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Anticoagulation and In-Hospital Mortality From Coronavirus Disease 2019: A Systematic Review and Meta-Analysis

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Abstract

Hypercoagulability in coronavirus disease 2019 (COVID-19) may aggravate disease severity during hospitalization but the reported survival benefits from anticoagulation (AC) vary among studies. We performed a literature research to estimate pooled odds ratios (ORs) of in-hospital mortality and major bleeding comparing among intermediate-to-therapeutic dose AC, prophylactic dose AC, and no AC. Until October 22, 2020, PubMed, EMBASE, and Cochrane Library Database were searched for studies reporting AC utilization and mortality in COVID-19. Studies with suspected risk of bias were excluded before the synthesis of pooled ORs with 95% confidence intervals (CIs) using random-effects models. Of 37 identified studies (N = 19,510), 17 (N = 17,833) were aggregated in the meta-analysis. The overall mortality rate was 23.1% (95% CI 18.7-28.2). The pooled odds of mortality comparing anticoagulated to non-anticoagulated patients were similar, but lower in prophylactic dose AC group (OR 0.83; 95% CI 0.73-0.95). Notably, intermediate-to-therapeutic dose AC increased mortality (OR 1.60; 95% CI 1.11-2.31) and major bleeding compared to prophylactic dose AC (OR 3.33; 95% CI 2.34-4.72). Our findings support the optimal efficacy and safety profiles of prophylactic dose AC in hospitalized COVID-19 patients.

Keywords

COVID-19, SARS-CoV-2, anticoagulation, mortality, meta-analysis

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Introduction

By the end of January 2021, the global spread of coronavirus diseases 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected more than 100 million people worldwide with approximately 2-3% case fatality, which could be up to 15-27% in hospitalized patients.[1] Although SARS-CoV-2 primarily infects respiratory organs, significant numbers of patients encounter systemic complications associated with proinflammatory cytokine overproduction, endotheliopathy, hypercoagulability, and thromboembolism.[2-5] Supported by the high prevalence of elevated plasma D-dimer levels[6] and postmortem findings of alveolar capillary microthrombi among critical cases,[2,7] activation of pulmonary intravascular coagulation may play an important role in the pathophysiology of severe COVID-19 pneumonia and acute respiratory distress syndrome. Moreover, emerging studies reveal the apparently high prevalence of arterial and

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venous thromboembolisms among hospitalized COVID-19 population, 18-28% in the intensive care unit (ICU) and 5-11% in non-ICU circumstances.[8] Notably, the thrombosis is associated with the higher mortality (pooled odds ratio [OR] 1.74; 95% confidence interval [CI] 1.01-2.98).[9] Anticoagulation (AC) therapy has been proposed to counteract the underlying prothrombotic mechanisms. Although several randomized controlled trials (RCTs) are ongoing,[10] the expert consensus recommends AC in all hospitalized COVID-19 patients in the absence of absolute contraindications,[11,12] primarily aiming for thromboprophylaxis.

The rationale behind AC is not only derived from evidence-based recommendations on thromboprophylaxis for hospitalized medical illness,[13] but also from a few cohort studies observing impact of AC on COVID-19 mortality. The first retrospective study from China[14] reported the association between prophylactic dose AC, using low molecular weight heparin (LMWH) or unfractionated heparin (UFH), and better survival of patients with severe COVID-19 pneumonia in a subgroup of markedly activated coagulation defined by high D-dimer levels and sepsis-induced coagulopathy score. A subsequent larger United States cohort[15] demonstrated lower mortality in COVID-19 subjects who received any doses of AC, compared to those without AC. Because thromboembolic rates are still high in COVID-19 patients despite prophylactic dose AC,[16] higher doses of AC are increasingly prescribed. Nevertheless, in-hospital mortality rates of prophylactic dose and therapeutic dose AC groups were not significantly different, while therapeutic dose AC possibly increased bleeding complications.[15,17] Therefore, the role of high-intensity AC in COVID-19 remains controversial.[12]

Consequently, we conducted a systematic review and meta-analysis of published data to estimate the associations between the AC utilization/intensity and mortality, as well as bleeding rates, of COVID-19 patients during hospitalization.

Methods

The protocol for this literature research was prespecified before study initiation. Relevant randomized and non-randomized studies were systematically reviewed, and extractable data were analyzed, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The primary aim of this research was to evaluate the impact of AC, either prophylactic or intermediate-to-therapeutic doses, on mortality of hospitalized patients with COVID-19. The effects of different AC dosages on major bleeding complication were determined as the secondary objectives.

Eligibility Criteria

Research articles published between the inception of COVID-19 and October 22, 2020 in any formats (i.e. full-length original articles, brief reports, letters, or conference abstracts) and languages, were eligible for inclusion into the systematic review. The inclusion criteria consisted of the studies reporting mortality and the AC uses among adult patients (age $\geq$18 years) hospitalized due to objectively confirmed COVID-19. Prospective or retrospective observational studies and RCTs recruiting at least 10 participants were included. Non-original studies (i.e. reviews, commentaries, guidelines, or trial protocols), duplicated studies, and studies with inappropriate designs for estimating mortality from COVID-19 (i.e. autopsy studies, case reports or case series which exclusively enrolled patients with trauma, surgeries, or thrombotic complications) were excluded. Finally, only studies which adequately described mortality based upon the AC utilization and dose intensities were qualified for statistical estimations in the comparative meta-analysis.

