



Efficacy of different anticoagulant doses for patients with COVID-19: a systematic review and network meta-analysis

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Abstract

Purpose As no reported randomized control trials (RCTs) directly compare the three administration doses of anticoagulants (prophylactic dose, treatment dose, and no treatment), the most recommended dose to be administered to patients with coronavirus disease 2019 (COVID-19) remains unclear. The purpose of this study was to examine the effects of anticoagulant doses administered to patients with COVID-19, using a network meta-analysis (NMA) including high-quality studies.

Methods All eligible trials from the Cochrane Central Register of Controlled Trials, MEDLINE, and Clinicaltrials.gov were included. We included RCTs and observational studies adjusted for covariates for patients aged ≥ 18 years and hospitalized due to objectively confirmed COVID-19. The main study outcome was mortality.

Results In patients with moderate COVID-19, the prophylactic (relative risk (RR) 0.64 [95% confidence interval (CI) 0.52–0.80]) and treatment dose (RR 0.57 [95% CI 0.45–0.72]) were associated with a lower risk of short-term mortality than that with no anticoagulant treatment. However, the prophylactic and treatment dose groups were not significantly different. The hierarchy for efficacy in reducing short-term mortality was treatment dose (P score 92.4) > prophylactic dose (57.6) > no treatment (0.0). In patients with severe COVID-19, due to the absence of trials with the no-treatment group, NMA could not be conducted. However, pairwise comparison did not show a significant difference between the prophylactic and treatment dose groups.

Conclusions Treatment and prophylactic doses of anticoagulants showed similar effects on mortality; however, the treatment dose is preferred over the prophylactic dose for patients with both moderate and severe COVID-19.

Trial registration number and registration dates PROSPERO (registration number: CRD42021245308, 05/21/2021).

Keywords Network meta-analysis · COVID-19 · Anticoagulation · Mortality · VTE · Bleeding

Introduction

One of the main pathologies of coronavirus disease 2019 (COVID-19) is thrombosis, associated with abnormal blood coagulation [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, damages the high-affinity type II alveolar epithelium and alveolar capillaries, resulting in the formation of fibrin and microthrombi [2, 3]. Furthermore, in COVID-19, the expression of tissue factors by alveolar resident macrophages infected with SARS-CoV-2 activates mainly the extrinsic system and increases the production of inflammatory cytokines, which stimulate the platelets and vascular endothelium, resulting in a thrombogenic mechanism [4].

These mechanisms of thrombus formation lead to deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with COVID-19, resulting in multiple organ failure,

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which is frequently observed in these patients [5]. Heparin is mainly used in anticoagulation therapy and assumed to have anticoagulant effects as well as anti-inflammatory and antiviral effects through neutralization of ribonucleic acid histones and cytokines [6]. Many studies have reported the efficacy of prophylactic and therapeutic doses of anticoagulants in patients with COVID-19 [7–9], but only a few high-quality randomized controlled trials (RCTs) have been conducted [10–14]. Therefore, when considering anticoagulation in COVID-19, physicians must refer to the results of systematic reviews and meta-analyses that integrate previously reported observational studies. However, the systematic reviews and meta-analyses reported so far are based on observational studies, the results of which have not been adjusted with covariates, resulting in several biases [15, 16]. Additionally, as there are no RCTs directly comparing the three administration doses (prophylactic dose, therapeutic dose, and no treatment), it is not clear which of the three anticoagulant doses is the most recommended for patients with COVID-19. Therefore, we conducted a systematic review and network meta-analysis (NMA) using only data from previously reported RCTs and observational studies, adjusted for appropriate confounders.

Methods

Protocol and registration

This systematic review and NMA was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) extension statements for reporting systematic reviews that incorporate NMA [17]. The review protocol was registered with PROSPERO (CRD42021245308).

Studies, participants, interventions/comparators, and outcomes

We included all observational studies and RCTs, regardless of the publication status (published, unpublished, or academic abstract) and language. The following types of RCTs were excluded: crossover, cluster randomized, and quasi-experimental trials.

This meta-analysis included studies involving patients aged ≥ 18 years hospitalized due to objectively confirmed COVID-19 and those that used multivariable analysis to determine the effect of anticoagulation on outcomes in case observational studies. We also included RCTs that compared different types of anticoagulation, including no treatment, in the NMA. Pregnant females and patients treated with extracorporeal membrane oxygenation were excluded. The outcomes of this study were short-term mortality (1) at the

end of the follow-up period for each trial within 30 days, (2) at intensive care unit (ICU) discharge, and (3) at hospital discharge; venous thromboembolism (VTE); major bleeding, requiring endoscopic or surgical interventions; or blood transfusion. The definition of anticoagulation (prophylactic dose, intermediate dose, treatment dose, and no treatment) is listed in Supplemental Table 1.

Data sources and search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, and Clinicaltrials.gov for eligible trials from inception until August 13, 2021. If data was missing in a study, we contacted the respective author. Details regarding the search strategy and searches are shown in Supplemental Table 2.

