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Integrating the Left Atrium Diameter to Improve the Predictive Ability of the Age, Creatinine, and Ejection Fraction Score for Atrial Fibrillation Recurrence After Cryoballoon Ablation

ABSTRACT

Background: Several clinical trials have assessed predictors for atrial fibrillation recurrence following cryoballoon catheter ablation. With these predictors, a practical and new scoring system can be developed to evaluate atrial fibrillation recurrence. The present study aimed to analyze the predictive value of the age, creatinine, and ejection fraction-left atrium score for potential recurrence of atrial fibrillation following cryoballoon catheter ablation in patients with symptomatic paroxysmal or persistent atrial fibrillation.

Methods: We retrospectively analyzed records of patients undergoing cryoballoon catheter ablation. atrial fibrillation recurrence was defined as an emerging atrial fibrillation episode around 12-month follow-up (with the exclusion of a 3-month blanking period). Univariate and multivariate analyses were performed to assess predictors of atrial fibrillation recurrence. In addition, receiver operating characteristic analysis was harnessed to evaluate the performance of the age, creatinine, and ejection fraction, left atrium score in determining the risk of atrial fibrillation recurrence.

Results: The study population comprised 106 subjects (age 52 ± 13 years, 63.2% women) with paroxysmal (84.9%, n = 90) or persistent (15.1%, n = 16) atrial fibrillation. age, creatinine, and ejection fraction, left atrium score was significantly higher in subjects with atrial fibrillation recurrence in comparison to those with the maintenance of sinus rhythm. However, on multivariate logistic regression analysis, only the age, creatinine, and ejection fraction, left atrium score (OR = 12.93, 95% CI: 2.22-75.21, *P* = .004) served as an independent predictor of atrial fibrillation recurrence following cryoballoon catheter ablation.

Conclusion: Age, creatinine, and ejection fraction, left atrium score had an independent association with the risk of atrial fibrillation recurrence in subjects with atrial fibrillation undergoing cryoballoon catheter ablation. Therefore, this score might potentially serve as a useful tool for risk stratification of patients with atrial fibrillation.

Keywords: Age, atrial fibrillation, creatinine, cryoballoon ablation, ejection fraction, left atrium, recurrence

ORIGINAL INVESTIGATION

Gökay Taylan[1]
Murat Gök[1]
Alparslan Kurtul[2]
Abdulkadir Uslu[3]
Ayhan Küp[3]
Serdar Demir[3]
Kamil Gülşen[3]
Servet Altay[1]
Taylan Akgün[3]
Kenan Yalta[1]

[1]*Department of Cardiology, Faculty of Medicine, Trakya University, Edirne, Türkiye*
[2]*Department of Cardiology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Türkiye*
[3]*Department of Cardiology, Kartal Koşuyolu High Specialization Training and Research Hospital, İstanbul, Türkiye*

Corresponding author:
Gökay Taylan
✉ taylan1091@hotmail.com

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INTRODUCTION

Catheter cryoballoon ablation (CCA) of atrial fibrillation (AF) primarily targeting pulmonary vein (PV) isolation has been a safe and efficient strategy in subjects with drug-refractory and symptomatic AF.[1,2] Catheter cryoballoon ablation therapy of AF limits disease progression by interrupting progressive pathophysiological changes, improves clinical outcomes, and reduces the risk of adverse cardiovascular outcomes, including stroke.[3-5] Notwithstanding the significant improvement in procedural outcomes largely due to advanced ablation techniques, AF recurrence still remains a major challenge following CCA (encountered in 25-50% of subjects on follow-up).[6] Therefore, it seems imperative to identify specific predictors of AF recurrence following CCA that has been increasingly adopted in clinical practice.

