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# Serum Beta-2 Microglobulin: A Possible Biomarker for Atrial Fibrillation

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**Conflict of interest:**

None declared

**Background:** Atrial fibrillation (AF) is the most common persistent arrhythmia that can cause complications (including stroke). Therefore, its diagnosis and treatment require increased attention. Although beta-2 microglobulin ( $\beta$ 2-MG) is a novel marker of cardiovascular disease, its role in AF has not been evaluated.


**Material/Methods:** We conducted a case-control study with 61 patients who had normal heart rhythm (control group) and 60 patients with AF (research group). We analyzed the serum  $\beta$ 2-MG levels in both groups and performed multivariate analysis to assess the correlation between  $\beta$ 2-MG and left atrial remodeling. In addition,  $\beta$ 2-MG levels were compared between the left atrial blood and peripheral venous blood of another set of 57 patients with AF, who underwent cryoballoon ablation.

**Results:** There were no statistically significant differences in the baseline characteristics (age, sex, history of hypertension, diabetes mellitus, previous stroke, coronary heart disease, and estimated glomerular filtration rate) of the control and research groups. The left atrial anteroposterior diameters (LAD) and left ventricular end-systolic diameters in the AF group were significantly larger compared to the control group ( $P < 0.01$ ). Serum  $\beta$ 2-MG levels in patients with AF were significantly higher ( $P < 0.01$ ) and positively correlated with the LAD (B-coefficient 25.482, 95% CI 14.410~36.554,  $P < 0.01$ ), serum  $\beta$ 2-MG levels in the left atrial blood were significantly higher than those in peripheral venous blood ( $P < 0.01$ ), and serum  $\beta$ 2-MG levels were an independent predictor of AF.

**Conclusions:** With the development of atrial fibrillation, the serum  $\beta$ 2-MG levels increase and are closely related to the left atrial remodeling due to AF. Therefore,  $\beta$ 2-MG can be an effective biomarker for predicting AF.

**Keywords:** **Arrhythmias, Cardiac • Atrial Fibrillation • Cardiology**

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## Background

Atrial fibrillation (AF) is one of the most common arrhythmias. It refers to the loss of normal and ordered atrial electrical activity, which is replaced by disorderly fibrillation waves [1]. The incidence and prevalence of AF are increasing globally. The Framingham Heart Study demonstrated that the prevalence of AF has tripled in the last 50 years [2,3]. In addition, future projections indicate that the absolute burden of AF could increase by >60% by 2050 [4]. AF can cause serious complications (including heart failure and arterial embolism) and the most common complication is cardiogenic stroke [5-7]. However, patients with AF lack its typical clinical symptoms and about 15% to 30% of AF patients are asymptomatic [8]. Many patients fail to receive effective treatment and have complications as an AF diagnosis can be easily missed or misdiagnosed [9]. Therefore, the early and timely diagnosis of AF is particularly important for an improved prognosis.

Previous studies have shown that the pathogenesis of AF is related to myocardial strain, myocardial fibrosis, and inflammation [10,11]. Over the past decade, there is growing evidence of the use of the natriuretic peptide system in AF, which includes brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). A cohort study showed that patients with elevated BNP levels are at greater risk of progression to persistent or permanent forms of AF. In addition, BNP and NT-proBNP are associated with AF incidence, post-operative AF incidence, and prognosis in AF [12,13]. Biomarkers that suggest myocardial fibrosis (including soluble suppressor of tumorigenicity 2 and galectin-3 [gal-3]) and inflammation indicators (C-reactive protein and interleukin 6) increased in patients with AF [14-18]. However, there is a lack of serum markers for the early diagnosis of AF [19].

