



# Impact of the COVID-19 pandemic on hyperacute stroke treatment: experience from a comprehensive stroke centre in Singapore

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## Abstract

The Coronavirus disease 2019 (COVID-19) pandemic is rapidly evolving and affecting healthcare systems across the world. Singapore has escalated its alert level to Disease Outbreak Response System Condition (DORSCON) Orange, signifying severe disease with community spread. We aimed to study the overall volume of AIS cases and the delivery of hyperacute stroke services during DORSCON Orange. This was a single-centre, observational cohort study performed at a comprehensive stroke centre responsible for AIS cases in the western region of Singapore, as well as providing care for COVID-19 patients. All AIS patients reviewed as an acute stroke activation in the Emergency Department (ED) from November 2019 to April 2020 were included. System processes timings, treatment and clinical outcome variables were collected. We studied 350 AIS activation patients admitted through the ED, 206 (58.9%) pre- and 144 during DORSCON Orange. Across the study period, number of stroke activations showed significant decline ( $p=0.004$ , 95% CI 6.513 to  $-2.287$ ), as the number of COVID-19 cases increased exponentially, whilst proportion of activations receiving acute recanalization therapy remained stable ( $p=0.519$ , 95% CI  $-1.605$  to  $2.702$ ). Amongst AIS patients that received acute recanalization therapy, early neurological outcomes in terms of change in median NIHSS at 24 h ( $-4$  versus  $-4$ ,  $p=0.685$ ) were largely similar between the pre- and during DORSCON orange periods. The number of stroke activations decreased while the proportion receiving acute recanalization therapy remained stable in the current COVID-19 pandemic in Singapore.

**Keywords** Acute ischaemic stroke · COVID-19 · Stroke activation · Recanalization therapy

## Highlights

- The Coronavirus disease 2019 (COVID-19) pandemic has increased healthcare burden globally and may hamper time-critical acute ischaemic stroke (AIS) care.

- In Singapore, there was a decline in number of stroke activations as the number of COVID-19 cases increased exponentially.
- Proportion of activations receiving acute recanalization therapy remained largely stable.
- System process timings such as door-to-needle and door-to-puncture time remained unaffected.
- Carefully designed protocols ensure efficient delivery of AIS care during pandemics.

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## Introduction

The Coronavirus disease 2019 (COVID-19) pandemic is rapidly evolving and affecting healthcare systems across the world [1]. In Singapore, the first case was reported in a

tourist from Wuhan, China, on 23 January 2020 and its first cluster of local transmission on 4 February 2020 [2]. WHO subsequently declared COVID-19 as a global pandemic [3]. The Ministry of Health, Singapore, escalated the country's alert level to Disease Outbreak Response System Condition (DORSCON) Orange, the second highest alert status, on 7th February 2020 [4]. The DORSCON status is a government mandated threshold of the disease status in the community and DORSCON Orange indicates that the disease is severe, spreads easily from person to person and there will be moderate disruption to daily life [5]. During this, citizens are advised to stay at home as much as possible, and to leave home only to obtain food and daily essentials.

Despite the pandemic, stroke remains an acute medical emergency. The initial treatment of acute ischaemic stroke (AIS) is both time-sensitive and has a large impact on functional outcomes [6]. It is crucial to continue delivering this service to patients who need it [7]. However, given the current pandemic, it will be a dilemma to balance appropriate delivery of care with reducing unnecessary exposure of healthcare staff to SARS-CoV-2. Healthcare systems across the world are increasingly overwhelmed by sharp rises in the number of COVID-19 cases, which may hamper the delivery of acute stroke care. This has led to various suggestions to modify the stroke code for stroke patients who concurrently fulfil the screening criteria for COVID-19 exposure or symptoms [8].

It is not clear how long COVID-19 will continue to plague healthcare systems across different regions of the world. This is an unprecedented situation for the current generation. It is all the more necessary to have a workable system of stroke care in place that is adapted to the current situation. Stakeholders involved with this care need to be well informed about the modified protocol and the necessary precautions to continue providing much needed timely stroke care. We aim to study the overall volume of stroke cases and delivery of hyperacute stroke service in a comprehensive stroke centre in Singapore. We compared the situation in the preceding months before and after DORSCON Orange was activated in the current COVID-19 pandemic.

