Uric Acid-HDL Ratio as Predictor of Major Cardiovascular Events in Very High Cardiovascular Risk Patients Treated with High-Intensity Statin Therapy

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KEYWORDS
Major Cardiovascular Events; Uric Acid-HDL Ratio; High Intensity Statin.

ABSTRACT
Introduction: Uric acid levels are positively correlated with cardiovascular disease. High Density Lipoprotein (HDL) cholesterol plays a role in suppressing blood oxidation reactions and protecting vascular endothelial cells. The combination of these two metabolic parameters, the Uric Acid-HDL Ratio (UHR) makes it a very useful predictor marker for metabolic disorders. Statins are known to be the gold standard for raising HDL cholesterol. Some types of statins are also known to reduce serum uric acid levels by involving pleiotropic actions. The aim of this study was to determine baseline UHR as a predictor of MACE after administration of high-intensity statins.
Objectives: The Objective of this study was to determine baseline UHR as a predictor of MACE after administration of high-intensity statins.
Methods: This study was conducted at the cardiac center of Dr Zainal Abidin Regional General Hospital. This study is an observational study with a prospective cohort design. The target population was patients classified as patients with very high cardiovascular risk and using consecutive sampling techniques.
Results: During the study period, a total of 82 patients with ischemic heart disease with very high cardiovascular risk met the inclusion and exclusion criteria. Of these, 49 patients (59.8%) were identified as having major cardiovascular events (MACE) while the remaining 33 patients (40.2%) did not had MACE. The results of this study are that statin therapy may not significantly affect the uric acid-HDL ratio in the context of major cardiovascular events.
Conclusions: The uric acid-HDL ratio had no significant predictive ability for major cardiovascular events in patients with very high cardiovascular risk who were treated with high-intensity statin therapy.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide with an estimated 17.9 million deaths each year, representing 32% of all global deaths.(1) Cardiovascular disease is a major cause of morbidity and mortality, responsible for one-third of all deaths in Indonesia.(2) Based on Basic Health Research (Riskesdas) data in 2018, 1.017.290 Indonesians suffered from coronary heart disease. The prevalence of cardiovascular disease increases with age.(3) High uric acid levels can increase the oxidation reaction of low density lipoprotein (LDL) cholesterol, thus exacerbating the process of atherosclerosis and increasing damage to the walls of coronary arteries. Several studies have proven that uric acid levels are one of the risk factors for cardiovascular disease including coronary heart disease (CHD). Uric acid is an indicator of metabolic abnormalities that can aggravate CHD. Every 1 mg/dl increase in blood uric acid levels will increase CHD mortality by 15%.(4) High density lipoprotein (HDL) cholesterol plays a role in suppressing blood oxidation reactions and protecting blood vessel endothelial cells. HDL cholesterol can interact directly or indirectly with other lipids and various substances in the blood. Decreased serum HDL cholesterol levels tend to be associated with very poor metabolic status and decreased HDL cholesterol is even a marker of a metabolic syndrome.(5)

Statins are the most efficient agents for reducing plasma LDL cholesterol, and also have an acceptable safety profile. The pleiotropic effects of statins are reduced accumulation of esterified cholesterol into macrophages, increased endothelial nitric oxide synthesis, reduced inflammation, improved atherosclerotic plaque stability, and antioxidant, anti-inflammatory and antithrombotic properties. Statins can also produce a meaningful reduction in serum uric acid levels, implying a pleiotropic action associated with certain drugs.(6) The effect of statins on HDL cholesterol levels varies from an increase of 1% to 10%, depending on the dose. The success of statins in the clinical setting confirms the epidemiological evidence that points to elevated LDL as a direct cause of atherosclerosis development. However, statins can also increase HDL based on strong epidemiological

evidence, most likely independently contributing to their benefits. Four large prospective studies estimated that an increase in HDL-C by 1 mg/dl was associated with a 2-3% lower risk of CHD.(7) The combination of these both metabolic parameters, the uric acid-HDL ratio (UHR) makes it a very useful predictor measure of metabolic decline. UHR is suggested to be a better predictor of metabolic syndrome than any other marker of metabolic syndrome. UHR is an easy, affordable, and economical measure that can be useful in predicting cardiovascular risk at routine screening.

2. Objectives

The Objective of this study was to determine baseline UHR as a predictor of MACE after administration of high-intensity statins.

