Original Article

Anticoagulant therapy in adult with COVID-19: a systematic review and meta-analysis of randomized controlled trial

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Background: Blood coagulation dysfunction is a risk factor for adverse outcomes in patients with coronavirus disease 2019 (COVID-19), especially in severe cases. The evidence for the effects of anticoagulation therapy on prognosis of COVID-19 patients and its risk of causing bleeding events is accumulating. Here we conducted a meta-analysis to assess the efficacy and safety of anticoagulants in COVID-19 patients of different severity.

Methods: We searched PubMed, Embase databases, Cochrane Trials, OVID MEDLINE from December 2019 to April 2023. We included randomized controlled trials (RCTs) involving COVID-19 patients over 18 years of age, which explored the effect of anticoagulant and its dose on outcomes including all-cause mortality, bleeding events or thrombotic events. We calculated the risk ratio (RR) and its 95% confidence interval (CI) for each outcome. We also performed subgroup analyses to assess the impact of disease severity, using a fixed-effect model to test for heterogeneity. The risk of bias, publication bias, and the quality of evidence were also evaluated.

Results: A total of 20 RCTs were included for final analysis. When compared with standard care, anticoagulation treatment reduced all-cause mortality (RR 0.47, 95% CI: 0.29–0.76) and thrombotic events (RR 0.35, 95% CI: 0.15–0.83) in the whole population with COVID-19 (n=2,365), without increase in bleeding events (total: RR 1.47, 95% CI: 0.54–4.00). Most of the studies only enrolled non-severe patients (n=2,329), while the number of severe patients (n=36) was scarce. In RCTs compared therapeutical and prophylactic doses of anticoagulants, no significant difference in on all-cause mortality was found in the whole population and non-severe and severe subgroups (total: RR 1.01, 95% CI: 0.92–1.10; non-severe: RR 1.03, 95% CI: 0.81–1.32; severe: RR 1.00, 95% CI: 0.91–1.11). Therapeutical dose reduced risk of thrombotic events (total: RR 0.59, 95% CI: 0.48–0.73; subtotal of non-severe: RR 0.57, 95% CI: 0.39–0.84; Subtotal of severe: RR 0.61, 95% CI: 0.47–0.78), while risk of bleeding was increased (total: RR 1.98, 95% CI: 1.47–2.66; non-severe: RR 2.38, 95% CI: 1.56–3.62; severe: RR 1.63, 95% CI: 1.07–2.47). Study heterogeneity was found only in the analysis of effects of anticoagulants on risk of thrombotic events.

Conclusions: Anticoagulant therapy reduces all-cause mortality and risk of thrombosis in non-severe COVID-19 patients. Therapeutic dose of anticoagulant therapy can be considered in both non-severe and severe COVID-19 patients to reduce thrombosis, but may be associated with increased bleeding events.

Keywords: Anticoagulant therapy; coronavirus disease 2019 (COVID-19); all-cause mortality; bleeding events; thromboses

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Introduction

Coronavirus disease 2019 (COVID-19), triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dealt a great blow to global health. According to the relevant data of World Health Organization (WHO), as of April 2023, 764 million confirmed cases and 6.9 million deaths had been reported globally (1). In addition to common respiratory symptoms, COVID-19 patients are also accompanied by blood coagulation disorders, such as hypercoagulable state, extensive micro-thrombosis, consumptive thrombocytopenia and hyperfibrinolysis, which are particularly common in critically ill patients. It has become one of the main factors affecting the disease severity and prognosis of COVID-19 patients (2). Meanwhile, the variability of COVID-19 could have significant implications for controlling the pandemic and assessing the emergence of virus strains with different characteristics, including increased or decreased transmissibility and lethality (3). Given the rapid mutation rate of COVID-19, it underscores the necessity for personalized treatment approaches tailored to the specific characteristics of emerging variants.

For the treatment of COVID-19, in addition to oxygen therapy, anti-inflammatory, antiviral therapy and other symptomatic treatment, anticoagulation therapy has been underlined (4). After infection with COVID-19, massive inflammatory factors released during acute immune response cause damage to vascular endothelial cells, which subsequently result in imbalance of coagulation, anticoagulation, and fibrinolysis processes (5). In addition, the activation of neutrophils during inflammatory storm further promotes formation of micro-thrombosis that causes thrombotic complications in COVID-19 patients, such as acute pulmonary embolism, deep venous thrombosis, ischemic stroke, and myocardial infarction, this cytokine storm not only exacerbates systemic inflammation but also triggers a cascade of coagulation abnormalities, significantly increasing the risk of life-threatening thromboembolic events (6,7). Klok *et al.* (8) found that the cumulative incidence of thrombotic complications in patients with COVID-19 was high, where the incidence of acute pulmonary embolism reached 87%; in addition, patients with thrombotic complications were usually associated with a higher risk of all-cause death. However, latest guidelines from many countries and organizations are inconsistent in recommended patient subpopulation and optimal dose for anticoagulants therapy. According to the 10th edition of the

Highlight box

Key findings

- Anticoagulants reduces all-cause mortality and the risk of thrombotic events in non-severe coronavirus disease 2019 (COVID-19).
- Therapeutic doses of anticoagulants reduce thrombotic events in non-severe and severe COVID-19, while increasing bleeding events.

What is known and what is new?

- Blood coagulation dysfunction is a risk factor for adverse outcomes in patients with COVID-19, especially in severe cases. The evidence for the effects of anticoagulation therapy on prognosis of COVID-19 patients and its risk of causing bleeding events is accumulating.
- This study indicates that anticoagulant therapy reduces all-cause mortality and risk of thrombosis in non-severe COVID-19 patients. Therapeutic dose of anticoagulant therapy can be considered in both non-severe and severe COVID-19 patients to reduce thrombosis, but may be associated with increased bleeding events.

