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Different anticoagulant regimens for non-ICU COVID-19 patients：a systematic review and meta-analysis

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Abstract: Objective: *The findings from current studies comparing the feasibility and safety of anticoagulant dosages for non-ICU COVID-19 patients were inconsistent. We conducted the meta-analysis to examine the feasibility and safety of anticoagulants therapy versus no anticoagulants therapy.****Methods:*** *We searched PubMed, Web of Science, Embase, CINAHL, Cochrane Library, Ovid, ClinicalTrials.gov, and Google Scholar until July 15, 2021. The primary outcomes were thrombosis and any bleeding events. Secondary outcomes included pulmonary embolism, deep venous thrombosis, major bleeding, and invasive mechanical ventilation. Pooled risk ratios (RRs) and pooled incidence were reported.* ***Results:*** *18,835 patients of 22 articles were selected in the systematic review and meta-analysis. The pooled incidence of any bleeding events and thrombosis were 3.4% and 9.3%. Compared with the group with no anticoagulants, the result showed that the group receiving anticoagulants was significantly associated with a 55% reduction in the risk of thrombosis(RR:0.45, 95% CI: 0.24-0.85; I2: 62.3%) but it was not significantly associated with the risk of bleeding events (RR:1.01,95% CI: 0.72-1.41; I2:23.3%). In addition, we found a lower risk of 29% in the group with prophylactic therapy (pooled RR:0.71, 95%CI: 0.57-0.88; I2:0%)in the invasive mechanical ventilation compared with no use group.****Conclusions:*** *Overall, prophylactic-dose anticoagulation was safe and feasible. We recommend it as the first consideration for non-ICU COVID-19 patients.****Trial registration****: The review protocol was registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42021259911).*

Keywords: *COVID-19, Anticoagulant dosages, Bleeding events, Thrombosis.*

1. Introduction

The prevalence of Coronavirus Disease 2019 (COVID-19) all over the world has caused more than 199 million people infected and more than 4 million deaths up to August 2021. Reports suggest that excessive inflammation, platelet activation, endothelial dysfunction, and stasis occur in patients affected by COVID-19[1], which may predispose patients to thrombotic or bleeding events. Additionally, coagulation markers such as D-dimer are elevated in COVID-19 patients, which is correlated with increased mortality. Therefore, some guidance recommend conventional anticoagulation therapy to prevent thrombosis and bleeding events, and to reduce the rate of mortality in COVID-19 patients. For non-ICU hospitalized COVID-19 patients, international clinical guidelines recommended a routine thromboprophylaxis with standard-dose UFH or LMWH should be used.[2] But some centers increased anticoagulation regimen for patients with certain risk factors. Martinelli. et.al[3] observed a 50% reduction of venous thromboembolism and low bleeding rate in patients treated with high enoxaparin dosages compared to standard dosage prophylaxis, which may due to the typical hypercoagulable state in severe Covid-19 patients. While few studies pay close attention to whether the non-ICU crowds should use anticoagulant and what dosage is effective and safe, which are controversial questions.

Therefore, the aim of the meta-analysis is to estimate the feasibility and safety of anticoagulant regimen in non-ICU COVID-19 patients in the clinical therapy.

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2. Methods

2.1 Inclusion criteria

We included adult patients who were confirmed SARS-CoV-2 infection and were hospitalized in non-ICU or general wards. And the participants in a study should be more than 10 cases. We selected studies which performed anticoagulants therapy on participants. This review selected studies that reported thrombosis events, incluidng deep venous thrombosis (DVT), pulmonary embolism (PE), invasive mechanical ventilation, and bleeding events. Randomized controlled trials(RCT), prospective and retrospective cohort studies, and cross-sectional studies were selected. We excluded articles without full text. Articles with unclear reporting methods and results were not included.

2.2 Search strategy

The research methods and manuscript were prepared based on the Cochrane Handbook for Systematic Reviews of Interventions, and it was registered with PROSPERO (CRD42021259911). We searched for all articles from Web of Science, PubMed, EMBASE, CINAHL ,Ovid and Cochrane Libraries, ClinicalTrials.gov, and Google Scholar until July 15, 2021. The search strategy is reported in Appendix I. We included only English articles.

