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Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis

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ABSTRACT

Background The purpose of this meta-analysis was to confirm if the global longitudinal systolic function of the left ventricle (LV) is altered in patients with heart failure with preserved ejection fraction (HFpEF).

Methods We searched in different databases (Medline, Embase and Cochrane) studies that analysed LV global longitudinal systolic strain (GLS) in patients with HFpEF and in controls (such as healthy subjects or asymptomatic patients with arterial hypertension, diabetes mellitus or coronary artery disease).

Results Twenty-two studies (2284 patients with HFpEF and 2302 controls) were included in the final analysis. Patients with HFpEF had significantly lower GLS than healthy subjects (mean −15.7% (range −12% to −18.9%) vs mean −19.9% (range −17.1% to −21.5%), weighted mean difference −4.2% (95% CI −3.3% to −5.0%), p < 0.001, respectively). In addition, patients with HFpEF had also significantly lower GLS than asymptomatic patients (mean −15.5% (range −13.4% to −18.4%) vs mean −18.3% (range −15.1% to −20.4%), weighted mean difference −2.8%(95% CI −1.9% to −3.6%), p < 0.001, respectively). In line, 10 studies showed that the rate of abnormal GLS was significantly higher in patients with HFpEF (mean 65.4% (range 37%–95%)) than in asymptomatic subjects (mean 13% (range 0%–29.6%)). Regarding the prognostic relevance of abnormal GLS in HFpEF, two multicentre studies with large sample size (447 and 348) and high number of events (115 and 177) showed that patients with abnormal GLS had worse cardiovascular (CV) outcomes than those with normal GLS (HR for CV mortality and HF hospitalisation 2.14 (95% CI 1.26 to 3.66) and 1.94 (95% CI 1.22 to 3.07)), even adjusting these analyses for multiples clinical and echocardiographic variables.

Conclusion The present meta-analysis analysing 2284 patients with HFpEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFpEF. Further large multicentre studies with the aim to confirm the prognostic role of abnormal GLS in HFpEF are warranted.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) has long been considered a disorder characterised principally by left ventricular (LV) diastolic alterations.[1–3] While it is correct, recent studies using two-dimensional speckle-tracking echocardiography (2DSTE) have suggested that the longitudinal systolic function of the LV is altered in HFpEF.[4–26] Nonetheless, despite these interesting pathophysiological insights, other studies including old control patients and well-characterised patients with HFpEF did not find any difference in LV global longitudinal systolic strain (GLS) between HFpEF and controls as well as any clinical relevance of GLS in HFpEF.[27–33] Accordingly, given these contradictory results, at this time it is difficult to confirm the magnitude of an altered LV longitudinal systolic function in patients with HFpEF. In addition, it remains uncertain the exact rate of abnormal GLS in HFpEF or whether the prevalence of this LV systolic alteration is significantly different to asymptomatic controls. In line, a global examination or meta-analysis addressing all these important issues in HFpEF is lacking.

Therefore, the purpose of this meta-analysis was to analyse the global longitudinal systolic function of the LV in all published studies that included HFpEF and control patients with the aim to confirm if the global longitudinal systolic function of the LV is altered in patients with HFpEF.

METHODS

Search process

We searched in different databases (Medline, Embase and Cochrane) published studies

KEY QUESTIONS

What is already known about this subject?

- Heart failure with preserved ejection fraction (HFpEF) has long been considered a disorder characterised principally by left ventricular (LV) diastolic alterations. While it is correct, recent studies using two-dimensional speckle-tracking echocardiography have suggested that the longitudinal systolic function of the LV is altered in HFpEF. Nonetheless, despite these interesting pathophysiological insights, other studies including old control patients and well-characterised patients with HFpEF did not find any significant difference in LV global longitudinal systolic strain (GLS) between HFpEF and controls. Accordingly, given these contradictory results, at this time it is difficult to confirm the magnitude of an altered LV longitudinal systolic function in patients with HFpEF. In addition, it remains uncertain the exact rate of abnormal GLS in HFpEF or whether the prevalence of this LV systolic alteration is significantly different to asymptomatic controls. In line, a global examination or meta-analysis addressing all these important issues in HFpEF is lacking.

What does this study add?

- On the basis of 22 studies, 2284 patients with HFpEF and 2302 controls, the findings of this meta-analysis confirm that patients with HFpEF have significantly lower LV longitudinal systolic function than asymptomatic controls and that a longitudinal systolic dysfunction of the LV is common among patients with HFpEF.

How might this impact on clinical practice?

- Several clinical trials have been conducted to restore the diastolic function of the LV in patients with HFpEF with the aim to improve the prognosis of these patients. However, none of these treatments has been shown to decrease mortality in patients with HFpEF. For this reason, additional pathophysiological mechanisms should be taken into consideration in the design of new clinical trials in this heterogeneous disease. The present meta-analysis analysing 2284 patients with HFpEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFpEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to cardiovascular mortality and HF hospitalisation in these patients. Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFpEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

until 15 June 2017 that analysed the global longitudinal systolic function of the LV using 2DSTE in patients with HFpEF. We searched the following Medical Subject Heading terms: 'heart failure', 'echocardiography' and 'strain'. In addition, we reviewed the citations in the selected articles to search for additional studies.

Selection criteria

The criteria to include the studies were: (1) patients with diagnosis of HFpEF using a cut-off of left ventricular ejection fraction (LVEF) ≥ 45%; (2) available LV GLS analysed by 2DSTE at rest in at least 12 LV segments and (3) available control group or data regarding the prevalence of abnormal GLS or data regarding the prognosis of GLS. Control group in the analysis was defined as healthy subjects or as asymptomatic patients with some cardiovascular (CV) risk factor or disease such as arterial hypertension, diabetes mellitus or history of coronary artery disease (CAD). Furthermore, in order to avoid analysing twice the same population, we selected only one study when the same population was included in two or more HFpEF studies for the same research group.

