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Short Title: Global longitudinal strain in asymptomatic aortic stenosis
Total Word count: 4582

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Disclosure: MF, CB, CHG, DJ, DMY, KL, LP, MT, SK, TM, ZC, CAC, MD, PL, HG and DE: None. PBA has received research support and lecture honoraria from GE Healthcare.

Structured Abstract
Objectives: In this individual participant data (IPD) meta-analysis on left ventricular global longitudinal strain (LVGLS), our objective was to (1) describe its distribution, (2) identify the most predictive cut-off values, and (3) assess its impact on mortality in asymptomatic patients with significant AS and preserved LV ejection fraction (EF).
Background: The evidence supporting the prognostic role of LVGLS in asymptomatic patients with aortic stenosis (AS) has been obtained from a number of relatively small studies.
Methods: A literature search was performed for studies published between 2005 and 2017 without language restriction according to the following criteria: "aortic stenosis" AND "longitudinal strain". The corresponding authors of selected studies were contacted and invited to share their data that we computerized in a specific database. The primary end-point was all-cause mortality.
Results: Among the 10 studies included, 1067 asymptomatic patients with significant AS and LVEF>50% were analyzed. The median of LVGLS was 16.2% (from 5.6% to 30.1%). There were 91 deaths reported during follow-up with median of 1.8 [0.9-2.8] years, resulting in a pooled crude mortality rate of 8.5%. The LVGLS performed well in the prediction of death (area under the curve=0.68). The best cut-off value identified was LVGLS= 14.7% (sensitivity=60%, specificity=70%). Using random effects model, the risk of death for patients with LVGLS <14.7% is multiplied by >2.5 (HR=2.62, 95%CI: 1.66-4.13, p<0.0001), without significant heterogeneity between studies (I^2=18.3%, p=0.275). The relationship between LVGLS and mortality remained significant in patients with LVEF≥60% (p=0.001).
Conclusion: This IPD meta-analysis demonstrates that in asymptomatic patients with significant AS and normal LVEF, impaired LVGLS is associated with reduced survival. These data emphasize the potential usefulness of LVGLS for the risk stratification and the management of these patients.

Key words: aortic valve stenosis, left ventricular global longitudinal strain, mortality, meta-analysis

List of Abbreviations:
AS: Aortic stenosis
AVAi: Indexed aortic valve area
CI: Confidence intervals
GLS: Global longitudinal strain
HR: Hazard ratio
LV: Left ventricular
LVEF: Left ventricular ejection fraction

Introduction

The assessment of left ventricular (LV) function using LV ejection fraction (LVEF) has a central place in the current guidelines for the management of patients with severe aortic stenosis (AS), particularly when still asymptomatic. The current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommend as class I indication (level of evidence B) to perform aortic valve intervention in asymptomatic patients when LVEF becomes <50% (1,2). However, these concomitant findings are rare (3) and symptoms generally occur well before decrease in LVEF which, in turn, remains preserved for long in patients with AS. Several recent studies demonstrate, using cardiac magnetic resonance, that LV structural and functional abnormalities may be frequent despite LVEF >50%(4–9). This may partially explain the reduced postoperative survival of patients with LVEF 50-60%(3,10). Furthermore, aortic valve intervention in patients with LVEF <50% frequently results in suboptimal postoperative LV function recovery, contributing to persistent symptoms, limited functional capacity and quality of life and increased risk of events. Consequently, this underlines the need to identify echocardiographic parameters better than LVEF to more accurately assess the consequences of AS-related LV pressure overload, on LV function.

The impairment of LV longitudinal shortening is associated with myocardial fibrosis(11,12), which is, in turn, a potential prognostic marker in patients with AS(6,13). Hence, LV longitudinal function assessment, using speckle-tracking echocardiography, may provide a surrogate imaging marker of myocardial damage. Indeed, there is growing evidence suggesting the potential prognostic role of LV myocardial longitudinal function, as assessed by global longitudinal strain (GLS), in asymptomatic patients with AS. However, the available data are mainly derived from relatively small series and/or from single center studies. In addition, current series report various unstandardized cut-off values.

Our objective was therefore to perform an individual participant data meta-analysis in order to (1) describe the distribution, (2) identify the most predictive cut-off values, and (3) assess the impact of LVGLS on mortality in asymptomatic patients with significant AS and preserved LVEF.

Methods

We searched MEDLINE, Embase, and the Cochrane Library database using the key terms "aortic valve stenosis" and "longitudinal strain" between 2005 and 2017 without language restriction. The protocol of this individual participant data meta-analysis was validated by the Research & Innovation Committee of the European Association of Cardiovascular Imaging (EACVI) and the study was conducted on behalf of all members of the Committee. The PRISMA statement(14) was followed to conduct the individual participant data meta-analysis.

Inclusion criteria

Studies were selected for the meta-analysis if they included patients with all of the following criteria: (1) asymptomatic, (2) preserved LVEF (i.e. >50%), (3) ≥ moderate AS as defined by current guidelines at the time of the study, (4) quantification of the LVGLS using 2-dimensional speckle tracking, (5) availability of outcome of interest for the current analysis i.e. all-cause death.

No inclusion criterion was applied regarding sample size.

Selection of studies

A first selection of the studies was based on the title and on the abstract. The full articles of all selected studies were then consulted in order to verify all pre-specified inclusion criteria. The selection of the studies was performed simultaneously during specific meeting (JM, BC and ED). The flow chart illustrating the selection of the studies process is reported in Figure 1. Great care

was taken to avoid inclusion of various studies based on the same cohort population in order to avoid redundancy in the meta-analysis.

Finally, all corresponding authors and/or first, second or last authors of the paper were contacted by email in order to propose them to participate to the meta-analysis. Responding authors were invited to share a short anonymized database including a limited number of variables. The required variables were age, gender, comorbidities (coronary artery disease, hypertension, diabetes, dyslipidemia), AS severity, LVEF, LVGLS and outcome data.

The data were then computerized in a dedicated database.

Primary end-point

The primary end-point of this individual participant data meta-analysis was all-cause death. Purposely, combined end-point including need for aortic valve intervention was not used in the meta-analysis. This is justified by the fact that the decision-making regarding indication for intervention may considerably vary between centers.

Statistical analysis

Extraneous data was removed from the database and units of continuous variables were standardized and continuous variables were dichotomized.

