Global Longitudinal Strain (GLS) in Elderly and Its Associated Factors

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ABSTRAK

Latar belakang: *penyakit kardiovaskular sangat umum dan bisa berakibat fatal pada pasien usia lanjut. Hal ini sering diawali oleh disfungsi sistolik ventrikel kiri (LVSD) asimptomatik atau subklinis. Deteksi dini LVSD dapat mengurangi morbiditas dan mortalitas akibat penyakit kardiovaskular. Salah satu metode yang digunakan dalam deteksi dini LVSD adalah penilaian global longitudinal strain (GLS). Penelitian ini bertujuan untuk menentukan nilai rerata faktor GLS dan terkait GLS.* ***Metode:*** *penelitian cross-sectional dilakukan di antara pasien usia lanjut berusia >60 tahun di poliklinik geriatri dan kardiologi, Departemen Ilmu Penyakit Dalam, RS Cipto Mangunkusumo. Data diperoleh dengan menggunakan metode wawancara, rekam medis, dan pemeriksaan ekokardiografi transthoracic. Variabel usia, frailty, hipertensi, penyakit arteri koroner, dislipidemia, dan diabetes mellitus dianalisis sebagai faktor penentu penurunan GLS. Analisis univariat dilakukan untuk setiap variabel. Analisis bivariat dilakukan dengan menggunakan uji chi-square dengan signifikansi p<0,25 dan interval kepercayaan (CI) 95%, dan analisis multivariat menggunakan uji regresi logistik.* ***Hasil:*** *sebanyak 194 pasien dirawat sesuai dengan kriteria penelitian, usia rerata 66 tahun. Proporsi wanita adalah 60,8%. Studi ini mengungkapkan bahwa faktor penentu dengan p<0,25 adalah frailty, hipertensi, dislipidemia, dan diabetes mellitus, dengan analisis multivariat frailty memperoleh nilai OR 2,002 (95% CI 1,042-3,925) dan diabetes mellitus memiliki OR 2,8278 (95% CI) 1.033–5.025).* ***Kesimpulan:*** *nilai rerata GLS pada orang tua adalah -21,6% (nilai minimum -5,3% dan nilai maksimum 29,9%). Faktor-faktor yang mempengaruhi penurunan GLS adalah frailty dan diabetes mellitus.*

Kata kunci: *global longitudinal strain (GLS), disfungsi sistolik ventrikel kiri (LVSD), frailty.*

ABSTRACT

Background: *cardiovascular disease is very common and can be fatal in elderly patients. It is often preceded by asymptomatic or subclinical left ventricular systolic dysfunction (LVSD). Early detection of LVSD can reduce morbidity and mortality due to cardiovascular disease. One method used in the early detection of LVSD is an assessment of global longitudinal strain (GLS). This study aimed to determine the mean value of GLS and GLS-related factors.* ***Methods:*** *this cross-sectional study was conducted among elderly patients aged > 60 years in the geriatric and cardiology clinic, Internal Medicine, CMH Hospital. Data were obtained from interviews, medical records, and transthoracic echocardiography examination. The variables of age, frailty, hypertension, coronary artery disease, dyslipidemia, and diabetes mellitus were analyzed as the determinants of a decrease in GLS. Univariate analysis was conducted for each variable. Bivariate analysis was conducted using the chi-square test with a significance level of p<0.25 and confidence interval (CI) of 95%, and multivariate analysis used a logistic regression test.* ***Results:*** *a total of 194 patients were admitted according to the study criteria, with*

a mean age of 66 years. The proportion of women was 60.8%. The study revealed that the determinants with p<0.25 are frailty, hypertension, dyslipidemia, and diabetes mellitus, with multivariate analysis frailty having an OR of 2.002 (95% CI 1.042–3.925) and diabetes mellitus having an OR of 2.278 (95% CI 1.033–5.025). ***Conclusion:*** *the mean value of GLS among the elderly was -21.6% (minimum value -5.3% and maximum value 29.9%). The factors that influence the decrease of GLS are frailty and diabetes mellitus.*

Keywords: *global longitudinal strain (GLS), left ventricular systolic dysfunction (LVSD), frailty.*

