AKSONA

Role of Procalcitonin in Intracerebral Hemorrhage Stroke with COVID-19

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Article info	ABSTRACT
  	Introduction: As COVID-19 has rapidly spread worldwide, it is an urgent health problem. Some evidence suggests that SARS-CoV-2 also affects the central nervous system. Stroke is the most common disease of the central nervous system. In contrast to ischemic stroke, which can occur due to the hypercoagulation effect of COVID-19, the study of Intracerebral Hemorrhage (ICH) associated with COVID-19 is still unclear. **Objective:** This paper investigated the characteristics of an inflammatory biomarker and compared the outcomes of ICH patients with COVID-19 and ICH patients without COVID-19. **Methods:** We conducted a retrospective, observational analysis case-control of patients (n = 42) admitted with ICH with positive COVID-19 and ICH with negative COVID-19 at the National Brain Center Hospital Prof.Dr.dr. Mahar Mardjono from March 2020 to August 2021. We took blood samples and COVID-19 swab PCR on the first day of admission, and GOS was measured when the patients were discharged. **Results:** There were 21 ICH patients with positive COVID-19 who had a significantly procalcitonin ($p < 0.05$) compared to control patients. From Spearman's correlational analysis, there is a significant value between early procalcitonin and the Barthel Index ($r_s = -0,374$, $p < 0.05$), early CRP and GOS ($r_s = -0.329$, $p < 0.05$), which indicates weak-inverse correlation, and between early PCT and GOS ($r_s = -0.438$, $p < 0.05$) which indicates moderate-inverse correlation. **Conclusion:** The level of procalcitonin was increased in ICH patients with COVID-19. Maybe PCT could be a predictor of outcome in ICH patients with COVID-19.

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INTRODUCTION

The case of COVID-19 was first reported in Wuhan, China, on December 12, 2019. COVID-19 is spread through droplets produced when talking, coughing, or sneezing.[1] By clinical symptoms, it presents more commonly as respiratory problems such as fever, dry cough, and shortness of breath. However, some COVID-19 patients also reported neurological symptoms like headaches, unconsciousness, and epilepsy.[2]

The mechanism of ischemic stroke in COVID-19 patients is related to hypercoagulability due to COVID-19, vasculitis, and cardiomyopathy, while the pathophysiology of hemorrhagic stroke in COVID-19 patients is still unknown.[3,4] However, several mechanisms are thought to play a role in the occurrence of hemorrhagic stroke. First, it has been postulated that SARS-CoV-2 is neurotropic and can invade and directly damage cerebral blood vessels. The early investigation confirmed that SARS-CoV-2 has a strong affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, which is present on many cell types, including endothelial and arterial smooth muscle cells in the brain.

Downregulation of ACE2 expression may impair endothelial function and increase the risk of hemorrhagic shock.[2,5] Then, most COVID-19 patients develop a systemic hyperinflammatory syndrome characterized by fulminant hypercytokinemia, which may mediate vascular remodeling and predispose them to ICH. The pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), as potent activators of matrix metalloproteinase, degrade the extracellular matrix, which leads to loss of wall vascular integrity, increasing the risk of hemorrhage.[2,5–7] Coronaviruses induce an exaggerated and prolonged cytokine/chemokine response known as a "cytokine storm."[7] The cytokines may activate the coagulation cascades that lead to arterial wall hypoxia due to thrombotic microangiopathy, undermining vascular integrity.[5] Another possible cause is the risk of ICH due to the routine use of anticoagulants and antiplatelet agents.[6]

A single-center, retrospective cohort study found that patients with new-onset stroke were elderly, had some comorbidities (hypertension and diabetes), and elevated plasma D-dimer levels.[3] Other studies regarding ICH patients with COVID-19 are limited. Zhang et al. investigated the impact of the inflammatory response as well as the predictive ability of the NLR for the adverse outcome of spontaneous cerebral hemorrhage over 30 days.[8]

The limited data concerning ICH patients with COVID-19 attracted our attention to how COVID-19-associated inflammatory factors can affect the prognostic and clinical outcomes of ICH patients with COVID-19.