Beta-2 microglobulin ( $\beta$ 2-MG) is an endogenous low-molecular-weight serum globulin produced by the lymphocytes, platelets, and leukocytes [20]. It is widely distributed in the human body, exists in free form in serum, and its concentration remains relatively stable in the serum of healthy individuals [21]. The serum level of  $\beta$ 2-MG is commonly used to assess early renal impairment and as a marker for multiple myeloma [22-24]. In recent years, increasing evidence has shown that  $\beta$ 2-MG is associated with the occurrence of coronary heart disease, heart failure, and hypertension and  $\beta$ 2-MG levels are positively related to the incidence and mortality of cardiovascular diseases [25-27]. The pathogenesis of AF has not been fully elucidated. Most pathophysiological mechanisms of AF are mainly ectopic excitation and reentry mechanisms, and these changes include ion-channel dysfunction, Ca<sup>2+</sup>-handling abnormalities, structural remodeling, and autonomic neural dysregulation [1]. Atrial fibrosis can promote atrial arrhythmogenesis, leading to AF with local conduction

slowdown and a unidirectional blockade [28-30]. The expression of  $\beta$ 2-MG is associated with fibrosis of the kidneys, liver, lungs, and heart. Previous studies have shown that  $\beta$ 2-MG is an indicator of the severity of pulmonary fibrosis [31]. In addition, exogenous  $\beta$ 2-MG has a profibrotic effect on cardiac fibroblasts [32]. Therefore, we proposed the hypothesis that serum  $\beta$ 2-MG is associated with AF. In this study, we determined serum  $\beta$ 2-MG levels in patients with AF and analyzed the relationship between serum  $\beta$ 2-MG levels and AF.

## Material and Methods

### Study Population

We conducted a case-control study on patients with or without AF who were hospitalized in the Second Hospital of Tianjin Medical University between December 2018 and December 2019. The study was conducted while the patients were in hospital and patient information was obtained from the hospital's electronic medical record system (including sex, age, comorbidities, and laboratory test results). Transthoracic echocardiography was performed on the enrolled patients for related parameters, including left atrial anteroposterior diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septum thickness, left ventricular posterior wall thickness, right ventricular anterior wall thickness, right ventricular end-diastolic diameter, and left ventricular ejection fraction. These parameters were measured in the parasternal long-axis view using 2-dimensional methods. The inclusion criteria were patients with AF or non-AF who were hospitalized in the Department of Cardiology of the Second Hospital of Tianjin Medical University and patients diagnosed with AF who met the diagnostic criteria of the 2016 Atrial Fibrillation Management Guidelines developed by the European Society of Cardiology and the European Heart Rhythm Association [33]. The exclusion criteria were patients with severe cardiac insufficiency (ejection fraction <40% or New York Heart Failure Classification IV), severe hypertension (3 measurements of systolic blood pressure  $\geq$ 180 mmHg and/or diastolic blood pressure  $\geq$ 110 mmHg on different days), acute or chronic autoimmunity or infectious diseases, liver, kidney, gallbladder diseases or abnormal liver and kidney function, other heart diseases (dilated cardiomyopathy, hypertrophic cardiomyopathy, rheumatic heart disease, congenital heart disease, malignant arrhythmia), and systemic blood diseases.

Subsequently, to explore the possible source of serum  $\beta$ 2-MG in AF patients, another set of 57 patients with AF who underwent cryoballoon ablation were chosen as the research subjects to determine the  $\beta$ 2-MG levels in left atrial blood and peripheral venous blood. The selection criteria for these patients were the same as described above for patients in the

**Table 1.** Baseline characteristics of the study participants.

	Control group n=61	Atrial fibrillation n=60	P value
Age, year	68.51±6.55	70.93±8.53	0.082
Male gender, n (%)	31 (50.8%)	27 (45.0%)	0.522
<b>Complications</b>			
Hypertension, n (%)	46 (75.4%)	43 (71.7%)	0.641
Diabetes mellitus, n (%)	17 (27.9%)	17 (28.3%)	0.955
Previous stroke, n (%)	9 (14.8%)	10 (16.7%)	0.772
Coronary heart disease, n (%)	34 (55.7%)	35 (58.3%)	0.773
<b>Laboratory indicators</b>			
eGFR, mL/min	86.49±15.08	91.12±20.23	0.156

eGFR – estimated glomerular filtration rate. Data are means±standard deviation (SD).

control and research groups. In addition, these patients underwent cryoballoon ablation (a treatment for atrial fibrillation). We collected atrial blood samples before the cryoballoon ablation (between September 2019 and January 2021).

