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Relationship between estimated glomerular filtration rate and severity of intracerebral hemorrhage

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Abstract. *Background and aim:* The effect of estimated glomerular filtration rate (eGFR) on intracerebral hemorrhage (ICH) severity is rarely studied. Meanwhile, the National Institute of Health Stroke Scale (NIHSS) is the gold standard scale for assessing stroke severity. Therefore, this study aimed to determine the relationship between eGFR and ICH severity. *Methods:* A cross-sectional study was conducted at Dr. Wahidin Sudirohusodo General Hospital. eGFR values were divided into 4 levels namely severe, moderate, mild, and normal, while the severity of stroke based on NIHSS was mild (<5), moderate (6–14), and severe (>15). Analysis to compare eGFR group values with NIHSS used chi-square analysis, and a p-value <0.05 was considered significant. *Results:* The results showed that the participants were mostly aged 45-70 years and male. Bleeding mostly occurred in the upper part of the brain (supratentorial) by 89.1%. The mean eGFR of participants was 84.65 mL/min/1.73 m² and the severity based on the NIHSS score ranged from 2-28. Furthermore, there was a significant relationship between eGFR values and NIHSS scores (p<0.001). Decreased eGFR tended to be associated with higher NIHSS indicated by a p-value of 0.018.*Conclusions:* Based on the results of this study, eGFR has a relationship with the severity of ICH. (www.actabiomedica.it/)

Key words: stroke, intracerebral hemorrhage, chronic kidney disease, national institutes of health stroke scale, estimated glomerular filtration rate

Introduction

The incidence of hemorrhagic stroke is estimated at 12-15% of cases per 1,000,000 population per year. The occurrence in males is higher than in females with a tendency to increase at age above 55 years and having a relative risk after 70 years (1). Mortality due to intracerebral hemorrhage (ICH) remains high at 50% on the 30th day (2). Chronic Kidney Disease (CKD) also increases the risk of ICH and micro bleeding from the brain, where estimated glomerular filtration rate (eGFR) values <45 mL/minute/1.73 m2 indicate a 3-fold greater risk of increased hematoma volume which can cause death (3).

The occurrence of hemorrhagic stroke includes various events that cause primary and secondary brain injury (4,5). Primary brain injury occurs due to the mass effect (edema) and mechanical disruption of the bleeding blood while secondary brain injury occurs due to toxic biochemical effects and metabolic effects in response to the bleeding components (6). Edema that occurs after ICH can reduce the clinical outcome of patients (6–8).

In assessing a person level of consciousness, the Glasgow Coma Scale (GCS) can be used to objectively determine impaired consciousness (9). The National Institute of Health Stroke Scale (NIHSS) is the gold standard scale for assessing stroke severity. Initial

NIHSS values correlate with early and long-term clinical outcomes, response to therapy, neurological decline, and mortality (10). It has been reported that ICH mortality can be better predicted using NIHSS than GCS. An increase in NIHSS scores on admission has a negative impact on ICH outcomes. There are NIHSS score categories, with a score of ≤ 5, 6-14, and ≥ 15 representing mild, moderate, and severe stroke respectively (11).

eGFR is a clinical measurement used to assess kidney function and diagnose CKD. It is calculated using serum creatinine levels, age, gender, and race (12). The values have rarely been studied to evaluate ICH and are a significant predictor of clinical outcomes. Studies have shown that lower eGFR levels correlate with increased mortality (13), poor outcomes (14), and higher complication rates (15). These associations underscore the importance of kidney function in the prognosis of ICH. Therefore, this study aimed to determine the relationship between eGFR and the severity of ICH.

Materials and Methods

This cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar in 2024 with 55 participants who met the inclusion criteria. The inclusion criteria for this study were the population whose first stroke symptoms appeared suddenly (onset less than 7 days) aged 18 years to 80 years in the South Sulawesi region who were admitted through the Emergency Room at our institution. The patient's educational background varies from elementary school to college. Apart from that, the employment status of the research subject is employee or self-employed. Exclusion criteria included patients under the age of 18 years, onset of ICH more than 7 days, as well as history of recurrent stroke, CKD, severe systemic disease, malignancy, and autoimmune disease.