## Methods

### Study population

This was a single-centre, observational cohort study performed at a comprehensive stroke centre responsible for AIS cases in the western region of Singapore, as well as providing care for COVID-19 patients. We included all AIS patients who were reviewed as an acute stroke activation in the Emergency Department (ED) from November 2019 to April 2020. Patients were then stratified into pre-DORSCON

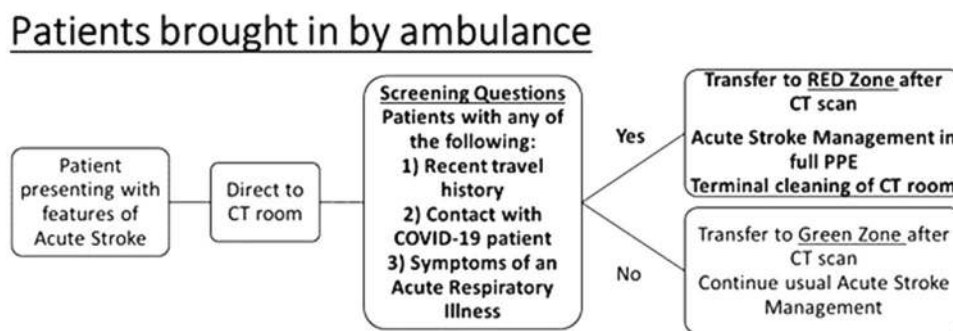
Orange (from 1st November 2019 to 7th February 2020) and during DORSCON Orange (from 7th February to 30th April 2020). AIS patients from the preceding year during the period of 7th February to 30th April 2019 (similar period as DORSCON Orange 1 year ago) were also included as an additional control group. Ethics approval was obtained from a local institutional review board. AIS was defined as new-onset neurological deficit lasting more than 24 h caused by brain ischaemia. Stroke patients were evaluated in the hyperacute setting with appropriate neuroimaging and vascular imaging when indicated: namely computed tomography (CT), multiphase computed tomography angiography (CTA) and computed tomography perfusion (CTP) of the brain. Patients who fulfilled the relevant indications and without exclusion criteria would undergo acute recanalization therapy. Eligible patients who presented up to 4.5 h of ischaemic stroke symptoms onset received intravenous thrombolysis (IVT) with recombinant-tissue plasminogen activator (r-TPA) [9]. Stroke patients would be indicated for endovascular thrombectomy (EVT) if they met the following criteria: pre-stroke modified Rankin Scale (mRS) 0–1, anterior circulation large vessel occlusion, National Institute of Health Stroke Scale (NIHSS) score equals or more than 6, Alberta Stroke Program Early CT score (ASPECTS) equals or more than 6 and within 6 h of symptom onset. Selected AIS patients within 6 to 24 h of last known normal may be included if they meet other DAWN or DEFUSE 3 eligibility criteria [9–11]. Time variables related to stroke activation including symptom onset-to-door time, door-to-activation time, door-to-neurology review time, door-to-needle time and door-to-puncture time were collected prospectively. The NIHSS and mRS were used to assess patient's initial stroke severity, premorbid status and functional outcomes on discharge.

### Workflow during COVID-19 pandemic (Supplementary Table 1)

After the initial cases of COVID-19 were reported in Singapore, the ED was divided into Green and Red Zones in order to segregate potential COVID-19 patients from non-COVID-19 ED patients with other presenting complaints. Potential COVID-19 patients were seen in the Red Zones, where patients were housed in separate cubicles and rooms, according to the acuity of care required. Staff members were required to review these patients while donning full Personal Protective Equipment (PPE) (i.e. N95 mask, protective eye wear, cap, splash-resistant gown and gloves) [12]. In the Green Zone, staff members would also wear a surgical mask to see patients. (Fig. 1).

