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Association of Left Ventricular *Global Longitudinal Strain* (GLS) and NT Pro BNP Levels with Major Cardiovascular Events in Chronic Heart Failure Patients with Reduced Ejection Fraction

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ABSTRACT

Background: Chronic heart failure (CHF) impairs the heart's pumping ability due to structural or functional issues. Global Longitudinal Strain (GLS) is a precise method for assessing left ventricular function, while NT-proBNP is used to diagnose heart failure and predict outcomes. This study examines the relationship between GLS and NT-proBNP as predictors of major cardiovascular events in CHF patients with reduced ejection fraction. ***Methods:*** Chronic heart failure patients with LVEF ≤49% were observed in a cohort study. After echocardiography and NT-proBNP blood sampling, they were followed for 3 months to monitor rehospitalization and/or mortality. Baseline characteristics included demographic, clinical, comorbidity, laboratory, and echocardiographic data. GLS and NT-proBNP cutoff values were determined via ROC curves, and survival analysis was conducted using Kaplan-Meier curves and Cox Regression in SPSS 26.0. ***Results:*** A total of 65 samples were enrolled with no drop-outs. The optimal GLS cutoff was -7,5% (AUC 0,763, p=0,017) with 62,5% sensitivity and 86% specificity. NT-proBNP's cutoff was 689 pg/mL (AUC 0,556; p=0,611) with 50% sensitivity and 87,7% specificity. Survival analysis showed lower survival rates in patients with GLS ≥-7,5% (66,7% vs. 92,5%; p=0,022) and NT-proBNP ≥689 (63,6% vs. 92,6%; p=0,012). However, neither GLS ≥-7,5% nor NT-proBNP ≥689 pg/mL were significant independent predictors of major cardiovascular events within 3 months. Higher LAVI (≥41 ml/m2) was found to be a significant independent predictor, associated with GLS ≥-7,5 (r -0,329; p=0,007), high NT-proBNP (r 0,632; p=0,03), EF (r -0,610; p<0,001), E/e' (r -0,32; p=0,014), and medial E (r 0,28; p=0,024).

Keywords: GLS; NT-proBNP; chronic heart failure; major cardiovascular events

INTRODUCTION

Cardiovascular disease is a major health issue globally, with high mortality and morbidity rates. In the United States, approximately 5,7 million adults have been diagnosed with heart failure, and 870,000 new cases arise annually. In Indonesia, over 1 million people suffer from cardiovascular disease, with 20% experiencing heart failure. While hospital mortality rates for heart failure have decreased, readmission rates have risen, reflecting the growing burden of chronic heart failure (CHF) as life expectancy increases [1,2].

Chronic heart failure (CHF) results from structural or functional heart abnormalities that impair its ability to pump blood effectively. The European Society of Cardiology (ESC) classifies heart failure into three categories based on left ventricular ejection fraction (LVEF): HFpEF, HFrEF, and HFmrEF. HFrEF accounts for nearly half of heart failure cases and is associated with worse outcomes compared to other phenotypes. The ASIAN-HF study highlighted that Southeast Asia has the highest mortality rates among heart failure patients, particularly in Indonesia and the Philippines [3–5]

Transthoracic echocardiography is the gold standard for assessing left ventricular function in heart failure patients. LVEF is a key measure but has limitations, particularly in patients with LVEF over 45%. Global longitudinal strain (GLS) offers a more precise assessment of heart function and is a stronger predictor of outcomes than LVEF. GLS is particularly valuable in patients with HFmrEF and HFpEF, where LVEF may not be as prognostic.

GLS's reliability and sensitivity make it a crucial tool for evaluating left ventricular function [6].

Brain natriuretic peptide (BNP) and NT-proBNP are key biomarkers used to diagnose and predict outcomes in heart failure. These peptides indicate ventricular stress and are crucial in guiding treatment, though their use in Indonesia is limited due to cost and lack of insurance coverage. High levels of BNP and NT-proBNP correlate with worse heart failure prognosis, making them essential in the clinical management of HFrEF [7].

This study aims to explore the relationship between GLS and NT-proBNP in predicting major cardiovascular events (MACE) such as rehospitalization and mortality in CHF patients with reduced ejection fraction. The potential for GLS to be as effective as NT-proBNP in predicting outcomes could make it a routine tool for monitoring and guiding therapy in CHF patients, offering a non-invasive, sensitive, and accessible method for assessing heart function.

METHOD

This study is an observational analytic research with an ambidirectional cohort design. The study involves measuring GLS and NT-proBNP levels in patients who presented to the echocardiography lab. The research begins with the assessment of the left ventricular ejection fraction when patients undergo echocardiography at the Integrated Heart Center (PJT) of RSUP Prof. I.G.N.G. Ngoerah Denpasar within a maximum of 7 days after the echocardiography examination, NT-proBNP levels are measured. GLS analysis is conducted using software that processes images from previous echocardiography examinations, including the apical 4 Chamber (CH), 3 CH, and 2 CH views. Subsequently, follow-up is conducted to monitor the occurrence of MACE, such as rehospitalization and/or death due to cardiovascular disease, within 3 months in heart failure patients with reduced ejection fraction.

Samples are selected according to the inclusion criteria when patients undergo echocardiography at the Integrated Heart Center (PJT) of RSUP Prof. I.G.N.G. Ngoerah Denpasar. Blood samples will be collected at the Clinical Pathology Laboratory of RSUP Prof. I.G.N.G. Ngoerah within a maximum of 7 days after the echocardiography examination.

