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The impact of COVID-19 on patients with stroke: an integrative review

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Abstract

Purpose – This review aims to evaluate the evidence of the impact of COVID-19 on patients with stroke.
Design/methodology/approach – The author carried out a review following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for a review article. PubMed, the Web of Science and CINAHL Plus Full Text were searched from January 2019 to October 2020. Twenty-three studies were included in the final review, incorporating a total of 9,819 stroke patients.
Findings – The most commonly reported effects of COVID-19 on patients with stroke were delayed stroke treatment (n = 14 studies), thrombotic, blood and immune system complications (n = 8), increased risk of stroke severity and disability (n = 6), increased mortality (n = 8), elevated D-dimer levels (n = 4), comorbidity and acute respiratory distress syndrome (ARDS) (n = 6) and prolonged hospitalization (n = 4).
Originality/value – COVID-19 has affected patients with stroke in various ways, either directly or indirectly, prior to admission or in hospital. The findings should help guide further investigation of the long-term impact of COVID-19 on patients with stroke and help to establish proper guidelines for the provision of efficient treatment for affected patients.

Keywords Stroke, COVID-19, Coronavirus, Impact, Integrative review
Paper type Review

Introduction

Stroke is the foremost cause of death and disability globally, taking almost 6.5 million lives each year [1]. In 2016, approximately 13.7 million people had a primary stroke. Furthermore, around 2.7 million people died as a result of ischemic stroke, and 2.8 million deaths were due to hemorrhagic stroke [2, 3]. Notwithstanding the improvement in stroke treatment, the mortality rate is increasing [4].

At the beginning of December 2019, the first novel pneumonia cases of unknown origin were recognized in Wuhan, Hubie province, China [5] and later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 [6]. As of February 2020, a total of almost 81,000 COVID-19 cases had been confirmed globally. The World Health Organization (WHO) then declared COVID-19 a public health emergency of international concern [7]. On October 3, 2020, COVID-19 has killed around 1 million people from all over the world, with roughly 34 million accumulated verified cases [8]. Numerous institutions from

This article is dedicated to the frontline workers worldwide whose sacrifice has saved many lives throughout the COVID-19 pandemic. The author hopes that information from this review will, in some measure, help them overcome this pandemic.

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different countries are attempting to develop a COVID-19 vaccine to prevent this disease [9], with some success already announced [10]. Limitations on travel, either internationally or domestically, have been established in several countries [11]. These restrictions impact ordinary people's lives, especially vulnerable groups like patients with stroke [12].

The previous literature pointed out that COVID-19 is affecting stroke care in all parts of the world [12]. Generally, patients with stroke seem to be more susceptible to severe infection than other patients. Yet, the pandemic of COVID-19 has made it more difficult for patients with stroke to receive treatment and healthcare professionals to deliver stroke care, given restricted and hazardous conditions [12]. Statistics illustrate that the recorded number of acute stroke admissions has decreased by 50% to 80% in some countries during the pandemic [12, 13]. This number can be interpreted as implying that many patients were not admitted to the hospital despite sustaining moderate or even severe stroke [12, 13]. To date, possible mechanisms by which COVID-19 might increase stroke risk have been recognized. Nevertheless, the link between COVID-19 and an increased stroke risk needs further investigation; some literature implies that COVID-19 infection may actually cause a stroke [12]. In a previous study, 214 COVID-19 patients were included, and almost 37% showed neurological complications, particularly among patients with a severe form of the condition [14]. As there has been only limited investigation of the impact of COVID-19 on patients with stroke, this review aims to evaluate the impact of COVID-19 on patients with stroke. The current review was carried out in the hope that it would guide the treatment of patients with stroke affected by the current outbreak of COVID-19.

