Association Between Serum Levels of Sestrin-2 and Galectin-3 and Atrial Remodelling in Patients with Atrial Fibrillation

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ABSTRACT

Objective: To explore the prognostic significance of Sestrin-2 and Galectin-3 levels in atrial fibrillation complicated by left atrial remodelling, aiming to offer novel insights for prevention, treatment, and follow-up strategies.

Study Design: Analytical study.

Place and Duration of the Study: Department of Cardiology, Second People's Hospital of Anhui Province, Hefei, China, from January 2021 to December 2023.

Methodology: A total of 188 patients with atrial fibrillation were enrolled and divided into two groups based on the presence or absence of atrial remodelling. Serum levels of Sestrin-2 and Galectin-3, along with baseline clinical data, laboratory examinations, and Doppler echocardiography results, were compared between the groups.

Results: The atrial remodelling group showed significantly higher levels of age, AST, Sestrin-2, Galectin-3, and left atrial diameter compared to the non-atrial remodelling group ($p < 0.05$). Multivariate logistic regression analysis indicated that both Sestrin-2 and Galectin-3 were independent risk factors associated with atrial remodelling in patients with atrial fibrillation ($p < 0.05$). The combined assessment of Sestrin-2 and Galectin-3 yielded an area under the receiver operating characteristic (ROC) curve of 0.854, facilitating precise identification of the incidence of atrial fibrillation.

Conclusion: The study found that serum levels of Sestrin-2 and Galectin-3 were significantly elevated in the atrial remodelling group compared to the non-atrial remodelling group, suggesting their potential clinical utility in predicting atrial remodelling in patients with atrial fibrillation. These findings are significant for the prevention and treatment of this condition.

Key Words: *Atrial fibrillation, Sestrin-2, Galectin-3, Atrial remodelling.*

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INTRODUCTION

Atrial fibrillation (AF) is characterised by the loss of organised atrial electrical activity, which is replaced by rapid and disordered fibrillatory waves, which results in the absence of coordinated contractions and diastoles. Atrial contractile function deteriorates or is lost, and reduced conduction of the atrioventricular junction to atrial excitation results in irregular ventricular contraction, leading to disturbances in ventricular rate, impaired cardiac function, and formation of atrial mural thrombosis.[1] It not only exacerbates the healthcare burden but also intensifies familial stress.

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The Global Burden of Disease project estimated a worldwide prevalence of AF of around 46.3 million individuals in 2016.[2] In China, the prevalence of atrial fibrillation reaches approximately 12 million patients, with its incidence increasing significantly with advancing age. Among individuals aged 75 years and above, males exhibit a higher prevalence compared to females. It is plausible that the actual prevalence of atrial fibrillation in China exceeds the aforementioned estimated figure.[1,3] The prevailing pathogenesis theory posits that a combination of a trigger and a substrate is the primary contributor to this condition. Ectopic electrical activity, which may arise from changes in calcium ion flow and ion channels within cardiomyocytes at specific heart locations such as the pulmonary vein *ostium*, coronary sinus, and Marshall ligament, can act as triggers for this arrhythmia.[4,5] As the disease progresses, the atrial matrix undergoes changes in its electrical and structural properties, a process known as atrial remodelling. This remodelling primarily involves electrical changes, such as alterations in ion channel numbers and distribution, and gap-junction protein expression. It also includes structural changes marked by progressive collagen deposition, as well as nerve remodelling, which is characterised by an imbalance in sympathetic and parasympathetic

nerve activities. These modifications create an environment that favours the heterogeneity of electrical conduction, thereby facilitating the perpetuation of atrial fibrillation.[6,7] Numerous studies have shown a close association between oxidative stress and the pathogenesis of myocardial remodelling,[8,9] Notably, the Nrf2/ARE signalling pathway has been implicated in providing cardiac protection against oxidative myocardial injury, cardiac remodelling, and cardiac dysfunction.[8,10] Sestrin-2 has been reported to have the potential to mitigate Angiotensin II-induced apoptosis of smooth muscle cells by activating the Nrf2 signalling pathway.[11]