Descriptive analysis was performed and mean ± standard deviation or proportion was reported. The distribution of LVGLS was compared according to each included study using one-way analysis of variance.

A univariate Cox proportional hazards model was used to derive, for each study, the hazard ratio (HR), standard error and 95% of confidence interval (95%CI) related to LVGLS (as continuous variables) and occurrence of death. Log transformation was performed and inverse variances as weights were then calculated for each study. The meta-analysis was performed using random

effects models and forest plots were generated to express the pooled effect. Heterogeneity was assessed using I^2. Stratified analysis were performed according to LVEF with a pre-specified arbitrary cut-off value of 60%.

In order to assess the potential impact of vendor difference on the results, a stratified analysis was performed according to vendor.

The best cut-off value of LVGLS associated with death was derived from receiver operating characteristics curve analysis and selected using the best compromise between sensitivity and specificity and the Youden index. This cut-off was then used to generate Kaplan-Meier analysis and to assess the impact of LVGLS on death in multivariate Cox proportional Hazard model.

To assess the incremental prognostic value of LVGLS over LVEF, we calculated integrated discrimination improvement as recommended(15).

To simplify the interpretation and discussion of the results, although negative, LVGLS is reported as positive values.

All statistical analyses were performed using SPSS V23 and STATA V13.

Results

A total of 10 studies, including 1 067 asymptomatic patients with LVEF >50% were used for the present individual participant data meta-analysis. The dataset was completed for LVGLS and outcome data. There was 0.8% of missing values for LVEF (i.e. patients with LVEF >50% but without exact value).

The selected studies are summarized in Table 1, the description of the population is reported in Table 2.

The median LVGLS was 16.2% (from 5.6% to 30.1%). A LVGLS>13.7% was observed in 75% of patients and less than 15% of patients had LVGLS>20% (i.e. preserved LV longitudinal

function). In patients with severe AS (i.e. indexed aortic valve area [AVAi] <0.6cm²/m²), the median LVGLS was 16.3% (from 6% to 30.1%).

The distribution of LVGLS according to selected studies is reported in Figure 2. Although the study from Sato et al.(16) reported significantly higher values and the study of Yingchoncharoen et al.(17) significantly lower values (p<0.0001), there was a good homogeneity between studies regarding LVGLS values (Figure 2). In studies using equipment only from the most commonly used vendor (GE Medical Systems), the median LVGLS was 16.6% (from 6% to 30.1%).

LVGLS and mortality

Among the 10 selected studies, 91 deaths were reported during a median follow-up of 1.8 years, from 0-8.5 years, resulting in a pooled crude rate of death of 8.5% (range 2.8% to 18.5%). In patients with LVEF≥60% (n=734), 61 deaths occurred (8.3%, range 3.0% to 17.3%).

In the whole cohort, LVGLS was well associated with occurrence of death (area under the curve=0.68). The best cut-off value identified was LVGLS=14.7% (sensitivity=60%, specificity=70%). By comparison, LVEF depicted lesser association with occurrence of death (area under the curve=0.56). In patients with severe AS (i.e. AVA <0.6cm²/m²), area under the curve for LVGLS was 0.69).

The relationship between LVGLS and risk of death is assessed using spline function. The spline curve suggest a marked increase risk of mortality when LVGLS decrease below 15% (Online supplement Figure 1).

In studies performed with the GE machine, the predictive value of LVGLS was similar (area under the curve=0.69) and the best cut-off value was 14.7% (sensitivity=62%, specificity=74%). The predictive value in studies without GE machine was lower (area under the curve=0.62) and

the best cut-off value was 11.9% with markedly lower sensitivity (35%) but higher specificity (86%).

In the whole cohort, impaired LVGLS<14.7% was found in 32.3% of patients, with significant difference between the studies (from 15.5% to 56%, p<0.0001). Applying this cut-off value to all selected studies allowed to generate a forest-plot (Figure 3, Panel A) showing that the risk of death for patients with LVGLS<14.7% was multiplied by >2.5 (HR=2.62, 95%CI: 1.66-4.13, p<0.0001), without significant heterogeneity (I^2=18.3%, p=0.275). The relationship between LVGLS<14.7% and mortality was also significant in patients with LVEF≥60% (Figure 3, Panel B). With a stratification according to vendor (i.e. GE vs. others, Online supplement Figure 2), similar results were found.

Because all patients from the Dahl et al.(18) study were referred for surgery, we performed a sub-analysis excluding this study. Similar results than in the whole cohort were found (HR=2.25, 95%CI: 1.47-3.43, p<0.0001; I^2=8.0%, p=0.369).

In patients with severe AS (i.e. AVAi <0.6cm²/m²), forest-plot showed that the risk of death in patients with LVGLS<14.7% was higher than in the whole cohort (HR=3.58, 95%CI: 1.84-6.99, p<0.0001, I^2=0, p<0.0001).

Using the cut-off of 14.7%, impaired LVGLS was associated with markedly reduced survival both in the whole cohort (p<0.0001, Figure 4, Panel A) and in patients with LVEF≥60% (p<0.0001, Figure 4, Panel B). Patients with LVGLS>18% have similar survival (at 2-year: 97±1%) than those with LVGLS between 16.2% and 18% (at 2-year: 95±2%, p=0.445) or even those with LVGLS between 14.7% and 16.2% (at 2-year 95±2%, p=0.207).

In patients with severe AS (i.e. AVAi<0.6cm²/m²), 2-year survival was significantly lower in patients with impaired LVGLS than in those with preserved LVGLS (94±1% vs. 81±4%, p<0.0001, Online supplement Figure 3).

In multivariate analysis, after adjustment for age, gender, indexed aortic valve area and LVEF, impaired LVGLS (i.e. <14.7%), was a strong independent determinant of survival (HR=3.59, 95%CI: 2.16-5.98, p<0.0001).

Adding impaired LVGLS to the multivariate model (i.e. including age, gender, indexed aortic valve area and LVEF) markedly improve its prediction (from χ^2=13.1 to χ^2=40.5). Comparing with LVEF, integrated discrimination improvement was positive for both LVGLS (i.e. as continuous variable) or LVGLS <14.7% suggesting its incremental prognostic value over LVEF (0.028 and 0.026, respectively).

Publication bias assessment

Funnel plots, regarding impaired LVGLS and risk of death (Figure 4 in Online supplement) demonstrated significant asymmetry (Egger's test, p=0.01) suggesting potential presence of publication bias. Funnel plots analysis demonstrates that this asymmetry may be related to discrepancy in publication in favor of studies reporting large effect size despite small sample size or large variance. In contrast, Begg's test demonstrated no significant risk of publication bias (p=0.18).

