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Journal of Clinical Cardiology and Cardiovascular Interventions
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Research Article

Decreased Mortality of COVID-19 with Anticoagulants and Antiplatelet Therapy in Patients with High Risk of Thromboembolism a Meta-Analysis

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Received Date: March 18, 2021; **Accepted Date:** April 26, 2021; **Published Date:** May 03, 2021

Citation: Qiao Deng, Fengweng Feng, (2021) Decreased Mortality of COVID-19 with Anticoagulants and Antiplatelet Therapy in Patients with High Risk of Thromboembolism a Meta-Analysis. *J. Clinical Cardiology and Cardiovascular Interventions*, 4(9); **Doi:10.31579/2641-0419/153**

Abstract

BACKGROUND: The clinical presentation of patients with COVID-19 varied considerably, ranging from asymptomatic infection to severe pneumonia that may lead to coagulation abnormality and pulmonary thromboembolism. Targeted antithrombotic therapy may be beneficial to reduce the incidence of thromboembolism in patients with COVID-19.

METHODS: We will conduct a systematic review based on searches of major databases (PUBMED, Web of Science and EMBASE) and clinical trial registries from inception to present. The search strategy included clinical date published until Aug 12, 2020. All published randomized retrospective, control and quasi-randomized trials, and observational studies related to antiplatelet/anticoagulant therapy for COVID-19 patients with high risk of thromboembolism will be included. The primary outcome was death events, secondary outcome was disease severity of COVID-19. We used Review Manager 5.3 software to calculate the odds ratio and corresponding 95% CI. The $\chi 2$ test (assessing the P) and the I2 statistic were performed to estimate the heterogeneity.

RESULTS:

Compared with non-antiplatelet/anticoagulant therapy, antiplatelet/anticoagulant therapy was not associated with disease severity (odds ratio, 0.70 [95% CI, 0.41–1.21], P=0.20, I2=52%) but was related to lower mortality of COVID-19 in patients with high risk of embolism (odds ratio, 0.33 [95% CI, 0.24–0.47], P<0.001, I2=8%).

CONCLUSION: Current evidence suggested that antiplatelet/anticoagulant therapy should be continued in COVID-19 patients with high risk of thromboembolism. the majority of patients with severe COVID-19 should have received similar supportive treatment after admission.

Keywords: COVID-19; SARS-CoV-2; Coronavirus associated coagulation

Introduction

Severe coronavirus disease 2019 (COVID-19) usually complicated with coagulopathy requiring effective treatment urgently. Coronavirus associated coagulation (CAC) disease can cause various thrombotic complications especially in critical illness patients with SARS-CoV-2, its pathogenesis may be related to endothelial injury and increased prothrombotic factors.[1] The incidence rate of thrombotic complications was 31% in patients with SARS-CoV-2, pulmonary embolism is the most common thrombotic complication which accounts for 81% of thrombotic complications. [2] The formation of hyaline thrombus in small blood vessels was also described in the autopsy of COVID-19 patients. In addition, long-term immobility and hormone replacement therapy may increase the risk of venous thromboembolism in severe COVID-19. Although preventive anticoagulation or antiplatelet is recommended for all hospitalized patients, treatment data are limited. Thus, we performed a meta-analysis of the current studies to explore whether the use of antiplatelet/anticoagulant therapy was associated with disease severity and mortality in COVID-19 patients with a high risk of thromboembolism.

Materials and methods

Literature search

To ensure high quality evidence, we followed the preferred reporting project for Systematic Reviews and Meta-analysis statements. A comprehensive search of the PubMed, Web of Science, EMBASE and

clinical trial registries was performed to identify all relevant articles published between Dec 27, 2019 and Aug 12, 2020. The search terms were as follows: 'COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR Coronavirus OR 2019 novel coronavirus' AND 'antithrombotic OR antiplatelet OR anticoagulant OR ticagrelor OR low molecular weight heparin OR acetylsalicylic acid OR P2Y12 inhibitor OR tirofiban'. Additionally, manual searches were performed on articles, related comments articles and meta analyses retrieved.

