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Review Article

Prevalence of Thromboembolic Events, Including Venous Thromboembolism and Arterial Thrombosis, in Patients with COVID-19: A Systematic Review with Meta-Analysis

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Abstract

Background: *Many studies have evaluated thromboembolic events in COVID-19 patients, and most of them have reported a high estimation of the prevalence of such events. The present study sought to evaluate the prevalence of thromboembolic events in patients with COVID-19.*

Methods: *This study is a systematic review with meta-analysis that investigated thromboembolic events in patients with COVID-19 from the start of the pandemic to August 31, 2021. The 4 main databases for collecting articles were Medline, Scopus, Google Scholar, and Web of Science. Deep vein thrombosis, pulmonary embolism, arterial thrombosis, and the overall rate of thromboembolic events were considered primary outcomes.*

Results: *In a total of 63 studies (104 920 patients with COVID-19), the overall thrombosis rate was 21% (95% CI, 18% to 25%), the rate of deep vein thrombosis was 20% (95% Cl, 16% to 25%), the rate of pulmonary embolism was 8% (95% Cl, 6% to 10%), and the rate of arterial thrombosis was 5% (95% Cl, 3% to 7%). The prevalence of all primary outcomes in critically ill patients admitted to the intensive care unit (ICU) was significantly higher ($P<0.05$). In older patients, the prevalence of overall thrombosis, pulmonary embolism, or deep vein thrombosis was significantly higher ($P<0.05$).*

Conclusion: *This study showed that COVID-19 increases the risk of thromboembolic events, especially in elderly and critically ill patients admitted to the ICU. Therefore, more strategies are needed to prevent thromboembolic events in patients with COVID-19, especially in ICU-admitted and elderly patients.*

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Keywords: *COVID-19; Venous thromboembolism; Pulmonary embolism*

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Introduction

In late December 2019, in Wuhan, China, there was a report of an unknown pneumonia case whose clinical manifestations were very similar to viral pneumonia. The World Health Organization named this virus "COVID-19". This virus belongs to the Betacoronavirus family.[1]

By September 2022, about 600 million people across the globe had been infected by COVID-19, and about 6.5 million of them died. Most of the deaths caused by this disease occurred in older men with underlying diseases such as diabetes, hypertension, cardiac diseases, chronic respiratory disease, and cancer. This virus can also affect young and healthy people and cause serious complications.[1, 2]

In addition to the lungs, this virus damages other tissues such as the heart, vessels, kidney, and liver. COVID-19 can cause cardiovascular complications by forming thrombosis in the veins and arteries. The mechanism of vascular thrombosis in this disease is acute inflammatory reactions, increased coagulation factors, platelet activation, blood vessel dysfunction, endothelial damage, blood circulation immobility, and vessel obstruction. The entire Virchow's triad, consisting of excessive coagulation, blood flow stasis, and endothelial damage, can be present in this disease.[3]

Many investigations have researched thromboembolic events in COVID-19 patients, and in some studies, the prevalence of venous thrombosis has been estimated as high as 86%.[4] Nonetheless, only a few systematic reviews have investigated the prevalence of thromboembolic events, specifically in patients with COVID-19.

The purpose of this systematic review and meta-analysis was to evaluate the prevalence of thromboembolic events, including venous thromboembolism and arterial thrombosis, in patients with COVID-19. The acquired data will help us choose the right thromboprophylaxis or thrombosis treatment in COVID-19 patients.

Methods

Search strategy

The present systematic review with meta-analysis investigated thromboembolic events in patients with COVID-19 from the start of the pandemic to August 31, 2021. The meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5]

According to all authors, deep vein thrombosis, pulmonary embolism, arterial thrombosis, and the overall rate of thromboembolic events were considered primary outcomes. First, review articles were checked, keywords were defined based on MeSH terms, and the search strategy was defined. Then, keywords in the 4 main databases, namely Medline (via PubMed), Scopus, Google Scholar, and Web of Science, were selected separately by 2 colleagues. Next, they compared their data to unify the desired information. In case of any disagreement regarding the selection or rejection of an article, a third colleague would act as a judge in this field.

After articles and full texts based on titles were searched, they were all reviewed and selected if they had information related to the topic. Investigations in which the diagnosis of COVID-19 was confirmed in the studied subjects were selected. Repetitive studies, non-English language studies, case studies, studies with a sample size of fewer than 10 patients, systematic reviews, meta-analyses, and studies on children under 18 years of age were excluded.

Outcome measures

Deep vein thrombosis, pulmonary embolism, arterial thrombosis, and the overall rate of thromboembolic events were considered primary outcomes.

Deep vein thrombosis diagnosis was confirmed by compression ultrasound or computed tomography (CT) phlebography. Pulmonary embolism was confirmed by pulmonary CT angiography or ventilation-perfusion scanning. Arterial thrombosis was confirmed by ultrasound or CT angiography.

Secondary outcomes consisted of an investigation of the relationship between disease severity, age, male gender, diabetes mellitus, chronic kidney disease, body mass index (BMI), and D-dimer levels and the incidence of each primary outcome.

Data collection and quality assessment

The required items collected from the studies were composed of the name of the first author, the countries of the studies, the type of study, the sample size of the studies, the average age of the patients, gender, the percentage of patients hospitalized in the general ward and the ICU, clinical features (BMI, diabetes, and chronic kidney disease), laboratory tests (D-dimer), and the prevalence of pulmonary embolism, deep vein thrombosis, and arterial thrombosis. These extracted data were initially entered into the Excel software by 2 colleagues according to the desired variables. In the next step, the data were entered into Stata, version 14, for analysis. The selected articles and the data extracted from them were each numbered by a code.

The risk of bias assessment was evaluated, and the quality of the articles was assessed using study quality assessment tools suggested by the National Heart, Lung and Blood Institute (NIH) (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools).

The studies were assessed and divided into overall rating qualities of good, fair, and poor. Our team determined good

studies to be those fulfilling at least 70% of the items in the assessment tool. Fair studies fulfilled 50% to 69%, and poor studies fulfilled fewer than 50% of the items in the tool. Two researchers independently extracted data on the principal characteristics of the populations and data related to the predicted outcomes, if available. Any disagreement was discussed until it was resolved with the cooperation of the third researcher.

Statistical Analysis

Data were analyzed using Stata with Metafunnel, Begg, and Egger tests to determine the diffusion curve. The Cochran test and I-squared statistics were employed to calculate the pooled estimator's common mean based on the rejection or acceptance of the hypothesis of the homogeneity of the samples using the random effect or the fixed effect model to determine the homogeneity of the samples. Thereafter, the proportions of the primary studies were aggregated with the appropriate method (random or fixed), and summary measures were calculated. In case of inconsistency, the Galbraith diagram was utilized to identify outlier studies and detect the cause of heterogeneity. Afterward, the effects of factors related to the heterogeneity of the studies were investigated using statistical methods of subgroup meta-analyses or meta-regression.

