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Estimated Glomerular Filtration Rate (eGFR) as a Predictor of 1-Month Clinical Outcome in First-Ever Acute Ischemic Stroke Patients

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ABSTRACT

Introduction: Renal dysfunction is a new risk factor that is thought to influence the clinical outcome of acute ischemic stroke. In this case, the estimated glomerular filtration rate (eGFR) value is used as an approach to assess kidney function status in acute ischemic stroke patients. This study aims to find the relationship between eGFR and clinical outcomes of acute ischemic stroke.

Method: 70 samples were obtained according to inclusion criteria. eGFR is calculated within first week of stroke onset using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. A normality test was carried out on the data, then determined the correlation and compared eGFR with good [modified Rankin Scale (mRS) 0-2] and poor (mRS 3-6) clinical outcomes on the 30th day.

Results: In this study, the average age of the sample was 61.37 years. The largest population was in the 45-59 mL/min/1.73 m2 eGFR group (38,6%). The mean eGFR ($p<0.001$) for all samples, good, and bad outcome groups was respectively 59.90 ± 21.09, 79.79 ± 19.21, and 52.49 ± 16.57. In this study the poor outcome group had a lower mean eGFR than the good outcome group (52.49 mL/min/1.73 m2 vs 79.79 mL/min/1.73 m2), with a cut-off value of 62 mL/min/1.73 m2 (sensitivity 80.39%, specificity 84.21%) tended to have worse clinical outcomes.

Conclusion: Based on the results of this study, eGFR has a relationship with clinical outcomes ($p<0.001$) and can objectively predict clinical outcomes on the 30th day of acute ischemic stroke.

Keywords

Stroke, Chronic kidney disease epidemiology collaboration, CKD-EPI, Modified rankin scale, mRS, Estimated glomerular filtration rate, eGFR

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INTRODUCTION

Stroke is an acute clinical syndrome associated with vascular injury of the central nervous system. Stroke is the main cause of physical disability in adults, and the second cause of death in developed countries. Stroke is not a single disease but can be caused by various risk factors, disease processes and mechanisms.[1,2]

Stroke can trigger kidney dysfunction through inflammatory and immune responses which then mediate kidney dysfunction after a stroke.[3,4] Severe acute renal dysfunction increases the expression of proinflammatory chemokines in the brain, increases neuronal pyknosis, induces microgliosis and astrogliosis in the brain, and disrupts the blood-brain barrier.[5]

In recent years, renal dysfunction has been identified as a new risk factor thought to influence stroke prognosis.[6] In acute ischemic stroke, low estimated glomerular filtration rate (eGFR) is significantly associated with death during hospitalization and death/disability after the patient is discharged.[6-8] The aim

of this study was to find the relationship between eGFR as a predictor of clinical outcomes in acute ischemic stroke.

METHOD

Subject

This prospective cohort study was conducted at Dr. Wahidin Sudirohusodo Makassar in 2023 until 70 samples were obtained that met the inclusion criteria. Exclusion criteria include patient age under 18 years, onset of ischemic stroke more than 7 days, history of recurrent stroke, history of chronic kidney disease, history of severe systemic disease, and history of renal replacement therapy. Figure 1 showed how this study was conducted.

