ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Predictive Value of the Inflammatory Prognostic Index for Ischemic Stroke in Patients with HFpEF and Atrial Fibrillation

HFpEF ve Atriyal Fibrilasyon Hastalarında Enflamatuvar Prognostik Endeksin İskemik İnme Öngörüsündeki Değeri

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ABSTRACT

Aim: *This study aimed to evaluate the predictive value of the inflammatory prognostic index (IPI) for ischemic cerebrovascular events in patients with heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF).*

Materials and methods: *A total of 1.286 patients with HFpEF and AF followed between 2020 and 2024 were retrospectively included. The primary endpoint was ischemic stroke during a mean follow-up of 651±167 days. Inflammatory prognostic index and CHA_2DS_2-VA scores were calculated, and Cox regression, receiver operating characteristic (ROC), and Kaplan-Meier analyses were performed.*

Results: *Ischemic stroke occurred in 67 patients (5.2%). Patients with stroke were older and had higher rates of hypertension, coronary artery disease, and prior stroke/TIA, while oral anticoagulant use was lower. They also exhibited higher levels of creatinine, CRP, and neutrophils, and lower lymphocyte counts. Both IPI and CHA_2DS_2-VA scores were significantly higher in the stroke group. In multivariable analysis, creatinine (HR: 1.828), CHA_2DS_2-VA (HR: 2.081), and IPI (HR: 1.909) remained independent predictors of stroke. ROC analysis showed that IPI had superior discriminative ability compared to CHA_2DS_2-VA (AUC: 0.783 vs. 0.726). Kaplan-Meier analysis demonstrated a significantly higher incidence of stroke in patients with elevated IPI levels (log-rank p<0.001).*

Conclusion: *IPI is a strong and independent predictor of ischemic stroke in patients with HFpEF and AF. Integration of inflammation-based biomarkers into conventional clinical risk scores may improve risk stratification, particularly in high-risk populations.*

Key words: *atrial fibrillation; HFpEF; inflammatory prognostic index; ischemic stroke*

ÖZET

Amaç: *Bu çalışmanın amacı, korunmuş ejeksiyon fraksiyonlu kalp yetersizliği (HFpEF) ve atriyal fibrilasyon (AF) hastalarında enflamatuvar prognostik endeksin (IPI), iskemik serebrovasküler olay gelişimini öngörmedeki değerini değerlendirmektir.*

Gereç ve Yöntem: *Bu retrospektif kohort çalışmasına 2020–2024 yılları arasında HFpEF ve AF tanısı ile izlenen toplam 1.286 hasta dâhil edildi. Primer sonlanım noktası izlem süresince gelişen iskemik inme olarak belirlendi. Ortalama takip süresi 651±167 gün idi. Enflamatuvar prognostik endeks ve CHA_2DS_2-VA skorları hesaplandı. İstatistiksel analizlerde Cox regresyon, ROC analizi ve Kaplan-Meier yöntemleri kullanıldı.*

Bulgular: *İzlem süresince 67 hastada (%5,2) iskemik inme gelişti. İnme gelişen hastalar daha yaşlı olup hipertansiyon, koroner arter hastalığı ve geçirilmiş inme/TIA öyküsü daha sık, oral antikoagülan kullanımı ise daha düşüktü. Ayrıca kreatinin, CRP, nötrofil, IPI ve CHA_2DS_2-VA skorları daha yüksek, lenfosit düzeyleri daha düşüktü. Çok değişkenli analizde kreatinin (HR: 1,828), CHA_2DS_2-VA (HR: 2,081) ve IPI (HR: 1,909) iskemik inmenin bağımsız prediktörleri olarak belirlendi. ROC analizinde IPI, CHA_2DS_2-VA skoruna göre daha yüksek ayırt edici güce sahipti (AUC: 0.783 vs. 0,726). Kaplan-Meier analizinde yüksek IPI düzeyine sahip hastalarda iskemik inme insidansı anlamlı olarak daha yüksekti (log-rank p<0,001).*

Sonuç: *IPI, HFpEF ve AF hastalarında iskemik inme gelişiminin güçlü ve bağımsız bir öngördürücüsüdür. IPI'nin mevcut klinik risk skorlarına entegrasyonu, özellikle yüksek riskli hasta grubunda risk sınıflamasını iyileştirebilir.*

Anahtar kelimeler: *atriyal fibrilasyon, HFpEF, enflamatuvar prognostik endeks, iskemik inme*

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a leading preventable cause of ischemic stroke. As populations age, the growing burden of AF is associated with increasing thromboembolic morbidity and mortality, posing a major challenge to healthcare systems (1).