NT-proBNP levels are measured at the Cakra Vidya Usadha (CVU) Integrated Biomedical Laboratory (LBT) FK Udayana using the human NT-proBNP ELISA E-EL-H6126 kit. GLS values are analyzed from previous echocardiography examinations (control patients) obtained during prior outpatient visits. The study is conducted at RSUP Prof. I.G.N.G. Ngoerah from February to August 2024.

The research samples are obtained from an accessible population through consecutive sampling, where all subjects meeting the eligible sample criteria are included in the study until the required sample size is reached. Inclusion criteria: Patients aged ≥18 years with LVEF ≤ 49%. Exclusion criteria: 1) Acute coronary syndrome; 2) Acute heart failure; 3) Significant valvular heart disease; 4) Congenital heart disease; 5) Significant arrhythmias; 6) Severe renal dysfunction; 7) History of chemotherapy; 8) Patients with poor echocardiography views; 9) Patients who refuse to participate after informed consent.

All collected data for each group will be analyzed using the SPSS program. Data analysis will be performed using descriptive analysis, Receiver Operating Characteristic (ROC) curve analysis, proportion comparison tests, and survival analysis using the Kaplan-Meier curve and Cox regression.

RESULT

This am bidirectional cohort study was conducted from June to October 2022 and then continued from March to July 2024, during which samples meeting the inclusion and exclusion criteria underwent echocardiography and blood sampling for NTproBNP level testing. During the study period, a total of 65 samples of patients with chronic heart failure with reduced ejection fraction were included as participants. Based on GLS values and NTproBNP levels, the samples were divided into groups with GLS values of ≥ -7,5, GLS < -7,5, NTproBNP ≥ 689 (high), and NTproBNP < 689 (low). All samples were then followed until rehospitalization and mortality were recorded. During the follow-up period, no samples were categorized as drop-outs. The characteristics of the samples are presented in detail in Table 1.

TABLE 1: Sample Characteristics Based on MACE.

Variable	MACE	Not MACE	p-value
Age	52,38 ± 13,06	58,18 ± 9,37	0,124#
Gender			
Man	5 (9,1%)	50 (90,9%)	0,098#
Woman	3 (30%)	7 (70%)	
BSA (m2)	1,65 ± 0,21	1,74 ± 0,18	0,259
BMI (kg/m2)	24,11 ± 5,21	25,57 ± 4,47	0,396
HbA1C	6,15 (5,2-7,5)	6,30 (4,5 – 12,4)	0,214#
Total cholesterol	140,62 ± 30,79	160,56 ± 40,37	0,185#
LDL	90,12 ± 33,08	106,31 ± 37,68	0,253
HDL	39,25 ± 17,86	38,68 ± 8,43	0,881
TG	106,20 ± 25,79	143,28 ± 65,87	0.122#
eGFR	70,27 ± 25,02	72,19 ± 21,77	0,819

Variable	MACE	Not MACE	p-value
GLS	-8,4 ± -1,91	-11,19 ± 3,52	0,036*#
NT-ProBNP (pg/ml)	990,38 ± 1401,90	432,31 ± 571,38	0,042*#
EF BP %	32,80 ± 6,85	39,35 ± 8,59	0,043*#
EA Ratio	1,34 (0,79-2,41)	0,96 (0,51-5,30)	0,633
Mean E/e'	4 (14,4%)	22 (84,6%)	0,703
TAPSE (mm)	21,00 ± 6,14	21,50 ± 3,92	0,751
LAVI	41,87 ± 13,46	31,68 ± 12,52	0,037*#
Smoking History			**0,685**
Yes	5 (11,1%)	40 (88,9%)	
No	3 (15,8%)	16 (84,2%)	
Hypertension			**0,709**
Yes	4 (10,5%)	34 (89,5%)	
No	4 (14,8%)	23 (85,2%)	
Diabetes Mellitus			**1,000**
Yes	3 (10,7%)	25 (89,3%)	
No	5 (13,5%)	32 (86,5%)	
Dyslipidemia			**0,717**
Yes	4 (10,8%)	33 (82,9%)	
No	4 (14,3%)	24 (85,7%)	
Compliance with taking medication			**0,071#**
Yes	6 (9,8%)	55 (90,2%)	
No	2 (50%)	2 (50%)	
HF classification			***0.066#***
HFmrEF	1 (3,1%)	31 (96,9%)	
HFrEF	7 (21,2%)	26 (78,8%)	
Obesity			***0,258***
Yes	2 (6,3%)	30 (93,8%)	
No	6 (18,2%)	27 (81,8%)	
Anemia			***0,015*#***
Yes	6 (24,4%)	19 (76%)	
No	2 (5%)	95%)	

Note: Numeric data are presented as mean ± standard deviation (SD). The analysis of numeric data was performed using the independent Student's t-test. Categorical data are presented as frequency (n) and percentage (%), and were analyzed using the Chi-square test. BSA = body surface area; BMI = body mass index; HbA1C = hemoglobin A1C; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; TG = triglycerides; eGFR = estimated glomerular filtration rate; GLS = global longitudinal strain; NT-proBNP = N-terminal pro-B-type natriuretic peptide; EF BP = ejection fraction biplane; TAPSE = tricuspid annular plane systolic excursion; LAVI = left atrial volume index. Indicates a statistically significant difference between the two groups ($p < 0,05$).

