BMJ Open

Thromboembolic events in hospitalised patients with COVID-19: ecological assessment with a scoping review

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ABSTRACT

Objectives Thrombosis is a common complication of the novel COVID-19. Pre-COVID-19 studies reported racial differences in the risk of developing thrombosis. This study aimed to describe the geographical variations in the reported incidences and outcomes of thromboembolic events and thromboprophylaxis in hospitalised patients with COVID-19. The final search for randomised clinical trials was carried out in January 2022. Screening eligible articles and data extraction were independently performed in duplicate by multiple reviewers.

Design Scoping review. MEDLINE, Embase, Cochrane Libraries were searched using terms related to COVID-19 and thromboembolism.

Setting Hospitals all over the world.

Participants In-hospital patients with COVID-19.

Outcome measures The incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE), and the prophylactic anticoagulation therapy.

Results In total, 283 studies were eligible, representing (239 observational studies, 39 case series and 7 interventional studies). The incidence of DVT was the highest in Asia (40.8%) and hospital mortality was high (22.7%). However, the incidence of PE was not very high in Asia (3.2%). On the contrary, the incidence of PE was the highest in the Middle East (16.2%) and Europe (14. 6%). Prophylactic anticoagulation therapy with low-molecular-weight heparin was the main treatment provided in all areas. Four of the seven randomised clinical trials were conducted internationally.

Conclusions The incidence of DVT was the highest in Asia. The incidence of PE was higher in the Middle East and Europe; however, detection bias during the pandemic cannot be ruled out. There were no major differences in the type or dose of prophylactic anticoagulants used for thromboprophylaxis among the regions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A thorough scoping review was performed to assess regional differences in the incidence, outcomes and prophylactic anticoagulation of thromboembolic events in hospitalised patients with COVID-19.

⇒ COVID-19 was a single common disease that suffered worldwide simultaneously, which minimised biases when comparing geographical/ecological variations in the thromboembolic complications related to an illness.

⇒ The scoping review included 239 observational studies, 39 case series and 7 interventional studies and extracted relevant data using a rigorous approach.

⇒ There were regional differences in the incidences; however, detection bias during the pandemic cannot be ruled out.

INTRODUCTION

The number of patients infected with SARS-CoV-2 continues to increase because of the global pandemic. SARS-CoV-2, the cause of the novel COVID-19, has been reported to cause not only an increased inflammatory response due to viral propagation[1] but also an excessive immune response in the host,[2] resulting in severe illness[3] and high mortality.[4] In addition, thromboembolic events have been noted as a characteristic complication of COVID-19 since the early phase of the pandemic.[5] As thromboembolic events contribute to poor clinical outcomes in patients with COVID-19,[6] it is important to identify the predisposing factors.

Before the COVID-19 era, racial differences in the frequency of thromboembolic events have been reported.[7] Reportedly, African-Americans have a higher risk of venous thromboembolism (VTE) than Caucasians or other racial groups, and Asians have a lower risk.[8] The variation was partly explained by the differences in the coagulation-fibrinolysis profile among different racial groups.[7 9–19]

Some studies have reported racial differences in the risk of hospitalisation[20 21] or mortality[22–24] from COVID-19, although the reason for this is unclear. The reportedly high incidence of thromboembolic events in patients with COVID-19, which are associated with high severity and mortality, might be related to the disparity in the care received. However, it is unclear whether there are racial differences in the incidence of thromboembolic events in patients with COVID-19.

Clinical trials examining the efficacy of anticoagulant therapy for the prevention of thromboembolic events associated with COVID-19 have been conducted globally.[25 26] However, the applicability of the results of these clinical trials depends on racial features and regional situations. Therefore, it is important to investigate the differences in the incidence and usual practices to prevent thromboembolic events associated with COVID-19. This study aimed to describe the geographical variations in the reported incidences and outcomes of thromboembolic events and thromboprophylaxis in hospitalised patients with COVID-19.

STUDY DESIGN AND METHODS

This scoping review (SR) conformed to the guidelines of the Cochrane Collaboration and Centre for Reviews and Dissemination and reported data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for SR statement[27] (online supplemental file 1).

We included all the studies that assessed any aspect of thromboembolic complications in hospitalised adult patients with COVID-19, including, but not limited to, descriptive studies of the incidence of thromboembolic events, observational studies of COVID-19 reporting thromboembolic events as outcomes, and interventional studies assessing the effect of prevention or treatment of thromboembolic events in patients with COVID-19. The following types of articles and studies were excluded: reviews, editorials or commentaries, where no original data were reported; studies of autopsy cases; studies in which the number of patients was less than five; studies that included children (aged <18 years); and studies published in languages other than English.

We searched the MEDLINE (Ovid), Embase (Ovid) and Cochrane Library databases using medical subject heading terms, a list of keywords, truncations and Boolean operators. The search was updated on 3 January 2021, for all relevant studies and on 24 January 2022, for randomised clinical trials (RCTs). We also searched the National Institute of Health Clinical Trials Register (https://clinicaltrials.gov/) and WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). The detailed search strategy is available in online supplemental file 2.

