Clinical implications of serum myoglobin in trauma patients: A retrospective study from a level 1 trauma center

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ABSTRACT

Background: We aimed to study the clinical implication of high serum myoglobin levels in trauma patients.

Methods: A retrospective analysis was conducted on data from trauma patients who were admitted to a level 1 trauma center between January 2012 and December 2015. A receiver operating characteristic (ROC) curve analysis was performed for the optimum myoglobin cutoff plotted against hospital length of stay of >1 week. Patients were divided into two groups (Group 1; low vs. Group 2; high myoglobin), and a comparative analysis was performed.

Results: There were 898 patients who met the inclusion criteria with a mean age of 35.9 ± 14.6 years. Based on ROC, the myoglobin optimum cutoff was 1000 ng/ml (64% of patients were in Group 1 and 36% in Group 2). The mean myoglobin level was 328 ng/ml in patients with the Injury Severity Score (ISS) <15 versus 1202 ng/ml in patients with ISS ≥15 (P < 0.001). Patients in Group 2 had higher ISS (22.2 ± 10 vs. 18.8 ± 10), more musculoskeletal injuries (18.3% vs. 4.2%), more blood transfusion (74% vs. 46.5%), intubation (57% vs. 46.5%), and sepsis (12% vs. 7.3%). The length of hospital stays was significantly higher in Group 2, but mortality was comparable. High myoglobin levels had a crude odd ratio 2.41; 95% confidence interval (1.470–3.184) for a longer hospital stay with a positive predictive value of 89% and a specificity of 77%.

Conclusions: One-third of the admitted trauma patients have elevated serum myoglobin level, which is associated with the prolonged hospital stay. The discriminatory power of myoglobin value of 1000 in trauma is fair, and further prospective assessments are needed.

Key Words: Hospital length of stay, injury, myoglobin, rhabdomyolysis, trauma

INTRODUCTION

Myoglobin is a muscle protein released into circulation due to damage to the muscles following either by inherited causes or by acquired etiology, mainly trauma.\(^1\) Rhabdomyolysis is a serious syndrome in which muscle fiber lysis occurs, and their contents are released into the bloodstream, often diagnosed with elevated creatine kinase (CK) and myoglobin levels. Disproportionately higher burden of traumatic injuries among males puts...
them at high risk of high serum myoglobin level and its complications. The main sources for higher myoglobin release into circulation are extremities and trunk. Although there is no guideline yet, delayed diagnosis and treatment of patients with elevated myoglobin level may result in high morbidity and mortality since it causes acute kidney injury (AKI), compartment syndrome, sepsis, acute respiratory distress syndrome (ARDS), or pneumonia.[1]

The clinical consequences of high serum myoglobin are not well defined due to the lack of clinical diagnostic criteria and prognostic indicators and well-established treatment guidelines. Treatment of rhabdomyolysis associated high serum myoglobin varies considerably depending on the clinical scenario from close observation to active interventions such as dialysis and treatment of complications. However, the distinction between cases who will recover quickly and uncomplicated and those who will have prolonged hospital stay due to significant myoglobin level may be difficult early in the management. Since every injury is unique with different degrees of associated muscle damage; it is difficult to develop appropriate precise decision-making algorithm for treatment, and therefore, risks of rhabdomyolysis often remain unidentified on the initial presentation. Interestingly, there is a paucity of information in the literature on cutoff levels of myoglobin to determine significant muscle damage. In this study, we retrospectively reviewed the injury characteristics, complications, and outcome of trauma patients based on myoglobin level from a single institute over 4 years. We hypothesized that a high myoglobin level is associated with the prolonged hospital stay. The study aims to identify patients’ characteristics, complications associated with elevated serum myoglobin level and in-hospital outcomes.

