Heliyon 8 (2022) e12509

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Elevated body temperature and leukocyte count are associated with elevated creatine kinase after seizures

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ARTICLE INFO

Keywords:
Creatine kinase
Seizures
hyperCKemia
Body temperature
Leukocyte count
Infection

ABSTRACT

Objective: To evaluate the independent risk factors for elevated creatine kinase (hyperCKemia) after seizures.
Methods: Data included in this retrospective study were obtained from two hospitals from July 1, 2017, to March 31, 2022. Clinical and laboratory data were acquired from the emergency department or within 24 h after patient admission. Variables that exhibited statistical differences ($P < 0.05$) were selected for further analysis. Associations between body temperature (BT), leukocyte count (LEU), percentage of neutrophils (NEU), and C-reactive protein (CRP) and creatine kinase (CK) levels were assessed using binary logistic regression analysis.
Results: One hundred twenty-three patients who exhibited seizures were included in the study, and 39 (31.7%) patients exhibited hyperCKemia based on a CK level that was >1.5 times the upper limit of the normal range for CK. No statistical differences were observed among the patient characteristics, seizure-related parameters, or electrolyte levels. However, BT, LEU, NEU, and CRP were elevated in patients with hyperCKemia compared to patients with normal CK levels. Specifically, a BT $\geq$ 37.5 °C (fever) and LEU $>9.5\times10^9$/L (elevated LEU) exhibited positive correlations with hyperCKemia, and presented an adjusted OR of 8.87 (95% CI: 2.11–37.24, $P = 0.003$) and 3.01 (95% CI: 1.12–8.05, $P = 0.029$), respectively.
Conclusion: In this study, hyperCKemia occurred in 31.7% of patients after seizures. Fever and elevated LEU were independent risk factors for seizure-related hyperCKemia. Earlier recognition of risks for seizure-related hyperCKemia would be beneficial in taking prophylactic measures.

1. Introduction

Creatine kinase (CK) is a vital enzyme in muscle for energy metabolism, it catalyzes rephosphorylation of ADP to maintain the intracellular concentration of ATP [1]. Elevated serum CK is associated with various etiologies, such as acute myocardial infarction, physical exertion, viral illnesses, and particularly muscle damages [1, 2, 3, 4, 5], which can disrupt the sarcolemma. Numerous molecules within muscle cells are excreted through a damaged sarcolemma and are involved in myoglobinuria, acute kidney injury (AKI), and possibly cardiac dysrhythmia [6, 7].

Epileptic seizures are known to induce an acute increase in CK [8, 9]. Elevation of CK of ≥15 U/L from the first to second day after a seizure is helpful in distinguishing generalized tonic–clonic seizures (GTCS) from syncope [10]. Tonic, clonic, and myoclonic movements associated with seizures or status epilepticus (SE) can be considered as involuntary muscle overuse [6, 11, 12]. A recent study identified seizures have the potential contribution to CK elevation [13], and seizures are commonly recognized as one cause of rhabdomyolysis (RM) [6, 14, 15, 16]. Another study indicated that renal replacement therapy or in-hospital mortality due to seizures within three days after admission accounted for 6.0% of patients with CK > 5,000 U/L [17]. Elevated CK with few symptoms and without renal failure at the condition of chronic or intermittent muscle overuse can be called hyperCKemia [14, 18].

Cardiopulmonary function support and seizure control are the most concern in the emergency department after the onset of seizures or SE [19]. Thus, it is likely that CK elevation due to seizures could be overlooked initially. CK increases gradually after muscle injury and reaches its peak within three to five days [20], due to the time lag, the insidious progression of hyperCKemia might be overlooked. The ability to identify the risk of hyperCKemia after seizure occurrence would be beneficial in

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https://doi.org/10.1016/j.heliyon.2022.e12509
Received 26 May 2022; Received in revised form 15 October 2022; Accepted 13 December 2022

taking prophylactic measures and improving the patient's prognosis. However, current studies concerning the risk factors for seizures related to hyperCKemia have not been conducted. In this study, we used clinical and laboratory data to evaluate the risk factors for hyperCKemia after seizure onset.

2. Methods

2.1. Study population

In this retrospective study, we obtained data from electronic medical records from two hospitals (the First Affiliated Hospital of Anhui Medical University [FAH] and Anhui Provincial Hospital [APH] located in Hefei, China). The records included patients admitted from July 1, 2017, to March 31, 2022.