Literature Search Strategy

A systematic search was performed on 3 online databases including PubMed, EMBASE, and Cochrane Library Database. A manual search of relevant journals and eligible abstracts from the international conferences was supplementally conducted. The search terms used on the electronic databases were the combination of the following words: anticoagulation, anticoagulant, anticoagulated, mortality, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, novel coronavirus 2019, 2019-nCoV, coronavirus disease 2019, and COVID-19. Before screening for eligibility, duplicated search results from different databases were excluded. Two researchers (C.M. and D.S.) independently searched the literatures, screened titles and abstracts, and thoroughly evaluated full-texts to identify potentially eligible studies. A study was primarily included according to the discretions of these 2 researchers. In case of disagreement, the third reviewer (P.R.) was consulted for the final decision. All researchers are hematologists who have clinical and research experiences on thrombosis and hemostasis. The PRISMA flowchart illustrates the results of the literature search and study selection (Figure 1).

Data Extraction and Data Synthesis

Included studies were reviewed for data extraction. If different studies reported the results from the same cohort or trial population, only the study with more maturity of data would be quantitatively appraised. Prespecified independent and dependent variables were extracted from each study as follows: study design, number of total study participants, number of patients with critical illness,[19] invasive mechanical ventilators or requiring ICU hospitalization, baseline characteristics (mean age, gender, comorbidities, and laboratory profiles), adjuvant treatments for COVID-19,[20] administration of AC, and outcomes of interest (in-hospital death and major bleeding).

In this review, prophylactic dose AC[13] was defined as subcutaneous enoxaparin 40-60 mg or 0.5-1.0 mg/kg once daily, subcutaneous nadroparin 2,850-5,700 IU once daily, subcutaneous UFH 5,000 U every 8-12 hours, subcutaneous

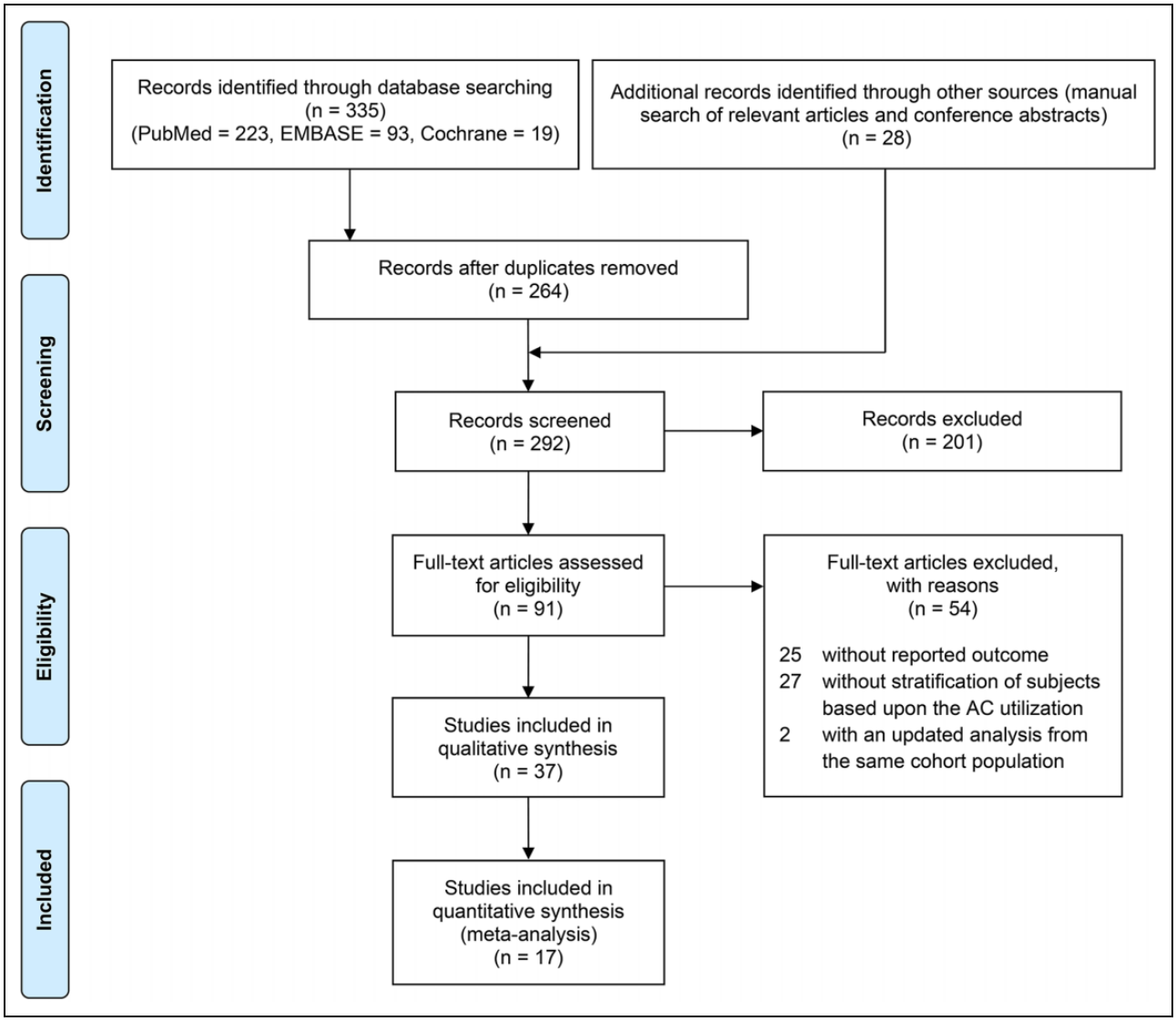

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection. Abbreviation: AC, anticoagulation.

fondaparinux 2.5 mg once daily, or oral apixaban 2.5 mg twice daily. Intravenous UFH, oral vitamin K antagonists targeting therapeutic international normalized ratio, or any AC doses higher than the prophylactic levels were categorized as intermediate-to-therapeutic dose AC. If these details of AC administration were not described, the AC doses would be defined according to the authors in each study.

