Retrospective analysis of 116 cases of exertional rhabdomyolysis in newly enrolled cadets of a military academy in Beijing

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Research

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Abstract

Background

Exertional rhabdomyolysis (ER) often occurs during prolonged intense exercise in hot environments, posing a threat to the health and safety of military personnel.

Objective

To investigate possible risk factors of ER and provide further empirical data for prevention and clinical treatment strategies for ER.

Methods

In this study, a systematic retrospective investigation on 116 concurrent cases of ER was conducted. Demographic, clinical, and exercise-related data were collected from both ER cases and controls which were allotted by 1:3 proportion. Conditional logistic regression analyses were performed to calculate the significance of the association between each potential risk (or protective) factors and ER.

Results

The adjusted ER prediction model finally included the following variables that significantly increased (or decreased) the risk of acquiring ER: age (odds ratios [OR] 0.59, 95% confidence interval [CI] 0.45–0.79), body mass index (BMI, OR 1.11, 95%CI 1.01–1.24), dark-colored urine after training (OR 2.98, 95%CI 1.58–5.64), frequent fruit consumption (OR 0.54, 95%CI 0.29–0.98), active hydrating habit (OR 0.31, 95%CI 1.58–5.64), water replenishment ≥ 2L on the training day (OR 0.18, 95%CI 0.06–0.54), water replenishment ≥ 500 ml within 1 hour before training (OR 0.32, 95%CI 0.11–0.90), lack of physical exercise in the last half-year (OR 3.23, 95%CI 1.34–7.80).

Conclusions

In military training, emphasis should be placed on incremental adaptation training prior to more intense training, and close attention should be paid to overweight and previously sedentary recruits. Fluid replenishment before exercise, increased fruit intake, and proper potassium supplementation may help to prevent ER.

1. Introduction

Rhabdomyolysis is defined as the breakdown of striated muscle with subsequent release of toxic cellular contents, such as myoglobin, into the circulation, causing a clinical syndrome characterized by fatigue, myalgia, myoglobinuria, and thereby accompanied by an increase in serum creatine kinase (CK) concentration. Prolonged and unaccustomed intense physical activity, especially exercise that involves eccentric contractions of muscles in hot environments, would put trainees at risk of skeletal muscle injury,
also known as exertional rhabdomyolysis (ER) or exercise-induced rhabdomyolysis. The severity of the disease ranges from self-limited mild conditions, such as asymptomatic elevated levels of serum muscle enzymes, to potentially life-threatening complications including extreme enzyme elevations, electrolyte imbalances, metabolic acidosis, and renal failure \[1\].

As military training is often tied to high intensity and high temperature, ER is a serious threat to military personnel. It is reported that the annual incidence of ER in the US army varied from 35.2 per 100,000 people to 42.4 per 100,000 people in the past 5 years, mainly occurring between May and October (75.3%). Compared with officers and enlisted members, the incidence of ER in new recruits (active service soldiers with service level E1-E4) was significantly higher (231.6 per 100,000 person-years). Besides, the incidence of ER may be related to multiple factors such as gender, race, occupational category, and years of service. Most of the existing studies have reported the possible association between demographic characteristics and ER; however, few studies have been conducted on training factors, health status, prevention measures, and other characteristics that may affect the occurrence of the disease. In particular, the key factors leading to the concentrated outbreak of large numbers of cases are still to be explored.

This article presents 116 concurrent ER cases during the summer enrollment in a military academy in Beijing. The new cadets received physical tests (including long-distance running, sprint, push-ups, sit-ups, horizontal bar, parallel bars) in the first two days after their enlistment (maximum temperature of the days was 33°C), and routine medical examination (ME) and blood test were performed on the next day. 116 patients with significantly elevated CK level (CK > 1000) were screened out through biochemistry tests, among which 71 were admitted to the First Medical Center of PLA General Hospital for treatment. Afterwards, we conducted a questionnaire survey on all the trainees and collected the ME data and in-hospital data. The purpose is to analyze the association between ER and the features of demographics, medical history, and exercise-related factors of the population through case-control study, and investigate the risk factors of ER onset, to improve the prevention strategies of ER in the military training setting.

