Acute review

Acute ischemic stroke outcomes in patients with COVID-19: a systematic review and meta-analysis

Sophia R Ferrone,1 Maria X Sanmartin,1,2 Joseph Ohara,3 Jean C Jimenez,3,4 Chinara Feizullahayev,3 Zachary Lodato,1 Shaya Shahsavaran,1 Gregory Lacher,1 Seleshi Demissie,4 Jaclyn Morales Vialot,5 Tim G White,6 Jason J Wang,1,2 Jeffrey M Katz,7 Pina C Sanelli 1,2,3

ABSTRACT

Background Although patients with COVID-19 have a higher risk of acute ischemic stroke (AIS), the impact on stroke outcomes remains uncertain.

Aims To determine the clinical outcomes of patients with AIS and COVID-19 (AIS-COVID+).

Methods We performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Our protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020211977). Systematic searches were last performed on June 3, 2021 in EMBASE, PubMed, Web-of-Science, Scopus, and CINAHL Databases. Inclusion criteria: (1) studies reporting outcomes on AIS-COVID+; (2) original articles published in 2020 or later; (3) study participants aged ≥18 years. Exclusion criteria: (1) case reports with <5 patients, abstracts, review articles; (2) studies analyzing novel interventions. Risk of bias was assessed using the Mixed Methods Appraisal Tool. Random-effects models estimated the pooled OR and 95% confidence intervals (95% CI) for mortality, modified Rankin Scale (mRS) score, length of stay (LOS), and discharge disposition.

Results Of the 43 selected studies, 46.5% (20/43) reported patients with AIS without COVID-19 (AIS-COVID−) for comparison. Random-effects model included 7294 AIS-COVID+ and 158,401 AIS-COVID−. Compared with AIS-COVID−, AIS-COVID+ patients had higher in-hospital mortality (OR=3.87 (95% CI 2.75 to 5.45), P<0.001), less mRS scores 0–2 (OR=0.53 (95% CI 0.46 to 0.62), P<0.001), longer LOS (mean difference=4.21 days (95% CI 1.96 to 6.47), P<0.001), and less home discharge (OR=0.31 (95% CI 0.21 to 0.47), P<0.001).

Conclusions Patients with AIS-COVID had worse outcomes, with almost fourfold increased mortality, half the odds of mRS scores 0–2, and one-third the odds of home discharge. These findings confirm the significant impact of COVID-19 on early stroke outcomes.

INTRODUCTION

Since the inception of the COVID-19 pandemic, over 676 million people have been infected worldwide, with more than 6.8 million deaths. Serious neurological manifestations, including stroke, were frequently reported in patients with COVID-19. Acute ischemic stroke (AIS) was the most common stroke subtype and was predominantly characterized by multiple cerebral infarctions. The risk of AIS was reported to be twice as high for patients with COVID-19 compared with non-COVID patients of the same age, sex, and ethnicity. In comparison with patients with AIS but without COVID-19 (AIS-COVID−), patients with AIS and...
COVID-19 (AIS-COVID+) were more likely to be younger, male, Black or Hispanic, and have diabetes and/or obesity. Furthermore, patients with AIS-COVID had more severe strokes with higher National Institutes of Health Stroke Scale (NIHSS) scores, and stroke was more often caused by large artery occlusion. While clinical evidence suggests that COVID-19 has a strong association with AIS due to underlying proinflammatory and hypercoagulable states, the magnitude of its impact on stroke outcomes among patients with AIS-COVID remains poorly elucidated.

Some previous research showed that AIS-COVID+ patients had worse clinical outcomes than AIS-COVID− patients, with extended hospital length of stay (LOS) and higher likelihood of discharge to a destination other than home. Many studies also reported higher in-hospital mortality and worse functional outcomes in AIS-COVID+ patients. However, a subset of studies described AIS-COVID+ patients with favorable outcomes based on the modified Rankin Scale (mRS) scores at discharge, which warrants further evaluation. Thus, synthesizing the available evidence in the literature from globally representative individual studies is critically important to more accurately quantify the impact of COVID-19 on stroke outcomes from different cohorts.