The primary outcome of the meta-analysis was in-hospital mortality, which was referred to deaths from any causes during hospitalization due to COVID-19. Major bleeding adverse events (AEs) following the International Society on Thrombosis and Haemostasis (ISTH) criteria for non-surgical patients[21] were the secondary outcome. For the primary analysis, mortality outcomes were stratified based upon the AC uses (AC versus no AC) and subsequently by the AC intensities (prophylactic versus intermediate-to-therapeutic dose AC). Two authors (C.M. and D.S.) separately performed data extraction from eligible studies. The consensus with the third author (P.R.) was necessary in a discordance.

Quality Assessment

Methodological quality of eligible studies was evaluated independently by 2 authors (C.M. and D.S.) using validated tools for assessing risk of bias: the Newcastle-Ottawa Scale (NOS)[22] for cohort studies, and the modified Cochrane Collaboration tool[23] for RCTs. The NOS assigns 0-9 points according to 3 quality domains: selection, comparability, and outcome. Total NOS scores <5 points, 0-1 point in the selection, 0 point in the comparability, or 0-1 point in the outcome domains define a study with low quality or at potential risk of bias. The Cochrane risk-of-bias tool comprises 7 items from 6 bias domains. Overall risk of bias based upon the summary of responses to all

7 items categorizes a RCT into low, high, or unclear risks of bias. Scoring discrepancies were resolved by a joint re-assessment of the article (C.M., D.S., and P.R.).

Statistical Methods

Statistical operations were performed using Comprehensive Meta-Analysis version 3.0 (Biostat Inc., Englewood, NJ, USA). Using the DerSimonian and Laird method with random-effects models, we calculated the pooled event rates and risk estimates (pooled ORs and 95% CIs) for in-hospital mortality by the AC uses and intensities. The prespecified subgroup analyses comparing no AC to prophylactic dose or intermediate-to-therapeutic dose AC were subsequently conducted. The pooled event rates and ORs for major bleeding AEs by the AC intensities were estimated in the secondary analysis. Results from the studies with zero outcome event, the studies with low methodological quality, or the studies at high risk of bias were not aggregated in the comparative meta-analysis. Continuous variables reported as medians with interquartile ranges were converted to estimated means with standard deviations[24] before quantitative synthesis into the pooled means and 95% CIs within random-effects models.

Between-study heterogeneity was measured by the I^2 statistic.[25] The I^2 of 0-25%, 26-50%, 51-75%, and >75%, indicated insignificant, low, moderate, and high heterogeneity, respectively. When at least 10 studies were aggregated in the meta-analysis, potential publication bias was assessed by visual inspection of the funnel plots and statistical estimation by the Egger's regression test.[26]

Table 1. Methodological Characteristics of 37 Studies Included in the Systematic Review.

Characteristics	No. of studies	No. of participants
Study design		
Randomized controlled trial	1	20
Prospective cohort	11	1,964
Retrospective cohort	25	17,526
Single-center study	24	5,328
Multi-center study	13	14,182
Geographical location		
Asia	4	1,464
Europe	21	5,121
North America	11	12,905
South America	1	20
Hospitalization or disease severity setting		
ICU/critically ill	34	6,118
Non-ICU/non-critically ill	17	10,434
Unstratified hospitalization setting	2	2,958
AC utilization		
No AC	37	3,840
Prophylactic dose AC	33	9,748
Intermediate-to-therapeutic dose AC	33	3,886
Undefined doses of AC	4	2,036
Reported mortality outcome		
No AC	15	3,648
Prophylactic dose AC	20	9,109
Intermediate-to-therapeutic dose AC	20	3,657
Any AC	36	15,484

Abbreviations: AC, anticoagulation; ICU, intensive care unit.

Results

From 363 studies identified by the literature search, titles and abstracts of 292 unique studies which fulfilled the inclusion criteria were screened for eligibility. Since 201 studies were excluded according to at least 1 criterion of exclusion, 91 studies remained for the full-text evaluation. Of those, 37 studies[14-16,27-60] which enrolled 19,510 patients hospitalized due to COVID-19 were eligible for data extraction. The PRISMA flow diagram demonstrating the process of study screening and selection is displayed in Figure 1.

Methodological characteristics of 37 eligible studies reporting the AC uses and in-hospital mortality of COVID-19 patients are summarized in Table 1. Although 56.8% of the studies were conducted in Europe, the largest fraction of participants (66.1%) belonged to 11 studies from North America. All except 1 RCT were retrospective or prospective observational studies determining mortality as the primary (15/36, 41.7%) or secondary (21/36, 58.3%) outcomes. An eligible RCT[44] from South America primarily evaluated the surrogate endpoint of gas exchange improvement, and secondarily for mortality. Major bleeding complications were reported as the primary outcome in 3 eligible cohorts,[47,50,51] while as the secondary outcome in the other 9 studies.

Among the included studies, anticoagulants were prescribed in 80.3% of hospitalized patients with COVID-19. More than half of those received prophylactic dose AC. Among 3,840 patients who were not exposed to AC during their hospital courses, 1,086 cases (28.3%) came from 4 studies in Asian population.[14,32,34,59] Compared with the studies from the other continents, the Asian studies reported substantially lower rates of the AC utilization (25.8% versus 82.7% in the North American and 89.8% in the European populations).

