The Effect of Heparinoid as Systemic Prophylactic Anticoagulants on COVID-19 Patient Mortality and Its Safety Profiles: A Systematic Review and Meta-Analysis

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ABSTRACT

Coagulopathy is one of the complications of COVID-19 and is associated with a higher risk of mortality. However, evidence regarding the effectiveness and safety of anticoagulant therapy in various doses among COVID-19 patients is limited. This systematic review and meta-analysis aims to review and explore the effect of using heparinoids as a systemic anticoagulant at prophylactic doses on mortality in COVID-19 patients. Systematic searches were conducted of various databases (Pubmed, ScienceDirect, SpringerLink, Scopus, and ProQuest) covering the period 2019-2021. We assessed the quality of the articles using the STROBE checklist. Studies with a high risk of bias were excluded before pooled effect size was synthesized with 95% confidence intervals (CI) using random-effects models. From the 12 identified studies (N=8,968), six observational studies (N=7,176) were involved in the meta-analysis. The studies reviewed in the paper used a retrospective cohort design in various settings. The pooled effect size of mortality comparing prophylactic anticoagulant and no anticoagulant in three studies showed that there was an association between using prophylactic anticoagulant and a lower risk of in-hospital mortality (pooled OR= 0.47; 95% CI 0.19-0.76). A prophylactic dose of heparinoid anticoagulant was also associated with lower mortality (pooled OR= 0.51; 95% CI 0.21-0.82) and with lower bleeding events compared to intermediate-to-therapeutic dose anticoagulants. Administration of heparinoid anticoagulants at prophylactic doses was associated with reduced mortality risk in hospitalized COVID-19 patients. Due to the increased risk of bleeding with therapeutic doses, the use of prophylaxis anticoagulant is suggested in COVID-19 patients who are not critically ill.

Keywords: *anticoagulants; prophylaxis; covid-19; mortality; therapeutic safety*

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INTRODUCTION

In late December 2019, the highly infectious coronavirus rapidly spread worldwide and caused coronavirus disease 2019 (COVID-19). Severe respiratory illness can be induced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Zhu et al., 2020). Several studies have shown that SARS-CoV-2 virus infection is linked to substantial coagulation system activity, leading to prothrombotic conditions (Abou-Ismail et al. 2020; Bikdeli et al., 2020). Coagulopathy is one of the COVID-19 complications that can cause mortality (chiefly in patients with severe COVID-19) (Zhou et al., 2020). It can lead to vascular complications, especially venous thromboembolism (VTE), also known as Deep Vein Thromboembolism (DVT) or Pulmonary Embolism (PE), which have been widely reported to have significant implications for the clinical outcome of COVID-19 patients (Klok et al., 2020; Langer et al., 2020). A cohort study of 191 patients with COVID-19 reported that 50% of in-hospital deaths

were in individuals who had coagulopathy (Zhou et al., 2020). The occurrence of coagulopathy as part of the systemic inflammatory response syndrome is a frequent feature of severe COVID-19. Almost 20% – 50% of COVID-19 hospitalized patients had hematologic abnormalities in coagulation testing, and up to 71.4% of COVID-19 deaths are caused by Disseminated Intravascular Coagulopathy (DIC) (Gómez-Mesa et al, 2021). Prophylactic anticoagulant has been linked to a reduction in the incidence of thrombosis and death in patients; as a result, it can help prevent and decrease COVID-19 mortality (Langer et al., 2020). The use of Low Molecular Weight Heparin (LMWH) as an initial anticoagulant in COVID-19 patients has been shown to lower mortality by 48% after 7 days, and 37% after 28 days (Gómez-Mesa et al., 2021). Therefore, managing coagulopathy, including thromboembolic prophylaxis and anticoagulant treatment, is essential for optimizing specific therapy and reducing mortality. Guidelines from the International Society of Thrombosis Haemostasis (ISTH) recommend prophylactic systemic anticoagulant

using LMWH among all hospitalized patients, regardless of their coagulopathy status (Thachil et al., 2020). Heparin is recommended because, apart from being an anticoagulant, it theoretically acts as an anti-inflammatory and antiviral (Hippensteel et al., 2020). Systemic heparinoid anticoagulants, both Unfractionated Heparin (UFH) and LMWH, have been reported to be more beneficial than oral anticoagulants for use in COVID-19 hospitalized patients. There is a higher risk of interaction between antivirals or other drugs with oral anticoagulants, rather than with systemic anticoagulants (Weeks, Connors, & Connell, 2021).

Several clinical studies regarding the assessment of the effect of prophylactic anticoagulants are ongoing. Tang et al. (2020) reported that prophylactic anticoagulants had a greater survival rate than no anticoagulant in a severely ill patient COVID-19, elevated D-dimer values, and coagulopathy (Tang et al., 2020). Dosage increases may be necessary because the incidence of thrombosis is still high, despite prophylactic anticoagulants (Patel et al., 2020). However, in-hospital mortality in prophylactic and therapeutic doses has been reported to be not significantly different, while therapeutic doses have increased bleeding complications more than prophylactic doses (Klok et al., 2020; Nadkarni et al., 2020). Therefore, it can be seen that the role of anticoagulants at higher doses remains controversial today.

For this reason, we accomplish a systematic review of several previous studies with more recent time on the effect of the prophylactic use of systemic anticoagulants on all-cause mortality in hospitals. We assessed the safety of therapy related to bleeding to provide clinical insight and consider using systemic anticoagulants in the treatment of COVID-19 patients in the hospital. A previous meta-analysis has asessed the association of administration of anticoagulants in various types (heparinoids, vitamin K antagonists, direct anticoagulants, etc.) on all-cause mortality in hospitalized COVID-19 patients (Flumingnan et al., 2020). However, in our study, we focus on the systemic use of heparinoid anticoagulants, i.e. unfractionated heparin and low molecular weight heparin, and pentasaccharides (a synthetic and selective anticoagulant drug similar to low molecular weight heparin), as heparin is more recommended for inpatients due to safety reasons related to drug interactions (heparin does not interact with other drugs administered to hospitalized COVID-19 patients). We hope this systematic review and meta-analysis will help clinicians when considering the use of heparinoid as a systemic prophylactic anticoagulant for COVID-19 patients.

METHODS

The systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guideline (Figure 1) (Page et al., 2021).

