Arterial Thrombotic Events in Hospitalized COVID-19 Patients: A Short Review and Meta-Analysis

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Abstract

It is well established that the risk of venous thromboembolism is high in coronavirus disease 19 (COVID-19). The frequency of arterial thromboembolic events (ATEs) in hospitalized patients with COVID-19 is unclear, as is the magnitude of these events in comparison with other infections. We searched MEDLINE from February 2020 to February 2022 for prospective or retrospective cohort studies and randomized clinical trials that reported the number of acute myocardial infarction (AMI), acute ischemic stroke (AIS), acute limb ischemia (ALI), or other ATE as defined by the original authors in hospitalized patients with COVID-19. The pooled frequencies were calculated through meta-analysis using random effects model with logit transformation and presented with relative 95% prediction intervals (95% PI). We retrieved a total of 4,547 studies, 36 of which (28 retrospective cohorts, five prospective cohorts and three randomized trials) were finally included in our analysis. The resulting cohort counted 100,949 patients, 2,641 (2.6%) of whom experienced ATE. The pooled ATE frequency was 2.0% (95% PI, 0.4–9.6%). The pooled ATE frequency for AMI, AIS, ALI, and other ATE was 0.8% (95% PI, 0.1–8.1%), 0.9% (95% PI, 0.3–2.9%), 0.2% (95% PI, 0.0–4.2%), and 0.5% (95% PI, 0.1–3.0%), respectively. In comparison with the ATE incidence reported in three studies on non-COVID viral pneumonia, we did not detect a significant difference from the results in our analysis. In conclusion, we found a non-negligible proportion of ATE in patients hospitalized for COVID-19. Our results are similar to those found in hospitalized patients with influenza or with non-COVID viral pneumonia.

Keywords
- COVID-19
- stroke
- myocardial infarction
- ischemia
- thromboembolism

Coronavirus disease 2019 (COVID-19) has affected over 400 million patients worldwide during the period February 2020 to February 2022.[1] The various mechanisms of action of this new Coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) are still partially undetermined. The clinical course spans from a completely asymptomatic disease to a critical clinical situation that requires mechanical ventilation and/or sophisticated management in the intensive care unit.

Among other sequelae, COVID-19 has been associated with higher incidence of venous thrombotic events. In a recent meta-analysis of 20 studies that included 1,988 patients with COVID-19, Di Minno et al found a weighted mean prevalence of venous thromboembolism (VTE) of 31.3% (95% confidence interval [CI], 24.3–39.2%).[2] Increasing age and high body mass index were also associated with higher VTE prevalence.[2]

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In an additional study that confirmed the high prevalence of VTE in COVID-19, the incidence of arterial thrombotic events (ATEs) in 16 studies with 7,939 patients was 3.9% (95% CI, 2.0–3.0%).[3]

Another systematic review of 4,466 patients with COVID-19 from the early phase of the pandemic until May 2020, reported a pooled incidence of acute ischemic stroke (AIS) of 1.2%.[4] Furthermore, the presence of myocardial injury seems to predict more severe COVID-19.[5] However, a global and updated assessment of ATE frequency in patients hospitalized for COVID-19 is still missing. Hence, the aim of this review and meta-analysis was to estimate the pooled frequency of ATE in these patients.

Methods

We searched MEDLINE from February 2020 to February 2022. The full search history is shown in ►**Supplementary Table S1** (available in the online version only). Retrospective and prospective studies involving patients hospitalized for COVID-19 and that reported the number of any ATE during the hospitalization or within 3 months from discharge were included. We excluded case reports and case series and limited our search to the English language and cohorts with ≥200 patients.

Baseline characteristics as age, sex, intensive care unit (ICU) admission, and treatment with antiplatelet drugs were retrieved. Events of interest were acute myocardial infarction (AMI), AIS, acute limb ischemia (ALI), and a composite of all the other ATE, as defined by the original authors. For the assessment of the quality of studies, we used the Jadad score for randomized controlled trials (RCTs), and the methodological index for non-randomized studies (MINORS) tool for observational studies.[6,7]

Statistical Analysis

Random-effects model with logit transformation was used to calculate pooled frequency for ATE with relative 95% CI assessed with Clopper-Pearson method.

