Journal of Thrombosis and Thrombolysis (2022) 53:96–102
https://doi.org/10.1007/s11239-021-02507-2

Impact of pre-admission antithrombotic therapy on disease severity and mortality in patients hospitalized for COVID-19

Mariana Corrochano[1] · René Acosta-Isaac[1] · Sergi Mojal[1] · Sara Miqueleiz[2] · Diana Rodriguez[2] · María Ángeles Quijada-Manuitt[3] · Edmundo Fraga[4] · Marta Castillo-Ocaña[3] · Kristopher Amaro-Hosey[3] · Nil Albiol[1] · José Manuel Soria[5] · Rosa Maria Antonijoan[3,6] · Joan Carles Souto[1]

Accepted: 7 June 2021 / Published online: 17 June 2021

Abstract
Anticoagulant therapy is a cornerstone treatment for coronavirus disease 2019 (COVID-19) due to the high rates of thromboembolic complications associated with this disease. We hypothesized that chronic antithrombotic therapy could play a protective role in patients hospitalized for COVID-19. Retrospective, observational study of all patients admitted to our hospital for ≥ 24 h from March 1 to May 31, 2020 with SARS-CoV-2. The objective was to evaluate clinical outcomes and mortality in COVID-19 patients receiving chronic anticoagulation (AC) or antiplatelet therapy (AP) prior to hospital admission. A total of 1612 patients were evaluated. The mean (standard deviation; SD) age was 66.5 (17.1) years. Patients were divided into three groups according to the use of antithrombotic therapy prior to admission (AP, AC, or no-antithrombotic treatment). At admission, 9.6% of the patients were taking anticoagulants and 19.1% antiplatelet therapy. The overall mortality rate was 19.3%. On the multivariate analysis there were no significant differences in mortality between the antithrombotic groups (AC or AP) and the no-antithrombotic group (control group). Patients on AC had lower ICU admission rates than the control group (OR: 0.41, 95% CI, 0.18–0.93). Anticoagulation therapy prior to hospitalization for COVID-19 was associated with lower ICU admission rates. However, there were no significant differences in mortality between the patients receiving chronic antithrombotic therapy and patients not taking antithrombotic medications. These findings suggest that chronic anticoagulation therapy at the time of COVID-19 infection may reduce disease severity and thus the need for ICU admission.

Keywords Anticoagulants · Antiplatelet drugs · Covid-19 · Intensive care · Mortality

Highlights

- COVID-19 patients have a higher risk of developing thromboembolic events
- Chronic antithrombotic therapy prior to admission may play a protective role in COVID-19 patients
- ICU admission rates were lower in patients on anticoagulation therapy but with no impact on mortality risk
- Mortality rates are not modified by previous antithrombotic therapy.

Introduction

Thromboembolic events are a well-documented complication of coronavirus disease-2019 (COVID-19). The pooled incidence of venous thromboembolism (VTE) among

✉ Mariana Corrochano
mcorrochano@santpau.cat

1 Haemostasis and Thrombosis Unit, Hospital de La Santa Creu I Sant Pau. Carrer de Sant Quintí 89, 08041 Barcelona, Spain

2 Clinical Trials Unit (AGDAC), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

3 Clinical Pharmacology Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

4 ALBA Synchrotron, Barcelona, Spain

5 Unit of Genomics of Complex Diseases, Institut d'Investigació Biomèdica Sant Pau, IIB-Sant Pau, Barcelona, Spain

6 Drug Research Center, Institut d'Investigació Biomèdica Sant Pau, IIB-Sant Pau, Barcelona, Spain

hospitalized COVID-19 patients is estimated to range from 14 to 31% based on data from meta-analyses [1–8]. In most cases, the patients developed VTE despite prophylactic treatment with low-molecular-weight heparin (LMWH). VTE rates are even higher in critically ill patients [9]. Acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 patients. However, autopsy data from a small series suggest that thrombotic events—mainly pulmonary embolism (PE)—are directly responsible for up to 30% of deaths [10]. Moreover, numerous studies have found that the mortality rate in COVID-19 patients who develop VTE is higher than in patients without VTE [8, 11–18].