**METHODS**

Following required institutional approval, data were acquired retrospectively for all trauma patients identified from the trauma registry database who were admitted to the Hamad Trauma Center (HTC) between January 2012 and December 2015. The HTC is the national Level 1 trauma center facility in Qatar, which admits and treats all patients with traumatic injury in the country. Serum myoglobin was checked for trauma patients on admission to our center, based on the physician’s discretion; however, there is no institutional protocol for that.

There is a lack of specific criteria to diagnose rhabdomyolysis in trauma settings, and therefore, a combination of clinical and laboratory data is used. Serum CK levels exceeding five times the upper limit of normal levels are often used for the diagnosis. However, in our patient population, CK level was not routinely requested along with myoglobin, and the diagnosis usually relied on the combination of clinical signs and symptoms and myoglobin level. Only the maximum or peak CK levels were reported in this study because of the lack of availability of data. AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 h or urine output of <0.5 mL/kg/h for >6 h. Our study included trauma patients (14 years and above) with serum myoglobin level order written with admission order. Children (<14 years) and those who do not have a test for serum myoglobin on admission were excluded. If the myoglobin level was above the normal range (reference range was 72 ng/mL), it was checked every 8 h until it was normalized. On arrival, all trauma patients underwent a thorough clinical assessment and resuscitation according to advanced trauma life support guidelines.[2] Collected data included demographic information (age, gender, and nationality); injury characteristics such as the mechanism of injury, injured body sites; injury characteristics Glasgow Coma Score (GCS), Abbreviated Injury Score (AIS), and Injury Severity Score (ISS); management (blood transfusion, Open Reduction and Internal Fixation Surgery [ORIF], hemodialysis and intubation); complications such as compartment syndrome, sepsis, ARDS, pneumonia, and AKI; relevant laboratory findings and outcomes including intensive care unit (ICU) days, ventilator days, hospital length of stay (LOS), and mortality.

**Statistical analysis**

Data were expressed as proportions, medians, or mean ± standard deviation, as appropriate. A receiver operating characteristic (ROC) curve analysis was performed for the optimum myoglobin cutoff plotted against hospital LOS (<7 vs. >7 days). The cutoff value of 1000 ng/mL in this study was based on the ROC curve analysis, which correlated myoglobin level and the length of hospital stay for >7 days. Discriminatory power was determined using sensitivity, specificity, and positive and negative likelihood ratio (LR). Patients were divided into two groups based on the myoglobin cutoff (low vs. high myoglobin group), and comparative analysis was performed. Differences in categorical variables between respective comparison groups were analyzed using the Chi-square test or Fisher exact. Continuous variables were analyzed using the Student’s t-test or ANOVA test. The correlation coefficient was performed for the relation between myoglobin, ISS, and hospital stay days. A subanalysis was performed to look for the association between hospital course and complications in different myoglobin levels (<200, 200–400, 400–600, 600–800, 800–1000, and >1000 ng/mL). Two-tailed $P < 0.05$ was considered to be statistically significant. Data analysis was carried out using the Statistical Package for the Social Sciences IBM® SPSS version 18 (IBM Inc., Armonk,
USA). This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[3]

RESULTS

A total of 898 patients met the inclusion criteria; the mean age of patients was 35.9 ± 14.6 years with male predominance (n = 837, 93%). A ROC curve analysis for the optimum myoglobin cutoff plotted against prolonged hospital LOS revealed a myoglobin cutoff 1000 ng/mL. Patients were divided into two groups based on the myoglobin level; <1000 ng/mL (Group 1; 64%) and ≥1000 ng/ml (Group 2; 36%). The age and male predominance were comparable between the 2 groups.

The main mechanism of injury was road traffic-related (n = 500, 56%), followed by falls (n = 235, 26%) and hit by heavy objects (n = 78, 9%). Mechanisms of injuries in both groups showed significant differences; road traffic-related was mainly associated with Group 2, whereas falls were significantly higher in Group 1.

Head injuries were more frequent in Group 1 when compared to Group 2, whereas chest, abdomen, pelvic, and solid organ injuries were more common in Group 2. Eighty-three patients (9%) had musculoskeletal injuries, more frequently reported in Group 2 patients.