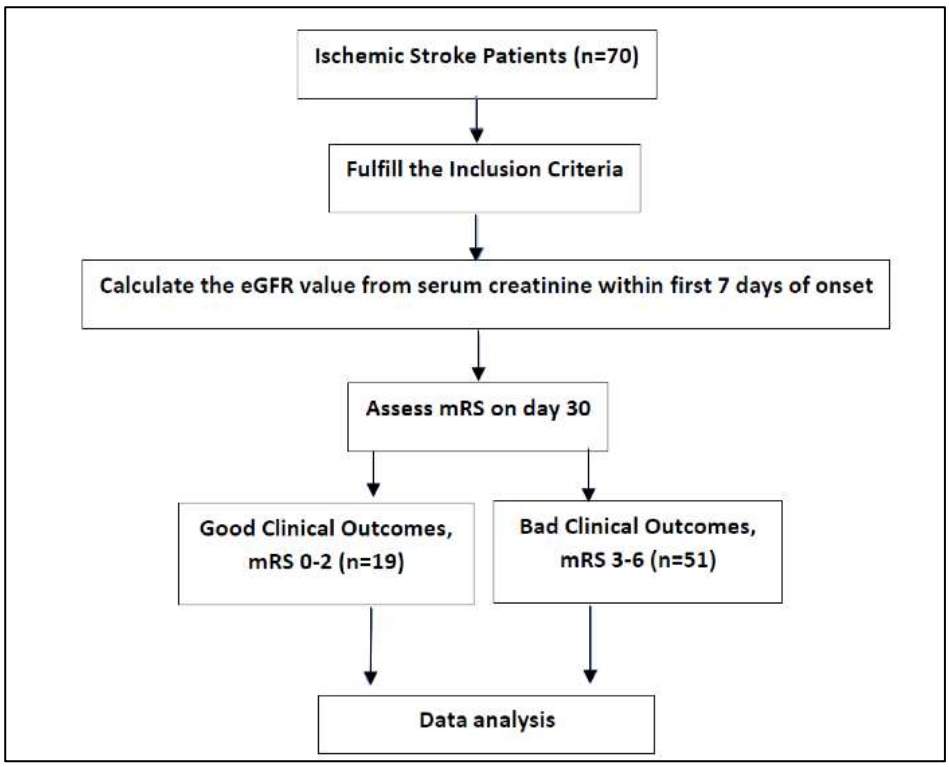

Figure 1. Study flowchart (eGFR: estimated glomerular filtration rate; mRS: modified Rankin Scale)

Determining Stroke

Stroke is confirmed by anamnesis in the form of a sudden focal neurological deficit, which is proven by the presence of a focal neurological deficit on neurological examination, and is supported by a computerized tomography (CT) scan of the head without contrast which shows a hypodense image or the absence of cerebral hemorrhage in the brain tissue.

Variable and Clincal Outcomes

Sample data included age, gender, body weight, comorbidities (hypertension, diabetes mellitus, atrial fibrillation, smoking, and dyslipidemia), and modified Rankin Scale (mRS). Clinical outcomes are changes in the level of health, function and quality of life, assessed by the mRS score on the 30th day with a value of 0 - 6. A score of 3 - 6 is categorized as poor clinical outcome, while 0 - 2 is categorized as good clinical outcome.

Renal Function Evaluation

Serum creatinine was measured within the first 7 days of acute ischemic stroke onset. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: 141 × min (Scr/κ, 1) $^{\alpha}$ ×

max (Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [in women] x 1.159 [in black races], where Scr is serum creatinine, κ 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/κ or 1, and max indicates Maximum sc/κ or 1.[9] eGFR is categorized into <45, 45-59, 60-89, and ≥90 mL/minute/1.73m^2.

Statistical Analysis

Continuous variables are presented as appropriate means, and categorical variables as proportions. Data normality test using Kolmogorov-Smirnov, then determines the correlation and compares eGFR with the two clinical outcome groups on the 30th day. Determining the eGFR binary cut-off value and measuring the sensitivity and specificity of eGFR to predict clinical outcomes based on the optimal cut-off. The data obtained was processed using statistical analysis applications. p value <0.05 were considered significant.

RESULT

Characteristics of Research Subjects Based on Clinical Outcomes and eGFR Categories

Table 1 presents the characteristics of research subjects based on clinical outcomes. The average age of the research sample was 61.37 years. The median eGFR value (p<0.001) in the poor outcome group was 52 (14-89) and in the good outcome group was 82 (41-107).

Table 1. Basic characteristics of research subjects in both groups

Characteristics	Total (n=70)	1 month clinical outcome		P value
		Bad (n=51)	Good (n=19)	
Gender (n)				
• Man	38 (54,3%)	24 (63,2%)	14 (36,8%)	0,086*
• Woman	32 (45,7%)	27 (84,4%)	5 (15,6%)	
Ages (n)				
• ≥75 years	11 (15,7%)	10 (90,9%)	1 (9,1%)	
• 60-74 years	30 (42,9%)	25 (83,3%)	5 (16,7%)	
• 44-59 years	24 (34,3%)	13 (54,2%)	11 (45,8%)	0,058*
• 25-43 years	4 (5,7%)	2 (50%)	2 (50%)	
• 18-24 years	1 (1,4%)	1 (100%)	0 (0%)	
Risk Factors (n)				
• Hypertension	51 (72,9%)	40 (78,4%)	11 (21,6%)	0,157*
• Diabetes	17 (24,3%)	13 (76,5%)	4 (23,5%)	1,000*
• Atrial Fibrilation	14 (20%)	8 (57,1%)	6 (42,9%)	0,181*
• Dislipidemia	26 (37,1%)	20 (76,9%)	6 (23,1%)	0,757*
• Smoking	24 (34,3%)	14 (58,3%)	10 (41,7%)	0.091*
• Obesity	25 (35,7%)	15 (60%)	10 (40%)	0,128*
eGFR (median)	55 (14-107)	52 (14-89)	82 (41-107)	<0,001**