INTRODUCTION

Cardiovascular disease is very common and potentially fatal in elderly patients. Heart failure is the end stage of all cardiovascular diseases and is often preceded by asymptomatic or subclinical left ventricular systolic dysfunction (LVSD).[1,2] Subclinical LVSD is LVSD without the signs and symptoms of heart failure detected by global longitudinal strain (GLS).[3] It can be classified as stage A and B heart failure according to the American College of Cardiology/American Heart Association 2013.[4] The early detection of LVSD prior to it developing into heart failure can reduce morbidity and mortality due to cardiovascular diseases.[5] Subclinical LVSD management is currently controversial as it is a new event that requires further research and adjustment to the stage of heart failure obtained.[6]

LVSD can be diagnosed by measuring the left ventricular ejection fraction (LVEF), which progressively decreases with age. However, LVEF examination is not sensitive to subclinical LVSD assessment.[7,8] One potential early detection method that can be carried out is to measure echocardiography using the speckle tracking echocardiography (STE) method. Using this STE method, the strain ability of the heart muscle can be assessed by evaluating GLS. A decrease in GLS is generally caused by a change in left ventricular geometry with or without any accompanying damage to or decrease in the left ventricular function. GLS is thus able to provide an early assessment of changes in the left ventricular systolic function when LVEF is still within normal limits.[9-11] Other factors that may affect a decrease in GLS values are changes in left ventricular geometry associated with various comorbidities: (1) Type 2 diabetes mellitus presents a 2.26 times greater risk of a decrease in GLS compared to patients without type 2 diabetes mellitus; (2) Hypertension is closely related to a decrease in GLS. Patients that have been hypertensive for more than 10 years have a 3.51 times greater risk of a decrease in GLS, while patients with uncontrolled hypertension are at a 3.55 times greater risk of a decrease in GLS; (3) Dyslipidemia presents a 2.26 times greater risk of a decrease in GLS compared to patients without dyslipidemia.[10,11] Dyslipidemia is a single major risk factor of coronary artery disease (CAD). CAD also affects a decrease in GLS.[12] A study by Liou et al. found that GLS can be used to detect CAD in symptomatic patients.[13] The management of various risk factors and diseases will inhibit the process of the disease becoming symptomatic heart failure.[12]

Cardiovascular dysfunction plays an important role in the development of frailty. Frailty is a condition in which there is an increased susceptibility to stressors that causes multisystem dysregulation. It is influenced by age and is associated with a high risk of physical dysfunction and increased mortality in the elderly.[14] A study by Russo et al.[15] found that black ethnicity was associated with a greater degree of subclinical LVSD by GLS than for other race-ethnic groups. Other study, meanwhile, have shown the existence of reference ranges based on age, gender, and ethnicity. The data for the research were gathered from Africans, Americans, Asians, Australians, and those of Middle Eastern and Pacific descent. However, based on the research, Indonesian data is not yet known.[16] We sought to investigate the relationship between GLS, elderly and its comorbidities.

METHODS

This is an observational study with a cross-sectional design with the aim of adding data on GLS in elderly patients and its related factors. The

data were collected from elderly patients aged > 60 years old in the geriatric and cardiology clinic, Internal Medicine, CMH Hospital. Data were obtained from interviews, medical records, and transthoracic echocardiography examinations, using the consecutive sampling method, from December 2018 to April 2019. This study was approved by the Ethics Committee, Faculty of Medicine, Universitas Indonesia, with ethical approval no. 1212/UN2.F1/ETIK/2018.

Registered patients at the geriatric and cardiology clinic aged >60 years old who met the inclusion criteria of having one of the comorbidities needed in this study were included. The comorbidities for inclusion were hypertension, CAD, dyslipidemia, and diabetes mellitus. Meanwhile, any patients who had symptomatic heart disease, were involved in drug research, had pulmonary diseases and kidney disorders (stage 4 and 5 chronic kidney disease), had arrhythmia, had poor echo window, and who were unwilling to take part in the study were excluded. The subjects were given oral and written explanations regarding the study and were asked to sign an informed consent form. Frailty was determined based on a questionnaire comprising a 40-item frailty index. Echocardiography was carried out by one operator (MSA), with two operators (SAN, LR) who already had the echocardiography examination certification providing confirmation of the post-processing data. The results were recorded and analyzed.

