Clinical characteristics and outcomes of acute ischemic stroke in patients with COVID-19: A systematic review and meta-analysis of global data

Zhelv Yao, Lili Huang, Yue Cheng, Ruowen Qi, Biyun Xu, Qingxiu Zhang, and Liqun Zhang

Department of Neurology of Drum Tower Hospital, Medical School and the State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210008, China
Department of Neurology, Affiliated Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China
Nanjing Neurology Clinic Medical Center, Nanjing 210008, China
Institute of Brain Science, Nanjing University, Nanjing 210008, China
Medical Statistics and Analysis Center, Nanjing Drum Tower Hospital, Nanjing University Medical School, 321 Zhongshan Road, Nanjing, 210008, China
St George’s University Hospital NHS Foundation Trust, London, Blackshaw Rd, London SW17 0QT, United Kingdom

Abstract

Objective. There is increased concern regarding acute ischemic stroke (AIS) in patients with coronavirus disease 2019 (COVID-19). The aim of this study was to depict the manifestations and outcomes of COVID-19-associated AIS.

Methods. We systematically searched for eligible studies describing AIS in patients with COVID-19 using PubMed, Embase, and Web of Science up to November 29, 2021. We complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and used the Newcastle–Ottawa Scale to assess data quality. The data were pooled using fixed- and random-effects models.

Results. Thirty-eight eligible studies involving 76,894 participants were included in this meta-analysis. Compared with AIS patients who did not have COVID-19, patients with COVID-19 were more likely to have anterior circulation stroke (odds ratio [OR]: 2.29, 95% confidence interval [CI]: 1.03 – 5.10; I²: 37%), particularly involving the internal carotid artery (OR: 1.85, 95% CI: 1.19 – 2.88; I²: 0%); more severe neurological deficit (National Institutes of Health Stroke Scale [NIHSS]) (weighted mean difference [WMD]: 3.21, 95% CI: 2.13 – 4.29; I²: 64%); higher proportion of cryptogenic stroke (OR: 1.83, 95% CI: 1.24 – 2.70; I²: 62%); large vessel occlusion (OR: 1.68, 95% CI: 1.10 – 2.57; I²: 75%), and multi-territory involvement (OR: 2.64, 95% CI: 1.24 – 2.70; I²: 62%), higher C-reactive protein levels (WMD: 55.90, 95% CI: 33.32 – 78.49; I²: 67%), and D-dimer levels (standardized mean difference: 0.81, 95% CI: 0.52 – 1.10; I²: 59%). The proportion of poor outcomes were higher among patients with COVID-19, including increased risk of in-hospital death (OR: 3.70, 95% CI: 2.73 – 5.02; I²: 64%) and lower possibility of favorable discharge (OR: 0.49, 95% CI: 0.39 – 0.61; I²: 0%). However, COVID-19 did not increase the risk of hemorrhagic transformation (OR: 1.34, 95% CI: 0.91 – 1.98; I²: 39%) and symptomatic intracerebral hemorrhage (OR: 1.46, 95% CI: 0.81 – 2.62; I²: 0%).

Conclusion. AIS patients with COVID-19 seem to display a pattern of large vessel occlusion and multi-territory infarcts. These patients have high inflammatory marker...
levels and increased D-dimer levels, which implies that thrombosis and/or thromboembolism might be the underlying mechanism. These patients tend to have worse prognosis regardless of whether they receive reperfusion treatment.

Keywords: Acute ischemic stroke; COVID-19; Clinical characteristics and outcomes

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide since December 2019, with more than 258 million confirmed cases and 5.17 million deaths as of November 24, 2021[1]. Even though the infection mainly results in respiratory symptoms, an increasing number of cases in cerebrovascular disease, particularly acute ischemic stroke (AIS), have been confirmed[2]. The incidence of AIS varied from 1% to 3%, and reached up to 6% in seriously ill patients[3,4]. Emerging data suggest that stroke in the context of COVID-19 may be associated with increased mortality and disability and presents with unique manifestations[5,6]. Although most of these studies have limited sample sizes or are restricted to particular geographic regions, thus showing considerable heterogeneity among studies, these individual studies provide valuable data on patients with COVID-19 who have AIS. Therefore, the meta-analysis can break the regional limitations and collect outcomes and characteristics of patients with COVID-19 in the real world can provide new insights.

The previous meta-analyses have mainly focused on stroke risk factors and outcomes[7,8]. With emerging evidence, we performed an updated systemic review and meta-analysis to illustrate the specific clinical features, laboratory findings, neuroimaging findings, and short-term outcomes of patients with COVID-19 who have AIS, to assist with better identification and management of these patients.

2. Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[9].

2.1. Search strategy

We conducted a systematic search of PubMed, Embase, and Web of Science databases from their inception to November 29, 2021, with no language restrictions. The search algorithm was modified by an information specialist; details are available in Table S1. References cited in retrieved articles as well as any review articles were also reviewed to identify additional studies.

2.2. Inclusion and exclusion criteria

Two investigators independently screened the identified articles and selected studies using pre-specified criteria, with disagreements resolved through consensus. Studies were deemed eligible if they (1) were observational studies with information on clinical features and outcomes of new-onset ischemic stroke in patients with COVID-19; (2) included at least 20 patients with AIS over 18 years of age; (3) SARS-CoV-2 infection was confirmed with a positive polymerase chain reaction test or International Classification of Diseases, Tenth Revision (ICD-10) codes[10]; and (4) the diagnosis of stroke was based on neuroimaging and clinical symptoms. We excluded comments, editorials, letters, reviews, case reports, small case series (<20 cases), animal studies, and duplicate publications involving the same patient cohorts.