Given the high incidence of thromboembolic complications, anticoagulation therapy administered at higher than usual doses has been proposed for prophylaxis in hospitalized patients [19, 20]. However, some authors have postulated that prophylactic anticoagulation therapy initiated after hospital admission may not be effective because the thrombotic process likely begins shortly after viral infection (i.e., prior to hospitalization) through the formation of micro-thrombi secondary to viral spread involving the neutrophil extracellular trap system [21]. This hypothesis, if true, suggests that patients receiving chronic anticoagulation (AC) or antiplatelet therapy (AP) may be at least partially protected from COVID-19-related thromboembolic complications and should theoretically be expected to have better clinical outcomes than patients not on antithrombotic therapy prior to admission. However, the available evidence from observational studies is contradictory, and thus the role of antithrombotic therapy in these patients remains unclear [22–34].

In this context, the objective of the present retrospective study was to evaluate the effects of chronic antithrombotic therapy on clinical outcomes and mortality in patients hospitalized for COVID-19.

Material and methods

This was a retrospective, single-centre observational trial (clinicaltrials.gov NCT04518735). Adult patients (≥ 18 years old) diagnosed with COVID-19 and admitted to our hospital (Barcelona, Spain) for ≥ 24 h from March 1, 2020, to May 31, 2020 were included in the analysis. COVID-19 diagnosis was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab specimens. The primary outcome was all-cause mortality and need for ICU admission. The study was approved by the hospital ethics committee.

We collected and analyzed clinical data from the day of admission through day 28 after admission. The following data were obtained from electronic health records: age; sex; co-morbidities; previous anticoagulant or antiplatelet therapy (and type of drug used); laboratory results; treatment received during admission (antivirals, hydroxychloroquine, antithrombotic therapy, etc.); thromboembolic events; hemorrhagic complications; intensive care unit (ICU) admission; type of respiratory support received and vital status (alive or deceased) at the end of the follow-up. The Charlson co-morbidity index (CCI) was calculated and patients were classified into three categories by CCI score according to co-morbidity severity, as follows: none or mild (CCI, 0–2); moderate (CCI, 3–4), and severe (CCI, ≥ 5) [35].

For study purposes, patients were divided into three groups according to the treatment received prior to admission for COVID-19. Group 1 was comprised of patients receiving chronic anticoagulation with vitamin K antagonists (VKA; warfarin or acenocoumarol), direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban or edoxaban), or heparins for any indication. Group 2 consisted of patients receiving antiplatelet therapy (aspirin, clopidogrel, prasugrel, ticagrelor, cangrelor, or dipyridamole) for any indication. Group 3 (the control group) included patients who did not receive either chronic anticoagulation or antiplatelet therapy.

Statistical analysis

Descriptive analyses were performed. Categorical variables were described as frequencies and percentages while continuous variables were summarized as means with standard deviation (SD) or medians and 25^{th} and 75^{th} percentiles, depending of the distribution of the variable.

We performed a univariate analysis of the baseline variables to assess the mortality and ICU admission outcomes. For the categorical variables, the Chi-square test or Fisher's exact test was used, as appropriate. The Mann–Whitney U test was performed to assess differences in continuous variables. All variables with a p value < 0.1 on the univariate analysis were initially entered into a multivariate binary logistic regression model. Non-significant variables (p value > 0.1) were then manually removed in a stepwise procedure until the final model was obtained. Both models (mortality and ICU admission) were adjusted by sex, age, CCI and antithrombotic therapy. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the final variables. The Hosmer–Lemeshow test was used to assess the calibration of the model. To evaluate the discriminative power of the model, the area under the ROC curve (AUC) was calculated. P values < 0.05 were considered statistically significant for all analyses. All statistical analyses were performed with the IBM-SPSS statistical package, v. 26.0 (IBM Corp).

Results

Of 1680 patients with confirmed COVID-19 admitted in our centre in the given dates, 68 were excluded because they were hospitalized for less than 24 h. The final study sample was of 1612 patients. At admission, 14 patients were on both anticoagulant and antiplatelet therapy and were therefore excluded from the multivariate model analyses for mortality and ICU admission. There were no missing values in any of the variables included in the analyses.

Study population

The mean (SD) age was 66.5 (17.1) years. Slightly more than half (n = 857; 53.2%) of the patients were men. The median [P_{25}–P_{75}] score on the CCI was 3 [1–5] points.

Antithrombotic therapy prior to admission

Most patients (n = 1135, 70.4%) were not receiving any type of antithrombotic (AC or AP) therapy prior to admission. Of the remaining patients, 155 (9.6%) were taking anticoagulants, 308 (19.1%) antiplatelet therapy, and 14 (0.9%) both.