2.3 Study selection

Following the search, Clarivate NoteExpress (version 3.4.0) was used to manage all identified articles and to remove duplicates. Two independent reviewers (L.M and L.W.) screened titles and abstracts for assessment against the inclusion criteria for the review. Potentially relevant studies were screened in full-text. After full-text screening, articles which did not meet the inclusion criteria were removed. Any disagreements and controversy between the reviewers were resolved through the third reviewer(X.L.).

2.4 Assessment of methodological quality

Two investigators (L.M. and L.W.) assessed the quality of each included study separately, JBI Critical Appraisal Checklist for Randomized Controlled Trials was used to appraise randomized controlled trials. Newcastle-Ottawa Quality Assessment Scale was used to appraise cohort studies. And JBI critical appraisal checklist for prevalence study was used to appraise cross-sectional studies. The controversies existed were resolved by a third investigator (Q.L).

2.5 Data extraction

Two reviewers (L.M. and L.W.) extracted data after reading full-text articles separately. The following data were extracted: name of author(s), time of publication, country, study design, study period, patients, setting, sex, age, intervention. In addition, important outcome variables reported by the articles were Thrombosis events, DVT, PE, Invasive mechanical ventilation, bleeding events, major bleeding. Any disagreements between the two reviewers were resolved through a third reviewer. We also tried to contacted authors of articles when we request missing or additional data for clarification. If we received no response, quantitative data should be abandoned.

2.6 Data synthesis

We estimated the effect of anticoagulation therapy or no anticoagulation by performing meta-analysis for each outcome separately. We calculate risk ratio (RR) and 95% confidence intervals (95%CIs) for each included study. What's more, we performed a meta-analysis for the pooled incidence of bleeding events, thrombosis, DVT, PE, and major bleeding for further exploration. We estimated pooled frequencies through a Freeman-Tukey double arcsine transformation using random effect models, as appropriate. Heterogeneity between studies was assessed by Higgins I2 analysis. When the statistical heterogeneity was high (I2>50%), the results were obtained by a random effects model. Through omitting the studies (once a time) and then calculating the combined estimates for the remaining studies, we use a sensitivity analysis to explore the source of heterogeneity and ensure the robustness of the results. Moreover, we conducted subgroup analysis including regions, study design, population characteristics, interventions and sample size to explore the heterogeneity source among studies. Publication bias was assessed by Begge's test, Eggers'test and funnel plot. And we performed the analyses by STATA 16.0

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(Stata Statistical Software: Release 15, 2019, StataCorp LLC, College Station, Texas)

2.7 Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of the evidence was followed, and a Summary of Findings was created using GRADEpro GDT Version 4 (McMaster University, ON, Canada). The Summary of Findings presents the following information where appropriate: outcomes, effect size (we reported the pooled incidence or risk radio), impact, number of participants and studies, a certainty grade of the evidence-based on the risk of bias.

3. Results

3.1 Study inclusion

The initial search identified 18,034 records through databases. Following a title and abstract screening, a total of 1,052 articles were reviewed in full text. Finally, 22 studies were included according to our eligibility criteria. A flow diagram is listed for study selection.

3.2 Methodological quality

The overall risk of bias for the 1 RCT, 14 retrospective cohort studies, 2 prospective cohort studies and 5 cross-sectional studies was varied, but we included all studies to provide a comprehensive review. The critical appraisal scores were calculated using the checklist from the Joanna Briggs Institute for randomized controlled trials, cohort studies and cross-sectional studies; they are provided in Appendix II. The quality of the randomized controlled trial was judged as high. For cohort studies, the lowest recorded score was 7, while the highest was 11 out of a total of 11, indicating that the quality of those studies was moderate to high. In these articles, the measurement of the exposure, outcomes and confounding variables were judged to be reliable and of good quality, which were one of the advantages of the studies. However, in some articles, no information was provided followed-up time and some studies provided outcomes at different follow-up time, resulting in heterogeneity. For cross-sectional studies, the scores were judged as 8 in 3 studies and only one study was judged as 3 for the lower quality of the identification and management of confounding variables. Therefore, the quality of the studies was low and high.

