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Left atrial appendage volume as a new predictor of atrial fibrillation recurrence after catheter ablation

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Abstract

Purpose Recurrence of atrial fibrillation (AF) after catheter ablation is common, being clinically relevant to identify predictors of recurrence. The left atrial appendage (LAA) role as an AF trigger is scarcely explored. Our aim was to identify if LAA volume is an independent predictor of AF recurrence after catheter ablation.

Methods We analysed 52 patients (aged 54 ± 10 years, 58% male) with paroxysmal and persistent AF who underwent a first AF catheter ablation and had performed contrast-enhanced cardiac computed tomography (CT) prior to the procedure.

Results The mean left atrial and LAA volumes measured by cardiac CT were 98.9 ± 31.8 and 9.3 ± 3.5 mL, respectively. All patients received successful pulmonary vein isolation and were followed up for 24 months. AF recurrence occurred in 17 patients (33%). LAA volume was significantly greater in patients with AF recurrence than in those without recurrence (11.3 ± 2.9 vs. 8.2 ± 3.4 mL; $p = 0.002$). Multivariable analysis using Cox regression revealed that LAA volume (hazard ratio 1.32; 95% confidence interval 1.12–1.55; $p = 0.001$) and persistent AF (hazard ratio 4.22; 95% confidence interval 1.48–12.07; $p = 0.007$) were independent predictors for AF recurrence. An LAA volume greater than 8.825 mL predicted AF recurrence with 94% sensitivity and 66% specificity. The Kaplan-Meier analysis showed a lower rate free from AF recurrence in the group with an LAA volume >8.825 mL ($p < 0.001$).

Conclusions Larger LAA volume was associated with AF recurrence after catheter ablation in patients with paroxysmal and persistent AF.

Keywords Atrial fibrillation · Ablation · Left atrial appendage · Cardiac computed tomography

1 Introduction

The overall success rate of catheter ablation to treat atrial fibrillation (AF) ranges from 60 to 90% [1–6]. To enhance the procedure's success rate, it is important to identify predictors of AF recurrence.

Some factors have been reported to have a role in predicting AF recurrence after ablation, namely AF duration, left atrial (LA) dimensions and cardiovascular comorbidities [6–10]. In this context, little is known about the left atrial appendage (LAA), which has an underrecognized role as an AF trigger despite being an acknowledged source of focal automaticity [11–15]. Di Biase et al. reported the LAA as a site of triggers and focal firing in 27% of 987 patients undergoing redo catheter AF ablation [16]. Recently, a randomized trial showed that electrical isolation of the LAA improved long-term freedom from atrial arrhythmias in patients with long-standing persistent AF submitted to catheter ablation [17]. However, the potential role of LAA volume in the prediction of AF recurrence has not yet been solved. LAA volume can be accurately measured using cardiac computed tomography (CT), which is routinely performed before AF ablation for assessment of the LA and pulmonary vein anatomy and for image integration of the three-dimensional (3D) CT-derived images with the real-time acquired electroanatomical mapping data during ablation [18–20].

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The aim of this study was to explore the association between LAA volume and AF recurrence after catheter ablation in patients with paroxysmal and persistent AF.

2 Methods

We analysed patients with symptomatic paroxysmal and persistent AF who underwent a first AF catheter-based radiofrequency ablation in our centre between July 2013 and December 2014 and had performed cardiac CT prior to the procedure. Paroxysmal AF was characterized by episodes of AF that terminate spontaneously or with intervention within 7 days of onset. Persistent AF was defined as continuous AF that is sustained more than 7 days and long-standing persistent AF as continuous AF lasting more than 12 months [21].

Patients with incomplete circumferential pulmonary vein isolation and patients with inadequate image quality for LA and LAA volume measurements were excluded from the study.

