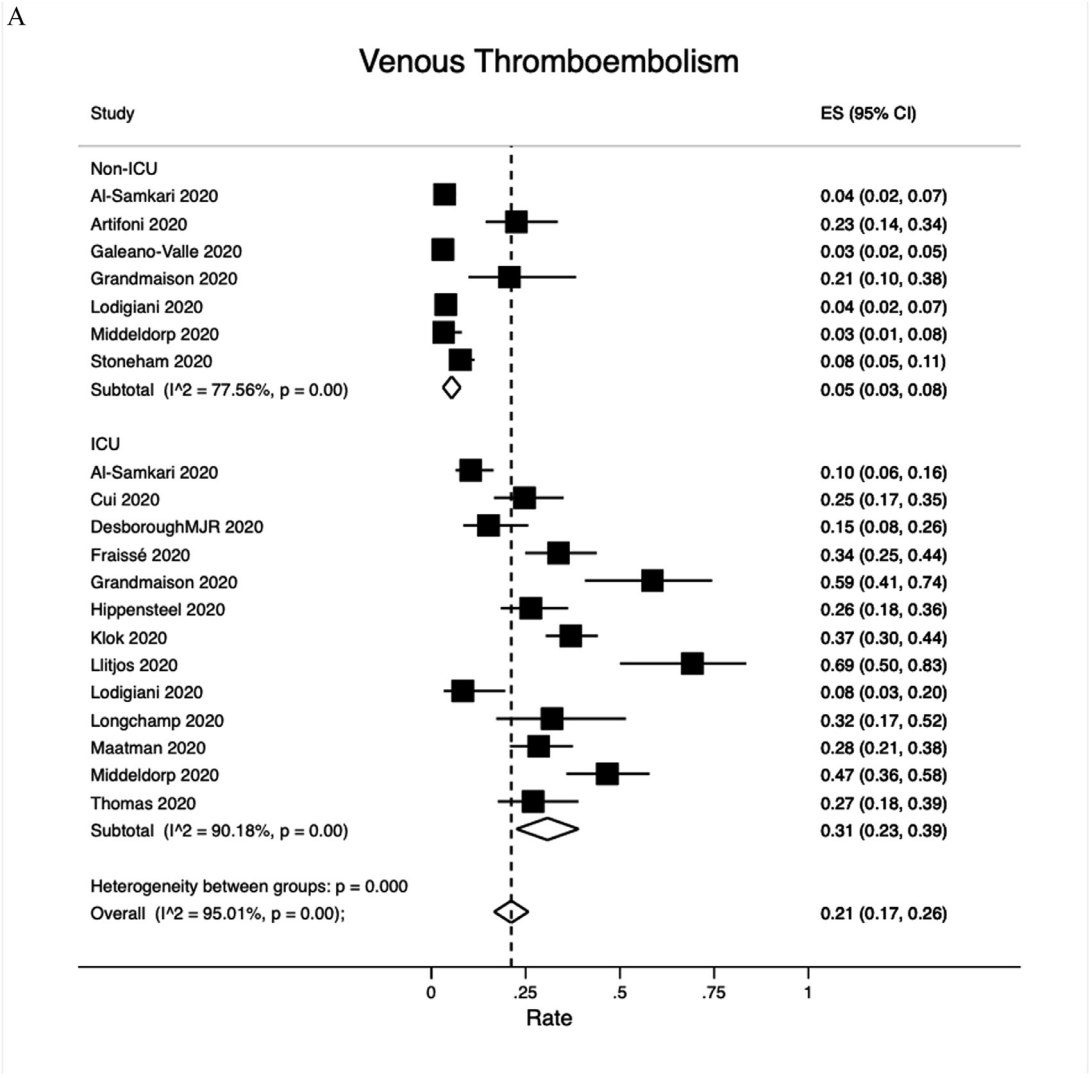

Fig. 2. Venous thromboembolism rates. A. Overall; B. Deep vein thrombosis; C. Pulmonary embolism. Abbreviation: ICU, intensive care unit.

