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HIGHLIGHTS

- Only measurement of maximal left atrial volume index is included in current echocardiographic guidelines
- Left atrial emptying fraction is superior to maximal left atrial volume index
- Left atrial emptying fraction predicts all-cause mortality in HFrEF

ABSTRACT

Background: The prognostic value of LA functional measures in heart failure patients with reduced ejection fraction (HFrEF) is unclear. Hence, this study investigated the prognostic value of left atrial (LA) functional measures such as the left atrial emptying fraction (LAEF) and the minimal LA volume in comparison to left atrial volume index (LAVI) in HFrEF patients.

Methods and results: A total of 818 HFrEF patients with left ventricular ejection fractions <45% underwent echocardiography. LA volumes were determined by the area-length method from the apical 2 chamber and apical 4 chamber view. LAEF, MinLAVI (minimal LA volume indexed to body surface area) and LAVI was calculated. End-point was all-cause mortality. During a median follow-up of 3.3 years (IQR: 1.8-4.6 years), 121 patients died (14.8%). Follow-up was 100%. In a final multivariable model adjusting for clinical and echocardiographic parameters, LAEF, but not MinLAVI or LAVI, was an independent predictors of all-cause mortality in HFrEF patients (LAEF: HR 1.11, p=0.033, per 5% decrease)(MinLAVI: HR 1.03, p=0.57, per 5mL/m^2 increase)(LAVI: HR 1.06, p=0.16, per 5 mL/m^2 increase).

Conclusion: LAEF is an independent predictor of all-cause mortality in HFrEF patients after multivariable adjustment. LAEF provides incremental prognostic value over LAVI in risk stratification of HFrEF patients.

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KEY WORDS

Heart failure with reduced ejection fraction; left atrial function; Prognosis; Risk stratification; Mortality; Echocardiography

INTRODUCTION

Heart failure (HF) represents a large societal burden of disease and has recently been characterized as an emerging epidemic[1]. HF is associated with significant mortality, morbidity and healthcare expenditures[1]. Echocardiography is an essential tool in the diagnosis, management and risk stratification of HF patients[2]. Echocardiographic assessment of HFrEF patients may improve survival and overall prognosis due to better and more intensified medical treatment [3].

Left atrial (LA) size and the LA volume index (LAVI) measured by echocardiography are established predictors of mortality in HF[4], [5]. Accordingly, measurement of LAVI is included in contemporary echocardiographic guidelines[6]. However, the prognostic value of left atrial (LA) functional parameters in HFrEF patients has not been a major area of interest thus far[7]. In a study of 982 patients admitted with suspicion of HF, LA emptying fraction (LAEF) measured by cardiac magnetic resonance imaging (CMRI), but not left ventricular ejection fraction (LVEF), was an independent predictor of death, and the prognostic value of LAEF in this population was superior to maximal LA volume[8]. These findings suggest that atrial functional measures, such as LAEF and the minimal LA volume calculated from the measurements of both maximal and minimal LA volume, may contribute with incremental prognostic value in HFrEF. However, little is known about the prognostic value of LA functional parameters measured by two-dimensional echocardiography in HFrEF.

This study therefore aimed to investigate whether left atrial functional measures, such as LAEF and the minimal LA volume, hold incremental prognostic value over LAVI and other established prognosticators in predicting all-cause mortality in HFrEF patients.

METHODS

Data

Routine echocardiographic examinations are conducted at the Department of Cardiology, Herlev-Gentofte University Hospital according to a standardised protocol[9]. Results have been stored on a local hard drive since 2005.

Study sample

For this retrospective study, we identified 1102 nonacute consecutive HFrEF patients with a LVEF < 45% who were referred to the HF clinic of a large University Hospital in Copenhagen in the period 2005-2013. The HFrEF population in the present study has previously been described in detail[9]. All patients had been diagnosed with HFrEF by a senior clinician according to contemporary guidelines[10], and all patients had a history of angiography to determine coronary artery status. We searched the Hospital Database for echocardiograms pertaining to each patient. We considered echocardiograms performed at a maximum of 1 year from first admittance to the HF clinic (median 30 days before admittance, interquartile range 6 to 56 days before admittance). A total of 22 patients did not have an examination within this window and were therefore excluded. Furthermore, 15 patients were excluded due to inadequate exam quality. This resulted in 1065 patients with echocardiograms of sufficient quality within the specified time frame. Then 247 patients were excluded due to insufficient image quality for the measurement of LA functional parameters. This resulted in final study sample of 818 HFrEF patients. Baseline clinical characteristics and medications were retrieved from the HF clinic database and were recorded upon

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first visit to the clinic. Mortality status was retrieved from the Danish National Registry of Mortality at follow-up, and follow-up was 100%.

Clinical characteristics

Diabetes mellitus (DM) was defined as either fasting plasma glucose levels over 7 mmol/L, non-fasting glucose above 11.1 mmol/L or the use of glucose-lowering medications. Ischemic cardiomyopathy (ICMP) was defined either as a history of myocardial infarction, previous percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery (CABG). Hypertension was defined as a systolic blood pressure ≥ 140mmHg or a diastolic blood pressure ≥ 90 mmHg.

Echocardiography

Vivid 7 or 9 ultrasound machines (GE Healthcare, Horten, Norway) were used by experienced sonographers in all echocardiographic examinations. Echocardiograms were stored in a GE Healthcare Image Vault and underwent offline analysis by a single investigator blinded to all patient data and outcomes, using Echopac version 12 (GE Healthcare, Horten, Norway).

Conventional echocardiography

The acquisition of conventional echocardiographic parameters has previously been described in detail[9]. We measured the maximum LA volume using the biplane area length method[6] from the apical 4 chamber and apical 2 chamber view in end-systole using the frame just prior to mitral valve opening. We measured the minimal LA volume using the biplane area length method from the apical 4 chamber and apical 2 chamber view in end-diastole using the frame just prior to mitral valve closure. LAEF was calculated as LAEF = (maximal LA volume – minimal LA volume)/

