

## Cognitive Outcome of Intracerebral Hemorrhage Patients with and without Pneumonia

Carissa Vania Pratama,<sup>1</sup> Cep Juli,<sup>2</sup> Chandra Calista,<sup>2</sup> Suryani Gunadharma,<sup>2</sup>  
Yusuf Wibisono,<sup>2</sup> Paulus Anam Ong<sup>2</sup>

<sup>1</sup>Faculty of Medicine Universitas Padjadjaran, <sup>2</sup>Department of Neurology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

### Abstract

**Background:** There is high prevalence of cognitive impairment in patients with intracerebral hemorrhage (ICH) that may worsen the patients' outcomes. Pneumonia, as the significant infection complication in stroke patients, may aggravate the decline in the cognitive outcome of patients. This study aimed to explore the cognitive outcomes among patients with or without pneumonia among patients with intracerebral hemorrhage.

**Methods:** A cross-sectional retrospective analytical comparative numeric study was conducted from September 2020 to February 2021, using secondary data of patients with intracerebral hemorrhage admitted to the Department of Neurology Dr. Hasan Sadikin General Hospital in the year 2019. A total sampling method was employed. Data on pneumonia in stroke patients was retrieved, consisting of patients with pneumonia and without pneumonia. Data on Mini-Mental State Examination (MMSE) scores as the measures of cognitive outcomes were compared using the Mann-Whitney U test.

**Results:** There were 108 patients with intracerebral hemorrhage included. There was a statistically significant difference ( $p$ -value=0.049) in MMSE scores with median MMSE score for pneumonia patients ( $n$ =27) and non-pneumonia patients ( $n$ =81) were 21 and 25, respectively.

**Conclusion:** Cognitive outcome is worse in patients with pneumonia than those without pneumonia. Early intervention is needed for intracerebral hemorrhage patients who develop pneumonia as a complication to improve the cognitive outcome.

**Keywords:** Cognition, intracerebral hemorrhage, MMSE, pneumonia

### Introduction

According to the definition by the American Heart Association/American Stroke Association, intracerebral hemorrhage (ICH) is a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.<sup>1</sup> The ICH is one of the mechanisms of stroke that is rapidly developing clinical signs of neurological dysfunction that lasts more than 24 hours or even leads to death.<sup>1</sup> Stroke itself is the second leading global cause of death, with hemorrhagic stroke as a significant source of mortality and disability despite its prevalence is lower than ischemic stroke.<sup>2</sup> Patients may develop infections after the onset of stroke. One of the causes of primary infectious complications in ICH is a respiratory infection

with a prevalence of 17%.<sup>3</sup> The ICH itself is also known to be a predictor of pneumonia development.<sup>4</sup> Complications of infection, especially respiratory infection, may lead to worse functional outcomes in patients.<sup>3,5</sup>

Cognitive impairment is one of the neurological manifestations in stroke patients. Post-stroke cognitive impairment (PSCI) occurs in over 20% of patients 3 months after the first stroke.<sup>6</sup> In the acute phase of ICH, PSCI occurs in 27-84% of patients.<sup>7</sup> This manifestation indicates worse long-term mortality and functional outcome, and is associated with lower long-term quality of life in stroke patients.<sup>6,8</sup> Therefore, it is crucial to run an early screening assessment of cognitive functioning in stroke patients in order to preserve the later outcome. Mini-Mental State Examination (MMSE) is a widely used

**Correspondence:** Carissa Vania Pratama, Faculty of Medicine Universitas Padjadjaran, Jalan Raya Bandung-Sumedang Km. 21 Jatinangor, Sumedang, Indonesia, E-mail: carissa17001@mail.unpad.ac.id

screening tool to assess a patient's cognitive function. This test has an 82% sensitivity and 76% specificity on the cut-off value <27 from a maximum score of 30 for the cognitive impairment.<sup>9</sup> Thus, MMSE is considered to be a valid assessment tool for cognitive outcomes.