Our study aimed to perform a systematic review and meta-analysis to summarize and analyze the clinical outcomes of AIS-COVID+ patients during the early COVID-19 pandemic (pre-omicron variants). To our knowledge, this will be the first meta-analysis to synthesize and quantify the effect of COVID-19 on several stroke outcomes (in-hospital mortality, discharge mRS score, LOS, and discharge disposition) during the more severe initial COVID-19 pandemic, prior to the emergence of the omicron variants. Understanding the impact of COVID-19 on stroke outcomes may influence management and treatment strategies of AIS associated with other viral illnesses during future pandemics.

**Methods**

We performed a systematic review and meta-analysis to assess the clinical outcomes of AIS in patients with COVID-19 following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Our study protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020211977).

A senior medical librarian performed a systematic search for studies reporting clinical outcomes of AIS in patients with COVID-19 in EMBASE, PubMed, Web-of-Science, Scopus, and CINAHL databases. The details of the search strategy are provided in online supplemental A. The searches were last performed on June 3, 2021. The inclusion criteria to select studies were: (1) studies reporting clinical outcomes on patients with AIS and COVID-19; (2) original articles using quantitative or qualitative methods published in 2020 or later; (3) study participants aged ≥18 years; and (4) studies published in the English language from all countries. The exclusion criteria were: (1) case reports, case series with fewer than five patients, abstracts, conference posters, editorial letters, and review articles; (2) studies analyzing any novel treatments or interventions, except standard stroke treatment with intravenous thrombolysis and endovascular thrombectomy (EVT); (3) studies on the risk of AIS in COVID-19 without clinical outcomes data; and (4) studies reporting clinical outcomes of patients with AIS combined with hemorrhagic stroke.

**Study Selection and Data Extraction**

The identified literature was screened for study selection by six trained reviewers according to the inclusion and exclusion criteria using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The title/abstract screening, full-text review, and data extraction of each study were evaluated by two independent reviewers, with discrepancies resolved by a senior independent arbitrator. The following data variables were collected: (a) study characteristics: first author’s last name, title, publication year, journal name, study time-period, country in which the study was conducted, study purpose/objective, study design and interventions, data source, study cohort description (inclusion/exclusion criteria), sample size, and comparison group (AIS-COVID−) if reported; (b) clinical data: age, biological sex, race, admission National Institutes of Health Stroke Scale (NIHSS) score, intravenous thrombolysis, endovascular therapy, and COVID-19 diagnostic method; (c) outcomes data: mortality (in-hospital, 1 year, 5 year), case fatality rate, life expectancy, mRS score (at discharge, 30-day, 90-day), discharge NIHSS score, functional disability, discharge disposition, LOS, thrombolysis in cerebral infarction score, complications, quality-of-life and quality-adjusted life-years, utilities, patient outcome assessment, patient-reported outcome measures, critical care outcomes, neurologic and vascular outcomes.

Following data extraction, studies were included in the meta-analysis if clinical outcomes were reported for both the AIS-COVID+ and AIS-COVID− patients.

**Risk-of-Bias Assessment**

The quality of the selected studies for data extraction was assessed using the Mixed Methods Appraisal Tool—a checklist to assess the methodology in qualitative, quantitative, and mixed methods studies. Each study was evaluated by two independent reviewers for the screening and relevant questions, with discrepancies resolved by the senior independent arbitrator.

**Statistical Analysis**

For the systematic review, we performed a narrative synthesis with a structured summary of the selected studies’ characteristics and findings on the clinical outcomes in patients with AIS-COVID. Furthermore, we explored relevant aspects of the study findings both within and across the studies, with possible causes of heterogeneity in the study designs, data variables, and statistical analyses.

For the meta-analysis, the primary outcome measure was in-hospital mortality since this outcome was most consistently...
reported in the selected studies. The association between AIS-COVID+ and in-hospital mortality was described using the OR with 95% confidence interval (95% CI). The pooled estimate of an overall OR was calculated as a weighted average of individual ORs using the random-effects model. A restricted maximum likelihood method was used to estimate the regression parameters for the random-effects model. The outcome measures of discharge mRS score 0-2 and home discharge disposition were analyzed using the same methods. However, age, NIHSS score, and LOS were evaluated by computing the mean differences with 95% CIs. Statistical significance was considered for P values <0.05.