2. Patients And Methods

2.1 Study Population

The new cadets enrolled in the summer of 2019 were included in our study. The ME information was obtained from the Outpatient Service Center of the academy, and the clinical information of inpatients was from the Patient Administration System of the hospital. A total of 116 individuals who were diagnosed with ER were incorporated into the case group. Every case was matched to 3 non-ER controls who were from the same squad (or platoon) and experienced the same training course. Those who did not participate in physical training or ME were excluded.

2.2 Survey Contents and Risk Factors
The contents of the questionnaire covered the demographics, medical history, exercise-related factors, and other health-related information. Potential risk (or protective) factors considered included the following statistical variables: age, body mass index (BMI), the long-term residence before enrolling, length of military service, symptoms, clothing and extra weight worn during training, mental and physical fitness before training, history of heat injuries, sleep conditions, dietary situations, hydrating statuses, cooling facilities in the dormitory, physical adaptability to training after enrolling, exercise frequency and intensity in the past half-year.

2.3 Diagnostic Criteria

Diagnostic criteria for ER include a history of physical training and elevated serum CK level greater than or equal to 5 times the upper limit of normal (1000 U/L).

2.4 Quality Control

The investigation team was composed of 10 investigators and 2 experts (1 expert in clinical medicine and 1 expert in epidemiology). Investigators were divided into 5 groups with 2 people in each group. To ensure investigation quality, every investigator had been uniformly instructed by the expert panel before the formal investigation. The contents included: definition and diagnostic criteria of ER, investigation methods, contents and key points of the questionnaire, standards of audit, sorting, and input the questionnaire, and other matters needing attention in the process. All the investigators had fully understood the significance and implementation plan of this investigation, and made clear all the requirements and precautions. Each group appointed one investigator to review the questionnaires, focusing on the standardization, accuracy, and completeness of the questionnaires. The questionnaires which were incomplete or had obvious mistakes or contradictions would be returned to the investigators for supplementary investigation. EpiData V3.1 was used to record survey data, with one investigator inputting and the other reviewing. All data were summarized after verification. The expert panel took random inspection on the consistency between the data recorded and the original to ensure accuracy.

2.5 Analytical Methods

Statistical analysis was performed on the summarized data. Initially, the exposure ratio of each variable was calculated, and chi-square test was used to evaluate the significance of differences between cases and controls. Since the data of age and BMI in the two groups were not completely normally distributed, the differences in age and BMI distribution between the two groups were compared by the Mann-Whitney U test. Then, with the occurrence of ER as the dependent variable (the outcome) and each risk factor to be evaluated as the independent variable, binary logistic regression univariate analyses were conducted to determine the unadjusted odds ratio (crude OR) of each individual variable, and the risk factors were filtered to eliminate the independent variables that had no significant influence on the incidence of ER. Finally, conditional logistic regression was performed to set up an adjusted predictive model for ER. Variables were removed one at a time to assess each one's influence on the stability and predictive power using − 2 log likelihood ratio test. The variables with no significant impact on the predictive power and the variables with strong multicollinearity were further eliminated.
In this study, EpiData V3.1 was used for data recording and IBM SPSS Statistics V 25.0 was used for statistical analyses. *P* values less than 0.05 were considered statistically significant in all the above tests.

### 3. Results

After preliminary screening, the following variables were found to have significantly different exposure ratios between the case group and the control group: age, BMI, length of service, symptoms (dark-colored urine, myalgia), mental and physical status before training (fatigue, return from vacation), history of heat injuries (previous ER diagnosis or darkened urine which seemed obviously abnormal after exercise), eating habits (frequency of fruit consumption), hydrating situation (hydrating habits, daily water consumption in the week before, water replenishment on training day, water replenishment within 1 hour before training), the adaptability to physical training after enrolling (subjective answer to whether kept physical exercising regularly or not, the intensity of exercise in the past six months, training intensity after enrolling), and abnormal blood biochemical manifestation (increased alanine transaminase [ALT] level) (Table 1); Those variables with no significant differences between the two groups included: environmental suitability (long-term residence before enrolling), clothing and extra weight worn during training, sleep conditions, diet (poor appetite, fasting, vegetarian or carnivorous), living environment (indoor cooling facilities), water replenishment during training (data not shown).

The adjusted ER predictive model finally incorporated the following variables as ER risk factors: younger age, overweight, dark-colored urine, low frequency of fruit consumption, inactive hydrating habit, insufficient water replenishment on the training day, insufficient water replenishment within 1 hour before training, insufficient physical exercise in recent half-year (Table 2).

