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REVIEW ARTICLE

Left ventricular global longitudinal strain and cardiorespiratory fitness in patients with heart failure: Systematic review and meta-analysis

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ABSTRACT

BACKGROUND There is no definition for strain deformation values in relation to cardiorespiratory fitness (CRF) in different heart failure (HF) phenotypes.

AIM To identify the relationship between echocardiographic systolic function measurements and CRF in HF patients.

METHODS Systematic review and meta-analysis following the PRISMA recommendations. Studies reporting echocardiographic assessments of left ventricular global longitudinal strain (LVGLS), left ventricular ejection fraction (LVEF), and direct measurement of peak oxygen uptake (VO_{2peak}) in HF patients with reduced or preserved LVEF (HFrEF, HFpEF) were included. The patients were divided into Weber classes according to VO_{2peak}.

RESULTS A total of 25 studies involving of 2,136 patients (70.5% with HFpEF) were included. Mean LVEF and LVGLS were similar in HFpEF patients in Weber Class A/B and Class C/D. In HFrEF patients, a non-significant difference was found in LVEF between Weber Class A/B (30.2% [95%CI: 29.6 to 30.9%]) and Class C/D (25.2% [95%CI: 20.5 to 29.9%]). In HFrEF patients, mean LVGLS was significantly lower in Class C/D compared to Class A/B (6.5% [95%CI: 6.0 to 7.1%] and 10.3% [95%CI: 9.0 to 11.5%], respectively). The correlation between VO_{2peak} and LVGLS ($r^2 = 0.245$) was nearly twofold stronger than that between VO_{2peak} and LVEF ($r^2 = 0.137$).

CONCLUSIONS Low LVGLS values were associated with low CRF in HFrEF patients. Although a weak correlation was found between systolic function at rest and CRF, the correlation between VO_{2peak} and LVGLS was nearly twofold stronger than that with LVEF, indicating that LVGLS may be a better predictor of CRF in patients with HFrEF.

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1. INTRODUCTION

Heart failure (HF) is a disease that results in significant reductions in quality of life and the performance of activities of daily living. HF affects approximately 26 million people throughout the world and is associated with high morbidity and mortality rates.[1,2] Echocardiography is considered essential for the establishment of the diagnosis and prognosis of patients with HF and helps determine the most appropriate treatment. Assessments of left ventricular systolic and diastolic function are performed to classify the HF phenotype according to left ventricular ejection fraction (LVEF) into preserved (HFpEF), reduced (HFrEF), or mildly reduced (HFmrEF).[1,2] LVEF, left atrial volume index (LAVI), E/e' ratio, and pulmonary systolic pressure with the estimation of left ventricular filling pressure are also well-established markers that play an important role in predicting outcomes in patients with HF.[3-5] More recently, myocardial strain imaging—especially the measurement of left ventricular global longitudinal strain (LVGLS)—has been claimed to be a well-validated, reliable, easy-to-perform method available in current echocardiographic devices, providing additional information for the evaluation of myocardial mechanics.[6] Some studies consider LVGLS to be a prominent variable for the detection of HF and the prognosis of patients.[7,8] Cardiopulmonary exercise testing (CPET) is another well-established method for the evaluation of cardiorespiratory fitness (CRF) in patients with HF via the direct measurement of peak oxygen uptake (VO_{2peak}), which is considered a powerful prognostic marker.[9,10] Along with other CPET-related variables, VO_{2peak} is reported to be the main parameter for the assessment of HF severity.[11-14] LVEF may be preserved in some patients with low exercise capacity and reduced in patients with normal exercise capacity. Thus, CPET variables can assist in the determination of low CRF, and the mechanisms involved. However, the availability of CPET is limited in clinical practice.[15,16]

LVGLS has been documented as a predictor of outcomes in patients with heart diseases, such as HF, hypertrophic cardiomyopathy, valvular heart disease, and cardiotoxicity.[17-22] However, there is no definition in the literature for strain deformation values in relation to LVEF and CPET variables in patients with different HF phenotypes. Indeed, these correlations remain uncertain or poorly described.[22-24]

Therefore, the aim of the present study was to conduct a systematic review with a meta-analysis of the current literature to identify mean LVEF and LVGLS values and associations with different levels of CRF in HF patients with preserved and reduced LVEF.

2. METHODS

This study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement). The protocol for this study was registered in the PROSPERO database (CRD42020196918).

2.1. SEARCH STRATEGY AND STUDY SELECTION. The MEDLINE via PubMed, EMBASE, CINAHAL, MEDLINE Complete, SPORTDiscus via EBSCOhost, SciELO Citation Index, and Web of Science (Clarivate Analytics) electronic databases were searched employing a prospectively defined literature and data retrieval strategy. We also screened the Cochrane Library and searched the reference lists of all articles included in an effort to identify additional studies.

The scope of the search was determined to identify patients with HF in whom CRF was measured by CPET, and LVGLS was determined by transthoracic echocardiography. The search terms were "cardiovascular diseases" [Mesh] OR "heart diseases" [Mesh] OR "heart failure" [Mesh] OR "myocardial ischemia" [Mesh] OR "cardiomyopathies" [Mesh] AND "ultrasonography" [Mesh] OR "echocardiography" [Mesh] OR "echocardiography, three-dimensional" [Mesh] AND "global longitudinal strain" [All fields] OR "myocardial strain" [All fields] OR "longitudinal strain" [All fields] OR "speckle tracking" [All fields] OR "speckle tracking echocardiography" [All fields] AND "ergometry" [Mesh] OR "exercise test" [Mesh] OR "cardiopulmonary exercise test" [Mesh] and respective relevant variations. Studies from 2009 to 2020 were included.

