

Predictive value of HMGB1 for atrial fibrillation recurrence after catheter ablation in paroxysmal atrial fibrillation patients

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Abstract

Background: To evaluate the clinical efficacy of serum high-mobility group box-1 (HMGB1) released from the left atrium to predict atrial fibrillation (AF) recurrence in paroxysmal AF (pAF) patients after catheter ablation (CA) at 1-year follow-up.

Methods: We included 72 pAF patients who underwent CA. To determine the expression levels of HMGB1, left atrial blood samples were collected from the patients prior to CA and after the procedure through the transseptal sheath placed into the left atrium. Patients were followed-up for AF recurrence after 1 year of CA.

Results: A total of 19 (26%) patients of the 72 experienced AF recurrence. No significant differences were noted in the clinical baseline data between the AF recurrence and AF nonrecurrence groups. The level of postoperative HMGB1 (HMGB1post) was higher in the AF recurrence group than in the AF nonrecurrence group (298.51 μ g/L vs. 278.17 μ g/L; $P = 0.03$). However, no differences were noted in the levels of other biomarkers such as preoperative high-sensitivity C-reactive protein (hs-CRPpre), postoperative hs-CRP (hs-CRPpost), and preoperative HMGB1 (HMGB1pre) between the two groups. Multiple logistic regression analysis revealed that a higher level of serum HMGB1post from the left atrium (HMGB1post: ≥ 279.35 μ g/L) was an independent predictor of AF recurrence (odds ratio [OR]: 5.29 [1.17–23.92], $P = 0.04$). Receiver operating characteristic (ROC) analysis revealed that HMGB1post had a moderate predictive power for AF recurrence (area under the curve [AUC]: 0.68; sensitivity: 72%; specificity: 68%). The 1-year AF-free survival was significantly lower in patients with a high serum HMGB1post level than in those with a low HMGB1post level (hazard ratio [HR]: 3.81 [1.49–9.75], $P = 0.005$).

Conclusion: In pAF patients who underwent CA, the level of HMGB1 from the left atrium immediately after CA was associated with AF recurrence and demonstrated a moderate predictive power. Thus, we offer a potential predictor to identify pAF patients at high risk of AF recurrence.

Background

Atrial fibrillation (AF), a frequent type of supraventricular arrhythmia, is the most common atrial arrhythmia among adults worldwide, and its prevalence has been increasing (1). AF is a progressive disease, and its early stage is paroxysmal AF (pAF); more than 50% of the pAF patients progress to persistent AF or die within 10 years (2). Thus, early intervention in pAF is of great significance.

Currently, catheter ablation (CA) is recommended for patients with symptomatic drug refractory pAF (3, 4), especially because CA techniques for AF have significantly evolved over the past decade (5). However, substantial AF recurrence is common during follow-up, which overshadows the potential benefits of the procedure (6). To stratify the risk of AF recurrence in pAF patients undergoing CA, several risk factors such as Age (>75 years), AF duration, Congestive heart failure, Hypertension, Diabetes, previous Stroke/transient ischemic attack-vascular disease, CHA₂DS₂-VASc score [congestive heart failure, hypertension, age ≥ 75 y (doubled), diabetes mellitus stroke (doubled), vascular disease, age 65-74 and

sex category (female)], left atrial size, and presence of structural heart disease are considered (7-9). However, all these factors show great population heterogeneity for AF recurrence prediction.

Recently, inflammatory processes were reported to play important roles in AF recurrence (10). A study found that the level of high-sensitivity C-reactive protein (hs-CRP) at baseline has an independent prognostic value in predicting AF recurrence (11). However, the study population included both persistent AF and pAF patients. Moreover, hs-CRP, a nonspecific acute-phase reactant synthesized by hepatocytes, is easily affected by other comorbidities (12). High mobility group protein 1 (HMGB1) is both a nuclear factor and secreted protein. The release of HMGB1 by necrotic cells can trigger inflammation (13). The expression levels of HMGB1 were significantly higher in AF patients and in the left atrium than in normal patients and in the periphery, respectively (14). A review concluded that HMGB1 may be released by the left atrium, and it may mediate inflammatory processes after CA and influence the occurrence and development of AF (15).

Although these studies have presented the association between HMGB1 and AF, the possibility of HMGB1 released from the left atrium predicting AF recurrence remains unclear. Therefore, this study investigated the predictive value of serum HMGB1 released from the left atrium for AF recurrence.

