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Serum Presepsin and GDF-15 levels in patients with acute myocarditis and their correlation with inflammatory level and cardiac function

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Abstract: Objective To investigate the levels of serum soluble leukocyte differentiation antigen subtype 14 (Presepsin) and growth differentiation factor 15 (GDF-15) in patients with acute myocarditis and their correlation with inflammation factor level and cardiac function indexes. **Methods** Fifty patients with acute myocarditis diagnosed and treated in the Affiliated Hospital of Inner Mongolia Medical University from October 2020 to October 2021 were selected as the case group, and 80 healthy people who received physical examination in the same period were selected as the control group. Enzyme linked immunosorbent assay (ELISA) was used to determine the serum levels of Presepsin, GDF-15, and inflammatory factors [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), hypersensitive C-reactive protein (hs-CRP)].The indexes of cardiac function [left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and left ventricular end diastolic diameter (LVEDD)] were measured by ultrasonic diagnostic apparatus. Pearson method was used to measure and analyze the correlation between serum Presepsin and GDF-15 levels in patients with myocarditis, and the correlation of the two indexes levels with the inflammation and cardiac function. ROC curve was applied to determine the diagnostic value of serum Presepsin and GDF-15 levels for acute myocarditis. **Results** Compared with the control group, the proportion of hypercholesterolemia, the serum levels of Presepsin, GDF-15, IL-6, TNF-α, hs-CRP and the values of LVEDD and LVMI in the case group were significantly higher (P<0.05), but LVEF was significantly lower (P<0.05). Pearson analysis showed that serum Presepsin was positively correlated with GDF-15 levels in patients with myocarditis (P<0.05), and they were respectively correlated with IL-6, TNF-α, hs-CRP, LVEDD and LVMI levels, while negatively correlated with LVEF (P<0.05). ROC curve analysis showed that the area under the curve (AUC) of serum Presepsin and GDF-15 levels in diagnosis of acute myocarditis was 0.873 and 0.816, respectively. When the optimal cut-off values was 77.62 pg/mL and 96.80 pg/mL, the sensitivity was 68.00% and 80.00% and the specificity was 95.00% and 70.00%, respectively. The AUC, sensitivity and specificity of the combined diagnosis for acute myocardit is were 0.908, 86.00% and 81.25%, respectively. **Conclusion** The levels of serum Presepsin and GDF-15 in patients with acute myocarditis are obviously increased, which are closely related to the level of inflammation and left ventricular remodeling. The two indexes have specific diagnostic value for the development of acute myocarditis, and their combined diagnostic value is higher.

Keywords: Acute myocarditis; Soluble leukocyte differentiation antigen 14 subtype; Growth differentiation factor 15; Human tumor necrosis factor-α; Interleukin-6; Hypersensitive C-reactive protein; Left ventricular ejection fraction; Left ventricular mass index; Left ventricular end diastolic diameter

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Acute myocarditis is the leading cause of sudden death in young adults under the age of 40, and it is a myocardial injury disease with a large number of patients clinically, which is mainly triggered by physical, chemical, or myocardial infections. Due to the initial symptoms not being specific, the patient's condition is easily neglected. The rapid development of the condition of some patients may easily lead to cardiogenic shock, heart failure, and cardiac arrhythmia, which may threat patients' lives[1]. Therefore, it is clinically significant to find molecular markers with high specificity and sensitivity for acute myocarditis to prevent the development of acute myocarditis[2]. Soluble leukocyte differentiation antigen subtype 14 (Presepsin), with a size of about 13,000, is a soluble N-terminal fragment of the cluster of differentiation 14 (CD14). Presepsin is a Toll-like receptor that recognizes pathogen-associated molecular patterns and initiates an innate immune response. It is present in macrophages, monocytes, and granulocytes, where it is responsible for intracellular transduction of endotoxin signals and is often used as a diagnostic and prognostic biomarker of sepsis risk stratification[3]. Presepsin is an immune biomarker used to diagnose infections in the past decade, but few studies have been reported for acute myocarditis[4]. Growth differentiation factor-15 (GDF-15) is a cytokine belonging to the transforming growth factor beta (TGF-β) family. GDF-15 is involved in cell growth, cell differentiation, and tissue repair， and can be used as a prognostic marker for acute coronary syndromes, coronary artery bypass grafting, and heart failure[5]. Thus, it is hypothesized that Presepsin and GDF-15 may be involved in developing acute myocarditis. The correlation of Presepsin and GDF-15 with inflammation level and cardiac function in the serum of patients with acute myocarditis is explored in this article, aiming to provide a

reference for clinical diagnosis and intervention of acute myocarditis.

1 Material and methods

1.1 General information

Fifty patients with acute myocarditis diagnosed and treated at the Affiliated Hospital of Inner Mongolia Medical University from October 2020 to October 2021 were selected as the case group, in which the duration of the disease ranged from 3 to 15 (8.84±2.90) days.

