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Left atrial reservoir strain as a predictor of cardiac outcome in patients with heart failure: the HaFaC cohort study

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Abstract

Background: The left atrium (LA) is a key player in the pathophysiology of systolic and diastolic heart failure (HF). Speckle tracking derived LA reservoir strain (LAS_r) can be used as a prognostic surrogate for elevated left ventricular filling pressure similar to NT-proBNP. The aim of the study is to investigate the correlation between LAS_r and NT-proBNP and its prognostic value with regards to the composite endpoint of HF hospitalization and all-cause mortality within 1 year.

Methods: Outpatients, sent to the echocardiography core lab because of HF, were enrolled into this study. Patients underwent a transthoracic echocardiographic examination, commercially available software was used to measure LAS_r. Blood samples were collected directly after the echocardiographic examination to determine NT-proBNP.

Results: We included 174 HF patients, 43% with reduced, 36% with mildly reduced, and 21% with preserved ejection fraction. The study population showed a strong inverse correlation between LAS_r and log-transformed NT-proBNP ($r = -0.75, p < 0.01$). Compared to NT-proBNP, LAS_r predicts the endpoint with a comparable specificity (83% vs. 84%), however with a lower sensitivity (70% vs. 61%).

Conclusion: LAS_r is inversely correlated with NT-proBNP and a good echocardiographic predictor for the composite endpoint of hospitalization and all-cause mortality in patients with HF.

Trial registration: <https://www.trialregister.nl/trial/7268>

Keywords: Left atrial strain, HFrEF, HFmrEF, HFpEF, NT-proBNP

Background

Heart failure (HF) is among the leading causes of morbidity and mortality worldwide [1]. Early recognition and prompt treatment of heart failure are crucial for the prognosis. Although HF is primarily a clinical diagnosis, N-terminal pro-B-type natriuretic peptide (NT-proBNP)

is a valuable diagnostic marker of HF given the fact that symptoms can be aspecific [2]. Patients with normal NT-proBNP levels are unlikely to have HF, contrary to patients with elevated levels who need further cardiac evaluation.

Echocardiography is the modality of choice to establish the diagnosis of HF. The classification is based primarily on measurement of left ventricular ejection fraction (LVEF) into HF with reduced ($\leq 40\%$), mildly reduced (41–49%), or preserved ($\geq 50\%$) ejection fraction [3]. Currently, the evaluation of HF is mainly focused on the left ventricle (LV). This is remarkable since left atrial (LA)

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volume and function has a pathophysiological significance in different types of HF [4, 5]. Accumulating evidence suggests an added value of measuring the left atrial reservoir strain (LAS_r) by speckle-tracking echocardiography for both diagnosis and prognosis of HF [6, 7]. Previous studies showed that LAS_r is around 40% in healthy controls [8] and that it is impaired in HF patients [6, 7]. Additionally, LAS_r can be used as a prognostic marker similar to NT-proBNP [9].

The aim of the study is to investigate the correlation between LAS_r and NT-proBNP and its prognostic value in an outpatient population with HF with regards to the composite endpoint of HF hospitalization and all-cause mortality within 1 year.

Methods

Study design

The present study was performed as part of the Heart Failure Classification (HaFaC) project (<https://www.trialregister.nl/trial/7268>). This prospective, non-randomized, observational, single-center study was designed to develop a HF classification based on objective measurement data. The local ethics committee and the Institutional Review Board approved the study (Medical Research Ethics Committees United study number NL60579.100.17) and all subjects gave written informed consent. The primary outcome was a composite of all-cause mortality or hospitalization for heart failure.

Population

From December 2017 to September 2019, patients referred to the Echocardiography Lab with HF based on the ESC guidelines [10] were prospectively included in the study. To be included, patients needed to be ≥ 18 years old and able to provide written informed consent. Exclusion criteria were: recent cardiothoracic surgery (≤ 90 days) or pregnancy. Patients were also excluded for further analysis in case of inadequate acoustic LA window on echocardiography (> 2 non-visible LA segments), and severe renal failure (glomerular filtration rate ≤ 30 mL/min, calculated by the CKD-EPI formula). Also patients with atrial fibrillation were excluded, because atrial fibrillation on its own induces LA remodeling and influences LAS_r . All patient data was entered into a prospective database, including demographical, clinical and echocardiographic variables, medications and laboratory biomarkers.