Discussion

In asymptomatic patients with significant AS and preserved LV ejection fraction, the present individual participant data meta-analysis suggests that (1) LVGLS is relatively homogeneous across available published cohorts, (2) LVGLS better than 20% is rare in this population, and (3) LVGLS is strongly associated with mortality, with >2.5-fold increase in risk of death in patients

with impaired LVGLS. Of interest, the close independent relationship between LVGLS and mortality is sustained even when LV ejection fraction is ≥60%. A cut-off value of 14.7% appears to be associated with patients at a higher risk of death.

LV longitudinal function and myocardial fibrosis

The alteration of LV longitudinal function occurs in parallel to AS severity(19), LV morphological changes(20), LV myocardial damage and fibrosis proliferation(11). Weidemann et al.(11) reported that the severity of myocardial fibrosis estimated with histological analysis was associated with impairment of LV longitudinal shortening as assessed by mitral annulus displacement using M-mode echocardiography. In addition, the presence of LV myocardial fibrosis may predict the risk of lack of LV function recovery following aortic valve replacement(13), and outcome(6). Based on these studies, it appears that the development of LV fibrosis is the main pathophysiological mechanism involved in the reduction in LV longitudinal shortening in patients with AS. Nevertheless, these findings were obtained in cohorts with surgical indications or with markedly reduced LV ejection fraction, limiting the clinical usefulness of LV longitudinal function assessment. Indeed, the LV longitudinal function evaluation could be more relevant to detect sub-clinical LV dysfunction and manage asymptomatic patients with preserved LV ejection fraction.

The presence of transthyretin cardiac amyloidosis(21), which, in patients with AS, is frequently associated with impaired longitudinal LV shortening without apical sparing, could also partially explain the reduction in LVGLS.

LVGLS derived from speckle tracking echocardiography

Speckle tracking echocardiography is a non-Doppler modality, angle-independent, allowing measurement of myocardial deformation (22). The quantification of LVGLS is now the most

common application of speckle tracking echocardiography and has already demonstrated added diagnostic and prognostic value in a wide range of conditions including valvular heart disease(23). Moreover, LVGLS during exercise may identify LV dysfunction associated with the development of symptoms (24).

Derived from 2-, 3- and 4-chamber apical views, LVGLS can be easily calculated with good feasibility and both inter- and intra-observer reproducibility(25,26), even better than LVEF. The relative inter-observer and intra-observer variability of GLS approximately varies from 5% to 8% according to vendors. By contrast, 8% and 10% of variability are reported for LVEF, respectively(25). Nevertheless, LVGLS remains load and geometry dependent and needs to be carefully interpreted in many cases.

LVGLS and LVEF

The obvious advantages of LVGLS over LVEF are its ability to unmask subclinical LV dysfunction, to identify early structural and morphological myocardial damage, and to better predict postoperative LV dysfunction and outcome(27). Many cardiac magnetic resonance studies recently reported myocardial alterations, despite preserved LVEF. The presence of LV late gadolinium enhancement has been highlighted in patients with various degrees of AS, despite normal LVEF(4–6). A graded relationship between AS severity and longer T1 time, regardless of LVEF (assessed using cardiac magnetic resonance), has been shown(5,7) and there have been good correlations between native T1 values and collagen volume fraction obtained by myocardial biopsies(7,28). Of interest, a large proportion of patients with AS and with high presence of LV late gadolinium enhancement or with markedly elevated T1 values still have preserved LV ejection. Furthermore, LVEF does not follow AS severity whereas LVGLS has been found to gradually worsen when AS becomes more severe(19). Altogether, these recent

data highlight the superiority of LVGLS over LVEF to assess LV myocardial function and predict outcomes of asymptomatic patients with AS.

Clinical implication

The present individual participant data meta-analysis shows, in a large cohort of patients, that LVGLS may have a close association with survival and could suggest a better risk stratification value than LVEF. However, the existing evidence has often considered aortic valve intervention in a composite end-point, with the consequence that intervention influenced event-free survival. In the present study, LVGLS demonstrated its strong impact on mortality and, therefore, the crucial role that it may have in the risk stratification and management of patients with asymptomatic AS. The close relationship between death and impaired LVGLS suggests that this echocardiographic parameter could be implemented in future guideline recommendations, if the present results are confirmed by large multicenter studies. Indeed, a “Heart Team” discussion of early intervention (i.e. including transcatheter aortic valve replacement if necessary) in asymptomatic patients with preserved LVEF but impaired LVGLS<14.7% may be envisaged. Further confirmation about the need for intervention, related to myocardial morphological and structural damage, may be obtained by performing cardiac magnetic resonance and assessment of the presence of late gadolinium enhancement and/or quantification of native T1. Furthermore, the use of exercise stress echocardiography in these patients may also be discussed(29,30). Patients with good LVGLS>18% had an excellent outcome (i.e. 97±1% 2-year survival) supporting a conservative approach with clinical and echocardiographic assessment every 1-2 years, in the absence of other indications for intervention or abnormality during exercise stress echocardiography. Our results show that the survival of patients with depressed LVGLS between 14.7% and 18% is similar to those with preserved LVGLS>18% up to 2 years follow-up. With

worse LVGLS values beyond 14.7% a marked increase in mortality seems to occur. This may rather promote shorter follow-up intervals (every 6-12 months), in order to assess subtle changes in LVGLS and/or symptoms and to propose prompt intervention.

Limitation

This study holds similar limitations to all meta-analyses. However, the use of individual data rather than data derived from publication only, may substantially improve the robustness of the reported results. Furthermore, the low degree of heterogeneity found indicates a relative consensus in the published data.

Although uncommon in asymptomatic patients with preserved LVEF, we cannot exclude that the presence of low flow/low gradient AS in the present cohort.

The lack of sub-analysis according to brain natriuretic peptide may limit our conclusion. However, this biomarker was not available in all selected studies and were not incorporated into guidelines when they were published.

The Egger's and Begg's tests produced discrepant results. However, analysis of the funnel plot suggests an asymmetry between studies' effect sizes and, therefore, a limited but potential publication bias. This is to be expected since positive studies may generally have higher chance to be published than negative ones. However, the studies selected in the present meta-analysis were positive on the basis of combined end-points, including aortic valve intervention. Of note, half of studies selected were negative with regards to all-cause mortality, further limiting the potential publication bias.

