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High Density Lipoprotein (HDL) Level and Blood Urea Nitrogen (BUN)/Creatinin Ratio Relationship with One-Month Outcome in Acute Ischemic Stroke Patients

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ABSTRACT

Introduction: Stroke has caused around 15.5% of all deaths. Evaluation of factors that worsen clinical outcomes is necessary to avoid complications such as renal dysfunction and secondary dyslipidaemia. This study aims to determine the relationship between increasing serum HDL levels and blood urea nitrogen–serum creatinine ratio (BUN/Cr) on clinical outcomes of acute ischemic stroke.

Method: Prospective cohort study was used with subjects being first-onset acute ischemic stroke patients. Demographic, clinical data, and assessment of BUN/Cr and HDL ratios were collected. Subjects were divided into good clinical outcome (mRS 0-2) and poor clinical outcome (mRS 3-6) groups, and then analysed using multiple linear regression multivariate analysis with confidence interval of 95%.

Results: 60 participants met the inclusion criteria. There was a significant relationship between serum BCR levels and poor clinical outcomes ($p < 0.001$) relationship between serum HDL levels and poor clinical outcomes also shown significances ($p < 0.001$) Mean BCR in good and poor clinical outcomes of acute ischemic stroke were (17.08±30.13) and (29.35±67.30) respectively. Mean HDL in good and poor clinical outcomes were (39± 62) and (41 ± 92) respectively. A multiple linear regression analysis showed a positive correlation ($p < 0.001$) between increasing Serum HDL levels and Bun/Cr ratio simultaneously to poor clinical outcomes in acute ischemic stroke patients. The Cut-off point was 20.9 for BUN to creatinine ratio and 46 mg/dL at serum HDL. Both of BUN/Cr ratio and HDL were shown high specificity and could be used as predictors of clinical outcome in acute ischemic stroke patients.

Conclusion: Increased BUN/Cr ratio and increased serum HDL levels were associated with clinical outcomes in patients with acute ischemic stroke.

Keywords

Stroke, Blood urea nitrogen ratio (BUN/Cr ratio), creatinine, HDL, mRS

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INTRODUCTION

Recent studies shown that hydration played a significant role in the outcomes of Acute ischemic stroke patient.[1] Another factors that indicated a significant correlation is a secondary dyslipidaemia which can be measured with HDL serum levels. HDL serum level has been said to have a direct and indirect relationship with the incidence of cerebrovascular disease including acute ischemic stroke. In several studies, the incidence of Acute Ischemic Stroke was associated with low and high HDL levels. A previous study stated there was a relationship between increased BUN/Creatinine and the clinical outcomes of acute ischemic stroke patients accompanied by increased markers of High-Density Lipoprotein levels (HDL).[2]

A 2016 study published in the Journal of Stroke and Cerebrovascular Diseases found that a higher BUN to creatinine ratio was associated with poor clinical outcomes at 3-months post-stroke.[2] An increase in the BUN/Cr ratio indicates a decrease in kidney function. It has been reported that a decrease in kidney function can be the reciprocal effect. An inflammatory response to blood vessel occlusion occurs in stroke causing brain tissue injury and kidney function decreases by brain-kidney interaction.[3] Decreased kidney function also occurs due to microvascular disorders caused by high HDL levels.[4] Researchers are interested in conducting this research to determine the relationship between serum HDL levels and the BUN/Cr ratio as prognostic facts and predictors of clinical outcomes to help identify the risk of mortality, morbidity, and the need for intensive care in acute ischemic stroke patients.

METHOD

Subject

This is a prognostic study with a prospective cohort method. The research sample was patients with first-attack ischemic stroke at Wahidin Sudirohusodo Hospital and network hospitals in Makassar whom were diagnosed with Head CT (computed tomography) scan, sorted through onset duration, and a patient who was not went home without mutual consent. Sample collection was carried out with a consecutive sampling technique in a homogenous group consist of acute stroke ischemic patient and 60 samples were obtained that met the inclusion criteria. The independent variables are serum HDL cholesterol levels and serum Bun/Creatinine ratio and the dependent variable is the clinical outcome of ischemic stroke.

