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Effect of Anticoagulants or Antiplatelets Administration on Mortality Case in COVID-19 Patients with Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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ABSTRACT

Acute ischemic stroke (AIS) is a life-threatening complication of COVID-19. This study aims to compare anticoagulant or antiplatelet administration on mortality cases in patients with COVID-19 and AIS. To know the mortality rate in COVID-19 patients with AIS after anticoagulants or antiplatelets therapies. We searched PubMed, ScienceDirect, and Google Scholar for a retrospective cohort study of anticoagulant or antiplatelet effects on mortality cases in COVID-19 and AIS patients. The retrospective cohort was screened using our eligibility criteria, and quality was assessed using the Newcastle Ottawa Scale. Heterogeneity was assessed using the I^2 test, and publication bias was evaluated using a funnel plot. All analyses were performed using Review Manager 5.4. Seven retrospective cohort studies involving 58 patients (38 of whom received anticoagulant therapy) met the inclusion criteria. Our combined analysis showed that anticoagulation versus antiplatelet therapy in COVID-19 patients with AIS on the forest plot chart did not significantly affect mortality (OR: 0.9 95% CI 0.42-1.91 I^2=0 %). The study showed no significant difference in the incidence of death between anticoagulants or antiplatelet agents to COVID-19 patients with AIS.

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INTRODUCTION

In six months since its emergence, the number of severe acute respiratory distress syndrome coronavirus 2 (SARS-Cov-2) has exceeded six million, with more than 360.000 deaths. WHO named coronavirus disease 2019 (COVID-19) and declared it a pandemic on March 11, 2020. Even though the lung is the main target, this virus is also neurovirulent and neuroinvasive. Hence, it can be present with a neurological manifestation. Acute ischemic stroke (AIS) is one of the life-threatening complications of COVID-19. There is a 0.9-2% incidence of stroke between COVID-19 inpatients. Furthermore, there is a high mortality rate in COVID-19 followed by stroke.[1] The etiology of AIS in COVID-19 patients is presumably related to coagulopathy which is caused by inflammation of COVID-19 infection.[2,3]

To date, information regarding AIS following COVID-19 infection is still rare. In this pandemic situation, a better understanding of the pathophysiological mechanism related to COVID-19 and the characteristics of cerebrovascular disease are essential to estimate the outcome and guide for therapy selection. The purpose of this research is to know the mortality rate in COVID-19 patients with AIS after being given anticoagulants or antiplatelet therapies.

REVIEW

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. From December 1, 2019, to November 15, 2021, a complete literature search was undertaken in PubMed, ScienceDirect and Google Scholar. The search strategy consisted of various keywords, including AIS, anticoagulant, antiplatelet, COVID-19, and mortality. Our search through the database provided 959 studies that included AIS, anticoagulant, antiplatelet, COVID-19, and mortality. After deleting the duplicates, we filtered 793 abstracts. After excluding several studies, only seven articles qualified to be included in the quantitative synthesis. All of the retrospective cohort studies that reported COVID-19 patients with AIS were included in the initial search. We eliminated studies that did not include full text, did not have English translation, and studies that gave combination therapy of anticoagulant and antiplatelet (Figure 1).

Three authors extracted relevant qualitative and quantitative data. Data extracted included the patient's demographics (age and gender), the time between infected with COVID-19 until developing neurological deficit, NIHSS (National Institute Health Stroke Scale), the ischemic stroke subtype according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification, D-dimer level, treatment (anticoagulant or antiplatelet), and the outcome (mortality). Retrospective cohort studies were filtered using eligibility criteria, and the quality was assessed using the Newcastle Ottawa Scale. Heterogeneity was assessed with the I^2 test, and publication bias was evaluated with a funnel plot. All analyses were done using Review Manager 5.4.