What is the implication, and what should change now?

- The severity of the patients should be considered when applying anticoagulant therapy for COVID-19, and attention should be paid to the efficacy and safety of medication duration and dosage.
- Our results are of significance for clinicians and also for clinical guidelines to guide precise use of anti-coagulants in patients with COVID-19.

"Diagnosis and Treatment Plan for COVID-19" of China, a therapeutic dose of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is suggested for moderate cases with high risk factors for severe disease and rapid disease progression, and for severe and critical cases (9). The COVID-19 treatment guidelines from the National Institutes of Health (NIH) recommends a prophylactic dose of heparin for patients who require intensive care unit (ICU)-level care, while in patients require low-flow oxygen, a therapeutic dose of heparin is recommended for those with elevated D-dimer levels and a prophylactic dose for those without (10). Similarly, a therapeutic dose of LMWH or UFH is recommended for non-critically hospitalized patients, but no preferred over prophylactic dose in critically ill patients according to International Society on Thrombosis and Haemostasis (ISTH) guidelines (11).

To date, the evidence for effects of various anticoagulants on COVID-19 mortality, thrombotic events, and bleeding is controversial (12-16). Previous meta-analyses showed inconsistent results on associations between therapeutic and prophylactic doses of heparin and reduced mortality in hospitalized COVID-19 patients, while therapeutic doses of anticoagulants were associated with increased risk of bleeding, noting the effect of disease severity (17-21). These meta-analyses mainly included observational studies, and most of the studies recruited patients without full-course vaccination during the first waves of the initial variants of SARS-CoV-2. More randomized controlled trials (RCTs) on anti-coagulation treatment among patients with COVID-19 have been published during subsequent phases of the pandemic, which permits a further estimation of anti-coagulants at different dose and in different subpopulations.

Here we conducted a comprehensive meta-analysis of high-quality RCTs to examine the efficacy and safety of therapeutic and prophylactic anticoagulant treatment in patients with severe or non-severe COVID-19. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-744/rc).

Methods

Information sources and search strategy (Appendix 1)

We searched PubMed, Embase databases, Cochrane Trials, Medline from December 2019 to April 2023. Each search query included the following terms: "anticoagulants", "heparin", "warfarin", "factor *Xa* inhibitors", "COVID-19", and "randomized controlled trial". After excluding duplicate records, two researchers (Y.Z. and Y.Y.) independently screened title and abstracts to exclude review, meta-analysis, case report, comment and apparently irrelevant studies. Then the full text was further screened by the two researchers independently.

(I) Type of study: RCTs.
(II) Population: adult patients (≥18 years old) with COVID-19 of any severity.
(III) Intervention and control:
  (i) Assess the effect of anticoagulants versus no anticoagulant. Intervention: any dose of anticoagulants, including heparin, warfarin, factor Xa inhibitors and so on; Control: placebo or no intervention or intervention without anticoagulants.
  (ii) Assess the anticoagulants at different doses: compared at least two dosing regimens of anticoagulants.
(IV) Outcomes: evaluated at least one of the following outcomes: all-cause mortality, bleeding events included major bleeding or nonmajor clinically relevant bleeding, or thrombosis included venous or arterial thromboembolism.

We excluded studies that had at least one of the following characteristics: observational study; no intervention or outcome information; does not meet the inclusion criteria. This meta-analysis was registered with number CRD42023428671.

We used "thrombosis" to define the composite end point of deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular events, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the study period (22). We defined "bleeding events" as fatal bleeding, a combination of bleeding types with symptoms or clinical manifestations at critical sites or organs.

Data extraction and management

The data extraction strategy was discussed and designed by the two authors to extract the following information from the published articles: (I) basic information: the first author and the year of publication; (II) demographic and clinical information: disease type, sample size, mean age, and sex ratio; (III) anticoagulants information: types and doses of anticoagulants used and measures taken in the study and control group; (IV) outcome information: the occurrence of all-cause mortality, bleeding events or thromboses. After the extraction strategy was determined, the two researchers

used a standardized table to conduct data extraction independently and verify the results.

Assessment of risk of bias

Based on the criteria recommended by the Cochrane Collaboration (23), two researchers independently assessed the risk of bias in the included studies. Each study was evaluated using the Cochrane Risk of Bias tool, which consists of several domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. For each domain, the risk of bias was categorized as low, unclear, or high, depending on the presence of methodological flaws or insufficient information. Discrepancies between the two researchers were resolved through discussion.

Evaluation of publication bias

R software (package "meta", version 4.3.0) was used to obtain the funnel plot of different outcomes. The publication bias was evaluated by testing the symmetry of the funnel plot. Based on the characteristics of outcomes, the test method was selected according to the heterogeneity. We evaluated heterogeneity by estimating the variance between studies (χ^2 test and I^2 statistic). The heterogeneity was considered not significant when $P>0.1$ or $I^2<50\%$. Harbord test or Peter test was used if studies had non-significant heterogeneity, otherwise AS-Thompson test was preferred (24). When $P>0.05$, there was no publication bias.

Rating of the quality of evidence

We evaluated strength of evidence for each outcome based on the system framework provided by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines, using the software GRADE Profiler Version 3.6.1 (25). The factors leading to downgrade quality of evidence included risk of bias, inconsistency, indirectness, imprecision, and publication bias. The factors leading to upgrade quality of evidence included large effect, possible confounding factors would change the effect and dose response relationship.

Statistical analysis

Review Manager Version 5.4 was used for statistical analysis. According to the purpose, we divided the included studies into two types: (I) assessing the use of anticoagulants versus no anticoagulants; and (II) assessing different dosage regiments of anticoagulants by using risk ratio (RR) and its corresponding 95% confidence intervals (CI). All the statistical scores were two-sided and the α level was stipulated as 0.05. and then the fixed effect model and the Mantel-Haenszel method was used (26,27).

