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Original Contribution

Higher serum level of myoglobin could predict more severity and poor outcome for patients with sepsis☆,☆☆

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ABSTRACT

Background: There have been sporadic case reports published focusing on myoglobin and sepsis. However, there are no systematic studies evaluating the correlation between myoglobin level and sepsis. This study investigated the correlation between the serum myoglobin level and the severity of septic patients. Next, we assessed the predictive value of the serum myoglobin level for the prognosis of septic patients.
Methods: Seventy septic patients were included and subdivided into the following 3 groups: sepsis group, severe sepsis group, and septic shock group. We collected blood samples at 0, 6, 12, 18, and 24 hours after admission. The serum levels of myoglobin, C-reactive protein, and procalcitonin were analyzed. We also evaluated the levels of malondialdehyde, which is a biomarker for oxidative stress.
Results: The data indicate that the myoglobin level increased gradually within 24 hours after admission. The median myoglobin levels of the sepsis, severe sepsis, and septic shock groups were 635.7, 903.6, and 1094.8 μg/L, respectively ($P < .05$). The elevated myoglobin level was positively correlated with Sequential Organ Failure Assessment score, C-reactive protein, and procalcitonin level in septic patients. The increased myoglobin level was also associated with the mortality of septic patients. The Kaplan-Meier survival curves indicated that patients with high myoglobin levels had an elevated mortality rate. Moreover, an elevated myoglobin level indicated more oxidative stress.
Conclusions: The myoglobin level can be detected in the early stage of sepsis and may serve as a potential biomarker for evaluating sepsis severity and further prognosis.

1. Introduction

Myoglobin is a heterodimer composed of a peptide chain and a heme group. The molecular weight is approximately 17.9 kDa. The protein is found in the cytoplasm of myocardial and skeletal muscle cells [1]. When muscle tissue damage occurs, the cytosolic myoglobin is rapidly released into the blood circulation [2]. Thus, myoglobin is often used as a biomarker in the diagnosis of myocardial injury in clinical settings [3]. Recent studies have shown that, in addition to myocardial and skeletal muscle injury, there are also elevated serum myoglobin levels in the following diseases: severe infection, systemic inflammation, organ failure, severe trauma, gastrointestinal bleeding, and severe pancreatitis [4]. Critical diseases may cause ischemia, hypoxia, local hypoperfusion, endotoxin, and other pathogenic factors. In addition, excessive inflammatory responses may induce the secretion of cytokines and elevate reactive oxygen species, which leads to oxidative stress [5–6]. Oxidative stress causes a positive feedback loop by aggravating tissue injury and causing further myoglobin outflow into the bloodstream. Therefore, elevated myoglobin levels in critical diseases indicate widespread and severe injury [7–8]. The myoglobin protein catalyzes oxidation reactions and hydrogen oxidation reactions in conditions of oxidative stress. The peroxidase-like activity of myoglobin may be involved in oxidative stress and promotes the generation of ferroferric oxide, lipid peroxides, isoprostanes, and other cytotoxic products. Excessive myoglobin levels may aggravate the injury caused by oxidative stress [9–11]. Therefore, monitoring serum myoglobin levels may facilitate our understanding of critical disease progression and may be used to evaluate the severity of critical diseases or multiple organ injury. Although sporadic case reports have been published, there are no systematic studies examining the correlation between serum myoglobin level and sepsis. Therefore, this study investigated the correlation between the serum myoglobin level and severity of septic patients. We also determined the clinical prognostic value of myoglobin as a potential biomarker.

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2. Materials and methods

2.1. Patient selection

The study population consisted of 70 consecutive septic patients who were admitted to the First Hospital of Lanzhou University between April 2013 and May 2014. The diagnosis of sepsis was based on the guideline of American College of Chest Physicians and the American Society of Critical Care Medicine. *Sepsis* was defined as the presence of systemic inflammatory response syndrome (SIRS) associated with infection. *SIRS* was further defined as the presence of 2 or more of the following criteria: temperature <36.8°C or >38.8°C, heart rate >90 beats per minute in the absence of a pacemaker, respiratory rate >20 times per minute or $Paco_2$ less than 4.3 kPa (32 mm Hg), and white blood cell count $>2 \times 10^9$/L or $<4 \times 10^9$/L, or >10% immature band cells. The patients included in the study were subdivided into the following 3 groups: sepsis group, severe sepsis group, and septic shock group. *Sepsis complicated with organ dysfunction* was defined as severe sepsis in accordance with the criteria of the 2001 American Society of Critical Care Medicine/European Society of Intensive Care Medicine/American Thoracic Society/Surgical Infection Society International Sepsis Definitions Conference. In addition, sepsis complicated with hypotension refractory to adequate volume resuscitation in the absence of an alternate cause is termed *septic shock*. The exclusion criteria in this study were the following: (1) age <18 years; (2) coronary heart disease, myocardial infarction, or coronary syndrome; (3) malignant tumors; (4) rhabdomyolysis; (5) pregnancy; and (6) autoimmune disease.