Data abstraction and variable definition

Data were independently extracted by two reviewers (DAM and X-XM). Clinical characteristics, design, imaging modalities for quantification of GLS, baseline values of GLS in HFpEF and controls, rate of abnormal GLS and hazard ratio (HR) or odds ratio (OR) that linked GLS to CV outcomes were extracted from each study. The key variable under study was GLS (ie, peak systolic LV strain) derived from the myocardial analysis of the LV in longitudinal direction in the apical 4-chamber, 2-chamber and 3-chamber views (ie, ≥12 LV segments) and using 2DSTE at rest.

Statistical analysis

We used Review Manager (V.5.3, Cochrane) to analyse the data. All analyses were in accordance with the PRISMA-IPD Statement recommendations.[34] Mean, 95% confidence interval (CI) and range were calculated for each variable from all studies. In line, we determined the weighted mean difference (WMD) for each variable in each study. A fixed model was used to obtain WMD. Statistical heterogeneity in GLS values among studies was evaluated using the I^2 statistics. In addition, we performed a meta-regression analysis in order to detect the possible sources of statistical heterogeneity on GLS values in the study population. Moreover, a sensitivity analysis was performed in order to decrease the possible bias or sources of statistical heterogeneity on GLS. In this regard, we performed subgroup analyses including studies with ≥ 100 patients with HFpEF and studies with < 100 patients with HFpEF as well as studies with patients with HFpEF without atrial fibrillation. Furthermore, with the purpose of evaluating the association of GLS with CV outcomes in HFpEF, we analysed the link of GLS to CV outcomes analysing the OR and HR in logistic and Cox regression analysis in the studies. Differences were considered statistically significant when p value was < 0.05.

RESULTS

Study population

We identified 953 potential studies from published literature (see figure 1). Twenty-nine studies met the eligibility criteria analysing the different databases (Medline, Embase and Cochrane) (see table 1). Twenty-two studies had a control group (2284 patients with HFpEF and 2302 controls) and nine studies had follow-up with outcomes analyses (1847 patients with HFpEF) (see table 1).

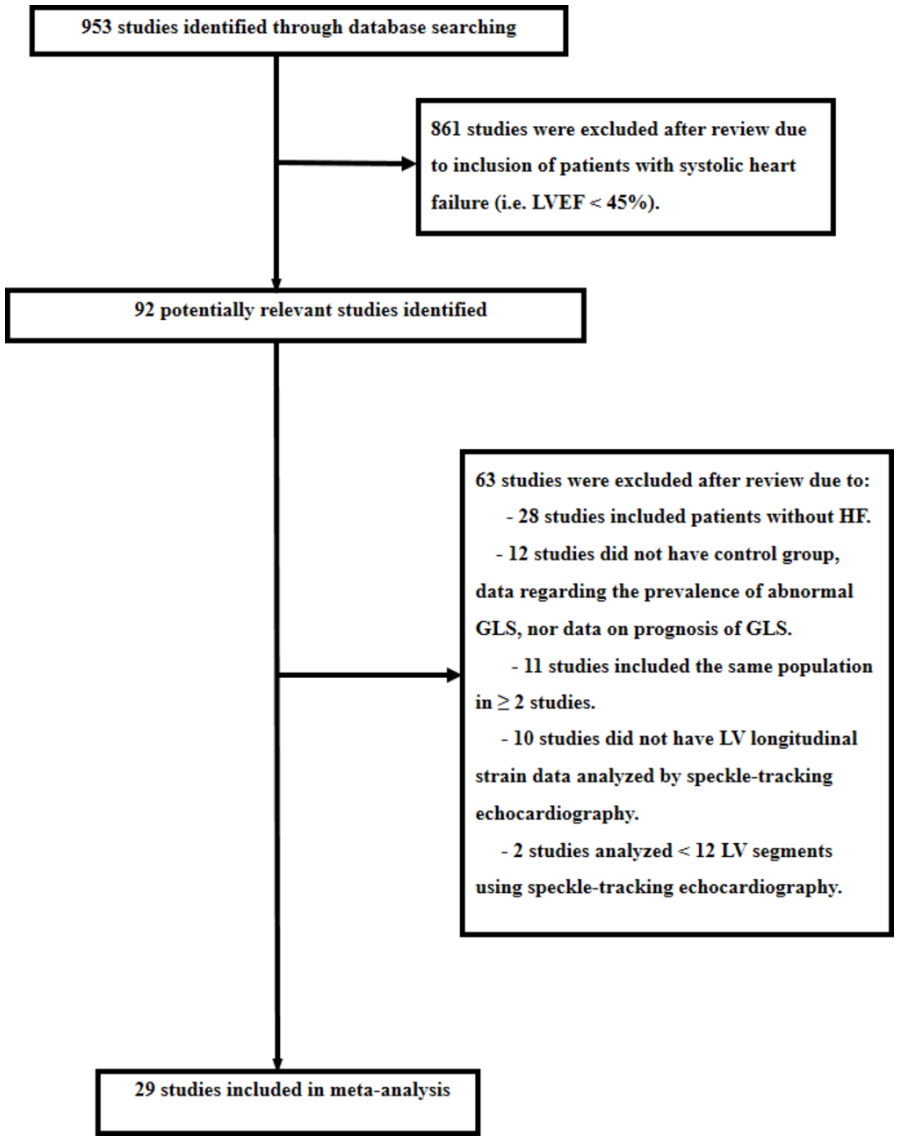

Figure 1 Search process. We searched in different databases (Medline, Embase and Cochrane) published studies until 15 June 2017 that analysed the global longitudinal systolic function of the left ventricular (LV) (global longitudinal systolic strain (GLS)) using two-dimensional speckle-tracking echocardiography in patients with heart failure with preserved ejection fraction. We searched the following Medical Subject Heading terms: 'heart failure', 'echocardiography' and 'strain'. HF, indicates heart failure; LVEF, indicates left ventricular ejection fraction.

Concerning the clinical and LV characteristics of the study population, there were differences between HFpEF and controls regarding comorbidities such as arterial hypertension, diabetes mellitus and history of CAD and regarding LV characteristics such as LV mass and LV filling pressures (table 2). Nonetheless, in a meta-regression analysis, the severity of LV filling pressures was the main factor linked to GLS in patients with HFpEF (see table 3).

