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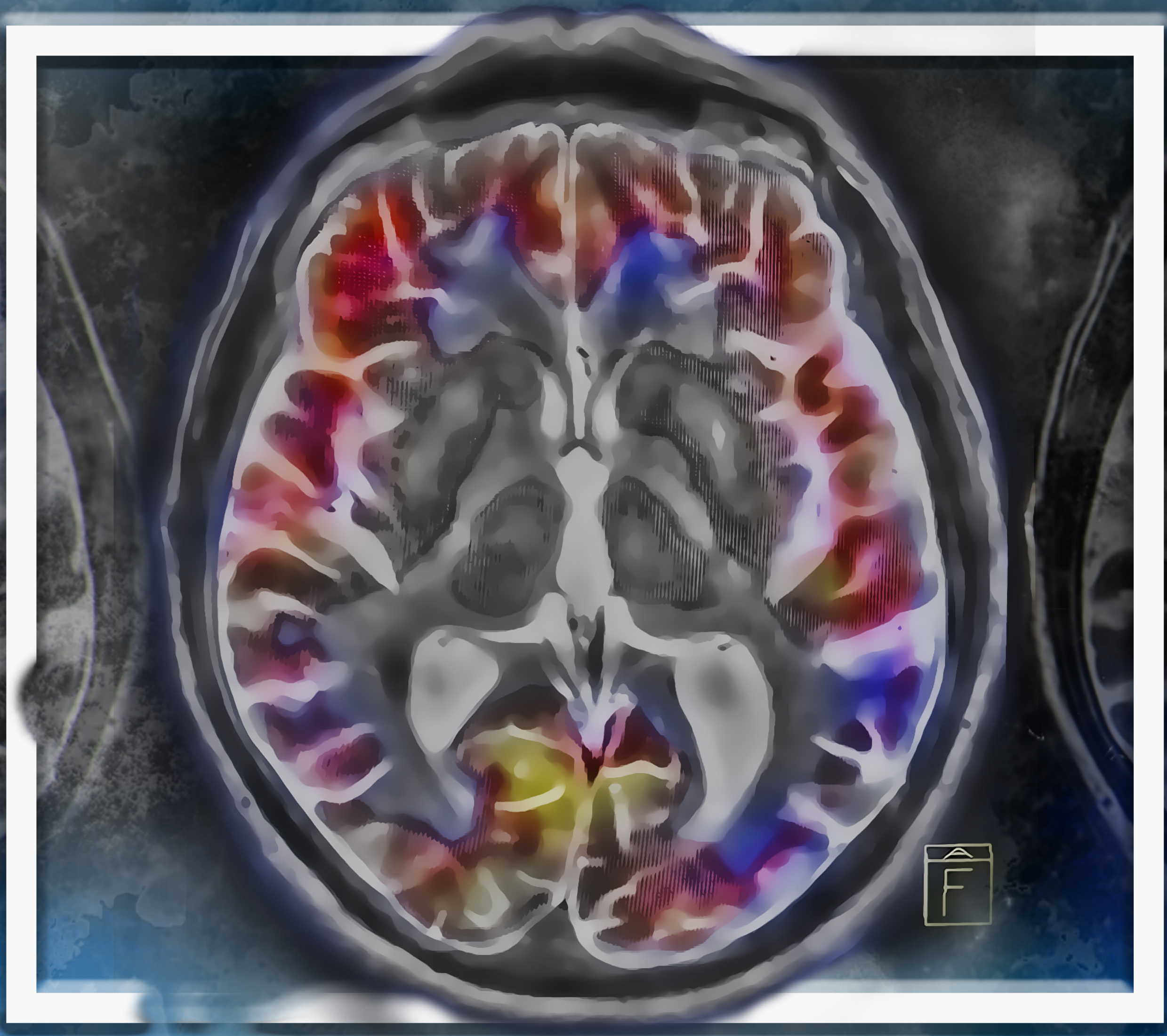

Outcome after decompressive craniectomies of middle cerebral artery infarcts in a new neurosurgical unit | Possibility of covid-19 reinfection with clinical manifestation of stroke: A case report

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OUTCOME AFTER DECOMPRESSIVE CRANIECTOMIES OF MIDDLE CEREBRAL ARTERY INFARCTS IN A NEW NEUROSURGICAL UNIT

Aiman Asyraf Ahmad Sukari[1*], Muhammad Hafiz Bohari[2], Rahmat Haron[1].

[1]Neurosurgical Unit, General Surgical Department, Hospital Tuanku Jaafar Seremban, Negeri Sembilan, Malaysia.
[2]Neurosurgical Department, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.

***Corresponding author**:
Dr. Aiman Asyraf Sukari, Neurosurgical Unit, General Surgical Department, Hospital Tuanku Jaafar Seremban, Negeri Sembilan, Malaysia. Telephone: +6017-2272532. Email: asyraf114@gmail.com

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ABSTRACT
Background: In the absence of thrombolytic therapy, decompressive craniectomy is a treatment option for patients with middle cerebral artery (MCA) infarcts. This study aimed to review the mortality and morbidity of patients with MCA infarct treated surgically at the Neurosurgical Unit, General Surgical Department, Hospital Tuanku, Jaafar Seremban, Negeri Sembilan, Malaysia.
Methods: From August 2016 to December 2017, 29 patients underwent decompressive craniectomy for MCA infarct. The patients were evaluated based on their demographics and risk factors including the presence of diabetes, hypertension, cardiac disease, renal problems, and pneumonia. Clinical neurological presentation was evaluated with the Glasgow Coma Scale (GCS). Patient outcome was defined as the occurrence of mortality within one month and modified Rankin Scale score in the following six months after surgical intervention.
Results: Mortality was 41% (12/29) within 30 days and good functional outcome (mRS $\leq$ 3) in surviving patients was achieved by 47% (8/29) at 6 months post-operation. The factors associated with higher mortality were low preoperative GCS score (Odds ratio; OR = 2.33; 95% CI 1.35-38.33), impaired renal function (OR = 16.0; 95% CI 1.57-162.5), and pre-existing cardiac problems (OR = 14.0; 95% CI 2.3-85.2). There was a tendency for lower mortality among patients with right side MCA compared to those with left side MCA. Patients above 60 years old had higher mortality compared to younger age groups, but the relationship was not statistically significant. Likewise, there was no association between any of the preoperative factors and the outcomes at 6 months post-operation.
Conclusion: Preoperative GCS, renal function and pre-existing cardiac problems should be considered during patient selection for surgery for MCA infarct. Age may have a lesser role in determining mortality. However, the 6-month outcome is unpredictable and should be highlighted to family members when offering surgery for these patients.

