

Rhabdomyolysis and acute kidney injury in patients with traumatic spinal cord injury

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Abstract

Background: Patients with acute traumatic spinal cord injuries (SCIs) exhibit factors that, in other populations, have been associated with rhabdomyolysis. **Purpose:** The aim of the study is to determine the incidence of rhabdomyolysis in patients with acute traumatic SCI admitted to the Intensive Care Unit (ICU), as well as the development of secondary acute kidney injury and associated factors. **Study Design and Setting:** This was an observational, retrospective study. **Patient Sample:** All adult patients admitted to the ICU with acute traumatic SCI who presented rhabdomyolysis, diagnosed through creatine phosphokinase (CPK) levels >500 IU/L. **Outcome Measures:** Incidence of rhabdomyolysis and subsequent renal dysfunction was calculated. **Materials and Methods:** Data about demographic variables, comorbidity, rhabdomyolysis risk factors, and variables involving SCI, severity scores, and laboratory parameters were obtained from clinical records. Multivariate logistic regression was used to identify renal injury risk factors. **Results:** In 2006–2014, 200 patients with acute SCI were admitted to ICU. Of these, 103 had rhabdomyolysis (incidence = 51.5%; 95% confidence interval [CI]: 44.3%–58.7%). The most typical American Spinal Injury Association classification was A (70.3%). The injury severity score was 30.3 ± 12.1 and sequential organ failure assessment (SOFA) score was 5.6 ± 3.3 points. During their stay, 57 patients (55.3%; 95% CI: 45.2%–65.4%) presented renal dysfunction (creatinine ≥ 1.2 mg/dL). In the multivariate analysis, variables associated with renal dysfunction were creatinine at admission (odds ratio [OR] = 9.20; $P = 0.006$) and hemodynamic SOFA score the day following admission (OR = 1.33; $P = 0.024$). Creatinine was a better predictor of renal dysfunction than the peak CPK value during the rhabdomyolysis (area under the receiver operating characteristic curve: 0.91 vs. 0.63, respectively). **Conclusions:** Rhabdomyolysis is a frequent condition in patients with acute traumatic SCI admitted to the ICU, and renal dysfunction occurs in half of the cases. Creatinine values should be requested starting at the admission while neither the peak CPK values nor the hemodynamic SOFA scores could be used to properly discriminate between patients with and without renal dysfunction.

Keywords: Acute kidney injury, rhabdomyolysis, spinal cord injuries

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.190370

Quick Response Code:



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How to cite this article: Galeiras R, Mourelo M, Pértega S, Lista A, Ferreiro ME, Salvador S, *et al.* Rhabdomyolysis and acute kidney injury in patients with traumatic spinal cord injury. *Indian J Crit Care Med* 2016;20:504-12.

Introduction

Rhabdomyolysis is a clinical emergency characterized by the rapid breakdown of skeletal muscle cells. It may be caused by trauma or nontraumatic factors,^[1-3] such as drugs, alcohol, ischemia, infectious diseases, and genetic disorders, though it is often impossible to detect a specific trigger mechanism. Regardless of the cause, however, the physiopathological events include an increased concentration in intracellular calcium resulting either from direct damage to the sarcolemma (acquired) or from the failure to produce energy (genetic), which leads to the dysfunction of the Na/K₂-ATPase and Ca²⁺-ATPase pumps and to necrosis of skeletal muscle fibers.^[4-6]

Rhabdomyolysis in an awake patient is characterized by myalgia, weakness, and reddish urine. Acute renal failure is the most significant complication, occurring at a rate of 17%–33% in various series.^[7-9] The mechanisms involved in kidney injury in patients with rhabdomyolysis include blockage of the renal tubules with myoglobin, damage from free oxygen radicals, and myoglobin-induced vasoconstriction of renal arterioles.^[6]

Patients with acute traumatic spinal cord injuries (SCIs) exhibit factors that, in other populations, have been associated with rhabdomyolysis, such as high-impact injuries, other relevant traumas, immobilization, need for drugs during a hospital stay, thermal dysregulation, and hemodynamic instability, and could comprise a population at risk of rhabdomyolysis. A high index of suspicion is required for an early diagnosis of rhabdomyolysis, especially in the absence of pain and motility. The rate of rhabdomyolysis, however, and the factors related to the development of subsequent renal dysfunction have not been studied in patients with acute traumatic SCI. Identifying the risk of kidney injury would allow for establishing diagnostic and therapeutic strategies relevant to the prognosis.