2.3. Data extraction

Data extraction was conducted independently by two investigators using a pre-designed form. For each eligible article, we extracted the first author, publication year, study design, geographic region, recruitment period, clinical definition of COVID-19 used in the study, sample size, age, gender, clinical manifestations, laboratory findings, neuroimaging findings, and short-term (in hospital or on discharge) outcomes of AIS.

Stroke etiology was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria[11]. Stroke severity was measured using National Institutes of Health Stroke Scale (NIHSS). Functional independence (i.e., favorable functional outcome) was defined as modified Rankin scale score 0–2.

2.4. Quality appraisal

We used the Newcastle-Ottawa Scale (NOS) to assess the methodologic quality of the selected studies[12]. Specifically, the NOS scale evaluates quality in three aspects, including selection of study groups, comparability of the study groups, and assessment of exposure or outcome of interest. A total of seven out of nine points is considered a low risk of bias, a score of 4 – 6 points a moderate risk, and a score <4 points a high risk of bias.

2.5. Statistical analysis

Because most included studies only reported raw data, we used unadjusted estimates for meta-analysis. To obtain a more conservative estimate of effect size, zero-events
studies were included with 0.5 continuity correction\textsuperscript{13}. We converted median and range in the reported data into mean and standard deviation\textsuperscript{14}. We used $Q$ and $I^2$ statistics to assess statistical heterogeneity among studies\textsuperscript{15}. Heterogeneity was considered to be present with an $I^2$ value >40%. We used a fixed-effects
Table 1. Characteristics of the included studies.

| Author          | Year | Design       | Country                      | Continent          | Confirmation of COVID-19 | Study period                          | COVID-19 positive | COVID-19 negative |
|-----------------|------|--------------|------------------------------|--------------------|--------------------------|---------------------------------------|-------------------|-------------------|
| Sasanejad et al.| 2021 | Prospective  | Iran, Greece, Germany        | Asia, Europe       | PCR                      | 18 February 19 – 31 December 20       | 101               | 444               |
| Sobolewski et al.| 2021 | Retrospective| Poland                       | Europe             | RT-PCR                   | 15 September 20 – 30 November 20       | 22                | 48                |
| Kasab et al.    | 2020 | Prospective  | North America, South America | Europe             | RT-PCR                   | February – March or March – April 20   | 13                | 445               |
| Havenon et al.  | 2020 | Retrospective| USA                          | North America      | WHO Guideline            | 1 April – 31 July 20                   | 104               | 3061              |
| Sobolewski et al.| 2020 | Prospective  | Poland                       | Europe             | RT-PCR                   | 1 March 20 – 15 April 20               | 10                | 27                |
| Pezzini et al.  | 2021 | Prospective  | Italy                        | Europe             | RT-PCR                   | 8 March – 30 April 20                  | 34                | 262               |
| Qureshi et al.  | 2021 | Retrospective| USA                          | North America      | Not specified            | 1 December 19 – 1 January 21          | 2122              | 22217             |
| Requena et al.  | 2020 | Retrospective| Spain                        | Europe             | RT-PCR                   | 2 March – 30 April 20                  | 10                | 19                |
| Akhtar et al.   | 2021 | Prospective  | Qatar                        | Asia               | Not specified            | March – May 20                         | 32                | 216               |
| Altschul et al. | 2020 | Retrospective| USA                          | North America      | RT-PCR                   | 1 March – 17 April 20                  | 13                | 23                |
| Benny et al.    | 2020 | Retrospective| India                        | Asia               | RT-PCR                   | 4 April – 15 September 20              | 78                | 100               |
| Calmettes et al.| 2021 | Retrospective| France                       | Europe             | PCR                      | 17 March – 2 May 20                    | 40                | 176               |
| Escalard et al. | 2020 | Prospective  | France                       | Europe             | RT-PCR                   | 15 March – 30 April 20                 | 12                | 34                |
| Herna´ndez-Ferna´ndez et al. | 2020 | Retrospective| Spain                       | Europe             | WHO Guideline           | 1 March – 19 April 20                  | 23                | -                 |
| John et al.     | 2020 | Retrospective| The United Arab Emirates     | Asia               | PCR                      | 1 March – 10 May 20                    | 19                | 220               |

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### Table 1. (Continued).

