Application value of hypersensitive C-reactive protein, lactic acid and myoglobin in the combined detection of myocarditis

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Abstract. Application value of hypersensitive C-reactive protein (hs-CRP), blood lactic acid (LAC) and myoglobin (Mb) in the combined detection of myocarditis was explored. A total of 107 patients with suspected myocarditis treated in The Second Nanning People's Hospital from January 2015 to December 2017 were retrospectively analyzed, of whom 81 patients diagnosed with myocarditis were enrolled into the research group, and 26 non-myocarditis individuals were enrolled into the control group. Fasting venous blood was drawn from all patients to detect the hs-CRP, LAC and Mb, and their levels were compared and analyzed between the two groups. Moreover, the coincidence rate, sensitivity and specificity of single detection and combined detection by hs-CRP, LAC and Mb in the diagnosis of myocarditis were compared and analyzed. There were no significant differences in the sex, age, smoking status, alcohol consumption, chest distress, palpitation, angina and dyspnea between the two groups (P>0.05), proving that patients in both groups were comparable. The levels of hs-CRP, LAC and Mb in the research group were significantly higher than those in the control group, displaying statistically significant differences (P<0.05). According to the receiver operating characteristic (ROC) curve, the area under the curve (AUC), coincidence rate, sensitivity and specificity in the diagnosis of myocarditis, respectively, were 0.610 (95% CI: 0.495-0.725), 58.88, 51.85 and 80.77% for hs-CRP, 0.657 (95% CI: 0.551-0.763), 58.88, 54.32 and 73.08% for LAC, 0.747 (95% CI: 0.651-0.843), 69.16, 64.20 and 84.62% for Mb, and 0.773 (95% CI: 0.680-0.867), 76.64, 79.01 and 69.23% for combined detection. Hs-CRP, LAC and Mb are highly expressed in the serum of patients with myocarditis, and their combined detection has guiding significance for the prevention and treatment of myocarditis.

Introduction

Myocarditis is a severe myocardial injury, and the dysfunction of cardiac electrical pathway caused by myocarditis is also one of the major causes of sudden death in young adults (1). In the early stage of the disease, patients only suffer from chest distress and palpitation, so it is often ignored by them. Besides, the diagnosis of non-specific symptoms is difficult, so the optimal treatment opportunity is often missed (2). Currently, the pathogenesis of myocarditis remains unclear in clinic. Myocarditis can be caused by a variety of factors, and it is characterized by acute onset, rapid progression, and even death in severe cases. Therefore, the early diagnosis of myocarditis plays a key role in clinical treatment and prevention (3).

It is very difficult to diagnose myocarditis, and the optimal means of diagnosing the type of myocarditis and determining its cause is an endomyocardial pathological biopsy. However, there is psychological repellence in patients due to the invasive examination and complications (4). C-reactive protein (CRP) is the most commonly-used acute-phase response index in clinic, which is involved in multiple stress responses and serves as an important index for the diagnosis of cardiovascular and cerebrovascular diseases (5). Hypersensitive CRP (hs-CRP) is not affected by diet, time and corticosteroid therapy, which can reflect the severity of cardiovascular and cerebrovascular injury in patients more quickly and effectively (6). Blood lactic acid (LAC) is a product of anaerobic glycolysis closely related to the metabolism and movement, which cannot only detect whether there are disorders in the respiratory system and circulatory system in human body, but also reflect the severity of disease (7). Myoglobin (Mb) is a kind of protein for cell storage and oxygen distribution in mammals, and serves as an important index for myocardial and skeletal muscle injury (8). However, hs-CRP and Mb are non-specific diagnostic indexes, so the single detection has no high diagnostic value in myocarditis. The combined detection can provide more complete indexes for clinicians and high reference value in the diagnosis of myocarditis, so

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Table I. Basic data of patients in the research and control groups [n (%)].