Heart failure and AF frequently coexist and are associated with worse outcomes than either condition alone. Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases and is associated with a high prevalence of AF (2). Patients with HFpEF and AF have an increased risk of ischemic stroke because of shared risk factors, including advanced age, hypertension, diabetes, and obesity (3,4).

The CHA_2DS_2-VA score is widely used to stratify thromboembolic risk in AF (1). However, thromboembolism in patients with HFpEF and AF involves mechanisms beyond clinical variables, including atrial remodeling, endothelial dysfunction, a prothrombotic state, and inflammation (5).

Chronic low-grade inflammation contributes to AF initiation and maintenance, atrial fibrosis, and thrombus formation. Through cytokine release, oxidative stress, and coagulation activation, inflammatory pathways increase thromboembolic risk (6). However, most current risk scores do not account for inflammatory burden, a limitation particularly relevant in patients with HFpEF and AF, who often exhibit pronounced systemic inflammation.

Accordingly, inflammation-based biomarkers have attracted increasing interest. The Inflammatory Prognostic Index (IPI), which combines C-reactive protein (CRP), albumin, and the neutrophil-to-lymphocyte ratio, reflects systemic inflammation and immune homeostasis in a single metric (7). However, its value for predicting ischemic stroke in patients with HFpEF and AF remains unclear.

This study aimed to evaluate the role of IPI in predicting ischemic cerebrovascular events in patients with HFpEF and AF.

Material and Methods

Study Design and Patient Population

This study was designed as a retrospective observational cohort study including patients diagnosed with HFpEF and AF between January 2020 and December 2024. After applying predefined inclusion and exclusion criteria, a total of 1.286 consecutive patients were included in the final analysis Fig. 1.

HFpEF was diagnosed in accordance with current guideline recommendations, requiring the presence of signs and symptoms of heart failure, a left ventricular ejection fraction ≥50%, and supportive echocardiographic findings (8). Atrial fibrillation was confirmed by standard 12-lead electrocardiography or 24-hour Holter monitoring, in line with current guideline definitions (1).

Patients with active infection, malignancy, severe hepatic failure, hematological disorders, or incomplete laboratory data were excluded. Additionally, patients with valvular AF, defined as severe mitral stenosis or a mechanical prosthetic valve, were excluded.

Data Collection

Demographic, clinical, and laboratory data were retrospectively obtained from institutional electronic medical records. Recorded variables included age, sex, comorbidities (hypertension, diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease), and medications.

Laboratory parameters at the time of index admission included serum creatinine, CRP, glucose, N-terminal pro-B-type natriuretic peptide (NT-proBNP), albumin, lipid profile, neutrophil and lymphocyte counts, hemoglobin, and platelet count. All laboratory parameters used for IPI calculation were obtained from the same blood sample collected at hospital admission

Risk Score Calculations

The CHA_2DS_2-VA score was calculated for each patient according to established criteria (1). The IPI was calculated using the following formula: IPI=(CRP (mg/L) × neutrophil count ($\times 10^9$/L)) / (lymphocyte count ($\times 10^9$/L) × albümin (g/L)) (7).

Study Endpoint and Follow-up

The primary endpoint was ischemic stroke during follow-up, confirmed by clinical evaluation and neuroimaging. Patients were followed from the index admission until stroke or the end of the study period. Follow-up data were obtained from hospital electronic records and patient files.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. Normality was assessed with the Kolmogorov-Smirnov test. Between-group comparisons used the independent samples t-test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Univariable and multivariable Cox proportional hazards regression analyses identified independent predictors of ischemic stroke, with variables showing $p < 0.05$ in univariable analysis entered into the multivariable model. Correlations between the CHA_2DS_2-VA score and clinical variables (age, hypertension, and prior stroke/TIA) were assessed using Spearman's rank correlation. Predictive performance was evaluated by ROC curve analysis with AUC calculation, and optimal cut-off values were determined using the Youden index. Kaplan-Meier analysis with the log-rank test was used for time-to-event analyses. A two-sided $p < 0.05$ was considered statistically significant.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Decision No: 2025/12-343).

Results

A total of 1.286 patients with HFpEF and atrial fibrillation were included, and ischemic stroke occurred in 67 patients (5.2%) during a mean follow-up of 651±167 days Table 1.