Keywords: Decompressive Craniectomy, Middle Cerebral Artery Infarct, Ischaemic Stroke

INTRODUCTION
Stroke remains a major cause of death among Malaysians. The latest report from the National Health Statistics (NHS, 2020) indicated that stroke accounts for 8% of the annual deaths of Malaysians (1). Middle cerebral artery (MCA) ischaemic stroke occurs due to sudden disruption of blood flow to the brain supplied by the middle

cerebral artery or its branches, causing brain ischaemia. The area of ischaemia is dependent on the vessel/branch disrupted, which subsequently determine the degree of neurological deficit of the patient. Ischaemic brain results in surrounding tissue oedema which may lead to further brain swelling, mass effect, and death if not promptly prevented. Therefore, the current management of MCA infarct aims at preventing ischaemia by restoring blood supply as soon as possible. If otherwise, the prevention of secondary brain damage is the next target. Good prognoses were observed when stroke patient are provided with chemical thrombectomy within 4.5 hours (previously 3 hours) and mechanical thrombectomy within 24 hours (2). These surgical interventions are the latest recommendations by AHA for the management of stroke patients (2).

As per similar guidelines, decompressive hemicraniectomy has been described for the management of MCA infarct, with mixed outcomes. A recent paper showed that decompressive craniectomies for malignant MCA infarct patients still had severe disability despite improvement in mortality (3). Early surgical intervention within 6 hours from deterioration or significant radiological findings were found to be significant predictor of favourable clinical outcome in a separate study (4). Although current evidence shows the benefit of surgical intervention by reducing mortality, information is still lacking on patient selection and the impact of surgery on the quality of life of patients.

A neurosurgical unit was established in General Surgical Department, Hospital Tuanku, Jaafar Seremban, Negeri Sembilan, Malaysia in June 2016 to cater for neurosurgical referrals in the state. However, for MCA infarct cases, a dedicated stroke unit, chemical and mechanical thrombectomy strategies are not available. Thus, the best medical care offered currently revolves around preventing the occurrence of secondary stroke. In view of current recommendations and evidence available regarding surgery, decompressive craniectomy has been applied to manage patients referred to the medical centre for MCA infarcts due to the absence of any other treatment modalities. For each case referred, surgery was offered with an explanation to family members regarding potential benefit, risk and the associated complications. Surgery is only undertaken following informed and signed consent by the patient's family members.

OBJECTIVE

This study aimed to review the outcome of patients with MCA infarct who underwent hemicraniectomy at the neurosurgical unit, General Surgical Department, Hospital Tuanku, Jaafar Seremban, Negeri Sembilan, Malaysia from August 2016 to December 2017. The outcome of patients was based on their mortality and morbidity at 1 month and 6 months post-operation, respectively.

METHODOLOGY

All the patients who were referred to the neurosurgical unit for MCA infarct were considered for enrolment into this retrospective cohort study. Inclusion criteria are patients referred for MCA infarct to the neurosurgical unit from August 2016 to December 2017. Patients whose family refused to consent to the surgical procedure were excluded from the study.

The data collected include patients' demography, operational condition, and outcome of surgery. Demographics included age, sex, and race, whereas variables considered under operational condition were the time from onset of MCA infarct to surgery (more or less than 2 days), site of infarct; the presence of diabetes, hypertension, any pre-existing heart problems (defined as having either atrial fibrillation or congestive cardiac failure or ischaemic heart disease), ongoing pneumonia, impaired renal function (i.e. elevated creatinine more than 110 mmol/dl) and smoking. The outcome was defined as mortality within the first 1 month and patients' modified Rankin score (mRS) 6 months after surgical intervention. Based on the hypothesis that each variable is independently associated with the outcome; the relationship was analysed using Chi-square statistic and Fischer exact test. The latter test was considered due to the small number of patients in the study, which may result in the violation of the conditions in performing Chi-square statistics. A p-value less than 0.05 was considered for statistical significance and the parameters were estimated at 95% confidence interval (CI).

ETHICAL APPROVAL

Ethical approval was obtained from the National Medical Research Registry Medical Research Ethics Committee (MREC) Malaysia (Ref. No: NMRR-18-2032-43448). Permission for the data extraction was obtained from the Director of the neurosurgical unit, General Surgical Department, Hospital Tuanku, Jaafar Seremban, Negeri Sembilan with the research ID 43448.

RESULTS

Descriptive results

Table 1 shows the demographics of the study population. A total of 47 patients with MCA infarct were referred to the neurosurgical unit of the medical centre between August 2016 and December 2017. Twenty-nine cases underwent decompressive hemicraniectomies with a corresponding mean (± SD) age of 54.8 (± 12) years old. A higher proportion of the patients were male (69%) and Malay (55%). The majority of patients with MCA infarct had a history of either diabetes, hypertension or were smokers. Postoperative mortality rate within 1 month was 41%, whereas patients achieving a relatively good functional outcome (mRS score ≤ 3) at 6 months was 47%.

