Title of the manuscript

Low molecular weight heparin is associated with better outcomes than unfractionated heparin for thromboprophylaxis in hospitalized COVID-19 patients: a meta-analysis

Running head: LMWH vs. UFH in COVID-19 thromboprophylaxis

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Abstract

Aims: This study aimed to compare the outcomes of administration of LMWH and UFH in hospitalized COVID-19 patients.

Methods and results: We systematically searched several databases and included observational studies or clinical trials that compared the outcomes of administration of LMWH and UFH in hospitalized COVID-19 patients. A total of nine studies comprising 9637 patients were included. Metanalysis showed that LMWH administration was associated with a lower in-hospital mortality, and 28/30-day mortality compared with UFH administration ([RR 0.44; 95%CI 0.32-0.61; I^2:87.9%] and [RR 0.45; 95%CI 0.24-0.86; I^2:78.4%], respectively). Patient with LMWH had shorter duration of hospital and ICU length of stay compared with UFH ([WMD -2.20; 95%CI -3.01 to -1.40; I^2:0%] and [WMD -1.41; 95%CI -2.20 to -0.63; I^2:0%], respectively). The risk of ICU admission or mechanical ventilation was lower in patients who received LMWH than those who received UFH (RR 0.67; 95%CI 0.55-0.81; I^2:67.3%). However, there was no difference in the incidence of bleeding with LMWH compared with UFH (RR 0.27; 95%CI 0.07-1.01; I^2:64.6%).

Conclusion: Our meta-analysis showed that administration of LMWH was associated with better outcomes compared with UFH in hospitalized COVID-19 patients. Prospective cohorts and RCTs are urgently needed in exploring the definitive effect of LMWH to provide direct high-certainty evidence.

Keywords: COVID-19, low molecular weight heparin, unfractionated heparin, thromboprophylaxis, mortality

PROSPERO registration number: CRD42021271977

Introduction

Coronavirus Disease 2019 (COVID-19) has spread rapidly around the world, causing high morbidity and mortality. Although respiratory symptoms dominate the clinical manifestations of COVID-19, some patients have an increased risk of thromboembolism due to coagulopathy complications [1,2]. Coagulopathy is one of the severe complications with a high incidence in COVID-19 patients [3,4]. Elevated coagulation parameters, including D-dimer, prothrombin time, and fibrinogen, are significantly associated with poor prognosis in patients with COVID-19 [5–7]. Activation of the coagulation pathway during the immunologic response to infection may also lead to overproduction of pro-inflammatory cytokines resulting in multiorgan damage [8].

Early reports demonstrated that anticoagulant thromboprophylaxis was associated with better outcomes in hospitalized COVID-19 patients [9,10]. Currently, several recommendations suggest venous thromboembolism (VTE) risk stratification and the use of prophylactic anticoagulants in all hospitalized COVID-19 patients. In contrast, evidence is insufficient to support thromboprophylaxis with therapeutic doses of anticoagulants [11–13]. A meta-analysis showed that anticoagulant regimens in therapeutic and prophylactic doses decreased in-hospital mortality in COVID-19 patients. However, prophylactic doses may be preferred due to the increased risk of bleeding in therapeutic doses of anticoagulants [14]. Another study also demonstrated a similar result that intermediate-to-therapeutic doses of anticoagulant increased mortality and major bleeding compared with prophylactic doses [15]. These findings demonstrate a favourable profile of the efficacy and safety of prophylactic anticoagulation in hospitalized COVID-19 patients.

Although the choice of prophylactic dosing regimen for anticoagulation becomes more evident, the type of anticoagulant itself remains a question. A spectrum of anticoagulants

such as low molecular weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux, and direct oral anticoagulant (DOAC) are used in the management of COVID-19 patients, with UFH and LMWH as the most commonly prescribed [16]. A recent study in matched cohorts of COVID-19 patients showed that enoxaparin was associated with lower 28-day mortality compared with UFH [17]. The plausible superiority of LMWH over UFH was also demonstrated in previous studies with different settings [18–21]. Therefore, the objective of our systematic review and meta-analysis was to compare the outcomes of administration of LMWH and UFH in hospitalized COVID-19 patients.

Methods

Eligibility criteria

Our analysis included studies that assessed the outcomes of LMWH and UFH administration in hospitalized COVID-19 adult patients. We included articles published in English and studies with extractable data for analysis. Other publications such as case reports, case series, review articles, editorial, and in-vitro or animal studies were excluded. Studies on special populations such as pregnant women and children were also excluded.

