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Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019

A Systematic Review and Meta-analysis

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BACKGROUND: Individual studies have reported widely variable rates for VTE and bleeding among hospitalized patients with coronavirus disease 2019 (COVID-19).

RESEARCH QUESTION: What is the incidence of VTE and bleeding among hospitalized patients with COVID-19?

METHODS: In this systematic review and meta-analysis, 15 standard sources and COVID-19-specific sources were searched between January 1, 2020, and July 31, 2020, with no restriction according to language. Incidence estimates were pooled by using random effects meta-analyses. Heterogeneity was evaluated by using the I^2 statistic, and publication bias was assessed by using the Begg and Egger tests.

RESULTS: The pooled incidence was 17.0% (95% CI, 13.4-20.9) for VTE, 12.1% (95% CI, 8.4-16.4) for DVT, 7.1% (95% CI, 5.3-9.1) for pulmonary embolism (PE), 7.8% (95% CI, 2.6-15.3) for bleeding, and 3.9% (95% CI, 1.2-7.9) for major bleeding. In subgroup meta-analyses, the incidence of VTE was higher when assessed according to screening (33.1% vs 9.8% by clinical diagnosis), among patients in the ICU (27.9% vs 7.1% in the ward), in prospective studies (25.5% vs 12.4% in retrospective studies), and with the inclusion of catheter-associated thrombosis/isolated distal DVTs and isolated subsegmental PEs. The highest pooled incidence estimate of bleeding was reported for patients receiving intermediate- or full-dose anticoagulation (21.4%) and the lowest in the only prospective study that assessed bleeding events (2.7%).

INTERPRETATION: Among hospitalized patients with COVID-19, the overall estimated pooled incidence of VTE was 17.0%, with higher rates with routine screening, inclusion of distal DVT, and subsegmental PE, in critically ill patients and in prospective studies. Bleeding events were observed in 7.8% of patients and were sensitive to use of escalated doses of anticoagulants and nature of data collection. Additional studies are required to ascertain the significance of various thrombotic events and to identify strategies to improve patient outcomes.

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ABBREVIATIONS: CAT = catheter-associated thrombosis; COVID-19 = coronavirus disease 2019; IDDVT = isolated distal DVT; ISSPE = isolated subsegmental pulmonary embolism; PE = pulmonary embolism; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Coronavirus disease 2019 (COVID-19), a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), results in substantial respiratory pathology and also causes important manifestations outside the pulmonary parenchyma.[1,2] COVID-19 may predispose patients to venous thromboembolic events (DVT and/or pulmonary embolism [PE]) due to hypoxia, excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[3] Accumulating evidence suggests that hospitalized patients with COVID-19 may have a high incidence of VTE, including those receiving standard thromboprophylaxis according to guidelines for acutely ill medical patients.[4-7]

However, an accurate estimate of the incidence of VTE in hospitalized patients diagnosed with COVID-19 remains unclear, with incidence rates reported between 4.8% and 85%.[5,8-11] This variability might have been influenced by the type of events counted, the type of testing for VTE, assessment setting, and the use and type of thromboprophylaxis. Furthermore, the assessment of PE in patients with COVID-19 is conflated by the presence of immunothrombosis.[12] It is likely that in some patients with COVID-19, local inflammation in the lungs with subsequent endothelial inflammation, complement activation, thrombin generation, platelet and leukocyte recruitment, and the initiation of innate and adaptive immune responses culminate in in situ small pulmonary vessel thrombosis.

In addition to an increased risk of thrombosis, patients with COVID-19 might be at risk of excess bleeding due to factors such as imbalances in platelet production and destruction, coagulation factor consumption in the setting of severe inflammation, and use of antiplatelet or anticoagulant agents.[13] A recent retrospective study, which included 144 critically ill patients primarily receiving standard-dose prophylactic anticoagulation, found a major bleeding event rate of 5.6%.[14]

Comprehensive assessment of the thrombotic and hemorrhagic event rates is critical in the thorough assessment of the disease course for COVID-19 and for considering strategies to mitigate patient outcomes. Our goal, therefore, was to conduct a comprehensive systematic review and meta-analysis to assess the overall incidence of VTE and bleeding among hospitalized patients with COVID-19.

Materials and Methods

We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42020198864) (e-Appendix 1). We followed the Reporting Checklist for Meta-analyses of Observational Studies (MOOSE)[15] to conduct and report this systematic review (e-Table 1).

Selection Criteria and Search Strategy

From January 1, 2020, to July 31, 2020, we included observational studies such as cohort and cross-sectional studies in any geographical area evaluating the incidence of VTE and/or bleeding among hospitalized patients with World Health Organization-defined confirmed or probable COVID-19. Studies enrolling < 10 consecutive patients initially hospitalized for COVID-19 were excluded.

We searched MEDLINE (using the Ovid platform), PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (using the Ovid platform), the Cochrane Library, COVID-19 Open Research Dataset Challenge, COVID-19 Research Database (World Health Organization), Epistemonikos (COVID-19 Living Overview of the Evidence platform), EPPI Centre living systematic map of the evidence, and reference lists of included papers. Preprint servers (bioRxiv, medRxiv, and Social Science Research Network First Look) and coronavirus resource centers of the *Lancet*, *JAMA*, and the *New England Journal of Medicine* (e-Appendix 2) were hand-searched. The search was not limited by language. The search strategy is available in e-Appendix 2.

