Prevalence and associated factors with rhabdomyolysis

Prevalência e fatores associados à rabdomiólise
Prevalencia y factores asociados a la rabdomiolisis

Ana Paula de Souza Cunha[ID], Bianca Oliveira Souza[ID], Cícero Santos Souza[ID], Danilo Miranda Bomfim[ID], Marcos Vinicius Santos de Jesus[ID], Gisele da Silveira Lemos[ID], Rafael Pereira[ID], Lucas Brasileiro Lemos[ID]

ABSTRACT

Introduction: Rhabdomyolysis (RB) is a frequent syndrome defined as skeletal muscle injury whereby intramuscular molecules, such as myoglobin and creatine phosphokinase, are released into the bloodstream. This study aimed to identify the prevalence of RB and associated factors to this outcome in in-hospital patients. Methods: This is an observational study - cross-sectional, retrospective, with a descriptive and analytical approach. The sample was composed of all in-hospital patients from a Brazilian public hospital that presented serum creatine phosphokinase measures recorded in medical records in the period from April 2020 to September 2021. Descriptive analysis was carried out with frequencies (absolute and relative) and means±standard deviation. The Chi-square test was used to infer the association to RB, and the variables presenting p-value ≤ 0.2 were included in a multivariate logistic regression technique applied to investigate the interaction among the selected independent variables and the RB. Results: Among 388 patients included in the present study, the prevalence of RB was 3.89% and the mortality rate was 39.43%. The main cause of hospitalization was circulatory system-related diseases. The frequency of RB was higher in males and in younger adults. The variables sex, age group, presence of comorbidities, trauma as the hospitalization cause, and history of recent exhaustive physical effort were significantly associated with RB. Conclusion: Our data share light on the profile of hospitalized patients prone to develop RB, a relevant clinical condition that could be unrecognized in many mild cases, but also lead to acute signals of renal failure. Additionally, our data brings a better understanding regarding mortality associated with RB, requiring greater attention from health professionals and managers.

Keywords: Rhabdomyolysis, Acute renal injury, Hemodialysis.

RESUMO

Introdução: A rabdomiólise (RB) é uma síndrome frequente definida como uma lesão do músculo esquelético em que moléculas intramusculares, como a mioglobina e a creatina fosfoquinase, são liberadas na corrente sanguínea. Este estudo teve como objetivo identificar a prevalência de RB e os fatores associados a esse desfecho. Métodos: Trata-se de um estudo observacional - transversal, retrospectivo, com abordagem descritiva e analítica. A amostra foi composta por todos os pacientes internados de um hospital público brasileiro que apresentaram medidas séricas de creatinofosfoquinase registradas em prontuários no período de abril de 2020 a setembro de 2021. A análise descritiva foi realizada com frequências (absolutas e relativas) e médias± desvio padrão. O teste qui-quadrado foi utilizado para inferir a associação com RB e as variáveis que apresentaram p-valor ≤ 0,2 foram incluídas em uma técnica de regressão logística multivariada aplicada para investigar a interação entre as variáveis independentes selecionadas e a RB. Resultados: Entre os 388 pacientes incluídos no presente estudo, a prevalência de RB

foi de 3,89% e a taxa de mortalidade foi de 39,43%. A principal causa de internação foram as doenças relacionadas ao aparelho circulatório. A frequência de RB foi maior no sexo masculino e em adultos mais jovens. As variáveis sexo, faixa etária, presença de comorbidades, trauma como etiologia da internação e história de esforço físico exaustivo recente apresentaram associação significativa com RB. Conclusão: Nossos dados trazem luz sobre o perfil de pacientes hospitalizados propensos a desenvolver RB, uma condição clínica relevante que pode não ser reconhecida em muitos casos leves, mas também pode levar a sinais agudos de insuficiência renal. Além disso, nossos dados trazem um melhor entendimento sobre a mortalidade associada à RB, exigindo maior atenção dos profissionais de saúde e gestores.