| Author          | Year | Design       | Country          | Continent | Confirmation of COVID-19 | Study period                  | COVID-19 positive | COVID-19 negative |
|-----------------|------|--------------|------------------|-----------|-------------------------|------------------------------|------------------|------------------|
| Naval-Baudin et al. | 2021 | cross-sectional | Spain           | Europe    | PCR                     | 13 March – 15 May 20        | Sample size: 19  | Age, mean: 70.2 (8.4)  | Male, n: 12 (63)  | Sample size: 81  | Age, mean: 70.1 (15.3) | Male, n: 56 (69) |
| Ntaios et al.  | 2020 | Prospective cohort | Multicenter     | Multicenter | PCR, serology        | 27 January – 19 May 20      | Sample size: 174 | Age, mean: 71.2 (12.3) | Male, n: 108 (62.07) | Sample size: NA  | Age, mean: 70 (15)  | Male, n: 178 (51) |
| Topcuoglu et al. | 2021 | Case-Control cohort | Turkey          | Asia, Europe | RT-PCR                | 16 April 20 – 14 January 21 | Sample size: 37  | Age, mean: 70 (15)  | Male, n: 31 (83)  | Sample size: 355 | Age, mean: 70 (15)  | Male, n: 178 (51) |
| Yaghi et al.    | 2020 | Retrospective cohort | USA             | North America | RT-PCR                | 15 March – 19 April 20      | Sample size: 32  | Age, mean: 63 (17)  | Male, n: 23 (71.9) | Sample size: 46  | Age, mean: 70 (15)  | Male, n: 178 (51) |
| Perry et al.    | 2020 | case-control   | UK               | Europe      | RT-PCR                | 9 March – 5 July 20         | Sample size: 86   | Age, mean: 74.5 (67 – 84) | Male, n: 47 (54.7) | Sample size: 1384 | Age, mean: 73 (61 – 82) | Male, n: 731 (52.8) |
| Srivastava et al. | 2021 | Retrospective cohort | USA             | North America | Not specified          | 4 February – 29 June 20     | Sample size: 1143 | Age, mean: 68 (57 – 79) | Male, n: 615 (53.8) | Sample size: 40 828 | Age, mean: 71 (60 – 81) | Male, n: 209 550 (51.3) |
| Dahoon et al.   | 2021 | Retrospective cohort | USA             | North America | PCR                    | 1 March – 30 April 20       | Sample size: 83  | Age, mean: NA       | Male, n: NA       | Sample size: 121 | Age, mean: NA       | Male, n: NA       |
| Thomas et al.   | 2020 | Retrospective cohort | India           | Asia        | RT-PCR                | 1 June – 31 Aug 20          | Sample size: 60  | Age, mean: NA       | Male, n: NA       | Sample size: 104 | Age, mean: NA       | Male, n: NA       |
| Ramos et al.    | 2021 | Retrospective cohort | USA             | North America | RT-PCR                | 13 March – 19 May 20        | Sample size: 33  | Age, mean: NA       | Male, n: NA       | Sample size: 37  | Age, mean: NA       | Male, n: NA       |
| Majdi et al.    | 2020 | Retrospective cohort | USA             | North America | RT-PCR                | 21 March – 12 April 20      | Sample size: 24  | Age, mean: 59 (13)  | Male, n: 19 (79.2) | Sample size: 21  | Age, mean: 73 (18)  | Male, n: 9 (42.9)  |
| Martí-Fàbregas et al. | 2021 | Prospective cohort | Spain           | Europe      | PCR                    | Mid March – 15 May 20       | Sample size: 91  | Age, mean: 71.6 (12.3) | Male, n: 58 (63.7) | Sample size: 610 | Age, mean: 72.4 (13.5) | Male, n: 366 (60.0) |
| Shais et al.    | 2021 | Prospective cohort | Netherlands     | Europe      | PCR                    | 1 March – 1 Aug 20          | Sample size: 38  | Age, mean: 74.5 (66.8 – 82.0) | Male, n: 22 (57.9) | Sample size: -  | Age, mean: -       | Male, n: -         |
| Ramos-Araque et al. | 2021 | Retrospective cohort | USA, Spain, Egypt, Romania | North America, Europe, Asia, Africa | PCR, serology | 1 March – 16 June 20 | Sample size: 156 | Age, mean: - | Male, n: 94 (60.6) | Sample size: -  | Age, mean: -       | Male, n: -         |
| Lin et al.      | 2020 | cross-sectional | USA             | North America | PCR                    | Late March – early May 20   | Sample size: 9  | Age, mean: 58.2 (18.3) | Male, n: 3 (33.3)  | Sample size: 51  | Age, mean: 65.9 (13.9) | Male, n: 24 (45.3) |
| Merkler et al.  | 2020 | Retrospective cohort | USA             | North America | PCR                    | 4 March – 2 May 20          | Sample size: 31  | Age, mean: 69 (66 – 78) | Male, n: 18 (58)  | Sample size: -  | Age, mean: -       | Male, n: -         |
| Rothstein et al. | 2020 | Retrospective cohort | USA             | North America | RT-PCR                | 15 March – 3 May 20         | Sample size: 20  | Age, mean: 64 (12)  | Male, n: 12 (60)   | Sample size: -  | Age, mean: -       | Male, n: -         |
| Kremer et al.   | 2020 | Retrospective cohort | France          | Europe      | RT-PCR                | 16 March – 9 April 20       | Sample size: 17  | Age, mean: 75 (59 – 92) | Male, n: 11 (65%)  | Sample size: -  | Age, mean: -       | Male, n: -         |

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model with the Mantel–Haenszel method to combine data when results were homogeneous. Otherwise, a random-effects model with the DerSimonian and Laird method was applied. In this study, we calculated the odds ratio (OR), standardized mean difference (SMD), or weighted mean difference (WMD) with the associated 95% confidence interval (CI) using both the fixed- and random-effects models, and compared them to assess potential heterogeneity.

Sensitivity analyses were performed by omitting one study at a time to investigate the robustness of the pooled results. When ten or more studies were proven eligible for meta-analysis, publication bias was assessed using funnel plots and Begg’s test. All reported P-values are two-tailed, and a P < 0.05 was defined as statistically significant. Statistical analyses were conducted using RevMan version 5.0 (The Cochrane Collaboration, 2020) and Stata version 16.0 (StataCorp LLC, College Station, TX, USA).

| Author            | Year | Design        | Country                                      | Continent                          | Confirmation of COVID-19 | Sample size | Mean age [SD or median [IQR] (years)] | Male, n (%) |
|-------------------|------|---------------|----------------------------------------------|------------------------------------|--------------------------|-------------|---------------------------------------|-------------|
| Shahjouei et al.  | 2020 | Prospective cohort | USA, Canada, Brazil, Greece, Turkey, Lebanon, Iran, India, New Zealand | North and South America, Europe, Asia, Oceania | History of exposure, symptomatology, and chest CT with or without PCR | 123 | 68.6 (13.9) | 67 (54.5) - - |
| Peng et al.       | 2021 | Retrospective cohort | USA | North America | RT-PCR | 3 January – 28 Aug 20 | 44 | 64.0 (19.9 – 81.5) | 25 (56.8) - - |
| Qureshi et al.    | 2021 | Retrospective cohort | USA | North America | Not specified | December 19 – April 20 | 103 | 68.8 (15.1 – 46 (44.7), 199 | 71.0 (14.9) 110 (55.3) |
| Bach et al.       | 2020 | Retrospective cohort | USA | North America | RT-PCR | 15 March – 30 April 20 | 20 | 63 (107) | 14 (63) - - |
| Khandelwal et al. | 2021 | Cross-sectional | USA, UK, Spain, Italy | North America, Europe | NA | 1 March – 1 May 20 | 66 | 51 (27 – 87) | - - - - |

COVID-19, coronavirus disease 2019; IQR, interquartile range; NA, not available; PCR, polymerase chain reaction; RT-PCR, reverse-transcriptase polymerase chain reaction; SD, standard deviation.