All patients who presented to the ED were screened for travel history, contact history with COVID-19 patients as well as symptoms of acute respiratory illnesses. Patients

**Fig. 1** Current Emergency Department workflow for suspected stroke cases in light of COVID-19 situation



who were screened positive for any of the above would be seen in the Red Zones, regardless of their primary presenting complaint in the ED. These patients were deemed as COVID-19 suspect cases and COVID-19 PCR testing from a nasopharyngeal swab were subsequently carried out. Patients with symptoms suggestive of an AIS were placed in the highest acuity area in the Red Zone to expedite early imaging, neurology consultation and relevant acute intervention. Patients with stroke-like symptoms who were brought in by public ambulances could be brought directly from the ambulance to the CT room for an early CT scan—these patients were also screened with the same criteria as stated earlier and transferred to the Red or Green zone as appropriate after the CT scan. Neurologists who reviewed patients in the ED red zones donned the PPE as described earlier. After a COVID-19 suspect patient underwent a CT scan in the ED, terminal cleaning of the CT room would be performed, and the room kept vacated and ventilated for at least 30 min before another CT scan could be performed. Any other patient who urgently required a CT scan during these 30 min had to be transferred to another CT imaging facility outside the ED.

Both intubation and extubation are potential aerosol generating procedures and high risk for viral particle transmission. COVID-19 suspect patients undergoing EVT are electively intubated in an isolation area in ED by emergency physicians or anesthesiologists wearing appropriate PPE and powered air-purifying respirators (PAPR) prior to transport to the angiography suite on a closed loop transport ventilator. EVT for intubated COVID-19 suspect patients would be performed with the neurointerventionist and rest of the neurointerventional team donning N95 masks and protective eyeshields. Post-procedure, the patient is transported to a suitable area for extubation in a negative pressure isolation room, with personnel taking the necessary precautions. The angiography suite would undergo terminal cleaning rendering it not usable for approximately 30 min and contingency plans need to be made for concurrent or immediately sequential thrombectomy patients. This reduces the number of facilities at risk of contamination, and conserves limited resources such as PAPR.

Prior to DORSCON Orange, all neurologists, emergency physicians, neurointerventionists, stroke nurses, and angiography suite staff were trained in infection control measures and PPE use. Our concern that this would lengthen the door-to-needle time led us to include additional training and reorganization for the stroke-response team, with emphasis on early notification of suspected stroke cases and pre-emptive donning of pre-issued PPE.

### Study outcomes and statistical analyses

The primary outcome measures were (1) the total number of acute stroke activations and (2) the proportion of acute recanalization therapy instituted amongst all AIS activations. Secondary clinical outcomes were (1) process efficiency timings related to stroke activations including symptom-to-door time, door-to-activation time, door-to-neurologist review time, door-to-needle time and door-to puncture time; and (2) early neurological improvement measured by change in NIHSS at 24- and 48-h interval.

Categorical variables were presented as frequency and percentages, normally distributed continuous variables as mean  $\pm$  standard deviation and non-normally distributed continuous variables as median and interquartile range. We performed statistical analyses using independent *t* test for normally distributed continuous variables, Mann-Whitney *u* test for non-normally distributed continuous variables comparing two groups, Kruskal–Wallis one-way analysis of variance for multiple groups and Chi-square test for categorical variables. A linear regression model was performed to identify trend of total activation and acute intervention frequency across the weeks. All *p* values  $< 0.05$  were considered statistically significant. Analyses were performed with SPSS, version 24 (IBM Corp., Armonk, NY, USA).

### Results

A total of 350 AIS activation patients admitted through the ED from November 2019 to April 2020 were included in this study. The mean age was  $65.2 \pm 14.3$  years and 35.1%

( $n = 123$ ) were female. There were 206 (58.9%) stroke activations pre-DORSCON Orange, while 144 occurred during DORSCON Orange (Table 1). Amongst all stroke activations during the study period, 30.3% ( $n = 106/350$ ) of patients received acute recanalization therapy. The proportion that received acute recanalization therapy was similar when comparing pre- and during DORSCON Orange (28.6% versus 32.6%,  $p = 0.423$ ). The proportion of patients receiving IVT only (12.1% versus 16.6%,  $p = 0.229$ ), bridging IVT with EVT (11.7% versus 11.1%,  $p = 0.876$ ), or EVT only (4.9% versus 4.9%,  $p = 1.000$ ) were also similar when comparing between the two time periods. Amongst patients that received EVT, there was no difference in the proportion that received bridging IVT pre- and during DORSCON Orange (70.6% versus 69.6%,  $p = 0.934$ ).

