



## Impact of raising serum myoglobin on resuscitation of trauma patients with high injury severity score (ISS)

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### ABSTRACT

**Introduction:** Recent studies recommend limiting the amount of crystalloid perfused during resuscitation for trauma patients. Severely injured patients sustain extensive muscle damage with subsequent high serum myoglobin levels precipitating acute renal injury if not treated immediately. To timely identify patients at risk of acute renal injury, we proposed determining the strength of the correlation between the American College of Surgeons–defined injury severity score with serum and urine myoglobin level in the early hours of arrival to the emergency department to determine the patient at higher risk of raising serum myoglobin level and subsequent renal injury.

**Method:** A retrospective analysis was conducted at a 400-bed community teaching hospital with a level 2 trauma section and annual admission of 750–800 patients using the data in the trauma registry (2010–2017). Patients with an injury severity score of 15 or above were selected, and Student *t* test and Pearson correlation 2-tailed analysis were used to identify the relationship with serum myoglobin.

**Result:** There were 306 patients total, with 200 men (70.3%) and 106 women (29.7%) and a mean age of 60.64 (SD = 23.6) (range 18–96) years. The mean injury severity score was 22.3 (SD = 8.5) (range 16–75). The median level of serum myoglobin in the first 24 hours of admission was 848.56 ng/mL (range 22–11,197). There was a strong and significant correlation between the 2 variables ( $r = 0.397, P < .0001$ ).

**Conclusion:** The appearance of urine myoglobin with serum level of 39 ng/mL suggests that with higher injury severity score, the potential for acute kidney injury is likely and should be addressed early in the patient management.

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### INTRODUCTION

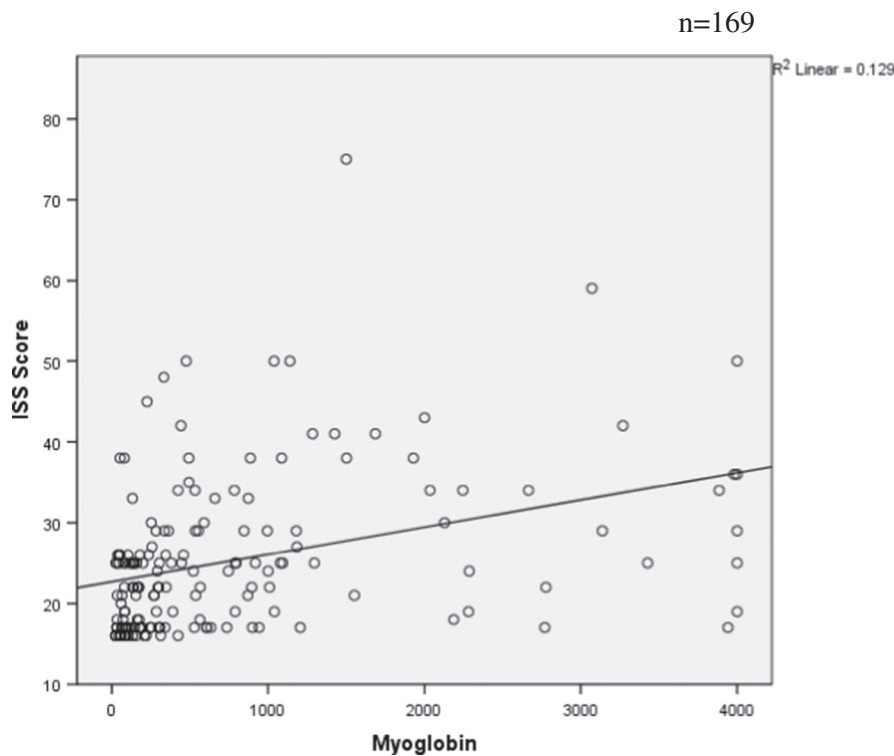
High serum myoglobin levels have been continuously implemented as the primary cause of renal toxicity in rhabdomyolysis secondary to tubular obstruction, renal vasoconstriction, and direct toxicity secondary to lipid peroxidation of the heme portion of the myoglobin [1,2]. Although trauma and crush injuries are a common cause of rhabdomyolysis [3–6], burns, malignant hyperthermia, and seizures, as well as alcohol and medications, can also be precipitating factors [7–10]. The precipitation of myoglobin in the tubules can be exacerbated by intravascular volume reduction and acidosis [7,10]. Skeletal muscle injury and the significantly increased levels of serum myoglobin have devastating effects on renal function [11–15]. Serum myoglobin levels greater than

368  $\mu\text{g/L}$  indicate risk for acute kidney injury (AKI), and levels greater than 15,000  $\mu\text{g/L}$  have a strong correlation to AKI necessitating renal replacement therapy. Early and aggressive fluid hydration remains the main intervention to prevent and treat AKI in the hopes of preventing progression to oliguria and renal failure necessitating renal replacement therapy [4,11,16].