Data Collection

We screened titles and abstracts, reviewed full texts, and extracted data. Risk of bias was assessed by two authors (D. J. and A. G.-S.) and independently using standardized prepiloted forms. Disagreements were resolved by discussion within the wider team (P. R., B. B., and M. M.).

Outcomes

The primary outcome was the incidence of nonfatal or fatal VTE during hospitalization for COVID-19, expressed as the proportion

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of patients with a diagnosis of VTE. VTE included upper and lower limb DVT and PE diagnosed by using accepted imaging tests, either following clinical suspicion or by routine screening. The secondary outcome was the incidence of bleeding during hospitalization for COVID-19. The incidence of major bleeding (including fatal bleeds) was also determined. Definitions of major bleeding were according to definitions in the individual studies. The outcomes data from the first available time point identified as a primary end point from each study were incorporated into the primary analysis.

Data Analysis

Because of high heterogeneity (as expected and observed), pooled data on the incidence of VTE and major bleeding were analyzed by using a random effects (DerSimonian and Laird method) model approach. Statistical heterogeneity was measured by using the Higgins I^2 statistic.[16,17] The Newcastle-Ottawa Scale was used to rate risk of bias for comparative nonrandomized studies corresponding to each study's design (cohort or cross-sectional).[18,19] The Begg rank correlation method was used to assess for publication bias.

Prespecified Subgroup Analyses: Data for subgroup effects were analyzed according to VTE type (ie, DVT vs PE), as well as setting (ward vs ICU), type of assessment for VTE (ie, screening vs clinical diagnosis), intensity of pharmacologic thromboprophylaxis (no pharmacologic thromboprophylaxis [arbitrarily predefined as ≤ 40% of the study population receiving any pharmacologic prophylaxis] vs standard-dose thromboprophylaxis [arbitrarily predefined as ≥ 70% of the study population receiving standard-dose thromboprophylaxis] vs intermediate-dose thromboprophylaxis or therapeutic anticoagulation), geographical area (North America vs Europe vs rest of the world), and study design (prospective vs retrospective). We also analyzed the incidence of PE and DVT after excluding episodes of isolated subsegmental PE (ISSPE) and catheter-associated thrombosis (CAT)/isolated distal DVT (IDDVT), respectively.

Prespecified Sensitivity Analyses: Two sensitivity analyses were conducted to test the robustness of the study findings. First, outcomes were analyzed from the longest available follow-up points in studies reporting outcomes at multiple time points to ensure no significant changes in outcome estimates. Second, supplemental analyses with inverse variance fixed effects models were run. Analyses were conducted by using Stata version 14.2 (StataCorp).

Results

The searches yielded 10,141 citations. After duplicates were removed and the titles and abstracts reviewed, 9,889 articles were excluded. Of the remaining 252 studies, 203 were excluded after reviewing the full-text manuscript. A total of 49 studies reporting the incidence of venous thrombosis (n = 44), bleeding (n = 1), or both (n = 4) were included in the review.[4,5,8-11,20-62] Two studies included overlapping patient populations,[5,39] and only outcomes data from the first publication were considered for the analyses (Fig 1).

Descriptive Characteristics

This review is based on a pooled sample of 18,093 patients with reported information related to VTE, 1,273 of whom experienced a VTE event (47 studies),[4,5,8-11,20-37,39-51] and a pooled sample of 1,411 patients with reported information related to bleeding, 148 of whom experienced a bleeding event (five studies).[8,36,50,51,60] The sample sizes ranged widely across studies (median, 108 patients; range, 10-1,477). Among the 47 studies that reported information related to VTE, eight (17%) were conducted in the United States,[8,22,37,39,43,48,50,59] 32 (68%) in Europe,[4,5,10,11,20,21,23,26,28-36,40-42,44,46,47,49,52-58,61] and seven (15%) elsewhere.[9,24,25,27,45,60,62] The most common study design was retrospective (33 of 47 [70%]),[4,8,10,11,20-25,27,29-32,34,35,37,39-41,43-46,48,50,54-56,58-60] followed by prospective (n = 10 [21%])[5,28,36,42,47,49,52,53,57,61] and cross-sectional (n = 4 [9%]).[9,26,33,62] Twenty-one studies (21 of 47; [45%]) were conducted exclusively in the ICU setting,[4,5,9,10,21,25,27,29,32,35-37,40,42,43,49,55,57,59,61,62] whereas 10 studies (23%) only enrolled patients in the ward setting[20,23,28,30,31,44,46,47,53,56] (Table 1). None of the studies identified by this systematic review had VTE and bleeding events independently adjudicated.

The mean age was consistently between 52 and 71 years. The proportion of male subjects ranged from 46% to 81%. Approximately 0% to 12% of patients had a history of VTE, and up to 24% of patients had cancer. The follow-up duration varied from 2 to 55 days (e-Table 2). In 19 studies (19 of 31 [61%]), clinicians used standard thromboprophylaxis for ≥ 70% of the patients[8-10,20,22,23,25,28-30,33,36,42,43,48,53,55,57,58]; in four studies (4 of 31 [13%]), clinicians prescribed any kind of pharmacologic thromboprophylaxis for ≤ 40% of the study population.[27,60-62]

With respect to VTE assessment, 13 studies (13 of 47 [28%]) systematically examined all patients for VTE (screening).[9,25,26,28,33,40,44,47,49,53,57,61,62] VTE was suspected based on clinical or laboratory parameter evolution in 29 studies (29 of 47 [62%]),[4,5,8,10,21,22,24,27,29-32,34-37,39,41,43,45,46,48,50,52,54-56,58,59] and five studies combined both modalities to assess for VTE[11,20,23,42,60] (Table 1).