Results

Overview of trials

The flowchart of study selection is shown in Figure S1. Our retrieval strategy identified 2,878 records; 1,552 articles remained after duplicate records were removed. Finally, 20 studies (14,15,22,28-44) were eligible (*Table 1*), of which 9 trials enrolled patients with severe COVID-19, while the others enrolled non-severe COVID-19. There were 20, 17, and 15 trials reported all-cause mortality, bleeding events, and thrombosis respectively. For the study arms and outcomes, 7 trials (28-34) enrolled 2,365 patients assessed efficacy between anticoagulants and placebo or standard care (one study included severe COVID-19 patients). Thirteen trials (14,15,22,35-44) enrolled 6,342 patients compared different types or regimens of anticoagulants (including 8 trials of severe COVID-19 patients).

Evaluation of risk of bias and publication bias

The summary in *Figure 1* shows that random sequence generation was carried out in all studies, but most of the studies were open-label. Based on the original study or the comprehensive evaluation of the whole experiment, there was confounding bias in some studies (Figure S2).

Peter test was used for test publication bias of all studies, except for the studies evaluating the effect of therapeutic doses of anticoagulants on thrombosis, where AS-Thompson was used due to heterogeneity ($P=0.05$, $I^2=45\%$). The results showed publication bias in the studies evaluating anticoagulants on the risk of thrombotic events receiving ($P=0.03$). No publication bias was found in other analyses (Figure S3). Funnel plots are shown in Figure S4.

Table 1 Baseline characteristics of the 20 selected studies on anticoagulant therapy in COVID-19 patients

Article	The severity of COVID-19	Sample size (study/control)	Mean age, years	Male, n (%)	Study group	Control group	Outcome
Ananworanich *et al.*, 2022 (28)	Non-severe	219/230	49	177 (39.4)	Rivaroxaban: 10 mg once daily, 21 days	–	All-cause mortality, bleeding events
Barco *et al.*, 2022 (29)	Non-severe	234/238	N/A	255 (54.0)	Enoxaparin: 40 mg once daily, 14 days	–	All-cause mortality, bleeding events, thromboses
Cools *et al.*, 2022 (30)	Non-severe	105/114	59	122 (55.7)	Enoxaparin: weighed <100 kg, 40 mg once daily; weighed ≥100 kg: 40 mg twice daily, 21 days	–	All-cause mortality, bleeding events, thromboses
DeNucci *et al.*, 2023 (31)	Non-severe	38/32	N/A	N/A	Heparin: 5,000 IU/0.25 mL being diluted with 4 mL of 0.9% saline, 6 hourly intervals	–	All-cause mortality
Ramacciotti *et al.*, 2022 (32)	Non-severe	159/159	N/A	191 (60.1)	Rivaroxaban: 10 mg once daily, 35 days	–	All-cause mortality, bleeding events, thromboses
Toshner *et al.*, 2022 (33)	Non-severe	402/399	N/A	472 (58.9)	Apixaban: 2.5 mg twice daily, 14 days	–	All-cause mortality
Barrett *et al.*, 2022 (34)	Severe	19/17	60	25 (69.4)	Tissue plasminogen activator + heparin: 90 mg tPA + 5,000 units UFH, 7 days	–	All-cause mortality, bleeding events
Connors *et al.*, 2021 (35)	Non-severe	143/135	N/A	132 (40.1)	Therapeutic-dose apixaban: 5 mg twice daily, 45 days	Prophylactic-dose apixaban: 2.5 mg twice daily, 45 days	All-cause mortality, bleeding events, thromboses
ATTACC Investigators *et al.*, 2021 (36)	Non-severe	1,180/1,046	N/A	1,310 (58.8)	Therapeutic-dose unfractionated or low-molecular-weight heparin: does N/A	Low or intermediate-dose thromboprophylaxis: N/A	All-cause mortality, bleeding events, thromboses
Lopes *et al.*, 2021 (15)	Non-severe	310/304	56.6	368 (59.9)	Therapeutic anticoagulation: rivaroxaban 20 mg or 15 mg daily or enoxaparin 1 mg/kg twice daily or UFH 0.3–0.7 IU/mL, 30 days	Prophylactic anticoagulation: standard in-hospital enoxaparin or UFH, 30 days	All-cause mortality, bleeding events, thromboses
Marcos-Jubilar *et al.*, 2022 (37)	Non-severe	33/32	N/A	41 (63.1)	Therapeutic-dose bemiparin: 115 IU/kg daily, 10 days	Prophylaxis-dose bemiparin: 3,500 IU daily, 10 days	All-cause mortality, bleeding events, thromboses

Table 1 (*continued*)

Table 1 (*continued*)

