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ORIGINAL RESEARCH

The HALP Index Is Associated with the Recurrence of Persistent Atrial Fibrillation Following Radiofrequency Catheter Ablation

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Purpose: To evaluate the relationship between the HALP Index and the recurrence of persistent atrial fibrillation (AF) following radiofrequency catheter ablation (RFCA).

Methods: We retrospectively analyzed 471 patients with persistent AF treated with RFCA between January 2019 and June 2022 at Yantai Yuhuangding Hospital of Qingdao University. The relationship between the Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Index and AF recurrence outcomes was assessed using Kaplan-Meier survival curve analysis and multifactorial Cox proportional hazards regression modeling. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value of the HALP Index for recurrence in patients with persistent AF undergoing RFCA.

Results: After a mean follow-up of 43.6 months, recurrence occurred in 130 patients (27.6%). There was a significant difference in the recurrence rate after RFCA of AF among the different HALP Index groups (44.9% vs 26.3% vs 22.9% vs 16.2%, $F = 9.347$, $P < 0.001$). Multifactorial Cox proportional hazards regression analysis indicated that the HALP Index was significantly associated with recurrence after RFCA of AF (HR = 0.967, $P < 0.001$). The HALP Index was treated as a categorical variable in the multifactorial Cox proportional hazards regression analysis, which revealed that the recurrence rate of RFCA of AF was significantly higher in the low HALP Index group compared to the high HALP Index group (HR = 6.080, $P < 0.001$). The results of the Kaplan-Meier survival analyses suggested a significant difference in recurrence after RFCA of AF among the various HALP Index groups (Log-rank $P < 0.001$). The ROC curve analysis demonstrated the predictive value of the HALP Index for recurrence after RFCA of AF, with an area under the curve (AUC) of 0.659 (95% CI 0.603–0.715, $P < 0.001$).

Conclusion: The HALP Index was an independent protective predictor of recurrence following RFCA of persistent AF.

Keywords: the HALP index, atrial fibrillation, radiofrequency catheter ablation, recurrence

Introduction

Atrial fibrillation (AF) is the most common and persistent cardiac arrhythmia, with its incidence and prevalence rising globally.[1] The estimated global prevalence of AF in 2020 was 50 million.[2] AF is associated with increased healthcare utilization and costs, placing a significant burden on society and elevating the risk of death by 1.5 to 2 times.[3] Additionally, AF is linked to a higher risk of several adverse outcomes, including a 2.4-fold increase in the risk of stroke, a 1.5-fold increase in the risk of myocardial infarction (MI), a 2-fold increase in the risk of sudden cardiac death, and a 5-fold increase in the risk of heart failure (HF).[3,4] Radiofrequency catheter ablation (RFCA) is increasingly utilized to treat patients with AF; however, the rate of post-procedural recurrence remains high. Previous studies have indicated that the postoperative success rate for patients with paroxysmal AF is approximately 85%, while for those with persistent AF, it is only about 60% to 70%.[5,6] Several studies have shown that there is a close correlation between inflammation and AF, indicating that the occurrence of AF is the result of necrosis and fibrosis caused by inflammatory processes.[7,8] Lymphocytes are involved in the occurrence and development of AF through inflammatory and immunomodulatory mechanisms, and low lymphocyte count may reflect a chronic inflammatory state.[9] Albumin, the most abundant protein

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in humans, has antioxidant and anti-inflammatory effects and inhibits platelet aggregation and activation.[10] Platelets not only participate in the thrombosis of AF, but also directly promote atrial structural remodeling and myocardial fibrosis by releasing pro-fibrotic factors (such as TGF-β1, PDGF, etc) and mediating inflammatory response, thus maintaining the persistence and recurrence of AF.[11] When anemia occurs, free hemoglobin increases, releasing heme iron catalyzes free radicals to generate oxidative stress that damages atrial muscle cell membrane and induces electrical remodeling, which may lead to AF.[12] The HALP Index is a novel immune marker that integrates several routinely collected indicators of immune status, including platelet counts, lymphocyte counts, albumin levels, and hemoglobin levels. Several previous studies have utilized the HALP Index in the prognostic assessment of tumor patients.[13–15] However, the predictive value of the HALP Index for recurrence following RFCA of AF has been infrequently reported. Our primary objective was to investigate the impact of the preoperative HALP Index on recurrence in patients with persistent AF undergoing RFCA.

Population and Methods

The flowchart of our study is presented in Figure 1. We retrospectively analyzed 471 patients with persistent AF who underwent their first RFCA from January 2019 to June 2022 at the Affiliated Yantai Yuhuangding Hospital of Qingdao University. Persistent AF was defined as episodes lasting seven days or more or requiring cardioversion. Relevant blood indicators, including complete blood count, biochemical markers, and coagulation function, were collected within 24 hours of admission for all patients. Transthoracic echocardiography was performed on all patients to measure left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF). Transesophageal echocardiography was conducted to exclude thrombus and to measure left atrial appendage strain (LAAS). All patients were followed up for at least three months after the ablation procedure. We excluded patients based on the following criteria: (1) failure to follow up; (2) missing information regarding the HALP Index; (3) valvular heart disease; (4) malignant tumors; and (5) recent myocardial infarction. The study adhered to the Declaration of Helsinki and