OBJECTIVE

In this study, we tried to find differences in the characteristics of inflammatory biomarkers in ICH patients with COVID-19 swab negative compared to ICH patients with COVID-19 swab positive. The study participants were patients in the COVID-19 isolation room at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono from March 2020 to August 2021. We studied each patient's laboratory results and outcomes, and we compared them to ICH patients without COVID-19 infection, including the association with mortality risk, length of hospital stay, and the patient's condition after the recovery phase. We understand that the low number of ICH patients with COVID-19 is one of our limitations in collecting data in this study, but along with the small number of ICH patients with COVID-19 swab positive, it becomes an attraction for us to carry out further investigations.

METHODS

Study Design and Participants

We performed a retrospective, observational study using clinical data from the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono (NBC), Jakarta. We took data from March 2020 to August 2021 (n = 42). We reviewed the electronic health record (EHR) to collect data on age, sex, comorbidities (hypertension, diabetes mellitus), clinical symptoms of COVID-19 infection, level of consciousness, NIHSS score, and laboratory findings on the first day of admission. The inclusion criteria were acute intracerebral hemorrhage patients hospitalized in our hospital with confirmed COVID-19. For the control group, we took patients admitted during the same period with negative COVID-19. We defined the confirmed case of COVID-19 as a positive result on reverse transcription-polymerase chain reaction (PCR) analysis of nasopharyngeal swab specimens.

We have diagnosed patients with ICH based on clinical presentation and non-contrast axial head MSCT scan. We took laboratory examinations including inflammatory biomarkers, i.e., neutrophil-lymphocyte ratio (NLR), absolute lymphocyte count (ALC), C-reactive protein (CRP), D-dimer, and Procalcitonin (PCT) on the first day of admission. The clinical outcome is evaluated at discharge using the Glasgow Outcome Score (GOS) and Barthel Index. The Research Ethics Board approved the study protocol from NBC Hospital. We have coded all the patient's records anonymously to ensure confidentiality during analysis.

Statistical Analysis

We used SPSS Statistic version 25 to analyze the

data. We described the characteristic variables and hematologic biomarkers in frequencies (%) and mean (range) by using Mann-Whitney and Chi-square comparative studies as the non-normal distribution of sample size. After that, we did a correlation study between hematologic biomarkers and the subject outcome by using Spearman's rank.

RESULTS

Demographic and Clinical Characteristics

We included 46 ICH patients with COVID-19 symptoms in the analysis. According to the results of the PCR swab, we divided the subjects into two groups: ICH with Positive COVID-19 and ICH with Negative COVID-19 (Figure 1).

The baseline characteristics of 42 subjects, including sex, age, clinical symptoms, and NIHSS on admission, are shown in Table 1. We used the Mann-Whitney and Chi-square comparisons to describe the characteristics of the variables and the relatable biomarkers. We found that ICH patients with positive COVID-19 had no significant difference from those with negative COVID-19.

Laboratory Findings

In addition, we also compared inflammatory biomarkers between ICH with positive COVID-19 and ICH with negative COVID-19 in Table 2. Procalcitonin levels were higher in ICH patients with positive COVID-19 than those with negative COVID-19 (0.6 IQR 0.4-3.1 vs 0.4 IQR 0.4-0.6, p < 0.05).

We calculated a correlation between inflammatory biomarkers and the subject outcome as shown in Table 3. We found that there is a significant inverse correlation between PCT and the Barthel Index (rs = -0,374, p <0,05), CRP and GOS (rs = -0,329, p <0,05), and PCT and GOS (rs = -0,438, p < 0,05).

DISCUSSION

SARS-CoV-2, a human respiratory virus that invades the respiratory tract, which, similar to SARS-CoV, has the neuroinvasive and neurotropic capabilities to infect the central nervous system.[1] The viruses invade and directly damage the blood vessels by binding with Angiotensin-Converting Enzyme-2 (ACE-2) receptors expressed in endothelial cells.[3] It will trigger the release of chemokines and proinflammatory cytokines, leading to the activation of inflammatory responses.[2] Downregulation of ACE2 levels may impair endothelial function in cerebral arteries and increase local Ang-II levels, which elevates blood pressure by activating of the AT1 receptor (AT1R). Simultaneously, it will decrease Ang

(1-7) levels/Mas receptor (MasR) signal, thus preventing its vasodilatation, growth-inhibiting, and antifibrotic actions.[2] It will increase the risk of hemorrhagic stroke in COVID-19 patients. The majority of the patients in this study had hypertension as their comorbidity in both categories (81% vs 100%). Chronic hypertension also leads to structural and functional alterations in the endothelium due to atherosclerosis.[2] Figure 2 depicts a suggested mechanism for COVID-19