2.2. DATA EXTRACTION. Two independent reviewers (L.D. and A.L.) extracted and reviewed the data using the Covidence platform. Potentially relevant articles were assessed for eligibility based on the inclusion and exclusion criteria. Articles were first screened by title and abstract, followed by a full-text analysis. In the full-text assessment for eligibility, agreement between reviewers was moderate (Kappa value of 0.548), the resulting sets of references for inclusion were compared and the disagreements were resolved by consensus. Authors of the primary studies were contacted if the data were incomplete. The selection criteria were cross-sectional, prospective cohort, or case-control studies involving patients with HF, and the assessment of LVGLS and LVEF via echocardiogram analysis, and the determination of VO_{2peak} by CPET. When available, LAVI and E/e' ratio by echocardiogram and CPET data on the carbon dioxide ventilatory equivalent slope (VE/VCO_2 slope) were also collected.

2.3. INCLUSION CRITERIA. Studies involving male and female adults (18 years of age or older) with a diagnosis of HF from all etiologies selected by clinical, laboratory criteria, or imaging tests based on international guidelines were included. All patients need to have undergone transthoracic echocardiography with the determination of LVGLS and LVEF as well as CPET for the determination of VO_{2peak}, enabling the classification of CRF according to Weber's criteria (Class A: >20 ml/kg/min; Class B: 16-20 ml/kg/min; Class C: 10-15.9 ml/kg/min; Class D: <10 ml/kg/min)[(25)] Both tests needed to be performed within a maximum of three months to minimize the occurrence of potential changes in clinical condition or pharmaceutical prescriptions.

2.4. EXCLUSION CRITERIA. Studies were excluded due to incomplete data or CRF determined by the indirect measurement of VO_{2peak} using methods other than CPET. Detailed information on the excluded studies is provided in Supplementary Table S1.

2.5. METHODOLOGICAL QUALITY APPRAISAL. The methodological quality and risk of bias of the studies included were appraised by the same two independent observers (L.D. and A.L.) using the method described by Joanna Briggs Institute (JBI) Systematic Reviews[26] (Supplementary Table S2).

2.6. STATISTICAL ANALYSIS. Data were expressed as absolute and relative frequency for categorical variables as well as mean and 95% confidence interval (95% CI) or mean and standard deviation (SD) for continuous variables. Data (mean ± SD) from the selected studies were analyzed using the OpenMeta (Analyst)® program. Heterogeneity among the studies was assessed using the Cochrane Q-test and I^2 inconsistency test. As heterogeneity was low, a fixed-effects model was used for the analysis.[27]

To assess heterogeneity among the studies for primary outcome groups and subgroups, the I^2 statistic was used as a proportionate measure of the total variance in pooled estimates. The random-effects method was used for this analysis.

For each individual study, the mean, SD, and sample size of the variables LVEF, LVGLS, VO_{2peak}, and VE/VCO_2 were used to calculate linearity (r^2; $p < 0.05$) for the curve using second-order regression and the power estimation of the convergence of the values for the proposed model (GraphPad Prism 9.2).[28]

3. RESULTS

3.1. SEARCH RESULTS AND STUDY SELECTION. **Fig. 1** displays the flowchart of the article selection process in accordance with the PRISMA guidelines. The search of the databases led to the retrieval of 924 records, which were imported for screening and 287 duplicates were removed. The title and abstract of 637 articles were analyzed and 68 articles were then submitted to full-text analysis for eligibility, resulting in 25 relevant publications.[29-53] The characteristics of the selected studies and the number of patients evaluated are summarized in Supplementary Table S3.

Using the JBI critical appraisal checklist tool for prevalence studies[26], one study achieved a full score of 9, 23 studies achieved a score of 8, and one study achieved a score of 7.