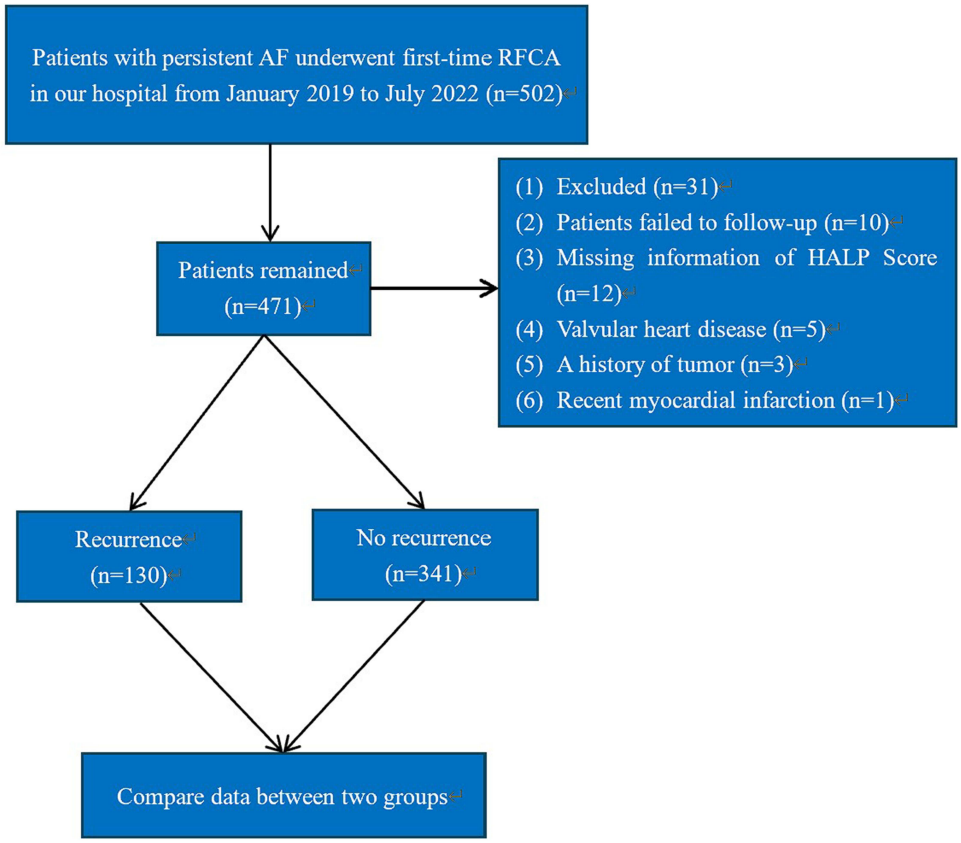

Figure 1 The flowchart of our study.

was approved by the Institutional Review Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University.

The HALP Index is calculated using the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L) ÷ platelets (/L). The neutrophil-to-lymphocyte ratio (NLR) is determined by dividing the neutrophil count (/L) by the lymphocyte count (/L). The HALP Index is categorized into four groups based on quartiles: Q1, <37.38; Q2, 37.39–48.70; Q3, 48.71–62.40; Q4, >62.41. Hypertension is defined as a blood pressure of ≥140/90 mmHg in the absence of antihypertensive medication.[16] Diabetes mellitus (DM) is defined by fasting blood glucose levels of ≥7.0 mmol/L, HbA1c levels of ≥6.5%, or an oral glucose tolerance test (OGTT) result of ≥11.1 mmol/L after 2 hours.[17] Coronary artery disease (CAD) is characterized by a narrowing of more than 50% in the left or right main coronary artery or its major branches. Cerebral ischemic stroke (CIS) is defined as a narrowing of more than 50% or occlusion of the intracranial or extracranial major arteries, accompanied by vascular lesions consistent with atherosclerosis. Chronic heart failure (CHF) is diagnosed according to the Heart Failure Guidelines of the European Society of Cardiology.[18] The diagnosis of chronic obstructive pulmonary disease (COPD) is based on clinical data, including a history of exposure to risk factors, symptoms, pulmonary function tests, and the presence of persistent airflow limitation, which is evident when the FEV1/FVC ratio is <70% after the administration of bronchodilators.[19]

Ablation Procedure

After two transseptal punctures, the three-dimensional geometry of the left atrium was reconstructed using the CARTO 3 navigation system (Biosense Webster, Inc., Diamond Bar, CA, USA). Angiography was performed on all patients to examine the openings of the pulmonary veins (PVs). All patients underwent circumferential pulmonary vein isolation (CPVI). Additional linear ablation techniques, such as left anterior atrial linear ablation, roof linear ablation, tricuspid isthmus linear ablation, mitral isthmus linear ablation, and complex fractionated atrial electrogram (CFAE) ablation, were employed as needed based on the surgeon's discretion. Radiofrequency energy of 40–45 W was applied at each site, with a flow rate of 20 mL/min, a target temperature of 43°C, and a maximum duration of 60 seconds. If sinus rhythm could not be maintained, cardioversion was performed following ablation. The endpoint of the ablation was defined as the absence or dissociation of electrical potentials in the isolated regions. All patients ultimately returned to sinus rhythm and were monitored for 30 minutes without any recurrence of arrhythmia. During the radiofrequency ablation, pericardial tamponade occurred in six patients (1.3%), with symptoms improving after drainage of the pericardial effusion. Five patients (1.1%) developed pseudoaneurysms during femoral vein puncture; these pseudoaneurysms resolved after post-operative pressure was applied to ensure their disappearance.

Follow-Up

All patients were prescribed dabigatran or rivaroxaban for a minimum of three months following ablation to prevent thrombosis. Clinical follow-up included outpatient visits, which involved 24-hour Holter monitoring or 12-lead ECG monitoring at 3, 6, and 12 months post-ablation, and every 6 months thereafter. All patients underwent 12-lead electrocardiograms or 24-hour Holter monitoring when experiencing palpitations. Recurrence was defined as any recorded AF, atrial flutter (AFL), or atrial tachycardia (AT) lasting longer than 30 seconds during the follow-up period. Early recurrence (ER) was defined as the recurrence of AF ≥30 s during the first 3 months of follow-up after RFCA. During the follow-up period, two patients (0.4%) developed new CIS, which were later determined to be unrelated to AF. All 471 patients with AF survived, and no deaths occurred.