Search strategy and study selection

We conducted a systematic literature search based on the search strategy presented in table S1 and finalized the search on June 21, 2022. We searched several databases, including PubMed, ScienceDirect, Scopus, Cochrane Library, and Europe PMC. After eliminating duplication from the literature search, three authors (E.P.B.M., I.M., Y.A.) independently screened the title and abstract. Eligibility criteria were used to assess the full article. The differences in article assessment were solved by a discussion with the senior authors (M.Y.A., B.P.S.). The research protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42021271977). This research followed the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

Data collection process

Piloted data extraction forms were used independently by three authors (D.A.R., A.Y., L.H.A.) to extract data that consisted of the author, publication date, design of the study, population studied, intervention administered, comparison or control, and outcomes. The comparative intervention assessed in this study was the administration of LMWH and UFH

in hospitalized COVID-19 patients. The primary outcome was in-hospital mortality, while the additional outcomes were 28 or 30-day mortality, intensive care unit (ICU) admission or mechanical ventilation, hospital and ICU length of stay, and bleeding complication. We presented categorical and continuous variables as mean ± standard deviation (SD) and frequency (percentage), respectively.

Quality assessment

All included observational studies were assessed by three authors (E.P.B.M., I.M., Y.A.) independently using the Newcastle-Ottawa score (NOS), which consisted of three domains that include sample selection, comparability of cohorts, and outcomes assessment [23]. The risk of bias for the included randomized controlled trial (RCT) was assessed by the modified Cochrane Collaboration tool [24]. Discussions were held to resolve the discrepancies between authors.

Data analysis

Data used for each included study was following univariate analysis in the original study. Pooled effect estimates of the outcomes were reported as weighted mean difference (WMD) and relative risk (RR) for the continuous and dichotomous variables, respectively. Data with low heterogeneity (I2 statistic <50% or P-value > 0.1) were pooled with a fixed-effects model, and data with high heterogeneity (I2 statistic >50% or P-value < 0.1) were pooled with a random-effects model. P-value < 0.05 was determined as statistical significance. We used funnel-plot analysis to assess the publication bias qualitatively. Egger's test and Harbord's test were used to further assessed publication bias on continuous and dichotomous variables, respectively. Furthermore, univariate meta-regression analysis was performed to determine which factors contributed to in-hospital mortality in hospitalized

COVID-19 patients receiving two different anticoagulants of LMWH and UFH. Meta-analysis was performed on Stata software V.14.0 (College Station).

Results

Study characteristics

We identified 6243 articles from the initial database search and 2 articles through additional search and then removed the duplicates. The remaining 4701 articles were screened for titles and abstracts, which resulted in 4406 articles being excluded. Using the eligibility criteria, 295 potential full-text articles were assessed. Finally, seven observational studies [10,17,25–29] and two RCTs [30,31] consisting of 9637 patients were included for qualitative analysis and meta-analysis (Figure 1 and Table 1).

Outcome comparison between low molecular weight heparin and unfractionated heparin

The meta-analysis showed that LMWH administration was associated with a lower risk of in-hospital mortality compared with UFH administration (relative risk, RR 0.44; 95%CI 0.32-0.61; I^2:87.9%] and [RR 0.45; 95%CI 0.24-0.86; I^2:78.4%], respectively). These effects were comparable to the pooled risk estimates comprising both doses of therapeutic and prophylactic (RR 0.28; 95% CI 0.17-0.47; P = 0.001; I^2:86.3%) and solely prophylactic doses (RR 0.63; 95% CI 0.46-0.87; P = 0.005; I^2:65.6%) (Figure 2). Similar results were obtained at one month follow-up that LMWH was associated with a lower 28 or 30-day mortality compared with UFH (RR 0.45; 95%CI 0.24-0.86; I^2:78.4%) (Figure 2).

Patient who received therapeutic and prophylactic doses of LMWH had shorter duration of hospital and ICU length of stay than those who received therapeutic and prophylactic doses of UFH ([weighted mean difference, WMD -2.20; 95% CI -3.01 to -1.40; P < 0.001; I^2:0%] and [WMD -1.41; 95% CI -2.20 to -0.63; P < 0.001; I^2:0%], respectively) (Figure 3). The risk of ICU

admission or mechanical ventilation was also lower in patients who received LMWH than those who received UFH (RR 0.67; 95% CI 0.55-0.81; P = 0.016; I^2:67.3%) (Figure 4). However, there was no significant difference in the incidence of bleeding with LMWH compared with UFH (RR 0.27; 95% CI 0.07-1.01; P = 0.052; I^2:64.6%) (Figure S1).