2.2. Study design

The patients' age, sex, Sequential Organ Failure Assessment (SOFA) score, and other clinical information were recorded. The patients received routine vital sign monitoring, breathing and blood gas parameter testing, and pathogen cultures at admission. The blood samples were collected at 0, 6, 12, 18, and 24 hours after admission. The serum myoglobin, C-reactive protein (CRP) and procalcitonin (PCT) levels were also analyzed. The malondialdehyde (MDA) level was evaluated as a biomarker for oxidative stress. All patients provided informed consents, and the protocol was approved by the Ethics Committee of the First Hospital of Lanzhou University.

2.3. Statistical analysis

The data analyses were performed using SPSS18.0 software (SPSS Inc, Chicago, IL). The data with a normal distribution were expressed as the mean ± SD, and data with a nonnormal distribution were expressed as the median. A 1-way analysis of variance was performed to compare multiple groups and was followed by the least significant difference test for parametric data. The nonparametric data were analyzed using the Mann-Whitney test to compare groups. The difference in frequency distribution between groups was determined using the χ^2 test. A Spearman correlation analysis was also performed. The 28-day survival was calculated using the Kaplan-Meier curves and the log-rank test. A P value < .05 was considered statistically significant.

3. Results

The demographic characteristics of all included patients are shown in Table. There were 20, 35, and 15 patients in the sepsis, severe sepsis, and septic shock groups, respectively. The age, sex, site of infection, and pathogen culture results were comparable among groups ($P > .05$). The SOFA score, serum CRP, and PCT levels (at 24 hours after admission) were higher in the septic shock group than in the sepsis and severe sepsis groups ($P < .05$). The sepsis group had the lowest SOFA score, CRP, and PCT level ($P < .05$).

3.1. The serum myoglobin level is elevated in septic patients

Fig. 1 shows the blood samples collected from patients at the indicated time points after admission. The data demonstrate that the median myoglobin level increased significantly with time (510.6 μg/L at 0 hour vs 541.5 μg/L at 6 hours vs 673.4 μg/L at 12 hours vs 764.2 μg/L at 18 hours vs 886.5 μg/L at 24 hours, all Ps < .05).

3.2. The elevated myoglobin level is correlated with the severity of sepsis

At 24 hours after admission, the median levels of myoglobin in patients with sepsis, severe sepsis, and septic shock were 635.7, 903.6, and 1094.8 μg/L, respectively ($P < .05$, Fig. 2). As shown in Fig. 3, the septic shock group displayed higher SOFA score, CRP, and PCT levels than the sepsis and severe sepsis groups ($P < .05$). The correlation analysis (Fig. 4) showed that the myoglobin level (at 24 hours after admission)

Table
Clinical characteristics of the subjects enrolled

	Sepsis patients ($n = 70$)			P value
	Sepsis subgroup ($n = 20$)	Server subgroup ($n = 35$)	Septic shock subgroup ($n = 15$)	
Median age (y)	52 (36-62)	55 (40-71)	54 (42-69)	NS
Sex				
Male	9	20	7	NS
Female	11	15	8	
Blood culture				
Negative	2	2	3	NS
Bacterial (G+)	6	10	3	
Bacterial (G−)	10	20	8	
Fungi	2	3	1	
Primary infection site				
Lower respiratory tract	2	5	4	NS
upper respiratory tract	3	3	2	
Urinary tract	4	8	3	
Abdomen	11	19	6	
SOFA score	6 (4-8)	7 (5-10)	9 (6-11)	<.05
CRP (mg/L)	72.3 (53.2-91.3)	95.5 (57.5-119.9)	135.7 (100.1-158.3)	<.05
PCT (μg/L)	2.9 (0.9-5.7)	6.8 (3.4-11.6)	12.8 (9.9-18.3)	<.05
Median ICU stay (d)	10 (6-18)	15 (15-22)	20 (18-27)	<.05
28-d survival				
Yes	15	25	5	<.05
No	5	10	10	

Abbreviations: ICU, intensive care unit; NS, no significance.