

CORRELATION ANALYSIS OF SERUM sTREM-1 AND sHLA-DR LEVELS WITH THE PROGNOSIS OF PATIENTS WITH ATRIAL FIBRILLATION

KORELACIONA ANALIZA NIVOVA STREM-1 I SHLA-DR U SERUMU U ODNOSU NA PROGNOZU KOD PACIJENATA SA ATRIJALNOM FIBRILACIJOM

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Summary

Background: To observe the expression levels of serum soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) and serum soluble Human Leukocyte Antigen-DR (sHLA-DR) in patients with atrial fibrillation (AF) and their clinical significance.

Methods: 136 patients with atrial fibrillation who were admitted from April 2023 to September 2025 were selected as the research group, and 100 healthy individuals who underwent physical examinations during the same period were selected as the control group. ELISA was used to detect serum levels of sTREM-1 and sHLA-DR, and interleukin-6 (IL-6) and C-reactive protein (CRP) were measured using an automatic biochemical analyser.

Results: The study group exhibited elevated blood levels of sTREM-1 and sHLA-DR compared with the control group ($P < 0.05$). Regarding patient age, sex, type of atrial fibrillation, and EHRA classification, there were statistically significant differences in sTREM-1 and sHLA-DR levels between the study and control groups ($P < 0.05$). The study group had greater levels of CRP and serum IL-6 than the control group ($P < 0.05$). The expression levels of sTREM-1 and sHLA-DR in serum were positively correlated with those of IL-6 and CRP ($P < 0.05$) using Pearson correlation analysis. Serum levels of the inflammatory markers IL-6 and CRP, as well as sTREM-1 and sHLA-DR, were strongly associated with AF in the logistic regression analysis.

Kratak sadržaj

Uvod: Cilj je bio da se ispituju nivoi ekspresije rastvorljivog receptora izraženog na mijeloidnim ćelijama-1 (sTREM-1) i rastvorljivog humanog leukocitnog antigena-DR (sHLA-DR) u serumu kod pacijenata sa atrijalnom fibrilacijom (AF), kao i njihov klinički značaj.

Metode: Za grupu ispitanika je odabrano 136 pacijenata sa atrijalnom fibrilacijom hospitalizovanih u periodu od aprila 2023. do septembra 2025. godine, dok je kontrolnu grupu činilo 100 zdravih ispitanika koji su u istom periodu bili podvrgnuti sistematskim pregledima. Nivoi sTREM-1 i sHLA-DR u serumu su određivani ELISA metodom, dok su interleukin-6 (IL-6) i C-reaktivni protein (CRP) mereni pomoću automatskog biohemijškog analizatora.

Rezultati: Ispitivana grupa je pokazala povišene koncentracije sTREM-1 i sHLA-DR u krvi u poređenju sa kontrolnom grupom ($P < 0,05$). U odnosu na starost, pol, tip atrijalne fibrilacije i EHRA klasifikaciju, utvrđene su statistički značajne razlike u nivoima sTREM-1 i sHLA-DR između grupa ($P < 0,05$). Nivoi CRP i serumskog IL-6 su bili viši u ispitivanoj nego u kontrolnoj grupi ($P < 0,05$). Pirsonovom korelacionom analizom je utvrđeno da su nivoi sTREM-1 i sHLA-DR u serumu pozitivno korelisali sa nivoima IL-6 i CRP ($P < 0,05$). Logistička regresiona analiza je pokazala da su serumski nivoi inflamatornih markera IL-6 i CRP, kao i sTREM-1 i sHLA-DR, značajno povezani sa atrijalnom fibrilacijom.

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Conclusion: Serum levels of sTREM-1 and sHLA-DR are increased in patients with atrial fibrillation, which may be related to the onset and progression of AF. Clinically, these can be considered relevant biological indicators for monitoring AF.