Variables	**n (%)**
Age	
> 60 years old	9 (31%)
≤ 60 years old	20 (69%)
Mean age in years (±SD)	**54.8 (±12)**
Mean Glasgow Coma Scale (±SD)	**10.97 (±2.32)**
Gender	
Female	9 (31%)
Male	20 (69%)
Race	
Malay	16 (55%)
Chinese	4 (14%)
Indian	8 (28%)
Other	1 (3%)
MCA Stroke Lateralization	
Left	13 (45%)
Right	16 (55%)
Time to surgery, Days	

≤ 2 days	20
> 2 days	9
Patient Comorbidities	
Diabetes	15 (52%)
Hypertension	23 (79%)
Cardiac Disease	12 (41%)
Pneumonia	15 (52%)
Renal Injury	7 (24%)
Smoking	19 (66%)
Mortality in 1 month	**12 (41%)**
mRS in 6 months in surviving patients (n=17)	
mRS 2	1 (6%)
mRS 3	7 (41%)
mRS 4	6 (35%)
mRS 5	3 (18%)

Table 1: Demographic Analysis of the patients with MCA stroke who underwent surgery (mRS = modified Rankin Scale)

Table 2 shows the relationship between patients' demographic and mortality within 1-month post-operation for MCA infarct. Only preoperative GCS had a significant association with the outcome (OR = 7.2; 95% CI 1.352-38.33, p = 0.025). Accordingly, 64% of patients with GCS less than 10 died within the first month after surgery. Other factors had no significant relationship with the mortality of patients, excluding MCA stroke. There was a tendency for lower mortality among patients with right side MCA (p = 0.06) compared to those with left side MCA

Age	Alive (n=17)	Dead (n=12)	Odds ratio	95% CI	p-Value
< 40 years old	0 (0%)	4 (33%)	2.3	0.47 - 11.55	0.42
40 - 60 years old	13 (76%)	3 (25%)			
> 60 years old	4 (24%)	5 (42%)			
GCS					
≤ 10	5 (29%)	9 (75%)	7.2	1.35 - 38.33	0.03
11 - 15	12 (71%)	3 (25%)			
Gender					
Female	5 (29%)	4 (33%)	1.2	0.25 - 5.89	1.00

Male	12 (71%)	8 (67%)			
Race					
Malay	11 (64%)	5 (42%)	0.4	0.09 - 1.78	0.27
Chinese	2 (12%)	2 (17%)	1.5	0.18 - 12.46	1.00
Indian	4 (24%)	4 (33%)	1.6	0.32 - 8.39	0.68
Other	0 (0%)	1 (8%)			
MCA Stroke Side					
Left	5 (29%)	8 (67%)	4.8	0.98 - 23.54	0.07
Right	12 (71%)	4 (33%)			
Time to Op					
≤ 2 days	13 (76%)	7 (58%)	0.4	0.09 - 2.14	0.42
> 2 days	4 (24%)	5 (42%)			

Table 2: Demographic factors associated with mortality among patients that underwent surgical intervention for MCA infarct; CI = confidence interval, MCA = middle cerebral artery

The association between the various comorbidities and mortality 1-month post-operation is presented in Table 3. Higher number of patients with cardiac disease (OR = 14.0; 95% CI 2.3-85.2, p = 0.003) and renal injury (OR = 16.0; 95% CI 1.57-162.1, p = 0.011) died within 1month post-operation compared to those without such comorbidities. There was no association between the other patients' comorbidities and mortality within 1 month.

Comorbidities	Alive (n=17)	Dead (n=12)	Odds Ratio	Confidence Interval	p-Value
Diabetes	9 (53%)	6 (50%)	0.9	0.20 - 3.90	1.00
Hypertension	14 (82%)	9 (75%)	0.6	0.11 - 3.91	0.67
Cardiac Disease	3 (18%)	9 (75%)	14.0	2.30 - 85.22	<0.01
Pneumonia	7 (41%)	8 (67%)	2.9	0.61 - 12.34	0.26
Renal Injury	1 (6%)	6 (50%)	16.0	1.58 - 162.1	0.01
Smoking	10 (59%)	9 (75%)	2.1	0.41 - 10.66	0.45

Table 3: Analysis of patient comorbidities to mortality outcome

Table 4 shows the association between patients' factors and mRS score 6-month after operation. None of the factors (i.e. demographics and comorbidities) was associated with the outcome.

Comorbids	mRS <4, (n=8)	mRS 4-5 (n=9)	Odds Ratio	Confidence Interval	p-Value
Age <60	6 (75%)	7 (78%)	1.2	0.12 - 10.99	1.00
GCS 11-15	5 (63%)	7 (78%)	2.1	0.25 - 17.59	0.62
Left MCA Infarct	3 (38%)	2 (22%)	0.5	0.06 - 3.99	0.62
Time to Op <48hrs (2 days)	6 (75%)	7 (78%)	1.2	0.12 - 10.99	1.00
Presence of					
Diabetes	3 (38%)	6 (67%)	3.3	0.46 - 24.44	0.35
Hypertension	6 (75%)	8 (89%)	2.7	0.19 - 36.76	0.58
Cardiac Disease	0 (0%)	3 (33%)	-	-	0.21
Pneumonia	2 (25%)	5 (56%)	3.8	0.47 - 29.75	0.33
Renal Injury	0 (0%)	1 (11%)	-	-	1.00
Smoking	6 (75%)	4 (44%)	0.3	0.03 - 2.12	0.33

Table 4: Association between demographics, comorbidities, and mRS score at 6 months post-operation for MCA infarct patients; mRS = modified Rankin Scale

DISCUSSION

In the absence of thrombolysis therapy, neurosurgical intervention is an important treatment option for patients with MCA infarcts. This study was designed to determine the factors influencing patients' outcome (i.e., mortality and mRS score within 1- and 6-months post-operation) following surgical intervention for MCA infarcts at a newly established neurological unit in Malaysia. The rationale for conducting this study was to tailor future treatment towards reducing patients' morbidity and mortality at the medical centre.