Characteristics	Research group (n=81)	Control group (n=26)	χ^2 value	P-value
Sex			0.090	0.764
Male	44 (54.32)	15 (57.69)		
Female	37 (45.68)	11 (42.31)		
Age (years)			0.104	0.747
<45	63 (77.78)	21 (80.77)		
≥45	18 (22.22)	5 (19.23)		
Smoking status			0.363	0.547
Yes	58 (71.60)	17 (65.38)		
No	23 (28.40)	9 (34.62)		
Alcohol consumption			0.060	0.806
Yes	52 (64.20)	16 (61.54)		
No	29 (35.80)	10 (38.46)		
Chest distress			0.051	0.822
Yes	64 (79.01)	20 (76.92)		
No	17 (20.99)	6 (23.08)		
Palpitation			0.509	0.476
Yes	53 (65.43)	15 (57.69)		
No	28 (34.57)	11 (42.31)		
Angina			0.359	0.549
Yes	49 (60.49)	14 (53.85)		
No	32 (39.51)	12 (46.15)		
Dyspnea			0.708	0.400
Yes	57 (70.37)	16 (61.54)		
No	24 (29.63)	10 (38.46)		
Pathological type			-	-
Viral myocarditis	36 (44.44)	-		
Bacterial myocarditis	15 (18.52)	-		
Immune response myocarditis	12 (14.81)	-		
Idiopathic myocarditis	18 (22.22)	-		

it can be used as an effective means for the early diagnosis and determination of risk factors for prognosis of patients with myocarditis (9). At present, there are few studies on the diagnosis of myocarditis via combined detection of hs-CRP, LAC and Mb. In this study, the expression levels of hs-CRP, LAC and Mb in patients with myocarditis were studied, and the coincidence rate, sensitivity and specificity of single detection and combined detection of hs-CRP, LAC and Mb in the diagnosis of myocarditis were analyzed, so as to determine whether the single detection and combined detection of hs-CRP, LAC and Mb can be used as diagnostic methods for myocarditis, and provide efficient and reliable references for the clinical treatment of patients with myocarditis in the future.

Patients and methods

Data of patients. A total of 107 patients with suspected myocarditis treated in the Second Nanning People's Hospital (Nanning, China) from January 2015 to December 2017 were selected, of whom 81 patients diagnosed with myocarditis were enrolled into the research group, and 26 non-myocarditis individuals were enrolled into the control group. In the research group, there were 37 females and 44 males aged 22-64 years with an average of 37.91±4.72 years. In the control group, there were 11 females and 15 males aged 19-63 years with an average of 41.17±4.38 years. Inclusion criteria were: patients diagnosed with suspected myocarditis via electrocardiography, echocardiography and X-ray examination, patients with complete data, patients aged >18 years, and patients who did not receive relevant treatments before admission. Exclusion criteria were: patients with other basic heart disease, pregnant or lactating patients, patients with other severe diseases or tumors, patients who were unwilling to undergo endomyocardial biopsy to diagnose myocarditis, or patients with communication or cognitive disorders.

This study was approved by the Ethics Committee of The Second Nanning People's Hospital. All the patients and their families signed an informed consent and cooperated with medical workers in relevant diagnoses and treatments.

Table II. Comparisons of expression levels of hs-CRP, LAC and Mb between the two groups.

Factors	Research group (n=81)	Control group (n=26)	t value	P-value
hs-CRP (mg/l)	10.79±1.63	9.67±1.22	3.222	0.002
LAC (mg/l)	106.24±14.08	98.15±11.43	2.659	0.009
Mb (μg/l)	82.31±7.15	77.87±5.54	3.372	0.001

Table III. Effectiveness of single detection by hs-CRP.

Factors	Pathological results (+)	Pathological results (-)	Total
hs-CRP diagnosis (+)	42	5	47
hs-CRP diagnosis (-)	39	21	60
Total	81	26	107

Table IV. Effectiveness of single detection by LAC.