To assess the between-study variability, we used Cochrane’s Q test and the proportion of between-study heterogeneity was measured as the I² statistic. Graphical visualization of the pooled estimates was presented in forest plots for each clinical outcome. Publication bias was evaluated using funnel plot asymmetry. All analyses were conducted using R software, version 3.6.1.

**RESULTS**

**Study selection**

The PRISMA flow diagram (figure 1) displays the three-step study selection process using title/abstract screening, full-text review, and data extraction. The initial search yielded 15032 studies. After removing 8271 duplicates and 6446 irrelevant studies which did not meet the inclusion criteria, 315 studies advanced to full-text review. An additional 262 studies were excluded for the following reasons: unsuitable study designs (n=124), only reported patients with hemorrhagic stroke (n=62), incompatible outcomes (n=46), different patient populations (n=21), incompatible indication (n=3), not written or translated to English (n=3), abstracts only (n=2), and retracted from the literature (n=1). During data extraction of the remaining 53 studies, an additional 10 studies were eliminated because outcome metrics could not be extracted separately for patients with ischemic stroke. A total of 43 studies were included in the systematic review, of which 46.5% (20/43) reported clinical outcomes in AIS-COVID− patients as a comparison cohort for inclusion in the meta-analysis.

![Figure 1](http://jnis.bmj.com/ J NeuroIntervent Surg: first published as 10.1136/jnis-2023-020489 on 17 July 2023. Downloaded from http://jnis.bmj.com/ on April 14, 2024 by guest. Protected by copyright.)

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the selection of studies in the systematic review using a three-step process for title/abstract screening, full-text review, and data extraction.
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Study characteristics
Seventy-two percent (31/43) of studies were published in year 2020, and 28% (12/43) were published in year 2021 (Table 1). Studies were conducted in the United States, France, Spain, China, United Kingdom, Iran, Brazil, India, Egypt, Qatar, United Arab Emirates, and multinational. Of the 43 selected studies, 62.8% (27/43) used data from single centers, 11.6% (5/43) from multicenters, and 25.6% (11/43)...
from data registries. COVID-19 diagnosis was confirmed by PCR laboratory testing in 95.3% (41/43) of studies, with 14.6% (6/41) using CT, clinical diagnosis, or antibody testing when PCR was not available.

**Study population**

In the systematic review of 43 studies, 8438 AIS-COVID+ and 159579 AIS-COVID− patients were identified (online supplemental table 1, table 2). The mean age ranged from 39.3 to 77.0 years for AIS-COVID+ and from 54.9 to 75.2 years for AIS-COVID−. Men represented 58.0% (4874/8403) of AIS-COVID+ and 51.9% (82 159/158 401) of AIS-COVID−. The mean NIHSS scores ranged from 6.0 to 22.0 in AIS-COVID+ and from 3.0 to 16.0 in AIS-COVID−.

In the meta-analysis of 20 studies, 7294 AIS-COVID+ and 158 401 AIS-COVID− patients were included (table 2). Using a random-effects model, AIS-COVID+ had significantly lower age (mean difference −3.93 years (95% CI −6.09 to −1.78), P<0.001), more men (OR=1.25 (95% CI 1.01 to 1.56), P=0.043), and higher NIHSS score (mean difference 4.97 (95% CI 3.11 to 6.82), P<0.001), compared with AIS-COVID−.

**Comorbidity status**

Of the 20 studies included in the meta-analysis, 95% (19/20) reported the underlying comorbidities in AIS-COVID+ and AIS-COVID− patients. Univariate analyses were performed in 73.7% (14/19) of studies comparing the proportion of AIS-COVID+ and AIS-COVID− patients with individual comorbidities, of which 64.3% (9/14) of studies reported statistically significant differences between groups. Compared with AIS-COVID− patients, AIS-COVID+ patients had significantly higher proportions of diabetes and obesity, and significantly lower proportions of hypertension, hyperlipidemia/dyslipidemia, atrial fibrillation, and congestive heart failure. Logistic regression analyses for in-hospital mortality and/or favorable mRS score/discharge status adjusted by comorbidities were performed in 31.6% (6/19) of studies. The statistically significant adjusted ORs for in-hospital mortality ranged from 4.34 to 15.13 and favorable mRS score/discharge status ranged from 0.33 to 0.65.