Palavras-chave: Rabdomiólise, Lesão renal aguda, Hemodiálise.

INTRODUCTION

Rhabdomyolysis (RB) is a common syndrome, defined as skeletal muscle damage that results in the release of creatine kinase (CK) and myoglobin into the bloodstream.[1] It is estimated that, in the United States of America, around 1 in 10,000 people may be affected by RB in their lifetime, then, knowledge about the prevalence and associated factors to this outcome could help clinicians.[2]

Hereditary, such as metabolic myopathies, history of recent trauma, infections, medication use, alcohol abuse, illicit drugs abuse, exhaustive physical efforts, and excessive heat, among others are reported as the most common etiologies of RB. [3, 4, 5]

Regarding the clinical presentation some studies have described clinical features ranging from asymptomatic serum CK elevations (more than 5 times the upper limit of normality), myoglobinuria, hydroelectrolytic disturbances, disseminated intravascular coagulation, and acute renal injury (ARI), which can be potentially fatal, especially when serum CK levels are greater than 5,000U/L, since it is highly associated with ARI. [5, 6, 7] Indeed, it is reported a prevalence of 13 to 50% of ARI among patients with RB. [8, 9] While it is estimated that ~78% of these patients recover renal function. [10, 11]

The classic triad of symptoms of rhabdomyolysis includes muscle pain, weakness, and dark urine. However, less than 10% of patients presented all signs of this classic triad, and up to 50% of patients do not report muscle pain or weakness. [12] Despite this, treatment should be instituted immediately after diagnostic confirmation, and vigorous volume replacement is reported as the main intervention to prevent acute renal failure. Bicarbonate can be used to alkalinize the urine, reducing the risk of tubular obstruction by myoglobin. Mannitol and diuretics can be used, but have little scientific evidence [5, 13].

The clinical consequences of RB are often dramatic in terms of morbidity and mortality, with mortaliy rates as high as 59% in severe cases.[14] Generally, the triggering factors are not recognized, so that clinical prevention strategies are often ineffective. Thus, it is necessary to broaden the epidemiological and clinical/laboratorial data on the subject. Therefore, the present study aimed to identify the prevalence and associated factors with rhabdomyolysis in in-hospital patients.

METHODS

Sample and data recordings

This is a cross-sectional, retrospective, descriptive and analytical study, based on medical records from April 2020 to September 2021. The study was conducted in a Brazilian public hospital, structured to support 27 municipalities of Southern Bahia (approximately 600 thousand inhabitants). The unit offers specialties in clinical medicine, clinical surgery, orthopedics, neurology, neurosurgery, pediatrics, psychiatry, and intensive care, guaranteeing the population access to medium and high-complexity procedures.

The studied sample comprised patients who presented serum CK > 1300 U/L. Patients with an incomplete medical history recorded at hospital admission, aged less than 18 years old, and patients with an established diagnosis of chronic kidney disease stage V (terminal) were excluded.

In this study, RB was defined by CK values five fold the upper limit of the normal reference value, i.e. > 1300 U/L, regardless of the inpatient ward.[15]

Previously trained graduate and undergraduate students recorded data from medical records using a form developed using Google Forms®. A pilot test of the data-collection instrument was conducted to identify necessary adjustments. The medical records analyzed in the pilot test were included in the total sample of the study, after the necessary adjustments.

This study was approved by the ethics and research committee of the Universidade Estadual do Sudoeste da Bahia (protocol number 4.684.585). Finally, the identification of patients was preserved using the medical record number and acronyms of the names in the data recording tables.

Study Variables

Dependent Variable

RB severity was classified as mild (CK < 4000 U/L) and moderate to severe (CK ≥ 4000 U/L) according to serum CK levels.

Independent variables

The sociodemographic variables were categorized as sex (female and male), age group (non-elderly < 60 years or elderly equal to or > 60 years), race/skin color (white or non-white), and marital status classification (with a partner or without a partner). The marital status defined as without a partner included single, widowed, and divorced people.