The following inclusion criteria were used in this study. (1) Patients were older than 18 years. (2) Motor signs of seizures complied with the terms described by the International League Against Epilepsy as diagnostic criteria for seizures, including tonic, clonic, myoclonic, or a combination of these motor signs [11]. (3) Clinical and laboratory data were available in the emergency department or within 24 h after admission. The following exclusion criteria were used in this study. (1) Patients who presented with other distinguishable diseases that resulted in CK elevation, including acute myocardial infarction, acute massive cerebral infarction, and muscle trauma. (2) The patient exhibited impaired liver function with a level of alanine aminotransferase that was greater than three times the upper limit of the normal range (ULN) and a total bilirubin level $\geq$2 ULN [21]. Because we should exclude the possibility of the patients taking hepatotoxic drugs, which might cause an elevated baseline CK [14]. 3) Patients were excluded if they did not have complete clinical or laboratory data, including vital signs, detailed medical records, CK, liver and kidney function, and electrolytes.

2.2. Data collection

We obtained information on the following: (1) Patient demographics, including age, gender, weight, height, and body mass index (BMI), which was calculated as weight (kg) divided by height (m) squared; (2) History of smoking, alcohol consumption, hypertension, diabetes, seizures, and drugs; (3) Body temperature (BT), systolic blood pressure (SBP), and diastolic blood pressure (DBP) on admission; (4) Seizure-related parameters, including seizure duration, recurrence before admission, bilateral or unilateral convulsions, the interval between the first onset to admission (IT), and motor signs. The term "convulsion" was used usually to indicate "motor signs" in the medical records as most witnesses could not describe "tonic, clonic, or myoclonic" precisely; (5) Laboratory tests, including CK, creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), leukocyte count (LEU), percentage of neutrophils (NEU), C-reactive protein (CRP), potassium, sodium, chlorine, albumin, bicarbonate, uric acid, creatinine, and the estimated glomerular filtration rate (eGFR). We did not collect data for urea nitrogen because it is a nonspecific marker for renal function and an inferior marker relative to creatinine [22]. The eGFR was calculated using an equation validated in the Chinese population [23]. We were unable to collect data for calcium, phosphate, myoglobin, and myoglobinuria for all patients as these tests were not performed for some patients.

2.3. Categorical standards of the variables

The cutoffs used for each variable were consistent with existing studies. (1) Age was based on the lower differences of CK activity between exercise and inactive in patients <50 years compared to patients who were $\geq$50 years [24]. A determination of a patient as overweight was based on a BMI $\geq$25 kg/m^2 [25]. (2) A current smoker or drinker was defined as smoking $\geq$ seven cigarettes per day or consuming one to seven drinks per week (a drink was determined to contain approximately 12–14 g of ethanol), respectively [26, 27]. (3) We defined fever as having a BT $\geq$ 37.5 °C [28]; hypertension as having a SBP $\geq$140 mmHg, a DBP $\geq$90 mmHg, or current use of antihypertensive medications [24]; diabetes as a history of diabetes, use of hypoglycemic agents, or HbA1c $\geq$ 6.5% [24]; renal impairment as an eGFR <60 ml/min/1.73m^2 [29]. (4) Drugs that were associated with muscle damage primarily included statins, antiepileptic drugs, and antipsychotics [14, 15, 30]. (5) Bilateral convulsions were noted when motor signs were described as "convulsions of all four limbs or the whole body." Otherwise, the motor signs were considered unilateral or indicative of a focal convulsion. Seizure duration was based on the duration of the "motor signs," and the longest duration was used if recurrences happened; a cutoff of $\geq$5 min was utilized as the duration that required emergency treatment [12]. IT was defined as the interval of time from seizure onset to laboratory tests, and the intervals were categorized as $\leq$ 1 day and $\leq$5 days, because CK begins to increase two to 12 h after muscle injury and exhibits a peak within three to five days [20]. (6) HyperCKemia was defined as CK > 1.5 ULN, as proposed by the EFNS guidelines [18] in which the cutoffs are 403.5 U/L and 465 U/L in APH (reference value: 22–269 U/L) and FAH (reference value: 50–310 U/L), respectively, without gender differences. (7) The cutoffs for LEU, NEU, and CRP were reference values that were used at the two hospitals, which were the same.

