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Triglyceride Glucose Index as a Predictor of 30–Day Readmission and 6 Months Mortality After Hospitalization in Acute Decompensated Heart Failure

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Abstract

Background: Acute decompensated heart failure (ADHF) is a cardiovascular disease with high mortality and readmission rates. Currently, insulin resistance has been reported to predict the prognosis of ADHF patients. Triglyceride glucose index (TyG) has now been proposed as an independent predictor of cardiovascular risk and a simple marker of insulin resistance. However, the association between TyG and 30-day readmission and 6 months of mortality after hospitalization remains unclear.

Objective: To investigate TyG as a predictor of 30-day readmission and 6-month mortality after hospitalization in ADHF patients.

Methods: The study was conducted in a retrospective cohort. Data were taken from medical records based on the admission of patients who met the inclusion criteria from January 2018 – November 2021. The clinical outcomes were 30 days readmission and 6 months mortality. The data were analyzed by multivariate analysis and the survival rate of the subjects.

Results: This study included 467 subjects, with 158 subjects having clinical outcomes. The readmission rate is 29% (135 subjects), and the 6-month mortality after hospitalization is 5% (23 subjects). Multivariate analysis showed that the factors associated with 30-day readmission were hypertension (p 0.03, HR 1.547, CI 95% 1.044 – 2.291), systolic blood pressure > 140 mmHg on admission (p< 0.001, HR 0.441, CI 95% 0.296 – 0.658), triglyceride 150 mg/dL (p 0.012, HR 1.812, CI 95% 1.139 – 2.881), and TyG index (p <0.001, OR 4.594, CI 95% 2.717 – 7.767). Independent factors for 6 months mortality were only no diuretic medication (p 0.02, HR 6.015, CI 95% 1.975 – 18.320).

Conclusion: Triglyceride glucose index can predict 30-day readmission, but is not associated with 6-month mortality in ADHF patients.

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Keywords: Acute decompensated heart failure, triglyceride glucose index, 6 months mortality, 30-day readmission.

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Introduction

Insulin is one of the hormones that are cardioprotective.[1] Therefore, insulin resistance or hyperinsulinemia can interfere with the metabolic status of a patient. This condition typically develops well long before prediabetes or type 2 diabetes occurrences.[2] Multiple studies demonstrate the associations between insulin resistance and cardiovascular outcomes, including heart failure (HF).[3] Heart failure is a fundamental health issue because of the economic burden and the leading contributor to high treatment costs. In addition to high prevalence and mortality, the burden of HF also includes the risk of hospital readmission. According to the Atherosclerosis Risk in Communities Study (ARIC), the hospital readmission rates for patients with ADHF were highest in the first 30 days after discharge from the initial hospitalization and were greater for patients with lower ejection fraction than those with normal ejection fraction.[4] The susceptible phase of acute HF begins with an acute HF exacerbation and lasts for up to six months after hospitalization. This phase was related to a 30% and 10% increase in the risk of hospital readmission and mortality, respectively, in the first few weeks. Accordingly, early detection of insulin resistance is essential.[5]

Insulin resistance is determined by performing the hyperinsulinemic-euglycemic clamp (HIEC) method as the gold standard of diagnosis, but it is impractical in daily practice. Triglyceride glucose index (TyG) is a simple surrogate biomarker for insulin resistance. Consequently, the TyG index has been suggested as the initial screening for insulin resistance.[6] Insulin resistance is caused by inefficient oxidation and more utilization of fatty acids. The rapid influx of free fatty acids from adipose tissue to non-adipose tissue induces anomalies in fat metabolism, thereby increasing many metabolic problems that characterize insulin resistance. Hepatic triglycerides are a strong determinant of hepatic insulin resistance and intramyocellular triglycerides in muscular insulin resistance.[16] Consequently, the TyG Index should represent the metabolic state of insulin resistance.[7] Some studies demonstrated that a high TyG index increases the cumulative risk for the incidence of T2DM.[8] A large cohort study found that a high TyG index at baseline is correlated with a 15 percent greater risk of HF, as well as remodeling and left ventricular dysfunction.[4]

Hitherto, there are not enough studies looking at the relationship between insulin resistance as assessed by the TyG index with 30-day readmission and 6-month mortality after hospitalization in acute decompensated heart failure (ADHF) patients treated for the first time.