The age distribution of all participants ranged from 18 to 24 years old, with 19 to 20 years old as the majority (62.7%, *n* = 291). In cases, patients ≤ 20 years old accounted for 91.38%, significantly higher than that of controls (60.06%) (Table 1); while age was added to the model as a continuous variable, the risk of ER decreased with every year of getting older (adjusted OR 0.594, 95% confidence interval [CI] 0.446–0.790). In terms of the service length, all cadets were classified as new recruits and enlisted cadets (had joined the PLA for 2 years or 3 years, namely private first class or corporal respectively), and new recruits had significantly higher odds of developing ER than the enlisted (crude OR 9.06, 95% CI 4.09–20.06). In view of the problems of multiple collinearities with age and other factors, length of service was not included in the final model.

The cadets who excreted darkened urine during or after training were significantly more likely to develop ER. When brown or even darker colored urine was excreted, the likelihood of ER grew to over 18 times (adjusted OR 18.649, 95% CI 3.337–102.967).

With the increase of water replenishment on the training day or within 1 hour before training, there was a trend for decreased probability of ER. Moreover, when the water replenishment was more than 2L on the training day or more than 500 ml within 1 hour before training, this association with ER was statistically significant.
Table 2 also shows a clear tendency that people who were overweight, with no active hydrating habit, did not eat fruit frequently, or lacked physical exercise had a greater risk of ER.

Of the 71 hospitalized patients, the length of stay (LOS) was 16 days at most and 1 day at least, with a median of 5 days. The most severe case had a maximum serum CK value of 163148 U/L, myoglobin (Myo) 6555 ng/ml, lactate dehydrogenase (LDH) 4932.7 U/L, aspartate transaminase (AST) 793.4 U/L (Table 3). Using Spearman's rank correlation test, maximum CK (CK_{max}) was significantly positively correlated with LOS (Table 4, r = 0.701, P < 0.001). In addition, 41 patients (57.7%) were diagnosed with hypokalemia on admission.
Table 1
Demographic, clinical and exercise-related characteristics of ER cases and controls

| Variable                  | ER Cases          | Controls         | Univariate analysis |
|---------------------------|-------------------|------------------|---------------------|
|                           | No. (n = 116)     | Rate (%)        | No. (n = 348)      | Rate (%)        | OR     | 95% CI   |
| Age (years)               |                   |                  |                     |                  |        |          |
| Median (IQR)              | 19 (20 – 19)      |                  | 20 (22 – 19)       |                  | 0.57*  | 0.47–0.69 |
| 18–20                     | 106               | 91.38            | 209                 | 60.06           | Ref.   |          |
| 21–24                     | 10                | 8.62             | 139                 | 39.94           | 0.14   | 0.07–0.28 |
| BMI (kg/m²)               |                   |                  |                     |                  |        |          |
| Median (IQR)              | 22.34 (24.60–20.21) |                  | 21.46 (23.61–20.05) |                  | 1.12*  | 1.03–1.22 |
| <24                       | 80                | 68.97            | 277                 | 79.60           | Ref.   |          |
| ≥24                       | 36                | 31.03            | 71                  | 20.40           | 1.76   | 1.10–2.81 |
| Days of service           |                   |                  |                     |                  |        |          |
| <1 week (recruit)         | 109               | 93.97            | 220                 | 63.22           | 9.06   | 4.09–20.06 |
| 2/3 years (enlisted)      | 7                 | 6.03             | 128                 | 36.78           | Ref.   |          |
| Symptoms                  |                   |                  |                     |                  |        |          |
| Myalgia                   | 45                | 38.79            | 92                  | 26.44           | 1.76   | 1.13–2.75 |
| Urine color               |                   |                  |                     |                  |        |          |
| Colorless or light yellow | 29                | 25.00            | 201                 | 57.76           | Ref.   |          |
| Deep yellow               | 81                | 69.83            | 142                 | 40.80           | 3.95   | 2.46–6.36 |
| Brown/ darker colors      | 6                 | 5.17             | 5                   | 1.44            | 8.32   | 2.39–29.00 |
| Pre-training condition    |                   |                  |                     |                  |        |          |