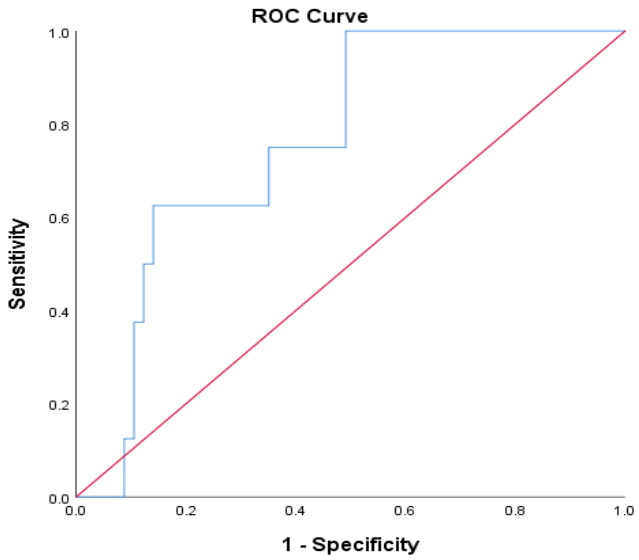

FIGURE 1: ROC Curve of GLS Value Against MACE.

Figure 1 shows the Receiver Operating Characteristic (ROC) curve for GLS values in predicting MACE. The discrimination value of GLS based on the area under the curve (AUC) was 0,763, with a cut-off of -7,5, yielding a sensitivity of 62,5% and a specificity of 86,0%, p = 0,017.

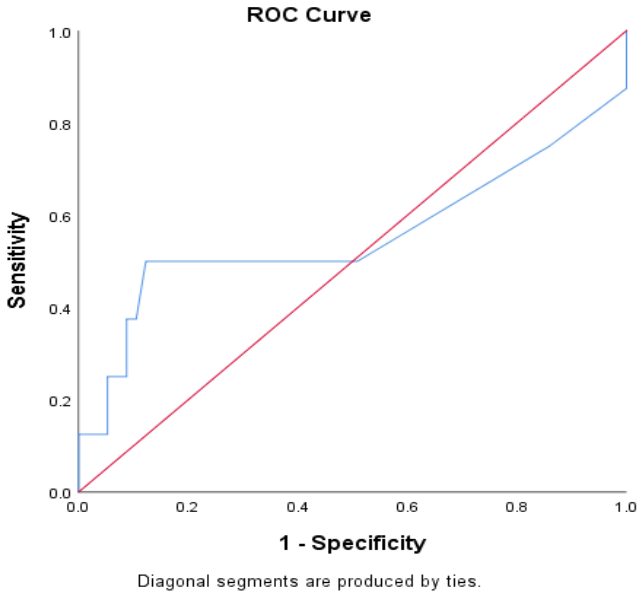

FIGURE 2: ROC Curve of NT-ProBNP Levels Against MACE.

Figure 2 shows the ROC curve for NT-proBNP levels as a predictor of MACE. The discrimination value of NT-proBNP based on the area under the curve (AUC) was 0,556, with a cut-off of 689,0. The sensitivity obtained was 50,0% and specificity was 87,7%, p = 0,611.

TABLE 2: Chi-square Test of GLS Value Against MACE in Chronic Heart Failure Patients with Reduced Ejection Fraction.

GLS	MACE, n (%)	No MACE, n (%)	RR	IK	p
≥ -7,55	4(33,3)	8(66,7)	4,417	(1,283-15,204)	0,033*
< -7,55	4(7,5)	49(92,5)			

Note: GLS = global longitudinal strain. Indicates a statistically significant difference between the two groups (p < 0,05).

TABLE 3: Chi-square Test of NT-ProBNP Levels Against MACE in Chronic Heart Failure Patients with Reduced Ejection Fraction.

NT-ProBNP	MACE, n (%)	No MACE, n (%)	RR	IK	p
≥689	4(36,4)	7(63,6)	4,909	(1,422-16,170)	0,023*
<689	4(7,4)	50(92,6)			

Note: NT-proBNP = N-terminal pro-B-type natriuretic peptide. Indicates a statistically significant difference between the two groups (p < 0,05).

The Chi-square test was conducted to determine the relationship between each variable (GLS value and NT-proBNP levels) and the occurrence of MACE. GLS values were categorized into ≥ -7,5 and < -7,5, while NT-proBNP levels were categorized into ≥ 689 and < 689. Tables 2 and 3 show the results of the Chi-square test to determine the relationship between each variable (GLS value and NT-proBNP levels) and the occurrence of MACE. GLS values of ≥ -7,5 were significantly associated with MACE within 3 months, with an RR of 4,417 (1,283-15,204), p = 0,03. Patients with NTproBNP ≥ 689 pg/mL also showed a statistically significant association with MACE within 3 months, with an RR of 4,909 (1,422-16,170); p = 0,023.

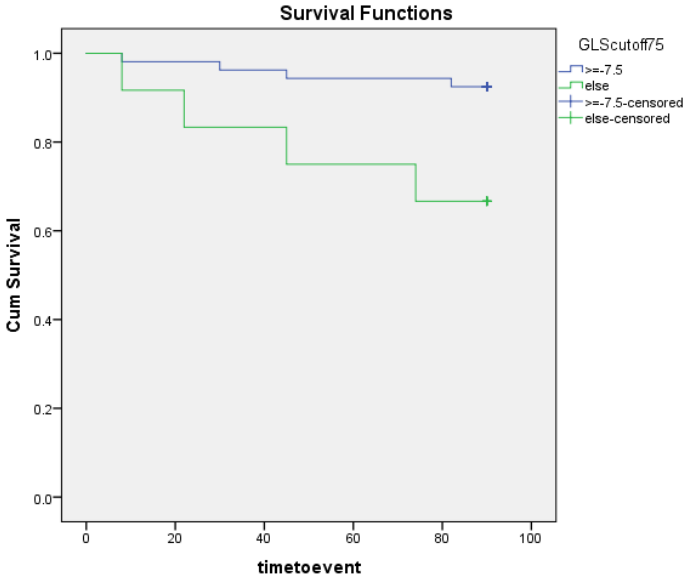

FIGURE 3: Kaplan-Meier Curve of GLS ≥ -7,5 as a Predictor of MACE.