Methods

Identify relevant studies

Three electronic databases incorporated PubMed, Web of Science and CINAHL Plus Full Text were searched in October 2020 to identify preliminary case reports, case series, observational studies and randomized controlled trials (RCTs) reporting patients with stroke affected by COVID-19. The author combined the search terms: *(Stroke OR cerebrovasc* disorders OR cerebrovasc* disease OR cerebrovasc* accident OR brain isch?emi* OR isch? emi* cerebral attack OR brain attack OR intracranial h?emorrhage* OR CVA) AND (severe acute respiratory syndrome coronavirus 2 OR 2019-nCoV OR Wuhan coronavirus OR SARS-CoV-2 OR 2019 novel coronavirus OR COVID-19 virus OR coronavirus disease 2019 virus OR ncov OR COVID-19 OR SARS-CoV-2).* The search was limited to reports in English, with studies involving human adults ≥ 18 years old, with a time limit from January 2019 until October 2020. The detailed search strategy is shown in Supplementary Table 1. The search terms were adopted according to the guidelines of each database. In addition, the author reviewed the reference lists of relevant literature, but no additional articles were identified. The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] were applied to the identification, screening, exclusion and inclusion of the literature, as shown in the flow diagram of Figure 1. The author identified and reviewed data from primary resources. The review does not involve additional human participation and is therefore exempt from the need for Institutional Review Board approval.

Study selection

Firstly, the author screened titles and abstracts of eligible studies. Subsequently, the full text was also assessed to decide whether or not it was relevant. Inclusion criteria were implemented to guarantee that only studies considered relevant to the study objective were included. Similarly, exclusion criteria were utilized to eliminate literature not affiliated with a review (Table 1). The summary data (Supplementary Table 2) included the following data for

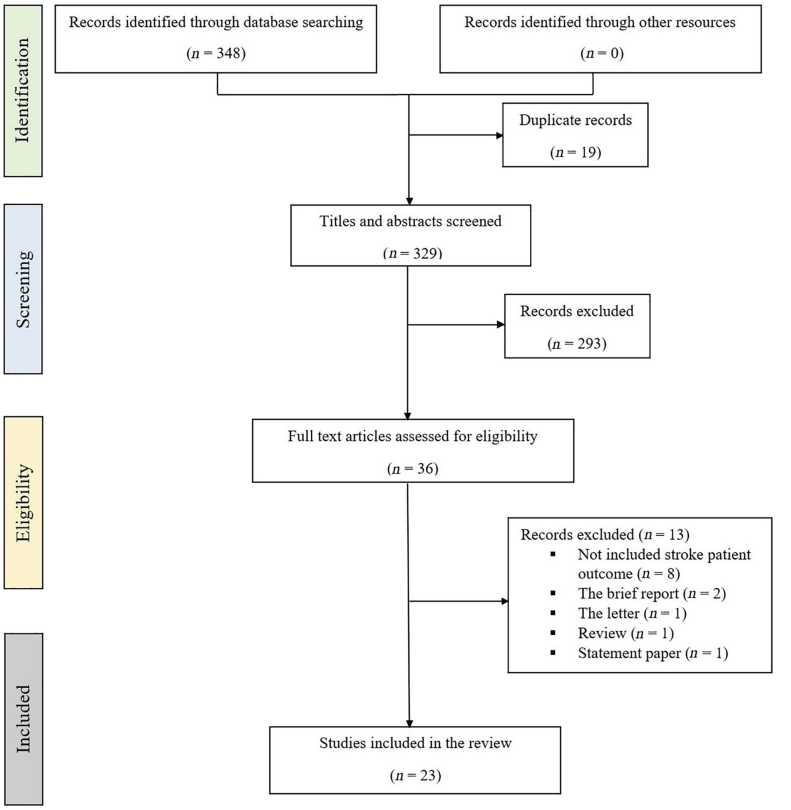

Figure 1.
Flow chart diagram displaying the selection method of eligible studies

	Inclusion	Exclusion
1	Adult patients (18 years or older)	Stroke as a complication/comorbidity
2	Diagnosis of stroke (including ischemic stroke, hemorrhagic stroke, or transient ischemic attack)	Studies including children or adolescents <18 years old
3	Case reports, case series, observational studies and randomized controlled trials reporting patients with stroke affected by COVID-19	Conference proceedings, abstracts, review articles, pilot study, protocol, dissertation, letter to the editor, brief report and statement paper
4	Described in the English language	Concerns animal subjects
5	Included an outcome measure of the impact of COVID-19 on patients with stroke (e.g. stroke complication, stroke severity, mortality, hospitalization, comorbidities, or disability)	