In the AC group, the most common medication was VKA (n = 94, 60.6%), primarily acenocoumarol (91/94; 96.8%). Fifty-one patients (32.9%) were on some type of DOAC, as follows: apixaban (n = 24, 47.1%), dabigatran (n = 11; 21.6%), edoxaban (n = 9; 17.6%), and rivaroxaban (n = 7; 13.7%). Ten (6.5%) patients were anticoagulated with LMWH. After admission, 80% of the patients on prior AC received therapeutic anticoagulation during their hospital stay (70% with therapeutic dose LMWH, 15.5% with DOACs and 14.5% with VKA).

Mortality

The overall mortality rate was 19.3% (n = 311). In the patients receiving antithrombotic therapy (AC or AP), the mortality rates were 35.5% (n = 55) and 35.7% (n = 110), respectively. The univariate analysis according to vital status at day 28 post-admission is shown in Table 1.

CCI Charlson comorbidity index, *MI* myocardial infarction, *CVA* cerebrovascular accident, *PVD* peripheral vascular disease, *CRD* chronic respiratory disease, *AC* Anticoagulation therapy, *AP* antiplatelet therapy, *ICU* intensive care unit.

*All values given as number (%) except where indicated.

**14 patients received both oral anticoagulants and antiplatelet therapy and were excluded from the analysis.

The only variables independently associated with mortality on the multivariate analysis (Table 2) were age and CCI score. Compared to the younger age groups, patients ≥ age 80 had a significantly higher mortality risk (OR, 11.20; 95% CI: 2.84–44.25). Similarly, patients with severe comorbidity (CCI ≥ 5) also had a higher mortality risk (OR: 7.70; 95% CI: 3.41–17.39) than those with less severe comorbidities. When adjusted by sex, age, and CCI score, pre-admission treatment with AC or AP did not significant influence mortality rates.

Table 1 Characteristics of hospitalized COVID-19 patients by vital status

Variable, n (%)*	Alive (n = 1294)**	Deceased (n = 304)**	P value
Age, mean (SD)	62.9 (16.5)	81.5 (10.5)	< 0.001
Sex (male)	682 (52.7)	163 (53.6)	0.774
CCI, median [P_{25} – P_{75}]	2 [1–4]	6 [4–7]	< 0.001
Any previous comorbidity	879 (67.9)	275 (90.5)	< 0.001
Diabetes	232 (17.9)	87 (28.6)	< 0.001
Hypertension	585 (45.2)	226 (74.3)	< 0.001
Vascular disease (MI, CVA, PVD)	195 (15.1)	103 (33.9)	< 0.001
Active cancer	60 (4.6)	35 (11.5)	< 0.001
CRD	185 (14.3)	50 (16.4)	0.341
ICU	133 (10.3)	55 (18.1)	< 0.001
Days ICU, median [P_{25} – P_{75}]	10 [5–27]	14 [9–20]	0.419
Days hospitalization, median [P_{25} – P_{75}]	6 [3–10]	4 [2–9]	< 0.001
Thromboembolic events	66 (5.1)	19 (6.3)	0.422
Hemorrhagic events	28 (2.2)	10 (3.3)	0.246
No previous AC or AP	996 (77.0)	139 (45.7)	< 0.001
AC	100 (7.7)	55 (18.1)	
AP	198 (15.3)	110 (36.2)	

Table 2 Multivariate analysis for mortality

Variable	OR (95% CI)	P value
Sex (male)	1.24 (0.93–1.67)	0.150
Age (< 50)	Ref	–
Age (50–59)	1.21 (0.28–5.23)	0.802
Age (60–69)	4.55 (1.23–16.89)	0.023
Age (70–79)	5.22 (1.32–20.58)	0.018
Age (≥ 80)	11.20 (2.84–44.25)	0.001
CCI: 0–2	Ref	–
CCI: 3–4	3.47 (1.60–7.51)	0.002
CCI: ≥ 5	7.70 (3.41–17.39)	< 0.001
No previous AC or AP	Ref	–
AC	1.07 (0.70–1.62)	0.757
AP	1.18 (0.84–1.66)	0.339

CCI Charlson comorbidity index, *AC* anticoagulation therapy, *AP* antiplatelet therapy

Discrimination power of the model, AUC (95% CI): 0.831 (0.809 – 0.853)

Calibration of model, Hosmer–Lemeshow Test: p = 0.516

ICU admission

The ICU admission rate was 11.7% (n = 188). Among the patients receiving AC or AP prior to hospitalization, the ICU admission rate was 4.5% (n = 7) and 11.7% (n = 36), respectively.