The articles retrieved from the database search were screened independently by two authors (SK, NM, KO, KW and KA). The titles and abstracts were screened to determine whether the studies met the eligibility criteria. The full texts were then reviewed for eligibility independently by two authors. Disagreements were resolved through discussion or consultation with a third reviewer (TF), as needed. As for interventional studies, RCTs comparing the efficacy of therapeutic or moderate dose anticoagulants and usual prophylactic dose of anticoagulants for patients with COVID-19 were included. The authors reviewed the study period, location and inclusion/exclusion criteria of all RCTs so as not to count same populations more than once.

The authors independently extracted the data in duplicate using an Excel spreadsheet. We extracted the following data: title of the article, name of the authors, country of study setting, whether the study included patients in the intensive care unit (ICU), number of patients, study characteristics, patient characteristics (age, sex, body mass index (BMI)), medical history (hypertension, diabetes, cardiovascular disease, atrial fibrillation, coronary artery disease, smoking, chronic kidney disease, cancer, prior thromboembolic events, stroke), laboratory data (platelets, activated partial thromboplastin time, D-dimer, prothrombin time-international normalised ratio), intervention (invasive mechanical ventilation, renal replacement therapy, extracorporeal membrane oxygenation), deep venous thrombosis (DVT) prophylaxis, thromboembolic events (total thromboembolic events, VTE, DVT, pulmonary embolism (PE), ischaemic stroke, myocardial infarction, limb ischaemia) and mortality at hospital discharge. For interventional studies, we added data on major bleeding events.

We classified the eligible studies according to the area of the countries in which they were conducted: Africa, Asia, Europe, Middle East, North America, Oceania, South America and Global, that is, a study conducted collaboratively in more than one area. If the data for the overall study population were not reported and only data for stratified groups (eg, a patient group with DVT and a group without DVT) were available, the reported values were combined to obtain the data for the overall study population.

The continuous variables in each study were summarised as means and SDs or as medians and IQRs, calculated using the formulae reported elsewhere.[28 29] The numerical data in each study were summarised as proportions (%), and the proportions were summarised as medians and IQRs. We additionally performed exploratory pooled analyses of the proportions of DVT and PE.

An exploratory meta-analysis of interventional studies was conducted to assess heterogeneity by area.[30] Pooled estimates were calculated using the Mantel-Haenszel method with a random-effects model. Heterogeneity was evaluated using I^2 with >75% as high, >50% as moderate and >25% as a low degree of heterogeneity, in addition to visual inspection. The meta-analysis was performed using R (V.4.1.1; R Core Team, Vienna, Austria).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

In total, 3045 articles were identified. After title, abstract and full-text screening, 283 articles were included in the SR (figure 1): 239 observational studies, 39 case series and
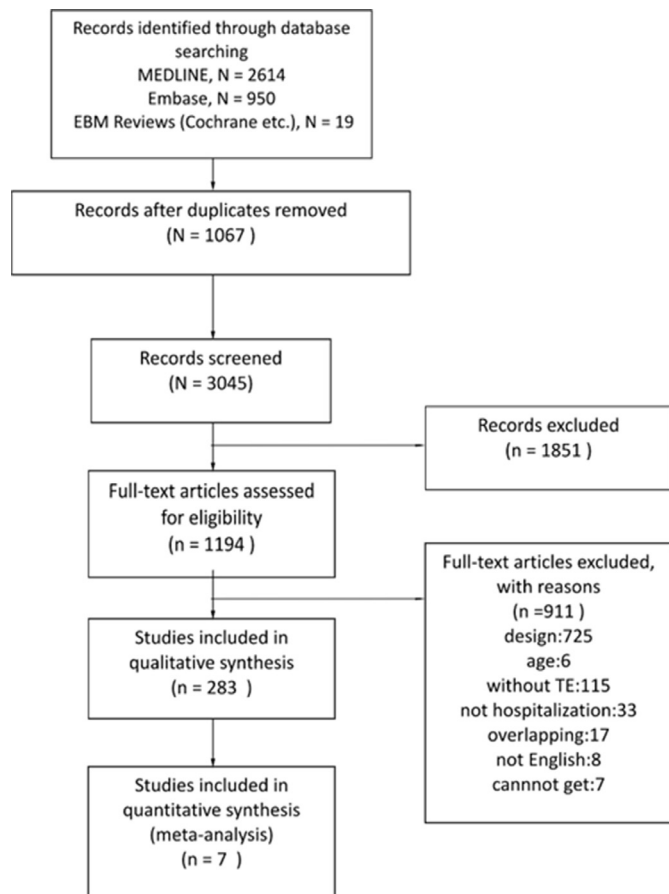
Figure 1 Study flow diagram.

