

# Ratio of End-Systolic Volume to Left Atrial Area Is a Solid Benchmark of Systolic Dysfunction in Non-Ischemic Cardiomyopathies

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# Ratio of End-Systolic Volume to Left Atrial Area Is a Solid Benchmark of Systolic Dysfunction in Non-Ischemic Cardiomyopathies

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Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** Impairment of systolic function and late gadolinium enhancement (LGE) are well-known negative prognostic markers in non-ischemic cardiomyopathies (NICMPs). There is limited knowledge of the geometrical rearrangements of the ventricle volumes over size of the left atrium and their connections with systolic dysfunction and existence of LGE.

**Material/Methods:** Consecutive cases of NICMPs with impaired systolic function and controls were included from a computerized database of cardiac magnetic resonance exams for a 2.5-year period. Ratios made from volumetric parameters over left atrial area (LAA) area were calculated.





**Results:** Our study included 205 cases referred to cardiac magnetic resonance (CMR); age was 48.7±17.0 years (range 15.2–80.4), male-to-female ratio 137 (66.8%): 68 (33.2%), (both p>0.05). LGE was significantly correlated with impairment of systolic function (Rho CC=0.395; p<0.001). For detection of systolic impairment, a critical value of end-systolic-volume (ESV)/LAA of ≥2.7 had an area under curve (AUC) of 0.902 (0.853–0.939), p<0.001; stroke-volume (SV)/LAA ≤3.0 had AUC=0.782(0.719–0.837), p<0.001, and end-diastolic volume (EDV)/LAA <7.4 had an AUC of 0.671 (0.602–0.735); p<0.001. In analyses of LGE, a value of SV/LAA of ≤3.0 had an AUC of 0.681 (0.612–0.744), p<0.001; while ESV/LAA and EDV/LAA were not significant (both p<0.05). ESV/LAA was correlated with systolic dysfunction (Rho-correlation-coefficient: 0.688; p<0.001) and existence of linear midventricular LGE stripe (Rho-CC=0.446; p<0.001).

**Conclusions:** ESV/LAA was the most effective for detection of systolic impairment and was associated with the existence of LGE. Prospective validation for clinical applicability and prognostic relations are warranted in future studies.

**MeSH Keywords:** **Atrial Function, Left • Cardiomyopathy, Dilated • Cardiomyopathy, Hypertrophic • Contrast Media • Diffusion Magnetic Resonance Imaging • Heart Failure**

**Abbreviations:** **NICMP** – non-ischemic cardiomyopathy; **CMR** – cardiac magnetic resonance imaging; **ESV** – end-systolic volume; **EDV** – end-diastolic volume; **SV** – stroke volume; **LAA** – left atrial area; **LGE** – late gadolinium enhancement; **CMR** – cardiac magnetic resonance; **AUC** – area under curve; **LVEF** – left ventricle ejection fraction; **HASTE** – half-Fourier acquisition single-shot turbo-spin echo; **SSFP** – steady-state free precession; **STIR** – short-tau inversion-recovery; **TSE** – turbo-spin echo; **ROC** – receiver operating curve; **Rho-CC** – Spearman's rank correlation coefficient

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## Background

Non-ischemic cardiomyopathies (NICMPs) are of low prevalence in the general population [1]. Prognosis is poor in many of these patients due to risk of arrhythmias, heart failure, and sudden cardiac death [2]. NICMPs are becoming an increasingly important chronic condition that impairs quality of life, causes numerous disabilities, and has high medical costs of treatment [3]. Cardiac magnetic resonance (CMR) is a well-respected imaging tool, which has diagnostic value and a profound clinical impact on therapeutic management of patients and prognostic outcomes [4]. Due to good resolution, availability of tissue characterizations, 3-dimensional planimetry, and being the most precise tool for noninvasive assessment of systolic function, it is reasonable to expect that further innovative clinical applications of CMR will be emerging in NICMPs [4,5].

Ventricular geometry is a useful diagnostic and prognostic tool in numerous heart diseases and conditions. Remodeling of the ventricle was found to be connected with disease stage and symptomatology in patients with Anderson Fabry disease [6]. Similarly, changes in ventricle geometry were identified as a landmark of infrastructural changes caused by arterial hypertension and obesity [7]. Moreover, the prevalence of arrhythmias and activity of implanted cardioversion defibrillators were also found to be associated with left ventricle shape [8]. Sphericity of the left ventricle is closely connected with ejection fraction and brain natriuretic peptide concentrations [9]. These geometric changes could as well in part be responsible for non-scarring perfusion deficits seen in non-ischemic cardiomyopathies [10]. The left atrium (LA) is also profoundly associated with systolic or diastolic function and is a promising diagnostic parameter [11,12]. Dimensions and contractile function of the left atrium carry independent prognostic information in patients with new-onset heart failure [13,14]. Currently, there are no studies on associations between left atrial size and left ventricle volume. We hypothesized that changes in ratio of end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) of the left ventricle to left atrial dimensions reflect impairment of systolic function or existence of late gadolinium enhancement; the latter also has well known prognostic implications [15,16].