Clinical variables: comorbidities, hypertension, diabetes mellitus, non-dialytic nephropathy, overweight or obesity, trauma < 24 hours, infection, statin use, exhaustive exercise < 48 hours, seizures, licit and illicit drug use, antipsychotic use, and diagnosis of new coronavirus 19 disease (COVID19), were dichotomized as yes or no.

The cause of hospital admission was categorized according to the International Classification of Diseases (ICD-10).[16] In addition, recording of volume replacement (yes or no), inter-consultation with a nephrologist (yes or no), ARF (yes or no), and hemodialysis (HD) (yes or no), as well as the amount of performed HD and the outcome death (death and non-death)

were also analyzed.

Prevalence was calculated by the number of patients with RB per all patients who were admitted to the hospital (9963 patients), and mortality was calculated by the number of deaths of patients with RB per all patients seen with RB (CK > 1300 U/L), in both periods corresponding to the study.

The 'trauma' etiology was defined as muscle injury resulting from an external force, such as a vehicle accident and/or crush injury, in the absence of contributing medical factors, such as syncope or falls. [8]

Regarding dialysis nephropathy, the terms end-stage V nephropathy and dialysis chronic kidney disease were considered in the medical record. Infection was defined by the presence of an increase in the total leukocytes above the reference value, fever, and/or use of antibiotics. The antipsychotic use was defined as before admission, within 24 hours of hospital admission, and within 24 hours of hospitalization. Positive RT PCR and/or positive antigen test was considered for the diagnosis of COVID-19.

In this study, volume replacement was defined as > 500 mL of fluid (saline, glucose, and/or ringer lactate) being replaced within 24 hours. ARF was defined as a 1.5-fold increase from baseline creatinine value at hospital admission, according to the Kidney Disease Improving Global Outcome (KDIGO) criteria. [17] In outcome, no death refers to hospital discharge, transfer, or evasion.

Data Analysis

For descriptive analysis, absolute and relative frequencies, and mean±standard deviation, were used for categorical and continuous variables, respectively. Pearson's chi-square test was used to compare the proportions of categorical variables.

The variables that achieved a significance level of $p < 0.2$ in the Chi-square test were included in a logistic regression model. The magnitude of association was calculated using the prevalence ratio with 95% confidence intervals and a significance level was set as $p < 0.05$. Data were analyzed using IBM SPSS V.21.0 (SPSS, IBM Corporation, Armonk, New York, USA).

RESULTS

From the studied sample, 388 patients presented CK dosage > 1300 U/L and meet all inclusion criteria (figure 1). Initially, 408 patients were selected, but 20 patients were excluded owing to incomplete hospital admission data (n = 1), chronic renal disease with dialysis (n = 8), and aged less than 18 years (n = 11).
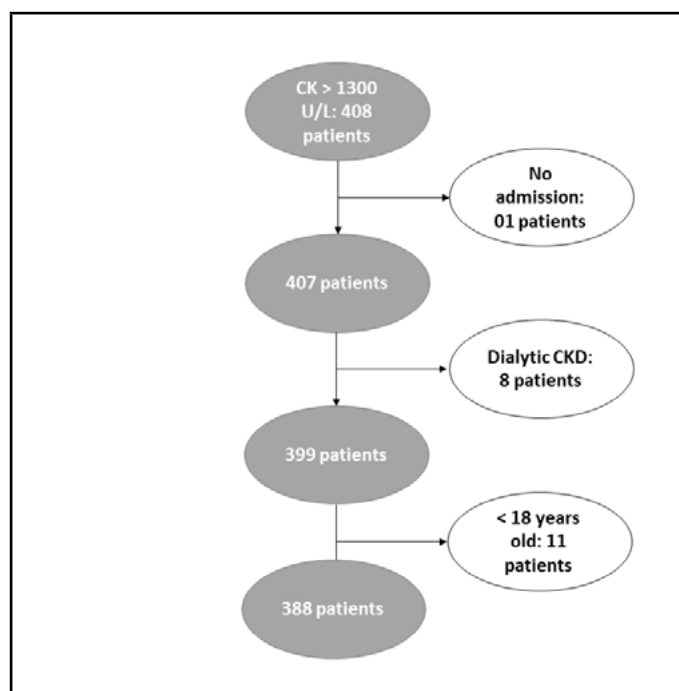
Figure 1 - Flow chart of the sample selection process. Bahia, Brazil, 2020 - 2021.