The average age (± SD) of the patients referred to the medical centre for MCA infarcts was 54 (± 12) years old. This mean age is consistent with the reported age group (54.5 to 62.6 years old) susceptible to stroke in Malaysia, based on the available records between 2000 and 2014 (5). Likewise, males constituted a higher percentage of the patients (68%) which is comparable to previous reports where males made up 60.5% of stroke patients. The proportion of patients with comorbidities found in this study is also consistent with the risk factors of stroke reported by Cheah et al (6), which included hypertension and diabetes. The racial distribution of the cases reported to the medical centre revealed that the majority of patients were Malay. A study conducted by Tan et al. (5) found that Malay constituted the highest population in Kuala Lumpur compared to other races, which may explain the finding in our study. In contrast, other studies conducted in different parts of Malaysia reflected geographical variation in ethnic distribution, rather than ethnic-specific differences (7,8).

Age has been reported as an independent predictor of mortality. Bansal et al (9) reported that 78% of its patients under 60 years old had good outcome compared to only 38% of patients over the age of sixty. On the contrary, Suyama et al. (10) reported that age was not a significant predictor of mortality in the Japanese population. In the present study, we found that 24% of all the patients that died following surgical intervention for MCA infarcts were under 60 years old. However, the findings were not statistically significant which is consistent with the reports by Sundseth et al. (11). Upon further analysis, we found that this is probably because all 4 patients below the age of 40 did not survive beyond 1 month after hemicraniectomy. Further review of the data shows that these 4 patients also suffered from heart failure and one had end-stage renal failure before the age of 40.

Existing cardiac and renal disease are other risk factors that were found to influence mortality in patients undergoing decompressive craniectomies in this study. These events may explain the early deaths in those with stroke under the age of 40. In this study, only 3 out of 15 patients with cardiac problems that underwent hemicraniectomy survived beyond 30 days. Furthermore, the patients had 14 times higher odds of dying compared to those without heart problems. Such cardiac disease and complications from surgery may further increase the mortality risk among patients. However, other studies reported that patients' risk factors – including atrial fibrillation, diabetes, hypertension and ischaemic heart disease were not significantly associated with mortality (11,12).

Another important finding in this study was the significant association between mortality among patients and the presence of renal dysfunction. Patients suffering from kidney injury had 14 times higher odds of dying within one month after operation compared to those without such kidney issues. The relationship between renal function and mortality is not well understood since such association has not been previously reported. Therefore, further analysis is required to elucidate the role of kidney failure and risk of mortality in patients undergoing surgery for MCA infarcts. In addition, preoperative GCS was an independent predictor of mortality in this study. Patients operated at a GCS of ≤ 10 had higher odds of dying within one month after operation compared to those with a preoperative of GCS > 10.

The mRS score was used to measure neurological deficit in our study, which is different to the NIHSS employed in another (12) for the same purpose. Our review revealed that none of the demographic factors and patients' comorbidities was associated with mRS score at 6 months post-operation. These results corroborate the report by another author (12) where they found no significant relationship between either mRS or preoperative GCS score (or NIHSS score) and patients' outcome. Furthermore, more than half of our surviving patients were moderate to severely debilitated. A recent meta-analysis by Back et al (13) has shown that although mortality in these group of patients decreases, a large proportion of these patients still end up with substantial disability, and our study's findings conform to this trend.

LIMITATIONS

The power of this study is limited due to the descriptive and retrospective nature hence, no conclusive causation could be drawn from the available data. Furthermore, broader comparisons could not be undertaken due to data paucity on the patients' outcomes with MCA infarct that were not operated on. Such information would have improved the power of the study. A cohort study consisting of a larger sample size would be better in evaluating the impact of patient comorbidities on surgical outcome and mortality.

CONCLUSION

We found that low preoperative GCS score, impaired renal function and presence of cardiac problems were associated with an increase in 1-month mortality post decompressive craniectomy for patients with MCA infarcts. Thus, these factors may be considered when offering surgery for patients with MCA infarcts. However, none of the available factors can predict morbidity. Such information should be made available to family members of the patient before they consent to surgery.

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POSSIBILITY OF COVID-19 REINFECTION WITH CLINICAL MANIFESTATION OF STROKE: A CASE REPORT

Septy Aulia Rahmy[1], Eko Arisetijono[2], Yuyun Yueniwati[3].

[1]Resident of Neurology Departement of Universitas Brawijaya Malang.
[2]Neurologist of Neurology Departement of Universitas Brawijaya Malang.
[3]Radiologist of Radiology Departement of Brawijaya University Malang.

***Corresponding author:**
Dr. Septy Aulia Rahmy, Neurology Department, Saiful Anwar General Hospital, Malang, East Java, Indonesia. E-mail: septy_aulia@student.ub.ac.id

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ABSTRACT

Background: SARS-CoV-2 virus was first detected in December 2019 and became pandemic. It can spread from the respiratory to the central nervous system due to its neuroinvasive abilities. The information on SARS-CoV-2 recurrence or reinfection is still limited. We reported COVID-19 with stroke manifestation and a history of positive COVID-19, possibly reinfection of the disease.

Case presentation: Male, 55-years old, with a medical history of diabetes mellitus, hypertension, and acute coronary syndrome, was first diagnosed with COVID-19 based on his nasopharyngeal swab without any clinical manifestation. The evaluation of his swabs then showed negative results, and he was declared cured of COVID-19. After 13 days, he came to ER with acute onset of slurred speech, left-sided hemiparesis, dysarthria, and left-sided facial drop. His nasopharyngeal swab showed a positive result, and he was diagnosed with COVID-19. His chest radiography was normal, and his head CT scan showed an ischemic brain. He received treatment for stroke and COVID-19 infection. Five days after admission, the patient spontaneously became hypoxic with oxygen saturation 60%, and the patient died due to respiratory failure.