Further review revealed that there was no significant difference in the Elixhauser comorbidity score between AIS-COVID+ and AIS-COVID− patients.15 24 Additionally, no significant difference in the proportion of patients without any comorbidities in the AIS-COVID+ and AIS-COVID− patients was reported.13 Furthermore, another study performed specific analyses to assess the impact of individual comorbidities on in-hospital mortality in AIS-COVID+ patients.25 There were no significant differences in the adjusted ORs of in-hospital mortality in patients with AIS-COVID with hypertension, atrial fibrillation, diabetes, prior stroke or transient ischemic attack, coronary artery disease, peripheral vascular disease, heart failure, and serum creatinine >2 mg/dL, compared with patients with AIS-COVID without these underlying comorbidities.25

**Stroke outcomes**

In the systematic review, in-hospital mortality was 27.8% (1990/7152) in AIS-COVID+ and 6.4% (10 093/158 327) in AIS-COVID− (online supplemental table 1, table 2). Discharge mRS score 0–2 was 26.9% (67249) in AIS-COVID+ and 26.8% (11 260/42 054) in AIS-COVID−. Mean LOS ranged from 6.0 to 18.7 days in AIS-COVID+ and from 3.0 to 9.1 days in AIS-COVID−. Home discharge disposition was 37.7% (2308/6130) in AIS-COVID+ and 64.0% (97 751/152 716) in AIS-COVID−.

In the meta-analysis, the OR and 95% CI for the individual studies included in each random-effects model are shown in figure 2. Compared with AIS-COVID−, the AIS-COVID+ had significantly higher mortality (OR=3.87 (95% CI 2.75 to 5.45), P<0.001), less discharge mRS scores 0–2 (OR=0.53 (95% CI 0.46 to 0.62), P<0.001), longer LOS (mean difference 4.21 days (95% CI 1.96 to 6.47), P<0.001), and less home discharge disposition (OR=0.31 (95% CI 0.21 to 0.47), P<0.001).

**Risk-of-bias assessment**

The quality assessment of studies using the Mixed Methods Appraisal Tool is summarized in online supplemental table 2. For all 43 of the selected studies, there were clear research questions/objectives, and 95.3% (41/43) of studies had appropriate data collection to answer the research question. Of these studies, 69.8% (30/43) were considered retrospective cohort and quantitative non-randomized studies. Participants were recruited in ways that minimized selection bias in all of these studies, and differences between comparison groups were considered in 93.1% (27/29) of studies. Data collection and outcome measures were relevant in 100% (29/29) and 96.3% (26/27) of studies, respectively. The remaining 30.2% (13/43) of studies were considered quantitative descriptive studies. For these studies, the sampling strategy and sample were relevant to address the study objective in 92.3% (12/13) and 100% (11/11) of studies, respectively. Data collection and outcome measures were relevant in 100% (12/12) and 100% (10/10) of studies, respectively.

To assess the between-study heterogeneity in the meta-analysis, the I^2 statistic measured 86.7% (P<0.001) for in-hospital mortality, 0% (P=0.376) for discharge mRS score 0–2, 95.6% (P<0.001) for LOS, and 93.0% (P<0.001) for home discharge disposition. Significant heterogeneity between studies was seen in the study cohorts, data variables, and statistical analyses.

The funnel plots for in-hospital mortality and discharge mRS score 0–2 (online supplemental figure 1) indicate no significant publication bias for these main outcomes.

**DISCUSSION**

Our meta-analysis revealed that patients with AIS-COVID had approximately fourfold higher in-hospital mortality, half the odds of good functional outcomes (mRS score 0–2), and one-third the odds of home discharge disposition. Our results are consistent with more recent studies published after our systematic search. In a large, multicenter retrospective study, patients with AIS-COVID had 2.51 higher odds of 60-day mortality than historical controls after propensity score matching.26 Although several studies reported on mortality in patients with AIS-COVID, our meta-analysis contributes to the literature by synthesizing and combining these individual studies from different cohorts to quantify the impact of COVID-19 more accurately in patients with AIS. In prior meta-analyses, a range of 1.32–5.21 higher odds of in-hospital mortality was found in patients with AIS-COVID during the first 8–10 months of the COVID-19 pandemic.3 27 Our study adds to the existing literature by including a larger sample size of patients with AIS-COVID, a longer time-period studied during the early pandemic, comparison with AIS-COVID− patients, and assessing several stroke outcomes. To our knowledge, there are no meta-analyses studying other relevant stroke outcomes in addition to mortality, such as discharge mRS score, LOS, and discharge disposition, in patients with AIS-COVID during the early (pre-omicron) COVID-19 pandemic.