Results

Study selection and the characteristics of the included studies

Figure 1 shows the process of selecting studies. At the beginning of the search in the databases (Medline, Scopus, Google Scholar, and Web of Science), 6599 articles were extracted. After duplicates and irrelevant items were removed, 485 articles were chosen based on their title and summary. The full texts of the articles were read, and non-English language studies, case studies, studies with a sample size of fewer than 10 patients, systematic reviews, meta-analyses, and studies on children under 18 years old were excluded. Subsequently, 63 studies (104 920 patients with COVID-19) meeting the inclusion criteria were selected and analyzed. These studies included patients from Europe, Asia, and America. The principal characteristics of the included studies are presented in Table 1.

Primary outcome measures

In data analysis, the overall thrombosis rate (pulmonary embolism, deep venous thrombosis, and arterial thrombosis) was 20% (95% CI, 17 to 24%) among COVID-19 patients. After the exclusion of low-quality studies (quality assessment score <50% of the total score), 11 studies were excluded, and the overall thrombosis rate in high-quality studies was 21% (95% CI, 18% to 25%). The overall thrombosis rate among patients hospitalized in the ICU was 41% (95% CI, 33% to 49%) and 19% (95% CI, 13% to 27%) in general wards (Figure 2 and E-Figure 1 in Supplement 1).

The overall rate of arterial thrombosis in all patients was 5% (95% CI, 3% to 7%), 9% (95% CI, 5% to 15%) among patients hospitalized in the ICU, and 4% (95% CI, 2% to 7%) among non-ICU patients (Figure 3 and E-Figure 2 in Supplement 1). The overall rate of pulmonary embolism in all patients was 8% (95% CI, 6% to 10%), 14% (95% CI, 9% to 19%) among patients hospitalized in the ICU, and 5% (95% CI, 3% to 7%) among non-ICU patients (Figure 4 and E-Figure 3 in Supplement 1). The rate of deep vein thrombosis was also 20% (95% CI, 16% to 25%) in all

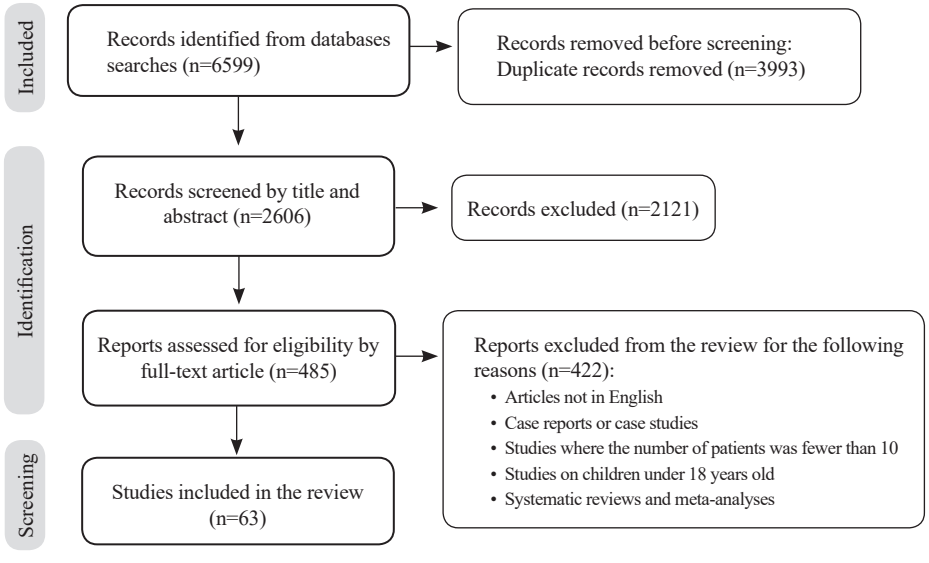


Figure 1. The image presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of the present study.

Table 1. Characteristics of the included studies

Study	Year	Type of Study	Country	Number of Patients	ICU (%)	General Ward (%)	Age, (y)	Sex (%)		Prevalence (%)		
								Male	Female	PE	DVT	AT
Motaganahalli RL, et al [6]	2021	Nonrandomized cohort study	USA	71	NR	NR	61	54	46	NR	47.8	NR
Zhang Y, et al [7]	2020	Single-center cross-sectional study	China	19	100	0	65	52.6	47.4	NR	5	21
Monfardini L, et al [8]	2020	Monocentric observational study	Italy	34	NR	NR	61	59	41	76	97	NR
Zhang L, et al [9]	2020	Cross-sectional	China	143	0	100	63	74	26	NR	46	NR
Stoneham SM, et al [10]	2020	Cohort and a case–control	England	274	NR	NR	67	67	33	0.05	7.7	NR
Stefely JA, et al [11]	2020	Observational cohort	USA	102	NR	NR	61	68	32	23	23	9
Roberts LN, et al [12]	2020	Observational cohort	England	1877	11	NR	NR	NR	NR	NR	0.04	NR
Rieder M, et al [13]	2020	Retrospective observational cohort	Germany	49	16	NR	60	61	39	NR	6.1	NR
Ren B, et al [4]	2020	Cross-sectional study	China	48	100	NR	70	54	46	NR	85	NR
Piazza G, et al [14]	2020	Observational cohort	USA	1114	15	21	50	54	46	0.07	3.5	1
Patell R, et al [15]	2020	Retrospective observational cohort	Israel	163	NR	NR	>18	NR	NR	0.6	2.5	2.5
Betoule A, et al [16]	2020	Retrospectively	France	76	NR	NR	62	50	50	2	NR	1
Middeldorp S, et al [17]	2020	Single-center cohort study	Netherlands	198	38	62	61	66	34	NR	20	NR
Medetalibeyoglu A, et al [18]	2021	Retrospective cross-sectional study	Turkey	309	10	NR	57	61	39	NR	0.9	0.3
Lodigiania C, et al [19]	2020	Retrospective cohort study	Italy	388	16	84	66	68	32	2.5	36	NR
Llitjos JF, et al [20]	2020	Retrospective study	France	26	100	NR	68	77	23	23	69	NR
Kapoor S, et al [21]	2021	Prospective observational study	USA	107	100	NR	60	62	38	12	20	NR
Inciardi RM, et al [22]	2020	Retrospective study	Italy	99	NR	NR	67	81	19	NR	12	3
Ierardi AM, et al [23]	2021	Observational study	Italy	234	20	NR	61	30	70	NR	10.7	NR
Le Jeune S, et al [24]	2021	Observational study	France	42	0	100	65	55	45	9.5	19	NR
Longchamp A, et al [25]	2020	Retrospective study	Switzerland	25	100	0	68	64	36	20	24	NR
Helms J, et al [26]	2020	Historical prospective cohort	French	150	100	0	63	81	19	16	8	NR
Hanif A, et al [27]	2020	Retrospective cohort study	USA	921	NR	NR	62	37	63	NR	1.7	0.2
Chuen Wen Tan, et al [28]	2021	Retrospective observational study	Singapore	108	100	0	62	69	31	NR	1.8	9.9
Edler C, et al [29]	2020	Prospective cohort study.	Germany	80	21	38	79	58	42	NR	40	NR

