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ORIGINAL RESEARCH

Elevated Serum HMGB1 Levels and Their Association with Stroke Risk of Paroxysmal Atrial Fibrillation

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Purpose: This study aimed to investigate the association between serum high mobility group box 1 (HMGB1) levels and stroke through the long-term follow-up of patients with paroxysmal atrial fibrillation (AF).

Patients and Methods: The study was a prospective cohort study. A total of 304 patients with paroxysmal AF were enrolled, including 66 who underwent radiofrequency ablation (RFA). Serum HMGB1 levels were measured using an enzyme-linked immunosorbent assay. The primary endpoint was the first occurrence of a major adverse cerebrovascular event (MACE), defined as an acute ischemic stroke or all-cause mortality.

Results: During the median follow-up of 81.5 months, 76 MACEs were recorded. Patients were categorized into MACE and no-MACE groups based on the occurrence of MACE. The MACE group showed significantly higher age, CHA_2DS_2-VASc scores, and serum HMGB1 levels than the non-MACE group ($p<0.05$). The areas under the curve (AUC) for HMGB1 and CHA_2DS_2-VASc were 0.779 [95% (confidence interval, CI): 0.728–0.824)] and 0.818 (95% CI: 0.770–0.860), respectively. The combination of HMGB1 and CHA_2DS_2-VASc yielded an AUC of 0.895 (95% CI: 0.855–0.927), which was significantly higher than that of either metric alone ($P < 0.05$). Kaplan-Meier analysis showed that patients with high HMGB1 levels had a significantly lower event-free survival rate for MACE than those with low HMGB1 levels ($P < 0.05$). Multivariate Cox regression analysis identified HMGB1 level [(Hazard ratio, HR), 4.161; 95% CI, 2.518–6.878)] as an independent predictor of MACE in paroxysmal AF, along with the CHA_2DS_2-VASc score (HR: 5.567, 95% CI: 3.089–10.032).

Conclusion: Elevated serum HMGB1 level was identified as a significant predictor of stroke or mortality in patients with paroxysmal AF, and may enhance the predictive capacity of current risk stratification tools while supporting more personalized anticoagulation strategies.

Keywords: high-mobility group box-1, paroxysmal atrial fibrillation, stroke

Introduction

Paroxysmal atrial fibrillation (AF), which accounts for approximately 25–62% of all AF cases, is one of the most common clinical arrhythmias.[1] Studies have found that AF increases the risk of stroke five-fold, doubles all-cause mortality, and is a leading cause of disability worldwide.[2,3] Although anticoagulation strategies based on the CHA_2DS_2-VASc score can reduce the risk of stroke in patients with AF by 60%-80%, the incidence of stroke and stroke-related mortality continues to increase annually.[4,5] Moreover, paroxysmal AF is regarded as a potential cause of cryptogenic stroke, which constitutes 15–40% of ischemic strokes.[6] Thus, identifying reliable predictors of stroke and death in patients with paroxysmal AF is of great clinical importance.

While traditional clinical factors—such as age, hypertension, AF type, and anticoagulation history—remain central to stroke risk prediction in AF, growing interest has emerged in the potential role of inflammatory cytokines as novel biomarkers of both ischemic and hemorrhagic complications.[7,8] Several studies have explored biomarkers predictive of

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stroke and mortality in patients with AF. A prospective observational cohort study demonstrated that elevated plasma trimethylamine-N-oxide levels were associated with increased cardiovascular mortality and stroke risk in patients with AF.[9] Similarly, the RE-LY trial identified several inflammatory and stress-related biomarkers, including growth-differentiation factor 15 and interleukin-6, as predictors of stroke and all-cause mortality.[10,11] However, limited evidence is available regarding the prognostic markers of paroxysmal AF.

Among emerging mediators linking inflammation, atrial remodeling, and thrombogenesis, high-mobility group box-1 (HMGB1) has garnered increasing attention.[12,13] HMGB1 has been reported to be closely associated with both AF and stroke. HMGB1 levels were significantly elevated in the peripheral and left atrial blood of patients with paroxysmal AF.[12,14] Moreover, atrial tissue samples from AF patients also showed increased HMGB1 expression.[13] In patients with paroxysmal AF undergoing cryoballoon ablation, elevated left atrial HMGB1 levels were predictive of AF recurrence.[15] Furthermore, HMGB1 levels are markedly increased in stroke patients and have been linked to prognosis, supporting its role as a prognostic biomarker.[16–18] However, the relationship between HMGB1 level and stroke in patients with paroxysmal AF remains unclear. Therefore, this study aimed to investigate the association between serum HMGB1 levels and stroke through long-term follow-up of patients with paroxysmal AF.