Patients who developed ischemic stroke were older than those who did not (72.3±3.1 vs. 67.8±4.0 years; $p < 0.001$) and had higher rates of hypertension (76.1% vs. 63.6%; p=0.037), coronary artery disease (55.2% vs. 35.8%; p=0.001), and prior stroke/TIA (23.9% vs. 13.9%; p=0.023). Sex, diabetes mellitus, and chronic obstructive pulmonary disease were similar between the groups (all $p > 0.05$) Table 1.

Regarding medical therapy, oral anticoagulant use was significantly lower in patients who developed ischemic stroke (64.2% vs. 76.0%; p=0.028). No significant differences were observed between the groups in the use of other medications (all $p > 0.05$).

Patients who developed ischemic stroke had higher creatinine (1.22±0.46 vs. 1.10±0.41 mg/dL; p=0.014), CRP (18.49±4.38 vs. 14.39±6.83 mg/L; $p < 0.001$),

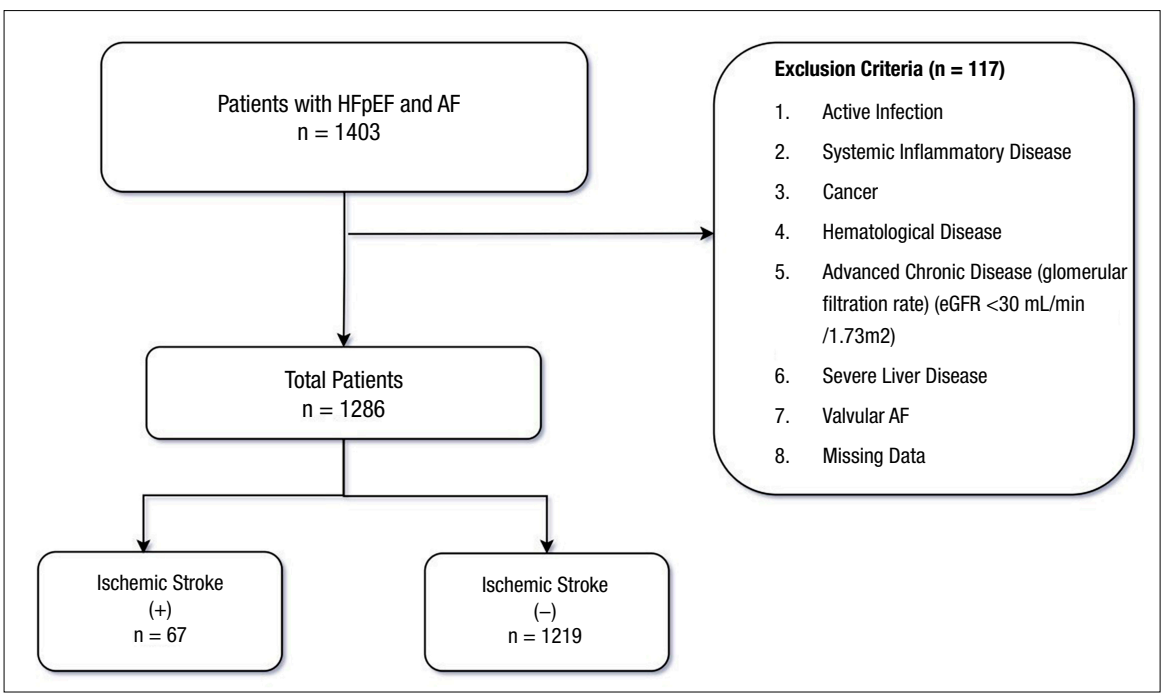

Figure 1. *Flowchart of study population.*

Table 1. *Baseline clinical, laboratory, and treatment characteristics of patients according to ischemic stroke status*