Inclusion criteria: (1) Diagnostic criteria were consistent with World Health Organization (WHO) criteria, and all were moderate acute myocarditis; (2) the clinical manifestations were pallor, dyspnea, anorexia, nausea, vomiting, fatigue, weakness, fever, etc.; (3) all of them were myocarditis caused by viral infections, and did not receive relevant treatment prior to admission; (4) general information was complete.
Exclusion criteria: (1) combination of liver, kidney and other serious diseases; (2) the presence of malignant tumors; (3) congenital atrioventricular block, primary endocardial elastin fibroplasia, primary cardiomyopathy; (4) electrocardiographic changes triggered by medications and abnormalities of cardiac autonomic nerve function; (5) rheumatic cardiomyopathies, dilated and peripheral cardiomyopathies, toxic cardiomyopathies, connective tissue diseases, congenital heart diseases and metabolic diseases. Myocardial damage caused by heart disease and metabolic diseases, etc.; (6) Combined autoimmune diseases, respiratory diseases, and blood diseases.

Another 80 healthy controls (without systemic immune diseases) who underwent a physical examination at the same time were selected as the control group. Informed consent for the study was signed by patients and their families. Approval was obtained from the Ethics Committee of the hospital [Approve No: 2020 (27)].

1.2 Major reagents and instruments

Reagent kit of enzyme-linked immunosorbent assay (ELISA):interleukin-6 (IL-6) (Shanghai C-reagent Biotechnology Co. Ltd., Lot No.: CS-E12859), high-sensitivity C-reactive protein (hs-CRP) (Shanghai C-reagent Biotechnology Co. Ltd., Lot No.: CS-12210E), tumor necrosis factor (TNF)-α (Shanghai Enzyme-linked Biotechnology Co., Ltd. , Lot No.: ml077385), Presepsin (Wuhan Amyjet Scientific Co., Ltd, Lot No.: EKL60088), GDF-15 (Wuhan Mershak Biotechnology, Lot No.: kt22190). High-speed centrifuge (Shanghai Jingmi Co. Ltd., Model: TGL-16G); Color Doppler Ultrasound Diagnostic Instrument (Philips USA, Model: PHILIPS IE33); Automatic enzyme-linked immunosorbent assay systems (Shandong Yunke Intelligent Technology, Model: YK-SY96S).

1.3 Sample collection

A total of 5 mL of fasting elbow venous blood from the control group and the case group were collected, respectively. The control group was collected during the physical examination, and the case group was collected within 24 hours of admission to the hospital. The blood was centrifuged at 3,500 r/min for 10 minutes, with a centrifugation radius of 10 cm. Then, the upper layer of the serum was divided into tubes and stored in a refrigerator at -20 ℃, avoiding a repeated freeze-thaw process.

1.4 ELISA detection of IL-6, TNF-α, hs-CRP, Presepsin and GDF-15 levels in serum

All reagents were mixed well, while the standards were diluted according to the ratio, the supernatant was added to the enzyme wells, and the reaction wells were sealed with sealing paper and incubated at room temperature, and three replicate wells were made for each sample, after which the working solution and chromogenic substrate were added sequentially. The absorbance value at 450 nm was detected by the enzyme counter and the corresponding standard curve was plotted to calculate the concentrations of IL-6, TNF-α, hs-CRP, Presepsin and GDF-15 in serum, respectively.

1.5 Detection of cardiac function indexes

Color Doppler ultrasound diagnostic instrument was used to collect images of the control group and case group researchers respectively. Statistics of left ventricular ejection fraction (LVEF), left ventricular muscle mass index (LVMI) and left ventricular end-diastolic diameter (LVEDD).

1.6 General data collection

General information was collected from all patients: age, gender, diabetes mellitus, hypertension, history of smoking, history of alcohol consumption, history of high cholesterol.

1.7 Statistical analysis

SPSS 24.0 software was used to process the data. The normal distribution of measurement data was described by $\bar{x} \pm s$ and independent samples t test was used; the count data was described by case (%), and the chi-square test was performed. Correlation analysis was carried out by Pearson analysis and ROC curve was used to analyse the diagnostic value of serum Prespsin, GDF-15 levels in acute myocarditis. $P < 0.05$ was considered as the statistical significance of the difference.

2 Results

2.1 Comparison of general information between the

two groups

The proportion of high cholesterol in the case group was higher than that in the control group, and the difference was statistically significant (P<0.05).There was no statistically significant difference in other general information between the two groups **[Table 1]**

2.2 Comparison of serum inflammatory factors and cardiac function indexes between the two groups

Compared with the control group, the serum levels of IL-6, TNF-α, hs-CRP, LVEDD, and LVMI in the case group were significantly higher, and LVEF was significantly lower, and the difference was statistically significant (P < 0.05). **[Table 2]**

Tab.1 Comparison of general information between two groups

Groups	Case	Age (years, $\bar{x}\pm s$)	Gender (male/female, case)	High cholesterol (case)	Hypertension (case)	Diabetes (case)	Smoking (case)	Alcohol consumption (case)
Control group	80	52.50±9.36	40/40	39	32	34	50	44
Case group	50	53.40±8.22	28/22	38	22	25	26	24
***t*/x^2 value**		0.558	0.444	9.462	0.203	0.698	1.397	0.604
***P* value**		0.578	0.505	0.002	0.653	0.403	0.237	0.437

Tab.2 Comparison of serum inflammatory factors and cardiac function indicators between two groups ($\bar{x}\pm s$)

