



Severe Acute Respiratory Syndrome Coronavirus 2 Infection is Associated with Homocysteine Level and Clinical Outcomes in Ischemic Stroke Patients

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Abstract

BACKGROUND: Since its emergence in December 2019 and declared as pandemic in March 2020, the drastic increase in cases of coronavirus disease 2019 (COVID-19) is alarming the importance of disease monitoring in order to prevent further complication, such as ischemic stroke. One of the efforts is utilizing the biomarkers. For instance, elevated homocysteine level, already known risk factor of ischemic stroke, is currently identified in COVID-19 patients.

AIM: The aim of the study is to assess factors associated with homocysteine level and clinical outcomes in ischemic stroke patients with and without COVID-19.

METHODS: A cross-sectional study was conducted at Dr. Zainoel Abidin Hospital di Indonesia between March and August 2021. Ischemic stroke patients who had physical and neurology examinations, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time polymerase chain reaction swab, chest X-ray, electrocardiography, head computed tomography-scan and the total homocysteine level were included. To assess the factors associated with homocysteine level and the outcomes of ischemic stroke patients, the independent Student t-test or analysis of variance and Chi-squared were used, respectively.

RESULTS: We included 62 ischemic stroke patients of which 32 (51.6%) were male and the age ranged between 30 and 80 years. Out of total, 60 patients (96.8%) were survived after the hospital admission. There was a significant association between gender and having COVID-19 with homocysteine level ($p = 0.012$ and $p = 0.020$, respectively). Having COVID-19 was the only variable significantly associated with the outcome of the ischemic stroke patient ($p = 0.035$).

CONCLUSION: COVID-19 is associated with homocysteine level and the clinical outcome in ischemic stroke patients. Therefore, SARS-CoV-2 infection in ischemic stroke or vice versa needs to be monitored closely in hospital settings.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and stroke have been occurring as double burden worldwide, interrelating to each other [1]. Although effective COVID-19 vaccines are available, the acceptance rate is quite low and vaccine hesitancy is high in some countries [2], [3], [4]. COVID-19 presumably could cause chronic illness [5], [6] and more prone for the patients to develop ischemic stroke and its complications [7], [8]. According to the World Stroke Organization, it is estimated 5% risk of ischemic stroke during COVID-19 [9]. During COVID-19, some occlusions are built up in large arteries due to embolization. The embolus might come from deep vein thrombosis or released from intracardiac. Ischemic stroke in COVID-19 patients is associated with vasculitis, hypercoagulation, and cardiomyopathy [10]. Furthermore, both ischemic stroke and COVID-19 were

identified to be associated with hyperhomocysteinemia – a condition with a characteristic of increased plasma homocysteine level ($>15\mu\text{mol/L}$) [11], [12], [13].

Homocysteine levels have been found to be positively correlated with venous and pulmonary thromboembolism [14]. A study in Italy suggested that homocysteine levels were significantly higher in non-survivors and could be used as a predictive marker for the outcome of hospitalized COVID-19 patients [15], [16]. Since high level of homocysteine in blood was associated with endothelial injuries leading to embolies formation, it underlies the high incidence and more severity of ischemic stroke [11], [17]. However, more data is required to provide more robust evidence. Studies have shown that COVID-19 patients with acute ischemic stroke had a higher mortality rate [18], [19], [20]. Those who had ischemic stroke and COVID-19 had a higher rate of thrombotic events and a higher mortality rate (15% vs. 2.8%) [18]. A multicenter study in Spain found that ischemic stroke patients with COVID-19 had a mortality rate up to 39.3% compared

to 16.1% only among those without COVID-19 [19]. Another study also found that the probability of survival in patients with ischemic stroke and COVID-19 was significantly higher compared to those without COVID-19 (91.0% vs. 78.3%) [20].

A study using images of chest computerized tomography scan (CT-scan) had reported a significant increase of plasma homocysteine among COVID-19 patients with imaging progression [21]. Nevertheless, whether homocysteine level in COVID-19 patients could be used as risk predictor for ischemic stroke is unknown and more studies are required. The aim of this study was to assess factors associated with the level of homocysteine and clinical outcomes among ischemic stroke patients with and without COVID-19.

