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Review Article

Neutrophil-lymphocyte ratio: A simple and accurate biomarker for the prognosis of patients with intracerebral bleeding, a study of 115 cases

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ABSTRACT

Background: Stroke is high in both mortality and disability; this makes stroke the world's second leading cause of death and the number one cause of long-term impairment. Surprisingly, intracerebral hemorrhage (ICH), the second largest type of stroke, is deadlier than ischemic strokes, with a high mortality rate and lack of effective treatment for ICH. This case report aims to identify and collect the various factors that increase the mortality rate of patients with ICH.

Methods: A retrospective review was done on 115 patients who experienced ICH at neurosurgical unit care between 2021 and 2024. Data were collected from medical record post admission reports. The study concentrated on factors such as the initial Glasgow coma scale (GCS) score, the volume of intracerebral bleeding, the ratio of neutrophils to lymphocytes, leukocyte count, and the administration of neuroprotective medications. We first ran univariate tests. Next, to evaluate the relationship between each component and patient mortality, we performed bivariate analyses with Spearman's correlation test. To determine the predictor factor from all the various variables that have been evaluated, we use multivariate analysis with logistic regression.

Results: Univariate analysis results show that ICH often occurs at the age of 41–50 years in males. Meanwhile, most of the patients who died were men aged 51–60 years. The results of the bivariate analysis showed that each predictor had a significant relationship with mortality. GCS has a negative relationship with mortality (−0.633 with $P < 0.001$). The neutrophil-to-lymphocyte ratio (NLR) (0.418), leukocyte count (0.527), and ICH blood volume (0.671) had a positive effect on ICH mortality. Multivariate analysis with logistic regression demonstrated that all predictor factors had a significant impact ($P < 0.05$) on mortality patients with hemorrhagic stroke. The most common neuroprotective therapy used in hemorrhagic stroke is the combination of citicoline and mecobalamin. The co-administration of citicoline and mecobalamin showed the highest number of survivors and deaths, indicating that no effective therapy for ICH has been found among all the neuroprotectants administered.

Conclusion: This study showed that GCS, ICH volume, leukocyte count, and NLR are predictors of mortality in ICH patients. At present, no ICH therapy can reduce complications and improve the physical and mental condition of ICH patients. Therefore, further research is needed to find an effective therapy for ICH.

Keywords: Glasgow coma scale (GCS), Leukocyte, Hematome, Neutrophil-to-lymphocyte ratio (NLR), Neuroprotektan

INTRODUCTION

Stroke is a clinical syndrome of focal or global neurological deficit that lasts more than 24 hours or causes death as a result of disorders or diseases of the cerebral blood vessels.[38] Intracerebral hemorrhage (ICH) is a subtype of stroke that is marked by bleeding that occurs in the brain after a rupture of the arteriole in the cerebral parenchyma.[49] Several risk factors contribute to ICH, including old age, hypertension, cerebral amyloid angiopathy, smoking, excessive alcohol intake, sympathomimetic drugs, anticoagulants, and antiplatelet drugs.[23]

Stroke is a major health issue that leads to both mortality and disability. It is the second most common cause of death in the world and the leading reason patients with stroke experience long-term physical and mental challenges. ICH, the second most common type of stroke, has a higher mortality rate than ischemic strokes, causing twice the number of fatalities.[30] About 10% of strokes are caused by intracerebral bleeding. Data sources from the Stroke Data Bank mention that at least 1 in 10 stroke cases is caused by cerebral parenchymal bleeding. Populations with high frequencies of hypertension, such as American-Africans and Chinese, Japanese, and Thai descendants, have a higher frequency of intracerebral bleeding. Intracerebral bleeding can occur over a wide age range, which can occur in decades 7, 8, and 9. Although the highest percentage of ICH cases is at the age of 40 years, intracerebral bleeding can also occur at a later age as well.[33]

The incidence of ICH in the Asian population is much higher than on any other continent. In addition, the incidence of ICH increases with age, with a marked difference in the age of 85 and over. Men have a higher risk of developing ICH than women, and the basal ganglia area is the most common location for ICH.[39] The mortality rate in Asia is high, with 40–54% of patients diagnosed with ICH dying every year, and after being exposed to ICH, only 12–39% can live independently in the long term.[2] Compared to its neighbors, the Philippines, Singapore, Brunei, Malaysia, and Thailand, Indonesia has a far higher stroke mortality rate, which makes Indonesia the country with the highest burden of stroke deaths in Southeast Asia. An estimated 500,000 Indonesians suffer strokes annually, and mortality is about 125,000. Of these cases, many of the survivors suffer from various forms of disability.[43] 10–15% of strokes in Indonesia are hemorrhagic strokes; this corresponds to an incidence rate of approximately 25 cases/100,000 individuals each year.[44]

