Efficacy and Safety of Anticoagulants for COVID-19 Patients in the Intensive Care Unit: A Systematic Review and Meta-Analysis

Yulistiani[1,3], Vina Neldi[2], Budi Suprapti [1,3], Alfian Nur Rosyid[4,5]

[1]Department of Pharmacy Practice, Faculty of Pharmacy, Airlangga University, Surabaya, East Java Indonesia; [2]Master of Clinical Pharmacy Programme, Faculty of Pharmacy, Airlangga University, Surabaya, East Java, Indonesia; [3]Department of Pharmacy, Universitas Airlangga Hospital, Surabaya, East Java, Indonesia; [4]Department of Pulmonology, Universitas Airlangga Hospital, Surabaya, East Java, Indonesia, [5]Medical Faculty, Universitas Airlangga, Surabaya, East Java, Indonesia

Corresponding author: Yulistiani, Department of Pharmacy Practice, Faculty of Pharmacy, Airlangga University, Surabaya, East Java, Indonesia, Department of Pharmacy, Universitas Airlangga Hospital, Surabaya, East Java, Indonesia; TEL: +62 (031) 5933150; email: yulistiani@ff.unair.ac.id

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ABSTRACT—Purpose: This study aims to analyze the efficacy and safety of anticoagulants for COVID-19 patients in the intensive care unit. **Methods:** A comprehensive search was conducted using databases such as MEDLINE, PubMed, EuropePMC, Science Direct, Google Scholar, Clinicaltrial.gov, The Cochrane Central Register of Controlled Trial (CENTRAL, Cochrane Library) and several other published articles from the systematic review up to March 31, 2021. The Newcastle-Ottawa Scale (NOS) was used for the studies' qualitative assessment. The primary outcome examined was mortality rate, while the secondary included the length of stay (LOS) in thei care unit; hospital length of stay (HOS), coagulation markers including D-dimer, Platelet count, aPTT, PT and fibrinogen; markers of inflammation specifically C-reactive protein; and other adverse events ranging from hemorrhage to thrombosis. Additionally, the quantitative synthesis was conducted using fixed and random effects model in "The Revman 5.4", while heterogeneity was tested using the I-squared (I^2) measure. **Results:** A total of 1,062 articles were found during the initial search step and eventually 12 were chosen to be analyzed quantitatively in a meta-analysis. Comparison of the results related to anticoagulant group with no anticoagulant or standard care treatment showed that anticoagulant group significantly reduced mortality rate with RR= 0.53; 95 % CI, 0.30-0.95; P= 0.03, with I^2 = 88% and venous thromboembolism (VTE) RR = 0.53; 95% CI, 0.37-0.76; P = .0007 with I^2 =35%. **Conclusions:** Based on the results, anticoagulants can mitigate mortality rate and VTE in COVID-19 patients.

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus was first identified in Wuhan, China in December 2019 (1,2). It was initially assumed that the virus can damage the respiratory system, but according to recent studies, SARS-CoV-2 also causes coagulation disorder namely COVID-19 Associated Coagulopathy or CAC (3–5). In a study of 184 critically ill COVID-19 patients in the intensive care unit (ICU), 31% were found to experience thrombotic complications (6). One of the most common complications is venous thromboembolism (VTE) with a prevalence of 27%, and the majority of cases are pulmonary embolism (6). Contrast-enhanced CT analysis in COVID-19 patients case series in the ICU showed a pulmonary artery thrombosis rate of 20.6% from 107 participants (7). In another study of 183 patients, 15 or 71.4% who died met the criteria for disseminated intravascular coagulopathy (DIC) based on the scoring system of the International Society of Thrombosis and Haemostasis (ISTH) with a score ≥ 5 (8). Meanwhile, Fogarty et al., found no signs of DIC, such as a significant decrease in platelets and fibrinogen in 83 patients (9).

The SARS-CoV-2 infection excessively increases the production of cytokines such as interferon and interleukin, causing a systemic inflammatory reaction known as a cytokine storm (10) which leads to systemic thrombus formation. Furthermore, this virus causes vascular endothelial damage associated with thrombogenesis (11). Aside from cytokine storm, COVID-19 patients also experience hypoxia characterized by vasoconstriction which reduces blood flow. Hypoxia plays a role in the pathogenesis of coagulopathy in COVID-19 patients causing a shift from antithrombotic and endothelial inflammation phenotypes into procoagulant and proinflammatory (11).