Noted: * *Chi square* test; ** Mann Whitney test

Table 2 showed the characteristics of the research sample for the eGFR category. Of the total 70 patients, 18 people (25.7%) with eGFR ≤45 mL/min/1.73 m^2, 27 people (38.6%) with eGFR 45-59 mL/min/1.73 m^2, 19 people (27.1%) with eGFR 60-89 mL/min/1.73 m^2, and 6 people (8.6%) with eGFR >90 mL/min/1.73 m^2.

Comparison of Mean eGFR Values in Acute Ischemic Stroke Patients with Good and Bad Clinical Outcomes

This study assessed differences in characteristics between good and poor clinical outcome groups with eGFR values (p<0.001). Table 3 shows a comparison of eGFR values for clinical outcomes of acute ischemic stroke.

Comparison of Mean eGFR Values in Acute Ischemic Stroke Patients with Good and Bad Clinical Outcomes

In receiver operating characteristic (ROC) curve analysis, it was found that the area under the curve (AUC) for eGFR was 0.848. Based on the coordinate of the curve table and using the Youden index, the cut off threshold for eGFR is 62 mL/min/1.73 m^2 (Figure 2), with a sensitivity of 80.39% and a specificity of 84.21%.

Table 2. Basic characteristics of research subjects regarding eGFR categories

Characteristics	eGFR (mL/min/1.73 m^2)				
	≤45 (n=18)	45-59 (n=27)	60-89 (n=19)	>90 (n=6)	P value
Gender (n)					
• Man	8 (21,1%)	11 (28,9%)	14 (36,8%)	5 (13,2%)	0,055*
• Woman	10 (31,3%)	16 (50%)	5 (15,6%)	1 (3,1%)	
Ages (n)					
• ≥75 years	3 (27,3%)	5 (45,5%)	2 (18,2%)	1 (9,1%)	
• 60-74 years	7 (23,3%)	14 (46,7%)	8 (26,7%)	1 (3,3%)	
• 44-59 years	4 (16,7%)	8 (33,3%)	9 (37,5%)	3 (12,5%)	0,248*
• 25-43 years	3 (75%)	0 (0%)	0 (0%)	1 (25%)	
• 18-24 years	1 (100%)	0 (0%)	0 (0%)	0 (0%)	
Risk Factors (n)					
• Hypertension	15 (29,4%)	18 (35,3%)	14 (27,5%)	4 (7,8%)	0,649*
• Diabetes	5 (29,4%)	6 (35,3%)	6 (35,3%)	0 (0%)	0,448*
• Atrial Fibrilation	5 (35,7%)	3 (21,4%)	4 (28,6%)	2 (14,3%)	0,441*
• Dislipidemia	6 (23,1%)	11 (42,3%)	6 (23,1%)	3 (11,5%)	0,816*
• Smoking	4 (16,7%)	9 (37,5%)	7 (29,2%)	4 (16,7%)	0,259*
• Obesity	5 (20%)	7 (28%)	10 (40%)	3 (12%)	0,210*
Clinical Outcomes					
• Bad	17 (33,3%)	25 (49%)	9 (17,6%)	0 (0%)	<0,001*
• Good	1 (5,3%)	2 (10,5%)	10 (52,6%)	6 (31,6%)	

Noted: * *Chi square* test

Table 3. Comparison of mean eGFR values in acute ischemic stroke patients with good and bad clinical outcomes

Characteristic	Total (n=70)	Clinical Outcomes		p value
		Good (n=19)	Bad (n=51)	
eGFR (mean)	59,90 ± 21,09	79,79 ± 19,21	52,49 ± 16,57	<0,001*