Materials & Methods

Study Design and Population

This is a single-center retrospective cohort study at the National Cardiovascular Centre Harapan Kita Hospital, Jakarta. From January 1st, 2018 to November 31st, 2021, 2785 consecutive patients were admitted to the emergency room with their first admission for ADHF. Of the 2785 patients, 2265 patients were excluded for meeting the exclusion criteria, namely: acute coronary syndrome, valvular heart disease, congenital heart disease, history of valve surgery, and hypertrophic obstructive cardiomyopathy/restrictive cardiomyopathy. Loss to follow-up was noted in 53 patients (11.3%). Finally, 467 patients were included in this study. This study was approved by the ethics committee of the National Cardiovascular Centre Harapan Kita Hospital, Jakarta.

Data Collection and Definition

Demographic, medical history, medications, laboratory results, and other examinations were conducted from the electronic medical record system. Length of stay was the duration of hospitalization. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (SBP) ≥ 90 mmHg, using antihypertensive medication, or having a history of hypertension. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% or routine of using antidiabetic medication. Body mass index (BMI) was defined as weight (kg)/height (m^2). TyG formula was [Ln(triglyceride x fasting blood glucose)/2]. Laboratory data were collected during admission.

Outcome and follow-up

The primary and secondary outcomes were

Table 1. Clinical characteristic of study population.

Variabel	Kelompok					
	30-days readmission N=135	P value	Mortality in 6 months N = 23	P value	Without outcome N = 309	Total N=467
Age	57±11.6	0.025a	62±7.2	0.123	59±11.3	58.6±11.3
Man	93(68.9%)	0.03a	18(78.3%)	0.888	243(78.6%)	354(75.8%)
Length of Stay	8 (3 – 40)	0.13	10 (3 – 51)	0.04 a	7 (2 – 33)	8 (6 – 51)
Hypertension	77 (57%)	0.207	13 (56.5%)	0.885	192 (62.1%)	282 (60.4%)
Diabetes Mellitus	80(59.3%)	0.022 a	15(65.2%)	0.22	142(46.0%)	237(50.7%)
Body Mass Index						
Normal	39 (28.9%)	0.267 (ref)	11 (47.8%)	0.294 (ref)	113 (36.6%)	163 (34.9%)
Overweight	14 (10.4%)	0.172	3 (13%)	0.20	22 (7.1%)	39 (8.4%)
Obese	82 (60.7%)	0.16	9 (39.1%)	0.193	174 (56.3%)	265 (56.7%)
ECG						
Sinus rhythm	126(93.3%)	0.025 (ref)	22(95.7%)	0.442 (ref)	254(82.2%)	402(86.1%)
Atrial Fibrillation	8(5.9%)	0.007a	0(0.0%)	0.20	52(16.8%)	60(12.8%)
Others	1(0.7%)	0.753	1(4.3%)	0.207	3(1.0%)	5(1.1%)
Ejection Fraction						
HFrEF	103(76.3%)	0.026a	20(87.0%)	0.207	213(68.9%)	336(71.9%)
HFmEF	15(11.1%)	0.263	2(8.7%)	0.14	23(7.4%)	40(8.6%)
HFpEF	17(12.6%)	0.027 (ref)	1(4.3%)	0.267 (ref)	73(23.6%)	91(19.5%)
ACE/ARB/ARNI	121(89.6%)	0.399	19(82.6%)	0.125	285(92.2%)	425(91.0%)
Beta-blocker	111 (82.2%)	0.968	13 (59.1%)	0.005 a	255 (82.5%)	379 (81.3%)
MRA	87(64.4%)	0.798	13(56.5%)	0.27	205(66.3%)	305(65.3%)
Loop Diuretics	126(93.3%)	0.851	18(78.3%)	0.007 a	289(93.5%)	433(92.7%)
Systolic blood pressure at admission	130 (79 – 197)	0.005a	119 (73 – 179)	0.493	123 (65 – 233)	124 (65 – 233)
Diastolic blood pressure at admission	78.5 (46 – 120)	0.049a	76 (56 – 110)	0.216	72 (55-100)	76 (46 – 120)
Heart rate predischarge	82 (52 – 160)	0.218	85 (46 – 114)	0.487	85 (48 – 122)	85 (46 – 160)
Triglyceride	159 (59 – 513)	<0.001a	148 (41 – 513)	0.001 a	100 (90 – 449)	112 (41 – 513)
Fasting blood glucose	117 (34 – 306)	<0.001a	133 (83 – 276)	0.001 a	99 (64 – 277)	103 (34 – 306)
Ureum	46 (11 – 178)	0.504	51.5 (28.5 – 264)	0.023	41.2 (12 – 199)	43.5(11 – 264.4)
BUN	21.5 (5 – 83)	0.525	24 (13 – 124)	0.033	20 (17.5 – 93)	20 (17.5 – 124)
Creatinin	1.88 (0.5 – 3.7)	0.165	1.2 (0.85 – 6.66)	0.952	1.24 (0.43 – 1.5)	1.23 (0.43 – 6.66)
eGFR	57 (13-125)	0.532	54 (7 – 97)	0.423	57 (3 – 129)	57 (3 – 129)
TyG index	4.9 (4.37 – 5.68)	<0.001a	4.94 (4.53 – 5.83)	0.001	4.6 (4.04 – 5.68)	4.69 (4.04 – 5.83)

