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Original Article

Predictive value of serum myoglobin and lactate dehydrogenase in rhabdomyolysis-induced acute kidney injury from severe heatstroke

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Abstract: Objective: To explore the predictive utility of serum myoglobin (Mb) and lactate dehydrogenase (LDH) for acute kidney injury (AKI) secondary to rhabdomyolysis (RM) in severe heatstroke patients. Methods: A retrospective analysis of 58 RM patients with severe heatstroke at Shanghai Ninth People's Hospital from June 2019 to May 2022 was conducted. Patients were categorized into AKI and non-AKI groups. Laboratory indices were compared, and receiver operating characteristic (ROC) curves were used to assess the predictive value of serum biomarkers for AKI. Results: Creatine kinase, Mb, LDH, creatinine, and blood urea nitrogen levels were significantly higher in the AKI group ($P<0.05$). Serum Mb and LDH were positively correlated with serum creatinine ($r=0.6772$ and $r=0.6816$, respectively; $P<0.05$). The area under the ROC curve (AUC) for serum Mb was 0.6692 (95% CI: 0.5253-0.8131) with a cut-off of 1024 ng/ml, while for LDH it was 0.8277 (95% CI: 0.7182-0.9371) with a cut-off of 1342 U/L. Combining serum Mb and LDH improved the AUC to 0.9116 (95% CI: 0.8219-1.001). Conclusion: Serum Mb and LDH levels are elevated in RM-induced AKI following severe heatstroke, and their combination offers substantial predictive value for AKI in these patients.

Keywords: Serum myoglobin, lactate dehydrogenase, acute kidney injury, rhabdomyolysis, severe heatstroke

Introduction

Heatstroke is a clinical syndrome characterized by an imbalance between heat production and heat dissipation under prolonged exposure to high temperature or humidity [1]. It primarily results from excessive endogenous heat production and reduced heat stress tolerance, leading to heat-induced cellular necrosis and apoptosis [2]. This imbalance, if prolonged, exacerbates the symptoms of heatstroke, potentially progressing to severe heatstroke [3]. Severe heatstroke disrupts thermoregulation and water-electrolyte balance, often causing rhabdomyolysis (RM), nervous system dysfunction, and multi-organ damage [4]. RM, a hallmark of severe heatstroke, involves primary or secondary skeletal muscle damage, releasing potentially toxic substances into the bloodstream. This condition is marked by striated muscle injury and muscle fiber necrosis, causing substantial cellular content release into the renal tubules, leading to acidic urine deposition and renal obstruction, subsequently precipitating acute kidney injury (AKI) [5]. AKI, a critical RM complication, has an incidence rate of 13%-50% and a mortality rate of 20%-50% [6]. The clinical manifestations of RM-induced AKI, such as oliguria, anuria, and dark urine, are often non-specific, contributing to a high rate of clinical underdiagnosis. This underdiagnosis delays optimal treatment timing and increases mortality risk. Thus, early prediction of AKI in severe heatstroke-associated RM is crucial for improving clinical outcomes.

Myoglobin (Mb), abundant in skeletal and cardiac muscles, facilitates oxygen transport and storage within muscle cells. Its levels can surge due to strenuous exercise, hyperthermia, or muscle damage [7, 8]. Lactate dehydrogenase (LDH), a glycolytic enzyme found in various tissues, catalyzes the conversion of pyruvate to lactic acid [9]. It is associated with conditions