We report all-cause mortality as it is more objective, especially in retrospective studies. Cardiovascular death is difficult to assess in retrospective studies(31) and was not available in all publications. The need to perform aortic valve intervention with class I indication as

recommended in current guidelines is a frequent end-point in patients with AS. However, the variety of centers and countries involved in the meta-analysis does not allow sufficient standardization to assess this end-point.

Exercise testing aimed at confirming the asymptomatic status of patients, was not systematically performed in all selected studies. Some apparently asymptomatic patients have abnormalities during exercise testing, and these may have been included in the meta-analysis.

The majority of studies included in the meta-analysis performed LVGLS measurement using a GE machine. Consequently, the present results could not be automatically transposed to all echocardiographs. However, LVGLS is known to have good reproducibility, limited difference between vendors and to be superior to conventional echocardiographic measurements (25).

Conclusion

This individual participant data meta-analysis demonstrates the strong relationship between LVGLS and all-cause mortality in asymptomatic patients with AS and preserved LVEF. These results support the systematic measurement of LVGLS for the risk stratification and the management of these patients and may promote its use in clinical practice as an important additive parameter for decision-making. A LVGLS<14.7% could be considered as a trigger for further imaging investigations and for early intervention. Nonetheless, a limited but potential risk of publication bias may be present in current literature, suggesting the value of a large prospective international study for confirming this key impact of GLS for our AS-patients.

Clinical Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE:

The prognostic value of LVGLS in patients with AS often arise from small, single center studies, including heterogeneous grade and stage of AS. Impaired LVGLS (i.e. <14.7%) is strongly associated with mortality in asymptomatic patients with significant AS. This is confirmed in patients with severe AS (i.e. indexed aortic valve area $<0.6 cm^2/m^2$) and in patients with LV ejection fraction >60%. This individual participant data meta-analysis confirmed the usefulness of LVGLS in the management and risk stratification of these patients and may have incremental value as compared the LV ejection fraction.

TRANSLATIONAL OUTLOOK:

The effort to improve reproducibility of LVGLS measurement between vendors should be sustained. Large multicenter prospective study aiming to confirm our results is now mandatory. The usefulness of LVGLS, as trigger for surgery, should also be tested in experimental trial, more particularly to test its benefit as compared to LV ejection fraction.

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Table 1: Description of selected studies

References	**Years**	**Design**	**Population available n=1 067**	**AVAi** (cm^2/m^2)	**Vendor**	**LVGLS cut-off**	**Outcome**
Lancellotti et al.(32)	2010	Prospective/bi-centric	n=163	0.45±0.09	GE	15.9%	MACE
Zito et al.(33)	2011	Prospective/monocentric	n=82	0.40±0.10	GE	18%	MACE
Dahl et al.(18)	2012	Prospective/monocentric	n=65	0.46±0.19	GE	Quartile	MACE
Kearney et al.(34)	2012	Prospective/monocentric	n=77	0.56±0.23	GE	15%	All-cause death
Yingchoncharoen et al.(17)	2012	Prospective/monocentric	n=78	0.39±0.13	Siemens	15%	MACE
Kusunose et al.(35)	2014	Retrospective/monocentric	n=137	0.42±0.2	Siemens	Quartile	All-cause death
Sato et al.(16)	2014	Retrospective/multicentric	n=142	0.42±0.11	GE	17%	MACE
Carstensen et al.(36)	2015	Prospective/multicentric	n=104	0.49±0.13	GE	15%	MACE
Nagata et al.(37)	2015	Prospective/multicentric	n=102	0.42±0.10	TomTec	17%	MACE
Salaun et al.(38)	2017	Prospective/multicentric	n=117	0.47±0.11	GE	Tertile	All-cause death

GE indicates General Electrics, AVAi, indexed aortic valve area and MACE, major adverse cardiac event.

Table 2: population characteristics.

Variables	Whole pooled cohort (n=1 067)
Age, years	74±10
Body surface area, m^2	1.79±0.26
Male gender, %	56
Comorbidities	
Coronary artery disease, %	26
Hypertension, %	63
Diabetes, %	28
Dyslipidemia, %	44
Echocardiographic data	
Indexed aortic valve area, cm^2/m^2	0.49±0.17
Severe AS*, %	82
LVEF, %	63.5±8
LVEF >60%, %	65
LV global longitudinal strain, %	16.2±3.6

LV indicates left ventricular. * severe AS is defined as an indexed aortic valve area <0.6cm^2/m^2