During DORSCON Orange, 13.9% ( $n = 20/144$ ) of stroke activation patients were deemed as COVID-19 suspects upon ED screening, and 10 of them received acute recanalization therapy. Five patients underwent IVT only, four patients had bridging IVT with EVT, while one underwent EVT only. All COVID-19 suspects eventually tested negative on the COVID-19 PCR nasopharyngeal swab.

Across the months from November 2019 to April 2020, the number of stroke activations showed significant decline during DORSCON orange and there was a negative linear correlation with exponential increase in COVID-19 cases in Singapore ( $B = -4.400$ ,  $R^2 = 0.893$ ,  $p = 0.004$ , 95%

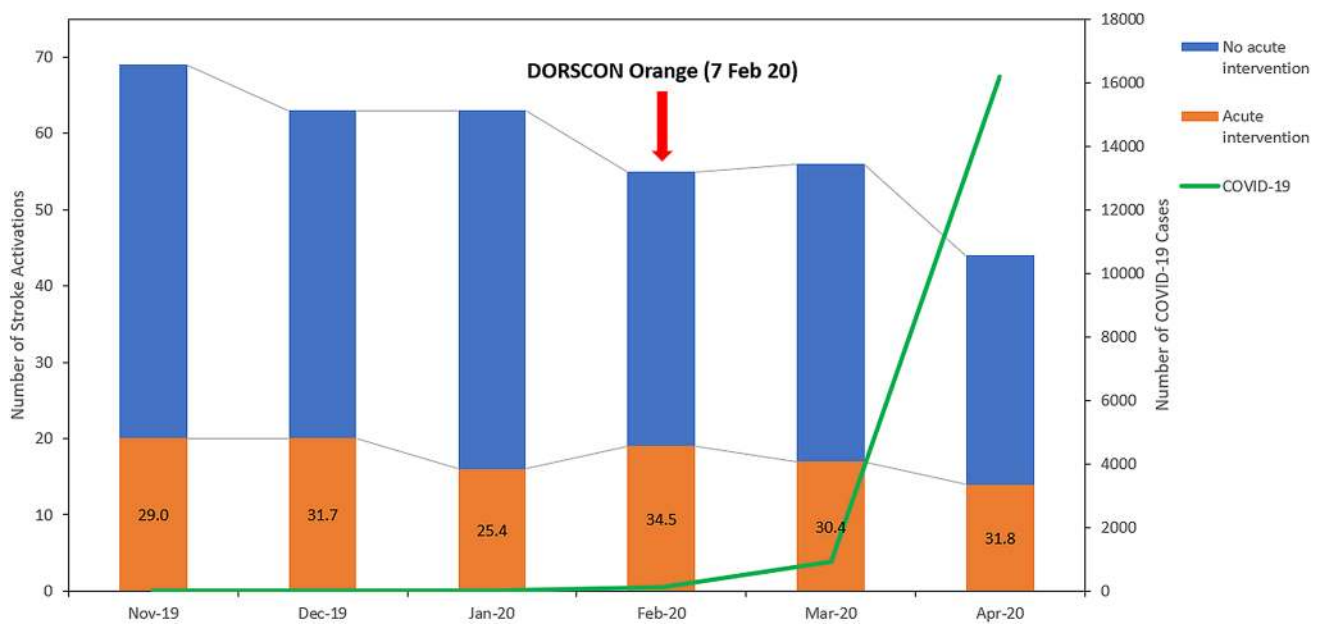
CI  $-6.513$  to  $-2.287$ ). However, proportion of activations receiving acute recanalization therapy remained largely stable ( $B = 0.549$ ,  $R^2 = 0.111$ ,  $p = 0.519$ , 95% CI  $-1.605$  to  $2.702$ ) (Fig. 2). In patients undergoing acute intervention, door-to-activation (median 11 min versus 14 min,  $p = 0.015$ ) and door-to-neurologist review time (median 19 min versus 27 min,  $p = 0.004$ ) were longer during compared to pre-DORSCON Orange (Fig. 3). Median door-to-needle time across the months remained within the target of 60-min. Six patients had recorded a door-to-needle time beyond the recommendation of 60-min during DORSCON Orange; two of them were COVID-19 suspects (with door-to-needles times 69 and 70 min). Their delays were attributed to donning of PPE and additional time taken to isolate the patient. There were no significant differences in all process timings when comparing COVID-19 and non-COVID-19 suspects (Table 2).