The previous study has shown that patients' hospitalization due to pneumonia is associated with an increased probability of developing cognitive decline and dementia.<sup>10</sup> This indicates that the presence of pneumonia complications may also worsen ICH patients' cognitive outcomes. Hence, this study aimed to explore the difference in the cognitive outcomes of ICH patients with or without pneumonia complications by comparing the MMSE score. Knowing the impact of such complications, preventive efforts to improve patients' outcomes are imperative.

## Methods

A retrospective analytical study using a comparative numeric method for two independent groups was conducted. Secondary data from the medical resume of all ICH patients admitted to the Department of Neurology Dr. Hasan Sadikin General Hospital Bandung in 2019 were retrieved. The data collection was conducted from September 2020 to February 2021 using a cross-sectional method. This study had been approved by the Research Ethics Committee Universitas Padjadjaran Bandung with ethical clearance No.026/UN6.KEP/EC/2021.

The inclusion criteria were those who had MMSE score data at discharge. MMSE score was used as the measurement of cognitive outcome. Patients without MMSE scores, those who were deceased, were illiterate, and had an unimproved consciousness until discharge time were excluded. Furthermore, the data on demographic, level of consciousness on admission, vascular risk factors, location of ICH, National Institute of Health Stroke Severity (NIHSS) score, and volume of ICH (cm<sup>3</sup>), if any, were also collected. The data were grouped into patients with a presence or absence of pneumonia, of which the diagnosis of pneumonia was determined by chest X-Ray results and/or final diagnosis in the medical resume.

Both categoric and numeric data of patients' characteristics were analyzed using descriptive and analytical statistics. The comparison between categorical data was conducted using the Chi-square test and Fisher's exact test. The numerical data were compared using

the Independent t-test or Mann-Whitney U test according to the normality of the data. To compare cognitive outcome, the normality distribution of MMSE score for groups with pneumonia or without pneumonia were analyzed first using the Kolmogorov-Smirnov test and Shapiro-Wilk test, before assessing by the Mann-Whitney U test. The significance of (p-value) <0.05 was considered statistically significant.

## Results

From 267 data of ICH patients admitted to Dr. Hasan Sadikin General Hospital in 2019, 159 (59.5%) were excluded, due to lack of MMSE examination results (n=108; 40.4%) and deceased (n=51; 19.1%). The lack of MMSE result was due to incomplete medical resume data for MMSE score (n=45; 16.8%), aphasia (n=23; 8.6%), decreased consciousness (n=39; 14.6%) and illiteracy (n=1; 0.4%).

Of the remaining 108 data that met the inclusion criteria of this study, 27 had pneumonia and 81 had no pneumonia. The patients' characteristics were presented in Table 1. The majority of patients in this study were female (53.7%), unemployed (46.3%), had somnolent consciousness (28.1%), had hypertension as vascular risk factor (91.7%), experienced first stroke attack (75.9%), and had deep ICH location (62%). Although there were some slight differences, the pattern of subjects' demographics and clinical characteristics in both groups were relatively the same.

Analytical statistics results of cognitive outcome comparison between those with pneumonia or without pneumonia patients can be seen in Table 2. Shapiro-Wilk test showed that the data in the pneumonia group were normally distributed (p=0.646). However, in the non-pneumonia group, the Kolmogorov-Smirnov test did not show that the data were normally distributed (p<0.0001). Therefore, the Mann-Whitney U test was used to make a comparison between the two groups, resulting in a significance value (p-value) of 0.049.

## Discussion

Other than the acute expansion of hemorrhagic lesions, cognitive decline in ICH patients may occur due to deterioration of underlying neurodegenerative processes or cerebral small vessel disease (CSVD) which are also associated with the mechanism of ICH.<sup>7,11</sup> Some vascular risk factors such as