Keywords: atrial fibrillation, serum sTREM-1s, serum sHLA-DR, prognosis analysis

Introduction

Atrial fibrillation (AF) is a prevalent form of arrhythmia in clinical settings. Its incidence increases with age, reaching 9% among individuals aged 80 years or older (1). AF is often accompanied by other complications, which can lead to serious, disabling, and fatal events. With the increasingly severe aging of the population, the harm caused by AF will continue to increase. Current research suggests that AF results from the combined action of multiple mechanisms. Some foreign scholars have reported that AF is related to inflammation (2). Leukocyte differentiation antigen 14 (sTREM-1) is a marker of the body's inflammatory response and is present in body fluids in the form of soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) (3); sHLA-DR is a specific scavenger receptor of haemoglobin and is expressed on the surface of monocytes and macrophages, and upon inflammatory stimulation, sHLA-DR detaches to form soluble Human Leukocyte Antigen-DR (sHLA-DR), thereby exerting an anti-inflammatory effect (4).

However, the roles of sTREM-1 and sHLA-DR in the development of AF disease remain unclear. This study measured serum levels of sTREM-1 and sHLA-DR in patients with atrial fibrillation (AF), analysed correlations between their expression levels and clinical characteristics, and explored the significance of sTREM-1 and sHLA-DR expression in the onset and development of AF.

Materials and Methods

General information

A total of 136 individuals with atrial fibrillation admitted to our institution between April 2023 and September 2025 were selected. Among them, 80 were male, and 56 were female, with ages ranging from 35 to 82 (67.38 ± 12.12) years. According to the European Heart Rhythm Association Symptom Score (EHRA score) (5), the risk of atrial fibrillation was categorized into four grades: 58 instances in grade I, 22 cases in grade II, 16 cases in grade III, and 18 cases in grade IV. They were divided into a spontaneous atrial fibrillation group (40 cases) and a nonspontaneous atrial fibrillation group (96 cases) based on whether they could return to normal rhythm spontaneously.

Zaključak: Serumski nivoi sTREM-1 i sHLA-DR su povišeni kod pacijenata sa atrijalnom fibrilacijom, što može biti povezano sa nastankom i progresijom bolesti. U kliničkoj praksi, ovi parametri mogu predstavljati značajne biološke pokazatelje za praćenje atrijalne fibrilacije.

Ključne reči: atrijalna fibrilacija, serumski sTREM-1, serumski sHLA-DR, analiza prognoze

80 healthy adults, comprising 40 males and 40 females aged 38-79 years (mean age 65.74 ± 9.89), were concurrently selected as the control group following physical examinations.

Inclusion criteria: Patients who were diagnosed with AF through medical history inquiry and electrocardiogram; patients who had not received any treatment before admission; and patients, along with their families, who executed the informed consent form.

Exclusion criteria: Patients with concurrent infections, tumours, or immune system diseases; patients with diabetes; patients with impaired liver or kidney function; and patients with primary heart diseases.

EHRA classification criteria

Based on the patient's symptoms and their impact on daily life, atrial fibrillation (AF) is classified into 4 grades. Grade I: No symptoms; Grade II: Moderate symptoms that do not interfere with day-to-day activities; Grade III: Severe symptoms that make it difficult to go about daily tasks; Grade IV: Incapable of carrying out any tasks.

Sample collection

For AF patients, before receiving treatment after diagnosis, 3 mL of venous blood was collected in the morning on an empty stomach. The blood was centrifuged, and the supernatant was placed in a sterile EP tube and stored at -20°C in the refrigerator; serum was collected from the control group in the same way in the morning.

Detection of serum sTREM-1 and sHLA-DR levels

The concentrations of sTREM-1 and sHLA-DR in the serum were detected by enzyme-linked immunosorbent assay (ELISA). The sTREM-1 detection kit (item number: DsTREM-10C) and the sHLA-DR detection kit (item number: DCD163B) were both purchased from R&D Systems in Minneapolis, Minnesota, USA. These kits use the double-antibody sandwich method and exhibit high specificity and

sensitivity. The microplate reader used in the experiment was the Model 680 enzyme-labelled microplate reader produced by Bio-Rad Laboratories, equipped with a 450nm wavelength filter. The detection process was carried out strictly in accordance with the kit instructions. First, the serum samples were thawed at room temperature, centrifuged at 3000rpm for 10 minutes to obtain the supernatant. Then, the standard curve was prepared by diluting the standards in a gradient. Each sample was set up with three duplicate wells. The pre-bound antibody-coated 96-well plate was added, and incubated at room temperature for 2 hours. After washing, the biotin-labelled detection antibody and streptavidin-horseradish peroxidase conjugate were added, and finally, the TMB substrate solution was added for colour development. After termination, the absorbance value was measured. To ensure the accuracy of the results, all samples were detected by the same experimental personnel on the same equipment. The intra-batch coefficient of variation was controlled within 5%. The sample concentrations were calculated using the four-parameter logistic curve fitting.