The clinical characteristics and outcomes of AIS activation patients are shown in Table 1, stratified by pre- and during DORSCON Orange phase. In terms of stroke severity, the median NIHSS on arrival was similar pre- and during DORSCON Orange amongst all AIS patients (median 5 both pre- and during DORSCON orange,  $p = 0.854$ ) and amongst patients who received acute recanalization therapy (median 16 versus 14,  $p = 0.250$ ). Amongst AIS patients that received acute recanalization therapy, early neurological outcomes in terms of change in median

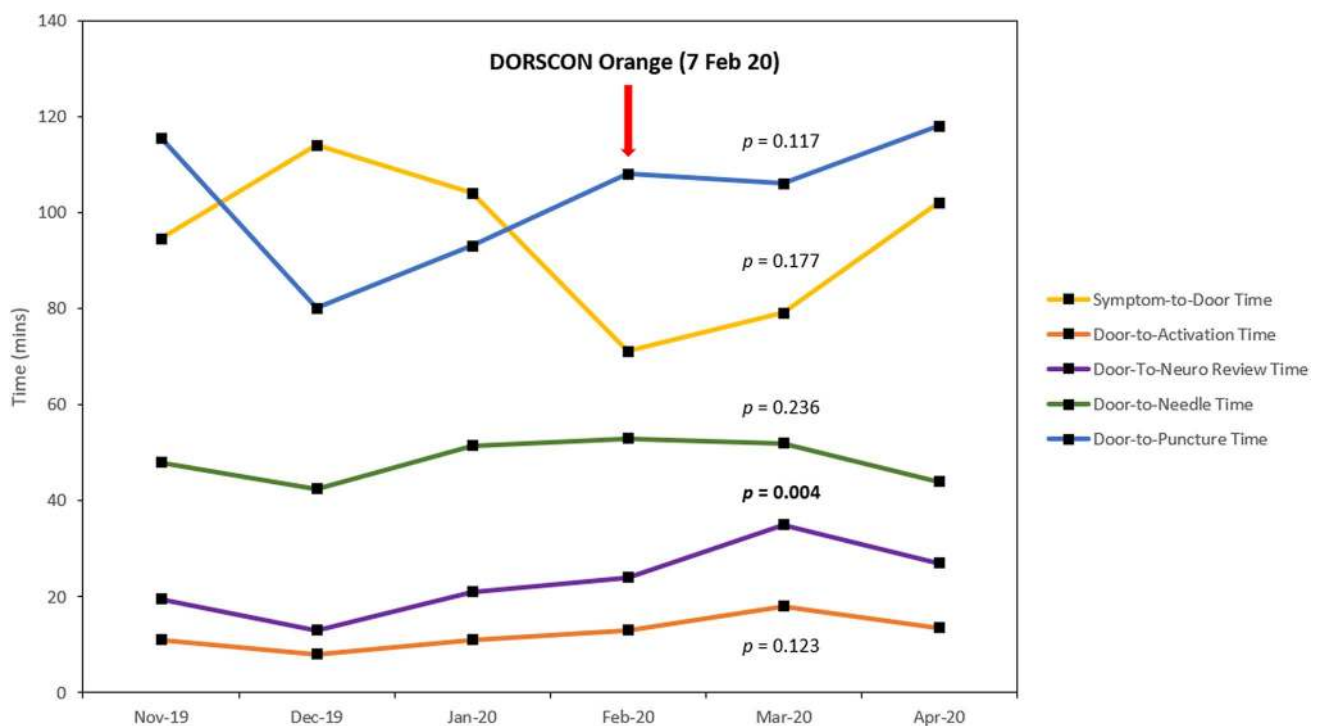
**Table 1** Clinical characteristics of stroke patients before and during DORSCON Orange