CKD: Chronic kidney disease.

The prevalence of RB was 3.89% and the mortality among these patients was 39.43%, with a mean serum CK = 5289.49 ± 20804.41 U/L, with values ranging from 1303 to 394050 U/L. Regarding the causes of hospital admission, according to ICD-10 (WHO, 2016), the two most frequent reasons were circulatory system diseases (39.50%) and injuries, poisoning and some other external causes (19.90%). Regarding the number of HD sessions performed, it ranged from 1 to 15 sessions, and 51.9% performed 1 to 3 sessions. Regarding the in-hospital days, we found an average of 16.00 ± 17.01 days.

Regarding the sociodemographic variables, there was a predominance of males (74%) and of young adults (51.8%), as shown in table 1.

Table 1 - Sociodemographic and clinical variables of in-hospital patients with rhabdomyolysis. Bahia, Brazil, 2020 - 2021.

Variables	N	(%)
Sex (n=388)		
Men	287	74
Women	101	26
Age group (n=388)		
Young adult	201	51.8
Elderly	187	48.2
Race/skin color (n=308)		
Non-white	305	99.0
White	3	1.0
Marital status (n=317)		
Without a partner	195	61.5
With a partner	122	38.5
Comorbidity (n= 350)		
Yes	262	74.9
No	88	25.1
Hypertension (n= 350)		
Yes	203	42.0
No	147	58.0
DM (n=350)		
Yes	87	24.9
No	263	75.1

Non-dialytic nephropathy (n=350)

Yes	5	1.4
No	345	98.6

Overweight and obesity (n=350)

Yes	31	8.9
No	319	91.1

DM: Diabetes mellitus

Table 2 shows the clinical variables of the in-hospital patients with RB, highlighting that 74.9% exhibited some comorbidity, 38.9% had ARF at some point during hospitalization, 13.9% needed HD procedure, and 39.4% died.

Table 2 - Clinical variables of in-hospital patients with rhabdomyolysis. Bahia, Brazil, 2020 - 2021.

Variables	N	(%)
Antipsychotics (n= 250)		
Yes	49	19.6
No	201	80.4
Statins (n= 246)		
Yes	155	63.0
No	91	37.0
Trauma (n= 167)		
Yes	70	41.9
No	97	58.1
Infections (n= 355)		
Yes	293	82.5
No	62	17.5

Exhaustive physical exercises (n= 65)

Yes	6	9.2
No	59	90.8

Seizures (n= 126)

Yes	34	73.0
No	92	27.0

Licit and/or illicit drugs (n= 118)

Yes	94	79.7
No	24	20.3

COVID-19 (n= 150)

Yes	41	27.3
No	109	72.7

ARF (n= 386)

Yes	150	38.9
No	236	61.1

Volume replacement (n= 336)

Yes	257	76.5
No	79	23.5

Consultation with a nephrologist (n= 388)

Yes	87	22.4
No	301	77.6

Hemodialysis (n= 388)

Yes	54	13.9
No	334	86.1

Outcome (n= 388)

Survive	**235**	**60.6**
Death	**153**	**39.4**

ARF: Acute renal injury. RB: Rhabdomyolysis.