Meta-regression

Univariate meta-regression analysis revealed that the association of two different anticoagulants of LMWH and UFH with in-hospital mortality in COVID-19 patients was not significantly affected by age (P = 0.463), gender (P = 0.954), hypertension (P = 0.571), diabetes (P = 0.912), chronic kidney disease (P = 0.597), cancer (P = 0.802), chronic lung disease (P = 0.604), heart failure (P = 0.812), coronary artery disease (P = 0.901), asthma (P = 0.742), chronic liver disease (P = 0.358), and stroke and cerebrovascular disease (P = 0.398) (Table S2).

Quality assessment and publication bias

Seven studies were of high quality based on the assessment using NOS (Table S3), and two RCTs showed a low overall risk of bias based on the assessment using the modified Cochrane Collaboration tool (Table S4). The asymmetric shape was obtained by visually qualitative assessment of the funnel plot for analysis on the variables of anticoagulant selection and mortality, indicating possible publication bias (Figure S2). However, quantitative analysis using regression-based Harbord's test showed no small-study effects (p = 0.876) on the same variable.

GRADE assessment

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment indicated a very low certainty of the evidence for the effect of LWMH and UFH on in-hospital mortality, 28 or 30-day mortality, hospital and ICU length of stay, ICU

admission or mechanical ventilation, and bleeding complication. The certainty of the evidence was very low for both subgroups of in-hospital mortality outcomes (Table S5).

Discussion

This systematic review and meta-analysis highlighted the differences in outcomes associated with the administration of LMWH and UFH in hospitalized COVID-19 patients. We found that LMWH was associated with lower in-hospital mortality, 28 or 30-day mortality, ICU admission or mechanical ventilation, and bleeding complication compared with UFH. Furthermore, we found that patients treated with LMWH had a shorter hospital and ICU length of stay compared with those treated with UFH.

A spectrum of anticoagulants, including LMWH, UFH, fondaparinux, and DOAC, are used in managing COVID-19 patients, both as prophylactic and therapeutic approaches [32]. Heparin is one of the anticoagulant drugs that is classified according to its molecular weight and is used for the prophylaxis and treatment of venous and arterial thrombosis [33]. Only UFH comprising at least 18 saccharide sequences can bind to and potentiates the activity of antithrombin. However, UFH of any length comprising a unique pentasaccharide sequence can inhibit the action of factor Xa [34]. This pentasaccharide sequence is used as the basis for developing LMWH. In contrast to UFH, whose main action is mediated by thrombin inhibition, LMWH inhibits prothrombin activation more robustly through its action on factor Xa [35].

The proposed mechanisms of using heparin in COVID-19 management are to block uncontrolled blood clotting and prevent VTE and other thrombotic events [36]. However, heparin may also offer anti-inflammatory, anti-complement activity, anti-viral, and immunomodulatory effects, which may benefit beyond the anticoagulation in COVID-19 [37].

Recent studies have also reported that soluble heparin inhibited viral entry by competing with heparan sulfate proteoglycan for binding to the SARS-CoV-2 spike protein, thereby inhibiting the attachment of SARS-CoV-2 to the surface of the host cell [38].

The superiority of LMWH over UFH has been demonstrated by previous studies in several different settings. A meta-analysis of RCTs comparing the administration of anticoagulant thromboprophylaxis in intensive care patients showed that LMWH was associated with a better net clinical benefit and a lower risk of DVT compared with UFH [21]. Another meta-analysis of patients with VTE showed that compared with UFH, initial treatment with LMWH was more effective in preventing recurrent VTE, reduced the risk of bleeding, and was associated with a lower mortality rate at follow-up [19]. In addition, the incidence of pulmonary embolism and proximal DVT was lower in patients undergoing orthopedic surgery who received LWMH than UFH [20].