Variables	Pre-DORSCON ( $N = 206$ )	During DORSCON ( $N = 144$ )	$p$ value
<i>All acute stroke activations</i>			
Age (years), mean (SD)	65.6 (14.2)	64.6 (14.5)	0.531
Female gender, % ( $n$ )	38.8 (80)	29.9 (43)	0.084
NIHSS on arrival, median (IQR)	5 (2–15)	5 (2–17)	0.854
Acute recanalization treatment	28.6 (59)	32.6 (47)	0.423
IVT only	12.1 (25)	16.6 (24)	0.229
Bridging IVT with EVT	11.7 (24)	11.1 (16)	0.876
EVT only	4.9 (10)	4.9 (7)	1.000
Received acute treatment (IVT, EVT) ( $N = 106$ )			
<i>Stroke activation timings (mins), median (IQR)</i>			
Symptom-to-door time	102 (54–150)	77 (52–145)	0.184
Door-to-activation time	11 (0–16)	14 (11–19)	0.015
Door-to-neuro review time	19 (4–28)	27 (20–37)	0.004
Door-to-CT time	0 (0–7)	0 (0–0)	0.077
Door-to-needle time	47 (39–59)	49 (38–57)	0.792
Door-to-puncture time	93 (81–128)	110 (94–132)	0.073
<i>Outcome measures, median (IQR)</i>			
NIHSS on arrival	16 (8–21)	14 (6–21)	0.250
NIHSS change (in 24 h)	−4 (−9 to 0)	−4 (−8 to 1)	0.685
NIHSS change (in 48 h)	−4 (−8 to 0)	−5 (−8 to 1)	0.680

DORSCON disease outbreak response system condition, EVT endovascular thrombectomy, IVT intravenous thrombolysis, mRS modified Rankin scale, NIHSS National institutes of health stroke scale



**Fig. 2** Proportion of stroke activations undergoing acute intervention (r-TPA, EVT) by months



**Fig. 3** Median timings of stroke activations by months from November 2019 to March 2020

NIHSS at 24 h (median -4 versus -4,  $p = 0.685$ ) and 48 h (median -4 versus -5,  $p = 0.680$ ) were largely similar between the two groups. When comparing AIS activation patients during DORSCON Orange and from the same

period in the preceding year, stroke characteristics, the proportion receiving acute recanalization therapy and process timings were largely similar (Supplementary Table 2).



**Table 2** Comparison of stroke activation timings between COVID-19 and non-COVID-19 suspects that received acute intervention during DORSCON Orange (N = 33)

Variables	Non-COVID-19 suspects (N = 37)	COVID-19 suspects (N = 10)	p value
<i>Stroke activation timings (mins), median (IQR)</i>			
Symptom-to-door time	82 (56–150)	58 (28–83)	0.152
Door-to-activation time	13 (10–19)	16 (10–23)	0.600
Door-to-neuro review time	27 (20–37)	26 (18–40)	0.949
Door-to-CT time	0 (0–0)	0 (0–1)	0.908
Door-to-needle time	49 (39–57)	48 (34–62)	0.679
Door-to-puncture time	112 (95–130)	106 (73–139)	0.745

## Discussion

We report the following key findings from our study: (1) The number of stroke activations showed significant decline during DORSCON orange and there was a negative linear correlation with exponential increase in COVID-19 cases in Singapore; (2) The proportion undergoing acute recanalization therapy remains stable; (3) A slight delay in door-to-activation and door-to-neurologist review time during DORSCON Orange period was observed which can be attributed to the additional time from screening potential COVID-19 suspects and donning of PPE, both of which are necessary infection control measures; (4) Other process efficiency timings and early neurological outcome measures remained similar.