Figure 2. Begg’s funnel plots of associations between coronavirus disease 2019 (COVID-19) and in-hospital mortality.

Figure 3. Begg’s funnel plots of associations between coronavirus disease 2019 (COVID-19) and favorable discharge.
Table 2. Characteristics and outcomes of acute ischemic stroke patients with COVID-19 versus those without COVID-19.

| Variables                              | No. of studies | AIS patients with COVID-19 | AIS patients without COVID-19 | OR (95% CI) or pooled MD Random effects | OR (95% CI) or pooled MD Fixed effects | P | I² heterogeneity % | P heterogeneity |
|----------------------------------------|----------------|---------------------------|-------------------------------|-----------------------------------------|----------------------------------------|---|-------------------|----------------|
| Demographics                           |                |                           |                               |                                         |                                        |   |                   |                |
| Age                                    | 20             | 3962                      | 26897                         | −2.31 (−3.88, −0.75)                   | −0.91 (−1.43, −0.38)                   | 0.004***                             | 64             | < 0.0001***       |
| Gender (male)                          | 23             | 2350/4154                 | 36522/70867                   | 1.29 (1.09, 1.54)                      | 1.20 (1.13, 1.28)                     | 0.004**                             | 60             | 0.0001***         |
| Stroke subtype (TOAST)                 |                |                           |                               |                                         |                                        |   |                   |                |
| Small vessel atherosclerosis           | 13             | 62/564                    | 579/3402                      | 0.64 (0.38, 1.08)                      | 0.65 (0.49, 0.87)                     | 0.10                                | 59             | 0.004**           |
| Large artery atherosclerosis           | 12             | 96/542                    | 645/3354                      | 0.91 (0.67, 1.24)                      | 0.90 (0.70, 1.16)                     | 0.56                                | 24             | 0.21              |
| Cardioembolic                          | 12             | 151/542                   | 939/3354                      | 1.01 (0.82, 1.26)                      | 1.00 (0.81, 1.24)                     | 0.91                                | 0              | 0.58              |
| Other known cause                      | 11             | 23/470                    | 100/2198                      | 1.11 (0.58, 2.13)                      | 0.99 (0.62, 1.58)                     | 0.75                                | 32             | 0.14              |
| Cryptogenic                            | 11             | 199/470                   | 654/2198                      | 1.83 (1.24, 2.70)                      | 1.69 (1.36, 2.10)                     | 0.002**                             | 62             | 0.003**           |
| Stroke territories                     |                |                           |                               |                                         |                                        |   |                   |                |
| Anterior circulation                   | 7              | 146/168                   | 675/913                       | 2.29 (1.03, 5.10)                      | 2.97 (1.77, 4.98)                     | 0.04*                               | 37             | 0.15              |
| MCA                                    | 9              | 118/281                   | 421/946                       | 0.79 (0.42, 1.50)                      | 0.87 (0.65, 1.18)                     | 0.48                                | 72             | 0.0004***         |
| ICA                                    | 7              | 47/229                    | 88/736                        | 1.85 (1.19, 2.88)                      | 1.88 (1.22, 2.90)                     | 0.007*                              | 0              | 0.73              |
| Posterior circulation                  | 7              | 12/168                    | 155/913                       | 0.42 (0.19, 0.95)                      | 0.32 (0.17, 0.59)                     | 0.04*                               | 28             | 0.21              |
| Multiple territories                   | 4              | 37/167                    | 86/930                        | 2.64 (1.62, 4.29)                      | 2.68 (1.66, 4.32)                     | < 0.0001***                         | 0              | 0.39              |
| Laboratory findings                    |                |                           |                               |                                         |                                        |   |                   |                |
| CRP, mg/L                               | 6              | 310                       | 2120                          | 55.90 (33.32, 78.49)                   | 47.29 (36.16, 58.42)                  | < 0.0001***                         | 67             | 0.009*            |
| WBC, ×10³/µL                           | 8              | 316                       | 1772                          | 0.21 (−0.46, 0.88)                     | 0.19 (−0.20, 0.59)                    | 0.54                                | 42             | 0.10              |
| APTTb                                   | 7              | 316                       | 1937                          | 0.33 (0.02, 0.64)                      | 0.40 (0.28, 0.52)                     | 0.04*                               | 82             | < 0.0001***       |
| PTb                                     | 6              | 214                       | 1236                          | 0.41 (0.04, 0.79)                      | 0.44 (0.29, 0.59)                     | 0.03*                               | 79             | 0.0003***         |
| PLT, ×10³/µL                            | 9              | 397                       | 2945                          | 14.78 (−5.31, 34.87)                   | 7.46 (−3.19, 18.12)                   | 0.15                                | 62             | 0.008*            |
| D-dimerb                               | 5              | 195                       | 1082                          | 0.81 (0.52, 1.10)                      | 0.84 (0.68, 1.00)                     | < 0.0001***                         | 59             | 0.04*             |
| Other stroke characteristics           |                |                           |                               |                                         |                                        |   |                   |                |
| NIHSS at admission³                     | 17             | 1697                      | 45017                         | 3.21 (2.13, 4.29)                      | 3.79 (3.33, 4.25)                     | < 0.0001***                         | 64             | 0.0002***         |
| Large vessel occlusion                 | 8              | 437/1428                  | 9358/4256                     | 1.68 (1.10, 2.57)                      | 1.41 (1.25, 1.59)                     | 0.02*                               | 75             | 0.0002***         |
| Volume of infarction, cm³              | 2              | 31                        | 115                           | 33.30 (−12.44, 79.04)                  | 20.27 (4.45, 36.10)                   | 0.15                                | 75             | 0.04*             |
| ASPECT score⁵                          | 5              | 88                        | 829                           | −0.22 (−1.31, 0.87)                    | 0.29 (−0.19, 0.78)                    | 0.69                                | 74             | 0.004**           |
| Overall outcomes of AIS                |                |                           |                               |                                         |                                        |   |                   |                |
| HT                                      | 6              | 130/2392                  | 1074/23226                    | 1.34 (0.91, 1.98)                      | 1.11 (0.92, 1.35)                     | 0.14                                | 39             | 0.15              |
| sICH                                    | 6              | 15/190                    | 79/1245                       | 1.46 (0.81, 2.62)                      | 1.40 (0.78, 2.49)                     | 0.21                                | 0              | 0.55              |
| In-hospital mortality                  | 19             | 659/2871                  | 2290/29187                    | 3.70 (2.73, 5.02)                      | 3.46 (3.13, 3.82)                     | < 0.0001***                         | 64             | < 0.0001***       |
| Favorable discharge                    | 10             | 136/415                   | 2811/5250                     | 0.49 (0.39, 0.61)                      | 0.49 (0.39, 0.61)                     | < 0.0001***                         | 0              | 0.93              |