IQR, inter-quartile range; Ref. reference; ALT alanine transaminase; Cr creatinine. * Calculated as a continuous variable. ** Prior heat injury includes the medical history of darkened urine which seemed obviously abnormal after exercise. *** Physical exercise should last at least 1 hour each time.
|                                | ER Cases | Controls | Univariate analysis |
|--------------------------------|----------|----------|---------------------|
| Fatigue                        | 30       | 52       | 1.99                |
|                                |          |          | 1.19–3.31           |
| Return from vacation           | 30       | 40       | 2.69                |
|                                |          |          | 1.58–4.57           |
| Prior heat injury**            | 17       | 24       | 2.32                |
|                                |          |          | 1.20–4.49           |
| Dietary habit                  |          |          |                     |
| Frequency of fruit consumption  |          |          |                     |
| <3/ week                       | 44       | 89       | Ref.                |
|                                |          |          |                     |
| ≥3/ week                       | 72       | 259      | 0.56                |
|                                |          |          | 0.36–0.88           |
| Hydrating habits               |          |          |                     |
| hydrating initiatively         | 27       | 169      | 0.32                |
|                                |          |          | 0.20–0.52           |
| no hydration until thirsty/extremely irregularly | 89    | 179      | Ref.                |
| Water replenishment            |          |          |                     |
| Daily water consumption in the week before |      |          |                     |
| <1L                            | 7        | 9        | Ref.                |
|                                |          |          |                     |
| 1L-2L                          | 55       | 107      | 0.66                |
|                                |          |          | 0.23–1.87           |
| 2L-3L                          | 43       | 156      | 0.35                |
|                                |          |          | 0.13–1.01           |
| ≥3L                            | 11       | 76       | 0.19                |
|                                |          |          | 0.06–0.60           |
| Water replenishment on training day |      |          |                     |
| <1L                            | 14       | 15       | Ref.                |
|                                |          |          |                     |
| 1L-2L                          | 46       | 68       | 0.73                |
|                                |          |          | 0.32–1.64           |
| 2L-3L                          | 36       | 127      | 0.30                |
|                                |          |          | 0.13–0.69           |

IQR, inter-quartile range; Ref. reference; ALT alanine transaminase; Cr creatinine. * Calculated as a continuous variable. ** Prior heat injury includes the medical history of darkened urine which seemed obviously abnormal after exercise. *** Physical exercise should last at least 1 hour each time.
| ER Cases | Controls | Univariate analysis |
|----------|----------|---------------------|
| ≥3L      | 20       | 17.24               | 138 | 39.66 | 0.16 | 0.07–0.37 |

Water replenishment within 1 hour before training

| <100 ml  | 26       | 22.41               | 37  | 10.63 | Ref. |
| 100 ml-500 ml | 70   | 60.34               | 219 | 62.93 | 0.46 | 0.26–0.80 |
| 500 ml-1L | 18       | 15.52               | 86  | 24.71 | 0.30 | 0.15–0.61 |
| 1L-2L    | 2        | 1.72                | 6   | 1.72  | 0.47 | 0.09–2.54 |
| ≥2L      | 0        | 0.00                | 0   | 0.00  | -    | -    |

Physical exercise

Regularly or not (subjectively)

| no       | 76       | 65.52               | 144 | 41.38 | Ref. |
| yes      | 40       | 34.48               | 204 | 58.62 | 0.37 | 0.24–0.58 |

Intensity in the past six months ***

| almost every day | 11       | 9.48                | 145 | 41.67 | Ref. |
| ≥ once a week    | 65       | 56.03               | 135 | 38.79 | 6.35 | 3.21–12.54 |
| ≥ once a month   | 21       | 18.10               | 33  | 9.48  | 8.39 | 3.69–19.08 |
| < once a month   | 19       | 16.38               | 35  | 10.06 | 7.16 | 3.12–16.40 |

Training intensity after enrolling (compared to the intensity of physical exercise before)

| lower or equal | 22       | 18.97               | 150 | 43.10 | Ref. |
| higher        | 94       | 81.03               | 198 | 56.90 | 3.24 | 1.94–5.39 |

Blood Chemistry

IQR, inter-quartile range; Ref. reference; ALT alanine transaminase; Cr creatinine. * Calculated as a continuous variable. ** Prior heat injury includes the medical history of darkened urine which seemed obviously abnormal after exercise. *** Physical exercise should last at least 1 hour each time.
|                      | ER Cases | Controls | Univariate analysis |
|----------------------|----------|----------|---------------------|
| ALT (>40U/L)         | 27       | 23.30    | 21                  | 6.03 | 4.72 | 2.55–8.75 |
| Cr (>110 µmol/L)     | 1        | 0.86     | 0                   | 0    | -    | -        |