LV longitudinal systolic function in HFpEF versus controls

Patients with HFpEF had significantly lower GLS than control subjects (see table 2 and figures 2 and 3). These differences in GLS between HFpEF and controls were significant between patients with HFpEF and asymptomatic patients (figure 2) as well as between patients with HFpEF and healthy subjects (figure 3). In line, 19 out of 22 studies showed that patients with HFpEF had significantly lower values of GLS than controls (see figures 2 and 3). On the other hand, there were minimal differences in LVEF between patients with HFpEF and controls and the mean range of LVEF in HFpEF and controls was within the normal range for LVEF (ie, 55%–75%) (see table 2 and figure 4).

In a statistical variability analysis (I^2), a statistical heterogeneity in GLS values among studies was found (see figures 2 and 3). In this regard, in order to detect the possible sources of statistical heterogeneity on GLS values in the study population, a meta-regression and sensitivity

Table 1 Characteristics and design of the studies

Study	Number of patients with HFpEF	Age (years)	Women	LVEF criteria	LV strain (GLS)	Control group	Follow-up
Wang *et al*[4]	20	63 ± 16	35%	≥ 50%	18 LV segments - EchoPac	yes	no
Liu *et al*[5]	26	68 ± 13	31%	≥ 50%	18 LV segments - EchoPac	yes	no
Phan *et al*[27]	40	67 ± 10	73%	> 50%	12 LV segments - EchoPac	yes	no
Tan *et al*[6]	56	72 ± 7	69.6%	> 50%	12 LV segments - EchoPac	yes	no
Kasner *et al*[28]	21	51 ± 4.2	52%	≥ 50%	18 LV segments - EchoPac	yes	no
Morris *et al*[7]	119	70 ± 10	44%	> 50%	18 LV segments - EchoPac	yes	no
Yip *et al*[8]	112	74 ± 12	64%	≥ 50%	18 LV segments - EchoPac	yes	no
Abe *et al*[9]	10	65 ± 12	30%	≥ 50%	16 LV segments - TomTec	yes	not reported in HFpEF
Obokata *et al*[10]	40	77 ± 13	65%	> 50%	18 LV segments - EchoPac	yes	no
Pellicori *et al*[29]	138	78 ± 10	37%	≥ 50%	18 LV segments - EchoPac	yes	28 months
Kraigher-Krainer *et al*[11]	219	71 ± 9	61%	≥ 45%	12 LV segments - TomTec	yes	no
Menet *et al*[12]	40	70 ± 13	77%	≥ 50%	18 LV segments - EchoPac	yes	no
Luo *et al*[13]	58	70 ± 10	40%	≥ 50%	16 LV segments - Toshiba	yes	no
Donal *et al*[19 20]	356	76 ± 9	55.9%	> 45%	18 LV segments - EchoPac	no	28 months
Wang *et al*[30]	80	66 ± 8	37%	> 50%	18 LV segments - EchoPac	no	36 months
Stampehl *et al*[14]	100	60 ± 1	76%	≥ 50%	18 LV segments - EchoPac	no	12 months
Shah *et al*[15]	447	70.3 ± 9.8	53.7%	≥ 45%	12 LV segments - TomTec	yes	31 months
Kosmala *et al*[16]	207	63.7 ± 8.6	73%	≥ 50%	18 LV segments - EchoPac	yes	no
Morris *et al*[17]	218	72 ± 10.5	52.3%	> 50%	18 LV segments - EchoPac	yes	no
Toufan *et al*[18]	126	57.5 ± 10	69.8%	≥ 50%	16 LV segments - EchoPac	yes	no
Freed *et al*[31]	308	65 ± 13	64%	≥ 50%	12 LV segments - TomTec	no	13 months
Carluccio *et al*[21]	46	75 ± 8	52%	≥ 50%	18 LV segments - EchoPac	yes	no
Iwano *et al*[22]	50	59 ± 16	70%	≥ 50%	12 LV segments - QLab	yes	no
Hung *et al*[23]	58	64.3 ± 12.4	53.4%	> 50%	18 LV segments - EchoPac	yes	no
Obokata *et al*[32]	102	77 ± 11	57%	≥ 45%	18 LV segments - Epsilon	no	12 months
DeVore *et al*[33]	187	69 ± 2.5	48.1%	≥ 50%	18 LV segments - TomTec	no	6 months
Huang *et al*[24]	129	75.1 ± 10.7	58%	≥ 45%	18 LV segments - EchoPac	no	36 months
Lo *et al*[25]	74	73.8 ± 17	60.8%	≥ 50%	18 LV segments - EchoPac	yes	no
Bosch *et al*[26]	159	68 ± 11	52%	≥ 50%	18 LV segments - EchoPac	yes	24 months

In the study by Bosch *et al*,[26] 159 out of 219 patients were feasible to perform GLS analyses and the reported follow-up with outcomes analysis did not include GLS. The studies by Donal *et al*[19 20] included a first outcomes analysis on GLS using a continuous Cox regression analysis and a second post hoc outcomes analysis on GLS using a dichotomous Cox regression analysis.
GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

Table 2 Global clinical and echocardiographic characteristics of studies with patients with HFpEF and control subjects