The purpose of this study is to determine the incidence of rhabdomyolysis in patients with acute traumatic SCI who require admission to the Intensive Care Unit (ICU), their characteristics and mortality, as well as the development of secondary acute kidney injury and associated factors.

Materials and Methods

We conducted an observational, retrospective study to determine the characteristics of adult patients (≥18 years old) with rhabdomyolysis and traumatic SCI who were admitted to an ICU between 2006 and 2014.

The study included patients admitted to the ICU diagnosed with acute traumatic SCI who presented with rhabdomyolysis, diagnosed through creatine phosphokinase (CPK) levels in excess of 500 IU/L, as defined in the literature.^[10-13] Patients under 18 years of age and those whose admission had been delayed by 48 h or more from the time of the injury were excluded from the study.

Our center is a highly specialized hospital, and the Spinal Cord Injury Unit is a benchmark in the region of Galicia, which had an average population of 2,778,875 during the study period. Patients with acute traumatic SCI are admitted to the ICU if they need or are expected to need support for a failing organ. The CPK determination is a part of the laboratory test parameters requested for these patients on admission. When required, the acute kidney injury associated with rhabdomyolysis is prevented and/or treated by fluid resuscitation to prevent hypovolemia, by correcting metabolic acidosis, and by administering osmotic diuretics such as mannitol and loop diuretics. Identifying and treating the precipitating cause are of paramount importance. The rhabdomyolysis was treated in accordance with the instructions of the patient's intensivist.

Definitions

A diagnostic criterion for rhabdomyolysis was CPK in excess of 500 IU/L. The catalytic activity of the CPK was determined according to the International Federation Clinical Chemistry (Dimension[®] clinical chemistry system, Newark, USA).

The trauma of the spinal cord was classified based on the categories of the American Spinal Injury Association (ASIA).^[14] The overall gravity of the trauma was assessed using the injury severity score (ISS).^[15] The level of consciousness was quantified using the Glasgow coma scale (GCS).^[16] Organ dysfunction was defined according to the sequential organ failure assessment (SOFA) scale.^[17] The body mass index was used to classify the patients as obese when its value was ≥30 kg/m².

Parameters

The parameters collected from medical records on admission were demographic (age and gender) and comorbidity (Charlson comorbidity index and arterial hypertension) variables, risk factors related in the literature to rhabdomyolysis (muscular necrosis, obesity, consumption of statins, antipsychotics, sedatives or alcohol, convulsions, anxiety, and hypo/hyperthermia), variables involving the SCI (area of the

spinal column affected with the column's sensory/motor level and the ASIA index), GCS, ISS, and laboratory analysis parameters relative to renal function (urea and creatinine) on admission. The SOFA score was calculated on admission in the first 24 h after admission and when the rhabdomyolysis was diagnosed. The time between admission and the rhabdomyolysis diagnosis, as well as the duration of the episode, was recorded. During the rhabdomyolysis episode, the initial and worse laboratory test values for CPK, creatinine, urea, potassium, calcium, phosphorus, lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT), uric acid, albumin, and metabolic acidosis were recorded. Variables related to preventing and/or treating kidney dysfunction, ICU stay, and intrahospital mortality were also recorded.

Sample size justification

From 2006 to 2014, 200 patients with an acute SCI were admitted to the ICU. Of these, 103 had rhabdomyolysis (CPK >500 IU/L). This sample size makes it possible to determine the characteristics of patients with rhabdomyolysis and the incidence of renal dysfunction with a confidence interval (CI) of 95% ($\alpha = 0.05$) and a precision of $\pm 9.6\%$.

Statistical analysis

A descriptive analysis was performed. Quantitative variables were described as mean \pm standard deviation (SD) and median (range). Categorical variables were described as counts and percentages.

The incidence of renal dysfunction during ICU stay was determined, together with its 95% CI. The Mann-Whitney test was used to compare the quantitative variables between patients with and without renal dysfunction. The Chi-square or Fisher's exact test was employed to compare qualitative variables between these groups of patients. The correlation among quantitative variables was assessed using Spearman's rho correlation coefficient. For multivariate analysis, a multiple logistic regression model was used to identify those variables independently associated with presenting kidney dysfunction during ICU stay.