7 interventional studies. Two case series were embedded in observational studies with wider study population. The full list of included studies is available in online supplemental file 3. The main continents and countries of publication, with the numbers of studies, were as follows: Asia: China (11); Japan (2); Africa: Egypt (1), Morocco (2); Europe: Belgium (3), Denmark (2), France (25), Germany (7), Italy (51), the Netherlands (12), Norway (2), Spain (18), Sweden (3), Switzerland (6), the UK (18), multiple European countries (6); Middle East: Iran(1), Iraq (1), Israel (2), Saudi Arabia (5), Turkey (3), the United Arab Emirates (UAE) (3); North America: Canada (2), the USA (89); Oceania: Australia (1); South America: Brazil (2); Global—global collaboration of 42 healthcare organisations (1); collaboration of Lithuania, Italy, Spain and Iraq (1); collaboration of Brazil, Canada, Ireland, Saudi Arabia, UAE and USA (1); collaboration of USA, Canada, the UK, Brazil, Mexico, Nepal, Australia, the Netherlands and Spain (1): collaboration of countries around the world that participated in three RCTs (1) .

Characteristics of patients in cohort studies

Observational cohort studies that included hospitalised patients with COVID-19 were summarised to explore the patients' characteristics and incidence of thromboembolic events. Cohort studies that included patients with only confirmed thromboembolic events were excluded. Accordingly, 134 studies were from Europe, 75 from North America, 13 from Asia, 12 from the Middle East, 2 from Africa and 1 each from Oceania, and South America (figure 2). Further, 50 studies from Europe, 14 from North America, 8 from the Middle East, 5 from Asia and 1 global collaboration study involved patients in the ICU.

The characteristics of the study population are summarised in table 1. The study populations were predominated by men in all regions, and the median age
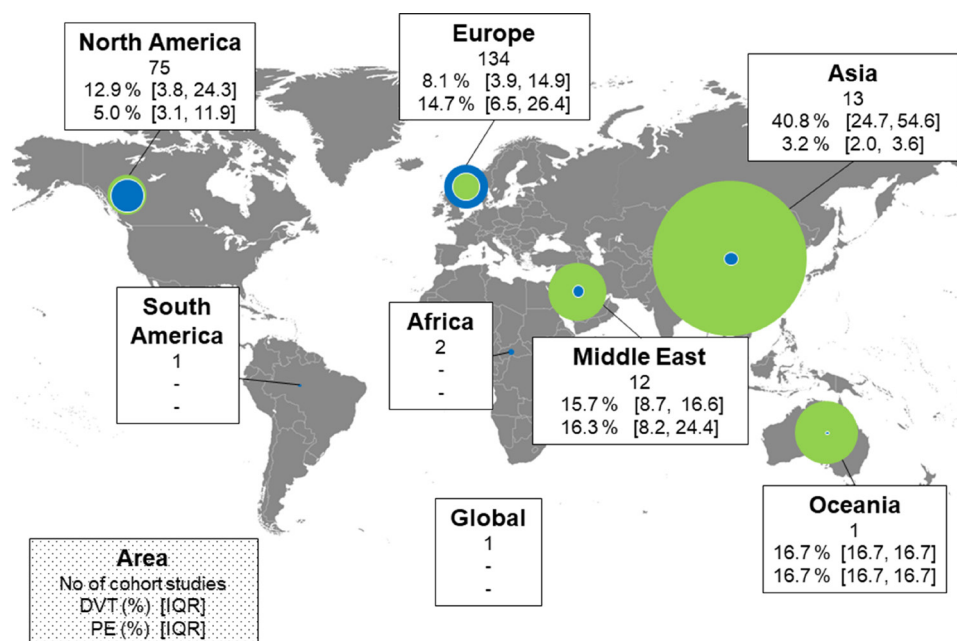

Figure 2 Number of observational studies and incidences of deep venous thrombosis (DVT) and pulmonary embolism by areas. The size of blue circles represents the number of eligible studies (square rooted) and the size of green circles represents the incidence of DVT in the area.

Table 1 Patients' characteristics and outcomes in cohort studies of hospitalised patients with COVID-19

