Postprint of a Meta-Analysis of the Impact of COVID-19 Infection on Stroke Incidence and Mortality

Authors: Li Litao, Huangfu Xiaojuan

Date: 2022-07-09T00:00:00+00:00

Abstract

Background Coronavirus disease 2019 (COVID-19) has spread globally, severely impacting human health and life. Studies have reported that COVID-19 infection can cause thrombotic diseases, and stroke is closely associated with thrombotic events. Objective To evaluate the impact of COVID-19 infection on stroke mortality and explore its potential mechanisms, thereby providing reliable clinical theoretical evidence for the scientific prevention and treatment of COVID-19 patients. Methods By searching literature published from December 2019 to January 2022 in databases including Web of Science, PubMed, Embase, Cochrane, CNKI, and Wanfang, screening relevant literature on COVID-19 complicated with stroke, using the NOS risk assessment criteria to evaluate the quality of included studies, using meta-analysis to evaluate the impact of COVID-19 infection on stroke mortality, and using funnel plots to assess publication bias. Results A total of 20 studies were included. Meta-analysis results showed: the mortality rate of stroke patients infected with COVID-19 was higher than that of the non-COVID-19 infection group (RR=4.16, 95% CI: 2.82-6.13, P<0.001); COVID-19 infection had a greater impact on prothrombin time (PT) (MD=0.93, 95% CI: 0.26-1.60, P=0.007); D-dimer levels were higher in COVID-19 patients complicated with stroke (MD=1.34, 95% CI: 0.83-1.84, P<0.001). There was no statistically significant difference in activated partial thromboplastin time (APTT) between the two groups (MD=2.51, 95% CI: -2.69-7.71, P=0.34); Stroke patients infected with COVID-19 were younger (MD=-1.70, 95% CI: -3.11-0.28, P=0.02); The prognosis of stroke patients infected with COVID-19 was associated with higher NIHSS scores at admission (MD=6.66, 95% CI: 4.54-8.59, P<0.01). Conclusion COVID-19 infection can increase stroke mortality, changes in the coagulation system such as PT and D-dimer may play an important mechanistic role, and its prognosis is associated with risk factors such as age and NIHSS at admission.

Full Text

Meta-Analysis of the Impact of COVID-19 Infection on Stroke Mortality

Huangfu Xiaojuan[1,4], Li Xiaojuan[2,4], Chen Min[3,4], Liu Jihong[2,4], Zhai Rui[2,4], Cai Zhipeng[1,4], Li Litao[4,*]

[1]Graduate School of Hebei North University, Zhangjiakou, Hebei Province, China
[2]Graduate School of North China University of Science and Technology, Tangshan, Hebei Province, China
[3]Graduate School of Hebei Medical University, Shijiazhuang, Hebei Province, China
[4]Department of Neurology, Hebei Provincial People' s Hospital, Shijiazhuang, Hebei Province, China

Corresponding author: Li Litao, Professor; Email: dingding51800@163.com

Abstract

Background: The novel coronavirus disease (COVID-19) has spread globally, seriously affecting human health and livelihood. It has been reported that COVID-19 infection can lead to thrombotic disease, and stroke is closely related to thrombotic events.

Objective: To evaluate the impact of COVID-19 infection on stroke mortality and explore its possible mechanisms, thereby providing a reliable clinical theoretical basis for the scientific prevention and treatment of COVID-19 patients.

Methods: We searched literature published from December 2019 to January 2022 in Web of Science, PubMed, Embase, Cochrane, CNKI, and Wanfang databases to screen studies related to COVID-19 and stroke. The NOS risk assessment criteria were used to evaluate the quality of included literature. Meta-analysis was used to evaluate the impact of COVID-19 infection on stroke mortality, and funnel plots were used to assess publication bias.