Article	The severity of COVID-19	Sample size (study/control)	Mean age, years	Male, n (%)	Group 1	Group 2	Outcome
Morici *et al.*, 2022 (38)	Non-severe	91/92	59	115 (62.8)	Enoxaparin 40 mg twice daily, 7 days	Enoxaparin 40 mg once daily, 6 days	All-cause mortality, bleeding events, thromboses
Bikdeli *et al.*, 2022 (39)	Severe	276/286	62	325 (57.8)	Intermediate-dose enoxaparin 1 mg/kg once daily, 30 days	Standard prophylactic-dose enoxaparin 40 mg once daily, 30 days	All-cause mortality, bleeding events, thromboses
REMAP-CAP Investigators *et al.*, 2021 (22)	Severe	534/564	N/A	772 (70.3)	Heparin: N/A	Low or intermediate-dose thromboprophylaxis: N/A	All-cause mortality, bleeding events, thromboses
Labbé *et al.*, 2023 (40)	Severe	110/114	N/A	155 (69.2)	Therapeutic anticoagulation: N/A	Standard-dose prophylactic anticoagulation: N/A	All-cause mortality, bleeding events, thromboses
Lemos *et al.*, 2020 (41)	Severe	10/10	N/A	16 (80.0)	Therapeutic enoxaparin: the dose according to age and adjusted daily by the creatinine clearance	Prophylactic anticoagulation: the dose according to age and adjusted daily by the creatinine clearance	All-cause mortality, bleeding events, thromboses
Oliynyk *et al.*, 2021 (42)	Severe	42/42	N/A	53 (63.1)	Therapeutic dose enoxaparin: 100 anti-Xa IU/kg once daily	Preventive dose enoxaparin: 50 anti-Xa IU/kg twice daily	All-cause mortality
Perepu *et al.*, 2021 (43)	Severe	87/86	64	99 (57.2)	Intermediate dose enoxaparin: BMI <30 kg/m^2: 1 mg/kg daily; BMI ≥30 kg/m^2: 0.5 mg/kg twice daily, 30 days	Standard prophylactic dose enoxaparin: BMI <30 kg/m^2, 40 mg daily; BMI ≥30 kg/m^2, 30 mg or 40 mg twice daily	All-cause mortality, bleeding events, thromboses
INSPIRATION Investigators *et al.*, 2021 (44)	Severe	276/286	N/A	325 (57.8)	Intermediate-dose enoxaparin: 1 mg/kg daily, 30 days	Standard prophylactic-dose enoxaparin: 40 mg daily, 30 days	All-cause mortality, bleeding events, thromboses
Spyropoulos *et al.*, 2021 (14)	Severe	129/124	66.7	136 (53.8)	Therapeutic-dose enoxaparin: CrCL ≥30 mL/min/1.73 m^2, 1 mg/kg twice daily; CrCL 15–29 mL/min/1.73 m^2, 0.5 mg/kg twice daily	Standard prophylactic or intermediate-dose heparins: heparin, up to 22,500 IU twice or thrice daily; enoxaparin: 30 or 40 mg once or twice daily; dalteparin: 2,500 IU or 5,000 IU daily	All-cause mortality, bleeding events, thromboses

Summary of subjects, interventions and outcomes of 20 articles. Seven trials enrolled 2,365 patients assessed efficacy between anticoagulants and placebo or standard care (one study included severe COVID-19 patients). Thirteen trials enrolled 6,342 patients compared different types or regimens of anticoagulants (including 8 trials of severe COVID-19 patients). tPA, tissue plasminogen activator; UFH, unfractionated heparin; BMI, body mass index; CrCL, creatinine clearance; COVID-19, coronavirus disease 2019; N/A, not applicable.

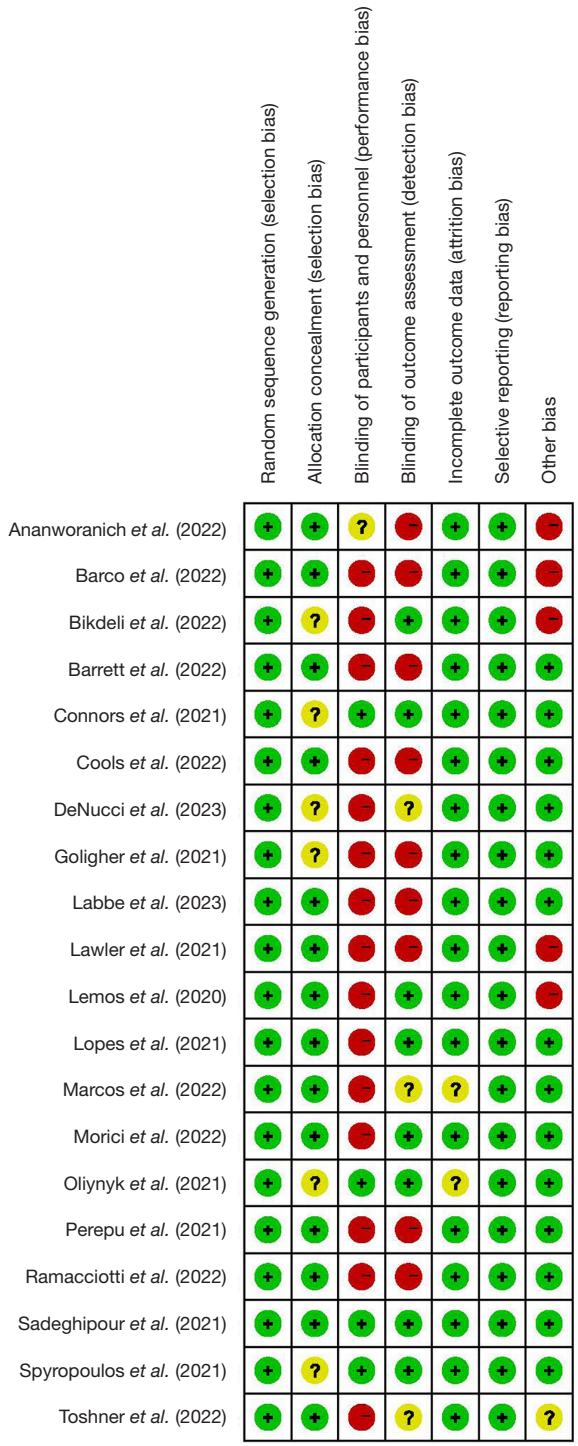


Figure 1 Summary of bias risk in 20 studies. "Green" means that the risk of bias is low, "red" means that the risk of bias is high, and "yellow" means that the risk of bias is unknown because it is not mentioned or cannot be determined.