2.4. Statistical analysis

The distributions of continuous variables were evaluated using P–P plots and calculation of kurtosis and skewness. Some skewed data were transformed into log scales (Log LEU: kurtosis -0.23, skewness 0.07; Log CRP: kurtosis 0.43, skewness 0.12; Log creatinine: kurtosis 0.43, skewness 0.53; Log uric acid: kurtosis 0.43, skewness -0.05).

Descriptive data were presented as means ± SD, medians (interquartile ranges [IQR]), and as numbers (frequency) for variables with normal distributions, skewed distributions, and as categories, respectively. The Student's *t*-test, Mann-Whitney U test, and Chi-square test (Fisher exact test) were used to compare means, medians, and frequencies, respectively. Variables with $P < 0.05$ determined from the results of the univariate analyses were considered confounders in the binary logistics regression analysis. Spearman's rank correlation was used to assess associations between continuous variables. A two-sided $P < 0.05$ was considered statistically significant. All analyses were conducted using SPSS software 22 (SPSS, Inc, Chicago, USA).

3. Results

3.1. Patient characteristics and seizure-related parameters

One hundred twenty-three patients with seizures were eligible for further evaluation in this study, and 39 (31.7%) patients exhibited hyperCKemia based on a CK value that was >1.5 ULN (Table 1). The ranges for age, BMI, BT, seizure duration, and IT in all patients were 16–90 years, 16.0–26.2 kg/m^2, 36.0–39.2 °C, 0.2–60 min, and 0.5–10 days, respectively (data not shown). The numbers of male patients, current smokers or drinkers, recurrence before admission, and bilateral convulsions were higher in patients with hyperCKemia (PHCK) than patients with normal CK (PNCK). The numbers of patients with a history of hypertension or diabetes, seizures, and taking drugs associated with muscle damage were slightly lower in PHCK than PNCK. There were no differences in the rate of occurrence between groups ($P > 0.05$) of the variables listed above. The means or medians of additional variables between PHCK and PNCK are shown in Table 1, which also revealed no differences ($P > 0.05$). However, BT was higher in PHCK (median: 36.8 °C, IQR: 36.5–37.6 °C) than PNCK (median: 36.6 °C, IQR: 36.5–36.8 °C), which was statistically significant ($P = 0.018$). Based on previously published studies [15, 24, 25, 31], we performed additional comparisons between the different categories related to hyperCKemia (Table 3). The results demonstrated that the

Table 1. Patient characteristics and seizure-related parameters.

Variables	PNCK (n = 84)	PHCK (n = 39)	*P value*
Age (years)	55.0 (32.0–75.0)	50.0 (33.0–66.0)	0.307
Gender, male (n, [%])	48 (57.1)	28 (71.8)	0.120
Weight (kg)	64.40 ± 10.5	65.4 ± 7.7	0.585
Height (cm)	166.0 ± 8.1	168.7 ± 5.4	0.058
Body mass index (kg/m^2)	23.3 ± 2.9	23.0 ± 2.6	0.575
Body temperature (°C)	36.6 (36.5–36.8)	36.8 (36.5–37.6)	0.018 *
Systolic blood pressure (mmHg)	129.6 ± 26.9	130.5 ± 16.8	0.860
Diastolic blood pressure (mmHg)	78.0 ± 13.7	79.1 ± 11.6	0.678
Current smoker (n, [%])	9 (10.7)	9 (23.1)	0.071
Current drinker (n, [%])	7 (8.3)	7 (17.9)	0.118
History of hypertension or diabetes (n, [%])	42 (50.0)	16 (41.0)	0.354
Drugs associated with muscle damage (n, [%])	24 (28.6)	9 (23.1)	0.552
History of seizures (n, [%])	42 (50)	15 (38.5)	0.232
Recurrence before admission (n, [%])	47 (56.0)	24 (61.5)	0.560
Bilateral convulsions (n, [%])	73 (86.9)	36 (92.3)	0.380
Seizures duration (minutes)	4.0 (2.0–8.8)	4.0 (3.0–7.0)	0.683
Interval time from first onset to admission (days)	2.0 (0.5–3.0)	1.0 (0.5–3.0)	0.593

PNCK: patients with normal creatine kinase; PHCK: patients with hyperCKemia. Values are means ± SD, n (%) or medians (interquartile ranges) as indicated. *P value: P < 0.05 indicates statistical differences between groups.

rate of fever in PHCK (25.6%) was significantly higher than in PNCK (3.6%) ($P = 0.001$). There were no statistical differences in other categories between PHCK and PNCK ($P > 0.05$).

