Comparison of the Mortality and Bleeding Risk of Anticoagulant Doses in COVID-19 Patients: A Systematic Review and Meta-analysis

Athaya Febriantyo Purnomo[1], Mokhamad Fahmi Rizki Syaban[2]*, Icha Farihah Deniyati Faratisha[2], Firstya Diyah Ekasiwi[2], Muthi'ah Adira Juwono[2], Nur Hudayana[2], Edwin Kinesya[2], Yusuf Mannagalli[2] and Erwin Alexander Pasaribu[2]

[1.] Department of Urology, Faculty of Medicine, Universitas Brawijaya, Malang, East Java 65145, Indonesia
[2.] Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia

Info Article	ABSTRACT
	Anticoagulant therapy becomes critical to preventing further complications caused by the hypercoagulative state in COVID-19 patients. The optimal dose and time-dependent administration of anticoagulants for COVID-19 patients remains unknown. The purpose of this study was to determine the mortality and bleeding risks of anticoagulants administered based dose dependent and time-dependent manner for COVID-19 patients. We collected data from articles that compared prophylactic and therapeutic anticoagulants in COVID-19 patients recorded online from studies that were published around 2020 to 2021. We were obtained the articles from a scientific database such as ScienceDirect, Cochrane, ProQuest, PubMed, and Google Scholar based on the inclusion criteria. Data analysis was conducted using Review Manager Version 5.4.1. Based on time dependent-manner, prophylactic anticoagulant showed benefit in reducing mortality (RR = 0.85; 95% CI = 0.75 to 0.95). Beside, based on dose-dependent manner, prophylactic anticoagulant was found beneficial to prevent mortality (RR = 0.49; CI 95%; 0.26 to 0.91) compared to therapeutic. Therapeutic anticoagulants also showed higher risk of bleeding (RR = 0.27; CI 95%; $p < 0.000001$) compared to prophylactic. Administer prophylactic dose is recommended using for COVID-19 patients due to the decreased mortality rate and fewer bleeding risks compared to the therapeutic dose. **Keywords**: Anticoagulants, COVID-19, Bleeding, Mortality.

INTRODUCTION

COVID-19 is associated with coagulopathy. Hypercoagulability may induced venous thromboembolism (VTE), increasing the mortality rate of COVID-19 patients. The severity of COVID-19 viral pneumonia, infection, and respiratory dysfunction may worsen into sepsis (Tang *et al.*, 2020). During the early stages of the COVID-19 pandemic as knowledge about associated coagulopathy and thrombosis complications of COVID-19, anticoagulants become recommended as initial treatment for patients with severe COVID-19 infection (Tang *et al.*, 2020; Yu *et al.*, 2021). Initially, all patients hospitalized for severe COVID-19 were advised to take a prophylactic or therapeutic dosage of anticoagulant and further evaluation of coagulopathy (Yu *et al.*, 2021).

Prior to the pandemic, anticoagulants are indicating as treatment for some diseases such as in cardiac infarction, ischemic stroke, and venous thromboembolism (VTE) (Hawes & Viera, 2014). VTE comprising of deep vein thrombosis (occurs mostly in the leg vein) and pulmonary embolisim afflicting nearly 10 million peoples per year, with annual incidence of acute VTE is 1-2 cases per 1000 population (Khan *et al.*, 2021). During the pandemic, anticoagulants have become a recommended treatment for COVID-19 induced hypercoagulability (Rico-Mesa *et al.*, 2020). Anticoagulants worked by inhibiting factors in the coagulation cascade, lowering the risk of coagulation and concomitantly increasing the risk of bleeding. Anticoagulants can be divided into vitamin K antagonists, heparins, factor Xa

inhibitors, direct thrombin inhibitors, and fibrinolytic. Before administration of anticoagulants, physicians need to consider renal dysfunction, intracranial hemorrhage, peptic ulcer, major bleeding, and bleeding disorders (DeWald *et al.*, 2018; Harter *et al.*, 2015)

For non-critically ill patients hospitalized with COVID-19, therapeutic dose heparin appears beneficial, but for critically ill patients, therapeutic dose heparin did not improve outcome or may result in harm. Administration of anticoagulants on post-hospitalised COVID-19 patients also not warranted (Bradbury & McQuilten, 2022). Therefore indication, dosage, efficacy, and adverse events of anticoagulants for COVID-19 patients need to be studied further. This systematical review and meta-analysis objectives are to determine the pooled efficacy, adverse effects, and dosage of anticoagulants usage either as prophylaxis or therapeutic in patients with COVID-19.