Determination of stroke patients

Stroke was confirmed by anamnesis in the form of a focal neurological deficit (impaired motor function, for example, weakness in the extremities or sensory function) that occurred suddenly on neurological examination. It was supported by the results of a computed tomography (CT) scan with Siemens Somatom Go Top 128 Slice (Erlangen, Germany) of the head without contrast, showing a hyperdense image indicating cerebral hemorrhage in the brain tissue.

Variables and degree of severity

Participants data included age, gender, bleeding location, GCS score, comorbidities (hypertension, diabetes mellitus, and smoking), eGFR, and NIHSS. Severity refers to the change in health level, function, and quality of life assessed by the NIHSS score at hospital admission with values of mild (<5), moderate (6–14), and severe (>15).

Kidney function evaluation

eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (12). The CKD-EPI formula (2021 revision) used is GFR = 141×min(Scr/k,1) α × max(Scr/k,1) -1.209× 0.993age × 1.018 [in women] × 1.159 [in black], where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is 0.329 for women and -0.411 for men, min indicates minimum Scr/k or 1, and max indicates maximum Scr/k or 1. The different levels include severe (<45 mL/min), moderate (45–59 mL/min), mild (60–89 mL/min), and normal (≥90 mL/min).

Glasgow coma scale

The Glasgow Coma Scale is a quantitative examination of the degree of consciousness of research subjects. The assessment component includes 3 elements: eye (E), motor (M) and verbal (V). Component E is given a value of 1-4, M scores 1-6, and V scores between 1-5. GCS score is the sum of the scores of each component, so the minimum value is three, and the maximum 15 (9).

National institute of health stroke scale

The National Institute of Health Stroke Scale (NIHSS) is the gold standard for assessing stroke severity. At admission, motor, sensory, and cognitive function

change scores comprise 11 assessment components. In this study, it is used to indicate the degree of severity (16).

Statistical Analysis

Continuous variables are presented as appropriate means and categorical variables as proportions. The collected data were processed using SPSS software (version 26), in which normality was tested with Kolmogorov-Smirnov. The relationship between eGFR and severity was tested using the Pearson correlation test, where the value range is -1 to 1. The positive or negative sign indicates the direction of the relationship. It is said to have a strong relationship if the value is close to 1. eGFR group values were compared to NIHSS using chi-square analysis, and a p-value <0.05 was considered significant.

Results

Characteristics of participants

Among the 63 patients with ICH included in the study, 8 died after follow-up and were excluded. Table 1 shows the results of the characteristics of the study participants.

As shown in Table 1, the mean age of participants was 53.35 years, with the majority falling within the age range of 45-70 years (60.0%). A total of 36 patients (65.5%) were males, and the location of the most bleeding was supratentorial, namely 89.1%. The degree of consciousness based on the GCS scale ranged from 3-15. In terms of consciousness, 32 patients (58.2%) were in a state of compos mentis.

The most common risk factors were hypertension at 80% followed by smoking at 45.5%. The mean eGFR was 84.65 mL/min/1.73 m² while the severity based on NIHSS score was between 2–28. Analysis was performed by grouping all patients based on eGFR values. In general, 6 patients were classified as severe eGFR group (Table 2).

Table 2 shows the characteristics of the study participants against the eGFR value. The mean age of patients with severe disease was 55.33 years (SD±18.47).

Table 1. Characteristics of study participants.

Variables	Results
Age (years, mean ± SD)	53.35 ± 13.59
18-45	16 (29.1)
45-70	33 (60.0)
>70	6 (10.9)
Sex	
Male	36 (65.5)
Female	19 (34.5)
Bleeding Location	
Supratentorial	49 (89.1)
Infratentorial	6 (10.9)
GCS score,	15 (3–15)
median (min-max)	32 (58.2)
Compos Mentis	0 (0)
Somnolence	14 (25.5)
Delirium	9 (16.4)
Diabetes Mellitus	
Yes	8 (14.5)
No	47 (85.5)
Hypertension	
Yes	44 (80.0)
No	11 (20.0)
Smoke	
Yes	30 (54.5)
No	25 (45.5)
eGFR (mean±SD)	84.65 ± 31.16
NIHSS median (Min-Max)	(2–28)

Note: GCS, Glasgow Coma Scale; eGFR, estimated glomerular filtration rate; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

The majority aged 18-45 years fell within the normal category (21.8%), while those aged 45-70 years were spread across all categories, with the largest proportion in normal (30.9%). Patients over 70 years were mostly in the mild category (5.5%) and males were more in the normal category (36.4%). Female patients were spread across all categories, with the largest proportion in the normal.