Search Procedure

We organized a systematic review to analyze and synthesize some of the latest studies regarding assessment of the effect of prophylactic anticoagulants. A systematic search was performed of the online database of Pubmed, SpringerLink, ScienceDirect, Scopus, and ProQuest to discover compatible articles. The primary search was restricted to articles published during the COVID-19 pandemic from 2019 to 2021. The language was limited to English, and we used a specific key search term ("Anticoagulant" OR "LMWH" OR "Heparin") AND ("Prophylaxis" OR "Prophylactic" OR "Subtherapy") AND "COVID" AND "Mortality." Employing these data, a systematic review was conducted on the effect of heparinoid anticoagulant at prophylactic doses on mortality amongst COVID-19 patients. Duplicate studies were excluded from this meta-analysis. We used EndNote tools to help that process. Two investigators independently explored the literature, screened titles and abstracts, and carefully evaluated full text to analyze potentially eligible studies. In case of disagreement, it was consulted and solved by the consensus of all authors.

Criteria for Inclusion and Exclusion

The patients' inclusion and exclusion criteria were established by the Population, Intervention, Comparison, Outcomes (PICO) formula. The population comprised patients with confirmed COVID-19 with RT-qPCR results and those undergoing hospitalization (any patients COVID-19 as long they were hospitalized). Intervention referred to heparinoid anticoagulants at prophylactic doses (both LMWH and UFH), while the comparison was based on patients not being given systemic prophylactic anticoagulants or heparionoid anticoagulants at intermediate-to-therapeutic doses. The outcomes related to establishing the clinical outcome of using systemic anticoagulants in the prophylactic dose and their effect on patient mortality. On the other hand, the exclusion criteria were: (1) non-original articles (review articles); (2) non-clinical studies; (3) non-COVID-19 patients; (4) patients not hospitalized; and (5) no comparison made between heparinoid anticoagulants at prophylactic and therapeutic doses or between prophylactic heparinoid anticoagulant and without anticoagulant treatment.

Schemes and Search Results

5,186 articles were discovered based on an online database search using specified keywords, including

259 from Pubmed, 708 from SpringerLink, 1,058 from ScienceDirect, 1,248 from Scopus, and 1,903 from ProQuest. After screening the title, abstract and full-text articles, 12 articles were found to match the stipulated inclusion criteria, and the review process was resumed (included in qualitative synthesis). The search results schemes are summarized in Figure 1.

Data Extraction and Quality Assessment
The extracted data for characteristics comprised the author's name and year, inclusion/exclusion criteria, population characteristics (age, sex), setting, follow-up period, and the dosage of anticoagulant treatment. All-cause mortality was documented for the primary outcomes, and for the treatment, safety assessment was bleeding. We collected and provided results in the form of narration and a table.

The authors used the STROBE checklist to assess the quality and authenticity of the observational researches (von Elm et al., 2014). This checklist STROBE covers 22 quality assessment domains. Items with fully reported detailed data received a score of 1, items with partially reported detailed data received a score of 0.5, and items with not reported detailed data received a score of 0. As a result, each study had a STROBE score rate ranging from 0 to 22. Two authors reviewed each study independently and scored them according to the STROBE checklist. All of the disagreement was consulted and solved by the consensus of all authors.

Data Synthesis
We planned to initiate meta-analyses only where this was consequential, that is, if the treatments, subject, and the underlying clinical investigation were similar enough for
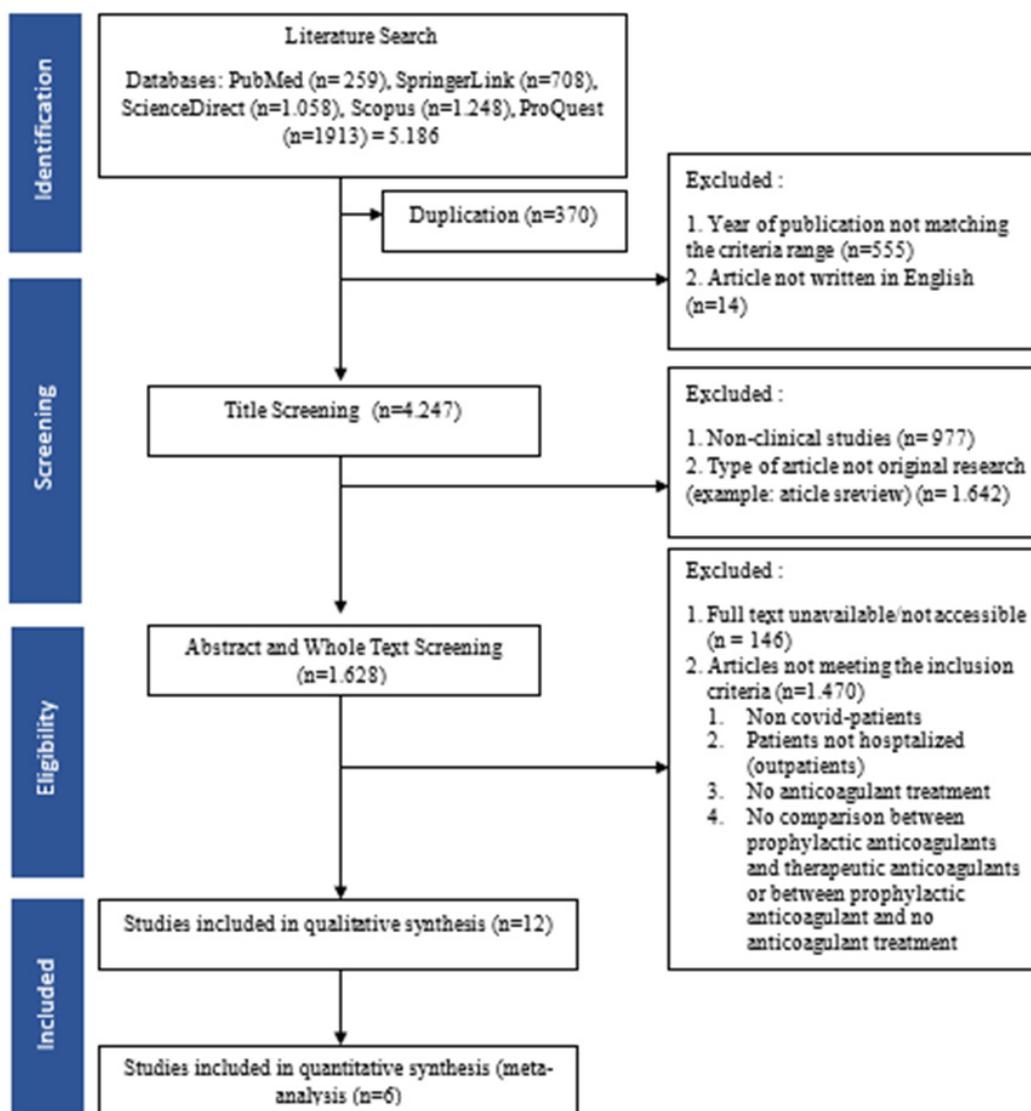

Figure 1. Literature Search Scheme with PRISMA flow

pooling to succeed. The comparative meta-analysis did not include results from studies with no outcome event, studies with poor methodological quality, or studies with a high risk of bias. The main meta-analysis included all studies that described adjusted estimates of the effects of prophylaxis anticoagulant on in-hospital mortality compared to no anticoagulant use in COVID-19 patients who were hospitalized. We also added to the meta-analysis the effect estimate of the thromboprophylaxis dosage compared to different dose (intermediate-to-therapeutic) anticoagulants.