Conclusion: We reported the case possibility of COVID-19 reinfection with clinical manifestation of stroke, without any respiratory manifestation of COVID-19.

Keywords: COVID-19, Stroke, Reinfection.

BACKGROUND

In December 2019, pneumonia caused by *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2), identified as *Coronavirus Disease* (COVID-19), became pandemic, infected millions of people worldwide, and was responsible for many deaths.[1] Globally, as of Feb 24 2021, there have been 111,762,965 confirmed cases of COVID-19, including 2,479,678 deaths, reported to World Health Organization (WHO)[2]. The patient's symptoms range from asymptomatic to severe. The most prevalent symptoms include fever, cough, and dyspnea.[3] SARS-CoV-2 virus also can spread from the respiratory to the central nervous system due to its neuroinvasive abilities. Some patients with COVID-19 were reported to have neurological symptoms, such as anosmia, headache, dizziness, dysgeusia, and impaired consciousness. Ischemic stroke was reported to occur in 0.9% to 2.3% of patients with COVID-19.[4] Study by Li Y et al.[5] reported that ischemic stroke incidence in COVID-19 patients was about 5% with a mean age of 71 years. These patients had risk factors like diabetes, hypertension, coronary artery disease, and previous cerebrovascular disease. The average time from COVID-19 infection to stroke manifestation was 12 days. Lee et al.[6] conducted a systematic review of twenty-eight studies and a meta-analysis of seven studies and reported the incidence of stroke in COVID-19 was 1.1%. Although stroke incidence among patients with COVID-19 infection is low, patients with COVID-19 infection and who suffered from stroke concurrently with severe infection had a worse prognosis with a higher mortality rate (46.7%) than if only suffering from COVID-19 and stroke.

The information on SARS-CoV-2 recurrence or reinfection is still limited. A study by Ye et al.[7] reported 55 patients with a history of COVID-19, five patients (9%) had reactivation after discharge from the hospital. The mean time from SARS-CoV-2 reactivation from negative to positive ranged from 4 to 17 days. The reactivation timing can vary depending on 3 points: host status, virologic factors, and immunosuppression type. We reported a case of COVID-19 with stroke manifestation and a history of positive COVID-19 earlier, possibly reinfection of the disease.

CASE REPORT

Male, 55 years old, came to the emergency department with a medical history of diabetes mellitus on insulin, hypertension treated with ramipril, heart failure treated with bisoprolol, atorvastatin, and history of acute coronary syndrome history of double-J stent (DJ stent) in February 2020. He worked as an administrative officer in the hospital. He was diagnosed with COVID-19 on 26th June based on his nasopharyngeal swab without any clinical manifestation, then isolated himself in his home. His second and third nasopharyngeal swabs on 14th and 15th July then showed negative results, and he was declared cured of COVID-19 infection. On 27th July, he came to emergency departments with acute onset slurred speech, left-sided hemiparesis, dysarthria, and left-sided facial drop two hours before admission when he woke up. The patient denied fevers, cough, nor dyspnea symptoms. There was no history of travels abroad or recent contact with any individuals known to be positive for COVID-19. The patient was fully alert with vital signs: blood pressure of 150/60 mm Hg, pulse of 82 beats per minute, respiratory rate of 20 breaths per minute, body temperature of 36.8ºC, and blood oxygen saturation of 98% on nasal cannula.

Physical examination revealed slurred speech, left-sided facial droop, and left-sided hemiparesis affecting the upper and lower extremities; there were no visual nor neglected symptoms from the patient. The sensation was intact. Babinski and Chaddock's reflex was positive on the left side. Cardiopulmonary examinations showed no abnormality. The laboratory studies (Table 1) were within normal limits, but his nasopharyngeal swab with positive result, he was diagnosed with COVID-19. He performed chest radiography (Figure 1) with normal result, and his head CT scan (Figure 2) showed ischemic in the right insular lobe and ischemic in the right parietal lobe with senile brain atrophy. Unfortunately, we did not do CT angiography to assess large-vessel occlusion (LVO). He was hospitalized in the high care unit for COVID-19 patients. He received Aspirin for stroke therapy, antibiotics (intravenous Levofloxacin 750 mg; Azithromycin 500 mg), antiviral drugs (Oseltamivir 75 mg bid; Hydroxychloroquine 400 mg) for COVID-19 therapy with supportive care. On 31st July, five days after admission, the patient spontaneously became hypoxic and somnolence with oxygen saturation 60%. D-dimer and Fibrinogen results were still normal. We suspected the reason for sudden deterioration was because of his pneumonia COVID-19. The respiratory status still deteriorated, with significant desaturation despite 15L of oxygen. We planned to perform endotracheal intubation, but suddenly the patient became apnea fifteen minutes later, and the patient died due to respiratory failure.

	June 2020	July 2020				Normal Value
	26	14	15	27	31	
Rapid Test SARS Antibody	**Reactive**			**Reactive**		
Nasopharyngeal swab	**(+)**	(-)	(-)	**(+)** CT Value: 37.6		
Hb (g/dL)				13.3	13.7	13.4-17.7
Erythrocyte (10^6/uL)				4.9	5.03	4-5.5
Leukocytes (10^3/uL)				8.4	**12**	4.3-10.3
Hematocrit (%)				39.3	41	40-47
Platelets (10^3/uL)				250	242	142-424
Blood Glucose (mg/dL)				174		
Blood gas analysis						
• pH				7.4	7.33	7.35-7.45
• pCO_2 (mmHg)				29.5	30.3	35-45
• pO_2 (mmHg)				113.5	100.3	80-100
• HCO_3 (mmol/L)				18.2	16.2	21-28
• O_2 saturation (%)				98	97.4	>95
CRP (mg/dL)				0.39	**4.16**	<0.3
Procalcitonin (ng/mL)				<0.02	<0.02	<0.5
Total cholesterol (mg/dL)				**171**		60-100
Triglycerides (mg/dL)				**162**		<150
HDL (mg/dL)				45		>50
LDL (mg/dL)				75		<100
Fibrinogen (mg/dL)				301.3	396.7	154.3-397.8
D-Dimer (mg/L FEU)				0.26	0.37	<0.5