The process stated above can provoke

endotheliopathy where Von Willebrand Factor (vWF) are released and cause platelet aggregation, initiating microvascular thrombogenesis which leads to microthrombus formation. Platelets, monocytes, neutrophils, and microparticles adhere to the activated endothelium, which in turn trigger the coagulation cascade along with tissue factor (TF) and neutrophil extracellular traps (NETs). The increase in thrombin potentially causes of hypercoagulability (11) which worsens with the escalation of prothrombotic factors including Von Willbrand (vWF), VIII, fibrinogen, NETs, and thrombotic microparticles (12–14). Anticoagulant is one of several recommended therapies for COVID-19 patients (15). Besides, previous studies supported anticoagulant application as both therapy and prophylaxis. Anticoagulants potentially decrease coagulopathy, microthrombus, and organ damage (16), but there are still no general guidelines for their application in COVID-19 patients, and further studies are required to ensure effectiveness (17).

A study conducted by Tang et al. included 449 severe COVID-19 patients, a total of 99 were given heparin therapy for seven days or longer. Enoxaparin at a dose of 40-60 mg/day was also given to 94 patients, and 5 were given unfractionated heparin (UFH) at a dose of 10,000-15,000 units/day. The result showed no difference in the mortality rate of patients with heparin usage amounting to 30.3% and those without heparin usage 29.7% with p=0.910 on their 28th day. However, patients with ≥4 Sepsis-Induced Coagulopathy (SIC) showed a mortality rate drop on their 28th day with values of 40% and 62.9% for patients with and without heparin usage respectively (p=0.029). Patients with > 3.0 μg/mL D-dimer showed a 32.7% mortality rate if they were given heparin and 52.4% if they were not given heparin (p=0.017) (18,19).

Although several studies support the use of anticoagulants in COVID-19 patients, many also reported insignificant effects and the risk of hemorrhaging due to inappropriate anticoagulation. Recent investigations are needed to support the effectiveness of anticoagulation in COVID-19 patients. Therefore, this systematic review and meta-analysis aim to determine the efficacy and safety of anticoagulants for COVID-19 patients in the intensive care unit. The primary outcome is to determine whether anticoagulants affect the mortality in the patients.

The secondary outcomes are to determine whether anticoagulants affect: 1) length of stay (LOS) in the ICU, 2) hospital Length of Stay (HOS), 3) coagulation markers including D-dimer, platelet count, aPTT, PT, and fibrinogen; 4) inflammation markers specifically C-reactive protein, and 5) other adverse events such as hemorrhage and thrombosis. The systematic review protocol has been registered in PROSPERO (ID: CRD42021242877) entitled "Efficacy and Safety of Anticoagulant for COVID-19 Patients in Intensive Care Unit: A Systematic Review and Meta-Analysis".

MATERIALS AND METHODS

Search Strategy

This systematic review and meta-analysis were carried out based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. VN conducted a systematic literature search using the primary databases in MEDLINE, PubMed, EuropePMC, Science Direct, Google Scholar, and the Cochrane central register of controlled trial (CENTRAL, Cochrane Library). In addition to subscription databases, the team searched trial registries in ClinicalTrials.gov. The search was carried out up to March 30, 2021, with relevant keywords and controlled vocabulary were carefully selected without language restrictions as shown in Appendix I.

Eligibility Criteria

The PICOS model was used to select the study population, and the inclusion criteria include: 1) Patients: adult aged ≥ 18 years and diagnosed with severe COVID-19 in ICU, 2) Intervention: Studies that compared parenteral anticoagulant therapy such as Unfractionated heparin (UFH), Low Molecular Weight Heparin (LMWH), and Fondaparinux (FDP) with all appropriate doses and regimens both prophylactic and therapeutic, 3) Comparison: no anticoagulant or standard treatment, 4) Outcomes: primary outcomes was mortality, while secondary included length of stay (LOS) in the ICU, hospital Length of Stay (HOS), coagulation markers comprising D-dimer, platelet count, aPTT, PT, and fibrinogen; inflammation markers specifically C-reactive protein; other adverse events such as hemorrhage and thrombosis, and, 5) Study design: randomized controlled trials (RCTs), and observational studies. Meanwhile, the exclusion criteria were review articles, case-control studies, case reports and case series, studies with incomplete data, animal and unpublished studies including conference papers, theses, and expert opinions.