	Asia	Africa	Europe	Middle East	North America	Oceania	South America	Global
No of studies	13	2	134	12	75	1	1	1
Patients in a study, n, mean (SD)	109.3 (100.3)	133.5 (0.7)	179.3 (479.7)	103.4 (94.3)	535.8 (1488.8)	6.0	27.0	630.0
Characteristics of patients in included studies, summarised in median (IQR)								
Proportion of male	54.2 (51.7–61.3)	54.6 (54.5–54.7)	68.4 (59.9–76.8)	74.0 (58.3–82.5)	58.7 (51.4–66.2)	83.3	70.3	56.9
Mean age	61.9 (54.8–63.3)	50.5 (50.3–50.7)	64.0 (61.3–67.6)	50.3 (46.4–50.8)	61.8 (59.5–64.5)	68.6	56.0	61.0
Mean BMI	23.7 (23.5–24.8)	NA	28.1 (27.1–29.1)	26.6 (26.3–26.7)	29.8 (28.9–30.7)	NA	28.8	NA
Past medical history (%), summarised in median (IQR)								
Hypertension	37.1 (30.3–39.9)	26.9 (26.9–27.0)	47.3 (39.8–57.1)	49.1 (38.3–50.0)	58.3 (48.8–69.5)	NA	25.9	NA
Diabetes	15.1 (12.1–18.0)	14.1 (NA)	21.4 (16.6–29.0)	38.4 (29.0–39.4)	36.4 (30.3–44.3)	NA	7.4	NA
Cardiovascular disease	11.8 (8.6–12.4)	14.2 (14.2–14.2)	15.4 (9.3–25.1)	10.0 (7.0–11.7)	14.6 (9.2–21.9)	NA	NA	NA
Coronary artery disease	7.4 (4.9–9.8)	NA	15.5 (12.5–20.0)	17.0 (8.0–21.0)	14.8 (11.6–16.7)	NA	3.0	NA
Af	NA	NA	10.0 (3.7–16.3)	11.0 (9.0–13.0)	13.6 (10.2–15.1)	NA	7.4	NA
CKD	7.6 (2.6–12.9)	2.2 (2.2–2.2)	11.6 (7.6–17.3)	10.3 (8.2–11.1)	13.5 (8.0–19.7)	NA	NA	NA
Stroke	4.2 (3.5–12.5)	0.7 (0.7–0.7)	7.5 (4.7–10.1)	11.0 (11.0–11.0)	10.0 (4.9–11.1)	NA	3.7	NA
Malignancy	5.6 (5.1–6.5)	1.8 (1.6–2.0)	10.2 (4.8–12.5)	4.6 (4.4–4.8)	10.1 (7.0–14.8)	NA	7.4	NA
DVT	NA	NA	3.0 (1.3–3.7)	NA	5.6 (4.6–6.7)	NA	NA	NA
PE	NA	NA	2.4 (0.0–3.0)	NA	5.2 (5.0–5.5)	NA	NA	NA
Any thrombosis	0.7 (0.7–0.7)	NA	4.9 (1.8–7.2)	NA	6.9 (4.6–10.8)	NA	NA	NA
Smoking	24.7 (6.3–47.6)	5.6 (5.4–5.7)	14.8 (8.3–24.0)	14.2 (7.6–27.7)	18.9 (13.5–30.9)	NA	3.7	NA
Outcomes (%), summarised in median (IQR)								
DVT	40.8 (24.6–54.5)	NA	8.0 (3.9–14.9)	15.6 (8.6–16.4)	12.8 (3.8–24.2)	16.6	NA	NA
PE	3.2 (1.9–3.5)	NA	14.6 (6.4–26.3)	16.2 (8.1–24.4)	5.0 (3.0–11.8)	16.6	NA	NA
VTE	NA	NA	8.7 (6.1–36.0)	NA	9.0 (4.3–19.7)	NA	NA	NA
Myocardial infarction	0.7 (0.7–0.7)	NA	1.5 (0.9–3.1)	NA	2.6 (0.7–4.7)	NA	NA	NA
Stroke	33.8 (19.2–48.5)	NA	2.3 (0.8–3.1)	NA	3.1 (1.5–14.0)	NA	NA	NA
Limb ischaemia	NA	NA	3.0 (0.6–7.4)	1.0 (1.0–1.0)	6.6 (3.4–13.3)	NA	NA	NA
Mean hospital length of stay	9.5 (9.5–9.5)	NA	21.4 (11.8–28.5)	9.6 (8.9–10.3)	10.0 (8.5–14.7)	NA	11.0	NA
Need for mechanical ventilation	37.5 (21.7–63.4)	10.4 (10.4–10.5)	68.4 (18.5–93.1)	86.3 (65.2–100.0)	41.9 (30.6–77.9)	83.3	29.6	NA
Need for renal replacement therapy	10.5 (10.5–10.5)	NA	19.7 (11.2–26.4)	65.3 (48.0–82.6)	15.2 (8.5–30.0)	33.3	NA	NA
Need for ECMO	52.6 (28.9–76.3)	NA	12.1 (6.6–77.5)	6.4 (5.6–8.0)	8.1 (3.9–16.9)	0.0	NA	NA
Hospital mortality	22.7 (15.0–31.2)	10.4 (10.4–10.5)	20.9 (12.9–30.7)	29.0 (26.3–31.5)	20.6 (14.2–26.5)	NA	3.7	NA

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 2 Patients' characteristics and outcomes in cohort studies of COVID-19 conducted in the ICU