Factors	Pathological results (+)	Pathological results (-)	Total
LAC diagnosis (+)	44	7	51
LAC diagnosis (-)	37	19	56
Total	81	26	107

Table V. Effectiveness of single detection by Mb.

Factors	Pathological results (+)	Pathological results (-)	Total
Mb diagnosis (+)	52	4	56
Mb diagnosis (-)	29	22	51
Total	81	26	107

Table VI. Effectiveness of combined detection.

Factors	Pathological results (+)	Pathological results (-)	Total
Combined diagnosis (+)	64	8	72
Combined diagnosis (-)	17	18	35
Total	81	26	107

Statistical analysis. SPSS 18.1 (Beijing ND Times Technology Co., Ltd.) software system was used for the statistical analysis. The basic enumeration data of patients were expressed as percentage (%), and Chi-square test was adopted. The expression levels of hs-CRP, LAC and Mb were expressed as mean ± standard deviation, and t-test was used for the difference between the two groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of clinical data of patients. To make the experimental results accurate and reliable, the sex, age, smoking status, alcohol consumption, chest distress, palpitation, angina and dyspnea were compared between the two groups, and it was found that there were no significant differences (P>0.05), proving that patients in both groups were comparable. The basic data of patients are shown in Table I.

Comparison of expression levels of hs-CRP, LAC and Mb between the two groups. The expression levels of hs-CRP, LAC and Mb in the research group were all significantly higher than those in the control group (10.79±1.63 mg/l vs. 9.67±1.22 mg/l, 106.24±14.08 mg/l vs. 98.15±11.43 mg/l, 82.31±7.15 μg/l vs. 77.87±5.54 mg/l), and there were statistically significant differences (t=3.222, 2.659 and 3.372, P=0.002, 0.009 and 0.001, respectively) (Table II).

Effectiveness analysis of single and combined detection by hs-CRP, LAC and Mb in the diagnosis of myocarditis. There were 107 patients with suspected myocarditis, including 81 patients pathologically diagnosed with myocarditis and 26 non-myocarditis individuals. There were, respectively, 47, 51 and 56 cases of myocarditis diagnosed in the single detection by hs-CRP, LAC and Mb and there were 72 cases of myocarditis diagnosed in the combined detection. Respectively 42, 44 and 52 cases were correctly diagnosed in the single detection by hs-CRP, LAC and Mb (Table III-VI).

Methods and equipment. Fasting venous blood was drawn from all patients to detect hs-CRP, LAC and Mb, and their levels were compared and analyzed between the two groups. After fasting for 12 h, venous blood was taken, placed at room temperature for 30 min and centrifuged at 2,800 x g for 5 min at 20˚C using a centrifugal machine (Beijing TideRadar Technology Co., Ltd.) to separate the serum. The hs-CRP kit was purchased from Shanghai Fanke Biotechnology Co., Ltd. (art. no. GD-XS3103), and hs-CRP was detected via immunoturbidimetry using the XL full-automatic biochemical analyzer (Shanghai Yuyan Instruments Co., Ltd.). The LAC kit was purchased from Shanghai Yubo Biological Technology Co., Ltd. (art. no. YB-60026), and LAC was detected via spectrophotometry using the XL full-automatic biochemical analyzer. The Mb kit was purchased from Shanghai Xinfan Biotechnology Co., Ltd. (art. no. XFSH20581), and Mb was detected via chemiluminescence using the XL full-automatic biochemical analyzer.

Diagnostic criteria. According to relevant literature (9), the criteria in single detection in the diagnosis of myocarditis are as follows: hs-CRP >10 mg/l, LAC >100 mg/l, and Mb>80 μg/l. The criteria in combined detection in the diagnosis of myocarditis are as follows: hs-CRP, LAC and Mb levels are higher than the threshold value.

