

Intravenous Thrombolysis in Acute Ischaemic Stroke Two Years into the COVID-19 Pandemic: A Retrospective Study

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Abstract

Introduction: Changes in intravenous thrombolysis treatment rates for acute ischaemic stroke during the COVID-19 pandemic have been reported. We examined the differences in the provision of intravenous thrombolysis in patients with acute ischaemic stroke, two years prior to and two years into the COVID-19 pandemic.

Methods: Data were compared between March 1, 2018 to February 28, 2020 (Pre-COVID-19) and March 1, 2020 to February 28, 2022 (COVID-19). Data collected included patients' demographics, intravenous thrombolysis rates, and patient outcomes.

Results: There was an increase in ischaemic stroke patient admissions during the COVID-19 period (Pre-COVID-19 n=1041, vs COVID-19 n=1087). Yet, fewer stroke patients received intravenous thrombolysis (19.2% vs 13.9%, $p<0.001$), and there were more stroke mimics thrombolysed (8.3% vs 15.6%, $p=0.021$) during this period. During the COVID-19 period, there was a significant delay in hospital presentation for patients who were thrombolysed (Pre-COVID-19 = 86 minutes vs COVID-19 = 107 minutes, $p = 0.004$); and delay in giving thrombolysis (median door to needle time: Pre-COVID-19 = 59 minutes vs COVID-19 = 65 minutes, $p = 0.002$). Fewer patients had severe stroke symptoms (National Institute of Health Stroke Scale score = >15) (12.2% vs 4.8%, $p=0.009$) during the COVID-19 period. There was no significant difference in patients' post-thrombolysis outcome (median National Institute of Health Stroke Scale score = 1, $p=0.136$; discharge modified Rankin Scale score = 1, $p=0.647$; and mortality $p=0.655$).

Conclusion: This study showed that during the first 2 years of the COVID-19 pandemic, there was a significant decline in the thrombolysis rates and delay in the administration of the intravenous thrombolysis treatment.

Keywords: Ischaemic stroke, COVID-19 pandemic, Intravenous Thrombolysis

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DOI: 10.21307/ajon-2024-003

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Introduction

The COVID-19 pandemic impacted healthcare systems Worldwide, affecting the delivery of various medical interventions. Stroke, a life-threatening event that requires prompt medical treatment, was particularly affected (Hurford, Sekhar, Hughes, & Muir, 2020). The provision of intravenous thrombolysis (IVT), a well-established treatment for acute ischaemic stroke (AIS) (Wardlaw et al., 2012), was challenging during this unprecedented time (Jala et al., 2022). Of note there was a reduction in the number of patients receiving IVT and delay in the initiation of thrombolysis reported internationally (Cadilhac et al., 2021; Ishaque et al., 2022; Jala et al., 2022; Mag Uidhir et al., 2020; Xu et al., 2022).

Disruptions in healthcare systems due to the COVID-19 pandemic led to a number of changes in protocols including personal protective equipment and infection control requirements, resource allocation, and patient management (Filip, Gheorghita Puscaselu, Anchidin-Norocel, Dimian, & Savage, 2022). The pandemic posed unique challenges to patients resulting in altered healthcare-seeking behaviour and changes in stroke presentations (Padmanabhan, Natarajan, Gunston, Raseta, & Roffe, 2021). These factors may have influenced the diagnosis and treatment of AIS, potentially leading to variations in thrombolysis utilisation and outcomes. As we have reached the two-year mark of the COVID-19 pandemic, it is crucial to assess the impact of this global health crisis on the administration and outcomes of IVT in stroke patients and the implications on hospital policy, clinical practice guidelines, and quality of essential care, to intervene and

improve at a systems level if required. Thus, we examined the differences in the provision of IVT in acute stroke two years into the COVID-19 pandemic in our acute stroke service. Officially, the World Health Organisation declared on the 5th of May 2023, that COVID-19 is no longer a global public health emergency (Rahman, Cronmiller, Victoros, Shanjana, & Islam, 2023).