When feasible, we conducted meta-analysis and forest plot using a Microsoft Excel Spreadsheet to calculate a summary effect size (Neyeloff, Fuchs, & Moreira, 2012). By entering step-by-step formulas, statistics such as Q and I^2 can be calculated using basic arithmetic operations. Heterogeneity was determined using the I^2 value, and low heterogeneity is defined as I^2 less than 50%, moderate heterogeneity as I^2 between 50% and 75%, and high heterogeneity as I^2 higher than 75%. A random-effect model would be used to report the result of heterogeneous data. If meta-analysis is not possible, for example if there are substantial clinical, methodological, or statistical heterogeneity across studies prevented the pooling of data, the results will be synthesized narratively.

RESULTS

Characteristics of the Included Studies
The review was compiled systematically to examine the development of the latest studies (2019-2021) regarding the impact of prophylactic systemic anticoagulants on COVID-19 patients' mortality through clinical reviews. A systematic method was utilized to help readers easier to understand the content and to avoid bias. Figure 1 shows the study selection process. In the initial literature search using predetermined keywords, we identified a total of 5,186 articles. After screening of the the title, abstract and full text, 12 articles (N=8,968 patients) were selected, which were considered suitable because they met the inclusion criteria set. Furthermore, only 6 studies (N=7,176 patients) continued for quantitative synthesis by meta-analysis. The other 6 studies had heterogeneous characteristics, different settings, and outcome units, so meta-analysis could not be carried out.

All of the researches are retrospective observational studies, and most are from European countries. All the studies were based on a hospital setting, including ICU and medical wards. Three studies focused on ICU patients (Helms et al., 2021; Jonmarker et al., 2020; Zheng et al., 2021). The nine other studies were based on an all-hospitalized patient setting, apart from Pesavento et al. (2020), who only used a medical ward patient

setting. In general, the study was conducted by collecting retrospective data on treatment, outcome, the severity of COVID-19 and comorbidities, obtained from patients' medical records, with hospital mortality defined as any death that occurred during hospitalization for whatever reason. In most of studies, the primary endpoint was "all-cause death" (Table 2).

In the 12 studies, the sample size ranged between 150 and 5000 patients; The smallest sample size was 152 patients in the study of Jonmarker et al. (2020) and the most sample used was 4,297 patients found in the study of Rentsch et al. (2021). All the studies involved adult men and women (≥18 years), with the majority being male (>55%), apart from the study of Shen et al. (2021), in which the percentage of men was lower (49.3%) than that of women (Shen et al., 2021) The median age for the study was 63, with the age range varying from 54 to 73.7 years (Table 1).

Table 1 displays the overall quality assessment score of the included studies using the STROBE guidelines (von Elm et al., 2014). The included studies' total scores varied from 17 to 21, indicating that the studies' quality ranged from moderate to high. In general, the quality of the studies in this systematic review is suitable based on the scores obtained. A summary of the overall STROBE checklist assessment is available in the Supplementary file.

Qualitative Review: Association of Anticoagulant Treatment with mortality

Anticoagulant prophylaxis versus non-use of anticoagulants
In the 12 studies that were reviewed, four studies compared prophylactic anticoagulant versus no anticoagulant with their related with a decreased risk of in-hospital mortality patients with COVID-19 (Albani et al., 2020; Rentsch et al., 2021; Shen et al., 2021; Zheng et al., 2021). Of these four studies, all used an LMWH systemic anticoagulant (enoxaparin) at a prophylactic dose of 40 mg daily (Albani et al., 2020; Shen et al., 2021) or 100 IU Axa/kg once per day (Zheng et al., 2021). In contrast, Rentsch et al. (2021) did not list the prophylactic dose of enoxaparin used (Albani et al., 2020) (Table 2). Overall, the four studies (N=6,375 patients) showed that prophylactic heparinoid anticoagulant (LMWH/enoxaparin) was related with decreased odds of mortality in patients with COVID-19: adjusted OR 0.53, 95% CI 0.40-0.70; 1,376 participants (Albani et al., 2020); adjusted HR 0.69, 95% CI 0.61-0.77; 4,297 participants (Rentsch et al., 2021); adjusted OR 0.20, 95% CI 0.09-0.46; 525 participants (Shen et al., 2021); unadjusted OR 0.60; 95% CI 0.32-1.01; 180 participants (Zheng et al., 2021).

Table 1. Characteristics of the included studies

Author	Year	Study Design	Country	COVID-19 Patient Type	N	Age	Male sex (%)	Quality Analysis Score
Jonmarker et al.	2020	Retrospective cohort study	Sweden	ICU Patients	152	Median (IQR): 61 (52-69)	125 (82.2)	19
Canola & Saylan	2020	Retrospective study	Turkey	All COVID-19 inpatients	154	Median (IQR): 55 (48-66)	96 (62.34)	18
Pesavento et al.	2020	Retrospective cohort study	Italy	Medical Wards Patients	324	Median (IQR): 71 (59-82)	181 (55.9)	17
Albani et al.	2020	Retrospective cohort study	Italy	All COVID-19 inpatients	1376	Median (IQR) : 68 (58-76)	379 (67.15)	20
Grandone et al.	2021	Retrospective cohort study	Italy	All COVID-19 inpatients	264	Median (IQR): 72 (58-80)	149 (56.4)	19
Mennuni et al.	2021	Retrospective cohort study	Italy	All COVID-19 inpatients	436	Mean (SD): 71.2 (15.6)	159 (55.4)	21
Shen et al.	2021	Retrospective cohort study	China	All COVID-19 inpatients	525	Median (IQR): 64 (52-72)	259 (49.3)	20
Martinelli et al.	2021	Retrospective cohort study	Italy	All COVID-19 inpatients	278	Median (IQR): 59 (49-67)	181 (65.1)	20
Zheng et al.	2021	Retrospective study	China	ICU Patients	180	Median (IQR): 64 (51-72)	113 (62.7)	19
Farrar et al.	2021	Retrospective cohort study	United State	All COVID-19 inpatients	803	Median (IQR): 54 (42-65)	446 (55.5)	19
Rentsch et al.	2021	Retrospective cohort study	United States	All COVID-19 inpatients	4297	Median (IQR): 68 (58-75)	4015 (93.4)	21
Helms et al.	2021	Bicenter cohort	France	ICU Patients	179	Median (IQR): 62 (51-70)	130 (72.6)	18