MATERIAL AND METHODS
Study design
We performed a systematic review and meta-analysis study (PRISMA) in July 2021 using Review Manager Version 5.4.1 (Liberati *et al.*, 2009). Published papers from a database such as ScienceDirect, Cochrane, ProQuest, PubMed, and Google Scholar based on the inclusion criteria around 2020 to 2021 were analyzed using the Comprehensive Meta-Analysis tool and estimated using fixed-effects or random-effects models. We searched and collected data used search term "COVID-19 OR Coronavirus OR Sars-CoV-2 OR 2019-nCoV'' AND "anticoagulant OR thrombolytic OR low molecular weight heparin OR LMWH OR heparin OR warfarin OR fibrinolytic OR Dabigatran OR Rivaroxaban" AND "efficacy or adverse event or mortality" AND "RCT OR randomized controlled trial OR cohort OR case-control OR cross-sectional study". We Also collected all relevant articles from all accessed articles. The effect of using anticoagulants is our primary outcome as (1) mortality, (2) Bleeding, (3) VTE.

Study selection
The inclusion criteria of this study were patients >18 years older with confirmed cases of COVID-19 who received prophylactic dose and therapeutic dose with primary outcome mortality, VTE and bleeding. We included all articles that met the criteria such as (1) randomized controlled trial, retrospective, prospective, case-control, or cross-

sectional studies compared treatment time-dependent, and dose-dependent of anticoagulant; (2) Studies with the purpose to investigate the efficacy and/or safety profile of anticoagulant in COVID-19 patients for prophylactic, therapeutic, or both; (3) availability of data about mortality, and bleeding. We excluded articles with one or more theses following criteria: (1) duplications; (2) published not in the English language; (3) irrelevant titles and/or abstracts, reviews, comments, dissertations that were not published into the journal, incomplete data, and inferior availability; and (4) outcome of interest not reported.

Data extraction
The following details were taken from each study: (1) first author; (2) publication year; (3) country of center study; (5) duration; (6) time followed; (7) sample population; (8) criteria of study; (9) mortality; (10) bleeding event.

Data analysis
The statistical analysis was using the Review Manager (Revman) version 5.4.1 tool. The Z test was used to examine the significance of the pooled data ($p < 0.05$ was considered statistically significant). A p-heterogeneity and I-square (I2) Q-analysis was used to measure the degree of heterogeneity. A random-effect model was used if there was heterogeneity ($p < 0.05$) or I2>50%, and a fixed-effect model was used if there was not. For the pooled bleeding event with the corresponding 95% CI (Cleophas & Zwinderman, 2017; Waranugraha *et al.*, 2021).

Quality assessment
The paper quality was assessed using the quality assessment of Newcastle-Ottawa quality assessment scale (NOS) tool. The authors critically appraised the quality of the product. The NOS was composed of patient selection, comparability, and exposure (Lo *et al.*, 2014; Syaban *et al.*, 2022).

RESULTS AND DISCUSSION
The flowchart for the process of selecting a research can be seen in Figure 1. In this analysis, we only included high-quality papers that were evaluated by NOS. The general characteristics of 9045 patients from 7 study included in this meta-analysis are detailed (Table I). Some of the included studies compare using of anticoagulant by dose-dependent and other compare by time-dependent.