Group	Case	IL-6 (ng/mL)	TNF-α (ng/mL)	hs-CRP (mg/L)	LVEF (%)	LVEDD (mm)	LVMI (g/m^2)
Control group	80	15.63±1.57	92.21±9.23	1.29±0.38	60.64±6.07	43.15±4.32	78.61±7.87
Case group	50	27.82±2.79	152.42±15.25	5.66±1.47	42.37±4.24	54.82±5.49	122.82±12.29
***t* value**		31.871	28.066	25.323	18.620	13.481	25.023
***P* value**		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

2.3 Comparison of serum Presepsin and GDF-15 levels between the two groups

Compared with the control group, the serum levels of Presepsin and GDF-15 in the case group were significantly higher, and the difference was statistically significant (P < 0.05). **[Table 3]**

Tab.3 Comparison of serum presepsin and GDF-15 levels between two groups ($\bar{x}\pm s$)

Groups	Case	Presepsin (pg/mL)	GDF-15 (pg/mL)
Control group	80	70.38±7.04	91.24±9.13
Case group	50	80.01±8.01	105.55±10.56
***t* value**		7.193	8.181
***P* value**		<0.01	<0.01

2.4 Correlation of Presepsin and GDF-15 levels in serum of patients with acute myocarditis

Pearson's analysis showed a positive correlation between Presepsin and GDF-15 levels in serum of patients with acute myocarditis (r=0.445, P<0.01). **[Figure 1]**

2.5 Correlation of serum Presepsin and GDF-15 levels with inflammatory factors and cardiac function indexes in patients with acute myocarditis

Results of *Pearson*'s analysis showed the serum levels of Presepsin and GDF-15 in patients with acute myocarditis were positively correlated with the levels of IL-6, TNF-α, hs-CRP, LVEDD, and LVMI (P<0.05), but both were negatively correlated with LVEF (P<0.05). **[Table 4]**

2.6 Diagnostic value of serum Presepsin and GDF-15 levels in patients with acute myocarditis

The AUC of serum Presepsin and GDF-15 levels for diagnosis of acute myocarditis were 0.873 and 0.816, respectively, with sensitivities of 68.00% and 80.00%, and specificities of 95.00% and 70.00%. The optimal cut-off values were 77.62 pg/mL and 96.80 pg/mL, respectively. The AUC, sensitivity, and specificity of the two combined for the diagnosis of acute myocarditis were 0.908, 86.00%, and 81.25%, respectively. **[Figure 2]**

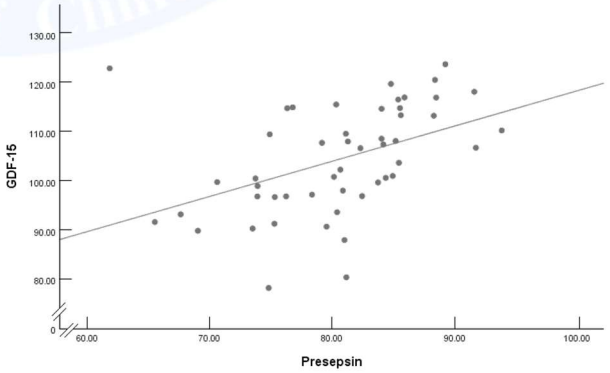

Fig.1 Correlation analysis of serum levels of Presepsin and GDF-15 in patients with acute myocarditis

Tab.4 Correlation between serum levels of Presepsin and GDF-15, inflammatory factors, and cardiac function indicators in patients with acute myocarditis

Indicator	Presepsin		GDF-15	
	r	*P* value	*r*	*P* value
IL-6	0.446	<0.01	0.393	<0.01
TNF-α	0.526	<0.01	0.410	<0.01
hs-CRP	0.482	<0.01	0.465	<0.01
LVEF	-0.400	<0.01	-0.533	<0.01
LVEDD	0.560	<0.01	0.480	<0.01
LVMI	0.579	<0.01	0.457	<0.01

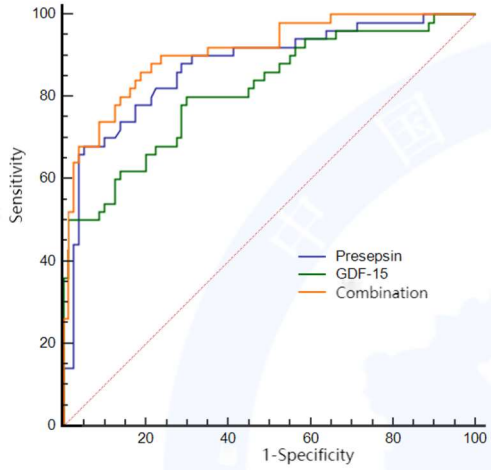

Fig.2 ROC curve of serum Presepsin and GDF-15 levels in the diagnosis of acute myocarditis

3 Discussion

Myocarditis may present in acute, fulminant, subacute, or chronic forms. Acute myocarditis, which can be defined as a period of less than one month between the onset of symptoms and diagnosis, is a severe, under-diagnosed inflammatory disease of the heart with a wide variety of clinical manifestations, ranging from mild symptoms to high-risk cardiac disease with refractory arrhythmias, severe heart failure, and cardiogenic shock[6]. The etiology of myocarditis is wide-ranging, including infections, inflammatory conditions, and exposure to toxic substances, and effective diagnosis remains a challenge[7].