Study	Year	Type of Study	Country	Number of Patients	ICU (%)	General Ward (%)	Age, (y)	Sex (%)		Prevalence (%)		
								Male	Female	PE	DVT	AT
Demelo-Rodríguez P, et al [30]	2020	Prospective study	Spain	156	10.3	NR	66.7	65.4	34.6	NR	14.7	NR
Cui S, et al [31]	2020	Retrospective study	China	81	100	0	60	46	54	NR	25	NR
Contou D, et al [32]	2020	Retrospective study	France	92	100	0	61	79	21	17	3.2	NR
Chen S, et al [33]	2021	Retrospective study	China	88	100	0	63	61	39	NR	45	NR
Artifoni M, et al [34]	2020	Retrospective cohort study,	French	71	18	NR	64	60.6	39.4	10	22.5	NR
Chang H, et al [35]	2021	Retrospective analysis	USA	443	18.6	NR	62	58	42	8	31	NR
Voicu S, et al [36]	2020	Observational study	France	92	41	NR	62	72	28	NR	43	NR
Longhitano Y, et al [37]	2020	Retrospectively reviewed	Italy	62	100	0	53	75	25	18	19.3	NR
Cho ES, et al [38]	2021	Retrospectively reviewed	USA	158	NR	NR	67	54	46	NR	33	NR
Thondapu V, et al [39]	2021	Retrospective observational cohort study	USA	138	68.8	NR	59.2	40	60	5	20	NR
Muñoz-Rivas N, et al [40]	2021	Single-cohort retrospective study	Spain	1127	6.4	NR	65	65	35	NR	3.8	1.6
Koleilat I, et al [41]	2021	Single center retrospective case-control	USA	135	NR	NR	61	53	47	3	13.3	NR
Alfageme M, et al [42]	2020	Retrospective	Spain	23	100	0	59	69.5	30.5	NR	60	NR
Ameri B, et al [43]	2021	Retrospective review	Italy	689	NR	NR	67.3	69.4	30.6	7.5	NR	NR
Atallah B, et al [44]	2021	Retrospective review	UAE	188	100	0	49	82	18	5	8	1
Avruscio G, et al [45]	2020	Observational cohort	Italy	85	48	52	67	72	28	9.8	42.4	NR
Mouhat B, et al [46]	2020	Retrospective single center	France	162	42	58	65.57	67.3	32.7	27	NR	NR
Rashidi F, et al [47]	2021	Prospective multi center	Iran	1529	7.8	NR	56	54.4	45.6	0.19	NR	NR
Kampouri E, et al [48]	2020	Observational retrospective	Switzerland	443	70	NR	68.6	57	43	6	2	NR
Planquette B, et al [49]	2021	Retrospective nested case-control	France	1259	24.7	NR	63	59.8	39.2	5.6	NR	NR
Kerbikov O, et al [50]	2021	Prospective cohort	Russia	75	0	100	63	48	52	NR	20	NR
Giorgi-Pierfranceschi M, et al [51]	2020	Single-center cross-sectional	Italy	66	NR	NR	71.5	69.6	28.4	7.5	13.6	NR
Hill JB, et al [52]	2020	Retrospective cohort	US	2748	NR	NR	61	48	52	12	15	NR
Jonmarker S, et al [53]	2020	Retrospective cohort	Sweden	152	100	0	61	82.2	17.8	11.2	2.6	NR

Study	Year	Type of Study	Country	Number of Patients	ICU (%)	General Ward (%)	Age, (y)	Sex (%)		Prevalence (%)		
								Male	Female	PE	DVT	AT
Daughety MM, et al [54]	2020	Retrospective cohort	US	192	10	90	63.5	61.5	38.5	6	1	NR
Chen S, et al [55]	2021	Retrospective cohort	China	1030	NR	NR	44	65.9	44.1	NR	45	NR
Chen B, et al [56]	2021	Prospective cross-sectional	China	23	NR	NR	42.7	60.1	39.9	NR	82.6	NR
Boyd S, et al [57]	2021	Retrospective review	Ireland	38	100	0	57.9	70	30	10.5	5.3	NR
Lee E, et al [58]	2021	Retrospective review	USA	192	51	49	62	54	46	15	25	3
Budimir Mršić D, et al [59]	2021	Retrospective	Croatia	280	NR	NR	71	62.8	37.2	27	NR	NR
`oscar Miro´, et al [60]	2021	Retrospective, case–control	Spain	74814	0	100	66	58	42	0.49	NR	NR
Calabrese C, et al [61]	2021	Retrospective, single-center observational case-control	Italy	68	100	0	58.5	69.1	30.9	36.8	1.5	NR
Taccone FS, et al [62]	2020	Retrospective	Belgium	40	100	0	61	70	30	3	NR	NR
Faqihi F, et al [63]	2021	Retrospective Analysis	Saudi Arabia	160	100	0	49	78	22	34	18	4
Nicholas S. Hendren, et al [64]	2021	Cohort	USA	7606	NR	NR	63	55	45	1.4	2.2	NR
Young Erben, et al [65]	2021	Prospectively collected, retrospective study	USA	915	30	70	60.8	56.7	43.3	4.1	4.9	NR
Trigonis RA, et al [66]	2020	Single-center retrospective review	USA	45	100	0	60.8	NR	NR	NR	42.2	NR
Iván J. Núñez-Gil, e al [67]	2021	Multicenter retrospective review	In several countries	2798	7	93	67	60	40	1.4	NR	NR
Total				104920								

ICU, Intensive care unit; PE, Pulmonary embolism; DVT, Deep vein thrombosis; AT, Arterial thrombosis; NR, Not reported

patients, 36% (95% CI, 28% to 45%) in ICU patients, and 14% (95% CI, 6% to 23%) in non-ICU patients (Figure 5 and E-Figure 4 in Supplement 1).

Secondary outcome measures

The correlations between disease severity, age, male gender, diabetes mellitus, chronic kidney disease, BMI, and D-dimer and each of the primary outcomes were also investigated.

As shown in Table 2, with both univariate regression (the unadjusted effect) and multivariate regression (the adjusted effect) models, the prevalence of overall thrombosis, arterial thrombosis, pulmonary embolism, and deep vein thrombosis in critically ill patients admitted to the ICU (end stages) was significantly higher (P<0.05).