The aim of our study was to analyze the association between individual volumetric parameters over left atrial area and impairment of systolic function or existence of late gadolinium enhancement in patients with non-ischemic cardiomyopathy and in healthy controls.

## Material and Methods

This study was performed in accord with the Declaration of Helsinki and the good clinical practice guidelines. Patients were included after signing the informed consent before imaging data acquisition. The study was not sponsored and there were no additional sources of funding, compensations, or in-kind type of financing. The study was approved by our hospital's Ethics Committee.

Imaging data on patients were recruited from CMR computer data base, for 2.5-year period (1470 exams). Patients with non-ischemic cardiomyopathy and systolic dysfunction, for purposes of this study defined with left ventricle ejection fraction (LVEF) <50% were consecutively included. Control group was made up from matching sample of cases from same period with no structural heart disease. Study did not include patients with significant chest wall deformities, cardiac tumors, sarcoidosis, congenital heart disease, previous heart surgery, ischemic heart disease (known coronary artery disease with at least one vessel having atherosclerotic lesion >30%; non-negative adenosine stress testing or with existent ischemic type of late gadolinium enhancement). Geometric ratios for purposes of this study were developed by study principal investigator (MB). Ratios were made up from left ventricle end-systolic volume (ESV), end diastolic value (EDV) and stroke volume (SV) where each was divided with left atria area (LAA), obtained from standard 4 chamber view cine sequences at end systole, and those were calculated for all cases included in the study.

Imaging studies were performed on 1.5 T Magnetom Avanto, Siemens® (Erlangen, Germany, EU), applying Body Matrix chest and spine coil, obtaining sequences using ECG gating and respiratory control. Imaging protocol consisted of setting localizers, Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) sequences, steady-state free precession (SSFP) of standard heart 2, 4, 3, chamber planes and 6-mm stack of short axial slices, with adding of right ventricle and its outflow tract in case of clinical question. Those were followed by short-tau inversion-recovery (STIR) or turbo spin-echo (TSE) T1 and in cases with clinical question also the T2 sequences dark blood, followed by fat saturation sequences. Gadolinium contrast was applied at a dose 0.2 mL/kg (0.1 mmol/kg). An intravenous bolus of Omniscan® [Gadodiamide] or Dotarem® [gadoterate meglumine] was applied, prior inversion time recovery scout, with acquisition of phase-sensitive inversion-recovery (PSIR) and STIR late gadolinium enhancement (LGE) sequences at 20–30 min after contrast application. Postprocessing analyzes were done on standard Siemens AG- NUMARIS/4, Syngo MR B17® software (Erlangen, Germany, EU) and volumetric measurements were made using Siemens AG- Syngo Console VA 30 Argus®, by 2 high-throughput cardiologists (performing over 400 exams per year) and a radiologist. The standard diagnostic

**Table 1.** Differences and correlations of diagnostic parameters based on preservation of left ventricle systolic function.

	Preserved LVEF (n=138)	Impaired LVEF (n=67)	Mann-Whitney U	Correlation with LVEF	
	Mean ±SD	Mean ±SD		Rho CC	p
LVEDD (cm)	5.2±0.6	6.2±1.0	<b>&lt;0.001</b>	-0.590	<b>&lt;0.001</b>
IVS (cm)	1.4±0.6	1.2±0.3	<b>&lt;0.001</b>	0.238	<b>0.001</b>
RV (cm)	3.7±0.7	3.62±0.9	0.389	-0.068	0.335
LA (cm <sup>2</sup> )	25.8±6.6	30.8±10.2	<b>0.001</b>	-0.185	<b>0.008</b>
RA (cm <sup>2</sup> )	24.2±6.6	26.3±8.3	0.171	-0.170	<b>0.015</b>
LVEF (%)	62.1±5.3	35.6±12.1	<b>&lt;0.001</b>	n/a	n/a
EDV (mL)	142.1±39.2	215.0±100.4	<b>&lt;0.001</b>	-0.557	<b>&lt;0.001</b>
ESV (mL)	54.7±24.5	151.7±107.3	<b>&lt;0.001</b>	-0.862	<b>&lt;0.001</b>
SV (mL)	88.6±23.1	96.6±22.9	<b>&lt;0.001</b>	0.460	<b>&lt;0.001</b>
MM (gram)	125.2±46.6	144.7±60.2	<b>0.015</b>	-0.113	0.107