There are several reasons that explain the plausible superiority of LMWH over UFH. Heparin-induced thrombocytopenia (HIT) is less common with LMWH than with UFH. A meta-analysis evaluating the incidence of HIT in patients at risk for VTE treated with prophylactic doses of anticoagulant showed that the incidence of HIT was lower with LMWH (0.2%) than with UFH (2.6%) [39]. The peak anti-Xa activity (Cmax) and area under the curve (AUC) are higher with enoxaparin and dalteparin compared with UFH [40]. In addition, administration of heparin increases the release of TPFI antigen, an inhibitor of tissue factor that plays a role in the antithrombotic effect of heparin. However, unlike UFH, the LMWH administration can increase TPFI that lasts longer in circulation. This finding may explain the different antithrombotic efficacy of LMWH and UFH in clinical settings [41]. LMWH is also better than UFH at suppressing inflammatory tissue factor expression and contributes to endothelial hemostatic properties in the microvasculature, where endothelial dysfunction is

associated with poor outcomes in COVID-19 patients [42,43]. Finally, LMWH is preferred over UFH because of its good predictability, dose-dependent plasma levels, and longer plasma half-life, allowing it to be administered subcutaneously once or twice daily and reducing healthcare worker exposure [33].

Clinical implication

Our meta-analysis suggests that LMWH may provide better outcomes in COVID-19 patients. These results may provide evidence for the current recommendation that LMWH is preferred over UFH as thromboprophylaxis for COVID-19 [12,16,44,45]. However, this new evidence does not justify changing existing guidelines and is insufficient to support or oppose using UFH as thromboprophylaxis in hospitalized COVID-19 patients. Currently, the selection of anticoagulant agents may still be based on the availability of anticoagulants, the experience of the physicians, treatment objectives, and other patient-specific factors [11]. Further evidence from RCTs is urgently needed to determine the most effective anticoagulant agents for thromboprophylaxis in COVID-19 patients.

Limitations

There are several limitations to this meta-analysis. Possible publication bias was noted in several outcomes, as well as substantial heterogeneity. Most of the included studies were retrospective observational, which were not matched or adjusted for confounders, so the strength of the association could not be measured accurately. The dose definition of the prophylactic or therapeutic LMWH or UFH, including the route of administration, also varied slightly across studies. Another issue is that the presence of both prophylactic and therapeutic dosing in the studies included outcome, especially in noncritically ill COVID-19 patients, as shown in the recent studies [46,47]. Some studies did not mention the specific type of LMWH, and not all studies provide details regarding the selection criteria for LMWH or

UFH (reason for using LMWH or UFH at an individual level cannot be identified), such as the use of UFH, which is the preferred choice for patients with renal dysfunction or disseminated intravascular coagulation. These problems may translate into uncertain effect estimates from these individual studies. Most studies also did not mention pre-existing conditions that have been anticoagulated before admission. The definition of bleeding also varied across studies. Lastly, one study by Lopes et al. [30] only included hospitalized adult patients with elevated D-dimer levels.

Conclusion

Our meta-analysis highlighted current evidence that administration of LMWH was associated with better outcomes compared with UFH in hospitalized COVID-19 patients. Nevertheless, this meta-analysis does not provide guidance for therapeutic decision-making or changing the existing guidelines for COVID-19 thromboprophylaxis. Until direct high-certainty evidence comparing these two types of anticoagulants is available, clinical inference from this analysis should be drawn with caution. Prospective cohorts and RCTs are urgently needed in exploring the definitive effect of LMWH and UFH to provide direct high-certainty evidence.

Disclosure statement

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None.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. The corresponding author (A) can be contacted for more information.

Credit authorship contribution statement

M.Y.A. and B.P.S. contributed to the study conception and design. E.P.B.M., I.M., and Y.A. performed article screening and quality assessment of the studies. D.A.R., A.Y., and L.H.A. performed literature retrieval and data extraction. E.P.B.M. and Y.A wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

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Table 1. Characteristics of included studies.