Kaplan-Meier curve analysis with a log-rank test for low left ventricular Global Longitudinal Strain (GLS) values in predicting MACE over the observation period in patients with chronic heart failure with reduced ejection fraction (HFmrEF and HFrEF) showed that patients with GLS ≥ -7,5 had a survival rate of 66,7%, which was significantly different from those with GLS < -7,5, who had a survival rate of 92,5%. The average duration until the occurrence of MACE for GLS ≥ -7,5 was 72 days compared to 86,321 days for GLS < -7,5. Cox regression analysis indicated that GLS ≥ -7,5 was statistically significant as a predictor of MACE occurrence, with an HR of 5.065 (95% CI 1,264-20,293; p = 0,022).

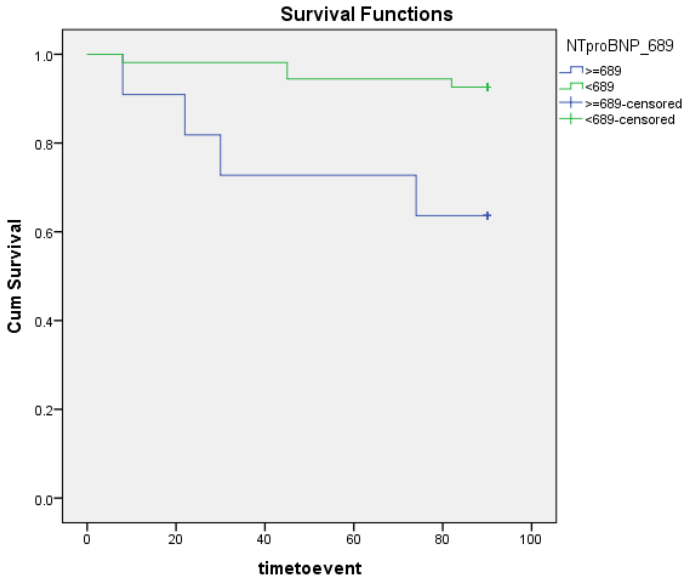

FIGURE 4: Kaplan-Meier Curve of High NTproBNP as a Predictor of MACE.

Kaplan-Meier curve analysis for high NTproBNP levels (≥ 689 pg/mL) in predicting MACE (mean survival time) in patients with chronic heart failure with HFrEF and HFmrEF showed that patients with high NTproBNP levels had a survival rate of 63,6%, while those with low NTproBNP levels had a survival rate of 92,6%. The mean survival time for NTproBNP was 69 days, and for low NTproBNP, it was 86 days (p = 0,004) (Figure 4). Cox regression analysis indicated that high NTproBNP levels were statistically significant as a predictor of MACE occurrence, with an HR of 5,932 (95% CI 4,179-23,800; p = 0,012).

Numerical variables that were significant were then categorized by finding cutoffs using ROC, and the following cutoffs were obtained: HbA1C at 6,25% (specificity 0,491, sensitivity 0,500), Cholesterol at 149 mg/dL (specificity 0,439, sensitivity 0,500), and LAVI at 41 ml/m^2 (specificity 0,842, sensitivity 0,625). A multivariate Cox Regression analysis was then performed with significant categorical variables until the final step.

TABLE 4: Results of Cox Regression Analysis of GLS and NT-proBNP Against Other Variables Based on Determined Cutoff Values.

Variable		AHR	95.0% CI for AHR		p-value
			Lower	Upper	
Step 1	Compliance with taking medication	10,343	,926	115,564	0,058
	GLS≥ -7,5	1,347	,225	8,070	0,744
	NTproBNP ≥ 689	1,060	,109	8,132	0,958
	HbA1C ≥ 6.25	3,588	,044	1,772	0,176
	LAVI ≥ 41 ml/m²	13,296	,011	,521	0,009
	Total cholesterol	2,507	,501	12,555	0,263
Step 5	Compliance with taking medication	6,881	1,244	38,072	0,027*
	LAVI ≥ 41 ml/m²	7,389	,031	,582	0,007*

Explanation: HbA1C = hemoglobin A1C; NT-proBNP = N-terminal pro-B-type natriuretic peptide; EF = ejection fraction; LAVI = left atrial volume index; GLS = global longitudinal strain.

Medication adherence and LAVI were found to be other variables that could not be excluded. An adjusted Hazard Ratio measurement was then performed, adjusted with other variables, as shown in Table 5 and 6.

TABLE 5: Results of Cox Regression Analysis of GLS as the Main Variable Against Other Variables Based on Determined Cutoff Values.

Variable	AHR	95.0% CI for AHR		p-value
		Lower	Upper	
GLS ≥ 7,5	2,082	0,484	8,951	0,324
Compliance with taking medication	5,523	0,954	31,990	0,057
LAVI ≥ 41 ml/m²	6,678	1,496	29,798	0,013*

Explanation: LAVI = left atrial volume index; GLS = global longitudinal strain.

TABLE 6: Results of Cox Regression Analysis of NT-proBNP Levels as the Main Variable Against Other Variables Based on Determined Cutoff Values.

Variable	AHR	95.0% CI for AHR		p-value
		Lower	Upper	
NTproBNP ≥ 689	2,004	0,335	11,971	0,446
Compliance with taking medication	4,150	0,520	33,301	0,179
LAVI ≥ 41 ml/m²	6,324	1,364	29,318	0,018*

Explanation: NT-proBNP = N-terminal pro-B-type natriuretic peptide; LAVI = left atrial volume index.