Inclusion criteria

Observational studies that meet these criteria are included: (1) study design: cohort study, self-controlled case series or case control; (2) antithrombotic drugs treatment: antiplatelet/anticoagulant use versus Non- antiplatelet/anticoagulant use; (3) outcomes: the severity and mortality rate of COVID-19; (4) appropriate data were used to incorporate the risk estimates if the adjusted data were not available in these articles. If adjusted data are not provided in publications, appropriate data are used to extract risk estimates. When detailed information was fragmentary in the article, attempts were made to contact the research investigators to acquire absent information. Two investigators independently extracted useful data from the article in a double-blind manner. This information including (research type, first author's name, publication year, gender, drugs, risk factors, number of participants, confounder adjustments) is extracted. The Newcastle Ottawa Scale was used to appraise the methodological quality of the comprised content, the included observational studies were judged as high quality with a score of 8/9~6/9.

Synthesis and analysis

All meta-analytical calculations were performed with Review Manager software (version 5.3). To provide a quantitative evaluate of the severity and mortality risk in COVID-19 patients, the odds ratios (ORs) and the corresponding 95% CIs were extracted from research. Statistical heterogeneity of the studies was calculated through utilize the χ^2 test and the I^2 statistic (substantial heterogeneity: I^2 >50 % or $P < 0.05$). A random or fixed-effects model was applied to statistical heterogeneity. The potential publication bias was not methodically assessed because every meta-analysis contained fewer than 10 studies.

Results

Search results

The search strategy identified 1183 studies, of which 778 articles were repeated. A total of 357 articles were excluded by reviewing the title and abstract, the remaining articles were meta-analyzed. Ultimately, 6 articles were qualified for this meta-analysis. Together, the included articles evaluated more than 3,600 COVID-19 patients. The details list of excluded studies and reasons (**Figure. 1**).

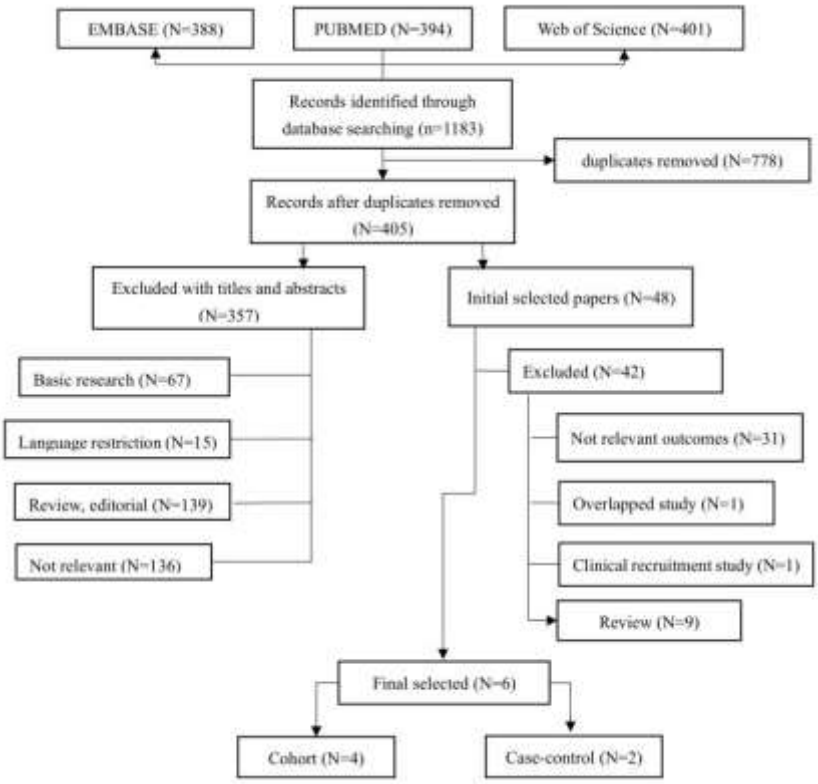

Figure 1: *Flow chart showing the meta-analysis studies selection.*

All eligible studies were published this year or online in advance, with sample patient sizes ranging from 10 to 2773 patients. The overall average age of the subjects was greater than 40 years. The primary outcome was death events, secondary outcome was disease severity of

COVID-19. The patient characteristics and antithrombotic drugs of the included studies are shown in Table 1.

