Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: September, 30, 2022

Citation: Sutil-Vega M, Rizzo M, et al., 2022. The role of myocardial global longitudinal strain in etiological stratification of heart failure and left ventricular systolic dysfunction, Medical Research Archives, [online] 10(9). https://doi.org/10.18103/mra.v10i9.3035

DOI
https://doi.org/10.18103/mra.v10i9.3035

ISSN: 2375-1924

RESEARCH ARTICLE

The role of myocardial global longitudinal strain in etiological stratification of heart failure and left ventricular systolic dysfunction

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ABSTRACT

Introduction: In patients with heart failure, global longitudinal strain (GLS) early detects decreased ventricular contractility, with prognostic value, but there is no evidence that GLS properly differentiates etiologies in patients with left ventricular ejection fraction <50%.

Methods and aims: 147 patients with heart failure and left ventricular ejection fraction <50% were included retrospectively. The aims were to compare the GLS in patients with heart failure with reduced (<40%) to those with mildly reduced ejection fraction (40-49%) and, to compare GLS between the different etiologies in each of these two subpopulations.

Results: 78 patients presented mildly reduced (53%) and 69 reduced ejection fraction (47%). The mean GLS was -13.4% ± 3.3% (mildly reduced -14.9% ± 2.9%, reduced -11.7% ± 3.0%, p <0.001). In mildly reduced ejection fraction, the etiologies were ischemic (47.4%), idiopathic (25.6%), tachycardiomyopathy (12.8%), valvular (11.6%), and toxic (2.6%), with similar mean GLS (p = ns among all etiologies). In reduced ejection fraction, the etiology of 50.7% patients was ischemic, 24.6% idiopathic, 10.1% valvular, 8.7% tachycardiomyopathy, and 5.8% toxic, with similar mean GLS (p = ns among all etiologies).

Conclusions: There were no significant differences in GLS between the etiologies of heart failure in any subpopulation. The reduced ejection fraction patients presented worse GLS.

INTRODUCTION

Heart failure (HF) is a highly prevalent disease worldwide, with severe economic impact on the health system. It is the result of cardiac functional deterioration due to different etiologies, each of which has diagnostic, therapeutic management and prognostic particularities[1].

The assessment of systolic ventricular function is a fundamental element in the clinical follow-up and for prognosis prediction of patients with HF. Echocardiographic determination of the left ventricular (LV) ejection fraction (LVEF) is the most widely used method in clinical practice to measure systolic ventricular function[1,2], and according to clinical practice guidelines it allows HF to be classified as preserved LVEF (HFpEF) with LVEF ≥50%; mildly reduced LVEF (HFmrEF) when it is in the range of 40-49%; and reduced LVEF (HFrEF) when it is <40%[1-3]. However, this parameter is strongly influenced by loading conditions and, importantly, it presents low sensitivity to detect an incipient deterioration in ventricular contractility[4].
Recently, the evaluation of global longitudinal strain (GLS) using the speckle tracking technique has become a clinically feasible alternative for the assessment of myocardial function[5-6]. GLS has greater sensitivity than LVEF for the detection of myocardial systolic function reduction (particularly useful in cardiotoxicity as a result of chemotherapy)[7]. Furthermore, GLS provides additional cardiovascular prognostic information in multiple scenarios, including general population[8] or elderly[9], as well as a number of pathologies that cause HF, for instance HFpEF, myocardial toxicity, hypertrophic cardiomyopathy (HCM), ischemic heart disease, aortic stenosis, aortic regurgitation, arterial hypertension or type 2 diabetes mellitus[10-25]. Moreover, GLS can help in the differentiation of the etiology in left ventricular thickening, cases consisting mainly of hypertensive heart disease, HCM or amyloidosis, in which LVEF is usually preserved[26-30]. Concretely, in HCM the longitudinal strain is decreased in the more hypertrophied and fibrotic segments[16], following a septal or apical distribution according to the type of HCM, and distinctly, in amyloidosis the longitudinal strain is preserved at the apex, and reduced in the basal and mid segments[28].

Despite GLS can properly classify HFpEF patients according to the etiology, there is no evidence regarding HF patients with LVEF <50% in this sense. We hypothesize that GLS might be useful to classify different etiologies within the categories of HFmrEF or HFrEF. The main clinical implication would be to speed up and strengthen the etiological diagnosis of cardiomyopathy with an initial echocardiography in patients with HF debut, before requiring additional tests, allowing to optimize the selection of necessary tests or initiate appropriate treatments early.
The aims of the study were to compare the GLS in patients with HFrEF to those with HFmrEF and, to compare GLS between the different etiologies in each of these two subpopulations.