maximal LA volume. MinLAVI was calculated as minimal LA volume indexed to body surface area (BSA) and LAVI as maximal LA volume indexed to BSA. Our lab has previously demonstrated good inter- and intraobserver variability in the measurement of LAEF, minimal LA volume and maximal LA volume[11]. In this analysis, the intraobserver coefficients of variation (CV) were as follows: LAEF CV = 9.0%; minimal LA volume CV = 10.7%; maximal LA volume CV = 10.7%. The interobserver CVs were as follows: LAEF CV = 19.9%; minimal LA volume CV = 29.3%; maximal LA volume CV = 24.6%.Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode in the apical 4 chamber view. Pulsed-wave Doppler echocardiography in the 4-chamber view was used to assess mitral valve inflow patterns and thus E, A, deceleration time (DT) and E/A ratio. In patients with atrial fibrillation, the left atrium does not contract in end-diastole, and thus no measureable A wave is present[12]. Therefore, we did not determine A or E/A in patients with atrial fibrillation. LVEF was obtained using the modified Simpson's rule[6]. LV end-diastolic dimensions were measured from the parasternal long axis view at the level of the mitral valve leaflets. These dimensions include the interventricular septum thickness, the LV internal diastolic diameter (LVIDd) and the LV posterior wall thickness. These measurements were used to calculate the LV mass by the Devereux formula and LV mass index (LVMI) by division with BSA[6]. The early diastolic peak tissue velocity (e') was determined by placing the range gate in each side of the mitral annular plane in a pulsed-wave tissue Doppler recording of the apical 4-chamber view with subsequent averaging of values to obtain e'. The degree of mitral valve regurgitation was graded according to contemporary guidelines using mitral valve morphology and Color Doppler imaging[13].

Speckle tracking echocardiography

Collection and calculation of strain parameters derived from speckle tracking echocardiography have been described in detail elsewhere[9]. Briefly, longitudinal speckle tracking was performed in the 3 apical views. A region of interest was defined and created by a semi-automated process, in which the operator placed 3 pointers at the endocardial-blood border, 2 in each side of the mitral annular plane and one at the apex of the LV, with the program subsequently detecting the endocardial border and the myocardial wall thickness. Global longitudinal strain (GLS) was calculated from a total of 18 heart wall segments obtained from the apical 4 chamber, apical 2 chamber and apical long axis views. Hence, 6 segments were averaged from each view to produce a single measure from each view. Then, values from each of the three apical views were averaged into a single GLS measure.

Ethics

This study was approved by a regional scientific ethics committee and by the Danish Data Protection Agency. The study complies with the second declaration of Helsinki. Informed consent is not needed for studies involving the use of hospital record and registry data in Denmark as long as the study has been approved by the Danish Data protection Agency and a regional ethics committee.

Statistics

All statistical analyses were carried out using STATA 13 for Mac OS. Statistical significance was defined as $p<0.05$. Continuous variables exhibiting Gaussian distribution were compared using Student's 2-tailed t-test. In table 1, untransformed continuous variables not exhibiting Gaussian distribution were reported as median with interquartile ranges (IQR) and were compared using the Mann-Whitney U test. Proportions were compared through use of the chi-square test. Linear

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regression of means was used to analyze trend over tertiles of LAEF. In case of non-Gaussian distribution, the Cuzick test for non-parametric trend was used to asses trend over tertiles of LAEF[14]. Survival curves were constructed using the Kaplan-Meier method. Poisson cubic spline regression was used to estimate mortality rates as a function of LAEF and MinLAVI. To determine the number of knots in these spline regression models, we calculated the Akaike Information criterion (AIC) for each model and selected the number of knots that yielded the lowest AIC value. Cox proportional hazards regression models were utilized to assess the prognostic value of LA functional parameters. To determine whether LA functional parameters contributed with independent prognostic value, we constructed multivariable models adjusted for known clinical and echocardiographic predictors of outcome in HFrEF.

In Model 1 we chose to adjust for important clinical variables (age, sex, mean arterial pressure, treatment with diuretics, diabetes and atrial fibrillation). Then, we evaluated the prognostic value of all echocardiographic variables available in our study when adjusted for the covariates specified in Model 1. The results of these analyses can be found in the Supplemental Material, Supplemental Table S1. The purpose of assessing the prognostic value of all available echocardiographic markers in Model 1 was to determine which variables proved to be important in this model such that they could be selected for entry into Model 2 using a forward-selection approach. Using an entry criterion of p≤0.15, we chose all echocardiographic variables which fulfilled this significance criteria in Model 1 and added these to the adjusting covariates from Model 1 to obtain the covariate adjustment for Model 2. Additionally, we also adjusted Model 2 for mitral valve regurgitation severity, since this is a known prognosticator in HFrEF. Then, we assessed the prognostic value of LAEF, MinLAVI and LAVI when entered individually into Model 2. Then, using an entry criterion of p≤0.15, we created a Model 3, which besides all the adjusting covariates from Model 2

additionally included LAEF, minLAVI and LAVI in the same model (unless they in Model 2 displayed a p-value > 0.15, in which case they were considered to have "dropped out" per the forward selection criteria). Thus, in Models 1 and 2, LAEF, minLAVI and LAVI were tested individually. However, in Model 3, to determine which LA parameter was the strongest predictor of outcome, LAEF and minLAVI were entered simultaneously into the same model (LAVI was not included in this model since it was not significant in Model 2). Harrell's C-statistics were calculated for each predictor to quantify prognostic strength. In this study we included HFrEF patients with a LVEF<45%. However, in the newest heart failure guidelines, HFrEF is defined using a LVEF<40%[2]. Therefore, we conducted a sensitivity analysis restricting our final multivariable model to consider only patients with a LVEF<40% to determine whether this would alter our results. Finally, since atrial fibrillation is very prevalent in HFrEF (In this study 15% had atrial fibrillation) we conducted a sensitivity analysis to determine whether atrial fibrillation modified the prognostic value of the LA functional measures (LAEF and MinLAVI). We conducted stratified analysis to analyze the association between LAEF and MinLAVI and outcome in patients with atrial fibrillation and in patients without atrial fibrillation. In these subgroup analysis the extent of our multivariable adjustment was limited by the number of events in each subgroup (28 events occurred in patients with atrial fibrillation, 93 events occurred in patients without atrial fibrillation). Hence, when considering only patients with atrial fibrillation we adjusted for age, sex and mean arterial pressure. When considering only patients without atrial fibrillation we adjusted for age, sex, mean arterial pressure, body mass index, heart rate, ischemic cardiomyopathy, coronary artery bypass graft, diabetes and left ventricular ejection fraction, since the higher number of events in this subgroup allowed for more extensive adjustment without the risk of overfitting the model. Also, in patients with atrial fibrillation, to assess whether the prognostic value of LA functional parameters was secondary to LV filling pressure, we assessed the prognostic value of LA functional parameters

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adjusting only for E, since E correlates well with LV filling pressure in patients with heart failure[15].