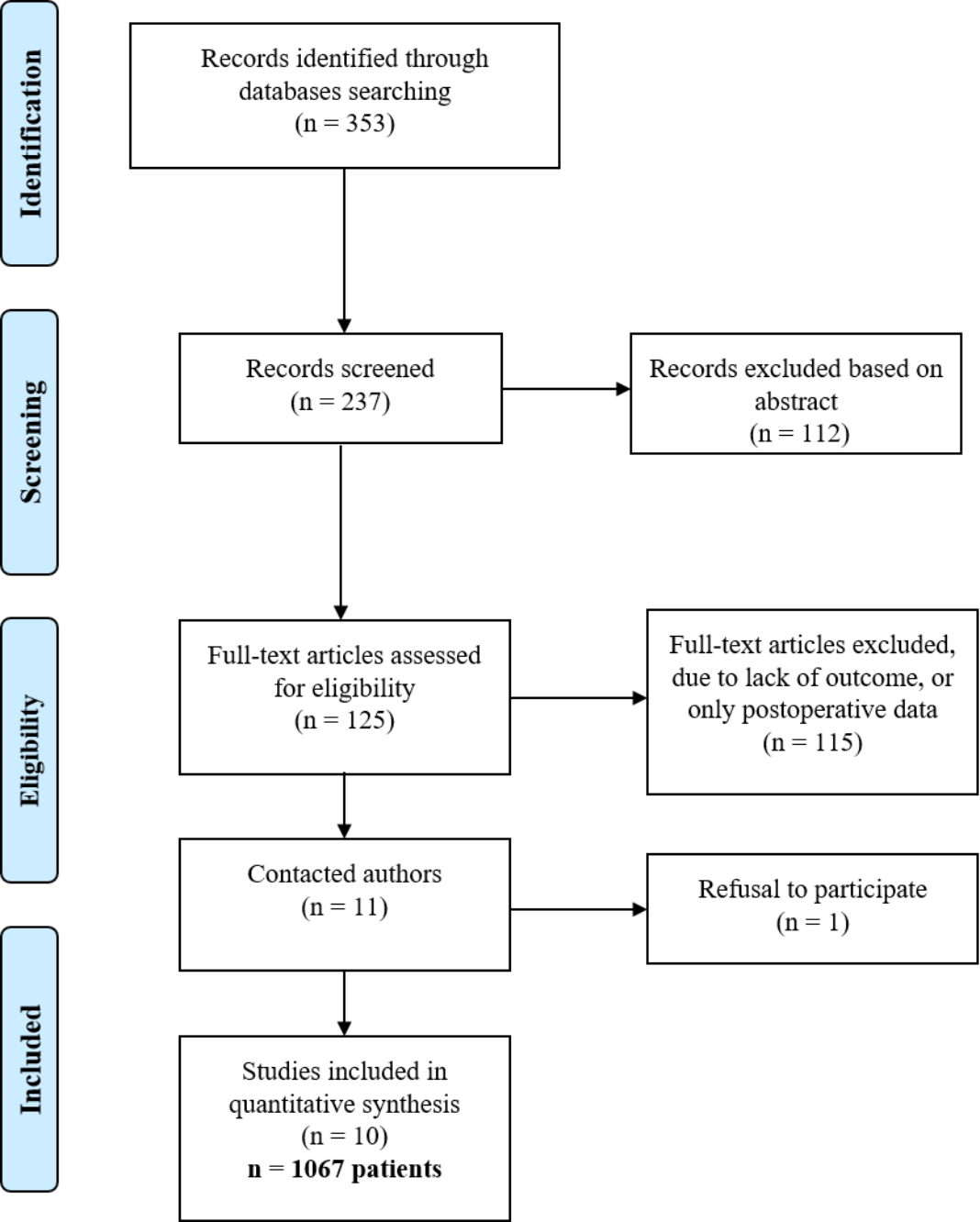
Figures Legend

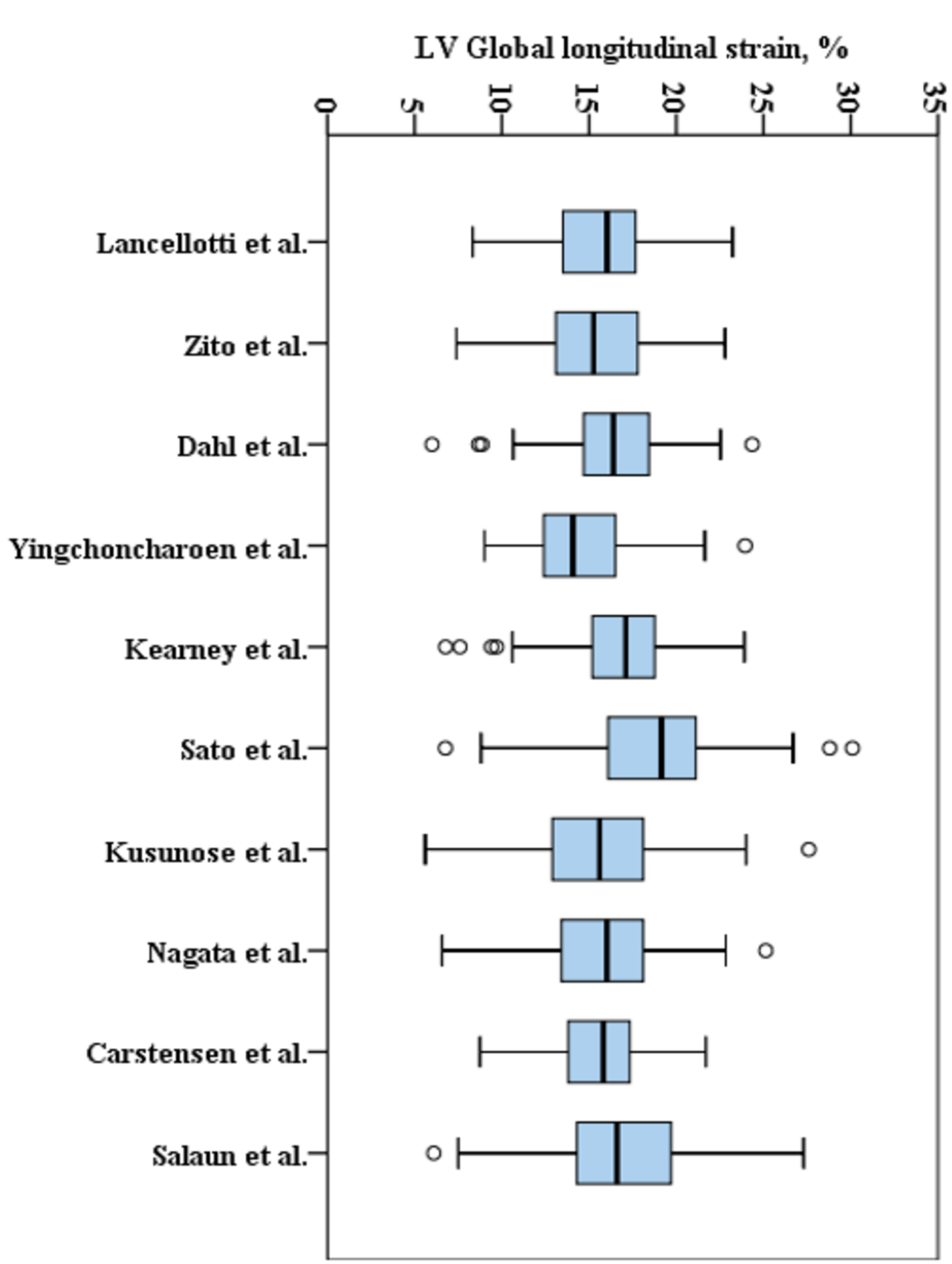
Figure 1
Flow chart
Selection and inclusion of the studies.