Variable	Ischemic Stroke (+) (n = 67)	Ischemic Stroke (–) (n = 1219)	P value
Age, years	72.3 ± 3.1	67.8 ± 4.0	<0.001
Male sex, n (%)	36 (53.7)	673 (55.2)	0.813
Hypertension, n (%)	51 (76.1)	775 (63.6)	0.037
Diabetes mellitus, n (%)	17 (25.4)	354 (29.0)	0.519
CAD, n (%)	37 (55.2)	436 (35.8)	0.001
COPD, n (%)	19 (28.4)	338 (27.7)	0.911
Prior Stroke/TIA, n (%)	16 (23.9)	169 (13.9)	0.023
Medications			
OAC, n (%)	43 (64.1)	927 (76.0)	0.028
ASA, n (%)	31 (46.2)	595 (48.8)	0.683
Statin, n (%)	47 (70.1)	873 (71.6)	0.784
BB, n (%)	43 (64.2)	792 (65.0)	0.896
CaKB, n (%)	18 (26.9)	287 (23.5)	0.534
ACEI / ARB, n (%)	46 (68.6)	885 (72.6)	0.624
Laboratory			
Creatinine, mg/dL	1.22 ± 0.46	1.10 ± 0.41	0.014
CRP, mg/L	18.49 ± 4.38	14.39 ± 6.83	<0.001
AST, U/L	21.5 ±4.3	18 ±4.7	0.091
Albumin, g/L	36.8 ± 4.0	37.1 ± 3.8	0.452
Glucose, mg/dL	123 ± 32	118 ± 29	0.102
NT-proBNP, pg/mL	486 ± 112	471 ± 124	0.241
Triglyceride, mg/dL	148 ± 35	139 ± 33	0.187
LDL cholesterol, mg/dL	112 ± 25	107 ± 28	0.240
HDL cholesterol, mg/dL	39.2 ± 3.6	40 ± 3.2	0.109
Neutrophil ($\times10^9$/L)	6.44 ± 0.73	5.66 ± 1.09	<0.001
Lymphocyte ($\times10^9$/L)	1.75 ± 0.34	1.85 ± 0.41	0.042
Hemoglobin, g/dL	13.18 ± 0.95	13.49 ± 0.96	0.074
Platelet ($\times10^9$/L)	253 ± 34	246 ± 40	0.173
CHA_2DS_2-VA score	3.60 ± 0.92	2.69 ± 1.11	<0.001
IPI	1.95 ± 0.67	1.28 ± 0.79	<0.001

AF: atrial fibrillation; HFpEF: heart failure with preserved ejection fraction; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; OAC: oral anticoagulant; ASA: acetylsalicylic acid; BB: beta-blocker; CaKB: calcium channel blocker; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CRP: C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TIA: transient ischemic attack; IPI: inflammatory prognostic index.

and neutrophil counts (6.44±0.73 vs. 5.66±1.09 $\times10^9$/L; p <0.001), while lymphocyte counts were lower (1.75±0.34 vs. 1.85±0.41 $\times10^9$/L; p=0.042). Glucose levels were similar between the groups (123±32 vs. 118±29 mg/dL; p=0.102), as were NT-proBNP, lipid parameters, AST, albumin, hemoglobin, and platelet counts (all p >0.05) Table 1.

The CHA_2DS_2-VA score was significantly higher in patients with stroke (3.60±0.92 vs. 2.69±1.11; p <0.001). Similarly, IPI levels were significantly higher in the stroke group (1.95±0.67 vs. 1.28±0.79; p <0.001).

In univariable Cox regression analysis, oral anticoagulant use (HR: 0.561; 95% CI: 0.341–0.925; p=0.024), creatinine (HR: 1.819; 95% CI: 1.108–2.984; p=0.018), CHA_2DS_2-VA score (HR: 2.063; 95% CI: 1.663–2.559; p <0.001), and IPI (HR: 1.788; 95% CI: 1.485–2.152; p <0.001) were significantly associated with ischemic stroke Table 2.

In multivariable analysis, creatinine (HR: 1.828; 95% CI: 1.079–3.098; p=0.025), CHA_2DS_2-VA score (HR: 2.081; 95% CI: 1.665–2.600; p <0.001), and IPI (HR: 1.909; 95% CI: 1.560–2.335; p <0.001)

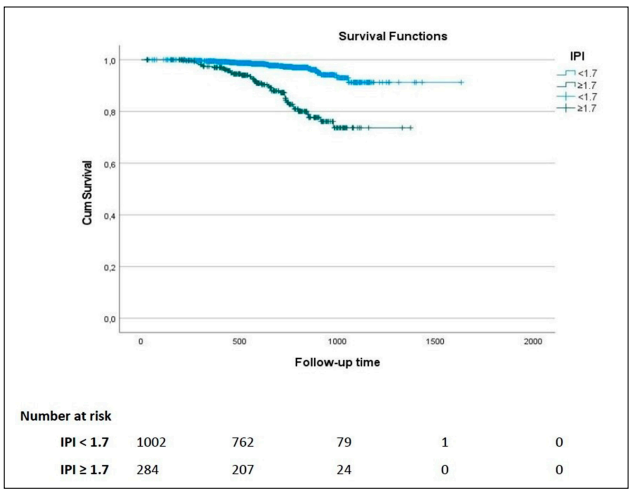

Figure 2. *Kaplan-Meier survival curves for ischemic stroke according to IPI levels.*