Methods

Study population

This study included 72 symptomatic patients with pAF who underwent CA at the First Hospital of the China Medical University between August 2017 and August 2018. All patients were older than 18 years, suitable for CA, and had voluntarily participated in the study. AF was diagnosed with a 12-lead electrocardiogram (ECG) or Holter-ECG. The diagnostic standard was in accordance with the pAF definition of the American Heart Association (16). Exclusion criteria were presence of persistent AF, severe heart failure, severe valvular disease, thyroid dysfunction, hepatic and renal dysfunction, LA thrombosis, malignant tumor, and autoimmune and inflammatory diseases or systemic disease and a 6-month history of surgery. Written informed consent was obtained from all patients before enrollment, and the study complied with the Declaration of Helsinki.

Echocardiographic measurements

All patients underwent transthoracic echocardiography within 72 hours before CA. Transthoracic echocardiography was performed using the Vivid E9 ultrasound system (GE Healthcare, Waukesha, WI, USA). The diameter of the left atrium was measured in the parasternal long-axis view on the 2-dimensional image. The Simpson's biplane method was used to measure left ventricular ejection fraction (LVEF) as well as left atrial volume in the apical 4-chamber and 2-chamber views. Notably, the left atrial appendage should not be included in tracing of the endocardial border. Left atrial volume index (LAVI) was calculated by dividing the estimated end-systolic left atrial volume by the body surface area. All

measurements were performed in accordance with the American Society of Echocardiography guidelines (17).

Ablation protocol

Transesophageal echocardiography was used to exclude any left atrium or left atrial appendage thrombosis. Multidetector computed tomography of pulmonary vein (PV) was performed 24 hours prior to CA to assess PV anatomy. Antiarrhythmic drugs were discontinued at least 5 half-lives before CA and anticoagulation drugs were administered during and after CA. The Seldinger technique was used to obtain venous access and perform fluoroscopy-guided transseptal puncture. We first chose the radiofrequency ablation (RFA), because of its longer history, more experienced for the operator and standard exposure duration than the cryoballoon ablation (CBA). However, for the patients with obvious symptoms, frequently arrhythmia occurring and poor general condition, which means less operation time is required, CBA was first preference, given that the CBA is similar and shorter procedure with fluoroscopy times than RFA[(18-20)]. In our study, 51 (79%) of the 72 pAF patients experienced RFA, whereas 21 (21%) patients underwent CBA. One patient only underwent one ablation, RFA or CBA. And the ablation mode was unified. For the patients went on RFA, they all underwent circumferential pulmonary vein isolation by an open-irrigated catheter tip with temperature adjusted at 50°C. For CBA, a cryoablation balloon was placed at the ostium of each PV, delivering 50°C cooling energy for 180x2 seconds. The balloon selection was based on the PV size. Further details about the CA procedure can be found in the international expert consensus that has been accepted in recently (21). The ablation was considered successful if all tested pulmonary potentials with a mapping catheter were completely blocked between the atrial tissue and PV.

Blood sample collection and post-processing

Transseptal puncture was performed using a transseptal sheath during CA. After access to the left atrium was achieved using the sheath, blood samples for determining the preoperative HMGB1 (HMGB1pre) level were obtained before the formal procedures of CA. Similarly, after successful CA, blood samples were immediately collected through the sheath placed in the left atrium. Thereafter, the blood samples were centrifuged at 3000 rpm for 10 minutes, and the serum samples were stored at -80°C until analysis. The inflammatory biomarkers, hs-CRP and HMGB1, were measured using commercial enzyme-linked immunosorbent assay (Boster Biological Technology, Wuhan, China) kits according to the manufacturer's instructions.

Follow-up

After CA, all patients underwent continuous electrocardiographic monitoring until discharge and were prescribed oral anticoagulation for at least 3 months based on the CHA₂DS₂-VASc score. The endpoint was 1-year AF recurrence after CA. Episodes of AF or atrial tachyarrhythmia lasting more than 30s diagnosed with a 12-lead ECG or Holter ECG within 3 months were classified as early AF recurrence and those after 3 months as AF recurrence (16). Patients' follow-up was conducted at 3, 6, and 12 months

after the ablation procedure and whenever required due to symptoms of AF, through outpatient clinic visits or contacting by phone from patients, their family members and referring physicians.