LVEF (%) – left ventricle ejection fraction; Rho CC – Spearman's rank correlation coefficient [Rho]; LVEDD (cm) – left ventricle end-diastolic dimension in 4-chamber view; IVS (cm) – interventricular septum thickness in 4-chamber view; RV (cm) – right ventricle end-diastolic dimension in 4-chamber view; LA and RA (cm<sup>2</sup>) – left and right atrial area in square centimeters in 4-chamber view; EDV (mL) – end-diastolic volume; ESV (mL) – end-systolic volume; SV (mL) – stroke volume; MM (gram) – myocardial mass in end-diastole. Data shown as means and standard deviations (SD). Statistically significant values (p<0.05) presented in bolded text.

report included referring cardiologist clinical questions, interpretation of all planes, sequences, tissue analyzes, and volumetrics, dedicated measurements of myocardial thickness in trabecula and solid part, indirect analyzes of valvular function, late gadolinium enhancement, and conclusion of exam, with final interpretation of results using guidelines and standardized myocardial segmentation with 17 divisions.

Sample size calculation was estimated using one-way ANOVA, with 95% confidence intervals, for 4 groups and considering random effects. Population and studied numeric groups were analyzed using descriptive statistics and are presented as means and standard deviations. Group data analyses were done using the chi-square test. Numeric variables were analyzed for differences by Mann-Whitney U test and volumes over LAA ratios to studied etiologies of controls were assessed using the Kruskal-Wallis test. Connections of studied CMR parameters with clinical data were done by Spearman's rho. We assessed the diagnostic potential of volumes over left atrial dimensions for characterization of impaired systolic function, defined with left ventricle ejection fraction (LVEF) cutoff point set at 50%, using the binomial regression model and receiver operator curve analyzes (ROC). P value less than 0.05 was considered significant. Statistical analyses were done by an experienced statistician using IBM-SPSS12® v 20 (IBM, Chicago, IL, USA) MedCalc v. 12.2® for Windows (MedCalc software co, Belgium, EU) and Statistica 10® for Windows (StatSoft, Tulsa, OK, USA).

## Results

### Studied sample

This study included 205 cases referred to CMR during a 2.5-year period (statistically estimated sample size; n=199). Mean age was 48.7±17.0 years (range 15.2–80.4) and male-to-female ratio was 137 (66.8%) to 68 (33.2%), respectively. There were 67 (32.7%) consecutive patients with non-ischemic cardiomyopathy and impaired systolic function. The leading diagnoses were: 66 (32.7%) with hypertrophic cardiomyopathy, 29 (14.1%) with dilated cardiomyopathy, and 45 (22.0%) with left ventricular non-compaction. The control group comprised 65 (31.7%) matching consecutive cases from the time same period, with no structural heart disease. There was no significant difference in sex or age (p=0.083, p=0.214, respectively) of studied cases within groups of preserved and impaired systolic function, while there was a significant difference in existence of LGE (1.6% versus 78.6%, respectively; p<0.001). LGE was significantly correlated with impairment of left ventricle systolic function (Rho CC=0.395; p<0.001).

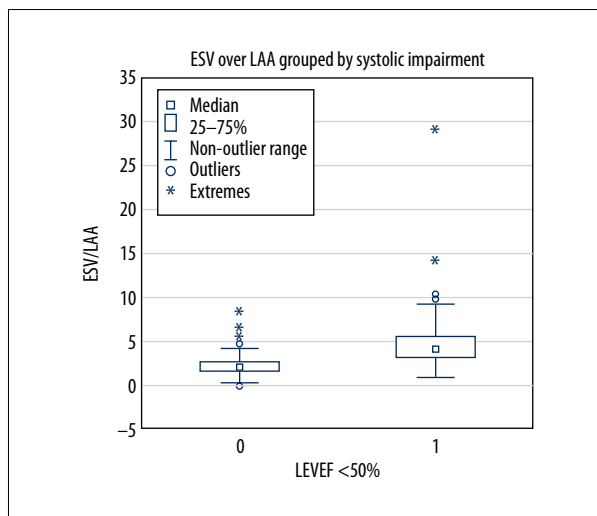
Differences and correlations of dimensions and volumetrics based on preservation of systolic function are shown in Table 1.