Due to the possibility of interaction between GLS, NT-proBNP, LAVI, and medication adherence variables—where medication adherence could influence NT-proBNP and GLS values, and vice versa—correlation analysis and Hazard Ratio calculations were performed with variable interactions regarding MACE occurrence over 3 months. The correlation analysis indicated that high LAVI (≥ 41 ml/m²) was associated with GLS ≥ -7,5 (r -0,329; p = 0,007), high NT-proBNP (r 0,632; p = 0,03), EF (r -0,610; p = <0,001), E/e' (r -0,32; p = 0,014), and medial E (r 0,28; p = 0,024).

GLS correlation analysis showed associations with EF (r -0,730; p = <0,001), NT-proBNP (r 0,245; p = 0,049), BMI (r -0,262; p = 0,035), SC (r 0,262; p = 0,035), eGFR (r -0,262; p = 0,035), HB (r -0,336; p = 0,006), E/A ratio (r 0,356; p = 0,004), peak E vel (r -0,306; p = 0,014), medial E (r -0,416; p = 0,001), E/e' (r 0,365; p = 0,003), TAPSE (r -0,367; p = 0,003), and LAVI (r 0,447; p = <0,001).

Correlation analysis indicated that high NTproBNP was associated with GLS ≥ -7,5 (r -0,526; p = <0,001), LAVI (r 0,362; p = 0,003), EF (r 0,334; p = 0,005), medication adherence (r -0,567; p = <0,001), E/e' (r -0,335; p = 0,006), peak A vel (r -0,290; p = 0,020), E/A ratio (r -0,393; p = 0,001), HB (r 0,284; p = 0,022), and triglycerides (r 0,315; p = 0.011).

Correlation analysis for medication adherence was not performed because medication adherence was assessed during the 3-month observation period and thus had no impact on baseline variables such as LAVI, GLS, and NTproBNP.

TABLE 7: Hazard Ratio and Adjusted Hazard Ratio of NTproBNP and GLS for MACE Occurrence Within 3 Months.

Variable	HR	IK	p-value	Adjusted HR	IK	p-value
GLS ≥ -7,5	5,065	1,264-20,293	0,022*	1,849	0,384-8,908	0,444
High NTproBNP	5,932	4,179-23,800	0,012*	1,497	0,218-10,294	0,682
LAVI ≥ 41 ml/m²	7,592	1,808-31,808	0,006*	6,215	1,328-29,089	0,020*
Compliance with taking medication	7,335	1,464- 36,764	0,015*	4,269	0,532-34,871	0,176
GLS ≥ -7,5* high NTproBNP	6,216	1,479-26,119	0,013*	2,309	0,471-11,325	0,303
GLS ≥ -7,5* high NTproBNP* medication adherence	3,803	0,467-31,007	0,212	5,611	0,620-50,798	0,125
GLS ≥ -7,5* high NTproBNP* LAVI ≥ 41 ml/m²	15,159	3,531-65,085	<0,001*	14,712	3,209-67,453	0,001*
GLS ≥ -7,5* high NTproBNP* LAVI ≥ 41 ml/m² * medication adherence	10,349	3,144-34,006	<0,001*	20,910	2,175-201,037	0,008*

*: Indicates a statistically significant difference between the groups (p < 0,05).

GLS and NTproBNP interacted with medication adherence and LAVI values, so multivariate analysis using Cox regression with several interaction models was performed. The GLS ≥ -7,5 + NTproBNP ≥ 689 pg/mL interaction model did not significantly predict MACE within 3 months (adjusted HR 2,309; p = 0,303). However, the GLS ≥ -7,5 + NTproBNP ≥ 689 pg/mL + LAVI ≥ 41 ml/m2 interaction model and the GLS ≥ -7,5 + NT-proBNP ≥ 689 pg/mL + LAVI ≥ 41 ml/m² + medication adherence interaction model significantly predicted MACE within 3 months (adjusted HR 14,712; p = 0,001 and adjusted HR = 20,910; p = 0,008, respectively).

DISCUSSION

Rehospitalization and mortality due to heart failure are major global health issues because of their impact on morbidity, decreased quality of life, increased risk of death, and contribution to high healthcare costs. Heart failure can occur as a result of progressive structural and functional changes in the heart.

As a compensatory adaptation mechanism to hemodynamic changes in heart failure patients, there is activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), changes in renal neurohormones, changes in peripheral blood vessels, and alterations in nitric oxide synthesis. This adaptive process aims to maintain hemodynamic balance. However, the continuous activation of these adaptive systems results in progressive myocardial damage, marked by a decline in left ventricular (LV) systolic function, increased LV filling pressure, and impaired LV diastolic function. Additionally, there is an increased release of natriuretic peptides by the atria and ventricles as a compensatory mechanism for increased ventricular wall stress. This continuous compensatory mechanism ultimately leads to the onset of heart failure symptoms [8].

This study evaluates the Global Longitudinal Strain (GLS) through echocardiographic examination and NT-proBNP levels through laboratory tests that reflect the hemodynamic congestion conditions of patients as risk factors for the occurrence of major adverse cardiovascular events (MACE) such as rehospitalization and death due to chronic heart failure with reduced ejection fraction. The results of this study are expected to provide information on the relationship between GLS and NT-proBNP levels with MACE in patients with chronic heart failure with reduced ejection fraction.