Most patients with supratentorial hemorrhage were in the normal category (47.3%). Infratentorial locations were spread across all categories but were fewer

Table 2. Characteristics of study participants regarding eGFR values.

Variables	Results			
	Severe	**Moderate**	**Mild**	**Normal**
Age (years, mean ± SD)	55.33 ±1 8.47	60.60 ± 12.34	59.20 ± 12.41	48.66 ± 12.05
18-45	2 (3.6)	0 (0)	2 (3.6)	12 (21.8)
45-70	3 (5.5)	3 (5.5)	10 (18.2)	17 (30.9)
>70	1 (1.8)	2 (3.6)	3 (5.5)	0 (0)
Sex				
Male	2 (3.6)	3 (5.5)	11 (20.0)	20 (36.4)
Female	4 (7.3)	2 (3.6)	4 (7.3)	9 (16.4)
Bleeding Location				
Supratentorial	5 (9.1)	4 (7.3)	14 (25.5)	26 (47.3)
Infratentorial	1 (1.8)	1 (1.8)	1 (1.8)	3 (5.5)
GCS score, median	12.5 (3–15)	9 (3–15)	11 (6–15)	15 (3–15)
(min–max)	3 (5.5)	2 (3.6)	5 (9.1)	22 (40.0)
Compos Mentis	0 (0)	0 (0)	0 (0)	0 (0)
Somnolence	2 (3.6)	1 (1.8)	7 (12.7)	4 (7.3)
Delirium	1 (1.8)	2 (3.6)	3 (5.5)	3 (5.5)
Diabetes Mellitus				
Yes	0 (0)	0 (0)	1 (1.8)	7 (12.7)
No	6 (10.9)	5 (9.1)	14 (25.5)	22 (40.0)
Hypertension				
Yes	6 (10.9)	3 (5.5)	12 (21.8)	23 (41.8)
No	0 (0.0)	2 (3.6)	3 (5.5)	6 (10.9)
Smoke				
Yes	3 (5.5)	4 (7.3)	8 (14.5)	15 (27.3)
No	3 (5.5)	1 (1.8)	7 (12.7)	14 (25.5)
eGFR (mean±SD)	25.5 ± 19.02	54.28 ± 5.40	74.71 ± 8.58	107.27 ± 16.41
NIHSS, median (Min-Max)	16.5 (8–28)	10 (3–27)	16 (2–27)	7 (2–24)

Note: *Pearson Correlation Test; GCS, Glasgow Coma Scale; eGFR, estimated glomerular filtration rate; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

than supratentorial. Most patients with compos mentis conditions were in the normal category. Patients with a history of diabetes mellitus (DM), hypertension, and smoking were mostly in the normal category, with values of 12.7%, 41.8%, and 27.3% respectively.

The highest mean eGFR was in the normal category, at 107.27 mL/minute/1.73 m², and the lowest was in the severe category, at 25.5 mL/minute/1.73 m². The eGFR values showed a decreasing trend as the disease severity category increased. The highest median NIHSS score was in the severe category, at 16.5 (with a range of 8-28). The NIHSS score decreased in the milder categories with the lowest value in the mild category (median 7, range 2-24).

Analysis of the relationship between eGFR values and NIHSS scores

There was a significant negative relationship between the eGFR and NIHSS scores. The correlation

coefficient (R) value of -0.501 indicates a moderate negative correlation, suggesting that the lower the eGFR value, the higher the likelihood of severity. Furthermore, a very small p-value (<0.001) indicates that the relationship is statistically significant at a high confidence level. This suggests that decreased eGFR may be associated with increased risk or severity of the condition (Table 3).

Comparison between eGFR and NIHSS Group

Table 4 shows that most patients with mild NIHSS scores had normal eGFR (21.85), indicating better kidney function. In severe NIHSS, most patients were in the mild eGFR category (14.4%), followed by the normal (3.6%) as well as severe and moderate groups with proportions of 5.5% and 3.6%, respectively. This suggests that decreased eGFR tends to be associated with increased stroke severity (higher NIHSS).

The p-value of 0.018 indicates that there is a statistically significant difference in the distribution of NIHSS based on eGFR categories. Therefore, decreased kidney function may be associated with higher stroke severity.