Echocardiographic evaluation

All patients underwent a comprehensive transthoracic echocardiographic examination using commercially available equipment (Philips iE33 or Philips EPIQ, Andover, MA, USA). Examinations were performed by 2

experienced and EACVI certified cardiac sonographers (SB or PH), blinded to other research data. Echocardiogram was stored as Digital Imaging and Communications in Medicine (DICOM) file on a secured server and analysed off-line using commercially available software (QLAB 13, Philips Healthcare, Eindhoven, the Netherlands). Standard 2D- and Doppler-echocardiographic measurements were performed following ASE/EACVI guidelines [11]. LVEF was calculated using the modified biplane Simpson's rule and maximum LA volume was calculated by the biplane method of disks at end-systole and indexed to body surface area (LAVI). The following parameters were used to determine diastolic dysfunction; average $E/e' > 14$, septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, tricuspid regurgitation velocity > 2.8 m/s, LAVI > 34 ml/m², pulmonary vein S/D ratio < 1 , mitral inflow velocities and ratio according to the published guidelines [11].

Speckle tracking echocardiography of the LA is a relatively new echocardiographic method. With dedicated software an unique pattern of speckles is identified within the LA wall and these speckles are tracked on frame-by-frame base throughout the cardiac cycle. The measured change in distance between the different speckles is used to calculate LA deformation. LA reservoir strain is a prognostic biomarker, which has been evaluated for patients with HF. Commercially available software (QLAB 13, Philips Healthcare, Eindhoven, the Netherlands) was used to measure LAS_r on non-foreshortened apical four- and two-chamber views of the LA with a frame rate of 60–80 frames per seconds. The LA endocardial border was automatically drawn followed by manual adjustment if required. The reference point for LA strain analysis was taken at the onset of the QRS-complex (R-R gating) (Fig. 1) [12].

Biomarker analysis

Blood samples were collected and analyzed directly after the echocardiographic examination while the patient was still in a supine position. Levels of NT-proBNP were determined at the department of Clinical Chemistry (Elecsys pro BNP II assay, Roche Diagnostics, Mannheim, DE) [13].

Follow-up

Patients were followed up at our outpatient clinic on a regular base by both clinical visits and telephone calls. All-cause mortality was recorded by consulting the Dutch civil registry. Information on HF hospitalization during the 1-year follow-up period was obtained from a systematic review of all hospital admissions performed by an independent reviewer unaware of clinical and echocardiographic data.