METHODS

Study design and ethics

A retrospective, observational, single-center study was designed to compare GLS between different etiologies in HFrEF and HFmrEF patients, as well as between these two subpopulations. The study was in compliance with the Declaration of Helsinki and its subsequent revisions, and reviewed by the Ethics Committee of the University Hospital of Sabadell (Autonomous University of Barcelona, Sabadell, Spain). Informed consent was received from all patients involved in the study.

Subject selection

Inclusion criteria:
- Outpatients followed at the HF Unit of the University Hospital of Sabadell with transthoracic echocardiography performed in the Cardiology Department of this hospital. All examinations were performed with two EPIQ 7C Digital Ultrasound Systems and S5-1 transducers (Philips Healthcare, Best, The Netherlands).
- LVEF <50% measured by the Simpson method.

Exclusion criteria:
- Technical impossibility to measure GLS (poor echocardiographic window, poor electrocardiographic recording, or poor image acquisition).
- Overlapped etiology of HF.

Variables

LVEF was assessed using 2-dimensional biplanar Simpson method with Intellispace Cardiovascular software (Philips Healthcare). GLS was assessed with speckle tracking using AutoStrain LV software (Philips Healthcare) as the average longitudinal systolic peak of three views with a model of 18 segments of the left ventricle (3 septal and 3 lateral in apical 4-chamber view, 3 septal and 3 lateral in apical 3-chambers view, 3 inferior and 3 anterior in apical 2-chambers view). The endocardial borders were traced semi-automatically by the software and manually adjusted by the operator, excluding segments with inadequate tracking. Any

plane with 3 or more excluded segments was invalidated, excluding the patient from the study. In patients with atrial fibrillation, GLS was analyzed in the longest cicle recorded.
Demographic data, etiology and clinical variables were obtained from medical record review.

Sample size

Given the exploratory and retrospective nature of this study, no formal hypothesis contrast is formulated (null hypothesis vs. alternative hypothesis) that allows the calculation of the sample size. Consequently, for this first exploratory study, it is proposed to collect between 10-20 subjects per group.

Statistical analysis

Results are presented as frequencies, mean ± standard deviation (SD) or median (interquartile range), as appropriate. Comparisons between patients with HFrEF and HFmrEF and comparisons between etiologies are performed using chi-squared test for categorical variables and t test or the Mann Whitney U test for continuous variables. The GLS between different etiologies is compared using a one-way analysis of variance (ANOVA). Spearman correlation analysis is used to determine correlations between GLS and LVEF. To explore associations between etiologies and clinical and echocardiographic variables including GLS and LVEF multinomial logistic regression analysis is used. For all statistical analysis IBM SPSS Statistics for Windows Version 25.0 (IBM Corp.; Armonk, NY) is used. A two-tailed $p<0.05$ is considered statistically significant.

RESULTS

The echocardiograms of 305 consecutive pacients between May 2019 and February 2020 were analyzed. Because of LVEF ≥50% and technically impossibility to properly measure GLS, 44 and 103 patients were excluded, respectively. In addition, 11 patients with overlapped etiologies were excluded. Thus, the recordings of 147 patients were included in the final analysis, 78 with HFmrEF (53.1%) and 69 with HFrEF (46.9%). Five groups of etiologies causing a reduction of LVEF were detected. The most frequent was ischemic, followed by idiopathic cardiomyopathy, tachycardio-myopathy, valvular, and finally toxic cardiomyopathy (including chemotherapy and alcohol). The proportion of etiologies was similar in the subpopulations of HFrEF and HFmrEF. Baseline characteristics of the subgroups are presented in Tables 1 to 4.

Table 1. Demographic characteristics of the cohort and the subgroups of HFrEF and HFmrEF.