Volumetric parameters over left atrium area in connection with systolic function

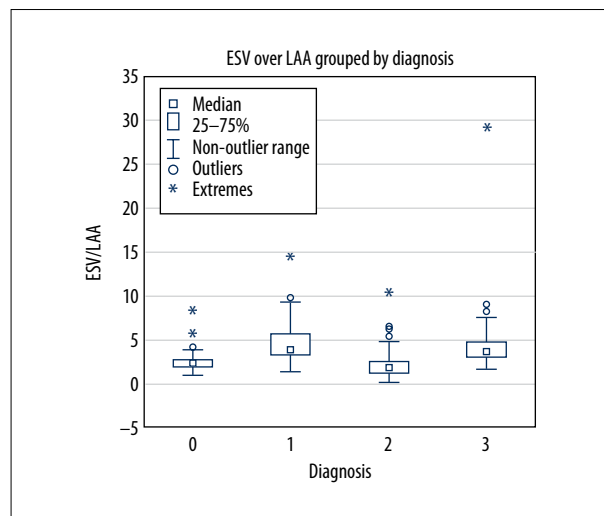
**Table 2.** Left ventricle volumetrics over left atrial area in connection with systolic function.

	Preserved LVEF (n=138)	Impaired LVEF (n=67)	Mann-Whitney U	Correlation with LVEF	
	Mean ±SD	Mean ±SD		Rho CC	p
EDV over LA	5.7±1.7	7.2±2.5	<b>&lt;0.001</b>	-0.369	<b>&lt;0.001</b>
ESV over LA	2.2±1.1	5.1±3.8	<b>&lt;0.001</b>	-0.824	<b>&lt;0.001</b>
SV over LA	3.5±1.0	2.5±1.1	<b>&lt;0.001</b>	0.486	<b>&lt;0.001</b>
	No LGE (n=93)	Existing LGE (n=111)	Mann-Whitney U	Correlation with LGE existence	
	Mean±SD	Mean±SD		Rho CC	p
EDV over LA	6.1±1.7	6.2±2.5	0.710	-0.026	0.710
ESV over LA	2.7±1.3	3.6±3.4	0.112	-0.112	0.111
SV over LA	3.5±0.8	2.9±1.2	<b>&lt;0.001</b>	-0.312	<b>&lt;0.001</b>

LVEF (%) – left ventricle ejection fraction; Rho CC – Spearman’s rank correlation coefficient [Rho]; LA (cm<sup>2</sup>) – left atrial area in 4-chamber view in square centimeters; EDV (mL) – end-diastolic volume; ESV (mL) – end-systolic volume; SV (mL) – stroke volume; LGE – late gadolinium enhancement; Part CC – partial correlations. Data shown as means and standard deviations (SD). Statistically significant values (p<0.05) presented in bolded text.



**Figure 1.** End-systolic volume over left atrial dimension grouped by preservation of systolic function. ESV – end-systolic volume; LA – left atrial area; LVEF – left ventricle systolic function. p<0.001.

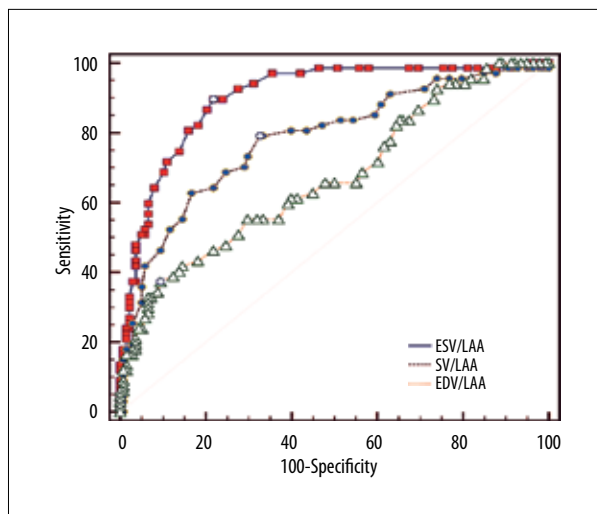


**Figure 2.** End-systolic volume over left atrial dimension grouped by diagnosis. ESV – end-systolic volume; LA – left atrial area; LVEF – left ventricle systolic function. 0 – no structural heart disease; 1 – hypertrophic cardiomyopathy; 2 – dilatative cardiomyopathy; 3 – left ventricular non-compaction. p<0.001.