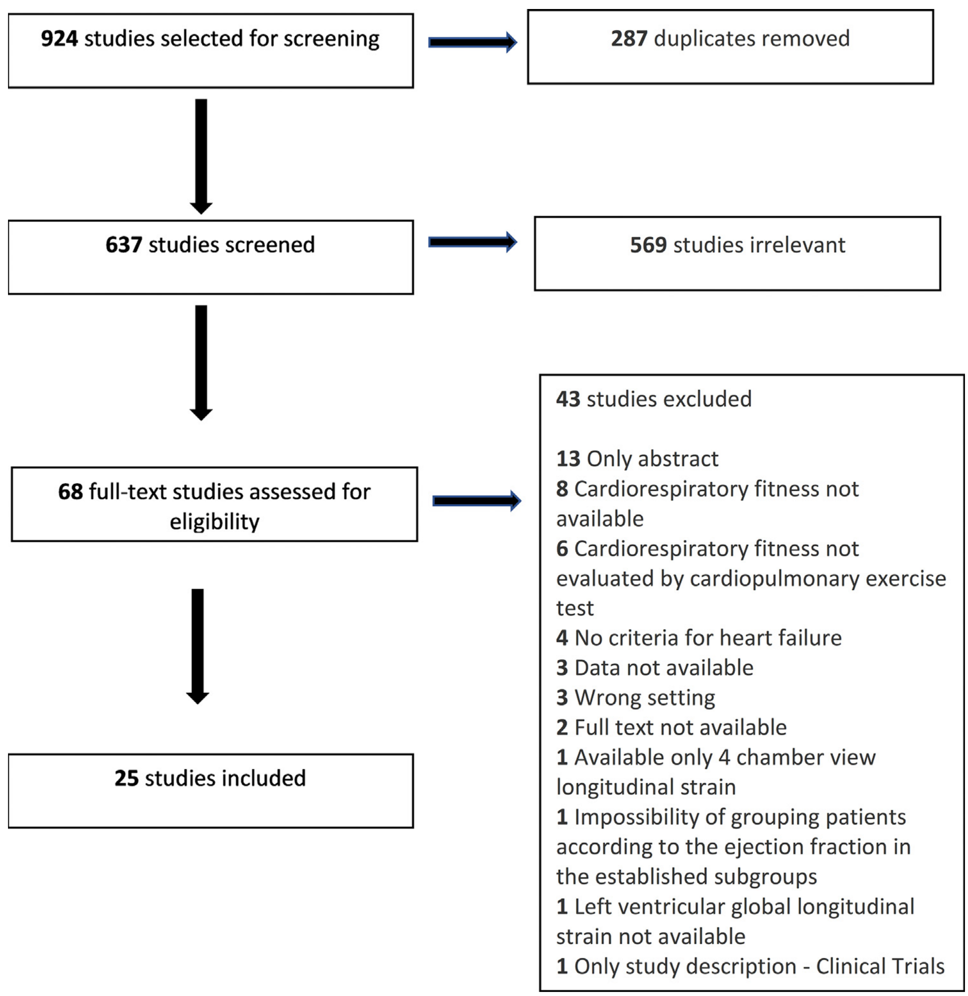
3.2. SAMPLE CHARACTERISTICS. A total of 2,136 patients with a mean age ranging from 44-70.8 years (51.1% females) were included in the analysis; 70.5% had HFpEF and most were in NYHA Class II (47.2%). Hypertension was the most common comorbidity in all groups. The characteristics of the participants are listed in **Table 1** and Table S3: Characteristics of studies included in meta-analysis.

3.3. ECHOCARDIOGRAPHY. Echocardiography was performed in most of the studies with the equipment manufactured by GE Healthcare and analyses were performed offline in most cases. Three studies used the Philips Medical System, one study used both GE and Philips, one study used the Toshiba Medical System, and one study did not report the equipment used **(Supplementary Table S2).**

The calculated mean LVEF was similar between HFpEF patients in Weber Class A/B and Class C/D (63.4% [95% CI: 60.9 to 65.9%] and 66.6% [95% CI: 60.8 to 72.4%], respectively). Among patients with HFrEF, mean LVEF was numerically lower in individuals in Class C/D compared to those in Class A/B, but the difference was not statistically significant (Weber Class A/B: 30.2% [95% CI: 29.6 to 30.9%] versus Class C/D: 25.2% [95% CI: 20.5 to 29.9%]) (**Table 2** and **Fig. 2**).

The distribution of LVGLS in the selected studies is shown in **Fig. 3**. Although all strain values are negative, these data were presented as absolute values. Hence, a decrease in strain (lower absolute value) is observed when LV function deteriorates. Mean LVGLS in patients with HFpEF in Weber Class A/B was 17.6% (95% CI: 16.8 to 18.3%) and was similar to that found in Weber Class C/D (16.7% [95% CI: 15.2 to 18.2%]). In contrast, mean LVGLS in patients with HFrEF in Weber Class A/B was 10.3% (95% CI: 9.0 to 11.5%) and was significantly lower among those in Weber Class C/D (6.5% [95% CI: 6.0 to 7.1%]). Only two studies qualified patients with HFmrEF, for

FIGURE 1 **PRISMA flowchart**



whom mean LVGLS was 12.6% (95% CI: 9.7 to 15.5%) (Table 2 and Fig. 3).

Mean LAVI and E/e' ratio values did not differ significantly according to Weber classes in patients with HFrEF or those with HFpEF (Supplementary Figs. S1 and S2).

3.4. CARDIOPULMONARY EXERCISE TESTING. Mean VO_{2peak} values (Supplementary Fig. S3) reflected the subdivision according to Weber classes among HF phenotypes. VO_{2peak} was equally low in Weber Class C/D in both patients with HFrEF and those with HFpEF. Unexpectedly, the VE/VCO_2 slope (Supplementary Fig. S4) did not follow the VO_{2peak} pattern and no statistically significant difference in mean VE/VCO_2 slope was found between Weber classes in patients with HFrEF or those with HFpEF.

Echocardiographic systolic function measurements (LVEF vs. LVGLS) were weakly correlated ($r^2 = 0.208$) (Fig. 4A). Despite both having a weak correlation ($r^2 < 0.4$; $p < 0.05$) (Fig. 4B and C), a positive association was found between CRF and systolic function, i.e., higher VO_{2peak} was correlated with higher LVEF and LVGLS values. However, the correlation between VO_{2peak} and LVGLS ($r^2 = 0.245$; $p < 0.001$) was nearly twofold stronger than that between VO_{2peak} and LVEF ($r^2 = 0.137$; $p = 0.034$). Additionally, the VE/VCO_2 slope was very weakly correlated with both LVGLS ($r^2 = 0.098$; $p = 0.022$) and LVEF ($r^2 = 0.070$; $p = 0.022$) (Supplementary Figs. S5B and S5C) as well as with VO_{2peak} ($r^2 = 0.056$; $p = 0.126$) (Supplementary Fig. S5A). Correlations between diastolic function measurements (E/e' and LAVI), LVGLS and VO_{2peak} were nonsignificant (Supplementary Fig. S6 e S7).