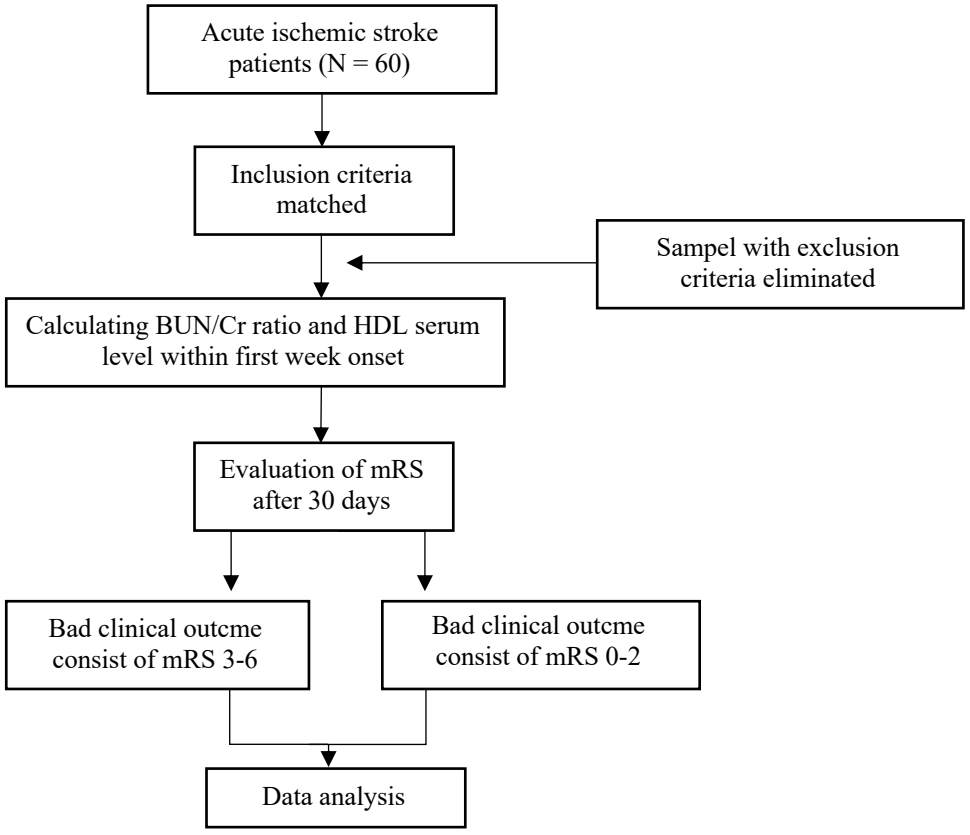

Figure 1. Flowchart for the selection of the study population

Determining Stroke

Stroke is determined by manifestation of first ever attack with one sided deficit of neurologic function, confirmed by examination, and diagnosed with a head computerized tomography (CT) scan of the head without contrast with a presentation of a hypodensity type lesion in the brain tissue.

Variable and Clinical Outcomes

Sample data included age, gender, body weight, comorbidities (hypertension, diabetes mellitus, atrial fibrillation, smoking), and modified Rankin Scale (mRS). Clinical outcomes are changes in the level of health, function and quality of life, assessed by the modified Rankin Scale (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.

Statistical Analysis

Data is processed through computerized statistical analysis. Descriptive analysis includes basic characteristic data for all study patients with univariate analysis. Statistical analysis includes Kolmogorov-Smirnov test to evaluate normality of the data and Mann-Whitney Test to compare the relationship between HDL cholesterol levels and clinical outcomes of ischemic stroke and Bun/Creatinine Ratio to clinical outcomes, as well as multivariate analysis using multiple linear regression analysis to evaluate both variables affect to the clinical outcomes. The data obtained was processed using statistical analysis applications. Value of the confidence used were 95% with Differences in a p value <0.05 were considered significant.

RESULT

Characteristics of Subjects Based on Clinical Outcome

In this study, 60 subjects met the research inclusion criteria. With 51 subjects (68.3%) in the good clinical outcome group and 19 subjects (31.7%) in the poor clinical outcome group. Based on gender, there are more men than women (55% vs 45%). The average age of the research sample was 62 years with the majority being in the age range 45-60 years (43%). Table 4 describes the basic characteristics of research subjects and all the variables were found homogenous.

The BUN /Cr ratio value was found to be 20.97 ± 9.66 mg/dl with the value in the poor outcome group being 29.35 ± 67.30 mg/dl and in the good outcome group being 17.08 ± 30.13 mg/dl. The mean serum HDL value was found to be 52.31 ± 59.45 g/dl with the value in the poor outcome group being 60.90 ± 92.00 g/dl and in the good outcome group being 38.57 ± 67.00 g/dl.