Selection of Studies and Data Extraction

Two authors (YL, BS) screened titles and abstracts to exclude irrelevant articles, then screening was carried out by reading the text thoroughly to assess

the article's suitability with the inclusion and exclusion criteria. When there are differences in their respective views, a joint discussion will be held by conferring with the third author (AN). Articles that met the inclusion criteria were then analyzed qualitatively, and the results were quantitatively analyzed (meta-analysis). Furthermore, the data were independently extracted by two authors (YL and BS) including patients' demographics, first author, year of publication, country, design of the study, population, intervention, sample size, anticoagulant regimen administered involving type, dose, and duration of anticoagulant therapy; and all outcome measures.

Quality Assessment

Two independent authors (YL, VN) evaluated the methodological quality according to the Cochrane Collaboration's tool. Any disagreements were resolved through discussion with the third author (AN). The quality assessment was carried out using the Newcastle Ottawa Scale (NOS) tool(20). NOS is a risk of bias (ROB) assessment tool for observational studies recommended by the Cochrane Collaboration (20). It is used for non-randomized studies in systematic review and/or meta-analyses based on 3 domains: the selection of the study groups; comparability; and the ascertainment of exposure and outcome for case-control or cohort studies, respectively. A maximum of 9 points can be assigned for the least risk of bias in these domains. The study quality is considered the lowest when the score is ≤ 4. Meanwhile, a study with a score of 5-6 is considered to have a moderate quality rate, while a score ≥ 7 is considered good/high quality (21).

Statistical Analysis

The meta-analysis was performed using the Review Manager Software (Revman), version 5.4 Windows. The effect estimation was in risk ratio (RR) for mortality and serious adverse events, as well as odds ratios (OR) for clinical improvement with 95% confidence intervals (CI). The pooled effect size estimation was performed by a fixed-effect or random-effect model after heterogeneity results were assessed. Furthermore, the heterogeneity was assessed using Cochran's Q test and I^2 statistic with I^2 of <25% indicating no heterogeneity; 25-50% low; 50-75% moderate; and >75% high. Significant statistical heterogeneity was defined by a $P<0.1$ or $I^2 >50\%$. When the P-value is defined by a $P\geq0.1$ or $I^2 \leq 50\%$, the fixed-effect model was used but when there is significant heterogeneity, the random-effect model was selected with $I^2 >50\%$ or $P <0.1$.

RESULTS

Study Results

A total of 1,062 studies were identified and 140 duplications were removed, hence, only 922 were screened. Among these, 71 were selected for full-text review after the irrelevant studies were removed. A total of 12 observational studies comprising 9 retrospective and 3 prospective were included in the meta-analysis. Studies were excluded after full-text review for the following reasons: 2 brief reports and letters to editor, 8 studies with different populations, 26 with unmatched eligibility, 7 with no comparing group, and 13 with inappropriate data. The PRISMA flowchart of study selection is depicted in Figure 1.

Study Characteristics

A total of 7,966 patients with a mean age between 60 to 70 years were analyzed in this meta-analysis. The most involved gender was male with 3,362, while females amounted to 1,831 and one study by Paranjpe did not attach the patients' gender (16). The participants involved consisted of certain races such as Caucasian, Asian, black, African American, Hispanic and all included studies were conducted on severe COVID-19 cases in the intensive care unit. Furthermore, multiple comorbidities were mentioned but the most common were hypertension, diabetes, pulmonary disorders, kidney, and cardiovascular diseases. The anticoagulants analyzed were Low Molecular Weight Heparin/LMWH including enoxaparin, nadroparin calcium, and fondaparinux; as well as Unfractionated Heparin (UFH). A total of 8 studies investigated the use of LMWH, especially enoxaparin, with prophylactic doses in 3 and therapeutic in 2, while both were examined in 3 studies. The use of UFH was reported in 3 studies consisted of therapeutic dose in 1 and prophylactic 2, while the use of nadroparin and fondaparinux was reported in 1 study, respectively. In addition, the most widely used anticoagulant with prophylactic doses was LMWH, especially enoxaparin. The characteristics of the included studies are presented in Table 1. Studies included were conducted in the United States (2,16,22,23), Italy (24,25), Turkey (26), France (27), and China (8,28–30).