Abbreviations: ICU, Intensive Care Unit; IQR, Interquartile; SD, Standard Deviation; N, Number

Table 2. Anticoagulant prophylaxis in COVID-19 mortality

Author/ Study	Intervention	Comparison	Follow up treatment follow up	Outcome assessment	Mortality A vs. B (%)	OR/HR
(Jonmarker et al., 2020)	*Standard dose thromboprophylaxis* (for ICU patients): 2500–5000 IU dalteparin, or 2500–4500 IU tinzaparin.	*Medium-dose thromboprophylaxis*: >4500 IU tinzaparin or <175 IU per kg of body weight; dalteparin >5000 IU or <200 IU/kilogram of body weight *Thromboprophylactic therapy at the high dose* (for patients with thromboembolic disease) ≥175 IU per kg tinzaparin or ≥200 IU/kilogram dalteparin	Patients were monitored until they died or until the 28th day after being admitted to the ICU	The primary outcome was mortality at 28-day	Patients who received high: lower : medium-dose prophylactic = 13.5% : 25.0% : 38.8%	In comparison to low-dose thrombophylaxis, the HR of death for high dose was 0.33 (95% CI 0.13–0.87) and 0.88 (95%.CI 0.43–1.83) for medium dose.
(Canoglu & Saylan, 2020)	prophylactic LMWH : 0.5 mg/kg twice daily	therapeutic Dose: 1 mg/kg twice daily	Patients were tracked from the time they were admitted to the hospital until the earliest data on outcomes were available.	In-hospital mortality	44.9% (98 patients) with prophylactic dose of LMWH died 17.9% (10 patients) of 56 patients with therapeutic Dose of LMWH died	Prophylactic dose LMWH had a higher risk of mortality than the therapeutic dose (OR 6.495; 95% CI 2.393-17.627)
(Pesavento et al., 2020)	Prophylactic doses: UFH 5000 UI TID, 40 mg OD of LMWH, 2.5 mg daily Fondaparinux	Subtherapeutic doses: 1 mg/kg BID of or 0.5 mg/kg BID of LMWH, 7.5 mg of Fondaparinux	Patients were tracked from the time they were admitted to the hospital until the earliest data on outcomes were available.	Overall mortality	Overall mortality rates were 12.2 per 100 people per month in the prophylactic group and 20.1 per 100 in the (sub) therapeutic group.	Overall mortality rates were 12.2/100-person/months (95% CI 8.1-17.8) in the prophylactic dose group and 20.1/100 person/month (95% CI 11-33.6) Anticoagulant sub-therapeutic dosages are associated with an increased risk of all-cause death (HR 3.89;95% 1.90-7.90)

Table 2. continued

Author/ Study	Intervention	Comparison	Follow up treatment follow up	Outcome assessment	Mortality A vs. B (%)	OR/HR
(Albani et al., 2020)	Enoxaparin: 40-80 mg in daily	without enoxaparin	Patients were tracked until they died or were discharged from the hospital.	the primary outcome was hospital mortality	No Enoxaparin: 154 (25.5 %) Enoxaparin: 200 (25%)	Compared to no enoxaparin treatment, enoxaparin was related to decreased in-hospital all-cause mortality (OR 0.53, 95% CI 0.40-0.70, with an E-value of 2.08 (upper CI 1.66).
(Grandone et al., 2021)	Prophylactic LMWH: 40 mg once a day	Intermediate and therapeutic dose of LMWH: 40 mg every 12 hours or 60 mg once a day Therapeutic dose: 100 U/Kg every 12 hours	Patients were tracked until they died or were discharged from the hospital.	Primary outcome: all-cause mortality	prophylaxis with LMWH reduces by almost 70% mortality in patients with mild/moderate disease	LMWH usage in prophylactic dosage has lowered mortality considerably (OR 0.31, 95% CI 0.13-0.85)
(Mennuni et al., 2021)	Prophylactic enoxaparin dosage: 40 mg per day	Enoxaparin at higher dose: >40 mg per day	The outcome of all events (both primary and secondary) was assessed from events that occurred at admission and after the patient received LMWH treatment.	Primary outcome: all-cause mortality	All-cause death Prophylactic dose (A) 25.4% vs Higher dose (B) 26.9%	Prophylactic dose LMWH is related to decreased risk of all-cause mortality: Adjusted OR 0.847 (95% CI 0.400-1.792)

Table 2. continued

Author/ Study	Intervention	Comparison	Follow up treatment follow up	Outcome assessment	Mortality A vs. B (%)	OR/HR
(Shen et al., 2021)	Prophylactic LMWH: 40 mg subcutan once a day or 40 mg every 12 hours	Without LMWH	Patients were tracked until they died or were discharged from the hospital.	Primary outcome: in-hospital all-cause mortality	In-hospital mortality in mild/moderate patients was 0% (LMWH) vs 1.7% (Non LMWH), in severe patient 2.4% (LMWH) vs 18.8% (non LMWH), and in critically ill patient 37.31% (LMWH) vs 63.63% (non LMWH)	LMWH was linked to decreased all-cause death (Adjusted OR 0.2; 95% CI, 0.09-0.46) than non-LMWH. In subgroup analysis, LMWH was related with lower death in severe (adjusted OR 0.08, 95% CI 0.01-0.06) and critical patients (Adjusted OR 0.32; 95% CI 0.10-0.996)
(Martinelli et al., 2021)	The standard dose of prophylactic enoxaparin: 40 mg once a day, increased to 60 mg a day in obese patients	High dose of prophylactic enoxaparin : 0.7-1 mg/kg twice daily	Patients were followed until endpoint (cumulative incidence at 21 days) or discharge from hospital or change in antithrombotic therapy	Primary outcome: in-hospital all-cause mortality	Cumulative incidence of death/in-hospital mortality in standard dose 23.6%) vs. 40.2 % in the higher dose.	Patients receiving standard-dose enoxaparin had a decreased cumulative incidence of mortality at 21 days than the higher dose (adjusted HR 0.39; 95 percent CI 0.18-0.76)
(Zheng et al., 2021)	Thromboprophylactic enoxaparin: enoxaparin was given once a day at a dose of 100 IU Axa/ kg for at least 5 days For COVID-19 inpatients with VTE suspects:100 IU Axa/ kg twice a day	No thromboprophylaxis	Estimation of ICU survival rate: 30-day survival after admission to the ICU	Primary outcome: survival rate/ mortality in ICU patient	Non-survivor in thromboprophylaxis group 21.67% vs 27.78% (non-thromboprophylaxis)	The thromboprophylaxis group had a lower 30-day mortality rate than the no-thromboprophylaxis group (OR 0.60; 95% CI 0.32-1.01)