Acute myocarditis can be considered an inflammatory condition. Presepsin, a circulating soluble isoform of a plasma protease-activated glycoprotein of CD such as monocytes, macrophages and neutrophils, was first identified in 2004 and is capable of regulating cellular and humoral immune responses through direct interaction with T and B cells and is a novel biomarker for the diagnosis of inflammatory diseases[8]. Previous studies have shown that Presepsin has high sensitivity and specificity for the diagnosis of diseases associated with systemic inflammation, such as sepsis[9]. In acute myocardial infarction (AMI) studies, serum Presepsin levels were significantly elevated in patients, which is expected to be a new marker for acute myocardial infarction detection[10]. Serum Presepsin levels peaked 12 hours after hospitalization in patients with cardiogenic shock, suggesting that cardiogenic shock due to acute myocardial infarction is accompanied by an inflammatory response[11]. Based on the above research, it is hypothesized that Presepsin may be closely related to the development of acute myocarditis. The results of this study showed a significant increase in serum Presepsin levels in patients in the case group, suggesting that Presepsin levels are abnormally expressed in patients with acute myocarditis, and that a decrease in Presepsin levels may signal clinical improvement, reflecting therapeutic efficacy[12].

GDF-15 is a cytokine of the TGF-β family and is found at low levels in tissues and plasma, except in the placenta and prostate[13]. GDF-15 has been used as a biomarker of cardiovascular events in most studies[14]. Wang *et al.*[15] found that plasma levels of GDF-15 were significantly higher in children with heart disease and growth defects than in healthy controls and children with normal growth heart disease. Andersson *et al.*[16] showed that elevated levels of GDF-15 were associated with an increased risk of sudden cardiac death within 24 hour of myocardial infarction, which could be a primary intervention to guide this disease. Based on the above research, it is hypothesized that GDF-15 may be involved in the development of acute myocarditis. The results of the present study showed a significant increase in serum levels of GDF-15 in the case group of patients, suggesting that GDF-15 may be involved in the pathogenesis of acute myocarditis for the following reasons: the onset and progression of acute myocarditis may lead to a compensatory upregulation of GDF-15, which may reduce the apoptosis of cardiomyocytes, thus exerting a myocardial protective effect. In addition, *Pearson's* analysis showed a positive correlation between serum Presepsin and GDF-15 levels in patients with acute myocarditis, suggesting that both may be involved in the development of acute myocarditis.

TNF-α and IL-6 are involved in the immune process of myocardial inflammatory injury, which is clinically instructive for determining the presence of myocarditis[17]. hs-CRP can be one of the indicators for the diagnosis and assessment of viral myocarditis[18]. Left ventricular dysfunction is a common cause of heart failure. Echocardiographic measurements of left ventricular function and structure are highly accurate and have the advantage of being non-invasive and safe, but there are also measurement biases. LVEF, LVEDD, and LVMI are important indicators for predicting left ventricular remodeling[19]. In this study, serum levels of IL-6, TNF-α, hs-CRP and LVEDD, LVMI were significantly higher but LVEF was significantly lower in the case group, indicating the presence of inflammatory response and ventricular remodeling in patients with acute myocarditis. *Pearson*'s analysis showed that serum levels of Presepsin, GDF-15 in patients with acute

myocarditis were significantly higher than those of IL-6, TNF-α, respectively, hs-CRP, LVEDD, LVMI levels showed a positive correlation, and all of them showed a negative correlation with LVEF, suggesting that serum Presepsin and GDF-15 levels have a reference value in reflecting inflammatory response and left ventricular remodeling. Both of them may be involved in the development of acute myocarditis by influencing the inflammatory factors and cardiac function indexes. In addition, ROC curve analysis showed that serum Presepsin and GDF-15 levels have a diagnostic value for acute myocarditis, and the combined diagnosis of the two can improve the AUC and the sensitivity, and the diagnostic efficacy is even higher, and the combined detection of serum Presepsin and GDF-15 levels can be considered for the early evaluation and treatment of acute myocarditis in the clinical application.

In conclusion, serum Presepsin and GDF-15 levels were significantly elevated in patients with acute myocarditis, which were closely related to the level of inflammation and left ventricular reconstruction, and had a specific diagnostic value for the development of acute myocarditis, and the combination of the two had a higher diagnostic value. However, due to the limited number of sample size, the results still need to be further verified.