Table 3 compares the clinical and demographic characteristics of patients who required ICU admission versus those who did not (univariate analysis).

On the multivariate analysis, the following variables were independently associated with ICU admission: sex, age, CCI score, and pre-admission AC. By age group, the highest ICU admission rates were observed in the 60–69 year age group (OR: 3.49, 95% CI, 1.91—6.40). Similarly, by CCI score, the highest ICU admission rate was observed in those with moderate co-morbidity (CCI, 3–4 points) (OR, 1.78; 95% CI: 1.11 – 2.88). When the model was adjusted for sex, age, and CCI score, patients on AC had lower ICU admission rates than the control group. The results of the multivariate analysis are shown in Table 4.

In the group of patients on anticoagulant therapy prior to hospitalization (n = 155), we found no statistically significant differences in mortality between the group of patients that continued therapeutic anticoagulation during hospital admission and those who received lower doses of LMWH (intermediate or prophylactic) or no antithrombotic treatment (mortality of 32.3% vs. 48.4% respectively, p value = 0.093). Likewise, we found no statistically significant differences in need for ICU admission between these groups (4.8% vs 3.2% respectively, p value = 1).

Table 3 Characteristics of hospitalized COVID-19 patients according to ICU admission status

Variable, n (%)*	Patients not admitted to ICU (n = 1410)**	Patients admitted to ICU (n = 188)**	P value
Age, mean (SD)	66.8 (17.7)	63.5 (11.7)	0.002
Sex (male)	723 (51.3)	122 (64.9)	< 0.001
CCI, median [P_{25}–P_{75}]	3 [1–5]	3 [2–4]	0.108
Any previous comorbidity	1008 (71.5)	146 (77.7)	0.076
Diabetes	272 (19.3)	47 (25.0)	0.066
Hypertension	707 (50.1)	104 (55.3)	0.182
Vascular disease (MI, CVA, PVD)	267 (18.9)	31 (16.5)	0.418
Active cancer	87 (6.2)	8 (4.3)	0.297
CRD	207 (14.7)	28 (14.9)	0.938
Days ICU, median [P_{25} – P_{75}]	–	12 [7–22]	–
Days hospitalized, median [P_{25} – P_{75}]	5 [3–8]	20 [13–35]	< 0.001
Thromboembolic events	44 (3.1)	41 (21.8)	< 0.001
Hemorrhagic events	25 (1.8)	13 (6.9)	< 0.001
No previous AC or AP AC AP	990 (70.2) 148 (10.5) 272 (19.3)	145 (77.1) 7 (3.7) 36 (19.1)	0.011

CCI Charlson comorbidity index, *MI* myocardial infarction, *CVA* Cerebrovascular accident, *PVD* Peripheral vascular disease, *CRD* chronic respiratory disease, *AC* Anticoagulation, *AP* antiplatelet therapy, *ICU* intensive care unit

*All values given as number (%) except where indicated

**14 patients received both oral anticoagulants and antiplatelet therapy and were excluded from the analysis

Table 4 Multivariate analysis for ICU admission

Variable	OR (95% CI)	P value
Sex (male)	1.70 (1.22–2.38)	0.002
Age (<50)	Ref	–
Age (50–59)	2.05 (1.13–3.73)	0.019
Age (60–69)	3.49 (1.91–6.40)	<0.001
Age (70–79)	2.38 (1.15–4.94)	0.02
Age (≥80)	0.23 (0.08–0.66)	0.006
CCI: 0–2	Ref	–
CCI: 3–4	1.78 (1.11–2.88)	0.018
CCI: ≥5	1.23 (0.64–2.35)	0.538
No previous AC or AP	Ref	–
AC	0.41 (0.18–0.93)	0.034
AP	0.96 (0.60–1.53)	0.863

CCI Charlson comorbidity index, *AC* anticoagulation therapy, *AP* antiplatelet therapy, *OR* odds ratio

Discrimination power of the model, AUC (95% CI): 0.743 (0.710 – 0.776)

Calibration of model, Hosmer–Lemeshow Test: p = 0.967

Thrombotic and hemorrhagic complications

Overall, the incidence of thrombotic events was 5.4% (n = 87). In the patients receiving AC or AP, the incidence rates for thrombotic events were 4.5% (n = 7) and 3.9% (n = 12), respectively, with no statistically significant differences with the no-antithrombotic therapy group (n = 66, 5.8%). Two patients receiving both AC and AP prior to admission presented thrombotic complications.