2.1 LAA volume assessed by cardiac computed tomography

LAA volume was assessed from contrast-enhanced cardiac CT images acquired before the ablation, with the intent of studying the LA and pulmonary vein anatomy and providing 3D images to merge with the electroanatomical mapping during the procedure. Cardiac CT images were obtained using a 64-detector scanner (VCT LightSpeed, GE Healthcare®) after administration of iodinated contrast agent (90 to 110 mL of Ultravist 370) at 4 to 5 mL/s followed by 30 to 50 mL of normal saline at the same rate. Data were acquired using a retrospective ECG-controlled tube current modulation technique, where the highest tube current (450–500 mA) was applied only during the systolic phase of the cardiac cycle. Scanning was triggered once the contrast arrived at the ascending aorta and had higher intensity in the aorta than in the pulmonary trunk. Non-overlapped axial images were reconstructed from phase 20 to 50% of the R-R interval, with 5% interval increments and a slice thickness of 0.6 mm. Image analysis was performed on a dedicated cardiac CT workstation (iNtuition, TeraRecon®) with volume-rendering software. Maximal LAA and LA volumes were measured at the end-systolic phase (usually 40% of the R-R interval), just before the mitral valve opening, when the LA cavity was largest and the LV cavity was smallest. LA borders were traced on each axial slice, excluding the pulmonary veins and appendage at the ostia and using the mitral valve annulus as the landmark differentiating the LA from the left ventricle. Orthogonal views were used to accurately differentiate the LAA orifice from the LA. The LAA borders were traced manually on the axial slices, and LAA trabeculations were considered part of the LAA cavity. The volumes of the 3D LAA and LA were calculated by multiplying the area of each slice by its thickness and summing up all the volumes of each slice (Simpson method) (Fig. 1). Only patients with fully contrasted LA and LAA allowing for an accurate border delineation were included in the analysis.

Furthermore, we categorized the LAA shape into four different morphologies: cactus, chicken wing, windsock and cauliflower, as originally described by Wang et al. [22]. Briefly, the "cactus" is defined as a central lobe with one or more secondary lobes; "chicken wing" as a main lobe that bends from the proximal or middle part of the LAA; "windsock" as one dominant lobe with several secondary, or even tertiary, lobes; and "cauliflower" as limited overall length structure with complex irregular characteristics and often lacking a dominant lobe.

In addition to cardiac CT, patients performed transthoracic echocardiogram with measurement of LA volume and diameter as well as left ventricular ejection fraction estimation.

2.2 Electrophysiological study and catheter ablation procedure

All patients underwent catheter-based circumferential pulmonary vein (PV) isolation using radiofrequency energy delivered by catheter with an open, irrigated tip. Three-dimensional electroanatomical mapping systems were used, and merging with CT-derived images was achieved. The endpoint of pulmonary vein isolation was the electrical isolation of all pulmonary veins from the LA, confirmed by entry and exit block assessed with the ablation catheter tip at four positions around the circumference of the PV ostia. Further linear ablation, including LA roof line and mitral isthmus line, was added at the discretion of the operator. Ablation of complex fractioned atrial electrograms (CFAEs) was also attempted at the discretion of the operator in cases where AF persisted after pulmonary vein isolation and linear ablation. If AF continued after the ablation, biphasic direct current shocks were applied to restore sinus rhythm.