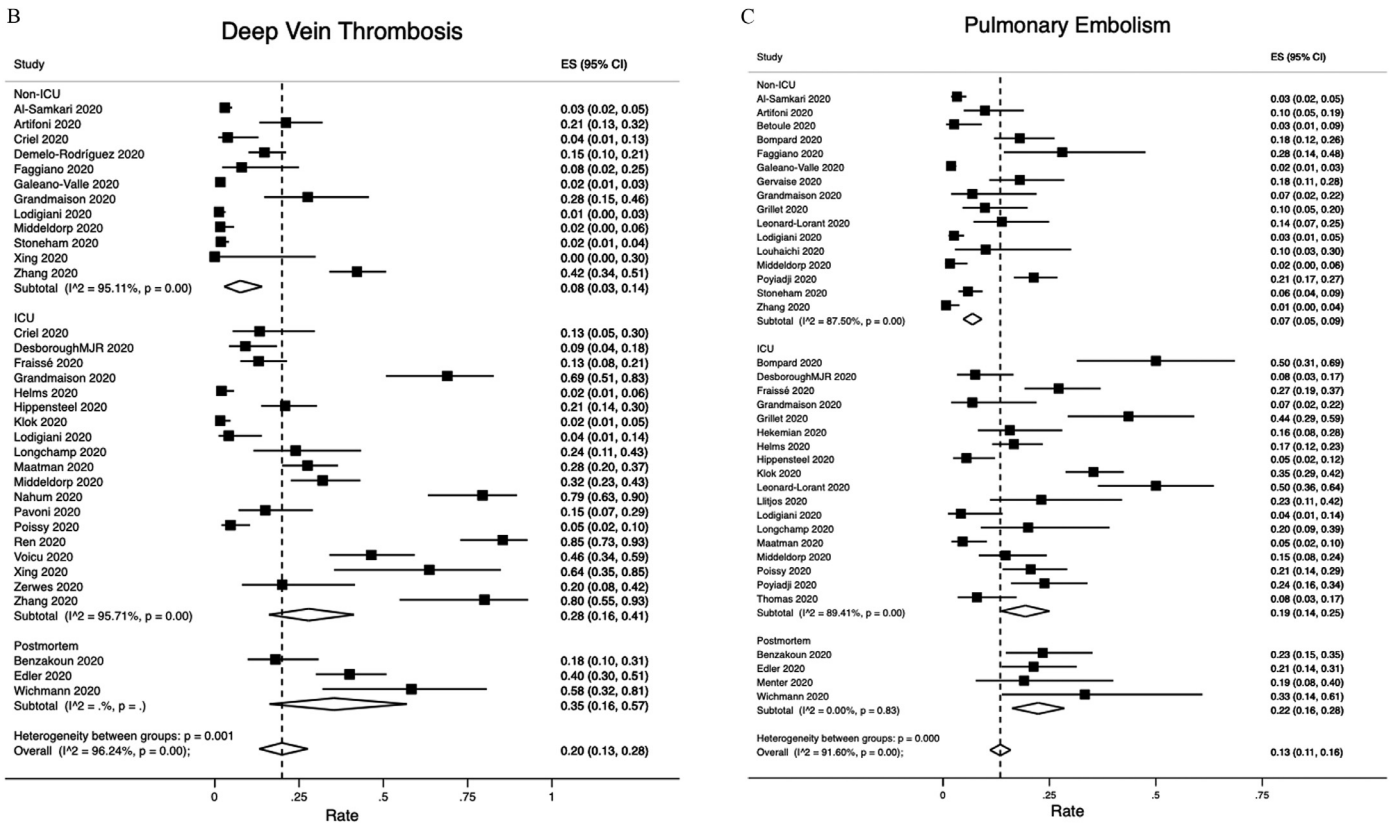

Fig. 2 Continued.

19 ICU studies and 35% (95% CI:16–57%) among the 3 postmortem studies. PE events were reported by 31 studies, 4 of which were post mortem studies (Fig. 2C). The overall PE rate was 13% (95% CI: 11–16%): 7% (95% CI:5–9%) among 16 non-ICU studies, 19% (95% CI: 14–25%) among 18 ICU studies and 22% (95% CI:16–28%) among postmortem studies.