Table 1.
Study criteria

each study: references, publication year, country or countries, sample size, target population, description of intervention/methodology, main finding/the impact of COVID-19 on patients with stroke, summaries and level of evidence (LOE). LOE for each study was appraised by the researcher using The Rating System for the Hierarchy of Evidence for Intervention and Treatment Questions by Melnyk and Fineout-Overholt [16]. The LOE of the literature is

characterized as follows: Systematic reviews or meta-analyses of RCTs and clinical guidelines based on systematic reviews or meta-analyses (Level 1); Well-designed RCTs (Level 2); Controlled trials with no randomization (Level 3); Case-control or cohort study (Level 4); Systematic reviews of descriptive and qualitative studies (Level 5); A single descriptive or qualitative study (Level 6); Expert opinion(s)s (Level 7).

Results

Search results

Three hundred forty-eight references were classified through the initial search, among which any duplicate was identified and eliminated either by using Endnote X7 or manually. After deduplication, 329 references were prepared for screening, of which 293 articles were excluded through the title and abstracts at the screening phase following the inclusion and exclusion criteria (Table 1), leaving 36 articles eligible for the full-text screening. During this phase, articles were excluded for following reasons: did not include stroke patient outcome ($n = 8$), being a brief report ($n = 2$), being a letter ($n = 1$), being a review ($n = 1$) and being a statement paper ($n = 1$). A total of 23 studies reached the inclusion-exclusion criteria and were incorporated in the final review (Figure 1).

Studies and participants' characteristics (Table 2)

All included studies were published in 2020. The included studies were conducted in several countries, including the United States ($n = 6$, 26.09%), China ($n = 4$, 17.39%), Spain ($n = 3$, 13.04%), Italy ($n = 2$, 8.70%), France (n = 2, 8.70%), Turkey ($n = 1$, 4.35%), Korea ($n = 1$, 4.35%), Singapore ($n = 1$, 4.35%), Iran ($n = 1$, 4.35%) and Multi-center ($n = 2$, 8.70%). The study designs were cohort study ($n = 8$, 34.78%), a retrospective study ($n = 7$, 30.43%), case series ($n = 3$, 13.04%), case reports ($n = 3$, 13.04%), a prospective study ($n = 1$, 4.35%) and a descriptive study ($n = 1$, 4.35%). Almost 66% of the selected articles were classified as level 6 of evidence and approximately 35% were classified as level 4 on the basis of the Melnyk and Fineout-Overholt [16] guidelines. The sample size varied according to the study design. For cohort studies, the sample size ranged from 13 to 894, 5 to 49 for case series, 1 to 4 for case reports, 55–2,737 for the retrospective study. Only one prospective and one descriptive study were included in the review; sample sizes were 1,513 and 277. The target population in the included studies were individuals with stroke, including acute ischemic stroke ($n = 10$ studies, 37.04%), ischemic stroke ($n = 6$ studies, 22.22%), hemorrhagic stroke ($n = 3$ studies, 11.11%), transient ischemic attack ($n = 3$ studies, 11.11%) and unspecified stroke ($n = 5$, studies 18.52%).

Description of the impact of COVID-19 on patients with stroke (Table 3)

A summary of the findings from the studies included in this review is provided in Table 3. Scrutiny of the table suggests that they can be placed into seven main categories, including (1) Delayed stroke treatment, (2) Thrombotic, blood and immune system complications, (3) Stroke severity and disability, (4) Mortality, (5) D-dimer levels, (6) Comorbidity and acute respiratory distress syndrome (ARDS) and (7) Prolonged hospitalization.