3.2. Laboratory tests

The CK range among all patients was 24–59,840 U/L. The CK ranges in PHCK and PNCK were 417–59,840 U/L and 24–444 U/L, respectively. As seen in Table 2, the levels of CK, CK-MB, LDH, AST, (Log) LEU, NEU, and (Log) CRP were significantly higher in PHCK than PNCK ($P < 0.05$). The levels of other variables, including potassium, sodium, chlorine, albumin, (Log) creatinine, eGFR, (Log) uric acid, and bicarbonate were not statistically different between the two groups ($P > 0.05$). As seen in Table 3, the rates for elevated LEU, NEU, and CRP in PHCK (59.0%, 56.4%, and 53.8%, respectively) were significantly higher than PNCK (25.0%, 33.3%, and 32.1%, respectively) ($P < 0.001$, $P = 0.015$, and $P = 0.022$, respectively).

3.3. Possible predictors for seizure-related hyperCKemia

Fever and elevated LEU, NEU, and CRP were positively correlated with hyperCKemia, with odds ratios (ORs) of 9.31 (95% confidence interval [CI]: 2.39–36.21, $P = 0.001$), 4.31 (95% CI: 1.92–9.66, $P < 0.001$), 2.59 (95% CI: 1.19–5.64, $P = 0.017$), and 2.46 (95% CI: 1.13–5.37, $P = 0.023$), respectively (see Model 1 in Table 4). We selected one variable from Model 1 as an independent variable with hyperCKemia as the dependent variable, and the remaining three variables were used for adjustment (Hosmer-Lemeshow, $P = 0.88$). HyperCKemia still was associated positively with fever and an elevated LEU with adjusted ORs (aOR) of 8.87 (95% CI: 2.11–37.24, $P = 0.003$) and 3.01 (95% CI: 1.12–8.05, $P = 0.029$), respectively (Model 2 in Table 4). Spearman's rank correlation was used to assess the associations within BT, LEU, NEU, and CRP (Table 5). The results demonstrated that LEU was positively correlated with NEU ($r_s = 0.56$, $P < 0.001$) and CRP ($r_s = 0.47$, $P < 0.001$). There were no correlations between BT and LUE, NEU, or CRP ($P > 0.05$).

Table 2. Results of laboratory tests.

Variables	PNCK (n = 84)	PHCK (n = 39)	*P* value
Creatine kinase (U/L)	150.5 (85.0–216.5)	1031.0 (648.0–2450.0)	<0.001 *
Creatine kinase isoenzyme (U/L)	13.5 (10.3–19.0)	27.6 (19.0–51.0)	<0.001 *
Lactate dehydrogenase (U/L)	206.5 (172.8–264.8)	312.0 (238.0–560.4)	<0.001 *
Aspartate aminotransferase (U/L)	22.0 (16.0–29.8)	49.0 (32.5–98.0)	<0.001 *
(Log) Leukocyte count (×10^9/L)	0.88 ± 0.18	1.03 ± 0.19	<0.001 *
Percentage of neutrophils (%)	69.5 (62.2–80.8)	79.4 (63.4–88.3)	0.024 *
(Log) C-reactive protein (mg/L)	0.72 ± 0.69	1.13 ± 0.68	0.003 *
Serum potassium (mmol/L)	3.8 ± 0.5	3.7 ± 0.5	0.264
Serum sodium (mmol/L)	139.1 ± 4.5	138.7 ± 5.9	0.683
Serum chlorine (mmol/L)	102.7 ± 4.9	102.1 ± 6.4	0.626
Serum albumin (g/L)	40.3 ± 5.4	40.5 ± 7.3	0.835
(Log) Creatinine (μmol/L)	1.81 ± 0.16	1.81 ± 0.20	0.054
eGFR (ml/min/1.73 m^2)	87.8 ± 20.2	84.8 ± 21.8	0.446
(Log) Uric acid (μmol/L)	2.51 ± 0.17	2.55 ± 0.26	0.295
Bicarbonate (mmol/L)	25.3 (22.9–27.9)	24.7 (22.5–26.5)	0.178

PNCK: patients with normal creatine kinase; PHCK: patients with hyperCKemia. Values are means ± SD or medians (interquartile ranges) as indicated. *P value: $P < 0.05$ indicates statistical differences between groups.