3.2.2. Arterial thromboembolism (ATE)

Overall ATE was reported by 8 studies (Fig. 3A). The overall ATE rate was 2% (95% CI: 1–4%): 1% (95% CI: 0–2% among 5 non-ICU studies and 5% (95% CI: 3–7%) among 5 ICU studies. The pooled rates of specific arterial thromboembolic events were as follows: MI, 0.5% (95% CI:0–1.3%), Fig. 3B; CVA, 1% (95% CI: 1–2%), Fig. 3C and ALI, 0.4% (95% CI:0.1–0.6%), Fig. 3D.

3.2.3. Comparative analysis

The pooled mortality rate among patients with TE was 23% (95%CI:14–32%, Fig. 4A) and among patients without TE it was 13% (95% CI:6–22%, Fig. 4B). The pooled odds of mortality were 74% higher among patients who developed TE compared to those who did not (OR, 1.74; 95%CI, 1.01–2.98; $P = 0.04$), (Fig. 4C).

4. Discussion

In this meta-analysis of 42 studies involving 8271 patients, we showed that thromboembolic events are high in SARS-CoV-2 infected individuals. Overall VTE rate was 21%, with DVT rate of 20% and PE rate of 13% while ATE rate was 2%. Among ICU patients, the VTE rate was 31%, DVT rate was 28%, PE rate was 19% and ATE rate was 5%. Thromboembolism significantly increased the odds of mortality by as high as 74% (OR, 1.74; 95%CI, 1.01–2.98; $P = 0.04$).

COVID-19 morbidity and mortality continue to remain significant in parallel with rising infection rates. The pathophysiology of COVID-19 is still being understood. The disease is known to primarily affect the respiratory system but the involvement of other systems is not uncommon. Involvement of the vascular system in particular is thought to contribute significantly to morbidity and more importantly mortality. Of note is the increased risk of thromboembolism that is now known to be associated with COVID-19. There are a number of mechanisms thought to contribute to this elevated thromboembolism risk of COVID-19. Abnormally elevated levels of proinflammatory cytokines have been found in patients infected with the novel coronavirus [52]. The resultant increased systemic inflammation coupled with endothelial injury triggered by attachment of the virus to the angiotensin-2 receptor of the endothelial cells and viral replication leads to a prothrombotic endothelial dysfunction [53,54]. Platelet activation, immobilization, mechanical ventilation and the use of central venous catheters are other factors that contribute to a prothrombotic state in COVID-19. Earlier reports have linked coagulopathy and development of TE with an increased risk of death [3,52]. Autopsy studies have provided some essential insights into this prothrombotic state in COVID-19 [34,44,55]. A recent autopsy study found that almost no organ in the body is spared of thrombosis [56]. Regardless of anticoagulation status and sometimes early in the disease course, significant macrovascular and microvascular thrombosis was found in multiple organs.

In order to mitigate the attendant prothrombotic state associated with COVID-19, the International Society of Thrombosis and Hemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19 recommends that in the absence of contraindications, “prophylactic dose low molecular weight heparin (LMWH) should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection” [57]. In a