The age, creatinine, and ejection fraction (ACEF) score, which might be regarded as quite practical, comprised 3 factors, and was originally suggested to evaluate mortality risk in elective cardiac surgeries.[7] In the course of time, this score has

been confirmed in a variety of procedures and clinical scenarios in the cardiovascular arena.[8-11] Given the several studies harnessing clinical features and laboratory data to analyze predictors of AF recurrence,[12-14] ACEF score might also have the potential to predict AF recurrence after CCA (can be considered as a minimally invasive surgical procedure). On the other hand, the ACEF score does not include left atrium (LA) diameter, which has been an important risk factor for AF recurrence following the procedure.[15] The addition of LA to this score might be based on the fact that this parameter appears to be routinely measured in clinical evaluation and has been one of the most rapidly evaluated parameters in transthoracic echocardiography (TTE). Furthermore, it has been potentially considered as one of the important independent parameters used to predict AF recurrence.[15] In this regard, its evaluation using the left atrial volume index may be easily applicable. Therefore, using the ACEF-LA score might be of significant predictive value in this context. In particular, the usefulness of preprocedural ACEF-LA score in the prediction of AF recurrence following CCA has not been tested so far.

Therefore, the goal of this study was to analyze the efficacy of the ACEF score and the modified ACEF-LA model (incorporating LA size) in the prediction of AF recurrence following CCA.

METHODS

Study Population

Between January 2018 and December 2019, 125 consecutive subjects undergoing CCA (for PV isolation) for documented symptomatic paroxysmal or persistent AF were enrolled in this 2 centered and retrospective study. In the present study, the primary end point was the first recurrence of AF lasting 30 seconds or longer after 90 days after the CCA procedure. Subjects with moderate to severe valvular disease, history of significant coronary artery disease, thyroid disorders, LA thrombus, myocardial infarction or cardiac operations within the last 3 months, a contraindication to anticoagulant therapy, pregnancy, or a LA size of >50 mm were initially excluded from the analysis. One hundred six patients were included in the final analysis. An episode of AF lasting more than 7 days (including episodes that were terminated by cardioversion) was defined as persistent AF. An episode of self-terminated AF within 7 days was defined as paroxysmal AF.[16]

Hypertension was defined as being on anti-hypertensive agents or as a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg or a definite history of hypertension. Hyperlipidemia was defined as being on lipid-lowering therapy, or a definite history of hyperlipidemia, or having a total cholesterol level of >200 mg/dL or a triglyceride level of >150 mg/dL. Diabetes was defined as a fasting blood glucose of ≥126 mg/dL or a definite history of diabetes. Finally, chronic kidney disease was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2 within the last 3 months or more, irrespective of the underlying etiology.

Standard TTE was performed to exclude any structural abnormality. In addition, LVEF (Simpson's method) and LA diameter (measured in the parasternal long axis view at end systole (when the left atrium has its maximum volume) were evaluated, and TTE images were evaluated by 2 different operators. Left atriun thrombus was excluded with transesophageal echocardiography, and PV configuration was analyzed with multidetector computed tomography. Age, creatinine, and ejection fraction-left atrium score was calculated as follows: age (years)/ejection fraction (%) + 1 (if creatinine ≥2.0 mg/dL) + 1 (if LA diameter >4.0 cm).

Informed consent was waived due to the retrospective feature of the study. However, the Local Research Ethics Committee endorsed the study that uniformly conformed to the Declaration of Helsinki.

Cryoballoon Ablation Procedure

The CCA procedures were implemented by electrophysiologists with extensive experience. Conscious sedation or general anesthesia was preferred at the discretion of the treating clinician. Continuous monitoring of vital parameters, along with electrocardiogram was implemented during the procedure. Technical details of CCA were explained elsewhere.[1,2] Follow-up evaluations were implemented at 3, 6, and 12 months following CCA, and every 6 months thereafter or in case of emerging symptoms. The blanking period was defined as the first 3 months following CCA. Arrhythmia recurrence was defined as an emerging AF episode of ≥ 30-second duration and was verified with 12-lead electrocardiography (ECG) 3 months after CCA.[17] Potential necessity for oral anticoagulation was assessed after 3 months according to CHA2DS2VASc score. Antiarrhythmic drug therapy (amiodarone) was preferred in the 3 months in the blanking period.

Statistical Analysis

The continuous variables were shown as the mean ± standard deviation (SD) along with categorical variables demonstrated as numbers and percentages. Assessment of normality was evaluated with Shapiro–Wilk criterion. Continuous variables were demonstrated as mean ± SD or median (25^{th}-75^{th} interquartile range). Comparisons of continuous variables were performed with Student's *t*-test or Mann–Whitney *U* rank sum. Categorical variables were shown as counts and percentages and were compared - based on chi squared or Fisher's exact test. Since no previous work with the ACEF score was available in the AF cryoablation population, we could not perform a power calculation.