2.3 Follow-up and AF recurrence assessment

All patients were followed up for 24 months after ablation. Assessment was performed at discharge and at the 3rd, 6th, 12th and 24th months by a clinic appointment, 12-lead ECG and 24-h Holter monitoring. In addition, patients who complained of palpitations or irregular pulse were instructed to seek immediate medical attention for prompt ECG recording. An external loop recorder was given to patients who developed symptoms suggestive of AF but had no documentation of AF on ECG or 24-h Holter monitoring. Oral anticoagulants were prescribed for a minimum of 6 months and eventually discontinued in case of a low thromboembolic score (CHADS$_2$VASC score 0 or 1). Antiarrhythmic drugs were
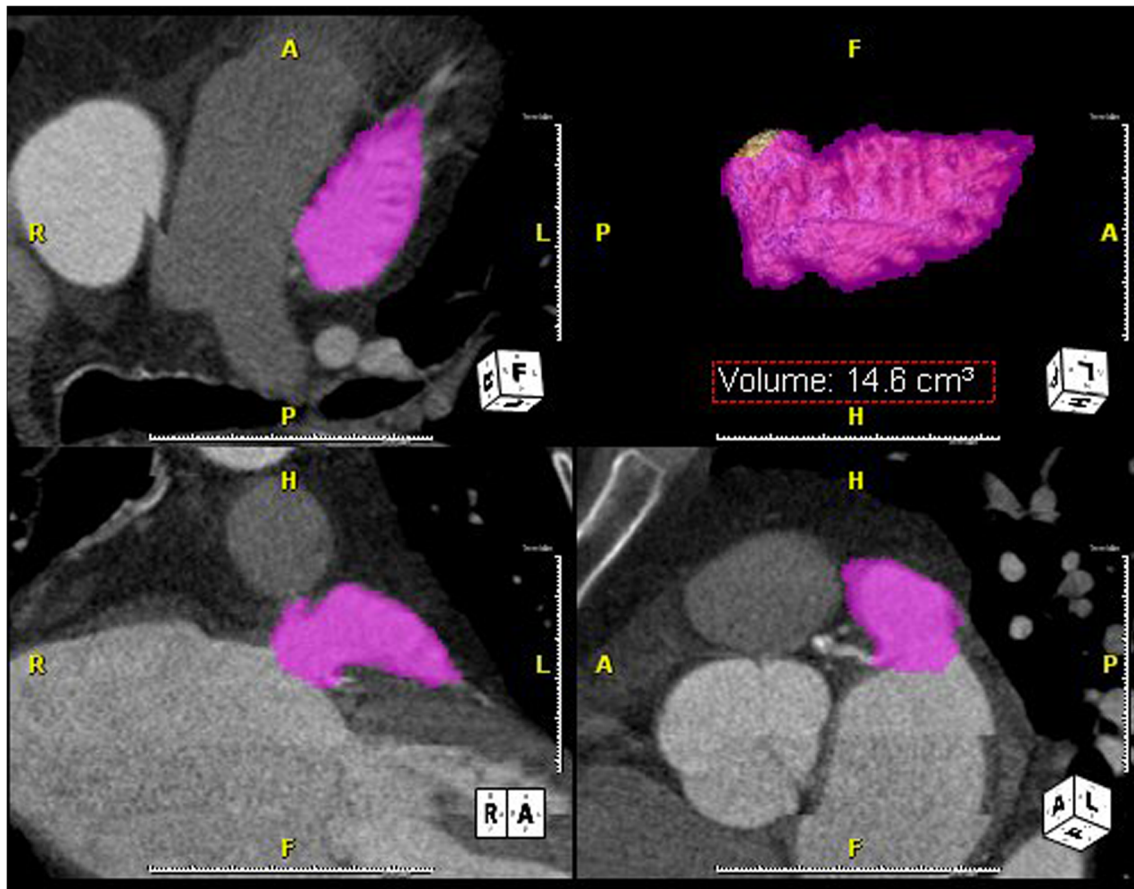
Fig. 1 Illustration of a large left atrial appendage (LAA) with a total volume of 14.6 mL. The depicted 3D LAA was obtained after manual tracing of its borders on axial slices for volume measurement

continued for at least 6 months in patients who were taking them prior to the procedure, and were interrupted in case of no AF recurrence at 6 months of follow-up. AF recurrence was considered as any episode of AF (recorded by 12-lead ECG, 24-h Holter monitoring or external loop recorder) lasting >30 s and occurring >3 months after ablation (blanking period) [23].