	Patients with HFpEF (n=2284)	Asymptomatic patients (n=1647)	Healthy subjects (n=655)
Clinical characteristics			
Age, years	68.5 (51–78)	64.7 (47–78)	55 (36.5–70)
Women	55.2% (30%–77%)	50.9% (32.4%–77%)	58.7% (40%–70.5%)
Arterial hypertension	82% (40%–100%)	70.3% (8%–100%)	0%
Diabetes mellitus	33.4% (5%–60%)	20.8% (0%–43%)	0%
Obesity	37.8% (29.4%–58.7%)	10.8% (8%–16.2%)	0%
History of CAD	31.7% (0%–91.3%)	13.6% (0%–33%)	0%
Atrial fibrillation	8.6% (0%–73%)	0.1% (0%–1%)	0%
Echocardiographic characteristics			
LV longitudinal systolic strain, %	−15.5 (−12 to −18.9)	−18.3 (−15.1 to −20.4)	−19.9 (−17.1 to −21.5)
LV ejection fraction, %	61.9 (58–72)	64 (56–71)	63.4 (60–67.6)
LV mass index, g/m²	105.7 (54–144)	85.7 (49–115)	78.8 (72.7–85)
LA volume index, mL/m²	37.7 (24.8–55)	26.9 (16–38)	25.4 (18–44)
Mitral septal-lateral e', cm/s	5.9 (3.4–8)	7.5 (4.8–12)	11.1 (9–13.5)
Mitral septal-lateral E/e' ratio	14.9 (10.2–19.9)	10 (6.8–12.6)	7.3 (6.3–8.5)

Data are expressed as mean and (range) (ie, the mean value of each variable from all studies as well as the range of the means from all studies). GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments).
CAD, coronary artery disease; GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction;e', septal and lateral annular mitral early diastolic peak velocity using pulsed-TDI; E, mitral inflow early diastolic peak velocity using pulsed Doppler; LA, left atrial.

analysis was performed. In effect, we found that the severity of LV filling pressures (measured by the mitral average septal-lateral E/e' ratio) was the main factor linked to heterogeneity on GLS values among HFpEF studies, whereas the sample size, age and the presence of AF were not significantly linked to GLS (see table 3). In addition, with the purpose of ruling out the possible role of the sample size on GLS values, we performed a

Table 3 Clinical and cardiac factors linked to LV global longitudinal systolic strain (GLS) in patients with HFpEF - Meta-regression analysis

	GLS, %	
Clinical and cardiac factors	**β (95% CI)**	**p Value**
Age, per 1 year	−0.05 (−0.15 to 0.05)	0.32
Prevalence of women, per 1%	0.08 (−0.04 to 0.12)	< 0.01
Prevalence of arterial hypertension, per 1%	0.02 (−0.03 to 0.07)	0.41
Prevalence of diabetes, per 1%	−0.02 (−0.08 to 0.02)	0.31
Prevalence of CAD, per 1%	−0.04 (−0.01 to −0.07)	< 0.01
Prevalence of AF, per 1%	−0.02 (−0.06 to 0.01)	0.27
LVEF, per 1%	0.29 (0.04 to 0.53)	0.03
LV mass, per 1 g/m²	−0.03 (−0.01 to −0.06)	0.05
Mitral septal-lateral e', per 1 cm/s	0.34 (−0.40 to 1.08)	0.38
Mitral septal-lateral E/e', per 1 unit	−0.39 (−0.17 to −0.61)	< 0.01
Sample size of the study, per one patient	0.01 (−0.01 to 0.02)	0.53

The meta-regression analysis was performed in all studies as shown in figures 2 and 3. GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments). The β coefficient indicates the estimated change in GLS for every estimated change in the independent variable analysed.
AF, atrial fibrillation; CAD, coronary artery disease; GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction; e', septal and lateral annular mitral early diastolic peak velocity using pulsed-TDI; E, mitral inflow early diastolic peak velocity using pulsed Doppler; β, beta coefficient; LV, left ventricular; LVEF, left ventricular ejection fraction.

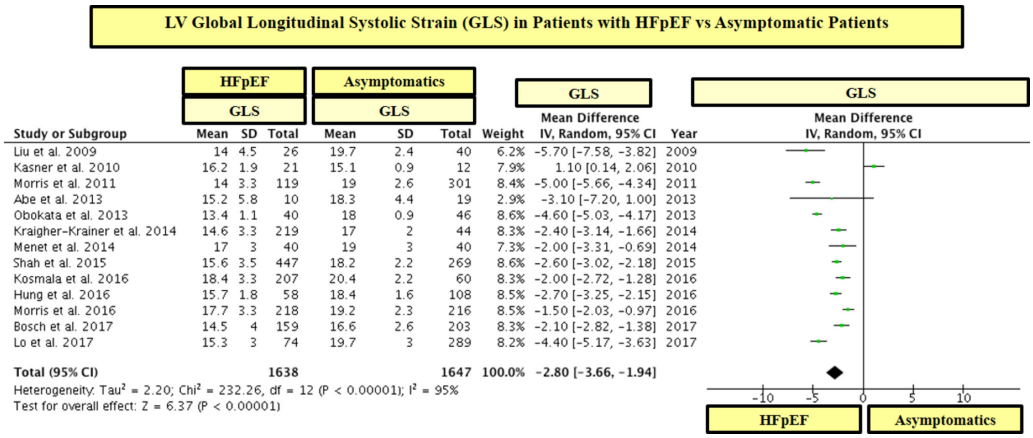

Figure 2 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFpEF) vs asymptomatic patients. GLS is shown in absolute values.

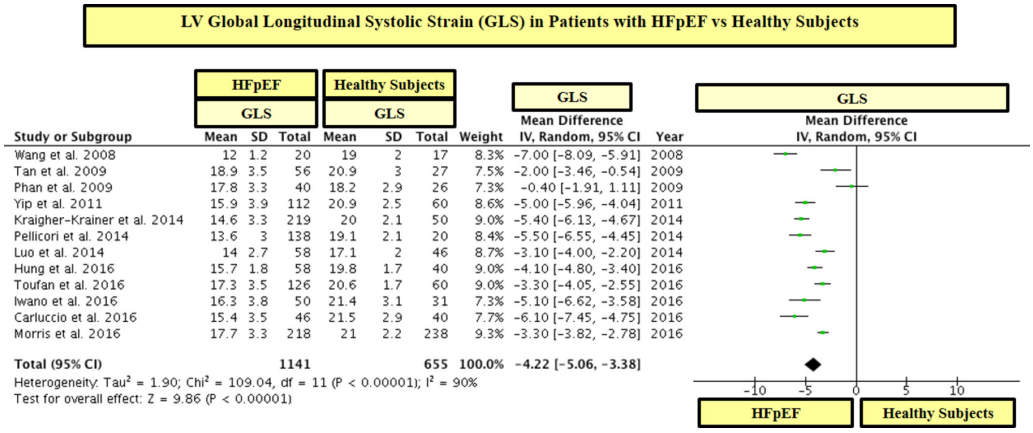

Figure 3 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFpEF) vs healthy subjects. GLS is shown in absolute values.