examined. The primary outcome was 30-day readmission and the secondary outcome was mortality in 6 months. Patients were followed up by phone and/or electronic medical records.

Statistical Analysis

After all patient data were collected, data entry, data editing, and variable coding were done. Data processing began with assessing the distribution of the data. The data will be presented in the form of categorical and numerical data. In the normal distribution, numerical data are presented with the mean ± standard deviation (SD), while in the non-normal distribution, the median ± minimum-maximum was presented.

The baseline characteristics of the patients will be assessed using the Cox regression test. In this analysis, if $p < 0.25$ will be included in the multivariate analysis and final model. Furthermore, the correlation between the TyG index and the length of survival was examined in the form of a Kaplan-Meyer curve. The limit of significance used is $p < 0.05$.

Then a test was conducted to determine the cut-off value of the TyG index by examining the receiver operating characteristic (ROC) and the area under the curve (AUC). This value was used to measure the association of the TyG index with clinical outcomes. All data analysis using SPSS.version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline characteristic of the study population

In this study, 467 patients with ADHF were recruited as subjects who met the inclusion and exclusion criteria. The results obtained 30-day readmission of 135 subjects (29%) and 23 subjects (5%) had mortality 6 months after hospitalization. **(Table 1)**

The mean age in the group with the clinical outcome of 30-day readmission had a younger age, which was 57±11.6, compared to the group without a clinical outcome. However, the mean age of mortality in 6 months was the oldest, which was 62±7.2. Based on the ECG in this study, the most common was sinus rhythm ECG (93.7%). Regarding ejection fraction, the highest proportion were patients with low ejection fraction

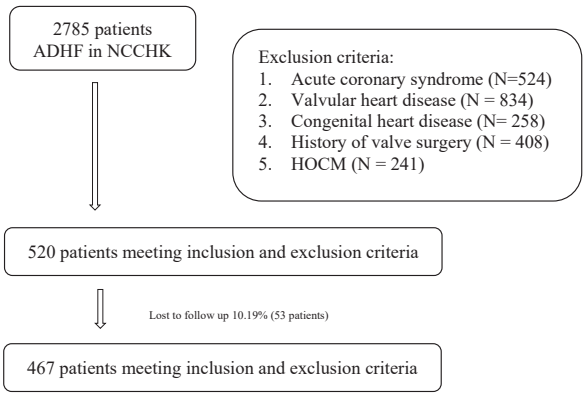

Figure 1. Flow diagram of subject selection.