**Table 1 Demographics and Characteristics of Study subjects**

Variables	(n=108)	Pneumonia (n= 27)	No pneumonia (n= 81)	p-value
Age, median (IQR)	108	53 (49–59)	55 (46–60)	0.670*
Years of education, median (IQR)	92†	12 (6–12)	12 (9–12)	0.157*
NIHSS, mean ± SD	95	12.08 ± 4.872	10.89 ± 4.783	0.279**
ICH volume (cm <sup>3</sup> ), median (IQR)	55 †	9.7 (3.5–39.7)	14.6 (5.3–21.4)	0.870*
Sex, n (%)				
Male	50 (46.3)	12 (44.4)	38 (46.9)	0.824***
Female	58 (53.7)	15 (55.6)	43 (53.1)	
Occupation, n (%)				
Unemployed	50 (46.3)	14 (51.9)	36 (44.4)	
Office worker	28 (25.9)	6 (22.2)	22 (27.2)	0.926***
Entrepreneur	6 (5.6)	2 (7.4)	4 (4.9)	
Farmer/fisherman/laborer	9 (8.3)	2 (7.4)	7 (8.6)	
Others	15 (13.9)	3 (11.1)	12 (14.8)	
Consciousness on admission, n (%)				0.837***
Compos mentis	38 (35.2)	8 (29.6)	30 (37.0)	
Conscious, inadequate contact	10 (9.3)	3 (11.1)	7 (8.6)	
Conscious, aphasic	6 (5.6)	1 (3.7)	5 (6.2)	
Somnolent	52 (48.1)	14 (51.9)	38 (46.9)	
Sopor	2 (1.9)	1 (3.7)	1 (1.2)	
Coma	-	-	-	
Vascular risk factors, n (%)				
Hypertension	99 (91.7)	26 (96.3)	73 (90.1)	0.315***
Dyslipidemia	33 (30.6)	10 (37.0)	23 (28.4)	0.399***
Diabetes mellitus	5 (4.6)	1 (3.7)	4 (4.9)	1.000****
Atrial fibrillation	2 (1.9)	1 (3.7)	1 (1.2)	0.439****
Ischemic heart disease	1 (0.9)	0 (0.0)	1 (1.2)	
No vascular risk factors	8 (7.4)	0 (0.0)	8 (9.8)	
History of stroke, n (%)				
First time	82 (75.9)	19 (70.4)	63 (77.8)	0.436***
Recurrent	26 (24.1)	8 (29.6)	18 (22.2)	
Location of ICH, n (%)				
Lobar	17 (15.7)	1 (4.3)	16 (22.2)	0.119***
Deep	67 (62)	18 (78.3)	49 (68)	
Mixed/multiple	11 (10.1)	4 (17.4)	7 (9.8)	

Note: \*Mann-Whitney U test, \*\*Independent t-test, \*\*\*Chi-square test, \*\*\*\*Fisher's exact test, ICH, intracerebral hemorrhage; IQR, interquartile range; MMSE, Mini-Mental State Examination; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation, † the number of patients as stated

**Table 2 Comparison of Cognitive Outcome in Intracerebral Hemorrhage Patients with or without Pneumonia**

	MMSE Score				p-value*
	n	Mean Rank	Median	IQR	
Pneumonia	27	44.24	21	17–24	0.049
No pneumonia	81	57.92	25	19.5–27.5	

Note: \*Mann-Whitney U test, IQR, interquartile range; MMSE, Mini-Mental State Examination

hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and ischemic heart disease are known to be associated with the event of CSVD in patients as well as vascular cognitive impairment.<sup>12,13</sup> The medical history of hypertension may lead to the development of white matter lesions, which is also a predictor for cognitive decline. In diabetes patients, the accumulation of proinflammatory cytokines and adhesion molecules is related to CSVD.<sup>12</sup> Meanwhile the neurodegenerative process is mostly related to the lobar location of ICH, CSVD is mostly related to the deep location of ICH.<sup>7</sup> Both neurodegenerative process and CSVD are potentially associated with pre-ICH, acute-phase ICH, and long-term post-ICH cognitive decline.<sup>11</sup> This study unfortunately was only able to seek the cognitive outcome of acute-phase ICH patients.