4. Discussion

Seizures also have the ability to cause elevated CK and even increase the rate of in-hospital mortality, as "motor signs" that occurred during seizures could be considered to involve involuntary muscle overuse [6, 11, 13, 17]. In the present study, we investigated the risk factors for hyperCKemia observed at admission in patients after seizure onset. The results observed for CK-MB, LDH, and AST demonstrated differences between PHCK and PNCK ($P < 0.05$, Tables 2 and 3), which indicated that it was feasible to define hyperCKemia as CK > 1.5 ULN because CK-MB, LDH, and AST also may be elevated with muscle injury [6, 14].

The average level of CK at 48 h was 1,422.9 U/L after performing experimental exercise trials that damaged muscle [3]. However, the average level of CK was 16,884.4 U/L in exertional RM [13]. RM has been diagnosed based on CK > 1,000 U/L in most studies [20]. HyperCKemia occurred in 31.7% of patients at admission in our study. The highest level of CK was 59,840 U/L, and the range for CK in PHCK and PNCK were 417–59,840 U/L and 24–444 U/L, respectively, which indicated the ability of seizures to cause RM and not just hyperCKemia. The responses of muscle cells to local damage depend on the sarcolemma repair system, and small tears within the sarcolemma are repaired rapidly in healthy muscles [3, 32]. These observations demonstrated that the higher CK levels correlated with a greater amount of muscle injury, and the muscle damage caused by seizures was persistent.

Considerable published evidence demonstrated that elevated CK is associated with age, gender, BMI, diabetes, certain drugs, and unhealthy lifestyles [14, 24, 25, 33]. However, in our study, these variables did not significantly influence seizure-related hyperCKemia. Compared to

Table 3. Comparisons between different categories related to hyperCKemia

Variables	Category	PNCK (n = 84)	PHCK (n = 39)	*P* value
Gender (n, [%])	Male	48 (57.1)	28 (71.8)	0.120
Age (years, n, [%])	≥50	51 (60.7)	20 (51.3)	0.324
Body mass index (kg/m^2, n, [%])	≥25	22 (26.2)	8 (20.5)	0.495
Body temperature (°C, n, [%])	≥37.5 (Fever)	3 (3.6)	10 (25.6)	0.001 *
Drugs associated with muscle damage (n, [%])	Yes	24 (28.6)	9 (23.1)	0.552
Bilateral convulsions (n, [%])	Bilateral	73 (86.9)	36 (92.3)	0.567
Seizure duration (minutes, n, [%])	≥5	39 (46.4)	17 (43.6)	0.769
Recurrent seizures before admission (n, [%])	Yes	47 (56.0)	24 (61.5)	0.560
Interval time from first seizure to admission (days, n, [%])	≤1	41 (48.8)	21 (53.8)	0.587
	≤5	34 (40.5)	16 (41.0)	
	>5	9 (10.7)	2 (5.2)	
Creatine kinase isoenzyme (U/L)	>25	6 (7.1)	24 (61.5)	<0.001 *
Lactate dehydrogenase (U/L)	>250	24 (28.6)	29 (74.4)	<0.001 *
Aspartate aminotransferase (U/L)	>40	6 (7.1)	23 (59.0)	<0.001 *
Leukocyte count (×10^9/L, n, [%])	>9.5	21 (25.0)	23 (59.0)	<0.001 *
Percentage of neutrophils (%, n, [%])	>75	28 (33.3)	22 (56.4)	0.015 *
C-reactive protein (mg/L, n, [%])	>10	27 (32.1)	21 (53.8)	0.022 *
eGFR (ml/min/1.73 m^2, n, [%])	<60	4 (4.8)	3 (7.7)	0.815

PNCK: patients with normal creatine kinase; PHCK: patients with hyperCKemia.
*P value: $P < 0.05$ indicates statistical differences between groups.

previous studies, our results might be explained by differences in the recruited population, exercise regimens, the cutoff used to determine the presence of hyperCKemia, how well underlying disease was controlled, type and dosage of drugs, and consumption of tobacco or alcohol. The small sample was an unavoidable limitation in this study. In contrast to variables that are typically associated with hyperCKemia, it was intriguing that BT was identified as being associated with hyperCKemia.