We then estimated the 95% prediction intervals (95% PI) for the pooled frequencies. We choose to present the results as pooled frequency and relative 95% PI, which estimates where the true effects are to be expected for 95% of similar studies that might be conducted in the future, and in case of heterogeneity. PI covers a wider range than CI.[8]

Subgroup analyses for AMI, AIS, ALI and all the other ATE were computed with the same method. All analyses were performed using R software, version 4.0.4, and Rstudio version 1.1.423 (2009–2018 RStudio, Inc.), meta package.

Results

The search and screening process are shown in ►**Fig. 1**. A total of 36 articles were included in the pooled analysis (►**Table 1**).[9–44] The majority (28; 78%) consisted of retrospective cohort studies whereas three (8%) were RCTs and five (14%) were prospective cohort studies (►**Table 1**).

The methodological quality of the 33 cohort studies is summarized in ►**Supplementary Table S2** and ►**Supplementary Fig. S1**, available in the online version only. In total, 17/33 studies had three out of eight MINORS' criteria assessed as inadequate whereas the items "loss to follow-up less than 5%" and "unbiased assessment of the study end point" was considered unclear for all the 33 studies.

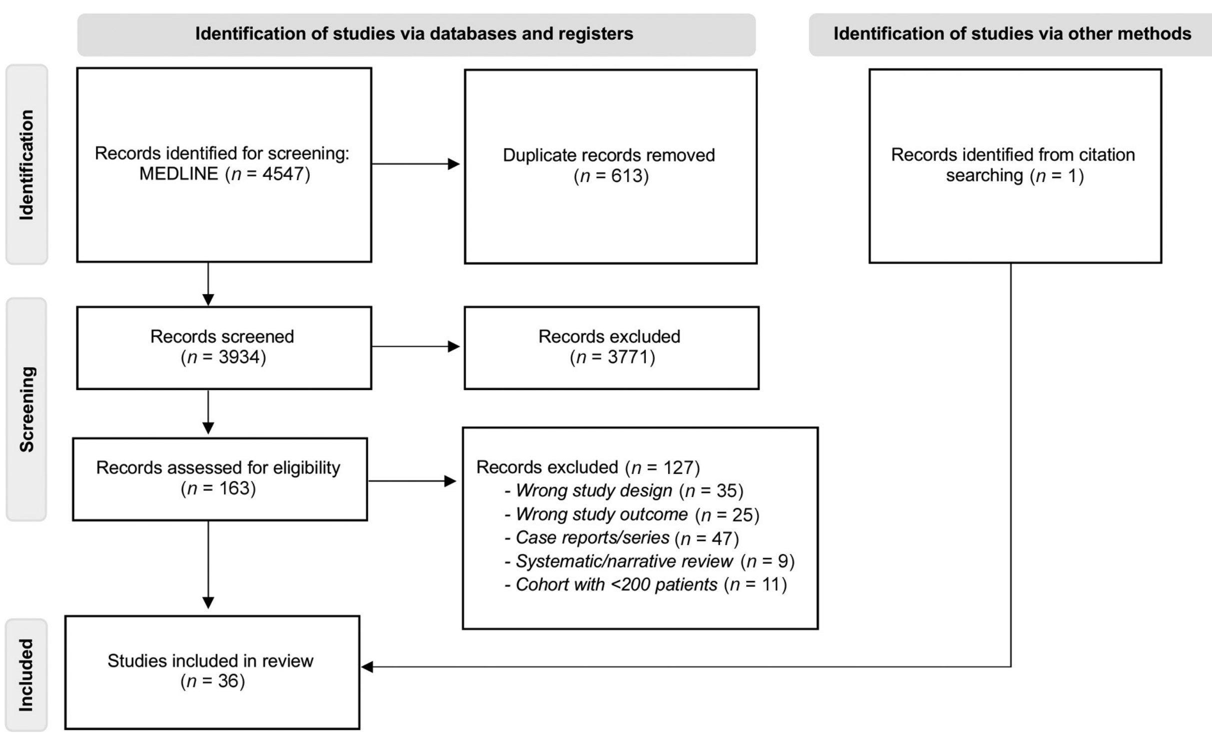

Fig. 1 Flow diagram of search results.