Our study showed that procalcitonin is higher in ICH patients with COVID-19 than those without COVID-19 (0.6 IQR 0.4–3.1 vs 0.4 IQR 0.4–0.6, p < 0.05). This result is different from the hypercoagulable state in ischemic stroke-related COVID-19 due to increased levels of D-dimer.[3] Procalcitonin (PCT) is a peptide precursor of calcitonin hormone, produced by parafollicular cells of the thyroid and neuroendocrine cells of the lung and intestine, which are triggered by bacterial infections. The extrathyroidal synthesis of PCT is activated by proinflammatory cytokines such as IL-6, IL-1β, and TNF-, while in viral infection, PCT levels may be decreased due to the inhibitory response of interferon-γ. PCT is a well-known, reliable biomarker to identify and assess the severity of sepsis.[9–11] Previous studies found that PCT levels increased in critical COVID-19 patients, suggesting that bacterial infection will promote aggravation of COVID-19.[10] Initial studies demonstrated that COVID-19 severity is directly correlated with cytokine storm and may result in shock and tissue damage, leading to multiple organ failure. From a recent study, COVID-19 complications are now largely due to immunosuppression, especially lymphopenia, rather than cytokine storm. Lymphopenia is continuous in critically ill COVID-19 patients and leads to increased secondary infections.[12] About 6.9% of COVID-19 patients were found to have bacterial co-infection. It was hypothesized that the increase in secondary bacterial infection was mediated by viral infection that damages the lung and holds the immune responses.[13]

Our study also showed that early PCT and GOS had a statistically significant value (r_s = -0.438, p = 0.005). It was interpreted as a moderate-inverse correlation. We also discovered a weak-inverse correlation between CRP and GOS (rs = -0.329, p < 0.05) and early PCT and Barthel Index (r_s = -0.374, p = 0.017). These findings are similar to some studies that have shown the role of procalcitonin as a prognosis marker for sepsis and organ dysfunction.[9,14] An et al. suggest using serum PCT levels to guide the initiation of antibacterial agents in patients with COVID-19. Regular PCT measurements can provide an overview of secondary bacterial infections that aggravate the patient's condition.[10] We acknowledge some limitations of this study. This was an observational, retrospective study. We could not prove

a cause-effect relationship. Second, we have difficulty comparing the role of PCT in ICH stroke because PCT has not been routinely evaluated in ICH stroke. We believe that further studies with more samples should be conducted to elaborate on our findings.

CONCLUSION

The level of procalcitonin was increased in ICH patients with COVID-19. We also discovered that early PCT levels had an inverse correlation to GOS and Barthel Index. Maybe PCT could be a predictor of outcome in ICH patients with COVID-19.

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ATTACHMENT

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┌─────────────────────────────────────┐
│ 46 ICH patients with COVID-19 symptoms│
│ reviewed retrospectively from the     │
│ electronic health records (EHR)       │
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┌──────────────────────────┐      ┌──────────────────────────┐
│        Group 1           │      │        Group 2           │
│ 24 ICH patients with     │      │ 22 ICH patients with     │
│ positive COVID-19 reviewed│     │ negative COVID-19 reviewed│
│ restrospectively form the │     │ restrospectively form the │
│ electronic health records │     │ electronic health records │
│ (EHR)                    │      │ (EHR)                    │
└──────────────────────────┘      └──────────────────────────┘
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┌──────────────────────────┐                    ┌──────────────────┐
│ 3 Subjects drop –out due  │                    │ 1 Subjects drop – │
│ to the type of            │                    │ out due to        │
│ haemorrhagic stroke       │                    │                  │
│ (SAH)                    │                    └──────────────────┘
└──────────────────────────┘
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21 subjects each of groups are enrolled into descriptive study of
➢ Characteristic variables: Age, Sex, Hypertension, diabetes mellitus, Pneumonia, NIHSS score, Los, GOS, Barthel index
➢ NLR, ALC, D-Dimer, CRP, and PCT)

