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SERUM C-SKI AS A BIOMARKER ASSOCIATED WITH ATRIAL FIBRILLATION PROGRESSION, INFLAMMATORY STATUS, AND PROGNOSIS

SERUMSKI C-SKI KAO BIOMARKER POVEZAN SA PROGRESIJOM ATRIJALNE FIBRILACIJE, INFLAMATORNIM STATUSOM I PROGNOZOM

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Summary

Background: To investigate the association between serum c-Ski levels and atrial fibrillation (AF) subtype, inflammatory status, and clinical prognosis.
Methods: A single-center observational study enrolled 164 patients with AF (paroxysmal, n=67; persistent, n=58; permanent, n=39) and 58 age- and sex-matched controls. Blood samples were collected within 24 h of admission and at discharge. Serum c-Ski, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were measured by ELISA; hs-CRP and echocardiographic indices (LVEF, LAVI) were recorded. Participants were followed at 1, 3, 6, and 12 months after discharge. Cardiovascular events and all-cause mortality were recorded for the full cohort, whereas AF recurrence was analyzed in 136 patients with complete rhythm follow-up and available discharge c-Ski measurement.
Results: Serum c-Ski was higher in AF patients than in controls and increased across AF subtypes (paroxysmal < persistent < permanent; all P<0.05). c-Ski showed moderate discrimination between AF and controls (AUC=0.794) and correlated positively with IL-6, TNF-α, hs-CRP, and LAVI and negatively with LVEF (all P<0.05). c-Ski decreased from admission to discharge (P<0.05). In exploratory prognosis analyses, higher discharge c-Ski was observed in patients who developed cardiovascular events (n=19/155) and in those who died (n=9/164) during follow-up (P<0.05). Among 136 patients included in the recurrence analysis, 64 experienced AF recurrence

Kratak sadržaj

Uvod: Cilj je ispitati vezu između nivoa c-Ski u serumu i podtipa atrijalne fibrilacije (AF), inflamatornog statusa i kliničke prognoze.
Metode: Sproveli smo studiju slučaj-kontrola koja je kao jednocentrična opservaciona studija obuhvatila 164 pacijenta sa atrijalnom fibrilacijom (paroksizmalna, n=67; perzistentna, n=58; trajna, n=39) i 58 kontrolnih ispitanika usklađenih po starosti i polu. Uzorci krvi su prikupljeni u roku od 24 sata od prijema i pri otpustu. Serumski c-Ski, interleukin-6 (IL-6) i faktor nekroze tumora-α (TNF-α) mereni su ELISA testom; zabeleženi su hs-CRP i ehokardiografski indeksi (LVEF, LAVI). Učesnici su praćeni 1, 3, 6 i 12 meseci nakon otpusta. Kardiovaskularni događaji i mortalitet od svih uzroka zabeleženi su za celu kohortu, dok je recidiv atrijalne fibrilacije analiziran kod 136 pacijenata sa kompletnim praćenjem ritma i dostupnim merenjem c-Ski pri otpustu.
Rezultati: Serumski c-Ski je bio viši kod pacijenata sa atrijalnom fibrilacijom (AF) nego kod kontrolne grupe i povećao se u svim podtipovima AF (paroksizmalna < perzistentna < permanentna; svi P<0,05). c-Ski je pokazao umerenu diskriminaciju između AF i kontrolne grupe (AUC=0,794) i pozitivno je korelirao sa IL-6, TNF-a, hs-CRP i LAVI, a negativno sa LVEF (svi P<0,05). c-Ski se smanjio od prijema do otpusta (P<0,05). U eksploratornim analizama prognoze, viši c-Ski pri otpustu je primećen kod pacijenata koji su razvili kardiovaskularne događaje (n=19/155) i kod onih koji su umrli (n=9/164) tokom praćenja (P<0,05).

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(47.06%); discharge c-Ski was higher in the recurrence group and showed moderate discrimination for recurrence (AUC=0.760).
Conclusion: Serum c-Ski is associated with AF subtype and inflammatory burden. Discharge c-Ski demonstrated moderate discrimination for AF recurrence and may contribute to risk stratification. These findings are exploratory and require external validation in larger, multicenter cohorts.