Statistical Analyses

SPSS 27.0 and GraphPad Prism 8 were used for statistical analysis and mapping. The Kolmogorov–Smirnov test was employed to assess whether the measurement data followed a normal distribution. Data that did not conform to a normal distribution were represented by the median and interquartile range [M (IQR)], and the Mann–Whitney nonparametric test was utilized for inter-group comparisons. Categorical data were expressed as percentage component ratios (n, %), and the χ^2-test was applied for comparisons between groups. The Spearman rank correlation coefficient was used for correlation analysis. Cox multifactorial regression analysis was performed to identify risk factors associated with postoperative recurrence of AF. The ROC curve was employed to evaluate the predictive value of the HALP Index

for postoperative recurrence of AF. The DeLong test was used to compare the areas under different ROC curves. Kaplan-Meier survival curves were generated to compare postoperative recurrence rates among HALP groups. A two-sided P-value of < 0.05 was considered statistically significant.

Results

Baseline Data

As shown in Table 1, significant differences were observed between the recurrent and non-recurrent groups in AF duration, history of CAD, history of CHF, albumin levels, hemoglobin levels, lymphocyte counts, neutrophil counts, the proportion of roof line ablation, the proportion of mitral isthmus ablation, LAD, LAAS, LVEDD, LVEF, proportion of ER, NLR and the HALP Index ($P < 0.05$).

Relationship Between the HALP Index and AF Recurrence After RFCA

There was a significant difference in recurrence rates after RFCA of AF between patients with varying HALP Index (44.9% vs 26.3% vs 22.9% vs 16.2%, $P < 0.001$). The HALP Index was lower in the recurrence group compared to the non-recurrence group ($P < 0.001$). Figure 2.

Table 1 Clinical Baseline Data of AF Populations

Variable	Total (n = 471)	No-Recurrence (n = 341)	Recurrence (n= 130)	P-value
Age (years)	63 (57, 69)	63 (57, 68)	64 (59, 69)	0.127
Gender (n, %)				0.726
Male	285 (60.5)	208 (61.0)	77 (59.2)	
Female	186 (39.4)	133 (39)	53 (40.8)	
AF duration (months)	20 (6, 48)	12 (3, 36)	36 (16, 84)	**<0.001**
Combined AFL (n, %)				0.803
Yes	41 (8.7)	29 (8.5)	12 (9.2)	
No	430 (91.3)	312 (91.5)	118 (90.8)	
Hypertension (n, %)				0.931
Yes	266 (56.5)	193 (56.6)	73 (56.2)	
No	205 (43.5)	148 (43.4)	57 (43.8)	
DM (n, %)				0.145
Yes	82 (17.4)	54 (15.8)	28 (21.5)	
No	389 (82.6)	287 (84.2)	102 (78.5)	
CAD (n, %)				**0.004**
Yes	87 (18.5)	52 (15.2)	35 (26.9)	
No	384 (81.5)	289 (84.8)	95 (73.1)	
CHF (n, %)				**0.019**
Yes	78 (16.6)	48 (14.1)	30 (23.1)	
No	393 (83.4)	293 (85.9)	100 (76.9)	
COPD (n, %)				0.180
Yes	11 (2.3)	6 (1.8)	5 (3.8)	
No	460 (97.7)	335 (98.2)	125 (96.2)	
CIS (n, %)				0.418
Yes	56 (11.9)	38 (11.1)	18 (13.8)	
No	415 (88.1)	303 (88.9)	112 (86.2)	
CHA2DS2-VAsc Score	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.212
Albumin (g/L)	40.42 (38.31, 42.28)	40.57 (38.54, 42.41)	39.82 (37.26, 42.04)	**0.037**
AST (U/L)	22 (18, 27)	22 (19, 28)	21 (18, 27)	0.299

(*Continued*)

Table 1 (Continued).

Variable	Total (n = 471)	No-Recurrence (n = 341)	Recurrence (n= 130)	P-value
ALT (U/L)	21 (16, 31)	22 (16, 31)	21 (16, 31)	0.785
GLU (mmol/L)	5.39 (4.86, 6.21)	5.35 (4.85, 6.08)	5.49 (4.90, 6.71)	0.109
Urea (mmol/L)	5.83 (4.82, 6.97)	5.79 (4.86, 6.87)	6.09 (4.79, 7.26)	0.385
SCr (umol/L)	66 (56, 75)	66 (56, 75)	65 (57, 77)	0.913
SUA (umol/L)	360 (301, 415)	357 (300, 411)	364 (305, 419)	0.427
TG (mmol/L)	1.09 (0.81, 1.53)	1.10 (0.81, 1.55)	1.08 (0.83, 1.49)	0.614
TC (mmol/L)	4.54 (3.79, 5.36)	4.58 (3.82, 5.39)	4.40 (3.64, 5.29)	0.402
HDL-C (mmol/L)	1.23 (1.05, 1.44)	1.24 (1.05, 1.46)	1.21 (1.06, 1.40)	0.603
LDL-C (mmol/L)	2.78 (2.21, 3.49)	2.78 (2.23, 3.49)	2.78 (2.10, 3.51)	0.737
Homocysteine (mg/L)	12.6 (10.7, 15.0)	12.7 (10.7, 15.0)	12.5 (10.5, 14.9)	0.637
BNP (pg/mL)	135.4 (64.48, 270.42)	126.6 (62.1, 259.9)	153.6 (72.7, 281.8)	0.116
D-dimer (mg/L)	0.58 (0.45, 0.79)	0.57 (0.45, 0.78)	0.61 (0.47, 0.84)	0.140
Hemoglobin ($\times10^9$ /L)	148 (137, 158)	149 (138, 160)	143 (134, 154)	**0.009**
Platelet ($\times10^9$ /L)	212 (183, 250)	211 (183, 247)	225 (182, 268)	0.099
Leucocyte ($\times10^9$ /L)	6.26 (5.28, 7.53)	6.24 (5.29, 7.52)	6.41 (5.21, 7.71)	0.585
Lymphocyte ($\times10^9$ /L)	1.75 (1.43, 2.16)	1.83 (1.47, 2.25)	1.62 (1.23, 1.95)	**<0.001**
Monocyte ($\times10^9$ /L)	0.47 (0.38, 0.58)	0.48 (0.38, 0.57)	0.47 (0.38, 0.60)	0.933
Neutrophil ($\times10^9$ /L)	3.87 (2.99, 4.63)	3.79 (2.98, 4.51)	4.18 (3.02, 5.31)	**0.020**
Anterior line ablation (n, %)				0.614
Yes	15 (3.2)	10 (2.9)	5 (3.8)	
No	456 (96.8)	331 (97.1)	125 (96.2)	
Roof line ablation (n, %)				**<0.001**
Yes	143 (30.4)	78 (22.9)	65 (50.0)	
No	328 (69.6)	263 (77.1)	65 (50.0)	
Mitral isthmus ablation (n, %)				**0.005**
Yes	25 (5.3)	12 (3.5)	13 (10.0)	
No	446 (94.7)	329 (96.5)	117 (90.0)	
Tricuspid isthmus ablation (n, %)				0.511
Yes	115 (24.4)	86 (25.2)	29 (22.3)	
No	356 (75.6)	255 (74.8)	101 (77.7)	
CFAE ablation (n, %)				0.151
Yes	99 (21.0)	66 (19.4)	33 (25.4)	
No	372 (79.0)	275 (80.6)	97 (74.6)	
Ablation to SR (n, %)				0.854
Yes	31 (6.6)	22 (6.5)	9 (6.9)	
No	440 (93.4)	319 (93.5)	121 (93.1)	
LAD (mm)	43 (39, 47)	42 (38, 45)	45 (41, 49)	**<0.001**
LAAS (cm/s)	40 (28, 51)	42 (29, 54)	34 (26, 43)	**<0.001**
LVEDD (mm)	46 (43, 50)	46 (43, 49)	48 (44, 52)	**0.005**
LVEF (%)	63 (58, 67)	64 (60, 67)	60 (57, 65)	**<0.001**
ER (n, %)				**<0.001**
Yes	95 (20.2)	27 (7.9)	68 (52.3)	
No	376 (79.8)	314 (92.1)	62 (47.7)	
NLR	2.12 (1.59, 2.91)	2.07 (1.52, 2.68)	2.41 (1.78, 3.62)	**<0.001**
HALP Index	48.70 (37.38, 62.41)	50.74 (40.90, 65.73)	43.05 (28.72, 54.84)	**<0.001**