All the procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional Research Committee (Medical Ethics Committee of the Second Hospital of Tianjin Medical University, approval number: KY2019K145) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from each patient.

### Blood Samples and Laboratory Assays

A fasting venous blood sample (5 mL) was taken from the patients within 24 h after hospital admission. Blood samples from the left atrial (5 mL) were collected from patients undergoing cryoballoon ablation. The supernatant serum from the blood samples was centrifuged at 3000 g for 5 min to 10 min and frozen at -80°C. The serum  $\beta$ 2-MG level was determined by an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA).

### Statistical Analysis

Continuous variables are expressed as means±standard deviations, and independent sample *t* tests and paired sample *t* tests were used for statistical analysis. Categorical variables are expressed as percentages and were compared by the chi-square test. Multiple linear regression analysis was used to evaluate the correlation between  $\beta$ 2-MG levels and left atrial anteroposterior diameters (LAD), and the estimated glomerular filtration rate (eGFR). The receiver operating characteristic (ROC) curve was used to assess the prediction accuracy of AF by  $\beta$ 2-MG.  $P < 0.05$  was considered statistically significant.

All analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

## Results

A total of 121 patients met the eligibility criteria – 60 patients with AF were the research group (50.8% men and 49.2% women), and 61 patients with normal heart rhythm were the control group (45.0% men and 55% women). The mean age of the control group was 68.51±6.55 years, and the mean age of the research group was 70.93±8.53 years. There were no exclusions due to complications or dropouts after enrolment.

### Relationship Between Serum $\beta$ -2 Microglobulin and Prevalence of Atrial Fibrillation

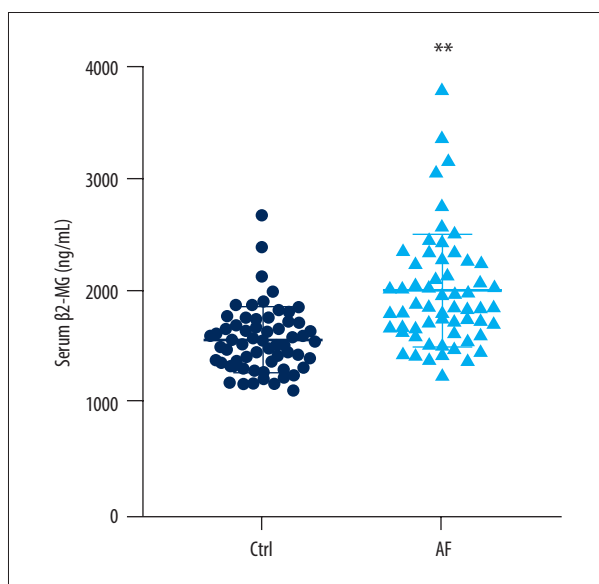
The baseline characteristics of the control and research groups are shown in **Table 1**. There were no statistically significant differences in the baseline clinical characteristics (age, sex, history of hypertension, diabetes, previous stroke, coronary heart disease, and eGFR) between the 2 groups. The antero-posterior of the left atrial diameters (LAD) (36.75±4.78 mm and 44.03±5.15 mm) and left ventricular end-systolic diameters (26.03±3.30 mm and 29.35±4.71 mm) in patients with AF were significantly larger compared to the control group ( $P < 0.01$ ) (**Table 2**). However, there were no significant differences between the 2 groups for the left ventricular end-diastolic diameter, left ventricular ejection fraction, and other parameters from the transthoracic echocardiography (**Table 2**).

We analyzed the serum  $\beta$ 2-MG levels between the 2 groups. These levels in the AF group (1999.68±498.26 ng/mL) were significantly higher than seen in the control group (1567.20±288.21 ng/mL) ( $P < 0.01$ ) (**Figure 1**). Multivariate analysis was performed to evaluate the correlation between  $\beta$ 2-MG levels and left atrial