The mean ISS score was higher in Group 2 (22.2 ± 10.4 vs. 18.8 ± 9.6, P < 0.001). The mean myoglobin level was 328 ng/ml in patients with ISS <15 versus 1202 ng/ml in patients with ISS ≥15 (P < 0.001). Serum myoglobin was correlated with ISS (r = 0.12, P = 0.001). Figure 1 shows that ISS was not directly increasing as the myoglobin levels increases; however, it was significantly higher in patients with myoglobin values between 400 and 600 and in those with values >1000 ng/mL. The mean GCS and AIS score for anatomical regions (head, chest, and abdomen) were comparable; however, pelvis AIS was higher in Group 2 [Table 1].

Baseline laboratory findings in the two groups are given in Table 2. Hemoglobin, hematocrit, urea, creatinine, and CK values showed significant differences across the study groups; all except hemoglobin and hematocrit were higher for Group 2 (P < 0.05). Sodium or potassium levels showed no significant difference (P > 0.05).

Based on the nature of injuries, blood transfusion was given in nearly half of the patients (n = 465, 52%) with a median of four units. Interventions included intubation (n = 451, 50%), ORIF of fractures (n = 225, 25%), and hemodialysis (n = 18, 2%). Blood transfusion, ORIF and intubation were performed more frequently in group 2 patients (P < 0.05). Hemodialysis was comparable in the two groups.

Complications included pneumonia (17%), sepsis (9%), ARDS, (3.2%), AKI (3%), and compartment syndrome (1%). Complications in both study groups were comparable [Table 3] except for sepsis and compartment syndrome that were more evident in Group 2. Figures 2 and 3 demonstrate the comparison of interventions and complications among six groups of myoglobin levels (ranging from <200 to >1000 ng/mL). It shows no significant statistical differences among different myoglobin levels regarding pneumonia, sepsis, ARDS, AKI, and mortality. However, the proportions of blood transfusion, intubation, compartment syndrome, and hospital stay were significantly higher in groups with higher myoglobin. The median ICU LOS was 5 days, and the median hospital LOS was 16 (1–232) days. Group 2 patients had a longer duration of ICU and hospital stay when compared to Group 1 patients. A large majority of the study cohort stayed in the hospital for more than 7 days (n = 740, 82%). Of these, Group 2 patients were larger in proportion than Group 1 (89% vs. 79%, P = 0.001). The overall in-hospital mortality was 7% (n = 58); comparable among the two groups.
Serum myoglobin was correlated with hospital LOS ($r = 0.20, P = 0.001$). High myoglobin levels had a crude odd ratio 2.1; 95% confidence interval (1.40–3.18) for longer hospital LOS (>1 week). The myoglobin cutoff 1000 ng/ml for longer hospital LOS had a sensitivity 39%, specificity 77%, positive predictive value 89%, negative predictive value 21%, −LR 0.79 and +LR 1.69 [Figure 4].

### DISCUSSION

The present descriptive study revealed that one-third of the patients admitted to the trauma center had high serum myoglobin level (>1000 ng/ml). These elevated serum myoglobin levels are associated with injury severity, sepsis, and prolonged hospital stay. However, there were no statistically significant differences in mortality based on serum myoglobin level. Patients with higher myoglobin levels often required blood transfusion and mechanical ventilation. Myoglobin value of 1000 ng/ml in trauma settings has fair discriminatory power to identify patients at higher risk.

This is a unique study with a large sample size from the Arab Middle Eastern region, which provides an insight on the injury characteristics, management, complications, and outcome of trauma patients based on myoglobin...
level. The study was based on data obtained from the only national trauma registry present in a level I trauma center in the country, and therefore, it is nationally representative.