The ACEF score and ACEF-LA score were harnessed in multiple logistic regression analysis with the use of

HIGHLIGHTS

- The age, creatinine, and ejection fraction, left atrium (ACEF-LA) score might be regarded as quite practical.
- Preprocedural ACEF-LA score is useful for the prediction of atrial fibrillation (AF) recurrence following cryoballoon catheter ablation (CCA).
- Patients with a high risk of AF recurrence following CCA should be under close follow-up.

Table 1. Baseline Demographic and Clinical Data of Study Patients

Variables	Atrial Fibrillation Recurrence		*P* value
	No (n = 88)	Yes (n = 18)	
Age (years)	52.1 ± 12.4	50.1 ± 15.8	.554
BMI (kg/m^2)	26.8 ± 2.7	27.1 ± 2.7	.685
Male gender, n (%)	34 (38.6)	5 (27.8)	.434
Hypertension, n (%)	36 (40.9)	6 (33.3)	.607
Diabetes mellitus, n (%)	17 (19.3)	4 (22.2)	.752
Hyperlipidemia, n (%)	15 (17.0)	5 (27.8)	.325
Coronary artery disease, n (%)	7 (8.0)	1 (5.6)	1.000
Chronic kidney disease, n (%)	5 (5.7)	2 (11.1)	.339
Antiarrhythmic drug therapy, n (%)	61 (69.3)	16 (88.9)	.095
Type of atrial fibrillation, n (%)			.099
Paroxysmal	77 (87.5)	13 (72.2)	
Persistent	11 (12.5)	5 (27.8)	

BMI, body mass index; n, number.

Hosmer–Lemeshow statistics. Optimum cut-off levels of ACEF-LA score for the prediction of AF recurrence was performed with receiver operating characteristic (ROC) curve analysis. All possible variables including type and duration of AF, follow-up time, and drug therapy were assessed through multivariable logistic regression analysis. A *P* value of less than .05 was regarded to have statistical significance.

Table 2. Procedural and Laboratory Data of Study Patients

Variables	Atrial Fibrillation Recurrence		*P* value
	No (n = 88)	Yes (n = 18)	
ACEF-LA score	1.04 ± 0.5	1.6 ± 0.6	<.001
CHA2DS2-VASc score	1.25 ±1.3	1.28 ± 1.07	.936
Total procedural time (min)	95.7 ± 8.9	96.8 ± 9.5	.649
Fluoroscopy time (min)	29.1 ± 5.4	29.4 ± 6.1	.856
AF diagnosis time (months)	31.8 ± 18.7	36.0 ± 14.4	.379
Left ventricular ejection fraction (%)	61.5 ± 6.2	56.3 ± 8.7	.004
Left atrium diameter (mm)	3.7 ± 0.4	4.2 ± 0.3	<.001
ACEF score	0.86 ± 0.24	0.91 ± 0.37	.098
Serum creatinine (mg/dL)	0.82 ± 0.20	0.89 ± 0.28	.214
White blood cell count (×10^9/L)	7.7 ± 2.1	8.0 ± 2.0	.586
Hemoglobin (g/dL)	13.8 ± 1.4	13.7 ± 2.0	.840
Platelet count (×10^9/L)	232 ± 42	220 ± 59	.314
Follow-up time (months)	23 (12-30)	30 (18-36)	.080

ACEF, age creatinine ejection fraction; ACEF-LA, age creatinine ejection fraction-left atrium; AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure hypertension ≥75 age diabetes mellitus stroke-vascular diseases 65-74 age sex; n, number.