Table 1 Characteristics of included studies

Author, year	Study type	Design	*N* tot	Age	Sex, female	Anti-platelets	Anti-coagulant	ICU	AMI	AIS	ALI	Other ATE	Total ATE	Death	FU days
Bekelis et al, 2020[11]	C	R	2,513	66[a]	1,111 (44.2)	–	–	–	–	22 (0.9)	–	–	22 (0.9)	–	–
Hanif et al, 2020[22]	C	R	921	62[b]	347 (37.7)	–	896 (97.3)	323 (35.1)	–	11 (1.2)	2 (0.2)	–	13 (1.4)	325 (35.3)	9[b]
Lodigiani et al, 2020[28]	C	R	388	66[b]	124 (32)	93 (24)	307 (79.1)	61 (15.7)	4 (1)	9 (2.3)	–	–	13 (3.4)	92 (23.7)	10[b]
Piazza et al, 2020[33]	C	R	399	62[a]	170 (42.6)	149 (37.3)	346 (86.7)	170 (42.6)	14 (3.5)	1 (0.3)	–	11 (2.8)	26 (6.5)	55 (13.8)	30[c]
Rothstein et al, 2020[36]	C	R	844	59[a]	439 (52)	–	–	–	1 (0.1)	20 (2.4)	–	–	20 (2.4)	–	–
Alabyad et al, 2021[9]	C	R	276	59[a]	130 (47.1)	–	–	158 (57.2)	4 (1.4)	5 (1.8)	–	–	9 (3.3)	31 (11.2)	10[b]
Brandão et al, 2021[13]	C	R	243	63[b]	97 (39.9)	–	222 (91.4)	243 (100)	6 (2.5)	3 (1.2)	3 (1.2)	–	12 (4.9)	77 (31.7)	28[c]
Caro-Codón et al, 2021[14]	C	P	3,042	62[a]	1372 (45.1)	434 (14.3)	307 (10.1)	–	5 (0.2)	18 (0.6)	–	11 (0.4)	34 (1.1)	626 (20.6)	59[b]
Cho et al, 2021[15]	C	R	2,699	59[b]	936 (34.7)	–	–	2,699 (100)	–	19 (0.7)	–	–	19 (0.7)	952 (35.3)	–
Constans et al, 2021[16]	C	P	211	65[a]	118 (55.9)	36 (17.1)	0 (0)	6 (2.8)	3 (1.4)	2 (0.9)	–	–	5 (2.4)	27 (12.8)	8[b]
De Michieli et al, 2021[17]	C	R	367	61[a]	147 (40.1)	–	–	102 (27.8)	8 (2.2)	–	–	–	8 (2.2)	33 (9)	30[c]
Fournier et al, 2021[18]	C	P	531	66[b]	180 (33.9)	137 (25.8)	267 (50.3)	0 (0)	9 (1.7)	8 (1.5)	6 (1.1)	7 (1.3)	30 (5.6)	93 (17.5)	20[b]
Fröhlich et al, 2021[19]	C	R	6,637	70[b]	3,132 (47.2)	912 (13.7)	–	720 (10.8)	99 (1.5)	72 (1.1)	–	–	171 (2.6)	1,372 (20.7)	–
Giannis et al, 2021[20]	C	P	4,906	61[a]	2,273 (46.3)	1,073 (21.9)	612 (12.5)	578 (11.8)	24 (0.5)	22 (0.4)	26 (0.5)	22 (0.4)	84 (1.7)	3,081 (62.8)	90[c]
Ilyas et al, 2021[23]	C	R	21,528	61[a]	9,884 (45.9)	7,066 (32.8)	16,300 (75.7)	6,604 (30.7)	655 (3)	168 (0.8)	44 (0.2)	168 (0.8)	1,035 (4.8)	3,326 (15.4)	10[b]
Kaptein et al, 2021[24]	C	R	947	66[a]	344 (36.3)	–	947 (100)	358 (37.8)	5 (0.5)	12 (1.3)	0 (0)	3 (0.3)	20 (2.1)	144 (15.2)	9[b]