Risk of Bias Results

Scores on the Newcastle-Ottawa Scale for the studies ranged from 4 to 9 (maximum, 9), with a higher score indicating a lower risk of bias. Twenty-eight studies (57%) scored 8 or above and were considered to be at

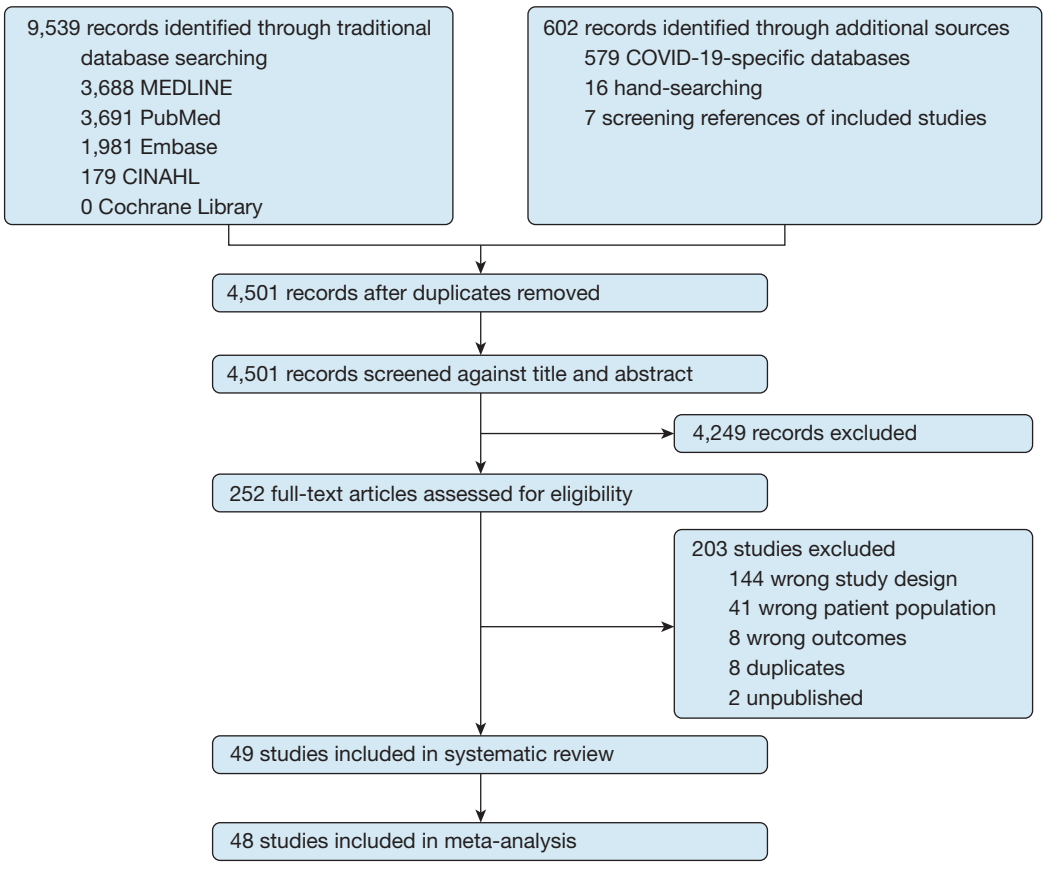

Figure 1 – *Study selection. CINAHL = Cumulative Index to Nursing and Allied Health Literature; COVID-19 = coronavirus disease 2019.*

low risk of bias.[8,10,11,20,23,25,28-33,36,40-43,45,48-53,56,57,60,62] A full assessment is presented in e-Table 3.

Meta-analysis of the Incidence of VTE

Table 2 presents the results of overall and subgroup meta-analyses. Estimates for the population-based studies ranged from 0% to 85.4% (Fig 2), and the random effects overall pooled-estimated incidence of VTE was 17.0% (95% CI, 13.4 to 20.9), with high heterogeneity (I^2 = 97%; $P < .001$). e-Figure 1 shows some evidence of publication bias, as indicated by visual inspections of the funnel plots and by the Egger test for small study effects for the primary outcome (bias coefficient for the main analysis, –0.003; 95% CI, –0.001 to –0.004; $P = .001$).

Meta-analysis of the Incidence of Bleeding

Table 2 presents the results of overall and subgroup meta-analyses. Estimates for the population-based studies ranged from 2.7% to 21.6% (Fig 3), and the random effects overall pooled-estimated incidence of bleeding was 7.8% (95% CI, 2.6 to 15.3), with high heterogeneity (I^2 = 95%; $P < .001$). No publication bias was found based on the funnel plot, Egger test (bias coefficient for the main analysis, –2.83; 95% CI, –11.88 to 6.22; $P = .39$), or Begg test ($P = 1.0$) (e-Fig 1).