Anticoagulant therapy versus standard care

Seven studies compared anti-coagulation therapy and standard care, of which 6 studies used factor *Xa* inhibitors (rivaroxaban or apixaban), enoxaparin, or heparin for intervention group. One study enrolled severe COVID-19 patients used a combination of tissue plasminogen activator and heparin. The detailed drug names and doses used in these RCTs are summarized in *Table 1*.

All-cause mortality

Seven studies involved 2,365 COVID-19 patients (1,176 with anticoagulants versus 1,189 with placebo or standard care). Results showed the use of anticoagulants reduced all-cause mortality in COVID-19 (RR 0.47, 95% CI: 0.29–0.76) with slight heterogeneity (P=0.33, I^2=13%). In subgroup analysis, the results of 6 studies on non-severe COVID-19 patients showed that it could reduce all-cause mortality (n=2,329, RR 0.46, 95% CI: 0.27–0.79, P=0.21, I^2=34%). An RCT with small sample enrolled severe COVID-19 patients showed no significant reduction in all-cause mortality in intervention group received heparin and tissue plasminogen activator (n=36, RR 0.51, 95% CI: 0.18–1.45) (*Figure 2A*).

Thrombotic events

Three studies involving 1,009 patients (498 with anticoagulants, 511 with placebo or standard care) compared the effects of anticoagulation on thrombotic events. A total of 27 thrombotic events were reported. The results showed that anticoagulants reduced the risk of thrombotic events in non-severe COVID-19 (n=1,009, RR 0.35, 95% CI: 0.15–0.83, P=0.90, I^2=0 for heterogeneity). None of the studies included severe COVID-19 patients (*Figure 2B*).

Bleeding events

Five studies involving 1,494 patients (736 with anticoagulants versus 758 with placebo or standard care) reported risk of bleeding events. A total of 15 bleeding events were reported. Anticoagulant therapy did not increase risk of bleeding events in the whole population and in severe and non-severe subgroup (total: n=1,494, RR 1.47, 95% CI: 0.54–4.00; severe: n=1,458, RR 1.34, 95% CI: 0.25–7.10; non-severe: n=36, RR 1.54, 95% CI: 0.44–5.37) when compared with standard care or placebo with no heterogeneity (*Figure 2C*).

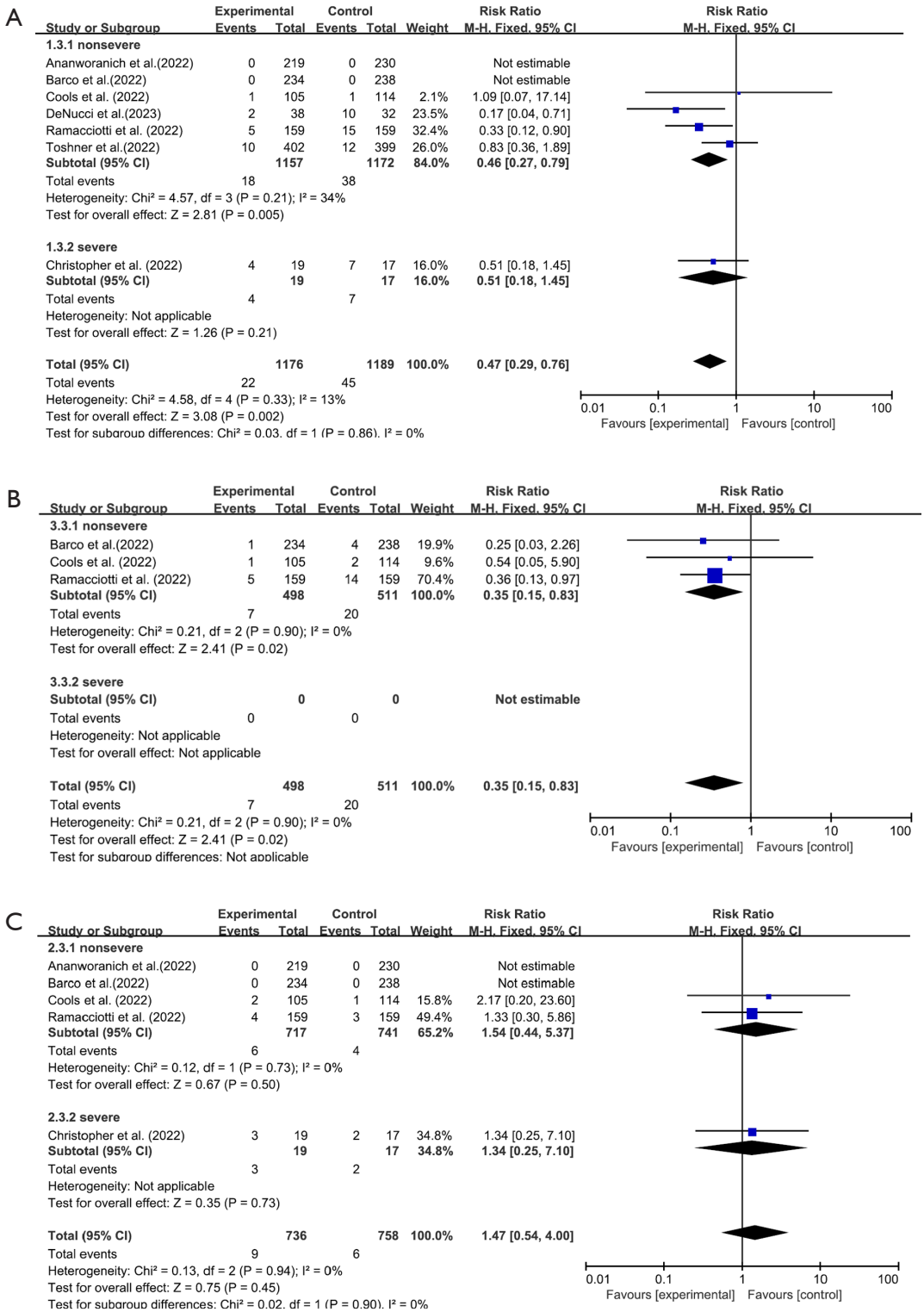


Figure 2 Mixed-effects models were used to analyze the effect of anticoagulants on total all-cause mortality (A), risk of thrombotic events (B), and risk of bleeding events (C) in the non-severe and severe COVID-19 subgroups. The solid vertical line of the forest plot represents RR =1 (invalid line). The short horizontal line for each study represents its confidence interval, the square on the short horizontal line represents its RR value and weight, and the diamond at the bottom of the graph represents the combined effect value. RR, risk ratio; CI, confidence interval; COVID-19, coronavirus disease 2019.