3.5. ANCILLARY ANALYSIS. In order to increase the applicability of our results to patients with advanced HFrEF, we performed an additional analysis of LVEF

TABLE 1 Demographic and clinical data of subjects enrolled in included studies

Characteristics	Patients assessed	Patients with condition
All N	2136	
Male	1045 (48.9)	
Female	1091 (51.1)	
Hypertension	1659 (77.7)	1170 (70.5)
Diabetes Mellitus	1609 (75.3)	535 (33.3)
Ischemic heart disease	605 (28.3)	271 (44.8)
Fabry Disease	35 (1.6)	35 (100)
Hypertrophic cardiomyopathy	168 (7.9)	133 (79.2)
NYHA I	1323 (61.9)	293 (22.1)
NYHA II	1323 (61.9)	624 (47.2)
NYHA III	1323 (61.9)	301 (22.8)
NYHA IV	1323 (61.9)	1 (0.1)
Weber A and B- HFpEF%	885 (41.4)	
Weber C and D- HFpEF%	622 (29.1)	
Weber A and B- HFmrEF%	115 (5.4)	
Weber A and B - HFrEF%	363 (17.0)	
Weber C and D- HFrEF%	151 (7.1)	

Data are presented as absolute and (relative) frequency. HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mildly reduced ejection fraction; HFrEF, Heart failure with reduced ejection fraction. NYHA (New York Heart Association functional class).

and LVGLS according to division into subgroups with VO_{2peak} above and below 14 mL/kg/min. Mean LVEF was numerically lower in individuals with VO_{2peak} < 14 mL/kg/min compared to VO_{2peak} > 14 mL/kg/min, and contrary to the analysis by division by Weber classes, the difference was statistically significant [30.0% (CI 95%: 29.4 to 30.6%) versus 24.2% (95% CI: 19.8 to 28.5%)].

Regarding the LVGLS, the results were similar to those found in the analysis by Weber classes. Mean LVGLS in patients with HFrEF and VO_{2peak} > 14 mL/kg/min was 9.8% (95% CI: 8.5 to 11.0%) and remained significantly lower among those with VO2peak <14 mL/kg/min [6.5% (95% CI: 5.7 to 7.3%)] (Supplementary Figs. S8 and S9).

4. DISCUSSION

In this meta-analysis including patients with HF in a broader range of presentations, we have tried to explore how the main prognostic variables on this condition are associated. We think this information may be clinically relevant, especially in patients with reduced ejection fraction, in which prognostic determination is tough, and the decision for heart transplantation depends mainly on CPET, that is not always available, compared to echocardiography.

LVEF and LVGLS values were grouped based on the HF phenotype according to CRF and we presented the discriminatory performance of LVGLS and LVEF comparing CRF classifications. We showed that a reduction in LVGLS was associated with a worse cardiorespiratory fitness (Weber Class C/D or subgroup with VO_{2peak} below 14 mL/kg/min) in patients with HFrEF. The correlation between VO_{2peak} and LVGLS (Fig. 4) was stronger than that between VO_{2peak} and LVEF, which may corroborate the powerful prognostic value of LVGLS, as VO_{2peak} is a marker of health, and lower values are associated with adverse outcomes.[9,10]

The clinical and prognostic value of CPET is well established as a functional assessment measure in HF. Pioneering studies by Weber et al.[25] introduced and proposed the use of CPET in daily practice. VO_{2peak} and, subsequently, the VE/VCO_2 slope became vital signs of disease severity, enabling a more precise definition on which to base treatment decisions.[54] In a landmark paper from 1982, Weber et al.[25] proposed a classification with four different VO_{2peak} categories that paved the way for considerable evidence and advances in care and risk stratification for patients with HF.[55] Weber's classification (A to D), which is based on exercise gas exchange patterns, reflects maladaptive exercise responses, defines disease severity and predicts a poorer outcome of the disease in the population with HF.

TABLE 2 Echocardiographic characteristics

	HFpEF Weber A/B	HFpEF Weber C/D	HFmrEF Weber A/B	HFrEF Weber A/B	HFrEF Weber C/D	Overall
LVEF, %	63.4 (60.9-65.9) N = 885	66.6 (60.8-72.4) N = 622	44.7 (42,4-47.0) N = 115	30.2 (29.6-30.9) N = 363	25.2 (20.5-29.9) N = 151	50.5 (45.3-55.7) N = 2136
LVGLS, %	17.6 (16.8-18.3) N = 885	16.7 (15.2-18.2) N = 622	12.6 (9.7-15.5) N = 115	10.3 (9.0-11.5) N = 363	6.5 (6.0-7.1) N = 151	14.0 (12.6-15.4) N = 2136
LAVI ml/m^2	33.7 (29.8-37.7) N = 605	38.3 (35.7-40.9) N = 560	30.8 (26.7-35.0) N = 115	40.1 (30.7-49.5) N = 125	38.4 (34.5-42.3) N = 54	35.7 (33.2-38.2) N = 1459
E/e', %	11.1 (10.2-12.0) N = 848	12.8 (11.1-14.4) N = 662	10.9 (10.1-16.7) N = 40	13.8 (11.4-16.2) N = 345	14.0 (10.0-17.9) N = 54	12.8 (11.5-13.0) N = 1949

Values are described as mean estimate, 95% confidence interval, and sample size. LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; LAVI, left atrial volume index; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF: heart failure with reduced ejection fraction; N, sample size.