Subgroup Analyses

Incidence of VTE: Separate meta-analyses were performed according to the type of VTE (ie, DVT vs PE) (e-Fig 2, Table 2). The graph shows that the incidence of DVT (36 studies; n = 11,566) was 12.1%, whereas the incidence of PE (32 studies; n = 13,424) was 7.1%.

A setting difference in the incidence of VTE was observed between the studies identified in the systematic review. Forty-one studies separately reported the number of ward and ICU patients with and without VTE. The pooled incidence of VTE was 7.1% for patients admitted to the ward and 27.9% for those admitted to the ICU (e-Table 3).

When the studies were categorized according to different diagnostic methods of VTE (ie, screening vs clinical diagnosis), significantly different pooled proportions of VTE were found among different subgroups (e-Fig 2, Table 2). Eighteen of the studies

TABLE 1] Characteristics of Included Studies

Study	No.	Country	Setting (No.)	Design	Assessment for VTE (No.)	Screening Method	Type of VTE	Bleeding Assessment	Intensity of Pharmacologic Thromboprophylaxis (%)	Risk of Bias
Al-Samkari et al[8]	400	United States	Ward (256) ICU (144)	Retrospective	Clinical diagnosis	…	SVT/DVT/PE	Yes (WHO grading system)	None (2) Standard dose (89) Intermediate dose (9)	8
Artifoni et al[20]	71	France	Ward	Retrospective	Screening for DVT (71) Clinical diagnosis for PE (71)	Lower limb ultrasound	DVT/PE	No	Weight-adjusted (99)	9
Beun et al[21]	75	The Netherlands	ICU	Retrospective	Clinical diagnosis	…	DVT/PE	No	NA	6
Bilaloglu et al[22]	3,334	United States	Ward (2,505) ICU (829)	Retrospective	Clinical diagnosis	…	DVT/PE	No	Standard dose	7
Cattaneo et al[23]	388	Italy	Ward	Retrospective	Screening (64) Clinical diagnosis (324)	Lower limb ultrasound	DVT	No	Standard dose	8
Chen et al[24]	1,008	China	NA	Retrospective	Clinical diagnosis	…	PE	No	NA	7
Chen et al[25]	88	China	ICU	Retrospective	Screening (88)	Ultrasound	DVT	No	Standard dose	8
Criel et al[26]	82	Belgium	Ward (52) ICU (30)	Cross-sectional	Screening (82)	Upper and lower limb ultrasound	DVT	No	None (4) Standard dose (60) Intermediate dose (37)	7
Cui et al[27]	81	China	ICU	Retrospective	Clinical diagnosis	…	DVT/PE	No	None	6
Demelo-Rodriguez et al[28]	156	Spain	Ward	Prospective	Screening (if D-dimer 1,000 ng/mL) (156)	Lower limb ultrasound	DVT	No	Standard dose	8
Desborough et al[29]	66	United Kingdom	ICU	Retrospective	Clinical diagnosis	…	DVT/PE	No	Standard dose	8
Dubois-Silva et al[30]	171	Spain	Ward	Retrospective	Clinical diagnosis	…	PE	No	Standard dose	9
Fauvel et al[31]	2,878	France	Ward	Retrospective	Clinical diagnosis	…	PE	No	NA	8
Fraissé et al[32]	92	France	ICU	Retrospective	Clinical diagnosis	…	DVT/PE	NA	Standard dose (47) Full dose (therapeutic) (53)	8

(Continued)

TABLE 1] *(Continued)*

Study	No.	Country	Setting (No.)	Design	Assessment for VTE (No.)	Screening Method	Type of VTE	Bleeding Assessment	Intensity of Pharmacologic Thromboprophylaxis (%)	Risk of Bias
Grandmaison et al[33]	58	Switzerland	Ward (29) ICU (29)	Cross-sectional	Screening (58)	Neck, upper and lower limb ultrasound	DVT	No	None (12) Standard dose (82) Full dose (therapeutic) (6)	8
Grillet et al[34]	280	France	NA	Retrospective	Clinical diagnosis	...	PE	No	NA	6
Hékimian et al[35]	51	France	ICU	Retrospective	Clinical diagnosis	...	PE	No	NA	5
Helms et al[36]	150	France	ICU	Prospective	Clinical diagnosis	...	DVT/PE	Yes (not reported)	Standard dose (70) Full dose (therapeutic) (30)	9
Hippensteel et al[37]	91	United States	ICU	Retrospective	Clinical diagnosis	...	DVT/PE	No	NA	7
Klok et al[5]	184	Netherlands	ICU	Prospective	Clinical diagnosis	...	DVT/PE	No	NA	7
Klok et al[38]	184	Netherlands	ICU	Prospective	Clinical diagnosis	...	DVT/PE	No	NA	7
Koleilat et al[39]	3,404	United States	NA	Retrospective	Clinical diagnosis	...	DVT	No	NA	7
Llitjos et al[40]	26	France	ICU	Retrospective	Screening (26)	Lower limb ultrasound	DVT	No	Standard dose (31) Full dose (therapeutic) (69)	8
Lodigiani et al[41]	388	Italy	Ward (327) ICU (61)	Retrospective	Clinical diagnosis	...	DVT/PE	No	None (14) Standard dose (45) Intermediate dose (22) Full dose (therapeutic) (20)	9
Longchamp et al[42]	25	Switzerland	ICU	Prospective	Screening for DVT (25) Clinical diagnosis for PE (25)	Lower limb ultrasound	DVT/PE	No	Standard dose	9
Maatman et al[43]	109	United States	ICU	Retrospective	Clinical diagnosis	...	DVT/PE	No	Standard dose	9
Mazzaccaro et al[44]	32	Italy	Ward	Retrospective	Screening (32)	Upper and lower limb ultrasound, and CTPA	DVT/PE	No	NA	7