Notes: The bold numbers were considered statistically significant (P<0.05).

Abbreviations: AFL, atrial flutter; DM, diabetes mellitus; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CIS, cerebral ischemic stroke; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate transaminase; GLU, glucose; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein C; LDL-C, low density lipoprotein C; BNP, B-type natriuretic peptide; CFAE, complex fractionated atrial electrogram; SR, sinus rhythm; LAD, left atrial diameter; LAAS, left atrial appendage strain; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ER, early recurrence; NLR, neutrophil to lymphocyte ratio.

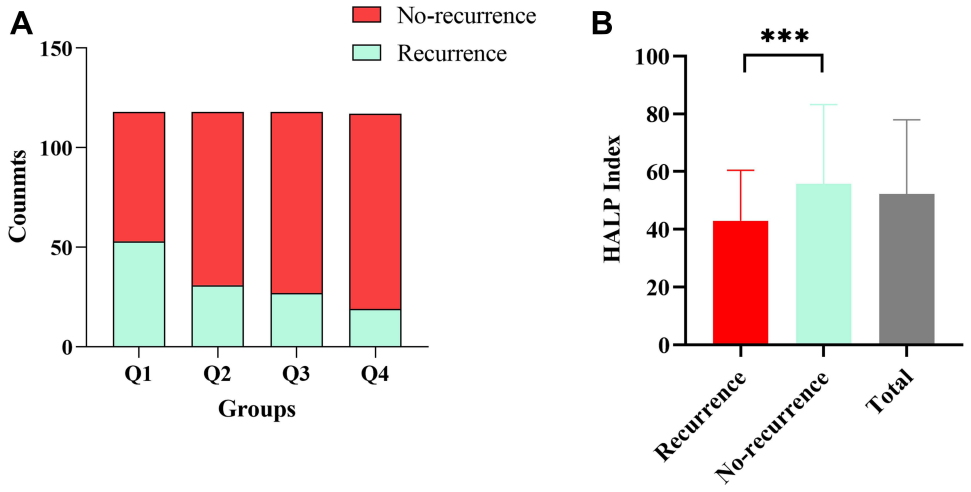

Figure 2 Recurrence in Different HALP Index Groups (**A**) and a Comparison of HALP Index Between the Recurrent and Non-Recurrent Groups (**B**) *** P< 0.001.

As shown in Table 2, univariate Cox regression analysis indicated that the AF duration, CAD, CHF, albumin levels, hemoglobin levels, lymphocyte levels, neutrophil levels, the proportion of roof line ablation, mitral isthmus ablation, LAD, LAAS, LVEDD, LVEF, ER, NLR and HALP Index were significantly correlated with recurrence after RFCA (P<0.05).

Multivariate Cox regression analysis indicated that the AF duration, CAD, LAD, ER, NLR and HALP Index were significantly associated with the recurrence of AF after RFCA. Table 3, Model 1.