Worse clinical outcomes in patients with AIS-COVID are probably related to more severe strokes at presentation as shown
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Table 2  Demographic characteristics and clinical outcomes of AIS-COVID+ and AIS-COVID– patients in the meta-analysis

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>First author (Last name)</th>
<th>AIS-COVID+ (N)</th>
<th>AIS-COVID− (N)</th>
<th>AIS-COVID+ Age (years) mean (SD)</th>
<th>AIS-COVID− Age (years) mean (SD)</th>
<th>Male sex % (N)</th>
<th>NIHSS score Mean (SD)</th>
<th>In-hospital mortality % (N)</th>
<th>Discharge mRS score 0–2% (N)</th>
<th>LOS Mean (SD)</th>
<th>Home discharge % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>Al Kasab et al</td>
<td>6</td>
<td>13</td>
<td>59.8 (17.4)</td>
<td>70.6 (14.9)</td>
<td>61.5% (8)</td>
<td>53.9% (240)</td>
<td>15.4% (2)</td>
<td>21.1% (94)</td>
<td>8 (2.8)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>2020</td>
<td>Altschul et al</td>
<td>18</td>
<td>23</td>
<td>63 (11.9)</td>
<td>68.3 (13.7)</td>
<td>38.5% (5)</td>
<td>56.5% (13)</td>
<td>23.1% (3)</td>
<td>17.4% (4)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2020</td>
<td>de Havenon et al</td>
<td>24</td>
<td>104</td>
<td>53.2 (13.7)</td>
<td>57.8 (13.2)</td>
<td>68.3% (71)</td>
<td>51.3% (1,571)</td>
<td>NR</td>
<td>NR</td>
<td>14.2 (15.4)</td>
<td>9.1 (10.6)</td>
</tr>
<tr>
<td>2020</td>
<td>Escalard et al</td>
<td>7</td>
<td>10</td>
<td>61.9 (15.1)</td>
<td>71.1 (16.8)</td>
<td>80.0% (9)</td>
<td>70.4% (19)</td>
<td>100% (1)</td>
<td>0% (0)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2020</td>
<td>Escalard et al</td>
<td>58</td>
<td>12</td>
<td>68.2 (13.0)</td>
<td>68.0 (14.7)</td>
<td>41.7% (28)</td>
<td>52.8% (28)</td>
<td>36.8% (7)</td>
<td>55.5% (12)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2020</td>
<td>Grewal et al</td>
<td>19</td>
<td>13</td>
<td>NR</td>
<td>63.0 NR</td>
<td>46.2% (6)</td>
<td>52.8% (28)</td>
<td>14.2 (15.4)</td>
<td>9.1 (10.6)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2020</td>
<td>Hernandez et al</td>
<td>8</td>
<td>17</td>
<td>68.2 (13.0)</td>
<td>68.0 (14.7)</td>
<td>76.5% (13)</td>
<td>72.7% (48)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2020</td>
<td>John et al</td>
<td>9</td>
<td>19</td>
<td>68.1 (18.0)</td>
<td>70.3 (15.3)</td>
<td>83.3% (10)</td>
<td>58.8% (20)</td>
<td>22.0 (1.7)</td>
<td>16 (1.8)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2020</td>
<td>Yaghi et al</td>
<td>13</td>
<td>53</td>
<td>61.6 NR</td>
<td>63.0 NR</td>
<td>46.2% (6)</td>
<td>52.8% (28)</td>
<td>14.2 (15.4)</td>
<td>9.1 (10.6)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2021</td>
<td>Majidi et al</td>
<td>24</td>
<td>21</td>
<td>59.0 (13.0)</td>
<td>73.0 (18.0)</td>
<td>79.2% (19)</td>
<td>42.9% (9)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>Tejada Meza et al</td>
<td>15</td>
<td>143</td>
<td>77.0 (10.5)</td>
<td>75.2 (12.6)</td>
<td>73.3% (11)</td>
<td>48.3% (69)</td>
<td>17.4 (6.9)</td>
<td>13.9 (6.3)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>Qureshi et al</td>
<td>25</td>
<td>32</td>
<td>48.9 (11.5)</td>
<td>54.9 (14.1)</td>
<td>85.7% (28)</td>
<td>77.8% (168)</td>
<td>9.8 (7.9)</td>
<td>5.6 (6.1)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>Benny et al</td>
<td>78</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>65.4% (51)</td>
<td>67.0% (87)</td>
<td>28.2% (22)</td>
<td>17.0% (17)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2021</td>
<td>Calmettes et al</td>
<td>40</td>
<td>17</td>
<td>64.8 (13.5)</td>
<td>68.1 (14.4)</td>
<td>62.5% (25)</td>
<td>63.1% (111)</td>
<td>10.2 (9.7)</td>
<td>7.1 (7.6)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>de Havenon et al</td>
<td>5517</td>
<td>111 418</td>
<td>61.6 (13.4)</td>
<td>61.5 (13.6)</td>
<td>58.0% (3,198)</td>
<td>51.9% (7,849)</td>
<td>11.6 (94)</td>
<td>7.5 (7.9)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2021</td>
<td>Nasal-Baudin et al</td>
<td>19</td>
<td>81</td>
<td>70.2 (8.4)</td>
<td>70.1 (15.3)</td>
<td>63.2% (12)</td>
<td>69.1% (56)</td>
<td>6 (3.3)</td>
<td>8 (3.8)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>Perry et al</td>
<td>81</td>
<td>1933</td>
<td>75.4 (13.6)</td>
<td>72.3 (16.3)</td>
<td>54.3% (44)</td>
<td>53.1% (833)</td>
<td>8 (3.4)</td>
<td>5 (2.8)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2021</td>
<td>Srivastava et al</td>
<td>1143</td>
<td>40828</td>
<td>67.6 (16.3)</td>
<td>70.7 (15.6)</td>
<td>53.8% (615)</td>
<td>51.3% (20,950)</td>
<td>8 (3.5)</td>
<td>4 (2.0)</td>
<td>21.5% (246)</td>
<td>4.6% (1,895)</td>
</tr>
</tbody>
</table>

