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Onset of Stroke in Patients with Post-COVID-19 Syndrome Following Hospitalisation for Severe COVID-19 Infection: A systematic literature review

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Introduction

Complications from SARS-CoV-2 infection are not limited to the respiratory system, with some patients presenting with systemic disease (1). An increased risk of acute cerebrovascular, thrombotic, and neurologic complications has been documented for certain patient subgroups with SARS-CoV-2, suggesting an association between infection and perturbed thromboinflammatory pathways (2-6). Acute ischemic stroke and large vessel occlusion has been documented following acute infection (7), with observational studies reporting a stroke incidence rate of between 1-3% (4, 8). Discharged hospitalised COVID-19 patients were three times more likely to suffer a new onset major adverse cardiovascular events (MACE), including stroke, when compared with matched controls (9). Post-acute COVID-19 syndrome (PACS), also known as 'long COVID', is an evolving topic of interest that is used to describe complications that extend ≥4 weeks beyond the initial symptoms (10). It is not yet known if patients in long-term recovery from severe hospitalised COVID-19 with PACS are at increased risk of cerebrovascular events. This systematic literature review (SLR) identified clinical studies reporting stroke outcomes associated with the onset of post-discharge cerebrovascular events following severe SARS-CoV-2 infection.

Methods

Sources: The SLR was performed in accordance with Cochrane and PRISMA guidelines (11). EMBASE®, MEDLINE® and Cochrane databases were searched 1st January 2020–14th June 2021 using OVID® to systematically identify studies reporting stroke outcomes associated with adults suffering a cerebrovascular event ≥4 weeks following hospitalisation for severe acute-COVID-19 (including time to stroke, epidemiological outcomes regarding onset stroke, disease characteristics of stroke and of SARS-CoV-2). Supplementary sources were hand searched from January 2020 to October 2021:

- Conferences (Brain, Behaviour, and Immunity; Stroke; Journal of Stroke; International Journal of Stroke)
- Websites (ClinicalTrials.gov; BMJ Stroke resources; ONS stroke outcome data)

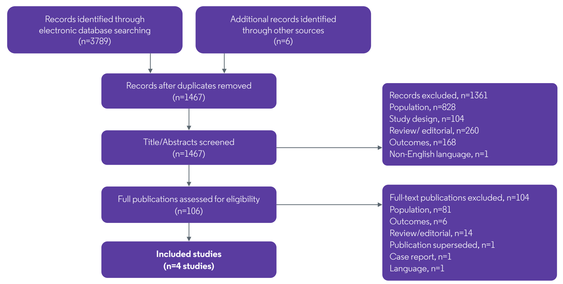
Eligibility criteria: All clinical studies that reported stroke outcomes associated with adults suffering a cerebrovascular event ≥4 weeks following hospitalisation for severe acute-COVID-19 were considered for inclusion, with no restriction by country/region.

Exclusion: Studies reporting patients with mild infection, studies without relevant stroke outcomes following hospitalisation for COVID-19, and patients with pre-COVID-19 prophylactic treatment for stroke. Non-English language publications.

Results

Of the 1,467 records screened in the SLR, a total of four published studies (12-19) were included (Figure 1). In addition, four ongoing clinical trials (16-19) were also identified.

FIGURE 1: PRISMA flow diagram for the SLR



Four studies (12-15) reported stroke outcome data associated with adults suffering a cerebrovascular event following hospitalisation for severe acute-COVID-19 (Table 1). Post-discharge timepoints across the studies ranged from 40 days (13) to 92 days (12). The incidence of stroke post-discharge ranged from 0.45% in the USA (12) to 11.5% in Ukraine (15). The post-discharge thrombotic outcomes ranged from 1.71% (12) to 2.5% (13) in the USA, with only one study reporting arterial thromboembolism (ATE). A single study reported the mortality due to stroke at 0.59% (14).

TABLE 1: Summary outcome table

Study Country	Data source	Study period; Design	Mean age, years (SD); Gender %	Post-discharge from hospital timepoint	Post-discharge stroke incidence, n/N (%)	Mortality due to stroke, n (%)	Post-discharge thrombotic outcomes	Author conclusion
Giannis, 2021 (12) USA, N=4906	CORE-19 registry	1 March to 31 May 2020; Prospective registry study	61.7 (17.5) Male: 53.7	92 days	22 (0.45)	NR	Composite ATE (including stroke): 84 (1.71)	ATE, VTE and ACM occur with a higher frequency during this post-discharge period than previously reported. Findings support extended thromboprophylaxis with an anticoagulant.
Vorokhta, 2021 (15) Ukraine, N=77,753	Odessa Regional Laboratory Center, Ukraine	December 2019 to 2020; Medical chart review	NR (All <50 years)	NR (Convalescents in recovery from COVID)	112 (11.5)	NR	NR	The incidence of stroke in Odessa in convalescents after COVID was 11.5%.
Patel, 2020 (13) USA, N=163	Beth Israel Deaconess Medical Center	March to May 2020; Medical chart review	Median (IQR: 58 (44-67) Male: 47.8	40 days	1 (<1)	NR	Thrombotic events: 4 (2.5)	The rates of thrombosis and haemorrhage appear to be similar following hospital discharge for COVID-19, emphasizing the need for randomized data to inform recommendations for universal post-discharge thromboprophylaxis.
Rashidi, 2021 (14) Iran, N=1529	Multi-center	February 20 to April 10 2020; Prospective cohort study	Median: 56 Male: 54.4	45 days	9 (0.59)	9 (0.59)	NR	We observed a low rate of symptomatic VTE and all-cause death in COVID-19 patients after hospital discharge. Due to the low number of events, we could not identify any risk factor for post-discharge VTE. The current evidence suggests that routine extended thromboprophylaxis after hospital discharge of COVID-19 patients may not have a net clinical benefit.