RESULTS

The study population comprised 106 subjects (age 52 ± 13 years, 63.2% women) with paroxysmal (84.9%, n = 90) or persistent (15.1%, n = 16) AF. Based on whether AF recurrence

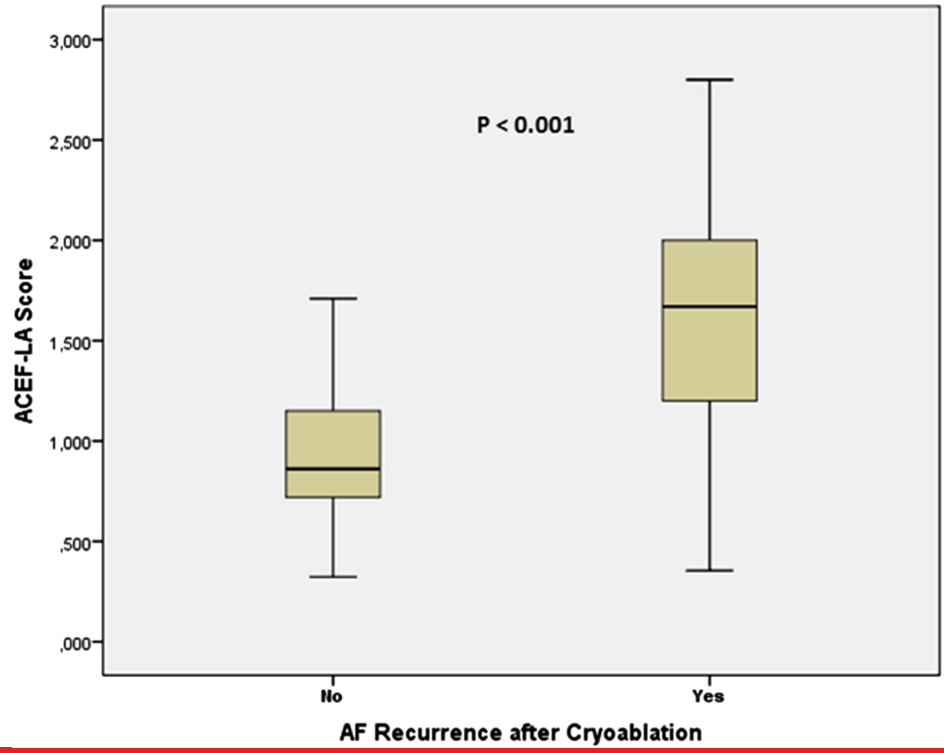

Figure 1. Comparison of precryoablation ACEF-LA score with development of postcryoablation atrial fibrillation recurrence. ACEF-LA, age, creatinine, and ejection fraction-left atrium.