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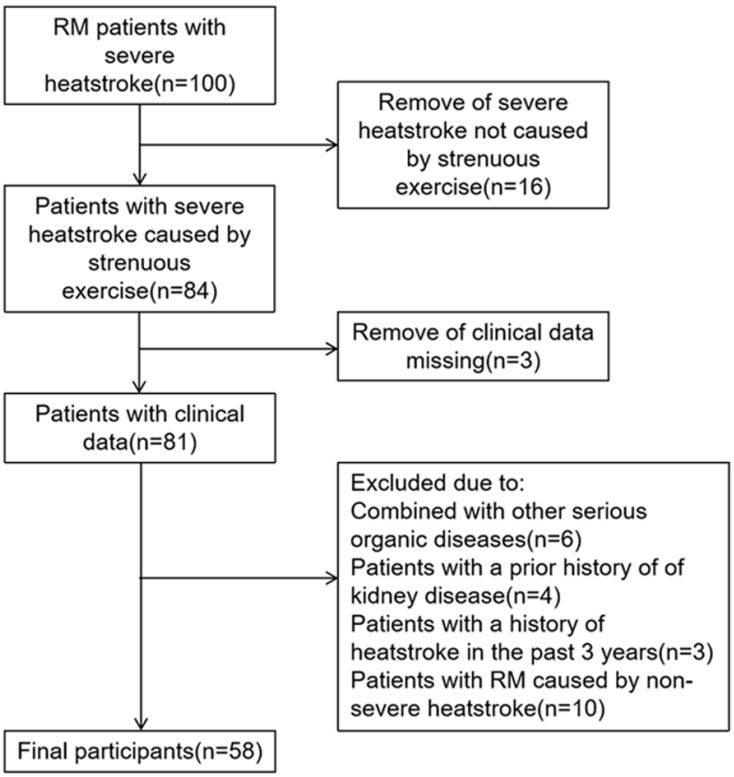

Figure 1. Flowchart of the study process. RM: rhabdomyolysis.

Table 1. Clinical data (n, %, $\bar{x}\pm s$)

Group	Non-AKI group (n=36)	AKI group (n=22)	χ^2/t value	*P* value
Sex			0.056	0.814
Male	24 (66.67%)	14 (63.64%)		
Female	12 (33.33%)	8 (36.36%)		
Age (years)	52.03±6.06	53.23±4.66	0.795	0.429
BMI (kg/m^2)	25.58±2.35	25.24±2.41	0.529	0.598
RM diagnosis time (h)	49.83±6.21	50.64±6.17	0.483	0.630
Underlying diseases				
Hypertension	19 (52.78%)	11 (50.00%)	0.042	0.837
Diabetes	14 (38.89%)	9 (40.91%)	0.023	0.879
Coronary heart disease	10 (27.78%)	6 (27.27%)	0.002	0.967
GCS score (points)	12.78±1.38	12.36±1.30	1.149	0.255

Note: t: data from t-test; χ^2: data from chi-square test; AKI: acute kidney injury; RM: rhabdomyolysis; BMI: body mass index; GCS: Glasgow coma scale.

like myocardial injury and sepsis, serving as a significant inflammation marker [10, 11].

Serum creatinine (Scr) is commonly used to assess kidney function clinically; however, it lacks sensitivity and only significantly increases with substantial kidney dysfunction, demonstrating a pronounced lag. Both Mb and LDH, as byproducts of rhabdomyolysis (RM), offer more timely insights into acute kidney injury (AKI) onset than Scr alone. Therefore, monitoring patient LDH and Mb levels can facilitate early AKI detection in RM scenarios. While some studies have indicated the efficacy of Mb and LDH in evaluating heatstroke-induced AKI [12, 13], comprehensive research on their combined impact in severe heatstroke RM patients remains limited. This study aims to address this gap by retrospectively analyzing data from 58 severe heatstroke patients with RM, focusing on the predictive value of Mb and LDH for AKI incidence.

Materials and methods

Research subjects

This study retrospectively analyzed data from 58 rhabdomyolysis (RM) patients with severe heatstroke admitted to Shanghai Ninth People's Hospital between June 2019 and May 2022 (**Figure 1**). Patients were categorized into non-AKI and AKI groups based on the occurrence of AKI. This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital.

Inclusion criteria included patients with severe heatstroke induced by strenuous exercise and exhibiting RM-related symptoms such as muscle soreness, pain, stiffness, weakness, and tea- or soy-sauce-colored urine, with potential muscle swelling and compartment syndrome in advanced stages. Comprehensive clinical data including symptoms, medical history, physical examination, and laboratory findings were required.