Discussion

In this study, the majority of patients were in the age range of 45-70 years (60%). Population studies from 1990-2021 showed an increasing trend in incidence and prevalence in Southeast Asia, East Asia, and Oceania after 2015, where 70.2% of people experienced a new stroke (17). Although stroke can affect people of all age groups, the incidence is more common in the elderly with an incidence that doubles in the age group over 55 years (18). The results showed that the number of males experiencing ICH was greater than females (65.5% vs 34.5%). A study conducted by Feign et al in 2023 found that males of productive age had a higher risk than females (19). Males have a 1.60 times greater risk of suffering a stroke than females. In males, stroke occurs more often due to the presence of the hormone testosterone which can increase blood LDL levels (20). Similar results were also shown in the study by Wang, et al who reported that more than 2/3 of patients were males. The decrease in GFR tended to be more significant in patients with a mean age of 61.4 years than in other groups (21).

The majority (85.5%) of patients did not suffer from type 2 DM, 80% suffered from hypertension, and 54.5% were smokers. Diabetes, male gender, history of alcohol consumption, underweight, and black or Hispanic race are also risk factors (22). Chronic hypertension and aging are associated with the incidence of spontaneous ICH. Specifically, chronic hypertension causes degenerative arterioles which will eventually lead to a Charcot-Bouchard aneurysm. Smoking habits, history of drug abuse, and uncontrolled hypertension are also included in the category of modifiable risk factors for ICH (23). History of statin use is also a risk factor (24) and similar results were also found in a study by Mayerhofer, et al. In this study, 86.2% of patients had hypertension, while only 23.4% had diabetes. In general, diabetes and hypertension, as well as smoking, can also increase the risk of cardiovascular and cerebrovascular disorders (25)

Table 3. Analysis of the relationship between eGFR values and NIHSS scores.

Variables	R	P
eGFR	-0.501	<0.001

Note: *Pearson Correlation Test; eGFR, estimated glomerular filtration rate.

Table 4. Comparison between the eGFR and NIHSS group.

NIHSS	Egfr				P
	Severe	Moderate	Mild	Normal	
Light	0 (0)	1 (1.8)	2 (3.6)	12 (21.8)	0.018
Medium	3 (5.5)	2 (3.6)	5 (9.1)	15 (27.3)	
Heavy	3 (5.5)	2 (3.6)	8 (14.5)	2 (3.6)	

Note: * Chi-square analysis; eGFR, estimated glomerular filtration rate; NIHSS, National Institute of Health Stroke Scale.

ICH has a significant correlation with tobacco use and according to a study by Cho et al., smoking increases the risk by 1.7x. Young smokers are also often associated with a high prevalence (26). The most common bleeding location was supratentorial hemorrhage (89.1%). Supratentorial ICH has a fairly high prevalence (15-30%) as one of the causes of stroke in the world and is among the highest causes of death (27). The next characteristic is the Glasgow Coma Scale (GCS) score, and in this study, the median result was (15) with the highest GCS level, namely compos mentis (58.2%). GCS is another important indicator used in assessing the severity of stroke/other ICH, apart from NIHSS. A low GCS score can also indicate poor outcomes in patients (28).

In assessing the severity of stroke or brain hemorrhage, several indicators can be used, ranging from eGFR to NIHSS. The mean eGFR value obtained in this study was 84.65 ± 31.16. Similar results were obtained in a study by Fukuda-Doi where the median eGFR value did not differ in patients after ICH. However, eGFR may be associated with subsequent events, up to death which can be predicted based on a decrease in the value. The risk of death can be predicted when the eGFR value is <60 mL/minute/1.73 m2. This study showed that the median NIHSS value was 10 (2-28). The mean NIHSS score in other studies was 5-15 in 51 patients, tended to be severe in 36 patients, and very severe in 28 patients. NIHSS can also be associated with worsening patient conditions when very severe values are found (11,29)

eGFR is the best global index to assess kidney function (Cusumano et al., 2021; Levey et al., 2011; Mihardja et al., 2018). The calculation of eGFR values used the CKD-EPI formula which provides more accurate results in the Asian population (Wang et al., 2014). In this study, eGFR values can be divided into 4 categories, namely <45, 45-59, 60-89, and > 90 mL/minute/1.73m^2. The severe, moderate, mild, and normal groups consisted of 6, 5, 15, and 29 patients respectively, with the highest mean age of patients occurring in the moderate group. Different results were found in gender, males tended to have normal GFR values and mild eGFR (56.4%) compared to other groups. Another study by Shemilt et al. showed that males tend to experience a faster decline in eGFR values than females, especially when there is multiorgan failure or a smoking habit (30).