Table 2. continued

Author/ Study	Intervention	Comparison	Follow up treatment follow up	Outcome assessment	Mortality A vs. B (%)	OR/HR
(Farrar et al., 2021)	Per-protocol (received thromboprophylaxis): Standard prophylactic doses could be recommended initially, the dose could be escalated based on patient-specific characteristics (admitted to the Hospital consensus). Specific dose not mentioned in studies	Off-protocol (other than prophylactic regiment)	Patients were tracked until they died or were discharged from the hospital.	Secondary outcome: all-cause mortality, major bleeding	All-cause mortality in per-protocol was significantly lower (6.3%) than off-protocol (11.8%)	Mortality in off-protocol had a higher death risk than on-protocol (OR: 2.5; 95% CI 1.36-4.56)
(Rentsch et al., 2021)	Prophylactic anticoagulant	No anticoagulant	Patients were tracked from the time they were admitted to the hospital until the earliest data on outcomes were available.	The primary outcome was mortality at 30-days	The cumulative incidence of mortality at 30 days for individuals receiving prophylactic anticoagulant: agents those getting no anticoagulant was 14.3 percent vs.18.7 percent	Prophylactic anticoagulant was associated with a lower risk of inpatient mortality compared to no anticoagulant use (aHR 0.69; 95% CI 0,61-0,77)

Table 2. continued

Author/ Study	Intervention	Comparison	Follow up treatment follow up	Outcome assessment	Mortality A vs. B (%)	OR/HR
(Helms et al., 2021)	A prophylactic dose of enoxaparin: 60 mg twice daily in obese patients or UFH 200 IU/kg once a day in individuals with creatinine clearance (ClCr) less than 30 mL/min.	Therapeutic dose: 100 IU/kg twice day of LMWH based on body weight, not to exceed 10,000 IU/12 h or 500 IU/kg daily of UFH for individuals with creatinine clearance (ClCr) less than 30 mL/min	Follow-up for the most recently admitted patients lasted 80 days.	Mortality in ICU	Prophylactic: 20 (18.5 %) Therapeutic: 11 (15.5%)	Therapeutic dose treatment was associated with decreased ICU mortality than prophylactic dose treatment (OR 0.84; 95%CI 0.43-1.13)

Abbreviations: LMWH, Low Molecular Weight Heparin; UFH, Unfractionated Heparin; ICU, Intensive Care Unit; BMI, Body Mass Index; IU, International Unit; VTE, Venous Thromboembolism Event; IPTW, Inverse Probability of Treatment Weighted OD, Once Daily; BID, Bis In Die (Twice in Daily); TID, Ter In Die (Three times in daily); RBC, Red Blood Cell OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval; NR: Not Reported

Shen et al. (2021) conclude that the use of prophylactic LMWH is related to decreased all-cause mortality when compared to no LMWH use (adjusted OR 0.2, 95% CI 0.09-0.46; 525 participants) after adjusting for some covariates age, sex, severity classification and comorbidities (Shen et al., 2021). These results align with Albani et al. (2020) study of 1376 hospitalized patients, which reported that mortality in enoxaparin intervention was 25% and in the comparator group was 25.5%. Enoxaparin is related to a decreased in-hospital mortality rate correlated to no enoxaparin usage (OR 0.53, 95% CI 0.40-0.70) (Albani et al., 2020). Furthermore, the study conducted by Rentsch et al. (2021), with a larger sample size (4.297 patients), reported an association between the use of prophylactic anticoagulants and reduced death rates within 30 days when compared to no use of prophylactic anticoagulants after multivariate adjustment (aHR 0,69; 95% CI 0,61-0,77) (Rentsch et al., 2021). In addition, Zheng et al. (2021) compared the thromboprophylaxis effect of enoxaparin versus no thromboprophylaxis using an ICU patient setting and assessing 30-day survival after ICU admission. The group of patients who received thromboprophylaxis had a lower 30-day mortality rate than the group who did not get thromboprophylaxis (21.67% vs. 27.78%), thromboprophylaxis group had a lower mortality rate than the non-thromboprophylaxis group (unadjusted OR 0.60, 95% CI 0.32-1.01;180 participants) (Zheng et al., 2021).

Anticoagulant prophylaxis dose versus anticoagulant therapeutic dose

Eight studies compared the use of different doses of anticoagulants. (Canoglu & Saylan, 2020; Farrar et al., 2021; Grandone et al., 2021; Helms et al., 2021; Jonmarker et al., 2020; Martinelli et al., 2021; Mennuni et al., 2021; Pesavento et al., 2020). The definition of the anticoagulant dose, either standard prophylactic, intermediate or therapeutic, was varied in each study (Table 2). Most studies used prophylactic anticoagulant systemic therapy LMWH/enoxaparin. Some of the standard prophylactic doses reported included enoxaparin 40 mg once daily or 0.5 mg per kg twice a day, UFH 5000 IU, 2.5 mg of fondaparinux, 2500-5000 IU dalteparin, and 2500-4500 Itinzaparin (Table 2) (Albani et al., 2020; Canoglu & Saylan, 2020; Jonmarker et al., 2020; Pesavento et al., 2020; Shen et al., 2021).

Pesavento et al. (2020) reported the study in 324 hospitalized patients that "all-cause mortality" at standard dose prophylaxis (12.2 per 100 person/month; 95%CI 8.1-17.8) was lower than subtherapeutic doses (20.1 per 100 persons/month; 95% CI 11.0–33.8) (Pesavento et al., 2020). These results are supported by research from Grandone et al. (2021) in 264 hospitalized patients; they reported that prophylactic LMWH administration significantly reduced mortality when compared to higher doses (OR 0.31, 95% CI 0.13-0.85) (Grandone et al., 2021). Furthermore, Mennuni et al. (2021) reported that prophylactic doses of LMWH were associated with lower in-mortality risk when compared to greater dosages (Adjusted OR 0.847; 95% CI 0.400-1.792; 436 participants) (Mennuni et al., 2021). Martineli et al. (2021) also reported results that the standard prophylactic enoxaparin had a lower percentage of mortality incidence than the higher dose group (adjusted HR 0.39; 95%CI 0.18-0.76) (Martinelli et al., 2021). However, these results are in contrast to those of Canoglu & Saylan. (2020), who reported that prophylactic doses of LMWH had a higher risk of death than therapeutic doses (OR 6,495; 95 percent CI 2,393-17,627; 154 participants) (Canoglu & Saylan, 2020).