Data Analysis

A data normality test was conducted using the Kolmogorov-Smirnov test. The variables of age, frailty, hypertension, coronary artery disease, dyslipidemia, and diabetes mellitus were analyzed as the determinants of a decrease in GLS. Univariate analysis was carried out in respect of each variable. Bivariate analysis was undertaken using a chi-square test with a significance level of $p<0.25$ and confidence interval (CI) of 95%, and multivariate analysis was carried out using a logistic regression test.

RESULTS

From a total of 203 patients who met the inclusion criteria, 9 were excluded owing to the presence of arrhythmia and poor echo window, which resulted in 194 research subjects meeting the criteria for analysis in this study. These 194 patients consisted of 76 males (38.2%) and 118 females (60.8%). The median age in this study is 66 years, with a range of 60–90 years old. A total of 184 patients (94.8%) have LVEF within normal limits, and 10 patients (5.2%) have decreased LVEF. The GLS assessment shows that 135 patients (69.6%) are within normal limits, while 57 patients (29.4%) have decreased GLS. Some of the patients with normal LVEF have decreased GLS. Frailty was present for 85 patients (43.8%), with non-frailty present in 109 patients (56.2%). In this study, 34 patients have CAD (17.5%), 149 have hypertension (76.8%), 105 have dyslipidemia (54.1%), and 44 patients have diabetes mellitus (22.7%).

Table 1. Characteristic of subjects

Characteristics	N (%)
Gender, n (%)	
- Women	118 (60.8)
Age, median (min-max)	66 (60-90)
- Young-old, n (%)	161 (83.0)
LVEF, median (min-max)	66 (24.7 - 82.2)
- Normal (≥ 55 %), n (%)	184 (94.8)
GLS, median (min-max)	21,6 (5.3 - 29.9)
- Normal (≥ -20 %), n (%)	135 (69.6)
Frailty index, median (min-max)	0.22 (0.03-0.9)
- Frailty (≥0,24), n (%)	85 (43.8)
CAD, n (%)	
- Yes	34 (17.5)
Hypertension, n (%)	
- Yes	149 (76.8)
Dyslipidemia, n (%)	
- Yes	105 (54.1)
Diabetes Mellitus, n (%)	
- Yes	44 (22.7)

From the echocardiography results, the measurements of Interventricular Thickness End-Diastole (IVSD), Left Ventricular Dimension End-Diastole (LVDD), and Left Ventricular Posterior Wall (LVPW) have average values of 1.26 cm, 4.39 cm, and 1.07 cm, respectively. The measurements of Left Atrial End-systolic Volume Index (LAVI) and E/A display average values of 28.40 ml/m^2 and 0.80, respectively. The