	Asia	Europe	Middle East	North America
No of studies	5	50	8	14
Patients in a study, n, mean (SD)	50.8 (38.2)	210.0 (714.9)	122.8 (110.8)	365.5 (1123.3)
Characteristics of patients in included studies,summarised in median (IQR)				
Proportion of male (%)	59.3 (54.1– 61.3)	76.7 (70.0– 81.4)	80.4 (76.0– 85.0)	62.5 (57.9– 63.6)
Mean age (mean)	63.7 (63.0– 65.0)	62.0 (60.4– 63.8)	50.3 (48.9– 50.7)	61.3 (60.0– 62.6)
Mean BMI (mean)	22.5 (21.0– 23.9)	29.0 (28.3– 30.0)	26.5 (26.2– 26.9)	30.3 (29.6– 32.2)
Past medical history (%), summarised in median (IQR)				
Hypertension	39.5 (37.4– 44.7)	44.9 (37.3– 56.0)	49.5 (42.6– 50.0)	59.5 (43.8– 64.5)
Diabetes	25.0 (17.6– 26.0)	26.0 (19.2– 36.8)	39.1 (38.5– 39.6)	40.1 (32.6– 42.2)
Cardiovascular disease	17.7 (15.1– 20.3)	14.2 (10.6– 24.0)	11.7 (10.8– 14.6)	21.8 (12.8– 27.6)
Coronary artery disease	2.2 (2.2– 2.2)	12.5 (9.6– 20.0)	8.0 (7.8– 18.7)	14.2 (12.2– 16.2)
Af	NA	1.7 (0.9– 2.5)	7.0 (7.0– 7.0)	6.8 (6.8– 6.8)
CKD	12.5 (12.5– 12.5)	8.0 (5.9– 13.6)	9.4 (7.5– 11.5)	14.6 (12.0– 15.6)
Stroke	12.5 (7.9– 13.5)	1.2 (0.6– 1.8)	NA	11.2 (11.2– 11.2)
Malignancy	9.0 (7.3– 10.8)	5.9 (2.8– 11.2)	4.2 (4.2– 4.26)	8.7 (4.7– 10.2)
DVT	NA	2.2 (0.9– 3.8)	NA	4.7 (4.7– 4.7)
PE	NA	5.5 (2.7– 8.3)	NA	4.7 (4.7– 4.7)
Thrombosis	NA	5.3 (3.2– 7.5)	NA	3.7 (3.5– 4.0)
Smoking	NA	24.0 (9.5– 30.3)	34.9 (27.7– 42.1)	17.5 (13.41– 27.9)
Outcomes (%), summarised in median (IQR)				
DVT	57.4 (44.0– 66.6)	9.0 (4.5– 23.3)	16.0 (15.3– 16.8)	20.8 (11.7– 28.6)
PE	NA	17.3 (9.1– 26.3)	16.2 (10.4– 24.1)	5.0 (2.7– 8.9)
VTE	NA	19.3 (14.0– 27.6)	NA	NA
Myocardial infarction	NA	3.1 (2.0– 3.1)	NA	2.6 (1.3– 2.8)
Stroke	63.1 (63.1– 63.1)	2.7 (1.9– 5.1)	NA	3.7 (3.4– 8.6)
Limb ischaemia	NA	0.8 (0.6– 1.5)	1.0 (1.0– 1.0)	6.6 (6.6– 6.6)
Need for mechanical ventilation	63.4 (37.5– 92.1)	91.1 (77.4– 100.0)	88.4 (76.9– 100.0)	84.6 (76.1– 93.3)
Need for renal replacement therapy	10.5 (10.5– 10.5)	23.9 (17.7– 29.7)	65.3 (48.0– 82.6)	33.1 (13.0– 54.0)
Need for ECMO	52.6 (28.9– 76.3)	22.5 (8.9– 100.00)	6.4 (5.6– 8.0)	9.3 (6.5– 14.2)
Hospital mortality	34.8 (29.1– 45.9)	27.6 (17.1– 33.1)	29.0 (26.3– 31.5)	22.0 (15.8– 28.4)

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

was 60 years. The patients in Asia had lower BMI; more frequent smoking history; and lower occurrences of hypertension, diabetes, chronic kidney diseases and cardiovascular diseases than the patients in Europe, Middle East and North America. The cohort studies involving patients in the ICU are summarised in table 2. The characteristics of the ICU study populations were similar to those of overall hospitalised patients for all the regions.

Incidence of thromboembolic events and other clinical outcomes

The incidence of DVT was the highest in Asia (40.8%), followed by 16.6% in Oceania, 15.6% in the Middle East, 12.8% in North America, and 8.0% in Europe (table 1). All patients were screened for DVT using lower extremity venous echocardiography in 6 of 13 Asian studies, and the incidence ranged from 24.7%[31] to 85.4%.[32] In several studies from Europe and North America that screened the patients for DVT using lower extremity venous echocardiography, the DVT incidence rates ranged from 10.7%[33] to 60.9%[34] and 13.3%[35] to 56.3%,[36] respectively. Two out of 12 studies from Middle East screened all patients for DVT, with incidence rates ranging from 16.9%[37] to 19.2%.[38] The pooled estimates of DVT incidence are reported in online supplemental file 4 (eResults).

The incidence of PE was higher in Europe (14.6%) and the Middle East (16.2%) than in Asia (3.2%) and North America (5.0%) (table 1). In 13 of 18 European studies that reported an incidence of >20%, all patients underwent CT pulmonary angiography (CTPA) to confirm the diagnosis of PE. Two studies conducted active screening to detect PE in patients using D-dimer cut-off levels of 1.0 µg/mL or greater.[39 40] Of the two Middle Eastern studies that reported an incidence rate of over 20%, one included all the patients who underwent CTPA, and the

other study did not specify the information. There were no studies from Asia in which all patients had undergone CT and, in North America, only in two studies with the PE incidence rates were over 20%, all patients had undergone CTPA. The pooled estimates of PE incidence are reported in online supplemental file 4 (eResults).