Materials and Methods

Study Population

The study was a prospective cohort study. Following established guidelines, this study included 304 adult patients diagnosed with paroxysmal AF between January 2016 and December 2018.[19] Among them, 238 patients received pharmacological treatment, 27 patients underwent radiofrequency ablation (RFA) during hospitalization, and 39 patients received RFA at a median of 24.5 months after discharge (Figure 1). This study was approved by the Ethics Committee of Jiangyin People's Hospital (approval number: 2015ER022) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment. The exclusion criteria were persistent AF, long-standing persistent AF, permanent AF, hyperthyroidism, impaired liver and kidney function, acute and chronic infections, malignant tumors, and other severe diseases. Patients who were unable to complete the follow-up were also excluded.

A priori power calculations were carried out using PASS software. Assuming a two-sided α of 0.05, 80% power, and an estimated cumulative incidence of 25% for the composite outcome (stroke or all-cause mortality) over the follow-up period—based on prior AF cohorts—we calculated that a minimum of 290 participants would be required to detect a hazard ratio of 1.8 for elevated HMGB1 levels (comparing the highest vs lowest tertile) using a Cox proportional hazards model. Accounting for an anticipated 10% loss to follow-up, we aimed to enroll at least 320 patients. Our final analytic cohort included 304 participants with complete baseline data and 76 outcome events, which provided sufficient power to test the primary hypothesis.

Clinical and Laboratory Assessments

All enrolled patients underwent a comprehensive physical examination and detailed review of their medical history by an experienced specialist. The CHA_2DS_2-VASc score was used to guide pharmacological management. All blood samples were collected on the second day of hospitalization from antecubital veins after an overnight fast, during sinus rhythm confirmed by electrocardiogram at enrollment. Levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and HMGB1 were measured as previously described.[17] In addition, all enrolled patients underwent echocardiography (Philips iE33 xMatrix) during hospitalization to measure left atrial diameter (LAD) and left ventricular ejection fraction (LVEF).

Follow-Up

Follow-up assessments were performed at intervals of 3–6 months through outpatient clinic visits or telephone communication with the patients' family members. By the end of 2024, the median follow-up time was 81.50 months (interquartile range: 73.00–89.75). The primary endpoint of this study was the first occurrence of a major adverse cerebrovascular event (MACE) outside the hospital, defined as an acute ischemic stroke or all-cause mortality. A total of 76 MACEs were observed during the study period (Figure 1).