Several factors increase the risk of mortality in ICH patients, including older age, larger blood clots (hematomas exceeding 30 cc), and bleeding within the fluid surrounding the brain (intraventricular hemorrhage [IVH]).[41] Previous studies have demonstrated a link between the initial Glasgow coma scale (GCS) score of patients and mortality after ICH. Higher GCS scores (above 8) show will have a lower rate of mortality, whereas lower GCS scorers (below 8) are more likely to experience problems or pass away during the first 2 days of therapy.[28] Furthermore, a GCS score of <7 and unequal pupil size, or anisocoria, were found to be significant predictors of death or impairment within 30 days in another study.[13] A more recent study revealed that the neutrophil-to-lymphocyte ratio (NLR) measured 72 h after admission is a reliable indicator of in-hospital death for patients with ICH.[32] This was further supported by another study that found a direct correlation between poor mortality and the 90-day outcome following ICH and high admission NLR levels. After ICH, NLR is a newly developed, widely accessible, and reasonably priced prognostic biomarker.[27] Sadly, there is currently no effective treatment available for ICH despite its high fatality rate.[42,47]

With a high mortality rate and lack of effective treatment for ICH, this case report aims to identify and collect the various factors that increase the mortality rate of patients with ICH. By analyzing this specific case, healthcare professionals can gain valuable insights and become more vigilant in monitoring ICH patients.

METHODS

This study was to identify and collect the various factors influencing the mortality of patients with ICH who were treated at RSUD M. Soewandhie between 2021 and 2023; a retrospective review was conducted. A total of 115 patients had their medical records examined. The study concentrated on factors such as the initial GCS score in the emergency department, volume of intracerebral bleeding, the ratio of neutrophils to lymphocytes (N/L), leukocyte count, and the administration of neuroprotective medications. Next, we looked at the relationship between each variable with mortality rates and determined the predictor factor.

This study employed Statistical Package for the Social Sciences Statistics 25 for statistical analysis. To get the lowest, maximum, and average values for each variable, we first ran univariate tests. Next, to evaluate the relationship between each component and patient mortality, we performed bivariate analyses with Spearman's correlation test. To determine the predictor factor from all the various variables that have been evaluated, we use multivariate analysis with logistic regression.

RESULTS

Univariate analysis

A study of the influence of factors on mortality was conducted on patients with hemorrhagic stroke who received treatment at M. Soewandhi Hospital, totaling 115 from 2021 to 2023. The patient profile can be seen in table 1.

Patients who died in the study sample were mostly between 41 and 50 years old (16 patients, 61.6%) and over 60 years old (16 patients, 61.6%). The majority of these patients were male (32 patients, 61.5%). The most common therapy profiles for deceased patients were citicoline and mecobalamin (33 patients, 63.5%).

On the other hand, the most common age group for surviving patients was 51–60 years old (33 patients, 52.4%). The most common gender among surviving patients was female (35 patients, 55.6%). The most common therapy profile for surviving patients was also citicoline and mecobalamin (48 patients, 76.7%).

The mean GCS score for patients who have passed away is 6.69, which is lower than the mean GCS score for patients who are still alive (12.51). The mean leukocyte count for patients who had passed away was noticeably greater than that of patients who were still alive (16927.50 vs. 11459.21). The same was observed for NLR and ICH volume. The mean NLR for deceased patients was 13.49, which is higher than the mean NLR for living patients of 6.70. Finally, the mean ICH volume for deceased patients was 35.01, which is higher than the mean ICH volume for living patients, 13.36. Details of the clinical data profile of the patients can be seen in table 2.

Table 1: Patient profile.

Patient profile	Alive		Deceased	
	n	%	*n*	%
Age				
≤30 years	1	1.6	0	0.0
31–40 years	3	4.8	6	11.5
41–50 years	8	12.7	16	30.8
51–60 years	33	52.4	14	26.9
>60 years	18	28.6	16	30.8
Gender				
Male	28	44.4	32	61.5
Female	35	55.6	20	38.5
Therapy				
No therapy	0	0.0	1	1.9
Citicoline	10	15.9	7	13.5
Mecobalamin	2	3.2	1	1.9
Piracetam	0	0.0	3	5.8
Citicoline and Mecobalamin	48	76.2	33	63.5
Citicoline and neurosanbe	3	4.8	6	11.5
Neurosanbe and mecobalamin	0	0.0	1	1.9

Bivariate analysis

Bivariate analysis was conducted on each factor in relation to the mortality that occurred. The analysis was performed using Spearman's rank correlation analysis because the mortality data are nominal in scale. The results of the bivariate analysis are presented in the table 3.