Collective data on clinical characteristics of 19,510 patients are presented in Table 2. The weighted mean of participant age was 61.7 years (95% CI 60.1-63.3) and 42.4% of overall population were female. Hypertension and diabetes mellitus were common comorbidities. Despite limited data on COVID-19 specific treatments, the administrations of hydroxychloroquine and systemic corticosteroids were implemented in 79.9% and 47.0% of patients, respectively. Pooled analyses of the potential coagulation parameters revealed the elevation of D-dimer and fibrinogen levels confirming the findings from the previous meta-analysis.[6] Based on the AC uses, patients who received AC had a higher proportion of ICU admission or critical illness (54.3% versus 17.7% in no AC group). Main characteristics of each included study are described in the supplementary Table S1.

Table 2. Patient Characteristics From 37 Studies Included in the Systematic Review.

Characteristics	No. of studies	No./total of participants (%) or estimated values
Mean age (years, 95% CI)	37	61.7 (60.1-63.3)
Gender		
Female	37	8,280/19,510 (42.4)
Male	37	11,230/19,510 (57.6)
No. of ICU or critically ill patients		
No AC	7	186/1,053 (17.7)
AC	25	5,106/9,403 (54.3)
Prophylactic dose AC	20	3,682/7,098 (51.9)
Intermediate-to-therapeutic dose AC	18	1,335/2,216 (60.2)
Overall population	34	6,118/16,228 (37.7)
Comorbidities		
Hypertension	21	6,821/14,485 (47.1)
Diabetes mellitus	22	4,313/14,774 (29.2)
Cardiovascular disease	16	893/12,343 (7.2)
Ischemic heart disease	11	1,622/12,829 (12.6)
Congestive heart failure	5	845/10,817 (7.8)
Cerebrovascular disease	4	392/4,510 (8.7)
Chronic pulmonary disease	16	1,856/11,404 (16.3)
Chronic liver disease	3	84/4,933 (1.7)
Chronic kidney disease	10	815/9,607 (8.5)
Malignancy	15	852/12,479 (6.8)
Current- or ex-smoker	13	1,721/11,962 (14.4)
Obesity	10	1,434/7,900 (18.2)
Prior VTE	10	255/4,428 (5.8)
Immunocompromised status	4	79/4,603 (1.7)
COVID-19 adjuvant treatments		
Remdesivir	5	40/562 (7.1)
Convalescent plasma	2	29/205 (14.1)
Interleukin-6 receptor inhibitors[a]	7	551/2,997 (18.4)
Corticosteroids	9	3,137/6,681 (47.0)
Hydroxychloroquine	9	5,223/6,541 (79.9)
Selected laboratory parameters		
Mean platelets (x 10^9 cells/μL, 95% CI)	26	230.1 (218.8-241.5)
Mean D-dimer (μg/mL, 95% CI)	30	2.32 (1.99-2.65)
Mean fibrinogen (g/L, 95% CI)	18	6.25 (5.25-7.25)
Crude in-hospital mortality rates		
No AC	15	772/3,648 (21.2)
AC	36	3,669/15,484 (23.7)
Prophylactic dose AC	20	2,076/9,109 (22.8)
Intermediate-to-therapeutic dose AC	20	1,148/3,657 (31.4)
Overall population	37	4,506/19,510 (23.1)

Abbreviations: AC, anticoagulation; CI, confidence interval; COVID-19, coronavirus disease 2019; VTE, venous thromboembolism.
[a]Reported uses of interleukin-6 receptor inhibitors included tocilizumab and sarilumab.

Risk of Bias

The quality assessment of 37 eligible studies was aimed to evaluate the potential risk of bias related to the exposure to AC and the reported mortality. Apart from appraising the generalizability of exposure and outcomes of interest, our evaluations were not judgment of the general quality or scientific merits of the included studies. The details on methodological assessment of 36 cohort studies and 1 RCT are presented in the supplementary Table S2 and Table S3, respectively. Eighteen studies were excluded from the meta-analysis due to their high risk of bias: 17 studies for limitations on comparability, and 8 studies for outcome assessment. Two studies,[43,48] albeit qualified by the NOS, were subsequently excluded due to the lack of stratification of mortality by the AC doses. Hence, 17 studies remained at the final for the comparative meta-analysis.

In the primary and the secondary analyses, 2 meta-analysis models comprising the results of at least 10 studies were evaluated for the publication bias. Although the funnel plot from 1 out of 2 evaluable models was asymmetrical, the Egger's regression intercept did not indicate a significant risk of publication bias. The funnel plots of both meta-analysis models are illustrated in the supplementary Figure S1.

Anticoagulation and In-Hospital Mortality

After methodological assessment, data from 17 qualified studies involving 17,833 hospitalized patients were analyzed. Clinical characteristics of the study subjects aggregated in the meta-analysis are summarized in the supplementary Table S4. The mean age of participants was 63.7 years (95% CI 62.3-65.1). Less than a half of patients were female (42.7%) and treated in ICU setting (33.9%). The pooled rates of in-hospital mortality of all, non-anticoagulated, and anticoagulated patients were 23.1% (95% CI 18.7-28.2; $I^2 = 98\%$), 21.4% (95% CI 16.3-27.7; $I^2 = 92\%$), and 24.3% (95% CI 19.5-29.8; $I^2 = 98\%$), respectively. For the primary analysis, the quantitative results from 10 studies (58.8%) reporting the number of patients with no AC, were pooled to determine the odds of in-hospital mortality comparing anticoagulated to no AC groups. Among 13,124 patients (1,911 critically ill, 9,105 non-critically ill, and 2,108 unclassified cases), the AC use was not associated with the lower in-hospital mortality from COVID-19 (OR 1.19; 95% CI 0.90-1.58; $I^2 = 74\%$; Figure 2A). However, in the prespecified analyses of subpopulations stratified by the AC intensities, the pooled odds of mortality were 17% lower in patients receiving prophylactic dose AC (OR 0.83; 95% CI 0.73-0.95; $P = 0.006$; $I^2 = 0\%$; Figure 2B), but 64% higher among the patients receiving intermediate-to-therapeutic dose AC, when compared to those with no AC (OR 1.64; 95% CI 1.15-2.35; $P = 0.007$; $I^2 = 68\%$; Figure 2C). A post hoc analysis in ICU/critically ill subgroup could not be performed due to the limited report on outcome stratified by COVID-19 severity.