subgroup analysis including studies with ≥ 100 and < 100 patients with HFpEF. In this respect, we found that patients with HFpEF had significantly lower values of GLS than controls in studies that included both ≥ 100 and < 100 patients with HFpEF (see figures 5 and 6). In addition, in order to exclude the role of AF on the statistical heterogeneity of GLS, we performed a subgroup analysis including only those studies that included patients with HFpEF without AF. In this regard, we found that patients with HFpEF without AF had also significantly lower values of GLS than controls (see figure 7).

Prevalence of LV longitudinal systolic dysfunction in HFpEF

Regarding the prevalence of LV longitudinal systolic dysfunction in HFpEF, 10 studies (1810 patients with HFpEF and 462 asymptomatic controls) showed that the rate of abnormal GLS was significantly high in patients with HFpEF (mean 65.4% (range 37%–95%)), whereas in asymptomatic subjects was only of 13% (range 0%–29.6%) (table 4). Nonetheless, only one study analysed the clinical and cardiac characteristics of patients with HFpEF with abnormal GLS.[33]

Prognostic relevance of LV longitudinal systolic dysfunction in patients with HFpEF

Nine studies analysed the prognostic relevance of GLS in patients with HFpEF (n=1847 patients with HFpEF; n of events=620) (see table 5). Four studies showed that GLS was associated with worse CV prognosis, but other five studies did not find any significant association of GLS with outcomes in patients with HFpEF (table 5). Six out of these nine studies analysed the association of GLS with outcomes using only continuous logistic or Cox regression analyses, whereas only three out of these nine studies analysed in a dichotomous analysis the link (ie, OR or HR) of an abnormal GLS to CV outcomes (table 5). Nonetheless, two out of these three studies were multicentre, with large sample size (447 and 348) and high number of events (115 and 177), and showed a significant association of an abnormal GLS with CV outcomes (HR for CV mortality and HF hospitalisation 2.14 (95% CI 1.26 to 3.66) and 1.94 (95% CI 1.22 to 3.07)) (see table 5).

Discussion

In the present study performing a meta-analysis regarding the longitudinal systolic function of the LV analysed by

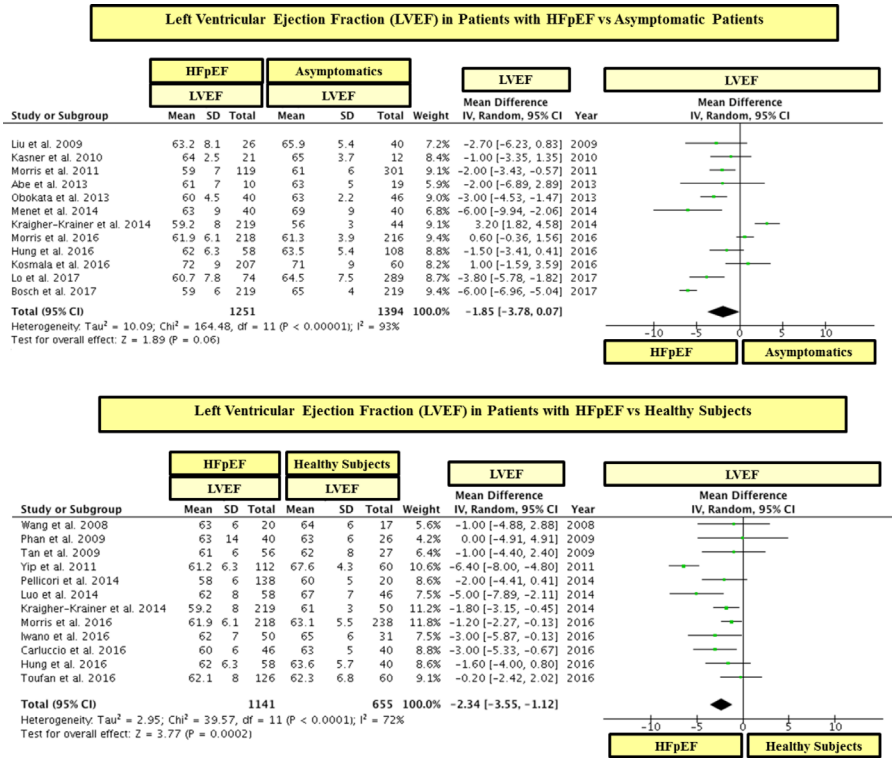

Figure 4 Left ventricular ejection fraction (LVEF) in patients with heart failure with preserved ejection fraction (HFpEF) vs asymptomatic and healthy controls. The study by Shah *et al*[15] was not included in this analysis because the value of LVEF in the control group was not reported.

2DSTE in HFpEF, patients with HFpEF had significantly lower GLS than control subjects and an abnormal GLS was common among patients with HFpEF. Moreover, two large multicentre studies analysing the association of an abnormal GLS with CV outcomes found that an abnormal GLS was significantly linked to CV mortality and HF hospitalisation.