2.4 Statistical analysis

Continuous variables are presented as mean value ± standard deviation and categorical variables as absolute numbers and relative frequencies. Student's t test was performed to compare continuous variables, and a chi-square test was used to compare categorical variables. A Cox proportional hazards regression model was used to identify parameters associated with AF recurrence following catheter ablation. Variables with a p value <0.20 in the univariate analysis were then considered in a multivariate analysis to determine any independent predictors associated with AF recurrence and calculate adjusted hazard ratios (HRs). LAA volume was further studied by using a receiver operating characteristic (ROC) curve to determine the optimal cut-off values for the prediction of AF recurrence. The best cut-off value was defined as the point combining the highest

sensitivity and specificity. The Kaplan-Meier method estimated the event-free survival rate, and comparisons between different groups were rendered by a log-rank test. Statistical significance was accepted at a p value <0.05. Statistical analysis was performed using SPSS Statistics, version 22.

Intraobserver variability and interobserver variability for LAA volume measurement were assessed using a randomly selected subset of 15 patients. Measurements were repeated by the same observer after an interval of ≥1 week and by a second independent blinded observer. Reproducibility was estimated by intraclass correlation coefficient, with good agreement defined as >0.80.

3 Results

3.1 Patients' characteristics

During the study period, 78 patients underwent radiofrequency catheter ablation of paroxysmal or persistent AF. From these, 11 patients were excluded due to incomplete electrical PV isolation from the LA, 9 were excluded due to a lack of pre-procedural cardiac CT and 6 were excluded because of

inadequate CT imaging with the LAA filling poorly with contrast. The final study population consisted of 52 patients (aged 54.4 ± 9.7 years, 58% male). AF recurrence occurred in 17 patients (33%) during the 24-month follow-up, with a mean time until recurrence of 305.9 ± 144.6 days. Table 1 compares the baseline characteristics between patients with and without AF recurrence. Patients who had AF recurrence did not differ significantly with respect to age, gender, comorbidities (e.g. hypertension, coronary artery disease), LA volume or diameter, when compared to patients who did not experience recurrent AF. Circumferential pulmonary vein isolation was achieved in all patients. Additional linear ablation was performed in 14 patients, and the proportion of them who received this procedure was comparable to those with and without AF recurrence. The study sample included 30 patients with paroxysmal AF and 22 patients with persistent AF, of whom seven had long-standing persistent AF. The recurrence rate was higher among patients with persistent AF (50 vs. 20% for patients with paroxysmal AF).

3.2 LAA volume and imaging characteristics

The mean LAA volume was 9.3 ± 3.5 mL. As depicted in Table 1 and Fig. 2, the LAA volume was significantly greater in patients with AF recurrence (11.3 ± 2.9 vs. 8.2 ± 3.4 mL; $p = 0.002$). This difference was notorious among the subgroup of patients with persistent AF: those who experienced AF recurrence had significantly larger LAA volume than those who did not (11.5 ± 2.2 vs. 7.8 ± 2.4 mL; $p = 0.005$). It is of note that the mean LA volume of patients with paroxysmal and persistent AF did not significantly differ (94.1 ± 33.8 vs. 105.3 ± 28.1 mL; $p = 0.2$).

LAA volume did not correlate with gender [9.8 ± 3.4 mL (male) vs. 8.5 ± 3.7 mL (female); $p = 0.22$], age ($r = 0.08$, $p = 0.58$), body mass index ($r = 0.15$, $p = 0.29$), left ventricular ejection fraction ($r = -0.01$, $p = 0.92$), persistent AF [9.4 ± 3.3 mL (with) vs. 8.9 ± 4.2 mL (without); $p = 0.46$] or hypertension [9.7 ± 2.9 mL (with) vs. 9.0 ± 3.9 mL (without); $p = 0.70$]. A good correlation was found between LAA volume and LA volume assessed by cardiac CT ($r = 0.71$, $p < 0.001$). The mean LA volume derived from CT (98.9 ± 31.7 mL) was larger than the mean LA volume measured by echocardiography (89.4 ± 28.0 mL) but with a strong correlation between each other ($r = 0.81$, $p < 0.001$).