Sestrins represent a highly conserved protein family involved in the cellular stress response. Distinct sub-types, namely Sestrin-1, Sestrin-2, and Sestrin-3, are expressed and their expression is induced upon cellular stress. Previous studies have demonstrated that Sestrins possess the ability to regulate metabolic homeostasis, lipid accumulation, apoptosis, fibrosis, and other pathophysiological processes through mechanisms dependent on or independent of oxidative stress.[12,13] The activation of Sestrin-2 expression is implicated in multiple processes, including the mitigation of ROS accumulation, maintenance of energy homeostasis, augmentation of autophagy, suppression of protein synthesis, deceleration of metabolic disease progression, and regulation of cellular growth.[14] The involvement of Galectin-3 in various physiological and pathological processes of the body is well-documented, as it actively facilitates macrophage migration, fibroblast proliferation, and collagen synthesis. The high expression of this marker signifies the activation of fibroblasts and macrophages, serving as a prominent indicator for myocardial remodelling.[15] With the advancement of research, it has been discovered that Sestrin-2 and Galectin-3 play pivotal roles in associated diseases. However, the precise underlying mechanism remains elusive. Therefore, it is imperative to further investigate the potential roles and regulatory pathways of Sestrin-2 and Galectin-3 in inflammatory diseases and immune cell responses. The aim of this study was to elucidate the association between serum levels of Sestrin-2 and Galectin-3 and atrial remodelling in patients with atrial fibrillation, thereby contributing to the prediction, prevention, and treatment of complications associated with atrial fibrillation. These findings offer novel insights for accurate clinical evaluation of patients with atrial fibrillation.

METHODOLOGY

An analytical study was conducted retrospectively to identify patients with non-valvular atrial fibrillation who were admitted or received outpatient care at the Department of Cardiology, Second People's Hospital of Anhui Province, between January 2021 and December 2023. The inclusion criteria were participants aged at least 18 years with atrial fibrillation waveforms captured *via* a 12-lead electrocardiogram and / or a 24-hour Holter electrocardiogram at the authors' hospital, adhering to the Atrial Fibrillation Guideline of 2023.[1] Atrial fibrillation was categorised as paroxysmal atrial fibrillation, characterised by the episodes lasting less than 7 days; persistent atrial fibrillation, defined as episodes lasting 7 days or more; long-standing persistent atrial fibrillation, having episodes persisting for over 1 year; and permanent atrial fibrillation, where the likelihood of converting to and maintaining sinus rhythm is minimal, and atrial fibrillation has persisted for 10 to 20 years, with the electrocardiogram displaying nearly linear, very small f waves. Exclusion criteria were patients who had recently undergone surgery, experienced a cerebral haemorrhage or cerebral infarction, sustained trauma, or were in acute severe conditions with primary cardiomyopathy, myocarditis, pericarditis, valvular heart disease (with the exception of mitral valve insufficiency), congenital heart diseases, severe hepatic and renal insufficiency [a glomerular filtration rate (GFR) of less than 30 ml/min, or transaminase levels at least three times the upper limit of normal (ULN)]. Those with tumours, haematological disorders, rheumatic connective tissue diseases, hyperthyroidism, and immune system diseases and conditions such as pulmonary embolism, bronchiectasis, pulmonary fibrosis, hepatitis B, and tuberculosis were excluded. Pregnant or lactating female patients with limited legal capacity were also excluded.

Based on the upper normal limit of the left atrial diameter from cardiac Doppler echocardiography (38 millimetres), patients were categorised into two groups. The atrial remodelling group (116 cases) and the non-atrial remodelling group (72 cases). The demographic data of the participants, encompassing age, gender, height, blood pressure, medical history, and type of atrial fibrillation, and recent medication use, were compiled to create a comprehensive patient database. Following a 12-hour fasting period, median elbow venous blood samples were collected for laboratory analysis to evaluate various indicators, such as complete blood counts, liver and kidney function tests, blood glucose levels, lipid profiles, and coagulation function assessments. On the subsequent day, fasting venous blood (4-5mL) was subjected to centrifugation at 3,500 revolutions per minute for 15 minutes in an EDTA-anticoagulant tube. The resultant upper serum was then transferred to an EP tube and preserved at -80℃ in a refrigerator. Thereafter, an extensive analysis of serum Sestrin-2 and Galectin-3 levels was conducted using enzyme-linked immunosorbent assay (ELISA) kits supplied by Shanghai Sinobestbio Co., LTD. Additionally, precise measurements of the left atrial diameter (LAD) were obtained *via* colour ultrasound imaging for all subjects.

The statistical analysis was performed utilising SPSS version 29.0. To evaluate the normality of the measurement data, the single-sample Kolmogorov-Smirnov (K-S) test was applied. Data points that followed a normal distribution were reported as mean ± standard deviation ($\bar{x}\pm s$). A t-test was utilised to compare data between the two groups. In cases where the data did not exhibit a normal distribution, the median and interquartile range (IQR) were employed for representation. The Mann-Whitney U rank-sum test was conducted to compare data between the two groups. Counting data were presented as cases with percentages (%), and group comparisons were executed using the Chi-square test, a widely recognised statis-

tical method. Binary logistic regression analysis was employed to examine the risk factors associated with atrial fibrillation and atrial remodelling. A significance level of $p < 0.05$ was deemed to denote statistical significance.