Clinical indicator examination

The levels of serum interleukin-6 (IL-6) and C-reactive protein (CRP) were measured using a Hitachi 766-020 automatic biochemical analyser produced by Hitachi (Japan). The IL-6 detection kit had the item number HS600B, and the CRP detection kit had the item number DRP00. Both were purchased from the US-based R&D Systems company. The reagents used employed a high-sensitivity chemiluminescent immunoassay (CLIA) method, with detection ranges of 0.7–10,000 pg/mL for IL-6 and 0.1–500 mg/L for CRP. Before the experiment, the serum samples were thawed at room temperature (25 °C) for 30 minutes and centrifuged at 3,000 rpm for 10 minutes to remove the precipitate. During testing, the instrument automatically performed sample dilution, sample addition, incubation, and signal collection. The IL-6 detection wavelength was 450 nm (reference wavelength 570 nm), and the CRP detection wavelength was 540 nm (reference wavelength 630 nm). Each batch of tests included standard samples (IL-6: 0, 31.2, 125, 500, 2,000 pg/mL; CRP: 0, 1, 5, 20, 100 mg/L) and quality control serum (low, medium, and high values) to ensure an intra-batch coefficient of variation (CV) <5% and an inter-batch CV <8%. All samples were tested by the same technician on the same instrument, with each sample set up for double-hole retesting. The results were averaged. The reagents were stored strictly according to the instructions, brought to room temperature before use, and thoroughly mixed to avoid repeated freezing and thawing, thereby ensuring test stability. The

instrument's accompanying software automatically analysed the data, and the final concentrations were calculated from the standard curve, with units uniformly converted to pg/mL (IL-6) and mg/L (CRP).

Statistical analysis

Statistical analysis was performed using SPSS 22.0. T tests were conducted, and measurement data are displayed as the mean \pm standard deviation ($\bar{x} \pm s$). Count data are presented as percentages (%), and χ^2 tests were performed; Pearson's method was employed to assess the correlation between serum sTREM-1 and sHLA-DR expression levels in AF patients and the inflammatory factors IL-6 and CRP. Logistic regression was used to assess risk factors for atrial fibrillation (AF).

Results

The expression levels of serum inflammatory factors in the two groups

Serum levels of the inflammatory markers IL-6 and CRP in the study group were significantly elevated compared with the control group ($P < 0.05$), as shown in *Table 1*.

The expression levels of sTREM-1 and sHLA-DR in the serum of patients with atrial fibrillation were significantly higher than those in the healthy control group, indicating that these two inflammatory markers were abnormally elevated in patients with atrial fibrillation. At the same time, serum levels of IL-6 and CRP in patients with atrial fibrillation were also significantly higher than in the healthy population, suggesting that the systemic inflammatory response may play an important role in the development and progression of atrial fibrillation. It is noteworthy that the expression levels of sTREM-1 and sHLA-DR showed significant positive correlations with IL-6 and CRP, suggesting that these inflammatory factors may exert a synergistic effect and jointly participate in the pathophysiological process of atrial fibrillation.

Table 1 Comparison of serum inflammatory factor expression levels between the two groups ($\bar{x} \pm s$).

Group	n	CRP (mg/L)	IL-6 (pg/L)
Control group	80	2.04 \pm 0.61	22.57 \pm 6.21
Research group	136	6.27 \pm 2.35	55.59 \pm 8.72
T value		-11.235	-20.85
P		<0.001	<0.001

Table II Comparison of serum sTREM-1 and sHLA-DR expression levels between two groups ($\bar{x}\pm s$).