Conflict of interest None

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·论　著·

急性心肌炎患者血清 Presepsin 和 GDF-15 水平及其与炎症水平和心功能的相关性

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摘要：目的　探讨急性心肌炎患者血清可溶性 CD14 亚型（Presepsin）、生长分化因子 15（GDF-15）水平及其与炎症因子水平、心功能指标的关系。**方法**　选取 2020 年 10 月至 2021 年 10 月于内蒙古医科大学附属医院诊治的 50 例急性心肌炎患者作为病例组，同期体检的 80 例健康人作为对照组。酶联免疫吸附法（ELISA）测定血清 Presepsin、GDF-15 和炎症因子[肿瘤坏死因子-α（TNF-α）、白细胞介素-6（IL-6）、超敏 C 反应蛋白（hs-CRP）]水平。超声心动图检测心功能指标[左室射血分数（LVEF）、左室质量指数（LVMI）、左室舒张末期内径（LVEDD）]。Pearson 法分析急性心肌炎患者血清 Presepsin 与 GDF-15 水平相关性，以及两者水平与炎症水平、心功能的相关性。ROC 曲线分析血清 Presepsin、GDF-15 水平对急性心肌炎的诊断价值。**结果**　与对照组相比，病例组患者高胆固醇比例、血清 Presepsin、GDF-15、IL-6、TNF-α、hs-CRP 水平以及 LVEDD、LVMI 显著升高，但 LVEF 显著下降，差异均有统计学意义（$P<0.05$）。Pearson 分析显示急性心肌炎患者血清 Presepsin 与 GDF-15 水平呈正相关，二者分别与 IL-6、TNF-α、hs-CRP、LVEDD、LVMI 呈正相关，与 LVEF 呈负相关（$P<0.05$）。ROC 曲线分析显示血清 Presepsin、GDF-15 水平诊断急性心肌炎的曲线下面积分别为 0.873、0.816，最佳截断值分别为 77.62 pg/mL、96.80 pg/mL 时，其敏感度分别为 68.00%、80.00%，特异度分别为 95.00%、70.00%；二者联合诊断急性心肌炎的曲线下面积、敏感度、特异度分别为 0.908、86.00%、81.25%。**结论**　急性心肌炎患者血清 Presepsin、GDF-15 水平显著增加，与炎症水平、左室重构密切相关，两指标对急性心肌炎有一定的诊断价值，两者联合诊断效能更高。

关键词： 急性心肌炎；可溶性 CD14 亚型；生长分化因子 15；肿瘤坏死因子-α；白细胞介素-6；超敏 C 反应蛋白；左室射血分数；左室质量指数；左室舒张末期内径
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Abstract: Objective　To investigate the levels of serum soluble CD14 subtype (Presepsin) and growth differentiation factor 15 (GDF-15) in patients with acute myocarditis and their correlation with inflammation factor levels and cardiac function indexes. **Methods**　Fifty patients with acute myocarditis diagnosed and treated in the Affiliated Hospital of Inner Mongolia Medical University from October 2020 to October 2021 were selected as the case group, and 80 healthy people who received physical examination in the same period were selected as the control group. Enzyme linked immunosorbent assay (ELISA) was used to determine the serum levels of Presepsin, GDF-15, and inflammatory factors [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), hypersensitive C-reactive protein (hs-CRP)]. The indexes of cardiac function [left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and left ventricular end diastolic diameter (LVEDD)] were measured by echocardiography. Pearson method was used to measure and analyze the correlation between serum Presepsin and GDF-15 levels in patients with myocarditis, and the correlation of

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the two indexes levels with the inflammation and cardiac function. ROC curve was applied to determine the diagnostic value of serum Presepsin and GDF-15 levels for acute myocarditis. **Results** Compared with the control group, the proportion of hypercholesterolemia, the serum levels of Presepsin, GDF-15, IL-6, TNF-α, hs-CRP and the values of LVEDD and LVMI in the case group were significantly higher (P<0.05), but LVEF was significantly lower (P<0.05). Pearson analysis showed that serum Presepsin was positively correlated with GDF-15 levels in patients with acute myocarditis (P<0.05), and they were respectively correlated with IL-6, TNF- α, hs-CRP, LVEDD and LVMI levels, while negatively correlated with LVEF (P<0.05). ROC curve analysis showed that the area under the curve of serum Presepsin and GDF-15 levels in diagnosis of acute myocarditis was 0.873 and 0.816, respectively. When the optimal cut-off values was 77.62 pg/mL and 96.80 pg/mL, the sensitivity was 68.00% and 80.00% and the specificity was 95.00% and 70.00%, respectively. The area under the curve, sensitivity and specificity of the combined diagnosis for acute myocarditis were 0.908, 86.00% and 81.25%, respectively. **Conclusion** The levels of serum Presepsin and GDF-15 in patients with acute myocarditis are obviously increased, which are closely related to the level of inflammation and left ventricular remodeling. The two indexes have certain diagnostic value for the occurrence of acute myocarditis, and their combined diagnostic value is higher.