In the USA and Italy, there are reports of reduction in acute stroke volume in hospitals [13–15]. This concern has also been raised by papers from China and the World Stroke Organisation [16, 17]. Similarly, our study reports a decline in number of stroke activations as the severity of the COVID-19 pandemic worsened in Singapore, however the proportion of patients receiving hyperacute interventions including EVT remained similar. We postulate that the psychological impact of COVID-19 amongst the general public has a role to play in the “vanishing stroke” cases seen, with the fear associated with contracting the COVID-19 disease being more than the impact of the disease itself [18]. As the number of COVID-19 cases increase exponentially, circuit breaker measures were introduced such as closure of non-essential work premises and controlled access to areas susceptible to crowding, which corresponds with the dip in stroke activations. Currently as of 7th May 2020, Singapore has a lower COVID-19 mortality rate than other countries, reporting a total of 20 deaths out of 20,198 cases (mortality rate of 0.09%), [19] compared to mortality rates in Italy and USA which are 13.8% and 5.9% respectively [20, 21]. Although this lower mortality rate should allay the public’s aversion to ED presentation, the recent exponential rise in COVID-19 cases may have deterred mild stroke patients from presenting to the ED despite stroke being an emergency [22]. Future studies to evaluate the psychological state of the

general public in the context of acute stroke and the COVID-19 pandemic are therefore warranted.

Interestingly, a decline in minor stroke and transient ischaemic attack presentations was recently reported during this COVID-19 pandemic [23]. These stroke patients with milder symptoms may have wanted to avoid coming to the hospital. However, whilst initial symptoms may be minor, there is a risk of neurological progression and deterioration which would result in these patients being ineligible for acute intervention [24]. Educational efforts need to be continued to inform and educate the general public on the importance of timely ED presentation if they have symptoms suggestive of AIS, even during this ongoing COVID-19 pandemic.

The COVID-19 situation has provided us with unprecedented challenges to acute stroke care. The American Heart Association in response has published temporary guidelines for the management of stroke patients during this COVID-19 pandemic [25]. Several issues with delivering stroke care in presence of ongoing COVID-19 pandemic were highlighted, including overwhelmed emergency and intensive care unit personnel, lack of availability of PPE, manpower shortages amongst neurologists and stroke care team members as a result of quarantine/stay home notices due to COVID-19 exposure or redeployment for COVID-19 care. In addition, intensive care units may face bed crunches which severely limit their availability for critical stroke cases.

With the worsening COVID-19 pandemic, the overall impact on stroke cases is likely to increase, with potential delays in process timings as described by Baracchini et al. [23] World Stroke Organization and Society of NeuroInterventional Surgery have also described these difficulties and has recommended certain guidelines such as screening for COVID-19 in all stroke patients requiring thrombectomy [26, 27]. Despite increase in door-to-activation and door-to-neurologist review time during DORSCON Orange period, door-to-needle and door-to-puncture time were maintained during DORSCON Orange by adopting a similar AIS activation protocol with simple modifications (Fig. 1). This required a multi-disciplinary team approach, with early discussion and planning by the emergency, neurology,

neuroradiology and anaesthesia teams. Singapore also has a relatively smaller number of COVID-19 cases mainly involving younger foreign workers from dormitories [28]. These younger patients with milder symptoms could be managed in Community Isolation Facilities thereby preventing hospitals from being overwhelmed. Furthermore, we have a robust system in place to screen patients quickly for COVID-19 upon ED arrival and well-described PPE and infection control measures to give confidence to hospital staff at this level of infection [22]. With time and further training, these processes may become more efficient and the delay can be further diminished.

### Limitations

Our study has several limitations. Firstly, it is a single center observational study with a modest sample size. Secondly, several trends and results observed may be specific to our unique setting, and may not apply to other countries with different healthcare systems and governance policies. Finally, the true impact of the COVID-19 pandemic on acute stroke care is largely determined by the strain it has on the healthcare system, and the challenge to maintain and improve urgent access is significant. We are likely to see progression in the number of COVID-19 cases in Singapore as time passes, and this may have an increasing toll on our healthcare system. Nonetheless, we report important trends concerning overall volume of stroke cases and delivery of hyperacute stroke services during a critical phase of the COVID-19 pandemic.

### Conclusion

Early treatment of AIS remains critical to reduce the burden of disability to society. Our study shows that the number of stroke activations decreased while the proportion receiving acute recanalization therapy remained stable in the current COVID-19 pandemic in Singapore. Carefully designed protocols for acute stroke care, COVID-19 screening, availability and familiarity of PPE and infection control measures, and multi-disciplinary team efforts can ensure that delivery of hyperacute stroke care remains efficient in healthcare systems.

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### Compliance with ethical standards

**Conflict of interest** None of the authors declare any conflict of interest.

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