**Table 2.** Echocardiographic parameters of the study participants.

	Control group n=61	Atrial fibrillation n=60	p-value
LAD (mm)	36.75±4.78	44.03±5.15**	<0.01
LVEDD (mm)	46.06±5.43	47.63±4.26	0.080
LVESD (mm)	26.03±3.30	29.35±4.71**	<0.01
IVST (mm)	9.14±1.35	9.46±1.61	0.238
LVPWT (mm)	9.13±1.28	9.41±1.45	0.257
RVAWT (mm)	3.45±0.53	3.62±0.51	0.071
RVDD (mm)	20.68±2.28	21.43±3.64	0.176
LVEF (mm)	64.21±4.92	62.57±5.35	0.081

LAD – left atrial anteroposterior diameter; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; IVST – interventricular septum thickness; LVPWT – left ventricular posterior wall thickness; RVAWT – right ventricular anterior wall thickness; RVDD – right ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction. Data are mean±standard deviation (SD). \*\*  $P<0.01$ .



**Figure 1.** Serum levels of beta-2 microglobulin in the control group and research group. Data are mean±standard deviation and an unpaired 2-tailed *t* test. \*\*  $P<0.01$  (GraphPad Prism 8.0.1, GraphPad Software, Inc., San Diego, CA, USA).

remodeling. The results showed that the increase in the  $\beta$ 2-MG levels was significantly correlated with the size of the LAD ( $P<0.01$ ) and negatively correlated to the eGFR (Table 3).  $\beta$ 2-MG showed a moderate predictive ability to diagnose AF according to the area under the ROC curve (AUC=0.80, 95% CI 0.720-0.876,  $P<0.01$ ) (Figure 2).

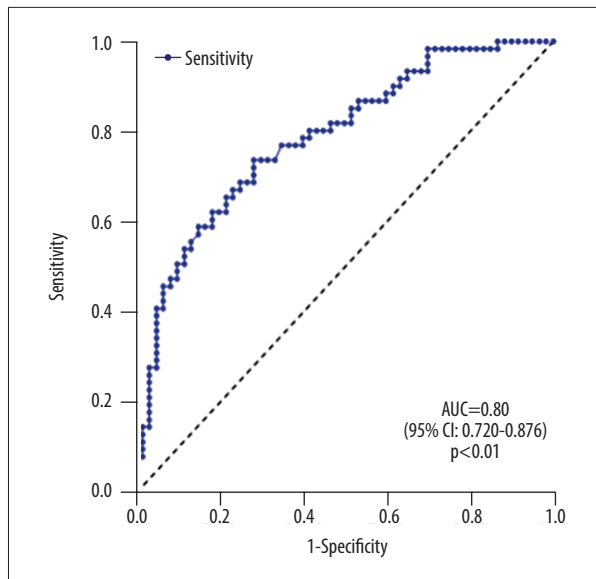
**Distribution of  $\beta$ 2-Microglobulin in Patients with Atrial Fibrillation**

In the light of the above results, we promote the hypothesis that the increase of serum  $\beta$ 2-MG contributes to the structural remodeling of the left atrial. Therefore, another set of 57 AF patients who underwent cryoballoon ablation were selected as the research subjects and we determined the concentration of  $\beta$ 2-MG in their left atrial blood and peripheral venous blood. The clinical characteristics of these patients are shown in Table 4. The mean age of these patients was 64.12±8.97 years, 57.9% were men and 42.1% were women. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score [34] was 2.21±1.29 points and the LAD was 41.16±4.77 mm. We determined the concentration of  $\beta$ 2-MG in the left atrial blood and peripheral venous blood of patients with AF using ELISA. The level of  $\beta$ 2-MG in the left

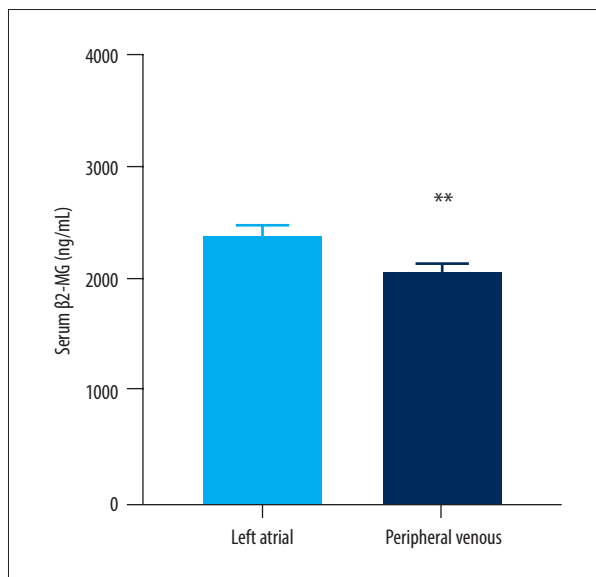
**Table 3.** Multivariate linear regression analysis for the association between serum beta-2 microglobulin levels and the left atrial diameter in the study participants.