Concerning the different rates of in-hospital thromboprophylaxis between Asian and Western studies, post hoc analyses stratified by the study continents revealed the similar pooled effects of AC as in the prespecified analyses. Nevertheless, the survival benefit of prophylactic dose AC compared to no AC was significant solely in the Western subgroup (OR 0.82; 95% CI 0.69-0.99; $P = 0.035$; $I^2 = 22\%$) but not in the Asian subgroup (OR 0.93; 95% CI 0.60-1.45; $I^2 = 0\%$; the supplementary Figure S2). The impact of intermediate-to-therapeutic dose

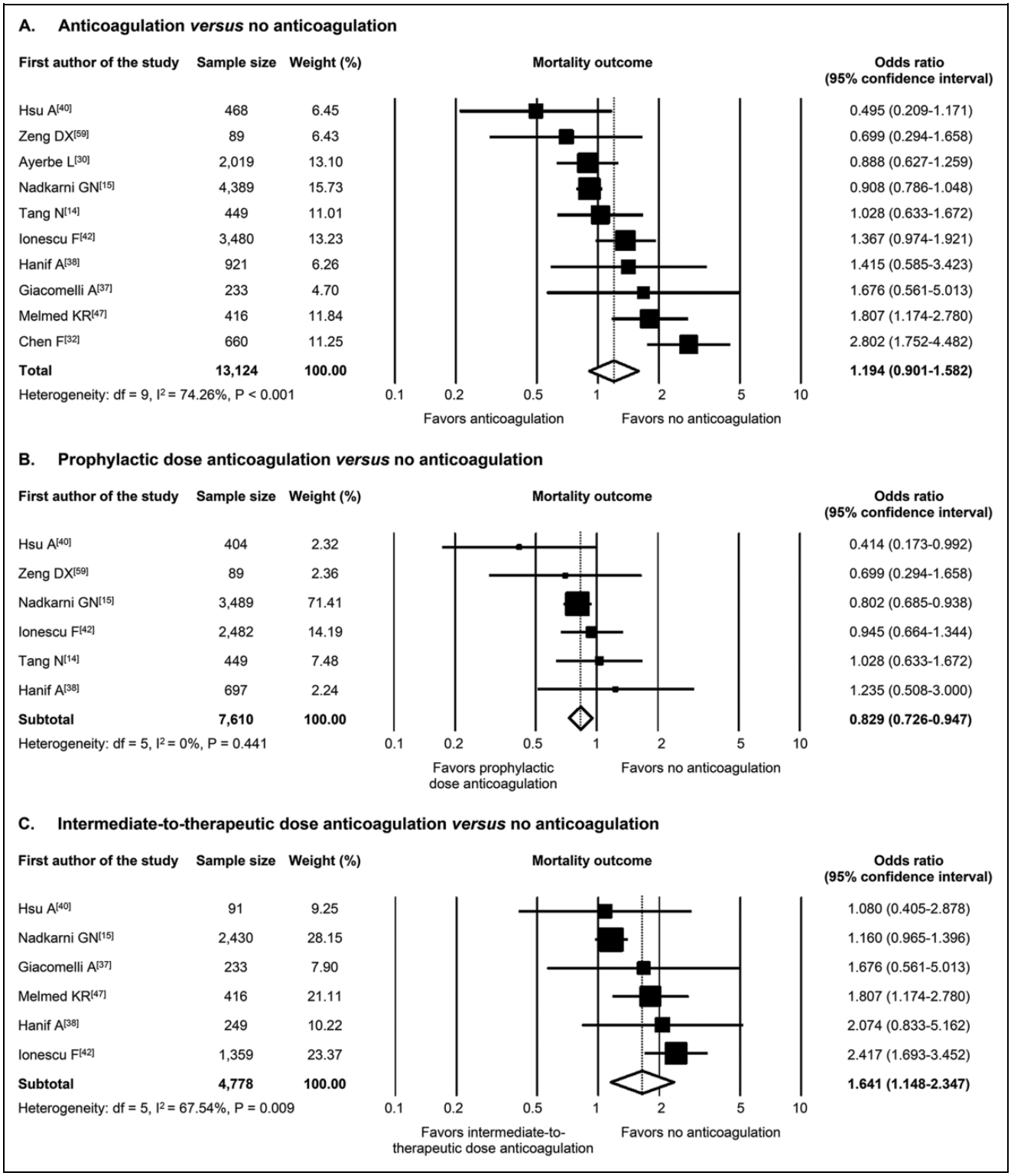

Figure 2. Pooled odds of mortality among hospitalized COVID-19 patients with anticoagulation compared to patients without anticoagulation: (A) any anticoagulation, (B) prophylactic dose anticoagulation, and (C) intermediate-to-therapeutic dose anticoagulation. Abbreviation: df, degree of freedom.