3.3 Characteristics of included studies

Finally 22 studies were selected, 16 were cohort studies (14[4-17]retrospective and 2[18, 19] prospective), 5[20-24]were cross-sectional studies and 1[25]was an RCT. We limited to English articles. COVID-19 patients (n=18,835) were selected, 17,537(93.11%) were non-ICU patients and 1,298 (6.89%) were ICU patients. The rest studies did not identify the population clearly. The sample size ranged from 43 to 4,389 participants. The majority of the studies (N=16) focused on non-ICU COVID-19 patients, 6 studies reported the proportion of ICU patients, while the remaining did not mention the clear population. In addition, 19 studies observed outcomes at treating with anticoagulant treatment or no use anticoagulants. Moreover, 8 studies only used anticoagulants of LMWH, Heparin or UFH, 9 studies included multiple anticoagulants, and 4 studies recorded no information on the type of anticoagulants. Specifically, studies had different anticoagulant regimens and dosages. The general characteristics of the 22 studies are shown in Appendix III. The clinical outcomes of included recorded in Appendix IV.

3.4 Review findings

To evaluate the feasibility and safety of anticoagulant therapy for COVID-19 patients, we performed a meta-analysis of outcome variables from two aspects. On the one hand, we estimated the pooled incidence of each outcome for patients receiving anticoagulant therapy, including bleeding, thrombosis, DVT and PE. According to the pooled incidence of outcomes, we compared them with those in previous studies. On the other hand, data for each outcome were made a comparison between anticoagulants therapy group and no use of anticoagulants group, including bleeding, major bleeding, thrombosis, DVT, and invasive mechanical ventilation. Additionally, only one RCT reported PE so that we can not perform a meta-analysis. **Table 1** shows the outcomes of included studies.

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Table 1A. The pooled incidence of outcomes for COVID-19 patients receiving anticoagulants therapy.

Variable	No. of studies	No. of patients	The pooled incidence (95% CI)
Thrombosis events	16	5,910	0.093 (0.059, 0.134)
DVT	13	5,161	0.045 (0.022,0.074)
PE	7	2,870	0.024 (0.003,0.058)
Bleeding events	13	9,748	0.034 (0.033, 0.048)

Table 1B. A comparison between anticoagulants therapy group and no use of anticoagulants group.

Variable	No. of studies	No. of patients	Relative radio (95% CI)
Thrombosis events	4	4,859	0.45 (0.24, 0.85)
DVT	3	4,858	1.42 (0.55, 3.71)
PE	1	3,480	NA
Invasive mechanical ventilation	3	3,771	1.05(0.45,2.44)
Bleeding events	7	14,463	1.01 (0.72, 1.41)
Major bleeding	1	3,480	NA

3.4.1 The pooled incidences of interesting outcomes in the population receiving anticoagulant therapy.

In the population receiving anticoagulants therapy, **Figure 1** presents the pooled incidence of overall bleeding events and thrombosis events. We estimated 13 studies, after using an double arsine fixed effects meta-analysis, the incidence of bleeding events ranged from 0.4% to 9.6% and the combined incidence estimate of bleeding was 3.4%, (95%CI: 0.033-0.048, I2:89.3%). Moreover, including studies only using heparin or LWMH (N=4,107), the pooled incidence of bleeding events was 1.9%(95% CI:0.010-0.029, I2:0.0%, double arcsine fixed effects) in subgroup meta-analysis. When it comes to the pooled incidence of thrombosis, we estimated for 16 included studies ranged from 0.0% to 28.6%, and pooled-estimated incidence of thrombosis was 9.3%(95%CI: 0.059-0.134, I2:95.0%) after using an double arcsine random effects meta-analysis. However, some evidence of publication bias was found, by visual inspections of the funnel plots and by Begg's Test (Pr > |z| = 0.008) and Egger' test (bias coefficient: 3.73; 95% CI: 2.01, 5.46; P > |z| = 0.001). What's more, the incidence of PE was 2.4%(95%CI: 0.003-0.058, I2:92.5%) and the incidence of DVT was 4.5%(95%CI: 0.022-0.074, I2:93.0%).