IQR, inter-quartile range; Ref. reference; ALT alanine transaminase; Cr creatinine. * Calculated as a continuous variable. ** Prior heat injury includes the medical history of darkened urine which seemed obviously abnormal after exercise. *** Physical exercise should last at least 1 hour each time.
Table 2
Odds ratios for ER associated with risk factors in the final conditional logistic regression model

| Variable                              | adjusted OR | 95% CI     |
|---------------------------------------|-------------|------------|
| Age                                   | 0.59        | 0.45–0.79  |
| BMI                                   | 1.11        | 1.01–1.24  |
| Urine color                           |             |            |
| colorless or light yellow             | Ref.        |            |
| deep yellow                           | 2.98        | 1.58–5.64  |
| brown/darker colors                   | 18.65       | 3.38-102.97|
| Frequency of fruit consumption         |             |            |
| <3/ week                              | Ref.        |            |
| ≥3/ week                              | 0.54        | 0.29–0.98  |
| Hydrating habits                      |             |            |
| initiative                            | 0.31        | 0.16–0.60  |
| no hydration until thirsty            | Ref.        |            |
| Water replenishment on training day   |             |            |
| <1L                                   | Ref.        |            |
| 1L-2L                                 | 0.89        | 0.29–2.74  |
| 2L-3L                                 | 0.18        | 0.06–0.54  |
| ≥3L                                   | 0.13        | 0.04–0.44  |
| Water replenishment within 1 hour     |             |            |
| <100 ml                               | Ref.        |            |
| 100 ml-500 ml                         | 0.50        | 0.22–1.12  |
| 500 ml-1L                             | 0.32        | 0.11–0.90  |
| 1L-2L                                 | 0.17        | 0.02–1.80  |
| Intensity of physical exercise in the past six months * | | |
| almost every day                      | Ref.        |            |

* Physical exercise should last at least 1 hour each time.
Table 3
Serum biochemical profile at admission of 71 inpatients with ER

| Biomarkers | Median | Range (MAX-MIN) | No. of abnormal (n = 71) | Rate (%) | Normal reference |
|------------|--------|----------------|-------------------------|----------|------------------|
| CK (U/L)   | 6726.8 | 163148.0-1115.1| 71                      | 100      | 2-200            |
| Myo (ng/ml)| 293.2  | 6555.0-82.7    | 71                      | 100      | 0-75             |
| LDH (U/L)  | 317.8  | 4932.7-189.6   | 56                      | 78.9     | 40-250           |
| ALT (U/L)  | 32.8   | 126.4-13.4     | 26                      | 36.6     | 0-40             |
| AST (U/L)  | 86.6   | 793.4-34.4     | 66                      | 93.0     | 0-40             |
| TBIL (µmol/L)| 12.5 | 41.3-6.2      | 10                      | 14.1     | 0-21             |
| DBIL (µmol/L)| 4.1 | 12.5-1.9      | 3                       | 4.2      | 0-8.6            |
| UA (µmol/L)| 424.7  | 780.5-235.6    | 32                      | 45.1     | 104-444          |
| K⁺ (mmol/L)| 3.41   | 3.98-3.02      | 41                      | 57.7     | 3.5-5.5          |

CK, creatine kinase; Myo, myoglobin; LDH, lactic dehydrogenase; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; DBIL, direct bilirubin; UA, uric acid; K⁺, potassium; MAX, maximum; MIN, minimum.
Table 4
Length of stay and of creatine kinase of 71 inpatients with ER

| LOS (days) | MIN-P<sub>25</sub> | P<sub>25</sub>-P<sub>50</sub> | P<sub>50</sub>-P<sub>75</sub> | P<sub>75</sub>-MAX | Total |
|------------|----------------|-----------------|-----------------|---------------|-------|
| < 4        | 10 (14.1)     | 1 (1.4)         | 0 (0.0)         | 0 (0.0)       | 11 (15.5) |
| 4          | 4 (5.6)       | 7 (9.9)         | 5 (7.0)         | 0 (0.0)       | 16 (22.5) |
| 5          | 3 (4.2)       | 5 (7.0)         | 6 (8.5)         | 4 (5.6)       | 18 (25.4) |
| 6          | 1 (1.4)       | 4 (5.6)         | 1 (1.4)         | 4 (5.6)       | 10 (14.1) |
| ≥ 7        | 0 (0.0)       | 0 (0.0)         | 6 (8.5)         | 10 (14.1)     | 16 (22.5) |
| Total      | 18 (25.4)     | 17 (23.9)       | 18 (25.4)       | 18 (25.4)     | 71 (100.0) |