Study selection, data collection process, and data items

Two review authors (HO, TM) screened the titles, abstracts, and full texts during the first and second screening for relevant studies and extracted data from eligible studies. Any disagreement between the two reviewers was resolved via discussion.

Risk of bias within individual studies

The risk of bias for all relevant outcomes was independently assessed by two reviewers (HO, TM) using the Cochrane Risk of Bias tool 2.0 for RCT [18] and ROBINS-I [19], a tool for assessing risk of bias in non-randomized intervention studies. Details of the assessment of risk of bias were described in Supplemental Methods.

Definition of severity

Studies wherein more than 50% of the patients were admitted to the ICU or undergoing invasive mechanical ventilation were considered to have severe COVID-19, and other hospitalized patients with COVID-19 were considered to have a moderate form of the disease.

Categorization of anticoagulants in meta-analysis

The anticoagulants used in the included studies were divided into four categories (Supplemental Table 1): no treatment, prophylactic dose, intermediate dose, and treatment dose. However, the definition of intermediate dose in some studies was included in that of the prophylactic dose. To perform meta-analysis and NMA, the intermediate-dose group was included in the prophylactic dose group; the anticoagulants

were finally classified into three groups (no treatment, prophylactic dose, and treatment dose).

Statistical analyses

Details of statistical analyses for a pairwise meta-analysis are described in “Supplemental Methods”.

Network comparison meta-analysis

A network plot was constructed to illustrate the number of studies and patients included in this study. NMA was performed with a frequentist-based approach using a multivariate random-effects meta-analysis; the effect size was expressed as relative risks (RRs) with 95% confidence intervals (CIs). In addition to pairwise comparison meta-analysis, if the outcome was expressed as odds (OR) or hazard ratio (HR) rather than RR in the included studies, OR and HR were transformed to RR based on the approximation suggested by VanderWeele [20]. The NMA was performed using the R package “netmeta” 0.9-5 (version 3.5.1); the certainty of evidence of the network effect estimate was evaluated using the GRADE Working Group Approach [21]. The transitivity assumption underlying the NMA was evaluated by comparing the distribution of clinical and methodological variables, which could act as effect modifiers across treatment comparisons.

The approach to imprecision involved a comparison of the range of treatment effects included in the 95% CI with the range of equivalence. We assessed the imprecision of treatment effects for a clinically important RR (< 0.8 or > 1.25) in CI. To assess the amount of heterogeneity, we compared the posterior distribution of the estimated heterogeneity variance with its predictive distribution [22]. The concordance between assessments based on CI and prediction intervals, which do and do not capture heterogeneity, respectively, was used to assess the importance of heterogeneity. We assessed the heterogeneity of treatment effects for a clinically important risk ratio of < 0.8 or > 1.25 in prediction intervals. The inconsistency of the network model was estimated from inconsistency factors and their uncertainty; consistency was statistically evaluated using the design-by-treatment interaction test [23]. For comparisons informed only by direct evidence, there was no disagreement between evidence sources; thus, there was “no concern” for incoherence. If only indirect evidence was included, there was always “some concern.” “Major concern” was considered when the P value of the design-by-treatment interaction test was < 0.05 . Ranking plots (rankograms) were constructed using the probability that a given treatment had the highest event rate for each outcome. P -scores were used to set the hierarchy of treatments [24]. The P scores were calculated from the point estimate and standard error of the network

estimate. The P score of a treatment can be interpreted as the average degree of confidence that the treatment is superior to other treatments.

Results

Study selection

A comprehensive search of electronic databases up to August 13, 2021, yielded 1495 records (Fig. 1). Of the 1495 records, 26 met the inclusion and exclusion criteria for this systematic review. Of the 26 references included in this NMA, 5 were RCTs [10–14], and the remaining 21 were observational studies [7–9, 25–42].

Network plot and study characteristics

Among the 26 studies included in this NMA, 15 and 11 studies were classified as moderate and severe cases of COVID-19, respectively. Regarding the outcome of short-term mortality, nine studies, including patients with moderate COVID-19, compared the three dosage groups, and six and eight studies compared the treatment and prophylactic dose groups, respectively, with the no treatment group. Only six studies compared the treatment and prophylactic doses in patients with severe COVID-19, in terms of short-term mortality. The number of studies comparing VTE and major bleeding outcomes is described in Table 1 and Supplemental Table 3.

In patients with moderate COVID-19, at least one study compared no treatment, prophylactic dose, and treatment dose for all the three outcomes; the network plot with the number of studies and patients included is shown in Supplemental Fig. 1. However, for the outcome of short-term mortality and severe bleeding in patients with severe COVID-19, only the prophylactic and treatment doses were compared; a network plot could not be drawn.

Risk of bias within studies

The risk of bias in the RCTs was either low risk or some concerns; none of them were at high risk. In contrast, the risk of bias in observational studies was serious for bias due to confounding factors in many studies (Supplemental Figs. 2 and 3).