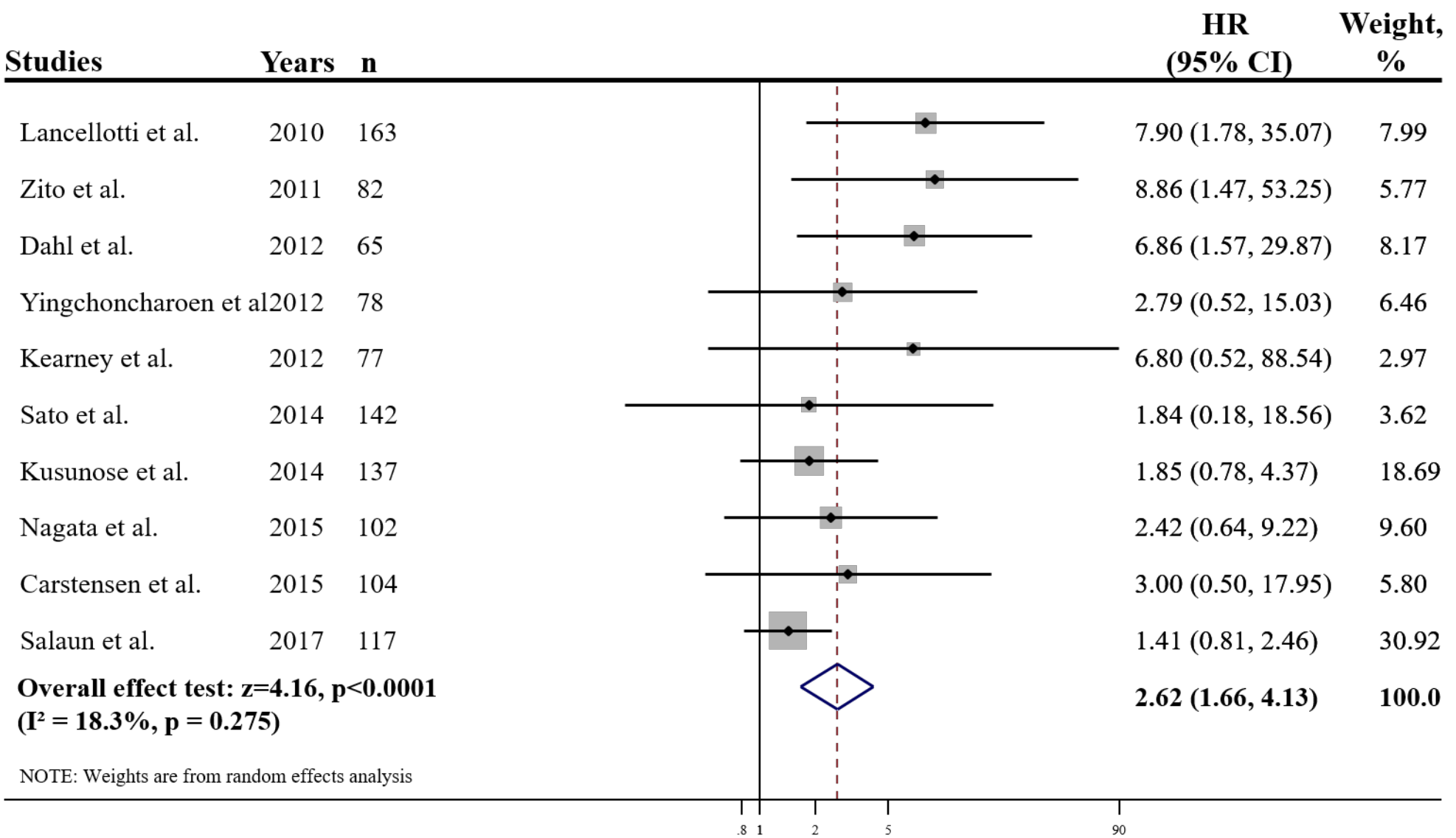
Figure 2
Distribution of left ventricular (LV) global longitudinal strain according to studies.
Circle indicates outliers.

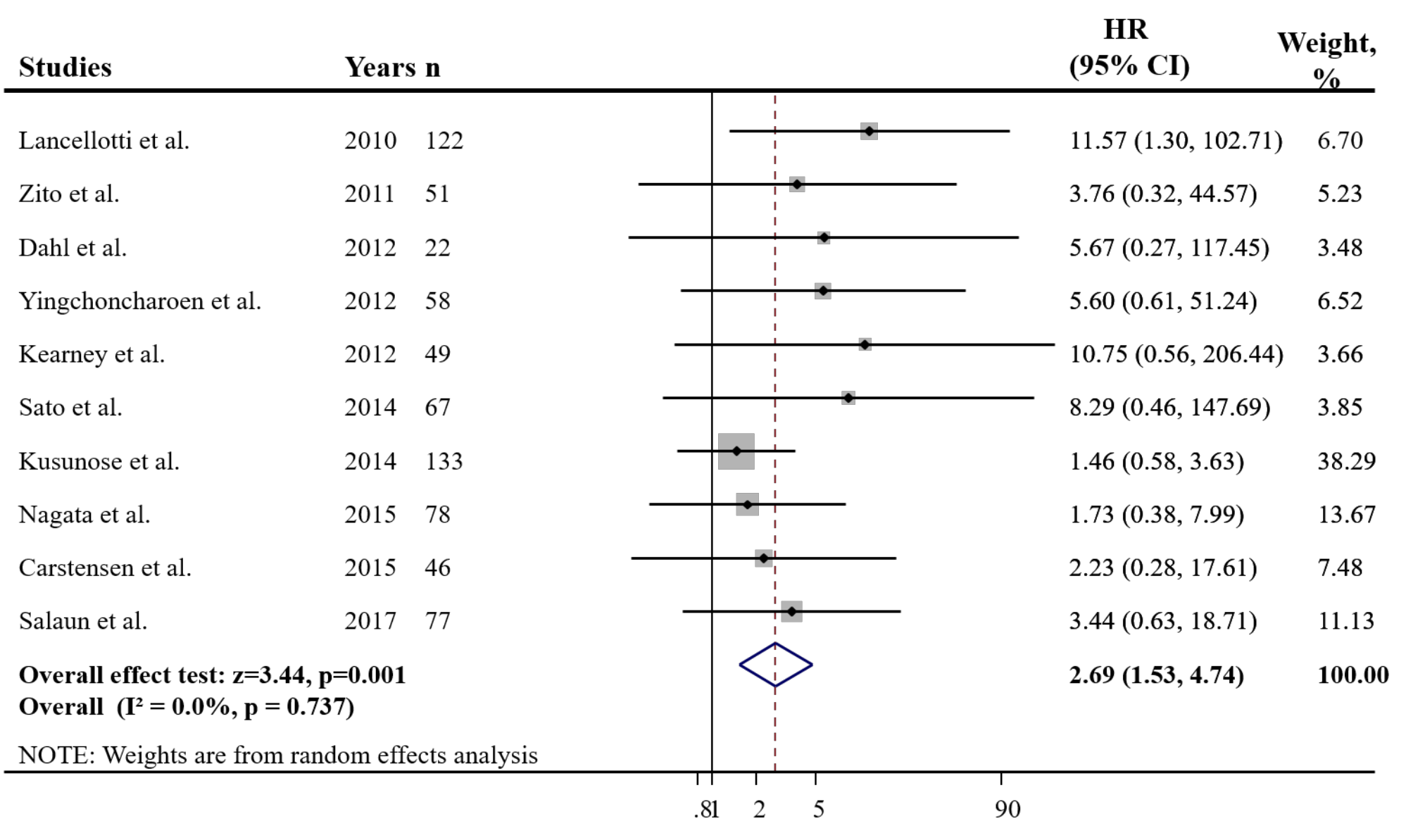
Figure 3
Forest-plot
Forest-plot reporting the pooled effect of impaired left ventricular (LV) global longitudinal strain (i.e. <14.7%) on mortality in the whole cohort (Panel A) and in patients with LVEF≥60% (Panel B).