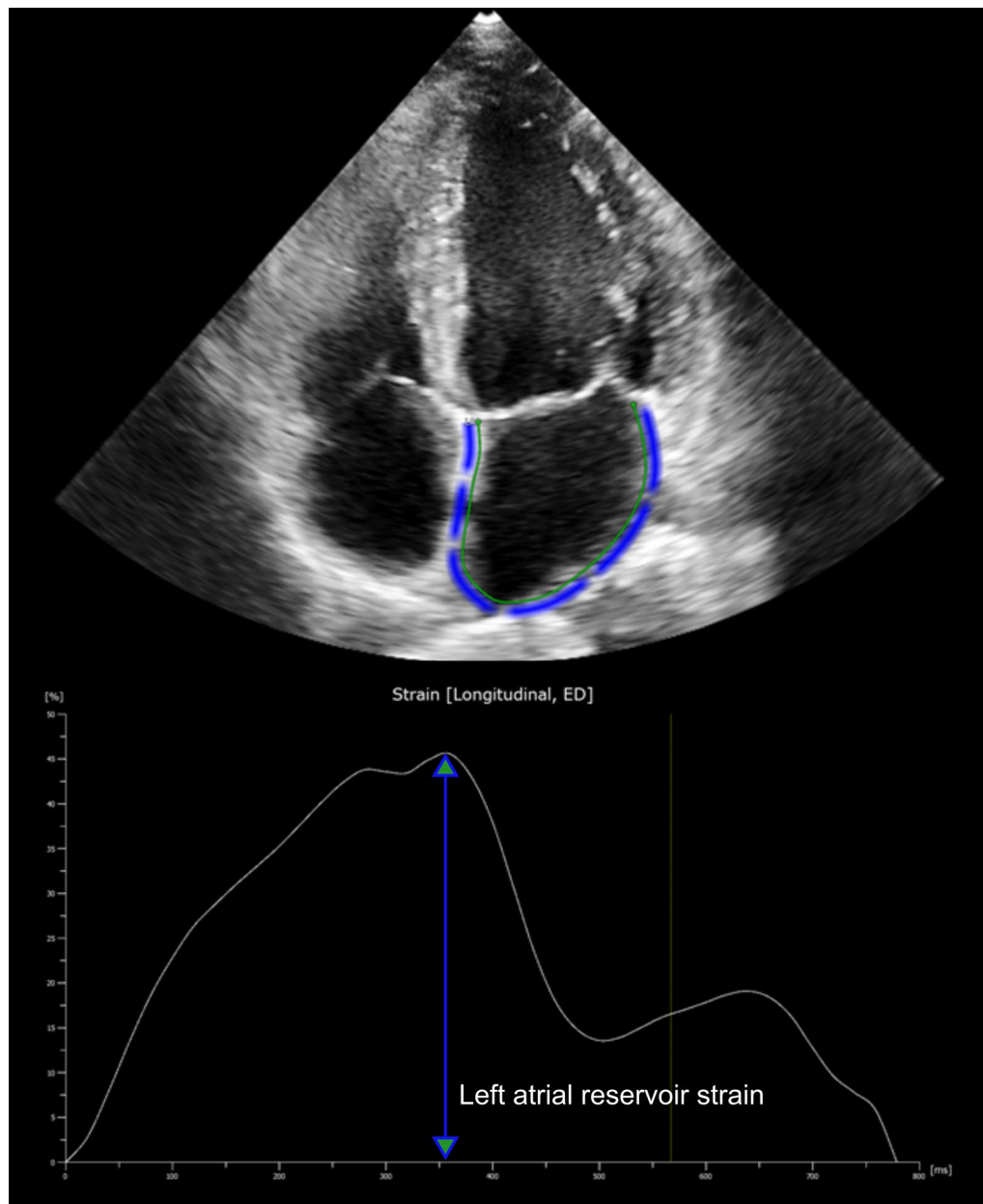


Fig. 1 Assessment of left atrial reservoir strain by 2D speckle-tracking echocardiography. This figure shows a non-foreshortened apical four-chamber view of the left atrium. Zero strain reference was set at end-diastole. Arrow represents left atrium reservoir strain (LAS_r)

Statistical analysis

Three groups were defined: HF with preserved ejection fraction (HFpEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with reduced ejection fraction (HFrEF) [10]. For continuous variables, normality of distribution was assessed with the Shapiro–Wilk’s test. Normal and skewed continuous variables are presented as means with standard deviation (SD) and medians with interquartile range [IQR], respectively. Statistical

comparisons of the three HF subgroups were made using one way ANOVA for normally distributed data or an Kruskal Wallis test for non-normally distributed data. Categorical variables were expressed as proportions and compared using a chi-squared test, or Fishers exact test when the number of positive cases in at least one of the heart failure categories is less than five. Multiple pairwise-comparison between subgroups was performed using Tukey Honest Significant Differences method for

normally distributed continuous variables, *p* values of the other multiple comparisons were corrected using Benjamini–Hochberg correction. A *p* value of less than 0.05 was considered to indicate statistical significance. The correlation between LAS_r and NT-proBNP were examined by Pearson’s correlation analysis. Prognostic value of the different parameters was assessed by a receiver-operator curve (ROC-curve), the optimal cut-off point was determined by maximizing the Youden Index. Kaplan–Meier curves are shown for the time-to-event distribution. All analyses were performed using R version 4.0.5 and Rstudio 1.2.1335 (R foundation for Statistical Computing, Vienna, Austria; RStudio InC, Boston, MA).

Results

Patient selection

Two hundred sixty-one outpatients were sent to the echocardiography Core Lab because of HF. Eighty-seven patients were excluded because of atrial fibrillation (n = 63), severe renal failure (n = 4) and insufficient

imaging quality for LAS_r analysis (n = 20). The remaining 174 patients were enrolled into the study; there were 37 patients with HFpEF (21%), 62 with HFmrEF (36%), and 75 with HFrEF (43%) (Fig. 2).

Baseline characteristics

Table 1 shows general characteristics of the total study population and HF subgroups. Patients were predominantly male (69%) with a median age of 68 years. The majority of patients were treated with beta blockers (79%), renin-angiotensin system antagonists (79%), and to a lesser extent with mineralocorticoid antagonists (31%) and loop diuretics (41%).

On echocardiography, median LVEF was 44% [34–49], median left ventricular end-diastolic volume (LVEDV) 142 ml [100–195], and median LAVI 37 ml/m² [28–47] with a median LAS_r 27% [20–35]. On subgroup analysis, patients with HFrEF had significantly larger LVEDV and prevalence of mitral valve regurgitation was higher compared with HFmrEF (*p* < 0.01). LA size did not differ