The following thrombotic events were observed: PE (n = 41, 2.5%); deep vein thrombosis (DVT) (n = 14, 0.9%); both PE and DVT (n = 4, 0.2%); cerebrovascular accident (CVA) (n = 18, 0.9%); acute myocardial infarction (MI) (n = 7, 4.3%); peripheral arterial embolism (n = 4, 0.2%); intraventricular thrombosis (n = 1, 0.06%); and superficial thrombophlebitis (n = 1, 0.06%);.

Hemorrhagic complications were reported in 39 patients (2.4%). No deaths were attributed to anticoagulant-induced hemorrhage. Bleeding was significantly more common in the AC group than in the AP group (11 [7.1%] vs. 8 cases [2.6%]) and compared to the controls (19 cases, 1.7%) (p = 0.001). One patient receiving both AC and AP prior to admission developed a hemorrhagic event.

Discussion

The present study was performed to determine the impact of chronic antithrombotic therapy on clinical outcomes in patients hospitalized for COVID-19. On the univariate analysis, patients receiving antithrombotic therapy prior to admission had a higher mortality rate than patients not receiving this therapy. However, on the multivariate analysis (adjusted for sex, age and CCI score), there were no significant differences between the antithrombotic and control groups. Interestingly, among the 14 patients receiving both AC and AP at admission, the mortality rate was 50%, probably due to their advanced age (mean age, 72.5 years) and the presence of multiple comorbidities (median CCI score, 6). Finally, elderly (≥age 80) and severely comorbid (CCI ≥ 5) patients had a significantly higher risk of hospital mortality (OR: 11.20 and 7.70, respectively) than younger patients with fewer underlying comorbidities.

In this cohort of hospitalized patients, patients on anticoagulant therapy prior to hospitalization had lower rates of ICU admission than the other groups. However, neither AC nor AP had a significant influence on mortality rates after adjusting for sex, age and comorbidities. In the group of previously anticoagulated patients, we also analysed mortality and need of ICU outcomes according to the antithrombotic treatment received *during* hospital admission and found no statistically significant differences between the groups. As a result, the impact of chronic antithrombotic therapy in patients with COVID-19 remains unclear. To our knowledge, the largest study to date to examine the role of pre-admission oral anticoagulation therapy was the nationwide registry-based cohort study by Flam et al. [22], who evaluated more than 100,000 DOAC users versus comparator groups. A total of 360 patients were hospitalized for COVID-19; of these, 160 patients presented the composite outcome (ICU admission and death due to COVID-19), but this did not differ significantly with the comparator group.

Other studies have also evaluated patients diagnosed with COVID-19 to determine complication and mortality rates in patients with previous antithrombotic therapy [23, 26, 30, 33, 34]. Those studies included from 110 to 731 anticoagulated patients and from 98 to 912 patients on antiplatelet therapy, with highly heterogenous findings. For example, in a nationwide registry-based study, Fröhlich et al. found that hospitalized patients who received DOACs or VKA had better composite (all-cause mortality or need for non-invasive or invasive ventilation or extracorporeal membrane oxygenation) outcomes compared to those on antiplatelet therapy [33]. Chocron and colleagues found that AC therapy prior to hospitalization was associated with better clinical outcomes (ICU admission and/or in-hospital mortality) [34]. By contrast, Tremblay et al. observed no improvement in all-cause mortality, time-to-mechanical ventilation, or need for hospitalization in either group (AC or AP) [26]. Rivera-Caravaca et al. found that patients on AC therapy at the time of hospital admission had lower survival rates and a greater mortality risk [23]. Finally, Chow and colleagues evaluated the role of previous antiplatelet therapy, finding that these patients had a lower risk of mechanical ventilation, ICU admission, and in-hospital

mortality [30], results that contrast with the findings of the other studies [26, 33].