Kolanko et al, 2021[25]	C	P	350	67[b]	139 (39.7)	163 (46.6)	347 (99.1)	124 (35.4)	8 (2.3)	4 (1.1)	–	–	12 (3.4)	47 (13.4)	14[b]
Lekoubou et al, 2021[26]	C	R	8,815	51[a]	4,977 (56.5)	–	–	–	–	77 (0.9)	–	–	77 (0.9)	–	–
Li et al, 2021[27]	C	R	2,804	70[b]	1,300 (46.4)	949 (33.8)	1,840 (65.6)	440 (15.7)	64 (2.3)	45 (1.6)	–	–	109 (3.9)	–	42[b]
Lopes et al, 2021[29]	RCT	P	615	57[a]	247 (40.2)	48 (7.8)	615 (100)	39 (6.3)	27 (4.4)	1 (0.2)	1 (0.2)	–	29 (4.7)	58 (9.4)	30[c]
Mendes et al, 2021[30]	C	R	265	86[a]	149 (56.2)	–	–	–	–	11 (4.2)	–	–	1 (0.4)	85 (32.1)	12.6[a]
Muñoz-Rivas et al, 2021[31]	C	R	1,127	65[b]	395 (35)	–	1127 (100)	13 (1.2)	6 (0.5)	13 (1.2)	1 (0.1)	8 (0.7)	28 (2.5)	–	14[b]
Purroy and Arqué, 2021[34]	C	R	1,737	66[a]	686 (39.5)	–	–	117 (6.7)	8 (0.5)	6 (0.3)	0 (0)	–	14 (0.8)	276 (15.9)	7[b]
Qureshi et al, 2021[35]	C	R	7,709	62[a]	4,088 (53)	–	–	272 (3.5)	–	103 (1.3)	–	–	103 (1.3)	–	–
Sahai et al, 2021[37]	C	R	496	–	–	258 (52)	258 (52)	–	7 (1.4)	10 (2)	–	–	17 (3.4)	–	–
Siegler et al, 2021[38]	C	R	14,483	–	–	–	–	–	–	156 (1.1)	–	–	156 (1.1)	1,694 (11.7)	–
Smadja et al, 2021[39]	C	R	1,044	63[b]	391 (37.5)	244 (23.4)	1044 (100)	157 (15)	9 (0.9)	5 (0.5)	3 (0.3)	–	17 (1.6)	93 (8.9)	–
Spyropoulos et al, 2021[40]	RCT	P	253	67[a]	117 (46.2)	40 (15.8)	253 (100)	83 (32.8)	3 (1.2)	2 (0.8)	2 (0.8)	1 (0.4)	8 (3.2)	56 (22.1)	30[c]
Tacquard et al, 2021[41]	C	R	538	63[b]	149 (27.7)	111 (20.6)	538 (100)	538 (100)	1 (0.2)	4 (0.7)	–	1 (0.2)	6 (1.1)	1 (0.2)	14[c]
Topcu et al, 2021[42]	C	R	681	63[b]	262 (38.5)	–	–	90 (13.2)	–	–	6 (0.9)	–	6 (0.9)	94 (13.8)	30[c]
Vallone et al, 2021[43]	C	R	1,621	73[b]	913 (56.3)	689 (42.5)	1,074 (66.3)	174 (10.7)	0 (0)	4 (0.2)	0 (0)	1 (0.1)	5 (0.3)	348 (21.5)	90[c]
Violi et al, 2021[44]	C	R	373	67[a]	145 (38.9)	56 (15)	–	67 (18)	15 (4)	10 (2.7)	9 (2.4)	–	34 (9.1)	75 (20.1)	18[b]
Arachchillage et al, 2022[10]	C	R	5,883	74[b]	2,636 (44.8)	1,093 (18.6)	5,883 (100)	789 (13.4)	12 (0.2)	49 (0.8)	–	18 (0.3)	79 (1.3)	1,719 (29.2)	90[c]
Bikdeli et al, 2022[12]	RCT	P	562	62[b]	237 (42.2)	172 (30.6)	562 (100)	562 (100)	0 (0)	2 (0.4)	–	–	2 (0.4)	250 (44.5)	90[c]