The prevalence of RB moderate to severe was 27.3%. Table 3 presents the associations between sociodemographic and clinical characteristics with the severity of RB. It was found that sex (PR= 2.66, CI = 1.46 - 4.86), age group (PR= 2.24, CI=1.41 - 3.57), comorbidities (PR =0.53, CI= 0.32 - 0.90) and trauma (PR = 2.56, CI= 1.31 - 5.00) were statistically associated with RB severity.

Table 3 - Prevalence ratio with its respective 95% confidence interval from regressions between sociodemographic and clinical characteristics and the rhabdomyolysis severity in in-hospita patients. Bahia, Brazil, 2020 - 2021.

	RB n (%)		p-valor	RP (IC)
	Mild	**Moderate to severe**		
Sex				
Men	196 (69.5)	91 (85.8)	0.001	2.66 (1.46 - 4.86)
Women	86 (30.5)	15 (14.2)	1	
Age group				
Young adult	131 (46.5)	70 (66.0)	0.001	2.24 (1.41 - 3.57)
Elderly	151 (53.5)	36 (34.0)	1	
Marital status				
Without a partner	134 (58.3)	61 (70.1)	0.054	1.68 (0.99 - 2.85)
With a partner	96 (41.7)	26 (29.9)	1	
Comorbidity				
Yes	203 (78.1)	59 (65.6)	0.019	0.53 (0.32 - 0.90)
No	57 (21.9)	31 (34.4)	1	
Hypertension			0,043	
Yes	159 (61.2)	44 (48.9)	0.043 0. 0.043 0.043	0.61 (0.38 - 0.99)
No	101 (38.8)	46 (51.1)	1	
DM				
Yes	70 (26.9)	17 (18.9)	0.131	0.63 (0.35 - 1.15)
No	190 (73.1)	73 (81.1)	1	
Trauma				
Yes	40 (34.8)	30 (57.7)	0.006	2.56 (1.31 - 5.00)
No	75 (65.2)	22 (42.3)	1	

Statins				
Yes	118 (65.6)	37 (56.1)	0.173	0.67 (0.38 - 1.19)
No	62 (34.4)	29 (43.9)	1	
Exhaustive physical exercise				
Yes	2 (4.1)	4 (25.0)	0.026	7.83 (1.28 - 47.96)
No	47 (95.9)	12 (75.0)	1	
Consultation with a nephrologist				
Yes	58 (20.6)	29 (27.4)	0.154	1.46 (0.87 - 2.44)
No	224 (79.4)	77 (72.6)	1	
Hemodialysis				
Yes	35 (12.4)	19 (17.9)	0.164	1.54 (0.84 - 2.83)
No	247 (87.6)	87 (82.1)	1	

PR: prevalence ratio. CI: confidence interval. RB: Rhabdomyolysis. DM: Diabetes Mellitus.

DISCUSSION

The present study investigated the prevalence of RB and its mortality among in-hospital patients. We found a prevalence of 3.89% and the mortality among these patients was 39.43%. Previous studies found a prevalence of 9.2%, but included only patients in an intensive care unit (ICU).[3] Indeed, methodological aspects, such as the diagnostic criteria (e.g., serum CK cut-off) and the investigated unit (e.g., ICU) could lead to divergent RB prevalence. Then, it is expected a higher prevalence of RB in in-hospital patients from the high complexity units, such as the ICU.

Regarding mortality, was found in study a mortality rate of 8.42%, which is lower than we found (39.43%)[18]. Again, the methodological aspects may explain the divergence, that included only patients from the hospital ward, which is characterized by low-complexity patients and lower risk of death, while we investigated RB prevalence among all hospital sections.

Trauma or excessive muscular efforts are pointed out as the most common cause of RB.[18] Indeed, RB secondary to trauma was reported as the most common cause of RB in that study, which excluded patients with acute myocardial infarction with elevated troponins, a relevant methodological aspect that was not possible in our study[18]. Despite this, we found that 41.9% of in-hospital patients with RB reported historic trauma before hospitalization.