Methods

Study Design, Participants, and Site

This observational study involved an audit of electronic health care records from a comprehensive acute stroke service in Sydney, Australia. A comparison of the administration of IVT during two time periods: 1 March 2018 to 28 February 2020 (pre-COVID-19) and 1 March 2020 to 28 February 2022 (COVID-19) was performed.

Patients diagnosed with stroke but not admitted to the stroke unit were also included in the dataset. Their electronic health records were reviewed by the members of the stroke research team.

The study included acute stroke patients with a primary diagnosis of ischaemic (I63.0-I63.9, and I64) or transient ischaemic attack (TIA) (G45.9) based on the International Classification of Diseases 10th Revision (ICD-10). Inclusion criteria were: adults (≥ 18 years) with signs and symptoms of an acute stroke who presented to the emergency department (ED) and had a confirmed diagnosis of stroke (either ischaemic or haemorrhagic) or TIA at discharge. Patients who had a stroke or TIA after admission (i.e., in-hospital stroke) were excluded.

Demographic and clinical variables were collected from the electronic health records including age, gender, indigenous identity, stroke severity using the National Institute of Health Stroke Scale (NIHSS) (Hage, 2011), pre-morbid function using modified Rankin Scale (mRS) (Broderick, Adeoye, & Elm, 2017), symptom onset to ED arrival, ED to CT scan time, ED to needle (treatment) time. Length of stay, discharge diagnosis. A full list of the variables is presented in the supplementary file.

Data Analysis and Statistics

Descriptive statistics were performed to summarise data and determine distribution. The Mann-Whitney U-test was used to explore differences in continuous outcomes and ordinal variables. Differences in categorical variables were assessed using Pearson's chi-square test or Fisher's exact test. A value of $p < 0.05$ was considered statistically significant. All analyses were conducted using IBM SPSS Statistics v.27.

Ethical Considerations

This study adhered to the National Health and Medical Research Council definition of quality assurance and evaluation and was reviewed and approved by the Northern Sydney Local Health District Human Research and Ethics Committee.

Results

This retrospective study showed that the demographics of the groups were similar: mostly non-indigenous (98.7%, pre-COVID-19 and 98.9% during COVID-19), almost half were females (pre-COVID-19 = 49.3% and during COVID-19 = 44.6%), with a median age of 77 (pre-COVID-19) and 76 (during COVID-19)

years. During the COVID-19 pandemic, there was an increase of 4.4% in stroke presentations (Pre-COVID-19 = 1041 vs during COVID-19 = 1087). Although both groups had mild to moderate symptoms at baseline, there were fewer patients with severe symptoms (NIHSS > 20) in the COVID-19 group (pre-COVID-19 = 12.2% vs during COVID-19 = 4.8%; $p = 0.009$).

During the COVID-19 pandemic, the IVT rate of ischaemic stroke significantly decreased (pre-COVID-19, 19.2% [$n = 200/1041$]; during COVID-19, 13.9% [$n = 151/1087$], $p < .001$). There was a delay in the administration of IVT treatment, with an increase of 6 minutes in the median door-to-needle time (DNT) during the same period (DTN: Pre-COVID-19 = 59 minutes and during COVID-19 = 65 minutes $p = 0.002$), which was significant. Further, the number of stroke mimics treated with IVT increased during the COVID-19 pandemic (pre-COVID-19 = 8.3% [$n = 19/229$] vs during COVID-19 = 15.6% [$n = 29/186$]; $p = 0.021$).

In terms of post-thrombolysis outcome, both groups had a similar median NIHSS score that is, 1. At hospital discharge, half of the patients from both groups had a discharge modified ranking score (mRS) of < 2 , and a mean length of hospital stay of 5 days ($p = 0.095$).