	B-coefficients	95% CI for B	p-value
LAD, mm	25.482	14.410~36.554**	<0.01
eGFR, mL/min	-13.968	-17.758~-10.177**	<0.01

LAD – left atrial anteroposterior diameter. \*\*  $P<0.01$ .



**Figure 2.** Receiver operating characteristic curve analysis for predictive values of beta-2 microglobulin in diagnosing atrial fibrillation. (GraphPad Prism 8.0.1, GraphPad Software, Inc., San Diego, CA, USA).



**Figure 3.** Left atrial and peripheral venous serum levels of beta-2 microglobulin in patients with atrial fibrillation. Data are mean $\pm$ standard deviation and an unpaired 2-tailed *t* test. \*\*  $P < 0.01$  (GraphPad Prism 8.0.1, GraphPad Software, Inc., San Diego, CA, USA).

atrial blood (2395.96 $\pm$ 604.47 ng/mL) was significantly higher than that in the peripheral venous blood (2036.33 $\pm$ 614.317 ng/mL) of patients with AF ( $P < 0.01$ ) (Figure 3).

**Table 4.** Clinical and laboratory characteristics of patients in the research.

Atrial fibrillation n=57	
Age, year	64.12 $\pm$ 8.97
Male gender, n (%)	33 (57.9%)
Heart rate, bpm/min	72.16 $\pm$ 17.68
Systolic blood pressure, mmHg	131.16 $\pm$ 16.31
Diastolic blood pressure, mmHg	79.21 $\pm$ 9.79
CHA <sub>2</sub> DS <sub>2</sub> VASc	2.21 $\pm$ 1.29
<b>Complications</b>	
Hypertension, n (%)	33 (57.9%)
Diabetes mellitus, n (%)	12 (21.1%)
Previous stroke, n (%)	8 (14.0%)
<b>History of drug use</b>	
Use of statins	23 (40.4%)
Use of ACEI/ARB	21 (36.8%)
<b>Laboratory indicators</b>	
eGFR, mL/min	109.78 $\pm$ 26.69
<b>Measurements on transthoracic echocardiography</b>	
LAD (mm)	41.16 $\pm$ 4.77
LVEDD (mm)	47.65 $\pm$ 4.11
LVESD (mm)	28.27 $\pm$ 4.88
LVPWT (mm)	9.11 $\pm$ 1.37
RVAWT (mm)	3.45 $\pm$ 0.57
RVEDD (mm)	21.06 $\pm$ 2.12
PAD (mm)	22.02 $\pm$ 2.46
LVEF (mm)	62.07 $\pm$ 5.33

eGFR – estimated glomerular filtration rate; LAD – left atrial anteroposterior diameter; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVPWT – left ventricular posterior wall thickness; RVAWT – right ventricular anterior wall thickness; RVEDD – right ventricular end-diastolic diameter; PAD – pulmonary artery diameter; LVEF – left ventricular ejection fraction. Data are means $\pm$ standard deviation (SD).

## Discussion

Atrial fibrillation is one of the most common tachyarrhythmias associated with many clinical outcomes, including stroke, extracranial systemic thromboembolism, dementia, heart failure, myocardial infarction, venous thromboembolism, and



mortality [3]. Besides the risk of death and disability, it greatly increases the burden on society. Therefore, early diagnosis and treatment of AF are critical. Our study revealed the correlation between serum  $\beta$ 2-MG levels and AF. Our findings are that the serum  $\beta$ 2-MG levels of AF patients were significantly increased ( $P < 0.01$ ),  $\beta$ 2-MG levels were positively correlated with LAD and were an independent predictor of AF, and serum  $\beta$ 2-MG levels in left atrial blood were significantly higher than the levels in peripheral venous blood for patients with AF ( $P < 0.01$ ).