Study Quality Assessment

The risk of bias was assessed using the NOS with 9 factors used to assess study quality. The results showed 3 studies (2,22,28) with high quality,

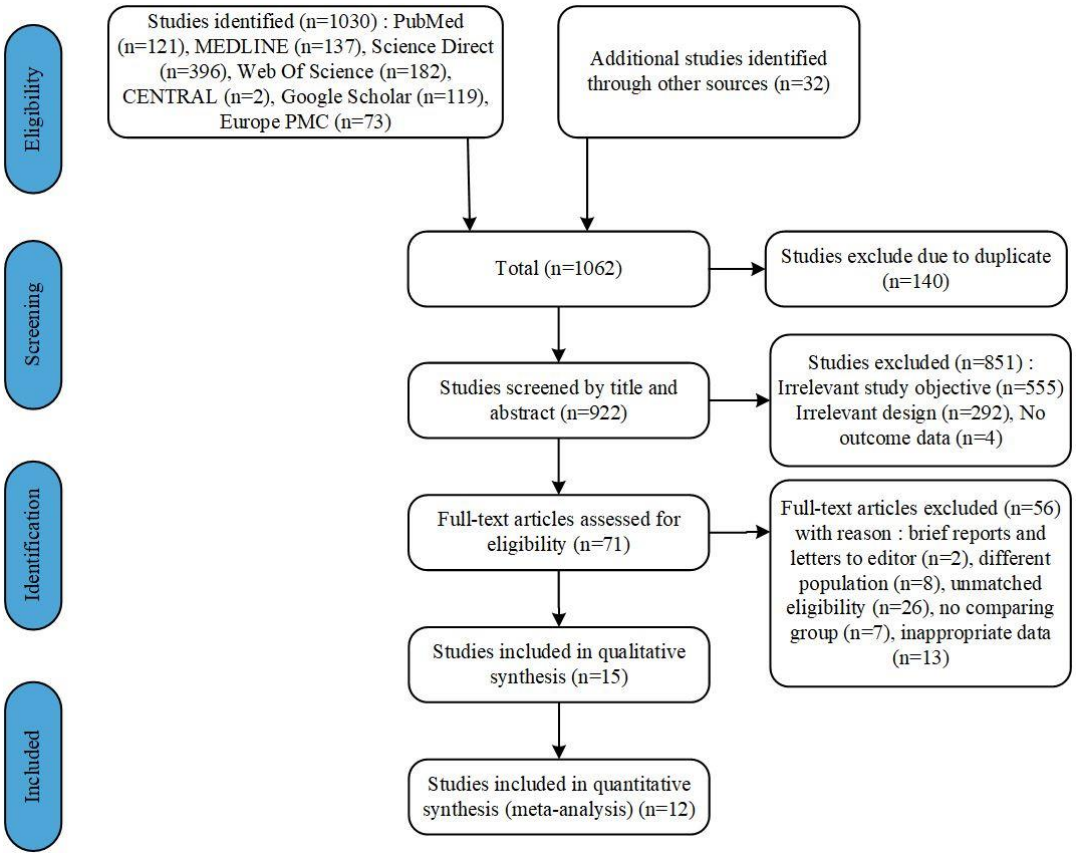

Figure 1. PRISMA flow chart and study selection process

3 with median quality (24,25,30) and 6 having low quality (8,16,23,26,27,29) (Table 2). The drawback of NOS in assessing the quality of studies is that there are no clear guidelines, making it possible for errors to occur in the assessment. Therefore, the evaluation must be carried out by more than one reviewer, and when there are differences in the evaluation, a joint discussion can be carried out. This tool has an adaptation index adjusted to the topic being assessed and provides a score ranging from 0-9, making it suitable for meta-regression analysis (31).