Furthermore, in patients with higher D-dimer levels, by both univariate and multivariate regression analyses, the prevalence of total thrombosis was significantly higher (P<0.05), while it was not significant for arterial thrombosis, pulmonary embolism, and deep vein thrombosis. In older patients, in the multivariable regression analysis, the prevalence of overall thrombosis, pulmonary embolism, and deep vein thrombosis was significantly higher (P<0.05), but there was not a significant relationship between the prevalence of arterial thrombosis and older age. In the multivariable regression analysis, the prevalence of deep vein thrombosis was significantly higher in men (P<0.05), but other primary outcomes were not significant in men.

No significant relationship existed between diabetes mellitus, chronic kidney disease, and BMI and the prevalence of each predicted primary outcome.

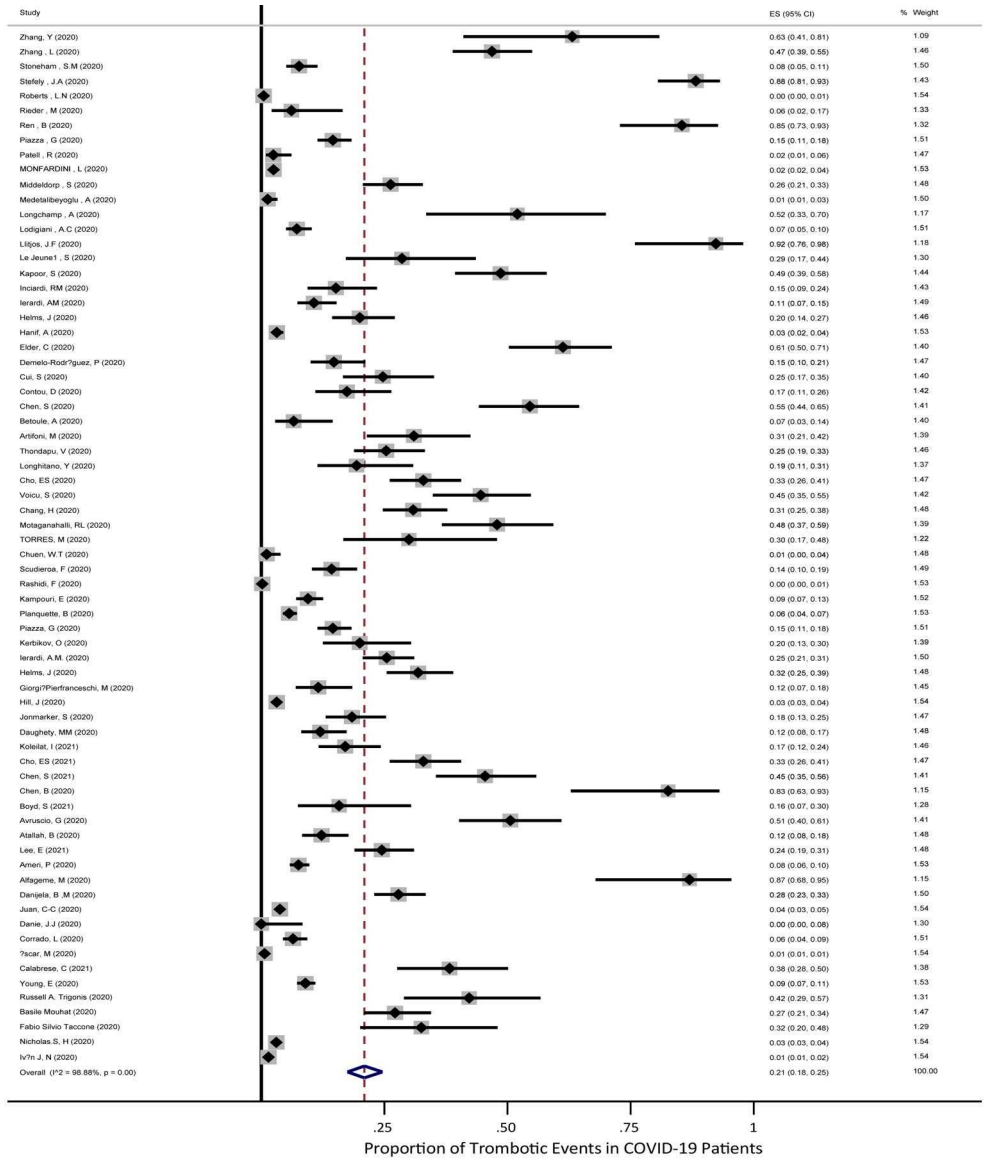
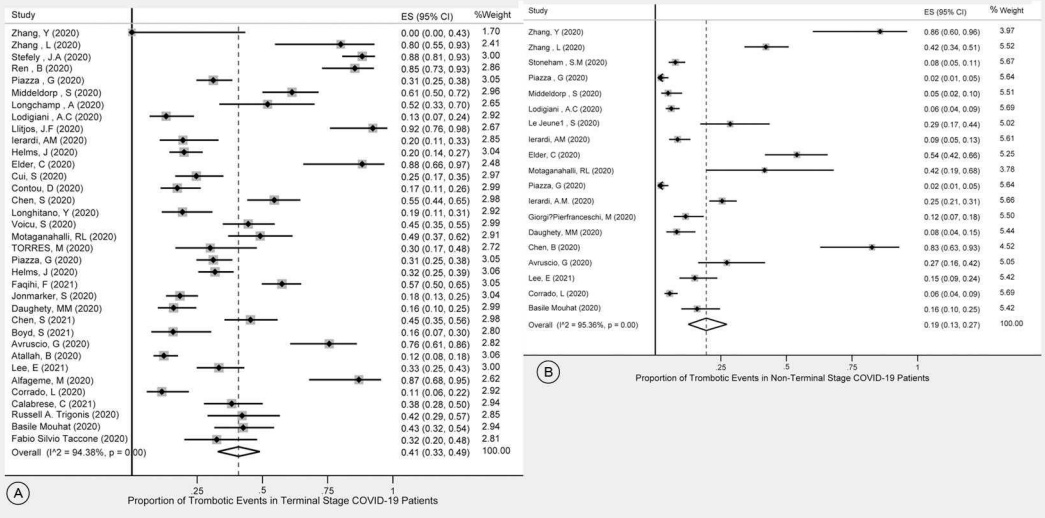


Figure 2. The image illustrates the proportion of total thromboembolic events in COVID-19 patients.

Supplement 1



E-Figure 1. Proportion of total thromboembolic events in COVID-19 patients: A) Terminal stage (ICU) patients, B) Non-terminal stage (general ward) patients.