Exclusion criteria encompassed individuals with significant organic diseases, a history of

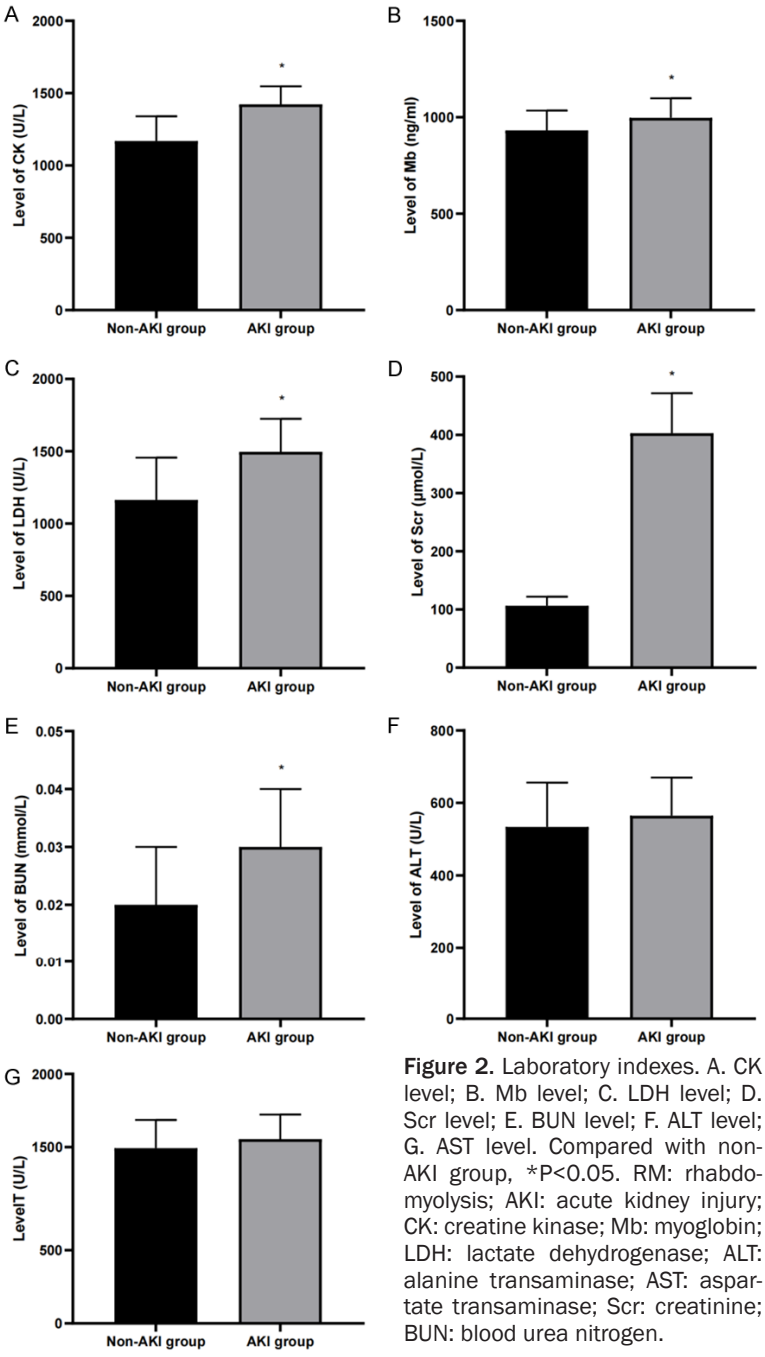

Figure 2. Laboratory indexes. A. CK level; B. Mb level; C. LDH level; D. Scr level; E. BUN level; F. ALT level; G. AST level. Compared with non-AKI group, *P<0.05. RM: rhabdomyolysis; AKI: acute kidney injury; CK: creatine kinase; Mb: myoglobin; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate transaminase; Scr: creatinine; BUN: blood urea nitrogen.

kidney disease, previous heatstroke within the last three years, or RM not resulting from severe heatstroke.

AKI is diagnosed based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria: a rise in Scr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours, an increase in Scr to ≥1.5 times the baseline within the previous 7 days, or urine output <0.5 ml/kg/hour for 6 hours [14].