Keywords: atrial fibrillation, c-Ski, inflammatory cytokines, prognosis, biomarker

Među 136 pacijenata uključenih u analizu recidiva, 64 su doživela recidiv AF (47,06%); c-Ski pri otpustu je bio viši u grupi sa recidivom i pokazao je umerenu diskriminaciju za recidiv (AUC=0,760).
Zaključak: Serumski c-Ski je povezan sa podtipom atrijalne fibrilacije (AF) i inflamatornim opterećenjem. Otpusni c-Ski je pokazao umerenu diskriminaciju za recidiv AF i može doprineti stratifikaciji rizika. Ovi nalazi su istraživačke prirode i zahtevaju eksternu validaciju u većim, multicentričnim kohortama.

Ključne reči: atrijalna fibrilacija, c-Ski, inflamatorni citokini, prognoza, biomarker

Introduction

Atrial fibrillation (AF) is the most prevalent persistent arrhythmia, with a global prevalence exceeding 2%. It significantly elevates the risk of stroke, heart failure, and mortality (1). Despite ongoing advancements in treatment modalities such as radiofrequency ablation and antiarrhythmic medications, the recurrence rate of AF remains alarmingly high at 30%–50%. The underlying pathological mechanisms driving atrial remodeling – comprising electrical remodeling, structural remodeling, and neural remodeling – have yet to be fully elucidated (2, 3). Recent studies have identified chronic inflammation as a critical factor in the onset and progression of AF. Inflammatory mediators (such as IL-6 and TNF-α) contribute to atrial fibrosis and abnormal electrical conduction by promoting fibroblast proliferation, collagen deposition, and oxidative stress (4, 5). However, the upstream regulatory network governing this inflammatory cascade remains largely unknown.

As a nuclear receptor co-repressor, c-Ski has been shown to inhibit myocardial fibrosis and inflammation by antagonizing the transforming growth factor-β (TGF-β) signaling pathway. This suggests that c-Ski may play a protective role in various cardiovascular diseases (6, 7). Animal studies indicate that overexpression of c-Ski can mitigate ventricular remodeling following myocardial infarction; however, its specific impact on atrial remodeling in AF has not been clearly defined (8). Most clinical investigations have concentrated on c-Ski expression within tumors or metabolic disorders (9, 10). Nonetheless, research examining dynamic changes in serum levels of c-Ski among AF patients – and their correlation with disease progression – is exceedingly limited. There is particularly a lack of comprehensive discussions regarding the regulatory mechanisms involved in inflammation.

Atrial fibrillation (AF) is the most common sustained arrhythmia and remains a major contributor to thromboembolic events, heart failure, and mortality (1, 11). Inflammation and structural remodeling are central to AF initiation and maintenance, but clinically applicable biomarkers that reflect these processes and inform risk stratification remain limited (4, 5). c-Ski, a regulator of TGF-β/Smad signaling, has been implicated in fibrosis and immune modulation; however, its circulating profile and clinical associations in AF have not been sufficiently characterized.

Materials and Methods

Subjects

Study populationThis was a single-center observational study. A total of 164 patients with AF treated in the Department of Cardiology of Shanghai Sixth People's Hospital from March 2024 to October 2024 were enrolled, including 67 paroxysmal AF cases, 58 persistent AF cases, and 39 permanent AF cases. Fifty-eight age- and sex-matched healthy subjects served as controls. Inclusion criteria were: (1) age ≥18 years; (2) AF diagnosed by ECG or 24-h Holter monitoring. Exclusion criteria were: (1) cardiac structural abnormalities (including valvular disease and cardiomyopathy); (2) acute infection, autoimmune disease, malignancy, or severe hepatic/renal dysfunction; (3) recent surgery or trauma; (4) pregnancy or lactation. The study was approved by the Institutional Ethics Committee of Shanghai Sixth People's Hospital (Approval No.: [to be inserted]), and written informed consent was obtained from all participants.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age between 18 and 80 years, regardless of sex; (2) Diagnosis of AF confirmed by a 12-lead electrocardiogram or a 24-hour Holter monitor (paroxysmal: duration <7 days with spontaneous cardioversion; persistent: duration ≥7 days or requiring intervention for cardioversion; permanent: rhythm control abandoned) (11); (3) Provision of informed consent and ability to cooperate in completing a one-year follow-up.