AIS-COVID+, acute ischemic stroke with COVID-19; AIS-COVID−, acute ischemic stroke without COVID-19; LOS, length of stay; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NR, metric not reported.
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The pandemic and neurointervention by higher NIHSS scores on admission \(^{13,21}\) and late last known well to hospital arrival time,\(^{28}\) affecting treatment eligibility and response during the early COVID-19 pandemic. The primary underlying mechanisms associated with arterial and venous thromboembolic disease, multiple cortical infarctions, and intracranial hemorrhage have been attributed to the proinflammatory and hypercoagulable states associated with COVID-19.\(^{29,30}\) Furthermore, worse outcomes are also related to complications of the multisystem involvement by SARS-CoV-2 infection.

Although we were unable to disentangle stroke-specific mortality from the independent lethality of COVID-19, the mortality rate of AIS-COVID+ was significantly higher than either COVID-19 or AIS alone, suggesting a synergistic effect when both are present.\(^{31}\) The postulated synergistic prothrombotic consequences of AIS-COVID+ have not been fully elucidated yet.\(^{15}\) However, other comorbidities such as diabetes and cancer are also known to be associated with worse outcomes in patients with AIS. For instance, patients with AIS with diabetes have 1.23 higher odds of mortality or dependency at 6 months, compared with patients with a stroke without diabetes.\(^{32}\) Although the mechanism of the interaction between stroke and diabetes is also not clear, it has been suggested that the proinflammatory processes associated with diabetes may exacerbate AIS.\(^{33}\) Likewise, patients with AIS and metastatic cancer have 2.16 higher odds of in-hospital mortality and 0.60 lower odds of routine discharges, compared with patients with AIS without cancer.\(^{34}\) The proposed etiology for this association is hypercoagulability of malignancy,\(^{15}\) especially in patients with metastatic or hematologic cancers. Our study indicates that COVID-19 might have an even greater impact on stroke outcomes relative to diabetes and cancer, possibly due to the combined effects of proinflammatory and hypercoagulable states associated with COVID-19, as well as the high transmission rate of SARS-CoV-2 affecting both the healthy population and vulnerable patients with underlying comorbidities across all age groups.