Jonmarker et al. (2020) and Helms et al. (2021) discovered that anticoagulant use was related to a survival advantage in ICU patients (Helms et al., 2021; Jonmarker et al., 2020). In Jonmarker et al. (2020) study reported that lower risk of ICU mortality was associated with higher dose thromboprophylaxis, both in high-dose thromboprophylaxis (HR 0.33; 95%CI 0.13–0.87) and medium-dose thromboprophylaxis (HR 0.88; 95% CI 0.43–1.83) compared to patients who received low-dose thromboprophylaxis (Jonmarker et al., 2020). These results are in line with Helms et al. (2021); their study of 179 ICU patients also reported that prophylactic anticoagulant administered to them resulted in higher mortality compared to therapeutic doses (18.5% vs.15.5%) (Helms et al., 2021).

In another study, Farrar et al. (2021) compared an on-protocol group (receiving prophylactic anticoagulant according to the protocol) and an off-protocol group, reporting a higher incidence of death in the latter than the former (OR: 2.5; 95 percent CI 1.36-4.56) in patients with D-dimer 1500ng/ml (Farrar et al., 2021).

Qualitative Review: The Anticoagulant Safety Profile in COVID-19 Patients

Safety assessment of the use of anticoagulants must also be considered when treating COVID-19 patients. Major bleeding events are one of the most frequent adverse effects of using systemic anticoagulants. Studies have reported various types of bleeding events (both major and non-major) in COVID-19 hospitalized patients receiving anticoagulant Treatment (Albani et al., 2020; Farrar et al., 2021; Grandone et al., 2021; Helms et al., 2021; Jonmarker et al., 2020; Martinelli et al., 2021; Mennuni et al., 2021; Pesavento et al., 2020; Rentsch et al., 2021; Shen et al., 2021); apart from two studies that did not assess such events (Canoglu & Saylan, 2020; Zheng et al., 2021).

A. Anticoagulation prophylaxis versus no anticoagulant
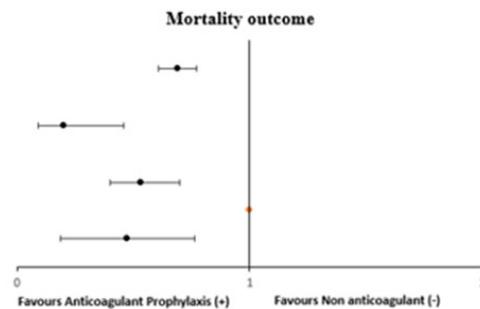
B. Prophylaxis dose anticoagulant versus Intermediate-to-therapeutic dose anticoagulation
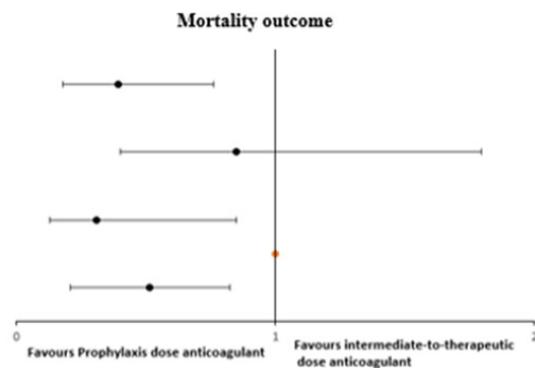

Figure 2. The Pooled Effect Size of mortality among COVID-19 patients in hospitalization with anticoagulant: (A) prophylaxis anticoagulant compared to patients without anticoagulant use, (B) Prophylaxis dose compared to intermediate-to-therapeutic dose anticoagulant, abbreviation: df, degree of freedom

Most studies report a higher incidence of bleeding with higher prophylactic doses of anticoagulants (intermediate/sub-therapeutic) than standard-dose prophylaxis (Grandone et al., 2021; Jonmarker et al., 2020; Martinelli et al., 2021; Mennuni et al., 2021; Pesavento et al., 2020). Pesavento et al. (2020) reported that the incidence of significant bleeding in the (sub) therapeutic dose group was higher (9.5%) than the standard prophylactic dose group (3.3%) (Pesavento et al., 2020). Jonmarker et al. (2020) also show similar results; the proportion of bleeding events in low dose prophylactic was lower (11.9%) than the higher dose prophylactic (14.6%), respectively (p=0.16) (Jonmarker et al., 2020). These results align with Mennuni et al. (2021); they reported a relatively low incidence of bleeding events in both groups. Major bleeding in the prophylaxis dose regimen was lower than the higher dose regimen, although the difference was insignificant (Mennuni et al., 2021). Furthermore, the research by Martinelli et al. (2021) also reported that major bleeding happened in 4/127 patients (3.1%) in higher dose enoxaparin, while no bleeding events were observed in the standard dose prophylactic group (Martinelli et al., 2021).

Several other studies reported bleeding events in the group receiving anticoagulants compared to those without anticoagulants (Albani et al., 2020; Farrar et al., 2021; Rentsch et al., 2021; Shen et al., 2021). Rentsch et al. (2021) report no risk of severe bleeding events; according to the results of a post hoc safety test, prophylaxis anticoagulant was not related to a higher incidence of bleeding with a need for transfusion when compared to non-anticoagulant use and bleeding events that required transfusion was rare (4.6%) (Rentsch et al., 2021). The study of Shen et al. (2021) also reported no statistical difference in the major bleeding event between individuals receiving LMWH anticoagulants (2 patients) and those who did not (1 patient) (Shen et al., 2021). Furthermore, the research conducted by Farrar et al. (2021) reported that the on-protocol group (receiving prophylactic therapy according to the protocol) had a considerably lower bleeding percentage than the off-protocol group (3.1% vs. 9.6%, p <0.001) (Farrar et al., 2021). Moreover, Albani et al. (2020) reported results, with its prophylactic enoxaparin group having a lower percentage of bleeding events than without enoxaparin (1.2% vs. 2.5%). However, the difference was not significant (Albani et al., 2020).

Quantitative: Meta-Analysis

Of the 12 research cited above, 3 were conducted in the ICU setting, while the other 9 were in the all-hospitalized setting (Helms et al., 2021; Jonmarker et al., 2020). Four of the 9 studies compared the use of prophylactic anticoagulants with non-anticoagulant usage (Albani et al., 2020; Farrar et al., 2021; Rentsch et al., 2021; Shen et al., 2021). The other 5 studies compared the use of standard prophylactic dose anticoagulants to higher dose (intermediate-to-therapeutic) anticoagulants (Canoglu & Saylan, 2020; Grandone et al., 2021; Martinelli et al., 2021; Mennuni et al., 2021; Pesavento et al., 2020).