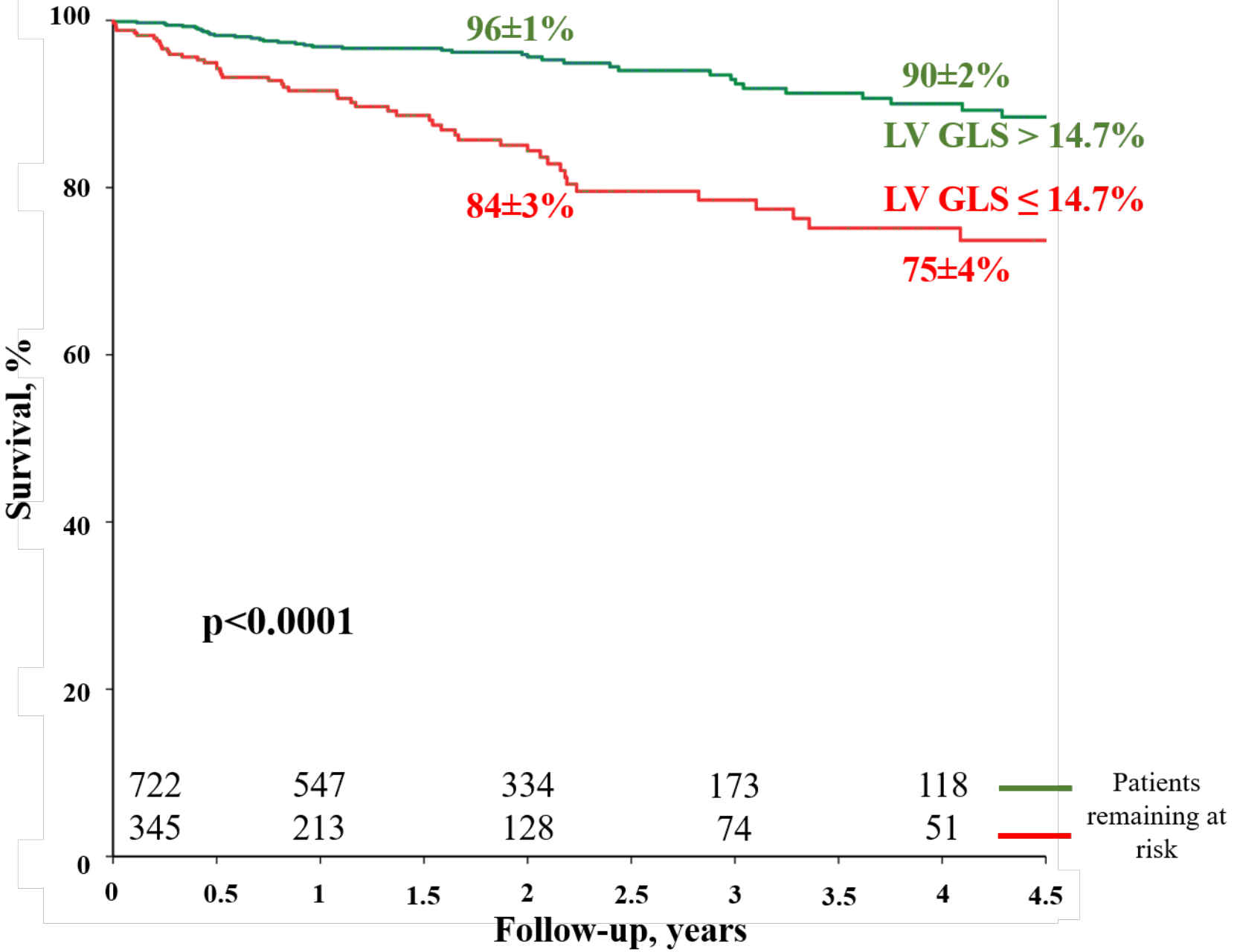
Figure 4
Kaplan-Meier survival curves
Kaplan-Meier survival curves stratified according to left ventricular global longitudinal strain (LVGLS) in the whole cohort (Panel A) and in patients with LVEF≥60% (Panel B). Percentage in the graphs are survival rate at 2- and 4-year follow-up.