Prophylactic versus therapeutic doses of anticoagulation

Of the thirteen RCTs compared different anticoagulant doses, one RCT used apixaban and the others used heparin or LMWH, including enoxaparin and bemiparin. The specific doses of anticoagulants in intervention and control group of trials are summarized in *Table 1*.

All-cause mortality

Thirteen studies involving 6,342 patients with COVID-19 receiving therapeutic dose (n=3,221) and prophylactic dose (n=3,121) of anticoagulants reported 1,282 all-cause mortality. Therapeutic doses of anticoagulants had no effect on all-cause mortality compared with prophylactic doses (RR 1.01, 95% CI: 0.92–1.10, heterogeneity: P=0.37, I^2=8%). Subgroup analysis in non-severe (n=3,366, RR 1.03, 95% CI: 0.81–1.32; n=2,976, I^2=47%, P=0.13 for heterogeneity) and severe (RR 1.00, 95% CI: 0.91–1.11, I^2=0%, P=0.51 for heterogeneity) found no difference in all-cause mortality between the two dose groups (*Figure 3A*).

Thrombotic events

Twelve studies involving 6,249 patients (3,175 with therapeutic dose versus 3,074 with prophylactic dose) reported 344 thrombotic events. Therapeutic doses of anticoagulants produced 41% reduction in risk of thrombotic events (RR 0.59, 95% CI: 0.48–0.73, P=0.05, I^2=45% for heterogeneity). Similar effect was also found in non-severe (n=3,366, RR 0.57, 95% CI: 0.39–0.84, I^2=54%, P=0.09 for heterogeneity) and severe subgroups (n=2,883, RR 0.61, 95% CI: 0.47–0.78, I^2=50%, P=0.06 for heterogeneity) (*Figure 3B*).

Due to the high heterogeneity of the studies, we repeated the analysis using one-by-one elimination method. A significant reduction in heterogeneity was observed in the non-severe subgroup excluding Morici *et al.* (38), while the effects on thrombosis remained (n=3,183, RR 0.69, 95% CI: 0.46–1.04, P=0.31, I^2=15% for heterogeneity). In the subgroup of severe patients, heterogeneity was reduced when excluding the study by Perepu *et al.* (43). Elimination of the study did not change the beneficial effect (n=2,710, RR 0.56, 95% CI: 0.43–0.73, P=0.14, I^2=39% for heterogeneity) (*Figure 3C*, Figure S5).

Bleeding events

Twelve studies involving 6,252 patients (3,174 treated with therapeutic dose versus 3,078 treated with prophylactic dose) reported 190 bleeding events. Therapeutic dose showed approximately doubled risk of bleeding events (RR 1.98, 95% CI: 1.47–2.66, P=0.62, I^2=0 for heterogeneity). In both non-severe (n=3,367, RR 2.38, 95% CI: 1.56–3.62, I^2=33%, P=0.21 for heterogeneity) and severe subgroups (n=2,885, RR 1.63, 95% CI: 1.07–2.47, I^2=0%, P=0.89 for heterogeneity), therapeutic dose also had higher risk of bleeding events (*Figure 3*).

Evaluation of the quality of evidence using the Grade method

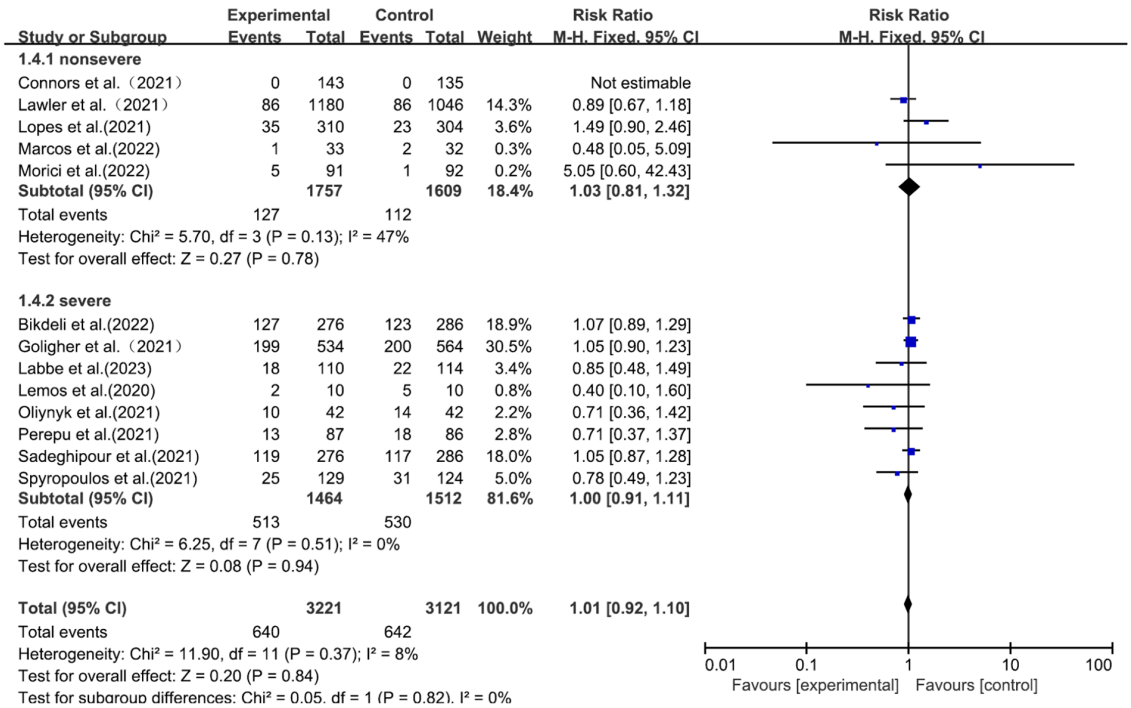
The grade of evidence for anticoagulants on all-cause mortality, thrombotic events and bleeding events was "High". The grade of evidence for the effect of different doses of anticoagulants on these outcomes was "Low", "Moderate", and "Low", respectively (Tables S1-S3).