A higher incidence of ischaemic stroke was reported in Asia (33.8%); however, the data were available only from two studies. Limb ischaemia and myocardial infarction were the least frequently reported conditions in all the regions. Hospital mortality was numerically lower in Africa (10.4%), but not significantly different across Asia (22.7%), Europe (20.9%), the Middle East (29.0%) and North America (20.6%; p value for all areas, 0.361).

Patients in the ICU had a higher incidence of DVT and mortality than hospitalised patients (table 2). The incidence of DVT was higher in Asia (57.4%) than in other areas. The mortality rate was the highest in Asia (34.8%).

Most patients were placed on mechanical ventilation in the studies from Europe (91.1%), Middle East (88.4%) and North America (84.6%). On the contrary, in Asia, 63.4% of patients in the ICU received mechanical ventilation; in one study, 37.5% of the patients were on mechanical ventilation.[32] Many studies had presented laboratory test data, but few had reported the timing of laboratory tests.

Prophylactic anticoagulation regimen

An Asian study in which all hospitalised patients were screened for DVT reported the use of prophylactic anticoagulation therapy with low-molecular-weight heparin (LMWH) at 30–40 mg/day.[32] One European study used intravenous unfractionated heparin (UFH) at 5–8 units/kg/hour or LMWH at 40 mg/day.[41] In North America, two studies reported the use of subcutaneous heparin or LMWH (dose not reported),[35 42] and one reported the use of enoxaparin at 40 mg or heparin at 5000 units every 8 hour as prophylactic anticoagulation therapy.[36] LMWH was used as the prophylactic anticoagulant in the ICUs in Asia, Europe, the Middle East and North America (table 3).

Studies on patients with thromboembolic complications

Case series of patients with thromboembolic complications related to COVID-19 were available from Europe (20 studies), North America (15 studies), Middle East (2 studies), Africa (1 study) and Global (1 study). The major thromboembolic complications reported in the case series

Table 3 The amounts and types of anticoagulants

Area	Anticoagulants	Daily dose		
		Observational cohort studies	ICU studies	Confirmed thrombosis (prophylaxis)
Asia	Low-molecular-weight heparin	10 000, 8000–12000 U 30–40 mg	10 000, 8000–12 000 U, 30–40 mg	NA
Europe	Unfractionated heparin	10 000, 12 000, 15000–20 000 U, 120–192 U/kg, 1500 or 2500+288 U/kg	NA	10 000,12 000 U, 1500 or 2500+288 U/kg
	Low-molecular-weight heparin	4000 U, 75–150 U/kg 40, 40–60, 40–100 mg, 1 mg/kg	4000 U 40 mg	NA
	Enoxaparin	40, 40–60, 40–80, 60–80, 80, 80–120 mg, 1–1.5 mg/kg	40, 40–60, 60–80, 80–120 mg	40, 40–60, 60–80 mg
	Nadroparin	2850–5700 U	5700–1 14 000 U	NA
	Dalteparin	5000,10000 U, 75–100 U/kg	5000, 75–100 U/kg	NA
	Findaparinux	2.5, 2.5–6.0 mg	NA	NA
	Bemiparin	3500 U	NA	NA
North America	Unfractionated heparin	10 000–15 000, 15 000, 15 000–22 500 U, 15 000 U+apixaban	NA	15 000–22500 U
	Low-molecular-weight heparin	40 mg, 0.5, 0.6 mg/kg	NA	NA
	Enoxaparin	30–40, 40, 40–60 mg 40 mg+apixaban	30–40 mg 40 mg+apixaban	40 mg
Middle East	Unfractionated heparin	10000 U	NA	NA
	Enoxaparin	40, 40–80 mg 1 mg/kg	40–80 mg	NA
South America	Enoxaparin	0.5 mg/kg	NA	NA

ICU, intensive care unit; NA, not available.

were PE in Europe (83.3%) and North America (43.0%) and DVT in the Middle East (60.0%). Prophylactic UFH or LMWH was administered to patients at doses similar to those reported in the observational cohort studies (table 3).

RCTs on thromboprophylaxis strategies

Seven RCTs, representing 4807 patients, compared the efficacy of two anticoagulation regimens in patients with COVID-19. All studies randomised patients hospitalised with COVID-19 to either a therapeutic/moderate dose or a prophylactic/low dose of anticoagulants. Three of the seven RCTs were conducted globally,[25 26 43] and three were conducted in the ICU.[26 44 45] Men accounted for 60% of

the trial participants, with a mean age of 60 years. Overall, the therapeutic/moderate dose anticoagulation regimen did not decrease DVT (6 trials, 4634 patients, OR 0.72 (95% CI 0.44 to 1.18)) but reduced the PE (6 trials, 4634 patients, OR 0.38 (95% CI 0.25 to 0.58)). However, it increased major bleeding (7 trials, 4807 patients, OR 1.73 (95% CI 1.12 to 2.67)) without affecting hospital mortality (7 trials, 4807 patients, OR 0.95 (95% CI 0.81 to 1.11), figure 3). Moderate heterogeneity was observed in the effect on hospital mortality but not for the other outcomes (figure 3).