Keywords: Acute myocarditis; Soluble leukocyte differentiation antigen 14 subtype; Growth differentiation factor 15; Tumor necrosis factor-α; Interleukin-6; Hypersensitive C-reactive protein; Left ventricular ejection fraction; Left ventricular mass index; Left ventricular end diastolic diameter

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急性心肌炎是 40 岁以下青壮年猝死的主要原因,属于临床患病人数较多的心肌损伤疾病,主要由物理、化学或心肌感染引发,由于初始症状特异性不高,容易造成病情被忽视,加上部分患者病情发展较快,易出现心源性休克、心力衰竭、心律失常等,可危及患者生命安全[1]。因此,寻找急性心肌炎特异度好、灵敏度高的分子标志物,预防其发生有着重要的临床意义[2]。可溶性 CD14 亚型(soluble CD14 subtype,又称 Presepsin)大小约为 13 000,是分化标记蛋白 CD14 簇的可溶性 N 端片段,是识别病原体相关分子模式并启动先天免疫反应的 Toll 样受体,存在于巨噬细胞、单核细胞和粒细胞中,负责内毒素信号的细胞内转导,常作为脓毒症风险分层的诊断和预后生物标志物[3]。Presepsin 是一种免疫生物标志物,在过去十年中已被用于感染的初步诊断,但对于急性心肌炎的研究鲜有报道[4]。生长分化因子 15(growth differentiation factor-15, GDF-15)是属于转化生长因子 β(transforming growth factor-beta, TGF-β)家族的细胞因子,GDF-15 参与细胞生长、分化与组织修复,可作为急性冠状动脉综合征、冠状动脉旁路移植术和心力衰竭的预后标志物[5]。结合上述研究推测 Presepsin、GDF-15 可能参与急性心肌炎发展,本研究探讨急性心肌炎患者血清中 Presepsin、GDF-15 与炎症水平、心功能的相关性,旨在为急性心肌炎的临床诊断及有效干预提供参考。

1　资料与方法

1.1　一般资料　选取 2020 年 10 月至 2021 年 10 月于内蒙古医科大学附属医院诊治的 50 例急性心肌炎患者作为病例组,病程 3~15(8.84±2.90) d。纳入标准:(1) 相关诊断标准符合世界卫生组织(World Health Organization, WHO)所制定的标准,均为中型急性心肌炎;(2) 临床表现为面色苍白、呼吸困难、食欲不振、恶心、呕吐、疲乏无力、发热等;(3) 由病毒感染引起的心肌炎,且入院前未接受相关治疗;(4) 一般资料完整。排除标准:(1) 合并肝、肾等其他严重性疾病;(2) 存在恶性肿瘤;(3) 先天性房室传导阻滞、原发性心内膜弹力纤维增生症、原发性心肌病;(4) 药物及心脏自主神经功能异常引发的心电图改变;(5) 风湿性心肌炎、扩张型及围生期心肌病、中毒性心肌炎、结缔组织病、先天性心脏病及代谢性疾病等引发的心肌损害者;(6) 合并自身免疫性疾病、呼吸系统疾病、血液疾病者。另选择同期接受体检的 80 例健康人(无全身免疫性疾病)为对照组。对研究内容患者及监护人签署知情同意书。获得医院伦理委员会批准,编号 2020 伦审字科研(27)号。

1.2　主要试剂仪器　酶联免疫吸附测定(enzyme-linked immunosobent assay, ELISA)试剂盒:人白细胞介素-6(interleukin-6, IL-6)(上海蕴试生物技术,批号:CS-E12859),超敏 C 反应蛋白(high-sensitivity C-reactive protein, hs-CRP)(上海蕴试生物技术,批号:

CS-12210E),肿瘤坏死因子(tumour necrosis factor, TNF)-α(上海酶联生物科技,批号:ml077385),Presepsin(武汉艾美捷科技,批号:EKL60088),GDF-15(武汉默沙克生物科技,批号:kt22190)。高速离心机(上海精密仪器仪表公司,型号:TGL-16G);彩色多普勒超声诊断仪(美国飞利浦公司,型号:PHILIPS IE33);全自动酶标仪(山东云科智能科技,型号:YK-SY96S)。

1.3　样本采集　采集对照组、病例组空腹肘正中静脉血 5 mL,其中对照组于体检时采血,病例组于入院 24 h 内采血,3 500 r/min 离心 10 min,离心半径 10 cm,取上层血清分装在管内,-20 ℃冰箱保存备用。

1.4　ELISA 检测血清中 IL-6、TNF-α、hs-CRP、Presepsin、GDF-15 水平　将所有试剂充分混匀,同时按照比例稀释标准品,取上清液加入酶标孔中,用封板胶纸封住反应孔,室温孵育,每个样品做三个复孔,之后依次加入工作液、显色底物,用酶标仪检测 450 nm 处的吸光度值,绘制相应标准曲线,依次计算血清中 IL-6、TNF-α、hs-CRP、Presepsin、GDF-15 浓度。

1.5　心功能指标检测　用彩色多普勒超声诊断仪分别采集两组对象的图像,统计左室射血分数(left ventricular ejection fraction, LVEF)、左室质量指数(left ventricular muscle mass index, LVMI)、左室舒张末期内径(left ventricular end-diastolic diameter, LVEDD)。

1.6　一般资料收集　收集两组年龄、性别、糖尿病、高血压、吸烟史、饮酒史、高胆固醇等资料。

1.7　统计学方法　采用 SPSS 24.0 软件处理数据。以 $\bar{x}\pm s$ 描述符合正态分布的计量资料并采用独立样本 t 检验进行组间比较;以例(%)描述计数资料,行 χ^2 检验;相关性采用 Pearson 法分析;采用 ROC 曲线分析血清 Presepsin、GDF-15 水平对急性心肌炎发生的诊断价值。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　两组一般资料比较　病例组高胆固醇者比例高于对照组,差异有统计学意义($P<0.05$);两组其他一般资料差异无统计学意义($P>0.05$)。见表 1。