The ability of different variables to predict renal dysfunction was expressed as the area under the receiver operating characteristics curve (AUC-ROC) and 95% CI. Sensitivity, specificity, predictive values, and likelihood ratios were also computed for different cutoffs in those variables potentially associated with kidney dysfunction.

Values of $P < 0.05$ were considered statistically significant. Statistical calculations were performed

using the SPSS 19.0 statistical software suite (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp).

Ethics

The study was carried out according to the principles laid in the Declaration of Helsinki and ensuring compliance with Spanish Decree 29/2009, which regulates the use of and access to electronic medical records. Confidentiality was maintained in accordance with the current Spanish Data Protection Law (15/1999). The study protocol was approved by the local Ethics Committee.

Results

From 2006 to 2014, 200 patients with an acute SCI were admitted to the ICU. Of these, 103 had rhabdomyolysis (CPK >500 IU/L). The incidence of rhabdomyolysis was therefore 51.5% (95% CI: 44.3%–58.7%).

Patient characteristics

The demographic characteristics relative to the SCI and severity indices for patients with rhabdomyolysis are shown in Table 1. The average age was 50.3 ± 18.9 years (median = 49.0 years), and 80.6% of the cases were in men. Most had a low comorbidity, with an age-adjusted Charlson comorbidity index at admission of 1.1 ± 2.0 (median = 1.7).

The most frequent sensory-motor level was cervical (41.7%) and the most typical ASIA index was A (70.3%). As for the severity scales at admission, the ISS was 30.3 ± 12.1 , the GCS was 13.7 ± 3.1 , and the SOFA was 5.6 ± 3.3 points.

Characteristics related to rhabdomyolysis

The average time between admission and the onset of rhabdomyolysis was 0.3 ± 0.5 days, with the condition being detected on admission in 78.6% of the patients and lasting 5.1 ± 3.1 days (median = 4.0 days). In addition to the presence of trauma, which is a common risk factor in patients who contract rhabdomyolysis, Table 2 shows the other relevant risk factors. Of note is the use of sedatives and/or analgesics in 100% of the cases and thermoregulatory alterations in 93 patients (90.3%). Rehydration in the first 24 h following the trauma was 4696.2 ± 1994.7 ml. The average SOFA score on the day of the rhabdomyolysis was 5.6 ± 3.4 points (0–5 scale), with 37.8% of patients presenting renal dysfunction at the time (determined using the SOFA renal score).

The laboratory variables are also shown in Table 2. Kidney function was evaluated at admission based on

Table 1: Demographic characteristics relative to spinal cord injury and severity indices

Variables	n (%)	Mean ± SD	Median	Minimum	Maximum
Age (years)	103	50.3 ± 18.8	49.0	18	87
Gender					
Male	83 (80.6)				
Female	20 (19.4)				
Age-adjusted Charlson comorbidity index	103	1.1 ± 2.0	1.7	0	9.7
Arterial hypertension	20 (19.4)				
Sensory/motor level					
Cervical	43 (41.7)				
Dorsal	50 (48.5)				
Lumbar	6 (5.8)				
Cauda equina	4 (3.9)				
ASIA classification	101				
A	71 (70.3)				
B	14 (13.9)				
C	8 (7.8)				
D	7 (6.9)				
E	1 (1.0)				
GCS	103	13.7 ± 3.1	15.0	3	15
≤ 8	9 (8.7)				
9-13	8 (7.8)				
≥ 14	86 (83.5)				
Injury severity score	103	30.3 ± 12.1	26.0	1	75
Total SOFA score at admission	103	5.6 ± 3.3	5.0	0	12
Total SOFA score in first 24 h following admission	103	5.8 ± 3.2	6.0	0	13
Length of ICU stay in days	103	18.8 ± 12.0	18.0	2	52
Days between injury and admission to ICU	103	0.6 ± 2.4	0	0	22
Intrahospital mortality	17 (16.5)				
Intra-ICU mortality	3 (2.9)				

SD: Standard deviation; ASIA: American Spinal Injury Association; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; GCS: Glasgow coma scale

creatinine levels, with the average being 1.2 ± 0.6 mg/dL. In 34% of the cases, it was ≥ 1.2 mg/dL. The average urea was 49.8 ± 22.1 mg/dL. In 67% of the patients, the maximum CPK value was recorded in the first 24 h after admission, with an average peak maximum CPK of 3761.3 ± 5095.2 IU/L (median = 2232.0). As for renal function, during the rhabdomyolysis, the average creatinine level was 1.3 ± 0.8 mg/dL, average urea was 69.3 ± 27.3 mg/dL, and the average hourly diuresis in the first 24 h after the rhabdomyolysis diagnosis was 88.5 ± 31.1 ml/h. As concerns the other laboratory analysis variables during the rhabdomyolysis episode, these showed the following average levels: LDH of 752.2 ± 369.8 IU/L, GOT 107.4 ± 109.4 IU/L, uric acid 4.2 ± 2.1 mg/dL, albumin 2.9 ± 0.5 g/dL, and a base deficit of -2.6 ± 6.5 .