Table 2. Characteristics of echocardiographic features of research subjects

Characteristics	Value	Frailty	Non frailty
Aorta diameter, cm (median)	2.50 (2.10-3.70)	2.50	2.50
Left Atrium, cm (mean)	3.56 (3.39-3.73)	3.43	3.46
E-Point Septal Separation, cm (median)	0.50 (0.20-1.40)	0.60	0.50
RV Dimension End-Diastole, cm (median)	1.97 (1.31-3.21)	1.97	2.01
IV Thickness End-Diastole, cm (mean)	1.26 (1.20-1.32)	1.23	1.22
LV Dimension End-Diastole, cm (mean)	4.39 (4.24-4.54)	4.29	4.49
LV Posterior Wall, cm (median)	1.07 (0.74-1.94)	1.06	1.00
LV Dimension End-Systole, cm (mean)	2.53 (2.41-2.64)	2.54	2.68
Fractional Shortening, % (median)	42.36 (16.80-52.70)	41.4	41.3
EF Teich, % (median)	75.00 (35.20-84.00)	72.7	74.15
Relative Wall Thickness (median)	0.50 (0.30-0.80)	0.50	0.40
LV Mass Index, g/m^2 (mean)	110.50 (106.42-121.30)	111.69	113.54
Pulmonary Acceleration Time, ms (mean)	120.41 (114.05-126.76)	114.58	116.0
EF 4-Chamber, % (median)	65.45 (24.70-82.20)	66.70	65.6
EF Biplane, % (median)	65.03 (25.30-77.60)	66.50	65.2
GLS, % (median)	-21.60 (-5.30 - -29.90)	-20.80	-22
TV D-E Excursion, cm (mean)	2.48 (2.37-2.57)	2.43	2.38
LA End-systolic Volume Index, ml/m^2 (mean)	28.40 (25.28-31.51)	28.12	27.23
IVC Expiration, cm (mean)	1.52 (1.45-1.57)	1.54	1.48
IVC Inspiration, cm (median)	0.68 (0.0-1.77)	0.69	0.69
Stroke Volume, ml (mean)	62.98 (57.94-68.03)	61.25	65.66
Cardiac Output, l/min (median)	4.30 (2.50-10.20)	4.2	4.35
Doppler Data			
- E, cm/s (mean)	76.65 (71.22-82.07)	73.67	76.69
- A, cm/s (mean)	86.84 (81.68-92.01)	91.33	93.36
- E/A (median)	0.80 (0.50-2.90)	0.70	0.80
- E' Medial, cm/s (mean)	6.87 (6.35-7.38)	6.47	7.81
- E' Lateral, cm/s (mean)	8.82 (8.20-9.44)	8.31	9.33
- E/E' (mean)	8.58 (8.01-9.15)	8.62	8.81

measurements of Ejection Fraction 4-Chamber (EF4C), Ejection Fraction Biplane (EFBp), Global Longitudinal Strain (GLS) and Tricuspid Annular Plane Systolic Excursion (TAPSE) have average values of 65.45%, 65.03%, -21.60%, and 28.40%, respectively.

From the bivariate analysis, this study revealed some determinants that have $p<0.25$; these are frailty, hypertension, dyslipidemia, and diabetes mellitus.

The multivariate analysis shows that frailty has an OR of 2.002 (95% CI 1.042–3.925) and diabetes mellitus has an OR of 2.278 (95% CI 1.033–5.025).

DISCUSSION

The patients in this study were predominantly female, with a proportion of 60.8% compared to the males. A study by Bendiab et al.[17] reported no significant difference between males and females on GLS changes. The age range of the patients in this study was 60–90 years old with a median age of 66 years. This age range is not in accordance with various studies from all over the world. Nadruz et al.[8], in a study using subjects with an average age of 75.6 (SD 5.0) years old, stated that elderly patients with frailty had a greater decrease in GLS. In addition, Hung et al.[7] used subjects with an average age of 76 (SD 5) years in their study about the relationship between

Table 3. Bivariate analysis for GLS deteminants

Variables	GLS		Total	PR	(95% CI)	P value
	Decreased (n,%)	Normal (n,%)				
Frailty						
- Frailty	31 (36.5)	54 (63.5)	85	1.728	1.092-2.735	0.018
- Non-frailty	23 (21.1)	86 (78.9)	109			
Usia						
- Old-old	6 (18.2)	27 (81.8)	33	0.610	0.285-1.306	0.174
- Young-old	48 (29.8)	113 (70.2)	161			
Hypertension						
- Yes	36 (24.2)	113 (75.8)	149	0.604	0.382-0.954	0.038
- No	18 (40.0)	27 (60.0)	45			
DM						
- Yes	17 (38.6)	27 (61.4)	44	1.566	0.983-2.495	0.069
- No	37 (24.7)	113 (75.3)	150			
CAD						
- Yes	8 (23.5)	26 (76.5)	34	0.818	0.426-1.573	0.675
- No	46 (28.7)	114 (71.2)	160			
Dyslipidemia						
- Yes	23 (21.9)	82 (78.1)	105	0.629	0.397-0.996	0.045
- No	31 (34.8)	58 (65.2)	89			

Table 4. Multivariate analysis for GLS determinants

	B Coefficient	Standard error	Wald (Forward)	Value p (Sig.)	OR	95% CI
Frailty	0.704	0.338	4.332	0.037	2.002	1.042–3.925
DM	0.824	0.404	4.164	0.041	2.278	1.033-5.025

age and sex and left ventricular remodeling. The differentiation in this study is that the younger ages were different from those in overseas studies. According to 2017 data from the United Nations, life expectancy in Indonesia falls within the range 65–69 years.