3. Methods

Study population

This study was conducted in the Cardiac Center of Dr. Zainoel Abidin Regional General Hospital. This study was a two-group paired numerical comparative analytical observational study with a prospective cohort design. The target population of this study were all patients with heart disease at hospital, while the affordable population were patients with ischemic heart disease who were classified as patients with very high cardiovascular risk.

In this study using a sampling technique in the form of consecutive sampling. The inclusion criteria in this study were patients with adult age > 18 years and age < 70 years, having complete lipid profile records (HDL, LDL, Triglycerides) and Uric Acid at the time of study recruitment measured as baseline UHR values, Patients with coronary heart disease with very high cardiovascular risk in the form of ASCVD which is proven both clinically and imaging and getting statin therapy with high intensity, having complete medical records and patient identity data. The exclusion criteria for this study were patients who had allergies to statin administration, were not compliant with taking the drugs given in the form of statins, pregnant or breastfeeding, malignancy, CKD stage IV-V, incomplete data.

Study measurements

Table 1

Characteristic	n (%) / Mean±SD / Median (Min-Max)
Age (years), Mean ± SD	57,79 ± 9,83
Gender, n (%)	59 (72)
- Male	23 (28)
- Female	
Body Weight (kg), Median (Min-Max)	65 (46-78)
Body Mass Index (kg/m2), Median (Min-Max)	23,6 (19,0-39,2)
Systolic Blood Pressure (mmHg), Mean ± SD	122,06 ± 22,38
Dystolic Blood Pressure (mmHg), Mean ± SD	70,44 ± 17,52
Ejection fraction (%), Mean ± SD	46,18 ± 14,17
Total cholesterol 0 month (mg/dL), Median (Min-Max)	166 (92-380)
HDL 0 month (mg/dL), Mean ± SD	34,86 ± 8,71
LDL 0 month (mg/dL), Mean ± SD	117,54 ± 51,76
Uric Acid 0 month (mg/dL), Median (Min-Max)	7,40 (3,10-17,70)

Chemical blood tests and lipid profiles were performed on patients by performing venous puncture at the cubital fossa as much as 3 cc aseptically for further assessment of the basic uric acid - HDL ratio with the following formula: serum uric acid level (mg/dL) divided by serum HDL level (mg/dL), then the patient will receive high-intensity statin management. Follow-up during the study period was conducted clinically to evaluate major cardiovascular events defined as acute myocardial infarction (AMI), admission for heart failure, and cardiovascular mortality. At 3 months and at the end of the 3-month follow-up period, uric acid and HDL levels will be re-evaluated.

Statistical analysis

The data obtained in this study will be assessed for statistical significance using paired t-test and independent t-test. Furthermore, if the data is not normally distributed based on the Kolmogorov Smirnov test data normality test, it will use the alternative test Wilcoxon rank test and Mann Whiney U Test with a confidence level of 95%.

Ethic Statement

The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics

committee of Zainal Abidin General Hospital (Approval No. 023/ETIK-RSUDZA/2024).

4. Results

Patient demographics

After collecting research data during the study period, the total number of patients with cardiovascular disease with very high cardiovascular risk who met the inclusion and exclusion criteria of the study was 82 patients. Furthermore, descriptive statistical analysis was carried out to determine the characteristics of the research subjects which can be presented in the following table:

Table 1. Baseline Characteristic

The characteristics of the study subjects with total distribution of 82 patients. The mean age was 57.79 years. The subjects included 59 male patients and 23 female patients. Furthermore, the mean value of body weight variables was 65kg and the mean BMI was 23.6 kg/m2. The mean values of systolic blood pressure, diastolic blood pressure, and cardiac ejection fraction were 122.06mmHg, 70.44mmHg, and 46.18%, respectively.

The mean value of 0 month total cholesterol level was 166mg/dL and the mean value of 0 month HDL was 34.86mg/dL. While the mean LDL 0 month was 117.54mg/dL. The mean value of 0-month uric acid levels was found to be 7.40mg/dL.

Results of the 3-Month Observation After Statin Treatment

After 3 months of observation, the following results were obtained:

Table 2. Observation Results 3 Months After Statin Treatment

Characteristic	n (%) / Mean±SD / Median (Min-Max)
Total cholesterol 3 months (mg/dL), Mean ± SD	170,91 ± 49,13
HDL 3 months (mg/dL), Median (Min-Max)	40 (20-110)
LDL 3 months (mg/dL), Mean ± SD	108,43 ± 39,31
Uric Acid 3 months (mg/dL), Mean ± SD	7,04 ± 2,20

Based on table 2, it is known that 3 months of observation after the treatment of statin therapy. The mean value of 3-month total cholesterol was 170.91mg/dL with the mean value of 3-month HDL was 40mg/dL and the mean value of 3-month LDL was 108.43mg/dL. The mean value of 3-month uric acid level was 7.04mg/dL.