The current concept of trauma resuscitation emphasizes on blood and blood product transfusion in the trauma bay while minimizing fluid resuscitation [17–20]. Therefore, with the limit on the amount of crystalloid given, it remains undetermined how the subsequent fluid resuscitation should be directed once the patient is past the initial insult of injury. Because trauma is associated with rhabdomyolysis and the potential for AKI, adequate and calculated fluid resuscitation must be put in place early to overcome the negative impact on renal function. To identify those trauma patients at risk, we studied the correlation between the injury severity score (ISS) [21,22] and serum and urine myoglobin level in acute trauma patients to identify the optimal timing for crystalloid fluid resuscitation.

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Correlation between the ISS score and serum myoglobin

Fig 1. Correlation between the ISS score and serum myoglobin

## METHOD

Retrospective analysis was conducted at a 400-bed community teaching hospital with a level II trauma designation with annual admission rate of 750–800 patients. Using the data in the trauma registry between January 2010 and December 2017, patients with an ISS score of 15 or above were included in the study, and the serum and urine myoglobin were analyzed during the first 3 days of admission, as were serum urea, creatinine, potassium, and sodium levels. Student *t* test and Pearson correlation 2-tailed analysis was used to identify the relationship of ISS with serum and urine myoglobin. Five patients with existing chronic renal failure were excluded from this study; however, 12 patients with blunt renal trauma (contusion and laceration grade I–V) were included. Institutional review board approval was obtained for this study.

## RESULT

There were a total of 306 patients admitted for trauma between January 2010 and December 2017 who were included in the study. The overall ISS score was 15 or more, with a mean score of 22.3 (SD = 8.5). Mechanism of injury included motor vehicle accidents for 87.1%, whereas 12.9% were blunt trauma and firearm. There were 12 patients with renal injury (contusion and laceration) on presentation to the emergency department. There were 200 men (70.3%) and 106 women (29.7%). The overall mean age was 60.6 (SD = 23.6) years. Average age was 51.1 (SD = 20.3) years for men and 60.5 (SD = 22.2) for women ( $P = .006$ ). Average ISS did not differ significantly by sex (men: 25.3 [SD = 9.6]; women 25.5 [SD = 9.6];  $P = .89$ ). Serum myoglobin levels were measured in the first 24 hours and subsequent days for a total of 3 days and ranged between 22 and 11,197 U with a mean of 848.6 (SD = 1301) for the total group. There was no significant difference in day-1 mean myoglobin levels between men (896.7; SD = 1404) and women (729.1; SD = 1002.9) ( $P = .45$ ).

The univariate association between ISS and day-1 myoglobin demonstrated a moderately strong and significant correlation ( $r = 0.46$ ,  $P = .02$ ,  $n = 169$ ), as well as age and sex ( $r = 0.55$ ,  $P = .01$ ), and we controlled for these factors in a regression analysis. ISS was independently significantly correlated with day-1 myoglobin when controlling for age and sex ( $r = 0.374$ ,  $P < .001$ ) (Fig 1). Urine myoglobin levels in the first 72 hours of admission were measured randomly in 40 patients (Table 1). The appearance of urine myoglobin was associated with serum myoglobin level as low as 39 ng/mL (Fig 2). Mean serum creatinine, potassium, sodium, and chloride measurements in the first 72 hours are in Table 2.

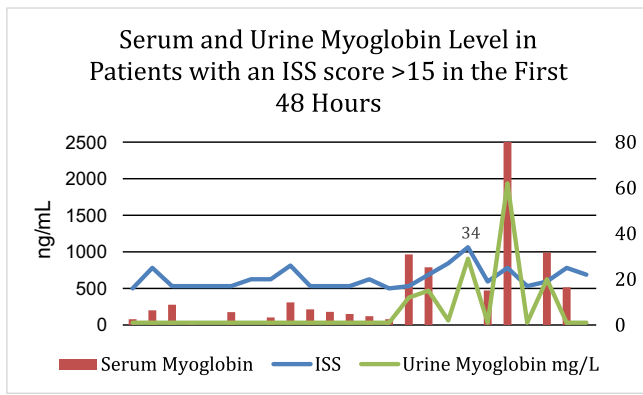
## DISCUSSION

A recent concept of acute trauma patient resuscitation advocates the use of blood and blood products in the trauma bay area [17] due to the higher risk of acute respiratory distress syndrome (ARDS) associated with the use of crystalloid in the resuscitation of trauma patients [19]. In addition, this recent damage control resuscitation which is heavily depended on more blood and blood product transfusions and less on utilization of crystalloids [20], reduces the risk of acute respiratory distress syndrome and coagulopathy which provides gains in survival advantages [17,18]. However, the rate and amount of crystalloid infused following initial resuscitation remains unsettled.