Table VII. Analysis of coincidence rate, sensitivity and specificity of single and combined detection by hs-CRP, LAC and Mb in the diagnosis of myocarditis.
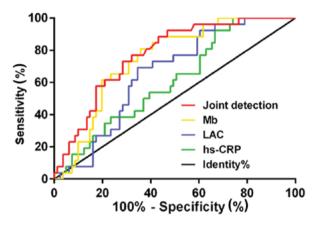
Factors	hs-CRP (%)	LAC (%)	Mb (%)	Combined detection (%)
Diagnostic coincidence rate	58.88	58.88	69.16	76.64
Sensitivity	51.85	54.32	64.20	79.01
Specificity	80.77	73.08	84.62	69.23

Figure 1. According to the ROC curve, the AUC in the diagnosis of myocarditis is 0.610 (95% CI: 0.495-0.725) for hs-CRP, 0.657 (95% CI: 0.551-0.763) for LAC, 0.747 (95% CI: 0.651-0.843) for Mb, and 0.773 (95% CI: 0.680-0.867) for combined detection.

Analysis of coincidence rate, sensitivity and specificity of single and combined detection by hs-CRP, LAC and Mb in the diagnosis of myocarditis. According to the receiver operating characteristic (ROC) curve, the area under the curve (AUC), coincidence rate as well as sensitivity and specificity, respectively, in the diagnosis of myocarditis were 0.610 (95% CI: 0.495-0.725), 58.88, 51.85 and 80.77% for hs-CRP, 0.657 (95% CI: 0.551-0.763), 58.88, 54.32 and 73.08% for LAC, 0.747 (95% CI: 0.651-0.843), 69.16, 64.20 and 84.62% for Mb, and 0.773 (95% CI: 0.680-0.867), 76.64, 79.01 and 69.23% for combined detection (Table VII and Fig. 1).

Discussion

Myocarditis can cause severe hemodynamic damage. The proportion of myocarditis is up to 13% in the cause of sudden death in adolescents, and its global incidence rate is 18.27/100,000 and prevalence rate is 21.83/100,000 (10). Pathogenesis of myocarditis has been studied by a large number of scholars, but its clinical manifestations are non-specific and diverse, and dependent on the range and severity of lesion due to the different etiology, and there may even be no clinical symptoms, making it one of the most challenging cardiovascular diseases (11). Moreover, it is hard to conduct multi-center large-scale experiments due to the limited incidence rate, so myocarditis is a major challenge in the medical field (12).

In this study, a total of 107 patients with suspected myocarditis were retrospectively analyzed, including 81 patients pathologically diagnosed with myocarditis and 26 non-myocarditis patients. The levels of hs-CRP, LAC and Mb were compared and analyzed between the two groups of patients, and the coincidence rate, sensitivity and specificity of single detection and combined detection by hs-CRP, LAC and Mb in the diagnosis of myocarditis were also compared. The expression level of hs-CRP in the research group was significantly higher than that in the control group (10.79±1.63 mg/l vs. 9.67±1.22 mg/l), and there was a statistically significant difference. There were 47 cases of myocarditis diagnosed in the single detection by hs-CRP, and 42 cases were correctly diagnosed. According to the ROC curve, AUC, coincidence rate, sensitivity and specificity in the diagnosis of myocarditis, respectively, were 0.610 (95% CI: 0.495-0.725), 58.88, 51.85 and 80.77% for hs-CRP. hs-CRP is an acute-phase reactive protein synthesized by the liver, and the changes in its expression level can rapidly reflect the subtle changes in the circulatory system. Besides, it is less affected by anti-inflammatory and hormone drugs, which can reflect the severity of cardiovascular injury more sensitively (13). However, hs-CRP is increased in acute myocardial infarction and stress response, so it is not a specific diagnostic index (14).