RESULTS

Outcome and follow-up

Median follow-up time was 3.3 years (IQR: 1.8-4.6 years), and follow-up was 100%. A total of 121 patients (14.8%) reached the end-point of all-cause mortality.

Baseline characteristics of the population stratified according to tertiles of LAEF

Decreasing LAEF was significantly associated with increasing age, decreasing systolic BP and increasing HR (Table 1). Increasing prevalence of previous pacemaker implantation, previous intracardiac defibrillator implantation, previous acute myocardial infarction (AMI) and previous episodes of angina pectoris were all significantly associated with decreasing LAEF (Table 1). Finally, increasing severity of mitral regurgitation was significantly associated with decreasing LAEF (Table 1).

Decreasing LAEF was significantly associated with increasing values of LAVI, MinLAVI, LVIDd, LVMI, E-wave, E/A ratio, and E/e' ratio (Table 1). Decreasing values of LVEF, GLS, TAPSE, A-wave and DT were all associated with decreasing LAEF (Table 1).

Prediction of all-cause mortality

LAEF, MinLAVI and LAVI were all significant predictors of outcome in univariable Cox regression (Table 2). LAEF and MinLAVI both displayed a significantly higher C-statistics than LAVI (p value for difference, p<0.001) (Table 2). Patients in the 1st tertile (worst) of LAEF displayed an approximately 4 times greater risk of death from any cause when compared to patients

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in the 3rd tertile (best) of LAEF (Figure 1). Patients in the 3rd tertile (worst) of MinLAVI displayed an approx. 3 times greater risk of death from any cause compared to patients in the 1st tertile (best) (Figure 2). Patients in the 3rd tertile (worst) of LAVI displayed an approx. 2.5 times greater risk of death from any cause compared to patients in the 1st tertile (best) (Figure 3). In unadjusted analysis, we found that the risk of death increased continuously as a function of LAEF, particularly at low values of LAEF(Figure 4). The same was true for the unadjusted relationship between MinLAVI and the risk of death (Figure 4).

LAEF, MinLAVI and LAVI all remained significant in a multivariable model adjusting for age, sex, mean arterial pressure, treatment with diuretics, diabetes and atrial fibrillation (Model 1) (Table 2). In a multivariable model adjusted for the same parameters as Model 1 with the addition of mitral regurgitation, LVEF, GLS, TAPSE, DT, E/e' and left ventricular end-systolic volume index, LAEF and MinLAVI were the only independent echocardiographic predictors of all-cause mortality (Model 2) (Table 2). Finally, in a final multivariable model, to determine which variable was the strongest predictor of outcome, we added both LAEF and MinLAVI to Model 2, obtaining Model 3: In this analysis, only LAEF remained a significant predictor of outcome (LAEF: HR 1.11, 95CI 1.01-1.23, per 5% decrease, p=0.033) (MinLAVI: HR 1.03, 95CI 0.93-1.15, per 5mL/m^2 increase, p=0.57) (Model 3) (Table 2). Also, since a LVEF<40% is used to diagnose HFrEF in the latest guidelines, we analyzed whether restricting our final multivariable model to consider only patients with LVEF<40% altered our results. We found that this did not significantly alter our results (LAEF: HR 1.10, 95CI 1.02-1.17, p=0.041, per 5% decrease) (MinLAVI: HR 1.02, 95CI 0.91-1.14, p=0.59, per 5 mL/m^2 increase).

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We also assessed whether atrial fibrillation modified the prognostic value of LAEF and MinLAVI. There was no statistically significant interaction between atrial fibrillation and LAEF or MinLAVI (LAEF: p for interaction p=0.41)(MinLAVI: p for interaction p=0.051). In a model considering only patients with atrial fibrillation adjusting for age, sex and MAP, LAEF and MinLAVI both remained independent predictors of outcome (LAEF: HR 1.31, 95CI 1.07-1.60, p=0.008, per 5% decrease)(MinLAVI: HR 1.10, 95CI 1.02-1.19, p=0.019, per 5 mL/m^2 increase). In a model adjusting only for E, only LAEF, not MinLAVI or LAVI, remained an independent predictor of outcome (LAEF: HR 1.27, 95CI 1.03-.55, per 5% decrease, p=0.023) (MinLAVI: HR 1.09, 95CI 0.97-1.24, per 5 mL/m^2, p=0.15) (LAVI: HR 1.06, 95CI 0.94-1.20, per 5 mL/m^2 increase, p=0.35). In a model considering only patients without atrial fibrillation adjusting for age, sex, MAP, BMI, HR, ICMP, CABG, DM and LVEF, LAEF and MinLAVI remained independent predictors of outcome (LAEF: HR 1.09, 95% CI 1.01-1.17, p=0.032, per 5% decrease)(MinLAVI: HR 1.11, 95% CI 1.03-1.20, p=0.009, per 5 mL/m^2 increase).

DISCUSSION

In this study, we found that both LAVI, minLAVI and LAEF were significant predictors of all-cause mortality in HFrEF patients, however, after adjusting for clinical and echocardiographic parameters, LAEF emerged as the strongest predictor of outcome.

Prognostic value of atrial volumes and function

Several studies have demonstrated increased LA size to be a consistent predictor of outcome in HF[4], [16]. Thus, it is well documented that the maximal LA volume conveys significant prognostic information in HFrEF, and assessment of maximal LA volume is included in current

guidelines[6]. In our study, we also found LAVI to be a significant univariable predictor of all-cause mortality in HFrEF. The prognostic value of the maximal LA volume relies on the assumption that LA size is a marker of chronically elevated LV filling pressure[17]. A restrictive LV filling pattern, determined by Doppler echocardiography, has previously been shown to predict all-cause mortality in HFrEF[18]. However, since mitral filling patterns are very dependent on loading conditions during examination and can vary widely, especially with volume depletion, the LA size may represent a more consistent marker of LV filling pressures[19]. The LA responds to increased LV filling pressures with dilation and fibrotic accumulation[19], and, in accordance, significant enlargement of the LA is often found in HFrEF[20]. Thus, LA volume is both an established and biologically plausible marker of the severity of HF. Recently though, in a study of 664 HF patients, LAEF measured by CMRI was a superior predictor of survival compared to LVEF[8]. Furthermore, in a study of 982 patients admitted with suspicion of HF, LAEF measured by cardiac magnetic resonance imaging CMRI, but not LVEF, was an independent predictor of death, and the prognostic value of LAEF in this population was superior to maximal LA volume[8]. This indicates that LA functional measures may offer more prognostic value than LAVI. This is supported by the results of our study, since we found LAEF to offer incremental prognostic value over to LAVI in HFrEF.