Results: A total of 20 studies were included. Meta-analysis results showed that the mortality of stroke patients infected with COVID-19 was higher than that of non-COVID-19 patients (RR=4.16, 95%CI: 2.82-6.13, P<0.001). The influence of COVID-19 infection on prothrombin time (PT) was greater (MD=0.93, 95%CI: 0.26-1.60, P=0.007). D-dimer was higher in patients with COVID-19 infection and stroke (MD=1.34, 95%CI: 0.83-1.84, P<0.001). There was no significant difference in activated partial thromboplastin time (APTT) between the two groups (MD=2.51, 95%CI: -2.69-7.71, P=0.34). Stroke patients infected with COVID-19 were younger (MD=-1.70, 95%CI: -3.11–0.28, P=0.02). The prognosis of stroke patients infected with COVID-19 was associated with

higher NIHSS at admission (MD=6.66, 95%CI: 4.54-8.59, P<0.01).

Conclusion: COVID-19 infection can increase stroke mortality. Changes in the coagulation system, including PT and D-dimer, may play an important mechanistic role. The prognosis is related to risk factors such as age and NIHSS at admission.

Keywords: COVID-19; Stroke; Novel coronavirus; Cerebrovascular disease; Mortality

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has spread globally, seriously affecting human health and livelihood. In early March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern [1], drawing widespread attention from researchers worldwide. Stroke represents a major global public health challenge, ranking as the second leading cause of death and third leading cause of disability worldwide, imposing tremendous burdens on society and individuals. In China, stroke has surpassed cardiovascular disease as the condition with the highest incidence, mortality, and disability rates.

COVID-19 infection affects not only the lungs but also multiple organs and systems [2], with several reports documenting its impact on the nervous system, particularly in causing cerebrovascular diseases [3,4]. Most published reports on COVID-19 and stroke have focused on patient care protocols [5], changes in healthcare delivery systems [6], or limited case series [7-10]. Facing this new disease spectrum, little is known about the interactions between diseases. Our scientific questions are: Does COVID-19 infection affect stroke prognosis? What is the underlying interaction mechanism? Some scholars suggest that COVID-19-associated stroke may result from hypercoagulability [11], vasculitis secondary to intracranial cytokine storms [12], and viral infection itself [13]. Therefore, this study aims to conduct a meta-analysis on this globally concerning issue, analyzing the relationship between COVID-19 infection and stroke to further evaluate the impact of COVID-19 infection on stroke mortality and explore its possible mechanisms, thereby providing reliable clinical evidence for the scientific prevention and treatment of COVID-19 patients.

Materials and Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

Study Subjects

All cases underwent COVID-19 testing using reverse transcription polymerase chain reaction on nasopharyngeal swab samples according to WHO standards. Stroke diagnosis was based on the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke. Patients were required to complete NIHSS assessment at admission and laboratory tests and outcome records during hospitalization.

Exclusion Criteria

We excluded: (1) studies with incomplete data or insufficient statistical analysis; (2) commentaries, reviews, and letters; (3) studies lacking information on diagnostic criteria for COVID-19 and stroke; (4) duplicate publications or multiple surveys based on the same population data (the most recent or most comprehensive study was included); (5) non-clinical study types such as case reports, case series, basic research, or laboratory studies.

Search Strategy

We systematically searched PubMed, Embase, Web of Science, Cochrane, CNKI (China National Knowledge Infrastructure), and Wanfang databases to collect clinical research literature on stroke in COVID-19 patients from December 2019 to January 2022. Search terms combined subject headings with free text. Chinese search terms included "COVID-19," "stroke," "novel coronavirus," "cerebrovascular disease,"and "mortality."English search terms included "Coronavirus Disease 2019 Virus," "Stroke," "novel coronavirus," "Cerebrovascular disease," and "Mortality." We also manually searched references of included articles to ensure comprehensive coverage.

Literature Screening and Data Extraction

Two reviewers independently assessed all identified articles by screening titles, abstracts, and full texts, with disagreements resolved through consensus. Full-text assessment was conducted when abstracts provided insufficient methodological information. We contacted authors of relevant articles if information was incomplete or unclear. The literature screening process is illustrated in [Figure 1: see original paper].

Data extraction included: first author, publication year, study country, study type, sample size, in-hospital mortality, National Institutes of Health Stroke Scale (NIHSS) score, age, and laboratory parameters.