Ratio of end-diastolic volume (EDV) over left atrium area (LAA) was 6.2±2.2, with interquartile range 4.7–7.0, and the end-systolic volume (ESV) over LAA was 3.15±3.27, with interquartile range 1.8–3.5 and stroke volume (SV) over LAA 3.2±1.11, with interquartile range 2.40–4.0. Associations of volumetric parameters over LAA with systolic dysfunction and existence of LGE are shown in Table 2.

Distribution of ESV over LAA based on groups of systolic impairment, as well as types of non-ischemic cardiomyopathies and controls, are shown in Figures 1 and 2.

Diagnostic value of studied volumetric parameters over left atrial area for assessing left ventricle systolic impairment or



**Figure 3.** Comparison of receiver operating curve analyzes for studied parameters in regard to preservation of systolic function. ESV – end-systolic volume; EDV – end-diastolic volume; SV – stroke volume; LAA – left atrial area; LVEF – left ventricle systolic function.

existence of LGE was tested using ROC analyzes and were ranked according to AUC value.

For detection of systolic dysfunction, a critical value of ESV over LA of  $\geq 2.7$  had a sensitivity of 89.6 (95% confidence intervals: 79.7–95.7), specificity 78.3 (70.4–84.8), +LR 4.1 (3.7–4.6) and –LR 0.1 (0.1–0.3), and AUC 0.904 (0.836–0.951),  $p < 0.001$ . SV over LA of  $\leq 3.0$  for LVEF  $< 50\%$  had a sensitivity 79.1 (67.4–88.1), specificity of 67.4 (58.9–75.1), +LR of 2.4 (2.0–2.9) and –LR 0.3 (0.2–0.5), and an AUC of 0.782 (0.719–0.837),  $p < 0.001$ . EDV over LA  $< 7.4$  for LVEF  $< 50\%$  had a sensitivity of 37.3 (25.8–50.0), specificity of 90.6 (84.4–94.9), positive likelihood ratio (+LR) 4.0 (2.9–5.4), and negative likelihood ratio (–LR) 0.7 (0.4–1.2), and the AUC was 0.671 (0.602–0.735);  $p \leq 0.001$ .

In analyzes of differences among ROCs for studied parameters, there were significant differences in AUC(ESV/LAA) vs. ROC (EDV/LAA)=0.231 (0.169–0.293);  $p < 0.001$ , and AUC(ESV/LAA) vs. ROC (SV/LAA)=0.120 (0.031–0.209);  $p = 0.008$ , Figure 3.

In ROC analyzes of late gadolinium existence, a critical value of SV over LAA of  $< 3.0$  had a sensitivity of 65.8 (56.2–74.5), specificity 73.1 (62.9–81.8), +LR 2.5 (2.0–2.9) and –LR 0.5 (0.3–0.7), and AUC 0.681 (0.612–0.744),  $p < 0.001$ . ESV over LAA and EDV over LAA were insignificant for existence of LGE (both  $p > 0.05$ ).

Correlations of morphologic type of late gadolinium enhancement were studied in regard to ESV/LAA, as follows: linear midventricular LGE (Rho-CC)=0.446,  $p < 0.001$ , and focal-LGE (Rho-CC)=–0.251,  $p < 0.001$ , while diffuse type of LGE was not significant ( $p > 0.05$ ).

## Discussion

Impairment of systolic function and existence of late gadolinium enhancement are well established adverse prognostic parameters in patients with non-ischemic cardiomyopathies [16,17]. This is the first study that analyzed ratios of volumetric parameters over left atrial area and associations with systolic impairment, as well as to late gadolinium enhancement [18]. Our study included a statistically representative number of patients with NICMPs and controls, without structural heart disease, to assess how specific phenotypes affect left ventricle volumetric and atrial size.