Meta-Analysis

In general, 7 studies reported a statistically significant association between anticoagulation administration and mortality. The random-effects model results indicated that the use of anticoagulants affected the relative risk of mortality with RR= 0.53; 95 % CI, 0.30-0.95; and p = 0.03 as shown in Figure 2A. In this analysis, the random effect model was selected because heterogeneity of the studies was high at I^2 = 88%. Regarding the secondary outcome, thrombotic events such as VTE was found in 6 studies while hemorrhage occurred in 1 study. Study outcomes related to coagulation markers including D-dimer, Platelet Count, aPTT, PT, and Fibrinogen; as well as inflammatory markers such as CRP were found in the baseline characteristics of each study. Furthermore, VTE was analyzed in the meta-analysis as a secondary outcome while hemorrhage was not assessed to avoid the risk of bias as the number of studies obtained was small. The fixed-effect model results showed that anticoagulant usage significantly reduced the risk of VTE compared to no anticoagulant or standard care treatment with RR = 0.53; 95% CI, 0.37-0.76; and p = .0007. The heterogeneity of the studies was low at I^2 = 35%, while the forest plots of the 2 quantitatively analyzed outcomes are shown in Figures 2A and 2B. This analysis showed a statistically significant relationship with p-value < 0.05 between the administration of anticoagulants and the observed outcome.

DISCUSSION

This study was conducted to evaluate the current evidence on the efficacy and safety of anticoagulants for COVID-19 patients in the intensive care unit. The meta-analysis results showed that compared to no anticoagulant or standard care treatment, anticoagulant significantly affects mortality outcome and VTE. The current diagnosis of COVID-19 infection majorly uses the real-time reverse transcription-polymerase chain reaction (rRT-PCR), which is a standard test for

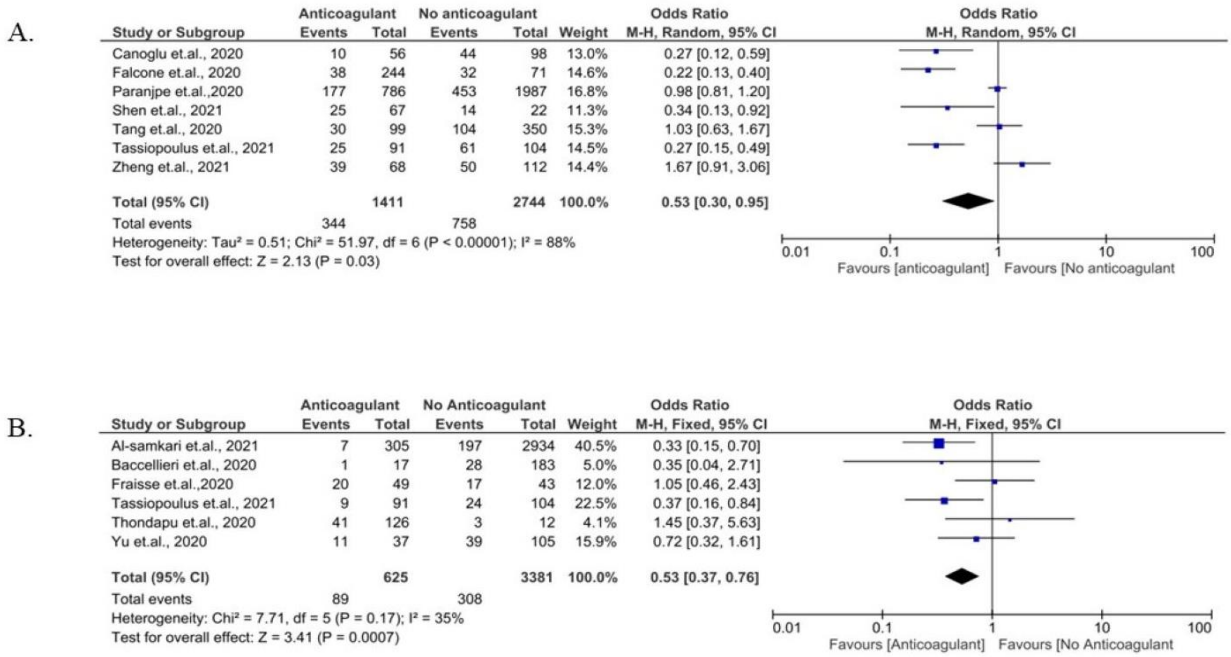

Figure 2. (A) Forest plot *Mortality*; (B) Forest Plot Venous Thromboembolism (VTE).