Statistical Analysis

We used RevMan 5.3 software for heterogeneity analysis. The I^2 test was used for heterogeneity assessment. If $I^2 \leq 50\%$, indicating low heterogeneity, a fixed-effects model was used; if $I^2 > 50\%$, a random-effects model was applied. For

high heterogeneity, sensitivity analysis was performed to identify sources. Categorical data were expressed as relative risk (RR) and continuous data as mean difference (MD), both with 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$. Funnel plots were generated to assess publication bias, and sensitivity analysis was performed to evaluate result robustness.

Results

Literature Search Results

Our search identified 2,805 articles. After screening with EndNote, 20 studies [15-34] were ultimately included, all published in English. The literature screening process and results are shown in [Figure 1: see original paper], and the basic characteristics of included studies are presented in .

Quality Assessment Results

All 20 included studies met "fair or good" quality standards and were selected for further analysis. Eight studies met "good" quality standards, while 12 met "fair" quality standards (see for cohort studies and for case-control studies).

Meta-Analysis Results

Impact of COVID-19 Infection on Stroke Mortality. Sixteen studies reported in-hospital mortality (<15 days) in stroke patients with COVID-19, totaling 4,791 patients. Meta-analysis results showed that stroke patients with COVID-19 infection had significantly higher mortality risk compared with non-COVID-19 patients (RR=4.16, 95% CI: 2.82-6.13). The results are shown in [Figure 2: see original paper]. Heterogeneity was I^2=84%, and the difference in mortality between groups was statistically significant under the random-effects model (P<0.001). Sensitivity analysis by sequentially removing each study did not significantly alter the results, confirming stability.

Impact of COVID-19 Infection on Prothrombin Time (PT) in Stroke Patients. Four studies reported PT at admission in stroke patients with COVID-19, totaling 889 patients. The meta-analysis result was MD=0.93, 95% CI: 0.26-1.60, I^2=50%. The difference in PT between groups was significant under the random-effects model (P=0.007) (see [Figure 3: see original paper]). Sensitivity analysis by sequentially removing each study did not significantly alter the results, confirming stability.

Impact of COVID-19 Infection on Activated Partial Thromboplastin Time (APTT) in Stroke Patients. Four studies reported APTT at admission in stroke patients with COVID-19, totaling 968 patients. Meta-analysis showed MD=2.51 (95% CI: -2.69-7.71) (see [Figure 4: see original paper]). Heterogeneity was I^2=83% under the random-effects model, but the difference was not statistically significant (P=0.34).

Impact of COVID-19 Infection on D-Dimer in Stroke Patients. Seven studies reported D-dimer levels at admission in stroke patients with COVID-19, totaling 1,100 patients. Meta-analysis results showed MD=1.34, 95% CI: 4.54-8.79, I^2=59% (see [Figure 5: see original paper]). The difference in D-dimer between groups was statistically significant under the random-effects model (P<0.01). Sensitivity analysis by sequentially removing each study did not significantly alter the results, confirming stability.

NIHSS Assessment in Stroke Patients with COVID-19 Infection. Five studies reported NIHSS at admission in stroke patients with COVID-19, totaling 1,141 patients. The meta-analysis result was MD=6.66, 95% CI: 4.54-8.79, I^2=59%. The difference was significant under the random-effects model (P<0.01) (see [Figure 6: see original paper]), indicating that NIHSS scores were higher in stroke patients with COVID-19 infection. Sensitivity analysis by sequentially removing each study did not significantly alter the results, confirming stability.

Age Assessment in Stroke Patients with COVID-19 Infection. Nine studies reported age in stroke patients with COVID-19, totaling 2,290 patients. Meta-analysis showed that stroke patients with COVID-19 infection were younger than non-COVID-19 patients (MD=-1.70, 95% CI: -3.11-0.28) (see [Figure 7: see original paper]). Heterogeneity was I^2=67%, and the difference was significant under the fixed-effects model (P=0.02). Sensitivity analysis by sequentially removing each study did not significantly alter the results, confirming stability.

Bias Analysis

We primarily used funnel plots of stroke mortality changes to assess publication bias. The funnel plot (see [Figure 8: see original paper]) showed that included studies were distributed relatively symmetrically on both sides of the axis, suggesting no significant publication bias and high credibility of results.