Most of the current literature on rhabdomyolysis is mainly based on retrospective studies and case series or case reports. However, Sousa et al. conducted a prospective study of small sample size (n = 57) to assess the risk factors and incidence of rhabdomyolysis in polytrauma patients and showed that many factors are implicated in CK and myoglobin variations.[4] The authors found that CK alone was not correlated with the incidence of acute renal failure (ARF) and therefore myoglobin level should be considered in these patients. Hackl et al. studied 34 polytrauma patients prospectively and demonstrated that although the myoglobin concentration increased over the period of study, there was no correlation with the creatinine clearance.[5] In our study, AKI was found not associated with increased levels of myoglobin; this could be related to the early, effective fluid resuscitation. Previous studies also demonstrated elevated myoglobin levels in crush injuries.[6] Unlike these patients, the majority of our patients were younger and victims of road traffic injuries. It was already shown that myoglobin could be used as a biomarker to evaluate the severity of critically ill patients and guide the treatment, especially in the ICU settings.[7]

Early diagnosis of rhabdomyolysis is challenging as the initial clinical evaluation in polytrauma patients cannot predict the severity of future complications. Prompt recognition is crucial as treatment should be initiated early to reduce the risk of complications. The severity of complications due to rhabdomyolysis mainly depends on the mechanism of injury, comorbidities, concomitant injuries, and anatomic site. It also shows that the greater the number of body sites involvement, the higher will be myoglobin level, as evident from the high ISS score of the group with a high myoglobin level.[9]

Due to the lack of specific criteria to diagnose rhabdomyolysis in the trauma setting, a combination of clinical and laboratory data is usually used to predict the outcome. Serum CK levels exceeding five times the upper limit of normal is often used for diagnosing rhabdomyolysis; however, in our patient population, CK level was not routinely requested along with myoglobin, and the diagnosis usually relied on the combination of clinical signs and symptoms and myoglobin level. Only a few studies put forward cutoffs for myoglobin level, which varies from 25 µg/ml to 5197 UI/L.[9] Studies

| Variables | Myoglobin < 1000 ng/mL (n = 576, 64.1%) | Myoglobin ≥ 1000 ng/mL (n = 322, 35.9%) | P |
|-----------|--------------------------------------|----------------------------------------|---|
| Hemoglobin | 13.3 ± 2.1                           | 12.4 ± 2.2                             | 0.001 |
| Hematocrit | 40.2 ± 6.7                           | 37.7 ± 7.4                             | 0.001 |
| INR | 1.1 ± 0.3                            | 1.2 ± 0.2                             | 0.001 |
| Urea | 4.7 ± 2.1                            | 5.4 ± 23.0                           | 0.001 |
| Creatinine | 86.1 ± 52.6                           | 101.5 ± 50.3                        | 0.001 |
| Sodium | 140.1 ± 5.2                           | 140.4 ± 11.6                        | 0.63 |
| Potassium | 4.0 ± 0.6                            | 4.0 ± 0.8                           | 0.50 |
| Creatinine Kinase (CK) [median, range] | 584 (1-3765)                        | 2436 (25-23115)                  | 0.001 |
| Lactate | 2.9 ± 1.9                            | 4.0 ± 2.3                           | 0.001 |

Data are expressed as mean ± SD or median (range) whenever appropriate. INR: International normalized ratio, CK: Creatinine kinase, SD: Standard deviation