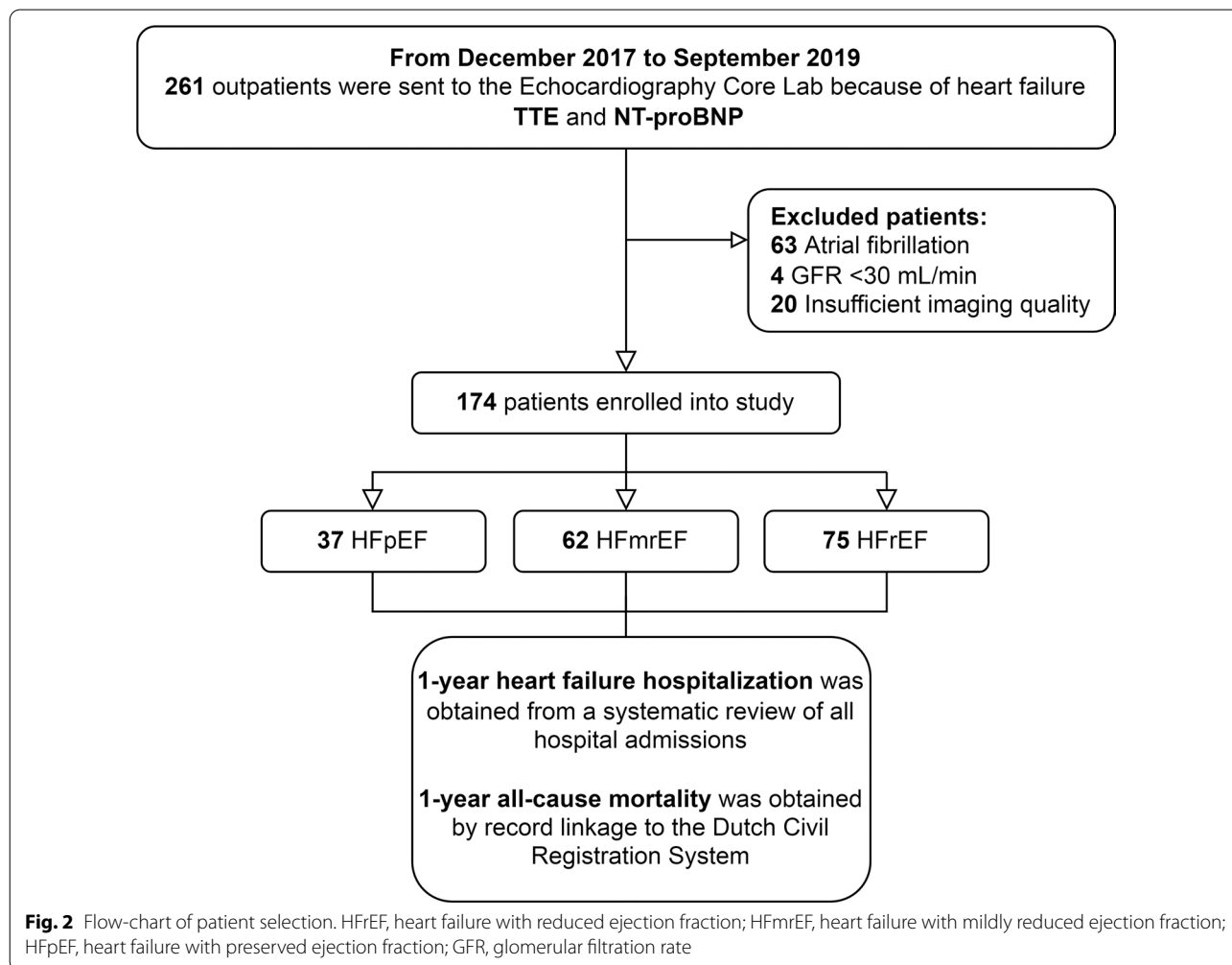


Fig. 2 Flow-chart of patient selection. HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; GFR, glomerular filtration rate

Table 1 General characteristics

	Total group (n = 174)	HFpEF (n = 37)	HFmrEF (n = 62)	HFrEF (n = 75)	p value
<i>Baseline demographics</i>					
Age—yr	68 [59–75]	74 [70–80]	62 [56–68]	68 [60–76]	< 0.01
Male	120 [69%]	18 [49%]	42 [68%]	60 [80%]	< 0.01
Body mass index—kg/m ²	26 [24–29]	28 [26–31]	26 [24–28]	26 [24–29]	0.03
Hypertension	88 [51%]	28 [76%]	28 [45%]	32 [43%]	< 0.01
Systolic blood pressure—mmHg	132 [118–145]	142 [132–164]	131 [120–141]	129 [116–141]	< 0.01
Diastolic blood pressure—mmHg	76 [71–85]	79 [70–88]	79 [72–86]	74 [71–80]	0.13
Heart Rate—bpm	66 [58–78]	68 [60–82]	69 [59–75]	65 [57–80]	0.76
Diabetes Mellitus	26 [15%]	3 [8%]	8 [13%]	15 [20%]	0.23
COPD	21 [12%]	8 [22%]	6 [10%]	7 [9%]	0.14
Chronic kidney disease	21 [12%]	6 [16%]	4 [6%]	11 [15%]	0.23
Coronary artery disease	67 [39%]	6 [16%]	23 [37%]	38 [51%]	< 0.01
<i>NYHA functional class</i>					
I	61 [37%]	8 [24%]	33 [54%]	20 [28%]	< 0.01
II	62 [37%]	13 [38%]	17 [28%]	32 [44%]	0.14
III	40 [24%]	11 [32%]	9 [15%]	20 [28%]	0.09
IV	4 [2%]	2 [6%]	2 [3%]	0 [0%]	0.08
<i>Heart failure medication</i>					
Beta-blocker	137 [79%]	26 [70%]	50 [81%]	61 [82%]	0.31
Renin-angiotensin system antagonist	137 [79%]	26 [70%]	52 [84%]	59 [80%]	0.27
Mineralocorticoid antagonist	54 [31%]	6 [16%]	19 [31%]	29 [39%]	0.05
Nephrilysine Inhibitor	5 [3%]	0 [0%]	2 [3%]	3 [4%]	0.72
Loop diuretics	71 [41%]	17 [46%]	16 [26%]	38 [51%]	0.01
<i>Endpoints</i>					
Heart Failure Hospitalization	18 [10%]	3 [8%]	3 [5%]	12 [16%]	0.09
Mortality	11 [6%]	3 [8%]	1 [2%]	7 [9%]	0.12
Composite endpoint	23 [13%]	4 [11%]	3 [5%]	16 [21%]	0.02