No	Author, year	Study design	Population	Setting	Time period	Prophylactic doses	Therapeutic doses	Outcome extracted	Bleeding definition	N	Age, year	Male, %	HTN	DM	CKD	Cancer	Quality
1	Volteas, 2022 [29]	Retrospective single center	Critically ill intubated adult patients	Stony Brook University Hospital	February 7 - May 17, 2020	Enoxaparin: 40 mg daily (D-dimer <1,000 ng/mL) or 40 mg twice a day (D-dimer ≥ 1,000 ng/mL but < 3000 ng/mL)	Enoxaparin: 1 mg/kg twice a day or UFH: IV starting rate of 18 units/kg/hr to achieve a goal PTT of 60 to 90	Mortality	NA	240 (LMWH proph: 70, ther: 65; UFH proph: 11, ther: 72)	≥ 18	NA	NA	NA	NA	NA	NA	7
2	Oliynyk, 2021 [31]	Randomized control trial single center	Severe hospitalized adult patients	Kyiv City Clinical Hospital No.4	July 1, 2020 - March 1, 2021	Enoxaparin: 50 anti-Xa IU/kg SC QD	Enoxaparin: 100 anti-Xa IU/kg SC BID; UFH: IV initial 80 U/kg/h, followed by 18 U/kg/h with APTT of 40–70 s	28-day mortality, mechanical ventilation	NA	126 (LMWH proph: 42, ther: 42; UFH ther: 42)	70.3 ±2.8	60.3	NA	NA	NA	NA	Low overall risk of bias
3	Gil, 2021 [25]	Retrospective single center	Hospitalized adult patients	Tertiary care center	March 20 - March 31, 2020	Enoxaparin: 40 mg SC once a day (BMI<40, GFR=30) or 30 mg SC twice a day (BMI=40); UFH: NA	Enoxaparin: 1-5 mg/kg/day or 1 mg/kg twice a day; UFH: 80 units/kg IV bolus followed by continuous IV infusion	Mortality	NA	225 (LMWH proph: 127, ther: 4; UFH proph: 20, ther: 10)	62.1 ± 14.4	57.8	64.9	38.7	19.1	8.4	8
4	Kirkup, 2021 [26]	Retrospective multicenter	Hospitalized adult patients	192 hospitals in 20 countries	Start time NA – January 4, 2021	NA	NA	Mortality, 28-day mortality, ICU admission, length of stay	NA	3196 (LMWH: 1939; UFH: 1012)	63.6 ± 28.2	57.1	54.0	34.9	12.8	6.7	9
5	Lopes,	Randomized	Hospitali	31	June 24,	Enoxaparin: 40	Enoxaparin: 1	Mortality,	Major	615	56.6	59.8	49.1	24.4	NA	0	Low

	2021 [30]	control trial multicenter	zed adult patients and elevated D-dimer concent ration	hospitals in Brazil	2020 – February 26, 2021	mg QD SC (GFR≥30, BMI<40), 60 mg QD SC or 40 mg BID SC (GFR≥30, BMI≥40); UFH: 5000 units TID/BID SC (BMI<40), 7500 units TID/BID SC (BMI≥40)	mg/kg BID SC or 1.5 QD SC mg/kg (GFR≥30, BMI<40), 0,75 mg/Kg BID SC (GFR≥30, BMI<40, age≥ 75), 1 mg/kg BID SC (GFR≥30, BMI≥40), 1 mg/kg QD SC (GFR<30, BMI<40); UFH: 60 unit/kg IV bolus, then 12 units/kg/hr	bleeding	bleeding by ISTH criteria	(LMWH: 256; UFH: 47)	± 14.3						over all risk of bias
6	Nadkarni, 2020 [27]	Retrospective multicenter	Hospitali zed adult patients	5 New York City hospitals	March 1 - April 3, 2020	Enoxaparin: once daily; UFH: SC	Enoxaparin: 1 mg/kg twice daily or 1.5 mg/kg daily; UFH: continuous IV infusions	Mortality, mechanic al ventilatio n, major bleeding	Major bleeding by ICD 10th Revision codes	2859 (LMWH: 445; UFH: 941)	66.5 ± 16.2	57.9	37.4	24.7	12.1	8.3	7
7	Pawlowski , 2020 [17]	Retrospective multicenter	Patients admitte d to hospital	19 Mayo Clinic sites in Arizona, Florida, Minnesot a, and Wisconsin	April 4 - August 31, 2020	Enoxaparin: ≤ 40mg/day SC; UFH: periodic administration	Enoxaparin: > 40mg/day SC; UFH: continuous administration	Mortality, 28-day mortality, ICU admission , length of stay, bleeding	Bleeding complicati ons from the physician notes	557 (LMWH: 441; UFH: 166)	58.4 ± 17.9	54.5	3.1	18.0	11.2	5.9	8
8	Piazza, 2020 [28]	Retrospective multicenter	Hospitali zed adult patients	The Mass General Brigham integrated health network	March 13 - April 3, 2020	NA	NA	ICU admission	NA	399 (LMWH: 277; UFH: 102)	61.1 ± 17.1	42.6	56.1	33.6	NA	6.5	7
9	Rentsch, 2020 [10]	Retrospective multicenter	Patients admitte d to	> 1200 points of care	March 1 - July 31, 2020	Enoxaparin: 40 mg QD or 30 mg BID SC; UFH:	Enoxaparin: >40 mg QD SC; UFH: IV dose	Mortality, 30-day mortality	NA	3627 (LMWH: 2506;	67.0 ± 12.3	93.6	66.6	43.4	19.1	13.6	9