Therapeutic anticoagulation did not affect the incidence rates of stroke (4 trials, 4149 patients, OR 0.87
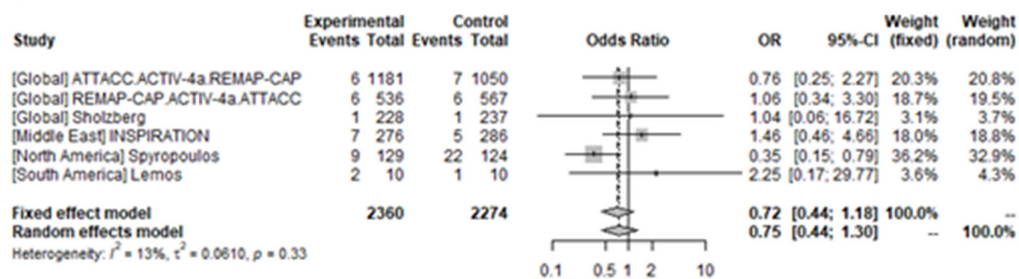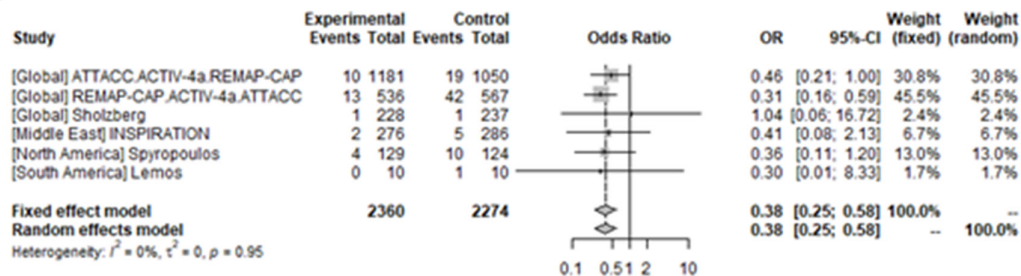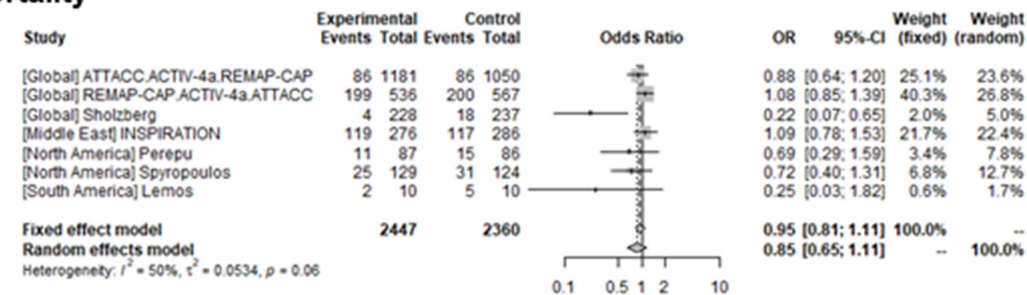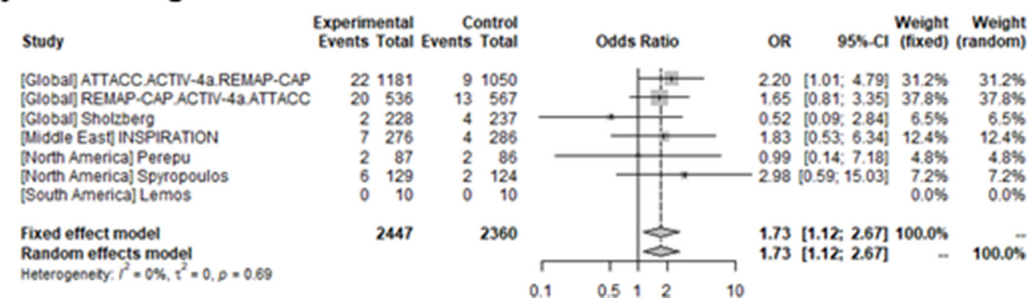

Figure 3 Forest plots of the meta-analysis of effect of therapeutic dose of anticoagulants in COVID-19. DVT, deep venous thrombosis; PE, pulmonary embolism.

(95% CI 0.39 to 1.96)), myocardial infarction (5 trials, 4614 patients, OR 0.62 (95% CI 0.27 to 1.44)) or limb ischaemia (2 trials, 815 patients, OR 4.88 (95% CI 0.23 to 102.72); online supplemental file 4.

DISCUSSION

In this SR, the incidence of DVT in patients hospitalised with COVID-19 was the highest in Asia (40.8%) and the lowest in Europe (8.0%). On the contrary, the incidence of PE was the highest in the Middle East (16.2%), followed by Europe (14.6%) and the lowest in Asia (3.2%). The incidence of DVT and PE in Africa were not available. Despite the variation in the reported incidence of thromboembolic complications, no significant difference was observed in the prophylactic anticoagulation regimen among the regions. The reported hospital mortality rates were not materially different across these areas. Pooled analysis of RCTs showed that therapeutic doses of anticoagulation reduced PE but increased major bleeding, without any apparent heterogeneity across the regions.