Discussion

This single-centre, retrospective observational study found a significant reduction (30%) in patients receiving IVT during the COVID-19 pandemic. This finding is consistent with results from studies conducted at other stroke centres (Cadilhac et al., 2021; Filip et al., 2022; Ishaque et al., 2022; Khunte et al.,

Table 1. Demographic and clinical characteristics

Characteristic	Statistic		P- value
	Pre- COVID	During COVID	
Ischaemic stroke admissions, n	1041	1087	
Received IVT, all stroke diagnoses, n	229	186	
Ischaemic stroke receiving IVT, n (%)	200 (19.2)	151 (13.9)	<0.001
Age, years, median (IQR)	77 (65-85)	76 (62-85)	0.434
Gender, female, n (%)	113 (49.3)	83 (44.6)	0.374
Non-indigenous identity, n, (%)	226 (98.7)	184 (98.9)	0.827
NIHSS score, on admission, median (IQR)	6 (2-13)	5 (3-9)	0.313
NIHSS score, 24 hours post IVT, median (IQR)	1 (1-4)	1 (1-4)	0.136
NIHSS score, on admission, categorised, n (%)			0.049
No symptoms	11 (4.8)	8 (4.3)	0.974
Minor	89 (38.9)	72 (38.7)	0.761
Moderate	84 (36.7)	87 (46.8)	0.024
Moderate to severe	17 (7.4)	10 (5.4)	0.400
Severe	28 (12.2)	9 (4.8)	0.009
mRS before stroke treatment, median (IQR)	0 (0-1)	0 (0-1)	0.327
mRS on discharge, median (IQR)	1 (1-4)	1 (1-4)	0.647
mRS on discharge, categorised, n (%)			0.522
Score 0-1	121 (52.8)	101 (54.3)	0.766
Score 2-3	32 (14.0)	19 (10.2)	0.246
Score 4-5	56 (24.5)	53 (28.5)	0.419
Score 6	20 (8.7)	13 (7.0)	0.655
Time: symptom onset to ED, minutes, median (IQR)	86 (62-130)	107 (74-166)	0.004
Time: Door to CT scan, minutes, median (IQR)	19 (13-29)	22 (16-32)	0.007
Time: Door to Needle (IVT), minutes, median (IQR)	59 (41-78)	65 (53-85)	0.002
Time: onset to needle (IVT), minutes, median (IQR)	160 (120-205)	188 (144-240)	<0.001
Length of stay: ED, minutes, median (IQR)	157 (113-202)	173 (131-216)	0.011
Length of stay: hospital, days, median (IQR)	5 (3-8)	5 (3-9)	0.095
Discharge stroke diagnosis, n (%)			0.063
Ischaemic	200 (87.3)	151 (81.2)	0.084
Transient ischaemic attack	10 (4.4)	6 (3.2)	0.548
Stroke mimic (Vilela, 2017)	19 (8.3)	29 (15.6)	0.021

Notes: Pre-COVID = 01 Mar 2018 – 28 Feb 2020; During COVID 01 Mar 2020 – 28 Feb 2022; IVT = intravenous thrombolytic medication, IQR = interquartile range, NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Score; ED = emergency department; CT = computerised tomography

2023; Xu et al., 2022). A recent meta-analysis reported a reduction in the rate of IVT administration of 27.2% during the COVID-19 pandemic (95% CI, 22.7 to 32.0%) for acute ischaemic stroke worldwide (Ishaque et al., 2022). The decline was highest in Asia (40.3%; 95% CI, 27.8 to 53.3), followed by North America (26.9%; 95% CI, 12.7 to 43.9), and Europe (25.7%; 95% CI, 19.7 to 32.1) (Ishaque et al., 2022).

The decrease in IVT administration during the COVID-19 pandemic could be attributed to several factors. Delay in stroke patients' presentation to hospitals could have resulted in an overall lower number of patients eligible for thrombolysis (Gu et al., 2022). On top of the delay presentation, the added COVID-19 infection control protocol / requirements contributed to the delay of assessment and diagnosis. A study reported that during the pandemic, the number of patients seeking urgent medical attention decreased as many feared contracting COVID-19 and were concerned about overwhelming the healthcare system (Padmanabhan et al., 2021). However, in our case, we had an increase in patient presentations with stroke symptoms. In addition, the pandemic may have overwhelmed and compromised healthcare systems, leading to delays in stroke recognition and treatment initiation. Healthcare resources and personnel may have been redirected to managing patients with COVID-19, causing delays in stroke evaluations and the administration of IVT. Further, the pandemic may have introduced additional challenges in accurately diagnosing acute ischaemic stroke. The presentation of stroke symptoms may have been confounded by COVID-19 and vaccination-related complications, such as respiratory distress or neurological manifestations

(Alam et al., 2021; Patone et al., 2021). This could have led to diagnostic uncertainty and increased caution in initiating IVT because of potential adverse events. It is worth noting that the decrease in IVT during the COVID-19 pandemic does not necessarily indicate a decline in the overall quality of stroke care. For example endovascular thrombectomy was used more in some centres during the COVID-19 pandemic (Khunte et al., 2023).