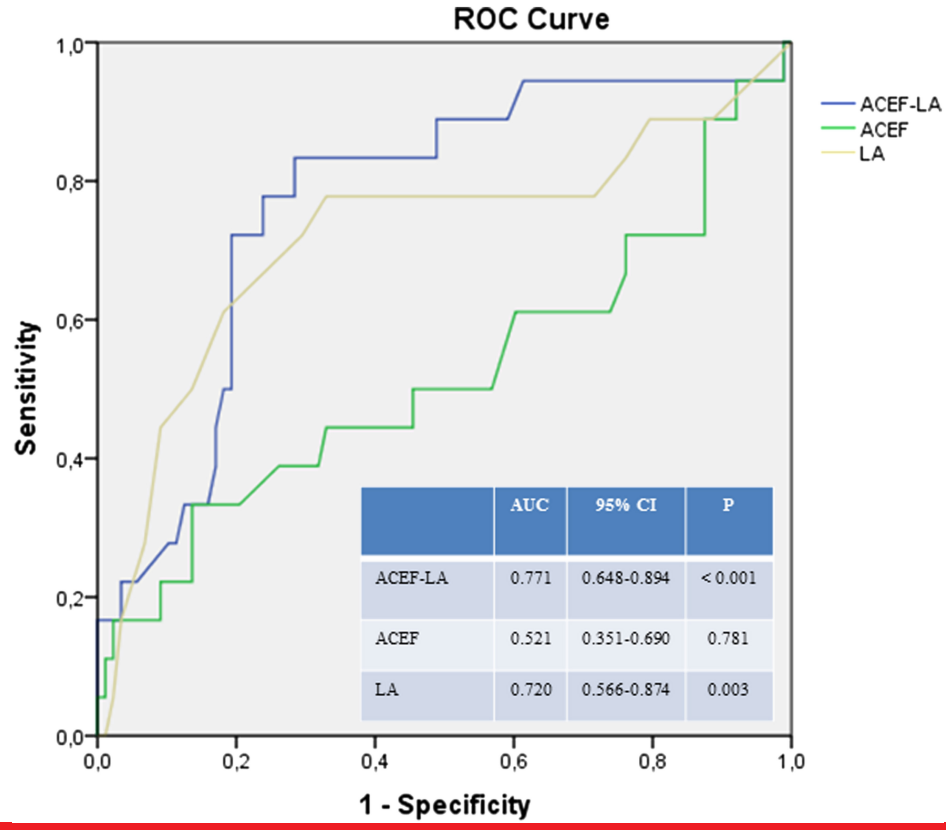

Figure 2. ROC curve of the ACEF-LA scoring system in predicting atrial fibrillation recurrence after cryoballoon ablation. ACEF-LA, age, creatinine and ejection fraction-left atrium; ROC, receiver operating characteristic.

developed during the follow-up period, all subjects were categorized into the AF recurrence group and no AF recurrence group. Following a mean period of 25 ± 14 months, recurrence was encountered in 18 patients (17.0%). Baseline clinical characteristics are presented in detail in Table 1. Age, gender, history of hypertension, coronary artery disease, diabetes mellitus, hyperlipidemia, chronic kidney disease, antiarrhythmic drug therapy, and type of AF were comparable between the 2 groups.

Procedural and laboratory data of subjects are presented in Table 2. The subjects with AF recurrence had reduced left ventricular ejection fraction (LVEF), increased LA size, and increased ACEF-LA score (Figure 1) in comparison to those who did not have AF recurrence. The subjects with AF recurrence also had increased ACEF scores and follow-up time in comparison to those without a recurrence (yet failing to attain a statistical significance ($P > .05$ for all).

In ROC curve analysis, the area under the curve of the ACEF-LA score for predicting AF recurrence was 0.771 (95% CI: 0.65-0.89; $P < .001$); sensitivity, 84%; specificity, 72%, and the optimum cut-off value was 1.075 (Figure 2).

In multiple logistic regression analysis, only the ACEF-LA score (OR = 12.93, 95% CI: 2.22-75.21, $P = .004$) served as an independent predictor for AF recurrence following CCA (Table 3). The ACEF score and LA did not serve as independent predictor in multiple analysis demonstrating a borderline statistical significance ($P = .055$ and $P = .780$).

Table 3. Multiple Regression Analysis of Clinical Parameters for Postcryoablation Atrial Fibrillation Recurrence Prediction

	Clinical Covariates Adjusted		
Variables	**Odds Ratio**	**95% CI**	***P* value**
ACEF-LA score	12.93	2.22-75.21	.004
Follow-up time	1.02	0.98-1.07	.163
Type of atrial fibrillation	0.92	0.18-4.53	.924
Duration of atrial fibrillation diagnosis	1.00	0.96-1.03	.971
Antiarrhythmic drug therapy	2.47	0.43-14.00	.306
ACEF score	2.30	0.97-3.08	.055
LA	1.28	0.21-7.69	.780

ACEF, age creatinine ejection fraction; ACEF-LA, age creatinine ejection fraction-left atrium diameter; LA, left atrium diameter.

DISCUSSION

In this study comprising subjects with persistent or paroxysmal AF, we, for the first time, were able to demonstrate that AF recurred more often in those who had higher ACEF-LA scores following CCA of PVs. In addition, this score had an independent association with AF recurrence in multivariable analysis. Therefore, this hypothetical ACEF-LA score might serve as a useful and relatively simple tool for the prediction of AF recurrence in patients undergoing CCA. However, the present study might be regarded as a hypothesis-generating

and preliminary study that needs to be confirmed by large-scale trials.