Delayed stroke treatment. Fourteen studies reported that the COVID-19 pandemic caused significantly delayed treatment such as alteplase administration, thrombolysis, thrombectomy, or patients' consultation [17–30]. One cohort study asserted that a trend toward more limited alteplase administration was recorded in patients with stroke throughout the COVID-19 pandemic than a year before the outbreak [17]. Likewise, another study shows that the time from stroke symptom onset to emergency room arrival was 22 hours during the pandemic, much longer than usual, resulting in delayed treatment

Characteristic		Number (*n*)	Percentage (%)
Publication year			
2020		23	100
Country			
United States		6	26.09
China		4	17.39
Spain		3	13.04
Italy		2	8.70
France		2	8.70
Turkey		1	4.35
Korea		1	4.35
Singapore		1	4.35
Iran		1	4.35
Multi-center		2	8.70
Study design	*Level of evidence*		
Cohort study	Level 4	8	34.78
A retrospective study	Level 6	7	30.43
Case series	Level 6	3	13.04
Case reports	Level 6	3	13.04
A prospective study	Level 6	1	4.35
A descriptive study	Level 6	1	4.35
*Target population**			
Acute ischemic stroke (AIS)		10	37.04
Ischemic stroke (IS)		6	22.22
Hemorrhagic stroke (HS)		3	11.11
Transient ischemic attack (TIA)		3	11.11
Unspecified		5	18.52

Sample size (n)	Maximum	Minimum
Cohort study	894	13
Case series	49	5
Case reports	4	1
A retrospective study	2,737	55
A prospective study**	1,513 ($n = 1$)	
A descriptive study**	227 ($n = 1$)	

Note(s): *One study consists of ≥ 1 target population; **Consists of only 1 study

Table 2.
The characteristics of the included studies

[18]. This phenomenon probably arose because several countries' governments restricted local travel and activity due to the COVID-19 pandemic. Consequently, stroke care either before hospital admissions, such as medical consultation and transfer to hospital, or treatment in hospital, such as alteplase administration, thrombolysis, thrombectomy, was affected [19, 20, 22].

Thrombotic, blood and immune system complications. Thrombotic, blood and immune system complications are the most common reported sequelae in patients with stroke diagnosed with COVID-19 [17–19, 31–35]. One cohort study shows that acute ischemic stroke patients diagnosed with COVID-19 developed a systemic thrombotic complication [17]. Similarly, another cohort study with 50 unspecified stroke patients with COVID-19 revealed that patients with a medical history of stroke had a higher neutrophil count and lowered lymphocyte and platelet counts than those without a stroke history [31]. In summary, patients with COVID-19 with a stroke history are more likely to have severe clinical symptoms and poorer outcomes than those without a stroke history.

Table 3. The impact of COVID-19 on patients with stroke

Reference##	Delayed treatment (alteplase/thrombolysis/ thrombectomy/ consultation)	Thrombotic/ blood and immune system complications	NIHSS (stroke severity)	mRS (disability)	Mortality	The D-dimer levels	Comorbidities	ARDS	Prolonged hospitalization
[17]	*v	*v	*v	*v					
[36]			*v	*v	*v				
[18]	***v	***v				***v			
[31]		****v			****v	****v	****v	****v	
[38]					****v		****v	****v	****v
[32]		***v	***v			***v			
[39]					****v		****v		****v
[37]			#^					#^	
[33]		***±	***±		***±		***±		***±
[19]	*v	*v							
[20]	*v								
[21]	*v								
[22]	*v				*v				
[23]	*v				*v				
[24]	*v								
[25]	*v								
[26]	*v								
[27]	*v								
[34]		***v					***v		
[28]	*v								
[29]	*v								*v
[30]	*v								
[35]		*v	*v		*v	*v			
Total (*n*)	*14*	*8*	*6*	*2*	*8*	*4*	*5*	*3*	*4*

Note(s): NIHSS National Institutes of Health Stroke Scale, mRS modified Rankin Scale, ARDS Acute Respiratory Distress Syndrome; **##** One study reported ≥ one impact; **#^** Outcome significantly improved (no comparison group); ***v** Outcome significantly worse compared to stroke patients without the diagnosis of COVID-19; *****v** Outcome significantly worse compared to stroke patients with the diagnosis of COVID-19; *****±** Outcome combined results compared to stroke patients with the diagnosis of COVID-19; ******v** Outcome significantly worse compared to non-stroke patients with the diagnosis of COVID-19

Stroke severity and disability. Six articles on the impact of COVID-19 on patients with stroke reported a correlation between stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) and a diagnosis of COVID-19 [17, 32, 33, 35–37]. Four out of the 6 stated that NIHSS was significantly higher in stroke patients with COVID-19 than those without the disease [17, 32, 35, 36]. In addition, two cohort studies examined the relationship between the level of disability measured by the modified Rankin Scale (mRS) and COVID-19 [17, 36]. Overall, patients with stroke with COVID-19 had a higher risk of severe disability than those without the infection.