Network meta-analysis

The results of pairwise comparisons are shown in Supplemental Figs. 4, 5, 6, 7, 8, and 9 (short-term mortality, VTE, and major bleeding in patients with moderate and severe COVID-19).

Fig. 1 Preferred reporting items for systematic review and meta-analyses (PRISMA) flow diagram (search, inclusion, and exclusion)

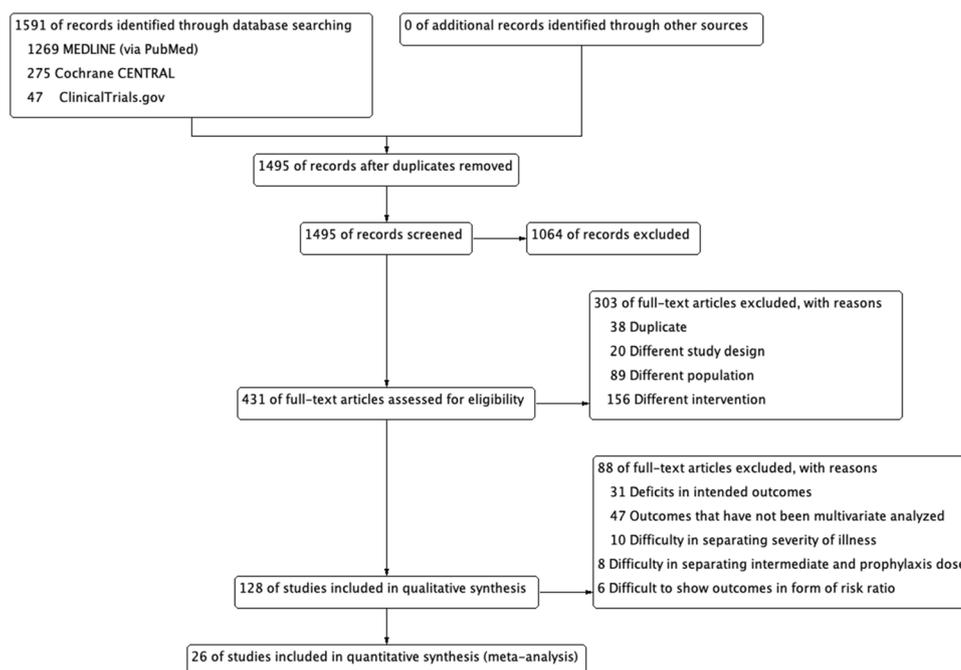


Table 1 The number of studies and patients included in each comparison

	Short-term mortality		VTE		Major bleeding	
	No. of studies	No. of patients	No. of studies	No. of patients	No. of studies	No. of patients
Moderate COVID-19						
Prophylactic dose vs. no treatment	8	15,764	1	1240	1	4297
Treatment dose vs. no treatment	6	6374	0	0	0	0
Treatment dose vs. prophylactic dose	9	11,907	4	5918	4	3722
Severe COVID-19						
Prophylactic dose vs. no treatment	0	0	1	142	0	0
Treatment dose vs. no treatment	0	0	0	0	0	0
Treatment dose vs. prophylactic dose	6	1955	4	1395	6	3884