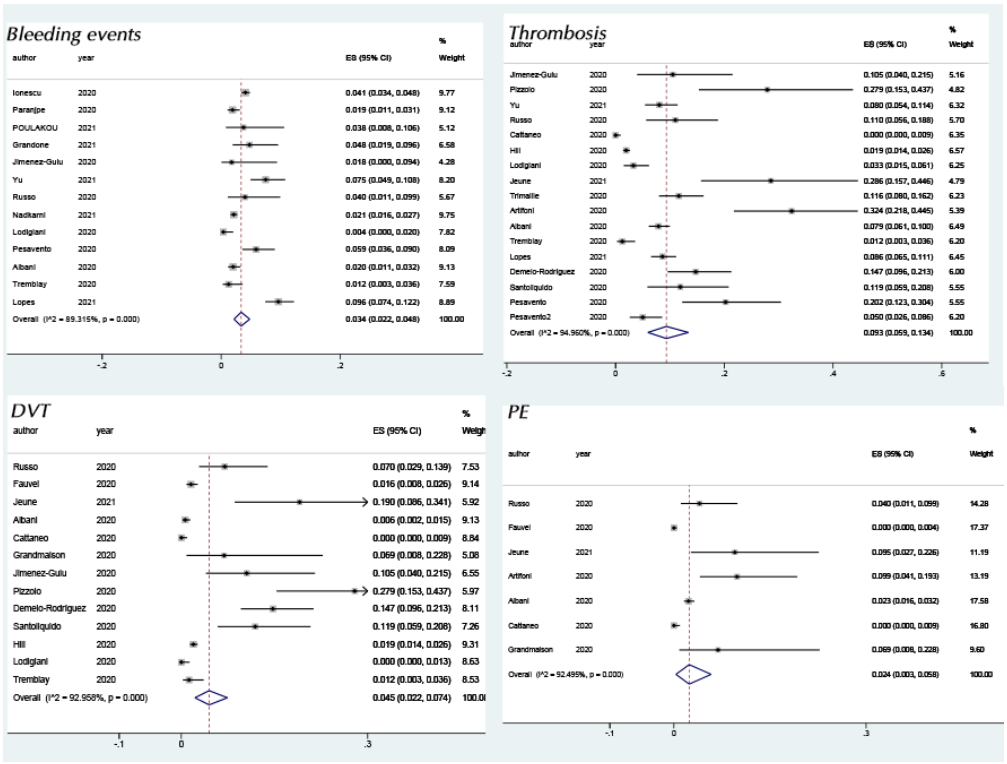

Figure 1. The pooled incidence of bleeding, thrombosis, DVT and PE.

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3.4.2 Feasibility and safety comparison between anticoagulant therapy group and no anticoagulant group.

The 8,841 non-ICU COVID-19 patients accounted for 87.74% of the total weight (excluded 4 articles of unclear proportion). The use of anticoagulant was not associated with bleeding compared with no use group (pooled RR: 1.01, 95% CI: 0.72--1.41; I2: 23.2%, random effects model;). To further analysis, the use of anticoagulant was also not associated with major bleeding in comparison with no use group (pooled RR: 1.45, 95% CI: 0.50--4.18; I2: 0.0%, random effects model).