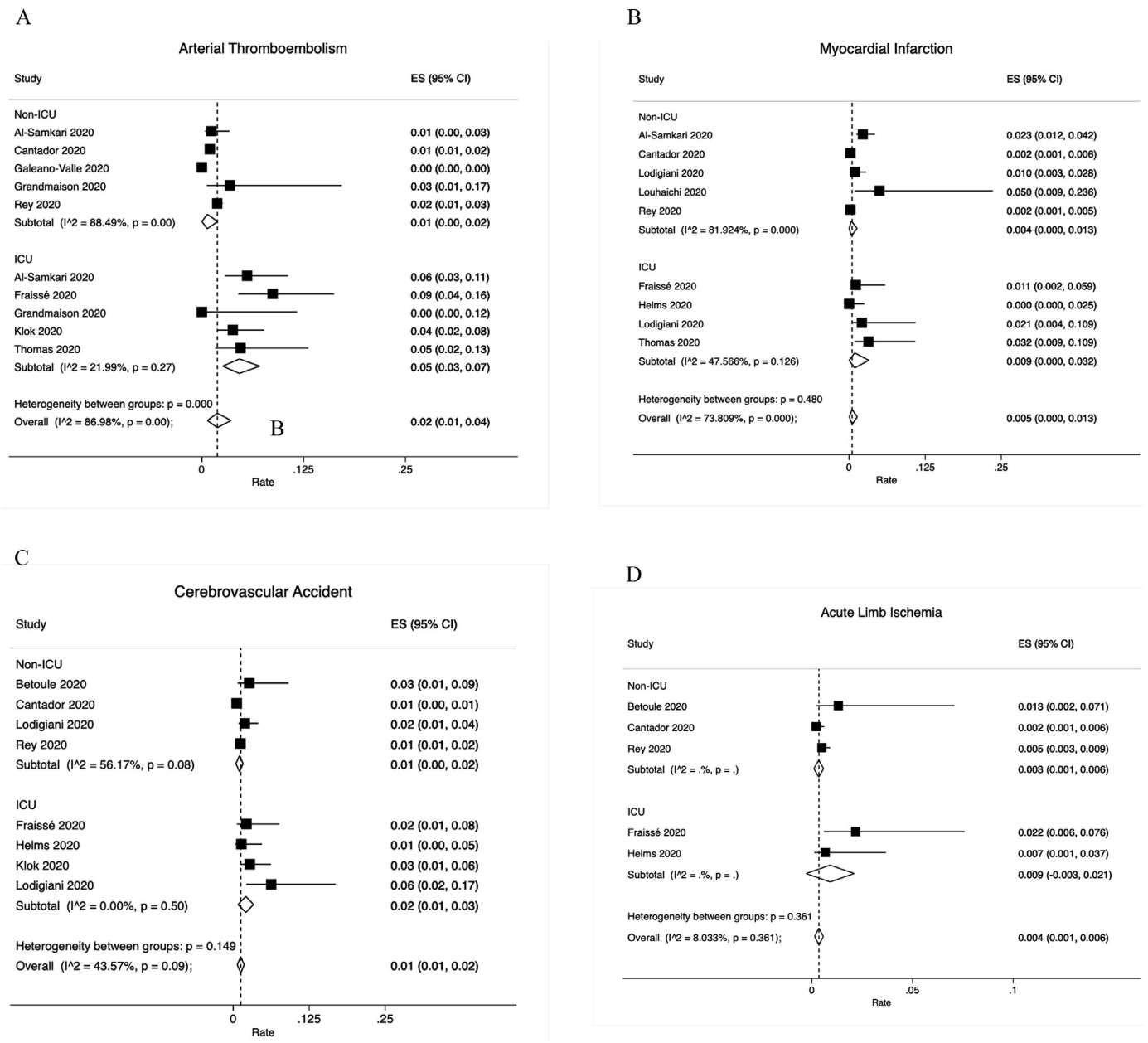

Fig. 3. Arterial thromboembolism rates. A. Overall; B. Myocardial infarction; C. Cerebrovascular accident; D. Acute limb ischemia. Abbreviation: ICU, intensive care unit.

similar manner, the American Society of Hematology also recommends that "all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux, unless they are judged to be at increased bleeding risk" [58]. Several other consensus statements, guidelines and reviews have also made similar recommendations of thromboprophylaxis for COVID-19 patients especially for hospitalized patients [59–61].

The VTE rates found in our study, particularly among ICU patients, are significantly higher than what is expected for hospitalized patients with acute infections. Previous studies have shown that hospitalization for acute infections can be associated with an estimated VTE risk as high as 15.5% [62], especially in hospitalization for pneumococcal and influenza infections [63,64]. Moreover, these rates are higher than what is reported in the literature for other viral pandemics experienced in the past. In the pandemic H1N1 influenza of 2009, studies reported VTE rates of about 6% [65]. Of note, the pooled VTE, DVT and PE rates were consistently higher among ICU versus non-ICU patients. This is in tandem with prior research indicating there is a correlation between disease severity and the risk of thromboembolism among SARS-CoV-2 infected individuals.