(*Continued*)

Table 1 (*Continued*)

Author, year	Study type	Design	*N* tot	Age	Sex, female	Anti-platelets	Anti-coagulant	ICU	AMI	AIS	ALI	Other ATE	Total ATE	Death	FU days
Gonzalez-Porras et al, 2022[21]	C	R	690	72[a]	274 (39.7)	–	615 (89.1)	80 (11.6)	3 (0.4)	2 (0.3)	1 (0.1)	–	6 (0.9)	263 (38.1)	–
Nemetski et al, 2022[32]	C	R	4,451	–	–	–	–	–	–	–	–		411 (9.2)	–	–

Abbreviations: AIS, acute ischemic stroke; ALI, acute limb ischemia; AMI, acute myocardial infarction; ATE, arterial thrombotic event; C, cohort; FU, follow-up; ICU, intensive care unit; P, prospective; R, retrospective.

[a]Mean.

[b]Median

[c]Planned follow-up duration.

We assessed one of the three RCTs as having a low quality with only one point on the Jadad scale (►**Supplementary Table S3**, available in the online version only).[12]

The resulting population included 100,949 patients. The age of the patients in the studies ranged from a mean of 51 to 86 years (18 studies) or a median of 59 to 74 years (15 studies). Point estimates for age were not available in three cohort studies.

Overall, 37,909 of 81,519 patients (46.5%, 33 studies) were female. Treatment in the ICU was required for 15,567 out of 66,040 patients (23.6%; 28 studies). Furthermore, 13,723 out of 52,181 patients (26.3%, 19 studies) were taking an antiplatelet agent at baseline. Information on anticoagulant treatment was available in 22 studies, and was given to 34,360 out of 49,099 patients (70.0%). Anticoagulant treatment included both prophylactic and therapeutic regimens with low molecular weight heparin, unfractionated heparin, vitamin K antagonists, or direct oral anticoagulants. The follow-up or mean/median hospital stay duration was reported by 17 studies and ranged from 7 to 90 days. Information on mortality was available in 28 studies and 15,293 of 72,190 patients (21.2%) died, with the proportion across the studies ranging from 0.2 to 62.8% (►**Table 1**).

Overall, there were 2,641 ATE (2.6%). The frequency of ATE ranged from 0.3 to 9.2% in the studies included. The pooled frequency was 2.0% with a quite large prediction interval (95% PI, 0.4–9.6%) (►**Fig. 2**).

The pooled frequency was lower for RCTs (1.2%) than for retrospective and prospective cohort studies (1.9 and 2.4%, respectively) (►**Fig. 2**).

The forest plots for the subgroup analyses are displayed in ►**Fig. 3**. In total, 27 studies provided data on AMI for a total of 1,000 of 58,412 (1.7%) patients. After meta-analysis, the pooled frequency turned out to be 0.8% with 95% PI ranging from 0.1 to 8.1%. AIS occurred in 896 of 95,450 patients (0.9%; 33 studies) for a pooled frequency of 0.9% (95% PI, 0.3 to 2.9%). The same figure for ALI was 104 of 37,217 patients (0.3%; 15 studies), pooled frequency 0.2% (95% PI, 0.0–4.2%) (►**Fig. 3**).

Other ATE events occurred in 251 of 40,775 patients (0.6%, 11 studies). These events included 16 systemic embolism, 1 mesenteric infarction, 11 catheter- or device-related arterial thrombosis (all in ICU patients), and the remaining 223 included aortic thrombosis, renal artery thrombosis, splenic infarction, upper-limb ischemia, and acute diffuse microvascular cerebropathy. The resulting pooled frequency for these events was 0.5% (95% PI, 0.1–3.0%) (►**Fig. 3**).

Discussion

In this systematic review we found a pooled frequency of ATE in COVID-19 hospitalized patients of 2.0% (95% PI, 0.4–9.6). In the subgroup analysis, AIS showed a pooled frequency of 0.9%, followed by AMI (0.8%), other ATE (0.5%), and ALI (0.2%).

Our study covered 2 years from the beginning of the pandemic. Compared with previous reviews and meta-analyses that analyzed only the first part of the pandemic, we found a frequency of AIS that was slightly lower (0.9 vs.