Group	n	sTREM-1 ($\mu\text{g/mL}$)	sHLA-DR ($\mu\text{g/mL}$)
Control group	80	4.75 \pm 1.20	0.50 \pm 0.16
Research group	136	12.37 \pm 3.82	0.85 \pm 0.24
T value		-11.991	-6.798
P		<0.001	<0.001

Table III Relationship between serum sTREM-1 and sHLA-DR expression levels and clinical characteristics in AF patients.

Indicator	Group	n	Age		Gender		Atrial fibrillation		EHRA grading	
			≤ 65 years old	> 65 years old	Male	Female	paroxysmal atrial fibrillation	Non-paroxysmal atrial fibrillation	I~II level	III~IV level
sTREM-1 expression level	Low-expression group	48	26	22	20	28	6	42	44	4
	High-expression group	88	26	62	60	28	36	52	58	30
	X ² value		3.989		4.501		5.875		5.498	
	P		0.049		0.037		0.018		0.012	
sHLA-DR expression level	Low-expression group	44	26	18	18	26	22	22	40	4
	High-expression group	92	26	66	62	30	20	72	62	30
	X ² value		5.993		4.302		5.562		4.393	
	P		0.017		0.031		0.011		0.039	

Serum sTREM-1 and sHLA-DR levels in the two groups

Compared with the control group, the study group showed a dramatic elevation in serum sTREM-1 expression ($P < 0.05$), and serum sHLA-DR expression also significantly increased ($P < 0.05$), see *Table II*.

Analysis of patients with atrial fibrillation with varying clinical characteristics revealed that sTREM-1 and sHLA-DR expression levels were closely associated with patient age, gender, atrial fibrillation type, and EHRA classification. This suggests that these inflammatory markers may reflect the varying severity and pathophysiological characteristics of atrial fibrillation. As important markers of monocyte/macrophage activation, increases in serum levels of sTREM-1 and sHLA-DR may indicate a persistent inflammatory state in patients with atrial fibrillation.

Relationships between the expression levels of sTREM-1 and sHLA-DR in the serum of AF patients and their clinical characteristics

Based on the mean expression levels of sTREM-1 and sHLA-DR in the serum of 136 patients with atrial fibrillation (AF), The serum was categorized into two groups: the high-expression group including 88 patients and the low-expression group consisting of 48 individuals, and the high-expression group (92 patients) and the low-expression group (44 patients). Statistically significant differences in sTREM-1 and sHLA-DR expression levels were observed in the serum of individuals with atrial fibrillation compared with those in patients with the same age, sex, type of atrial fibrillation, and EHRA classification ($P < 0.05$), as shown in *Table III*.

Correlation analysis of serum sTREM-1 and sHLA-DR levels in patients with AF

Using the Pearson method for analysis, it was found that sTREM-1 expression in the serum of AF patients was higher (*Figure 1*).