Regarding LAA shape assessed by cardiac CT, the following morphologies were detected: cactus in 15 patients (29%), chicken wing in 24 (46%), windsock in 10 (19%) and cauliflower in 3 (6%). The distribution of LAA morphologies did

Table 1 Patients' characteristics by subgroup (no AF recurrence vs. AF recurrence)	No AF recurrence	AF recurrence	*p* value
Clinical characteristics			
Age (years)	54.1 ± 10.9	54.9 ± 6.9	0.77
Male (*n*, %)	19 (54)	11 (65)	0.56
Body mass index (kg/m²)	28.6 ± 4.3	27.8 ± 4.1	0.73
Type of AF (*n*, %)			0.03
Paroxysmal AF	24 (69)	6 (35)	
Persistent AF	11 (31)	11 (65)	
Hypertension (*n*, %)	26 (74)	10 (58)	0.11
Dyslipidaemia (*n*, %)	19 (54)	8 (47)	0.76
Diabetes mellitus (*n*, %)	4 (11)	1 (6)	0.47
Coronary artery disease (*n*, %)	7 (20)	5 (29)	0.58
Obstructive sleep apnoea (*n*, %)	6 (17)	3 (18)	0.62
Imaging parameters			
Left atrial appendage volume (mL)[a]	8.2 ± 3.4	11.3 ± 2.9	0.002
Left atrial volume (mL)[a]	95.5 ± 30.0	105.7 ± 35.0	0.28
LV ejection fraction (%)[b]	53.9 ± 9.8	53.5 ± 10.9	0.64
Left atrial diameter (mm)[b]	43.8 ± 10.9	43.9 ± 10.9	0.54
Left atrial volume (mL)[b]	88.3 ± 32.7	91.9 ± 38.4	0.81
Ablation characteristics			
Additional linear ablation (*n*, %)	8 (23)	6 (35)	0.59
Additional CFAE ablation (*n*, %)	4 (11)	2 (12)	0.57

AF atrial fibrillation, *CFAE* complex fractioned atrial electrogram

[a] Assessed by cardiac CT
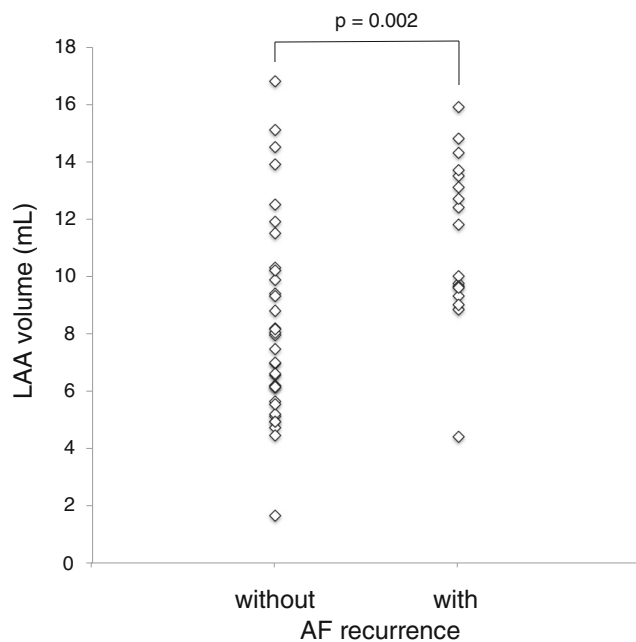
[b] Assessed by echocardiography

Fig. 2 Comparison of LAA volume between patients with and without AF recurrence. LAA volume was significantly larger in patients with AF recurrence than in those without AF recurrence (11.3 ± 2.9 vs. 8.2 ± 3.4 mL; $p = 0.002$)

not significantly differ between patients with and without AF recurrence ($p > 0.05$). Moreover, no compelling correlation could be established between volume and distinct LAA morphologies ($p > 0.05$).