Demography characteristics and clinical study

Quantitative analysis from the collected data found 58 COVID-19 patients with AIS. Of those patients, 46.15% were male. The average age was 58.82 $\pm$ 31.18. For the patients with COVID-19 symptoms, the duration from the emergence of the symptoms to neurologic deficit was 9.38 $\pm$ 5.5 days. The mean NIHSS during first admission or the first time a neurological deficit emerged was 17.09 $\pm$ 2.79. The laboratory results showed an increase in D-dimer level with a mean of 5,478.91 $\pm$ 55,521.09. According to TOAST criteria, the most common stroke subtype was undetermined stroke/cryptogenic stroke (58.70%). There were 38 (65.52%) COVID-19 patients treated with AIS with oral or intravenous anticoagulants, and the mortality rate was 14 (36.84%). On the other side, 20 (34.48%) of the patients were treated with a single antiplatelet, and the mortality rate was 7 (35%) (Table 1).

Administration of anticoagulant or antiplatelet on mortality rate of COVID-19 patients with AIS

There was no significant mortality rate difference between the administration of anticoagulant or antiplatelet in COVID-19 patients with AIS, with p-value = 0.78 and z-score = 0.28 (Table 2).

Bias risk of all study

Seven studies were included in the quantitative analysis. The funnel plot was symmetrical, indicating no bias in publication (Figure 2).

Based on the study results, the mean age was 58.82 $\pm$ 31.18. This is in accordance with a previous study comparing AIS with and without COVID-19, where the age of AIS patients with COVID-19 is younger. At the time of admission or the emergence of the neurological deficit, the mean NIHSS was 17,09 $\pm$ 2,79. Studies have shown that COVID-19 patients have a higher NIHSS. The D-dimer level was also increased with a mean of 5,478.91 $\pm$ 55,521.09. The most common AIS subtype in COVID-19 patients was a cryptogenic stroke. Compared with the control group of stroke history, patients with COVID-19 and stroke are more likely to be male (71.9% vs. 45.0%, p = 0.012).[4] Further bivariate analysis is needed to determine how strong the relationship between every prognostic factor and the mortality rate is.

Based on the presented retrospective cohort study, there is a tendency for treatment with anticoagulants compared to antiplatelet in COVID-19 patients with AIS to prevent secondary stroke. Studies

have shown no significant difference between the administration of anticoagulants and antiplatelets for COVID-19 patients with AIS. This diamond in the forest plot, cutting the line from the vertical axis, indicates that this study result is not significant and not precise.

Establishing a diagnosis in COVID-19 patients with neurologic symptoms of acute stroke is the basis for giving primary and secondary stroke therapy. A Computed Tomography (CT) scan of the head without contrast is a good first step, especially before beginning antithrombotics. Laboratory tests, such as a complete blood count and coagulation markers, are necessary before starting antithrombotic therapy.[5]

To identify optimal antithrombotics for secondary prevention of AIS associated with COVID-19, we need to better understand the mechanisms underlying these strokes. For example, thrombosis could occur through alteration in the walls of blood vessels in viral infections. This alteration could result from (1) an inflammatory response where the virus invades endothelial cells affecting coagulation factors and damaging the endothelial wall, and (2) direct invasion by viruses.[6]

Vasculopathy is a general principle to describe any condition affecting blood vessels. Several mechanisms explain the association between systemic viral infection and intracranial vasculopathy. One of the mechanisms is the systemic vascular response that can cause inflammation of the blood vessel walls, direct changes in the shape of the vessel walls, rupture of atherosclerotic plaques, including viral binding components to endothelial cells, and activation of adhesion molecules.[6]

Platelets are the main component in the primary hemostatic system. The presence of the virus influences thrombus initiation and growth through the induction of platelet aggregation and fibrin as an acute phase reactant. Active viral infection can result in a coagulation cascade, indicating a secondary hemostatic system. The primary etiology underlying hypercoagulation is characterized by increased levels of D-dimer, lactate dehydrogenase, and decreased fibrinogen levels in severe COVID-19 patients.[7] Hypercoagulation markers and high levels of inflammatory mediators may be associated with poor outcomes in acute respiratory distress syndrome (ARDS) and sepsis patients. Studies have shown that prophylactic or therapeutic doses of heparin may benefit COVID-19 patients with severe symptoms of coagulopathy caused by sepsis. Heparin can change the biological properties of the virus, not only through its anticoagulant properties but also because of its anti-inflammatory effect, especially on blood vessels.[8]

Although several studies have shown the possibility of hypercoagulation in COVID-19 patients with AIS, there are currently no guidelines on anticoagulant therapy in preventing secondary stroke, especially in cases where the coagulation marker is high, the etiology of ischemic stroke is unclear. Optimal secondary stroke prevention in the COVID-19 patient group differs from secondary prevention management in ischemic stroke patients and cardiovascular risk factors. Some patients may already be taking anticoagulants or antiplatelets for pre-existing cardiovascular conditions before COVID-19 treatment.