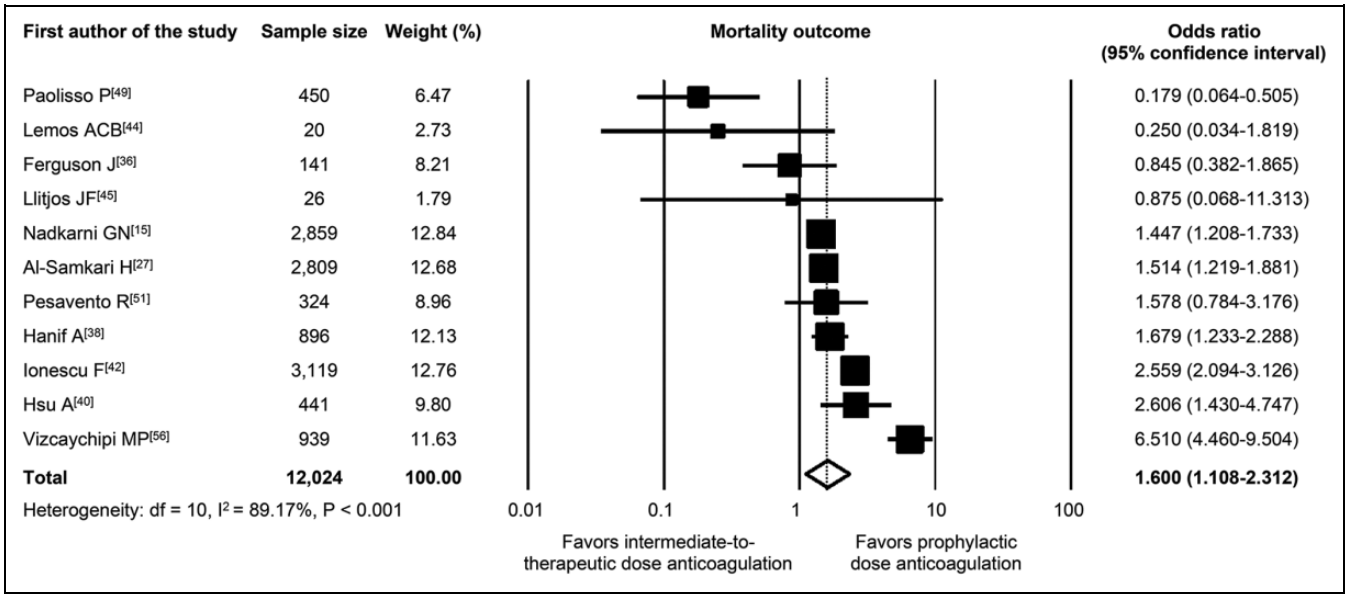

Figure 3. Pooled odds of mortality among hospitalized COVID-19 patients with intermediate-to-therapeutic dose anticoagulation compared to patients with prophylactic dose anticoagulation. Abbreviation: df, degree of freedom.

AC in the Asian population was undetermined since none of them specified AC doses higher than the prophylactic levels.

Intermediate-to-Therapeutic Versus Prophylactic Dose Anticoagulation and In-Hospital Mortality

Eleven studies (64.7%) reporting fatality in 3,385 patients who received intermediate-to-therapeutic dose (27.8%; 95% CI 21.5-35.2; $I^2 = 93\%$) and 8,639 patients who received prophylactic dose AC (20.4%; 95% CI 14.3-28.2; $I^2 = 98\%$) were aggregated in the secondary analysis. In a total of 12,024 cases, COVID-19 patients with intermediate-to-therapeutic dose AC had 60% significantly higher odds of mortality compared to those with prophylactic dose AC (OR 1.60; 95% CI 1.11-2.31; $P = 0.012$; $I^2 = 89\%$; Figure 3).

In a sensitivity analysis by removing a study with a unique protocol of AC titration using an individual risk of thrombosis,[56] the survival benefit of prophylactic dose AC was still present (OR 1.42; 95% CI 1.05-1.93; $P = 0.022$; $I^2 = 81\%$). Moreover, a post hoc analysis integrating multiple subgroups of the disease severities demonstrated the reproducibility of those pooled risk estimates (OR 1.50; 95% CI 1.07-2.11; $P = 0.018$; $I^2 = 89\%$). Including 4 studies which solely enrolled 2,996 critically ill patients, the higher AC intensity was not related to the greater risk of deaths during ICU hospitalization (OR 1.08; 95% CI 0.60-1.95; $I^2 = 41\%$; the supplementary Figure S3).

Anticoagulation and Major Bleeding Complications

For the secondary outcome, major bleeding AEs were documented clearly in 9 studies (52.9%) covering 10,609 hospitalized patients (2,560 patients with intermediate-to-therapeutic dose AC, 5,835 with prophylactic dose AC, and 2,214 with no AC). The pooled event rates of major bleeding among all patients, patients with no AC, prophylactic dose AC, and intermediate-to-therapeutic dose AC were 4.8% (95% CI 3.0-7.6; $I^2 = 94\%$), 3.5% (95% CI 1.9-6.6; $I^2 = 75\%$), 2.6% (95% CI 1.7-4.1; $I^2 = 78\%$), and 9.6% (95% CI 5.8-15.6; $I^2 = 89\%$), respectively.

The quantifiable results from 8 out of 9 studies reporting bleeding complications in both dose levels of AC were analyzed. The pooled odds of major bleeding were approximately 3 folds greater in intermediate-to-therapeutic dose compared to prophylactic dose AC groups (OR 3.33; 95% CI 2.34-4.72; $P < 0.001$; $I^2 = 30\%$; Figure 4). These effects were comparable to the pooled risk estimates from a post hoc analysis comprising all subgroups of COVID-19 severities (OR 3.34; 95% CI 2.22-5.04; $P < 0.001$; $I^2 = 30\%$) or solely ICU subpopulation (OR 3.58; 95% CI 1.49-8.62; $P = 0.004$; $I^2 = 0\%$; the supplementary Figure S4).

Furthermore, the odds of major bleeding comparing any doses of AC to no AC were collated using the quantitative data of 9,674 participants from 5 studies. Administration of intermediate-to-therapeutic dose AC increased the pooled odds of major bleeding (OR 2.11; 95% CI 1.18-3.76; $P = 0.011$; $I^2 = 56\%$). However, prophylactic dose AC was not significantly associated with an increase in major bleeding compared to no AC (OR 0.52; 95% CI 0.25-1.05; $I^2 = 59\%$; the supplementary Figure S5).