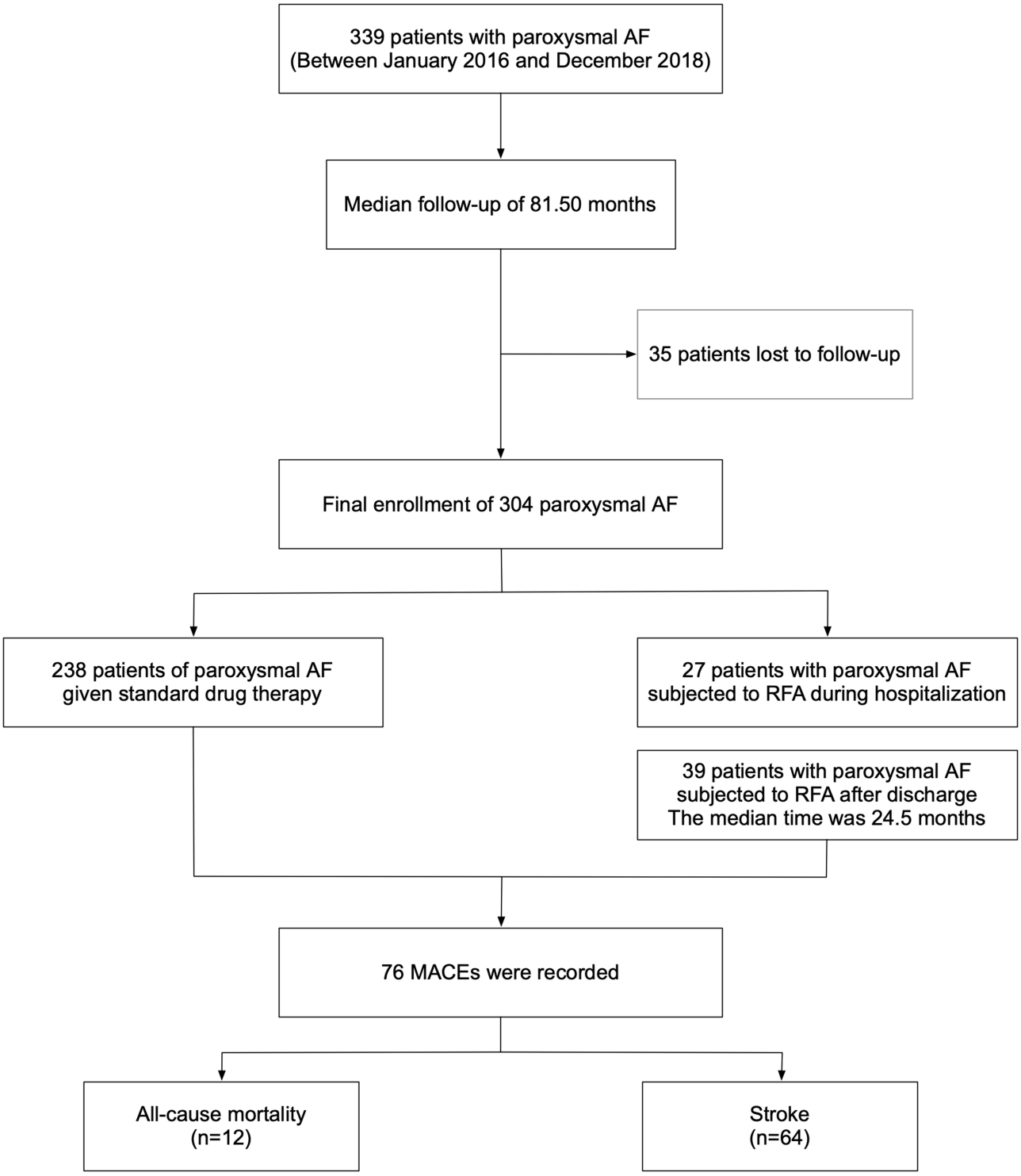

Figure 1 Flow chart of the study.
Abbreviations: AF, atrial fibrillation; RFA, radiofrequency ablation; MACE, major adverse cerebrovascular event.

Statistical Analysis

A priori power analysis was performed using PASS software (v14). Statistical analysis was conducted using the SPSS 25.0 statistical software package. Continuous variables are presented as mean ± standard deviation and compared between groups using Student's *t*-test, while categorical variables are expressed as absolute numbers (percentages) and

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compared using the chi-square test. The MedCalc software was used to compare the receiver operating characteristic (ROC) curves of the different variables. Kaplan–Meier survival curves were constructed to assess event-free survival, and group differences were evaluated using the Log rank test. To explore the relationship between HMGB1 levels and the prognosis of paroxysmal AF, univariate and multivariate Cox proportional hazards models were used with hazard ratios (HRs) and 95% confidence intervals (CIs). Variables that reached statistical significance in univariate Cox analysis were included in the multivariate model. Subjects were followed from enrollment until the earliest occurrence of endpoint event, loss to follow-up, or study completion. For subjects lost to follow-up, the last recorded date of clinical contact served as the censoring time point. Given the low missingness, all primary analyses used complete-case analysis. Statistical significance was set at a two-tailed p-value of < 0.05.

Result

The Comparison of Baseline Clinical Data

During a median follow-up of 81.5 months, 76 MACEs were documented in 304 patients with paroxysmal AF. Patients were categorized into MACE and no-MACE groups based on the occurrence of MACE. Compared to the non-MACE group, the MACE group was significantly older and had higher CHA_2DS_2-VASc scores and serum HMGB1 levels ($p < 0.05$) (Table 1). There were no statistically significant differences between the two groups in terms of sex, history of hypertension and diabetes mellitus, blood LDL-C and HDL-C levels, LAD, LVEF, or whether RFA was performed.