Analysis of the relationship between 4 predictor factors and mortality, as shown in Table 3, concluded that there was a significant relationship. The relationship between the GCS factor and mortality was the only one that differed from the other factors, with a significant negative relationship. The correlation coefficient of r between GCS and mortality was −0.633 with $P < 0.001$, indicating a strong relationship with a negative direction, it's means the lower the GCS score, the higher the mortality.

In the meantime, there is a strong positive correlation between mortality and the other three parameters. The NLR factor, with a coefficient of r 0.418, showed a moderate positive relationship, and the leukocyte and ICH volume factors, with coefficients of r 0.527 and 0.671, showed strong positive relationships. The results of the relationship between the four factors showed that the higher the leukocyte, NLR, and ICH volume values, the higher the probability of patient death.

Multivariate analysis

The results of the previous bivariate analysis concluded that all predictor factors have a significant relationship with mortality. Therefore, all predictor factors will be used in the multivariate analysis to determine the predictors of mortality. The results of the multivariate analysis on mortality in patients with hemorrhagic stroke with a sample of 115 can be presented as follows:

Multivariate analysis with logistic regression demonstrates that all predictor factors had a significant impact ($P < 0.05$)

Table 2: Clinical data profile of patients.

Clinical data	Alive		Deceased	
	Min-Max	Mean±SD	Min-Max	Mean±SD
GCS	3–15	12.51±3.53	2–15	6.69±3.55
Leukocyte	6450–19980	11459.21±3228.41	8510–33530	16927.50±5918.02
NLR	0.61–18.77	6.70±4.12	0.99–42.75	13.49±8.99
ICH	0.10–100	13.36±19.58	10–101	35.01±28.36

GCS: Glasgow coma scale, ICH: Intracerebral hemorrhage, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation

Table 3: Spearman rank correlation.

Mortality predictive factor	Rank spearman		Description
	r	*P*-value	
GCS	−0.633	<0.001	Significant
Leukocyte	0.527	<0.001	Significant
NLR	0.418	<0.001	Significant
ICH volume	0.671	<0.001	Significant

GCS: Glasgow coma scale, ICH: Intracerebral hemorrhage, NLR: Neutrophil-to-lymphocyte ratio, r: Spearman's correlation coefficient

Table 4: Logistic regression predictors of mortality.

Predictor factor	β	*P*-value	OR	CI 95%
GCS	−0.308	<0.001	0.735	0.632–0.856
Leukocyte	0.00024	0.006	1.000	1.000–1.000
NLR	0.115	0.019	1.122	1.020–1.235
ICH volume	0.031	0.015	1.031	1.006–1.058

OR: Odds ratio, CI: Confidence interval, GCS: Glasgow coma scale, ICH: Intracerebral hemorrhage, NLR: Neutrophil-to-lymphocyte ratio

on mortality patients with hemorrhagic stroke[Table 4]. It can be concluded that GCS, leukocyte count, NLR, and ICH volume are significant predictors of mortality in patients with hemorrhagic stroke.

The predictor factor GCS captured a β coefficient value with a negative direction, indicating that the GCS factor has a negative effect on the mortality of hemorrhagic stroke patients. It means the lower the GCS score, the higher the mortality rate. The odds ratio (OR) value for the GCS factor is 0.737, this showed that the lower the patient's GCS score, the 1.361 times more likely the patient is to die compared to when the patient's GCS score is higher.

Predictor factors of leukocyte count get a positive coefficient β, indicating that leukocyte count has a significant positive effect on the mortality of hemorrhagic stroke patients. This means that the higher the patient's leukocyte count, the higher the mortality rate. The OR value for the leukocyte count factor was 1.000240, which reveals that for every increase in the patient's leukocyte count, the risk of death is 1.000240 times higher than for a decrease in the patient's leukocyte count.

The predictor factors of NLR were obtained with a positive β coefficient value, indicating that the NLR factor has a significant positive effect on the mortality of hemorrhagic stroke patients. This means that the higher the NLR value of the patient, the higher the mortality rate. The OR value for the NLR factor was 1.122, indicating that for every increase in the NLR value of the patient, the patient's risk of death is 1.122 times higher compared to when the NLR.

Predictors of ICH volume were found to have a positive β coefficient, indicating that ICH volume has a significant positive effect on mortality in patients with hemorrhagic stroke. This means that the higher the ICH volume, the higher the mortality rate. The OR for ICH volume was 1.032, indicating that for every unit increase in ICH volume, the risk of death is 1.031 times higher.