➢ Measuring each data normality distribution
➢ Analysis study of Spearman's Rank correlation coefficient for each biomarker and BI-GOS-LoS
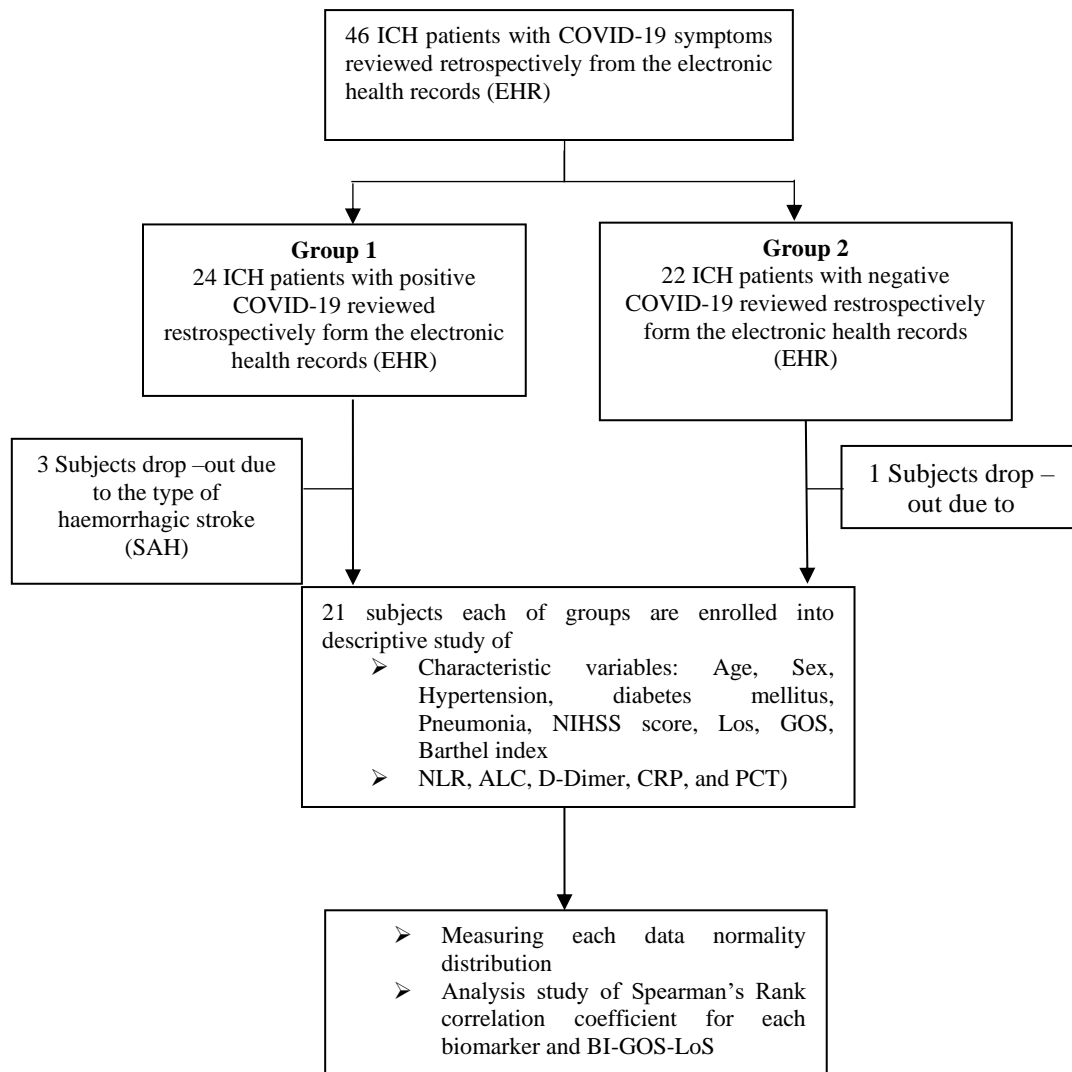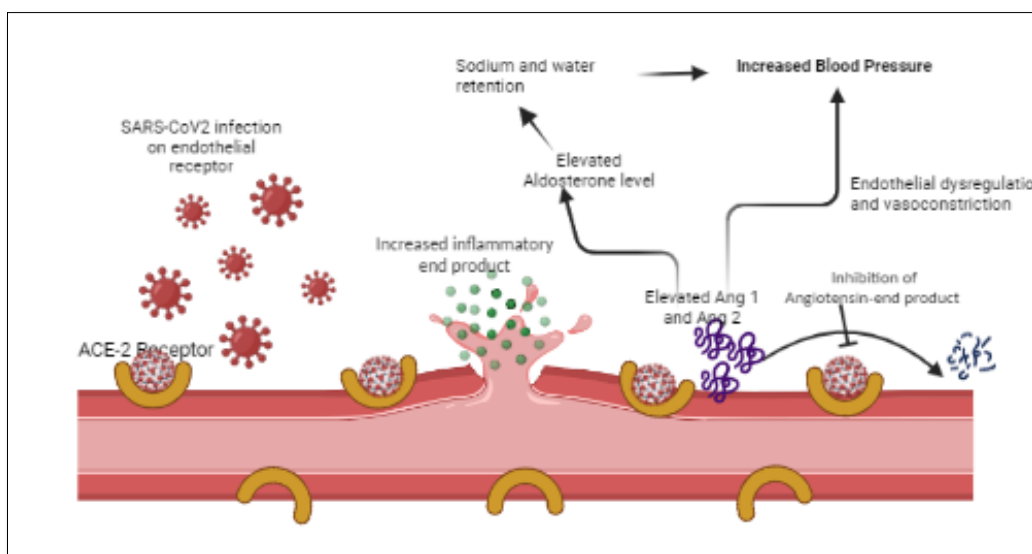
Figure 1. Flowchart of the study