Diagnostic criteria for severe heatstroke

Severe heatstroke is diagnosed in patients who, after high-intensity exercise in hot and humid conditions, exhibit severe central nervous system dysfunction (e.g., unconsciousness, convulsions, delirium), core temperature above 40°C, increased skin temperature or continuous sweating, significant liver transaminase elevation, marked platelet reduction, rapid onset of disseminated intravascular coagulation, muscle symptoms (weakness, pain), tea-colored urine, and creatine kinase (CK) levels exceeding 5 times the norm [15].

Data collection

Clinical and disease data were obtained from electronic medical records, reviewed by trained professionals. Recorded patient data included sex, age, body mass index (BMI), time of RM diagnosis, underlying diseases, and Glasgow Coma Scale (GCS) score.

Laboratory indices

Laboratory and disease data, gathered from electronic medical records and vetted by professionals, included post-admission serum CK, Mb, LDH, alanine transaminase (ALT), aspartate transaminase (AST), Scr, and blood urea nitrogen (BUN). The correlation between these indices and Scr in the AKI group was examined.

Statistical analysis

Data were analyzed using SPSS 22.0, with measurement data expressed as mean ± SD and compared using the t-test. Count data were expressed in percentages and analyzed with the χ^2 test. Pearson's analysis assessed the

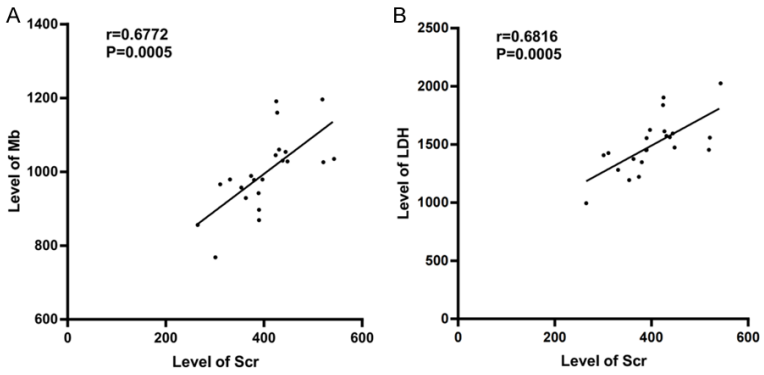

Figure 3. Correlation between serum Mb, LDH levels and Scr in RM patients with severe heatstroke complicated with AKI. A. Relationship between serum Mb and Scr; B. Relationship between serum LDH and Scr. RM: rhabdomyolysis; Mb: myoglobin; LDH: lactate dehydrogenase; Scr: creatinine.

correlation of laboratory indices with Scr in the AKI group, while the receiver operating characteristic (ROC) analysis evaluated the predictive efficacy of serum markers for AKI. ROC curve comparisons were made using DeLong's test, with $P<0.05$ denoting statistical significance.

Results

Clinical data

In the study of 58 severe heatstroke patients with RM, 22 (37.93%) developed AKI. There were no significant differences in sex, age, BMI, time of RM diagnosis, underlying diseases, and GCS score between the AKI and non-AKI groups ($P>0.05$), as detailed in **Table 1**.

Laboratory indexes

No significant differences were found in ALT and AST levels between the groups ($P>0.05$). However, CK, Mb, LDH, Scr, and BUN levels were significantly higher in the AKI group ($P<0.05$), as illustrated in **Figure 2**.

Correlation between serum Mb, LDH levels, and Scr in RM patients with severe heatstroke and AKI

In RM patients with severe heatstroke who developed AKI, serum Mb and LDH levels showed a positive correlation with Scr ($r= 0.6772$ and $r=0.6816$, respectively; $P<0.05$), as depicted in **Figure 3**.

Predictive efficacy of serum Mb and LDH levels for AKI in RM patients with severe heatstroke

The area under the curve (AUC) for serum Mb in predicting AKI in RM patients with severe heatstroke was 0.6692 (95% CI: 0.5253-0.8131), with a cut-off point of 1024 ng/ml. For serum LDH, the AUC was 0.8277 (95% CI: 0.7182-0.9371), with a cut-off point of 1342 U/L. These findings are summarized in **Table 2** and **Figure 4**.