Methods

Study design

This cross-sectional study was conducted at Dr. Zainoel Abidin Hospital in Banda Aceh of Indonesia between March and August 2021. All ischemic stroke patients admitted to the hospital who met the inclusion criteria (having physical and neurology examination, had COVID-19 tested by real-time polymerase chain reaction (RT-PCR) swab, chest X-ray, electrocardiography, head CT-scan, and complete blood count including the total homocysteine) were included. Ischemic stroke was confirmed by non-contrast head CT-scan showing the hypodensity that indicates embolic or thrombotic occlusion of certain cerebral artery [22]. The patients with the decrement of consciousness, extremities paralysis due to infection, tumor, head trauma or nucleus pulposus herniation, were excluded from this study. The written informed consent was obtained from each patient before the study.

Study variables

The demographic characteristics of ischemic stroke patients (age, gender) homocysteine level, COVID-19 status, and outcome were collected. In addition, hypertension, diabetes, and dyslipidemia were also recorded as they contribute as the major risk factor of ischemic stroke patients [23]. Age was divided into 30–40, 40–50, 51–60, 61–70, and 71–80 years old. Homocysteine was obtained from the vein blood and it was defined as high if it was $>15 \mu\text{mol/L}$ [24], [25]. Hypertension was defined based on American Heart Association [26]. Dyslipidemia was confirmed according to the Adult Treatment Panel III [27]. Diabetes diagnose was made based on Guideline for Diabetes Management in Indonesia, 2019 [28].

Statistical analysis

The characteristics of the patients were quantitatively described by univariate analysis. Factors associated with homocysteine level and the outcome of ischemic stroke patients were statistically analyzed by independent Student t-test or analysis of variance and Chi-squared as appropriate and considered as significant at $p < 0.05$.

Ethical statement

The protocol of this study was approved by the Ethical Committee Faculty of Medicine Universitas Syiah Kuala, Banda Aceh, Indonesia (080/EA/FK-RSUDZA/2021) and KEPPKN Republic of Indonesia registration 1171012P.

Results

Patients' characteristics

A total of 62 ischemic stroke patients were included in the study of which 32 were male patients (51.6%) (Table 1). There were 12 patients confirmed for COVID-19 and some comorbidities were reported such as hypertension 43 patients (69.4%), diabetes 20 patients (32.2%), and dyslipidemia 30 patients (48.4%). There were 60 patients (96.8%) were survived after the hospital admission.

Table 1: The mean of homocysteine level and its associated factors in ischemic stroke patients (n = 62)

Characteristics	n (%)	Homocysteine level ($\mu\text{mol/L}$) Mean \pm SD	p
Age (years)			
30–40	3 (4.8)	7.6 \pm 0.8	0.738 ^a
41–50	15 (24.2)	10.5 \pm 4.6	
51–60	15 (24.2)	9.3 \pm 2.3	
61–70	19 (30.6)	9.2 \pm 2.6	
71–80	7 (11.3)	11.0 \pm 7.9	
>80	3 (4.8)	9.7 \pm 0.6	
Gender			
Male	32 (51.6)	10.8 \pm 4.1	0.012 ^{b*}
Female	30 (48.4)	8.4 \pm 3.2	
COVID-19			
Yes	12 (19.4)	7.9 \pm 1.2	0.020 ^{b*}
No	50 (80.6)	10.1 \pm 4.2	
Hypertension			
Yes	43 (69.4)	9.7 \pm 3.7	0.825 ^b
No	19 (30.6)	9.5 \pm 4.3	
Diabetes			
Yes	20 (32.3)	9.8 \pm 5.2	0.899 ^b
No	42 (67.7)	9.6 \pm 3.1	
Dyslipidemia			
Yes	30 (48.8)	10.3 \pm 3.9	0.190 ^b
No	32 (51.6)	9.0 \pm 3.8	
Outcome			
Survive	60 (96.8)	9.7 \pm 3.4	0.568 ^b
Dead	2 (3.2)	8.6 \pm 2.0	

^aAnalyzed with Anova, ^bAnalyzed by student t-test, *Significant at P = 0.05. SD: Standard deviation.

Factors associated with homocysteine level

The mean homocysteine level among total of patients were $9.6 \pm 3.9 \mu\text{mol/L}$. The highest mean of

homocysteine level was found among patients within 71–80 years group (11.0 $\mu\text{mol/L}$), while the lowest was among those 30–40 years old (7.6 $\mu\text{mol/L}$) (Table 1). There was a significant association between gender and the homocysteine level ($p = 0.012$). COVID-19 was also significantly associated with the homocysteine level ($p = 0.02$). The rest of clinical characteristics, such as age, hypertension, diabetes, dyslipidemia, and outcome of the patients were not associated with homocysteine level in the blood (Table 1).