Comparative Predictive Value of HMGB1 and CHA2DS2-VASc for MACE in Patients with Paroxysmal AF

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of HMGB1 levels and CHA_2DS_2-VASc scores for MACE. The areas under the curve (AUC) for HMGB1 and CHA2DS2-VASc were 0.779 (95% CI: 0.728–0.824) and 0.818 (95% CI: 0.770–0.860), respectively (Figure 2). Although the Z-test showed no significant difference between the two groups, their combination yielded an AUC of 0.895 (95% CI: 0.855–0.927), which was significantly higher than that of either parameter alone ($p < 0.05$).

Table 1 The Comparison of Clinical Data Between the MACE and NO MACE Group in Paroxysmal AF Patients

Variables	MACE Group (n=76)	NO-MACE Group (n=228)	p
Male, n (%)	41 (53.94%)	126 (55.26%)	0.823
Age (years)	66.59±10.41	63.21±9.15	0.007
Hypertension, n (%)	50 (65.79%)	128 (56.14%)	0.139
Diabetes mellitus, n (%)	11 (14.47%)	27 (11.84%)	0.548
CHA_2DS_2-VASc	3.08±1.30	1.58±0.93	0.000
LDL-C (mmol/L)	2.36±1.49	2.49±0.85	0.392
HDL-C (mmol/L)	1.17±0.38	1.23±0.35	0.178
HMGB1 (μg/L)	5.89±2.36	3.54±1.91	0.000
LAD (mm)	42.91±5.57	42.07±5.44	0.280
LVEF (%)	61.48±4.07	61.78±5.23	0.680
RFA	13 (17.11%)	53 (23.25%)	0.261

Notes: Age, CHA_2DS_2-VASc, LDL-C, HDL-C, HMGB1, LAD and LVEF were presented as means ± standard deviations and compared using Student's *t*-test. Male, previous history of hypertension, diabetes mellitus, and RFA were presented as absolute numbers (percentages) and compared using the chi-square test.

Abbreviations: MACE, major adverse cerebrovascular event; AF, atrial fibrillation; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HMGB1, high mobility group protein box-1; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; RFA, radio-frequency ablation.

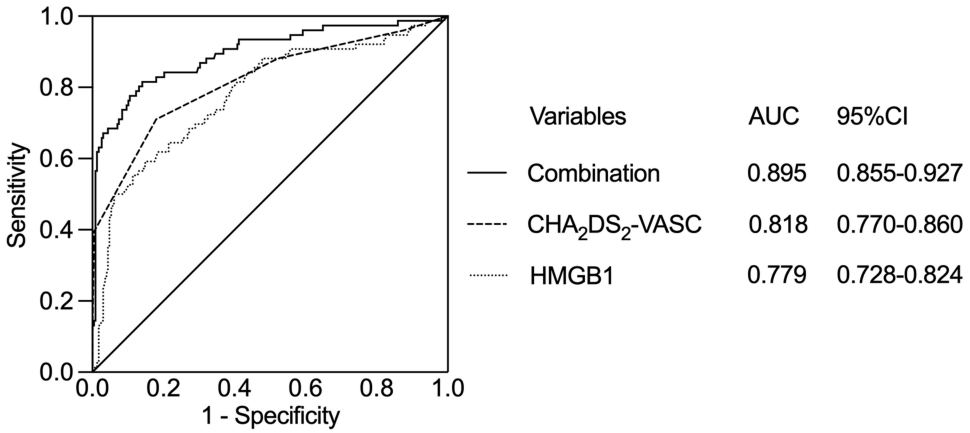

Figure 2 Comparative predictive value of HMGB1 and CHA2DS2-VASc for MACE in patients with paroxysmal AF. Receiver operating characteristic curves were used to determine the area under the curve for each variable and z-test comparisons were performed.
Abbreviations: HMGB1, high mobility group protein box-1; MACE, major adverse cerebrovascular event; AF, atrial fibrillation; AUC, area under the curve.

Kaplan-Meier Analysis of MACE in Paroxysmal AF Patients Based on HMGB1 Levels

After deriving the optimal cut-off value of HMGB1 (5.31 μg/L) based on ROC analysis, the patients were divided into high and low HMGB1 level groups for Kaplan-Meier analysis. Kaplan–Meier analysis revealed a significant difference in cumulative survival without MACE between the two groups (Figure 3). Patients with high HMGB1 levels had significantly lower event-free survival rates than those with low HMGB1 levels ($P < 0.05$).