In the current study we found a significant delay in providing IVT for stroke patients from arrival at the ED (6 minutes, $p=0.002$). The median door to needle time (DNT) during the COVID-19 period was 65 minutes compared to 59 minutes pre-COVID-19. A decrease in DNT was reported in a similar observational study conducted in China during the pandemic but the delay was lower (51.60 minutes, $p=0.026$) (Xu et al., 2022). During the pandemic delays in treatment initiation were attributed to various factors including increased infection prevention measures; changes in hospital workflows; reduced healthcare resources; and difficulty in clinical decision-making as COVID-19 and vaccination reaction signs and symptoms sometimes mimic stroke.

Further, we found more stroke mimics were treated with IVT during the COVID-19 period. Stroke mimics are patients who present with stroke symptoms, not caused by a cerebrovascular event. The administration of IVT to stroke mimics can be attributed to the challenges in accurately differentiating between stroke and stroke mimics based solely on initial emergency department clinical presentation. Time is of the essence in stroke treatment, and clinicians may err on the side of caution and initiate thrombolysis if there is

uncertainty about the diagnosis. Moreover, the concern for potential underdiagnosis or failure to correctly diagnose stroke due to the fear of overwhelming the healthcare system during the pandemic may result to a more liberal approach towards IVT.

Interestingly, during the COVID-19 pandemic, an upward trend in stroke mimic presentations was noted. For example an observational study exploring stroke mimic patterns in Lithuania, demonstrated an increase in hospital presentation of severe symptoms for stroke mimics (Melaika et al., 2021). In contrast, summary data for many studies suggests there was a decline in the rates of stroke mimics, which was demonstrated in a recent meta-analysis (2022). Nonetheless, there are limited reports for the thrombolysis treatment and outcomes of stroke mimics.

Limitation

In this current study the sample was relatively small and from a single site. Thus, the findings might not be generalisable. The findings may not be representative of healthcare settings in other states of Australia or countries. As this is an observational study, there may be some confounding variables thus we could not demonstrate causality.

Implications of the findings

Stroke Clinicians

The findings may prompt stroke clinicians to re-evaluate their approaches to thrombolysis treatment. Medical, nursing and allied health professionals may consider factors such as the risk benefit ratio of thrombolysis, resource allocation, and the potential impact of other contextual factors such as a pandemic on the effectiveness and safety of the treatment.

This could lead to clearer acute stroke pathways, protocols and guidelines to ensure standardisation and optimal care regardless of contextual factors. Further, healthcare institutions and organisations may need to adapt their practices and resources to account for reduced thrombolysis rates and delay treatment during this period. This may involve the provision of additional training and education to clinicians on screening, and diagnosing acute stroke patients during the pandemic, ensuring the availability of necessary resources, and implementing measures to minimise delay to treatment.

Nurses

The findings of the study have important implications for nursing practice. Nurses can play a crucial role in the initial assessment of stroke patients. This highlights the need for nurses to promptly recognise stroke signs and symptoms and initiate the appropriate protocols for stroke assessment. Moreover, the study findings suggests that the pandemic has led to changes in healthcare resources and protocols, potentially impacting the administration of thrombolysis. Nurses need to stay updated with the latest guidelines from stroke organisations and adapt their practices accordingly. This may involve modifying stroke assessment protocols, implementing alternative pathways for thrombolysis administration, and collaborating with medical and allied health teams to ensure appropriate care. Further, nurses can help in raising awareness about stroke symptoms and the importance of seeking medical attention. This emphasises the need for nurses to help in educating the public, both in healthcare settings and the community, about the signs of stroke and the urgency of calling 000.