Discussion

In this systematic review, we gathered data from 37 studies describing pharmacological thromboprophylaxis and mortality in 19,510 SARS-CoV-2-infected patients during

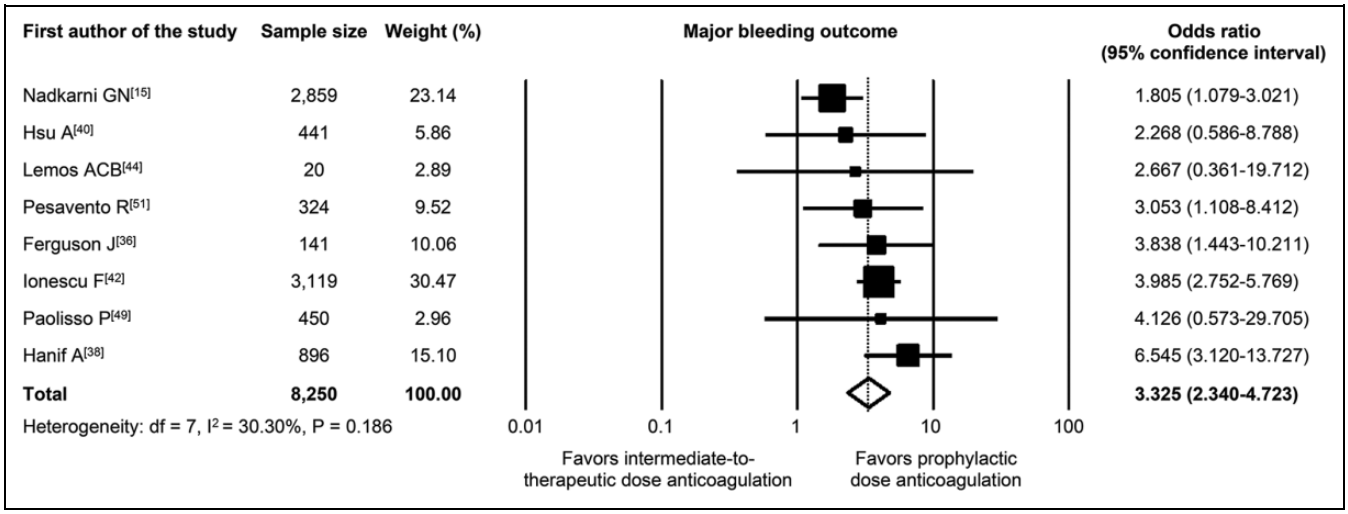

Figure 4. Pooled odds of major bleeding among hospitalized COVID-19 patients with intermediate-to-therapeutic dose anticoagulation compared to patients with prophylactic dose anticoagulation. Abbreviation: df, degree of freedom.

hospitalization. Considering data of 17,833 participants from 16 observational studies and 1 RCT aggregated in the comparative meta-analysis, the in-hospital mortality rates were substantially high regardless of the AC uses and intensities (27.8% in intermediate-to-therapeutic dose AC, 20.4% in prophylactic dose AC, and 21.4% in no AC groups). The mortality of anticoagulated versus non-anticoagulated patients were not different.

Comparing to no AC group, prophylactic dose AC significantly decreased the odds of in-hospital death by 17%, despite a lower proportion of critically ill patients in no AC group. This may suggest a beneficial role of prophylactic dose AC as part of COVID-19 treatment. On contrary, intermediate-to-therapeutic dose AC was associated with the higher odds of mortality. A possible explanation for this adverse outcome was a large proportion of critically ill patients in intermediate-to-therapeutic dose AC group (60.2% versus 17.7% in no AC and 51.9% in prophylactic dose AC groups). Consistently, an ICU subgroup analysis showed similar odds of mortality among critically ill patients with intermediate-to-therapeutic dose AC and those with prophylactic dose AC.

A proposed mechanism for AC benefit in COVID-19 treatment is to suppress prothrombotic coagulopathy preventing thrombosis in micro- and macro-vasculatures.[61] Furthermore, several inflammatory markers, i.e. C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and ferritin, are elevated in COVID-19 patients and correlated with thrombotic complications.[62] Therefore, anti-inflammatory effects of LMWH and UFH[63,64] including neutralization of cytokines, chemokines, and extracellular histones may be advantageous for COVID-19 patients beyond their anticoagulant properties. Laboratory profiles of the study participants in this meta-analysis (the supplementary Table S4) showing the increases in D-dimer, fibrinogen, CRP, and procalcitonin potentially support this hypothesis. Moreover, LMWH and UFH can also reduce SARS-CoV-2 cellular entry by competitively binding to heparan sulfate on host cell membrane.[63,64] While prophylactic dose AC does not reduce in-hospital mortality of patients with acute medical illnesses other than COVID-19,[13,65] the current evidence suggests a unique pathogenesis of SARS-CoV-2 infection that can be alleviated by an appropriate dose of AC and also support the guidelines recommending prophylactic dose AC in both critically ill and non-critically ill hospitalized COVID-19 patients.

A recent systematic review and meta-analysis of 35 studies disclosed that hospitalized COVID-19 patients who received AC developed substantially lower thrombotic rates (10.5-19.8% venous and 1.3-2.5% arterial thrombosis) compared to those without AC (41.9% venous and 11.3% arterial thrombosis), although thrombotic rates in prophylactic dose and high-intensity AC groups were not significantly different.[17] A post hoc quantitative synthesis of available data from 4 studies[40,44,45,51] involving 811 patients in this meta-analysis also revealed similar odds of venous thrombosis when comparing intermediate-to-therapeutic dose to prophylactic dose AC groups (OR 1.98; 95% CI 0.99-3.93; $I^2 = 0\%$). Within this frame of evidence, increased intensity of AC may be ineffective, not only in reducing thrombosis, but also in improving survival. Targeting systemic hyperinflammation in SARS-CoV-2 infection by immunomodulatory methods[20,66,67] should be considered rather than escalating dose of AC.