FIGURE 2 Forest plot of left ventricular ejection fraction according to Weber classes and heart failure phenotypes. Data expressed as mean values and 95% confidence interval

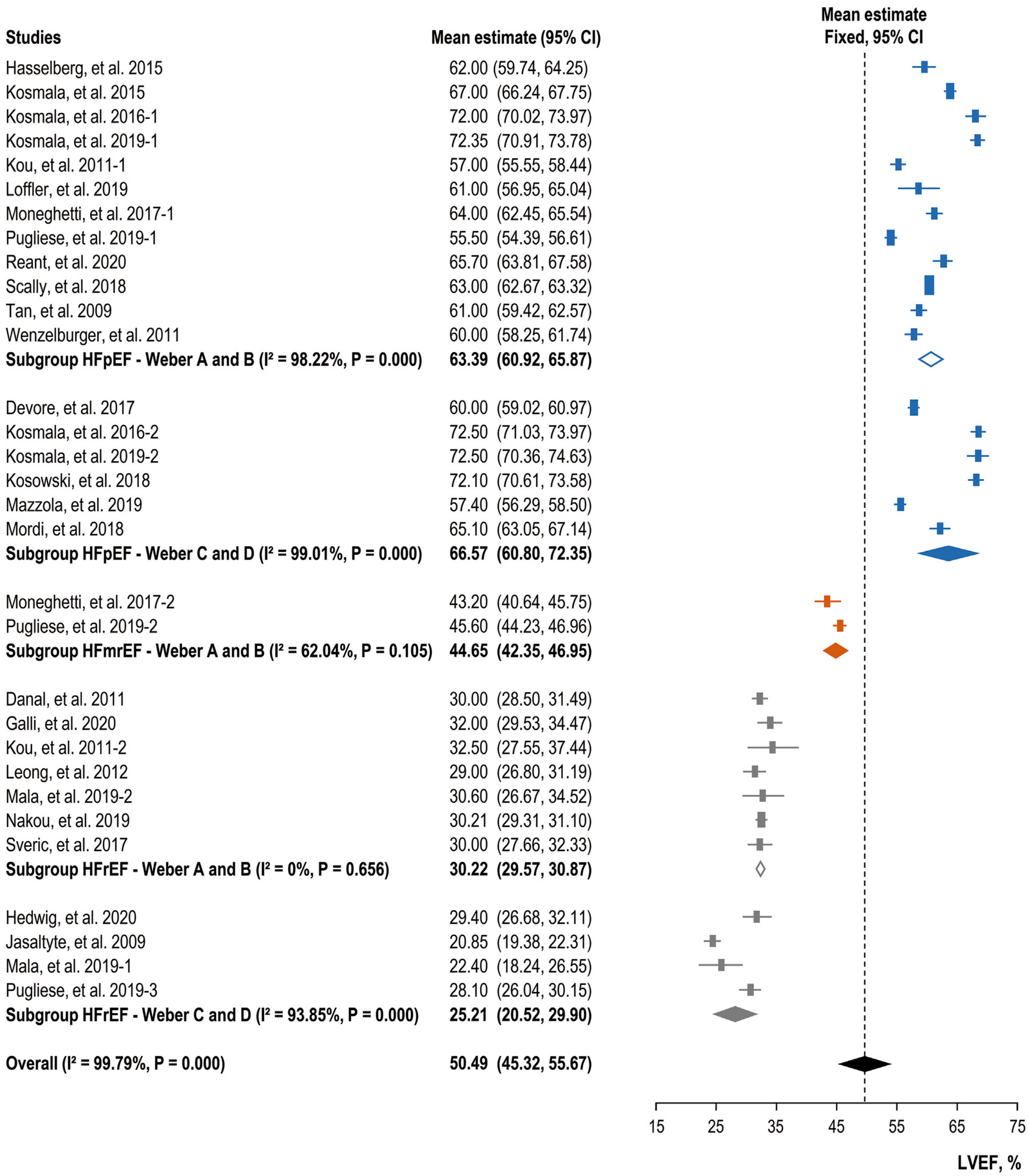
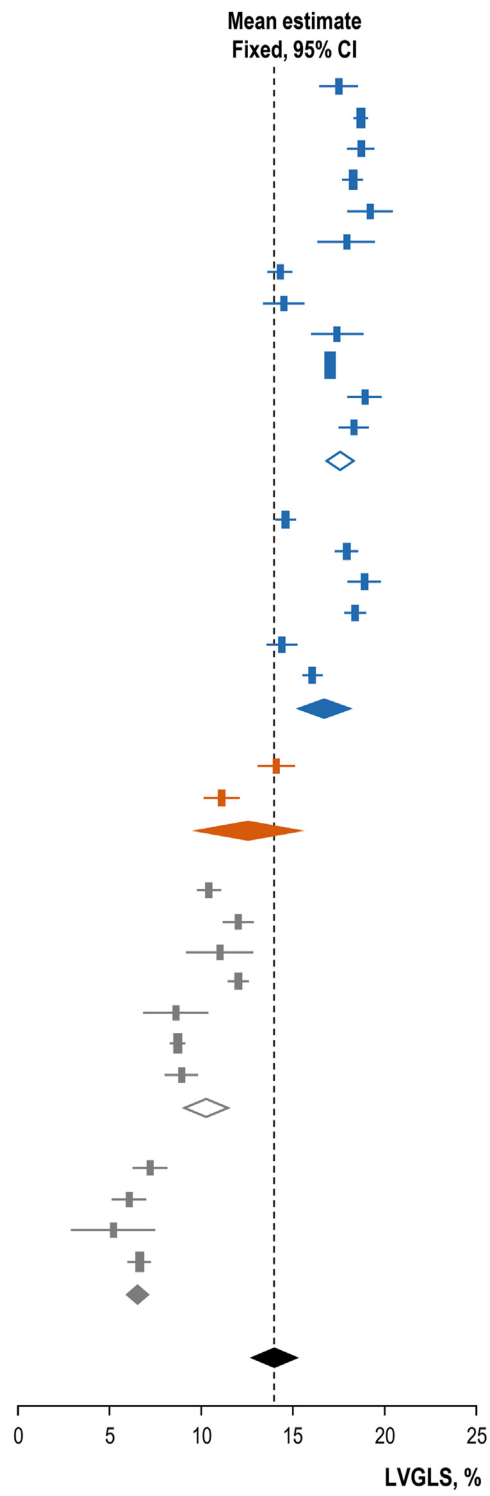