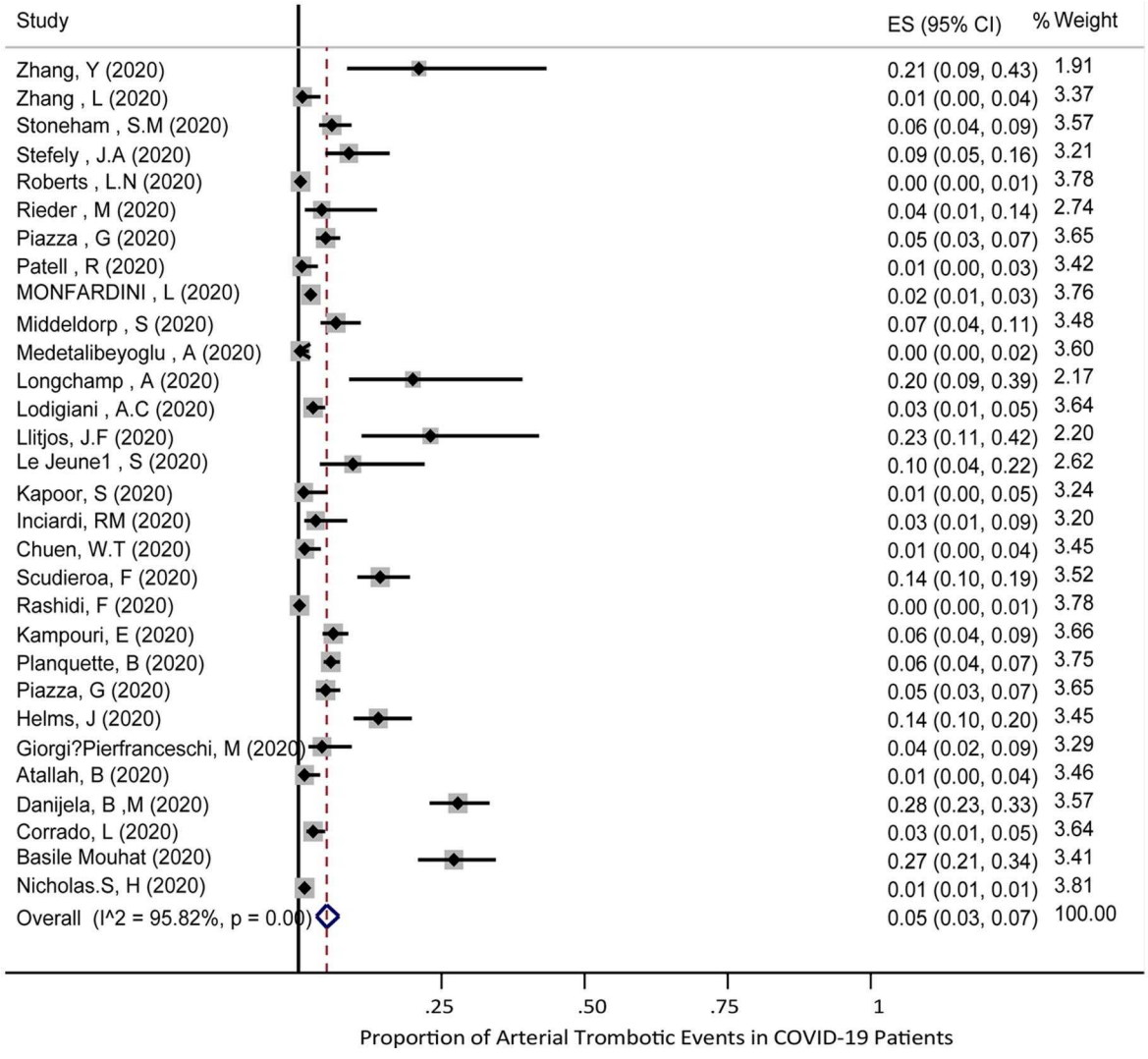
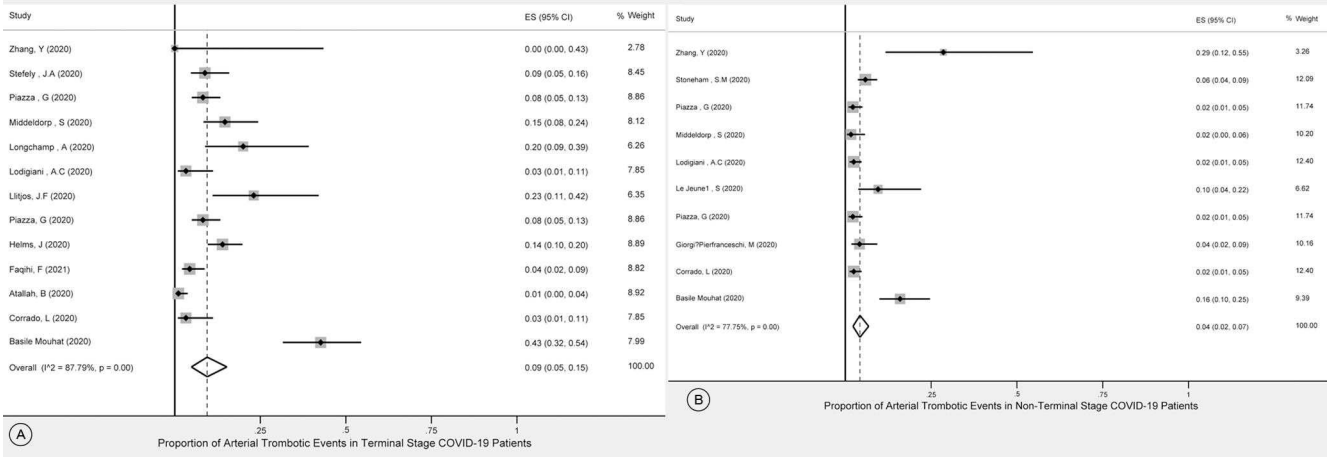


Figure 3. The image demonstrates the proportion of arterial thrombosis in COVID-19 patients.

Supplement 1



E-Figure 2. Proportion of arterial thrombosis in COVID-19 patients: A: terminal stage (ICU) patients, B: non-terminal stage (general ward) patients.