Table 1. Basic characteristics of subjects in both groups

Characteristics	Total (n=60)	1-month clinical outcomes		P value
		Bad (n=19)	Good (n=41)	
Gender (n)				
• Man	33	8 (24.2%)	25 (75.8%)	0,277*
• Woman	27	11 (40.7%)	16 (59.3%)	
Ages (n)				
• ≥75 years	6 (10%)	2(33.3%)	4(66.7 %)	
• 60-74 years	25 (41.7%)	8 (32%)	17(68%)	
• 44-59 years	26 (43,3%)	7(26.9%)	19(73.1%)	0,281*
• 25-43 years	2(3.3%)	2 (100%)	0 (0%)	
• 18-24 years	1 (1,7%)	0(0%)	1 (100%)	
Risk Factors (n)				
• Hypertension	44 (73.3%)	13 (29.5%)	31 (70.5%)	0,786*
• Diabetes	24 (40%)	13 (76,5%)	4 (23,5%)	0,533*
• Atrial Fibrilation	9 (15%)	8 (57,1%)	6 (42,9%)	0,705*
• Smoking	17(28.3%)	20 (76,9%)	6 (23,1%)	0,586*

Table 2. Relationship between HDL cholesterol levels and clinical outcomes of ischemic stroke.

Variable		MRS >2	MRS ≤2	Uji Mann Whitney (p value)
HDL Level	40 - 100	17 (85%)	3 (15%)	<0.001**
	<40 (low)	2 (5%)	38 (95%)	<0.001**

Noted: *Mann Whitney Comparison test

Mann Whitney Test was used to analyze is there a relationship between HDL cholesterol levels and the clinical outcome of ischemic stroke. The test can be used if the data distributed abnormally with Kolmogrov-Smirnov test. The result of Kolmogrov-Smirnov test showed an abnormally distributed data (p value < a), and Mann Whitney Test result show that there is a significant relationship between HDL cholesterol levels at hospital admission and the clinical outcome of ischemic stroke,

Table 3. Correlation of Bun Creatinine Ratio with clinical outcomes of ischemic stroke

Creatinin	0.88(0.46-1.50)	0.92(0.44-1.73)	0.589**
BCR	29.35(7.80-67.30)	17.08(8.00-30.13)	< 0.001**

Based on Kolmogorov Smirnov test, the data were not normally distributed. Using the Mann Whitney comparison test, the Bun/Cr ratio showed a significant relationship with the mRS score 30 days after acute ischemic stroke (p <0.001) Compared to Creatinin Alone.

Table 4. Multivariate analysis of the relationship between HDL cholesterol variables and Bun/Creatinine ratio on clinical outcomes of ischemic stroke using the mRS scale

Variable		P Value		R^2
		T-Test	F Test/ Significant test	
Bun-Creatinin Ratio	0.065	< 0.001		0.681
HDL	0.051	< 0.001	< 0.001	

Noted: *Multiple Linear Regression test

This study used the linear regression test to determine the influence of the BUN/Creatinine ratio and serum HDL levels separately or simultaneously to see whether there was an influence on the clinical outcome of acute ischemic stroke. It can be seen that the BUN/creatinine ratio and HDL levels simultaneously have a unidirectional relationship where the results of the F/significance test are p (<0.001) with the Bun/creatinine and HDL ratios said to have a simultaneous relationship with an influence of 68% (R2: 0.681) on clinical outcomes.

DISCUSSION

This study used a prospective cohort method which aimed to determine the relationship between serum HDL levels and the BUN/Creatinine ratio with clinical outcomes of acute ischemic stroke. Secondary data was taken from RSUP Dr. Wahidin Sudirohusodo Makassar and several educational network hospitals in Makassar City, South Sulawesi. 60 subjects of acute ischemic stroke patients met the inclusion and exclusion criteria, with 19 subjects in the poor clinical outcome group and 41 subjects with good clinical outcomes.

The average age in this study was 60.62 years with the majority in the 45-60 years age group. More males were found than females (55% vs 45%). It is similar to epidemiological research by Aliah et al., which found that strokes generally occur over the age of 40 years, and are found more in men than women.[5] A Study by Akbar, et al., also found that the incidence of ischemic stroke was higher in men than in women.[6] The poor outcome group in this study had a higher mean serum HDL level compared to the good outcome group (60.90 vs 38.57). It showed a significant relationship between serum HDL levels and clinical outcomes after acute ischemia stroke of p <0.001. The results of this study are similar to the study by Lu et al in 2023, which showed a U-shaped relationship between HDL levels and clinical outcomes of ischemic stroke. His research looked at the relationship between HDL levels and the risk and causes of mortality. When related to mortality due to cerebrovascular disease, an association between HDL levels and ischemic stroke and ischemic heart disease was found, but there was no association with hemorrhagic stroke. Patients with HDL-C <30 mg/dL (HR 1.40, 95% CI: 1.23–1.59) and >90 mg/dL (HR 1.15, 95% CI: 1.02–1, 30) had a significantly higher risk of death for ischemic heart disease compared to the reference group (70–79 mg/dL). Similarly, for ischemic stroke, the corresponding mortality rates for very low and high HDL-C were 1.38 (95% CI: 1.09–1.74) and 1.43 (95% CI: 1.17– 1.74) with 70–79 mg/dL as the normal range.[7]