(Continued)

TABLE 1] *(Continued)*

Study	No.	Country	Setting (No.)	Design	Assessment for VTE (No.)	Screening Method	Type of VTE	Bleeding Assessment	Intensity of Pharmacologic Thromboprophylaxis (%)	Risk of Bias
Mei et al[45]	256	China	Ward (211) ICU (45)	Retrospective	Clinical diagnosis	...	DVT/PE	No	NA	9
Mestre-Gómez et al[46]	452	Spain	Ward	Retrospective	Clinical diagnosis	...	PE	No	NA	5
Middeldorp et al[11]	198	Netherlands	Ward (123) ICU (75)	Retrospective	Screening (55) Clinical diagnosis (143)	Lower limb ultrasound	DVT/PE	No	Standard dose (62) Intermediate dose (38)	9
Minuz et al[47]	10	Italy	Ward	Prospective	Screening (10)	CTPA	PE	No	NA	7
Moll et al[48]	210	United States	Ward (108) ICU (102)	Retrospective	Clinical diagnosis	...	DVT/PE	No	Standard dose	8
Nahum et al[49]	34	France	ICU	Prospective	Screening (34)	Lower limb ultrasound	DVT	No	NA	8
Patell et al[50]	399	United States	NA	Retrospective	Clinical diagnosis	...	DVT/PE	Yes (ISTH criteria)	None (7) Standard dose (67) Intermediate dose (22) Full dose (therapeutic) (38)	9
Pesavento et al[51]	324	Italy	Ward	Retrospective	NA	...	NA	Yes (ISTH criteria)	Standard dose (74) Intermediate dose (26)	9
Poissy et al[4]	107	France	ICU	Retrospective	Clinical diagnosis	...	PE	No	NA	6
Ren et al[9]	48	China	ICU	Cross-sectional	Screening (48)	Lower limb ultrasound	DVT	No	Standard dose	7
Rieder et al[52]	49	Germany	Ward (41) ICU (8)	Prospective	Clinical diagnosis	...	PE	No	NA	8
Santoliquido et al[53]	84	Italy	Ward	Prospective	Screening (84)	Lower limb ultrasound	DVT	No	Standard dose	9
Stoneham et al[54]	274	United Kingdom	NA	Retrospective	Clinical diagnosis	...	DVT/PE	No	NA	5
Tavazzi et al[55]	54	Italy	ICU	Retrospective	Clinical diagnosis	...	DVT/PE	No	Standard dose	5

(Continued)

TABLE 1] *(Continued)*

Study	No.	Country	Setting (No.)	Design	Assessment for VTE (No.)	Screening Method	Type of VTE	Bleeding Assessment	Intensity of Pharmacologic Thromboprophylaxis (%)	Risk of Bias
Thomas et al[10]	63	United Kingdom	ICU	Retrospective	Clinical diagnosis	...	DVT/PE	No	Standard dose	8
Trimaille et al[56]	289	France	Ward	Retrospective	Clinical diagnosis	...	DVT/PE	No	None (11) Standard dose (59) Intermediate dose (11) Full dose (therapeutic) (20)	8
Voicu et al[57]	56	France	ICU	Prospective	Screening (56)	Ultrasound	DVT	No	Standard dose	8
Whyte et al[58]	1,477	United Kingdom	Ward (1,255) ICU (222)	Retrospective	Clinical diagnosis	...	PE	No	Standard dose	7
Wright et al[59]	44	United States	ICU	Retrospective	Clinical diagnosis	...	DVT/PE	No	NA	4
Xu et al[60]	138	China	Ward (123) ICU (15)	Retrospective	Screening for ICU patients (15) Clinical diagnosis for ward patients (123)	Lower limb ultrasound	DVT	Yes (not reported)	None (70) Standard dose (30)	8
Zerwes et al[61]	20	Germany	ICU	Prospective	Screening (20)	Lower limb ultrasound	DVT	No	None (40) Standard dose (30) Intermediate dose (15) Full dose (therapeutic) (15)	6
Zhang et al[62]	143	China	ICU	Cross-sectional	Screening (143)	Lower limb ultrasound	DVT	No	None (63) Standard prophylaxis (37)	8

CTPA = CT pulmonary angiogram; ISTH = International Society on Thrombosis and Haemostasis; NA = not available; PE = pulmonary embolism; SVT = superficial vein thrombosis; WHO = World Health Organization.