Main findings of this meta-analysis

On the basis of 22 studies, 2284 patients with HFpEF and 2302 controls, the findings of this meta-analysis confirm that patients with HFpEF have significantly lower LV longitudinal systolic function than asymptomatic controls and that a longitudinal systolic dysfunction of the LV is

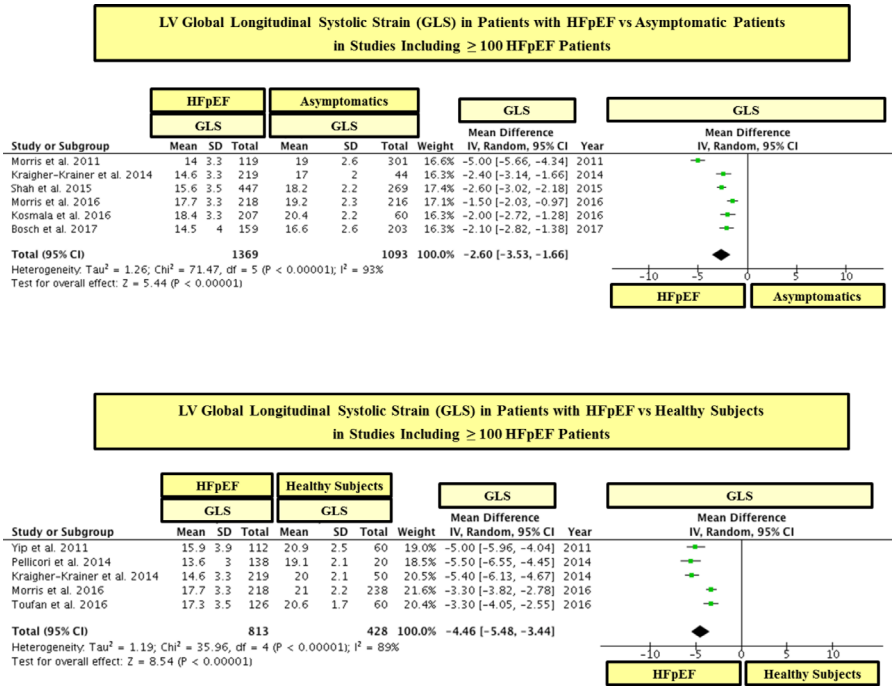

Figure 5 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFpEF) vs asymptomatic and healthy controls in studies including ≥ 100 patients with HFpEF. GLS is shown in absolute values.

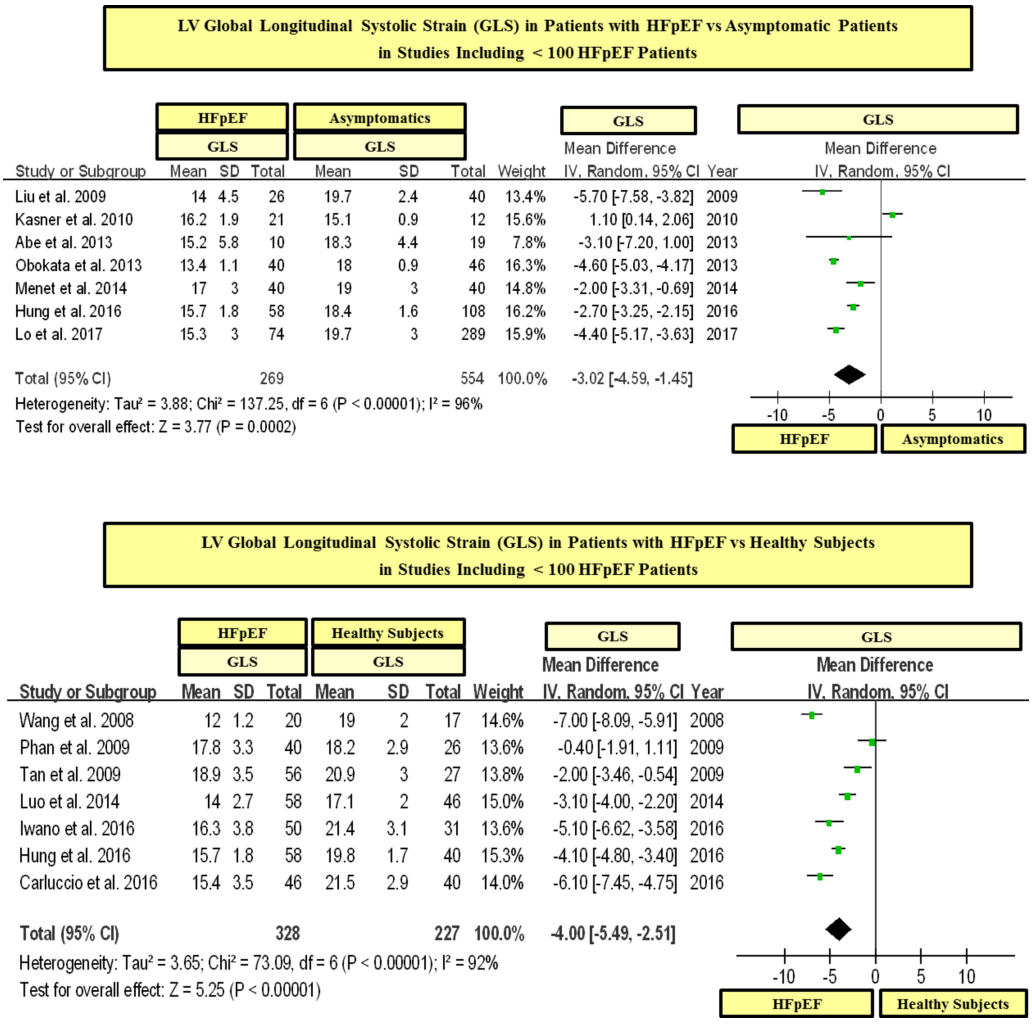

Figure 6 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFpEF) vs asymptomatic and healthy controls in studies including < 100 patients with HFpEF. GLS is shown in absolute values.

common among patients with HFpEF. Nonetheless, despite the fact that the number of studies and patients was large, the amount of studies reporting the characteristics of patients with abnormal GLS as well as the prognostic consequences of an abnormal GLS was lower. In fact, only one study analysed the clinical and cardiac characteristics of patients with HFpEF with abnormal GLS and only two large multicentre studies analysed in a dichotomous analysis the association of an abnormal GLS with CV outcomes.[15 20 33] Accordingly, on the basis of this meta-analysis, we can confirm that the longitudinal systolic function of the LV is altered in high proportion of patients with HFpEF, but the clinical and cardiac characteristics of this subgroup of patients as well as the clinical consequences of LV longitudinal systolic dysfunction in patients with HFpEF need to be confirmed.