In short, the studies carried out to date have reported highly variable outcomes, which can be explained by several factors. First, the analyses performed in these studies were variable. For example, Flam et al. [22] evaluated anticoagulated patients to determine the incidence of severe COVID-19 infection; by contrast, the other studies, in line with the present study—evaluated patients hospitalized for COVID-19 to assess whether pre-admission AC or AP influenced hospital outcomes. Second, although most of these studies evaluated severe disease and mortality, outcomes were measured differently. While some studies assessed combined outcomes (i.e., mortality plus the need for invasive measures), others evaluated these measures separately. Third, the study designs were heterogenous, ranging from single-center studies like ours to nationwide registry studies and multicentric studies. Clearly, differences in study design could influence data collection and outcomes.

In our study, the overall in-hospital thromboembolism rate was 5.4%, with no impact in mortality. The mean incidence of thromboembolism in our series was lower than in the other studies [1–8, 36], which leads us to think that we may have underdiagnosed this complication, probably because we did not have any screening protocol in place to systematically assess VTE in COVID-19 patients. Nevertheless, the incidence of thromboembolism in our cohort was consistent with other groups that have also reported lower rates of VTE [37].

Study strengths and limitations

The main limitation of this study is the observational, retrospective study design, which may have caused us to overlook or not collect relevant data. However, we made every effort to ensure the data was complete by checking all possible sources. A second potential limitation is that some potential confounding variables may not have been included in the multivariate analysis, the absence of which could have influenced the study outcomes, especially mortality. In this regard, patients on chronic AC are more likely to be older and have various comorbidities that could influence the reported outcomes. By contrast, an important strength of our study is that this study is, to our knowledge, the largest single-centre cohort of patients on antithrombotic therapy, and thus all patients included in this sample were diagnosed and treated according to the same institutional protocol, thus increasing the reliability of the data.

Conclusions

The association between antithrombotic therapy and outcomes in patients hospitalized for COVID-19 remains unclear. However, our findings show that ICU admission rates in patients receiving anticoagulation therapy prior to admission are lower than in patients on chronic antiplatelet therapy and patients not treated with antithrombotic therapy prior to hospitalization. Nonetheless, our data also show that chronic antithrombotic therapy does not appear to affect mortality rates in patients hospitalized for COVID-19. More studies—ideally prospective—are necessary to better elucidate whether chronic anticoagulant and/or antiplatelet therapy prior to COVID-19 infection influences outcomes in hospitalized patients.

Acknowledgements The authors wish to thank all the patients who were included in this study and the health care professionals involved in their care. We also would like to thank Bradley Londres for professional English language editing.

Authors' contributions All of the authors were involved in data collection. SM analyzed the data. MC and JS drafted the manuscript. All authors critically revised the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and material The data that support the findings of this study are available on request from the corresponding author.

Code availability Not applicable.

Declarations

Conflicts of interest No authors declare competing financial interests.

Ethical approval Ethical approval was waived by the local Ethics Committee of Hospital de la Santa Creu i Sant Pau in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

1. Lu Y, Pan L, Zhang W-W, Cheng F, Hu S-S, Zhang X et al (2020) A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. Int J Infect Dis 100:34–41
2. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M (2020) Venous thromboembolism in patients with COVID-19: Systematic review and meta-analysis. Thromb Res 196:67–74
3. Kunutsor SK, Laukkanen JA (2020) Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis. Thromb Res 196:27–30
4. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost [Internet]. 2020 Sep 25 [cited 2021 Feb 4]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7537137/.

5. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND (2020) COVID-19 and venous thromboembolism: A meta-analysis of literature studies. Semin Thromb Hemost 46(7):763–771
6. Al-Ani F, Chehade S, Lazo-Langner A (2020) Thrombosis risk associated with COVID-19 infection. A scoping review Thromb Res 192:152–160
7. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. CHEST [Internet]. 2020 Nov 17 [cited 2021 Feb 4];0(0). Available from: https://journal.chestnet.org/article/S0012-3692(20)35146-1/abstract.
8. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B (2020) Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 29:100639
9. Chi G, Lee JJ, Jamil A, Gunnam V, Najafi H, Memar Montazerin S et al (2020) Venous thromboembolism among hospitalized patients with COVID-19 undergoing thromboprophylaxis: A systematic review and meta-analysis. J Clin Med 9(8):2489
10. Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. Ann Intern Med [Internet]. 2020 May 6 [cited 2021 Feb 4]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7240772/.
11. Cui S, Chen S, Li X, Liu S, Wang F (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 18(6):1421–1424
12. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM et al (2020) Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 191:148–150
13. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA et al (2020) Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 18(8):1995–2002
14. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J et al (2020) Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: Prevalence, risk factors, and outcome. Circulation 142(2):114–128
15. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS (2020) Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 324(8):799
16. Trimaille A, Curtiaud A, Marchandot B, Matsushita K, Sato C, Leonard-Lorant I et al (2020) Venous thromboembolism in non-critically ill patients with COVID-19 infection. Thromb Res 193:166–169
17. Pizzolo F, Rigoni AM, De Marchi S, Friso S, Tinazzi E, Sartori G et al (2020) Deep vein thrombosis in SARS-CoV-2 pneumonia-affected patients within standard care units: Exploring a submerged portion of the iceberg. Thromb Res 194:216–219
18. Scudiero F, Silverio A, Di Maio M, Russo V, Citro R, Personeni D et al (2021) Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome. Thromb Res 198:34–39
19. Blasi A, von Meijenfeldt FA, Adelmeijer J, Calvo A, Ibañez C, Perdomo J et al (2020) In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. J Thromb Haemost 18(10):2646–2653
20. Mattioli M, Benfaremo D, Mancini M, Mucci L, Mainquà P, Polenta A et al (2020) Safety of intermediate dose of low molecular weight heparin in COVID-19 patients. J Thromb Thrombolysis 13:1–7
21. Arcanjo A, Logullo J, Menezes CCB, de Souza Carvalho Giangiarulo TC, dos Reis MC, de Castro GMM, et al. The emerging role of neutrophil extracellular traps in severe acute respiratory syndrome coronavirus 2 (COVID-19). Scientific Reports. 2020; 10(1):19630.
22. Flam B, Wintzell V, Ludvigsson JF, Mårtensson J, Pasternak B (2020) Direct oral anticoagulant use and risk of severe COVID-19. J Intern Med. https://doi.org/10.1111/joim.13205
23. Rivera-Caravaca JM, Núñez-Gil IJ, Vivas D, Viana-Llamas MC, Uribarri A, Becerra-Muñoz VM et al (2021) Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. Eur J Clin Invest 51(1):e13436
24. Bousquet G, Falgarone G, Deutsch D, Derolez S, Lopez-Sublet M, Goudot F-X et al (2020) ADL-dependency, D-Dimers, LDH and absence of anticoagulation are independently associated with one-month mortality in older inpatients with Covid-19. Aging (Albany NY) 12(12):11306–11313
25. Schiavone M, Gasperetti A, Mancone M, Curnis A, Mascioli G, Mitacchione G et al (2021) Oral anticoagulation and clinical outcomes in COVID-19: An Italian multicenter experience. Int J Cardiol 323:276–280
26. Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S et al (2020) Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study. Blood 136(1):144–147
27. Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D et al (2020) Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: A multicenter observational study. Pharmacol Res 159:104965
28. Rossi R, Coppi F, Talarico M, Boriani G (2020) Protective role of chronic treatment with direct oral anticoagulants in elderly patients affected by interstitial pneumonia in COVID-19 era. Eur J Intern Med 77:158–160
29. Brouns SH, Brüggemann R, Linkens AEMJH, Magdelijns FJ, Joosten H, Heijnen R et al (2020) Mortality and the use of antithrombotic therapies among nursing home residents with COVID-19. J Am Geriatr Soc 68(8):1647–1652
30. Chow JH, Khanna AK, Kethireddy S, Yamane D, Levine A, Jackson AM et al (2020) Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. Anesth Analg 132:930–941
31. Sivaloganathan H, Ladikou EE, Chevassut T (2020) COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol 190(4):e192–e195
32. Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized Covid-19 patients: A systematic review and meta-analysis of case-control and cohort studies. Rev Med Virol [Internet]. 2020 Oct 6 [cited 2021 Feb 4]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646049/.
33. Fröhlich GM, Jeschke E, Eichler U, Thiele H, Alhariri L, Reinthaler M et al (2021) Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. Clin Res Cardiol 8:1–10
34. Chocron R, Galand V, Cellier J, Gendron N, Pommier T, Bory O et al (2021) Anticoagulation prior to hospitalization is a potential protective factor for COVID-19: insight from a French multicenter cohort study. J Am Heart Assoc 8:e018288
35. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
36. Boonyawat K, Chantrathammachart P, Numthavaj P, Nanthatanti N, Phusanti S, Phuphuakrat A et al (2020) Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Thrombosis J 18(1):34
37. Hill JB, Garcia D, Crowther M, Savage B, Peress S, Chang K et al (2020) Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. Blood Adv 4(21):5373–5377