Statistical analysis

The baseline data were stratified by pAF recurrence after CA. Continuous data are expressed as means \pm standard deviation or medians (interquartile range), and categorical data are expressed as counts and percentages. Intergroup comparisons were performed using unpaired Student t-tests for normally distributed variables and the non-parametric Mann–Whitney U-test for non-normally distributed variables. Categorical variables were collated using the chi-square test or Fisher's exact test. Multivariate regression analysis was performed to analyze the risk factors for the prediction of AF recurrence. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Optimal cutoff values were determined by analyzing the sensitivity and specificity values derived from the receiver operating characteristic (ROC) curve data. The area under the curve (AUC) was calculated to assess the discriminatory power of meaningful biomarkers. The AF-free survival rates were determined using Kaplan–Meier curves and compared using the log-rank test. Data were analyzed using SPSS ver. 25 (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA). The results of the t-test and chi-square test were validated by bootstrapping (1000 repetitions). A P value of <0.05 was considered significant.

Results

Study population

Nineteen (26%) of the 72 pAF patients experienced AF recurrence, whereas 53 (74%) patients did not experience postoperative recurrence. Characteristics of patients were stratified by recurrence and nonrecurrence of AF. Age, sex, AF duration, CHADS-VASC score, concomitant diseases, biochemical index, and echocardiographic parameters (LAD, LVEF, and LAVI) were not significantly different between the AF recurrence and AF nonrecurrence groups. However, the early recurrence rates were significantly higher in the AF recurrence group than in the AF nonrecurrence group ($P = 0.001$). The results were consistent after bootstrapping (1000 times; Table 1).

All patients (N=72)	Nonrecurrence (N=53)	Recurrence (N=19)	P-value after bootstrapping	
Clinical characteristics				
Age (yrs)	61.5±8.8	61.6±8.9	61.2±8.8	0.84
Female [n (%)]	21 (29%)	16 (30%)	5 (26%)	1.00
AF period (months)	61.5±67.5	60.3±62.6	64.9±81.2	0.95
CHA2DS2-VASc score	2.00±1.50	1.98±1.52	1.76±1.25	0.31
Hypertension [n (%)]	32 (48%)	27 (51%)	5 (26%)	0.11
Diabetes mellites [n (%)]	10 (14%)	8 (15%)	2 (11%)	1.00
Peripheral arterial disease [n (%)]	14 (20%)	11 (21%)	3 (16%)	0.75
Fasting blood glucose (mmol/L)	5.41±1.48	5.40±0.96	5.44±2.45	0.92
Total cholesterol (mmol/L)	3.74±1.01	3.66±1.02	3.97±1.00	0.26
LDL-cholesterol (mmol/L)	2.15±1.02	2.23±1.04	2.07±0.98	0.92
HDL-cholesterol (mmol/L)	2.42±1.73	2.33±1.72	2.40±1.68	0.67
Triglycerides (mmol/L)	1.62±0.83	1.56±0.68	1.84±1.19	0.64
Uric acid (umol/L)	296.22±83.71	302.25±85.69	279.11±77.53	0.32
Creatinine (umol/L)	67.71±13.15	67.22±12.87	65.28±14.18	0.59
ERAF [n (%)]	16 (22%)	6 (11%)	10 (53%)	0.001
Echocardiographic parameters				
Left atrial diameter (mm)	39.65±5.06	40.15±4.90	38.48±5.70	0.24
Left atrial volume index (mL/m ²)	33.42±10.18	34.19±10.49	31.04±9.04	0.56
Left ventricular ejection fraction (%)	62.70±4.37	63.23±4.59	61.65±3.62	0.15

The values shown are mean ± SD or percentages.

Abbreviation: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Early recurrence refers the episode of symptomatic or asymptomatic documented atrial tachyarrhythmia > 30 seconds in the blanking period.

Laboratory test

The results revealed that no obvious differences existed between the two groups for the preoperative hs-CRP (hs-CRPpre) and HMGB1pre levels. The levels of hs-CRP and HMGB1 in the left atrium were significantly elevated after ablation. Moreover, the HMGB1post levels were obviously higher in the AF recurrence group than in the AF nonrecurrence group (298.51 μ g/L vs. 278.17 μ g/L; P = 0.03). However, the postoperative hs-CRP (hs-CRPpost) levels did differ between the two groups (Table 2).

Further, because two types of ablation procedures (RFA and CBA) were performed, we compared the association of HMGB1 between the two groups (RFA group and CBA group). The results revealed that in the RFA group, the HMGB1pre and HMGB1post levels did not differ between the AF recurrence and AF nonrecurrence groups (213.90 μ g/L vs. 218.21 μ g/L, P = 0.83 and 284.26 μ g/L vs. 260.28 μ g/L, P = 0.15, respectively). Similarly, in the CBA group, no significant differences in the HMGB1pre and HMGB1post levels were noted (281.82 μ g/L vs. 242.87 μ g/L, P = 0.43 and 295.22 μ g/L vs. 271.23 μ g/L; P = 0.52, respectively) between the AF recurrence and AF nonrecurrence groups (Table 2).