laboratory diagnosis. However, no RCT-based study was found during the search because it is still in the experimental stage. Each investigation has a different level of evidence with that of a systematic review depending on the study design. The primary study level is categorized based on the design from the highest to the lowest as follows: experimental; randomized or non-randomized controlled trials; quasi-experimental studies; and observational analytic studies including cohort and case-control.

Based on the variations between races, the results from each study cannot be generalized because racial differences can affect the outcome of a disease or the provision of specific therapies, one example is the variation of risk factors for VTE. A study reported that the incidence of VTE in an Asian population was in the low category with 21-29 cases per 100,000 individuals per year (32,33). Therefore, prophylactic anticoagulants such as LMWH might be considered with an adjusted dose. In this systematic review analysis, it was found that the use of anticoagulants is associated with the presence of coagulopathy in COVID-19 patients characterized by changes in several coagulation parameters such as D-dimer, platelet count, PT, and aPTT. The mechanism of coagulopathy in the COVID-19 pathophysiological process involves a procoagulant shift mechanism. An increase in the value of D-dimer was reported in COVID-19 patients, especially in those with severe symptoms and receiving treatments in the ICU (34). Moreover, an increase in the D-dimer value of more than 1 mg/dl is significantly associated with mortality (35).

According to Al-Samkari et al. (2020), 2/3 of most hemow1`` varrhaging events occur in patients receiving anticoagulants at therapeutic doses. The high mortality rate, especially in COVID-19 patients with critical conditions accompanied by hemorrhage, is an essential concern in the administration of anticoagulants. The results and stratification of patient groups are first considered before anticoagulant therapy is given. To date, guidelines for the administration of anticoagulants in COVID-19 patients have not been provided. They are currently still in the form of expert recommendations that require further studies (8,18,36–38). Meanwhile, the mechanism of anticoagulation in the COVID-19 treatment is related to the suppression of prothrombotic coagulopathy to prevent microvascular and macrovascular thrombosis. Several inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and ferritin reportedly increase in COVID-19 patients (39). Therefore, the administration of heparin (LMWH and UFH) is a profitable option because it provides anticoagulant and inflammatory effects such as neutralization of cytokines, chemokines, and extracellular histones (40). Heparin administration also reduces SARS-CoV-2 virus entry into cells through competitive binding with heparin sulfate on the host cell membranes (41).

These results support previous systematic reviews, stating that anticoagulants can reduce mortality and VTE.