		Cohort (N=147)	HFrEF (n=69)	HFmrEF (n=78)	p value
Women		55(37.4)	24(34.8)	31(39.7)	0.535
Age (years)		69.6±12.7	67.1±11.6	71.8±13.2	0.022
Left ventricular ejection fraction (%)		38.2±8.1	32.7±5.4	45.8±3.2	<0.001
Global longitudinal strain (%)		-13.4±3.3	-11.7±3.0	-14.9±3.0	<0.001
Ethiology	Ischemic	72(49)	35(50.7)	37(47.4)	0.379
	Tachycardiomyopathy	16(10.9)	6(8.7)	10(12.8)	0.192
	Valvular	16(10.9)	7(10.1)	9(11.5)	0.401
	Toxic	6(4.1)	4(5.8)	2(2.6)	0.149
	Idiopathic	37(25.2)	17(24.6)	20(25.6)	0.612
BMI (kg/m²)		27.1±4.6	26.5±4.3	27.6±4.9	0.122

BMI >25 kg/m²	96(65.3)	42(60.9)	54(69.2)	0.288
Smoking	77(52.4)	34(49.3)	43(55.1)	0.478
Type 2 diabetes mellitus	63(42.9)	30(43.5)	33(42.3)	0.886
High blood pressure	104(70.8)	52(75.4)	52(66.7)	0.247
Dyslipidemia	86(58.5)	46(66.7)	40(51.3)	0.059
Atrial fibrillation	55(37.4)	25(36.2)	30(38.5)	0.780
Beta-blockers	108(73.5)	57(82.6)	51(65.4)	0.018
ACEI/ARB	79(53.7)	33(47.8)	46(59.0)	0.176
Mineralocorticoid receptor antagonists	57(38.8)	42(60.9)	15(19.2)	<0.001
Sacubitril-valsartan	26(17.7)	22(31.9)	4(5.1)	<0.001
Loop diuretics	100(68.0)	47(68.1)	53(68.0)	0.983

Values: n(%), mean ± standard deviation. P value: differences between the ICFEr and ICFErm subgroups. HFrEF: heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. BMI: body mass index. ACEI: angiotensin-converting enzyme inhibitors. ARB: angiotensin-II receptor blockers.

Table 2. Demographic characteristics of the etiological groups in the cohort.

	Ischemic (n=72)	Idiopathic (n=37)	Valvular (n=16)	Tachy. (n=16)	Toxic (n=6)	p value
HFrEF	35(48.6)	17(46.0)	7(43.8)	6(37.5)	4(66.7)	0.796
Global longitudinal strain (%)	-13.0±3.0	-13.0±4.4	-12.5±2.3	-13.7±3.7	-12.6±2.9	0.820
Women	24(33.3)	14(37.8)	8(50)	5(31.3)	4(66.7)	0.101
Age (years)	67.8±10.7	73.4±13.6	73.3±10.6	66.0±18.4	66.3±12.9	0.399
BMI (kg/m²)	27.2±4.8	26.2±4.1	25.6±4.5	29.6±4.3	28.5±5.0	0.071
BMI >25 kg/m²	48(66.7)	23(62.2)	7(43.8)	13(81.3)	5(83.3)	0.188
Smoking	41(56.9)	19(51.4)	6(37.5)	7(43.8)	4(66.7)	0.557
Type 2 diabetes mellitus	34(47.2)	11(29.7)	10(62.5)	3(18.8)	5(83.3)	0.009
High blood pressure	48(66.7)	27(73.0)	14(87.5)	10(62.5)	5(83.3)	0.431
Dyslipidemia	53(73.6)	15(40.5)	8(50)	5(31.3)	5(83.3)	0.001

Atrial fibrillation	18(25)	14(37.8)	8(50)	13(81.3)	2(33.3)	0.001
Beta-blockers	59(82.0)	21(56.8)	12(75)	11(68.8)	5(83.3)	0.076
ACEI/ARB	39(54.2)	22(59.5)	8(50)	8(50)	2(33.3)	0.795
Mineralocorticoid receptor antagonists	34(47.2)	11(29.7)	2(12.5)	6(37.5)	4(66.7)	0.039
Sacubitril - valsartan	15(20.8)	3(8.1)	1(6.25)	4(25)	3(50)	0.057
Loop diuretics	42(58.3)	30(81.1)	13(81.3)	10(62.5)	5(83.3)	0.086

Values: n(%), mean ± standard deviation. P value: differences between etiological groups. Tachy.: tachycardia-induced myocardiopathy.

Table 3. Demographic characteristics of the etiological groups in patients with HFmrEF.