	hospital	nationwide of US Department of Veterans Affairs	5000 units BID or TID SC	adjusted on PTT		UFH: 1094)

N = number of samples; UFH = unfractionated heparin; HTN = hypertension; DM = diabetes mellites; CKD = chronic kidney disease; BMI = body mass index, GFR = glomerular filtration rate; NA = not available; QD = *quaque die* means once a day; BID = *bis in die* means twice a day; TID = *ter in die* means three times a day; IV = intravenous; SC = subcutaneous; ICU = intensive care unit; ISTH = International Society on Thrombosis and Haemostasis; proph: prophylactic, ther: therapeutic.

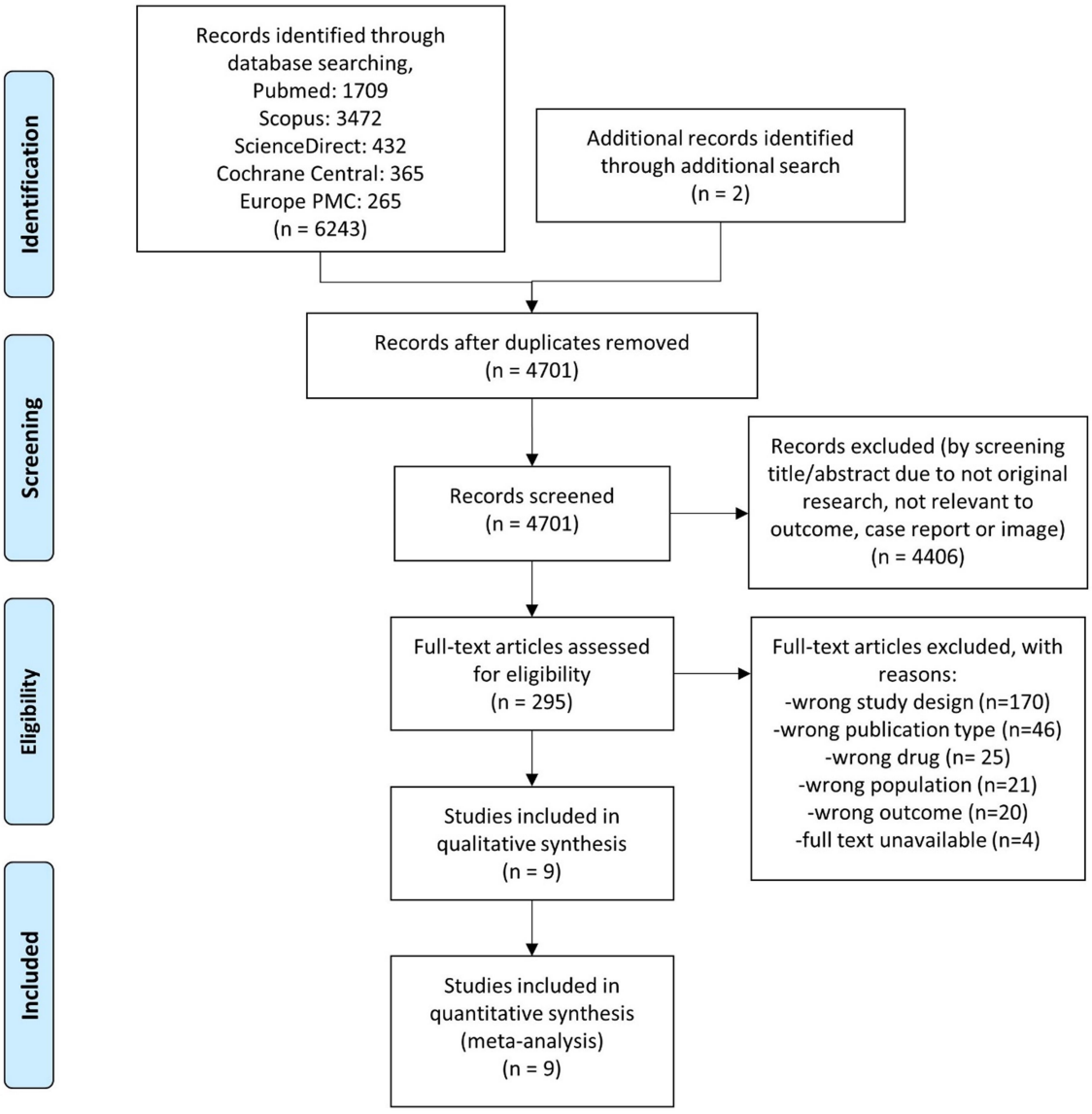

Figure 1. PRISMA flowchart.

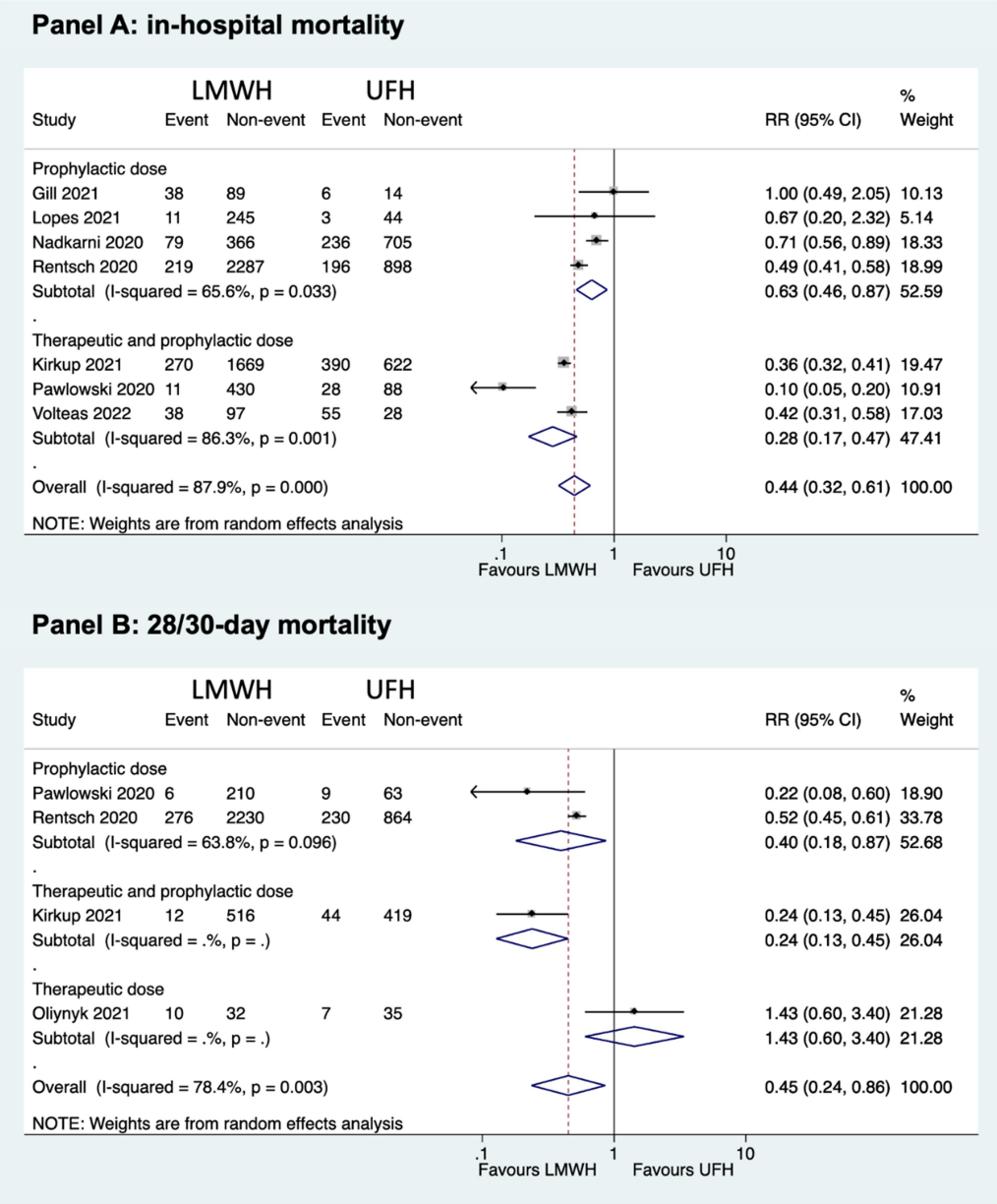

Figure 2. Panel A: forest plot for the association of two different types of anticoagulant (LMWH vs UFH) with in-hospital mortality in hospitalized COVID-19 patients. Panel B: forest plot for the association of two different types of anticoagulant (LMWH vs UFH) with 28 or 30-day mortality in COVID-19 patients.