Exclusion criteria: (1) Presence of valvular heart disease, congenital heart disease, acute myocardial infarction, or cardiomyopathy; (2) Severe liver or kidney dysfunction; (3) Malignant tumors, systemic lupus erythematosus, or other autoimmune diseases; (4) Use of immunosuppressive agents, high-dose corticosteroids, or anti-inflammatory drugs within the past month; (5) Pregnant or lactating women; (6) Inability to tolerate follow-up procedures or refusal to provide blood samples.

Inclusion criteria for controls: (1) Gender and age matched with AF patients; (2) No significant medical history; (3) Normal cardiac function confirmed through physical examination. The exclusion criteria for the control group were identical to those applied to the AF patient cohort. This study received approval from the ethics committee at our hospital.

Sample collection and pre-analysis

Blood samples were collected within 24 h of admission (baseline) and at discharge (post-treatment). Fasting venous blood (5 mL) was collected into serum tubes, allowed to clot for 30 min, and centrifuged at 3,000 rpm for 10 min. Serum was aliquoted and stored at −80 °C until analysis.

Laboratory tests

Serum c-Ski, IL-6, and TNF-α concentrations were measured by ELISA (R&D Systems). Blank Wells (dilution only), calibration Wells (6 multiple Wells), and sample Wells (double multiple Wells) were set up, 100 μL sample/calibrator was added to each well, and the plates were coated overnight at 4 °C. The liquid in the Wells was discarded, and 300 μL PBS-Tween 20 was added to each well. The plates were washed 5 times by a washing machine (soaking for 30 s each time), and the residual liquid was patted dry. 100 μL biotinylated detection antibody (1:100 dilution) was added to each well and incubated for 1 h at 37 °C. After washing, 100 μL of streptavidin-HRP (1:100 dilution) was added and incubated at 37 °C for 30 min. After washing, 100 μL of TMB chromogenic solution was added, and the color was developed in the dark at 37 °C for 15 min, followed by 50 μL of termination solution (yellow changed to blue). The absorbance (OD value) was read by microplate reader at 450 nm, zeroed with blank Wells, and the standard curve (concentration -OD value) was fitted by four-parameter logistic regression to calculate the sample concentration.

The level of hs-CRP was detected by automatic biochemical analyzer (Beckman Coulter AU5800). The device was turned on and preheated for 30 min, the reagents were loaded (equilibrated to room temperature in advance), and the calibrators, quality control materials and sample information were input. Select »hs-CRP« test item, set the parameters: wavelength 340 nm (turbidimetric transmission), reaction mode as endpoint method, reaction time 5 min. The hs-CRP in the sample was combined with the latex particle reagent to form a turbidity complex. The instrument calculated the concentration (mg/L) by measuring the absorbance change of the specific wavelength.

Quality Control

ELISA quality control: High-, medium-, and low-concentration quality control materials (R&D Systems, cat. No. QC001/QC002/QC003) were tested in duplicate for each batch. The intra-batch CVs were 3.2%–6.8% (high: 3.2%, medium: 4.5%, low: 6.8%), and inter-batch CVs were 7.5%–12.3% (high: 7.5%, medium: 9.1%, low: 12.3%), all meeting the criteria (intra-batch ≤10%, inter-batch ≤15%). Levey-Jennings control charts were used to monitor results: when the low-concentration QC exceeded +2SD in 1 batch, the reagent was re-calibrated and the sample retested, with consistent results after correction.

Automatic biochemical analyzer quality control: Daily calibration was performed with Beckman Coulter calibrators (cat. No. CAL6800), and QC materials (Beckman Coulter, cat. No. QC5800) were tested. The CVs of hs-CRP were 2.1%–4.3% (high: 2.1%, medium: 3.2%, low: 4.3%), meeting the requirement of ≤5%. The instrument's internal quality control system automatically flagged abnormal results (e.g., absorbance deviation >10%), which were verified by retesting with fresh samples.

Sample quality control: Venous blood was centrifuged at 3000 rpm for 10 minutes to separate serum. Hemolysis was detected by hemoglobin assay (Beckman Coulter AU5800), with 3 hemolyzed samples (hemoglobin >0.5 g/L) excluded and re-collected. Lipemic samples (triglycerides >10 mmol/L, n=2) were treated with lipid-clearing reagent (Beckman Coulter, cat. No. LCR001) before retesting. Serum aliquots (100 μL/aliquot) were stored at -80 °C, with no more than 1 freeze-thaw cycle allowed.