Gölbasi *et al* (15) reported that the level of hs-CRP in patients with acute myocarditis is increased, and the ST-T changes in more than 2 out of 4 leads (EKGI, II, aVF and V5) indicate the increased risk of myocarditis. The expression level of LAC in the research group was significantly higher than that in the control group (106.24±14.08 mg/l vs. 98.15±11.43 mg/l), and there was a statistically significant difference. There were 51 cases of myocarditis diagnosed in a single detection of LAC, and 44 cases were correctly diagnosed. According to the ROC curve, AUC, coincidence rate as well as sensitivity and specificity in the diagnosis of myocarditis, respectively, were 0.657 (95% CI: 0.551-0.763), 58.88, 54.32 and 73.08% for LAC. In patients with myocarditis, a large number of catecholamines are secreted due to the stimulation of inflammatory factors, thus leading to the increased level of fasting blood glucose. Then the high-level fasting blood glucose promotes anaerobic glycolysis, and a large amount of LAC is produced in the body. The increase in LAC in patients can suggest disorders in the respiratory or circulatory system. However, LAC can be easily affected by blood glucose, so it is not specific in the diagnosis of myocarditis (16). The expression level of Mb in the research group was obviously higher than that in the control group (82.31±7.15 µg/l vs. 77.87±5.54 mg/l), and the difference was statistically significant. There were 56 cases of myocarditis diagnosed in the single detection of Mb, and 52 cases were correctly diagnosed. According to the ROC curve, AUC, coincidence rate as well as sensitivity and specificity in the diagnosis of

myocarditis, respectively, were 0.747 (95% CI: 0.651-0.843), 69.16, 64.20 and 84.62% for Mb. Mb mainly exists in the striated muscle, which is a polypeptide chain widely distributed in myocardial and skeletal muscle tissues (17). As a small-molecule protein containing heme, Mb can display the tissue hypoperfusion and oxygenation dysfunction, so its level increases in the case of shortness of breath or chest pain in patients with myocarditis (18). Related studies (19) have demonstrated that if patients suffer from severe myocardial damage or ventricular systolic dysfunction, the level of Mb is increased, which has a significantly positive correlation with the degree of degeneration or necrosis of myocardial cells. The above research results are similar to this study, proving these findings. There were 72 cases of myocarditis diagnosed in the combined detection, and 64 cases were correctly diagnosed. According to the ROC curve, AUC, coincidence rate as well as sensitivity and specificity in the diagnosis of myocarditis, respectively, were 0.773 (95% CI: 0.680-0.867), 76.64, 79.01 and 69.23% for combined detection. hs-CRP, LAC and Mb are commonly-used indexes reflecting the myocardial damage of patients, as well as reference indexes in the diagnosis of myocarditis (20). According to literature (21), the peaks of hs-CRP, LAC and Mb indicate severe myocardial damage. Berg *et al* (22) conducted a 5-year follow-up study on child patients with myocarditis, and found that hs-CRP, LAC and Mb are risk factors for prognosis of patients. These research results can prove the conclusion in this study that the combined detection has high value in the diagnosis of myocarditis.

In this experiment, the sample size was small due to the limited medical resources in the hospital, so the results may have certain contingency. Therefore, further studies are needed for confirmation.

In conclusion, hs-CRP, LAC and Mb are highly expressed in the serum of patients with myocarditis, and their combined detection has guiding significance for the prevention and treatment of myocarditis.