(Contd...)
Table 2. (Continued).

| Variables                     | No. of studies | AIS patients with COVID-19 | AIS patients without COVID-19 | OR (95% CI) or pooled MD | OR (95% CI) or pooled MD | P       | I² heterogeneity | P heterogeneity |
|-------------------------------|----------------|---------------------------|------------------------------|-------------------------|-------------------------|--------|------------------|-----------------|
| Outcome following IVT        |                |                           |                              |                         |                         |        |                  |                 |
| HT                            | 2              | 28/117                    | 75/543                       | 1.96 (1.20, 3.19)       | 2.33 (0.96, 5.6)        | 0.007* | 51               | 0.15            |
| sICH                          | 3              | 11/139                    | 41/591                       | 1.34 (0.60, 2.99)       | 1.25 (0.63, 2.48)       | 0.52   | 8                | 0.34            |
| In-hospital mortality         | 2              | 31/123                    | 52/492                       | 2.84 (1.72, 4.68)       | 2.82 (1.71, 4.66)       | < 0.0001*** | 0                | 0.6             |
| Favorable discharge           | 2              | 32/123                    | 203/492                      | 0.52 (0.33, 0.81)       | 0.52 (0.33, 0.81)       | 0.004* | 0                | 0.75            |
| Outcome following MT          |                |                           |                              |                         |                         |        |                  |                 |
| HT                            | 1              | -                         | -                            | -                       | -                       |        |                  |                 |
| sICH                          | 4              | 4/51                      | 38/654                       | 2.04 (0.71, 5.86)       | 1.92 (0.66, 5.57)       | 0.18   | 0                | 0.76            |
| In-hospital mortality         | 4              | 46/137                    | 460/3552                     | 3.22 (2.16, 4.79)       | 3.27 (2.24, 4.78)       | < 0.0001*** | 1                | 0.39            |
| Favorable discharge           | 2              | 51/117                    | 1987/3506                    | 0.56 (0.38, 0.82)       | 0.56 (0.38, 0.81)       | 0.003* | 0                | 0.79            |

AIS, acute ischemic stroke; APTT, activated partial thromboplastin time; ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence intervals; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HT, hemorrhagic transformation; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; MD, mean difference; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odd ratio; PLT, platelets; PT, prothrombin time; sICH, symptomatic intracerebral hemorrhage; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WBC, white blood cell count. *P<0.05, ** P<0.005, *** P<0.001. *items were calculated with weighted MD. #items were calculated with standard MD.

3. Results

Literature searches of the three databases yielded a total of 7961 potentially relevant references. After removing duplicates and screening titles and abstract, 772 full-text articles were retrieved. Of these, 732 were removed as no data of interest were provided. Finally, 38 observational studies involving 76,894 individuals met the eligibility criteria and were included in the meta-analysis. The detailed process of study identification and selection is presented in Figure 1.

3.1. Study characteristics

The characteristics of the included studies are summarized in Table 1. Of these, 32 were cohort studies[46-48,44-45], two were case–control studies[46,47], and four were cross-sectional studies[48-51]. Patients number varied from 29 to 41,971. The most common geographic regions were North America (n = 19, 50%) and Europe (n = 19, 50%). Among these studies, there were several multiple geographic regions and only one study was conducted in Oceania and Africa. About clinical design, three studies compared COVID-19 patients with and without AIS; 30 studies compared AIS patients with COVID-19 versus those without COVID-19. The remaining five studies merely depict the characteristics and outcomes of AIS patients with COVID-19.

3.2. Study quality and publication bias

The methodological quality of each included study after critical appraisal using the NOS is summarized in Table S2. Most included studies were assessed as low risk of bias (n = 31, 81.6%) whereas the remaining studies were assessed as moderate risk of bias (n = 7, 18.4%). There was no evidence of publication bias in the meta-analyses (Figures 2 and 3).