Discussion

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported in Wuhan, China in December 2019, has spread worldwide. As of December 2021, COVID-19 had affected 2.78 billion people in 224 countries and territories, causing 5.3 million deaths [35]. With the emergence of variants such as Omicron [36], COVID-19 cases have grown exponentially, resulting in thousands of deaths. The disease can damage multiple systems and plays an important role in stroke pathogenesis [37]. Facing this new disease spectrum, little is known about interactions between diseases.

Many case reports suggest that COVID-19 infection can cause thrombotic diseases, which are closely related to stroke. However, whether COVID-19 infection affects stroke prognosis and the underlying interaction mechanisms remain unclear. During the COVID-19 pandemic, many countries reported a sharp

decrease in stroke admissions, suggesting that patients with mild stroke symptoms either did not seek hospitalization or voluntarily stayed home due to fear of COVID-19 infection, avoiding medical assistance during lockdowns. This aligns with reports from NOT and others showing reduced stroke hospitalization rates across regions [38]. Compared with the same period in 2019, stroke admissions decreased by more than 45% during the 2020 study period. All included patients were COVID-19 positive, and this decreased admission rate may be related to healthcare resource reallocation toward COVID-19 patients during the pandemic, precluding definitive conclusions about the relationship between stroke incidence and COVID-19.

This meta-analysis found that among stroke patients, those with COVID-19 infection had significantly higher mortality than non-COVID-19 patients (RR=4.16, 95% CI: 2.82-6.13, I^2=83%, P<0.001). This finding is consistent with a meta-analysis showing that COVID-19 infection increases stroke mortality risk threefold compared with non-COVID-19 patients [39]. Additionally, Yang et al. demonstrated that pre-existing cerebrovascular disease is associated with increased risk of poor prognosis in COVID-19 patients [40], possibly due to severe underlying infection and subsequent systemic and metabolic dysfunction.

Our analysis revealed that stroke patients with COVID-19 had higher rates of coagulation parameter abnormalities compared with non-COVID-19 patients, with statistically significant differences (MD=0.93, 95% CI: 0.26-1.60; MD=1.34, 95% CI: 0.83-1.84, I^2=54%). Consistent with our results, Garcia reported that stroke patients with COVID-19 had higher D-dimer levels and lower lymphocyte counts than ordinary patients, suggesting that COVID-19 infection causes immunosuppression [41]. A report from China also described higher rates of antiphospholipid antibodies and D-dimer abnormalities in COVID-19 patients with stroke [42]. D-dimer is a polymer composed of two D fragments of fibrin formed when the fibrinolytic system degrades fibrin networks after thrombosis [43], representing activation of the fibrinolytic system. Studies have shown that increased D-dimer and fibrinogen levels are associated with disease severity and increased mortality [44]. Additionally, we found no significant difference in APTT between COVID-19 and non-COVID-19 stroke patients. PT reflects the extrinsic coagulation pathway, with a normal range of 11-13 seconds; changes exceeding 3 seconds from normal controls are clinically significant. Shortened PT indicates a hypercoagulable state predisposing to thrombotic diseases such as coronary heart disease, myocardial infarction, and deep vein thrombosis, while prolonged PT indicates coagulation dysfunction. APTT reflects the intrinsic coagulation pathway. Based on 170 COVID-19 patients and 798 non-COVID-19 patients with stroke from included studies, results showed no statistically significant difference between groups.

Some literature reported NIHSS scores and age in stroke patients with COVID-19 infection, with adjusted analysis showing associations between NIHSS, age, and in-hospital mortality. In our stroke case series, COVID-19-infected cases

had lower mean age (MD=-1.70, 95% CI: -3.11-0.28, P=0.02) and higher NIHSS scores (MD=6.66, 95% CI: 4.54-8.79, P<0.01). A major finding of this study is that stroke severity is significantly affected by COVID-19 infection, with COVID-19 patients showing significantly higher stroke severity and in-hospital mortality compared with non-COVID-19 stroke patients.