Table I. Characteristics Study Included in Study

| No	Author, Year	Country	Design Study	Sample	Duration	Followed	Sample Population and Additional information	NOS
1	Albani *et al* 2020	Italy	Observational Cohort Study	1403	30 days	30 days	COVID (+) ICU admitted	7
2	Andrew *et al* 2020	USA	Observational Cohort Study	468	30 days	30 days	COVID (+) ICU admitted	7
3	Lopes *et al* 2021	Brazil	Randomised Control Trial	615	30 days	30 and 60 days after discharge	COVID (+) inpatient with elevated D-dimer	7
4	Pawlowski *et al* 2021	USA	Observational Cohort Study	1113	7 days	28 days	Severe COVID	8
5	Rentsch *et al* 2021	USA	Observational Cohort Study	4297	0-24 hours	< 30 days	Covid-19	8
6	Roomi *et al* 2021	USA	Retrospective Cohort Study	176	7 days	7 days	Confirmed Covid 19	6
7	Yu *et al* 2021	USA	Retrospective Cohort Study	973	not mentioned	not mentioned	Confirmed Covid 19	7
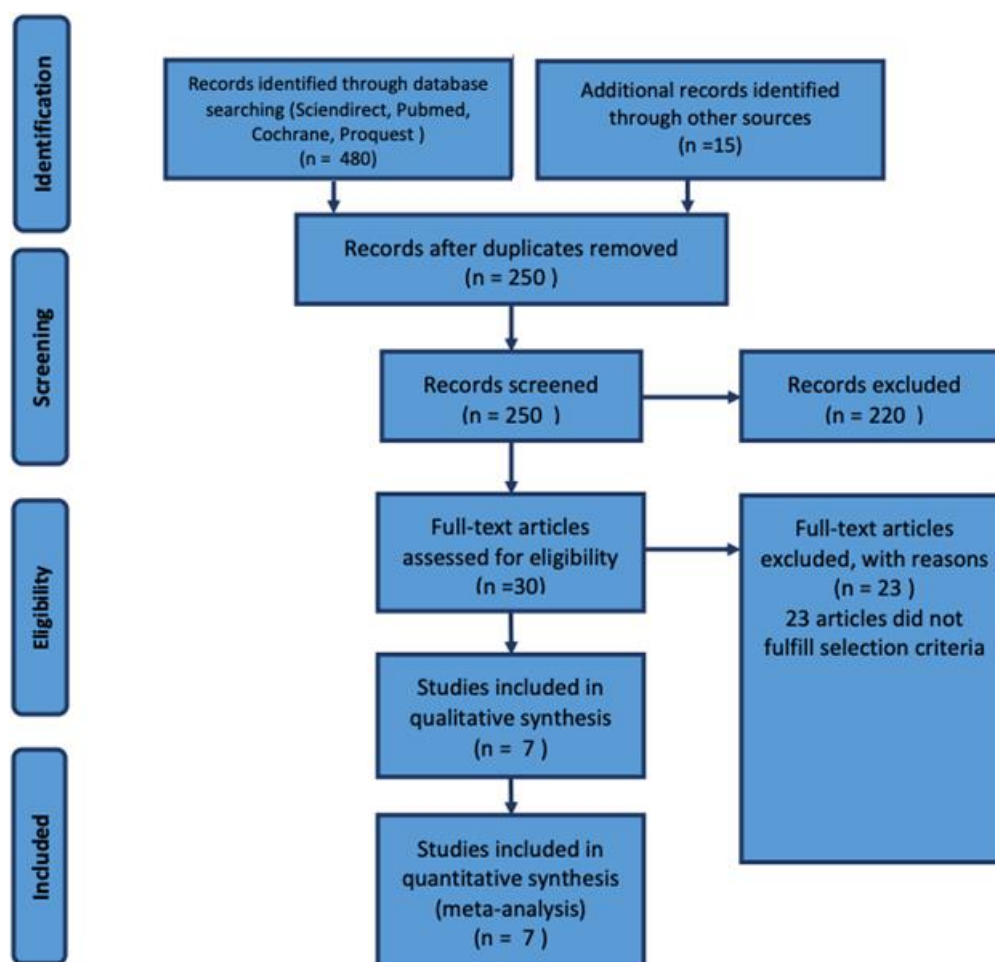
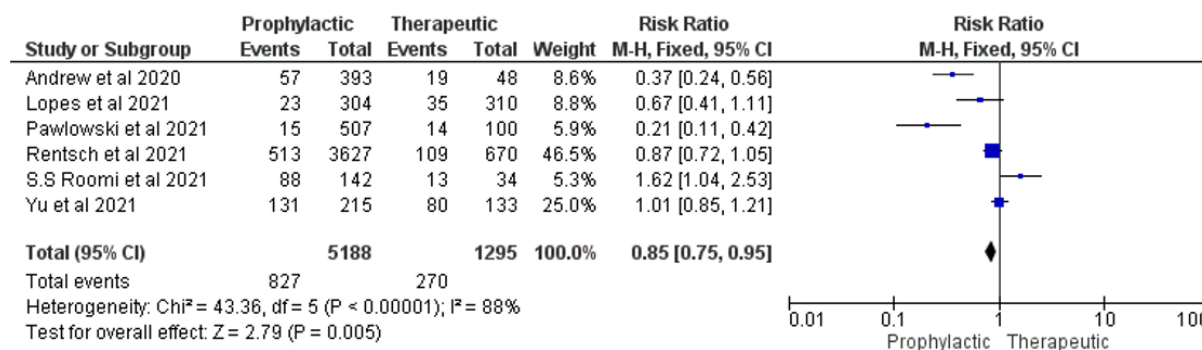Figure 1. Flowchart of the study the selection process of included studies