p values < 0.05 are shown as bold to indicate statistical significance

significantly between HFrEF and HFpEF patients, however LAS_r was lower in the HFrEF compared with HFpEF and HFmrEF patients ($p = 0.02$ and $p < 0.01$, respectively) (Table 2).

Median NT-proBNP (568 pg/mL [276–1114]) was significantly higher in the HFrEF group (HFmrEF $p < 0.01$, HFpEF $p = 0.02$) (Table 2).

Correlation between biomarkers and LAS_r

The study population showed a moderate inverse correlation between NT-proBNP and LAS_r ($r = -0.55$, $p < 0.01$), which improved after ¹⁰log-transformation of NT-proBNP ($r = -0.75$, $p < 0.01$) (Fig. 3). For the HF subgroups, no significant differences were found between the degree of correlation between ¹⁰log-transformed NT-proBNP and LAS_r .

Correlation between conventional echocardiographic diastolic parameters and LAS_r

Both deceleration time of early mitral inflow (E) and early diastolic mitral annular velocity (e') had a weak correlation with LAS_r ($r = 0.35$ and $r = 0.24$, respectively). E/A and E/e' ratio had a moderate inverse correlation with LAS_r ($r = -0.44$ and $r = -0.42$, respectively).

Follow-up

Twenty-three patients (13%) reached the composite endpoint of all-cause mortality and heart failure hospitalization (Table 1).

Prognostic value of LAS_r and biomarkers

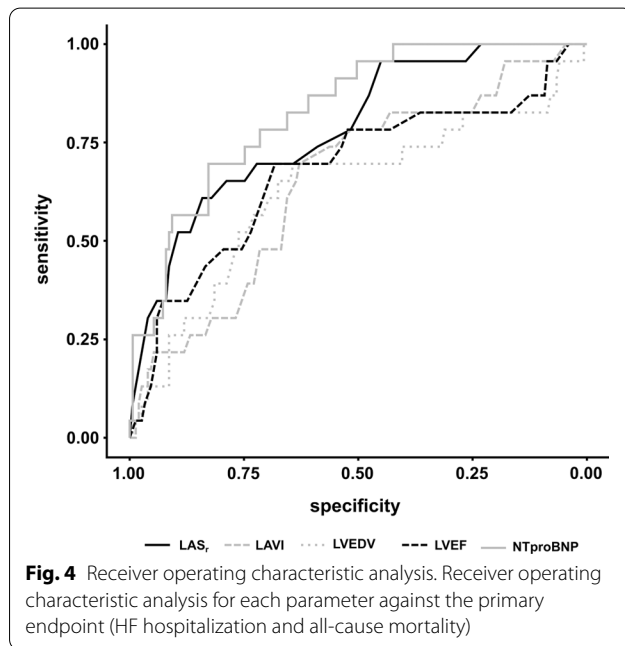
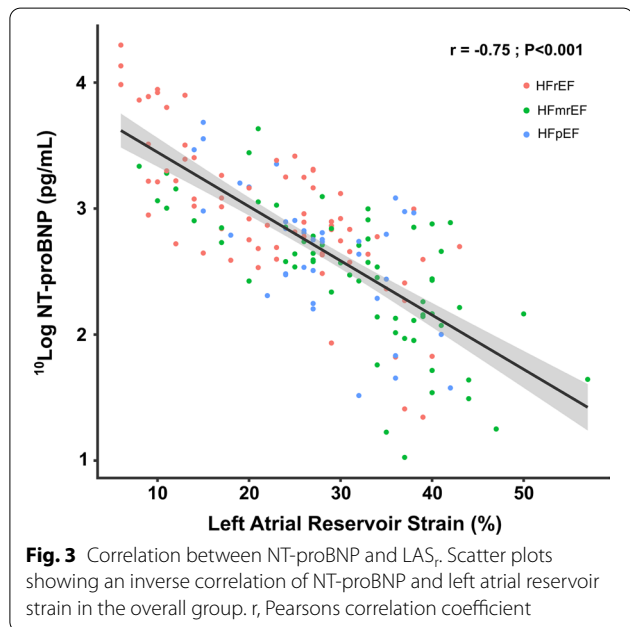
Results of receiver operating characteristic (ROC) analysis for all predictors of the endpoint are shown in Fig. 4 and Table 3. NT-proBNP showed the highest area under the ROC curve (AUC 0.83) to predict the primary endpoint of death or heart failure hospitalization up to 12 months of follow-up. As for echocardiographic