Our findings also highlight the potential impact of viral infections on stroke outcomes. Acute viral illnesses may contribute to various stroke subtypes, including large or small vessel occlusion, with multifocal strokes due to cardioembolic etiology from hypercoagulability and thrombosis from inflammation and vasculitis.\(^{36,37}\) A wide range of viral infections have been linked to increased risk of AIS,\(^{37}\) including varicella zoster, HIV, and severe respiratory infections from parvovirus and influenza.\(^{36}\) In particular, similarities have been drawn between SARS-CoV-2 and influenza viral infections. Experimental studies of mice with occlusion of the middle cerebral artery found significantly increased inflammatory mediators in those mice brains that were coinfected with influenza A, concluding that influenza infection aggravates stroke pathophysiology out of proportion to fever or hypoxemia.\(^{38}\) Similar pathophysiologic alterations are seen in patients infected with SARS-CoV-2 virus, with activation of inflammatory mediators resulting in hypercytokinemia or ‘cytokine storm’ that increases procoagulant mechanisms and stroke events.\(^{36,39,40}\) In a large retrospective study, patients

Figure 2  In the meta-analysis, the random-effects model compared AIS-COVID+ and AIS-COVID− patients for each clinical outcome. AIS-COVID+ patients had significantly higher in-hospital mortality (OR=3.87 (95% CI 2.75 to 5.45), P<0.001) (A), less discharge mRS scores 0–2 (OR=0.53 (95% CI 0.46 to 0.62), P<0.001) (B), longer length of stay (mean difference 4.21 days (95% CI 1.96 to 6.47), P<0.001) (C), and less home discharge disposition (OR=0.31 (95% CI 0.21 to 0.47), P<0.001) (D). The individual studies included in each random-effects model are shown in the forest plots. AIS, acute ischemic stroke; AIS-COVID+, patients with AIS and COVID-19; AIS-COVID−, patients with AIS without COVID-19; mRS, modified Rankin Scale.

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with COVID-19 had a 7.6 increased odds of AIS compared with patients with influenza. Thus, COVID-19 has an even stronger association with AIS relative to other well-known viral infections, raising concern given the worldwide spread of SARS-CoV-2 and the high mortality rate associated with patients with AIS-COVID. These findings have highlighted the importance of understanding the synergistic effect of acute viral illnesses in the AIS population. In the era of globalization, other prevalent or novel viral illnesses could also reach pandemic levels, with potentially similar manifestations in patients with AIS.

The COVID-19 pandemic has expedited the adoption of systemic and workflow changes in healthcare to accommodate massive volumes of patients requiring emergency care. Understanding the severe impact of COVID-19 on AIS outcomes supports prioritizing a more proactive and flexible approach in managing and treating patients with AIS and with other viral illnesses. Six key principles were described to ensure safe and timely EVT during the COVID-19 pandemic focused on transfer of key knowledge, clinical practice, standardization and simplification, individualization, flexibility, and teamwork. In particular, prehospital triage employing telemedicine resources for efficient decision-making and routing patients with AIS-COVID directly to comprehensive stroke centers may be necessary to minimize delays for EVT and prevent overwhelming the primary stroke centers during the pandemic. Furthermore, there were considerable variations in the treatment of patients with AIS-COVID with ongoing debates promoting prethrombectomy airway management, intravenous thrombolysis, and antithrombotics. Thus, the COVID-19 pandemic has prepared health systems to be flexible and promptly adapt to new developments and available resources in stroke workflows and treatment paradigms in a rapidly changing environment in the post-COVID era.