That said we believe that, the VTE rates reported in this study are conservative estimates of the overall VTE risk associated with SARS-CoV-2 infection. This position is informed by the fact some studies did not systematically search for VTE in all patients and this may have led to an underestimation of some of the VTE rates reported in the individual studies included in this meta-analysis. This is further supported by the fact that DVT rates in the postmortem studies were nearly two times higher than the DVT rates of antemortem studies. It is worth noting these autopsies were mostly performed on patients who were not suspected of VTE before death [44].

Understandably, it is sometimes not feasible to conduct the imaging studies needed to diagnose VTE especially in patients who are critically ill, intubated, unstable and might be in prone position. The potential for other patients and healthcare workers acquiring the infection through contact with SARS-CoV-2 infected individuals and contaminated imaging equipment may discourage clinicians from

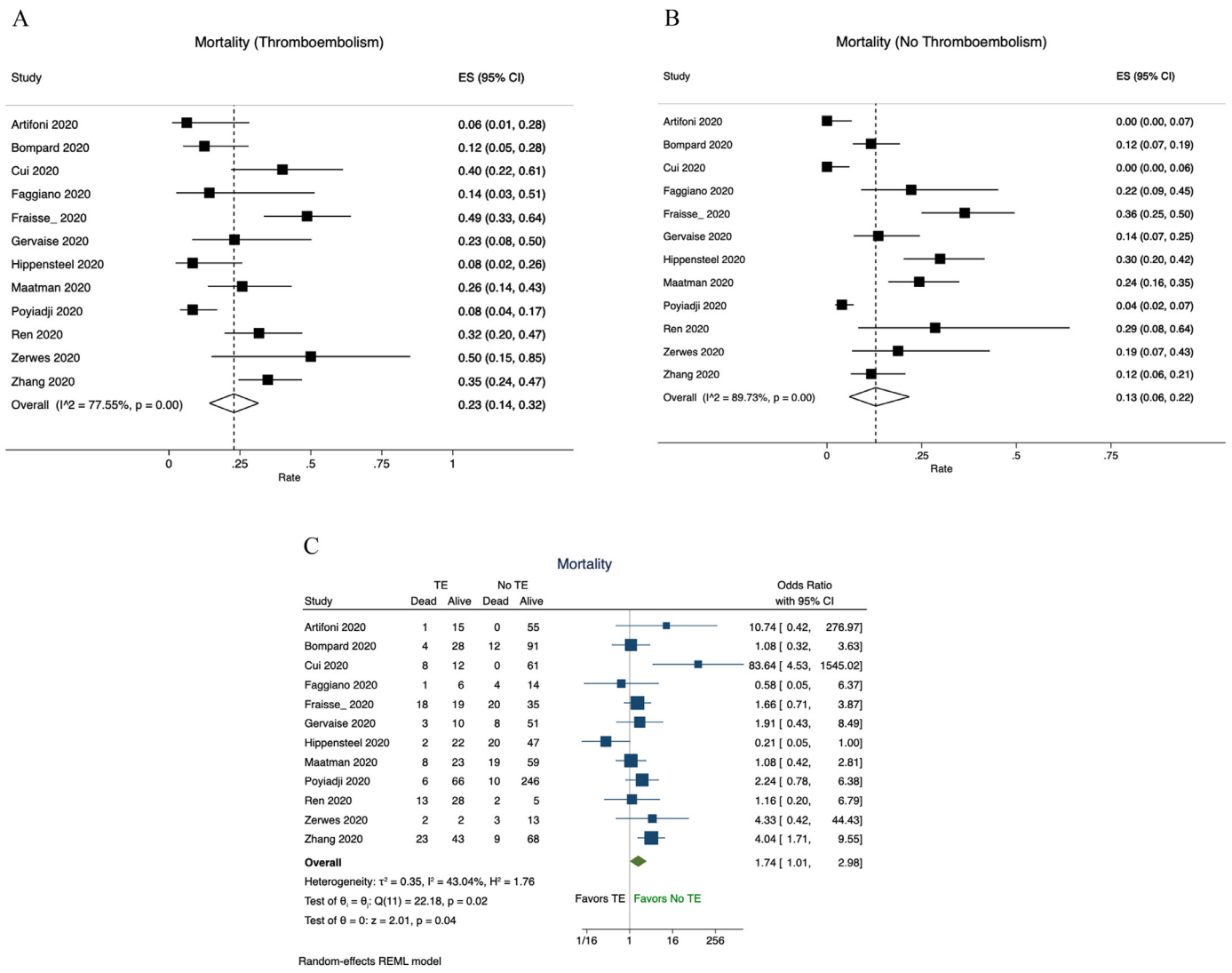

Fig. 4. Mortality among patients with and without thromboembolism. A. Mortality rate of patients with thromboembolism; B. Mortality rate of patients without thromboembolism; C. Pooled odds of mortality among patients with TE compared to patients without TE. Abbreviation: TE, thromboembolism.

systematically searching for TE in all patients. That said, the overall VTE rate of 21%, DVT rate of 20% and particularly PE rate of 13%, though likely conservative, are still high, and should prompt all to the heightened risk of VTE associated with COVID-19.

More importantly, whereas a prior study evaluating non-COVID-19 ICU patients found that patients with and without VTE had comparable mortality risk (16% vs 20%, $P = 0.72$) [66], our meta-analysis shows that concomitant TE and COVID-19 is associated with 74% increased odds of death compared to COVID-19 patients without TE (13% vs 23%, OR: 1.74, $P = 0.04$). The risk of death in COVID-19 posed by TE is therefore not negligible. It stands to reason that thromboprophylaxis may favorably change the clinical course and improve the prognosis of COVID-19 infected patients. In line with prior recommendations therefore, it is our position that standardized thromboprophylaxis protocols should be implemented in all COVID-19 patients in the absence of contraindications; to mitigate the risk of developing TE and to reduce the mortality risk associated with concomitant TE and COVID-19 [67]. The optimal dosing of antithrombosis drugs however remains unknown given