3.3. Clinical features

3.3.1. Etiology of AIS in patients with COVID-19

Regarding the etiology of stroke in patients with COVID-19 according to the TOAST criteria, cryptogenic stroke was the most common type (41.0%, 95% CI: 33.9 – 48.0%; I²: 76.1%; 17 studies), followed by cardioembolism (26.4%, 95% CI: 20.5 – 32.4%; I²: 76.3%; 18 studies), large vessel atherosclerosis (13.9%, 95% CI: 9.7 – 18.1%; I²: 72.9%; 18 studies), and small vessel stroke (7.6%, 95% CI: 4.8 – 10.3%; I²: 64.5%; 19 studies) (Table 2).

In comparison to patients who did not have COVID-19, those with COVID-19 were more likely to develop cryptogenic stroke (OR: 1.83, 95% CI: 1.24 – 2.70; I²: 62%; 11 studies); no differences were observed for other stroke subtypes (Table 3).
Table 3. Characteristics and outcomes of acute ischemic stroke patients with COVID-19.

| Variables                        | No. of studies | Proportion (95%CI) or pooled median Random effects | Proportion (95%CI) or pooled median Fixed effects | I² heterogeneity (%) | P heterogeneity  |
|----------------------------------|----------------|-----------------------------------------------------|--------------------------------------------------|---------------------|-----------------|
| **Demographics**                 |                |                                                    |                                                  |                     |                 |
| Age                              | 30             | 66.450 (64.569, 68.330)                             | 68.832 (68.431, 69.234)                          | 92.9                | <0.0001***      |
| Gender (male)                    | 33             | 0.646 (0.606, 0.687)                                | 0.583 (0.570, 0.597)                             | 80.4                | <0.0001***      |
| **Stroke subtype (TOAST)**       |                |                                                    |                                                  |                     |                 |
| Small vessel                     | 19             | 0.076 (0.048, 0.103)                                | 0.051 (0.037, 0.065)                             | 64.5                | <0.0001***      |
| Large artery atherosclerosis     | 18             | 0.139 (0.097, 0.181)                                | 0.109 (0.089, 0.129)                             | 72.9                | <0.0001***      |
| Cardioembolic                    | 18             | 0.264 (0.205, 0.324)                                | 0.219 (0.192, 0.245)                             | 76.3                | <0.0001***      |
| Other known cause                | 16             | 0.051 (0.030, 0.072)                                | 0.036 (0.023, 0.049)                             | 47.8                | 0.017*          |
| Cryptogenic                      | 17             | 0.410 (0.339, 0.480)                                | 0.392 (0.359, 0.425)                             | 76.1                | <0.0001***      |
| **Stroke territories**           |                |                                                    |                                                  |                     |                 |
| Anterior circulation             | 7              | 0.866 (0.765, 0.966)                                | 0.930 (0.892, 0.968)                             | 73.5                | 0.002**         |
| MCA                              | 10             | 0.456 (0.332, 0.581)                                | 0.390 (0.338, 0.441)                             | 79.8                | <0.0001***      |
| ICA                              | 8              | 0.204 (0.109, 0.298)                                | 0.141 (0.099, 0.182)                             | 73.0                | 0.001**         |
| Posterior circulation            | 7              | 0.067 (0.030, 0.104)                                | 0.067 (0.030, 0.104)                             | 0                   | 0.557           |
| Multiple territories             | 5              | 0.303 (0.172, 0.434)                                | 0.250 (0.192, 0.308)                             | 76.0                | 0.002**         |
| **Laboratory findings**          |                |                                                    |                                                  |                     |                 |
| CRP (mg/L)                       | 14             | 108.778 (77.845, 139.711)                           | 22.422 (19.568, 25.277)                          | 97.0                | <0.0001***      |
| WBC (×10^3/µL)                   | 12             | 9.242 (8.618, 9.866)                                | 9.037 (8.767, 9.306)                             | 75.6                | <0.0001***      |
| PLT (×10^3/µL)                   | 16             | 244.664 (231.336, 257.992)                          | 236.337 (229.980, 242.694)                      | 71.1                | <0.0001***      |
| **Other stroke characteristics** |                |                                                    |                                                  |                     |                 |
| NIHSS at admission               | 24             | 13.113 (11.717, 14.509)                             | 10.936 (10.539, 11.332)                          | 88.4                | <0.0001***      |
| Large vessel occlusion           | 13             | 0.406 (0.332, 0.481)                                | 0.304 (0.282, 0.326)                             | 76.5                | <0.0001***      |
| Volume of infarction (cm³)       | 2              | 47.536 (9.857, 85.215)                              | 37.324 (22.964, 51.684)                          | 66.3                | 0.085           |
| ASPECT score                     | 5              | 7.867 (6.533, 9.200)                                | 8.853 (8.419, 9.287)                             | 85.6                | <0.0001***      |
| **Overall outcomes of AIS**      |                |                                                    |                                                  |                     |                 |
| HT                               | 11             | 0.132 (0.085, 0.180)                                | 0.048 (0.040, 0.056)                             | 86.1                | <0.0001***      |
| sICH                             | 9              | 0.046 (0.017, 0.075)                                | 0.030 (0.013, 0.047)                             | 40.2                | 0.100           |
| In-hospital mortality            | 28             | 0.292 (0.244, 0.339)                                | 0.225 (0.211, 0.239)                             | 82.9                | <0.0001***      |
| Favorable discharge              | 14             | 0.290 (0.238, 0.342)                                | 0.287 (0.253, 0.321)                             | 49.5                | 0.018*          |
| **Outcomes following IVT**       |                |                                                    |                                                  |                     |                 |
| HT                               | 2              | 0.255 (0.124, 0.386)                                | 0.234 (0.158, 0.310)                             | 33.9                | 0.219           |
| sICH                             | 3              | 0.074 (0.031, 0.118)                                | 0.074 (0.031, 0.118)                             | 0                   | 0.660           |
| In-hospital mortality            | 2              | 0.252 (0.175, 0.328)                                | 0.252 (0.175, 0.328)                             | 0                   | 0.762           |
| Favorable discharge              | 2              | 0.266 (0.163, 0.369)                                | 0.256 (0.179, 0.333)                             | 22.5                | 0.256           |
| **Outcomes following MT**        |                |                                                    |                                                  |                     |                 |
| HT                               | 1              | -                                                   | -                                                | -                   | -               |
| sICH                             | 5              | 0.042 (−0.009, 0.093)                                | 0.024 (−0.006, 0.053)                             | 21.3                | 0.279           |
| In-hospital mortality            | 6              | 0.288 (0.206, 0.370)                                | 0.220 (0.203, 0.237)                             | 61.9                | 0.022*          |
| Favorable discharge              | 2              | 0.325 (0.014, 0.635)                                | 0.410 (0.324, 0.496)                             | 87.7                | 0.004**         |