As for the treatment when the rhabdomyolysis was diagnosed, rehydration was employed in 100% of the cases (average liquid in the first 24 h of 4614.8 ± 1957.0 ml). In 22.3% of the cases, diuresis was forced using loop diuretics, and in 11.7% of the cases, urine alkalization using bicarbonate was utilized. None of the patients required renal replacement therapy.

The mean length of ICU stay was 18.8 ± 12.0 days, with an in-hospital mortality of 16.5% (95% CI: 8.8%–24.1%)

(17 patients) and in-ICU of 2.9% (95% CI: 0.6%–8.3%) (3 patients) [Table 1].

Incidence of renal dysfunction and associated factors

During their stay, 57 patients (55.3%; 95% CI: 45.2%–65.4%) presented renal dysfunction (creatinine ≥ 1.2 mg/dL). These were compared with the 46 patients (44.7%) with normal renal function [Table 3]. We did not find significant differences between the two groups when assessing comorbidity as per the age-adjusted Charlson comorbidity index, traumatic injury scales, or SOFA score on admission. Similarly, there was no correlation between the values of the age-adjusted Charlson comorbidity index or the ISS and the serum creatinine value during the rhabdomyolysis. This was in contrast to the SOFA score on the day of admission ($\rho = 0.222$; $P = 0.024$). The average fluid intake in the first 24 h after admission was similar in both groups (4905.6 vs. 4424.9 ml; $P = 0.091$), unlike the creatinine values at admission (1.30 vs. 0.99 mg/dL; $P = 0.000$), the hemodynamic status on the 1st day in the hospital as determined by the hemodynamic SOFA (1.8 vs. 1.7 points; $P = 0.003$), and peak CPK (4639.6 IU/L vs. 2673.1 IU/L; $P = 0.023$), which were higher in the group with kidney injury. As concerns the rhabdomyolysis treatment, the group with renal dysfunction received significant mannitol treatment (14.0% vs. 2.2%; $P = 0.040$), this not being the case with other treatments. Both the ICU

Table 2: Variables related to rhabdomyolysis

Variables	n (%)	Mean ± SD	Median	Minimum	Maximum
Days from admission until rhabdomyolysis	103	0.3 ± 0.5	0	0	2
0	81 (78.6)				
1	17 (16.5)				
2	5 (4.9)				
Duration of the rhabdomyolysis (days)	103	5.1 ± 3.1	4.0	1	16
Rhabdomyolysis risk factors					
Muscle necrosis	1 (1.0)				
Obesity	4 (3.9)				
Statins	13 (12.6)				
Antipsychotics	17 (16.5)				
Alcohol	10 (9.7)				
Convulsions	1 (1.0)				
Anxiety	16 (15.5)				
Sedatives	103 (100)				
Hyperthermia (>39°C)	20 (19.4)				
Hypothermia (<36°C)	73 (70.9)				
Rehydration in the first 24 h after the trauma (ml)	101	4696.2 ± 1994.6	4300.0	1175	14,340
Laboratory analysis results at admission					
Potassium (mEq/L)	103	4.1 ± 0.7	4.1	1.9	6.2
Calcium (mg/dL)	81	7.6 ± 0.6	7.6	5.8	9.2
Phosphorus (mg/dL)	41	3.1 ± 0.9	3.0	1.2	4.8
Creatinine (mg/dL)	103	1.2 ± 0.6	1.1	0.39	6.00
Urea (mg/dL)	103	49.8 ± 22.1	46.0	10	141
Laboratory analysis values during rhabdomyolysis (worst value)					
CPK (IU/L)	103	3761.3 ± 5095.2	2232.0	544	34,768
Patients with peak CPK on day 0 or 1 since the spinal cord injury	69 (67)				
Creatinine (mg/dL)	103	1.3 ± 0.8	1.2	0.5	8.7
Creatinine ≥ 1.2 (mg/dL)	57 (55.3)				
Urea (mg/dL)	103	69.3 ± 27.3	64.0	25	169
LDH (IU/L)	101	752.2 ± 369.8	658.0	65	2222
GOT (IU/L)	102	107.4 ± 109.4	77.5	19	849
Uric acid (mg/dL)	90	4.2 ± 2.0	4.2	1.0	10.8
Albumin (gr/dL)	96	2.9 ± 0.5	2.9	1.7	4.4
Base deficit	102	-2.6 ± 6.5	-4.1	-19.6	11.0
Total SOFA score on 1 st day of rhabdomyolysis	103	5.5 ± 3.4	5.0	0	12
Renal SOFA score on 1 st day of rhabdomyolysis	103	0.4 ± 0.5	0	0	2
Renal SOFA score ≥ 1 on 1 st day of rhabdomyolysis	39 (37.8)				
Average diuresis during first 24 h of the rhabdomyolysis (ml/h)	103	88.5 ± 31.1	85.0	41	210
Treatment during the rhabdomyolysis	34 (33.0)				
Liquids (ml/24 h)	103 (100)	4614.8 ± 1957.0	4200.0	550	14,340
Mannitol	9 (8.7)				
Bicarbonate	12 (11.7)				
Loop diuretics	23 (22.3)				
Hemofiltration	0				
Albumin	0				

SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase; GOT: Glutamic oxaloacetic transaminase

stay (19.4 days vs. 18.1 days; $P = 0.717$) and mortality (1.8% vs. 4.3%; $P = 0.585$) were similar in both groups.

After adjusting in the multivariate analysis for creatinine at admission, maximum CPK value during the rhabdomyolysis, and the hemodynamic SOFA the day following admission, the variables significantly associated with renal dysfunction were creatinine at admission (odds ratio [OR] = 9.20; $P = 0.006$) and the hemodynamic SOFA score the day following admission (OR = 1.33; $P = 0.024$).

Creatinine at admission thus proved to be a better predictor of renal dysfunction than the peak CPK value during the rhabdomyolysis, with an AUC-ROC of 0.91 (95% IC = 0.85–0.97) and 0.63 (95% CI: 0.52–0.74), respectively [Figure 1]. Sensitivity, specificity, predictive values, and likelihood ratios were also calculated at various cutoff points for the initial creatinine, CPK, and hemodynamic SOFA on the day following admission [Table 4]. This showed that initial creatinine values ≥ 1.1 mg/dL exhibit good sensitivity (77.2%; 95% CI: 65.4–89.0), specificity (89.1%; 95% CI: 79.1–99.2),

Table 3: Bivariate analysis of factors associated with the development of renal dysfunction

Variables	Correlation coefficient	P	Creatinine \geq 1.2 (mg/dL) n=57 (55.34%)		Creatinine < 1.2 (mg/dL) n=46 (44.66%)		P
			Mean \pm SD	Median	Mean \pm SD	Median	
			Age	0.213	0.031	53.1 \pm 18.5	
Gender (%)		-					0.300
Male	-		84.2 (48)		76.1 (35)		
Female	-		15.8 (9)		23.9 (11)		
Comorbidity							
Age-adjusted Charlson comorbidity	0.174	0.079	1.9 \pm 2.0	1.5	1.5 \pm 2.0	0.5	0.140
Arterial hypertension, %			65.0 (13)		35.0 (7)		0.333
Injury scales							
Injury severity score	-0.157	0.114	29.1 \pm 11.7	26.0	31.9 \pm 12.6	26.0	0.422
ASIA level A			59.2% (42)		40.8% (29)		0.145
Total SOFA score at admission	0.222	0.024	6.1 \pm 3.2	5.0	5.0 \pm 3.4	5.0	0.062
Risk factors for kidney injury							
Hemodynamic SOFA score in the first 24 h after admission	0.235	0.017	2.3 \pm 1.8	3.0	1.3 \pm 1.6	0	0.003
Rehydration in the first 24 h after the trauma (ml)	0.128	0.198	4905.6 \pm 2131.7	4660.0	4424.9 \pm 1789.1	3800.0	0.091
Creatinine at admission (mg/dL)	0.734	0	1.3 \pm 0.3	1.2	1.0 \pm 0.8	0.90	0
Peak CPK (IU/L)	0.240	0.015	4639.6 \pm 6160.9	2459.0	2673.1 \pm 3069.6	1760.5	0.023
Laboratory test abnormalities							
Potassium (mEq/L)	0.128	0.197	4.2 \pm 0.7	4.20	4.0 \pm 0.6	4.10	0.259
Calcium (mg/dL)	0.036	0.752	7.7 \pm 0.7	7.80	7.5 \pm 0.8	7.60	0.466
Phosphorus (mg/dL)	0.243	0.126	3.3 \pm 0.9	3.20	3.0 \pm 1.0	2.85	0.430
Uric acid (mg/dL)	0.451	0	4.9 \pm 1.9	4.95	3.5 \pm 1.9	3.25	0
Albumin (g/dL)	-0.159	0.122	2.9 \pm 0.5	2.90	3.0 \pm 0.5	2.95	0.418
Base deficit	-0.180	0.070	-3.5 \pm 6.8	-4.7	-1.5 \pm 6.0	-3.5	0.191
Average diuresis in the first 24 h of the rhabdomyolysis (ml/h)	-0.030	0.015	87.1 \pm 29.2	85.0	90.2 \pm 33.5	83.5	0.763
Treatment following diagnosis, %							
Mannitol			14.0 (8)		2.2 (1)		0.040
Bicarbonate			17.55 (10)		4.3 (2)		0.061
Furosemide			22.8 (13)		21.7 (10)		0.545
Length of ICU stay in days	0.056	0.571	19.4 \pm 12.6	18	18.1 \pm 11.4	18	0.717
Intra-ICU mortality, %	-	-	1.8 (1)		4.3 (2)		0.585
Intrahospital mortality, %	-	-	17.5 (10)		15.2 (7)		0.752