Author	Study design	Study period	Male	Drugs	Risk factors	Anti throm-botic	Non-Anti throm-botic	Measurement of anti-thrombotic use
Maurizio et al. 2020	single-center retrospective case-control	April 9 to April16, 2020	80%	acetylsalicylic acid/oral clopidogrel + tirofiban	D-dimer, 3.038 ~ 4.038μg/ml	5	5	Medical record review
Brouns et al. 2020	Multi-center retrospective case-control	March 20 to May 1, 2020	25%	antiplatelet therapy + vitamin K antagonist / direct oral anticoagulant	Transient ischemic attack, myocardial infarction, Atrial fibrillation	38	29	Medical record review
Tang et al. 2020	Single-center retrospective cohort	Jan 1 to Feb 13, 2020	60%	low molecular weight heparin	D-dimer > 3.0 μg/ml.	99	350	Medical record review
Vincenzo et al. 2020	Multi-center retrospective cohort	Feb 2020 to April 2020	59%	P2Y12 inhibitor + acetylsalicylic acid	Atrial fibrillation, ARDS	55	111	Medical record review
Li et al. 2020	single center retrospective observational study	Jan 16 to Feb 19, 2020	55%	Aspirin or clopidogrel	Acute ischaemic stroke, higher D-dimer levels	10	209	Medical record review
Ishan et al. 2020	Single-center retrospective cohort	March 14 to April 11, 2020	50%	Systemic anticoagulation therapy	Invasive mechanical ventilation, coagulopat-hy	786	1987	Medical record review

Table 1: *Characteristics of the Included Studies.*

Antithrombotic and influence on COVID-19 When our analysis was limited to the studies that only included patients on antiplatelet/anticoagulant for antithrombotic therapy indications, we included 6 studies comprising 689 patients with high risk of thromboembolism and COVID-19 infection. Compared with non-antiplatelet/anticoagulant therapy, antiplatelet/anticoagulant therapy was not associated with disease severity (odds ratio, 0.70 [95% CI, 0.41–1.21], P=0.20, I^2=52%, **Figure. A**) but was related to lower mortality of COVID-19 in patients with high risk of embolism (odds ratio, 0.33 [95% CI, 0.24–0.47]; P<0.001; I^2=8%; **Figure. B**).