The non-ICU COVID-19 patients accounted for 99.12%(4,870/4,910) of the total weight(excluded 3 articles of unclear proportion). On the basis of our results, patients with anticoagulant therapy were lower risk of thrombosis events (RR: 0.45, 95% CI: 0.24-0.85; I2:62.3%) compared with no anticoagulant therapy group. In addition, using anticoagulants did not reduce the risk of DVT compared with no use group (pooled RR: 1.42, 95%CI:0.55-3.71; I2: 0.0%). To further analysis, patients treated with therapeutic dosage were not associated with the reductions or increases of DVT in cohort studies (pooled RR:3.29, 95% CI:2.21-9.68; I2: 0.0%) and RCT (pooled RR: 0.98, 95% CI:0.29-3.33; I2: 0.0%) compared with prophylactic dosage group. Similarly, patients treated with therapeutic dosage group were not significantly associated with the reduction of PE in the RCT (pooled RR: 0.53, 95%CI: 0.21--1.32; I2: 0.00%) compared with those of prophylactic dosage group.

Compared with no anticoagulant use, the meta-analysis showed no significant association between anticoagulant treatment group and no use of anticoagulant group in the field of invasive mechanical ventilation (pooled RR: 1.05, 95% CI: 0.45-2.44; I2:65.3%) after excluding Paranjpe et al. But we found a lower risk of 29% in prophylactic doses group (pooled RR: 0.71, 95% CI: 0.57-0.88; I2: 0%).

4. Discussion

Our systematic review and meta-analyses found three points. First, for bleeding complications, anticoagulant use did not bring a higher risk of bleeding events among non-ICU COVID-19 patients. Second, for thrombosis events, anticoagulant therapy also had a 55% decreased risk of compared with no use. Third, prophylactic doses were found a lower risk of 29% in comparison with no use group in the field of invasive mechanical ventilation.

4.1 Bleeding events

Our meta-analysis presented the pooled incidence of overall bleeding events in anticoagulant population was 3.4%. Al-Samkar et al[30] reported an incidence of major bleeding of 2.8% in a multi-center cohort study. Our results included overall bleeding events, and it could explain the higher incidence. In subgroup meta-analysis, the incidence decreased to 1.9% including studies only using heparin or LWMH (N=4,107), it is an interesting finding. Mattioli et al.[31] performed intermediate doses of LWMH in non-ICU COVID-19 patients, and they found it didn't increase the risk of bleeding events. LMWH was selected in the guidance due to the convenience of use and no need for laboratory monitoring. But if renal impairment occurred, heparin may be preferred. However, the types of anticoagulants for COVID-19 patients in clinical were not consistent. Although the incidence of bleeding events was low, major bleeding increased the risk of mortality, especially inpatients using therapeutic anticoagulants. Therefore, clinical nurses need to monitor coagulation indicators and bleeding signs of patients strictly. The HAS-BLED rating system or thromboelastography (TEG) could assess for bleeding risk of stratification and guide for anticoagulant regimens. We found using anticoagulants did not significantly increase the risk of bleeding compared with the no use of anticoagulants group, which was supported by Pesavento et al[29]. and Nadkarni et al[14]. What' more, prophylactic anticoagulants was not associated with an increase of bleeding events and major bleeding events.

4.2 Thrombosis events

The pooled incidence of thrombosis is 9.3% in patients receiving anticoagulants, it is similar to those reported in other reviews. A large systematic review[29](N=66) reported a VTE prevalence of 7.9% in non-ICU. Although the use of prophylaxis even therapeutic anticoagulation in patients, thrombosis events occurred in many patients. Therefore, risk in non-ICU hospitalized patients should not be ignored, it is essential to establish ideal anticoagulation regimens to reduce the high risk of thrombosis events, such as a biomarker-based personalized anticoagulant regimen.[30] The incidences of PE and DVT in non-ICU was 2.4% and 4.5%, respectively. However, a study[34] estimated a higher incidence of PE and

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DVT(8.5% and 8.2%) and this meta-analysis mixed a small proportion of ICU patients, which may be the reason of higher incidence. Above all, in our meta-analysis, the pooled incidence of PE and DVT lower than previous, it can be explained that COVID-19 patients with anticoagulant therapy had a reducing the occurrence of PE and DVT. It supported the effectiveness of anticoagulants in non-ICU patients.