Conclusion

The study identified a significant difference in IVT administration before and during the COVID-19 outbreak which highlights the impact of the pandemic on stroke management practices. These findings emphasise the need for continuing evaluation and adjustment of stroke care protocols to ensure that timely and appropriate treatment is provided to all eligible acute ischaemic stroke patients, particularly during health challenges such as a pandemic.

This study highlighted the need for further research to explore the underlying reasons for reduced thrombolysis rates and delayed IVT during the COVID-19 pandemic. This research could focus on understanding clinicians' clinical decision-making, patient preferences, biases, and system-level factors that contributed to the observed trends. Moreover, future studies and analysis are required to understand the long-term implications of the decrease in thrombolysis rate and delays in IVT treatment so as to identify strategies to mitigate their potential negative consequences on stroke outcomes.

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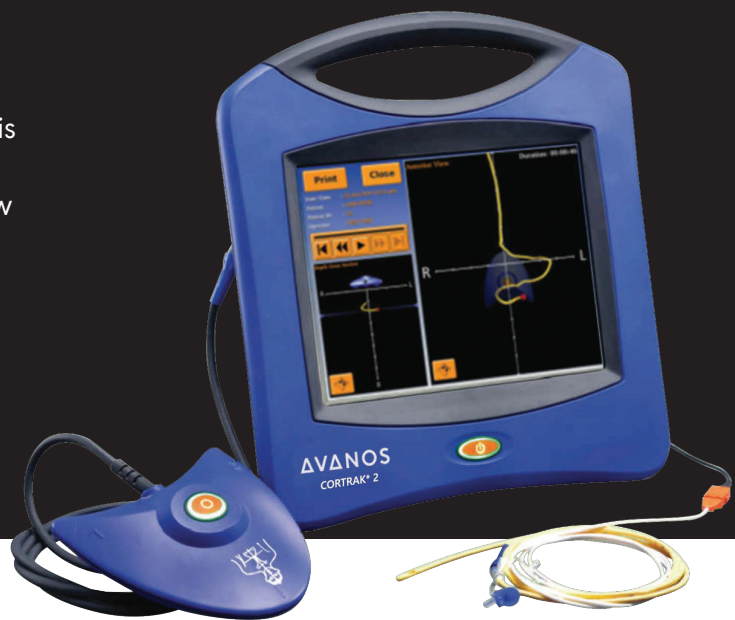
Supplementary list of variables considered for the study

Variables	Description
Demographics: Age Gender Indigenous identity	Age of patients in years Gender of patients (female, male, binary) Indigenous identity of patient (aboriginal/torres strait islander, non-aboriginal/torres strait islander)
Stroke presentation: Presentation Admission NIHSS mRS	Patient presented to hospital with stroke symptoms Patients admitted to the acute stroke unit Stroke severity scale (admission, 24 hours post IVT) No symptoms - 0 Minor = 1-4 Moderate = 5-15 Moderate to severe = 16-20 Severe = 21-42 Patient function (pre-stroke treatment, discharge) 0 = no symptom 1 = No significant disability. Able to carry out all usual activities, despite some symptoms 2 = Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities 3 = Moderate disability. Requires some help, but able to walk unassisted 4 = Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted 5 = Severe disability. Requires constant nursing care and attention, bedridden, incontinent 6 = Dead
Measure (Time in minutes): Symptom to ED time Door to CT time Door to Needle time Length of Stay	Time from onset of first symptoms to presentation to ED Time patient spent in ED before CT imaging Time from patient presentation to hospital to administration of bolus dose of alteplase Patient length of stay (ED in minutes, hospital in days)
Diagnosis Ischaemic Stroke TIA Stroke mimic	Neurological symptoms due to the effect of decreased blood flow to particular areas of the brain that correlate with examination findings and infarct on the diffusion-weighted Magnetic Resonance Imaging (MRI) Temporary focal neurological symptoms resulting from cerebral ischaemia that is not associated with infarction on diffusion-weighted MRI Non-vascular conditions that present with an acute neurological deficit simulating acute ischaemic stroke

NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Score; ED = emergency department; CT = computerised tomography

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