Table 2 Echocardiographic and laboratory parameters

	Total group (n = 174)	HFpEF (n = 37)	HFmrEF (n = 62)	HFrEF (n = 75)	p value
<i>LV parameters</i>					
LVEDV—ml	142 [100–195]	92 [68–115]	134 [98–168]	194 [151–230]	< 0.01
LVESV—ml	82 [52–121]	38 [30–48]	70 [53–94]	128 [102–164]	< 0.01
LV mass index—gram/m2	106 [89–132]	94 [82–120]	101 [86–121]	120 [97–139]	< 0.01
LVEF—%	44 [34–49]	57 [56–60]	47 [45–48]	33 [26–38]	< 0.01
<i>LA parameters</i>					
LAVI—ml/m2	37 [28–47]	39 [32–46]	32 [25–40]	41 [34–52]	< 0.01
LAS _r —%	27 [20–35]	27 [24–32]	33 [26–39]	23 [14–30]	< 0.01
<i>RV parameters</i>					
TAPSE—cm	2 [0.47]	2.1 [0.48]	2.0 [0.40]	1.9 [0.50]	0.08
Peak TR gradient—mmHg*	26 [20–34]	30 [26–38]	21 [18–5]	29 [22–36]	< 0.01
<i>Valvular heart disease</i>					
Aortic stenosis ≥ moderate	6 [3%]	2 [5%]	0 [0%]	4 [5%]	0.12
Aortic regurgitation ≥ moderate	3 [2%]	0 [0%]	2 [3%]	1 [1%]	0.60
Mitral stenosis ≥ moderate	0 [0%]	0 [0%]	0 [0%]	0 [0%]	-
Mitral regurgitation ≥ moderate	31 [18%]	5 [14%]	4 [6%]	22 [29%]	< 0.01
Tricuspid regurgitation ≥ moderate	8 [5%]	1 [3%]	0 [0%]	7 [9%]	0.02
<i>Laboratory biomarkers</i>					
CKD-EPI—mL/min	68 (22)	59 (16)	74 (21)	67 (23)	< 0.01
NT-proBNP—pg/mL	568 [276–1114]	568 [298–925]	357 [138–706]	788 [449–1913]	< 0.01

p values < 0.05 are shown as bold to indicate statistical significance

LVEDV = left ventricular end-systolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, LAVI = left atrial volume index, LAS_r = left atrial reservoir strain, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, NT-proBNP = N-terminal pro-B-type natriuretic peptide, *data available in 75 patients (39%)



parameters, LAS_r outperformed LVEF with a AUC-value of 0.79. The AUC of LAS_r differed significantly

from LAVI and LVEDV ($p < 0.01$ and $p = 0.03$), however not from LVEF and NT-proBNP ($p = 0.10$ and $p = 0.25$).

Table 3 Receiver operating characteristic to predict adverse events

	Cut-off	AUC	Sensitivity (%)	Specificity (%)
<i>Echocardiographic parameters</i>				
LVEDV—ml	≥ 166	0.63	70	64
LVEF—%	≤ 38	0.68	70	68
LAVI—ml/m ²	≥ 40	0.65	70	63
LAS _r —%	≤ 17	0.79	61	84
<i>Laboratory parameter</i>				
NT-proBNP—pg/mL	≥ 1191	0.83	70	83

LVEDV = left ventricular end-systolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, LAVI = left atrial volume index, LAS_r = left atrial reservoir strain, NT-proBNP = N-terminal pro-B-type natriuretic peptide