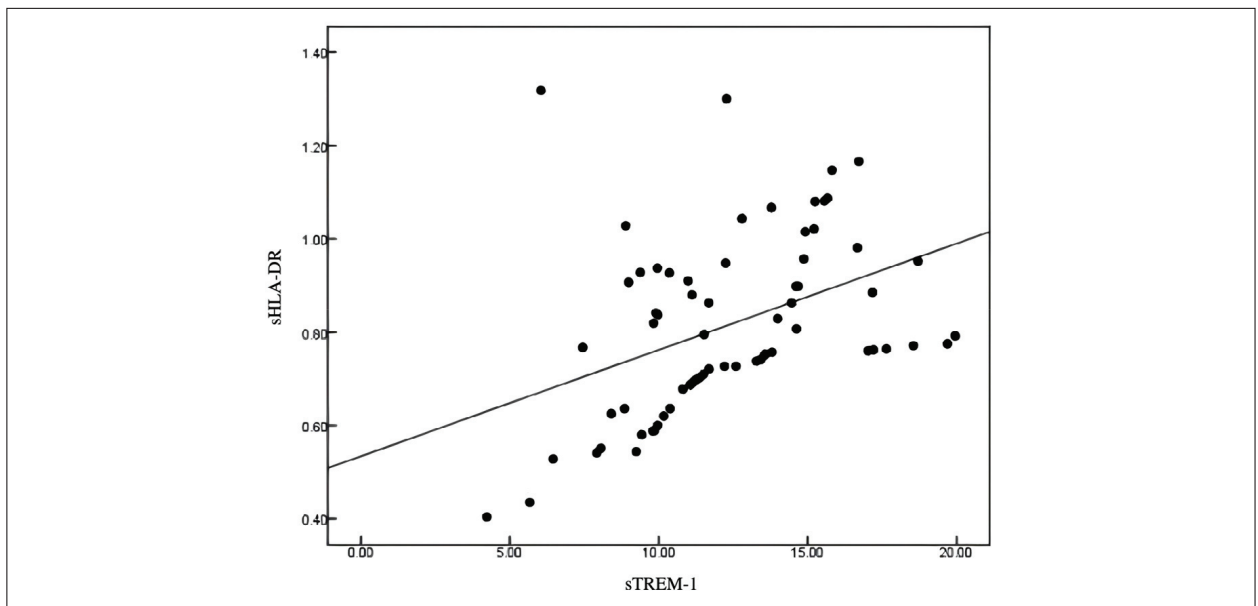


Figure 1 Correlation analysis of sTREM-1 and sHLA-DR expression levels in the serum of AF patients.

Table IV Correlation analysis between sTREM-1 and sHLA-DR expression levels and inflammatory factors in AF patients.

Analysis factors	Statistical analysis	IL-6	CRP
sTREM-1	r value	0.545	0.482
	P	0.001	<0.001
sHLA-DR	r value	0.475	0.524
	P	<0.001	<0.001

Correlation analysis revealed that the expression levels of sTREM-1 and sHLA-DR in the serum of patients with atrial fibrillation showed a significant positive correlation, suggesting that these markers of monocyte/macrophage activation may act synergistically in the pathogenesis of atrial fibrillation. Further analysis revealed that sTREM-1 and sHLA-DR levels were closely associated with patients' clinical characteristics, including age, gender, atrial fibrillation type, and EHRA classification. sTREM-1 and sHLA-DR also showed significant positive correlations with the traditional inflammatory markers IL-6 and CR.

Correlations between serum expression levels of sTREM-1 and sHLA-DR in patients with atrial fibrillation and inflammatory factor levels

The expression levels of sTREM-1 and sHLA-DR showed a positive correlation with the blood levels of the inflammatory markers IL-6 and CRP in patients with atrial fibrillation ($P < 0.05$; Table IV).

These single-nucleus/macrophage activation markers may be involved in the inflammatory response in patients with atrial fibrillation and are closely related to the systemic inflammatory state. sTREM-1, as the main receptor for lipopolysaccharide (LPS), can recognize and transmit inflammatory signals, while sHLA-DR is a marker of macrophage activation. Together, these two markers reflect the intensity and duration of the body's inflammatory response. In patients with atrial fibrillation, elevated inflammatory markers may indicate myocardial injury and fibrosis, thereby influencing the onset and progression of atrial fibrillation.

Logistic regression analysis of factors influencing the occurrence of AF

Logistic analysis revealed that the expression levels of sTREM-1 and sHLA-DR, along with the serum concentrations of the inflammatory markers IL-6 and CRP, were risk factors for AF (Table V).

Using logistic regression, the factors influencing atrial fibrillation were explored. The results showed that serum levels of sTREM-1, sHLA-DR, IL-6, and CRP were significantly correlated with atrial fibrillation. These inflammatory factors, as independent predictors, play an important role in the occurrence and development of atrial fibrillation. The analysis indicated that these inflammatory markers not only reflect the inflammatory status of atrial fibrillation patients but may also be involved in the pathophysiological process of atrial fibrillation. sTREM-1, as the main receptor for lipopolysaccharide, and sHLA-DR, as a marker of macrophage

Table V Logistic regression analysis results of AF related variables.

Variable	Partial regression coefficient	Standard error	Standard regression coefficient	P	OR	CI 95%
sTREM-1	0.366	0.175	4.457	0.035	1.432	1.278~1.626
sHLA-DR	0.255	0.167	2.364	0.012	1.289	1.041~1.571
IL-6	1.456	0.424	11.915	0.002	4.341	2.324~8.148
CRP	0.555	0.180	8.717	0.007	1.730	1.197~2.520

activation, their elevation indicates activation of the mononuclear-macrophage system, while IL-6 and CRP reflect the degree of systemic inflammatory response.