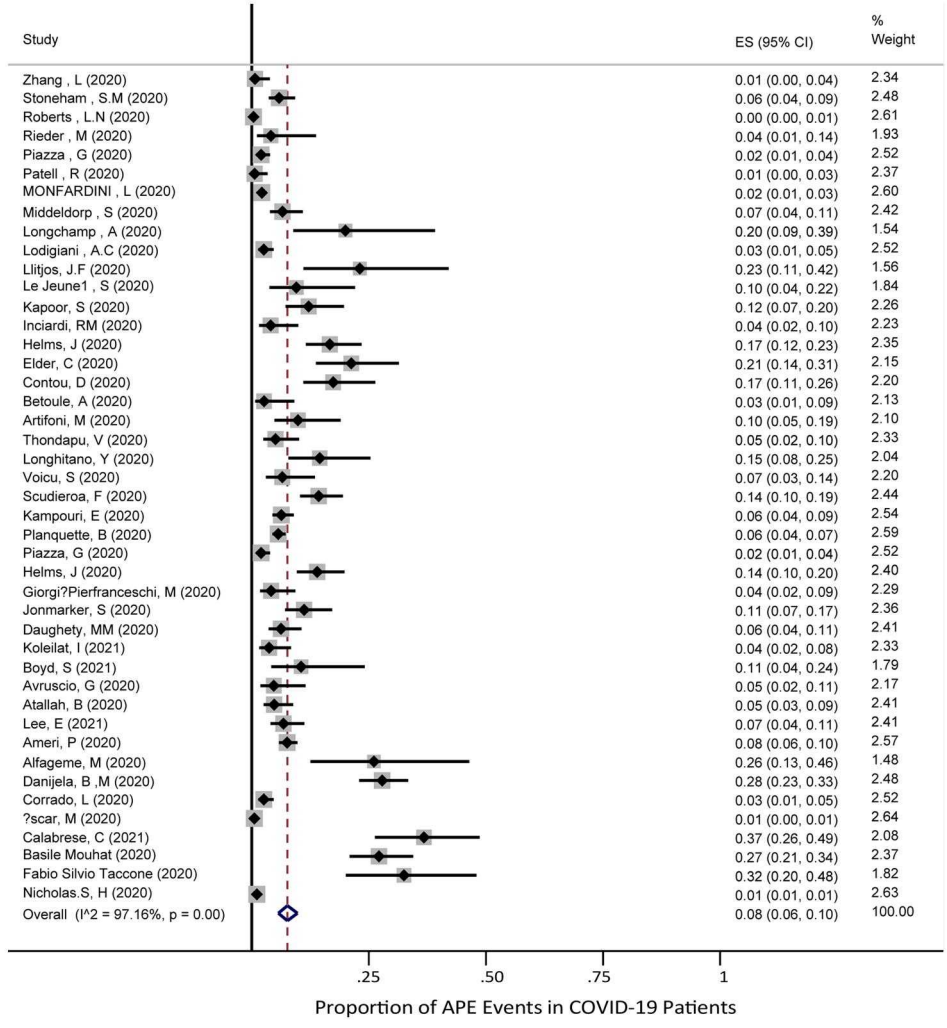
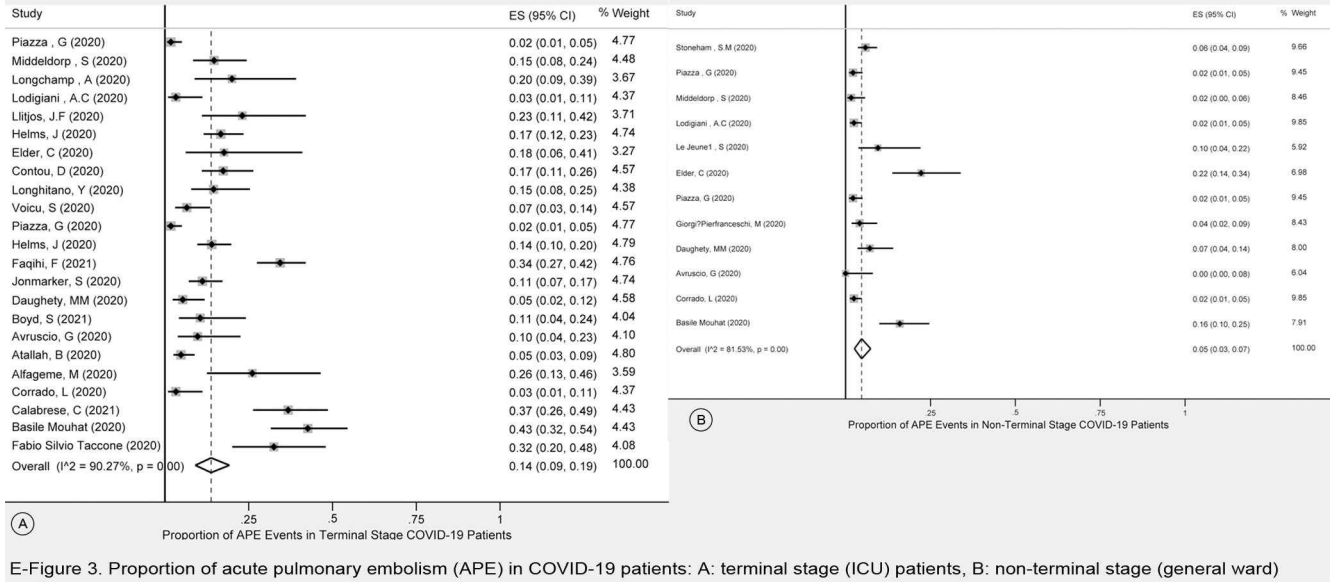


Figure 4. The image shows the proportion of acute pulmonary embolism (APE) in COVID-19 patients.

Supplement 1



E-Figure 3. Proportion of acute pulmonary embolism (APE) in COVID-19 patients: A: terminal stage (ICU) patients, B: non-terminal stage (general ward) patients.