LOS, length of stay; CK<sub>max</sub>, maximum value of creatine kinase during hospitalization; MIN, minimum = 1115.1 U/L; MAX, maximum = 163148.0 U/L; P<sub>25</sub>, the 25th percentile = 3984.7 U/L; P<sub>50</sub>, the median = 7106.8 U/L; P<sub>75</sub>, the 75th percentile = 11899.0 U/L.

4. Discuss

According to previous studies, the common potential risk factors of ER can be classified as intrinsic factors and extrinsic factors. Intrinsic factors include younger age, shorter length of military service (recruit), poor physical fitness, prior history of heat stroke, etc. [1, 2]; extrinsic factors include hot environments, unaccustomed strenuous training and so on [3]. In this study, the above risk factors were verified, and more potential risk factors or protective factors were systematically screened regarding demographics, medical history, exercise-related factors, and other health-related information, and the significance of association with ER was assessed.

4.1 Association Between Age (or Service Length) and ER

Several studies have confirmed that the incidence rates of ER were higher among younger people. In 2019, 512 incident cases of ER were reported in the US military, among whom patients under 20 years old accounted for 32.4% (n = 166), and the subgroup-specific incidence rate was 88 per 100,000 person-years (p-yrs), which was significantly higher than the total incidence (38.9 per 100,000 p-yrs) in 2019; and with getting older, the incidence is gradually decreasing [2]. Similarly, in this study, the risk of ER decreased by 40.6% with each one-year increase in the age of trainees, suggesting the protective effect of age on ER.

Length of service is one of the factors that are highly correlated with age. Recruits were more than twice as likely to develop ER compared to those who had served more than 90 days [1]. There were mainly two hypothetical reasons to explain this difference, one was that new recruits often lacked exercise before enlistment, while the other potential objective reason was that the period immediately after enlistment
was tight with a vigorous training schedule, and usually in the summer (August-September). In this study, both cases and controls had basically the same training subjects, and consistent training intensity and environment. The results showed that new recruits had over nine times the likelihood of ER versus the enlisted cadets (who had joined the PLA for 2 years or 3 years), it therefore can be concluded that new recruits were not used to the relatively intense daily physical training or military training, which was the most important reason for the high incidence of ER among new recruits.

4.2 Association Between Training Adaptability and ER

Studies have shown that a higher BMI could increase the risk of heat-related illnesses \[4\], which might be attributed to the fact that people with more body fat have poor heat resistance and slow adaptation to heat. However, in our study, we found that overweight people were less motivated to exercise than normal-weight people in both cases and controls (Table 5). Strenuous and unaccustomed exercise leads to focal disruption in the banding patterns of muscle fibers \[5\]. Therefore, we believe that the tendency to ER in overweight people is more likely to be related to their relative lack of daily exercise.

| BMI (kg/m²) | ER Cases [n = 116, n (%)] | Controls [n = 348, n (%)] |
|------------|----------------------------|---------------------------|
|            | Regularly                  | Irregularly               | Total a      | Regularly | Irregularly | Total b |
| ≥ 24       | 8 (6.9)                    | 28 (24.1)                 | 36 (31.0)    | 30 (8.6)  | 41 (11.8)   | 71 (20.4) |
| <24        | 32 (27.6)                  | 48 (41.4)                 | 80 (69.0)    | 174 (50.0)| 103 (29.6)  | 277 (79.6) |
| Total      | 40 (34.5)                  | 76 (65.5)                 | 116 (100.0)  | 204 (58.6)| 144 (41.4)  | 348 (100.0)|

| a. OR = 0.43, 95%CI 0.17–1.06; b. OR = 0.43, 95%CI 0.26–0.74 |

At present, there is still a lack of evidence to prove whether the adaptability to heat or to training plays a more critical role in the occurrence of ER. We investigated the following factors that related to heat adaptability: long-term residence (cold regions in the north or hot regions in the south), clothing during training (short-sleeved physical training uniform, long-sleeved combat uniform), and indoor cooling facilities (air conditioner, electric fan, no cooling facilities) of both the groups. None of the above factors was found significantly correlated with ER. However, the intensity of previous physical exercise and the adaptability to post-enrolling training had a significant impact on developing ER; additionally, a protective trend was observed when the intensity of previous exercise increased.