Why LA function may offer more prognostic value than LAVI has not been fully elucidated. One explanation may be that LAEF is a stronger correlate of LV filling pressure than the maximal LA volume. The LA is directly exposed to the LV filling pressure in end diastole during the LA contraction. Therefore, the minimal LA volume, which is included in the calculation of LAEF, is a balance between atrial afterload (LV filling pressure) and atrial contractile function. In a CMRI study of patients undergoing clinically indicated left heart catheterization, LAEF and the LA

minimal volume were superior to the maximal LA volume in identifying increased LV filling pressure[21]. Furthermore, the minimal LA volume measured by 3-dimensional echocardiography has been shown to display a stronger association to diastolic function than the maximal LA volume[22]. The minimal LA volume has also been shown to be more strongly correlated to Natriuretic peptide levels in a community based sample when compared to LAVI[23]. Hence, these considerations along with our results suggest that LAEF be a better marker of LV filling pressure and congestion than LAVI, and as a result, may offer prognostic value over LAVI in predicting outcome in HFrEF.

It is also possible that part of the prognostic value of LA functional measures found in this study is due to an ability to quantify primary myocardial disease independent of the relation to LV filling pressure. In a study of ischemic cardiomyopathy and idiopathic dilated cardiomyopathy patients, authors found that patients with idiopathic dilated cardiomyopathy had significantly lower LAEF even though they had similar systolic and diastolic function[24]. Likewise, in a study comparing patients with dilated cardiomyopathy to patients with aortic stenosis, atrial systolic function as determined by atrial active emptying fraction was significantly lower in patients with dilated cardiomyopathy even though there was no difference in maximal LA volume or in hemodynamically assessed LV filling pressure[25]. This difference in LA function cannot be explained by differences in LA maximal volume or LV filling pressure. In our study, we corrected our multivariable model for E/e', a marker of LV filling pressure, yet LAEF remained a strong predictor of outcome. Hence, it is possible that at least part of the prognostic value conveyed by LAEF in HFrEF may stem from an ability to quantify generalized myocardial disease.

LAEF and MinLAVI

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As discussed, it is likely that some of the prognostic value of LAEF is due to the strong correlation to LV filling pressure[21]. However, an interesting finding was the lack of prognostic value of MinLAVI when both LAEF and MinLAVI were entered into the final multivariable model. This suggests that the prognostic value of LAEF is not only carried by the minimal LA volume and its relation to LV filling pressure. LAEF is not only determined by LA contractile function, but also by LA reservoir and conduit functions[26], [27]. The LA has 3 important functions throughout the cardiac cycle, and all contribute to optimal cardiac performance[26]–[30]: 1) during the reservoir phase in systole, the left atrium acts as a reservoir for pulmonary venous return while the mitral valve is closed, 2) during the conduit phase in early diastole, the left atrium acts as a conduit for blood entering the left ventricle, and 3) during end-diastole, the left atrium acts as a booster pump augmenting left ventricular filling right before ventricular systole. Aging is associated with reduced LA compliance, reduced LA reservoir function and reduced conduit function, partly due to accumulation of LA fibrosis and increased LA stiffness[31]–[33]. This reduction in reservoir and conduit function associated with normal aging is compensated for by an increase in LA booster pump function[26], [30], [33]. Similarly, in early heart failure, increased LA pump function compensates for impaired LV function[26], [30], [33], [34]. However, as LV function deteriorates further with progression heart failure, the workload imposed on the LA exceeds its reserve capacity and LA pump failure ensues[35], [36]. To maintain LV filling and stroke volume, the reservoir and conduit functions must compensate for decreased LA pump function[26], [30], [35], [36]. Thus, since LAEF represents all three functions of the LA, LAEF may be able to identify patients with advanced disease in whom LA reservoir and conduit function cannot compensate for LA failure. This notion is supported by our finding that LAEF, but not MinLAVI, also predicted mortality in patients with atrial fibrillation: In atrial fibrillation, LA contractile function is absent and thus LAEF does not represent LA systolic function and booster pump function in atrial fibrillation rhythm. LA

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compliance is reduced and LA stiffness is increased in patients with atrial fibrillation due to LA fibrosis and impaired LA relaxation (due to constant fibrillation)[37], and since especially LA reservoir function is determined by LA compliance, this may result in impaired reservoir function[26], [27], [30]. Hence, the prognostic value of LAEF in patients with atrial fibrillation may stem from an ability to quantify reservoir and conduit function, allowing the identification of patients with poor LA compliance and high LA stiffness, who cannot compensate for the loss of contractile function. Alternatively, invasive hemodynamic studies have demonstrated that the irregular ventricular rate and the loss of atrial filling caused by AF significantly increase pulmonary capillary wedge pressure and contribute to diastolic dysfunction[8]. In HF patients with AF, pronounced diastolic dysfunction could potentially antagonize LA emptying during diastole and lead to reduced LAEF. Thus, this may also explain part of why LAEF was a strong predictor of mortality in patients with atrial fibrillation in our study. However, these considerations should be confirmed in future experimental studies.

Limitations

Some limitations to this study must be acknowledged. None of the patients were suspected of restricted cardiac amyloidosis. However, as is the case for all other HFrEF studies, and for HFpEF studies, the presence of cardiac amyloidosis as a cause of HF symptoms can never be excluded completely. Furthermore, we did not have information on whether some patients may have developed HFrEF in due to specific genetic mutations, rare conditions or viral infections. These considerations are important since myocarditis, amyloidosis and other infiltrative diseases may cause atrial myopathy and affect LA function independently of other disease mechanisms. Also, we did not have information on important clinical variables such as natriuretic peptide levels or New York Heart Association functional class. Since these variables contribute with valuable prognostic

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information in HFrEF[38], [39], this is another limitation. In this study we did not have access to information regarding the specific cause of death, and as a result we could not analyze the association between LA functional parameters and cardiovascular mortality. However, when considering that approximately 80% of HFrEF patients die from cardiovascular causes[40], we feel that our results remain valid even though our outcome was all-cause mortality. Furthermore, we did not have information on heart failure hospitalizations during follow-up. Since heart failure hospitalization is associated with significant healthcare costs[41], this would have been useful. Multiple statistical tests were performed in this study but no adjustment for multiple comparisons was made. Due to a high degree of multicollinearity between LAEF and MinLAVI, these variables were tested separately in the multivariable models. Therefore, it was difficult to assess whether one was superior to the other. However, since LAEF and MinLAVI remained independent predictors of outcome when tested separately in the final multivariable model but LAVI did not, we may still conclude that LAEF and MinLAVI are superior to LAVI in predicting outcome in HFrEF. Lastly, the study population was mainly of Caucasian ethnicity, and therefore our results cannot be applied to other ethnicities.