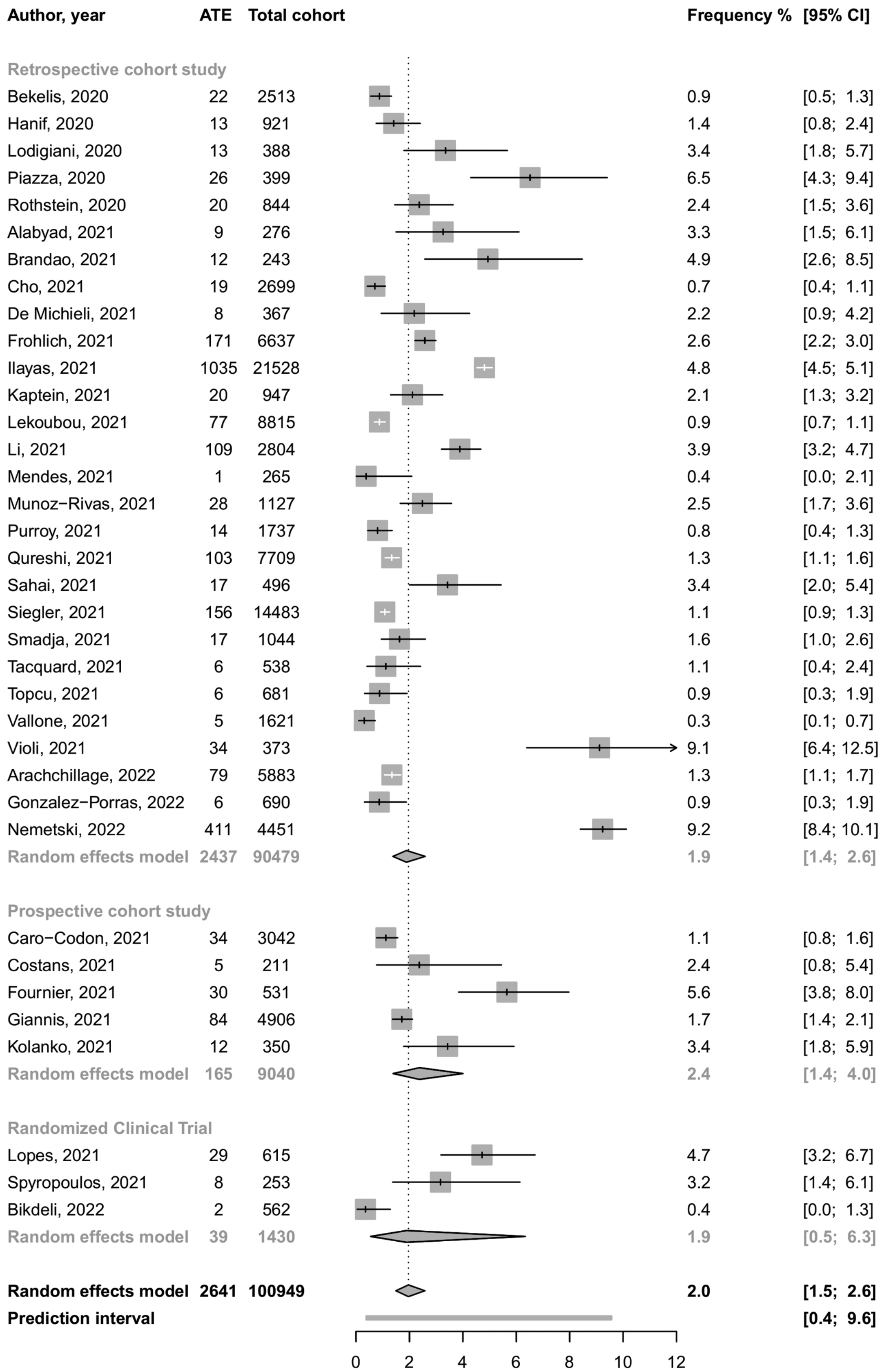

Fig. 2 Forest plot for ATE in overall cohort. ATE, arterial thrombotic events.