COVID coronavirus infectious disease, VTE venous thromboembolism

Patients with moderate COVID-19

Short-term mortality

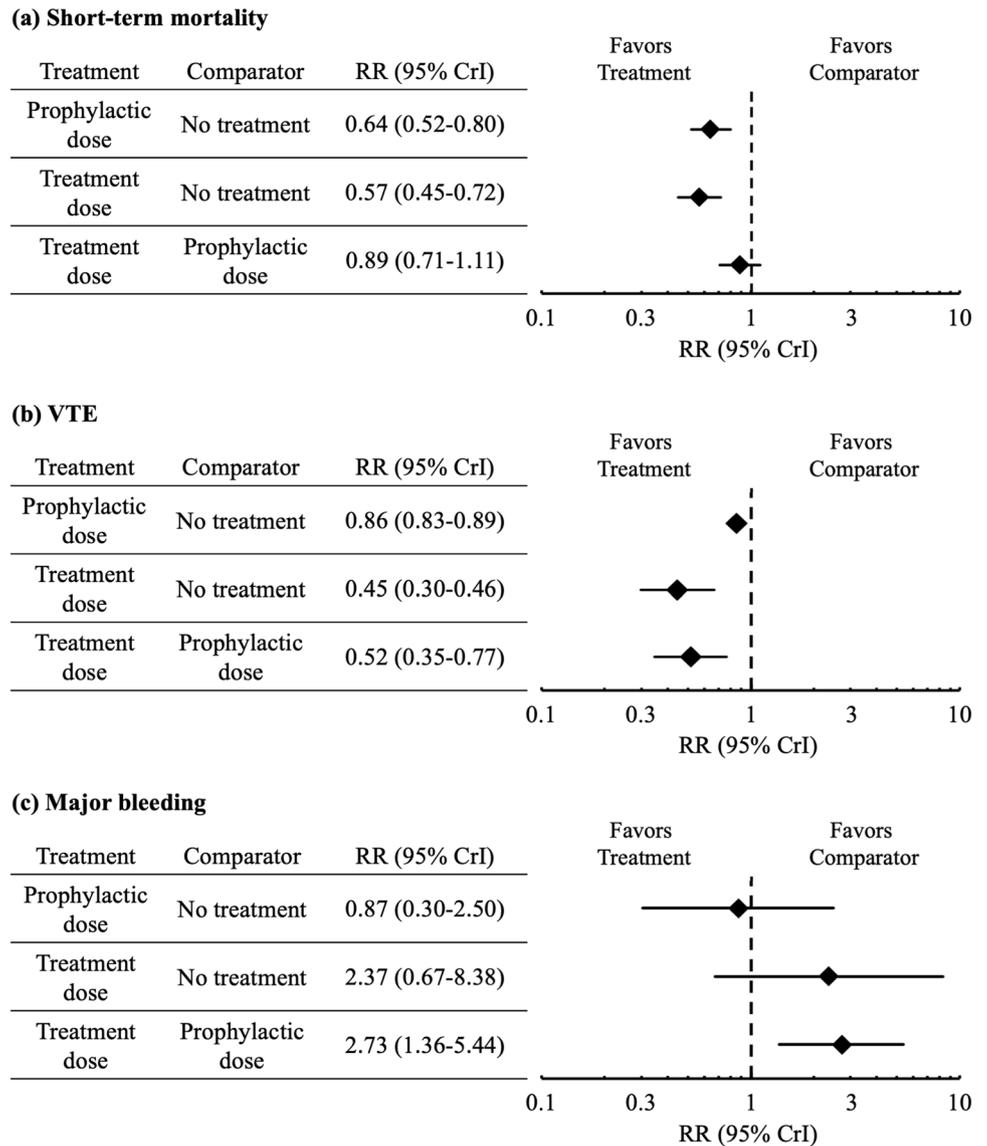
Twenty-three studies were included in the analysis of short-term mortality in patients with moderate COVID-19. The prophylactic dose [RR 0.64 (95% CI 0.52–0.80): low certainty] and treatment dose [RR 0.57 (95% CI 0.45–0.72): low certainty] were associated with a lower risk of short-term mortality (Fig. 2a) than that with no treatment. However, there was no significant difference in the association with short-term mortality between the prophylactic and treatment dose groups [RR, 0.89 (95% CI, 0.71–1.11): very low certainty]. Table 2a summarizes the estimates and certainty of the evidence of direct, indirect, and network

comparisons. Details of the NMA assessment of anticoagulants on short-term mortality in patients with moderate COVID-19 is shown in Supplemental Table 4.

GRADE system-based confidence in the RR of each comparison and short-term mortality, is shown in Supplemental Table 5a. The prediction interval required to assess heterogeneity in the network comparison is shown in Supplemental Fig. 10. Coherence was observed in the forest plots of short-term mortality in the direct, indirect, and network comparisons (Supplemental Fig. 11a). Inconsistency between direct and indirect RRs was not observed for any of the three comparisons (Supplemental Table 6; $P=0.70$).

The ranking analysis results (Table 3a) revealed that the hierarchy for efficacy in reducing short-term mortality was treatment dose (P score 92.4) > prophylactic dose (P score

Fig. 2 Forest plots of the network meta-analysis for the association of anticoagulation doses with short-term mortality, venous thromboembolism (VTE), and major bleeding in patients with moderate COVID-19. **a** Short-term mortality. **b** VTE. **c** Major bleeding



57.6) > no treatment (*P* score 0.0). Table 2a summarizes the NMA findings for short-term mortality.

VTE

Five studies were included in the analysis of patients with moderate COVID-19. The prophylactic dose [RR 0.86 (95% CI 0.83–0.89): very low certainty] and treatment dose [RR 0.45 [95% CI 0.30–0.46): low certainty] were associated with a lower risk of VTE than that with no treatment (Fig. 2b). Additionally, there was a significant difference in the association with VTE between the prophylactic and treatment dose groups [RR 0.52 (95% CI 0.35–0.77): very low certainty]. Table 2b summarizes the estimates and certainty of the evidence of direct, indirect, and network comparisons. Supplemental Table 7 summarizes the NMA

assessment of the estimates of anticoagulants on VTE in patients with moderate COVID-19.

GRADE system-based confidence in the RR of each comparison and VTE is shown in Supplemental Table 5b. The prediction interval required to assess heterogeneity in the network comparison is shown in Supplemental Fig. 10. Coherence was observed in the forest plots of short-term mortality in the direct, indirect, and network comparisons (Supplemental Fig. 11b). Inconsistency between direct and indirect RRs was not observed for any of the three comparisons (Supplemental Table 6).