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence intervals; CRP, C-reactive protein; HT, hemorrhagic transformation; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PLT, platelets; sICH, symptomatic intracerebral hemorrhage; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WBC, white blood cell count. *P < 0.05, **P < 0.005, ***P < 0.001.
3.3.2. Imaging findings and stroke severity in patients with COVID-19

Patients with COVID-19 showed a higher proportion of large vessel occlusion (LVO) (OR: 1.68, 95% CI: 1.10 – 2.57; I²: 75%; 8 studies) and multi-territory infarcts (OR: 2.64, 95% CI: 1.62 – 4.29; I²: 0%; 4 studies) than those without COVID-19. Stroke was more likely to occur in the anterior circulation (OR: 2.29, 95% CI: 1.03 – 5.10; I²: 37%; 7 studies), particularly in the internal carotid artery (OR: 1.85, 95% CI: 1.19 – 2.88; I²: 0; 7 studies) (Table 3).

The mean NIHSS score in AIS patients with COVID-19 was 13.113 (95% CI: 11.717 – 14.509; I²: 64%; 17 studies) (Table 2), which was higher than the score in patients without COVID-19 (WMD: 3.21, 95% CI: 2.13 – 4.29; I²: 64%; 17 studies) (Table 3).

3.3.3. Inflammation and coagulopathy in patients with AIS and COVID-19

As opposed to AIS patients without COVID-19, those with COVID-19 had higher levels of C-reactive protein (CRP) (WMD: 55.90, 95% CI: 33.32 – 78.49; I²: 67%; 6 studies) and D-dimer (SMD: 0.81, 95% CI: 0.52 – 1.10; I²: 59%; 5 studies), as well as prolonged activated partial thromboplastin time (APTT) (SMD: 0.33, 95% CI: 0.02 – 0.64; I²: 82%; 7 studies) and prothrombin time (PT) (SMD: 0.41, 95% CI: 0.04 – 0.79; I²: 79%; 6 studies). No difference was detected in leukocytes (WMD: 0.21, 95% CI: −0.46 – 0.88; I²: 42%; 8 studies) and platelets (WMD: 14.78, 95% CI: −5.31 – 34.87; I²: 62%; 9 studies) (Table 3).
3.3.4. Outcomes of patients with COVID-19 in developing AIS

In patients with AIS and COVID-19, 13.2% of patients had hemorrhagic transformation (95% CI: 8.5 – 18.0%; I²: 86.1%; 11 studies), 29.2% died during hospitalization (95% CI: 24.4 – 33.9%; I²: 82.9%; 28 studies), and 29.0% had a favorable outcome on discharge (95% CI: 23.8 – 34.2%; I²: 49.5%; 14 studies) (Table 2).

In contrast to patients who did not have COVID-19 infection, COVID-19 status was associated with high in-hospital mortality (OR: 3.70, 95% CI: 2.73 – 5.02; I²: 64%; 19 studies; Figure 4) and lower possibility of favorable
In patients who received intravenous thrombolysis, those with COVID-19 had a higher rate of hemorrhagic transformation (OR: 1.96, 95% CI: 1.20 – 3.19; I²: 51%; 2 studies) and increased risk of in-hospital mortality (OR: 2.84, 95% CI: 1.72 – 4.68; I²: 0%; 2 studies), in comparison with patients who did not have COVID-19 (Table 3). In patients who were treated with thrombectomy, those with COVID-19 were less likely to achieve functional independence on discharge (OR: 0.56, 95% CI: 0.38 – 0.82; I²: 0%; 2 studies), and these patients had a higher mortality rate (OR: 3.22, 95% CI: 2.16 – 4.79; I²: 1%; 4 studies; Table 3).

4. Discussion

In this systematic review and meta-analysis investigating the clinical characteristic and outcomes of stroke in patients with COVID-19, we found that in comparison with patients not infected with COVID-19, those with COVID-19 were more likely to develop cryptogenic large vessel stroke that involved multiple territories, present with more severe stroke syndromes, have higher CRP and D-dimer levels, and have prolonged APTT/PT. Furthermore, COVID-19 was associated with an increased risk of in-hospital mortality and lower rates of functional independence on discharge in ischemic stroke patients, especially after reperfusion treatment.

In this meta-analysis, we found that patients with AIS and COVID-19 tended to have multi-territory infarcts with LVO. In this study, we first observed abnormalities in several coagulation and inflammatory markers in patients with COVID-19. Compared with non-COVID-19 patients, AIS patients with COVID-19 had higher or longer D-dimer, PT, and APTT levels. These results suggested that AIS patients with COVID-19 may be a manifestation of SARS-CoV-2-related coagulation disorders [52]. Furthermore, recent clinical research reported that elevated CRP levels were closely related to increased stroke severity, hemorrhagic transformation, and in-hospital mortality [53,54], which suggested that CRP might not only be a biomarker of inflammation but also acts as a direct participant in the pathological process of ischemic stroke [55]. Accumulated studies have shown that several potential mechanisms with COVID-19 are involved in the occurrence of AIS, mainly inducing thrombo-inflammation or immune thrombosis. Viral translation through angiotensin-converting enzyme 2 receptors expressed in vessel walls may contribute to endothelial dysfunction and thrombosis. Thrombo-inflammation is secondary to activation of immune cells involved in the defense against the virus and amplification of the cytokine system and complement cascade, resulting in activation of downstream pro-coagulant pathways [56]. COVID-19 infection may also induce cardiac arrhythmias resulting in embolic infarcts [57]. Further studies are needed to explore the potential underlying mechanisms are needed.