The results of the echocardiography measurements from IVSD, LVDD, and LVPW illustrate a thickening of the left ventricular wall, with the dimensions being within normal limits for geriatric patients. The LAVI and E/A measurements illustrate early onset of diastolic dysfunction in geriatric patients with E/A ≥ 0.80, with LAVI within normal limits. The patients' measurements of EF4C, EFBp, GLS, and TAPSE are within normal limits. The LVEF measurement data show that 94.8% of the patients have normal LVEF, while 5.2% of the patients have decreased LVEF. The GLS measurement data show that 69.6% of the patients have normal GLS, while 30.4% of patients have decreased GLS. This reveals that 26.6% of patients with normal LVEF have decreased GLS. This is in line with a study by Yancy et al.[2], which stated that there are elderly patients who have decreased GLS with normal LVEF. In this study, it was also found that a decrease in GLS has a sensitivity of 100%, a specificity of 73.4%, and a positive predictive value of 100% compared to the decrease in LVEF. Plana et al.[18] stated that a decrease in GLS can predict subclinical LVSD before structural changes in the left ventricular and a decrease in LVEF, with high values for sensitivity, specificity, positive predictive value, and negative predictive value (65–96%, 73–95%, 50–83%, and 89–97%).

In this study, based on bivariate analysis, age was not associated with a decrease in GLS.

with a PR of 2.880 and a p value of 0.289 (95% CI 0.443–18.749). Statistically, the age variable was not suitable to be continued to multivariate analysis due to the p value ≥0.25, although we did continue to multivariate analysis because it was clinically meaningful. This finding differs from that in a study by Hung et al.[7], which stated that age should show a significant difference in terms of the decrease in GLS. Hung et al.[7] reported a decrease in GLS of 0.39–0.19% per decade. The value of GLS decreases every decade. In this study, the average GLS value for patients aged 60–70 years (n:141) was -21.08% (-7.4% – -29.9%), for patients aged 71–80 years (n:43) it was -20.76% (-5.3% – -29.5%), while for patients aged 81–90 years (n:10) it was -22.88% (-16.8% – -26.20%). The higher average value for the oldest group may be due to the low number of subjects, which totaled only 10 patients.

This study showed a statistically significant relationship between frailty and a decrease in GLS, with an OR of 2.002 and a p value of 0.037 (95% IK 1.042–3.925). This shows that patients with frailty have a 2.002 times greater risk of a decrease in GLS than non-frail patients. Seto et al.[14] stated that cardiovascular dysfunction plays an important role in the development of frailty, which is the condition of being frail. The incidence of frailty increases with age, female gender, African-American race, low education and income, poor health, and the presence of chronic comorbid diseases and disability. Some of the subjects in this study have diseases such as hypertension, diabetes mellitus, coronary heart disease, and dyslipidemia. Pathophysiologically, frail elderly patients can display sarcopenia and weakness of limbs, resulting in a decrease in body activity, including for the cardiovascular system.[19] A significant decrease in GLS has been shown in elderly patients without risk factors for cardiovascular disease, with a value of -20.9 (SD 1.9) %.[2] Elderly patients with frailty reported a greater decrease in GLS (22%) compared to the non-frail (12%).[8]