Cryoballoon catheter ablation, as first-line treatment, has been a more favorable option compared with antiarrhythmic drugs for the prevention of AF recurrence and improvement of patients' well-being in the settings of paroxysmal and persistent AF.[18,19] AF recurrence has long been a significant clinical challenge following CCA. Therefore, early recognition along with risk stratification might potentially mitigate the risk of AF recurrence in such patients. Several markers and scores have been suggested for the prediction of AF recurrence following CCA of AF.[20] In a previous study, it was inferred that an increased pre-CCA neutrophil to lymphocyte ratio might be associated with AF recurrence following CCA.[21] Aakash et al[22] suggested certain patient characteristics, including LA diameter of > 40 mm and early AF recurrence as significant predictors of AF recurrence. In another study, Hermida et al[23] evaluated the prevalence and predictors of LA tachycardia following CCA of PVs. The authors reported that baseline LVEF < 50% was found to be associated with an elevated risk of post-CCA LA tachycardia. The aforementioned risk factors for AF recurrence following CCA in the setting of persistent or paroxysmal AF are also included in the ACEF-LA score.

In the clinical setting, serum creatinine level is of crucial importance in the evolution of contrast nephropathy. However, this complication generally arises in the presence of contrast agent doses over 150 mL.[24] In the setting of the cryoablation procedure, the dose of the contrast agent used was below this value, and accordingly, no patient developed significant contrast nephropathy on follow-up.

The lower cut-off value of the LA diameter (which predicted AF recurrence) was not calculated. In this setting, the value of 4 cm is generally accepted as the lower limit for the enlarged LA diameter in the literature.[23] An LA diameter of 5 cm was accepted as an exclusion criterion due to the increased frequency of non-PV isolation (PVI) foci in this context, potentially leading to a preferential use of radiofrequency (RF) ablation by most operators. In this respect, we also excluded those undergoing RF ablation (which exclusively targets PVI in AF ablation) to prevent selection bias.[25]

In our study, although the ACEF score was not statistically different between the groups, the mean age and ejection fraction were lower in the recurrence group, along with higher creatinine levels. Importantly, the value of ACEF-LA score was found to be statistically different between the groups. However, this needs to be tested in larger populations. Of note, we hold the opinion that reduced compliance with the medical treatment after ablation in young patients might also have an impact on AF recurrence.

Moreover, the recurrence rate in our study was 17%, which is relatively lower compared with the literature. This might be due to the relatively short follow-up period (mean duration of 30 months) and higher incidence of subclinical AF (that might have gone unnoticed on follow-up). We hold the opinion that longer follow-up in the current study may potentially lead to similar recurrence rates (around 25-40%).[26] Therefore, we plan to expand our study (in terms of follow-up periods and possibly number of patients recruited) in the future.

The ACEF score was initially suggested to predict mortality risk following elective cardiac operations. Thereafter, its use has been extended to a variety of clinical conditions, such as acute coronary syndromes, percutaneous coronary interventions, and transcatheter aortic valve implantation. In these clinical settings, an increased ACEF score has been linked with adverse cardiovascular outcomes such as mortality. However, to date, the predictive value of the ACEF score in AF subjects managed with CCA has not been thoroughly assessed. However, the current study has demonstrated that ACEF-LA score is of more clinical value in comparison to ACEF score for the prediction of AF recurrence following CCA (Figure 2: In the ROC analysis, ACEF-LA score predicted recurrence with higher specificity and sensitivity than ACEF or LA alone).

Due to the high risk of recurrence in patients with ACEF-LA score above the cut-off value, these patients should be under close follow-up in terms of AF recurrence. Therefore, patient-specific evaluation, along with consideration of RF ablation with 3D mapping in certain settings seems as a plausible strategy. Based on current results, integration of LA size into the ACEF score might potentially create a novel and clinically useful clinical score, namely ACEF-LA score. This is largely based on the fact that the ACEF-LA score served as the sole independent factor for the prediction of AF recurrence in the post-CCA setting in subjects with paroxysmal or persistent AF. However, further studies are still necessary to confirm its clinical value in this context.

Study Limitations

There exists a variety of limitations in this hypothesis-generating study. This is a 2 center study harboring a small sample size and a preliminary design. Intermittent rather than continuous monitoring might have led to an underdiagnosis of AF recurrence in both groups. In addition, the follow-up period is relatively short. However, the monitoring protocol was comparable between the 2 groups and was analogous to previous reports.

CONCLUSION

ACEF-LA score might gain widespread recognition and clinical utility for the prediction of AF recurrence following CCA.

Availability of data and material: The data that support the findings of this study are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study was approved by the Local Ethics Board (TU-BAEK 2021/391 and date: 04.10.2021) and complies with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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