Table 2 Univariate Cox Proportional Hazards Regression Model

Variable	Levels	HR (95% CI)	P-value
Age		1.011 (0.991–1.031)	0.282
Gender	Male	Reference	0.756
	Female	1.057 (0.745–1.500)	
AF duration		1.004 (1.003–1.006)	**<0.001**
Combined AFL	No	Reference	0.831
	Yes	1.067 (0.589–1.932)	
Hypertension	No	Reference	0.843
	Yes	0.966 (0.683–1.366)	
DM	No	Reference	0.148
	Yes	1.362 (0.896–2.069)	
CAD	No	Reference	**0.003**
	Yes	1.812 (1.230–2.671)	
CHF	No	Reference	**0.011**
	Yes	1.697 (1.127–2.555)	
COPD	No	Reference	0.081
	Yes	2.217 (0.905–5.429)	
CIS	No	Reference	0.400
	Yes	1.238 (0.753–2.037)	
CHA2DS2-VAsc Score	-	1.076 (0.962–1.203)	0.199
Albumin	-	0.957 (0.924–0.992)	**0.017**
AST	-	1.000 (0.989–1.012)	0.990
ALT	-	1.000 (0.992–1.007)	0.929
GLU	-	1.083 (0.979–1.198)	0.122
Urea	-	1.061 (0.965–1.165)	0.224
SCr	-	1.000 (0.989–1.011)	0.979
SUA	-	1.000 (0.999–1.002)	0.652

(*Continued*)

Table 2 (Continued).

Variable	Levels	HR (95% CI)	P-value
TG	-	0.915 (0.689–1.215)	0.540
TC	-	0.955 (0.841–1.085)	0.479
HDL-C	-	0.866 (0.537–1.397)	0.555
LDL-C	-	0.997 (0.828–1.200)	0.976
Homocysteine	-	1.004 (0.998–1.011)	0.197
BNP	-	1.000 (1.000–1.001)	0.054
D-dimer		1.047 (0.795–1.380)	0.742
Hemoglobin	-	0.988 (0.979–0.997)	**0.009**
Platelet	-	1.003 (1.000–1.006)	0.083
Leucocyte	-	1.049 (0.963–1.142)	0.275
Lymphocyte	-	0.505 (0.365–0.699)	**<0.001**
Monocyte	-	1.425 (0.533–3.810)	0.480
Neutrophil	-	1.146 (1.041–1.261)	**0.005**
Anterior line ablation	No	Reference	0.526
	Yes	1.335 (0.546–3.265)	
Roof line ablation	No	Reference	**<0.001**
	Yes	2.899 (2.051–4.099)	
Mitral isthmus ablation	No	Reference	**<0.001**
	Yes	2.685 (1.512–4.768)	
Tricuspid isthmus ablation	No	Reference	0.478
	Yes	0.861 (0.570–1.301)	
CAFÉ ablation	No	Reference	0.081
	Yes	1.424 (0.958–2.117)	
Ablation to SR	No	Reference	0.855
	Yes	1.065 (0.541–2.097)	
LAD	-	1.109 (1.074–1.144)	**<0.001**
LAAS	-	0.976 (0.965–0.988)	**<0.001**
LVEDD	-	1.039 (1.012–1.067)	**0.004**
LVEF	-	0.964 (0.948–0.981)	**<0.001**
ER	No	Reference	**<0.001**
	Yes	7.841 (5.506–11.168)	
NLR	-	1.087 (1.049–1.126)	**<0.001**
HALP Index	-	0.974 (0.964–0.987)	**<0.001**

Notes: The bold numbers were considered statistically significant (P<0.05).

Abbreviations: AFL, atrial flutter; DM, diabetes mellitus; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CIS, cerebral ischemic stroke; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate transaminase; GLU, glucose; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein C; LDL-C, low density lipoprotein C; BNP, B-type natriuretic peptide; CFAE, complex fractionated atrial electrogram; SR, sinus rhythm; LAD, left atrial diameter; LAAS, left atrial appendage strain; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ER, early recurrence; NLR, neutrophil to lymphocyte ratio.

The HALP Index was included in the Cox multivariate regression analysis as a categorical variable. The results indicated that LAD, ER, NLR, and the HALP Index were independent risk factors for the recurrence of AF after RFCA. Furthermore, patients with a low HALP Index were more likely to experience recurrence after RFCA compared to those with a high HALP Index (HR=6.080, P<0.001). Table 3, Model 2.

As illustrated in Figure 3, the ROC curves examined the relationship between the HALP Index and the recurrence of AF. The area under the curve (AUC) was 0.659 (95% CI: 0.603–0.715, P < 0.001). With a cut-off level of 32.98, the HALP Index predicted AF recurrence during follow-up with a sensitivity of 36% and a specificity of 89%. The AUC for NLR was 0.627 (95% CI: 0.569–0.685, P < 0.001). The cut-off point for NLR was 2.71, which predicted AF recurrence

Table 3 Multivariate Cox Proportional Hazards Regression Model

Variable	Levels	Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value
AF duration	-	1.002 (1.000–1.004)	**0.030**	1.002 (1.000–1.004)	0.051
CAD	No	Reference	**0.029**	Reference	0.063
	Yes	1.629 (1.052–2.523)		1.512 (0.978–2.339)	
CHF	No	Reference	0.714	Reference	0.616
	Yes	0.905 (0.531–1.543)		0.870 (0.504–1.501)	
Neutrophil	-	0.968 (0.869–1.079)	0.560	0.959 (0.860–1.070)	0.457
Roof line ablation	No	Reference	0.254	Reference	0.309
	Yes	1.255 (0.849–1.854)		1.286 (0.868–1.903)	
Mitral isthmus ablation	No	Reference	0.318	Reference	0.352
	Yes	1.366 (0.740–2.522)		1.340 (0.724–2.479)	
LAD	-	1.058 (1.017–1.101)	**0.005**	1.059 (1.017–1.102)	**0.005**
LAAS	-	0.996 (0.982–1.010)	0.544	0.995 (0.981–1.009)	0.453
LVEDD	-	0.990 (0.954–1.028)	0.616	0.990 (0.954–1.027)	0.579
LVEF	-	0.977 (0.953–1.002)	0.074	0.978 (0.954–1.003)	0.084
ER	No	Reference	**<0.001**	Reference	**<0.001**
	Yes	8.487 (5.429–13.269)		8.822 (5.595–13.910)	
NLR	-	1.065 (1.010–1.123)	**0.021**	1.095 (1.039–1.154)	**<0.001**
HALP Index	Q4 >62.41	0.967 (0.957–0.976)	**<0.001**	Reference	**<0.001**
	Q1 <37.38			6.080 (3.396–10.886)	**<0.001**
	Q2 37.39–48.70			4.028 (2.176–7.455)	**<0.001**
	Q3 48.71–62.40			2.912 (1.562–5.428)	

Notes: Model 1, the HALP Index was included in regression analysis as continuous variables. Model 2, the HALP Index was included in regression analysis as categorical variables. The bold numbers were considered statistically significant (P<0.05).

Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; LAD, left atrial diameter; LAAS, left atrial appendage strain; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ER, early recurrence; NLR, neutrophil to lymphocyte ratio.

with a sensitivity of 44% and a specificity of 77%. The DeLong test indicated that there was no significant difference between the HALP Index and NLR in predicting AF recurrence after RFCA (Z = 1.089, P = 0.276). The predictive value derived from the model of established risk factors, which included AF duration, CAD, LAD, ER, plus NLR was 0.848 (95% CI: 0.804–0.892, P < 0.001). The predictive value of the established risk factor models, including AF duration, CAD, LAD, ER, and HALP Index, was 0.885 (95% CI: 0.848–0.922, P < 0.001). The DeLong test showed that there was a significant difference between the two sets of models (Z = 2.224, P = 0.026). The predictive value of the prediction model with HALP Index was significantly higher than that with NLR. When the established risk factors were combined with the HALP Index and NLR, the predictive value of the ROC curve increased to an AUC of 0.889 (95% CI: 0.851–0.926, P < 0.001). Table 4.

Correlation Analysis

The Spearman correlation analysis revealed that the HALP Index was negatively correlated with NLR (r = −0.54, P < 0.001). In contrast, it was positively correlated with triglycerides (r = 0.169, P < 0.001), leukocyte count (r = 0.189, P < 0.001), and monocyte count (r = 0.216, P < 0.001). See Figure 4.

Kaplan-Meier Survival Curve Analysis of AF Recurrence

The Kaplan-Meier survival curve analysis indicated that the postoperative recurrence of AF patients with varying HALP Index was significantly different (Log-rank P < 0.001). Figure 5.

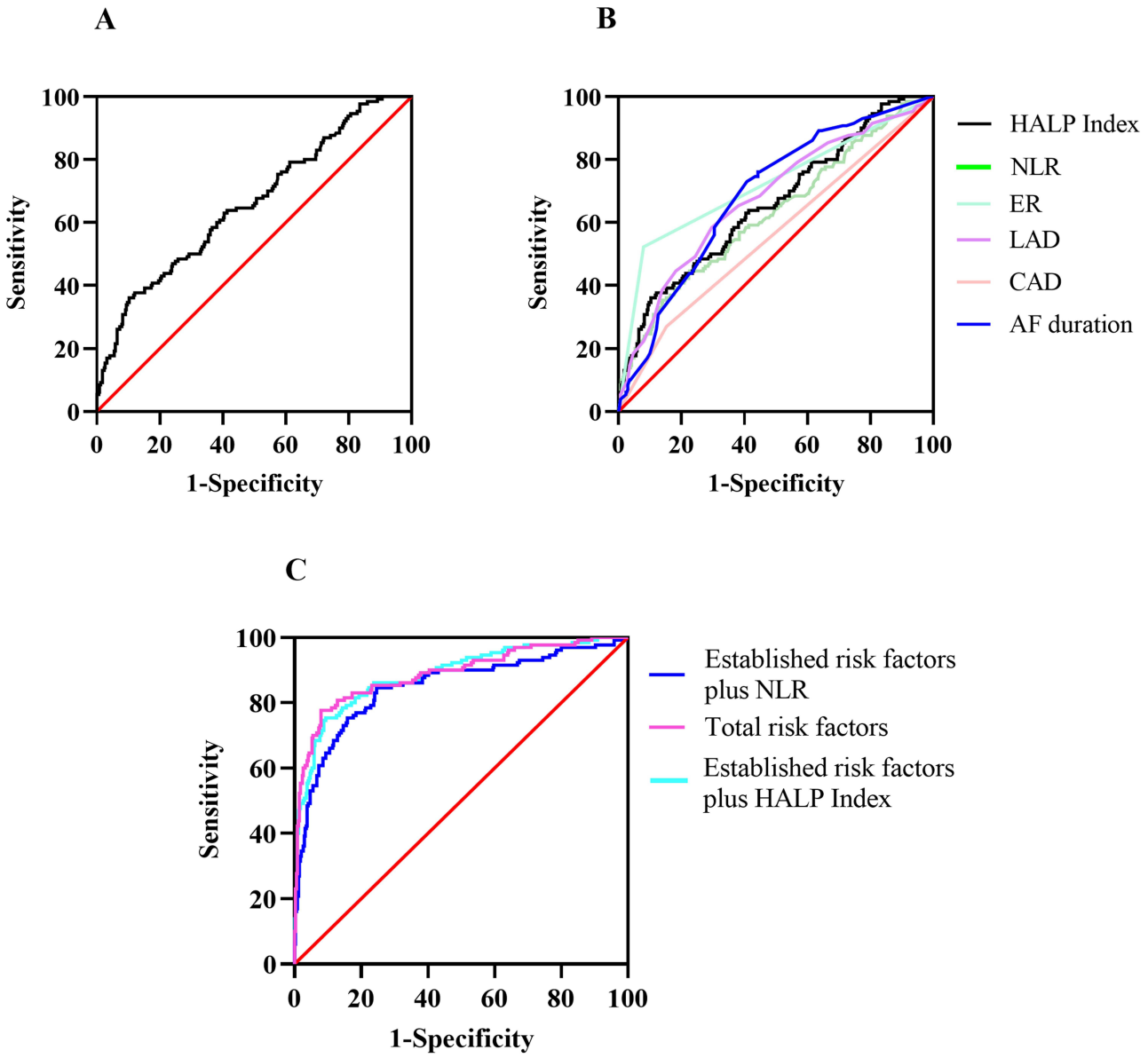

Figure 3 The ROC curve for the HALP Index (**A**), total risk factors (HALP Index, NLR, ER, LAD, CAD and AF duration) (**B**) and established risk factors (ER, LAD, CAD and AF duration) (**C**).