Discussion

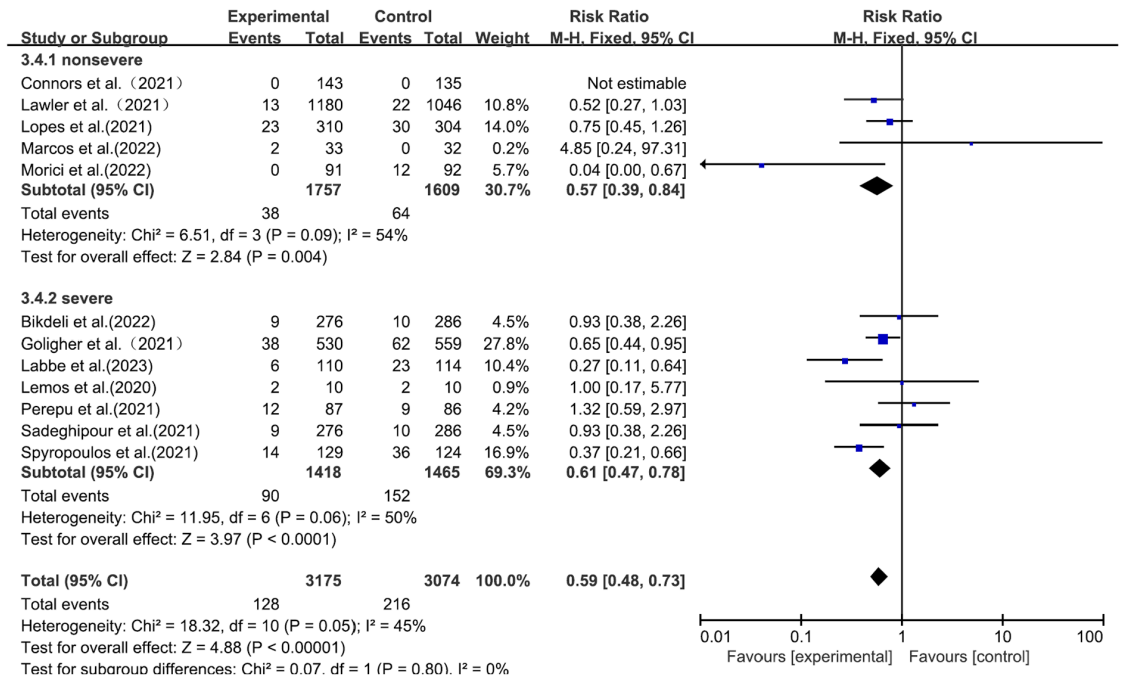
In this study, we evaluated the efficacy and safety of anticoagulant therapy in severe and non-severe patients with COVID-19 based on results from RCTs. Our results showed that high quality evidence suggesting that anticoagulants reduced all-cause mortality and risk of thrombotic events in non-severe COVID-19 patients, without significant increase in bleeding events. No difference was observed between therapeutic and prophylactic doses of anticoagulants on all-cause mortality both in non-severe and severe COVID-19 patients. However, therapeutic dose of anticoagulants reduced risk of thrombotic events while increasing bleeding events.

Previous studies suggested that anticoagulants may reduce mortality regardless of disease severity, but the results had been controversial. Zeng *et al.* (45) (13 observational studies) and Dai *et al.* (46) (12 observational studies) did not find an effect of anticoagulants. In contrast, Tunjungputri *et al.* (47) and Parisi *et al.* (19) included 32 (7 RCTs) and 29 (6 RCTs) studies to evaluate the correlation between anticoagulants and in-hospital death of COVID-19 patients through meta-analysis, they found that anticoagulants could reduce mortality with RR of 0.55 (95% CI: 0.43–0.66) and 0.30 (95% CI: 0.15–0.60), respectively. These results were inconsistent with our study. Another meta-analysis by Reis *et al.* (26), which included 13 RCTs, did not show an effect of anticoagulants in patients with COVID-19, mainly because the high heterogeneity of anticoagulant regimens reduced the certainty of the