TABLE 2] Incidence of VTE and Bleeding Using Random Effects Meta-analysis and Subgroup Meta-analysis

Variable	No. of Articles	No. of Participants	No. of Cases	Incidence (95% CI)	I^2, %	Subgroup Difference
Global analysis for VTE						
VTE	47	18,093	1,273	17.0 (13.4-20.9)	97	NA
Subgroup analyses for VTE						
Type of VTE						
DVT	36	11,566	614	12.1 (8.4-16.4)	97	.09
PE	32	13,424	649	7.1 (5.3-9.1)	93	
Type of assessment for VTE						
Screening	18	1,067	332	33.1 (21.3-46.0)	94	<.0001
Clinical diagnosis	34	17,122	941	9.8 (7.4-12.6)	96	
Setting						
Ward	20	9,350	458	7.1 (4.8-9.8)	93	<.0001
ICU	31	3,122	731	27.9 (22.1-34.1)	92	
Design						
Prospective	10	768	157	25.5 (16.0-36.3)	89	<.0001
Retrospective	33	16,994	980	12.4 (9.4-15.9)	97	
Geographical location						
North America	8	7,991	367	9.5 (4.4-16.2)	98	.15
Europe	32	8,340	720	17.9 (13.6-22.7)	96	
Rest of world	7	1,762	149	23.7 (6.2-47.9)	99	
Intensity of thromboprophylaxis						
None	4	382	94	21.0 (2.8-48.9)	97	.97
Standard dose	19	7,008	622	18.2 (12.6-24.5)	97	
Intermediate or therapeutic dose	8	1,549	204	19.4 (10.5-30.2)	95	
After exclusion of patients with CAT/ IDDVT (for DVT) and ISSPE (for PE)						
DVT	36	11,566	437	6.2 (4.1-8.7)	95	.02
PE	34	13,620	594	5.5 (4.0-7.1)	91	
Global analysis for bleeding						
Bleeding	5	1,411	148	7.8 (2.6-15.3)	95	NA
Major bleeding	5	1,411	75	3.9 (1.2-7.9)	90	NA
Subgroup analysis for bleeding						
Setting						

(Continued)

TABLE 2] (Continued)

Variable	No. of Articles	No. of Participants	No. of Cases	Incidence (95% CI)	I^2, %	Subgroup Difference
Ward	3	703	46	5.6 (1.9-10.9)	…	.48
ICU	3	309	16	4.4 (1.1-9.3)	…	
Design						
Prospective	1	150	4	2.7 (0.7-6.7)	…	<.001
Retrospective	4	1,261	144	9.4 (3.2-18.3)	95	
Intensity of thromboprophylaxis						
None	1	138	6	4.4 (1.6-9.2)	…	<.001
Standard dose	3	790	38	4.7 (3.1-6.6)	…	
Intermediate or therapeutic dose	2	483	104	21.4 (17.9-25.2)	…	

CAT = catheter-associated thrombosis; IDDVT = isolated distal DVT; ISSPE = isolated subsegmental pulmonary embolism; NA = not available; PE = pulmonary embolism.

diagnosing VTE were based on screening (n = 1,067), and the combined incidence estimate of VTE was 33.1%. Thirty-four studies were based on clinical diagnosis (n = 17,122), and the incidence estimate of VTE was 9.8%.

When the studies were categorized according to different intensity of thromboprophylaxis (no pharmacologic thromboprophylaxis vs standard-dose thromboprophylaxis vs intermediate-dose thromboprophylaxis or therapeutic anticoagulation), similar pooled proportions of VTE were found among different subgroups (e-Fig 2, Table 2). In four studies, < 40% of the patients received pharmacologic prophylaxis (n = 382), and the combined incidence estimate of VTE was 21.0%. In 19 studies, > 70% of the patients received standard dose prophylaxis (n = 7,008), and the combined incidence estimate of VTE was 18.2%. For the eight studies in which patients received intermediate-dose thromboprophylaxis or therapeutic anticoagulation (n = 1,549),[11,21,26,32,40,41,50,56] the combined incidence estimate of VTE was 19.4%.

Most of the studies were from Europe (n = 8,340), only eight were from North America (n = 8,014), and seven were from Asia (n = 1,739). The incidence of VTE was 17.9% in Europe, 9.5% in North America, and 23.7% in Asia (e-Fig 2, Table 2). e-Table 4 presents the subgroup meta-analyses according to geographical area.

After excluding patients with a diagnosis of CAT/IDDVT, the combined incidence estimate of DVT was 6.2%. The pooled incidence of PE was 5.5% when patients with ISSPEs were excluded from the analyses.

Incidence of Bleeding: The pooled incidence of major bleeding was 3.9%. The highest pooled incidence estimate of any bleeding was reported for patients receiving intermediate- or full-dose anticoagulation (21.4%) and the lowest was in the only prospective study that assessed bleeding events (2.7%) (Table 2). e-Figure 2 presents the forest plot of the incidence of bleeding across subgroups of patients.

Sensitivity Analyses

When we analyzed outcomes from the longest available follow-up points in studies reporting outcomes at multiple time points, the pooled incidence of VTE was 18.0%. We reconsidered our findings using an inverse variance fixed effects meta-analysis (e-Fig 3). The combined incidence estimate of VTE was 4.7%, and the incidence of bleeding was 9.4%.