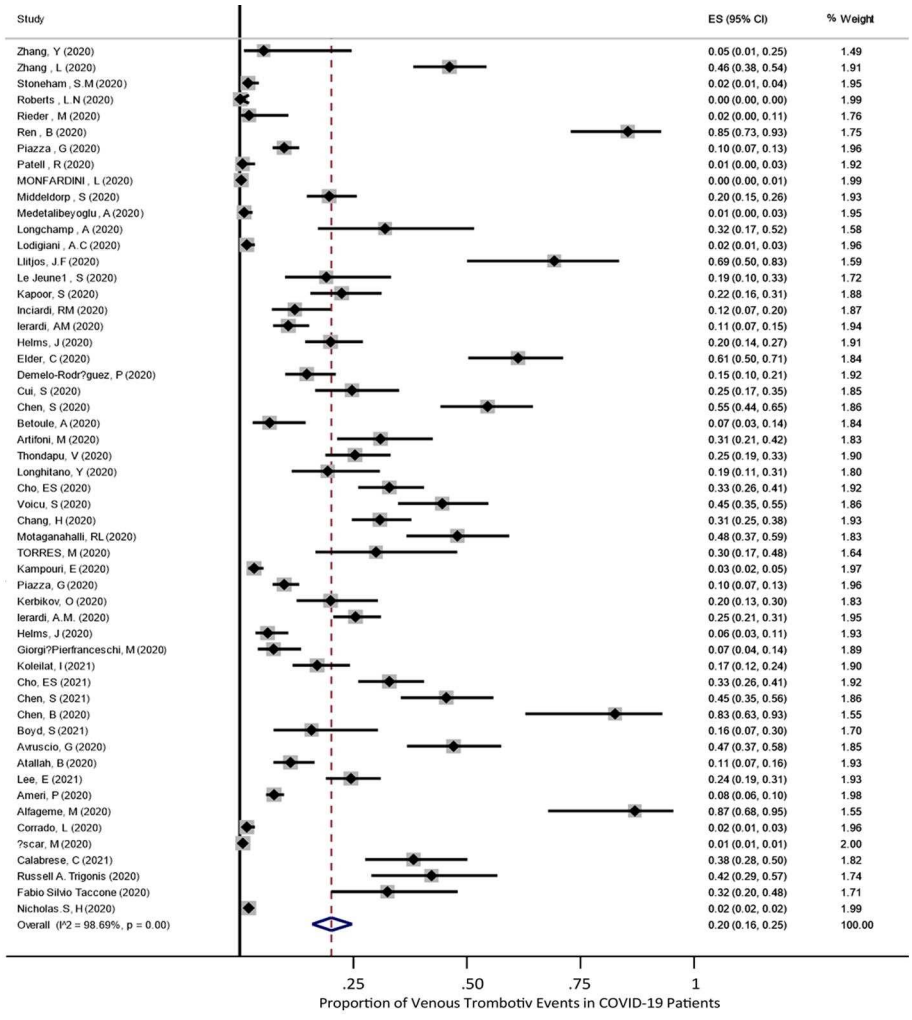
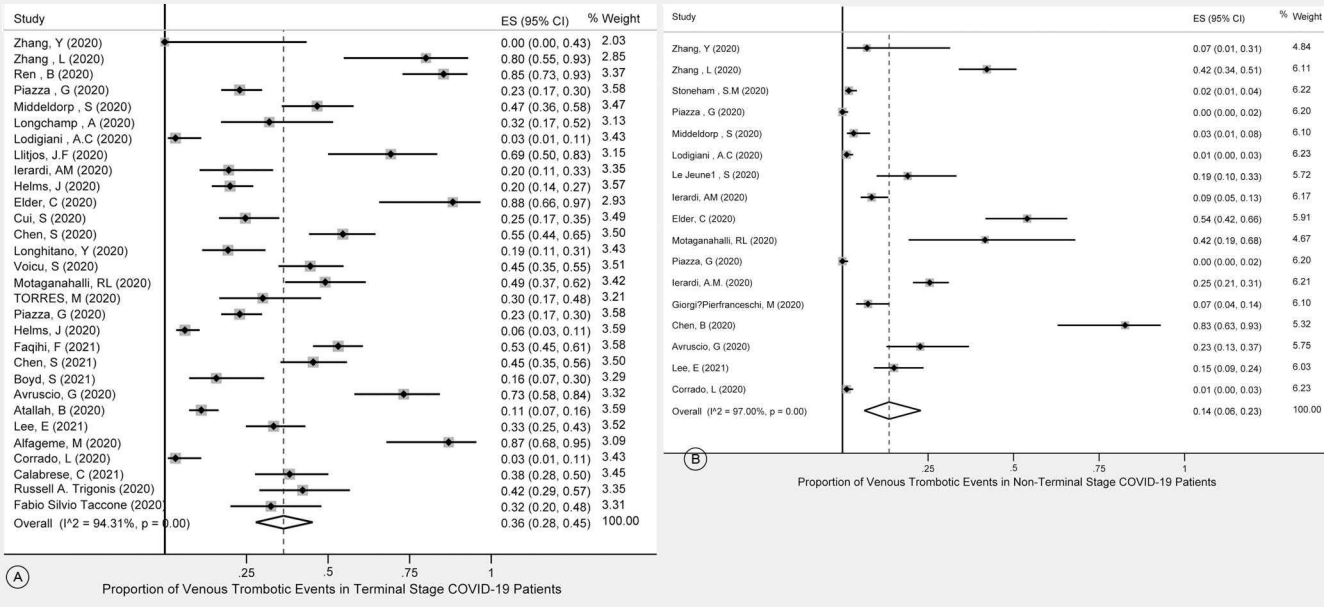


Figure 5. The image depicts the proportion of deep vein thrombosis in COVID-19 patients.

Supplement 1



E-Figure 4. Proportion of deep vein thrombosis in COVID-19 patients: A:terminal stage (ICU) patients, B: non-terminal stage (general ward) Patients.

Table 2. Meta-regression results of univariate and multiple (the adjusted effect) models assessing the effects of age, male proportion, body mass index, D-dimer, diabetes mellitus and chronic kidney disease on the prevalence of thromboembolic events (A, Total thromboembolic event; B, Arterial thrombosis; C, Pulmonary embolism; and D, Deep vein thrombosis) in COVID-19 patients.

A.	Unadjusted		Adjusted	
	β (95% CI)	P	β (95% CI)	P
Terminal Stage (ICU)	0.31 (0.14-0.49)	0.001	0.30 (0.01, 0.58)	0.040
Age	0.004 (-0.005, 0.02)	0.330	0.02 (0.002, 0.05)	0.035
Male	0.07 (-0.42, 0.57)	0.775	-0.40 (-1.11, 0.31)	0.261
Body Mass Index	-0.02 (-0.05, 0.009)	0.172	-0.01 (-0.05, 0.02)	0.415
D-Dimer	0.06 (0.02, 0.11)	0.008	0.05 (0, 0.1)	0.050
Diabetes Mellitus	0.23 (-0.49, 0.94)	0.510	-0.23 (-0.96, 0.5)	0.525
Chronic kidney Disease	-0.11 (-0.83, 0.6)	0.745	-0.22 (-1.05, 0.61)	0.581

B.	Unadjusted		Adjusted	
	β (95% CI)	P	β (95% CI)	P
Terminal Stage (ICU)	0.44 (0.18, 0.71)	0.002	0.46 (0.17, 0.75)	0.003
Age	0.009 (-0.005, 0.02)	0.215	0.02 (-0.002, 0.04)	0.081
Male	-0.02 (-0.75, 0.72)	0.970	-1.09 (-2.56, 0.38)	0.145
Body Mass Index	0.03 (-0.03, 0.1)	0.315	0.06 (-0.07, 0.19)	0.320
D-Dimer	0.08 (-0.03, 0.19)	0.133	0.04 (-0.11, 0.2)	0.572
Diabetes Mellitus	0.49 (-0.14, 1.12)	0.125	-0.19 (-1.03, 0.65)	0.655
Chronic kidney Disease	-0.14 (-1.29, 1.02)	0.820	-0.44 (-1.85, 0.97)	0.520