Mortality. Eight studies reported that increased mortality is one of the effects of COVID-19 on patients with stroke [22, 23, 31, 33, 35, 36, 38, 39]. Seven of the eight studies noted that the mortality rate of stroke patients with a diagnosis of COVID-19 has significantly increased during the pandemic. COVID-19 patients with a stroke history had more acute clinical symptoms and worse outcomes than those without a history of stroke and during the pandemic appeared to receive delayed treatment (either pre-admission or in-hospital) compared to before the pandemic (see above). Consequently, they were more likely to succumb [22, 23, 31, 35, 36, 38, 39].

D-dimer levels. Inflammation and blood clot formation in developing ischemia can be predicted by a high D-dimer level [32]. Four studies indicated that D-dimer levels were markedly higher in COVID-19 patients with a history of stroke [18, 31, 32, 35]. This result possibly indicates that the coronavirus causes or worsens stroke, perhaps by inducing inflammation. In addition to infectious symptoms, signs of cerebrovascular events should be investigated, particularly among elderly patients with prothrombotic risk factors.

Comorbidity and acute respiratory distress syndrome (ARDS). A number of papers stated that stroke patients diagnosed with COVID-19 are more likely to develop comorbidity and ARDS [31, 33, 34, 37–39]. Previous studies indicated that the COVID-19 patients with a medical history of stroke were more elderly, had more underlying comorbidities and greater illness severity than those without pre-existing stroke [31, 34, 38]. Likewise, another study found that patients with COVID-19 with a history of stroke (study cohort) had more comorbidities and worse clinical outcomes than those without a history of stroke (control cohort) (39). Furthermore, a cohort study [31] reported that stroke survivors who contracted COVID-19 were more likely to develop ARDS than non-stroke patients with the diagnosis of COVID-19. Correspondingly, the study from Zhang and colleagues [38] said patients with stroke had a higher risk of developing acute pneumonia and subsequent death than patients without stroke.

Prolonged hospitalization. Four investigations explored the possible connection between COVID-19 and prolonged hospitalization in patients with stroke [29, 33, 38, 39]. A previous case series revealed that in 49 patients with stroke with the diagnosis of COVID-19, they are more likely than non-stroke patients with the diagnosis of COVID-19 to develop comorbidities and greater severity of illness and consequently tended to have prolonged length of hospital stay [38]. Likewise, a prospective study in acute ischemic stroke patients suggested that the coronavirus pandemic caused delays in treatment, with patients needing to wait unusually long times to receive it, and this was a cause of increased duration of care [29].

Discussion

This review included a cohort study, a retrospective study, case series, case reports, a prospective study and a descriptive study of a moderate level of quality based on Melnyk and Fineout-Overholt guidelines [16]. Reported outcomes differed according to the research objective and design. Fourteen studies reported the impact of COVID-19 in delaying stroke treatment (e.g. alteplase, thrombolysis, thrombectomy, or consultation), eight studies reported on thrombotic, blood and immune system complications, six on stroke severity, two on level of disability, eight on mortality, four on D-dimer levels, five on comorbidities, three on ARDS and

four on hospitalization (Table 3). Delayed consultation or treatment, including alteplase administration, thrombolysis, thrombectomy, is the most frequently reported impact of COVID-19 on stroke patients. Stricter disease prevention measures and restrictions on activity and travel, both internationally and domestically, maybe the main reason for this [19, 20, 22]. The finding is consistent with the conclusion of the World Stroke Organization (WSO) that, during the pandemic, provision of stroke therapy, including critical interventions such as carotid endarterectomy, has been delayed or put on hold due to an insufficient number of trained healthcare professionals [12].