Standardization of testing

Give priority to using reagent kits certified by IFCC (International Federation of Clinical Chemistry) to ensure that the reference standards are traceable to international standards. The ELISA standard curve adopted four-parameter logistic regression (4PL), with a correlation coefficient (r^2) of ≥0.99. Verify

the linear range (such as c-Ski 15–180 ng/mL), take high-value samples, dilute them and compare them with the measured values. The recovery rate is 90%–110%. Biochemical analysis shows that the linear range of hs-CRP is 0.1–20 mg/ L. If it exceeds this range, it needs to be diluted with normal saline and retested.

Follow-up plan

The patients were followed up at 1, 3, 6, and 12 months after discharge. Endpoint events were recorded, including AF recurrence (documented AF/atrial flutter lasting >30 seconds during follow-up), cardiovascular events (stroke, hospitalization for heart failure, myocardial infarction), and all-cause death.

Statistical analysis

SPSS 25.0 was used for statistical analysis. Continuous variables are presented as mean ± SD or median (interquartile range) depending on distribution (assessed using the Shapiro–Wilk test). Between-group comparisons were performed using Student's t-test or the Mann–Whitney U test, and multiple-group comparisons were performed using one-way ANOVA or the Kruskal–Wallis test with appropriate post hoc testing. Categorical variables are expressed as n (%) and compared using the χ^2 test or Fisher's exact test. Correlations were assessed using Pearson or Spearman coefficients as appropriate. ROC analysis was used to evaluate discrimination, and the area under the curve (AUC) was reported. Optimal cut-offs were determined using the Youden index. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Comparison of clinical baseline data

Baseline characteristics. There were no significant differences in baseline data such as age, sex, BMI, and family history of disease between AF patients and controls ($P>0.05$). Standardized mean differences (SMDs) are provided to quantify group imbalance, and values were within 0.2 for the main baseline covariates, indicating acceptable comparability. In terms of cardiac function, the AF group had a significantly lower LVEF and a significantly higher LAVI than the control group ($P<0.05$, *Table I*).

Diagnostic efficacy of c-Ski for AF

The serum c-Ski level of AF patients was (22.31±4.93) ng/mL, which was higher than that of the control group ($P<0.05$). ROC analysis demonstrated moderate discrimination of c-Ski for differentiating AF patients from controls (cut-off >19.00 ng/mL; sensitivity 71.95%; specificity 74.14%; AUC=0.794; *Figure 1*). In different subtypes of AF, the level of c-Ski was highest in permanent AF and lowest in paroxysmal AF ($P<0.05$, *Figure 1*).

The relationship between c-Ski level and inflammatory factors and cardiac function in patients with AF

Correlation analysis showed that c-Ski was positively correlated with inflammatory factors IL-6, TNF-α and hs-CRP (all $P<0.05$). In terms of cardiac function, c-Ski was negatively correlated with LVEF but positively correlated with LAVI (all $P<0.05$, *Figure 2*).

The relationship between the dynamic changes of c-Ski and cardiovascular events and all-cause mortality

At discharge, the c-Ski level of AF patients was lower than that at admission ($P<0.05$). During the one-year follow-up, 9 patients (5.49%) died. For cardiovascular event analyses, deaths were excluded, leaving 155 patients; among them, 19 patients (12.26%) experienced cardiovascular events. Discharge c-Ski was higher in patients with cardiovascular events than in those without events ($P<0.05$). Similarly, discharge c-Ski was higher in patients who died than in those who survived ($P<0.05$, *Figure 3*).

The relationship between c-Ski and prognosis recurrence

Among 136 patients included in the recurrence analysis, AF recurrence occurred in 64 patients, and the recurrence rate was 47.06%. Compared with patients without recurrence, patients with recurrence had a higher discharge c-Ski level ($P<0.05$). ROC analysis showed that when discharge c-Ski >17.70 ng/mL, the sensitivity was 78.13% and the specificity was 63.89% (cut-off >17.57 ng/mL, AUC=0.760, *Figure 4*) for discriminating patients who developed AF recurrence during follow-up.

Table I Comparison of clinical baseline data.