CONCLUSION

LAEF is an independent predictor of all-cause mortality in HFrEF patients after multivariable adjustment. LAEF provides incremental prognostic value over LAVI in risk stratification of HFrEF patients.

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FIGURE LEGENDS
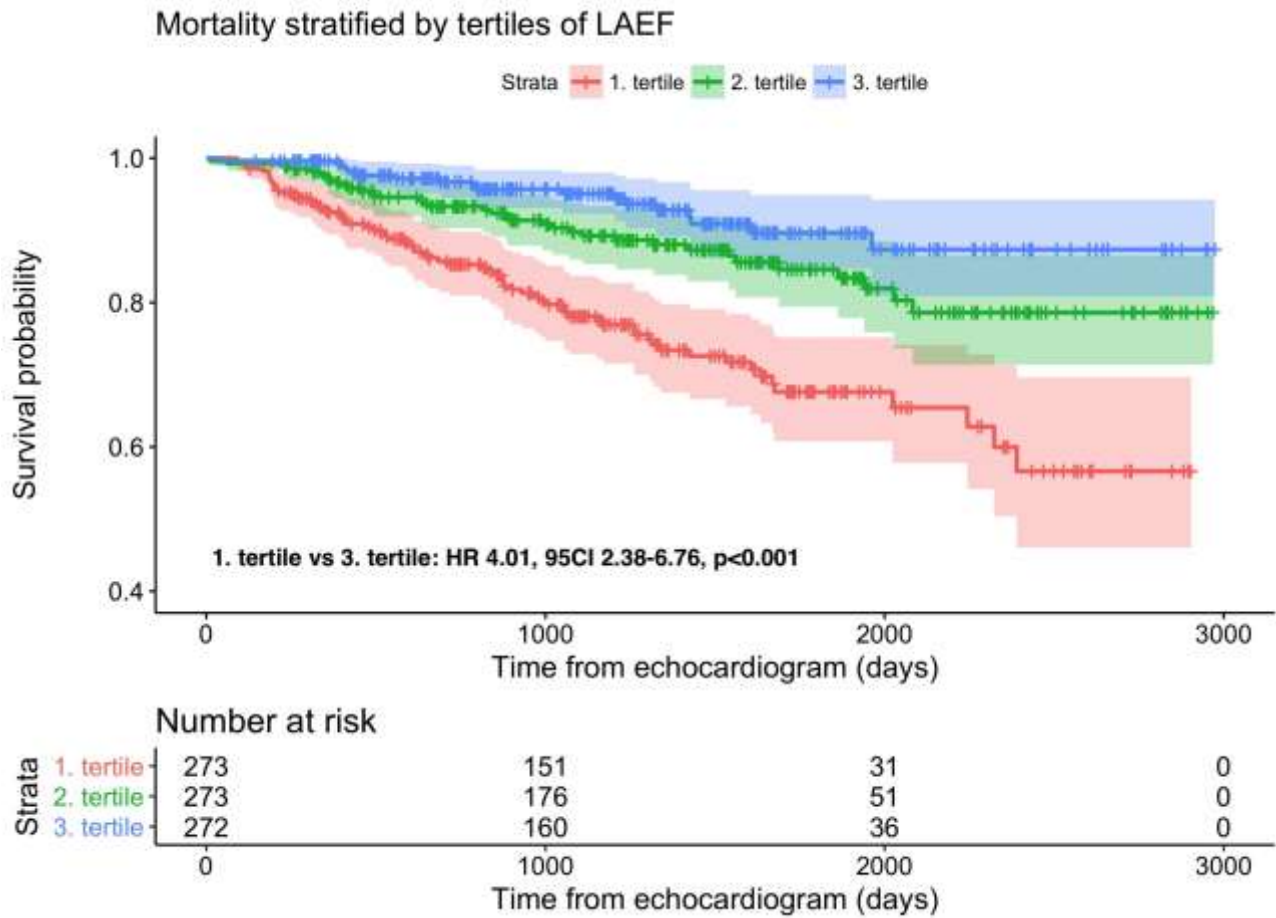
Figure 1: Mortality of the population stratified according to tertiles of left atrial emptying fraction

(LAEF). The tertile cut-offs are 1. tertile, LAEF < 28%; 2. tertile, LAEF = 28-43 %; 3. tertiler.

LAEF > 43%.

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Figure 2: Mortality of the population stratified according to tertiles of end diastolic (minimal) left atrial volume indexed to body surface area (MinLAVI) .The tertile cut-offs are 1. tertile, MinLAVI < 14 mL/m^2; 2. tertile, MinLAVI = 14-23 mL/m^2; 3. tertile MinLAVI > 23 mL/m^2.

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Mortality stratified by tertiles of LAVI

Strata ── 1. tertile ── 2. tertile ── 3. tertile

3. tertile vs 1. tertile: HR 2.83, 95CI 1.78-4.50, p<0.001

Number at risk

| Strata	0	1000	2000	3000
1. tertile	273	175	54	0
2. tertile	273	154	23	0
3. tertile	272	158	41	0

Time from echocardiogram (days)