Discussion

In this retrospective study, we aimed to focus on the relationship between the HALP Index and AF recurrence. We demonstrated that the HALP Index was a strong and independent predictor of recurrence in patients with persistent AF undergoing RFCA. Significant differences in AF recurrence were observed among patients with persistent AF who had varying HALP Index. Patients with a low HALP Index were more likely to experience recurrence after RFCA compared to those with a high HALP Index.

Atrial fibrillation (AF) is the most prevalent arrhythmia encountered in clinical practice, and its onset and progression are influenced by numerous factors. AF is a complex arrhythmia that can result from various pathophysiological processes. Paroxysmal AF typically involves drivers located around one or more pulmonary veins (PVs) within the myocardial cuff, which are caused by rapid focal activity or local reentry.[20] The natural progression of AF is characterized by the effects of atrial remodeling, which may occur due to the arrhythmia itself and/or the advancement of underlying heart disease, evolving from paroxysmal to persistent and ultimately to permanent forms.[21]

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Table 4 ROC Curve for Risk Factors

Variable	AUC	95% CI	Youden Index	P value
HALP Index	0.659	0.603–0.715	0.259	**<0.001**
NLR	0.627	0.569–0.685	0.220	**<0.001**
LAD	0.678	0.622–0.733	0.288	**<0.001**
ER	0.722	0.665–0.779	0.444	**<0.001**
AF duration	0.688	0.636–0.740	0.323	**<0.001**
CAD	0.558	0.499–0.618	0.117	**0.007**
Established risk factors plus NLR	0.848	0.804–0.892	0.599	**<0.001**
Established risk factors plus HALP Index	0.885	0.848–0.922	0.660	**<0.001**
Established risk factors plus HALP Index and NLR	0.889	0.851–0.926	0.697	**<0.001**

Notes: The bold numbers were considered statistically significant (P<0.05). Established risk factors included ER, AF duration, CAD and LAD.
Abbreviations: CAD, coronary artery disease; LAD, left atrial diameter; ER, early recurrence; NLR, neutrophil to lymphocyte ratio.

Inflammation plays a significant role in the development of AF and can trigger the onset of fibrillation by activating mechanisms as potent as those associated with pulmonary vein potentials.[22] Inflammation and oxidative stress are interconnected, leading to atrial fibrosis, which may play a significant role in the pathophysiology of AF pathophysiology.[23] Mediators of the inflammatory response are closely linked to the electrical and structural remodeling of the atria, resulting in an increased susceptibility to AF. Inflammation also impacts calcium homeostasis and connexins, which are associated with the triggers of AF and contribute to heterogeneous atrial conduction.[24] A recent report has shown that elevated levels of angiopoietin-2 and interleukin-6 are associated with relapse following the ablation of AF.[25] NLR is a reliable biomarker for

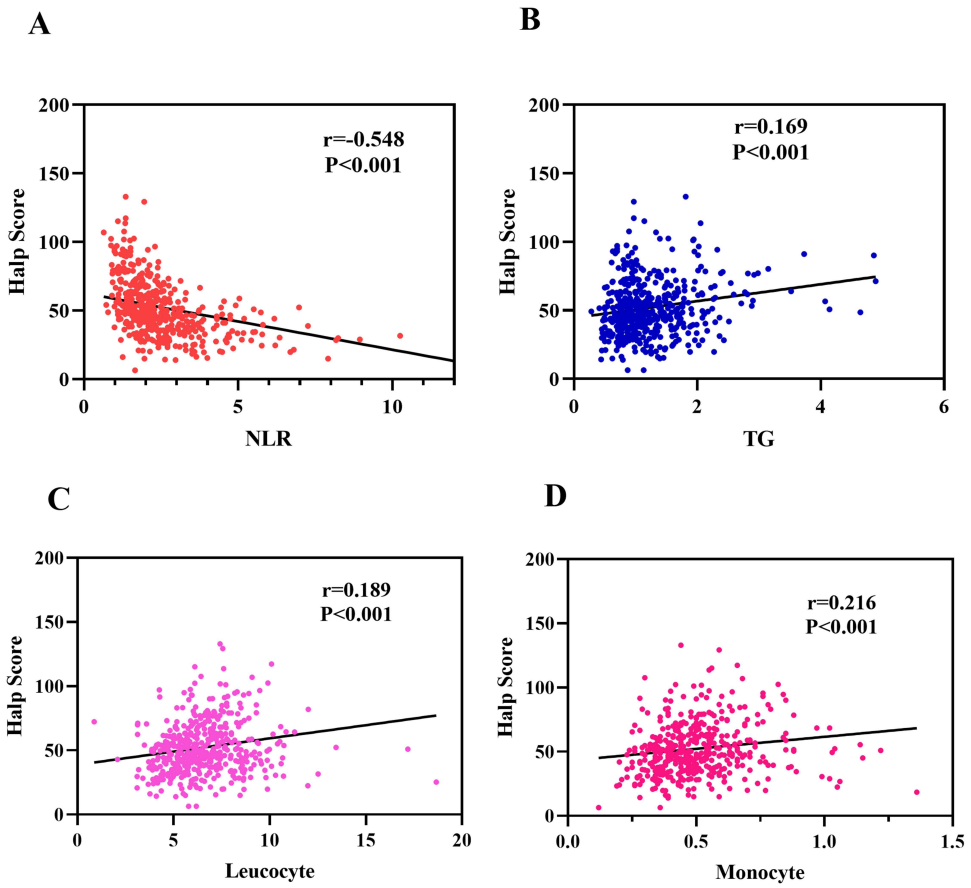

Figure 4 Correlation analysis between the HALP Index and the neutrophil-to-lymphocyte ratio (NLR) (**A**), triglycerides (TG) (**B**), leukocyte count (**C**), and monocyte count (**D**).