(71.9%). In using ACE-I/ARB/ARNI and diuretics, this study found that most patients had received these therapies, namely 91% and 92.7%, respectively. On the other hand, the proportion of using MRA in ADHF patients in this study was only 65.3%.

The outcome of a 30-day Readmission

Based on the bivariate results **(Table 1)**, all variables with $p<0.25$ were included in the multivariate analysis. The results of the multivariate analysis for the 30-day readmission showed that the initial variables were not all $p <0.05$, so statistically, those that were strongly associated with the outcome of the 30-day readmission were hypertension, systolic blood pressure, and TyG index **(Table 2)**.

The ROC analysis showed that the level of TyG index (AUC = 0.821, 95% CI = 0.781 – 0.860) with a cut-off value of 4.815 was statistically significant and included in the model. Kaplan-Meier analysis with log-rank test showed significant differences between the two groups (TyG index <4.815 and TyG index ≥4.815) **(Figure 3)**.

The outcome of 6-months Mortality

Multivariate analysis for 6-month mortality showed that those patients without the use of diuretics were the only independent and significant predictor (p 0.002; HR 6.015; CI 95% 1.975 – 18.320). The ROC analysis showed that the level of TyG index (AUC = 0.732, 95% CI = 0.634 – 0.831) with a cut-off value of 4.825 was statistically significant. The Kaplan-Meier analysis with log-rank test showed significant differences between the

Table 2. Multivariate analysis for 30-days readmission.

Variabel	Nilai P	HR	95% CI	
			Minimum	Maksimum
Hypertension	0.030	1.547	1.044	2.291
Triglyceride >150 mg/dL	0.012	1.812	1.139	2.881
Systolic blood pressure >140 mmHg	<0.001	0.441	0.296	0.658
TyG index	<0.001	4.594	2.717	7.767

two groups (TyG index <4.825 and TyG index ≥4.825) **(Figure 3.)**.

Discussion

Our study demonstrated that the TyG index is a significant predictor of 30-day hospital readmission in patients with ADHF. The other significant predictors of 30-day hospital readmission are hypertension, elevated triglyceride concentration (≥ 150 mg/dL), and systolic blood pressure ≥ 140 mmHg. The only significant predictor of 6-month mortality is those patients without the use of diuretics.

Thirty days of hospital readmission of ADHF in this study was 29%. A previous study reported a similar number of 30-day readmissions of ADHF in Indonesia [9]. In Europe and America, the hospital readmission rate was 19-30%. These data showed that hospital readmission is still the main health issue for ADHF. Many studies tried to find predictors of readmission in ADHF, however, hospital readmission in patients with HF is caused by multifactorial factors and also due to the health system and patient self-care behavior.[10] Mortality of ADHF during 6-month follow-up was encountered in 5% of the cohort, whereas INTER CHF in a 2016 study showed mortality in ASEAN about 15% in ADHF patients. This study showed that most patients were clinically treated according to the ESC Guideline for Heart Failure, for example, ACE-i/ARB/ARNI (91.0%), beta-blockers (81.3%), MRA (65.3%), and loop diuretics (92.7%).