Table 1. The characteristics of included studies

Study	Study design/location	Participants	Outcome						Intervention	NOS
			Mortality		VTE		Bleeding			
			n (A vs B)	(A vs B)	n (A vs B)	(A vs B)	n (A vs B)	(A vs B)		
Al-Samkari et al (2)	Multicenter Cohort prospective / United States	3239	NA	NA	305 vs 2934	7 vs 197	305 vs 2934	16 vs 74	Enoxaparin or UFH	8
Baccellieri et al (24)	Single-centre Cohort prospective / Italy	200	NA	NA	17 vs 183	1 vs 28	NA	NA	LMWH	6
Canoglu & Saylan (26)	Single-centre Retrospective / Turkey	154	56 vs 98	10 vs 44	NA	NA	NA	NA	LMWH (Enoxaparin)	3
Falcone et al (25)	Prospective Observational / Italy	315	244 vs 71	38 vs 32	NA	NA	NA	NA	LMWH (enoxaparin)	6
Fraissé et al (27)	Mono-Center Cohort Retrospective / France	92	NA	NA	49 vs 43	20 vs 17	NA	NA	Anticoagulant (no mention of AC)	4
Paranjpe et al (16)	Cohort Retrospective / USA	2773	786 vs 1987	177 vs 453	NA	NA	NA	NA	Anticoagulant systemic (no mention of AC)	4
Shen et al (28)	Multicenter Cohort Retrospective / China	89	67 vs 22	25 vs 14	NA	NA	NA	NA	LMWH (enoxaparin)	7
Tang, Bai et al (8)	Retrospective / China	449	99 vs 350	30 vs 104	NA	NA	NA	NA	LMWH (enoxaparin) or UFH	4
Tassiopoulos et al (22)	Single-centre Cohort Retrospective / New York	195	91 vs 104	25 vs 61	91 vs 104	9 vs 24	NA	NA	Enoxaparin	7
Thondapu et al (23)	Multi-Centre Cohort Retrospective Observational / United States	138	NA	NA	126 vs 12	41 vs 3	NA	NA	LMWH, Heparin	4
Yu et al (29)	Single-Center Retrospective / China	142	NA	NA	37 vs 105	11 vs 39	NA	NA	Anticoagulant (no mention of AC)	3
Zheng et al (30)	Retrospective / China	180	68 vs 112	39 vs 50	NA	NA	NA	NA	Enoxaparin	5

AC Anticoagulant, *ICU* intensive care unit, *LMWH* Low molecular weight heparin, *NOS* Newcastle Ottawa scale, *UFH* unfractionated heparin

Table 2. Quality of study based on Newcastle Ottawa scale (NOS)

Author/Year	Selection				Comparability	Outcome			Score total	Quality of study
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment Of exposure	Demonstration that outcome of interest was no present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Follow-up length	Adequacy of follow-up of the cohort		
Al-Samkari et al (2)	1	1	1	1	1	1	1	1	8	High
Baccellieri et al (24)	0	0	1	1	1	1	1	1	6	Median
Canoglu & Saylan (26)	0	0	0	1	1	1	0	0	3	Low
Falcone et al (25)	0	0	1	1	1	1	1	1	6	Median
Fraissé et al (27)	0	1	0	0	1	0	1	1	4	Low
Paranjpe et al (16)	1	1	0	1	0	0	1	0	4	Low
Shen et al (28)	0	1	0	1	2	1	1	1	7	High
Tang, Bai et al (8)	0	1	0	1	0	1	1	0	4	Low
Tassiopoulos et al (22)	0	1	0	1	2	1	1	1	7	High
Thondapu et al (23)	0	1	0	0	1	1	1	0	4	Low
Yu et al (29)	0	1	0	0	1	1	0	0	3	Low
Zheng et al (30)	1	1	0	0	1	1	1	0	5	Median

This analysis found a significant effect between anticoagulation and VTE including Pulmonary embolism (PE) and/or Deep Vein Thrombosis (DVT) thrombotic events. The anticoagulant dose given between prophylactic and therapeutic did not show a significant difference. However, prescribed types and doses of anticoagulants have not been described in detail. Some studies explained that therapeutic anticoagulants can reduce mortality in COVID-19 patients but are associated with the risk of hemorrhage, while other investigations recommended using prophylactic anticoagulants, hence, further studies are needed regarding the dose of anticoagulation in COVID-19 patients.

Several studies reported persistent risk of VTE in some patients even after receiving anticoagulant prophylaxis. For example, Singhania et al., reported that 2/3 of COVID-19 patients admitted to the Intensive Care Unit (ICU) still had VTE complications despite prophylactic anticoagulation (42). In addition, in the post-mortem examination conducted by Menter et al., alveolar microthrombi 45% and glomerular microthrombus 16.7% were found in 21 patients (43). Another analysis conducted to determine the relationship between anticoagulant administration and mortality showed that anticoagulants are significant in reducing mortality in COVID-19 patients. This is also supported by several other studies showing that prophylactic anticoagulation can reduce mortality, especially in patients with elevated D-dimer values and those on mechanical ventilation (16,18).