Complications in blood and the immune system in stroke patients diagnosed with COVID-19 have also been reported [17–19, 31–35]. In brief, stroke patients with COVID-19 are more likely to develop a systemic thrombotic, abnormal white blood cell level, inflammation and blood clot formation, predicted by a high D-dimer level. Although the association between COVID-19 and stroke still requires additional investigation, previous studies stated that hypercoagulability, as evidenced by increased D-dimer levels, exaggerated systemic inflammation and cardio-embolism virus-related cardiac injury, are potential risk factors among stroke patient with COVID-19 [14, 40, 41]. One study recommended that various factors possibly perform functions in the co-occurrence of stroke and COVID-19 and its outcome. Prospective examinations with long-term follow-up are needed to appraise and confirm prognostic factors [33].

Although a previous systematic review asserted that there was no statistically significant difference in NIHSS score between survivors and non-survivors among stroke patients with COVID-19 [42], in the present review, three studies [17, 35, 36] reported that the NIHSS score was significantly higher in stroke patients with the diagnosis of COVID-19 compared to stroke patients without the diagnosis of COVID-19. Furthermore, a couple of studies also demonstrated the potential connection between the level of disability as measured by the modified Rankin Scale (mRS) and the occurrence of COVID-19 [17, 36]. Patients with stroke who are COVID-19 positive tend to have higher mRS scores, indicating a more significant disability.

A previous systematic review [42] demonstrated that among 30 relevant studies involving 115 stroke patients, a higher death rate (47.9%) was reported in stroke patients with COVID-19 infection as compared with those without the infection. The factor correlated with this mortality was comorbidity, such as a history of hypertension, dyslipidemia, diabetes, or inflammatory and thrombotic conditions. This is consistent with conclusions from the current review, which noted that 7 out of 8 studies report that the mortality rate of stroke patients with COVID-19 has significantly increased during the pandemic [22, 23, 31, 35, 36, 38, 39], caused by comorbid conditions such as ARDS and acute pneumonia [31, 38]. The findings of the current review indicate that adequate preparation of public stroke services is essential. Strengthened public consciousness and corrective measures may minimize the harmful outcomes of the COVID-19 outbreak on acute stroke care.

Limitations

There are several limitations in this integrative review itself to note. Firstly, since the researcher did not include studies from the gray literature, such as conference proceedings or abstracts, this may introduce a publication bias. Moreover, solely English language studies were included. Because of this, the study in other languages that aimed to report stroke patients affected by COVID-19 may have been omitted. Finally, the researcher searched only three electronic databases, which could possibly lead to a limitation of this study's findings and generalizability.

Conclusions

Compared with the prior to the COVID-19 pandemic, the pandemic significantly interferes with stroke treatment efficacy such as stroke consultations and reperfusion treatment, particularly thrombolysis, which declined qualitatively. The delay in thrombolysis appeared

to continue through the pandemic so that healthcare providers are encouraged to reevaluate their local paradigms to expedite stroke treatment. The existing review confirms that the current pandemic of COVID-19 varyingly impacted patients with stroke either directly or indirectly. Delayed stroke treatment, increases in complications, increased stroke severity, disability, mortality, comorbidity and prolonged hospitalization are the most generally reported findings. This year until next year will be a challenging and uncertain time for stroke care. Therefore, the government, healthcare institutions, healthcare professionals and individuals will have to adjust their working practices. In the meantime, effectively following standard precautionary practice to ensure that both patients and workers are protected is necessary. Further, after this pandemic has ended, investigation of the long-term impact of the COVID-19 pandemic on patients with stroke should be undertaken.

Conflict of Interest: None

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Supplementary materials

Supplementary Table 1 can be found online at: https://www.researchgate.net/publication/350342543_Supplementary_table_1_Search_strategies_The_Impact_of_COVID-19_on_Patients_with_Stroke_An_Integrative_Review

Supplementary Table 2 can be found online at: https://www.researchgate.net/publication/350342451_Supplementary_table_2_Summary_data_The_Impact_of_COVID-19_on_Patients_with_Stroke_An_Integrative_Review

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