| Variables | Overall (n = 898) | Myoglobin < 1000 ng/mL (n = 576, 64.1%) | Myoglobin ≥ 1000 ng/mL (n = 322, 35.9%) | P |
|-----------|------------------|----------------------------------------|----------------------------------------|---|
| Management | Blood transfusion | 465 (51.8) | 227 (39.4) | 238 (73.9) | 0.001 |
| Blood units (median) | 4 (1-79) | 4 (1-79) | 6 (1-142) | 0.002 |
| ORIF | 225 (25.1) | 104 (18.1) | 121 (37.6) | 0.001 |
| Hemodialysis | 18 (2.0) | 12 (2.1) | 6 (1.9) | 0.82 |
| Intubation | 451 (50.2) | 268 (46.5) | 183 (56.8) | 0.003 |
| Complications | Compartment syndrome | 8 (0.9) | 0 | 8 (2.5) | 0.001* |
| Sepsis | 81 (9.0) | 42 (7.3) | 39 (12.1) | 0.02 |
| ARDS | 29 (3.2) | 22 (3.8) | 7 (2.2) | 0.20 |
| Pneumonia | 156 (17.4) | 95 (16.5) | 61 (18.9) | 0.35 |
| AKI | 23 (2.6) | 13 (2.3) | 10 (3.1) | 0.44 |
| Outcomes | ICU days (median) | 5 (1-124) | 5 (1-124) | 6 (1-82) | 0.009 |
| Ventilator days | 5 (1-63) | 6 (1-53) | 5 (1-63) | 0.59 |
| Hospital LOS | 16 (1-232) | 14 (1-232) | 22 (2-218) | 0.001 |
| ≤7 days (%) | 158 (17.6) | 122 (21.2) | 36 (11.2) | 0.001 |
| >7 days (%) | 740 (82.4) | 454 (78.8) | 286 (88.8) | 0.95 |
| Mortality | 58 (6.5) | 37 (6.4) | 21 (6.5) | 0.95 |

Data are expressed as n (%), mean ± SD or median (range) whenever appropriate. ORIF: Open reduction internal fixation, ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury, ICU: Intensive care unit, LOS: Length of stay, SD: Standard deviation
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Our study showed that baseline reading for troponin is statistically significant in high myoglobin level, but the level of troponin was not clinically significant for the diagnosis of acute myocardial infarction. A study by Li et al. found a false-positive troponin with rhabdomyolysis in up to 17% of cases. None of the patients in our study developed acute myocardial infarction.

A number of cytokines are increased in septic patients such as plasma calcitonin gene-related peptides, and myoglobin was found to be significantly higher in this group of patients. High myoglobin level was associated with sepsis, as shown in our study, in 9.0% of the study population. Yao et al. studied the relationship between serum myoglobin level and sepsis and assessed the predictive value of the serum myoglobin level for the prognosis in 70 septic patients. They concluded that 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. This association of high myoglobin level in septic shock trauma patients demonstrates that the early recognition of high myoglobin level and early management would result in a better outcome. Moreover, the elevated myoglobin level was found to correlate with the Sequential Organ Failure Assessment score, C-reactive protein, and procalcitonin level in septic patients.

The outcomes of a patient with elevated myoglobin depend on the nature of injuries and how aggressively these injuries are treated. The mortality rate of rhabdomyolysis with high myoglobin level was reported as 8%–10%.

**Limitations**

The retrospective nature of the study is one of the limitations. Selection bias cannot be ruled out since serum myoglobin was checked for trauma patients on admission were based on the physician’s discretion, and there was no institutional protocol. The study does not address the crush syndrome or rhabdomyolysis in detail as a direct complication of elevated myoglobin. However, there is no well-defined cutoff of serum myoglobin in trauma patients in these regards. As CK testing was not routinely requested in trauma patients, the diagnosis of rhabdomyolysis was not perfectly available in most of cases. Only the maximum or peak CK levels were reported in this study. The timing and frequency of serum myoglobin testing still need further assessment. In addition, several variables, including activated partial thromboplastin time, platelets, phosphate, calcium, liver function tests, lactate dehydrogenase were not available because of the retrospective design of the study. Surgical interventions such as ORIF were recorded from the operating room notes; however, complete records of nonoperative management were not available. Further studies are needed for much better discriminatory power and accuracy of the selected cut-off.

**CONCLUSIONS**

One-third of admitted trauma patients have elevated serum myoglobin levels, which is associated with prolonged hospital stay. Level of myoglobin should be...
checked on admission of polytrauma patients and if it is higher, it should be followed up to avoid complications. The discriminatory power of myoglobin value of 1000 in trauma is fair and therefore, further assessment in prospective studies is needed.