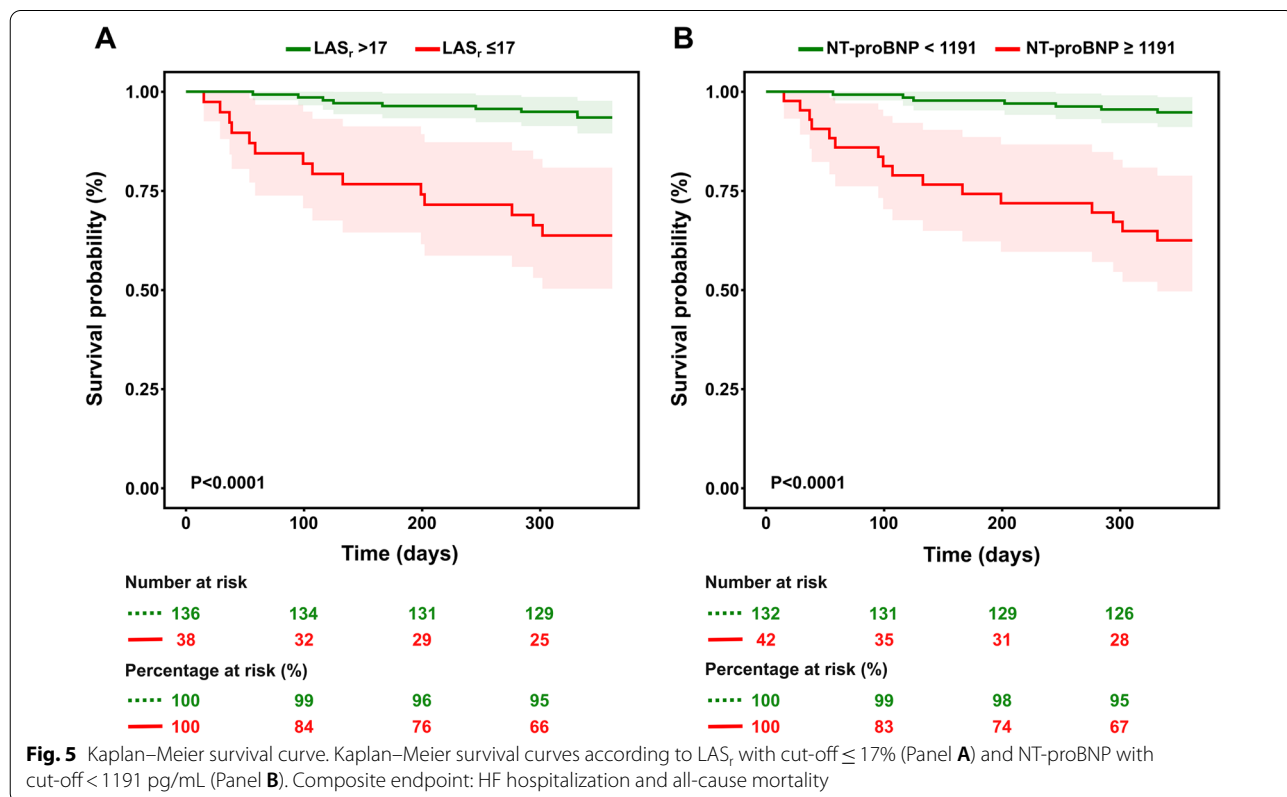
Figure 5 shows survival curves by Kaplan Meier analysis for patients stratified by LAS_r (Panel A) and NT-proBNP (Panel B). Patients with LAS_r ≤ 17% showed significantly worse survival than patients with LAS_r > 17%. Patients with NT-proBNP ≥ 1191 pg/mL also showed significantly worse survival.

Discussion

The key findings of the present study are as follows. First, LAS_r is a strong echocardiographic predictor of the composite endpoint of HF hospitalization and all-cause mortality. Compared to NT-proBNP, LAS_r predicts the endpoint with a comparable specificity (83% vs. 84%), however with a lower sensitivity (70% vs. 61%). Also, LAS_r correlates strongly with ¹⁰log-transformed NT-proBNP levels.

LAS_r has enhanced prognostic value beyond conventional echocardiographic measures to discriminate which heart failure patients are at greater risk for hospital admission or death. For HF subgroups, Carluccio et al. [15] and Freed et al. [16] showed that assessment of LAS_r by speckle-tracking strain echocardiography had powerful prognostication in patients with HF_rEF and HF_pEF, respectively.

Although limited in number, previous studies that investigated the correlation between NT-proBNP and LAS_r are in line with our results. Al Saikhan [7] demonstrated a modest inverse correlation in patients with both HF_pEF (r = -0.57) and HF_mEF (r = -0.53). Another study showed that LAS_r had moderate inverse correlation with NT-proBNP (r = -0.42) [14]. In both studies, the correlation between LAS_r and a log-transformation of NT-proBNP levels was not reported, although it has



been shown that plasma concentrations of NT-proBNP follow a log-normal distribution in patients with HF [13]. Prastaro [5] evaluated the relationship between NT-proBNP and LA function in patient with HFrEF. In their study, LA function was based on measuring fractional active and total emptying from M- and B-mode images and showed a significant correlation between NT-proBNP and LA function [5].