Discussion

AF is often accompanied by complications such as stroke and cerebral infarction, and can even lead to death due to thromboembolism, seriously endangering human health. The exact pathogenesis of AF is still unclear. Recent in-depth research has revealed that inflammatory responses may play important roles in the occurrence and development of AF. CRP and IL-6 are sensitive markers of inflammation. In 1997, first reported that IL-6 and CRP expression increased to varying degrees after coronary artery bypass surgery (6). The CRP expression level is a strong prognostic indicator of AF onset risk (7). Some studies have speculated that inflammatory responses in atrial myocardial cells and stroma can directly alter the transmembrane potential, triggering activity. Another study confirmed that inflammatory responses can cause atrial structural remodeling, increasing the likelihood that atrial fibrillation will persist (8). Serum levels of IL-6 and CRP were considerably higher in AF patients than in controls. Serum levels of CRP and IL-6 are correlated with the onset of AF, indicating that the body's inflammatory response may play a role.

sTREM-1 is a specific marker on the surface of monocytes and macrophages and belongs to the family of cell surface glycoproteins. sTREM-1 can be divided into two forms according to its location: the membrane-bound type (msTREM-1), which is expressed on the cell membranes of monocytes, macrophages, and neutrophils, and the soluble form (sTREM-1), which is found in body fluids such as human plasma (9, 10). Cells such as endothelial cells (ECs) that do not express sTREM-1 are activated by the action of the endotoxin lipopolysaccharide (LPS)-sTREM-1 complex, releasing interleukins, growth factors, nitric oxide, etc., and expressing adhesion molecules, which participate in the inflammatory response and cause tissue and

organ damage (11). Direct binding of sTREM-1 to LPS can reduce LPS binding to msTREM-1, thereby regulating the cellular responses of monocytes and other cells. sTREM-1 can promote the adhesion of monocytes to activated epithelial cells, interact with sTREM-1 ligands on the surface of activated lymphocytes, inhibit T-cell proliferation and B-cell antibody production, and promote the adhesion of macrophages to activated endothelial cells and T cells, thereby neutralizing and clearing LPS non-specifically and reducing the inflammatory response. Abnormal specific expression of monocytes and elevated sTREM-1 concentrations have good diagnostic and prognostic value for sepsis, sarcoidosis, and haematological diseases (12). Another study found that serum sTREM-1 levels are elevated in patients with common complications of AF (atrial fibrillation) (13). This study revealed that sTREM-1 expression in the serum of AF patients was higher than in control patients, suggesting that sTREM-1 may be associated with the development of AF. Serum sTREM-1 expression was associated with patient age, sex, atrial fibrillation type, and EHRA classification, suggesting that sTREM-1 expression is associated with disease progression in AF patients.

Macrophages are important components of the human innate immune system and can engulf pathogenic microorganisms and mediate inflammatory responses. sHLA-DR is specifically expressed on the surface of M2-type macrophages and is expressed only on the cell membranes of activated monocytes and macrophages (14). sHLA-DR belongs to the scavenger receptor cysteine structure family and exists in two forms in the body: a transmembrane macromolecular form on macrophages and a soluble form in serum or other tissue fluids (15). sHLA-DR can recognize tumour necrosis factor-like weak inducers of apoptosis and, upon binding, exert anti-inflammatory effects; it can also stimulate cell growth, induce angiogenesis, and promote the release of various inflammatory factors (16–19). There is a substantial rise in sHLA-DR expression in inflammatory bowel disease (20–22). According to studies, patients with acute coronary syndrome have higher levels of sHLA-DR expression, which makes it a perfect marker for diagnosing the condition (23–25).

Conclusion

Serum levels of sTREM-1 and sHLA-DR are markedly increased in patients with atrial fibrillation. These levels are associated with patient age, sex, type of atrial fibrillation, EHRA classification, and levels of inflammatory factors. These findings suggest that serum levels of sTREM-1 and sHLA-DR may be associated with the onset and progression

of AF and can serve as indicators for disease monitoring.

Conflict of interest statement

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

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