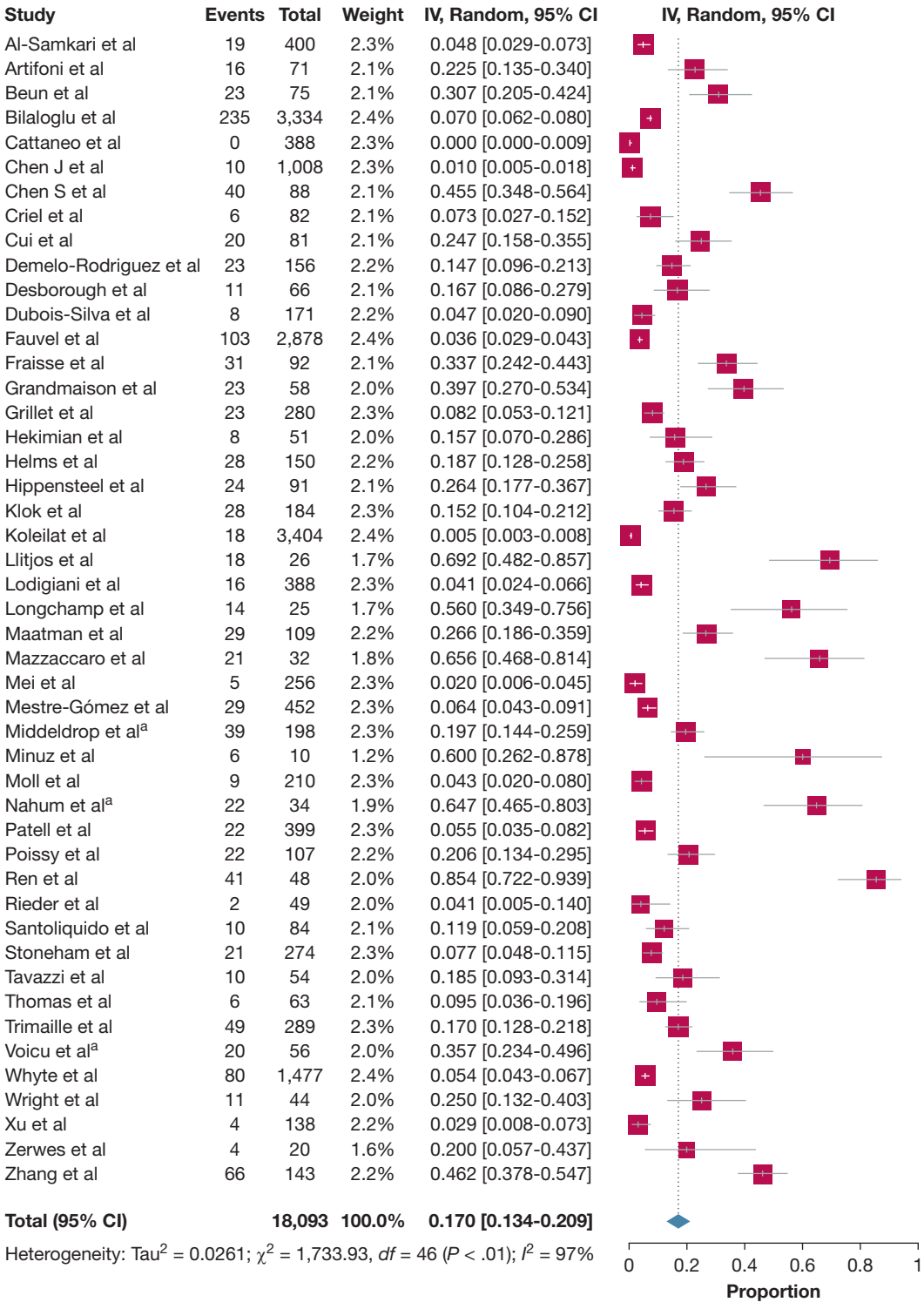

Figure 2 – *Forest plot showing the incidence of VTE among hospitalized patients with COVID-19.* [a]*Shortest assessment period. COVID-19 = coronavirus disease 2019; IV = Inverse-Variance.*

Discussion

This comprehensive systematic review and meta-analysis from several countries and hospital systems showed that the overall incidence rate of VTE among hospitalized patients with COVID-19 was 17.3%, with roughly two-thirds of the events being DVTs. The

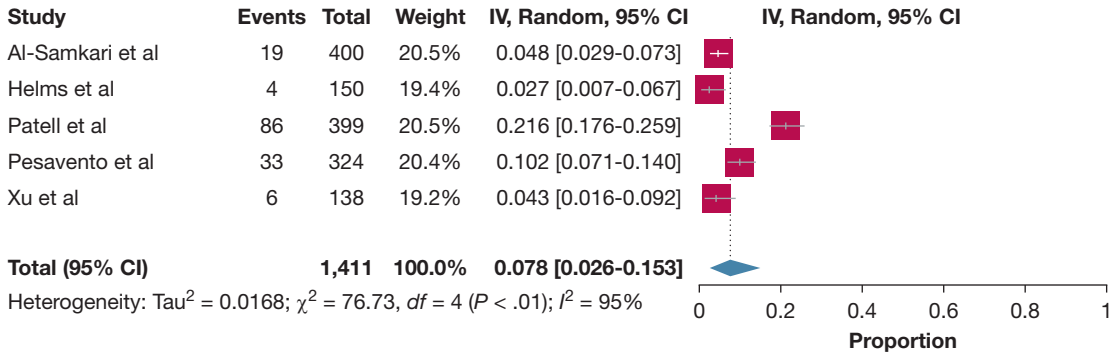

Figure 3 – *Forest plot showing the incidence of bleeding among hospitalized patients with COVID-19. COVID-19 = coronavirus disease 2019; IV = Inverse-Variance.*

results were sensitive to type of assessment for VTE, type of VTE, setting of hospitalization, and nature of data collection, with higher rates with routine screening, inclusion of CAT/IDDVT and ISSPE, in critically ill patients, and in prospective studies. In turn, bleeding events were observed in 7.8% of patients and were sensitive to use of escalated doses of anticoagulants and nature of data collection. Event rates both for VTE and for bleeding are clinically relevant and deserve urgent attention for assessment of the clinical significance and strategies to improve outcomes.