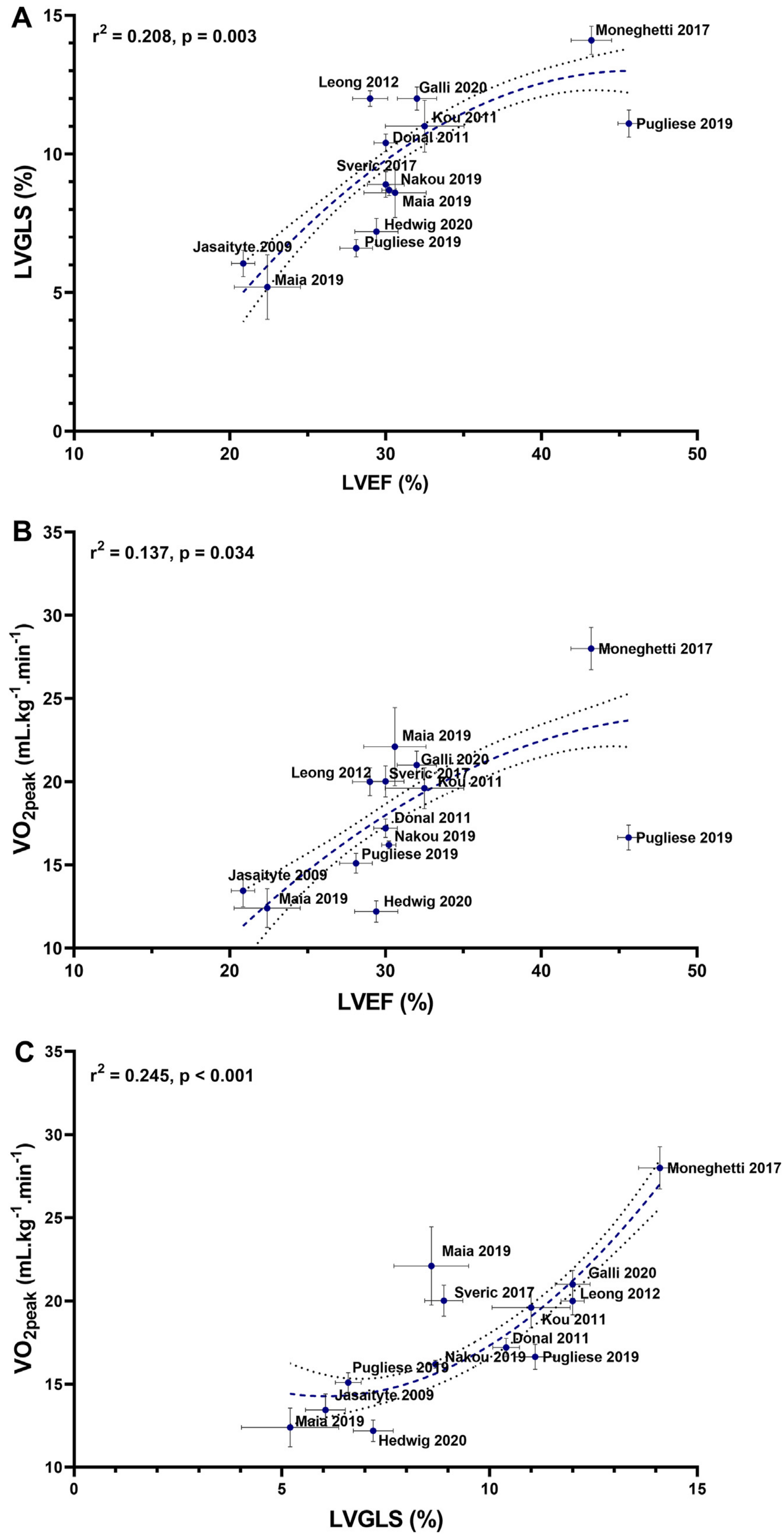
FIGURE 3 **Forest plot of left ventricular global longitudinal strain according to Weber classes and heart failure phenotypes**