According to univariate analysis, experiences of fatigue, vacation, or prior heat injury before training facilitated an increased risk of ER after training. Considering that the above conditions could directly affect individuals’ adaptability to physical training, thus further enhancement of physiological adaptation may play an important role to reduce ER occurrence.
4.3 Association Between Hydration and ER

Insufficient hydration is another critical risk factor for ER. Studies have revealed that dehydration can aggravate physiological strain, reduce sweating, increase perceived exertion, and raise core body temperature\(^6,7\). In addition, dehydration is also a risk factor for secondary acute renal failure\(^5\). Therefore, to ensure euhydration before training and to keep on rehydrating during the activity can effectively prevent the occurrence of ER and resultant complications\(^6\). According to our survey, cadets with active hydrating habits had a 68% reduction in the risk of ER compared with those who didn't rehydrate actively until thirsty (or hydrated extremely irregularly); and it can significantly reduce the risk of ER when daily water replenishment ≥ 3L in the week before training, water replenishment ≥ 2L on training day, and water replenishment ≥ 500 ml within one hour before training (Table 1&2).

Water replenishment during training was not found to have a significant impact on ER in this study. We assume that it might be because rehydrating during training could not relieve dehydration in a timely manner before the injuries were actually initiated, especially muscle damage caused by strenuous strength training. Furthermore, improper hydration during training may even induce dilutional hyponatremia and other electrolyte abnormalities, thus aggravating the illness.

4.4 Clinical Features of ER

Myalgia and darkened urine were the two main symptoms of ER. Especially when urine turned brown or even darker, the possibility of ER increased by 18 times (Table 2), indicating the occurrence of myoglobinuria; but the possibility of exercise-induced hematuria cannot be ruled out in practice\(^8\).

However, only 41.4% (n = 48) of the 116 cases had typical symptoms (myalgia or brown urine), suggesting that the majority of the cases were actually asymptomatic or subclinical rhabdomyolysis with mild atypical symptoms, which were detected by blood biochemical tests (elevated serum CK values) in ME.

Secondary renal insufficiency or failure is a vital complication of ER, whereas the reliability of CK elevation in predicting renal dysfunction after ER is still controversial\(^3,5,9\). Studies have proposed that rhabdomyolysis patients with a CK higher than 1000 U/L and a Cr lower than 1.3 mg/dl (114.92 µmol/L) at admission are not at risk of developing renal insufficiency or failure during hospitalization if treated promptly with fluid rehydration, regardless of their initial CK value\(^9\). Only one of the patients in our data, whose CK value at admission was 4923.4 U/L, had a post-exercise Cr exceeded the upper limit of the normal range (111.6 mol/L, Table 1), while 65% (n = 71) of the inpatients had higher CK but without renal dysfunction.

Comparison of other biochemical results showed that 27 cases (23.3%, n = 116) in the case group had an abnormally high ALT (the upper limit of normal value 40 U/L), which was significantly different from the control group, suggesting that there was a significant association between elevated aminotransferase and ER. But the sequential relationship between them could not be determined. At admission, there were just 26 inpatients (36.6%, n = 71) with ALT elevations, while 66 inpatients (93.0%, n = 71) with increased
AST, moreover, the maximum AST (793.4 U/L) was obviously higher than the maximum ALT (126.4 U/L). Thus, ALT elevated less sensitively than AST in ER cases, as a result of the different distribution in muscle cells—more AST is distributed in striated muscle cells than ALT\cite{3,10,11}. Accordingly, significantly elevated AST level with nearly normal ALT and TBIL levels—the phenomenon of dissociation—can indicate the occurrence of ER rather than liver dysfunction (Table 3).