The intraclass correlation coefficient for LAA volume measurements was 0.95 for intraobserver variability and 0.89 for interobserver variability.

3.3 LAA volume and prediction of AF recurrence

To explore the associations between the various clinical parameters and AF recurrence, a Cox proportional hazards regression analysis was executed. In the univariate analysis, persistent AF, hypertension and LAA volume were linked to AF recurrence. In the multivariable analysis, LAA volume (adjusted HR 1.32, 95% confidence interval 1.12–1.55; $p < 0.001$) remained as an independent predictor for AF recurrence, as well as persistent AF (adjusted HR 4.22, 95% confidence interval 1.48–12.07; $p < 0.001$).

The ROC curve analysis revealed that an LAA volume >8.825 mL was associated with AF recurrence after catheter ablation with a sensitivity of 94% and a specificity of 66% (area under the curve = 0.76). In our study population, only one patient out of 24 with an LAA volume <8.825 mL had AF recurrence. Furthermore, Kaplan-Meier curves demonstrated that patients with LAA volume above the 8.825 mL cut-off had a significantly higher rate of AF recurrence (Fig. 3).

4 Discussion

The main finding of our study was that a larger LAA volume was independently associated with AF recurrence after catheter ablation in patients with paroxysmal or persistent AF. To the best of our knowledge, this is the first study to describe such association.

Importantly, we found that among patients with persistent AF, those who experienced recurrence had considerably higher LAA volumes. It is known that the outcomes of ablation in patients with persistent and long-standing persistent AF are poorer [1–4]. In these patients, many non-PV areas seem to be the source for initiation and maintenance of AF. The most common sites are the superior vena cava, the coronary sinus, the ligament of Marshall, the crista terminalis, the LA posterior wall and the LAA [16, 24–27]. In the recent BELIEF trial, Di Biase et al. showed improved freedom from atrial arrhythmias in patients with long-standing persistent AF who performed empirical electrical isolation of the LAA in addition to *standard* catheter ablation [17]. Although there is increasing evidence of the LAA importance as a trigger for atrial arrhythmias, the literature is scarce on the mechanisms and factors that may contribute to it. Previous studies have demonstrated the value of LAA flow velocity in the prediction of sinus rhythm maintenance after electrical cardioversion and, recently, Kanda et al. described an association between low LAA flow velocity and AF recurrence after catheter ablation in patients with persistent AF [28–30]. The current research suggests that LAA volume may be a surrogate of increased LAA arrhythmogenicity, similar to what happens with the LA volume: an enlarged LA is associated with electrical remodelling, which provides an arrhythmogenic substrate for AF triggers [31]. The LAA has a complex architecture with extensive pectinate muscles and highly heterogeneous orientation of the muscle bundles, which may facilitate slow conduction and block, along with the development of re-entry [11, 32, 33]. These electrical circuits may be heightened in the setting of an enlarged LAA and increased fibrosis.

It is accepted that cardiovascular comorbidities, such as hypertension and obesity, strongly influence atrial remodelling and enlargement [9, 34]. However, it is unclear what factors contribute to the enlargement of the LAA, which has distinct embryology, anatomy and histology from the LA [32, 33]. This may explain why some patients may have very large LAA with small- or moderately sized LA. Moreover, our finding that LAA volume, but not LA volume, was significantly greater in patients with AF recurrence compared to those without recurrence, reinforces the role of the LAA volume as an independent predictor for AF recurrence. It might become appropriate to empirically isolate the LAA in patients who present to catheter ablation with large LAA, especially those with persistent or long-standing persistent AF. In addition, LAA volume measurement by cardiac CT is feasible and readily accessible, given that patients programmed for catheter ablation should undergo the scan for procedure planning.