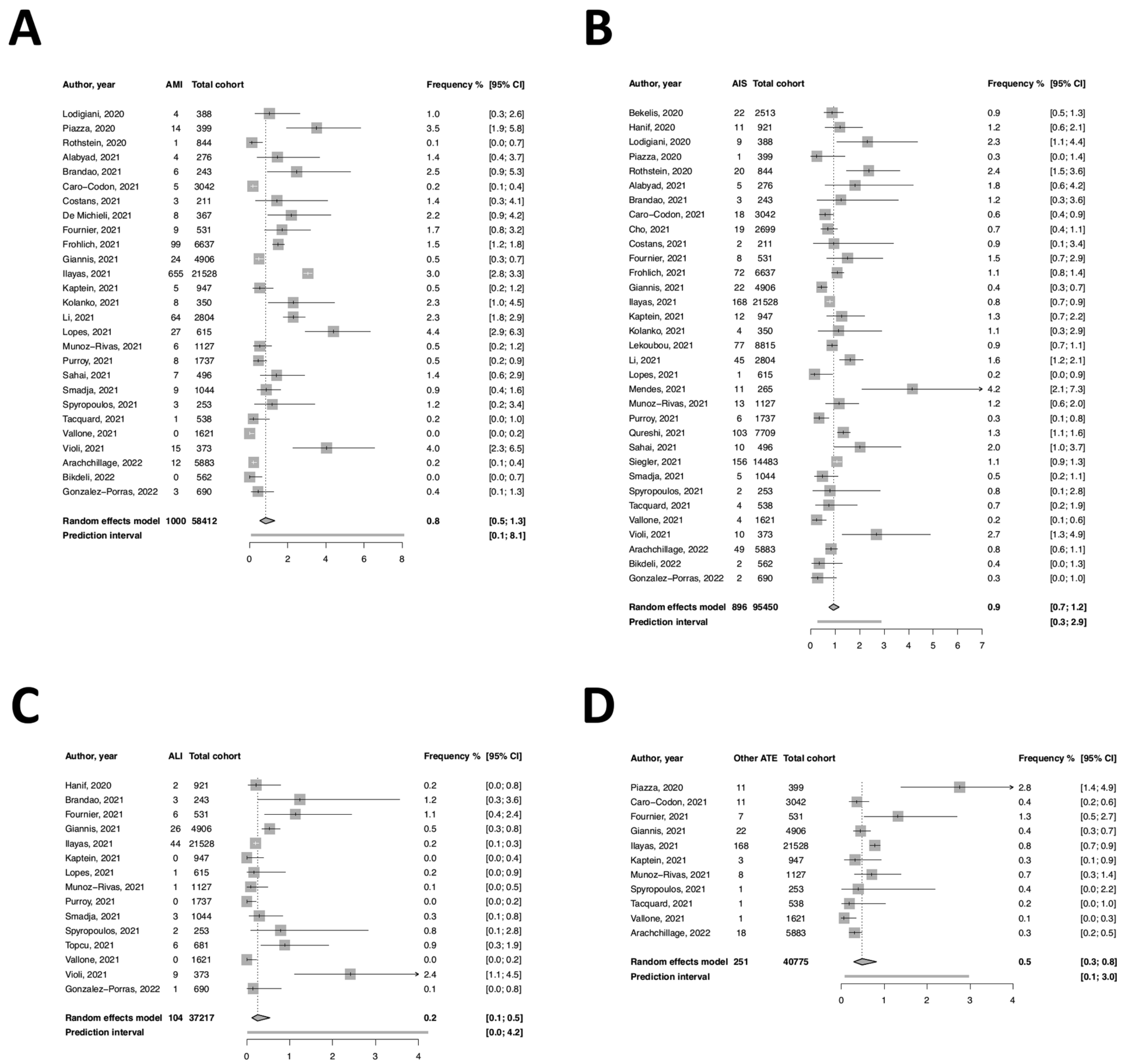

Fig. 3 Forest plots for subgroups analysis. **(A)** AMI, acute myocardial infarction; **(B)** AIS, acute ischemic stroke; **(C)** ALI, acute limb ischemia; **(D)** ATE, arterial thrombotic events.