The research have not been widely done. However, in research by Li H et al from China National Clinical Research for Neurological Disease which studied the incidence of stroke with HDL levels, it was also found that there was a U shape relationship. Research by Li H et al showed that in healthy people with HDL cholesterol values below and above the normal range, a higher risk of stroke was found in the 10 years study period.[8]

The mechanism underlying the U-shaped relationship between HDL levels is not yet known with certainty, but several things are considered to influence this condition. First, there are genetic variants, as in Cholesterol ester transfer protein (CETP) which is a protein responsible for transporting cholesterol esters and triglycerides between lipoproteins. This genetic variant is said to be associated with an increased risk of stroke.[8] Cholesterol ester transfer protein (CETP) enzyme deficiency may lead to the development of atherosclerosis despite high HDL cholesterol levels. In addition, studies are showing that increased serum HDL cholesterol caused by CETP deficiency mutations may be associated with a high prevalence of cardiovascular disease. Furthermore, other studies suggest that CETP may function as a protective factor against vascular disease. Therefore, deficiency or inhibition of the CETP pathway may explain the association between increased serum HDL cholesterol concentrations and mortality risk of cardiovascular disease.[9]

Second, an extreme increase in HDL can cause HDL to contain excess cholesterol (cholesterol-overloaded HDL particles), which is less significant in preventing atherosclerosis. Several studies show that HDL with a greater number of particles can be a predictor of cardiovascular events. Several observational studies have proven that the amount of HDL-P (HDL Particles) is more closely related to CVD risk than HDL-C. This is true even if HDL-C increases substantially, increasing excess cholesterol HDL-P There is evidence that excess cholesterol HDL-P may be harmful because it not only negatively impacts cholesterol transport from extrahepatic cells but also reduces the selective absorption of cholesterol heart.[10]

A third possible explanation underlying this condition is that extreme HDL levels contribute to endothelial dysfunction.[8] In this study, for the first time we show that endothelial function is impaired not only in subjects with low HDL-C levels but also in subjects with very high HDL-C levels. After adjustment for traditional cardiovascular risk factors, very high HDL-C levels were significantly associated with endothelial dysfunction. This mechanism is in research by Huang et al. in vitro studies using early endothelial progenitor cells (EPCs), which serve as a prognostic indicator of clinical atherosclerosis. In this study, it was demonstrated that although protective at low concentrations, moderate to high HDL concentrations from healthy subjects paradoxically impaired EPCs and associated angiogenesis in the absence of oxidized LDL thereby providing in vitro evidence of the potential toxic effects of elevated HDL concentrations.[11] In addition, it disrupts the release of HDL cholesterol cargo in the liver which is the final step in RCT (reverse cholesterol transport) and may be another possible mechanism that has not been studied to date. Such a defect can lead to a highly atherogenic state despite marked elevations in plasma HDL cholesterol.[9] The findings of the influence of HDL levels which form a U curve, as in this study, were also found in cardiovascular research conducted by Trimarco et al in 2022 showing that at low and high HDL levels (found a higher prevalence of cardiovascular events compared to patients with HDL levels of 40-60 mg/dL.[12]

The results of this study show that there is a significant relationship between increasing BUN/Cr and clinical outcomes in acute ischemic stroke patients (mRS score 30 days after stroke). Consideration that increased BUN/Cr is associated with poor hydration status and is associated with poor clinical outcomes in Acute Ischemic Stroke patients. Thirst is the main mechanism that prevents the body from experiencing severe dehydration. Acute Ischemic Stroke patients tend not to consume enough fluids due to dysphagia, physical limitations, and loss of consciousness.[2]

The Bun Creatinine ratio as a marker of dehydration is associated with a decrease in total plasma volume, a decrease in cardiac output, and an increase in blood viscosity as well as the risk of intravascular thrombo-inflammation.[13] In the early stroke recovery period, disruption of the autoregulatory system related to ischemia makes the brain more stressed and susceptible to changes in blood viscosity and pressure.[14] In this way, frequent dehydration reduces blood perfusion to the brain and simultaneously decreases the flow of

oxygen and nutrients, which then contributes to brain damage and affects clinical outcomes.[15] In addition, several studies have shown that cerebral perfusion after acute ischemic stroke is significantly associated with clinical outcomes and patient mortality.[16]