The ranking analysis results (Table 3a) revealed that the hierarchy for efficacy in reducing VTE was treatment dose (*P* score 99.9) > prophylactic dose (*P* score 50.0) > no treatment (*P* score 0.0). Table 2b summarizes the findings of the NMA for VTE.

Table 2 Estimate and certainty of the evidence of direct, indirect, and network comparison (a) short-term mortality, (b) venous thromboembolism, (c) major bleeding in patients with moderate COVID-19

Comparison	Estimate of direct comparison (95% CI)	Certainly of the evidence of direct comparison	Estimate of indirect comparison (95% CI)	Certainly of the evidence of indirect comparison	Estimate of network comparison (95% CI)	Certainly of the evidence in network comparison
(a) Short-term mortality						
Prophylactic dose vs. no treatment	0.63 (0.49, 0.81)	⊕⊕○○ Low	0.68 (0.45, 1.03)	⊕○○○ Very Low	0.64 (0.52, 0.80)	⊕⊕○○ Low
Treatment dose vs. no treatment	0.59 (0.43, 0.80)	⊕⊕○○ Low	0.54 (0.37, 0.79)	⊕⊕○○ Low	0.57 (0.45, 0.72)	⊕⊕○○ Low
Treatment dose vs. prophylactic dose	0.87 (0.66, 1.14)	⊕○○○ Very Low	0.94 (0.63, 1.41)	⊕○○○ Very Low	0.88 (0.71, 1.11)	⊕○○○ Very Low
(b) VTE						
Prophylactic dose vs. no treatment	0.86 (0.83, 0.89)	⊕⊕⊕○ Moderate	–	–	0.86 (0.83, 0.89)	⊕⊕⊕○ Moderate
Treatment dose vs. no treatment	–	–	0.45 (0.30, 0.87)	⊕⊕⊕○ Moderate	0.45 (0.30, 0.87)	⊕⊕⊕○ Moderate
Treatment dose vs. prophylactic dose	0.52 (0.35, 0.78)	⊕⊕⊕○ Moderate	–	–	0.52 (0.35, 0.78)	⊕⊕⊕○ Moderate
(c) Major bleeding						
Prophylactic dose vs. no treatment	1.15 (0.40, 3.31)	⊕○○○ Very Low	–	–	1.15 (0.40, 3.31)	⊕○○○ Very Low
Treatment dose vs. no treatment	–	–	0.42 (0.12, 1.49)	⊕○○○ Very Low	0.42 (0.12, 1.49)	⊕○○○ Very Low
Treatment dose vs. prophylactic dose	2.73 (1.36, 5.44)	⊕⊕○○ Low	–	–	2.73 (1.36, 5.44)	⊕○○○ Very Low

CI confidence interval, COVID coronavirus infectious disease, VTE venous thromboembolism

Table 3 P-scores of anticoagulants for patients with (a) moderate and (b) severe COVID-19

Dose	Short-term mortality	VTE	Major bleeding
(a) Moderate COVID-19			
Treatment dose	92.4	99.9	4.6
Prophylactic dose	57.6	50.0	80.0
No treatment	0.0	0.0	65.4
(b) Severe COVID-19			
Treatment dose	96.2	99.7	0.0002
Prophylactic dose	3.8	49.1	99.998
No treatment	–	1.2	–

COVID coronavirus infectious disease, VTE venous thromboembolism

Major bleeding

Five studies were included in the analysis of major bleeding in patients with moderate COVID-19. The prophylactic dose [RR 0.87 (95% CI 0.30–2.50): very low certainty] and treatment dose [RR 2.37 (95% CI 0.67–8.38): very low certainty] were not associated with a lower risk of major bleeding than that with no treatment (Fig. 2c). However, there was no significant difference in the association with major bleeding between the prophylactic and treatment dose groups [RR 2.73 (95% CI 1.36–5.44): very low certainty]. Table 2c summarizes the estimates and certainty of the evidence of the direct, indirect, and network comparisons. Details of the assessment of the estimates from NMA of anticoagulants on major bleeding in patients with moderate COVID-19 are shown in Supplemental Table 8.

GRADE system-based confidence in the RR of each comparison and major bleeding is shown in Supplemental

Table 5c. The prediction interval required to assess heterogeneity in the network comparison is shown in Supplemental Fig. 10. Coherence was observed in the forest plots of short-term mortality in the direct, indirect, and network comparisons (Supplemental Fig. 11c). Inconsistency between direct and indirect RRs was not observed for any of the three comparisons, as shown in Supplemental Table 6.

Table 3a shows the ranking analysis results, which revealed that the hierarchy for efficacy in reducing major bleeding was prophylactic dose (*P* score 80.0) > no treatment (*P* score 65.4) > treatment dose (*P* score 4.6). Table 2c summarizes the findings of the NMA for major bleeding.