However, the mechanisms of stroke in COVID-19 patients remain to be determined, with several plausible hypotheses: vascular wall invasion, coagulation disorders, cerebral embolism secondary to myocardial injury, or destabilization of existing atherosclerotic plaques. The virus can invade vascular walls because endothelial cells express ACE2 receptors [45], which the virus uses to enter cells, promoting thrombosis by disrupting vascular walls or inducing antiphospholipid antibodies [46] and activating the immune system [47], thereby affecting coagulation, platelet activation, and endothelial function, leading to a hypercoagulable state. Another potential mechanism involves interference with coagulation [48]; COVID-19 infection causes endothelial cell damage, activating the tissue factor-factor VIIa pathway to initiate coagulation and recruiting platelets and leukocytes to lesions, increasing local inflammation and further promoting coagulation system activation. The general inflammatory state or "cytokine storm" induced by COVID-19 in some patients also affects coagulation function [49]. Increased mortality after COVID-19 infection with stroke may represent a manifestation of systemic hypercoagulability, disrupting the balance between coagulation and anticoagulation systems and increasing stroke risk [50]. Some reports found that prophylactic anticoagulation in COVID-19 patients significantly reduced systemic thrombotic events [51], while others reported that anticoagulation reduced stroke mortality risk [52].

This study systematically analyzed current small-sample retrospective studies and found that stroke in COVID-19-infected patients is associated with higher in-hospital mortality compared with non-COVID-19 patients. This prognosis is significantly associated with laboratory parameters such as coagulation markers (D-dimer, PT), stroke severity, and age, opening new avenues for early identification and treatment of COVID-19 patients with stroke and providing evidence-based support. This meta-analysis has several limitations, including small sample sizes; none of the included studies mentioned blinding or allocation concealment, risking selection bias; descriptions of mindfulness interventions in included literature were not detailed or systematic; and the incidence of COVID-19 in stroke patients requires confirmation by high-quality randomized controlled trials.

Conflict of Interest: None declared.

References

[1] Alberto V, Luigi G G, Claudio B, et al. Stroke in patients with COVID-19: Clinical and neuroimaging characteristics[J]. Neuroscience Letters, 2021, 743.

[2] I G E, Yu M M, N B A, et al. [Novel coronavirus infection (COVID-19) and

nervous system involvement: pathogenesis, clinical manifestations, organization of neurological care][J]. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova, 2020, 120(6).

[3] Mehta P R, Apap Mangion S, Benger M, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases[J]. Brain Behav Immun, 2021, 95:514-517.

[4] C H D, Wael E, Elizabeth R. COVID-19-Related Stroke[J]. Translational stroke research, 2020, 11(3).

[5] Pandain J D, Panagos P D, Sebastian I A, et al. Maintaining Stroke Care During the COVID-19 Pandemic in Lower- and Middle- Income Countries: World Stroke Organization Position Statement Endorsed by American Stroke Association and American Heart Association[J]. Stroke, 2022, 53(3):1043-1050.

[6] Golomb M R, Hall G C. Letter by Golomb and Hall Regarding Article, "Temporary Emergency Guidance to US Stroke Centers During the COVID-19 Pandemic" [J]. Stroke, 2020, 51(7):e138.

[7] Bao Y, Lin S Y, Cheng Z H, et al. Clinical Features of COVID-19 in a Young Man with Massive Cerebral Hemorrhage-Case Report[J]. SN comprehensive clinical medicine, 2020, 2(prepublish).

[8] Kenichi S, Tatsuya M, Hideaki N, et al. [A case of cerebral embolism with Coronavirus disease 2019][J]. Rinsho shinkeigaku = Clinical neurology, 2021, 61(7).

[9] Bao Y, Lin S Y, Cheng Z H, et al. Clinical Features of COVID-19 in a Young Man with Massive Cerebral Hemorrhage-Case Report[J]. SN Compr Clin Med, 2020, 2(6):703-709.

[10] Shibata K I, Mukai T, Nakagaki H, et al. [A case of cerebral embolism with Coronavirus disease 2019][J]. Rinsho Shinkeigaku, 2021, 61(7):486-490.

[11] Ng Kee Kwong K C, Mehta P R, Shukla G, et al. COVID-19, SARS and MERS: A neurological perspective[J]. J Clin Neurosci, 2020, 77:13-16.

[12] Koncz J, Orosz V, Sulyok Z, et al. [Treatment options for enormous carotid thrombus as a complication of SARS-CoV-2 infection][J]. Ideggyogy Sz, 2021, 74(3-4):129-134.