HFmrEF	Ischemic	Idiopathic	Valvular	Tachy.	Toxic	p value
Women	14(37.8)	8(40)	4(44.4)	4(40)	1(50)	0.994
Age (years)	69.7±11.3	75.9±11.6	77.2±10.2	64.4±20.9	82.1±3.5	0.065
Global longitudinal strain (%)	-15.0±2.9	-15.8±3.5	-13.7±1.8	-14.7±2.9	-13.2±1.2	0.543
BMI (kg/m²)	27.8±5.2	27.1±4.3	26.4±4.9	29.4±5.3	27.1±1.4	0.715
BMI >25 kg/m²	25(67.6)	15(75)	5(55.6)	7(70)	2(100)	0.728
Smoking	23(62.2)	10(50)	4(44.4)	5(50)	1(50)	0.827
Type 2 diabetes mellitus	17(46.0)	7(35)	5(55.6)	2(20)	2(100)	0.195
High blood pressure	23(62.2)	14(70)	7(77.8)	6(60)	2(100)	0.710
Dyslipidemia	23(62.2)	7(35)	6(66.7)	3(30)	1(50)	0.162
Atrial fibrillation	10(27.0)	8(40)	3(33.3)	8(80)	1(50)	0.048
Beta-blockers	27(73.0)	11(55)	7(77.8)	5(50)	1(50)	0.439
ACEI/ARB	24(64.9)	12(60)	4(44.4)	5(50)	1(50)	0.786
Mineralocorticoid receptor antagonist	9(24.3)	4(20)	0(0)	1(10)	1(50)	0.338

Sacubitril-valsartan	1(2.7)	2(10)	0(0)	1(10)	0(0)	0.644
Loop diuretics	22(59.5)	16(80)	8(88.9)	5(50)	2(100)	0.147

Values: n(%), mean ± standard deviation. P value: differences between etiological subgroups.

Table 4. Demographic characteristics of the etiological groups in patients with HFrEF.

HFrEF	Ischemic	Idiopathic	Valvular	Tachy.	Toxic	p value
Women	10(28.6%)	6(35.3)	4(57.1)	1(16.7)	3(75)	0.210
Age (years)	65.9±9.6	70.4±15.4	68.2±9.4	68.6±14.7	58.4±4.8	0.386
Global longitudinal strain (%)	-11.5±2.8	-11.9±3.7	-13.1±3.2	-10.9±1.9	-11.6±2.3	0.687
BMI (kg/m²)	26.6±4.3	25.0±3.6	24.6±4.0	29.9±2.3	29.3±6.2	0.052
BMI >25 kg/m²	23(65.7)	8(47.1)	2(28.6)	6(100)	3(75)	0.062
Smoking	18(51.4)	9(52.9)	2(28.6)	2(33.3)	3(75)	0.553
Type 2 diabetes mellitus	17(48.6)	4(23.5)	5(71.4)	1(16.7)	3(75)	0.068
High blood pressure	25(71.4)	13(76.5)	7(100)	4(66.7)	3(75)	0.586
Dyslipidemia	30(85.7)	8(47.1)	2(28.6)	2(33.3)	4(100)	0.001
Atrial fibrillation	8(22.9)	6(35.3)	5(71.4)	5(83.3)	1(25)	0.014
Beta-blockers	32(91.4)	10(58.8)	5(71.4)	6(100)	4(100)	0.023
ACEI/ARB	15(42.9)	10(58.8)	4(57.1)	3(50)	1(25)	0.688
Mineralocorticoid receptor antagonist	25(71.4)	7(41.2)	2(28.6)	5(83.3)	3(75)	0.059
Sacubitril-valsartan	14(40)	1(5.9)	1(14.3)	3(50)	3(75)	0.020
Loop diuretics	20(57.1)	14(82.4)	5(71.4)	5(83.3)	3(75)	0.368

Values: n(%), mean ± standard deviation. P value: differences between etiological groups.

In the cohort, mean LVEF was 38.2% ± 8.1% and mean GLS was -13.4% ± 3.3%. LVEF was significantly correlated with GLS (Spearman's r = 0.614, p <0.001). Absolute value of GLS was higher in HFmrEF than in HFrEF, both in the entire cohort (-14.9% ± 2.9% vs -11.7% ± 3.0%, p <0.001) (Table 1), and in all etiologies (Table 5).

Table 5. Comparison of GLS between HFmrEF and HFrEF in the different etiology groups.