Forty-one ER inpatients (57.7%, n = 71) were diagnosed with hypokalemia through the initial blood biochemical test in the emergency department, but the actual situation might be worse, as almost all the ER patients had started the oral rehydration therapy with mineral soda water (containing sodium bicarbonate, potassium chloride) before admission. Prolonged physical exertion in hot environments can lead to large amounts of potassium loss due to excessive sweating, hypokalemia may be developed if the potassium supplement is delayed. Hypokalemia is also one etiological factor of rhabdomyolysis, for hypokalemia can reduce the muscles’ excitability \cite{3,12}, but the specific role of hypokalemia in the pathogenesis of ER remains unclear. Because serum potassium was not tested in the routine ME after enrolling, it is not clear whether there was a difference in serum potassium between the cases and the controls. 25.86% of the cases had experienced exercise fatigue before or during training, which was significantly higher than that of the controls. We speculate that this might be related to hypokalemia. In the study, we also found that eating fruit regularly (no less than 3 times a week) was conducive to reducing the risk of ER (Table 1). Combined with other factors discussed, fruit consumption is supposed to work by replenishing fluid and potassium, nevertheless, the precise links still need to be further verified.

5. Conclusion

5.1 Advantages

One advantage of this study is to systematically investigate and review the 116 concurrent cases of ER which happened in the enrolling season. Compared with collecting cases from the database of inpatients, this survey can effectively avoid missing data, and cover related factors on a broader scale. Furthermore, all the participants came from a population-based cohort that had equal education level, the same training environment, similar training intensity, and consequently good population homogeneity. Stratified analysis and multivariate analysis were utilized in data analysis so as to better control the selection bias and confounding bias.

In addition, large numbers of asymptomatic cases were detected due to the routine ME scheduled after the physical training tests, it allowed us to better understand ER and its risk factors; however, such conditions (post-exercise biochemical tests) are relatively rare in common life. In view of that, the tests of biochemical markers (CK, Myo) in non-invasive specimens, such as sweat or urine, may contribute to the early detection and early treatment of subclinical ER.

5.2 Limitations
(1) Although several intrinsic factors were analyzed in this study, some common extrinsic factors were not included (weather, training programs, different months of the year, etc.) or were not found to have statistical significance (clothing, extra-weight bearing, etc.);

(2) Investigations were conducted after the ER occurrence, some of the data were collected from the subjective answers of the survey respondents, which might generate certain recall bias and investigation bias. This case-control study was also limited by the inability to determine the sequential relationship, so the causal links were hard to demonstrate.

(3) There were limited biochemical items of ME, e.g., serum myoglobin and potassium were not routinely tested. The diagnostic criteria for ER could only be based on exercise history and elevated CK level, while other critical markers were not able to be evaluated, and their roles in the prediction and pathogenesis of ER might be overlooked.

5.3 Summary

Exertional rhabdomyolysis is a common and easily underestimated disease characterized by myalgia and darkened-brown urine during or after exercise. Younger age, overweight, lack of training adaptability and inadequate hydration have been proven to be core risk factors for ER. In military training, emphasis should be placed on incremental adaptation training prior to more intense training, and close attention should be paid to overweight and previously sedentary recruits (newly enrolled cadets). Fluid replenishment before exercise, increased fruit intake, and proper potassium supplementation may help to prevent ER. Biochemical tests, especially on noninvasive specimens, would be helpful for early detection of asymptomatic subclinical ER cases.

Abbreviations

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CI: confidence interval; CK: creatine kinase; Cr: creatinine; DBIL: direct bilirubin; ER: Exertional rhabdomyolysis; IQR: inter-quartile range; K⁺, potassium; LDH: lactate dehydrogenase; LOS: length of stay; MAX: maximum; ME: medical examination; MIN: minimum; Myo: myoglobin; OR: odds ratios; Ref: reference; TBIL: total bilirubin; UA: uric acid;

Declarations

Ethics approval and consent to participate

All protocols of the study were approved by the Ethics Committee of Chinese PLA General Hospital.

Consent for publication

Not applicable.
Availability of data and materials

The datasets generated or used during the current study are available in a repository or online in accordance with funder data retention policies.

Competing interests

No conflicts of interest to disclose.

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Authors' contributions

Song Q as the principal person in charge of this study, presided over the project design, discussion, and implementation. Mao H.D. analyzed and interpreted the patient data, and was a major contributor in writing the manuscript. Tan Z.J. and Sun H.L. assisted in statistical analysis and quality control of the survey. Other authors participated in literature review and data collection. All authors read and approved the final manuscript.

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- [Retrospectiveanalysisof116casesofexertionalRM.pdf](#)