Trauma patients with high ISS scores ( $\geq 15$ ) invariably sustain muscle injury with resultant rhabdomyolysis, high serum myoglobin level and a potential for acute kidney injury (AKI) [12]. In addition to trauma,

Table 1  
Forty Patients who had positive qualitative myoglobin measurement

Range of ISS ( $n = 40$ )	Range of serum myoglobin: ng/L ( $n = 40$ )	Urine myoglobin ( $n = 40$ )
16–26	39–4026	positive



**Fig 2.** Serum and urine myoglobin level in patients with an ISS score greater than 15 in the first 48 hours.

rhabdomyolysis also presents after strenuous exercise, particularly in hot humid weather [23], in prolonged neurosurgical procedures [24], adenovirus infection [25], burn patients [6,8–10,13,26] and exertional rhabdomyolysis as well as other etiological factors. The myoglobin precipitation and resulting tubular obstruction can be intensified by the intravascular volume depletion, vasoconstriction, and systemic acidosis [10]. Skeletal muscle injury, rhabdomyolysis, has pathophysiological effects on serum and urinary myoglobin with the devastating result of AKI [4,27]. Nonetheless, one has to consider that despite the significance of myoglobin in AKI development, in the trauma patients, other factors such as drug effects and hypovolemia from blood loss also impact renal function. The optimal treatment for trauma patients with rhabdomyolysis remains unclear [14,28], and the review of best available evidence failed to demonstrate the best protocol to treat rhabdomyolysis [28]. However, aggressive fluid resuscitation using crystalloid to restore renal perfusion and increase urine output, coupled with urine alkalization, in the early hours is associated with improved outcomes [3,5,28]. One must keep in mind that excessive crystalloid infusion may exacerbate the already existing coagulopathy in these trauma patients [17,18] and may result in greater negative outcomes than AKI. Sometimes, forced diuresis with mannitol and loop diuretics has also been used [3,29], although the benefits of these as well as urine alkalization remain uncertain [4,14]. Because creatinine kinase was not shown in prior studies to be a reliable predictor of AKI [14], we elected not to measure it. AKI in trauma patients occurs more commonly in the elderly and those with low base excess [12]. We admitted, annually to the trauma service, an average 700–850 patients with mean age of 63 years. The significance of an older group of patients is the associated comorbid conditions, mainly diabetes mellitus, coronary artery disease, and chronic renal insufficiency or renal failure. There were only 5 patients with documented renal failure in our studied group of patients, and they were excluded from our study. The elevated level of creatinine kinase in rhabdomyolysis has never been studied [3,4,13,27]. However,

its correlation with AKI in such patients had not been established yet, and therefore, we rely on serum and urine myoglobin measurement only in our study. The mean age of our patients in the study was 60.6 (SD = 23.6) years, with no difference in ISS score levels in men and women. Also, the serum myoglobin measurement in the first 24 hours did not show a significant difference between men (896.7 ng/mL) and women (729.1 ng/mL) ( $P = .45$ ).

Not surprisingly, there was a significant correlation between serum myoglobin and ISS score regardless of sex and age (Fig 1), whereas the appearance of myoglobin in the urine within the first 24 hours and with a level as low as 39 ng/mL was an alarming finding (Fig 2), and with the previous finding on the significance of serum and urine myoglobin levels in predicting AKI [28], one has to consider those trauma patients arriving to the hospital with a high ISS score as a potential candidate for AKI, and measurements to prevent it must be in place following initial resuscitation. Measurement of serum electrolytes as well as urea and creatinine during the first 72 hours of admission remains within normal range (Table 1). Therefore, one can reliably use ISS score as an indicator for high serum myoglobin and potential risk for AKI. We applied these changes to our trauma patients, including measurement of serum and urine myoglobin for all patients with ISS score of 15 and higher, and adjusted the IV crystalloid fluid resuscitation accordingly to achieve diuresis. The drawback of the study was that there were patients with missing data on the urine myoglobin. Additionally, in measuring urine myoglobin, only qualitative measures were included.

**CONCLUSION**

The association between the ISS score and serum myoglobin level should direct attention to potential AKI in trauma patients with high ISS scores and bring renewed focus to optimal renal perfusion using fluid resuscitation to achieve diuresis, following initial resuscitation with the option of urine alkalization.

**Author Contribution**

TW, BS and KB designed the study and prepared the manuscript. TK, JM, and KB contributed to the statistical analysis and interpretation. BD, AR, JH, and RY contributed to the data collection.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Funding Sources**

No funding was received for this study.

**Table 2**  
Mean level of creatinine and electrolytes in the first 72 hours of admission

	Measurement 1 Mean (SD)	Measurement 2 Mean (SD)	Measurement 3 Mean (SD)	Measurement 4 Mean (SD)	Measurement 5 Mean (SD)	Measurement 6 Mean (SD)
Creatinine	N = 40 1.01(0.30)	N = 37 0.99(0.43)	N = 34 0.95(0.61)	N = 29 0.90(0.63)	N = 26 0.69(0.36)	N = 23 0.64(0.32)
Potassium	N = 40 3.85(0.66)	N = 37 4.08(0.61)	N = 34 3.90(0.43)	N = 29 3.77(0.81)	N = 26 3.36(1.30)	N = 23 3.36(1.41)
Sodium	N = 40 138.45(3.48)	N = 37 138.11(5.61)	N = 34 139.35(4.02)	N = 28 124.04(41.08)	N = 23 134.43(26.94)	N = 20 125.35(35.16)
Chloride	N = 40 100.98(5.45)	N = 37 101.11(17.55)	N = 34 101.32(17.01)	N = 28 100.89(20.87)	N = 24 90.83(35.46)	N = 22 88.55(36.41)

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