Hypertension was one of the predictors associated with the incidence rate of 30-day hospital readmission. Akkineni et al. showed that HF patients with hypertension would increase the risk by 53% for 30-day readmission in those with acute HF ($p < 0.034$).[11] History of hypertension has been a factor influencing the clinical outcome of HF. The state of hypertension would increase the heart work and trigger the structural and functional changes in the myocardium. These changes include left ventricular hypertrophy, one factor that significantly increases morbidity and mortality in HF patients.[11] Systolic blood pressure (SBP) at admission was divided into two groups, ≥140 mmHg and <140 mmHg. This study showed that SBP of more than 140 mmHg is a protective factor for 30-day hospital readmission. Increasing SBP in acute settings has shown an appreciable protective effect. It is a result of high sympathetic tone, termed reactive hypertension. Elevated SBP indicates the presence of functional cardiac reserve in the face of an acute physiologic stressor.

contrast, low or even normal BP at presentation, which may be the goal of treatment in the ambulatory setting, maybe a more ominous finding, reflecting a low cardiac output and suboptimal or inadequate end-organ perfusion, including coronary hypoperfusion, thereby worsening the heart failure condition.[12] Triglyceride levels of ≥150 mg/dL had an 81% higher risk for 30-day hospital readmission in ADHF patients. The association may be direct, indirect, or both. Hypertriglyceridemia is a marker of insulin resistance and metabolic syndrome. It showed high serum levels of remnant lipoprotein, which are atherogenic and pro-inflammatory. Hypertriglyceridemia has a positive association with cardiovascular events, especially atherosclerotic disease leading to ischemic cardiomyopathy. Its condition can lead to the expansion of epicardial pad volume; and increased epicardial adiposity thereby accelerating lipotoxic cardiomyopathy.[13] The utilization of loop diuretics was administered in almost all patients, which was approximately 92.7% and statistically significant. In addition, Faselis et al. found that high use of potent diuretics reduced 30-day readmission independently.[14] Several other clinical trials have also shown that the administration of diuretics can improve the symptoms

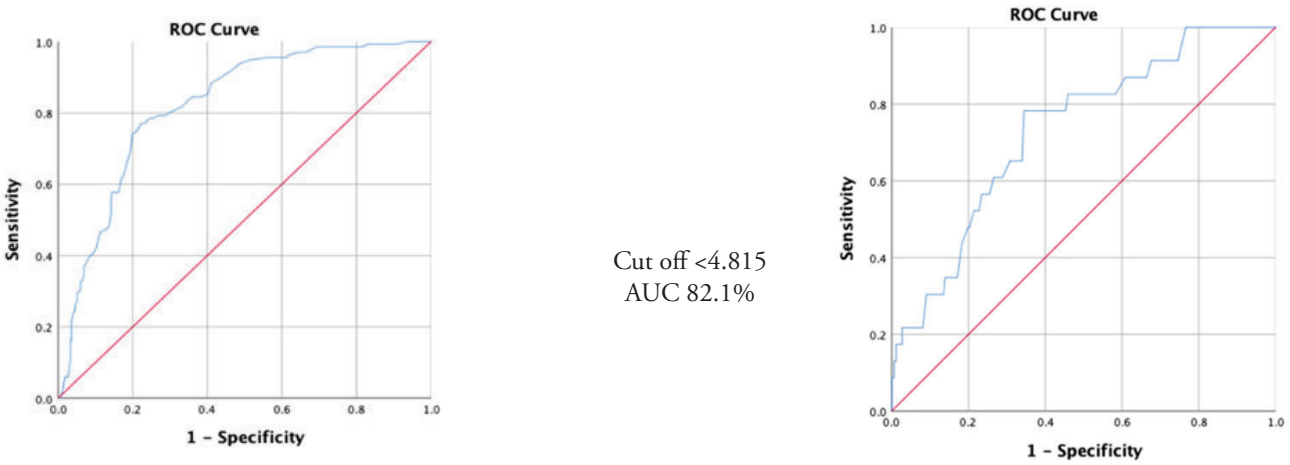

Figure 2. Receiver operating characteristic curve. Sensitivity represents true-positive results and 1-specificity the false-positive results. The best TyG index for predicting 30-days readmission (a) and 6-months mortality.