Studies	Mean estimate (95% CI)
Hasselberg, et al. 2015	17.50 (16.46, 18.53)
Kosmala, et al. 2015	18.70 (18.34, 19.05)
Kosmala, et al. 2016-1	18.70 (17.95, 19.44)
Kosmala, et al. 2019-1	18.25 (17.71, 18.78)
Kou, et al. 2011-1	19.20 (17.97, 20.42)
Loffler, et al. 2019	17.90 (16.32, 19.47)
Moneghetti, et al. 2017-1	14.30 (13.63, 14.96)
Pugliese, et al. 2019-1	14.50 (13.39, 15.61)
Reant, et al. 2020	17.40 (15.97, 18.82)
Scally, et al. 2018	17.00 (16.80, 17.19)
Tan, et al. 2009	18.90 (17.98, 19.81)
Wenzelburger, et al. 2011	18.30 (17.47, 19.12)
Subgroup HFpEF - Weber A and B (I^2 = 95.07%, P = 0.000)	**17.55 (16.75, 18.34)**
Devore, et al. 2017	14.60 (14.04, 15.15)
Kosmala, et al. 2016-2	17.90 (17.28, 18.51)
Kosmala, et al. 2019-2	18.90 (18.02, 19.77)
Kosowski, et al. 2018	18.40 (17.83, 18.96)
Mazzola, et al. 2019	14.40 (13.56, 15.23)
Mordi, et al. 2018	16.05 (15.51, 16.58)
Subgroup HFpEF - Weber C and D (I^2 = 96.94%, P = 0.000)	**16.70 (15.22, 18.19)**
Moneghetti, et al. 2017-2	14.10 (13.10, 15.09)
Pugliese, et al. 2019-2	11.10 (10.13, 12.06)
Subgroup HFmrEF - Weber A and B (I^2 = 94.46% , P = 0.000)	**12.59 (9.65, 15.53)**
Danal, et al. 2011	10.40 (9.77, 11.02)
Galli, et al. 2020	12.00 (11.17, 12.82)
Kou, et al. 2011-2	11.00 (9.16, 12.83)
Leong, et al. 2012	12.00 (11.45, 12.54)
Mala, et al. 2019-2	8.60 (6.84, 10.35)
Nakou, et al. 2019	8.70 (8.30, 9.09)
Sveric, et al. 2017	8.90 (7.99, 9.80)
Subgroup HFrEF - Weber A and B (I^2 = 95.21%, P = 0.000)	**10.25 (8.97, 11.53)**
Hedwig, et al. 2020	7.20 (6.26, 8.13)
Jasaltyte, et al. 2009	6.05 (5.11, 6.98)
Mala, et al. 2019-1	5.20 (2.91, 7.48)
Pugliese, et al. 2019-3	6.60 (5.98, 7.21)
Subgroup HFrEF - Weber C and D (I^2 = 30.52%, P = 0.229)	**6.53 (5.95, 7.10)**
Overall (I^2 = 99.36%, P = 0.000)	**13.98 (12.56, 15.40)**



Data expressed as mean values and 95% confidence interval.

FIGURE 4 **Non-linear regression analyses between systolic function measurements and peak oxygen uptake in studies of heart failure with reduced and mildly reduced ejection fraction**



Data expressed as the mean and standard error of the mean for each study and second-order polynomial regression curve with the 95% confidence bands.

Despite the solid scientific evidence supporting CPET, the method remains underused in clinical practice due to the cost as well as a lack of equipment and specialized professionals.[12,16,34]

HF is a heterogeneous syndrome in which disease progression is associated with a dynamic evolution of functional and structural changes that lead to unique disease trajectories, creating a spectrum of phenotypes with distinct and overlapping features.[56,57] Unlike CPET, transthoracic echocardiography is an easily accessible, low-cost test that can even be performed at the bedside.[16] LVEF is the stroke volume expressed as a fraction of the LV end-diastolic volume and has been the most widely used and accepted echocardiographic parameter of LV systolic function. This parameter occupies a unique position in cardiology, serving as a selection criterion for almost all reference therapeutic trials in HF and being incorporated into clinical guidelines.[58] However, LVEF alterations may not reflect ventricular contractility and remodeling, leading to a simplification of the scientific view of a complex syndrome, and contributing to delays in pathophysiological and therapeutic understanding, especially in patients with HFpEF.[56,57] Myocardial strain imaging, now available in most echocardiography machines, has been shown to be a more sensitive marker of LV systolic function than LVEF, with superior prognostic value in many heart diseases with wide-range myocardial dysfunction.[58] Thus, an easy-to-perform test can provide important information that can help in the management and medication adjustment of HF patients with a worse prognosis (HFrEF), and with low exercise capacity.[30,31] In the present study, we found a lower mean LVGLS value (6.5%) in patients with HFrEF and low CRF (Weber Class C/D), whereas the mean LVGLS value was higher (10.3%) in patients with similar LVEF but better CRF (Weber Class A/B), correlating with the data obtained for CRF and possibly revealing individuals with a poorer prognosis. Zhang et al.[59]showed that patients with HFrEF and low (<9.6%) or very low (≤6.5%) LGLS values had a markedly increased risk of adverse outcomes compared to patients with higher values (hazard ratio = 3.9; 95% CI: 2.5 to 6.1, $P < 0.001$). LVGLS has previously been correlated with mortality in patients with HFrEF independently of LVEF.[59,60]

Although the bivariate correlation between VO_{2peak} and LVGLS was considered weak ($r^2 = 0.245$), we should emphasize that we are comparing systolic function at rest to function during peak exercise. Thus, a single resting measurement that can explain one-fourth of the variation in the peak exercise variable may be considered relatively powerful, as other variables also exert an influence on CRF, such as, sex, age, anthropometrics, physical activity level, as well as regional or national heterogeneity.[61-63] Moreover, the correlation between VO_{2peak} and LVGLS was nearly twofold stronger than that between VO_{2peak} and LVEF ($r^2 = 0.137$), indicating that LVGLS is a better predictor of CRF than LVEF.