A



B



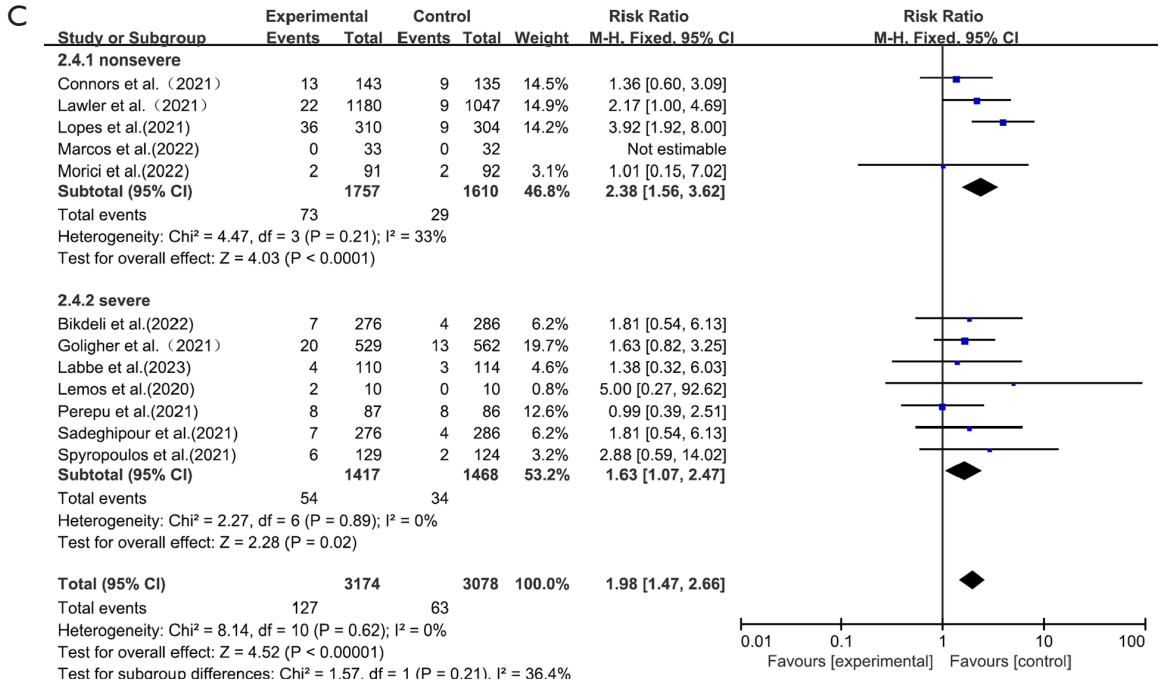


Figure 3 Mixed-effects models were used to analyze the effect of different doses of anticoagulants on total all-cause mortality (A), risk of thrombotic events (B), and risk of bleeding events (C) in the non-severe and severe COVID-19 subgroups. The solid vertical line of the forest plot represents RR =1 (invalid line). The short horizontal line for each study represents its confidence interval, the square on the short horizontal line represents its RR value and weight, and the diamond at the bottom of the graph represents the combined effect value. RR, risk ratio; CI, confidence interval; COVID-19, coronavirus disease 2019.

evidence. Above conclusions were inconsistent with ours, the type and number of studies included in the meta-analysis might influence the results.

The effects of anti-coagulants were compared with standard care mainly in non-severe patients in our study. We found no significant reduction in all-cause mortality in severe subgroup. This result is questionable due to the small sample size (1 RCT, 36 cases) and the combination of anticoagulants with plasminogen activator, which may additionally increase risk of bleeding. RCTs of severe pneumonia caused by other pathogens have demonstrated the effectiveness of anticoagulation in previous studies (48-51), so patients with severe COVID-19 may also benefit from anticoagulation. The study has shown that after receiving anticoagulant treatment, the incidence of chronic thromboembolic pulmonary hypertension in COVID-19 patients was comparable to that of non-COVID patients (52), which may offer further insights into the potential long-term benefits of anticoagulant treatment in COVID-19. However, because COVID-19 has a more prominent effect on coagulation and fibrinolysis than other pathogens (53,54), more RCTs are needed to evaluate the efficacy of anticoagulation in severely ill COVID-19 patients.

The COVID-19 treatment guidelines from NIH and ISTH both recommend prophylactic dose over therapeutic dose (10,11). In our analysis, the results showed no difference in all-cause mortality between prophylactic dose over therapeutic dose. Therapeutic dose decreased risk of thrombotic by 41%, but with 98% increase in risk of bleeding events, compared with prophylactic dose. In addition, we found that the risk of bleeding was more intensively increased in non-severe subgroup than severe subgroup (RR 2.38 *vs.* 1.63), while the risk of thrombotic events was comparable between the subgroups (RR severe 0.66 *vs.* non-severe 0.57). Therefore, the selection of anticoagulant dose should be combined with the severity of the disease. For non-severe patients, more precise evaluation for risk of thrombosis is required to determine the necessity of anti-coagulants, where level of D-dimers might be an alternative indicator (15).

This systematic review included comprehensive search

methodology and strict selection for high-quality RCTs, while most of the previous meta-analyses mainly included observational designs. The studies analyzed were from many regions such as America, Asia, and Africa, which ensures high population representation and good external scalability. In addition, we analyzed the effects of anticoagulation therapy in non-severe and severe subgroups, respectively, which provide essential information for clinical decision of prescription of anticoagulants.

There are some limitations in this study. First, majority of the included trials were open-label and might generate bias in the ascertainment of outcomes. More double-blind RCTs would substantiate the findings in the future. Second, the outcomes reported by the included RCTs were mostly short-term mortality or composite end points for thrombosis and bleeding, further studies with longer follow-up time and data of different sites of thrombosis or bleeding might be helpful for more targeted clinical recommendations. Third, there was large variation in sample size of the included trials, which affected stability of the results and may cause inconsistency. Forth, we included two studies from REMAP-CAP, ACTIV-4a, and ATTACC platform. There may be overlap in study population, which cannot be evaluated. Larger sample, multi-center and parallel group trials are needed to further determine the efficacy, safety, and optimal dose of anticoagulation in COVID-19.

Conclusions

Anticoagulants can reduce all-cause mortality and thrombosis in non-severe COVID-19. Therapeutic dose of anticoagulants reduced risk of thrombotic events, but not all-cause mortality compared with prophylactic dose while increasing bleeding events in both severe and non-severe patients.

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Footnote

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