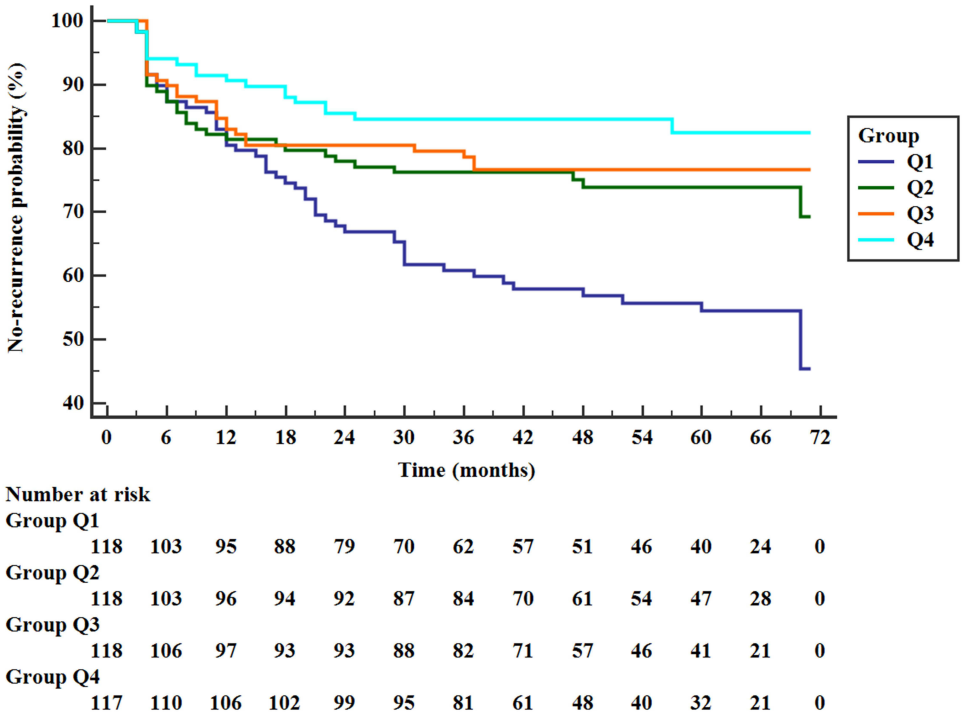

Figure 5 Comparison of AF recurrence in patients with different HALP Index.

systemic inflammation. Elevated NLR levels indicate increased inflammation in patients with AF.[26] Research has demonstrated a significant association between NLR and the recurrence of AF following RFCA.[27]

The HALP Index is an immune-inflammatory complex composed of hemoglobin, albumin, lymphocytes, and platelets. Compared to a single indicator, the HALP Index can more accurately predict patient prognosis. Lymphocytes play a crucial role in eliminating and repairing inflammation, while albumin provides a protective effect due to its antagonistic properties against oxidation, thrombosis, and white blood cell adhesion.[28,29] Inflammation reduces albumin synthesis, and elevated cytokine levels hinder red blood cell maturation, potentially leading to anemia.[30] Previous study has shown a correlation between albumin levels and an increased likelihood of developing AF.[31] In addition to its association with inflammation, albumin also affects blood viscosity, endothelial function, and platelet activation.[32] The HALP Index evaluates a patient's immune system and nutritional status and has been utilized to predict the prognosis of various diseases, including lung, bladder, and breast cancer.[33,34] In recent years, it has been demonstrated that the HALP Index is significantly associated with the prognosis of cardiovascular disease. Zheng et al confirmed that the HALP Index was significantly correlated with the prognosis of patients with coronary artery disease (CAD).[30] Eyiol et al demonstrated a significant association between the HALP Index assessed at admission and critically ill patients with AF.[35] Liu et al demonstrated that the HALP Index might serve as a potential predictor of mortality in patients with heart failure.[36] However, the relationship between the HALP Index and recurrence following radiofrequency catheter ablation (RFCA) of AF has not been previously reported. In our study, we discovered that the HALP Index was an independent predictor of recurrence after RFCA in patients with persistent AF. Patients with low HALP Index were more likely to experience recurrence after undergoing RFCA compared to those with high HALP Index. The ROC curve indicated that the HALP Index possesses a high predictive value for recurrence after RFCA, comparable to that of NLR. There was no statistical difference between the area under the ROC curve of HALP index and that of NLR. However, the predictive value of the established risk factors plus HALP was significantly better than the predictive value of the established risk factors plus NLR. Compared with established risk factors, incorporating the HALP Index into the predictive model demonstrated superior predictive value for recurrence after RFCA in persistent AF patients. Additionally, we identified a positive correlation between the HALP Index and levels of triglycerides,

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monocytes, and leukocytes. A large national retrospective study demonstrated a positive correlation between triglycerides and the HALP Index.[34]

The significance of these findings lies in the HALP Index, a complex immunoinflammatory marker that is more readily available in clinical settings. This index can enhance the timely identification of high-risk patients with AF. However, our study has some limitations. Firstly, the success rate of RFCA of persistent AF may have been overestimated, despite thorough follow-up. Secondly, as this is a retrospective study, further prospective research is needed to confirm our findings. In the future, we will examine the effect of HALP Index on AF recurrence after RFCA. Alternatively, HALP Index could be incorporated into the risk prediction model to further evaluate its effect on postoperative recurrence of AF.

Conclusion

In our study, we observed that the HALP Index was significantly associated with recurrence following RFCA of persistent AF. Patients with low HALP Index were more likely to experience recurrence after undergoing RFCA compared to those with high HALP Index.

Data Sharing Statement

The datasets utilized and analyzed in this study are available from the corresponding author upon reasonable request.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Yantai Yuhuangding Hospital of Qingdao University (No. 2024-784). All patients provided informed consent.

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Disclosure

The authors declare that there are no conflicts of interest.

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