Few previously published reports have discussed the relationship between BT and CK. One earlier study described a significant correlation between CK > 2,000 U/L and BT > 38.5 °C in children after cardiac surgery [34]. CK has been reported to increase for up to 48 h in cases involving whole-body hyperthermia systems used to treat cancer patients [35]. However, Cohen et al. did not observe any patients with a

Table 5. The associations within BT, LEU, NEU, and CRP (Spearman's rank correlation).

Variables	Body temperature (°C)		Leukocyte count (×10^9/L)	
	r_s	*P* value	r_s	*P* value
Leukocyte count (×10^9/L)	0.14	0.13	1.00	NV
Percentage of neutrophils (%)	0.00	0.95	0.56	<0.001 *
C-reactive protein (mg/L)	0.09	0.32	0.47	<0.001 *

BT: body temperature; LEU: leukocyte count; NEU: percentage of neutrophils; CRP: C-reactive protein.
NV: No values.
*P value: $P < 0.05$ indicates statistical differences.

body temperature of 41.8 °C that exhibited elevated CK after using a radiant heat device [36]. A sporadic case with an influenza A infection reported an elevated level of CK at approximately 6 h after a spike in temperature [4]. The diverse results that have been reported may be due to the existence of different etiologies and different cohorts of subjects. Several studies have pointed out that temperature elevation in severe febrile illnesses may not be related to elevated CK as other factors that affected CK could not be excluded, including peripheral hypoperfusion, muscle tissue breakdown, and hypoxia [4, 34, 36]. In addition, the elevation of BT and CK may be two independent clinical manifestations caused by the same adverse factor. A recent multi-center study revealed that BT was not correlated with RM in a study population that experienced acute recreational drug toxicity [37], indicating that some drugs have the potential to induce myocytotoxicity and hyperthermia simultaneously [37, 38]. All in all, the relationship between BT and CK is not entirely understood.

We observed that the rate of fever was significantly higher in PHCK than PNCK, the rate of BT < 37.5 °C was lower in PHCK than PNCK, and the OR of fever for hyperCKemia was 9.31 (95% CI: 2.39–36.21). Various infections have accounted for a considerable proportion of the causes of fever [39]. Therefore, other parameters associated with infection, including LEU, NEU, and CRP were investigated. The results indicated that elevated LEU, NEU, and CRP were risk factors for hyperCKemia. However, elevated NEU ($P = 0.345$) and CRP ($P = 0.465$) were not independent risk factors for hyperCKemia after adjusting for the other variables. LEU, NEU, and CRP elevations have been observed simultaneously in many infections [40, 41]. Therefore, we analyzed the correlations among these inflammatory markers. The results demonstrated that LEU was significantly correlated with NEU and CRP as well as the OR of LEU for hyperCKemia decreased from 4.31 to 3.01 after adjusting variables, indicating that NEU and CRP enhanced the impact of LEU in the development of hyperCKemia. In the present study, we determined that fever and elevated LEU were independent risk factors for hyperCKemia in patients after seizures.

Our results suggested that infection might be the underlying risk factor for hyperCKemia as fever and elevated LUE are markers of infection even though they are nonspecific [39, 40]. After further inspection

Table 4. Risk factors for seizure-related hyperCKemia (Binary logistics regression analysis).

Model 1				Model 2[#]			
Variables	β	OR (95% CI)	*P* value	Variables	β	aOR (95% CI)	*P* value
Fever	2.23	9.31 (2.39, 36.21)	0.001 *	Fever	2.18	8.87 (2.11, 37.24)	0.003 *
Elevated LEU	1.46	4.31 (1.92, 9.66)	<0.001 *	Elevated LEU	1.10	3.01 (1.12, 8.05)	0.029 *
Elevated NEU	0.95	2.59 (1.19, 5.64)	0.017 *	Elevated NEU	0.46	1.58 (0.61, 4.10)	0.345
Elevated CRP	0.90	2.46 (1.13, 5.37)	0.023 *	Elevated CRP	0.34	1.41 (0.56, 3.53)	0.465