Our study has several limitations. We limited the search to studies published in the early COVID-19 pandemic (2020–2021) to focus on the initial outcomes for patients with AIS-COVID, prior to emergence of the omicron variant, which could have excluded relevant studies published after 2021. However, this approach allowed us to capture the impact of COVID-19 amid the more severe initial pandemic, as the omicron variant is less likely to cause severe illness. Studies have reported a decline in mortality among patients hospitalized for COVID-19 from 17% to 21% in 2020 to 6% in 2022–2023, which may be due to changes in SARS-CoV-2 variants, increased immunity levels (from vaccination and prior infection), and improved clinical care. Future studies are also needed to explore further the impact of the post-omicron variants on AIS outcomes, and whether implementation of the vaccination program has significantly improved outcomes for patients with AIS during the COVID-19 pandemic. Lastly, there was significant heterogeneity between studies in the study cohorts, data variables, and statistical analyses that somewhat limited our ability to condense and analyze stroke outcomes in all selected studies. In particular, we were unable to perform propensity score matching on comorbidities in the meta-analysis to more accurately isolate the effect of COVID-19 on AIS outcomes. Further review of the studies included in the meta-analysis revealed that patients with AIS-COVID had significantly higher proportions of diabetes and obesity, and significantly lower proportions of hypertension, hyperlipidemia/dyslipidemia, atrial fibrillation, and congestive heart failure. However, the one study that specifically evaluated the impact of comorbidities on in-hospital mortality found no significant associations in patients with AIS-COVID. Furthermore, the logistic regression analyses adjusted by comorbidities ranged from 4.34 to 15.13 for in-hospital mortality and from 0.33 to 0.65 for favorable mRS score/discharge. Thus, even after adjusting for comorbidities, these findings are consistent with our meta-analysis results.

CONCLUSION
This systematic review and meta-analysis revealed that in the early (pre-omicron) pandemic, patients with AIS-COVID had almost fourfold higher in-hospital mortality, half the odds of good functional outcomes, and one-third the odds of home discharge disposition, compared with AIS-COVID—patients. The magnitude of these findings suggests that COVID-19 is a potent modulator of poor outcomes in AIS. A more accurate understanding of the impact of early COVID-19 on clinical outcomes in patients with AIS provides important insights that may guide the management and treatment of stroke associated with future viral pandemics, such as earlier adoption of more aggressive EVT criteria, anti-inflammatory and antithrombotic treatment strategies, flexible hospital workflow and triage protocols, and novel technologies. In this way the particularly poor outcomes associated with patients with AIS-COVID may be minimized or avoided during the next unexpected novel illness.

Author affiliations
1 Institute for Health System Science, Northwell Health Feinstein Institutes for Medical Research, Manhasset, New York, USA
2 Department of Radiology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, New York, USA
3 Department of Radiology, Northwell Health, Manhasset, NY, USA
4 Department of Biostatistics, Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY, USA
5 Medical Library Services, Northwell Health, Manhasset, NY, USA
6 Department of Biostatistics, Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY, USA
7 Department of Biostatistics, Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY, USA
8 Department of Neurology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, New York, USA
9 Department of Neurology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, USA
10 Department of Radiology, Northwell Health, Manhasset, NY, USA

Twitter Tim G White @timothywhiteMD

Contributors SRF made substantial contributions to the concept and design, critical review of the study protocol, data acquisition and organization, interpretation of results, manuscript preparation, and is guarantor of the scientific integrity. MXS served as a scientific advisor and made contributions to the interpretation of results and manuscript preparation. JO made contributions to the concept and design, study protocol preparation, review and submission, data acquisition and organization, and manuscript preparation. JCI, CF, ZL, SS, and GL made contributions to the data acquisition and organization. SD served as a scientific advisor and made contributions to the biostatistical analyses, interpretation of results, and manuscript preparation. JMV made contributions to designing and conducting the search strategy in the literature and data acquisition. TGW served as a scientific advisor and made contributions to the data acquisition, interpretation of results, and manuscript preparation. JKK served as a scientific advisor and made contributions to the interpretation of results and manuscript preparation. PSC made substantial contributions to the concept and design, critical review of the study protocol, data acquisition and organization, interpretation of results, manuscript preparation, and is guarantor of the scientific integrity.

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**ORCID IDs**
Jean C. Jimenez http://orcid.org/0000-0008-2880-2853
Tim G. White http://orcid.org/0000-0002-3604-4334
Pina C. Sanelli http://orcid.org/0000-0002-9633-3699

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The pandemic and neurointervention