[13] Balcom E F, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease[J]. Brain, 2021, 144(12):3576-3588.

[14] Page M J, Mckenzie J E, Bossuyt P M, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews[J]. Bmj, 2021, 372:n71.

[15] Dhamoon M S, Thaler A, Gururangan K, et al. Acute Cerebrovascular Events With COVID-19 Infection[J]. Stroke, 2021, 52(1):48-56.

[16] Qureshi A I, Baskett W I, Huang W, et al. Acute Ischemic Stroke and COVID-19: An Analysis of 27 676 Patients[J]. Stroke, 2021, 52(3):905-912.

[17] Katz J M, Libman R B, Wang J J, et al. Cerebrovascular Complications of COVID-19[J]. Stroke, 2020, 51(9):e227-e231.

[18] Rohit B, M P S, P S, et al. Clinical features and outcome of stroke with COVID-19. COVID-19 Stroke Study Group (CSSG), India[J]. Annals of Indian Academy of Neurology, 2021, 24(5).

[19] Mehrpour M, Shuaib A, Farahani M, et al. Coronavirus disease 2019 and stroke in Iran: a case series and effects on stroke admissions[J]. Int J Stroke, 2021, 16(9):1047-1052.

[20] Pablo N, Isabel R C, Cecilia R, et al. COVID-19 and Ischemic Stroke: Clinical and Neuroimaging Findings[J]. Journal of neuroimaging : official journal of the American Society of Neuroimaging, 2020, 31(1).

[21] Requena M, Olivé-Gadea M, Muchada M, et al. COVID-19 and Stroke: Incidence and Etiological Description in a High-Volume Center[J]. J Stroke Cerebrovasc Dis, 2020, 29(11):105225.

[22] Mathew T, John S K, Sarma G, et al. COVID-19-related strokes are associated with increased mortality and morbidity: A multicenter comparative study from Bengaluru, South India[J]. Int J Stroke, 2021, 16(4):429-436.

[23] Martí-Fàbregas J, Guisado-Alonso D, Delgado-Mederos R, et al. Impact of COVID-19 Infection on the Outcome of Patients With Ischemic Stroke[J]. Stroke, 2021, 52(12):3908-3917.

[24] Fernando S, Esther A R, Paz A G, et al. Increased Incidence of In-Hospital Ischemic Stroke During SARS-CoV-2 Outbreak: A Single-Center Study[J]. Neurocritical care, 2021, (prepublish).

[25] Bekelis K, Missios S, Ahmad J, et al. Ischemic Stroke Occurs Less Frequently in Patients With COVID-19: A Multicenter Cross- Sectional Study[J]. Stroke, 2020, 51(12):3570-3576.

[26] Lin C, Arevalo Y A, Nanavati H D, et al. Racial differences and an increased systemic inflammatory response are seen in patients with COVID-19 and ischemic stroke[J]. Brain, Behavior, & Immunity - Health, 2020, 8(prepublish).

[27] Merkler A E, Parikh N S, Mir S, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza[J]. JAMA Neurol, 2020.

[28] Correction to: SARS2-CoV-2 and Stroke in a New York Healthcare System[J]. Stroke, 2020, 51(8):e179.

[29] Topcuoglu M A, Pektezel M Y, Oge D D, et al. Stroke Mechanism in COVID-19 Infection: A Prospective Case-Control Study[J]. J Stroke Cerebrovasc Dis, 2021, 30(8):105919.

[30] Perry R J, Smith C J, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case- control study[J]. J Neurol Neurosurg Psychiatry, 2021, 92(3):242-248.

[31] John S, Hussain S I, Piechowski-Jozwiak B, et al. Clinical characteristics and admission patterns of stroke patients during the COVID 19 pandemic: A single center retrospective, observational study from the Abu Dhabi, United Arab Emirates[J]. Clin Neurol Neurosurg, 2020, 199:106227.

[32] Wang M, Zhang H, He Y, et al. Association Between Ischemic Stroke and COVID-19 in China: A Population-Based Retrospective Study[J]. Front Med (Lausanne), 2021, 8:792487.