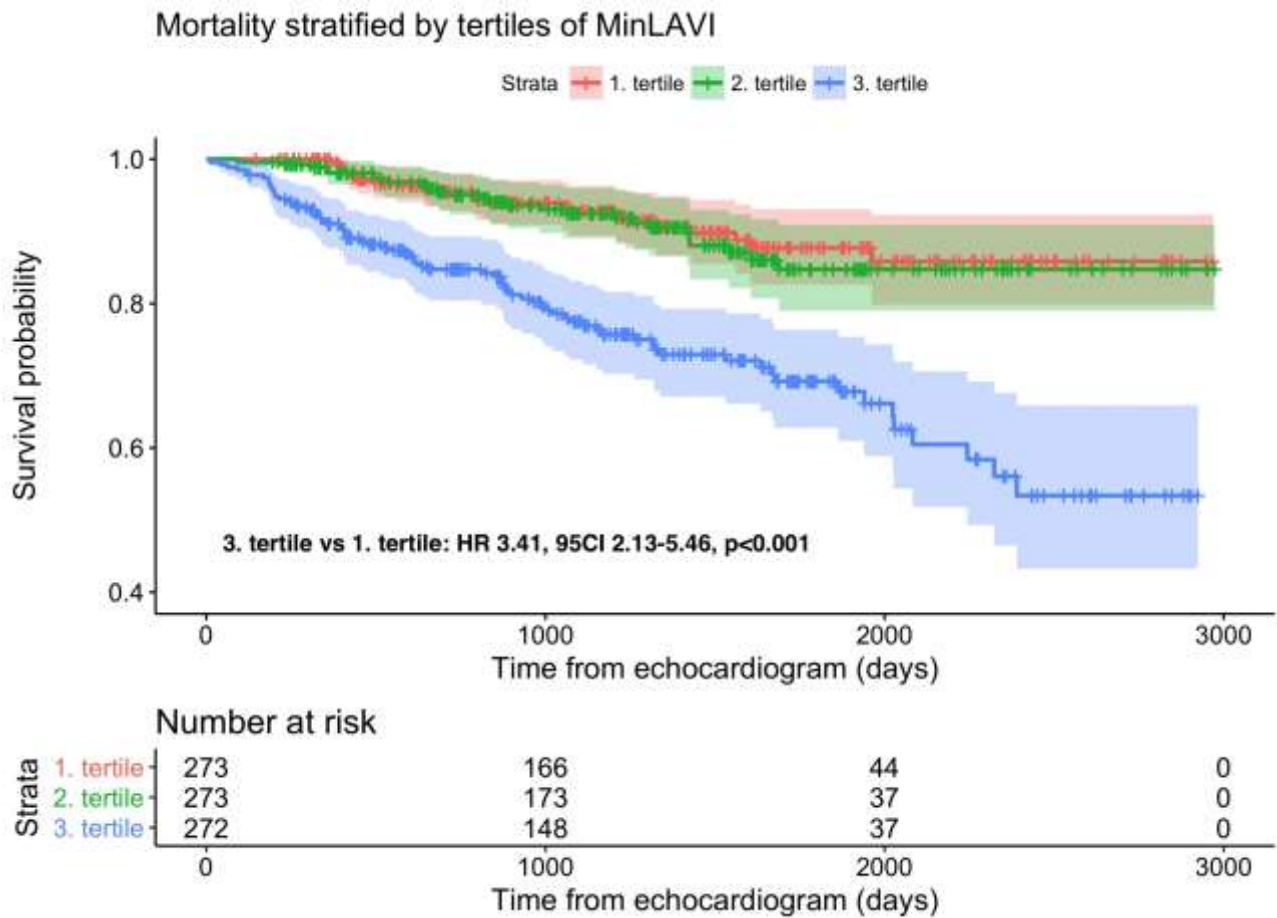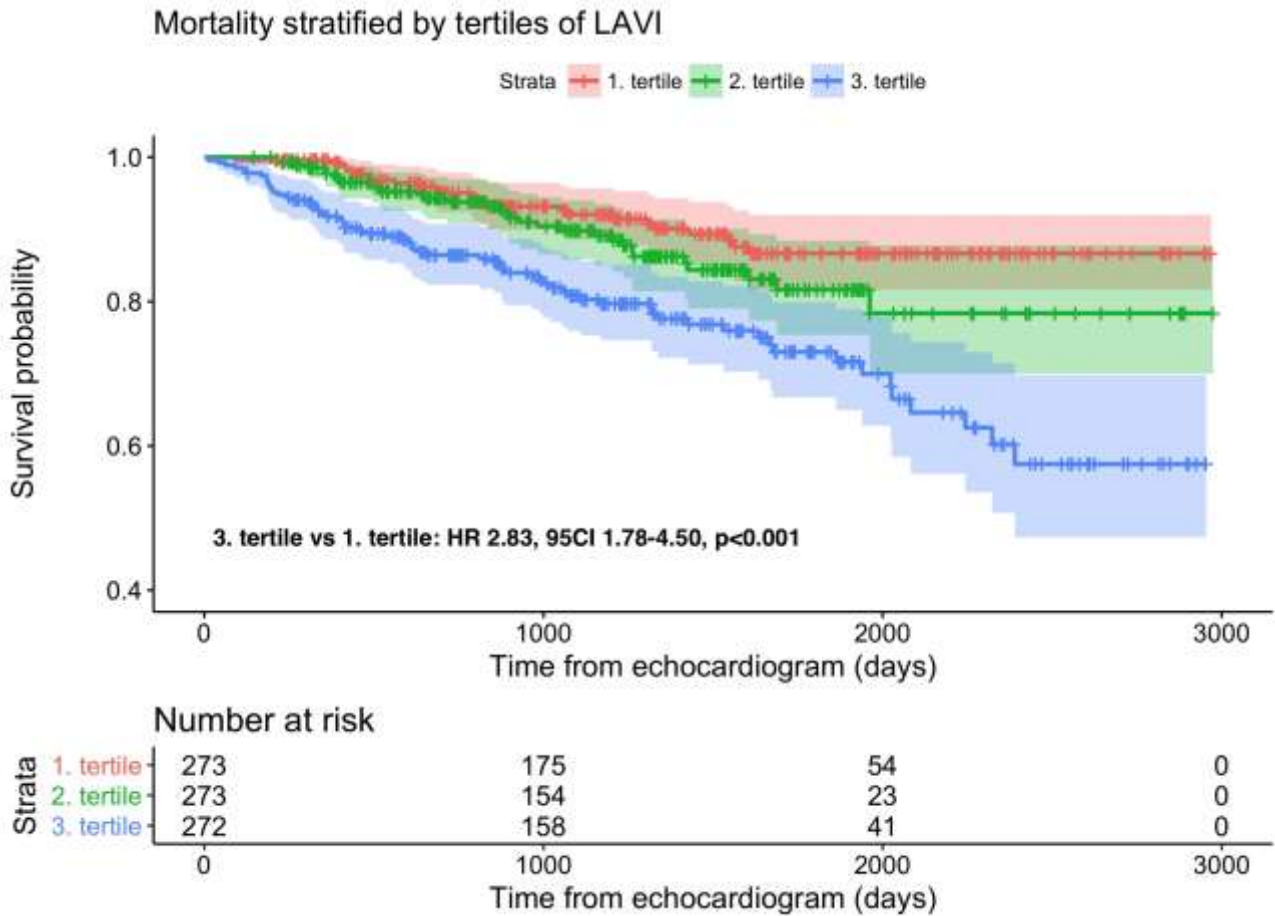*Figure 3: Mortality of the population stratified according to tertiles of left atrial volume index (LAVI). The tertile cut-offs are 1. tertile, LAVI < 24 mL/m^2; 2. tertile, LAVI = 24-34 mL/m^2; 3. tertile, LAVI > 34 mL/m^2.*

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All-cause mortality by left atrial emptying fraction

Mortality rate (per 1000 person-years)

p<0.001
— — 95% CI

Left atrial emptying fraction (%)

All-cause mortality by minimal left atrial volume index

Mortality rate (per 1000 person-years)

p<0.001
— — 95% CI

Minimal left atrial volume index (mL/m^2)

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Figure 4: The association between all-cause mortality and measures of left atrial function. The curves display the unadjusted mortality rate with 95% confidence intervals as a function of the left atrial emptying fraction and the minimal left atrial volume index. A Poisson regression model was used to estimate incidence rates.