	HFmrEF	HFrEF	p value
GLS in ischemic (%)	-15.0±2.9	-11.5± 2.8	<0.001
GLS in idiopathic (%)	-15.8±3.5	-11.9±3.7	0.008
GLS in valvular (%)	-13.7±1.8	-10.9±1.9	0.036
GLS in tachycardiomyopathy (%)	-14.7±2.9	-13.1±3.2	0.091
GLS in toxic (%)	-13.2±1.2	-11.6±2.3	0.132

Values: mean ± standard deviation. P value: differences between HFmrEF and HFrEF. GLS: global longitudinal strain.

One-way ANOVA indicated no significant differences in GLS between the different etiologies (ischemic -13.0% ± 3.0%, idiopathic -13.0% ± 4.4%, tachycardia-induced myocardiopathy -13.7% ± 3.7%, valvular -12.5% ± 2.3%, toxic -12.6% ± 2.9%, p = 0.820) (Table 2, Figure 1-A). Furthermore, absence of significant differences in GLS between etiologies was also detected both in HFmrEF (Table 3, Figure 1-B) and HFrEF subpopulations (Table 4, Figure 1-C).

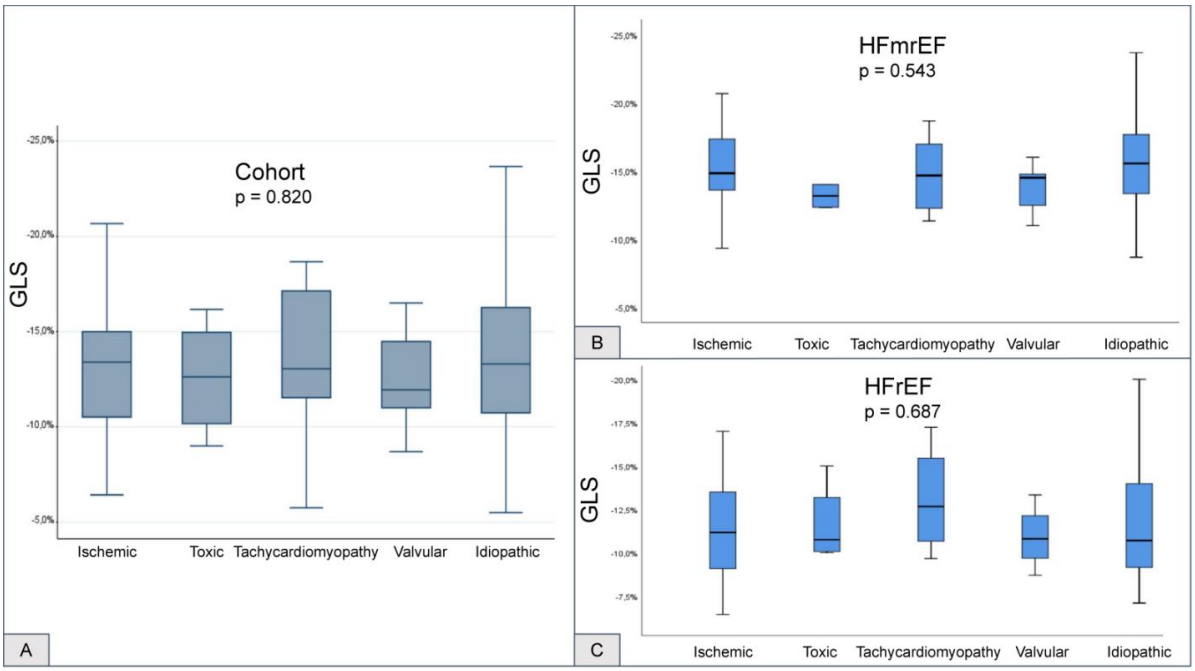

Figure 1. Comparison of GLS between the different etiologies. A) Comparison in the cohort. B) Comparison in the HFmrEF group. C) Comparison in the HFrEF group. GLS: global longitudinal strain. HFmrEF: heart failure with mildly reduced ejection fraction. HFrEF: heart failure with reduced ejection fraction.

In order to further explore the association between GLS, LVEF and etiologies, a multivariate analysis was performed. Multiple linear regression models showed that age and GLS were independently associated with LVEF (Table 6, Figure 2-A), and LVEF was independently associated with GLS (Table 7, Figure 2-B). However, in a multinomial logistic regression analysis adjusted by age, sex and LVEF, the GLS was not associated with etiologies (Table 8).