Thus, the decision regarding the optimal antithrombotic, either anticoagulant or antiplatelet, should be individualized considering the clinical and radiological features of the patient, further ischemic pathomechanisms, and the potential risk of bleeding. Other studies are needed to assess the effectiveness of the antithrombotic given, considering that long-term management after COVID-19 is still a challenge. In addition, the ideal duration of antithrombotic administration for secondary stroke prevention also requires further research.

CONCLUSION

The study indicates no significant difference in the incidence of mortality between anticoagulants or antiplatelet agents for COVID-19 patients with AIS. Further studies are needed to assess the optimal antithrombotic therapy through the use of anticoagulants, antiplatelets, or a combination of both.

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ATTACHMENT

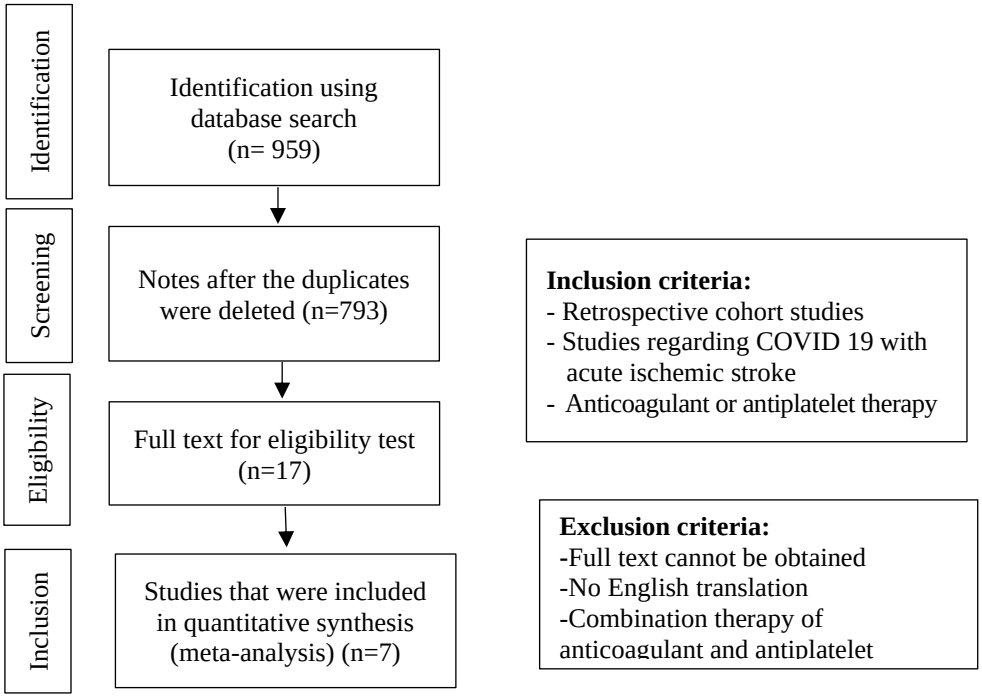

Figure 1. PRISMA chart

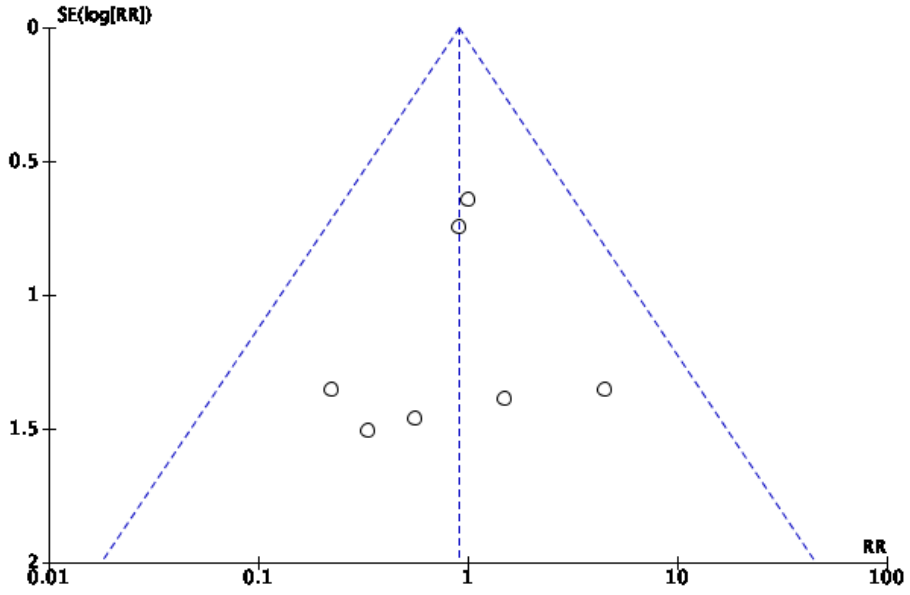

Figure 2. Funnel plot of the included studies (95%CI)

Table 1. Summary of comparative studies included in meta-analysis.[2–4,9–12]

Reference	COVID-19 case + AIS	Ratio M:F	Age ± SD	Days from COVID-19 to AIS	NIHSS value ± SD	D-dimer level ± SD	Stroke subtype					Therapy		Mortality		Newcastle Ottawa Scale