The sample population in this study consisted of heart failure patients with reduced ejection fraction, including heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF), the majority of which were caused by coronary heart disease. The average ejection fraction (EF) in HFmrEF patients was 46%, while in HFrEF patients, it was 32%. During the three-month observation period, MACE occurred in one HFmrEF patient and seven HFrEF patients. The average GLS value in those who experienced MACE was -8,4%, while in those who did not experience MACE, it was -11,19%. This is consistent with the study by Gaborit et al., which reported that the majority of chronic heart failure patients experienced impaired LV GLS. Patients with more impaired LV GLS had lower EF. As in previous findings, LV GLS reflects LV dysfunction in heart failure patients, including those with HFpEF, HFmrEF, and HFrEF [9]. A study by Mignot et al., on a population with systolic dysfunction (EF <45%) showed that GLS can be used in patients with left ventricular dysfunction and is very effective for risk

stratification in HFrEF patients, with better accuracy compared to EF, with a GLS cutoff >-7% that can predict MACE [10]. The average NT-proBNP level in those who experienced MACE was 990 pg/mL.

In this study, the majority of chronic heart failure patients were male, with an average age of 57 years. This is consistent with the study by Pastore et al., which reported that the majority of heart failure patients were male (73%) (Pastore et al., 2022), and in the ADHERE-AP study (Acute Decompensated Heart Failure National Registry-Asia Pacific) conducted on 10,171 acute heart failure patients from 2006-2008 in eight Asia-Pacific countries, including Indonesia, it was found that patients in Southeast Asia generally had a relatively younger age (median age in the Philippines was 53, Indonesia 60, Malaysia 61, Thailand 67, and Singapore 71 years) compared to East Asian countries (median age 77 years for Hong Kong and Taiwan) [11]. Heart failure patients often have one or more comorbidities, the most common being dyslipidemia, hypertension, type 2 diabetes mellitus, and smoking. In this study, the prevalence of comorbidities such as hypertension, type 2 diabetes mellitus, dyslipidemia, and smoking were observed.

Global Longitudinal Strain (GLS), assessed using speckle-tracking echocardiography (STE), is a novel technique for detecting and measuring left ventricular dysfunction. GLS is expressed as a negative percentage, with values closer to zero indicating greater LV dysfunction. GLS reflects longitudinal myocardial contraction, and its accuracy has been validated against MRI imaging [12]. A decrease in GLS is a strong predictor of adverse cardiovascular events, including hospitalization and death in heart failure patients. GLS has been shown to have high sensitivity and specificity for predicting MACE [13]. In some guidelines, the peak GLS value is around -20% in healthy individuals.

Based on the ROC curve analysis, a GLS cutoff value of ≥ -7,5 showed the best accuracy as a predictor of MACE during the three-month observation period, with an AUC of 0,763, sensitivity of 62,5%, and specificity of 86,0%; p = 0,017. This is in line with a multicenter study conducted by Mignot et al., which assessed Global Longitudinal Strain (GLS) as a predictor of MACE in 147 patients with reduced LV function (EF ≤ 45%) followed for more than 12 months. In the ROC curve analysis, GLS had the highest prognostic value (AUC 0,83) with a sensitivity of 73% and specificity of 83%, using a cutoff of -7% [10]. The same GLS cutoff of -7% was used in a study by Otani et al. to predict MACE using automated GLS in patients already known or suspected to have heart failure, with an average EF of ±46%.

Each 1% increase in GLS is associated with a 10% increase in the odds of composite outcomes and a 13% increase in the odds of decreased LVEF [14]. The findings of this study are supported by a study by Modin (2018), which stated that GLS has high sensitivity in predicting major cardiovascular events in HFrEF patients. GLS is also said to have fairly high specificity, indicating that GLS can identify patients who are not at high risk of experiencing major cardiovascular events [13].

The study by Brann (2023) stated that a decrease in GLS is a strong independent predictor of all-cause mortality and heart failure hospitalization. Patients with impaired GLS have significantly higher rates of adverse events compared to those with normal GLS. This study found that HFpEF patients with abnormal GLS had a 1,7-fold increased risk of cardiovascular death or heart failure hospitalization (HR 1,74, 95% CI 1,3-2,4, p < 0,001), mostly due to an increased risk of heart failure hospitalization (HR 1,81, 95% CI 1,2-4,3; p = 0,018). In this study, patients with GLS ≥ -7,5 had a fourfold increased risk of MACE within three months [14].

In chronic heart failure patients with reduced ejection fraction, GLS has been reported to have an independent relationship with all-cause mortality and long-term outcomes as an additional prognostic factor [15]. A cohort study involving 3,289 patients with symptomatic and asymptomatic heart failure found that GLS is associated with the severity of heart failure, as indicated by NT-proBNP levels after adjusting for heart structure and function (P < 0,001). GLS is associated with all-cause mortality with an HR of 2,32, 95% CI 1,57-3,42; p < 0,001 [16]. This is consistent with this study, which found that GLS is a significant predictor of MACE with an HR of 5,065 (95% CI 1,264-20,293; p = 0,022) in Kaplan-Meier analysis with the log-rank test.

In addition to GLS, NT-Pro BNP can also be used to predict MACE. NT-proBNP (N-terminal pro-b-type natriuretic peptide) is a biomarker widely used in the diagnosis and management of heart failure. NT-ProBNP is released by the heart in response to increased wall stress, making it a valuable indicator of heart dysfunction. Several studies have successfully demonstrated the role of NT-ProBNP in diagnosing acute heart failure and MACE [17]. Guidelines from the ESC, the American Heart Association/American College of Cardiology, and the American Diabetes Association recommend NT-proBNP for diagnosing heart failure and cardiac stress, as well as providing cutoff values for implementation and interpretation. In outpatient settings, elevated NP concentrations at the time of heart failure diagnosis are closely associated with the risk of rehospitalization and death [18].