SD: Standard deviation; ASIA: American Spinal Injury Association; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; CPK: Creatine phosphokinase

and adequate positive (89.8%; 95% CI: 80.3–99.3) and negative (75.9%, 95% CI: 63.6–88.3) predictive values. In contrast, no cutoff points were found for either CPK or hemodynamic SOFA values that could be used to properly discriminate between patients with and without renal dysfunction.

Discussion

We studied episodes of rhabdomyolysis in patients admitted to an ICU after an acute traumatic SCI and the factors related to secondary kidney injury in these patients.

51.5% of the patients with an acute traumatic SCI admitted to the ICU presented with rhabdomyolysis. CPK levels were moderately elevated (mean \pm SD: 3761.3 \pm 5095.2 IU/L) though the patients had endured serious accidents (ISS mean \pm SD: 30.3 \pm 12.1; ASIA A: 70.3% of cases) requiring immobilization for a certain period. The patients were young (median age: 49) and

mostly male, which could be explained by the higher rate of exposure to SCI and other risk factors. In addition to the trauma and sedation, 86.7% of the patients exhibited at least one of the other risk factors analyzed. The start of the rhabdomyolysis episode was detected as part of the admission laboratory work in 78.6% of the patients.

Rhabdomyolysis is a condition with a wide range of clinical expression.^[7] The kidney injury associated with rhabdomyolysis results from vasoconstriction with decreased renal perfusion and intraluminal deposits of myoglobin, of its breakdown products and of uric acid, which causes obstruction and tubular damage.^[18,19] The factors that appear to be involved in the appearance of kidney injury in patients with rhabdomyolysis are glomerular filtration rate, metabolic acidosis, CPK levels, and presence of myoglobin in urine.^[6,19] A small increase in serum creatinine could indicate a significant decrease in glomerular filtration. Acidemia could facilitate the precipitation of myoglobin in the renal tubule. The

Table 4: Sensitivity, specificity, predictive values and probability coefficients for values of creatinine at admission and for peak creatine phosphokinase and hemodynamic Sequential Organ Failure Assessment in 1st day following admission when predicting renal dysfunction