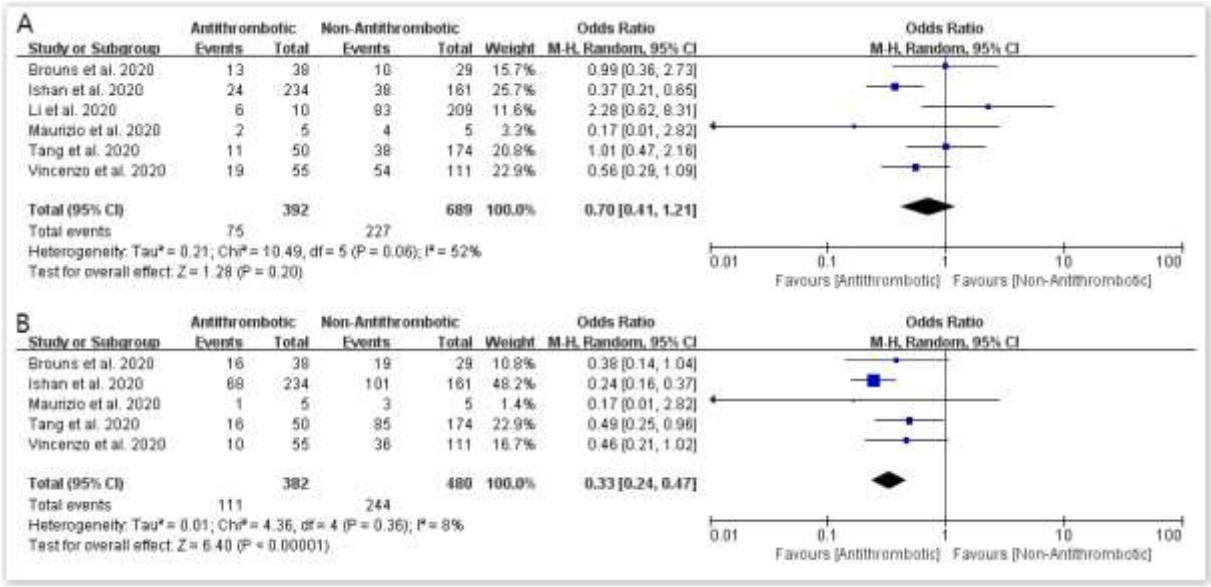

Figure.2: *Meta-analysis on effect of antiplatelet/anticoagulant therapy on coronavirus disease 2019 (COVID-19) patients with high risk of thromboembolism. Forest plots of (A) disease severity and (B) mortality in the antiplatelet vs the non-antiplatelet groups in COVID-19 patients with high risk of thromboembolism. M-H indicates Mantel-Haenszel.*

Discussion

There are several ways in which the COVID-19 pandemic may affect the drug prevention and clinical management of thromboembolic disease. [3] Through the direct or indirect action of the virus (mediated by systemic inflammatory response syndrome), the SARS-CoV-2 can cause thrombus complications of venous and arterial circulation. Two typical hemostatic abnormalities shown in COVID-19 patients were high levels of D-dimer and mild thrombocytopenia. [4] Other common abnormalities found in patients with COVID-19 include decreased lymphopenia, elevation in lactate dehydrogenase and inflammatory markers such as C-reactive protein, ferritin and interleukin-6. The severity of COVID-19 is variably associated with prolongation of the prothrombin time and international normalized ratio, and shortened activated partial thromboplastin time. Collectively, these hemostatic parameters changes demonstrate several forms of coagulopathy that can predispose to thromboembolic events. Nevertheless, it is unclear whether these hemostatic parameters changes are either particular effect of SARS-CoV-2 or caused by cytokine storm that precipitates the onset of systemic inflammatory response syndrome.

Antiviral therapies for treating COVID-19 (such as, azithromycin, bevacizumab, chloroquine/hydroxychloroquine, methylprednisolone, pirfenidone, and ribavirin) may have severe drug-drug interactions with antiplatelet/anticoagulants agents. [5] The specific interactions mechanism between these medications and oral anticoagulants remains to be further determined. Ritonavir/lopinavir may also affect selection and dosage of multiple anticoagulants, for instance, vitamin K antagonists, betrixaban and apixaban may require dose adjustment whereas rivaroxaban should not be used simultaneously with ritonavir/lopinavir. [6] Furthermore, parenteral anticoagulation therapy is recommended in most cases in which anticoagulant is required for thrombotic disease. Low molecular weight heparin (LMWH) is a reasonable alternative in the case of sudden venous thrombosis. Moreover, there are no major drug interactions between investigational COVID-19 therapies and parenteral anticoagulants such as LMWH, tirofiban and eptifibatide. [7]

In summary, Antiplatelet/anticoagulant therapy did not aggravate disease severity of COVID-19. Besides, antiplatelet/anticoagulant therapy can decrease the mortality of COVID-19. Current evidence suggested that antiplatelet/anticoagulant therapy should be continued in COVID-19 patients with high risk of thromboembolism. the majority of patients with severe COVID-19 should have received similar supportive treatment after admission.

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DOI:10.31579/2641-0419/154