In recent years, scientists and researchers have tried to identify biomarkers that can predict AF and its complications. Previous studies have found that elevated plasma levels of interferon- $\gamma$  were an independent risk factor for stroke and all-cause mortality in patients with AF [35], the serum levels of B-type natriuretic peptide are related to the AF load (chronic hemodynamic changes and anatomical changes) in patients with single AF and are strong predictors of arrhythmia recurrence after the ablation of AF [36], gal-3 is closely related to AF-induced left atrial remodeling, and gal-3 can be an effective biomarker in the AF population for risk stratification and prognosis prediction [37].

$\beta$ 2-MG is a non-lysogenic polypeptide of about 11.8 kDa, which is present in all nucleated cells. It is released into blood circulation at a constant rate. Part of the serum  $\beta$ 2-MG is reabsorbed and decomposed in the renal tubules after being freely filtered by the glomeruli. Previous studies have shown that  $\beta$ 2-MG is a risk factor for cardiovascular disease, which is associated with coronary heart disease, chronic heart failure, and hypertension. In our study, we found that  $\beta$ 2-MG is associated with AF and has a certain predictive value for AF, which could be related to the structural remodeling of the left atrium.

The risk factors of AF induce atrial structural and histopathological changes characterized by fibrosis, inflammation, and cellular and molecular changes. These changes increase the incidence of AF. Persistent AF leads to electrical and structural remodeling of the left atrium and further contributes to the persistence of AF. Previous studies have shown that the expression of  $\beta$ 2-MG is related to fibrosis of the kidneys, liver, and heart.  $\beta$ 2-MG plays a role in cardiac fibrosis, and it is released by cardiomyocytes during pressure overload as a novel secreted soluble factor. In addition,  $\beta$ 2-MG promotes profibrotic gene expression in cardiac fibroblasts in vitro and in vivo. Stretched cardiomyocytes release soluble  $\beta$ 2-MG, which, through paracrine communication with cardiac fibroblasts, activates the epidermal growth factor receptors to initiate acute signal transduction and upregulate the fibrosis genes, thus promoting cardiac fibrosis [32,38]. Research has shown that cardiomyocytes can activate the epidermal growth factor receptor by releasing  $\beta$ 2-MG, leading to the accelerated proliferation and differentiation of cardiac fibroblasts, and increased secretion and accumulation of the extracellular matrix, resulting in

the development of myocardial fibrosis. The knockdown of the  $\beta$ 2-MG gene using adenovirus 9 (AAV9) significantly reduced  $\beta$ 2-MG levels in the myocardium and inhibited the process of myocardial fibrosis and cardiac dysfunction [32].

In this study, we found that  $\beta$ 2-MG levels in venous serum were elevated in AF patients compared with those in the control group and that  $\beta$ 2-MG levels in left atrial blood were higher than those in peripheral venous blood. This suggests that cardiomyocytes can secrete  $\beta$ 2-MG or regulate the cellular metabolism and electrophysiological activity of the heart through this process, which leads to the development of AF.  $\beta$ 2-MG appears to be strongly associated with atrial structural remodeling.

### Limitations

There were several limitations in our research. Firstly, as this is a single-center study, the sample size is small compared to a multicenter study. Secondly, the level of serum  $\beta$ 2-MG is affected by many factors, and our research lacks further information on the specific mechanism of  $\beta$ 2-MG on AF. Therefore, the use of plasma  $\beta$ 2-MG levels to predict the occurrence of AF in the population could be biased. We hope to study a larger population in the future to verify the predictive value of  $\beta$ 2-MG in AF.

### Conclusions

We demonstrated that serum  $\beta$ 2-MG levels increased with the development of atrial fibrillation. The levels of  $\beta$ 2-MG are closely related to the left atrial remodeling due to AF.  $\beta$ 2-MG could be an effective biomarker for AF prediction. Therefore, in the future, we could diagnose early AF by measuring serum  $\beta$ 2-MG levels.

### Department and Institution Where Work Was Done

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### Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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