Table 2. Comparison of high-sensitivity C-reactive protein and high-mobility group box-1 from the left atrial serum between the two groups

All subjects	Nonrecurrence	Recurrence	P-value	
(N=72)	(N=53)	(N=19)		
Pre-operation				
hs-CRPpre (mg/L)	4.47 (3.79-5.15)	4.36 (3.74-5.08)	4.80 (3.74-8.03)	0.71
HMGB1pre (ug/L)	221.73 (191.18-250.50)	221.15 (193.35-246.98)	239.15 (189.63-360.70)	0.37
Post-operation				
hs-CRPpost (mg/L)	41.96 (36.48-50.13) *	43.17 (36.10-50.24) *	40.39 (36.97-69.60) *	0.63
HMGB1post (ug/L)	268.78 (244.24-298.79) *	260.28 (239.14-295.39) *	289.73 (270.29-365.42) *	0.03
RFA				
HMGB1pre (ug/L)	217.04(190.32-243.36)	218.21(192.47-245.12)	213.90(186.21-240.91)	0.83
HMGB1post (ug/L)	264.06(244.43-295.02)	260.28(241.41-295.39)	284.26(258.49-310.87)	0.15
CBA				
HMGB1pre (ug/L)	245.42(237.20-375.77)	242.87(232.50-346.02)	281.82(240.13-360.69)	0.43
HMGB1post (ug/L)	293.86(259.85-357.11)	271.23(228.57-527.95)	295.22(275.39-357.12)	0.52

The values shown are percentiles.

Abbreviation: hs-CRP, high sensitivity c-reactive protein; HMGB1, high mobility group 1 protein; RAF, radiofrequency ablation; CBA, cryoballoon ablation.

* P <0.05 vs. pre-operation

Univariate logistic regression analysis revealed that serum HMGB1post released from the left atrium was an independent predictor of AF recurrence (odds ratio [OR]: 3.90 [1.16–13.08], P = 0.03). After adjusting for common clinical risk factors for AF recurrence, such as age, female sex, AF period, CHADS2-VASc score, hypertension, diabetes mellitus, peripheral arterial diseases, left atrial diameter, LAVI, and LVEF, multiple logistic regression analysis confirmed that a high left atrial serum HMGB1post level was a significant prognostic predictor of AF recurrence(OR: 3.62 [1.02–12.77], P = 0.04; Table 3). ROC analysis revealed that serum HMGB1post released from the left atrium (AUC: 0.68; sensitivity: 72%; specificity: 68%) had a moderate predictive power for AF recurrence and the cutoff value of serum HMGB1post was calculated to be 279.35 µg/L (Fig. 1). Kaplan–Meier survival curves for AF recurrence using the

HMGB1post values revealed that the 1-year AF-free survival was significantly lower in patients with a high serum HMGB1post level (HMGB1post: ≥ 279.35 $\mu\text{g/L}$) than in those with a low HMGB1post level (HMGB1post: < 279.35 $\mu\text{g/L}$) (HR: 3.81 [1.49–9.75], P = 0.005; Fig. 2).

Table 3. Prediction of paroxysmal atrial fibrillation recurrence

Univariate	Multivariate			
	OR [95%CI]	P-value	OR [95%CI]	P-value
Age (yrs)	1.00 [0.94-1.06]	0.87	0.96 [0.88-1.06]	0.45
Female (%)	0.83 [0.25-2.68]	0.75	1.18 [0.26-5.46]	0.83
AF period (months)	1.00 [0.99-1.01]	0.80	1.00 [0.99-1.01]	0.64
CHA2DS2-VASc score	0.86 [0.60-1.23]	0.41	0.91 [0.44-1.87]	0.79
Hypertension (%)	0.34 [0.11-1.09]	0.07	0.71 [0.17-2.99]	0.64
Diabetes mellitus (%)	0.66 [0.13-3.44]	0.62	1.65 [0.19-14.43]	0.65
Peripheral arterial diseases (%)	0.72 [0.18-2.90]	0.64	1.64 [0.19-14.84]	0.66
Left atrial diameter (mm)	0.93 [0.84-1.04]	0.23	0.90 [0.76-1.07]	0.22
Left atrial volume index (mL/m ²)	0.98 [0.93-1.04]	0.48	1.02 [0.93-1.11]	0.69
Left ventricular ejection fraction (%)	0.91 [0.80-1.04]	0.15	0.88 [0.74-1.09]	0.27
HMGB1post (ug/L)	3.90 [1.16-13.08]	0.03	5.29 [1.17-23.92]	0.04

Abbreviation: HMGB1, high mobility group 1 protein.