1.2%).[5] A previous review reported an extremely high event rate of acute myocardial injury (20%; 95% CI, 17–23%), which is approximately 20 times higher than the pooled frequency we found in our study.[45] However, the authors included cohorts with at least 100 patients and did not perform a systematic search. Moreover, all the included cohorts but two were from China and the observation covered the early COVID-19 pandemic till May 2020,[45] and thus before emergence of new viral lineages which may possess lower virulence and pathogenicity.[46]

Accordingly, the pooled frequency of ATE in the included studies tended to decrease from 2020 to 2022, when the Omicron lineages BA.1 and BA.2 become worldwide dominant (data not shown).

If there truly is a decreasing frequency of ATE with time in this pandemic, this could be associated with some other reasons along with emergence of new SARS-CoV-2 variants. First, in the early part of the pandemic there were mainly case reports and studies based on small cohorts of COVID-19 patients. This could have been led to an overestimation of the true frequency of the ATE. Second, increased attention to antithrombotic prophylaxis during hospitalization in COVID-19 patients began to occur only after the initial months of the pandemic, as attested by the RCTs in this regard.[12,29,40] This might have reduced the frequency of ATE compared with the early stages of the pandemic. Third, since December 2020 and throughout 2021, a massive vaccine campaign was implemented in the countries where the studies have been performed. This has likely contributed to reduce the frequency of COVID-19 in its most severe form and probably also the frequency of ATE. Moreover, some studies addressed the importance of influenza vaccines in reducing the frequency of ATE in patients with influenza.[47] As a result, although on a purely conjectural level, this could also have happened in patients with COVID-19. Hence, if this trend is maintained as the vaccination campaign progresses,

Table 2 ATE frequency in our pooled cohort vs viral pneumonia cohort (influenza and non-influenza)

ATE type	COVID-19 Pooled cohort = 100,949	Non-COVID-19 viral pneumonia Total cohort = 455,629[a]
AMI	0.8%	1.3%
AIS	0.9%	0.7%
ALI	0.2%	0.07%

Abbreviations: AIS, acute ischemic stroke; ALI, acute limb ischemia; AMI, acute myocardial infarction; ATE, arterial thromboembolic event.
[a]Data are from Elgendy et al.[49]

we could expect a further decrease in the frequency of ATE in COVID-19.

Some studies have compared the incidence of ATE between COVID-19 and influenza. In a retrospective cohort, the unadjusted incidence of ATE (AIS + AMI) was more than double in COVID-19 than in influenza (7.1 vs. 3.0%).[48] However, after propensity score matching there was no difference between the two groups (hazard ratio 1.02, 95% CI, 0.95–1.10).[48] Nemetski et al found a slightly higher incidence of ATE in patients with COVID-19 ($n = 4,451$) when compared with patients hospitalized for influenza ($n = 468$) or non-COVID-19 illness ($n = 40,359$) and, notably, none of the influenza patients experienced an ATE.[32] However, the study was retrospective and the real incidence of ATE in the non-COVID-19 population could have been underestimated.

On the other hand, our data are comparable to those found in a large cohort ($n = 455,629$) of patients hospitalized with viral pneumonia (influenza and non-influenza).[49] Indeed, in this cohort the incidence of ATE was 1.3% for AMI, 0.7% for AIS, and 0.07% for ALI (►**Table 2**).[49] This supports the assumption that the incidence of ATE may be similar in patients hospitalized with COVID-19 or with viral influenza or pneumonia. Therefore, whereas it has been proposed that endothelial activation and dysfunction in COVID-19 could be a mechanism that explains the increase in pulmonary thrombosis,[50] this thromboinflammation might not affect the arteries in the systemic circulation.

This study has limitations that need to be considered. First, because of aggregate data we could not perform more granular subgroup analyses. However, we had enough information to estimate a pooled frequency of ATE as planned. Second, wide variations in duration of follow-up probably contributed to wide prediction intervals.

In conclusion, the frequency of ATE in patients hospitalized for COVID-19 is not negligible although it might have diminished compared with initial estimates from the pandemic onset. When compared with patients hospitalized for viral pneumonia the frequency of ATE is similar.

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Conflict of Interest
M.C. has nothing to disclose. S.S. reports grants and personal fees from Boehringer Ingelheim, grants from Octapharma, personal fees from Bayer, personal fees from Bristol-Myers Squibb, personal fees from Daiichi-Sankyo, personal fees from Pfizer, personal fees from Sanofi, personal fees from Alexion, outside the submitted work.

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