Patients with severe COVID-19

Short-term mortality

Six studies were included in the analysis of short-term mortality in patients with severe COVID-19. Since these studies did not include a no-treatment group, there was only a pairwise comparison between the prophylactic and treatment dose groups. The treatment dose [RR 0.77 (95% CI 0.58–1.03): low certainty] was not associated with a lower risk of short-term mortality than that observed with the prophylactic dose (Fig. 3a). Table 4a summarizes the estimates and certainty of evidence of the direct, indirect, and network comparisons. Details of the assessment of the estimates from the NMA of anticoagulants on short-term mortality in patients with severe COVID-19 are shown in Supplemental Table 9.

Fig. 3 Forest plots of the network meta-analysis for the association of anticoagulant doses with short-term mortality, venous thromboembolism (VTE), and major bleeding in patients with severe COVID-19. **a** Short-term mortality. **b** VTE. **c** Major bleeding

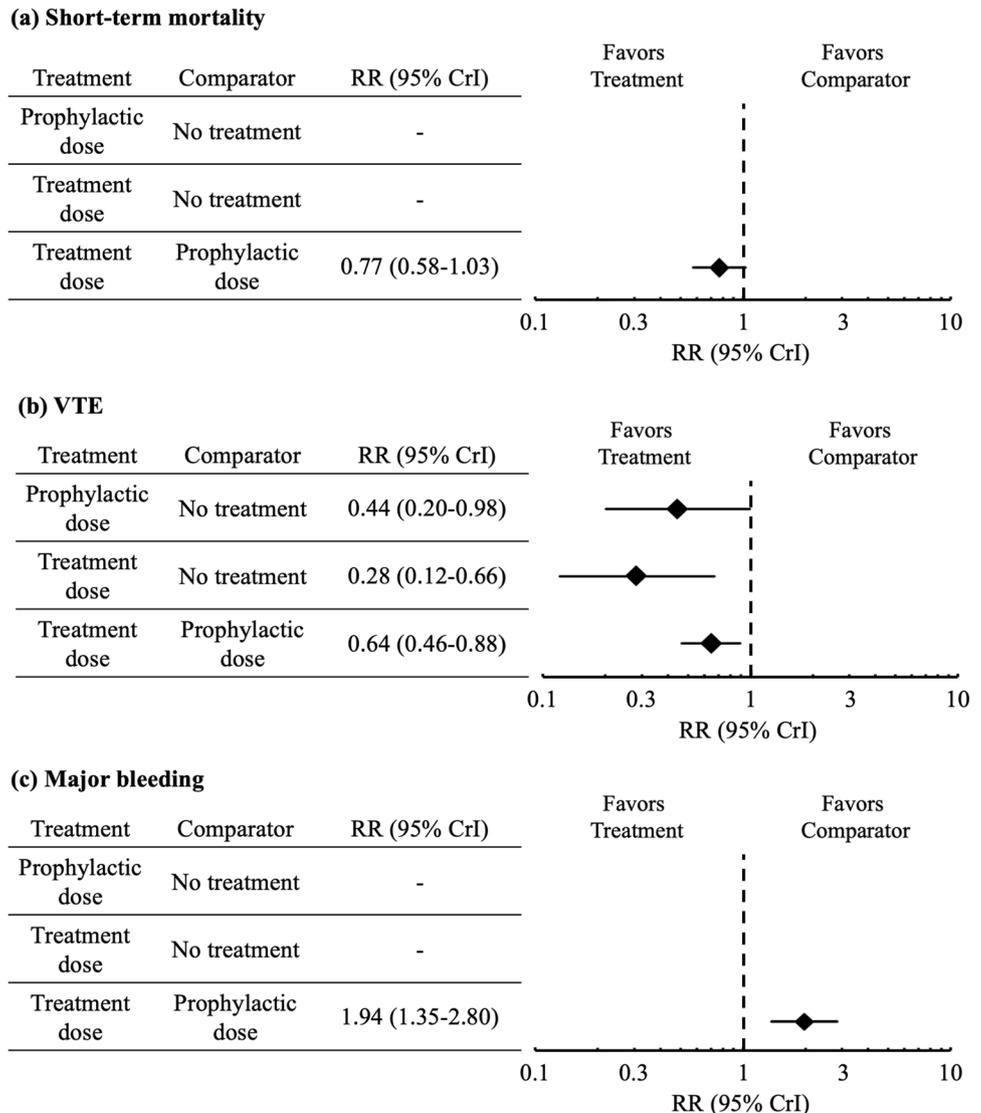


Table 4 Estimate and certainty of the evidence of direct, indirect, and network comparison (a) short-term mortality, (b) venous thromboembolism, (c) major bleeding in patients with severe COVID-19