From the bivariate analysis, 24.2% of the patients with hypertension show a decrease in GLS, with a PR of 0.604 and a p value of 0.038 (95% CI 0.382–0.954). Furthermore, multivariate analysis was carried out by logistic regression, although a p value of ≥0.05 meant it could not proceed to the multivariate final stage. This shows that hypertension is statistically not related to a decrease in GLS. However, this is not in accordance with a study by Bendiab et al.[17], which stated that hypertension is closely related to a decrease in GLS. Hypertensive patients with a duration of more than 10 years have a 3.51 times greater risk of a decrease in GLS, while patients with uncontrolled hypertension have a 3.55 times greater risk of a decrease in GLS. This difference is likely to be due to the majority of the subjects in this study being hypertensive patients undergoing routine treatment. In this study, the average duration of hypertension is 8.6 years. Most of the patients were using a combination therapy of several drugs, with amlodipine being the most used drug. The mean blood pressure of the subjects was 133/81 mmHg, thus indicating that the subjects had controlled hypertension. The echocardiographic characteristics did not show a change in the structure due to severe hypertension, which could have produced a decrease in GLS values.

This study succeeded in revealing elements that were in accordance with the existing research on the relationship between diabetes mellitus and decreased GLS. Patients with diabetes mellitus have a 2.278 times greater risk of experiencing a decrease in GLS than patients without diabetes mellitus, with a p value of 0.041 (95% CI 1.033–5.025). These results indicate that diabetes mellitus is the most influential factor in decreasing GLS compared to the other studied factors. This finding is in accordance with that of Mahalle et al.10, who found that patients with diabetes mellitus have a 2.26 times greater risk of a decrease in GLS compared to patients without diabetes mellitus. Pathophysiologically, on the theoretical framework, diabetes mellitus causes a decrease in GLS in terms of macroangiopathy (coronary arteries) and microangiopathy (non-ischemic cardiomyopathy). Diabetes mellitus and atherosclerosis-related cardiovascular events are also associated with comorbidities such as obesity, hypertension, and dyslipidemia. Diabetic cardiomyopathy is associated with an increase in adipocytes to release leptin and resistin, which

causes a direct change in cardiac structure, the occurrence of hypertrophy, and fibrosis.[20]

Ammirati et al.[1] stated that CAD can cause a decrease in GLS due to systolic dysfunction resulting from permanent damage from myocytes that turn into nonfunctional fibrotic tissue or dysfunctional myocytes. However, this study has shown different results. From the bivariate analysis, it was found that 23.5% of the patients with CAD had a decrease in GLS, with a PR of 0.818 and a p value of 0.675 (95% CI 0.426–1.573). The analysis was continued to multivariate analysis despite the p value ≥0.25 because CAD is an important parameter toward a decrease in GLS. This study also shows that there is no statistical relationship between CAD and decreased GLS. The results of this study are different from those of prior studies as the CAD diagnoses were established based only on the patients' medical records and not by the gold standard of an angiographic examination. This allows for a false negative on the incidence of CAD. Based on ESC 2013 guidelines, patients with age ≥60 years, male and female, with or without symptoms have a pretest probability of intermediate risk that requires further evaluation using a stress test to diagnose the presence or absence of CAD.[21] GLS itself is a significantly strong predictor of stenosis in stable CAD with a mean value of -17% and an OR of 1.25 per 1% reduction in GLS.[22]

According to Mahalle et al.[10] and Miller et al.[11], patients with dyslipidemia have a 2.26 times greater risk of a decrease in GLS, compared to patients without dyslipidemia. However, those studies are contrary to our finding. From the multivariate analysis, it was found that there is a statistically significant relationship between dyslipidemia and decreased GLS, with an OR of 0.401 and a p value of 0.011 (95% CI 0.199–0.808). This indicates that dyslipidemia is a protective factor against a decrease in GLS. Other studies have shown that GLS has a negative correlation with several risk factors, one of which is dyslipidemia, especially in children.[23] Vitarelli et al.[24] stated that children and young adults with dyslipidemia have more severe left ventricular disorders characterized by a decrease in GLS. The study used subjects with a mean age of 10.48 (SD 3.42). This significant difference is probably due to the characteristics of the subjects from different studies, especially with regard to the age and history of dyslipidemia. The subjects of this study were selected based only on their medical records, with no cholesterol check performed alongside the echocardiography examination.

CONCLUSION

From this study, the mean value of GLS in elderly is -21.6% (minimum value -5.3% and maximum value 29.9%). The factors that influence the decrease of GLS are frailty and diabetes mellitus.

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