Larger end-diastolic diameter of left ventricle, thicker interventricular septum, and larger left atrial area were found in patients with impaired systolic function compared to the control group [18,19]. Corresponding significant changes were also found within the entire set of volumetric parameters [5]. End-diastolic and end-systolic volumes were significantly greater in cases with systolic impairment, whereas stroke volume was lower. Corresponding to these baseline differences, all tested novel geometric parameters were significantly different between studied groups of systolic functions. Ratio based on end-diastolic volume over left atrial size had the lowest level of diagnostic utility, which was congruently verified with significant but lower-grade level of correlations and significant difference, where the difference was of close numeric range. These results came partially as a surprise, since left ventricle end-diastolic diameter is a well-established prognostic parameter of inverse correlations with systolic function and represents 2 dimensional parameters of structural derangements [20]. However, the lack of a clinically meaningful difference might be explained by the fact that left atrial area was also enlarged in patients with a dilated left ventricle, so their ratio might be relatively preserved as the systolic function further declines and structural rearrangements in terms of atrial dilatation progress in the failing heart. In addition, there were no significant differences, correlations, or ROC analyzes for the ratio based on end-diastolic volume with late gadolinium enhancement, which made expectations about clinical applicability of end-diastolic volume ratio less useful.

On the other hand, ratios based on end-systolic volume and stroke volume to left atrial area displayed statistically significant associations within all studied groups, which was reaffirmed by different tests, and was associated with prognostic parameters in a more meaningful way [21]. The greatest clinical impact of novel volumetric ratios was found for end-systolic volume over left atrial area, with the highest values of AUC. Sensitivity and specificity for systolic impairment was adequately high, with both parameters being around 80% [22]. ESV/LAA ratio had a high-grade positive correlation with left ventricle systolic impairment and was non-significant for

existence of late gadolinium enhancement [19]. Differences based on preservation of systolic function were more powerfully connected with significantly higher end-systolic volume rather than relatively smaller increase of left atrial area [23]. For this reason, the ratio of ESV to LAA was more than double that of patients with impaired systolic function versus controls [24]. The latter could be explained by the fact that relatively larger structural and functional derangements occur in ventricles alternated by cardiomyopathy at end-systole, but in the left atrium the changes are slightly less pronounced [23]. End-systolic volume also appears promising for further studies, especially those connected with clinical endpoints and functional changes, New York Heart Association-NYHA grade, or prevalence of arrhythmias, along with therapeutic interventions [25]. In this sense, geometric infrastructural changes that cause end-diastolic dilatation and loss of systolic function in terms of previously known negative prognostic value could be further characterized by end-systolic changes of volume and end-systolic geometric alternations. ESV/LAA also had moderately high correlations with more malignant mid-ventricular linear type of late gadolinium enhancement [26].

Stroke volume is generally a reliable marker of cardiovascular performance, particularly if it is meaningfully decreased. Luckily, this is not common, since compensation of minute volume is conveniently made by increased heart rate, where the latter is a very useful reservoir and the effect is relatively long-lasting [27,28]. Hence, a decrease of left ventricle ejection fraction is compensated for until severe grade of systolic impairment develops. Therefore, it was not surprising that SV/LAA was also significantly lowered in patients with systolic impairment and controls, as well as in those with existence of LGE and those without imbibitions [29]. SV/LAA also had a high correlation with systolic impairment, as well as a high AUC in the ROC analyzes, but slightly lower than the ESV/LAA. Thus, sensitivity and specificity were rather high but were marginally lower than the ESV/LAA ratio.

Late gadolinium enhancement was found in 80.6% of patients with non-ischemic cardiomyopathies who had impaired systolic function [30]. There was an inverse correlation between systolic function of the left ventricle and ESV/LAA, while the correlation of SV/LAA was highly positive. Previous studies showed that LGE is connected with symptoms of heart failure, increased prevalence of arrhythmias, and mortality [29].

The present study is limited due to the small population size and its case-control, retrospective design. Further limitations were inclusion criteria and sub-selection of a population recruited mostly from secondary or tertiary medical centers from around the country, as well as scheduling and waiting list effects, in which all mentioned parameters have the potential to influence consecutiveness of cases. Prospective validation in multicenter settings and with a larger population, as well as inclusion of clinical endpoints, would be important to improve reproducibility and clinical applicability.

## Conclusions

In conclusion, this study analyzed novel geometry analyses made from ratios of left ventricle volumetrics and left atrial area, which are convenient and easily available measurements. Of the studied parameters, end-systolic volume over left atrial size was the most effective for detection of systolic impairment, and was associated with existence of late gadolinium enhancement. Stroke volume over left atrial area index had marginally less diagnostic power than ESV/LAA and of divergent correlations, but its diagnostic utility also seems promising. The ratio of end-diastolic volume and left atrial area was not significantly associated with systolic function or existence of the late gadolinium enhancement. Prospective validation of tested parameters for their clinical applicability and prognostic relations is warranted in future studies. Also, it might be worthwhile to analyze their usefulness for therapy-based decisions in patients with non-ischemic cardiomyopathies [31].

## Conflict of interest

None.

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