Because of concerns related to thrombotic events, multiple individual studies had reported the rates of VTE in patients with COVID-19. The main strength of this study is that it provided an aggregate estimate. We are cautious not to be overly certain in the precise quantitative estimates of effects, although the qualitative effect and direction are probably of high certainty. Some of the variations across the studies, as shown in our pooled estimates, might be explained by the differences in end point definition, testing strategies, and patients' baseline risk. Studies that used broader end point definitions (such as inclusion of ISSPEs and CAT/IDDVTs) typically reported higher event rates. Systematic screening is also known to increase the diagnostic yield for detecting VTE.[63] Similarly, ICU stay has previously been shown to be a marker of high risk for VTE.[64] The lower rates of VTE in retrospective studies, many of which were from the United States, may be indicative of undertesting early in the course of the pandemic when the shortage in personal protective equipment and fluidity of policies in health systems may have precluded appropriate testing in some patients.

A critical unresolved question is whether all these VTE events, if any, correlate with mortality. Analyses from large observational studies will be informative in this regard. It should be specifically determined if events such as ISSPE, which in many cases may reflect immunothrombosis, or IDDVT, carry prognostic significance. This is particularly important considering that the bleeding events are not rare in patients with COVID-19 and will likely increase as a result of intensified antithrombotic therapy.

From a practical perspective, it is important to identify optimal strategies to avoid deterioration and thrombotic events across the spectrum of patients with COVID-19, including outpatients, inpatients in medical wards, and critically ill patients. In this context, results from several ongoing randomized trials will be informative.[65] These studies can indicate whether more intense antithrombotic therapy can reduce the rates of VTE but also mortality, which may be driven by VTE as well as microangiopathic thrombotic events and arterial thrombosis.

Studies included in this systematic review found a large proportion of patients with COVID-19 who had isolated distal DVT, catheter-associated thrombosis, and subsegmental PE, supporting the notion that the severe inflammatory response and thromboinflammation may have contributed to such events.[66] Although our meta-analysis was not designed to assess treatment efficacy, future studies should determine if immunomodulatory therapies may confer benefit to reduce both the rates of thrombotic events and mortality.[67] In this context, reporting of the thrombotic event rates from the trials testing immunomodulatory therapies, including Randomized Evaluation of COVID-19 Therapy (RECOVERY),[68] Intermediate vs Standard-dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomized

Controlled Trial (INSPIRATION-statin),[65] and others,[69] is highly awaited.

Although the main purpose of the current study was to report on the epidemiology, rather than comparative effectiveness, of health interventions, no association was found between the intensity of thromboprophylaxis and the rate of thrombotic events; however, the rate of clinically relevant bleeding complications among patients who received intermediate- or full-dose anticoagulation exceeded that recorded among those treated with preventive doses. Therefore, results from the ongoing randomized clinical trials are necessary to determine the optimal dose and course of thromboprophylaxis in patients with COVID-19.[65,70]

This study has several limitations. First, in the absence of individual patient data, we were unable to perform a detailed assessment of subgroups or to conduct time-to-event analyses. Second, missing or unreported data in individual studies limited the inferences from aggregate estimates for some of the outcomes. In addition, lack of independent adjudication might have introduced significant biases into this meta-analysis's estimates of the incidence of VTE and bleeding among hospitalized patients with COVID-19. Third, this study did not assess arterial thrombotic events. The existing literature indicates that the majority of thrombotic events in patients with COVID-19 are in the venous circulation.[3] Fourth, the risk of bias tool that we assessed may not have captured all the potential, methodologic limitations of the included studies. It should be noted that prospective, preferentially multicenter and international studies with prospective data collection and similar criteria for outcome assessment will be preferred to provide balanced estimates for disease incidence. Fifth, we were unable to explore the extent of association between incident thrombotic or hemorrhagic events and all-cause mortality. Finally, the high statistical heterogeneity in our study suggests that differences in prevalence estimates across the included studies were determined by factors such as differences in baseline characteristics and baseline risk of VTE, frequency and type of imaging modalities to assess for VTE, setting of hospitalization and acuity of illness, and thromboprophylactic regimens such as type, dose, and duration of antithrombotic therapy. The large difference in results between the random effects and the fixed effects models provides a useful description of the importance of heterogeneity in the individual estimates of included studies; it is for this reason that we had pre-specified to use random effects models for the primary analyses. In addition, small studies might have accounted for this difference,[71] and we encourage an updated analysis of incidence rates once several other large-scale studies become available.

Interpretation

In this systematic review and meta-analysis, nearly one in six hospitalized patients with COVID-19 had incident VTE, although the results were sensitive to hospitalization setting, mode of VTE diagnosis, and outcome definitions across studies; the rates of major bleeding were much lower but sensitive to use of escalated doses of anticoagulant agents. Additional studies are required to understand the utility of more potent antithrombotic or immunomodulatory therapies to safely mitigate the risk of thrombotic events, and mortality.

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Additional information: The e-Appendixes, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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