Comparison	Estimate of direct comparison 95% CI)	Certainly of the evidence of direct comparison	Estimate of indirect comparison (95% CI)	Certainly of the evidence of indirect comparison	Estimate of network comparison (95% CI)	Certainly of the evidence in network comparison
(a) Short-term mortality						
Prophylactic dose vs. no treatment	–	–	–	–	–	–
Treatment dose vs. no treatment	–	–	–	–	–	–
Treatment dose vs. prophylactic dose	0.77 (0.58, 1.03)	⊕○○○ Very Low	–	–	0.77 (0.58, 1.03)	⊕○○○ Very Low
(b) VTE						
Prophylactic dose vs. no treatment	0.44 (0.20, 0.98)	⊕⊕⊕○ Moderate	–	–	0.44 (0.20, 0.98)	⊕⊕⊕○ Moderate
Treatment dose vs. no treatment	–	–	0.28 (0.12, 0.66)	⊕⊕⊕○ Moderate	0.28 (0.12, 0.66)	⊕⊕⊕○ Moderate
Treatment dose vs. prophylactic dose	0.64 (0.46, 0.88)	⊕⊕⊕○ Moderate	–	–	0.64 (0.46, 0.88)	⊕⊕⊕○ Moderate
(c) Major bleeding						
Prophylactic dose vs. no treatment	–	–	–	–	–	–
Treatment dose vs. no treatment	–	–	–	–	–	–
Treatment dose vs. prophylactic dose	1.94 (1.35, 2.80)	⊕⊕⊕○ Moderate	–	–	1.94 (1.35, 2.80)	⊕⊕⊕○ Moderate

CI confidence interval, COVID coronavirus infectious disease, VTE venous thromboembolism

Confidence in the RR of each comparison and short-term mortality, assessed by the GRADE system, is shown in Supplemental Table 10a.

The ranking analysis results (Table 3b) revealed that the hierarchy for efficacy in reducing short-term mortality was treatment dose (P score 96.2) > prophylactic dose (P score 3.8) > no treatment (P score N/A. Table 4a summarizes the findings of NMA for short-term mortality.

VTE

Five studies were included in the analysis of patients with severe COVID-19. Compared with no treatment, the prophylactic [RR 0.44 (95% CI 0.20–0.98): moderate] and treatment doses [RR 0.28 (95% CI 0.12–0.66): moderate] were associated with a lower risk of VTE (Fig. 3b). Additionally, there was a significant difference in the association with VTE between the prophylactic and treatment dose groups

[RR 0.64 (95% CI 0.46–0.88): moderate]. Table 4b summarizes the estimates and certainty of the evidence of direct, indirect, and network comparisons. Details of the assessment of the estimates from NMA of anticoagulants on VTE in severe COVID-19 patients are shown in Supplemental Table 11.

GRADE system-based confidence in the RR of each comparison and VTE is shown in Supplemental Table 10b. The prediction interval required to assess heterogeneity in the network comparison is shown in Supplemental Fig. 10. Incoherence was not observed, referring to forest plots of short-term mortality in the direct, indirect, and network comparisons (Supplemental Fig. 11d). Inconsistency between direct and indirect RRs was not observed for any of the three comparisons, as shown in Supplemental Table 6.

The ranking analysis results (Table 3b), revealed that the hierarchy for efficacy in reducing VTE was treatment dose (P score 99.7) > prophylactic dose (P score 49.1) > no

treatment (P score 1.2). Table 4b summarizes the findings of the NMA for VTE.

Major bleeding

Six studies were included in the analysis of major bleeding in patients with severe COVID-19. As these studies did not include a no treatment group, there was only a pairwise comparison between the prophylactic and the treatment dose groups. The treatment dose [RR 1.94 (95% CI 1.35–2.80): moderate] was associated with an increased risk of major bleeding compared to that observed with the prophylactic dose (Fig. 3c). Table 4c summarizes the estimates and certainty of evidence of the direct, indirect, and network comparisons. Details of the assessment of the estimates from the NMA of anticoagulants on major bleeding in patients with severe COVID-19 are shown in Supplemental Table 12.

GRADE system-based confidence in the RR of each comparison and major bleeding is shown in Supplemental Table 10c.

The ranking analysis results (Table 3b), revealed that the hierarchy for efficacy in reducing short-term mortality was prophylactic dose (P score 99.9) > treatment dose (P score 0.0002) > no treatment (P score N/A). Table 4c summarizes the findings of the NMA for major bleeding.

Discussion

In patients with moderate COVID-19, a significant reduction in short-term mortality and VTE was observed with either the prophylactic or treatment dose of anticoagulants, compared to that observed with no treatment, although the certainty of the evidence ranged from low to very low. In contrast, although there was no difference in the incidence of short-term mortality between the prophylactic and treatment dose groups, the incidence of VTE was significantly lower with the treatment dose than with the prophylactic dose. However, there was a significant increase in bleeding complications with the treatment dose than that with the prophylactic dose. NMA could not be performed, except for VTE, in patients with severe COVID-19, due to lack of studies comparing no treatment with the anticoagulation doses. Additionally, the treatment dose significantly reduced the incidence of VTE than did the prophylactic dose, although there was no significant difference in short-term mortality. However, there was a significant increase in bleeding complications with the treatment dose.