2.2　两组血清炎症因子、心功能指标比较　与对照组相比,病例组血清中 IL-6、TNF-α、hs-CRP、LVEDD、LVMI 水平显著升高,LVEF 显著下降,差异有统计学意义($P<0.05$)。见表 2。

2.3　两组血清 Presepsin、GDF-15 水平比较　与对照组相比,病例组血清中 Presepsin、GDF-15 水平显著升高,差异有统计学意义($P<0.05$)。见表 3。

2.4　急性心肌炎患者血清 Presepsin 与 GDF-15 的相关性　Pearson 相关分析结果显示,急性心肌炎患者血清 Presepsin 与 GDF-15 水平呈正相关($r=0.445$, $P<0.01$)。见图 1。

2.5　血清 Presepsin、GDF-15 水平分别与炎症因子、心功能指标的相关性　Pearson 相关分析结果示,急性心肌炎患者血清中 Presepsin、GDF-15 水平分别与 IL-6、TNF-α、hs-CRP、LVEDD、LVMI 水平呈正相关($P<0.05$),但均与 LVEF 呈负相关($P<0.05$)。见表 4。

2.6　血清 Presepsin、GDF-15 水平对急性心肌炎患者的诊断价值　血清 Presepsin、GDF-15 水平诊断急性心肌炎的曲线下面积分别为 0.873、0.816,最佳截断值分别为 77.62 pg/mL、96.80 pg/mL 时,其敏感度分别为 68.00%、80.00%,特异度分别为 95.00%、70.00%;二者联合诊断急性心肌炎的曲线下面积、敏感度、特异度分别为 0.908、86.00%、81.25%。见图 2。

表 1　两组一般资料比较

Tab. 1　Comparison of general information between two groups

组别	例数	年龄(岁, $\bar{x}\pm s$)	性别(男/女,例)	高胆固醇(有/无,例)	高血压史(有/无,例)	糖尿病史(有/无,例)	吸烟史(有/无,例)	饮酒史(有/无,例)
对照组	80	52.50±9.36	40/40	39/41	32/48	34/46	50/30	44/36
病例组	50	53.40±8.22	28/22	38/12	22/28	25/25	26/24	24/26
t/χ^2 值		0.558	0.444	9.462	0.203	0.698	1.397	0.604
P 值		0.578	0.505	0.002	0.653	0.403	0.237	0.437

表 2　两组血清炎症因子、心功能指标比较　($\bar{x}\pm s$)

Tab. 2　Comparison of serum inflammatory factors and cardiac function indicators between two groups　($\bar{x}\pm s$)

组别	例数	IL-6(ng/mL)	TNF-α(ng/mL)	hs-CRP(mg/L)	LVEF(%)	LVEDD(mm)	LVMI(g/m^2)
对照组	80	15.63±1.57	92.21±9.23	1.29±0.38	60.64±6.07	43.15±4.32	78.61±7.87
病例组	50	27.82±2.79	152.42±15.25	5.66±1.47	42.37±4.24	54.82±5.49	122.82±12.29
t 值		31.871	28.066	25.323	18.620	13.481	25.023
P 值		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

表 3　两组血清 Presepsin、GDF-15 水平比较　($\bar{x}\pm s$)

Tab. 3　Comparison of serum Presepsin and GDF-15 levels between two groups　($\bar{x}\pm s$)

组别	例数	Presepsin(pg/mL)	GDF-15(pg/mL)
对照组	80	70.38±7.04	91.24±9.13
病例组	50	80.01±8.01	105.55±10.56
t 值		7.193	8.181
P 值		<0.001	<0.001

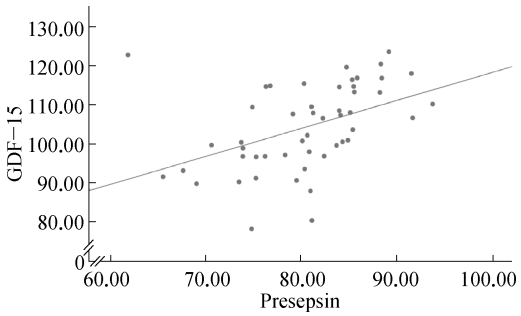

图 1　急性心肌炎患者血清中 Presepsin 与 GDF-15 水平的相关性

Fig. 1　Correlation between serum levels of Presepsin and GDF-15 in patients with acute myocarditis

表 4　急性心肌炎患者血清 Presepsin、GDF-15 水平分别与炎症因子、心功能指标的相关性

Tab. 4　Correlation of serum levels of Presepsin and GDF-15 with inflammatory factors, and cardiac function indicators in acute myocarditis patients

指标	Presepsin		GDF-15	
	r 值	P 值	r 值	P 值
IL-6	0.446	<0.01	0.393	<0.01
TNF-α	0.526	<0.01	0.410	<0.01
hs-CRP	0.482	<0.01	0.465	<0.01
LVEF	−0.400	<0.01	−0.533	<0.01
LVEDD	0.560	<0.01	0.480	<0.01
LVMI	0.579	<0.01	0.457	<0.01