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Conflicts of interest
There are no conflicts of interest.

Research quality and ethics statement
This study was approved by the local Institutional Review Board / Ethics Committee. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, during the conduct of this research project.

REFERENCES

1. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: A systematic review of rhabdomyolysis for clinical practice. Crit Care 2016;20:135.
2. Available from: https://www.facs.org/quality-programs/trauma/atls/about. [Last accessed on 2020 Mar 27].
3. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9.
4. Ciarambino T, Adinolfi LE, Giordano M. Acute rhabdomyolysis in healthy woman. Am J Emerg Med 2016;34:113.e1-2.
5. Sousa A, Paiva JA, Fonseca S, Raposo F, Valente L, Vyas D, et al. Rhabdomyolysis: Risk factors and incidence in polytrauma patients in the absence of major disasters. Eur J Trauma Emerg Surg 2013;39:131-7.
6. Hackl JM, Neumann M, Weirather E, Strosnieder E. Myoglobin release and renal function in polytraumatized patients in intensive care. Anaesthesist 1990;39:319-22.
7. Poznanović MR, Sulen N. Crush syndrome in severe trauma. Lijec Vjesn 2007;129 Suppl 5:142-4.
8. Ye J, Chen EZ, Wang TS, Jiang J, Li XG, Li Y, et al. A comparison between serum myoglobin and acute physiology and chronic health evaluation II score in the evaluation of disease severity and prognosis in critically ill patients. Zhongguo Wei Zhong Bing Ji Ji Yu Xue 2008;20:538-41.
9. Slater MS, Mullins RJ. Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: A review. Am Coll Surg 1998;186:693-716.
10. Thomas MA, Ibels LS. Rhabdomyolysis and acute renal failure. Aust N Z J Med 1985;15:623-8.
11. Ide M, Tajima F, Furusawa K, Mizushima T, Ogata H. Wheelchair marathon racing causes striated muscle distress in individuals with spinal cord injury. Arch Phys Med Rehabil 1999;80:324-7.
12. Köppel C. Clinical features, pathogenesis and management of drug-induced rhabdomyolysis. Med Toxicol Adverse Drug Exp 1989;4:108-26.
13. Koski A, Koljonen V, Vuola J. Rhabdomyolysis caused by hot air sauna burn. Burns 2005;31:776-9.
14. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine (Baltimore) 1982;61:141-52.
15. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int 1996;49:314-26.
16. Guechot J, Lioret N, Cynober L, Letort C, Saizy R, Giboudeau J. Myoglobinemia after burn injury: Relationship to creatine kinase activity in serum. Clin Chem 1986;32:857-9.
17. Mikkelsen TS, Toft P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patients with rhabdomyolysis. Acta Anaesthesiol Scand 2005;49:859-64.
18. Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJ, de Visser M. Rhabdomyolysis: review of the literature. Neuromuscul Disord (England) 2014;24:651-9.
19. Li SF, Zapata J, Tillem E. The prevalence of false-positive cardiac troponin I in ED patients with rhabdomyolysis. Am J Emerg Med 2005;23:860-3.
20. Onuoha GN, Alpar EK. Elevation of plasma CGRP and SP levels in orthopedic patients with fracture neck of femur. Neuropeptides 2000;34:116-20.
21. Yao L, Liu Z, Zhu J, Li B, Chai C, Tian Y. Higher serum level of myoglobin could predict more severity and poor outcome for patients with sepsis. Am J Emerg Med 2016;34:948-52.
22. Gupta KL, Kumar R, Sekhar MS, Sahuja V, Chugh KS. Myoglobinuric acute renal failure following electrical injury. Ren Fail 1991;13:23-5.
23. Nespoli A, Corso V, Mattarel D, Valerio M, Nespoli L. The management of shock and local injury in traumatic rhabdomyolysis. Minerva Anestesiol 1999;65:256-62.
24. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med 2007;2:210-8.