Noted: * Mann-Whitney Test

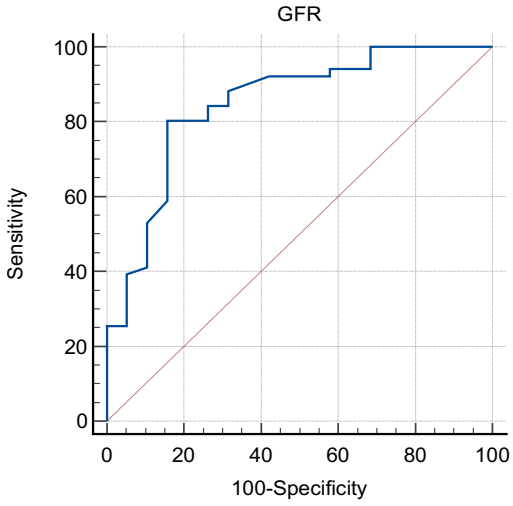

Figure 2. ROC curve of the relationship between eGFR and clinical outcomes

DISCUSSION

In this study, there were 70 samples that met the inclusion and exclusion criteria, with 51 samples belonging to the poor clinical outcome group, and 19 samples belonging to the good clinical outcome group. The average age of patients in this study was 61.37 years with the majority being in the 60-74 years age group. More males than females (54.3% vs 45.7%). The most reported risk factors were hypertension (72.9%) followed by dyslipidemia (37.1%), obesity (35.7%), smoking (34.3%), diabetes mellitus (24.3%), and atrial fibrillation. (20%).

Estimated Glomerular Filtration Rate (eGFR) is the best global index for assessing kidney function.[9-12] The calculation of eGFR values in this study uses the CKD-EPI formula, which provides more accurate results in Asian populations.[13] In all research samples, the mean eGFR was 59.90 mL/min/1.73 m2, with the highest eGFR group being 45-59 mL/min/1.73 m2 (38.6%). The poor outcome group had a lower mean eGFR than the good outcome group (52.49 mL/min/1.73 m2 vs 79.79 mL/min/1.73 m2). eGFR has a relationship with clinical outcomes on the 1 month after acute ischemic stroke ($p<0.001$). In Wang et al. study, it was found that 40% of samples were in the group of eGFR <60 mL/min/1.73 m2; then in Miwa et al. study it was found that 42% of the samples were in the group of eGFR <60 mL/min/1.73 m2. The similarities between the two studies concluded that the eGFR <60 mL/min/1.73 m2 had a significantly higher risk of 1 month mortality after acute ischemic stroke compared with the eGFR >60 mL/min/1.73 m2 group.[14,15]

Acute kidney dysfunction often appeared after an acute ischemic stroke and are associated with mortality during hospitalization.[16,17] Kidney dysfunction after an acute ischemic stroke is caused by disorders of several systems: the renin angiotensin aldosterone system (RAAS), the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis system. In addition, inflammatory and immune responses mediate kidney dysfunction after stroke. [3,4]

Until now, the mechanism underlying the relationship between kidney function and poor clinical outcomes of stroke is not fully known.[6] Several recent hypotheses explain that kidney dysfunction after acute ischemic stroke can cause disruption of the hemostasis system which results in a prothrombotic state and disruption of central nervous system autoregulation. Acute kidney dysfunction can also increase the expression of proinflammatory chemokines in the brain, increase neuronal pyknosis, induce microgliosis and astrogliosis in the brain, disrupt the blood brain barrier, and impair motor function in the brain. All of these things can contribute to morbidity and mortality, especially in acute ischemic stroke patients.[5,15,18]

One systematic review and meta-analysis study concluded that there was an increase in mortality rates in acute ischemic stroke patients with comorbid kidney dysfunction (acute kidney disorders) so that efforts to treat strategies to prevent kidney dysfunction are needed to improve the clinical outcomes of acute ischemic stroke patients.[19] In this case there are studies that conducting an approach to the effects of using nephrotoxic agents (radiological and medical contrast agents) used during the treatment of acute ischemic stroke patients was found to be associated with acute kidney disorders.[16]

According to a 2020 study by Delgado et al., during the treatment of acute ischemic stroke, renal dysfunction induced by contrast agents is a frequent complication and is associated with worse outcomes. [20] In the study of Chusiri et al. and Rachoin et al., it is stated that there are two most common risk factors that can causes nephropathy induced by the use of radiological contrast agents (contrast induced nephropathy). These two risk factors are mechanical thrombectomy procedure and initial eGFR value at admission below 30 mL/min/1.73 m2 (eGFR value before using contrast agent). The use of radiological contrast agents for the treatment of acute ischemic stroke patients with one/both of the above risk factors can still be done without delay with regular monitoring due to decreased kidney function.[21-23]