Cox Regression Analysis of MACE in Patients with Paroxysmal AF

Univariate Cox analysis revealed that elevated serum HMGB1 level, age, CHA2DS2-VASc score, and LAD were independent predictors of MACE in patients with paroxysmal AF (Table 2). Subsequent multivariate analysis of the statistically significant factors identified in the univariate analysis further validated the independent predictive value of CHA2DS2-VASc score (HR:5.567, 95% CI:3.089–10.032) and HMGB1 (HR, 4.161; 95% CI:2.518–6.878). However, variables such as sex, age, history of hypertension and diabetes, LDL-C, HDL-C, LVEF, and RFA did not show independent effects in the univariate and multivariate Cox analyses.

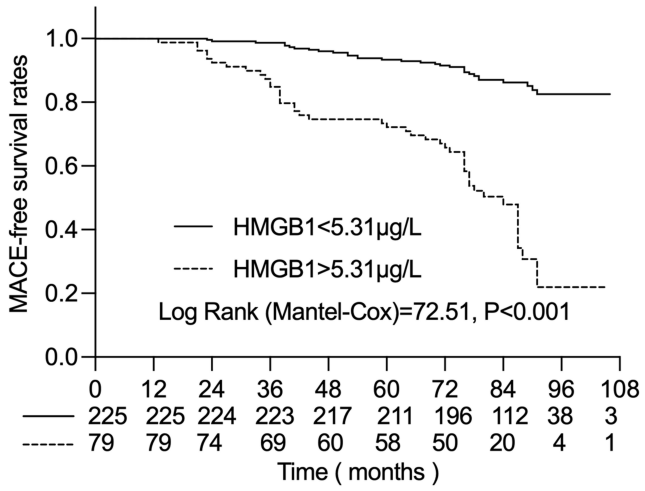

Figure 3 Kaplan-Meier analysis of MACE in paroxysmal AF patients based on HMGB1 levels. Kaplan-Meier survival curves were used to conduct survival analysis which were then compared using the Log rank test.
Abbreviations: MACE, major adverse cerebrovascular event; AF, atrial fibrillation; HMGB1, high mobility group protein box-1.

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Table 2 Univariate and Multivariate COX Analysis for MACE in Paroxysmal AF Patients

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Sex (male)	0.982	0.624–1.545	0.937	–	–	–
Age (years)	2.776	1.710–4.506	0.000	1.367	0.790–2.366	0.264
Hypertension	1.372	0.854–2.204	0.191	–	–	–
Diabetes mellitus	1.103	0.582–2.091	0.764	–	–	–
CHA2DS2-VASc	7.165	4.355–11.788	0.000	5.567	3.089–10.032	0.000
LDL-C	2.053	0.503–8.389	0.316	-	-	-
HDL-C	0.796	0.344–1.842	0.594	-	-	-
HMGB1	5.882	3.703–9.342	0.000	4.161	2.518–6.878	0.000
LAD	1.678	1.011–2.785	0.045	1.582	0.943–2.652	0.082
LVEF	2.293	0.318–16.531	0.410	-	-	-
RFA	0.719	0.396–1.306	0.279			

Notes: Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using univariate and multivariate Cox proportional hazards models.

Abbreviations: MACE, major adverse cerebrovascular event; AF, atrial fibrillation; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HMGB1, high mobility group protein box-1; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; RFA, radiofrequency ablation.

Discussion

This study found that serum HMGB1 levels were significantly correlated with the occurrence of MACE in patients with paroxysmal AF. Its predictive efficacy for MACE was comparable to that of the widely used CHA_2DS_2-VASc score, and the combination of both further improved its predictive ability. These findings suggest that HMGB1 may serve as a novel biomarker for risk stratification of paroxysmal AF.

Experimental and clinical studies have provided mechanistic insight into the role of HMGB1 in AF. In a rat model of hypertension with metabolic syndrome, elevated HMGB1 levels in the atrial tissue contributed to atrial remodeling by activating the RAGE/NF-κB inflammatory pathway, thereby creating a pathological substrate for AF.[20] In patients with valvular AF, HMGB1 expression is significantly upregulated and is identified as a ferroptosis-related gene that mediates inflammation and ferroptosis, thereby accelerating AF progression.[21,22] HMGB1 also regulates myocardial fibrosis in AF through its interaction with HSPA9.[23] Furthermore, in a minipig model of atherosclerosis, serum HMGB1 levels were inversely correlated with the thrombosis time.[24] Mechanistically, HMGB1 promotes thrombosis by activating platelets via autocrine and paracrine pathways and inducing neutrophil extracellular trap (NET) formation.[25] Collectively, these findings indicated that HMGB1 plays a pivotal role in the initiation, progression, and thromboembolic complications of AF.