Abbreviations: ACM, all-cause mortality; ATE, arterial thromboembolism; IQR, interquartile range; N, number; NR, not reported; SD, standard deviation; VTE, venous thromboembolism

Identified ongoing clinical trials

Four ongoing clinical trials were identified from the supplementary searches that will report relevant secondary outcome measures on the long-term effects of COVID-19 (Table 2):

TABLE 2: Ongoing clinical trials

Trial/ NCT number Country	Title	Secondary outcome measure	Estimated Study Completion Date
CV-COVID-19/ NCT04359927 Spain, Italy	Long-term effects of coronavirus disease 2019 on the cardiovascular system, CV COVID registry: A structured summary of a study protocol	Stroke rate at 1 year defined according to the Academic Research Consortium-2.	August 31, 2025 (Estimated primary completion date: August 31, 2021)
OPTIC-19/ NCT04838106 England, Wales	Outcomes of Patients Who Survived Treatment on an Intensive Care Unit for COVID-19 in England and Wales (OPTIC-19)	Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure).	November 1, 2021
CORONA-VTE NET/ NCT04535128 USA	COVID-19 Registry to Assess Frequency, Risk Factors, Management, and Outcomes of Arterial and Venous Thromboembolic Complications	30-day and 90-day frequencies of arterial (myocardial infarction, stroke or systemic embolism) and venous thromboembolic events	March 30, 2022
NCT04650087 USA	COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis	Composite outcome of symptomatic DVT, PE, other venous thromboembolism, ischemic stroke, other arterial thromboembolism, and all-cause mortality at 45 and 90 days after hospital discharge. New, symptomatic ATE (inclusive of stroke, MI or peripheral arterial thromboembolism) at 30 days.	August 2022

Management guidelines/recommendations at each stage of the PACS patient journey

Given the paucity of published evidence on the longitudinal follow up of patients with complications from PACS, this SLR reviewed available clinical guidelines and other consensus documents at each stage of the PACS patient journey (Table 3).

- The definition of PACS is varied and is still evolving (20-22).
- Although descriptions are varied, PACS is defined as collection of symptoms that develop >4 weeks after acute COVID-19 onset (23, 24), and may have symptoms that are persist at >12 weeks from the onset of acute COVID-19 symptoms (25, 26).
- NIH and WHO recommends prophylactic anticoagulation treatments to be prescribed only for hospitalised non-pregnant acute COVID-19 patients who are without any contraindication or need for higher dosage. Patients already on anticoagulation treatment pre-hospitalisation, anticoagulation should be continued unless contraindicated. In case of clinical deterioration, a switch to low molecular weight heparin (LMWH) is preferred over other therapy choices (25).
- Post-discharge continuation of thromboprophylaxis is generally not recommended, however evidence suggests that high-risk patients are typically discharged on a 10 day extended regimen (22).
- Concept of care for complications from PACS is heterogenous. Overall, advice considers the benefits of supportive management and symptom monitoring in patients' discharge period and knowing when to seek emergency care.
- From a triage viewpoint, specialty referral and rehabilitation should be organised for effective management of deteriorating neural and other life-threatening symptoms in PACS suspects (21, 22, 24, 26, 27). NICE recommend that follow up for symptom alerts of PACS occurs within 1-2 weeks (25); SIGN recommend this at 6 weeks post-discharge (26).
- PACS is clearly an evolving topic of interest; we expect to see treatment guidelines providing more detailed advice on managing the long terms complications in due course.

Evidence gaps

- Whilst there are other sources of COVID-19 evidence (e.g. large global registries, living SLRs), due to a lack of reporting of specific stroke-related outcomes in PACS, our SLR focussed on high-quality evidence from peer-reviewed publications reporting on longitudinal data from clinical trials, prospective observational studies, and retrospective medical chart review.
- There was a paucity of high-quality published evidence reporting cerebrovascular events in the post-discharge PACS period. Few studies documented the median time between COVID-19 hospitalisation and the identification of complications. More longitudinal follow up studies are needed.
- Longitudinal outcome data from severe hospitalised COVID-19 and PACS presents other challenges in analysis, including confounding variables (patient vaccination status, administered prophylactic stroke treatment, patients' existing prophylactic treatment). Further, if there is a strong relationship between PACS and stroke symptom onset, a paucity of high-quality data identified in this SLR could reflect a tendency for patients with PACS and minor stroke to stay away from primary and secondary care during the ongoing pandemic.

Conclusion

This SLR identified four published studies and four ongoing clinical trials that measure the onset of cerebrovascular events in PACS following hospitalisation for acute-COVID-19 . It is unclear if there is an elevated risk of suffering cerebrovascular events without the results on ongoing follow-up studies. Continued observations of the natural history of PACS are much awaited in order to update this SLR in the future.

TABLE 3: Summary of guidelines and recommendations

PATIENT JOURNEY

	Guideline on use of prophylactic anti-coagulation in hospitalised patients	Management of hospitalised patients with rapid neurological deterioration	Guidelines on post-discharge anti-coagulation or thromboprophylaxis treatment	Guideline on the definition of PACS	Guideline on management of any complication of PACS	Guideline on management of neurological or cognitive complications in PACS	Guideline on management of stroke complications in PACS
NIH	✓	✓	✓	✓	✓		
CDC				✓	✓	✓	
Nuffield Department of Primary Care Health Sciences, UK			✓	✓	✓	✓	✓
BMJ					✓		
WHO	✓		✓	✓	✓	✓	✓
NICE	✓			✓	✓	✓	
SIGN	✓				✓		

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