DISCUSSION

COVID-19 is Betacoronavirus that binds the ACE-2 receptor to enter the cell. ACE-2 receptors present in multiple organs, including the nervous system, so SARS-CoV-2 can infect neural cells and result in neurological manifestation.[8] In this case, the patient came to the emergency ward because of acute onset slurred speech, left-sided hemiparesis, dysarthria, and left-sided facial drop, without any manifestation of COVID-19 like fever, cough, dyspnea, nor sore throat; so, we diagnosed him as a stroke attack. Stroke is an uncommon complication in viral CNS infections. Umapathi et al.[9] reported large vessel strokes in five of 206 SARS-CoV patients in Singapore. In a retrospective study by Avula et al.[10], four elderly patients with multiple cardiovascular risk factors were diagnosed with COVID-19 developed stroke. Similarly, Guo et al.[11] reported five stroke cases with positive COVID-19 who had vascular risk factors, including dyslipidemia, diabetes, and hypertension. It is proven that COVID-19 infection is related to cardiovascular comorbidities, such as hypertension, diabetes mellitus, and dyslipidemia.

The pathophysiology of stroke following COVID-19 infection is still unclear and debatable. Three mechanisms seem to be responsible for the occurrence of ischemic strokes in COVID-19. These include (1) hypercoagulable state, (2) vasculitis, and (3) cardiomyopathy. It suggested that the virus's invasion triggers the activation of complement systems in vascular endothelium, which initiates the thrombotic process and inflammatory cascades. Vessels are also inflamed by the direct effect of SARS-CoV-2 on the ACE-2 receptors in vascular endothelium and by a systemic immune response to the pathogen called a cytokine storm. In addition, there is increased cardiac stress due to respiratory failure and hypoxemia from the infection, leading to stress cardiomyopathy.[11]

ACE-2 receptors are the primary entry for SARS-Cov-2 infection. Another hypothesis tries to explain the entry of SARS-CoV-2 into the nervous system, including direct injury to the blood and blood-brain barrier, immune-related injury, and hypoxic injury.[12] SARS-CoV-2 increases the risk of arterial thrombosis with acute ischemic stroke by induced hypercoagulable state and direct virus invasion and immune-mediated neuronal damage. SARS-CoV-2 can penetrate to the central nervous system via the hematogenous or retrograde neuronal route and activating the neuroimmune system making cytokine storm and induces a viral vasculopathy.[13]

In our case, the patient had comorbidities correlated with stroke accidents, namely diabetes mellitus, hypertension, and a history of coronary syndrome. WHO states that the elderly whose underlying medical conditions are at higher risk of developing severe COVID-19 disease. Diabetes is one of the severe comorbidities linked to the severity of coronavirus infections. Based on the global region, 20-50% of COVID-19 pandemic patients had diabetes.[14] Guan et al.[14,15] showed 173 of 1099 patients with COVID-19 in China had severe disease with comorbidities, in which 16.2% were diabetes mellitus. Hypertension patients in COVID-19 are also at high mortality risk. A systematic review and meta-analysis from Zuin et al.[16] showed that COVID-19 patients with hypertension have a significantly higher mortality risk. Hypertension and diabetes are proven associated with a higher risk of respiratory infection and an indicator of COVID-19 severity. Li et al.[17] reported a meta-analysis from six published studies from China; from 1527 patients with COVID-19, the most common comorbid conditions include diabetes (9.7%), cardiovascular disease (16.4%), and hypertension (17.1%). Poor outcomes in COVID-19 patients have been reported to be associated with vascular risk factors such as coronary artery disease, hypertension, and diabetes mellitus. It postulated that the SARS-CoV-2 virus causing cytokine storm through ACE-2 receptor binding leads to a hypercoagulable state and increasing incidence of vascular thromboses in patients with COVID-19.[18,19]

Reinfection can be defined as recurrent clinical symptoms compatible with COVID-19, accompanied by a positive PCR test (CT value <35), more than 90 days after the onset of primary infection, supported by close contact exposure, and no evidence of another infection. In the presence of significant exposure (epidemiological risk factors), if clinical symptoms from the first episode resolve and two PCR tests are negative before the new episode, reinfection should be considered during the first 90 days. Meanwhile, recurrence or relapse is defined as recurrent clinical symptoms compatible with COVID-19 by the absence of epidemiological exposure and accompanied by positive or persisting PCR within 90 days of primary infection.[20]

In this case, the patient has been diagnosed with pneumonia COVID-19 infection on 26th June and performing a nasopharyngeal swab twice (14th and 15th July) with a negative result. However, he became positive again after one month from his positive result with clinical manifestation of stroke but without any clinical manifestation of COVID-19. A study by Ye et al.[7] stated that the meantime from SARS-CoV-2 reactivation from negative to positive ranged from 4 to 17 days. In this case, the patient became positive again 13 days from his negative result or 45 days after the onset of primary infection with a CT value of 37.6. We could not know about environmental exposure from this patient, and he used to work in the hospital. Thus, we considered this patient as reinfection from the definition of reinfection in the presence of significant exposure. Unfortunately, we did not perform specific antibody IgM/IgG testing to differentiate whether this was reinfection or recurrence of the disease.