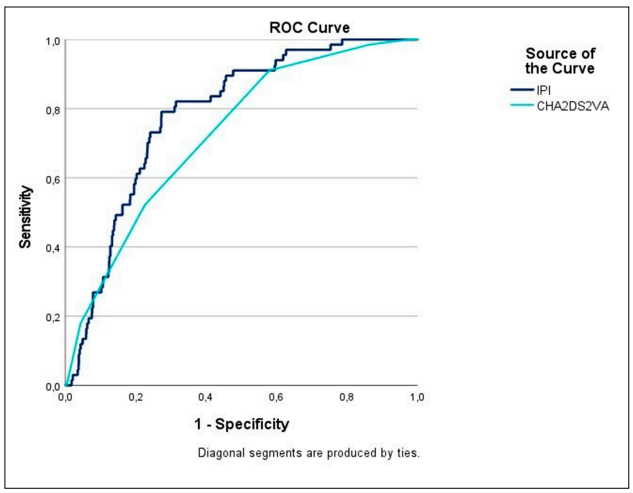

Figure 3. *ROC curve of the CHA_2DS_2-VA score and IPI for predicting ischemic stroke.*

Table 2. *Univariable and multivariable Cox regression analyses for predictors of ischemic stroke*

Variables	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
OAC	0.561 (0.341–0.925)	0.024	0.690 (0.412–1.156)	0.159
Creatinine	1.819 (1.108–2.984)	0.018	1.828 (1.079–3.098)	0.025
CHA_2DS_2-VA	2.063 (1.663–2.559)	<0.001	2.081 (1.665–2.600)	<0.001
IPI	1.788 (1.485–2.152)	<0.001	1.909 (1.560–2.335)	<0.001

HR: hazard ratio; CI: confidence interval; OAC: oral anticoagulant; IPI: inflammatory prognostic index.

remained independent predictors of ischemic stroke. Oral anticoagulant use was not independently associated with stroke after adjustment (HR: 0.690; 95% CI: 0.412–1.156; p=0.159) Table 2.

ROC analysis showed that IPI had a higher discriminative ability than the CHA_2DS_2-VA score (AUC: 0.783 vs. 0.726). The optimal IPI cut-off was 1.70, with 61.0% sensitivity and 79.7% specificity Fig. 2, Table 3.

Kaplan-Meier analysis showed a higher incidence of ischemic stroke in patients with elevated IPI than in those with low IPI (log-rank p <0.001) Fig 2.

Spearman correlation analysis revealed that the CHA_2DS_2-VA score was strongly correlated with age (r=0.924, p <0.001), hypertension (r=0.612, p <0.001), prior stroke/TIA (r=0.683, p <0.001), and coronary artery disease (r=0.715, p <0.001). Given their high correlation with the CHA_2DS_2-VA score, these variables were not included in the multivariable regression analysis to avoid multicollinearity.

Table 3. *Receiver operating characteristic (ROC) analysis of CHA_2DS_2-VA Score and IPI for predicting ischemic stroke*

Variables	AUC	95% CI	p value
CHA_2DS_2-VA	0.726	0.669–0.782	<0.001
IPI	0.783	0.737–0.829	<0.001

AUC: area under the curve; CI: confidence interval; IPI: inflammatory prognostic index; ROC: receiver operating characteristic.

Discussion

The present study demonstrates that the IPI is a strong and independent predictor of ischemic cerebrovascular events in patients with HFpEF and non-valvular atrial fibrillation. Moreover, incorporating IPI into the CHA_2DS_2-VA score significantly enhanced risk discrimination. To the best of our knowledge, this is among the first studies to specifically explore the association between IPI and ischemic stroke in patients with concomitant HFpEF and AF, highlighting the novelty of our findings.

Atrial fibrillation remains the most common sustained cardiac arrhythmia worldwide and is a leading cause of ischemic stroke (1). The presence of AF increases stroke risk approximately four- to five-fold, with annual stroke rates ranging from 1–2% in the general AF population to over 5% in high-risk individuals (9). When AF coexists with HFpEF, the risk of both stroke and mortality increases further (2,10).