Figure 2. Forest plot: Comparing prophylactic and therapeutic anticoagulant in time-dependent manner toward mortality in COVID-19 patients
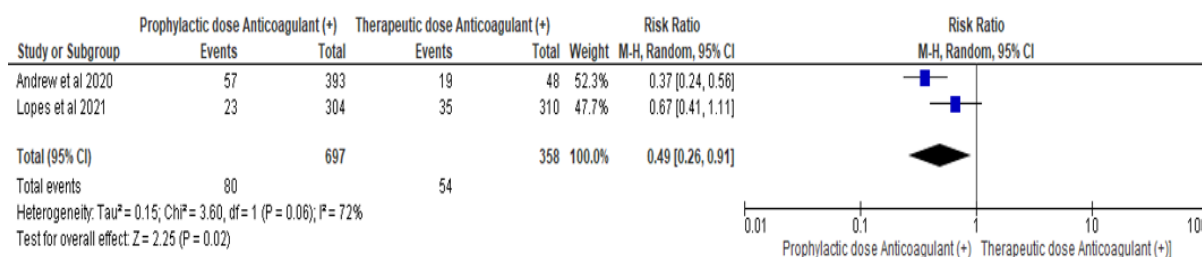

Figure 3. Forest plot: Comparing prophylactic and therapeutic anticoagulant in dose-dependent manner toward mortality in COVID-19 patients
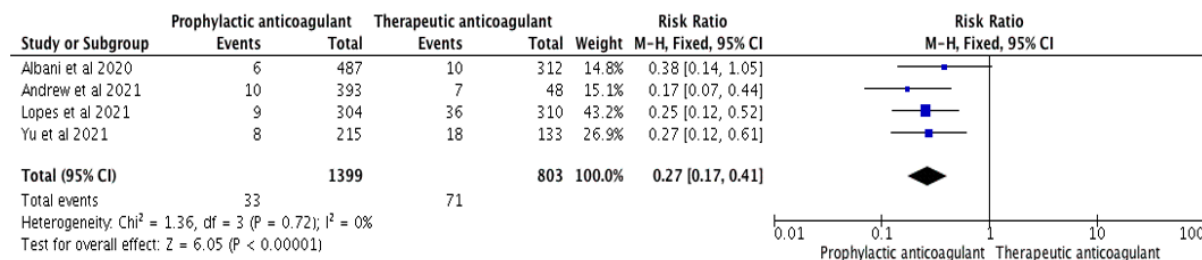

Figure 4. Forest plot: Comparing prophylactic and therapeutic anticoagulant in bleedings events in COVID-19 patients

The anticoagulant used compared by dose-dependent divided into two groups which are prophylactic dose anticoagulant group (lower dose, eg Rivaroxaban one times 40 mg) and therapeutic dose anticoagulant (higher dose, eg Rivaroxaban two times 40 mg) (Giossi *et al.*, 2021). The anticoagulants used compared by time-dependent were also divided into two groups. The first group was anticoagulants given before the venous thromboembolism event occurred (prophylactic anticoagulants). The second group was anticoagulants given at the time or after the venous thromboembolism event (therapeutic anticoagulants).

Our result, as shown in Figure 2, investigated the mortality rate of prophylactic anticoagulants compared to therapeutic in a time-dependent manner were found significant, statistically. Using therapeutic anticoagulant had a higher mortality rate than the prophylactic anticoagulant group (RR = 0.85; 95% CI = 0.75 to 0.95). As mentioned above, the therapeutic anticoagulants group was a group in which anticoagulants were given to Covid-19 patients who had already a venous thromboembolism event. We assume that the therapeutic anticoagulant group had a higher mortality rate because, in this group, the Covid-19 patients already had a venous thromboembolism

event compared to the prophylactic anticoagulants group, which the Covid-19 patients in this group had not a venous thromboembolism event yet. However, this statement needs to be reviewed more, especially regarding the time interval between drug administration and the incidence of venous thromboembolism.