Cardiovascular comorbidities are associated with high fatality rates of COVID-19 patients.[19] In the presence of systemic hyperinflammation and endotheliopathy due to COVID-19, coronary microvascular dysfunction and destabilized atherosclerotic plagues may aggravate underlying cardiac conditions and possibly lead to deaths.[68,69] In this meta-analysis, 18.4% of COVID-19 patients who received intermediate-to-therapeutic dose AC had ischemic heart disease, higher than those who received prophylactic dose AC (11.4%) and those who did not (10.8%; the supplementary Table S4). This factor may partially

contribute to the higher mortality rates among high-intensity AC group. Consequently, cardiologists should be involved early in the multidisciplinary management team for COVID-19 patients with preexisting cardiovascular diseases.[69]

Coagulopathy in COVID-19 is not only related to thrombotic but also to bleeding complications, particularly in the presence of overt disseminated intravascular coagulation, thrombocytopenia, or hypofibrinogenemia.[62] Although the elevated D-dimer levels and the prolonged clotting times were commonly observed in this meta-analysis (the supplementary Table S4), prophylactic dose AC did not increase major bleeding rates compared to no AC and yielded significantly lower rates than that of intermediate-to-therapeutic dose AC (2.6% versus 9.6%). This harmful effect, therefore, did not support the use of high-intensity AC. Moreover, exposure to LMWH or UFH possibly cause heparin-induced thrombocytopenia (HIT) which may lead to thrombosis via platelet-activating antiplatelet factor 4/heparin antibodies.[70,71] Recent retrospective studies[72,73] highlighted the burden of HIT among hospitalized COVID-19 patients who received LMWH or UFH as thromboprophylaxis. The impact of heparin dosages on HIT development is uncertain as data are lacking. One study[42] in our meta-analysis described HIT in only 0.05% of patients who received prophylactic dose AC (1/2,121) but 1.1% of patients who received increased intensity of AC (11/998). Exploring the HIT incidence in a larger COVID-19 population is warranted.

Two recently published systematic reviews[74,75] reported the uses of AC to improve survival of hospitalized COVID-19 patients. One review with a subsequent meta-analysis[74] concluded that any AC and intermediate-to-therapeutic dose AC were associated with the lower COVID-19 mortality based upon data from 6 observational studies. However, the other review[75] revealed conflicting effects of therapeutic dose AC on COVID-19 mortality based upon data from 8 observational studies. Our updated literature research accumulated more mature data from 17 studies in the meta-analysis, including several large cohorts and 1 RCT. We confirmed the survival benefit from prophylactic dose AC in hospitalized COVID-19 patients, but with the negative impact of high-intensity AC. Additionally, we conducted the pooled analysis on major bleeding which was undetermined in the prior reviews. This meta-analysis presents both efficacy and safety outcomes of AC that would be helpful for a clinical decision on COVID-19 management.

Study Limitations

The majority of included studies in this systematic review are retrospective or prospective cohorts that assign mortality as the secondary outcome. The meta-analysis assembling data from observational studies undeniably contain limitations, i.e. among-study heterogeneity, selection bias, and various confounders.[76] First, there may be a tendency to prescribe intermediate-to-therapeutic dose AC to more severe patients. Imbalance of baseline characteristics among comparative arms of interventions could limit an interpretation of their effects on outcomes. In this context, we tried to perform post hoc analyses in the ICU/critically ill subgroup when data were available. Second, the reported data on other adjunctive treatments for COVID-19 were limited. Third, subtherapeutic doses of AC used in the included studies were highly variable. Therefore, we combined any increased intensity of AC into intermediate-to-therapeutic dose AC group to ease the quantitative synthesis. Fourth, although direct oral anticoagulants (DOACs), i.e. apixaban 2.5 mg twice daily,[77] rivaroxaban 10 mg once daily,[78] and betrixaban 80 mg once daily,[79] may be used as pharmacological thromboprophylaxis in acutely ill medical patients, studies using prophylactic doses of DOACs other than apixaban[15,40] in COVID-19 population are lacking. Fifth, due to the limited number of the Asian studies, prophylactic dose AC did not significantly reduce the in-hospital mortality from COVID-19 compared to no AC in this subgroup (the supplementary Figure S2). The AC effects in various ethnic groups deserve further investigations.[80] Ongoing RCTs[10] which directly compare effectiveness of prophylactic dose to higher doses of AC in COVID-19 will provide stronger evidence for clinical practice.

Conclusions

We discovered that the standard prophylactic dose of AC was associated with lower in-hospital mortality from COVID-19 without excess bleeding. On contrary, the intermediate-to-therapeutic dose AC revealed no survival benefit but a 3-fold increase in major bleeding. Results from upcoming RCTs are required to confirm our findings.

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Author Contributions

CM contributed to study design, data collection, data interpretation, statistical analysis, and writing the first draft of manuscript; DS contributed to study design, data collection, and data interpretation; TC and NU contributed to study design and critical review of the manuscript; PR contributed to study design, data interpretation, and critical review of the manuscript; all authors contributed to revision of the final manuscript.

Ethics Approval

Our institution did not require ethical approval or informed consent from the patient(s) for reporting a systematic review and meta-analysis.

Declaration of Conflicting Interests

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Supplemental Material

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