Variables	95% CI					
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Initial creatinine (mg/dL)						
≥0.8	98.2 (94.0-100.0)	26.1 (12.3-39.9)	62.2 (51.7-72.8)	92.3 (51.7-72.8)	1.3 (1.1-1.6)	0.1 (0.0-0.5)
≥0.9	96.5 (90.9-100)	50.0 (34.5-65.5)	70.5 (59.8-81.3)	92.0 (79.4-59.8)	1.9 (1.4-2.6)	0.1 (0.0-0.3)
≥1	89.5 (80.6-98.3)	69.6 (55.2-83.9)	78.5 (67.8-89.2)	84.2 (71.3-97.1)	2.9 (1.9-4.6)	0.1 (0.2-0.1)
≥1.1	77.2 (65.4-89.0)	89.1 (79.1-99.2)	89.8 (80.3-99.3)	75.9 (63.6-88.3)	7.1 (3.1-16.4)	0.3 (0.2-0.4)
≥1.2	59.6 (46.0-73.3)	97.8 (92.5-100.0)	97.1 (90.2-100.0)	66.2 (54.2-78.2)	27.44 (3.9-192.9)	0.4 (0.3-0.6)
CPK (IU/L)						
≥1000	86.0 (76.1-95.9)	23.9 (10.5-37.3)	58.3 (47.2-69.5)	58.0 (33.1-82.7)	1.1 (0.9-1.4)	0.6 (0.3-1.3)
≥5000	22.8 (11.0-34.6)	89.1 (79.1-99.2)	72.2 (48.8-95.7)	48.2 (37.0-59.5)	2.1 (0.8-5.5)	0.9 (0.7-1.0)
≥10,000	8.8 (0.6-17.0)	97.8 (92.5-100.0)	83.3 (45.2-100.0)	46.4 (36.0-56.8)	4.0 (0.5-33.3)	0.9 (0.9-1.0)
Hemodynamic SOFA						
≥1	64.9 (51.7-78.2)	56.5 (41.1-71.9)	64.9 (51.7-78.2)	56.5 (41.1-72.0)	1.5 (1.0-2.2)	0.6 (0.4-1.0)
≥2	64.9 (51.7-78.2)	60.9 (45.7-76.1)	67.3 (54.0-80.6)	58.3 (43.3-73.3)	1.7 (1.1-2.5)	0.6 (0.4-0.9)
≥3	63.2 (49.8-76.6)	63.0 (48.0-78.1)	67.9 (54.4-81.4)	58.0 (43.3-72.7)	1.7 (1.1-2.6)	0.6 (0.4-0.9)

SOFA: Sequential Organ Failure Assessment; CPK: Creatine phosphokinase; CI: Confidential interval

extent of muscle damage was represented using various CPK cutoff points to identify at-risk populations.^[20] Identifying at-risk patients would allow early treatment strategies to be initiated in patients as appropriate.

In our study, acute kidney injury at the time of the diagnosis of rhabdomyolysis, as measured by the SOFA score, occurred in 37.8% of patients, with 55.3% of patients having creatinine values ≥ 1.2 mg/dL during the rhabdomyolysis episode. The incidence of kidney injury reported in the literature ranges from 4.7% to 94%,^[7,9,10,21] a variation that probably stems from the different patient populations evaluated and from differences in how rhabdomyolysis and acute renal dysfunction are defined. Whether these percentages reflect the natural progression of the rhabdomyolysis or the effects of treatments or concomitant conditions is unknown.

We evaluated the univariate relationship between kidney injury and demographic, injury, and organ dysfunction variables. We did not find significant differences ($P = 0.06$) in age distribution and the development of this complication, indicating that no age is immune to the risk of kidney injury. We also found no relationship with the Charlson index or with previous hypertension probably because of the population's low comorbidity. As in other research,^[18,22] the uric acid levels were more elevated in patients with renal dysfunction.

There is no consensus in the literature as to what marker best identifies rhabdomyolysis and which one can be used to monitor these patients. We used CPK due to the ease of the associated laboratory test. Patients with moderately high CPK levels during the

rhabdomyolysis had a lower incidence of kidney injury compared to patients with higher levels of CPK. This is consistent with findings in other studies.^[18] The figure for peak CPK, however, did not turn out to be a good predictor of kidney injury in the multivariate analysis, which had a low discriminatory capacity as evidenced by an AUC-ROC of 0.63 [Figure 1]. There are differences in the literature regarding the usefulness of this variable as a predictor of complications. Beetham^[20] found that CPK levels ≥ 5000 IU/L could mark the cutoff point for the development of kidney injury. In the work by Sharp *et al.*,^[19] CPK values ≥ 5000 IU/L measured at admission were not predictors of renal dysfunction in critical surgical patients.