RESULTS

No significant variations were noted regarding gender, BMI, HGB, WBC, Glu, Cr, TG, ALT, hypertension, coronary heart disease, diabetes mellitus, or the utilisation of anticoagulation therapy and medications such as statins and β-blockers between the remodelling group and the non-remodelling group ($p > 0.05$). Nevertheless, significant differences were observed in age, as well as in the levels of AST, Sestrin-2, and Galectin-3, along with LAD measurements ($p < 0.05$, Table I).

The multivariate logistic regression analysis indicated that Sestrin-2 and Galectin-3 are independent risk factors for atrial fibrillation, alongside atrial remodelling. A statistically significant difference was observed in Sestrin-2 levels between patients with atrial fibrillation and atrial remodelling (OR = 1.214, 95% CI 1.138 - 1.295, $p < 0.05$), suggesting that a 1 pg/ml increase in Sestrin-2 corresponds to a 21.4% higher risk of developing atrial fibrillation in conjunction with atrial remodelling. Similarly, Galectin-3 levels showed a statistically significant association with atrial fibrillation and atrial remodelling (OR = 1.058, 95% CI 1.028 - 1.088, $p < 0.05$), indicating that a 1 pg/ml increase in Galectin-3 was linked to a 5.8% increased risk of atrial fibrillation combined with atrial remodelling (Table II).

Upon performing ROC curve analysis, it was ascertained that the area beneath the curve for Sestrin-2 in the diagnosis of atrial fibrillation coupled with atrial remodelling amounted to 0.799. In a parallel assessment, Galectin-3 demonstrated an area beneath the ROC curve of 0.681 for the identification of atrial fibrillation in conjunction with atrial remodelling. Importantly, the concurrent use of both Sestrin-2 and Galectin-3 in the diagnostic process for atrial fibrillation alongside atrial remodelling led to a markedly enhanced area beneath the ROC curve, reaching 0.854 (Figure 1).

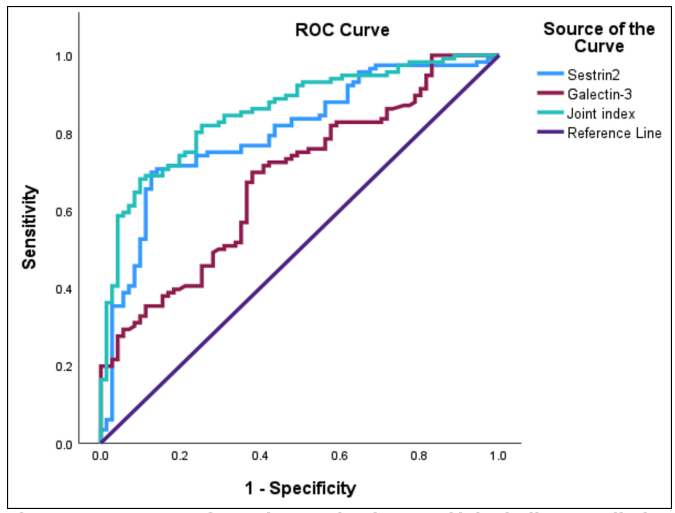

Figure 1: ROC curve of Sestrin-2, Galectin-3, and joint indices predicting atrial remodelling in atrial fibrillation.

Table I: Comparison of clinical features with and without atrial remodelling.

Index	Remodelling group (n = 116)	Non-remodelling group (n = 72)	H/t/χ^2	p-value
Male (%)	55 (47.4)	40 (55.6)	1.178	0.278
Age (year)	72.90 ± 8.62	68.97 ± 10.18	-3.012	0.003
BMI	25.07 ± 3.49	24.34 ± 3.37	-1.132	0.258
HGB (g/L, M (Q1, Q3))	128 (116, 141)	132 (120, 137)	-0.752	0.452
WBC ($\times 10^9$, M (Q1, Q3))	5.91 (4.80, 7.51)	6.00 (4.72, 7.75)	-0.245	0.806
Cr (μmol/L, M (Q1, Q3))	73 (61, 84)	66 (58, 80)	-1.860	0.063
Glu (mmol/L, M (Q1, Q3))	5.22 (4.63, 6.26)	4.94 (4.47, 6.97)	-1.293	0.196
TG (mmol/L, M (Q1, Q3))	3.89 (3.28, 4.32)	3.97 (3.33, 4.43)	-0.865	0.387
ALT (U/L, M (Q1, Q3))	19 (14, 28)	19 (13, 25)	-0.919	0.358
AST (U/L, M (Q1, Q3))	25 (20, 28)	21 (17, 26)	-2.804	0.005
Complications [case (%)]				
Hypertension	85 (73.3)	50 (69.4)	0.322	0.570
Coronary heart disease	86 (74.1)	45 (62.5)	2.848	0.091
Diabetes	21 (18.1)	14 (19.4)	0.053	0.818
Stroke	57 (53.8)	45 (62.5)	1.334	0.248
Drugs [case (%)]				
Anticoagulant	100 (86.2)	66 (91.7)	1.282	0.258
Statins	100 (86.2)	59 (81.9)	0.619	0.432
Beta-blockers	56 (48.3)	25 (34.7)	3.328	0.068
ACEI / ARB / ARNI	58 (50)	26 (36.1)	3.467	0.063
Sestrin-2 (pg/ml, M (Q1, Q3))	37.756 (32.635, 41.769)	29.937 (24.940, 34.017)	-6.645	<0.001
Galectin-3 (pg/ml, M (Q1, Q3))	46.716 (36.166, 58.515)	35.456 (29.988, 48.557)	-4.415	<0.001
LAD (mm, M (Q1, Q3))	43 (41, 48)	34 (32, 36)	-11.529	<0.001