A single-center study of cognitive outcomes in ICH patients found that the cognitive outcomes of patients in pneumonia and non-pneumonia groups were below the optimal cut-off of MMSE (<27), indicating that ICH patients as general had a poor cognitive outcome in the acute phase of the disease. In addition, a statistically significant difference was found when the cognitive outcome of ICH patients in both groups was compared. The MMSE median of the pneumonia group is lower than the non-pneumonia group, which denotes that the distribution of their cognitive outcome is lower than the non-pneumonia group. This result is parallel to the previous study which also reported worse functional outcomes in stroke patients with pneumonia complications at discharge.<sup>5</sup> Other studies also reported that the presence of infection in ICH patients lead to worse functional outcomes after 3 months, and the impact was greater in respiratory infection compared to urinary tract infection.<sup>3</sup> Particularly in cognitive functioning, pneumonia is related to a decline in cognition.<sup>10</sup> Stroke patients with pneumonia may have worse cognitive outcomes due to infection-induced inflammatory response, which is associated with the later occurrence of cognitive decline.<sup>14</sup> Other to inflammatory cascades, pneumonia patients may also experience hypoxia, which can disrupt neuronal physiology and lead to an increase in cell death numbers in the underlying stroke lesion. The presence of hypoxia is known to be associated with cognitive decline in patients.<sup>15</sup> However, this study did not observe the impact of such manifestation, and thus the exact consequences of hypoxia in ICH patients with pneumonia cannot be investigated.

Demographically, the gender distribution of the two groups showed that most of the subjects were female.<sup>5</sup> The slightly higher proportion of female patients in this study was a perchance due to the high exclusion number of male patients. However, this slight difference was found to be statistically insignificant. Moreover, the age distribution of included subjects in this study is lower in the pneumonia group, which is similar to the previous study conducted in New York, but different from the study conducted in England.<sup>3,5</sup> Although there was no statistically significant difference between both groups, this slight difference may occur due to the high number of exclusions for older patients in this study, especially in patients with pneumonia as a complication.

Other characteristics such as level of consciousness or GCS on admission, vascular risk factors, history of stroke, location of ICH, stroke severity, and ICH volume were also taken as these covariates may interfere with patients' outcomes.<sup>3,16-19</sup> In summary, patients with pneumonia had a slightly lower level of consciousness on admission, had a higher proportion of hypertension and dyslipidemia, had higher proportion of recurrent stroke, had a higher proportion of deep ICH location, had a higher NIHSS mean, and had lower ICH volume median, however, these differences were not statistically significant, similar to various studies.<sup>3,4,17</sup> In contrast, lower ICH volume in patient with pneumonia was in contrary to the result of the previous multicenter case-control study.<sup>3</sup>

Interestingly, of 108 patients in this study, 25% had developed pneumonia during ICH hospitalization, which is higher than in previous studies.<sup>3,5,17,20</sup> Although there were not statistically significant, overall slight proportion differences from patients' characteristics in this study support the high proportion of pneumonia in this study by providing the data of predictors and risk factors for pneumonia such as lower level of consciousness on admission, a higher proportion of deep ICH location, and higher NIHSS score in pneumonia group subjects.<sup>3,17</sup> Moreover, the higher proportion of recurrent stroke and higher stroke severity found in patients with pneumonia are also known as predictors for cognitive decline in ICH patients.<sup>16,19</sup> Other known predictors and risk factors for the development of cognitive decline in ICH patients such as older age, lobar ICH location, and ICH volume are found to be higher in patients without pneumonia.<sup>16,18</sup>

This study has several limitations, among others the feasibility of running the MMSE test at discharge that was limited to the patients' ability. Therefore, the measurement of cognitive outcome in patients with severe disability, low level of consciousness at discharge time, and older age tend to be difficult. Also, this study fails to exclude previous cognitive impairment before stroke onset due to a lack of available data. Other potential confounders to cognitive outcomes such as the presence of seizure, the degree of oxygen saturation, and other complications were also overlooked in this study.<sup>13,15</sup>

To conclude, ICH patients with pneumonia develop worse cognitive outcomes than patients without pneumonia. The worse cognitive outcome of patients within the pneumonia group tends to occur as the effect of the presence of pneumonia alone since the other characteristics between both groups showed no statistically significant difference. Therefore, more attention to preventive and curative measures for pneumonia in ICH patients is essential to improve patients' outcomes. A better understanding of the mechanism of cognitive decline in ICH patients with pneumonia is also substantial to maximize these efforts.

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