TABLE 1

Patients stratified according to tertiles of LAEF.

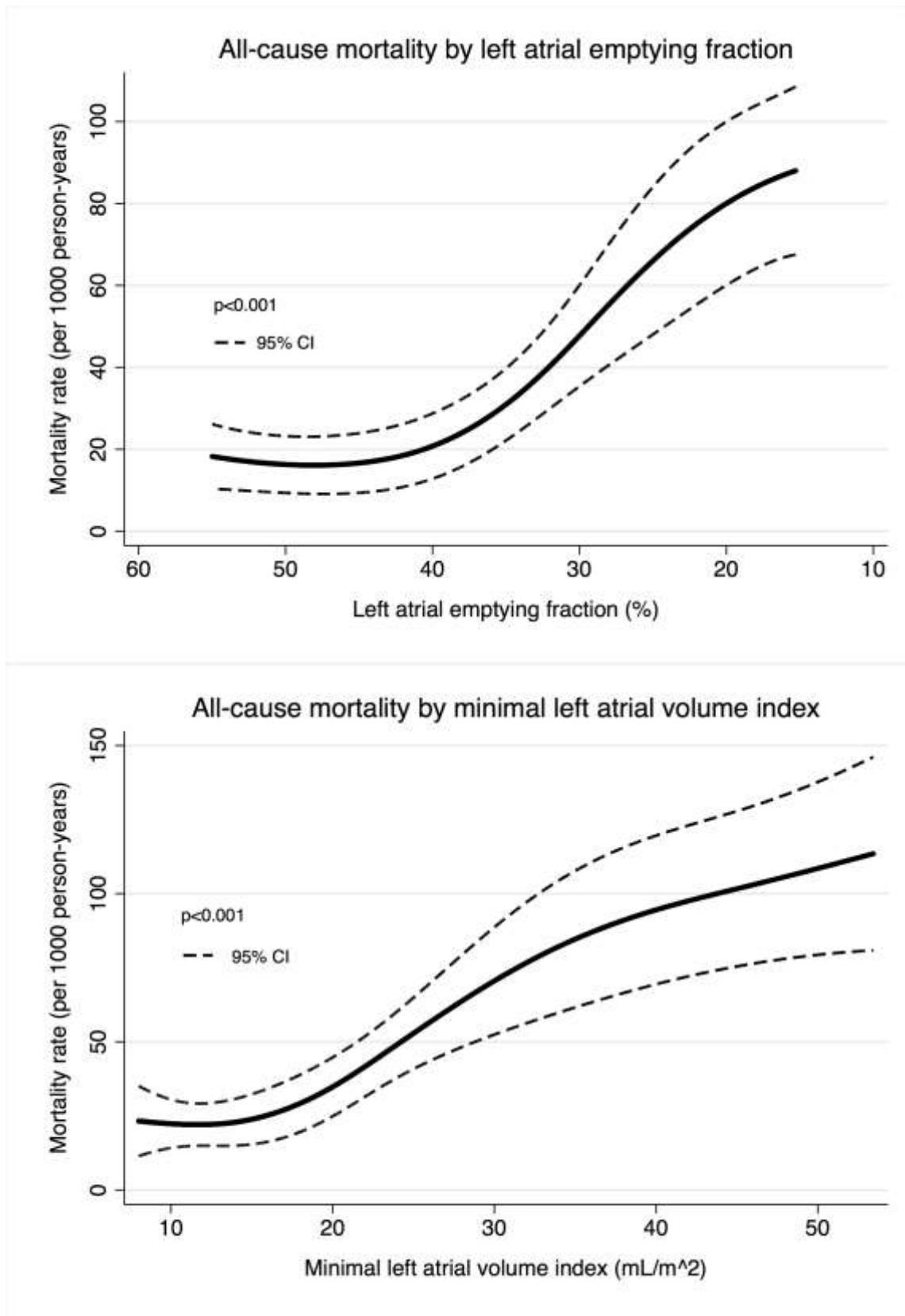| Demographics	All Patients	1. Tertile (LAEF < 28%)	2. Tertile (LAEF = 28-43%)	3. Tertile (LAEF > 43%)	P for trend
N	818	273	273	272	
Age (years)	66.4 (11.4)	68.6 (9.9)	66.0 (11.6)	64.5 (12.2)	<0.001
Male	600 (73.4%)	205 (75.1%)	198 (72.5%)	197 (72.4%)	0.48
Clinical Characteristics					
Systolic BP (mmHG)	129.9 (20.7)	126.9 (20.3)	131.3 (21.3)	131.6 (20.3)	0.008
Diastolic BP (mmHG)	74.7 (12.4)	74.5 (12.2)	74.9 (12.3)	74.6 (12.7)	0.96
Pulse Pressure (mmHG)	55.2 (16.8)	52.4 (16.1)	56.4 (17.7)	57.0 (16.3)	0.051
MAP (mmHG)	93.1 (13.5)	92.0 (13.4)	93.7 (13.5)	93.6 (13.6)	0.17
Hypertension	337 (41.2%)	107 (39.2%)	113 (41.4%)	117 (43.0%)	0.66
BMI (kg/m^2)	26.4 (4.8)	26.2 (4.1)	26.4 (4.8)	26.5 (5.3)	0.44
Diabetes Mellitus	93 (11.4%)	33 (12.1%)	29 (10.6%)	31 (11.4%)	0.80
Heart rate (BPM)	74 (16)	78 (17)	73 (15)	70 (13)	<0.001
Ischemic Cardiomyopathy	457 (55.9%)	135 (49.5%)	161 (59.0%)	161 (59.2%)	0.02
History of AMI	384 (46.9%)	111 (40.7%)	133 (48.7%)	140 (51.5%)	0.011
CABG	159 (19.4%)	56 (20.5%)	60 (22.0%)	43 (15.8%)	0.17
RAS Blockade	647 (79.1%)	218 (79.9%)	222 (81.3%)	207 (76.1%)	0.28
Beta Blocker	542 (66.3%)	183 (67.0%)	183 (67.0%)	176 (64.7%)	0.57
Spironolactone	122 (14.9%)	44 (16.1%)	33 (12.1%)	45 (16.5%)	0.89
Diuretics	412 (50.4%)	141 (51.6%)	141 (51.6%)	130 (47.8%)	0.37
Antiarrhythmics	37 (4.5%)	12 (4.4%)	12 (4.4%)	13 (4.8%)	0.83
Total Cholesterol (mmol/L)	4.46 (1.14)	4.44 (1.21)	4.43 (1.07)	4.51 (1.15)	0.49
Atrial Fibrillation	125 (15.3%)	93 (34.1%)	25 (9.2%)	7 (2.6%)	<0.001
Permanent Atrial Fibrillation	113 (13.8%)	87 (31.9%)	22 (8.1%)	4 (1.5%)	<0.001
Paroxysmal Atrial Fibrillation	12 (1.5%)	6 (2.2%)	3 (1.1%)	3 (1.1%)	0.47
Mitral Regurtitation					0.002
None	305 (37.3%	87 (31.9%)	109 (39.9%)	109 (40.1%)	
Mild	439 (53.7%)	148 (54.2%)	140 (51.3%)	151 (55.5%)	