There are several studies regarding nephrotoxic medicamentosa which are often used in cases of acute ischemic stroke. In the study of Laville et al, the use of oral anticoagulants was associated with an increased risk of acute renal dysfunction and an increased risk of bleeding if the eGFR value was <30 mL/min/1.73 m2. Meanwhile, the use of oral antiplatelets is not associated with acute renal dysfunction.[24] The risk of glomerular nephrotoxicity increases with antiprostaglandin drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), so their use must be monitored in patients with acute ischemic stroke.[25] There are multicenter studies examining the use of drugs commonly use in intensive care patients and reported that there are 14 classes of drugs that have a risk of causing acute kidney dysfunction, several groups whose use needs to be monitored include: Phosphodiesterase inhibitors-Antiarrhythmia (Enoximone and Milrinone), Loop Diuretics (Furosemide), Antihypertensives (Ketanserin), plasma products/ blood (albumin), and immunosuppressants (except corticosteroids).

In acute ischemic stroke patients who will be considered for nephrotoxic agents (radiological and medicemantose contrast agents according to indications), eGFR monitoring is required before and after administration of nephrotoxic agents.[26] There are references that determine the eGFR cut-off limit at a value of 60 mL/min/ 1.73 m2 as a consideration for administering nephrotoxic agents. In this situation, the use of nephrotoxic agents must be closely monitored, and if there is a significant deterioration in eGFR, an infusion of isotonic solution can be given to dilute the concentration level of the nephrotoxic agent in the blood.[27]

Using receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) for the eGFR value was 0.848 with a cut-off value of 62 mL/min/1.73 m2 (sensitivity 80.39%, specificity 84.21%). Based on the results above, eGFR values <62 mL/min/1.73 m2 tend to have worse clinical outcomes.

There are several studies regarding reference cut-off values for eGFR in acute ischemic stroke. In 2 studies it was found that a reference cut-off eGFR <60 mL/min/1.73 m2 was associated with an increased risk of hemorrhagic transformation, death while in hospital, and worse disability/disability within 1 year after acute ischemic stroke. However, in these two studies it was said that eGFR was less accurate for predicting short-term outcomes.[7,28] In Wang et al., study, a lower cut-off value was obtained, namely <45 mL/min/1.73 m2, which in this group was at mortality risk at 1 year was 2.5 times greater than in the eGFR >90 mL/min/1.73 m2 group [13] and was associated with worse disability in ischemic stroke caused by small vessel occlusion and cardioembolism.[15]

The relationship of kidney dysfunction assessed using eGFR in stroke is currently an important concern. There are several recent studies examining this matter. In Yao et al. study, it was reported that low eGFR in the cases of mechanical thrombectomy procedure caused worse 3-months clinical outcomes.[29] Another study reported that low eGFR increases the risk of 5-years mortality rate in cases of stroke due to stenosis of carotid artery [30], even increases the risk of first ischemic stroke attack [31], also correlated with development of post-stroke depression.[32] In cases of hemorrhagic stroke, it has also been reported that low eGFR is associated with complications of hydrocephalus, pneumonia, and expansion of the hematoma area.[33]

The strength of this study is that using a simple test (serum creatinine) to calculate eGFR can objectively predict clinical outcomes after 1 month of acute ischemic stroke. We also realize that this study has several limitations. First, the study was conducted at a single center, where bias may occur, so a multicenter study is necessary. Second, this study only took samples at the start of admission, so the prognostic effect of changes in eGFR values is still unknown. Third, we did not perform vascular neuroimaging examinations on each patient, so the determination of stroke subtype based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and its relationship to the predictive value of eGFR cannot yet be determined.

CONCLUSION

Based on the results of this study, eGFR has a relationship with clinical outcomes ($p<0.001$) and can objectively predict clinical outcomes on the 30th day of acute ischemic stroke.

DECLARATIONS

The research has received approval from the local Health Research and Ethics Committee of the Hasanuddin University RSPTN RSUP Dr. Wahidin Sudirohusodo Makassar (No. 751/UN4.6.4.5.31/PP36/2023). All participants were informed about subject of the study.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest in this research.

AUTHORS' CONTRIBUTIONS

All authors are responsible for conceptualization, manuscript preparation, manuscript editing, and manuscript assurance.

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