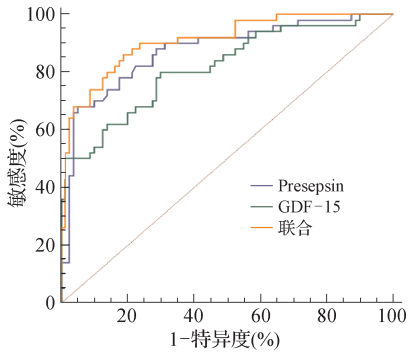

图 2　血清 Presepsin、GDF-15 水平诊断急性心肌炎的 ROC 曲线

Fig. 2　ROC curve of serum Presepsin and GDF-15 levels in the diagnosis of acute myocarditis

3　讨　论

心肌炎可能以急性、暴发性、亚急性和慢性形式出现,急性心肌炎可定义为症状出现到诊断的时间不超过 1 个月,是目前一种严重的、未被充分诊断的心脏炎症疾病,临床表现多样,从轻微症状到难治性心律失常、严重心力衰竭和心源性休克的高危心脏病[6],其病因较为广泛,包括感染、炎症状况及接触有毒物质,目前其有效诊断依然是一项挑战[7]。

急性心肌炎可以被认为是一种炎症状态。Presepsin 是单核细胞、巨噬细胞和中性粒细胞等白细胞分化抗原糖蛋白被血浆蛋白酶激活后形成的循环可溶性亚型,于 2004 年首次被发现,能够通过直接与 T 细胞和 B 细胞相互作用来调节细胞和体液免疫反应,是一种用于诊断炎症疾病的新型生物标志物[8]。先前研究表明,Presepsin 对诊断伴有全身炎症疾病(如败血症)具有高敏感性和特异性[9]。值得关注的是,在急性心肌梗死(acute mesenteric ischaemia, AMI)研究中,患者血清 Presepsin 水平显著升高,有望成为 AMI 的新标志物[10]。在心源性休克患者入院 12 h 后,血清 Presepsin 水平达到峰值,表明 AMI 引起的心源性休克伴随着炎症反应的发生[11]。基于以上调研,推测 Presepsin 可能与急性心肌炎的发生发展密切相关。本研究发现,病例组患者血清中 Presepsin 水平显著增加,提示 Presepsin 水平在急性心肌炎患者中异常升高,Presepsin 水平的降低可能预示着临床改善,反映治疗效果[12]。

GDF-15 是 TGF-β 家族的一种细胞因子,在组织和血浆中含量较低,但胎盘和前列腺除外[13]。大多数研究将 GDF-15 作为心血管事件发生的生物标志物[14-15]。Wang 等[16]研究发现在患有心脏病和生长缺陷的儿童血浆中 GDF-15 水平显著高于健康对照组和正常生长性心脏病儿童。Andersson 等[17]研究表明 GDF-15 水平升高与 AMI 发生后 24 h 内心源性猝死的风险增加相关,可用于指导该疾病的初级干预。基于以上调研,推测 GDF-15 可能参与急性心肌炎的发生发展。本研究结果显示,病例组患者血清中 GDF-15 水平显著增加,提示 GDF-15 可能参与急性心肌炎发病,原因为:急性心肌炎发病及病情进展时,可能导致 GDF-15 代偿性上调,减少心肌细胞的凋亡,从而发挥心肌保护作用。另外,Pearson 分析显示急性心肌炎患者血清 Presepsin 与 GDF-15 水平呈正相关,提示二者可能共同参与急性心肌炎的发生发展。

TNF-α 和 IL-6 二者参与心肌炎性损伤的免疫过程,对于判断心肌炎的发生具有临床指导意义[18]。hs-CRP 可作为诊断病毒性心肌炎及评估病情的指标之一[19]。左室功能降低是心力衰竭的常见原因,超声心动图测量左室功能、结构的准确性较高,但也存

在测量偏差,而 LVEF、LVEDD、LVMI 是预测左室重构的重要指标[20]。本研究中病例组患者血清 IL-6、TNF-α、hs-CRP 水平及 LVEDD、LVMI 显著升高,但 LVEF 显著下降,表明急性心肌炎患者存在炎性反应及心室重构。Pearson 分析显示急性心肌炎患者血清 Presepsin、GDF-15 水平分别与 IL-6、TNF-α、hs-CRP、LVEDD、LVMI 水平呈正相关,均与 LVEF 呈负相关,提示血清 Presepsin、GDF-15 水平在反映炎性反应及左室重构方面有一定的参考价值,二者可能通过影响炎症因子、心功能指标参与急性心肌炎的发生和发展。另外,ROC 曲线分析显示血清 Presepsin 和 GDF-15 水平对急性心肌炎具有一定的诊断价值,二者联合可提高诊断效能,在临床应用中,可考虑联合检测血清 Presepsin 及 GDF-15,以能早期评估及治疗急性心肌炎。

综上所述,急性心肌炎患者血清 Presepsin、GDF-15 水平显著增加,与炎症水平、左室重构密切相关,对急性心肌炎有一定的诊断价值,两者联合诊断效能更高,但由于样本量有限,该结果仍需进一步验证。

利益冲突　无

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