This study found that NT-ProBNP for predicting MACE had an AUC of 0,556 at a cutoff of 689,0, with a sensitivity of 50,0% and specificity of 87,7%. The AUC approached 0,5 because the overall area included an invalid area as a predictor. NT-proBNP levels below 235 pg/mL, representing the starting point of the line under the curve with a sensitivity of 50% and specificity of 50%, were not significant for predicting MACE within the three-month observation period. In both acute heart failure patients and outpatients, NT-proBNP levels used to

diagnose heart failure are adjusted based on age. This adjustment categorizes NT-proBNP levels as follows: patients under 50 years old ≥ 125 pg/mL, 50-70 years old ≥ 250 pg/mL, and patients over 75 years old ≥ 500 pg/mL. However, there is no standardized cutoff value used as a prognosis.

A previous study by Januzzi (2006) demonstrated that NT-ProBNP is highly effective in diagnosing acute heart failure. The diagnostic accuracy of NT-ProBNP for acute heart failure events was shown to have a sensitivity of 90%, specificity of 84%, positive predictive value (PPV) of 88%, negative predictive value (NPV) of 66%, and overall accuracy of 85% [19]. This study also successfully showed that NT-ProBNP had an area under the curve (AUC) of 0.76 (p<0,001) in diagnosing short-term mortality in acute heart failure patients. The NT-ProBNP cutoff value of 5180 pg/mL could predict mortality within 76 days with a sensitivity of 68%, specificity of 72%, PPV of 19%, and NPV of 96%. Higher levels of BNP and NT-ProBNP are associated with greater risk for adverse short-term and long-term outcomes in heart failure, including all-cause and cardiovascular mortality. NT-ProBNP has been validated as a prognostic marker in chronic heart failure patients with reduced EF [20]. NT-ProBNP levels have been widely used in assessing outcomes in patients with heart disease, especially heart failure. NT-ProBNP levels of ≥1594,5 pg/mL were found to be a predictor of major adverse cardiovascular events (MACEs) with an HR of 1,024 (p<0,001) in patients with coronary heart disease (CHD). The high tertile of NT-ProBNP levels showed a heart failure patient proportion of 10% compared to the medium tertile (4%) and low tertile (0,8%) (p<0.001) [21]. NT-ProBNP also plays a role in the incidence of heart failure and mortality. The incidence of MACEs was higher in the NYHA III-IV group compared to NYHA I-II, with mean NT-ProBNP levels of 9,320.2 ± 78.2 ng/L and 855.2 ± 34.8 ng/L, respectively. The prognostic value of NT-ProBNP for death and heart failure showed AUCs of 0,672 (sensitivity 75,7% and specificity 58,2%) and 0,901 (sensitivity 80,1% and specificity 81,6%), respectively. NT-ProBNP levels ≥ 6,335.1 ng/L were significantly predictive of mortality in heart failure patients [8,19,22,23].

The consensus "Practical Algorithms for Early Diagnosis of Heart Failure and Heart Stress Using NT-proBNP: A Clinical Consensus Statement from the Heart Failure Association of the ESC" recommends an NT-proBNP threshold of >2000 pg/mL in outpatients, which is associated with more than twice the risk of rehospitalization due to heart failure and a 50% higher risk of death compared to NT-proBNP levels of 400-2000 pg/mL [18].

Unlike the cutoff used in previous studies, this study used a cutoff of 689 pg/mL because the characteristic data showed that NT-ProBNP levels in the MACE group were higher, at 990,38 ± 1401,90 pg/mL, compared to 432,31 ± 571,38 pg/mL (120-2857) in the non-MACE group. The patients in this study had already received therapy, and the sample size was small. Moreover, other studies have mostly focused on the prognostic value of NT-ProBNP in acute heart failure patients, resulting in a higher cutoff value.

A meta-analysis of 66 studies involving 83,846 heart failure patients assessed BNP/NT-ProBNP levels for prognosis stratification. The subgroup meta-analysis found that high BNP and NT-ProBNP levels in heart failure patients significantly increased mortality, with an effect size of 11.16 (p<0,00001) compared to non-heart failure patients with an effect size of 6.45 (p<0,00001) [24]. Consistent with this study, the chi-square comparison test showed a significant difference (p=0.023). Kaplan-Meier analysis also showed significant results, with NT-ProBNP as a predictor of MACE, with an HR of 5,932 (95% CI 4,179-23,800, p=0,012).

Characteristic data revealed that left ventricular GLS values in chronic heart failure patients with reduced ejection fraction were higher in the MACE group, at -8,4 ± -1,91, compared to the non-MACE group, at -11,19 ± 3,52. The chi-square proportion comparison test found a significant difference in GLS values between MACE and non-MACE patients (p<0,05).

Left ventricular global longitudinal strain (GLS) is known to be associated with the risk of mortality and cardiovascular events in patients with heart disease [25]. Among patients with acute myocardial infarction, left ventricular GLS is associated with the development of heart failure and increased mortality [26]. In the study by Gaborit et al., the main finding was that impaired left ventricular GLS was associated with increased wall stress, as expressed by elevated plasma concentrations of NT-proBNP and pro-ANP in patients with chronic systolic heart failure [9]. Most patients with chronic systolic heart failure had impaired left ventricular GLS. Patients with impaired left ventricular GLS had lower left ventricular ejection fractions, and left ventricular GLS showed a stronger correlation with echocardiographic variables related to systolic function than diastolic function [12]. GLS provides additional prognostic information beyond traditional echocardiographic measures, such as GLS being strongly correlated with left ventricular ejection fraction (LVEF) (-0,7). GLS is also correlated with NTpro-BNP (0,2), LAVI (0,4), BMI (-0,2), SC (0,2), eGFR (-0,2), HB (-0,3), and echocardiographic parameters for diastolic function. From this data, GLS reflects not only systolic function but also diastolic function (LV relaxation impairment), and it is associated with increased LV filling pressure.