Observation Results of Major Cardiovascular Events

During period of 3 months observation, 33 patients who did not have MACE and 49 patients who had MACE were obtained, where 36 patients with MACE events were rehospitalized and 13 people had mortality. The following results of major cardiovascular events are shown in the graph as follows:

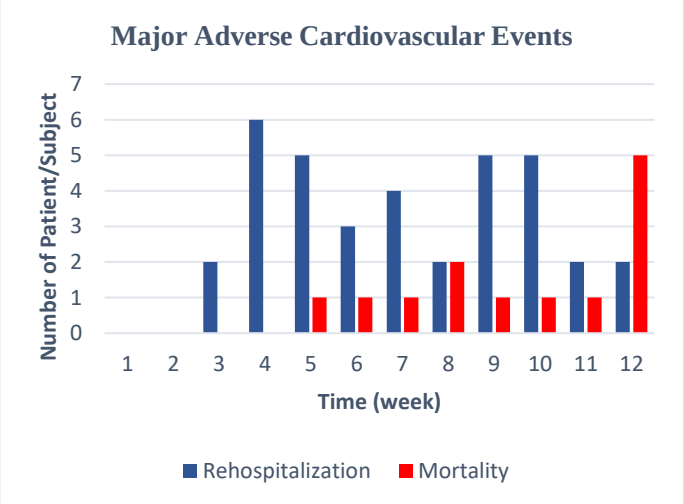

Figure 1. Major Adverse Cardiovascular Events

Based on Figure 1, it was shown that the initial incidence of rehospitalisation occurred in week 3 and the initial incidence of mortality occurred in week 5, then the highest incidence of rehospitalisation occurred in week 4

with an incidence of 6 people and the highest incidence of mortality was found in week 12 with an incidence of 5 subjects.

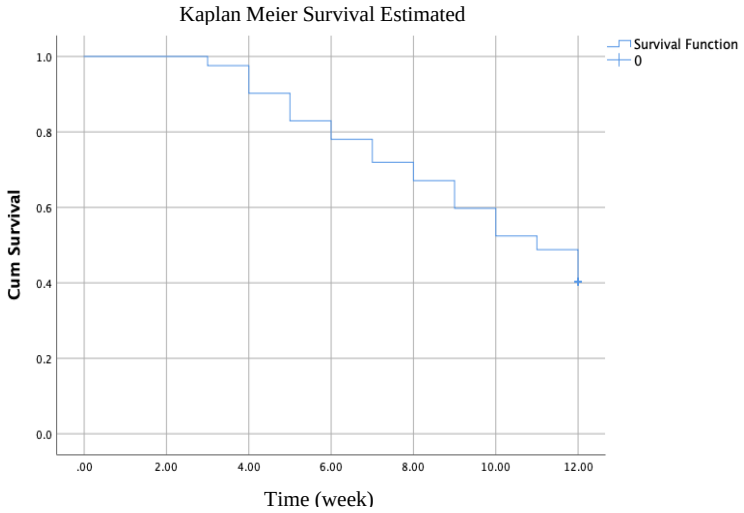

Figure 2. Analysis of Survival Rate Estimation in Patients with High Cardiovascular Risk

The figure above explains the survival analysis using Kaplan-Meier curves and found that the average incidence of MACE in patients who have high cardiovascular risk who receive high-intensity statins occurs at 9.48 week.

The Analysis of Differences in Baseline Uric Acid - HDL Ratio in Groups with and Without MACE

Analysis of the difference in baseline uric acid - HDL ratio in groups with and without MACE is shown in the table below.

Table 4. Analysis of Differences in Baseline Uric Acid - HDL Ratio in Groups with and Without MACE

	Median	Min – Max	P Value*
MACE (+)	0,188	0,09 – 0,58	0,806
MACE (-)	0,207	0,09 – 0,61	

* Mann Whitney test

Table 4 shows it was found that the mean baseline UHR of the group with MACE was 0.188 and without MACE was 0.207. Statistically, there was no significant difference in UHR in patients with very high cardiovascular risk with and without major cardiovascular events (p=0.806).