	Control group (n=58)	AF patients (n=164)	t (or χ^2)	P	SMD
Age	52.76±10.16	54.01±11.70	0.721	0.472	0.111
Gender			0.679	0.410	0.120
male	33 (56.90)	83 (50.61)			
female	25 (43.10)	81 (49.39)			
BMI (kg/m^2)	22.42±2.35	22.57±1.75	0.512	0.609	0.078
Family history of AF			0.339	0.561	-0.081
yes	8 (13.79)	28 (17.07)			
no	50 (86.21)	136 (82.93)			
Smoking			1.060	0.303	-0.160
yes	22 (37.93)	75 (45.73)			
no	36 (62.07)	89 (54.27)			
Hypertension			0.399	0.528	-0.102
yes	22 (37.93)	70 (42.68)			
no	36 (62.07)	94 (57.32)			
Type 2 diabetes mellitus			1.007	0.316	-0.146
yes	18 (31.03)	63 (38.41)			
no	40 (68.97)	101 (61.59)			
IL-6 (pg/mL)	14.40±4.36	23.49±5.77	10.931	<0.001	-
TNF-α (pg/mL)	7.61±2.87	16.74±4.29	15.114	<0.001	-
hs-CRP (mg/L)	3.57±0.89	7.70±2.23	13.713	<0.001	-
LVEF (%)	63.65±7.65	46.72±4.29	20.653	<0.001	-
LAVI (mL/m^2)	25.92±4.48	44.43±4.17	28.472	<0.001	-

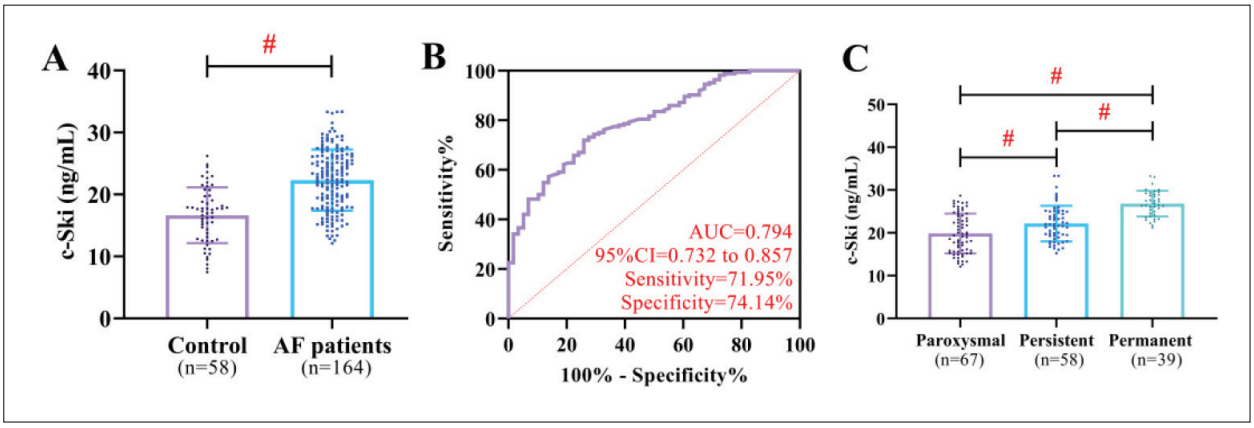

Figure 1 Relationship between c-Ski and AF.

(A) c-Ski comparison between AF patients and controls. (B) ROC curve of c-Ski for diagnosis of AF. (C) The difference of c-Ski in different AF subtypes. #P<0.05.