While nine studies have analysed the association of the longitudinal systolic function of the LV (analysed by GLS) with CV outcomes in patients with HFpEF,[14 15 20 24 29–33] only two of these studies were multicentric, enrolled large number of patients (>300) and had high number of events (>100).[15 20] In this regard, Shah *et al*[15]analysing the echocardiographic data of the TOPCAT trial found that an abnormal GLS was significantly linked to worse CV outcomes (CV death and HF hospitalisation) in patients with HFpEF. In agreement, Donal *et al*[20]analysing the echocardiographic data of the KaRen study found a significant association of an abnormal GLS with CV outcomes. However, other two smaller multicentre studies and three single-centre studies did not find any significant association of GLS with outcomes in HFpEF.[29–33] Nonetheless, it is important to highlight that the analyses in the TOPCAT and KaRen studies were dichotomous analyses (ie, analysing the HR of an abnormal GLS with CV outcomes),[15 20] whereas the other smaller studies analysed the association of GLS with CV outcomes using only continuous logistic or Cox regression analyses.[29–33] Accordingly, while it is not possible to confirm in this meta-analysis if an abnormal GLS is linked to worse CV outcomes in HFpEF, we consider that further large multicentre studies with the aim to confirm the prognostic role of abnormal GLS in HFpEF are warranted.

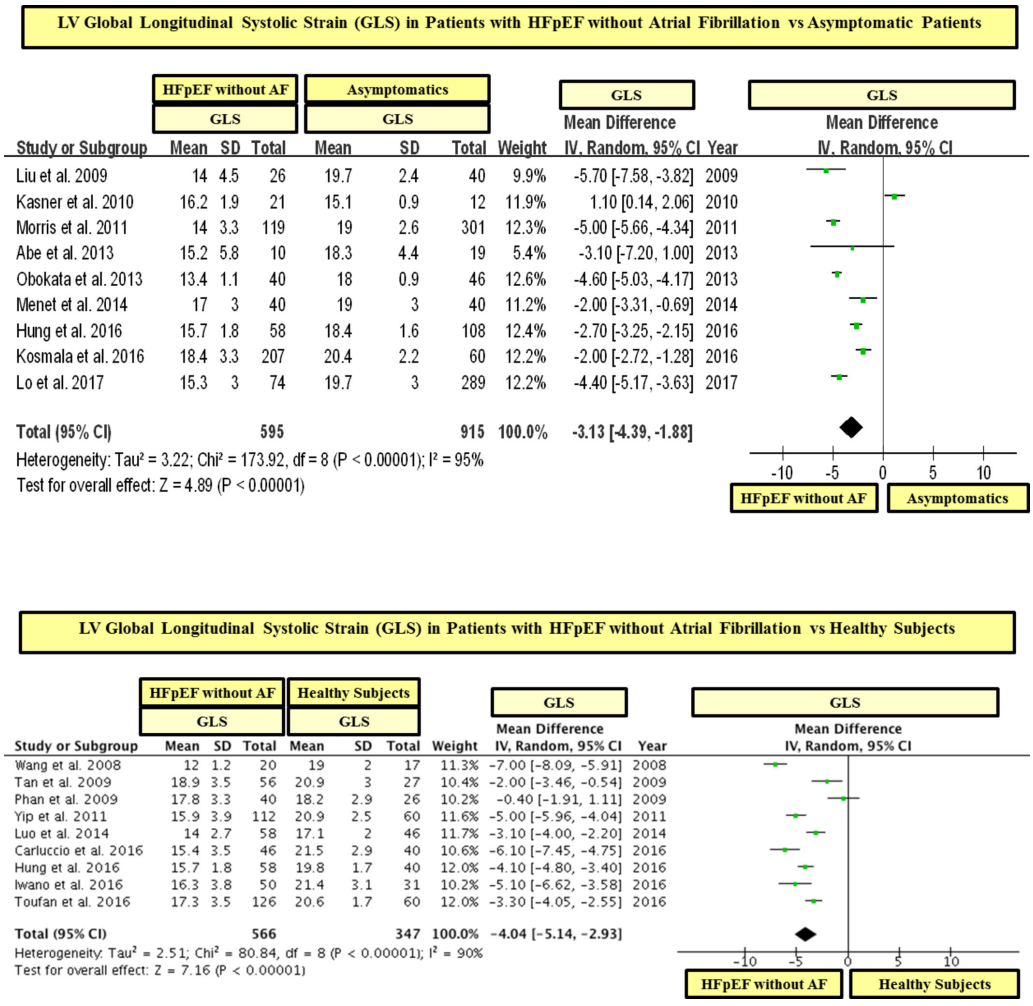

Figure 7 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFpEF) without atrial fibrillation vs asymptomatic and healthy controls. GLS is shown in absolute values.

Table 4 Prevalence of LV longitudinal systolic dysfunction in patients with HFpEF vs controls

Study	HFpEF patients rate of abnormal GLS	Asymptomatic controls rate of abnormal GLS	Cut-off of abnormal GLS	LV segments analysed	Software package
Wang *et al*[4]	95%	5%	–16%	18	EchoPac
Liu *et al*[5]	85%	15%	–17.5%	18	EchoPac
Morris *et al*[7]	81.5%	15.5%	–16%	18	EchoPac
Yip *et al*[8]	37%	0%	–16%	18	EchoPac
Kraigher-Krainer *et al*[11]	54.3%	29.6%	–15.8%	12	TomTec
Donal *et al*[19]	39%	No control group	–16%	18	EchoPac
Shah *et al*[15]	52%	Not reported	–15.8%	12	TomTec
Freed *et al*[31]	75%	No control group	–20%	12	TomTec
DeVore *et al*[33]	65%	No control group	–16%	18	TomTec
Huang *et al*[24]	75.9%	No control group	–15.8%	18	EchoPac
All studies	mean 65.4% (range 37%–95%)	mean 13% (range 0%– 29.6%)			

The rate of abnormal GLS indicates the prevalence of LV longitudinal systolic dysfunction. GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments).
HFpEF, heart failure with preserved ejection fraction; GLS, global longitudinal systolic strain.