5. Discussion

This study aimed to evaluate the relationship between uric acid-HDL ratio and major cardiovascular events in patients with very high cardiovascular risk stratification receiving high-intensity statin therapy. Based on the baseline UHR results, there was no significant difference between the group with MACE events and the group without MACE events. This indicates that after 3 months of high-intensity statin treatment, the uric acid-HDL ratio showed no significant difference between the two groups. The findings of this study may indicate that the uric acid-HDL ratio is not sensitive or specific enough as an indicator for major cardiovascular events. Other factors such as overall health condition, lifestyle, and history of disease may be more influential at an early stage.

The results of these analyses also suggest that statin therapy may not significantly affect the uric acid-HDL ratio in the context of major cardiovascular events. However, a study conducted by El-Tantawy & Temraz et al (2019) showed that the effect of statins on lipid profiles may vary depending on the dose and type of statin used.(8)Therefore, it should be noted that the study findings could also be influenced by the sample size, duration of observation, or other variables that were not controlled in the study. The results of this study are also in line with a study conducted by Cicero et al. (2015) which showed that the effect of statin administration on uric acid levels can vary and does not always have a direct impact on cardiovascular events.(9)

There was no significant difference between the groups with and without MACE, this significant change in UHR indicates a statin-induced biochemical effect. This is in line with the literature which states that the effects of

statins can alter lipid and uric acid profiles in the body.(10) Research conducted by Kastelein et al. (2008) showed that statin administration can affect various biochemical parameters, including uric acid and HDL, although the effects may vary in each individual.(11)

In the study of Anjan et al (2023), treatment with statins (Atorvastatin 10 mg, 20 mg and 40 mg) was highly effective in normalising lipid parameters and reducing uric acid. However, this study could not find a dose-dependent effect of Atorvastatin on uric acid, as participants had varying baseline serum uric acid values. In a study conducted by Stella-Maris et al also reported no significant relationship between statin dose and serum uric acid. (12)

As a result of decreased proximal tubular reabsorption, Atorvastatin significantly increases the amount of uric acid excreted through the urine. This occurs through an active transport process that is closely related to sodium reabsorption in the tubules. Another possibility is that lipophilic statins, such as atorvastatin, have stronger tissue effects. For example, these drugs can improve endothelial function and impact the renal vasculature, increasing renal blood flow and glomerular filtration rate (GFR), which in turn impacts uric acid levels.(13)

The results of a study conducted by Kastelein et al. (2008) also showed that lipid biomarkers often have limitations in predicting cardiovascular events if not used together with other risk factors.(11) In addition, Wei et al. (2019) emphasised the importance of considering the population and clinical setting when evaluating the effectiveness of biomarkers in cardiovascular research.(14) In accordance with Hu et al (2022), found that increased serum uric acid levels change the way HDL affects carotid atherosclerosis.(15) UHR levels are reported to be significantly increased in patients with haemodynamically significant coronary lesions. Beyond coronary conditions, UHR has shown associations with various non-coronary comorbidities.(13) Omer et al (2024) mentioned the ease of obtaining parameters such as UHR and its potential to predict in-hospital mortality in patients undergoing PPCI for STEMI highlights its clinical utility and the importance of its inclusion in risk assessment protocols.(16)

This is contrary to the study conducted by Yu Yang et al (2023) who reported for the first time, that high UHR may be associated with increased adverse clinical events in patients with ischaemic heart disease.(17) This prognostic value could possibly be due to increased uric acid and decreased HDL-C levels. Many studies have shown that uric acid/HDL ratio is a good predictor of ASCVD events.(18) In addition, additive interactions may explain part of the observed value of UHR for coronary heart disease prognosis. Yazdi et al showed that a high uric acid/HDL ratio increased the risk of metabolic syndrome by 2.9 times.(19) In the study, it was found that the mean level of UHR was significantly higher in coronary heart disease patients compared to the general population.(17) As stated by Kannel (2002), cardiovascular risk is often influenced by several other factors besides lipid profile, including blood pressure, smoking habits, and diabetes.(20)

In summary, the results of this study suggest that the UHR does not have a significant predictive ability of MACE in patients with very high cardiovascular risk who are given high-intensity statin therapy. Changes did not prove to be sensitive or specific enough to predict MACE. Cardiovascular risk is often influenced by factors other than lipid profile, including blood pressure, smoking and diabetes. Overall, RAH predictors did not perform well in predicting MACE incidence.(4) The results of this study emphasise the importance of considering various other risk factors and the need for further studies using larger samples and longer duration of observation to gain a more comprehensive insight into the relationship between UHR and major cardiovascular events. There was not significant predictive ability of MACE in patients with very high cardiovascular risk who are given high-intensity statin therapy.

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