The coexistence of HFpEF and AF represents an increasingly recognized and clinically significant phenotype (4). Large registry-based studies such as GWTG-HF, SwedeHF, and CHART-2 have shown that AF is highly prevalent in HFpEF and is closely linked to disease progression (11–13). Data from the ESC Heart Failure Long-Term Registry further indicate that AF is more strongly associated with mortality and hospitalization in HFpEF patients (14).

HFpEF and AF share a common risk profile, including advanced age, obesity, hypertension, diabetes, and sleep apnea (3,15). Mechanistically, their interaction is bidirectional: elevated filling pressures and atrial stretch promote AF development, while AF exacerbates diastolic dysfunction and accelerates HFpEF progression (15).

Although CHA_2DS_2-VA is widely used for thromboembolic risk assessment in AF, it does not account for inflammation, endothelial dysfunction, or thromboinflammation (1). This may contribute to residual thromboembolic risk, particularly in patients with HFpEF and AF.

Growing evidence highlights inflammation as a central driver of both AF and HFpEF. Chronic low-grade inflammation contributes to endothelial dysfunction, microvascular injury, and myocardial fibrosis, and promotes thrombus formation by activating coagulation pathways (5,6,16).

In this context, biomarkers such as CRP, NLR, and albumin have been associated with AF development and prognosis. Elevated CRP levels reflect systemic inflammation and have been linked to AF occurrence and recurrence, as well as poor outcomes in heart failure (17,18). Similarly, NLR has been identified as a marker of thromboinflammatory activity and is associated with AF burden and adverse cardiovascular outcomes (19). Low albumin levels, reflecting inflammation and oxidative stress, have also been associated with adverse cardiovascular outcomes (20).

The IPI, which combines CRP, NLR, and albumin, provides a comprehensive measure of systemic inflammation (7). Initially studied in oncology, IPI has more recently been shown to predict adverse outcomes in cardiovascular settings (21–23). It has been associated with contrast-induced nephropathy, no-reflow in STEMI, and adverse outcomes in NSTEMI (23–25). Additionally, IPI has been shown to predict new-onset AF after PCI and poor outcomes in stroke populations (26–27).

In our study, IPI was significantly higher in patients who developed ischemic stroke and remained an independent predictor after multivariable adjustment. ROC analysis showed that IPI had better discriminative ability than the CHA_2DS_2-VA score, while Kaplan-Meier analysis demonstrated a higher cumulative risk of ischemic stroke in patients with elevated IPI, supporting the role of inflammation in thromboembolic risk.

Consistent with previous studies, patients who developed stroke were older and had higher rates of hypertension, coronary artery disease, and prior stroke/TIA. Oral anticoagulant use was lower in this group, possibly reflecting higher baseline risk. However, anticoagulation quality, treatment adherence, and time in the therapeutic range were not assessed and may have contributed to residual risk.

From a laboratory perspective, higher creatinine, CRP, and neutrophil levels, along with lower lymphocyte counts, were observed in patients with stroke. The independent predictive value of creatinine is consistent with the well-established relationship between renal dysfunction and thromboembolic risk in AF, which is mediated by endothelial dysfunction, platelet activation, and coagulation abnormalities.

Taken together, these findings suggest that integrating inflammation-based biomarkers, such as IPI, into conventional risk models may improve risk stratification, particularly in high-risk populations, such as HFpEF with AF.

Limitations

This study has several limitations. Its retrospective, single-center design may limit generalizability. Inflammatory markers were assessed only at baseline, and residual confounding cannot be excluded despite multivariable analyses. In addition, specific inflammatory cytokines and detailed data on oral anticoagulant

adherence and dose optimization were unavailable. Finally, the optimal IPI cut-off may vary across different populations.

Conclusion

In conclusion, IPI is an independent predictor of ischemic cerebrovascular events in patients with HFpEF and atrial fibrillation. These findings support the role of inflammation in thromboembolic risk and suggest that incorporating inflammation-based biomarkers into conventional risk scores may improve risk stratification. Given its simplicity and availability, IPI may be a practical, cost-effective tool for identifying high-risk patients. Prospective multicenter studies are needed to validate these findings and define the clinical utility of inflammation-based risk models.

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Conflicts of Interest

The authors declare no conflicts of interest.

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