Factors associated with outcome of ischemic stroke patients

Focusing on the outcome of the ischemic stroke patients, our data suggested that COVID-19 was the only variable that was significantly associated with the outcome of the patient (odds ratio [OR]: 0.8; $p = 0.035$) (Table 2).

Table 2: Factors associated with outcome in ischemic stroke patients (n = 62)

Variables	Outcome		OR	p
	Dead (%)	Survive (%)		
Age (years)				
≤ 50	0	18 (29.0)	1.0 (0.9–1.1)	0.500
> 50	2 (3.2)	42 (67.7)		
Gender				
Male	1 (1.6)	31 (50.0)	0.9 (0.1–15.7)	0.738
Female	1 (1.6)	29 (46.8)		
COVID-19				
Positive	2 (3.2)	10 (16.1)	0.8 (0.6–1.1)	0.035*
Negative	0	50 (80.6)		
Hypertension				
Yes	1 (1.6)	42 (67.7)	0.4 (0.0–7.2)	0.522
No	1 (1.6)	18 (29.0)		
Diabetes				
Yes	1 (1.6)	19 (30.6)	2.2 (0.1–36.4)	0.545
No	1 (1.6)	41 (66.1)		
Dyslipidemia				
Yes	2 (3.2)	28 (45.2)	0.9 (0.8–1.0)	0.230
No	0	32 (51.6)		
Homocysteine				
Normal	2 (3.2)	49 (79.0)	0.9 (0.9–1.0)	0.674
High	0	11 (17.7)		

*Significant at $P = 0.05$. OR: Odds ratio.

Discussion

In this present study, we found that COVID-19 significantly determined the outcome of ischemic stroke patients. This is in agreement with a previous study analyzing 27,676 hospitalized patients with ischemic stroke, where they found COVID-19 could increase the risk of cardiovascular complications, such as myocardial infarction, intracerebral hemorrhage, and cerebral edema [10]. The risk of ischemic stroke in COVID-19 patients could be attributed to the formation of venous and arterial thromboembolism [29]. Moreover, a previous study also reported the induction of thrombosis through plaque rupture, inflammation, and increased oxygen demand in damaged tissue upon the SARS-CoV-2 infection [30].

Recently, homocysteine has been strongly associated with the severity of ischemic stroke with induced vascular damage as its main mechanism [31].

Other than vascular damage, the harmful effects of homocysteine are caused by endothelial dysfunction, oxidative stress imbalance, and acceleration atherosclerotic process [32], [33], [34]. In the case of viral infection, homocysteine has been found significantly increased in patients infected by hepatitis virus, human papilloma virus, and human immunodeficiency virus [35], [36], [37]. Newly published investigation on COVID-19 patients suggested a high level of homocysteine was associated with severe pneumonia [21]. A preliminary data from a previous study participated by 40 patients reported potential of homocysteine level as severe COVID-19 predictor [12]. Nonetheless, our current study reveals a contrary result, where significantly lower average level of homocysteine was observed in SARS-CoV-2-infected patients with ischemic stroke. To date, there have been no published reports pertaining to how SARS-CoV-2 infection plays a role in the induction of plasma homocysteine. Despite the absence of the pathological explanation, the limited number of participants could contribute to the difference between our findings and that of previously reported [12], [21].

As a biomarker, homocysteine has been reported predictive against the severity and poor outcome of ischemic stroke patients [21], [38]. On contrary, plasma homocysteine level was not found statistically significant in determining the clinical outcomes of ischemic stroke patients participated in this present study. It is worth noting that we found significantly produced homocysteine male patients, in comparison with female patients. It is attributed to the fact that women have a higher flux of the methionine cycle that consequently lead to lower production of homocysteine level [39]. Hence, the statistical insignificance of the association between homocysteine and ischemic stroke outcomes could be derived from the absence of men and women separation in our study. Besides, only 2 deaths were recorded during our investigation period making the result of this study is hard to be generalized.

The main limitation of this study is the number of samples. Further studies and validation with greater number of samples are required to clarify homocysteine level as a potential risk predictor for ischemic stroke patients infected with SARS-CoV-2. Future studies should also measure homocysteine level in periodical manner due to the possibility of its dynamic changing. Moreover, biomarkers such as red cell distribution width (RDW), erythrocyte sedimentation rate, D-dimers, and neutrophil-to-lymphocyte ratio should be included, as suggested by other previous studies [40], [41], [42].

Conclusion

COVID-19 is significantly associated with homocysteine level and clinical outcomes in patients with ischemic stroke. Further studies should be carried

out to confirm the potential of homocysteine as a predictor for the outcomes of patients with ischemic stroke and COVID-19.

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