ICH Patients with low eGFR values have a 5.5 times higher risk of death within 1 month and a 7.5 times higher risk within 1 year compared to those with normal values. Furthermore, ICH patients with high NIHSS values have a risk of impaired renal function, which leads to larger hematoma sizes (31). Intensive systolic blood pressure lowering therapy has also been shown to increase this risk in patients with low eGFR, while those with eGFR above 60 mL/min/1.73 m^2 did not show the same result. Several shared vascular risk factors including hypertension, diabetes, and dyslipidemia, as well as CKD-specific mechanisms namely coagulation disorders, endothelial dysfunction, chronic inflammation, and oxidative stress, may play a role (29).

Impaired renal function is an independent risk factor for mortality in patients with progressive ICH with eGFR levels serving as a prognostic indicator (21). Renal function is independently associated with the incidence of ICH after IV rtPA thrombolysis in ischemic stroke patients. Furthermore, renal dysfunction is an independent predictor of Secondary ICH according to the National Institute of Neurological Disorders and Stroke (sICHNINDS) and symptomatic ICH by the European Cooperative Acute Stroke Study II (sICHECASS II) criteria. This condition should be considered when evaluating the risk of intravenous thrombolysis with IV rtPA (32).

This study conducted an analysis related to the location of bleeding and eGFR results. The results showed that supratentorial bleeding locations often occurred in patients with mild or normal eGFR deficiency. The GCS score tended to be the lowest in the moderate eGFR compared to other groups. However, the score tended to be lower in the mild compared to the severe eGFR group. Several other studies have shown that renal dysfunction can be correlated with the location of ICH bleeding, while a study suggested deeper locations tend to have higher rates of renal dysfunction (33) GCS scores and comorbidities also correlate with the severity of eGFR. In patients with chronic diseases such as DM and HT, there may be a

brief decrease in eGFR indicating a decrease in renal function. This can be explained by a decrease in glycemic control and acute neuropathy. eGFR was considered a clinical marker to predict clinical outcomes on the 30th day after acute ischemic stroke (13,34)

The correlation between eGFR and NIHSS scores was analyzed using the Pearson and the chi-square tests with the results showing significant results ($p < 0.001$). Based on the chi-square test, a significant correlation was obtained ($p < 0.05$) between the eGFR and NIHSS groups. eGFR is the best global index for assessing kidney function. Calculation of eGFR can be carried out using the CKD-EPI formula which tends to be more accurate in the Asian population. The mean eGFR value was 59.90 mL/minute / 1.73 m^2 with the highest ranging from 45-59 mL/minute / 1.73 m^2. According to Billi, et al., eGFR values can have a significant correlation with clinical outcomes in ischemic stroke patients, which may also be assessed using the NIHSS severity level (13,34).

ICH potentially triggers AKI through several complex and interrelated mechanisms. The main mechanisms are exaggerated sympathetic response and hypertension leading to the release of catecholamines, such as adrenaline and noradrenaline, which increase blood pressure and cause renal vasoconstriction. This vasoconstriction reduces blood flow to the kidneys known as renal hypoperfusion. Activation of the Renin-Angiotensin-Aldosterone System (RAAS) causes increased vasoconstriction as well as sodium and water retention, thereby increasing systemic blood pressure and reducing renal perfusion. ICH triggers a systemic inflammatory response, with the release of proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β that promote local inflammation, leading to impaired renal cell function, reduced glomerular filtration, and increased risk of AKI. Furthermore, antidiuretic hormone (ADH) dysfunction causes excessive fluid retention and electrolyte imbalance, especially sodium, which directly affects kidney function. This condition can cause cerebral edema and fluid imbalance that worsens kidney damage. Disruption of the blood-brain barrier and other organ damage worsens the inflammatory process and increases the risk of toxic substances entering the kidney. When the blood-brain barrier is disrupted, inflammatory substances, cytokines, and metabolic products can reach the kidney and increase tissue damage (13,34). A limitation of this study is that it was conducted at a single institution and did not assess clinical outcomes.

Conclusion

In conclusion, this study found a relationship between eGFR and the severity of ICH. Multicenter studies are needed to reduce bias and further examine the relationship between eGFR and clinical outcomes of patients with ICH.

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