Accumulating evidence highlights the involvement of HMGB1 in stroke pathogenesis.[26] HMGB1 levels have been observed in brain tissue, serum, plasma, and cerebrospinal fluid after stroke.[27–29] HMGB1 released from damaged cells or activated platelets can act as a damage-associated molecular pattern (DAMPs) to trigger inflammation and immune responses.[30–32] Extracellular HMGB1 promotes inflammatory responses in ischemic stroke via toll-like receptor 4 (TLR4) and C–X–C chemokine receptor 4 (CXCR4).[33] HMGB1 can also promote thrombosis by inducing NETs formation via autophagy, thereby exacerbating brain tissue damage.[34]

Clinically, HMGB1 has been recognized as a potential biomarker for AF recurrence following cryoballoon ablation in patients with paroxysmal AF, outperforming CHA_2DS_2-VASc score.[15] Previous studies have confirmed that the CHA_2DS_2-VASc score predicts the stroke risk in patients with AF.[35] This result was consistent with the findings of the present study. Importantly, this study revealed that HMGB1 provides prognostic value comparable to the CHA_2DS_2-VASc score for stroke prediction in paroxysmal AF. Taken together, these results support HMGB1 not only as a critical mediator of AF pathophysiology through inflammation, fibrosis, and thrombosis but also as a promising prognostic biomarker and potential therapeutic target.[36]

Future studies should explore HMGB1 as a potential therapeutic target—particularly in light of emerging preclinical evidence that agents such as dapagliflozin may attenuate atrial remodeling via HMGB1 suppression.[37] Additionally, HMGB1-based risk prediction models warrant validation in independent multicenter cohorts. Finally, it remains to be

determined whether serial HMGB1 measurements could inform personalized antithrombotic or anti-inflammatory strategies in patients with AF.

This study has several limitations. First, although the overall sample size was adequate, the number of patients who underwent RFA was small, and neither medication adherence nor stroke severity were assessed. Second, as a single-center observational study, the findings may be subject to selection bias and cannot establish a causal relationship between HMGB1 and the outcomes, with residual confounding factors remaining possible. Third, baseline systemic inflammatory markers (eg, C-reactive protein or interleukin-6) were not measured. Although patients with acute or chronic infections were excluded at enrollment, the lack of objective inflammatory data limits our ability to fully account for subclinical inflammation that may influence HMGB1 levels. Fourth, the absence of validation in an independent external cohort limits the generalizability of the results. Finally, the extended follow-up period may introduce challenges related to data completeness and evolution of treatment strategies over time.

Conclusion

In summary, this study demonstrated that elevated serum HMGB1 levels were significantly associated with stroke and all-cause mortality in patients with paroxysmal AF. The predictive performance of HMGB1 rivaled that of the CHA_2DS_2-VASc score, and their combined use further improved risk stratification. These findings suggested that HMGB1 might emerge as a clinically useful biomarker. However, before incorporation into routine clinical practice, prospective validation in large multicenter cohorts, standardization of HMGB1 testing protocols across laboratories, and studies evaluating its effectiveness in guiding personalized antithrombotic or anti-inflammatory strategies are required.

Data Sharing Statement

Data from this study are available upon request from the corresponding authors. The data were not publicly available due to privacy and ethical restrictions.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Jiangyin People's Hospital (approval number: 2015ER022) and conducted in accordance with the Declaration of Helsinki. All enrolled patients provided written informed consent before enrollment.

Author Contributions

Lingyun Gu; Conceptualization, Funding acquisition, Methodology, Writing – review and editing. Jinfeng Zhou; Investigation, Methodology, Writing – original draft. Qi Jin; Methodology, Visualization, Writing – original draft. Zhuowen Xu; Funding acquisition, Methodology, Supervision. Weizhang Li; Conceptualization, Methodology, Visualization. Junyou Cui; Investigation, Project administration, Writing – review and editing. Hua Zhang; Conceptualization, Project administration, Writing – review and editing.

All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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