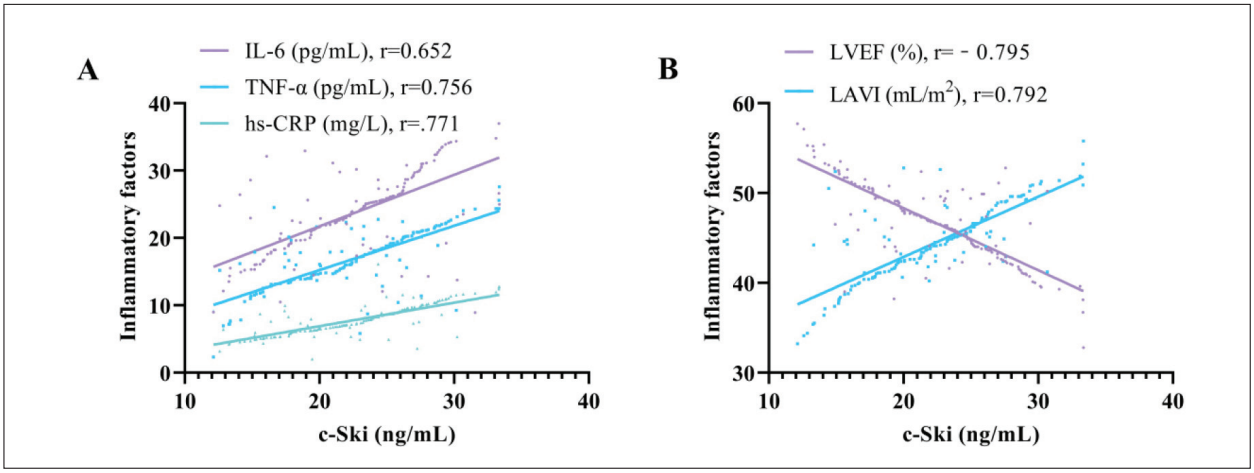

Figure 2 Relationship between c-Ski and inflammatory factors and cardiac function.

(A) Correlation between c-Ski and inflammatory cytokines IL-6, TNF-α, hs-CRP. (B) correlation between c-Ski and cardiac function LEVF and LAVI.

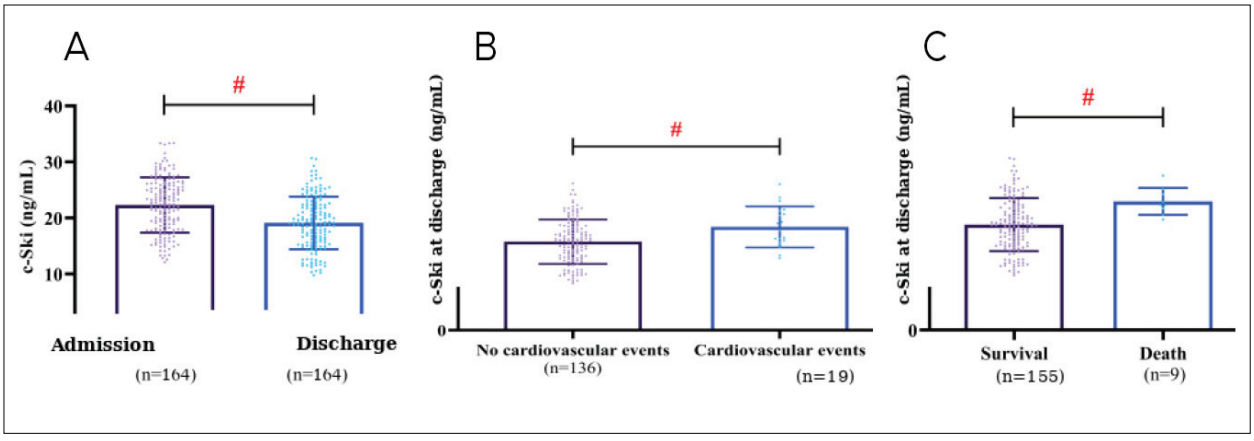

Figure 3 Dynamic changes of c-Ski.

(A) Changes of c-Ski at admission and at discharge (n=164). (B) Association between discharge c-Ski and cardiovascular events (events n=19; no events n=136). (C) Association between discharge c-Ski and all-cause mortality (death n=9; survival n=155). #P<0.05.