and signs of fluid retention in HF. In a short-term study, diuretics significantly reduced HF symptoms, for example, jugular venous pressure, pulmonary congestion, and peripheral edema. In an intermediate-term study, diuretics may improve patients' cardiac function, symptoms, and activity tolerance. Therefore, diuretics are vital in heart failure patients to reduce mortality and morbidity.[15]

In this study, the TyG index was statistically significant for 30-day readmission in patients with ADHF ($p < 0.001$). Furthermore, Huang et al. suggested that the TyG index was independently associated with poor prognosis.[16] A retrospective cohort study stated that the TyG index correlated with the prognosis of patients with chronic HF and T2DM.[17] Another study suggested that the TyG index could be a new biomarker for assessing myocardial fibrosis and significant risk stratification in HF.[18] Assessing the relationship between the TyG index and worsening acute HF showed a relationship between metabolic conditions and HF. Myocardial insulin resistance can alter myocardial carbohydrate metabolism. In a study by Bing et al., diabetic patients had an increase in the number of fatty acids from the myocardium. Fatty acids themselves can cause various effects on the myocardium. In the state of insulin resistance, plasma-free fatty acids increase triglycerides, and cellular free fatty acids, and increase fatty acids. The association of altered metabolism of HF to insulin resistance includes SNS and RAS activation, inflammation with TNF-alpha, changes in skeletal muscle function and mass resulting in decreased physical activity, and increased adipokines such as adiponectin and leptin.[19] Several studies discuss the interaction between insulin resistance and poor prognosis of HF. First, the state of insulin resistance is said to cause sodium retention, thereby triggering a worsening condition in patients with ADHF. Second, insulin resistance is known to cause sympathetic nervous system activation and RAAS activity that contributes to myocardial fibrosis and cardiac dysfunction.[20] Additionally, the TyG index is easy to obtain in clinical practice. Therefore, it can be routinely assessed in ADHF patients as a therapeutic target thence make a better prognosis in ADHF patients.

Anyway, there are still some limitations to this study. First, this is a retrospective study based on the medical records; therefore, the incomplete data or variables were not unavoidable. Second, this study did not assess medication adherence, knowledge, and lifestyle of HF patients, which are essential factors in predicting readmission in acute heart failure patients.

Conclusion

Our study suggests that the triglyceride-glucose index can predict 30-day hospital readmission but is not associated with 6-month mortality in ADHF patients.

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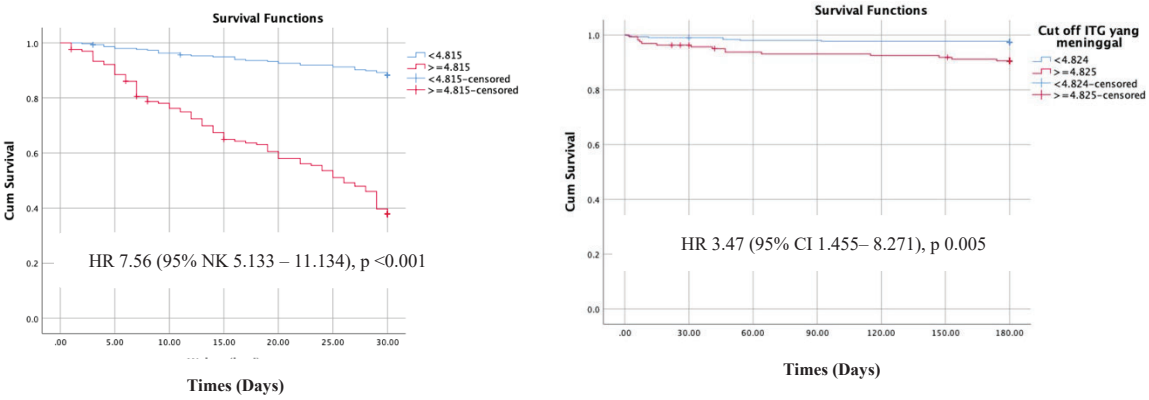

Figure 3. Kaplan Meier Curve for predicting 30-days readmission (a) and 6-months mortality.

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