Our results showed anticoagulants therapy lowered the risk of thrombosis compared with no use of anticoagulants. The results investigated the feasibility of anticoagulants in the reduction of thrombosis events. However, therapeutic doses tended to be risk factors of thrombosis complications among included cohort studies compared with the prophylactic treatment group. Patellindicated hospitalized COVID-19 patients with intermediate or therapeutic dosage were similar to those who received standard dosage anticoagulation. Their views verified our meta-analysis. Therapeutic doses not only failed to reduce the risk of thrombotic complications but also increased the hemorrhagic risk. So the use in patients with non-ICU COVID-19 should be cautious. The similar phenomenon also appeared in the meta analysis of DVT. A possible explanation of these variations may be COVID-19 patients with therapeutic dosages treatment had fierce inflammatory causing thrombosis, which may be an important mechanism for the high rate of VTE, and Helms et al.[31] also reported a high risk of thrombosis in patients receiving therapeutic anticoagulants.

4.3 Invasive mechanical ventilation

In comparison with no anticoagulants, using prophylactic dosages lower the occurrence of invasive ventilation compared with no use of anticoagulants. Invasive ventilation for long time was associated with a respiratory failure in COVID-19 patients. And invasive mechanical ventilation may cause an increasing mortality rate of 25 to 57%[32]. Therefore, a high mortality rate occurred in COVID-19 patients associated with mechanically ventilated patients. Our results reported anticoagulants group was associated with lower occurrence of invasive ventilation events. Anticoagulation may play an important role anti-thrombotic, anti-inflammatory and anti-viral mechanisms to improve clinical outcomes. Our results was consistent with Matli et al.[33] Nursing management should focus on supportive care and should control the use of invasive mechanical ventilation.

4.4 Heterogeneity

Substantial heterogeneity existed among our studies of pooled incidences and risk radio of bleeding and thrombosis. Possible explanations may be samples of patients from different countries and data sources, varying different species of anticoagulants and mixed few intensive patients. What's more, different studies adjusted for different covariates. Evidence from our rigorous meta-analysis of studies provides similar findings compared with the results from the RCT and other studies acting on non-critically ill COVID-19 patients despite high heterogeneity exited. Given the heterogeneity in meta-analysis of our studies, clinicians would be best to take consideration with caution to specific patients .

4.5 Strengths and Limitations

Our article has several advantages. First of all, it is the first study for non-ICU COVID-19 patients, while past studies (such as Hasan et al.[35]) paid attention to ICU population or all patients in the hospital. Secondly, our outcome indicators are more than other studies. Mansory et al.[34]paid attention to venous thromboembolism in non-critically COVID-19 patients, but we analyzed more indicators, such as thrombosis, DVT, PE, and invasive mechanical ventilation,bleeding and major bleeding events, which provided a stronger and more comprehensive evidence to evaluate the feasibility and safety of anticoagulant therapy. Thirdly, we included observational studies to estimate the pooled frequency of thrombosis and bleeding events.

Our study also has some limitations. First, different confounding factors exited in selected studies, and we could not compare the baseline characteristics of each study. Our study aims at non-ICU COVID-19 population, while a small proportion of ICU or critically ill COVID-19 patients were mixed, which may cause bias of results. Second, we found only a RCT and other are all cohort studies when we compared two groups of interest outcomes. Third, high heterogeneity existed in some meta-analysis results. In accordance with the JBI Grades of Recommendation, the quality of this systematic review was very low. Therefore, the results should be considered with caution, since the possibility of confounding could not be excluded fully.

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5. Conclusion

We report a significant reduction of thrombosis events and invasive mechanical ventilation in non-ICU COVID-19 patients receiving anticoagulants. At the same condition, the risk of bleeding has not significantly increased. However, due to limited time on the study (the outbreak of COVID-19 since 2019) and several studies for non-ICU patients, more multi-center randomized clinical controlled trials are required to verify the feasibility and safety of prophylactic anticoagulant therapy, and we are looking forward to further studies exploring suitable anticoagulants dosage for COVID-19 patients in different severity.

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