Predictive efficacy of combined serum Mb and LDH for AKI in severe heatstroke RM patients

The logistic model yielded the combined diagnostic prediction formula: -5.657 - 0.002 * Mb + 0.006 * LDH. The AUC for the combined serum Mb and LDH in predicting AKI among severe heatstroke RM patients was 0.9116 (95% CI: 0.8219-1.001), indicating superior predictive performance compared to Mb alone ($P<0.01$, DeLong's test) and similar to LDH alone ($P>0.05$, DeLong's test), as shown in **Figure 5**.

Discussion

Severe heatstroke patients often develop RM, possibly due to disrupted thermoregulatory center function and loss of water, electrolytes, and membrane channel integrity under prolonged high temperature and thermal radiation, affecting skeletal muscle energy metabolism [16]. Clinically, RM is frequently associated with AKI, attributed to reduced renal perfusion from effective circulatory volume depletion, potentially causing ischemic rhabdomyocyte necrosis and subsequent renal tubular obstruction [17, 18]. Existing biomarkers for AKI in severe heatstroke with RM are often insufficient and can be influenced by various factors. Therefore, identifying effective biomarkers is crucial for improving AKI diagnosis and therapeutic management in severe heatstroke RM patients.

Research by Zorova et al. indicates that Mb accumulation in the kidneys is implicated in RM pathogenesis, with Mb injections in rats inducing AKI, while Mb degradation ameliorates AKI progression and reduces nephrotoxicity [19]. Samuel HU's team, analyzing four cases, observed that Mb, freely filtered by the glomeruli, precipitates in acidic urine, forming tubular casts that obstruct and discolor the

Table 2. Predictive efficacy of serum Mb and LDH levels for AKI in RM patients with severe heatstroke

Variable	AUC	Asymptotic 95% confidence interval		Standard error	Progressive Sig	Sensitivity	Specificity	Youden index	Cut-off point
		Lower limit	Upper limit						
Mb	0.6692	0.5253	0.8131	0.07340	0.03181	0.4545	0.8611	0.3156	1024
LDH	0.8277	0.7182	0.9371	0.05584	<0.0001	0.8182	0.7778	0.5960	1342

Note: AUC: area under curve; Mb: myoglobin; LDH: lactate dehydrogenase; RM: rhabdomyolysis.

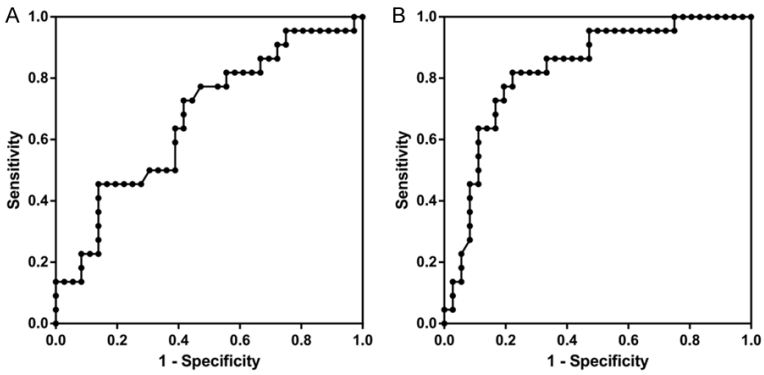

Figure 4. Predictive efficacy of serum Mb and LDH levels for AKI in RM patients with severe heatstroke. A. Predictive efficacy of serum Mb level for AKI in RM patients with severe heatstroke; B. Predictive efficacy of serum LDH level for AKI in RM patients with severe heatstroke. RM: rhabdomyolysis; Mb: myoglobin; LDH: lactate dehydrogenase; Scr: creatinine; AKI: acute kidney injury.