Fig. 3 Kaplan-Meier analysis of time to AF recurrence. Study patients were divided into two groups based on the best cut-off value of LAA volume for prediction of AF recurrence. Patients with an LAA volume >8.825 mL had a lower rate of freedom from AF recurrence

Kaplan-Meier analysis of time to AF recurrence

No. at risk				
LAA volume <8.825 mL	24	23	23	23	23
LAA volume >8.825 mL	28	23	17	13	12
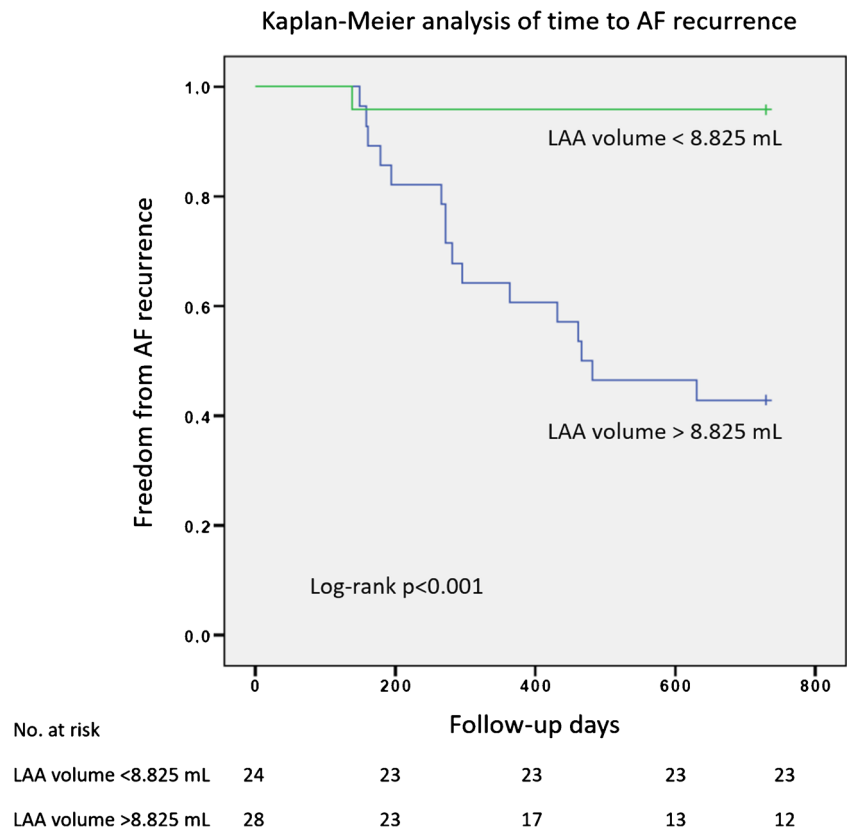
4.1 Study limitations

This was an exploratory study with important limitations. First, although we closely followed up patients with periodic clinic appointment, ECG and Holter monitoring, asymptomatic episodes of AF might not have been detected. Nonetheless, all patients included in our study had symptomatic AF before catheter ablation and, therefore, would probably seek medical attention if AF recurred. Second, the study design was retrospective and the sample size was modest; thus, we cannot rule out the bias of LA volume dependence. In addition, only a small number of patients had long-standing persistent AF. Those patients are probably the ones who might benefit more from LAA electrical isolation [17]. Prospective randomized studies are needed, particularly in the subgroup of patients with persistent and long-standing AF, to further clarify the clinical utility of LAA volume measurement as a predictor of AF recurrence and as a potential surrogate for electrical isolation of the LAA.

5 Conclusions

LAA volume, measured by cardiac CT, may be an independent predictor of AF recurrence in a population of patients with paroxysmal and persistent AF undergoing a first catheter ablation procedure. In patients with large LAA, the inclusion of empirical electrical isolation of the LAA might be appropriate. An LAA volume greater than 8.825 mL showed good accuracy to predict AF recurrence, with a sensitivity of 94% and a specificity of 66%.

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