Figure 2. Proposed Mechanism of Spontaneous Intracerebral Hemorrhage in Covid Patient
(created with BioRender.com)

Table 1. Characteristic Variables

Characteristic Variables	ICH with Positive COVID-19	ICH with Negative COVID-19	p-value
Age, median	56 (51 - 78)	62 (58 - 67)	0.598
Male (%)	4 (36.4)	7 (63.5)	0.394
Comorbidities			
Hypertension	81.8	100	0.476
Diabetes Mellitus	18.2	9.1	1.000
NIHSS score, IQR	11 (4.5-13)	14(9.5-17.5)	0.136
Blood Glucose Random, IQR	121 (107-163.5)	135 (111.5-173.5)	0.554
Systolic Blood Pressure, IQR	182 (154-210)	171 (150-202)	0.435
Type of Haemorrhage (%)			
Subcortex	38.1	38.1	
Cortex	9.5	9.5	
Brainstem	4.8	4.8	0.920
Intraventricular	42.9	47.6	
Cerebellum	4.8	0	
Length of Stay	11 (6 - 14)	9 (7 – 13.5)	0.810
Barthel index	20 (0 – 82.5)	25 (0 - 45)	0.582
GOS (%)			
Score 1	47.6	38.1	
Score 2	4.8	0	
Score 3	23.8	57.1	0.080
Score 4	23.8	4.8	
Score 5	0	0	
Pneumonia (%)	76.2	81	1.000

*p-values < 0.05

Table 2. Hematologic Biomarkers

Inflammatory Biomarker	ICH with Positive COVID-19	ICH with Negative COVID-19	p-value
Neutrophil-Lymphocyte Ratio (NLR)	7.46 (4.38 – 12.02)	5.43 (3.34 – 7.88)	0.201
Absolute Lymphocyte Counts (ALC)	1.34 (0.67 – 1.83)	1.74 (1.14 – 2.09)	0.107
D-dimer	1430 (780 - 2720)	985 (518.5 – 1687.5)	0.152
C-reactive Protein	41.45 (10.75 – 135.15)	32.25 (9.53 – 185.73)	0.693
Procalcitonin	0.6 (0.4 – 3.1)	0.4 (0.4 – 0.6)	0.043*

*p-values < 0.05

Table 3. Spearman's Rank Correlation Test between Inflammatory Biomarkers and Outcome

	Spearman's Rank Correlation Coefficient (r_s)	p-value
NLR and LOS	0.189	0.236
NLR and GOS	-0.012	0.939
NLR and Barthel Index	0.039	0.808
AlCand LOS	-0.120	0.447
ALC and GOS	-0.029	0.857
ALC and Barthel Index	-0.110	0.486
D-dimer and LOS	-0.081	0.626
D-dimer and GOS	-0.243	0.137
D-dimer and Barthel Index	-0.269	0.098
CRP and LOS	0.005	0.978
CRP and GOS	-0.329	0.044*
CRP and Barthel Index	-0.316	0.053
PCT and LOS	-0.027	0.867
PCT and GOS	-0.438	0.005*
PCT and Barthel Index	-0.374	0.017*

*p-values < 0.05