Discussion

HMGB1 is both a nuclear factor and secreted protein that can be released into the extracellular space by activated immune cells or damaged cells during infection or injury. In addition, HMGB1 could be an inflammatory mediator that participates in the pathogenesis of inflammatory diseases (13). After CA, HMGB1 expression increases, causing a continuous state of oxidative stress and inflammation process (27). Further, HMGB1 may bind to HMGB1 receptor (Toll-like receptor-2,4) located in the left atrium and mediate atrial remodeling (15). In conclusion, after CA, HMGB1 is released into serum by damaged myocardial cells of the left atrium. In addition, HMGB1 acts as a pro-inflammatory factor in atrium remodeling, making atrial arrhythmia more likely to occur. This might explain the moderate predictive power of HMGB1post released from the left atrium for AF recurrence. No significant difference was noted between the AF recurrence and AF nonrecurrence groups for the hs-CRPpre and hs-CRPpost levels, which may be because hs-CRP is easily affected by other comorbidities (12). This is similar to the findings of

Masson S study that in pAF patients with a history of AF and without significant left ventricular dysfunction or heart failure, hs-CRP is a weak predictor of AF recurrence (28).

Early recurrence of AF (ERAF) could be a transient phenomenon due to inflammation or a foretaste of late AF recurrence due to CA lesion reconnection (29). Recently, increasing number of studies have reported that the incidence rate of ERAF is highly related to late AF recurrence after CA, irrespective of RFA (30) or CBA (31). Similarly, we found that a higher ERAF rate was related to higher AF late recurrence at 1-year follow-up.

Several studies have indicated that enlarged left atrial size is a potential predictor of AF recurrence with AF patients after CA (32, 33). However, this conclusion is based on the study of patients with LA enlargement. In our small sample study, the mean LAVI was 33.42 mL/m² and LVEF was 62.70%, indicating that our patients had only slight structural remodeling of LA. Thus, this conclusion is not suitable for our study.

To clarify the association between HMGB1 and AF recurrence, we evaluated the clinical efficacy of HMGB1 released from the left atrium for predicting AF recurrence. In contrast to previous studies, we collected blood samples from the left atrium instead of peripheral vessels to verify the effect of HMGB1. CA damages the myocardium and hence, HMGB1 is released by the injured cardiomyocytes directly into the left atrium (13). Collection of blood samples from the left atrium was aimed to emphasize the influence of local inflammation caused by HMGB1 on AF recurrence. Previous study found that myocardial damage by CA may contribute to transient diastolic dysfunction and AF recurrence through systemic proinflammatory reaction (34). But a recent major study showed that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early AF(35). Therefore, the ablation not only could prevent the progression of AF, but also could cause an injury to atrium tissue aggravating the fibrillation. This paper is aimed to offer a potential predictor to identify patients at high risk of AF recurrence.

Our study had several limitations. First, our sample size was small and therefore, we adopted the bootstrapping method (1000 repetitions) to compensate for the small sample size. We intend to increase our sample size and follow-up our patients for further study. Second, two CA procedures, RFA and CBA, were performed in our study, which contributed to the disequilibrium of the study population. However, both the HMGB1pre and HMGB1post levels were not significantly different between the AF recurrence and AF nonrecurrence group patients who underwent RFA as well as CBA. Therefore, the effect of this asymmetry was relatively small. Third, some AF events were asymptomatic and our patients were intermittently followed-up depending on patient-reported symptoms. Thus, the AF recurrence rates might have been underestimated, which can be improved by shortening the follow-up duration.

Conclusion

Our study found that in pAF patients undergoing CA, HMGB1post released from the left atrium was associated with AF recurrence and had a moderate predictive power for AF recurrence. Therefore, we offer

a potential predictor to identify patients at high risk of AF recurrence. This predictor is helpful for clinical decision-making and postoperative management of AF patients.