Previous haematological studies have reported that intrinsic thrombogenicity differs among races.[7] Caucasians reportedly have a higher prevalence of factor V Leiden mutation, resulting in a higher prothrombotic status than Asians.[9] Therefore, it is possible that the incidence of thromboembolic events also varies among patients of different races with COVID-19.

Several COVID-19 studies have found differences in SARS-CoV-2 positivity, prognosis and complications among different racial groups in the USA.[20–24 46–49] They reported that Black and African-American patients had higher COVID-19 positivity rates,[48 50] higher rates of hospitalisation[20 21] and higher mortality rates[22–24 49] than white patients. The current study showed that the type and incidence of thromboembolic complications related to COVID-19 differed between regions, particularly Europe and Asia. Regional differences may support the racial differences in the risk of thromboembolism.

However, we did not find any differences in in-hospital mortality between these regions, possibly due to confounding factors that could not be adjusted because this study used aggregated data of the study populations and variables.

The incidence of DVT should be affected by screening methods and prophylactic anticoagulants. The current SR found that approximately half of the Asian reports performed DVT screening to all patients in the study cohort, which might have led to a high overall incidence. In addition to the incidence of DVT, the mortality rate was also higher in Asian studies. The possible reason is that the SR evaluated reports from the early days of the pandemic before the start of the vaccination—reports from the early days of the first wave of the pandemic in China might have played a central role in the high mortality rate. Perhaps, during the first wave, prophylactic anticoagulants and thromboembolic events were not as well understood in COVID-19 cases as they are

today. There were very few reports from Asian countries other than China, and it is unknown whether we accurately assessed Asian characteristics. Further investigation of granular patient-level data including other Asian countries is warranted.

The incidence of fatal PE was higher in Europe and the Middle East and lower in Asia and North America. Many European studies subjected all eligible patients to CTPA and may have included many asymptomatic patients, thereby contributing to the high incidence rate.

The incidence rates of DVT and PE were higher in ICU-admitted patients than in overall hospitalised patients, and thromboembolic events were associated with severity. In this SR, mortality did not differ between cohorts of hospitalised patients and ICU-admitted patients. One reason for this may be that many of the studies were conducted in the early days of the pandemic, when ICUs became full, and the general wards might have been used to provide care for critically ill patients. The incidence of DVT and mortality in the ICU were highest in Asia; PE was not reported but may have contributed to the relatively high mortality. There were no significant differences in the type and dose of anticoagulants used across the regions.

The common risk factors for thromboembolic events (such as cancer, obesity, older age and history of VTE)[51] were not evident in patients with COVID-19. D-dimer levels were elevated in patients with thromboembolic events and laboratory data should have played an important role in screening DVT and PE in the case of COVID-19.[52] However, very few studies clearly reported data when thromboembolic event occurred.

The current meta-analysis showed that therapeutic dose reduced the incidence of PE but not of DVT or mortality and increased major bleeding complications. We aimed to assess the heterogeneity across the regions; however, the small number of RCTs did not allow statistical assessment to interpret the regional difference. Also, major large trials were conducted globally.

Furthermore, in this study, the incidence of PE in Asia and North America was low; therefore, in such areas, therapeutic dose or moderate dose of anticoagulation might not be effective as observed in global studies, and the use of anticoagulants may only increase bleeding complications.

Limitations

Several limitations should be acknowledged. First, we summarised the studies at the continental level but did not evaluate them at the country level or by race. Many countries have populations of different ethnicities, and we were not able to accurately assess the characteristics of thrombosis by race or ethnicity. Second, COVID-19 is an emerging infectious disease, and it involves many unidentified features. Therefore, factors other than race might have a strong impact on the incidence of thromboembolic events, such as medical conditions, public health policies and social status at the time of reporting. We searched

cohort studies that were published before the mass vaccination programmes started. Now that many people are vaccinated, the outcomes may be different. However, we submit that this is the strength of this study—this study presents data from before the vaccination campaign, meaning that the natural course of COVID-19 unaffected by the vaccine were examined. Third, reporting formats, items and screening methods were not standardised among the studies. Therefore, there might be over-reporting and under-reporting of the patient characteristics or outcomes. The reported incidence could be biased by the indications for screening and testing in each study. Furthermore, many cohort studies did not follow up all patients until the final follow-up of the study probably with the aim to publish the paper rapidly. Fourth, the results of the meta-analysis in this study should be taken as exploratory as the statistical analysis plan had not been registered a priori, because the study was mainly designed as an SR. Finally, there were no data on DVT and PE related to COVID-19 from Africa and South America that were available.

CONCLUSIONS

The incidence of DVT was the highest in Asia and the lowest in Europe. The incidence of PE was the highest in Middle East and Europe. There were no regional differences in prophylactic anticoagulation therapy. No material difference in hospital mortality was observed across the regions.

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