

INPLASY PROTOCOL

To cite: Lu et al. The Relationship Between COVID-19 's Severity and Ischemic Stroke: a Systematic Review and Meta-Analysis. Inplasy protocol 2020120075. doi: 10.37766/inplasy2020.12.0075

Received: 12 December 2020

Published: 13 December 2020

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Support: None.

Review Stage at time of this submission: Data analysis.

Conflicts of interest:
None.

The Relationship Between COVID-19 's Severity and Ischemic Stroke: a Systematic Review and Meta-Analysis

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Review question / Objective: Whether the severity of COVID-19 is associated with the incidence of ischemic stroke. **Condition being studied:** Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection is associated with changes in blood coagulation and, and it increases the risk of thromboembolism (including arterial and venous embolism). These complications may be mediated by systemic inflammatory injury of vascular endothelial cells, platelet activation and stasis¹. Although the incidence of deep venous thrombosis and pulmonary embolism is high in many coronavirus disease 2019 (COVID-19) cohorts, it is not clear how acute ischemic stroke occurs in this disease. A study in China found that the incidence of cerebrovascular disease during hospitalization of severe COVID-19 patients was 5.7%, while that of non-severe patients was 0.8%. A multicenter study in Germany found that the total incidence of stroke in COVID-19 was 4.2%, with a stroke rate of 5.0% in severe patients and 2.2% in non-severe patients. However, in a multicenter study in Spain, the incidence of acute ischemic stroke in patients with COVID-19 was 1.2% in severe patients and 1.4% in non-severe patients. Therefore, we conducted a systematic review and meta-analysis to explore the possible link between SARS-CoV-2 infection and acute ischemic stroke.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 December 2020 and was last updated on 13 December 2020 (registration number INPLASY2020120075).

INTRODUCTION

Review question / Objective: Whether the severity of COVID-19 is associated with the incidence of ischemic stroke.

Rationale: We conducted a literature search, including PubMed, Cochrane Library, Embase and Web of Science databases. Studies including COVID-19 's

severity classification data and COVID-19 patients with acute ischemic stroke were included. Two independent evaluators extracted data, and the random effects model was used to calculate the risk ratios (RR) and 95% confidence interval (95% CI) of acute ischemic stroke associated with COVID-19 's severity.

Condition being studied: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with changes in blood coagulation and, and it increases the risk of thromboembolism (including arterial and venous embolism). These complications may be mediated by systemic inflammatory injury of vascular endothelial cells, platelet activation and stasis¹. Although the incidence of deep venous thrombosis and pulmonary embolism is high in many coronavirus disease 2019 (COVID-19) cohorts, it is not clear how acute ischemic stroke occurs in this disease. A study in China found that the incidence of cerebrovascular disease during hospitalization of severe COVID-19 patients was 5.7%, while that of non-severe patients was 0.8%. A multicenter study in Germany found that the total incidence of stroke in COVID-19 was 4.2%, with a stroke rate of 5.0% in severe patients and 2.2% in non-severe patients. However, in a multicenter study in Spain, the incidence of acute ischemic stroke in patients with COVID-19 was 1.2% in severe patients and 1.4% in non-severe patients. Therefore, we conducted a systematic review and meta-analysis to explore the possible link between SARS-CoV-2 infection and acute ischemic stroke.

METHODS

Search strategy: We conducted a literature search (the last search was on October 28, 2020), including PubMed, Cochrane Library, Embase and Web of Science databases. Studies including COVID-19 's severity classification data and COVID-19 patients with acute ischemic stroke were included. The search terms were as follows: "Coronavirus", "COVID 19", "2019-nCoV", "SARS-CoV-2", "stroke", "cerebrovascular", "transient ischemic

attack", "cerebral infarction", "brain infarction", "cerebral ischaemia".

Participant or population: COVID-19 patients with acute ischemic stroke.

Intervention: Patients with severe COVID-19.

Comparator: Patients with non-severe COVID-19.

Study designs to be included: Randomized or non-randomized observational study of at least 5 adult patients diagnosed with COVID-19.

Eligibility criteria: The studies were included according to the following criteria: (1) randomized or non-randomized observational study of at least 5 adult patients diagnosed with COVID-19; (2) available data on the incidence of ischemic stroke in COVID-19 patients; (3) there was a classification of the severity of COVID-19 patients.

Information sources: We conducted a literature search including PubMed, Cochrane Library, Embase and Web of Science databases.

Main outcome(s): A total of 8 studies were included, involving 5266 patients. Among all COVID-19 patients, the total incidence of ischemic stroke was 1.76% (95% CI: 0.82-3.01). Severe patients have an increased risk of acute ischemic stroke compared with non-severe patients (RR = 3.53, 95% CI: 2.06–6.07, $P < 0.0001$; $I^2 = 12.1\%$). This association was also observed when COVID-19 's severity was defined by clinical parameters (RR 2.91, 95% CI: 1.17–7.26, $P = 0.02$; $I^2 = 29.0\%$) and the need for intensive care (RR 4.47, 95% CI: 2.40–8.31, $p < 0.0001$; $I^2 = 0\%$).

Data management: We use endnote to manage literature and word to record data.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa scale was used to assess the quality of the included studies. Two investigators independently conducted

the quality assessment, and the differences were resolved by consensus.

Strategy of data synthesis: A comprehensive dichotomy of severity was used in our main analysis, which included all severity results reported in each study comprising severity based on clinical parameters, and the need for intensive care (ICU) and non-ICU. If the included studies divide the severity outcomes into two or more categories based on clinical parameters (for example, mild, moderate, severe, critical), these are classified as non-severe (including mild and moderate) and severe (including severe and critical) categories. Therefore, in our main analysis, we classified all patients as severe or non-severe COVID-19 according to the classification used in each study included. We performed this meta-analysis using R software. The variance-stabilizing double arcsine transformation was used in all proportion analyses. The random-effects model was used to calculate the outcomes through pooled proportion meta-analysis. The Mantel-Haenszel formula is used to calculate the binary variable to calculate the risk ratio (RR), and report it with its 95% confidence interval (CI). $P < 0.05$ indicated statistical significance. I^2 statistics were used to record and evaluate statistical heterogeneity (I^2 value of 0-40% indicated no or low heterogeneity, 30-60% indicated moderate heterogeneity, 50-90% indicated substantial heterogeneity, and 75-100% indicated considerable heterogeneity). Publication bias was evaluated using a funnel plot.

Subgroup analysis: Patients with severe COVID-19 and patients with non-severe COVID-19.

Sensibility analysis: The robustness of the results was assessed by sensitivity analyses.

Language: No restriction.

Country(ies) involved: China.

Keywords: Meta-analysis; COVID-19; Severity; Ischemic stroke.

Contributions of each author:

Author 1 - Yue Lu - Designed and supervised the study, planned and performed the statistical analyses, reviewed the systematic search, contributed to drafting the first version of the manuscript, and reviewed the manuscript for intellectual content.

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