[33] Ciolli L, Righi V, Vandelli G, et al. In-hospital and out-of-hospital stroke in patients with COVID-19: two different diseases?[J]. Neurol Sci, 2022, 43(4):2203-2210.

[34] Eric J G, Òscar M, Marcos F, et al. A case-control analysis of stroke in Covid-19 patients: Results of Unusual Manifestations of Covid-19-Study 11[J]. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 2021, 28(11).

[35] Ahmad Malik J, Ahmed S, Shinde M, et al. The impact of COVID-19 on the comorbidities: A review of recent updates for combating it[J]. Saudi J Biol Sci, 2022.

[36] Mohapatra R K, Kuppili S, Kumar Suvvari T, et al. SARS-CoV-2 and its variants of concern including Omicron: looks like a never ending pandemic[J]. Chem Biol Drug Des, 2022.

[37] Stamm B, Huang D, Royan R, et al. Pathomechanisms and Treatment Implications for Stroke in COVID-19: A Review of the Literature[J]. Life (Basel), 2022, 12(2).

[38] Yang Q, Tong X, Coleman King S, et al. Stroke Hospitalizations Before and During COVID-19 Pandemic Among Medicare Beneficiaries in the United States[J]. Stroke, 2021, 52(11):3586-3601.

[39] Galán J M T G Y. Stroke as a complication and prognostic factor of COVID-19[J]. Neurología (English Edition), 2020, 35(5).

[40] H K A, Lina P, Ramin Z, et al. The Impact of SARS-CoV-2 on Stroke Epidemiology and Care: A Meta-analysis[J]. Annals of neurology, 2020, 89(2).

[41] David G A, Abenza A M J, Erro A M E, et al. Neurological presentations of COVID-19: Findings from the Spanish society of neurology neuroCOVID-19 registry[J]. Journal of the Neurological Sciences, 2020, (prepublish).

[42] Hossri S, Shadi M, Hamarsha Z, et al. Clinically significant anticardiolipin antibodies associated with COVID-19[J]. Journal of Critical Care, 2020, 59(pre-publish).

[43] Zhang A, Leng Y, Zhang Y, et al. Meta-analysis of coagulation parameters associated with disease severity and poor prognosis of COVID-19[J]. Int J Infect Dis, 2020, 100:441-448.

[44] Milenkovic M, Hadzibegovic A, Kovac M, et al. D-dimer, CRP, PCT, and IL-6 Levels at Admission to ICU Can Predict In-Hospital Mortality in Patients with COVID-19 Pneumonia[J]. Oxid Med Cell Longev, 2022, 2022:8997709.

[45] Singh V, Beer A, Kraus A, et al. Stroke increases the expression of ACE2, the SARS-CoV-2 binding receptor, in murine lungs[J]. Brain Behav Immun, 2021, 94:458-462.

[46] Janardhan V, Janardhan V, Kalousek V. COVID-19 as a Blood Clotting Disorder Masquerading as a Respiratory Illness: A Cerebrovascular Perspective and Therapeutic Implications for Stroke Thrombectomy[J]. J Neuroimaging, 2020, 30(5):555-561.

[47] Rosas I O, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia[J]. N Engl J Med, 2021, 384(16):1503-1516.

[48] Nuthalapati P, Ghanta M K, Natesh N S, et al. Association of hypercoagulation with severe acute respiratory syndrome coronavirus 2 infection[J]. Blood Res, 2021, 56(2):61-64.

[49] Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review[J]. Thromb Res, 2020, 192:152-160.

[50] Souheil Z, Timothée K, Róbert K, et al. Acute Cerebral Stroke with Multiple Infarctions and COVID-19, France, 2020[J]. Emerging infectious diseases, 2020, 26(9).

[51] Flumignan R L G, Tinôco J D, Pascoal P I F, et al. Prophylactic anticoagulants for people hospitalised with COVID-19[J]. Cochrane Database of Systematic Reviews, 2020, (10).

[52] Alexandra K, Arooshi K, Shadi Y, et al. Anticoagulation use and Hemorrhagic Stroke in SARS-CoV-2 Patients Treated at a New York Healthcare System[J]. Neurocritical care, 2020, 34(prepublish).

Note: Figure translations are in progress. See original paper for figures.