All recently reported RCTs on the types of anticoagulants for patients with COVID-19 compare the efficacy of the treatment dose and the prophylactic dose [10–14]. Therefore, the effects of no treatment depend on those of observational studies. Considering that RCTs using no treatment as

a control arm are unlikely to be conducted in the future, it is necessary to examine the effect of no anticoagulation treatment for patients with COVID-19 by comparing the three categories of anticoagulant doses based on the present data of high-quality observational studies adjusted for covariates. When the results of observational studies are included in a meta-analysis, it is necessary to integrate only the results adjusted for confounding factors to enhance the quality of meta-analysis evidence. Most of the meta-analyses reported so far have integrated the results of studies that have not been adjusted for confounding [15, 16]; few systematic review were conducted with the integration of the adjusted results from observational studies [43]. According to this study [43], there is a significant reduction in mortality in the prophylactic and treatment dose groups compared to that in the no treatment group. Although this result is in-line with our study, the previous study included patients with both moderate and severe COVID-19, and differences in the severity of COVID-19 were not considered in the study. The results of our study in patients with moderate COVID-19 were in-line with the results of the previous study [43]; the results of the present study could be more robustly analyzed by NMA, including RCTs comparing the treatment and prophylactic dose. However, in patients with severe COVID-19, there was only one observational study that included a no-treatment group, with VTE as the outcome [25]; the results for mortality and major bleeding could not be presented because the network could not be formed. In case of critically ill patients, treatment with anticoagulants is recommended even in patients without COVID-19 [44], and no treatment may not be an option.

Along with the basic prophylactic and treatment doses of anticoagulants used in COVID-19, the use of intermediate prophylactic doses has also been reported [26, 45]. Some studies have included the intermediate dose in the prophylactic dose group [10, 11]; for comparability, we did not include the intermediate dose in this study. Large-scale RCTs were published in 2021, comparing the effect of treatment and prophylactic doses in patients with moderate and severe COVID-19, which showed no significant difference in mortality or major bleeding between the two groups but a slightly significant decrease in VTE with the treatment dose [10, 11]. In patients with severe COVID-19, there was no significant difference between the effects of prophylactic and treatment doses on mortality, VTE, or bleeding. In contrast, a meta-analysis integrating RCTs, comparing prophylactic and treatment doses reported to date, including these two large RCTs [10, 11], has been reported [46]. There was no significant difference in the incidence of mortality between the two anticoagulant regimens in patients with both moderate and severe COVID-19, but there was a significant difference in VTE and bleeding only in patients with severe COVID-19. The NMA results showed that there

was no significant difference in the incidence of mortality, but there was a significant decrease in VTE with the treatment dose compared to the prophylactic dose in patients with both moderate and severe COVID-19. Furthermore, major bleeding increased in the treatment dose group compared to that in the prophylactic dose group in patients with both moderate and severe COVID-19. The difference in the results between the NMA in our study and previously reported NMAs, including only RCTs [46] may be due to the increased sample size of the NMA in this study, which was able to incorporate the results of high-quality observational studies.

Study limitations

This study has several limitations. First, the study did not conduct a meta-analysis of thrombosis risk stratification. Although anticoagulants may be effective in patients with elevated D-dimer levels [47], most of the studies included in this NMA did not stratify by D-dimer levels, and meta-analysis accounting for the risk of embolism risk could not be conducted. Second, although the NMA increased comparability by increasing the number of patients in the meta-analysis, it may still not be enough to meet the required sample size at which significant differences can be detected, particularly for patients with severe COVID-19. In particular, the treatment dose tended to reduce mortality more than that by the prophylactic dose, but the difference was not significant. The results may vary with increase in sample size. Third, there is a possibility that the grouping of anticoagulants in this NMA is not appropriate. The prophylactic dose group, which was the control group in a recently reported large RCT reported in 2020 [10, 11], included treatment with both intermediate and prophylactic doses. To accommodate majority of the previously reported studies in this NMA, we included the intermediate-dose group in the prophylactic group. In future, it would be preferable to include a separate intermediate-dose group in the analysis. Finally, the observational studies included in this analysis were adjusted for confounders for the outcome; however, it is possible that there was improper adjustment for confounding, resulting in distorted results. If the number of studies increases in future, it may be necessary to conduct a sensitivity analysis by further excluding low-quality studies.

Conclusion

Both prophylactic and treatment doses of anticoagulants reduced mortality and VTE in patients with moderate and severe COVID-19. Additionally, therapeutic doses of anticoagulants effect mortality in a manner similar to that observed with prophylactic doses; however, therapeutic

doses of anticoagulants significantly reduced VTE, although it increased major bleeding.

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Declarations

Conflict of interest The authors have no conflict of interests.

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