C.	Unadjusted		Adjusted	
	β (95% CI)	P	β (95% CI)	P
Terminal Stage (ICU)	0.14 (0.07, 0.22)	0.001	0.19 (0.07, 0.31)	0.005
Age	0.004 (-0.003, 0.01)	0.295	0.01 (0.001, 0.02)	0.033
Male	-0.12 (-0.36, 0.12)	0.331	0.02 (-0.42, 0.47)	0.910
Body Mass Index	0.01 (-0.02, 0.04)	0.420	0.02 (-0.04, 0.07)	0.485
D-Dimer	0.007 (-0.02, 0.04)	0.645	0.004 (-0.03, 0.04)	0.830
Diabetes Mellitus	0.17 (-0.18, 0.51)	0.321	-0.41 (-0.93, 0.11)	0.115
Chronic kidney Disease	-0.21 (-0.75, 0.32)	0.420	-0.06 (-0.68, 0.57)	0.855

D.	Unadjusted		Adjusted	
	β (95% CI)	P	β (95% CI)	P
Terminal Stage (ICU)	0.18 (-0.02, 0.38)	0.085	0.27 (0.03, 0.5)	0.030
Age	0.002 (-0.01, 0.02)	0.765	0.02 (0.004, 0.04)	0.025
Male	-0.34 (-0.93, 0.26)	0.260	-0.71 (-1.42, -0.004)	0.040
Body Mass Index	-0.02 (-0.05, 0.007)	0.135	-0.02 (-0.05, 0.02)	0.285
D-Dimer	0.05 (0.004, 0.1)	0.041	0.04 (-0.02, 0.1)	0.151
Diabetes Mellitus	0.31 (-0.57, 1.19)	0.470	0.02 (-1, 1.04)	0.975
Chronic kidney Disease	-0.08 (-1.31, 1.15)	0.895	0.05 (-1.67, 1.77)	0.950

Discussion

The results of the present systematic review showed that the prevalence of overall thrombosis in all patients was 21%. The prevalence of deep vein thrombosis, acute pulmonary embolism, and arterial thrombosis in all patients was 20%, 8%, and 5%, respectively.

It seems that infection with COVID-19 increases thrombus or microthrombus formation in pulmonary arteries and veins and causes endothelial damage and endotheliitis.[68] Additionally, excessive cytokine release in the plasma of infected patients may play an interfering role in the coagulation cascade activation and cause hypercoagulable states.[69, 70] The proposed mechanisms for macrovascular and in situ microvascular thrombosis formation in pulmonary vessels include known risk factors, such as immobility, lung parenchymal infection, fever, and obesity, as well as an inflammatory response causing endothelial dysfunction and cytokine storm, well known in COVID-19.[71]

In addition, the prevalence of acute pulmonary embolism was 8% in general, 14% in critically ill patients admitted to the ICU, and 5% in patients admitted to the general wards. This increased rate compared with the normal population is probably due to 2 reasons. The first reason is macrovascular and in situ microvascular thrombosis in the pulmonary vessels, as mentioned earlier. The second one is the high prevalence of deep vein thrombosis in COVID-19 patients, supporting the hypothesis that pulmonary embolism is caused by peripheral thrombosis. Our study showed that the prevalence of deep vein thrombosis in all patients was 20%, and this rate was 36% in critically ill patients admitted to the ICU and 14% in patients admitted to general wards. Ren et al[4] reported that the incidence of deep vein thrombosis in critically ill patients admitted to the ICU was up to 85%, significantly different from the overall result of our study and similar studies. It seems that the reason for this difference is the routine ultrasound examination of all patients, multiple times, including symptomatic and asymptomatic ones (and CT angiography in all asymptomatic patients suspected of pulmonary embolism). In many similar studies, ultrasound or pulmonary CT angiography was done for only symptomatic patients.

The prevalence of arterial thrombosis was also 5% among all patients, 9% among patients hospitalized in the ICU, and 4% among patients admitted to general wards. Virchow's triad helps explain the mechanism of arterial thrombosis in these patients. Endotheliitis and diffuse endothelial damage caused by direct virus infection, prolonged immobility of COVID-19 patients, and the hypercoagulable state caused by the excessive release of cytokines describe the 3 sides of Virchow's triad. In a study conducted by Cheruiyot et al[72] in 2021, the prevalence of arterial thrombosis in critically ill COVID-19 patients was 4.4%. This lower prevalence compared with the 9% prevalence of arterial thrombosis in critically ill patients admitted to the ICU in our study may be due to the smaller population (90 COVID-19 patients) of the Cheruiyot study.

The current study showed that the prevalence of all predicted outcomes, including overall thrombosis, arterial thrombosis, pulmonary embolism, and deep vein thrombosis, in critically ill patients admitted to the ICU (end stages) was significantly higher. Avruscio et al[45] reported that among 85 COVID-19 patients (44 patients in general wards and 41 patients in the ICU), the prevalence of venous thromboembolism was significantly higher in ICU patients despite receiving thromboprophylaxis in both groups (75% vs 27%). These results indicate that ICU patients are at a higher risk of venous and arterial thromboembolism due to immobility, receiving sedative drugs, having central venous catheters, and considering that COVID-19 patients (as mentioned above) are susceptible to thromboembolism from all Virchow's triad aspects.

Moreover, the prevalence of overall thrombosis was significantly higher in patients with high D-dimer, while the association between high D-dimer and the prevalence of arterial thrombosis, pulmonary embolism, and deep vein thrombosis in COVID-19 patients was not significant. In fact, in addition to thromboembolism, D-dimer may be a manifestation of severe viral infection. Infection, followed by sepsis, may cause coagulation dysfunction. Further, an increase in D-dimer may be a sign of an inflammatory reaction because inflammatory cytokines can cause an imbalance between coagulation and fibrinolysis, followed by the activation of fibrinolysis and then a rise in D-dimer.[73]

In accordance with the normal population, where the risk of venous thromboembolism is higher in older individuals,[74] the prevalence of pulmonary embolism and deep vein thrombosis is also significantly higher in older patients with COVID-19.

Despite the association between high BMI and more thromboembolic events in the normal population,[74] we found no significant correlations between high BMI and the prevalence of any of the above outcomes in patients with COVID-19. Justifying this finding is, however, challenging. A systematic review by Singh et al[75] in June 2022 on the association between obesity and COVID-19 concluded that obesity was strongly and significantly associated with the severe form of the disease and higher mortality. In particular, a study by Wang et al,[76] performed last year specifically on the association between obesity and thromboembolic events among 609 patients with COVID-19 (not included in our study because it was conducted after our study design) showed that the prevalence of venous thromboembolism was significantly higher in obese patients with COVID-19.

Furthermore, we observed no significant relationship between diabetes mellitus or chronic kidney disease and the prevalence of each predicted outcome. One of the reasons can be the use of diabetes and hyperlipidemia drugs, such

as statins, and the anti-inflammatory effect of these drugs.[77]

The current study has some considerable limitations, the most salient of which is the lack of non-English language scientific literature reviews, considering the sizable number of studies in Chinese, especially earlier in the pandemic.

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