Declarations

Not applicable

Availability of data and materials

Not applicable. The study is currently ongoing on patient enrollment and data collection. Thus, no datasets were generated for analysis yet.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

CM and BY contributed the study conception and design. XxL was involved the data acquisition, data analysis and manuscript drafting. ML, HY, XpL and XS contributed to the acquisition of data. CZ and JQ performed the laboratory examination. YW was involved in the study data analysis. All authors reviewed and approved the final version of the manuscript.

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Abbreviations

AF, atrial fibrillation; AUC, area under the curve; CA, catheter ablation; CBA, cryoballoon ablation; CI, confidence intervals; ECG, electrocardiogram; HMGB1, high-mobility group box-1; HMGB1pre, preoperative high-mobility group box-1; HMGB1post, postoperative high-mobility group box-1; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-CRPpre, preoperative high-sensitivity C-reactive protein; hs-CRPpost, postoperative high-sensitivity C-reactive protein; LAVI, Left atrial volume index; LVEF, left ventricular ejection fraction; OR, odds ratio; pAF, paroxysmal atrial fibrillation; PV, pulmonary vein ; RAF, radiofrequency ablation; ROC, receiver operating characteristic.

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Figures

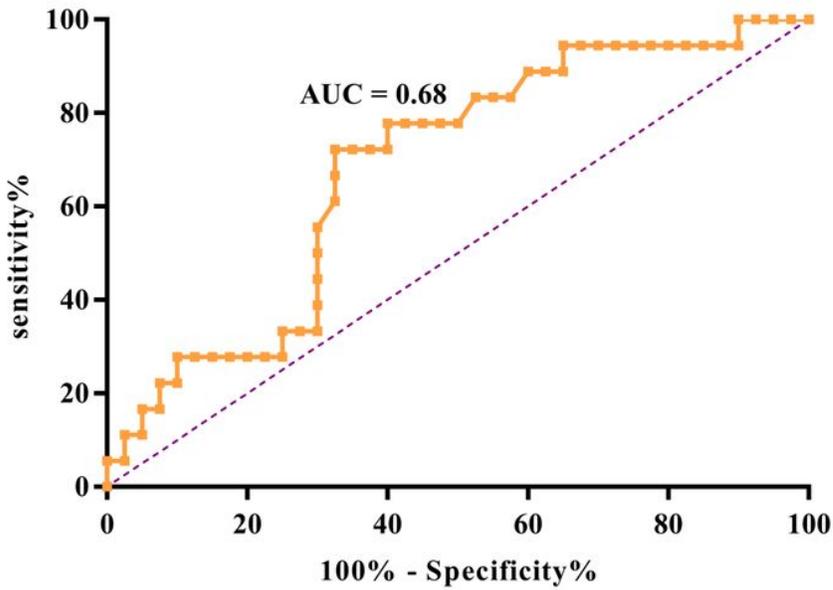


Fig. 1. Receiver-operating characteristic analysis of postoperative high-mobility group box-1

Figure 1

Receiver-operating characteristic analysis of postoperative high-mobility group box-1

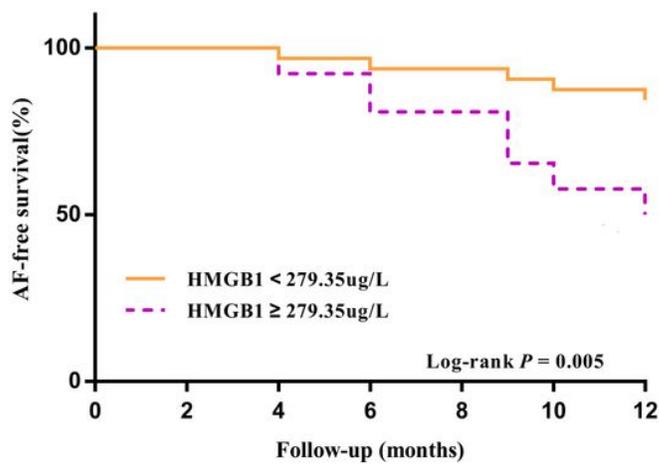


Fig. 2. Kaplan-Meier survival curve for atrial fibrillation recurrence. Analysis of 1-year atrial fibrillation-free survival to determine the impact of postoperative high-mobility group box-1 on atrial fibrillation recurrence in paroxysmal atrial fibrillation patients after catheter ablation.

Figure 2

Kaplan–Meier survival curve for atrial fibrillation reoccurrence Analysis of 1-year atrial fibrillation-free survival to determine the impact of postoperative high-mobility group box-1 on atrial fibrillation recurrence in paroxysmal atrial fibrillation patients after catheter ablation.