LA reservoir strain and elevated LV filling pressure

Assessment of LV filling pressure has important diagnostic and prognostic implications in patients with HF [10, 11]. Although right-sided cardiac catheterization is the gold standard to determine LV filling pressure, it is unattractive for routine clinical use given its invasiveness. In the continuing search for non-invasive markers to estimate LV filling pressure, NT-proBNP provides a reliable estimation, especially for left ventricular end-diastolic pressure (LVEDP) [17]. The prognostic value of NT-proBNP is well established [9, 10] and the results of our study are in line with previous reports. The LA, on the other hand, is more and more acknowledged as key player in the pathophysiology of systolic and diastolic HF [18]. Indeed, elevated LV filling pressure results in pressure overload that induces LA failure characterized by dilation and decrease in reservoir function. Wakami [19] showed that an increase in LVEDP is associated with a decrease in LAS_r . Moreover, LAS_r can accurately categorize patients based on a normal or elevated LV filling pressures [14, 20].

LA reservoir strain and heart failure

In HFpEF a fortiori, elevated filling pressures are the main physiologic consequence of the diastolic dysfunction [21]. Current guidelines [11] use various echocardiographic parameters for determination of diastolic dysfunction. LAS_r provides potentially clinical relevance in the detection of LV diastolic dysfunction, because LAS_r detects subtle dysfunction, even before the LA begins to enlarge [22]. LAS_r decreases in a linear fashion as LV diastolic dysfunction progresses [23]. In line with this, the latest EACVI document [24] encourages the use of LA strain in the assessment of diastolic function and filling pressures in HFpEF, however LAS_r should not be used in patients with atrial fibrillation [25]. We previously showed a relationship between increased coronary microvascular resistance and reduced LAS_r , that seemed to precede conventional measures of LV diastolic dysfunction [26]. Moreover, LAS_r is not only influenced by diastolic, but also by systolic LV function. As LA expansion is also determined by the base-to-apex displacement during LV systolic contraction [27], any condition that influences LV myocardial function is expected to

influence LAS_r . Thus, LAS_r correlates with both LV filling pressures and systolic performance.

Clinical implications

The LA seems to have a central role in HF. LA function can be easily studied using speckle-tracking strain echocardiography. The LA strain measurements should be included in the standard evaluation of outpatients with heart failure, because it can stratify their risk for hospital admission and death more reliable than LVEF. Further research is needed if a closer follow-up of these patients will reduce their morbidity and mortality.

Study limitations

Although the current study is based on a real-world, prospective, observational data of an outpatient HF population referred to the echocardiography lab, the subgroups of different HF types were relatively small. Second, the number of events was too small to perform a multivariate Cox regression analysis. A logistic regression with NT-proBNP and echocardiographic parameters did not result in an improvement in AUC. However, follow-up research with a larger population and more events is needed to draw conclusions on the AUC of combined laboratory and echocardiographic parameters. Third, the length of follow-up in the current study was limited to 1 year, so we were unable to determine the long-term prognostic value of LAS_r . Fourth, in this prospective study a combined endpoint of HF hospitalization and all-cause mortality has been chosen. Cardiovascular death might have been a stronger endpoint. However, the exact cause of death was not known in all of our HF patients. Finally, in 7% of the study population, LAS_r could not be analyzed due to poor image quality.

Conclusions

LAS_r is a strong echocardiographic predictor of the composite endpoint of HF hospitalization and mortality. LAS_r is inversely correlated with NT-proBNP and predicts the endpoint with a comparable specificity.

Abbreviations

HF: Heart failure; HFmrEf: Heart failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; LA: Left atrial; LAS_r : Left atrial reservoir strain; LAVI: Left atrial volume indexed to body surface area; LV: Left ventricle; LVEDP: Left ventricular end-diastolic pressure; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

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Authors' contributions

S.B. and J.S.: planning, conducting, patient enrollment, data collection, article writing and submission. S.L.: planning, conducting, patient enrollment and

data collection. N.R: article writing. A.B: planning, article writing. L.D: patient enrollment, article writing. V.S: planning, data collection and article writing. P.H: planning, conducting, patient enrollment, data collection and article writing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The investigation complied with the principles of the Declaration of Helsinki and was approved by the Catharina hospital ethics committee and the Institutional Review Board (Medical Research Ethics Committees United study number NL60579.100.17) and all subjects gave written informed consent.

Consent for publication

Not applicable.

Competing interests

None.

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