In our study, the average of in-hospital days was 16.00 ± 17.01 among patients with RB, very close from another study, which found a median of 13 days.[18] It is important to note that the cited study included only patients from the hospital ward, which is characterized by low-complexity patients, while we included patients from all hospital sections.

In our study, 13.9% of patients diagnosticated with RB needed HD and, despite a well-established relationship between serum CK levels and HD needs,[19] in our study HD need was not significantly associated with RB severity. Despite this, we found a prevalence of 38.9% of ARF among the patients with RB, which could be associated with longer hospitalization, since ARF is a condition that requires more attention and health care.

In our study, moderate to severe RB was more prevalent among men. Indeed, moderate to severe RB was 2,66 (1,46 - 4,86) greater in men than women. In this sense, another studies also showed a greater prevalence of RB among men. [8, 20] Regarding the age group, was found the mean age of RB involvement in an Australian trauma center was 49 years old.[8] In fact, young adults male show greater vulnerability to developing RB due to behaviors and activities associated with greater risk, including injuries by trauma. [21]

In another study was identified exhaustive physical exercise as the main etiology of RB with a frequency of 19.6%. [20] Unlike the present study, this study did not have a time criterion between the physical exercise carried out and hospital admission, which may justify the greater presence of this etiology.

The prevalence of hypertension and DM was greater among patients with RB in our study, which was also observed in the another study.[18] Despite this, in our study, only hypertension was significantly associated with RB severity. In addition, we found a 27.3% of patients with RB and tested positive for COVID-19, corroborating founds in the another study. [1] This result does not allow for the establishment of a cause-and--consequence relationship, since data was recorded during the pandemic period, then, it is suggested that future studies designed to investigate this issue, could be conducted.

Regarding the frequency of ARF, our founds agree with another study founds,[3] whereas a retrospective study conducted in the emergency department of a tertiary care hospital in Turkey where was found a lower frequency (8.8%). [20] Our higher prevalence of ARF could be justified by the main etiology of RB in our study, which was circulatory diseases and trauma, justifying the greater severity and development of ARF, while in other studies the main etiology was exhaustive physical exercise.

In a study was identified an association between comorbidities and death in patients with RB.[8] Unlike this trend, the present study found comorbidity associated with mild MB, but it could be explained by the profile of our sample since we found a higher prevalence of RB in patients aged > or equal to 60 years.

It is worth mentioning some aspects representing the limitations of this study. The present study was conducted in only one hospital and, about the traumatic etiology of RB, our study could exhibit a bias to find more high-energy traumas, while in the case of elderlies, low-energy traumas such as hospitalization after falling from own height can also lead to RB.

From the perspective of the benefits of our study, it was possible to identify the prevalence of RB and its associated factors at the in-hospital level with a significant sample of patients. In addition, it is possible to have a better understanding of this condition with high mortality, requiring greater attention from health professionals.

In further studies, the use of prospective methodology is suggested for a better understanding of the cause-and--consequence relationship between RB etiologies and the associated factors to RB severity as well as its mortality.

CONCLUSION

The prevalence and factors associated with RB at the in-hospital level were evidenced in the study. Regarding this, a high mortality rate in patients with RB was identified, as well as the association of sex, age group, comorbidities, trauma, and exhaustive physical exercise with the severity of RB.

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Contribuição dos autores:

APSC: Substantial contribution to the study outline and data interpretation; Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

BOS: Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

CSS: Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

DMB: Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

MVSJ: Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

GSL: Substantial contribution to the study outline and data interpretation; Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

RP: Substantial contribution to data interpretation; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

LBL: Substantial contribution to the study outline and data interpretation; Participation in writing the preliminary version; Participation in the review and approval of the final version; Compliance with being responsible for the accuracy or completeness of any part of the study.

Corresponding Author:
Ana Paula de Souza Cunha
souzacunhaanapaula@gmail.com