The multivariate analysis in our study shows that serum creatinine values at admission and the presence of hypotension on the 1st day in the ICU are related to the presence of renal dysfunction during the rhabdomyolysis episode. This is in keeping with the findings reported in other patient populations.^[9,18,19,23]

The serum creatinine value measured on admission to the hospital is probably related to preexisting kidney injury and to the preadmission treatment though we did not find differences in the initial rehydration regimens in the two groups. In the multivariate analysis, its effect was statistically significant ($P = 0.006$), with a good discriminative capacity to predict kidney injury and an AUC-ROC of 0.91. Initial creatinine values ≥ 1.1 show good sensitivity (77.2%; 95% CI: 65.4–89.0), specificity (89.1%; 95% CI: 79.1–99.2), and adequate positive (89.8%; 95% CI: 80.3–99.3) and negative (75.9%, 95% CI: 63.6–88.3) predictive values.

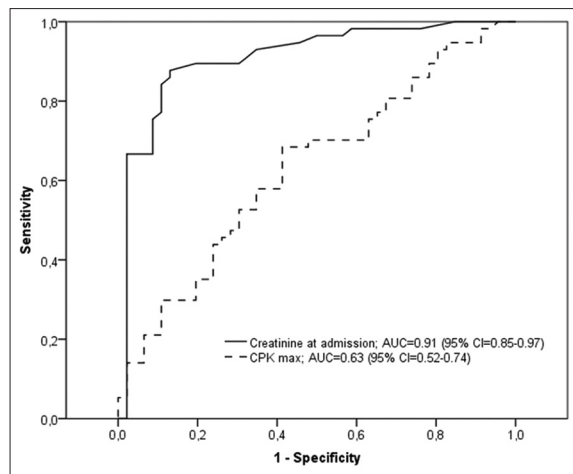


Figure 1: Receiver operating characteristics curve for predicting renal dysfunction based on values of creatinine at admission and maximum creatine phosphokinase during stay

Previous studies in diverse patient populations^[18,24,25] have pointed to dehydration and systemic hypotension as important factors. Morris *et al.*^[26] found that inadequate resuscitation contributed to kidney injury requiring hemodialysis. In our series, cardiovascular deterioration in the days immediately following the trauma in patients with acute SCIs and rhabdomyolysis were linked independently to kidney injury after adjusting for conventional variables. The hypotension immediately following the trauma probably involves a series of genetic and immune biological phenomena, cardiovascular ability to respond to the trauma, neurogenic damage after the SCI, presence of comorbidities, and initial treatment. Our results, however, show that the posttraumatic hemodynamic dysfunction does not invariably progress to renal dysfunction, with a sensitivity and specificity of around 60% for a hemodynamic SOFA ≥ 1 .

Of the 57 patients (55.3% of the patients with rhabdomyolysis) who developed kidney injury in our series, none required hemodialysis and all regained kidney function with conservative treatment. This is probably related to the population type (young and with a low comorbidity index), range of CPK values, and absence of nephrotoxic cofactors that are present in other types of rhabdomyolysis.

The mortality of patients with rhabdomyolysis was almost 3%, and the death rate had no direct relationship to the rhabdomyolysis or acute kidney injury. Kidney injury by itself was not a predictor of mortality in this series, probably due to the low impact on renal function.

To the best of our knowledge, this is the first series that studies the prevalence and prognosis of rhabdomyolysis

in patients with acute traumatic SCI requiring admission to an ICU. Our study was somewhat limited by its reliance on data from a single hospital and by its retrospective nature. We studied a small number of patients, but we included all those with SCIs and rhabdomyolysis over a given period. These patients were all subjected to the same diagnostic criteria and received similar treatments, which increase the internal validity of the study. While the retrospective nature of the study makes it vulnerable to information bias from inaccurate clinical records and missing data, the fact that the patients were in critical condition from the time of admission resulted in exhaustive clinical and laboratory analysis information. Finally, although residual confounding might be present, information regarding different sociodemographic and clinical variables was recorded and adjusted for in a multivariate regression analysis.

Conclusion

Rhabdomyolysis is a frequent (51.5%) and early condition in patients with acute traumatic SCI who were admitted to ICU and renal dysfunction occurred in over half of the cases (55.34%) though the prognosis is good. These data suggest that diagnostic markers should be requested starting at the admission. Initial creatinine values ≥ 1.1 mg/dL yielded a sensitivity of 77.2% and a specificity of 89.1% for the appearance of renal dysfunction. In contrast, neither the peak CPK values nor the hemodynamic SOFA score in the first 24 h exhibited a cutoff point that could be used to properly discriminate between patients with and without renal dysfunction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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