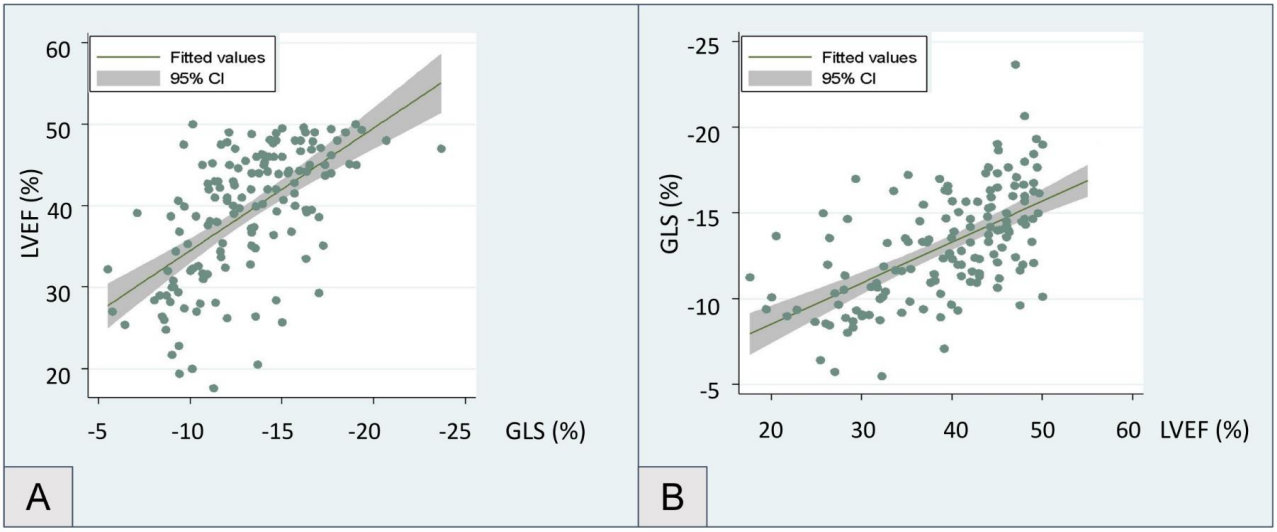

Figure 2. A) Regression line between GLS and LVEF in the cohort, 95% confidence bands. The regression coefficient is 1.504, p <0.001. **B)** Regression line between LVEF and GLS in the cohort, 95% confidence bands. The regression coefficient is 0.239, p <0.001. CI: confidence interval. GLS: global longitudinal strain. LVEF: left ventricular ejection fraction.

Table 6. Multiple linear regression analysis for LVEF.

Variables	Beta	T	p value	95% Confidence Interval for Beta	
				Lower	Upper
Global longitudinal strain	1.58	9.83	<0.001	1.26	1.90
Age	0.16	3.82	<0.001	0.08	0.24
Adjusted R^2 = 0.410, R^2 = 0.418					

Table 7. Multiple linear regression analysis for GLS.

Variables	Beta	T	p value	95% Confidence Interval for Beta	
				Lower	Upper
Left ventricular ejection fraction	0.25	9.83	<0.001	0.20	0.31
Age	-0.06	-3.54	0.001	-0.09	-0.03
Adjusted R^2 = 0.402, R^2 = 0.411					

Table 8. Multinomial logistic regression analysis for etiologies, adjusted by age, sex and LVEF.

Variables		OR	Standard error (OR)	p value	95% Confidence Interval	
					Lower	Upper
Global longitudinal strain	Ischemic (ref)	1				
	Toxic	1.08	0.19	0.683	0.76	1.53
	Tachy.	1.03	0.12	0.805	0.82	1.28

	Valvular	0.91	0.11	0.432	0.72	1.15
	Idiopathic	1.11	0.09	0.227	0.94	1.31
Left ventricular ejection fraction	Ischemic (ref)	1				
	Toxic	0.93	0.07	0.275	0.81	1.06
	Tachy.	1.02	0.05	0.699	0.93	1.12
	Valvular	1.03	0.05	0.518	0.94	1.14
	Idiopathic	0.97	0.03	0.347	0.91	1.04
Age	Ischemic (ref)	1				
	Toxic	0.99	0.04	0.812	0.92	1.07
	Tachy.	0.99	0.02	0.635	0.95	1.03
	Valvular	1.03	0.03	0.319	0.98	1.08
	Idiopathic	1.05	0.02	0.019	1.01	1.09
Sex	Ischemic (ref)	1				
	Toxic	4.83	4.50	0.091	0.78	30.03
	Tachy.	0.92	0.56	0.894	0.28	3.03
	Valvular	1.74	1.00	0.338	0.56	5.35
	Idiopathic	1.06	0.46	0.898	0.45	2.49

OR: Odds ratio. Ref: reference category. Tachy: tachycardiomyopathy.