In this study, the Multivariate Test with multiple linear regression in Table 5 was used to determine the influence of the BUN/Creatinine ratio and serum HDL levels separately or simultaneously to see whether there was an influence on the clinical outcome of acute ischemic stroke. It can be seen that the BUN/Creatinine ratio and HDL levels separately have a positive influence with the greatest influence on the Bun Creatinine ratio (0.065) while the serum HDL level (0.051). Simultaneously, serum HDL levels and the Bun/Creatinine ratio have a unidirectional relationship with worsening clinical outcomes where significant results were obtained ($p<0.001$) with the Bun/creatinine ratio and HDL simultaneously influencing 69% (R2: 0.691) on clinical outcomes.

The study conducted by Deng et al. also found a significant interaction between BUN/Cr and HDL as well as a positive correlation between the BUN/Cr ratio and three-month clinical outcomes in patients with high HDL levels (OR 1.03.95% CI 1.00- 1.07, p=0.04). This correlation was not significant at low HDL levels (p=0.41) or moderate HDL (p=0.15). High HDL levels have been reported to correlate with an increased risk of poor outcomes in AIS patients, which may potentiate the effect of BUN/Cr on three-month clinical outcomes.[2]

A relationship between serum HDL levels and decreased kidney function has been found in several studies. A retrospective cohort study examining the relationship between lipid parameters and the incidence of decreased kidney function showed several new findings, including confirmation of the U-shaped contribution of HDL-C to KFD. (Kidney Functional Decline). The relationship between HDL-C and KFD was U-shaped, consistent with findings that hyper-HDL cholesterolemia had an adverse effect on cardiovascular disease mortality in previous cohort analyses. In connection with these results, it is considered that severe hyper-HDL cholesterolemia may be atherogenic due to changes in the shape of HDL particles and their functional properties. ROC analysis from Nagayama et al (2023) shows the cut-off value of lipid parameters (HDL) in predicting KFD is 66mg/dL.[17]

The finding that the relationship between HDL-C levels and the risk of developing kidney disease follows a U-shaped curve suggests that at high concentrations, HDL-C loses its protective properties, the mechanism underlying this finding is not yet completely clear. Experimental evidence performed in healthy individuals suggests that HDL-C may have a biphasic effect (at low and high concentrations) and that at high concentrations of HDL-C there is impaired endothelial progenitor cell formation and angiogenesis, indicating loss of protective effects. The risk of CKD development associated with HDL-C may be related to inflammation and oxidative stress, which may result in functional impairment of the anti-atherogenic properties of HDL-C leading to microvascular disease and renal dysfunction.[4]

On the other hand, in conditions of impaired kidney function, HDL-C functional impairment occurs. In research by Moradi et al, a condition characterized by inflammatory cytokine activation, increased inflammatory burden, and oxidative stress was found. Furthermore, they found that increased concentrations of oxidized HDL were associated with increased mortality from cardiovascular disease. They concluded that excessive oxidative stress might produce dysfunctional HDL, and patients with high HDL cholesterol under conditions of oxidative stress, might have greater amounts of oxidized HDL, and then result in increased cardiovascular disease and death from cardiovascular disease. Therefore, in inflammatory states, HDL may not only be dysfunctional but also have adverse effects by increasing inflammation and increasing the burden of cardiovascular disease. [9]

On curve analysis receiver operating characteristic (ROC), we found that the area under the curve (AUC) was 90.2% for the bun creatinine ratio, with a specificity of 82.3 percent and a sensitivity of 94 percent. Meanwhile, for HDL, an area under the curve (AUC) of 90 percent was found for HDL, with a specificity of 92% and sensitivity of 89%. With this high specificity value, the ratio of BUN creatinine and HDL can be used as a predictor and can predict poor outcomes in 90 out of 100 cases of ischemic stroke with $P <0.001$ and a

threshold value (cut-off point) at a ratio of 20.9 for BUN creatinine, and serum HDL levels at 46 mg/dL. So these two examinations can be clinical tools to predict poor outcomes in patients with Acute Ischemic Stroke. Furthermore, findings such as the U-shaped HDL pattern influence clinical outcomes, as well as the association between HDL and BUN creatinine on poor clinical outcomes in Acute Ischemic Stroke need an investigation and further exploration.

CONCLUSION

Elevated HDL Serum and BUN/Creatinine levels separately or simultaneously have an Association with poor clinical outcomes in acute ischemic stroke patients.

DECLARATIONS

The research has received approval from the Hasanuddin University and RSUP Wahidin Sudirohusodo Health Research and Ethics Committee with Number (No. 345/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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