GLS is a widely studied biomarker for assessing heart function and has been evaluated for use in risk stratification in heart failure. In one study of patients with acute decompensated heart failure, GLS demonstrated superior prognostic value compared to LVEF [27].

In a study of 137 heart failure patients, it was found that plasma concentrations of brain-natriuretic peptide (BNP) were associated with functional class, decreased left ventricular ejection fraction, and

abnormalities in GLS in patients with systolic and diastolic dysfunction [28]. Previous studies up to the present suggest that left ventricular GLS reflects wall stress in heart failure patients since plasma concentrations of BNP and NT-proBNP reflect myocardial stress [12]. Notably, left ventricular GLS and natriuretic peptides are indirect measures of myocardial stress, and future studies are recommended to evaluate the relationship between myocardial stress, invasive measurements, left ventricular GLS, and plasma concentrations (Gaborit, 2015). In this study, high NT-proBNP was associated with GLS ≥-7,5 (-0,5), LAVI (0,3), EF (0,3), medication adherence (-0,5), peak A vel (-0,2), E/A ratio (-0,3), HB (0,2), and TG (0,3). NT-proBNP is associated with both LV systolic and diastolic function.

Characteristic data showed that NT-ProBNP levels in the MACE group were higher, at 990,38 ± 1401,90 pg/mL, compared to the non-MACE group, at 432,31 ± 571,38 pg/mL (120-2857). The chi-square comparison test found a significant predictor (p=0.023). Kaplan-Meier analysis also showed significant results, with NT-ProBNP as a predictor of MACE, with an HR of 5,932 (95% CI 4,179-23,800, p=0,012).

NT-proBNP, a biologically inactive peptide, is secreted from cardiomyocytes along with BNP, a biologically active peptide [29]. Due to different elimination mechanisms, NT-proBNP has a longer half-life and higher plasma concentration [30]. Additionally, the stability of NT-proBNP makes it easier to measure in routine clinical practice. Previous data have shown that NT-proBNP is a more sensitive predictor of MACEs in the general population [31].

Survival analysis of heart failure patients with NSTEMI and LVEF <40% revealed that high NT-ProBNP levels significantly increased patient mortality compared to medium and low levels, as evidenced by a log-rank test (p<0,0001) (Gong X et al., 2021). A study that assessed the prognostic role of NT-ProBNP levels applied clinically to evaluate the efficacy of treatment with Empagliflozin 10 mg/day found that Empagliflozin significantly reduced NT-ProBNP levels across various LVEF categories [19]. This research suggests that baseline NT-ProBNP can play a clinical role in the treatment of patients.

In this model, LAVI ≥ 41 ml/m^2 independently served as a predictor of MACE during the 3-month observation period in heart failure patients with reduced EF (AHR 6,215; p=0,020). LAVI can be used to assess left atrial reservoir function and indirectly reflects diastolic function and left atrial filling pressure. In heart failure patients, the dynamic relationship between LA and LV pressure plays a crucial role in cardiac hemodynamics. Increased left atrial volume is a predictor of adverse cardiac events in both healthy individuals and various cardiovascular conditions, including myocardial infarction, heart failure, stroke, mitral regurgitation, and atrial fibrillation [32]. This finding aligns with the study by Shang which investigated 146 heart failure patients admitted to Yamagata University Hospital, Japan, for worsening heart failure or evaluation of heart failure therapy, with a median follow-up of 448 days [7]. The study showed that LAVI is an independent predictor of MACE in heart failure patients (HR 1,427; 95% CI 1,024-1,934; P 0,05) [33]. In the study by Ahmeti et al., which investigated the prognostic value of LAVI in ACS across 2,705 patients from 11 cohort studies with an average of 18 months, enlarged LA was associated with comorbidities such as hypertension, diabetes, and prior ACS, known factors that impair LV diastolic function. Increased LAVI was an independent predictor of MACE in ACS patients (Ahmeti et al., 2020). LAVI, as another variable, independently served as a predictor of MACE during the 3-month observation period in heart failure patients with reduced EF. In this study, we sought to identify variables associated with high LAVI (≥41 ml/m^2). High LAVI (≥41 ml/m^2) was strongly associated with EF (-0,6), high NT-proBNP (0,6), GLS (-0,3), and LV diastolic function. High LAVI is a multifactorial process where the associated variables help explain why high LAVI can be an independent predictor of MACE during the 3-month observation period.

Medication adherence is crucial in managing patients with heart failure. The therapies given to heart failure patients, such as beta-blockers, ACE-i/ARBs, diuretics, and MRAs, aim to stabilize hemodynamics. Medication adherence helps maintain heart function, control symptoms, and prevent worsening conditions that could lead to MACE. Without good adherence, the effectiveness of therapy is significantly reduced, increasing the risk of worsening conditions and the likelihood of MACE. In this study, the interaction model of GLS ≥ -7,5 + NTproBNP ≥ 689 pg/mL + LAVI ≥ 41 ml/m^2 + medication adherence significantly predicted MACE within 3 months (adjusted HR = 20,910, p-value 0,008).

This study is a cohort study involving 65 heart failure patients at a single healthcare center, namely RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. The limitations of this study include the limited follow-up time, resulting in a low number of MACE events. Medication adherence was assessed during the 3-month observation period, while other variables were baseline data, so no correlation was assumed.

CONCLUSION

(1) GLS is associated with MACE in patients with chronic heart failure with reduced ejection fraction.
(2) GLS ≥ -7,5 and high NTproBNP (≥ 689 pg/mL) are not independent predictors of short-term MACE in patients with chronic heart failure with reduced ejection fraction.
(3) LAVI is an independent predictor of short-term MACE occurrence.

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