CONCLUSION

We reported the case possibility of COVID-19 reinfection with clinical manifestation acute onset slurred speech, left-sided hemiparesis, dysarthria, and left-sided facial drop, without any manifestation of COVID-19 like fever, cough, dyspnea, nor sore throat, and we diagnosed it as stroke attack. His nasopharyngeal swab result was positive, so we diagnosed him to be infected with COVID-19 infection. The patient has been diagnosed with COVID-19 one month before admission, his second and third nasopharyngeal swabs then showed negative results, and he was cured of COVID-19 infection after that. We hypothesized the manifestation of stroke as a neurological manifestation of COVID-19 without any respiratory manifestation and possibly reinfection of COVID-19. Unfortunately, we did not perform specific antibody IgM/IgG testing to differentiate whether this was the disease's reinfection or recurrence.

FIGURE LEGENDS

Figure 1. Chest Radiography showed normal.
Figure 2. Head CTScan showed ischemic in the right insular lobe and ischemic in the right parietal lobe with senile brain atrophy.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case and any accompanying images. A copy of the written consent is available for review.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

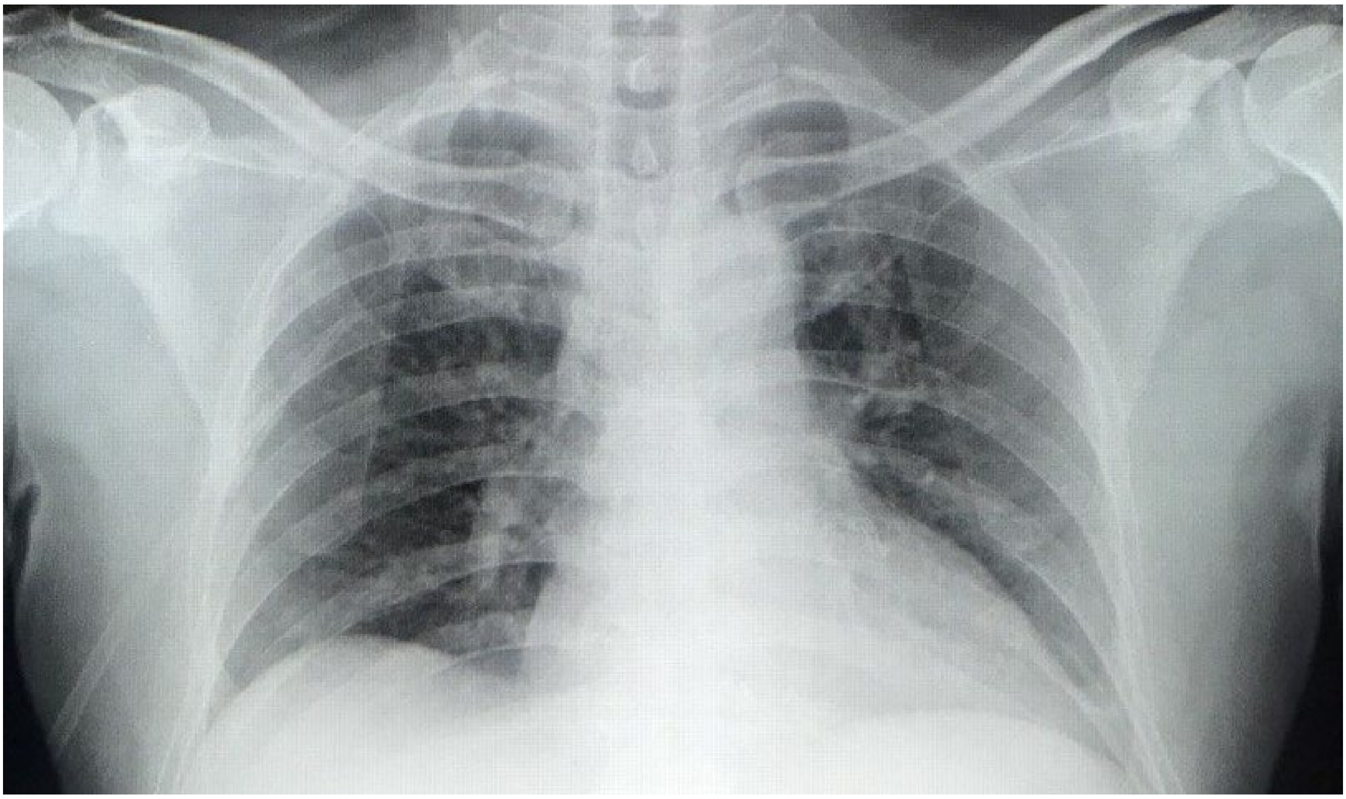

Figure 1

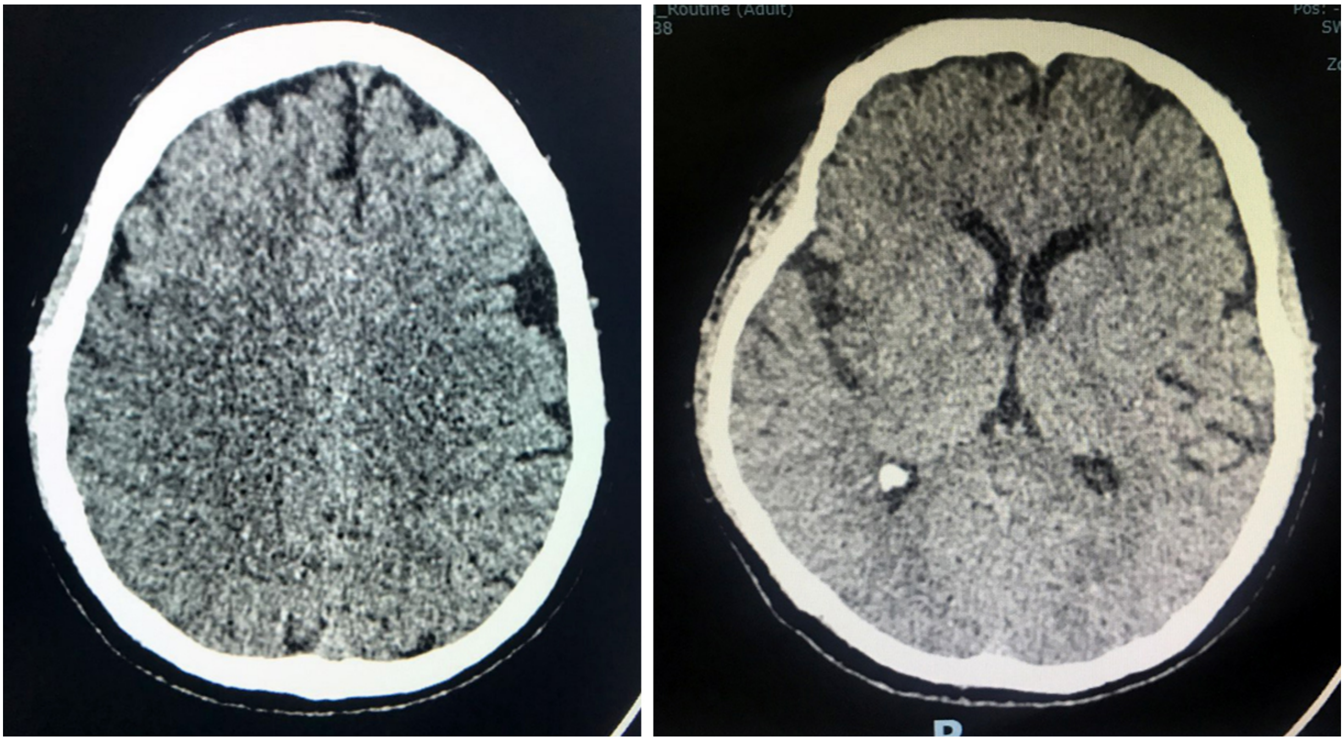

Figure 2

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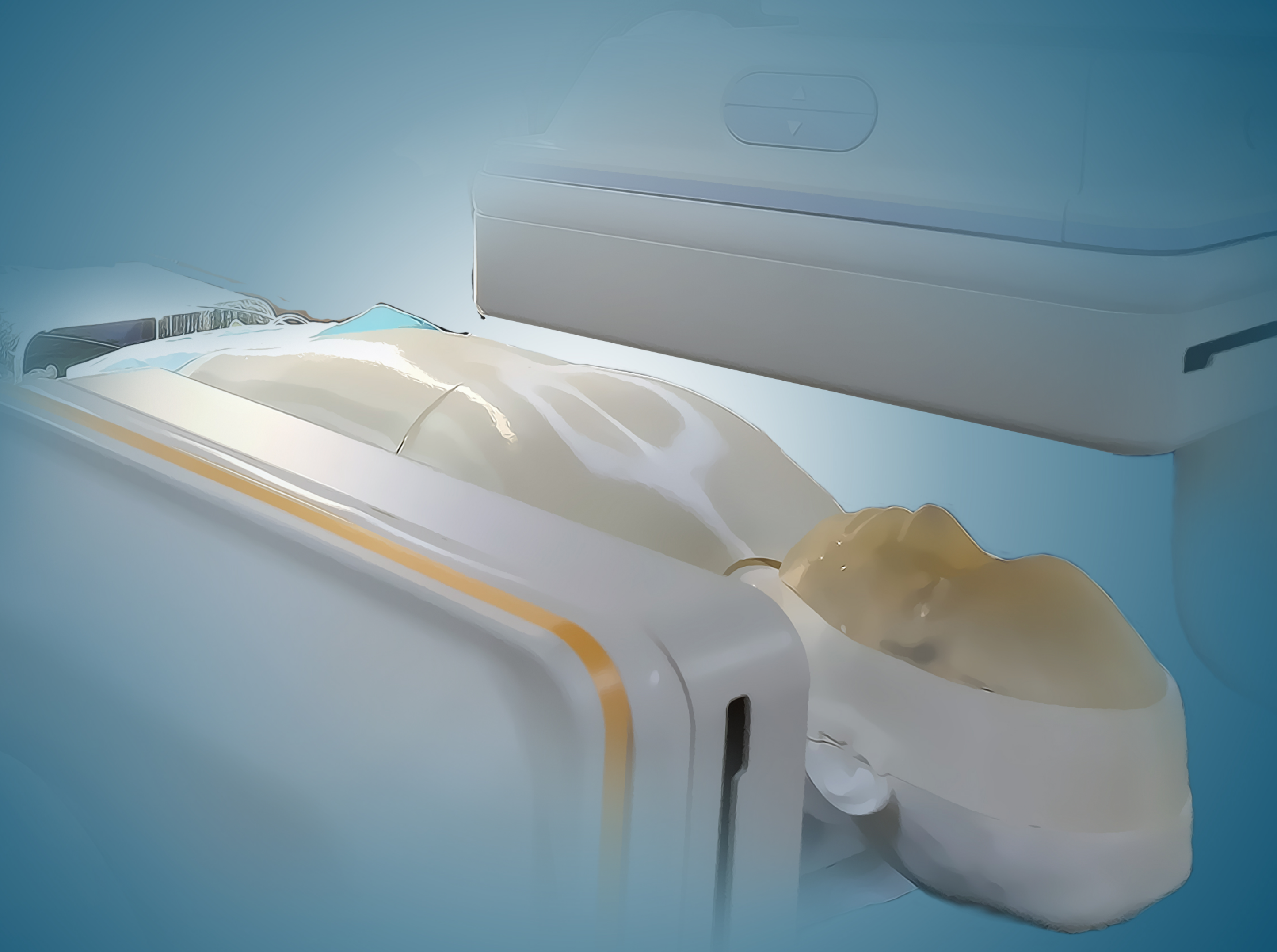

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