DISCUSSION

Main findings

The main finding in this study consisted of a neutral result of the differences in GLS between the etiologies of cardiomyopathy, both in HFrEF and HFmrEF. Thus, it suggests that the GLS is an echocardiographic parameter invalid to stratify patients according to the etiology of cardiomyopathies with LVEF <50%, and consequently with a poor impact on the choice of subsequent diagnostic tests or on the early initiation of treatment derived from a specific etiological suspicion in these patients.

This hypothesis was raised in patients with LVEF <50% due to the demonstrated value of the GLS for etiological differentiation in patients with left ventricular thickening, usually presenting preserved LVEF (i.e. hypertensive heart disease, HCM or amyloidosis). Conversely, in those patients, longitudinal strain can be useful in the diagnosis, either due to the magnitude of the decrease in its global value or due to its segmental distribution. Some studies found that patients with HCM[26,27], hypertensive heart disease[27] and amyloidosis[28] had worse GLS than controls, generally without differences in LVEF. Furthermore, the results suggest both that the GLS in HCM was significantly worse than in hypertensive heart disease[27], and in addition, GLS was worse in amyloidosis than in HCM[29]. In HCM, the longitudinal strain decreased in the more hypertrophied and fibrotic segments[16], following a septal or apical distribution according to the type of HCM. In amyloidosis, the longitudinal strain was preserved at the apex, and reduced in the basal and mid segments[28], with an apex / base ratio greater than 2.1 that provided good diagnostic precision to detect those patients[30].

One of the main hypotheses that justifies the neutral result in our study is that the patients had an LVEF <50%, while LVEF was preserved in the majority of patients with left ventricular thickening[26-29]. This suggests that in cardiomyopathies with preserved LVEF there may be an incipient impairment in systolic function due to GLS worsening, with a

different magnitude of decrease in GLS, dependent on the pathophysiological mechanism of myocardial damage of each etiology. However, in etiologies presenting more advanced systolic dysfunction, with reduced LVEF, the GLS is also more severely reduced, with a similar magnitude in all etiologies, becoming not useful to differentiate them.
In addition, another hypothesis for our neutral result is that GLS, like LVEF, is a parameter that evaluates the global systolic function of the ventricle, without considering peculiarities in segmental contractility that each etiology may have. For example, ischemic ethiology is the most prevalent one, and in this regard, GLS is not very helpful to assess global left ventricular systolic function in patients with ischemic cardiomyopathies since the impairment of the myocardium may be focal and distributed inhomogeneously. In this sense, it has been reported that segmental longitudinal strain can be useful in the determination of the culprit lesion in the acute phase of coronary disease[17,31]. Moreover, segmental longitudinal strain has demonstrated its diagnostic value in the location of hypocontractile segments in HCM[16] or amyloidosis[28]. In contrast, our study analyzed GLS, but not segmental longitudinal strain. Conversely, it is possible that with segmental analysis of longitudinal strain we may have detected differences between etiologies in our patients.

Finally, the design of the study as a retrospective and cross-sectional approach, with patients in different stages in the evolution of HF, may have additionally influenced the main result of the study.

The second main finding of the study is that GLS in patients with HFrEF was significantly worse than in HFmrEF. Both GLS and LVEF reflect LV systolic function. Even if they are not equivalent in certain diseases because of changes in load or of the earlier reduction in GLS, there is a wide evidence in patients with LVEF <50% on the correlation that the lower LVEF, the worse GLS, both in acute[32] and chronic HF[33].

Secondary findings

Baseline characteristics of the patients in the study were similar to other studies and large registries, favoring the external validity of the study.
The most frequent etiology causing cardiomyopathy was ischemic, both in the cohort (findings consistent with those reported in the literature[34]) and in the subpopulations of HFrEF and HFmrEF. In addition, HFrEF were younger, and similar age correlation has been reported between patients with HFpEF and HFrEF. The proportion of HFpEF conforming total HF patients increases with age, and is by far the most prevalent form of HF in the elderly[35]. Furthermore, patients with HFpEF are older than patients with HFrEF, both in acute[36] and in chronic HF[37]. Other finding in our study was a more frequent use of drugs such as beta-blockers, mineralocorticoid receptor antagonists and sacubitril / valsartan in HFrEF, consistent with the optimal treatment recommended by clinical practice guidelines[1].
Another finding from our study is that GLS can not be measured in all patients. A technical impossibility to properly analize GLS in routine echocardiograms acquired by the staff of the Imaging Department occurred in 103 of 294 patients (35%), therefore, reducing the usefulness for the overall population of patients with or at risk of HF.