the limited evidence in the literature [61]. In the face of life-threatening thromboembolic complications developing in the presence of standard dose thromboprophylaxis, some authors have pushed for higher anticoagulation targets in severely ill COVID-19 patients [8]. In this regard some physicians routinely increase the dose of anticoagulation beyond prophylactic dosing to intermediate or therapeutic dosing in the hope that this will reduce the widespread microvascular thrombosis and the thrombosis related mortality associated with SARS-CoV-2 infection [7,61,67]. The role and optimal dosing of anticoagulation in COVID-19 is the subject of ongoing trials. It is hoped that these clinical trials will provide the much-needed robust evidence on the impact of anticoagulation on the risk of TE and mortality among SARS-CoV-2 infected individuals.

This study has some limitations within which the results of the analysis should be interpreted. As noted earlier, not all studies included in the analysis systematically looked for the presence of TE. For most studies, the screening for TE was rather symptom driven, with the implication of missing asymptomatic events. This may have resulted in conservative estimates of the TE risk associated with SARS-CoV-2 infection. Also, the nature of the data available in the individual studies did not allow the meta-analysis to be stratified by some clinically relevant variables such as thromboprophylaxis status, race, and healthcare access/quality to assess their effect on the incidence of TE and mortality. The ability to stratify the analysis by thromboprophylaxis status, for instance, would have helped to determine the extent to which thromboprophylaxis reduces COVID-19-related TE and mortality.

Despite these limitations, our meta-analysis is novel in estimating the overall high TE rates of COVID-19 and the associated significant increase in mortality odds.

In this novel systematic review and meta-analysis involving 8271 SARS-CoV-2 patients, we determined the overall incidence of VTE to be 21%. Among ICU patients the VTE rate was as high as 31%. Patients who developed TE were at 74% increased odds of death compared to those who did not. Clinical trials are ongoing to elucidate the mortality benefit of thromboprophylaxis and optimal dosing in this population of patients.

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Data sharing statement

The data used in this study were gathered from publicly available studies and available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100639.

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