We found a significant difference between prophylactic and therapeutic doses of anticoagulants in a dose-dependent manner on the mortality rate of COVID-19 patients. Prophylactic dose anticoagulant had more protective ability than therapeutic dose anticoagulant in preventing the risk of mortality (Figure 3) (RR = 0.49; 95% CI=0.26 to 0.91; p = 0.02). The primary finding of the several studies included in our pooled analysis was insignificant; however, 5 out of 6 studies reported favoring prophylactic anticoagulants to prevent mortality, compared to only one study by Roomi *et al.* This finding corroborated a study published by Parisi *et al.*, which demonstrated that anticoagulants are associated with a significantly lower risk of inpatient all-cause mortality in COVID-19 patients (Parisi *et al.*, 2021; Xiang *et al.*, 2021). Both anticoagulant regimens significantly reduced in-hospital all-cause mortality in COVID-19 patients (Moonla *et al.*, 2021). Although, based on time-dependent comparation, there was no significant difference between the therapeutic and prophylactic group in mortality, it was discovered that therapeutic dosages were associated with an increased risk of bleeding. It is well established that excessive anticoagulant exposure can result in bleeding events, which frequently result in death but did not corellate with mechanical ventilation necessity (Yueniwati *et al.*, 2022).

In contrast, the bleeding was found statistically significant out of 4 studies with a total of 2202 samples. 1399 patients were allocated to the prophylactic anticoagulant group and 803 patients to the therapeutic anticoagulant group. The pooled risk ratio is around 0.27 or 27% (RR + 0.27; Cl 95%; 0.17 to 0.41, I2=0%) (Figure 4). Earlier, we already mentioned about dose-dependent, which prophylactic dose stands for a lower dose of anticoagulant, and therapeutic dose stands for a higher dose of anticoagulant. Therapeutic dose anticoagulant correlated with higher bleeding risk on Covid-19. Therefore, The International Society of Thrombosis and Haemostasis (ISTH) has developed the Sepsis-induced Coagulopathy (SIC) criteria to guide anticoagulant therapy. The SIC score system including prothrombin time (PT),

platelet count, and sequential organ failure assessment (SOFA). The anticoagulant treat was associated with lower 28-days mortality rate in Covid-19 patients with SIC score ≥ 4 4 (40.0% vs 64.2%, p = .029), but not in those with SIC score < 4 (29.0% vs 22.6%, p = .419) (Tang *et al.*, 2020).

According to a recent study, the incidence of bleeding caused by COVID-19 was significantly higher in patients treated with therapeutic dose anticoagulants than in patients treated with prophylactic dose anticoagulants (Pesavento *et al.*, 2020). Another study found that 61% of patients received prophylactic anticoagulant, while 7% and 29% received sub-therapeutic and therapeutic anticoagulant, respectively. Therapeutic dose anticoagulant caused significantly more bleeding than prophylactic dose anticoagulant (Musoke *et al.*, 2020).

This study shows that both prophylactic and therapeutic doses have a protective effect in influencing the risk of death in COVID-19 patients in a dose-dependent manner. However, it was also found that prophylactic doses of anticoagulants have better protective effect than therapeutic doses; this is maybe caused by various things: (1) therapeutic dose anticoagulant has a higher dose than prophylactic dose anticoagulant, thus the bleeding risk of therapeutic dose anticoagulant is also higher. This is thought to affect the effectiveness of drugs acting on the bodies of COVID-19 patients; (2) Prophylactic anticoagulant doses can eliminate the fatal condition of arterial thrombosis. Meanwhile, the therapeutic dose of anticoagulant, which has a higher dose, also can eliminate the fatal condition of arterial thrombosis, but there is also increase risk of bleeding. This also raises the suspicion that prophylactic doses of anticoagulant can prevent other complications of coagulation disorders in COVID-19 patients, with the low possibility of complications.

CONCLUSION

In sum, the prophylactic dose of anticoagulant is better than the therapeutic dose for COVID-19 patients, because it has decreased mortality and fewer bleeding risk compared to the therapeutic dose of anticoagulant.

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