DISCUSSION

The study revealed that the highest incidence of ICH occurred in the 51–60 age group with 47 patients; 14 of 47 patients are deceased. Male is the most common gender affected by ICH. The results of this study are in line with other studies that have shown the incidence of postictal seizure (PIS) increases significantly faster in the 18–44 and 45–64 age groups.[5] This is further strengthened by research in France that found an increased incidence of ICH in the 45–64 age group.[31] Older patients are more likely to have ICH because age increases the likelihood of systemic diseases such as diabetes, hypertension, and atrial fibrillation, as well as chronic illnesses, all of which can add to the pathophysiology of ICH.[40]

The highest mortality rate occurs in the 41–50 age group and patients over 60 years old. Males have a higher mortality rate when ICH happens. These results are also supported by other studies that show that death from ICH often occurs at older ages (over 67 years old).[20] This is supported by other studies that showed that compared to those under 65, those 65 years of age or older have a lower surgical intervention rate (16.00% vs. 43.33%) but a higher death rate (60.00% vs. 26.67%).[19] Mortality among the elderly is greater because the elderly often come with comorbidities such as atrial fibrillation, hypertension, diabetes mellitus, and renal diseases.[29] Although elderly patients were more likely to die from a stroke, the severity of the stroke typically lessened while they were in the hospital. One explanation is that older people are more likely to have brain atrophy, which gives the brain more space for compensatory growth. Hematoma volume and IVH have minimal effects on patient prognosis since they do not significantly alter intracranial pressure in older individuals. Elderly patients will simultaneously have a general decrease in the inflammatory immune response due to "immunosenescence," and secondary brain damage from hematomas may also be lessened.[46]

The Hemphill ICH score has proven to be a reliable indicator of spontaneous ICH (SICH) prognosis despite the development of several other measures for predicting functional outcomes and mortality following ICH. The functional status score (FUNC) also accounts for the presence of preICH cognitive impairment, whereas the Essen ICH score is based solely on clinical factors (age, degree of consciousness, and severity of neurological impairments). This means that the Essen ICH score has the advantage of not requiring the measurement of ICH volume.[11] In this study, we use GCS, leukocyte levels, NLR, and ICH volume as predictors of mortality rate, and our study shows that all factors are significant predictors in predicting the mortality of bleeding stroke patients where NLR is the most cost-effective and readily accessible biomarker for predicting ICH outcomes.

The GCS score can give a picture of a patient's clinical condition on arrival at the emergency room (ER) and can be a factor in determining the prognosis of ICH patients. This study found that the lower the GCS score, the higher the risk of death. The OR for the GCS factor was 0.737, suggesting the risk of death is 1/0.735 = 1.361 times higher for patients with a lower GCS score compared to those with a higher GCS score. This is consistent with other studies that showed ICH patients who die have a lower GCS score on arrival at the ER.[24] Furthermore, other studies have shown that the GCS score can be a predictor of mortality in ICH. Patients with a GCS score of <5 when arrival at the emergency department have a high 30-day mortality rate.[16] Other studies have shown that a GCS score of <10, in combination with other parameters such as hematoma volume >44.55 cm^3 and IVH, can be used as a predictor of mortality in ICH patients.[4]

Hematoma volume is a crucial factor in all ICH prognostic scores and has been shown to be the best independent predictor of clinical outcome after SICH.[15] This study demonstrates that the higher the ICH volume, the higher the mortality rate. The OR for the ICH volume factor is 1.032, indicating that for every unit increase in ICH volume, the patient's risk of death increases by 1.031 times. Studies showed that patients with hematoma volumes <30 mL have a 30-day mortality rate of <20%, but volumes >60 mL are linked to a mortality rate of more than 90%. At 30 days, patients who had hematoma volumes larger than 30 mL were more likely to be functionally dependent.[12] This is further supported by another literature that shows that patients who bleed more than 20 cc are 0.154 times more likely to die from a stroke than patients who bleed <20 cc due to compression of vital brain stem structures.[3] Other research explains that the mortality rate of ICH varies by location. All patients with a pontine hemorrhage >5 cm^3 or cerebellar hemorrhage >30 cm^3 died within 30 days.[6] A large volume of hematomas increases the mortality rate because ICH may lead to a midline shift, which, if severe, can result in herniation and compression of critical structures in the brainstem, ultimately leading to death.[7]