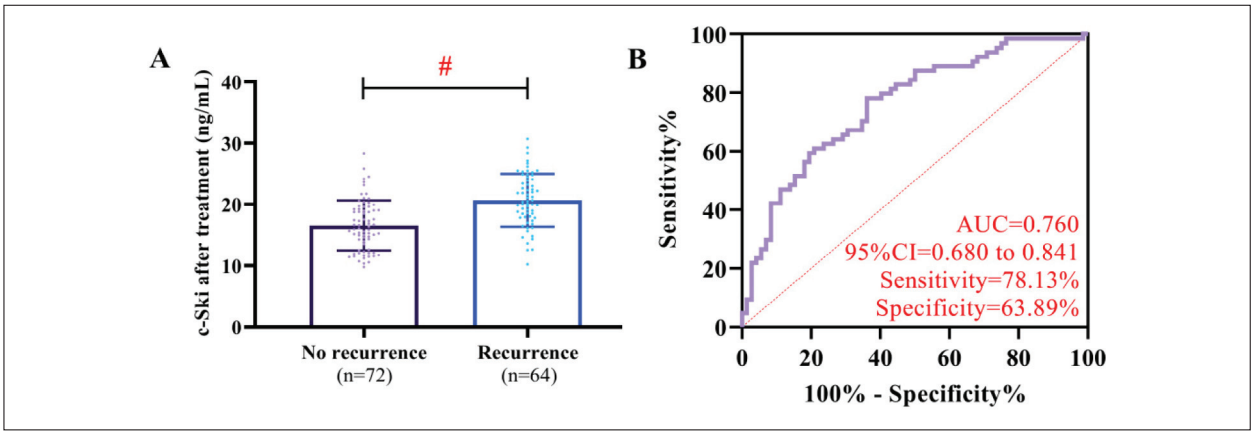

Figure 4 Association of c-Ski with AF recurrence (n=136).

(A) Comparison of discharge c-Ski between patients with and without AF recurrence. (B) ROC curve of discharge c-Ski for AF recurrence during follow-up. #P<0.05.

Discussion

This study evaluated serum c-Ski in a cohort of AF patients and found that circulating c-Ski was elevated in AF compared with controls and increased across AF subtypes. c-Ski correlated with inflammatory markers and indices of atrial remodeling (higher LAVI and lower LVEF). c-Ski decreased from admission to discharge, whereas higher discharge c-Ski was observed among patients who later developed adverse outcomes, including cardiovascular events, death, and AF recurrence. Collectively, these findings suggest that serum c-Ski is associated with inflammatory burden and disease severity in AF and may have potential utility for risk stratification.

The directionality of the association between serum c-Ski and inflammation warrants careful interpretation. Previous mechanistic studies have emphasized intracellular c-Ski as a negative regulator of TGF-β/Smad signaling and fibrosis (12, 13). In clinical settings, however, circulating c-Ski may reflect a compensatory response to ongoing inflammatory and remodeling stimuli, altered tissue expression, or release from stressed cells. Therefore, elevated serum c-Ski in AF could represent a marker of active remodeling rather than a direct anti-inflammatory effect. Further experimental work integrating tissue expression, circulating levels, and immune profiling is needed to clarify these relationships (14–16).

From a clinical perspective, the moderate discriminatory performance of discharge c-Ski for AF recurrence (AUC=0.760) indicates that c-Ski alone is unlikely to be sufficient as a stand-alone prognostic test. Instead, c-Ski may be considered as a candidate component of multimarker or clinical–biochemical models that capture inflammatory and structural remodeling pathways. Future studies should evaluate whether incorporating c-Ski improves risk prediction beyond established clinical predictors (17, 18).

Several limitations should be acknowledged. First, this was a single-center study with a modest sample size; subgroup analyses by AF type may be underpowered. Second, prognostic endpoints (cardiovascular events and death) were infrequent, and the corresponding analyses should be considered exploratory. Third, recurrence timing was not analyzed using time-to-event methods, as recurrence was assessed at prespecified follow-up visits and the exact time of recurrence was not systematically captured for all patients. Fourth, medication exposure and post-discharge management may have influenced c-Ski and outcomes but were not modeled in detail. Finally, the proposed cut-offs and discrimination metrics require external validation before clinical translation.

Conclusions

Serum c-Ski is elevated in AF, varies across AF subtypes, and correlates with inflammatory markers and echocardiographic indices of remodeling. Higher discharge c-Ski was associated with adverse outcomes in exploratory analyses and showed moderate discrimination for AF recurrence. Larger, multicenter studies with standardized follow-up and external validation are required to confirm these findings and to determine the incremental value of c-Ski in risk stratification.