Furthermore, Gonzales et al., reported a beneficial effect of anticoagulation in reducing mortality (44–46). Kamel et al. also confirmed the positive effects of anticoagulant application on the mortality rate of COVID-19 patients in hospitals with a steady association when made using a non-adjusted model (47). A systematic review reported by Moonla et al. showed a mortality rate reduction in patients receiving prophylactic anticoagulants compared to those who did not, with a 17% reduction. The example above has become a consideration in using prophylactic anticoagulants for COVID-19 patients. However, the safety of the anticoagulant must be considered when treating the patients. In the systematic review, two studies reported hemorrhaging events without significant data. Paranjpe et al. (16) found increased hemorrhage in COVID-19 patients receiving anticoagulant therapy, although it was not statistically significant. Therefore, stratification related to the need for anticoagulants, especially the administration of therapeutic doses in COVID-19 patients, is needed to provide maximum effectiveness and minimize side effects.

LIMITATIONS

This study has several limitations firstly, no randomized controlled trial was found, hence the design used was observational, both prospectively and retrospectively. Observational studies often use a limited number of populations, and the results provided are less representative of the general population. Second, there was no standard therapy for the use of anticoagulants in COVID-19 patients, making it difficult to determine the control group in the systematic review. Third, the development of the disease occurred very quickly, stating the need for more investigations. Fourth, several studies did not provide information regarding the type and dose of anticoagulant given hence, further subgroup analyses are needed.

CONCLUSION

Based on the systematic review and meta-analysis results, there is a relationship between anticoagulation administration, decreased mortality, and the incidence of VTE in COVID-19 patients. However, further studies are needed as there are no guidelines for the use of anticoagulants to achieve more effective and safer applications.

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CONFLICT OF INTEREST. All authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS. YL conceived and conceptualized the study idea. VN conducted comprehensive searches. YL and BS reviewed the search, performed the screening and full text assessment. AN resolved any conflicts. YL and VN completed the quality assessment and data extraction. YL performed the data analyses, VN and YL interpreted the results. YL and VN contributed to the draft manuscript. All authors contributed to the revisions and final proof reading.

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Appendix I. Search Strategies

Database	Keywords	Result
PubMed	(COVID-19∗[tw] OR "SARS-CoV-2" [tw] OR "2019-nCoV" [tw] OR "severe acute respiratory syndrome coronavirus 2" [tw] OR "coronavirus SARS-CoV-2" [tw] OR "COVID-2019 pneumonia" [tw] OR 2019-nCoV AND (anticoagulants OR "anti coagulants"[tw] OR "anti coagulate"[tw] OR "anti coagulated"[tw]) AND "Intensive Care Units")	121
MEDLINE	(COVID-19∗[tw] OR "SARS-CoV-2" [tw] OR "2019-nCoV" [tw] OR "severe acute respiratory syndrome coronavirus 2" [tw] OR "coronavirus SARS-CoV-2" [tw] OR "COVID-2019 pneumonia" [tw] OR 2019-nCoV) AND ("anticoagulants" OR "anti coagulants"[tw] OR "anti coagulate"[tw] OR "anti coagulated"[tw] "Heparin" OR "Unfractioned Heparin" OR UFH OR "Fondaparinux" OR "Enoxaparin") AND ("Intensive Care Units" OR "Critical Care Units") AND ("Randomized Controlled Trial" OR "Retrospective Studies" OR "Cohort Studies" OR "Observational Studies")	137
Science Direct	(COVID-19) AND (Anticoagulant OR Enoxaparin OR Fondaparinux OR Heparin) AND (Intensive Care Units OR Critical Illness) NOT Paediatric NOT Myocardial Infarction	396
Web Of Science	((COVID-19 OR SARS-CoV-2) AND (anticoagulants OR Enoxaparin OR Fondaparinux OR Heparin) AND (Intensive Care Units OR Critical Illness OR Hospital Mortality))	182
CENTRAL	COVID-19 and anticoagulant	2
Google Scholar	COVID-19 AND Anticoagulant OR Enoxaparin OR Fondaparinux OR Heparin AND Research Article	119
Europe PMC	COVID-19 AND anticoagulants OR Heparin OR Enoxaparin OR Fondaparinux AND Intensive Care Units OR Critical Illness OR Hospital Mortality	73
other study		32