We found a lower mean LVGLS value (16.7%) in patients with HFpEF in Weber Class C/D compared to those with similar LVEF but better CRF (Weber Class A/B) (17.6%). Although the value was lower in patients with poorer exercise capacity and both values were below the normal reference value, the confidence interval between groups was very close, precluding the differentiation of these individuals based on LVGLS alone.[59,60] This may be attributed to the distinct systemic and myocardial signaling in patients with HFpEF and the diversity of HFpEF phenotypes. HFpEF is a clinical syndrome with multiple contributing factors, etiologies, and pathophysiological expressions.[23,42] Despite a better understanding of the pathophysiology of the syndrome, diagnosing patients with HFpEF is a challenge and is based on stages.[23,39] The criteria include signs and symptoms of HF, evidence of preserved LVEF and the presence of diastolic dysfunction. The echocardiogram provides parameters that generate a sum score, such as septal e' velocity, lateral e' velocity, E/e' ratio, maximum LAVI, relative left ventricular wall thickness, left ventricular mass index, peak tricuspid regurgitation velocity, and LVGLS velocity.[39] In some cases, however, changes are found only during exercise, which may have interfered with the values found in the present study, as the LVGLS analysis was performed at rest.

In studies for which some diastolic function indices (E/e' ratio and maximum LAVI) were available, the data were collected and analyzed, but no correlation was found between those echocardiographic variables and the indices and CRF (Supplementary Figs. S1 and S2, S6, and S7).

Finally, only two studies presented the HFmrEF phenotype. Intermediate LVGLS values were found in these patients compared to those with preserved and reduced LVEF. However, the reduced sample highlights the need for more studies in this phenotype.

In summary, we think our data reinforces the powerful prognostic value of LVGLS in patients with HF, demonstrating its linear relationship with EF and, most importantly, with CRF, which could be clinically relevant for patient's clinical management.

4.1. LIMITATIONS. As occurs with other meta-analyses of observational studies, nonuniform designs and differences in the inclusion criteria and endpoints are potential sources of heterogeneity among studies. The data obtained in each study were means rather than raw values, which may have influenced the results. Data from LAVI, E/e' ratio, and VE/VCO2 slope were not available in the whole sample. Thus, conclusions about these variables can be limited due to selection bias and higher heterogeneity, mainly regarding VE/VCO_2 slope, in which data were available in only 43% of the included sample. Additional potential limitations of LVGLS include the dependence on high-quality 2D images and proper settings, as occurs in the calculation of LVEF. LVGLS is also dependent on both preload and afterload. Changes in loading can increase or reduce the strain, irrespective of myocardial status, such as in severe mitral regurgitation, which can cause disproportionate LVGLS due to reduced left ventricular afterload. A recent technique incorporated into echocardiography enables the analysis of myocardial work (MW) through non-invasive measurements using the pressure-strain loop (PSL) adjusted according to the duration of the isovolumetric and LV ejection phases. The advantage of MW and the corresponding indices is that they provide a more load-independent measure of LV function, considering afterload. MW is also highly reproducible and can provide additional LVGLS information about desynchronized contractions and segmental work. However, MW analysis was not the scope of this study, and the literature search did not include this variable.

An important limitation of LVGLS is the lack of standardization among equipment suppliers, leading to inter-supplier variability. This could have influenced our data. On the other hand, we believe that our data could be seen as "real-world data", demonstrating the correlation between HF variables independently of machine manufacturers, as the most important echocardiographic equipment suppliers were included in the studies reviewed.

Another limitation of the present study was that the correlation and regression analyses were performed with the data available in the studies (mean, SD, and sample size) rather than raw data. However, the present analysis could be helpful in demonstrating possible relationships between variables and stimulating future research that may enable a better understanding of such relationships. Due to this limitation, regression equations were not presented, as the real values could be different from our results.

5. CONCLUSION

LVGLS has good reproducibility, with little difference between equipment suppliers and is superior to conventional echocardiographic measures.[64-66]

This study offered the following novel findings:

1) Low LVGLS values were associated with low cardiorespiratory fitness (Weber functional Classes C and D) in patients with HF and a reduced ejection fraction.
2) Although a weak bivariate correlation was found between systolic function at rest and CRF, the correlation between VO_{2peak} and LVGLS was nearly twofold stronger than that between VO_{2peak} and LVEF, indicating that LVGLS may be a better predictor of CRF when used in association with other variables that influence exercise performance, such as sex, age, and anthropometrics.

DATA AVAILABILITY

The data supporting this article are available in the article and its online supplementary material and can be shared upon reasonable request to the corresponding author.

AUTHORS' CONTRIBUTIONS

L.D., A.L., and G.C.J. conceived the study. L.D. and A.L. performed the systematic searches, examined the eligibility and validity of the articles and performed the data extraction. I.C. and M.M. performed the analysis and interpretation of the results. The first draft of the manuscript was written by L.D. and all authors (A.L., M.M., J.M., G.C., D.B., I.C., and G.C.J.) revised it critically. Study supervision was performed by G.C.J. All authors gave final approval of the version to be published and agreed to be responsible for all aspects of the research.

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DECLARATION OF COMPETING INTEREST

The authors have no conflicts of interest to disclose. There is no relationship with the industry.

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APPENDIX A. SUPPLEMENTARY DATA Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2023.09.010.