Limitations

Reliability and reproducibility of the GLS values are ideally based on acquisition and analysis of the test by the same person, as well as ultrasound systems and software of the same model, but in this study the image acquisition was done by multiple operators with a high variability in technique, leading to a large case exclusion due to poor image quality (35% of patients with LVEF <50%), reducing the usefulness of this parameter for the overall population of patients with or at risk of HF. In addition, there was no random distribution or matching to create the groups to be compared, but the patients were distributed according to their basal characteristics, although despite this the different groups were quite homogeneous.

As already mentioned, this cohort shows similarities with other studies, such as a worse GLS is detected as LVEF decreases, or patients with HFmrEF and HFpEF are older than HFrEF patients. Even so, a series of threats to external validity have been detected, such as the non-randomized retrospective nature of the study or groups with a reduced sample size due to the significant exclusion for technical reasons, leading to the use of low-power statistical tests; or also the use of a variable such as the GLS, with values dependent on the hardware and software of each commercial company. A selection bias occurred when only patients who had been requested an echocardiography in HF Unit were included, probably with asymptomatic HFrEF and HFmrEF underrepresented because a lower follow-up in this Unit. Other selection bias was that infiltrative, congenital and other minority cardiomyopathies are not represented in the study

because they are followed-up in specific Units and not in the HF Unit. It should also be taken into account that only the GLS was measured, without analyzing the segmental longitudinal strain, which perhaps could have provided some diagnostic value, as in the case of the segmental differences in strain between the etiologies of left ventricular thickening.

One of the advantages that makes the GLS an attractive diagnostic tool is its ability to detect incipient myocardial damage. Decreased GLS is an early marker of myocardial structural alteration or incipient contractility deterioration before LVEF decreases, particularly useful in Cardio-Oncology after toxic treatments[7], but also in clinical scenarios like HFpEF[12], noncompaction cardiomyopathy[18], elderly[9], obesity[19], hypertensive heart disease[20] or diabetic heart disease[21]. Our study analyzed patients with an established LVEF reduction. Thus, the usefulness of GLS for an early diagnosis of systolic dysfunction could not be corroborated.
Furthermore, the worsening of GLS is consistently correlated with cardiovascular events and cardiovascular mortality, regardless of LVEF, in multiple scenarios, both in the elderly population[9] and in the general population[8], or in pathologies such as myocardial toxicity derived from oncohematological treatments[22], HFpEF[12], HCM[14,23], ischemic heart disease[13,24], aortic stenosis[15], aortic regurgitation[25], arterial hypertension[10], and type 2 diabetes mellitus[11]. Conversely, this is a cross-sectional study that did not evaluate the previous LVEF or GLS of the patients, and there are no echocardiographic or clinical data of the follow-up, thus no cardiovascular prognosis could be correlated to the GLS, and further studies are needed for this purpose.

CONCLUSIONS

In this cohort of HF patients with LVEF <50%, both in HFrEF and HFmrEF there are no differences in GLS between the etiologies of cardiomyopathy, suggesting GLS is not a useful tool to properly classify different etiologies in HF patients with LVEF <50%.
A prospective study, with a larger sample size and including segmental longitudinal strain, may find different results.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

FUNDING STATEMENT

Sources of funding: no funding was received in the publication of this article.

AKNOWLEDGEMENTS

We thank Mr. Joan Carles Oliva for the help in the statistical analysis and for the review of the data.
This work has been presented by the author Mario Sutil-Vega as a final Master's thesis in the University Master's Degree in Image Diagnosis in Cardiology (Spanish Society of Cardiology and UCAM [San Antonio Catholic University of Murcia, Spain]) in the 2019-2021 academic course.
We thank Dr. Teresa López Fernández as tutor of the final Master's thesis and Dr. Carlos Fernández Palomeque and Dr. Esther Pérez David as members of the jury that evaluated the work, for their help in reviewing the thesis and for suggestions on new lines of investigation.

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