In this study, we also found that D-dimer levels were high in most patients with COVID-19, surpassing the threshold that has been identified as a predictor of in-hospital death [58]. This highlights the need to closely monitor patients with high levels of CRP and D-dimer for potential stroke, although the prevalence is relatively low. Consistent with previous studies [59,60], our meta-analysis showed that patients with AIS and COVID-19 were more likely to have LVO and multi-territory infarcts; rapid patient evaluation is crucial for effective reperfusion treatment.

It is suggested that D-dimer and CRP levels may be associated with the severity of AIS in patients with COVID-19 [61,62]. Hence, for patients with hypercoagulable states, proper use of antithrombotic agents or antithrombotic therapy could be effective [63,64]. Tracking these biological markers will allow for early identification and even prediction of disease progression. Intensive studies on these markers may provide the basis for development of therapeutic and preventive strategies against COVID-19-related stroke.

Our meta-analysis demonstrated poor prognosis and high mortality in patients with COVID-19. The previous meta-analyses have reported a high mortality rate of 29.2% amongst patients with COVID-19 [65]. Our study reinforced this finding and found that patients with AIS and COVID-19 infection had a nearly 4-fold higher risk of mortality compared with their counterparts who did not have COVID-19 infection, as well as highly unfavorable outcome at discharge, even for younger patients. We noted that patients with AIS and COVID-19 who received intravenous thrombolysis treatment had higher rates of hemorrhagic transformation, which may be related to the deranged coagulation status in these patients. We found that patients with COVID-19 who developed AIS and who received reperfusion treatment tended to have poor outcomes and high mortality. Several aspects related to COVID-19 infection may explain our observation, including respiratory distress, multiorgan failure [21], a high proportion of LVO and multi-territory involvement.
Pezzini et al. found that patients with COVID-19 had suboptimal collateral status\(^{20}\), which may also contribute to the poor prognosis in these patients.

Only a few studies have reported 90-day functional outcome, making it difficult to draw conclusions in this meta-analysis. Martí-Fàbregas et al. concluded that 90-day functional outcome was comparable in patients with and without COVID-19\(^{35}\), whereas a recent study demonstrated that 3-month outcome tended to be worse in patients with COVID-19\(^{36}\). Additional well-designed studies are warranted to investigate functional outcomes beyond 3 months and factors contributing to long-term outcomes.

Our study has notable strengths. The large sample size and worldwide geographic coverage means that the findings of this meta-analysis have good generalizability. To minimize risk of bias, we restricted our meta-analysis to cohort, case-control, and cross-sectional studies with a large sample size and with low to moderate risk of bias based on strict quality assessment criteria. Our comparative data on patients with COVID-19 and AIS as well as patients without COVID-19 allow for clearer inferences regarding the impact of COVID-19 on the manifestations and outcomes of patients with AIS. Furthermore, we summarized data based on patients with AIS who received acute revascularization treatment and laboratory data in the context of COVID-19, which have not been explored in previous reviews.

Several potential limitations should also be noted. First, potential confounding variables may lead to an overestimation of association because we used unadjusted estimates for the meta-analysis. Second, we cannot fully exclude the possibility that there may be overlapping of some patients across the included studies. Third, the small number of events may reduce the reliability of some estimates. Fourth, the studies included in this analysis demonstrated significant methodological heterogeneity; although we tried to mitigate this using random-effects models; this should be considered when interpreting our results. Finally, because the follow-up duration for most included studies was short, long-term functional outcomes remain to be determined.

5. Conclusions

This systematic review and meta-analysis showed that patients with AIS who had COVID-19 infection tended to have cryptogenic LVO and multi-territory infarcts with high CRP and D-dimer levels. These patients had more severe stroke syndromes, worse functional outcome, and a higher in-hospital mortality rate, with or without reperfusion treatment. These findings provide evidence that vigilance regarding stroke is needed in patients with severe COVID-19 infection as well as a need for antithrombotic treatment. Further studies are required to elucidate the precise pathophysiological mechanism of cerebrovascular disease in patients with COVID-19 and best management.

5. Conclusions

This systematic review and meta-analysis showed that patients with AIS who had COVID-19 infection tended to have cryptogenic LVO and multi-territory infarcts with high CRP and D-dimer levels. These patients had more severe stroke syndromes, worse functional outcome, and a higher in-hospital mortality rate, with or without reperfusion treatment. These findings provide evidence that vigilance regarding stroke is needed in patients with severe COVID-19 infection as well as a need for antithrombotic treatment. Further studies are required to elucidate the precise pathophysiological mechanism of cerebrovascular disease in patients with COVID-19 and best management.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Qingxiu Zhang, Liqun Zhang
Data curation: Zhelv Yao, Yue Cheng, Ruowen Qi, Lili Huang
Formal analysis: Zhelv Yao, Biyun Xu, Lili Huang
Funding acquisition: Qingxiu Zhang
Methodology: Zhelv Yao, Biyun Xu, Yue Cheng
Supervision: Qingxiu Zhang, Liqun Zhang
Writing–original draft: Zhelv Yao
Writing–review & editing: Qingxiu Zhang, Liqun Zhang

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