Leukocyte count was also demonstrated to be correlated with death rates in this investigation. The mortality rate increases with leukocyte count. The leukocyte count OR was 1.000240, meaning that the chance of dying increased by 1.000240 times with each rise in leukocyte count. This is probably due to the fact that increased leukocyte counts have been linked to the development of hematomas and early neurological decline.[21]

NLR is the amount of neutrophils divided by the total number of lymphocytes in peripheral blood.[35] The N/L ratio in peripheral blood indicates inflammatory conditions in the patient's body.[17] Research has been done on the significance of NLR as a prognostic marker for cancer, stroke, and myocardial infarction. NLR of >5 has been linked to an increased risk of death, according to some evidence.[18] According to the majority of research, a higher NLR of more than 5–7 is associated with a worse prognosis. According to certain research, a healthy adult's typical NLR ranges from 0.78 to 3.53.[8] Recent research has demonstrated a clear correlation between inflammation and the risk of stroke. Although post-stroke inflammation is detrimental to brain damage, it may be beneficial for tissue regeneration and repair.[22] Both the systemic inflammatory response and the local central nervous system will become active following intracerebral bleeding. Within an hour after an ICH, neutrophils are the first type of white blood cells to actively migrate from the bloodstream into the brain. The production of inflammatory and cytotoxic mediators by infiltrating leukocytes promotes capillary permeability, cell swelling, and disruption to the blood–brain barrier, all of which worsen the perilesional edema.[25] Neutrophil infiltration surrounding brain tissue started as early as 8 h after hemorrhage in a population-based investigation of ICH. It is thought that lymphopenia is the primary indicator of brain injury during the acute stage of ICH. Lymphopenia is caused by apoptosis and inactivation of lymphocytes; these events are mostly brought on by catecholamines and steroids generated by sympathetic and hypothalamic-pituitary-adrenal axis activity.[45]

Recently, NLR has been used as an assessment to evaluate patient mortality rates, and numerous clinical models of brain disorders have confirmed the NLR's prognostic power for clinical outcomes.[36] In this study, NLR also showed a significant association with mortality. High NLR was associated with high mortality rates. The OR for the NLR factor was 1.122, indicating that the higher the patient's NLR, the 1.122 times more likely the patient will die compared to when the patient's NLR is lower. This is supported by other studies that greater neutrophil and lower lymphocyte counts correspond with a worse 3-month functional outcome, and the NLR is linked to both a worse functional outcome and a greater death rate. The NLR is also connected with both short- and long-term outcomes and mortality.[34] An analysis of the association between NLR and the long-term prognosis in patients with ICH discovered that NLR was an independent predictor of 180-day death and morbidity in cases of SICH.[9] This association between NLR and mortality can be explained by understanding NLR; after ICH occurs, the NLR is thought to reflect the equilibrium between the immune system and the systemic inflammatory response.[37] Moreover, elevated NLR levels are also associated with increased hematoma expansion, which further leads to brain tissue damage and increased mortality.[18] Another study suggested that the following reason could be the cause of the higher NLR correlation and higher mortality in ICH patients: First, neutrophils would disrupt the blood–brain barrier and cause neurological damage after ICH, which could further result in transient immunological suppression and lymphocytopenia. Consequently, the chance of infection would rise due to lymphocytopenia, ultimately leading to death. Thus, in ICH patients, a high level of NLR predicted an increased death rate. Second, the elevated levels of WBC, CRP, and NLR may indicate an exacerbation of the inflammatory condition, and this could lead to the enlargement of hematoma following ICH. The enlarged hematoma would then cause cerebral pressure, which would ultimately cause death.[10] Thus, NLR can be a predictor of hematoma expansion in patients with ICH.[1] By stopping the growth of hematomas and the release of inflammatory chemicals from them, surgery can intervene in the pathological processes that follow the start of the disease.[14]

This study has shown that the most common neuroprotective therapy used in hemorrhagic stroke is the combination of citicoline and mecobalamin. The co-administration of citicoline and mecobalamin showed the highest number of survivors and deaths, indicating that no effective therapy for ICH has been found among all the neuroprotectants administered. Other studies also highlight that no effective drugs have been developed for clinical use due to the complexity of ICH pathology.[48] According to another study, there is no FDA-approved medication or effective therapy that can help brain hemorrhage patients' physical or mental health.[26]

CONCLUSION

ICH is a subtype of stroke with a high mortality rate. This study showed that GCS, ICH volume, leukocyte count, and NLR are predictors of mortality in ICH patients. At present, no neuroprotector therapy for ICH can reduce complications and improve the physical and mental condition of ICH patients. Therefore, further research is needed to find an effective therapy for ICH.

Ethical Approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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