Table 5 Association of LV global longitudinal systolic strain (GLS) with outcomes in HFpEF

Study	Primary end point	Events (n)	Dichotomous univariate analysis Abnormal GLS HR (95% CI)	Dichotomous multivariate analysis Abnormal GLS HR (95% CI)	Continuous univariate analysis GLS 1SD or 1% decrease HR (95% CI)	Continuous multivariate analysis GLS 1SD or 1% decrease HR (95% CI)
Shah *et al*[15]	CV death or aborted cardiac arrest or HF hospitalisation	115	2.26 (1.53 to 3.34)	2.14 (1.26 to 3.66)	1.13 (1.08 to 1.19)	1.14 (1.04 to 1.24)
Donal *et al*[19 20]*	All-cause death or HF hospitalisation	177	not reported	1.94 (1.22 to 3.07)	not reported	not reported
Huang *et al*[24]	All-cause death	27	3.4 (1.02 to 11.3)	4.72 (1.25 to 17.8)	not reported	not reported
Pellicori *et al*[29]	CV death or HF hospitalisation	62	not reported	not reported	1.09 (1.00 to 1.19)	0.99 (0.90 to 1.11)
Freed *et al*[31]	All-cause death or CV hospitalisation	115	not reported	not reported	1.25 (1.03 to 1.52)	1.17 (0.95 to 1.43)
Obokata *et al*[32]	CV death, non-fatal MI and HF exacerbation	29	not reported	not reported	0.99 (0.87 to 1.13)	not reported
Stampehl *et al*[14]†	CV death or HF hospitalisation	17	not reported	not reported	not reported	not reported
Wang *et al*[30]‡	All-cause death or HF hospitalisation	43	not reported	not reported	not reported	not reported
DeVore *et al*[33]§	All-cause death or all-cause hospitalisation	35	not reported	not reported	not reported	not reported

*Donal *et al* did not find a significant link between GLS and CV outcomes at 28 months in a continuous Cox proportional hazards regression analysis in 356 patients (univariate analysis: p =0.1406; multivariate analysis: p =0.1192; the HR of this analysis was not reported).[19] However, in a post hoc analysis of these data in 348 patients,[20] an abnormal GLS (<16% in absolute values) was significantly linked to the combined end point of total mortality or HF hospitalisation at 18 months (HR 1.94 (1.22–3.07)), but an abnormal GLS was not linked to mortality-only at 18 months (HR 1.56 (0.84–2.89)).

†Stampehl *et al* found in a dichotomous univariate Cox proportional hazards regression analysis that an abnormal GLS (< 15% in absolute values) was linked to worse CV outcomes (X^2=4.0, p=0.04; the HR of this analysis was not reported). In addition, patients with events had significantly lower GLS than those without events (–11.6 ± 0.4% vs –16.5 ± 0.5%, p=0.03).[14]

‡Wang *et al* did not find a significant link in a continuous logistic regression analysis between GLS at rest and CV outcomes (the HR of this analysis was not reported). In line, patients with events had similar values of GLS at rest than those without events (–17.5 ± 3.7% vs –18.8 ± 2.9%, p > 0.05). However, GLS during exercise was significantly linked to CV outcomes (univariate analysis: HR 0.81 (0.72–0.92), p < 0.01; multivariate analysis: HR 0.79 (0.67–0.91), p < 0.01) in a continuous logistic regression analysis. In addition, patients with events had significantly lower GLS during exercise than those without events (–18.2 ± 3.9% vs –21.4 ± 3.9%; p=0.001).[30]

§DeVore *et al* did not find a significant link between the tertiles of GLS and a composite end point of time to death or all-cause hospitalisation (p=0.952).[33]

CV, cardiovascular; GLS, global longitudinal systolic strain (ie, average longitudinal peak systolic strain from ≥12 LV segments); HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction.

Clinical perspectives on the basis of the findings of this meta-analysis

Isolated LV diastolic dysfunction (ie, abnormalities of LV myocardial stiffness and relaxation with normal LVEF) has long been considered the main underlying mechanism in HFpEF.[1–3] On the basis of this pathophysiological model, several clinical trials have been conducted to restore the diastolic function of the LV in patients with HFpEF in order to improve the prognosis of these patients.[35 36] However, none of these treatments has been shown to decrease mortality in patients with HFpEF.[35 36] For this reason, additional pathophysiological mechanisms should be taken into consideration in the design of new clinical trials in this heterogeneous disease. The present meta-analysis analysing 2284 patients with HFpEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFpEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to CV mortality and HF hospitalisation in these patients.[15 20] Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFpEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

LIMITATIONS

Some considerations should be taken into account on this meta-analysis. Given that GLS values could vary among different software packages,[37 38] we consider that the cut-off of GLS used to define LV longitudinal systolic dysfunction should be considered according to the ultrasound software package used in each study. In addition, it is worth to note that GLS, like other 2D methods such as LVEF, depends on the imaging quality and for these reasons the patients included in all studies of this meta-analysis had adequate imaging quality for an analysis by 2DSTE. Hence, the results of this meta-analysis could not be extrapolated to patients with poor imaging quality of the LV. Furthermore, while in the present meta-analysis were analysed all published studies that analysed GLS in HFpEF, there was some statistical heterogeneity in GLS values in the study population. In this respect, we performed a meta-regression analysis in order to detect the possible sources of statistical heterogeneity on GLS values among the studies. In effect, we found that the severity of LV filling pressures was the main factor linked to heterogeneity on GLS values among HFpEF studies, whereas the sample size, age and the presence of AF were not linked to GLS values. Nonetheless, it is important to note that it was not possible to perform a subgroup analysis including studies with HFpEF without history of CAD because only one study excluded patients with history of CAD.[21]

CONCLUSIONS

The present meta-analysis analysing 2284 patients with HFpEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFpEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to CV mortality and HF hospitalisation in these patients. Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFpEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

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