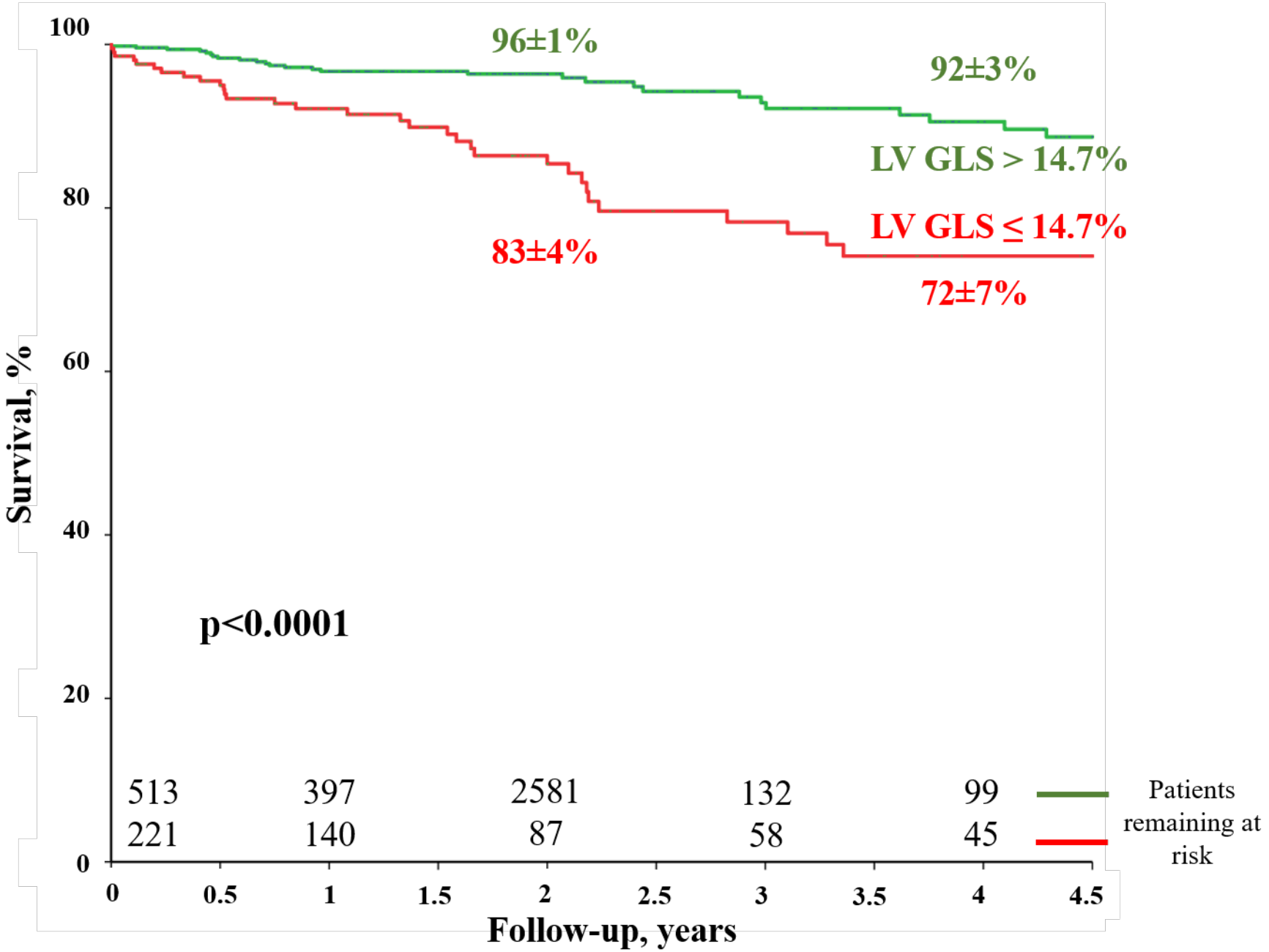

Identification
Screening
Eligibility
Included
Records identified through databases searching (n = 353)
Records screened (n = 237)
Records excluded based on abstract (n = 112)
Full-text articles assessed for eligibility (n = 125)
Full-text articles excluded, due to lack of outcome, or only postoperative data (n = 115)
Contacted authors (n = 11)
Refusal to participate (n = 1)
Studies included in quantitative synthesis (n = 10)
n = 1067 patients


LV Global longitudinal strain, %
0
5
10
15
20
25
30
35
Lancellotti et al.
Zito et al.
Dahl et al.
Yingchoncharoen et al.
Kearney et al.
Sato et al.
Kusunose et al.
Nagata et al.
Carstensen et al.
Salaun et al.


Studies
Years
n
HR (95% CI)
Weight, %
Lancellotti et al. 2010 163 7.90 (1.78, 35.07) 7.99
Zito et al. 2011 82 8.86 (1.47, 53.25) 5.77
Dahl et al. 2012 65 6.86 (1.57, 29.87) 8.17
Yingchoncharoen et al 2012 78 2.79 (0.52, 15.03) 6.46
Kearney et al. 2012 77 6.80 (0.52, 88.54) 2.97
Sato et al. 2014 142 1.84 (0.18, 18.56) 3.62
Kusunose et al. 2014 137 1.85 (0.78, 4.37) 18.69
Nagata et al. 2015 102 2.42 (0.64, 9.22) 9.60
Carstensen et al. 2015 104 3.00 (0.50, 17.95) 5.80
Salaun et al. 2017 117 1.41 (0.81, 2.46) 30.92
Overall effect test: z=4.16, p<0.0001
(I² = 18.3%, p = 0.275)
2.62 (1.66, 4.13) 100.0
NOTE: Weights are from random effects analysis
.8
1
2
5
90


Studies
Years n
HR (95% CI)
Weight, %
Lancellotti et al. 2010 122 11.57 (1.30, 102.71) 6.70
Zito et al. 2011 51 3.76 (0.32, 44.57) 5.23
Dahl et al. 2012 22 5.67 (0.27, 117.45) 3.48
Yingchoncharoen et al. 2012 58 5.60 (0.61, 51.24) 6.52
Kearney et al. 2012 49 10.75 (0.56, 206.44) 3.66
Sato et al. 2014 67 8.29 (0.46, 147.69) 3.85
Kusunose et al. 2014 133 1.46 (0.58, 3.63) 38.29
Nagata et al. 2015 78 1.73 (0.38, 7.99) 13.67
Carstensen et al. 2015 46 2.23 (0.28, 17.61) 7.48
Salaun et al. 2017 77 3.44 (0.63, 18.71) 11.13
Overall effect test: z=3.44, p=0.001 2.69 (1.53, 4.74) 100.00
Overall (I² = 0.0%, p = 0.737)
NOTE: Weights are from random effects analysis
.81
2
5
90


100
80
60
40
20
0
Survival, %
96±1%
90±2%
LV GLS > 14.7%
84±3%
LV GLS ≤ 14.7%
75±4%
p<0.0001
722
547
334
173
118
345
213
128
74
51
Patients remaining at risk
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Follow-up, years


100
80
60
40
20
0
Survival, %
96±1%
92±3%
LV GLS > 14.7%
LV GLS ≤ 14.7%
83±4%
72±7%
p<0.0001
513
397
2581
132
99
221
140
87
58
45
Patients remaining at risk
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Follow-up, years