							CE	LAA	SVO	OD	UD	Antiplatelet	Anticoagulant	Antiplatelet	Anticoagulant	
Khandelwal et al., 2021 [2]	6	3:3	40.75 ± 8.25	NA	19.88 ± 7.88	1,500.5 ± 3,461.5	NA	NA	NA	NA	NA	n=4	n=2	25%	0%	Good quality (7/9☆)
Lapergue et al., 2020 [3]	3	3:0	58.5 ± 4.5	11.75 ± 1.25	17 ± 13	4,052.5 ± 2,472.5	-	-	-	-	n=3	n=2	n=1	0%	100%	Poor quality (7/9☆)
Yaghi et al., 2020 [4]	24	NA	55.90 ± 15.90	7.83 ± 19.18	NA	3,611.5 ± 6,388.5	n=4	-	n=2	-	n=18	n=2	n=22	50%	45.50%	Good quality (7/9☆)
Shekhar et al., 2020 [9]	3	NA	50.5 ± 7.5	12.25 ± 6.75	NA	1,572.75 ± 488.25	NA	NA	NA	NA	NA	n=1	n=2	100%	0%	Fair quality (6/9☆)
Lodigiani et al., 2020 [10]	4	2:2	67.99 ± 10.99	NA	NA	18,666 ± 42,334	NA	NA	NA	NA	NA	n=1	n=3	0%	33.33%	Good quality (8/9☆)
Grewal et al., 2020 [11]	8	NA	60.56 ± 30.56	3.88 ± 11.13	15.13 ± 13.13	10,580 ± 16,920	n=1	n=1	n=1	-	n=6	n=4	n=4	25%	0%	Good quality (7/9☆)
Li et al, 2020 [12]	10	5:5	73.75 ± 23.75	11.21 ± 17.79	16.34 ± 18.67	NA	n=3	n=5	n=2	-	-	n=6	n=4	50%	50%	Fair quality (6/9☆)

AIS: Acute Ischemic Stroke; SD: Standard Deviation; NIHSS: National Institute Health Stroke Scale; CE: Cardioembolism; LAA: Large-artery Atherosclerosis; SVO: Small-vessel Occlusion; OD: Other Determined; UD: Undetermined/Cryptogenic stroke; NA: Not Available

Table 2. Forest plot mortality rate of COVID-19 patients with acute ischemic stroke after anticoagulant or antiplatelet therapy