Table II: Multi-factor logistic regression analysis.

Variable	B	SE	Wald χ^2	p-value	OR	OR (95% CI)
Sestrin-2	0.195	0.033	34.467	<0.001	1.214	1.138~1.295
Galectin-3	0.056	0.015	14.519	<0.001	1.058	1.028~1.088
Age	0.032	0.019	30.904	0.089	1.033	0.995~1.072

DISCUSSION

Atrial fibrillation is currently acknowledged as a progressive ailment, with atrial remodelling playing a pivotal role in its long-term pathogenesis. In their study, Teh *et al*. discovered that patients with atrial fibrillation exhibited an increased proportion of low-voltage regions, slower conduction, and more complex electrical signals in the left atrium compared to those with left supraventricular tachycardia.[16] Furthermore, these symptoms were more pronounced and consistent with the progressive remodelling process in the persistent atrial fibrillation compared to paroxysmal atrial fibrillation, indicating its continuous nature. The terminal phase of atrial fibrillation is characterised by the predominance of myocardial fibrosis in atrial remodelling, which underpins the perpetuation of the condition.[17]

The role of oxidative stress as a central molecular mechanism in the pathogenesis of cardiac remodelling has been well-documented. During normal physiological processes, the production of ROS is finely tuned by the endogenous antioxidant system, ensuring the preservation of REDOX balance, which is crucial for homeostasis. An increase in ROS production or a disruption of the endogenous antioxidant system can trigger oxidative stress, resulting in irreversible damage to micromolecules, bio-membranes, proteins, and DNA, thereby adversely affecting the organism. ROS plays a central role in the process of cardiac remodelling and heart failure, exerting its impact through the activation of various signalling pathways and the initiation of cardiac remodelling cascades.[18]

The present study undertook a comparative analysis of the core clinical features, biochemical markers, and echocardiographic data of patients diagnosed with atrial fibrillation alongside atrial remodelling, with the aim of pinpointing statistically significant disparities among these parameters. The analysis of the results revealed a significant elevation in the serum levels of Sestrin-2 and Galectin-3 among patients with atrial fibrillation accompanied by the left atrial fibrosis, exhibiting a close correlation with the extent of atrial fibrosis. It can serve as a crucial reference index for evaluating the extent of atrial fibrosis. This study demonstrated a positive correlation between serum levels of Sestrin-2 and Galectin-3 with left atrial fibrosis, suggesting their potential influence on atrial structural remodelling and fibrosis, thereby contributing to the onset and progression of atrial fibrillation ($p < 0.05$). The multivariate analysis revealed that elevated levels of serum Sestrin-2 and Galectin-3 were identified as the independent risk factors for atrial fibrillation complicated with left atrial fibrosis ($p < 0.05$).

The underlying cause lies in the pivotal role of the inflammatory response within the pathological progression of atrial fibrosis. Inflammatory-triggered activation of macrophages induces the release of a diverse array of pro-inflammatory cytokines, including Sestrin-2 and Galectin-3, which synergistically interact with myofibroblasts to promote extracellular matrix secretion, ultimately culminating in tissue structural impairment and fibrotic formation. The ROC curve analysis in this study demonstrated that serum Sestrin-2 and Galectin-3 exhibited superior predictive value for assessing atrial fibrillation complicated with left atrial fibrosis, while their combined detection further enhanced the predictive accuracy.

CONCLUSION

Serum levels of Sestrin-2 and Galectin-3 can serve as reliable indicators for assessing the extent of atrial fibrosis, thereby offering valuable guidance in evaluating left atrial fibrosis among patients with atrial fibrillation.

ETHICAL APPROVAL:
This study protocol was approved by the Second People's Hospital of Anhui Province with approval number HEC-AF-042-020.

PATIENTS' CONSENT:
The study was conducted on the medical records of patients who had provided informed consent.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
DL: Conception, acquisition, drafting, analysis, and critical revision for important intellectual content.
LR: Data collection and data analysis.
YG: Conception, design, and data collection.
WC: Literature search and editing of the draft.
SZ: Conception, intellectual input, and supervision of the study.
All authors approved the final version of the manuscript to be published.

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