Availability of data and materials

The de-identified data supporting the findings of this study are available from the corresponding author upon reasonable request for academic purposes, subject to institutional policies and ethics approval.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Saleh K, Haldar S. Atrial fibrillation: a contemporary update. Clin Med (Lond) 2023; 23(5): 437–41.
2. Liu L, Xie P, Zhu P, Zhuo W, Xu A. Role of the score for the targeting of atrial fibrillation (STAF) combined with D-dimer in screening ischemic stroke patients with atrial fibrillation. J Med Biochem 2024; 43(1): 5–62.
3. Zhao L, Li M, Zhang Y, Tang W, Huang D, Zhou G, et al. The correlation between ultrasonographic morphology and structure of the left atrial appendage, blood flow velocity, and plasma galectin-3 levels with thrombus formation in the left atrial appendage of patients with atrial fibrillation. J Med Biochem 2024; 43(4): 587–96.
4. Ou G, Zhang Y, Cai H, Yao K, Qiu Z, Chen Y, et al. Lipid-lowering drugs, circulating inflammatory factors, and atrial fibrillation: a mediation Mendelian randomization study. Frontiers in cardiovascular medicine. 2024; 11: 1446610.
5. Karamnov S, Muehlschlegel JD. Inflammatory Responses to Surgery and Postoperative Atrial Fibrillation. Anesthesiology 2022; 136(6): 877–9.
6. Han S, Wang J, Gao S, Sheng L, Li Y. c-Ski improves beagle atrial structural remodeling by suppressing TGF-beta1-SMAD signaling and p38 MAPK pathway. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2021; 37(10): 910–6.
7. Wang F, Fan K, Zhao Y, Xie ML. Apigenin attenuates TGF-beta1-stimulated cardiac fibroblast differentiation and extracellular matrix production by targeting miR-155-5p/c-Ski/Smad pathway. Journal of ethno-pharmacology 2021; 265: 113195.
8. Wang F, Zhang J, Niu G, Weng J, Zhang Q, Xie M, et al. Apigenin inhibits isoproterenol-induced myocardial fibrosis and Smad pathway in mice by regulating oxidative stress and miR-122-5p/155-5p expressions. Drug Dev Res 2022; 83(4): 1003–15.
9. Liao HY, Da CM, Wu ZL, Zhang HH. Ski: Double roles in cancers. Clin Biochem 2021; 87: 1–12.
10. Ran R, Gong CY, Wu ZL, Zhang SB, Zhang K, Zhou WM, et al. miR-204-5p Mitigates Disc Degeneration via SKI-Mediated Modulation of Apoptotic Signaling and Matrix Remodeling in Nucleus Pulposus. Am J Pathol 2025; 195(10): 1905–20.
11. Zhang J, Johnsen SP, Guo Y, Lip GYH. Epidemiology of Atrial Fibrillation: Geographic/Ecological Risk Factors, Age, Sex, Genetics. Card Electrophysiol Clin 2021; 13(1): 1–23.
12. Wang J, Li H, Lv Z, Luo X, Deng W, Zou T, et al. The miR-214-3p/c-Ski axis modulates endothelial-mesenchymal transition in human coronary artery endothelial cells in vitro and in mice model in vivo. Hum Cell 2022; 35(2): 486–97.
13. Yoon JH, Bae E, Nagafuchi Y, Sudo K, Han JS, Park SH, et al. Repression of SMAD3 by STAT3 and c-Ski induces conventional dendritic cell differentiation. Life Sci Alliance 2024; 7(9).
14. He W, Chen Z, Li H, Wu W, He P, Zhong D, et al. Decreased phosphorylation facilitates the degradation of the endogenous protective molecule c-Ski in vascular smooth muscle cells. Cell Signal 2021; 87: 110116.
15. Pola-Veliz V, Carrero D, Sagredo EA, Inostroza V, Cappelli C, Rivas S, et al. SKI regulates rRNA transcription and pericentromeric heterochromatin to ensure centromere integrity and genome stability. Neoplasia 2025; 67: 101204.
16. Gori I, George R, Purkiss AG, Strohbuecker S, Randall RA, Ogrodowicz R, et al. Mutations in SKI in Shprintzen-Goldberg syndrome lead to attenuated TGF-beta responses through SKI stabilization. eLife 2021; 10.
17. Latus H, Stammermann J, Voges I, Waschulzik B, Gutberlet M, Diller GP, et al. Impact of Right Ventricular Pressure Load After Repair of Tetralogy of Fallot. J Am Heart Assoc 2022; 11(7): e022694.
18. Karakasis P, Theofilis P, Vlachakis PK, Korantzopoulos P, Patoulias D, Antoniadis AP, et al. Atrial Fibrosis in Atrial Fibrillation: Mechanistic Insights, Diagnostic Challenges, and Emerging Therapeutic Targets. Int J Mol Sci 2024; 26(1).

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