CK: creatine kinase; ULN: upper limit of normal range; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval. Fever: body temperature (≥37.5 °C); Elevated LEU: leukocyte count (>9.5×10^9/L); Elevated NEU: percentage of neutrophils (>75%); Elevated CRP: C-reactive protein (>10 mg/L).
[#] Model 2 (aOR): One variable was selected from Model 1 as an independent variable with hyperCKemia selected as the dependent variable, and the other three variables remained for adjustments (Hosmer-Lemeshow, $P = 0.88$).
*P value: $P < 0.05$ indicates statistical differences.

of the cases in this study, the 13 PHCK with fever included patients with pulmonary infections (five), viral encephalitis (four), urinary tract infections (two), severe anemia (one), and diabetic ketoacidosis (one). The underlying etiology of the patient with severe anemia was gastrointestinal hemorrhage, for which the possibility of a gut-derived infection could not be excluded. Based on the evidence, it was possible that infection might be the risk factor for seizure-related hyperCKemia, which appeared a reasonable explanation for why not all instances of elevated BT caused an elevation in CK. However, further investigation is needed to improve the diagnostic accuracy for infections in patients after seizures.

Muscle damage can be induced by resistant exercise [3]. Several factors, including intensity and duration of exercise, the different muscle groups that are involved, and muscle contraction type, affect the degree of muscle damage [31]. An earlier study revealed that the average CK after GTCS increased from 116 U/L on the first day to 271 U/L on the second day [10]. An elevated CK above the normal limit (180 U/L) was observed in 15% of patients with GTCS, while no elevation in CK was observed in patients who experienced partial seizures [9]. The level of CK was 38.0 fold higher in patients with $\geq$ five seizures compared to a 7.5 fold increase in patients who experienced $<$ five seizures, indicating that CK was associated with the recurrence of seizures [42]. Nevertheless, there were no correlations between the parameters associated with seizures and hyperCKemia in this study. One possible reason for this result is that the inaccurate reports on seizure-related parameters described by witnesses. Gao H et al. have reported that the relatives of people with epilepsy had higher rates in mistaken descriptions on length of seizure, movement elements, and movements progression [43]. Indeed, retrospective seizure descriptions can be difficult tasks for witness who were not trained to understand the meaning and key points of the seizure movements. Additionally, the possible influence of a small sample size on the negative outcome cannot be excluded. Future studies with larger samples were conducted in epilepsy monitoring unit equipped with video electroencephalogram may facilitate to interpret the associations between seizure-related parameters and hyperCKemia induced by seizures.

5. Limitations

To our knowledge, this is the first retrospective study to evaluate the risk factors for hyperCKemia after the onset of seizures. However, there were several limitations in our study. First, the small sample size limited the number of fever patients that were included, which might limit the interpretation of the results. Second, we did not obtain data concerning the treatment of patients before admission to our hospitals. We collected data concerning CK levels and other variables at the time of admission as our aim was to evaluate the risk factors for hyperCKemia. Third, ULN of CK in different gender was not distinguished as our laboratories have not yet carried out such tests. Finally, our study lacked information that allowed for differentiation of seizures because syncope and nonepileptic psychogenic seizures could manifest “motor signs” of seizures. Thus, the results of this study were more applicable for “seizures” but possibly not for “epileptic seizures”. CK was evaluated as a marker for differentiating GTCS from syncope [44]; a level of CK $>$ 200 U/L was unlikely to be the result of vasovagal syncope [10]. In this study, we considered that PHCK should be patients with epileptic seizures.

6. Conclusion

This study revealed that hyperCKemia occurred in 31.7% of patients after seizures. Fever and elevated LEU were independent risk factors for seizure-related hyperCKemia, which might be associated with a potential role of infection in the development of hyperCKemia after seizures. Repeated assessment of CK should be performed after seizures, especially in patients with fever, elevated LEU or an infection. A larger sample size and a more rigorous study design should be utilized in future investigations.

Declarations

Author contribution statement

Lei Wang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yanan Lu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yujing Yang: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hanli Li: Performed the experiments.

Yu Wang: Conceived and designed the experiments; Wrote the paper.

Funding statement

Yu Wang was supported by National Natural Science Foundation of China [82071460].

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

Acknowledgements

None.

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