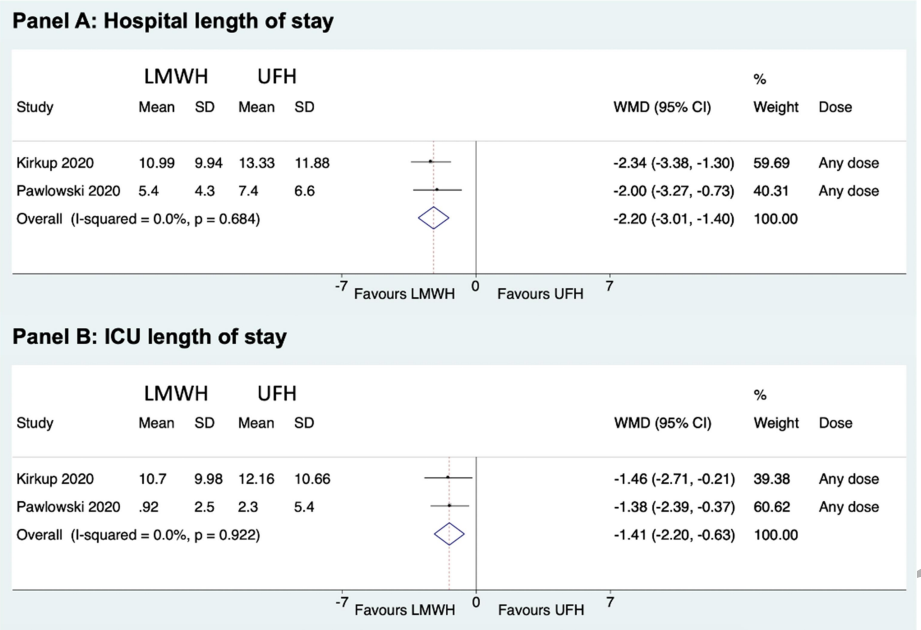

Figure 3. Panel A: forest plot for the association of two different types of anticoagulant (LMWH vs UFH) with hospital length of stay in COVID-19 patients. Panel B: forest plot for the association of two different types of anticoagulant (LMWH vs UFH) with ICU length of stay in COVID-19 patients.

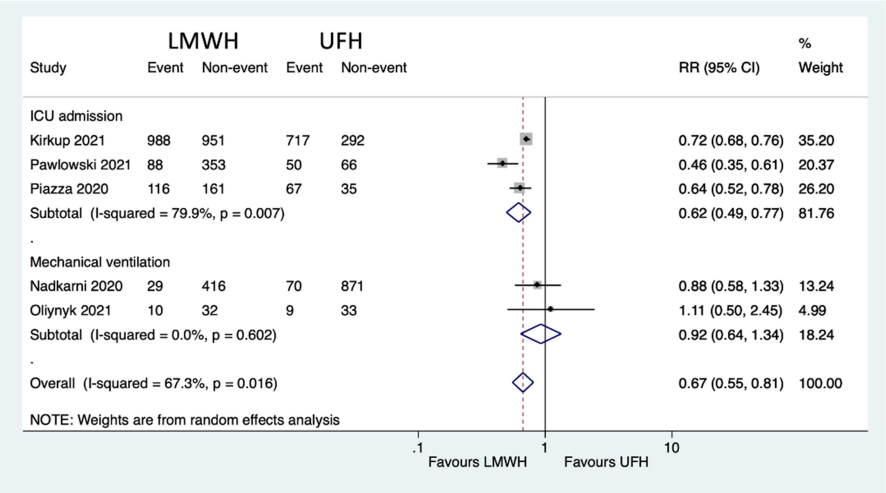

Figure 4. Forest plot for the association of two different types of anticoagulant (LMWH vs UFH) with ICU admission or mechanical ventilation in all hospitalized COVID-19 patients.