Six observational studies with 7.176 hospitalized COVID-19 patients were involved in the quantitative meta-analysis with some considerations (Albani et al., 2020; Grandone et al., 2021; Martinelli et al., 2021; Mennuni et al., 2021; Rentsch et al., 2021; Shen et al., 2021). We performed to compare prophylactic anticoagulant to without anticoagulant used. Moreover, we independently considered the association of heparinoid anticoagulant at prophylactic doses with in-hospital mortality compared to intermediate-to-therapeutic dose anticoagulant. Based on the pooling effect size results, the prophylactic dose of anticoagulant significantly reduces the risk of mortality by 40-50%. Administration of prophylactic doses of anticoagulants decreased mortality compared with no anticoagulants and intermediate-to-therapeutic anticoagulants.

In comparison between prophylactic anticoagulant versus no anticoagulant use, we performed a combined meta-analysis of 3 studies. Farrar et al. (2021) should be excluded because of methodological differences, and the adjusted association of anticoagulants to the use of anticoagulants in-hospital mortality was not reported. By pooling the result of the three studies on all COVID-19 patients, the risk of in-hospital mortality was reduced by 53% (pooled OR 0.47; 95% CI 0.19-0.76; I^2= 0%) (Figure 2A). In addition, compared with intermediate-to-therapeutic dose anticoagulants, prophylactic dose anticoagulants were also associated with decreased risk of in-hospital mortality in COVID-19 patients hospitalized (pooled OR 0.51; 95% CI 0.21-0.82, I^2=12.4%, three studies, N= 978) (Figure 2B). Canoglu & Saylan (2020) and Pesavento et al. (2020) were excluded from the meta-analysis because they reported different methodological and the adjusted effect size.

In our study, we could not perform a pooling meta-analysis of 3 studies in the ICU setting. This is due to the absence of reported adjusted associations between anticoagulant use and in-hospital all-cause mortality in the study of Helms et al. and Zheng et al., which prevented the pooling of data, so data were synthesized narratively. The pooling meta-analysis could not be reported in assessing bleeding events because most studies did not report adjusted association anticoagulant use in bleeding events. They only reported the proportion of bleeding events in each study that prevented the pooling of data, and the data were synthesized narratively (in the Qualitative review section).

DISCUSSION

The present study's main finding is that using heparinoid as a prophylactic systemic anticoagulant was related to a substantially reduced risk of in-hospital mortality in COVID-19 patients who were hospitalized. For hospitalized COVID-19 patients, heparin was suggested in some treatment guidelines. Not only employed as an anticoagulant, but heparin can also be used as an antiviral and anti-inflammatory treatment. It can bind to the spike protein in SARS-CoV-2 and act as a viral inhibitor to break down infectiousness (Buijsers et al.,2020). Previous in vitro studies reported that the SARS-CoV-2 spike protein interacts with a greater affinity for heparan sulfate than the SARS-CoV or MERS-CoV spike protein (Kim et al., 2020). Tree et al. (2021) also reported that UFH had a solid antiviral effect, with IC50 values ranging 25-41 µg/ml, while LMWH had a lower inhibitory ability (IC50 values range 3.4-7.8 mg/ml) (Tree et al., 2021). Heparin's ability to inhibit SARS-CoV-2 infection was reported to depend on the concentration used. Heparin was shown to effectively inhibit 70% of SARS-CoV-2 in Vero cells at a concentration of 100 mg/ml (Mycroft-West et al., 2020). As an anti-inflammatory, heparin is reported to reduce NF-B signaling to the endothelium, resulting in decreased synthesis of pro-inflammatory cytokines such as TNF, IL6, and IL-1. This mechanism can be used to prevent the occurrence of cytokine storms, which can worsen the prognosis of COVID-19 patients (Hippensteel et al., 2020).

Heparin's potential as a commonly used anticoagulant has proven to be very strong (Albani et al., 2020; Farrar et al., 2021; Grandone et al., 2021; Mennuni et al., 2021; Rentsch et al., 2021; Shen et al., 2021). However, its optimal dose and the possibility of bleeding are of particular concern in its use. Research on the optimal dose of anticoagulants is still at the development stage. The risk of bleeding especially concerns the administration of anticoagulant therapy, and the occurrence of inpatient mortality is also associated with that of major bleeding after such therapy (Khan et al., 2020).

Most of the studies obtained results showing that prophylactic doses of anticoagulants reduced mortality (Grandone et al., 2021; Mennuni et al., 2021; Shen et al., 2021; Martinelli et al., 2021; Albani et al., 2020; Martinelli et al., 2021; Pesavento et al., 2020). Most of them are studied from Italy and Iran (study Pesavento et

al.). However, two studies from the other country (study Canouglu et al. from Turkey and study Helms et al. from France) produced different results regarding the effect of prophylactic and therapeutic doses on mortality rates (Canoglu & Saylan, 2020; Helms et al., 2021). Canoglu & Saylan (2020) and Helms et al. (2021) reported that prophylactic doses of LMWH posed a higher risk than therapeutic doses of LMWH. Canoglu & Saylan (2020) established 0.5 mg per kg every 12 hours as a prophylactic dose and 1 mg per kg every 12 hours as a therapeutic dose. On the other hand, Helms et al. (2021) used prophylactic doses of UFH 6000 IU twice a day subcutaneously in patients with obesity or UFH 200 IU per kg daily in creatinine clearance (ClCr) less than 30 mL/min. Meanwhile, the therapeutic dose of LMWH is 100 IU per kg every 12 hours subcutaneously according to body weight, with a maximum dose of 10,000 IU twice every 12 hours or UFH 500 IU per kilogram daily for individuals with creatinine clearance less than 30 mL/min (Helms et al., 2021). However, most studies report that prophylactic doses have a lower risk of mortality than therapeutic ones.

The standard prophylactic doses reported include enoxaparin 40 mg once daily (Grandone et al., 2021; Mennuni et al., 2021; Shen et al., 2021; Martinelli et al., 2021), enoxaparin 40 mg-80 once daily (Albani et al., 2020), enoxaparin 60 mg twice daily in obese patients (Martinelli et al., 2021); and 2.5 mg fondaparinux (Pesavento et al., 2020) (see Table 2). Apart from the definition of different doses, the differences in results may be influenced by other factors, including the essential characteristics of patients, their clinical condition, and standard of care in each country which are pretty diverse. While studies reviewed are ongoing, the standard of care for thromboprophylaxis use for COVID-19 patients was still very diverse. Although in April 2020, the International Society on Thrombosis and Haemostasis (ISTH) published recommendations for thromboprophylaxis with enoxaparin for COVID-19 patients, they specified the prophylactic dosage of LMWH as enoxaparin 4,000UI or 40 mg subcutaneously every 12 hours. The evidence for this recommendation is inadequate, and evidence of a mortality advantage in individuals treated with enoxaparin is insufficient, primarily since COVID-19 is a novel disease (Thachil et al., 2020). The results of the studies reviewed can illustrate that standard prophylactic doses are shown to reduce patient mortality further. The standard dose commonly used in the studies reviewed is LMWH (enoxaparin) 40 mg once daily.