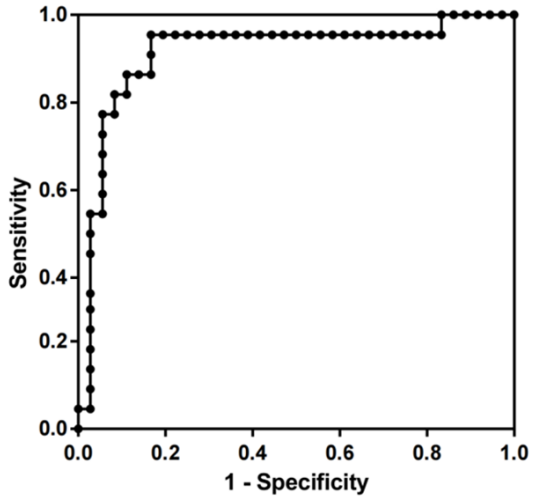

Figure 5. Predictive efficacy of serum Mb combined with LDH level for AKI in RM patients with severe heatstroke. RM: rhabdomyolysis; Mb: myoglobin; LDH: lactate dehydrogenase; Scr: creatinine; AKI: acute kidney injury.

urine. Clinically, it's vital to enhance renal blood flow, alkalize the urine to improve Mb solubility, and expedite its removal [20].

In this study, Mb levels were higher in the AKI group compared to the non-AKI group. The probable reasons are as follows: ① Severe heatstroke causing extensive skeletal muscle damage results in substantial Mb release into the bloodstream, reaching the renal tubules and combining with urinary proteins to form casts, which depend on Mb concentration. This can increase renal capsule pressure and reduce glomerular filtration rate [21]. ② High Mb levels can induce oxidative stress, leading to the production of pathogenic small-molecule cytotoxins, causing tissue stress injury. Furthermore, Mb's toxic effects directly damage renal tubular epithelium, causing mechanical blockage of the tubules [22, 23]. ③ In RM patients, muscle cell membrane damage and reduced effective blood volume activate the renin-angiotensin-aldosterone system. Elevated Mb levels may inhibit nitric oxide synthesis, causing renal ischemia and triggering inflammatory responses, thus promoting AKI development [24, 25]. Furthermore, an increase in serum LDH was observed in severe heatstroke RM patients with AKI. LDH, a metalloenzyme primarily found in the kidneys and liver, facilitates the conversion of pyruvate to lactic acid during glycolysis [26]. Its tissue-specific expression means LDH levels vary across different tissues. Elevated LDH indicates functional impairment due to conditions like infection, hemorrhage, RM, liver and kidney issues, respiratory coagulation disorders, or malignancies [27]. In severe heatstroke, vascular endothelial damage leads to increased secretion of tissue factors and collagenase, causing coagulation abnormalities and vascular dysfunction, which

in turn contributes to renal hypoperfusion [28]. Vascular endothelial injury in AKI disrupts tissue and cell integrity, increases cell membrane permeability, and significantly raises serum LDH levels [29, 30]. Studies have shown that LDH is indicative of the extent of tissue and cell damage and serves as a vital marker for monitoring disease severity [31].

The study found that in severe heatstroke RM patients with AKI, serum Mb and LDH levels were positively correlated with Scr. The AUC for predicting AKI using serum Mb and LDH levels were 0.6692 and 0.8277, respectively, indicating their role in AKI development and their effectiveness as early AKI biomarkers. Combining Mb and LDH yielded the highest AUC of 0.9116 for AKI prediction in severe heatstroke RM patients, enhancing sensitivity and specificity over individual markers. This combination offers a more reliable prediction for AKI onset in severe heatstroke with RM. Serum Mb and LDH testing are advantageous due to ease, cost-effectiveness, predictive efficiency, and practicality.

While the combined Mb and LDH AUC did not statistically differ from LDH alone, the combined AUC exceeding 0.9 suggests superior predictive capability with the addition of new biomarkers. LDH and Mb facilitate early AKI diagnosis before noticeable Scr level increases. Early identification of high-risk patients is possible through monitoring Scr, Mb, and LDH levels, alongside clinical and imaging assessments, aiding in AKI management and potentially improving patient outcomes.

In conclusion, elevated serum Mb and LDH levels in severe heatstroke RM patients with AKI highlight their predictive value for AKI. Given the retrospective nature and small sample size of this study, further research with larger, multicenter cohorts is needed to confirm these findings and address potential confounders.

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Disclosure of conflict of interest

None.

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