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Moderate	68 (8.3)	35 (12.8%)	21 (7.7%)	12 (4.4%)	
Severe	6 (0.7%)	3 (1.1%)	3 (1.1%)	0 (0.0%)	
Echocardiography					
MinLAVI (ml/m^2)	21.1 (13.3)	32.6 (15.3)	18.8 (7.0)	11.9 (5.1)	<0.001
LAVI (ml/m^2)	30.9 (13.8)	39.0 (16.7)	28.9 (10.1)	25.0 (9.4)	<0.001
LVEF (%)	27.8 (9.1)	23.9 (9.0)	28.7 (8.6)	30.7 (8.4)	<0.001
GLS (%)	9.7 (3.3)	8.0 (2.8)	10.0 (3.2)	11.1 (3.3)	<0.001
TAPSE (cm)	1.9 (0.6)	1.6 (0.5)	1.9 (0.6)	2.1 (0.5)	<0.001
LVIDd (cm)	5.6 (1.0)	5.9 (1.0)	5.6 (1.0)	5.5 (0.9)	<0.001
LVMI (g/m^2)	120.9 (38.9)	128.4 (36.4)	120.2 (37.6)	114.1 (41.5)	<0.001
E (m/s)	0.81 (0.2)	0.94 (0.31)	0.81 (0.27)	0.71 (0.23)	<0.001
A* (m/s)	0.71 (0.26)	0.56 (0.28)	0.72 (0.28)	0.77 (0.23)	<0.001
E/A*	1.02 (0.74-1.65)	1.93 (1.09-2.93)	1.03 (0.79-1.60)	0.84 (0.67-1.18)	<0.001
DT (ms)	189 (79)	168 (74)	190 (72)	210 (81)	<0.001
e' (cm/s)	6.9 (2.5)	7.1 (2.7)	6.8 (2.3)	6.7 (2.5)	0.15
E/e'	11.8 (8.9-15.9)	12.9 (9.5-17.6)	11.3 (9.0-15.7)	10.5 (7.9-14.3)	<0.001

*Measured only in patients without atrial fibrillation, since no A wave is present in atrial fibrillation rhythm

BP, blood pressure; MAP, mean arterial pressure; BMI, body mass index; BPM, beats per minute; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; RAS, renin-angiotensin system; LAEF, left atrial emptying fraction; LAi, left atrial expansion index; MinLAVI, minimal left atrial volume indexed to body surface area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; LVIDd, left ventricular inner diameter at end diastole; LVMI, left ventricular mass index; DT, deceleration time.

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TABLE 2

Prediction of all-cause mortality using Cox regressions.

Unadjusted (818 patients; 121 events)	Hazard Ratio	P-value
LAEF (per 5% decrease)	HR 1.21, 95CI 1.14-1.29, C-stat: 0.675	<0.001
MinLAVI (per 5ml/m^2 increase)	HR 1.16, 95CI 1.12-1.21, C-stat: 0.661	<0.001
LAVI (per 5 ml/m^2 increase)	HR 1.14, 95CI 1.09-1.19, C-stat: 0.620	<0.001
Model 1 (817 patients; 121 events)	Hazard Ratio	P-value
LAEF (per 5% decrease)	HR 1.17, 95CI 1.1.10-1.25	<0.001
MinLAVI (per 5ml/m^2 increase)	HR 1.13, 95CI 1.07-1.18	<0.001
LAVI (per 5 ml/m^2 increase)	HR 1.10, 95CI 1.05-1.16	<0.001
Model 2 (727 patients; 106 events)	Hazard Ratio	P-value
LAEF (per 5% decrease)	HR 1.13, 95CI 1.05-1.23	0.002
MinLAVI (per 5ml/m^2 increase)	HR 1.11, 95CI 1.02-1.21	0.0018
LAVI (per 5 ml/m^2 increase)	HR 1.06, 95CI 0.98-1.16	0.16
Model 3 (727 patients; 106 events)	Hazard Ratio	P-value
LAEF (per 5% decrease)	HR 1.11, 95CI 1.01-1.23	0.033
MinLAVI (per 5ml/m^2 increase)	HR 1.03, 95CI 0.93-1.15	0.57

Model 1 is adjusted for age, sex, diabetes, mean arterial pressure, treatment with diuretics and atrial fibrillation.
Model 2 is adjusted for the same variables as model 1 with the addition of mitral regurtitation, LVEF, GLS, TAPSE, DT, E/e' and LVESV index. LAEF, left atrial emptying fraction; MinLAVI, minimal left atrial volume index; LAVI, left atrial volume index, LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; LVIDd, left ventricular inner diameter at end-diastole; LVMI, left ventricular mass index; DT, deceleration time of the E-wave; LVESV, left ventricular end-systolic volume.
Model 3 is identical to Model 2 with the addition that LAEF and MinLAVI were entered simultaneously into the same model.