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Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YaL wrote the manuscript and was also involved in the conception and design of this study. XH and YuL detected and analyzed hs-CRP, LAC and Mb levels. DL and JZ collected and analyzed the general data of patients. LY and YaL were responsible for the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Second Nanning People's Hospital (Nanning, China). Signed informed consents were obtained from the patients or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Dominguez F, Kühl U, Pieske B, Garcia-Pavia P and Tschöpe C: Update on myocarditis and inflammatory cardiomyopathy: Reemergence of endomyocardial biopsy. Rev Esp Cardiol (Engl Ed) 69: 178-187, 2016.
2. Bowles NE and Towbin JA: Molecular aspects of myocarditis. Curr Opin Cardiol 13: 179-184, 1998.
3. Heymans S, Eriksson U, Lehtonen J and Cooper LT Jr: The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol 68: 2348-2364, 2016.
4. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, *et al*: Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 375: 1749-1755, 2016.
5. Guo JG: Detection of cardiac troponin and high-sensitivity C reactive protein in children with viral myocarditis. Nan Fang Yi Ke Da Xue Xue Bao 28: 1076-1077, 2008 (In Chinese).
6. Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y and Miyahara K: C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J 45: 441-445, 2004.
7. Garlotta D: A literature review of poly(lactic acid). J Polym Environ 9: 63-84, 2001.
8. Kottwitz J, Berg J, Baltensperger N, Elhassan M, Kissel CK, Lovrinovic M, Patriki D, Scherff F, Schmied C, Templin C, *et al*: Myoglobin is a strong predictor of extent of late gadolinium enhancement on cardiac magnetic resonance imaging in patients with acute myocarditis. Circulation 136 (Suppl 1): A15156, 2017.
9. Huang GY, Zhang LY, Long-Le MA and Wang LX: Clinical characteristics and risk factors for peripartum cardiomyopathy. Afr Health Sci 12: 26-31, 2012.
10. Sinagra G, Anzini M, Pereira NL, Bussani R, Finocchiaro G, Bartunek J and Merlo M: Myocarditis in clinical practice. Mayo Clin Proc 91: 1256-1266, 2016.
11. Rose NR: Viral myocarditis. Curr Opin Rheumatol 28: 383-389, 2016.
12. Huber SA: Viral myocarditis and dilated cardiomyopathy: etiology and pathogenesis. Curr Pharm Des 22: 408-426, 2016.
13. Henningsen KM, Nilsson B, Bruunsgaard H, Chen X, Pedersen BK and Svendsen JH: Prognostic impact of hs-CRP and IL-6 in patients undergoing radiofrequency catheter ablation for atrial fibrillation. Scand Cardiovasc J 43: 285-291, 2009.
14. Fett JD: Inflammation and virus in dilated cardiomyopathy as indicated by endomyocardial biopsy. Int J Cardiol 112: 125-126, 2006.
15. Gölbasi Z, Uçar O, Keles T, Sahin A, Cagli K, Camsari A, Diker E and Aydogdu S: Increased levels of high sensitive C-reactive protein in patients with chronic rheumatic valve disease: Evidence of ongoing inflammation. Eur J Heart Fail 4: 593-595, 2002.
16. Donald KW, Gloster J, Harris EA, Reeves J and Harris P: The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease. Am Heart J 62: 494-510, 1961.
17. Al Shamkhani W, Ajaz Y, Saeed Jafar N and Roy Narayanan S: Myocarditis and rhabdomyolysis in a healthy young man caused by salmonella gastroenteritis. Case Rep Infect Dis 2015: 954905, 2015.

18. Odum EP and Young EE: Elevated cardiac troponin I, creatine kinase and myoglobin and their relationship with cardiovascular risk factors in patients with type 2 diabetes. Diabetes Metab Syndr 12: 141-145, 2018.
19. Shorie M, Kumar V, Priyanka S and Ganguli AK: Carbon quantum dots-mediated direct fluorescence assay for the detection of cardiac marker myoglobin. Curr Sci 108: 1595-1596, 2015.
20. Khan R, Pal M, Kuzikov AV, Bulko T, Suprun EV and Shumyantseva VV: Impedimetric immunosensor for detection of cardiovascular disorder risk biomarker. Mater Sci Eng C 68: 52-58, 2016.
21. Thomas KN, Cotter JD, Williams MJ and van Rij AM: Diagnosis, incidence, and clinical implications of perioperative myocardial injury in vascular surgery. Vasc Endovascular Surg 50: 247-255, 2016.
22. Berg J, Kottwitz J, Baltensperger N, Kissel CK, Lovrinovic M, Mehra T, Scherff F, Schmied C, Templin C, Lüscher TF, *et al*: Cardiac magnetic resonance imaging in myocarditis reveals persistent disease activity despite normalization of cardiac enzymes and inflammatory parameters at 3-month follow-up. Circ Heart Fail 10: 10, 2017.