The studies' results proved that treatment with a systemic prophylactic anticoagulant during hospital stay reduce themortality. Moreover, when prophylactic anticoagulants are taken on the general ward, the probability of ICU admission is reduced (Albani et al., 2020). Nevertheless, ICU patients need a high-dose anticoagulant because adjusted dosing is influenced by characteristic patients, including the risk of thromboembolic complications (Mennuni et al., 2021). There is a consensus reporting an increased risk of thromboembolic events in 20-43% of COVID-19 patients admitted to ICUs despite receiving prophylactic anticoagulants. The most common occurrences are pulmonary embolism and vein thrombosis of the lower extremities (Pluta, Cieniewicz, & Trzebicki, 2021). A high rate of thrombotic complications has been reported in patients with COVID-19 in the ICU. In a systematic screening report, many events of thrombotic complications would be missed by relying solely on clinical suspicion, so increasing the dose of thromboprophylactic anticoagulants in the ICU should be considered (Jenner et al., 2021).

In our meta-analysis, compared to the non-anticoagulant group, using a prophylactic dosage anticoagulant reduced the risk of in-hospital mortality by 53%; this might imply that using a prophylactic dose anticoagulant as a part of COVID-19 treatments may be advantageous. In addition, standard-dose prophylactic heparinoid anticoagulant was associated with decreased in-hospital mortality more than intermediate-to-therapeutic dose anticoagulant (pooled OR 0.51; 95% CI 0.21–0.82, $I2= 12.4\%$, three studies, N=978). In contrast to the results of Kamel et al. (2021), they discovered that the prophylactic anticoagulant dosage might be related to increased in-hospital mortality compared to therapeutic anticoagulant dose (RR 1.58, 95 % CI 1.34-1.87, three studies, N=963) (Kamel et al., 2021). These conflicting results are because of the wide variety of the study setting, populations, the patient clinical condition, type of healthcare, and therapeutic approaches. In addition, when studies reviewed are ongoing, the primary guidance has not yet established a standardized regimen for managing patients with COVID-19, so the standard of care for thromboprophylaxis use for COVID-19 patients in each study was still very diverse. To ascertain a more apparent optimal dose, it is necessary to standardize the definitions of standard, intermediate, and therapeutic doses and monitor patients' clinical conditions. The studies included had varying degrees of COVID-19 severity and suggested that heparinoid (especially LMWH) may benefit patients in the mild/moderate and severe ill COVID-19. These results are per the ISTH interim guidance, which recommends using LMWH in COVID-19 patients who have been hospitalized (Thachil et al., 2020). The American Society of Hematology (ASH) recently proposed using the prophylaxis anticoagulants doses rather than the intermediate and therapeutic anticoagulant doses in COVID-19 patients. However, this suggestion was based on evidence with a low degree of certainty (Cuker et al., 2021).

In addition to the dose, the adverse effects of anticoagulants were also investigated, as bleeding needs to be considered in the administration of systemic anticoagulants. Bleeding remains a major safety concern when anticoagulant is administered in COVID-19 patients with coagulation disorders. Bleeding events, as measured by our study was relatively rare in anticoagulant therapy. Our result reported no statistically significant difference in major bleeding events between individuals receiving prophylactic anticoagulants and those who did not. Billet et al. (2020) reported that a higher probability of transfusion was not associated with any anticoagulant regimen (both prophylactic and therapeutic dose anticoagulant) (Billett et al., 2020). Jonmarker et al. (2020) stated no signs of higher bleeding in the critically ill patients with COVID-19 who received higher doses of anticoagulants; this could be due to the characteristics of patients who may not bleed easily even with larger doses (Jonmarker et al., 2020). According to our study, the incidence of the bleeding event was relatively low in both standard prophylactic dose group and intermediate-to-therapeutic dosage, despite the proportion of bleeding event in standard prophylactic dose was lower than the higher dose. However, this risk does not lead to death, indicating that it can be safely used in this clinical setting. The studies reviewed to establish that there is potential for standard prophylactic anticoagulants to reduce mortality rates. However, their use needs to be made with intensive monitoring of therapy and side effects.

LIMITATIONS

This systematic review's strength is that it provides systematic information on the effects of heparinoids as systemic anticoagulants prophylactic on all-cause-death from COVID-19 in hospitals. It also evaluates the safety of therapy related to bleeding that has not previously been made. However, the study has limitations because the population engaged is limited (confined to a few regions and does not cover all countries and continents). All of the identified studies in our analysis were observational and retrospective; as a result, the association's strength could not be adequately determined. There are variances across studies that will lead to bias, such as differences in the setting (ICU and general wards), variations in the type of health facilities where the study took place; varying standards of care or protocol therapy in each country; and differences in dose and type of thromboprophylactic anticoagulant. Moreover, some studies did not report the exact prophylactic dose used. Furthermore, item scoring in quality assessment is still a subjective process that might lead to subjective bias. However, we have minimized subjective bias by independently assessing the study using the STROBE statement by two investigators, and the differences were resolved by discussion. The last, although the results of this meta-analysis were

significant, extrapolation of these data studies should be done with caution because no randomized controlled trials were conducted on the systemic anticoagulants or LMWH included in this meta-analysis. Further research, including RCTs on the effects of systemic or heparinoid anticoagulants in patients with COVID-19, might help to explain and confirm the findings.

CONCLUSION

We discovered that using heparinoid as systematic prophylactic anticoagulant was associated with decreased in-hospital mortality in COVID-19 patients without an increase in bleeding events, despite the severity of their disease. The reduction in mortality associated with prophylactic heparinoid anticoagulant may be related to the prevention of the coagulopathy that commonly occurs in the development of COVID-19. Administration of prophylactic anticoagulants at higher doses (intermediate-to-therapeutic dose anticoagulant) benefits increasing survival rates, especially for ICU patients. However, the risk of bleeding is higher than with standard doses. Therefore, standard-dose prophylactic heparinoid anticoagulant (40 mg once daily of LMWH) should be considered for patients with non-critical or other conditions without contraindications. RCT clinical trials are required to establish conclusions about the potential effectiveness of this therapy in COVID-19 patients.

DECLARATION

ACKNOWLEDGMENT

CONFLICT OF INTEREST

There are no conflicts of interest stated by the authors.

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