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Original Article

Serum lactate concentration on admission to hospital predicts the postoperative mortality of elderly patients with hip fractures 30 days after surgery

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Abstract: Purpose: To determine whether serum lactate concentration on admission to hospital is a predictor for 30-day and 1-year mortality for patients who underwent hip-surgery. Methods: Data from elderly patients with hip fractures admitted to our hospital (Jan 2012-Dec 2016) were reviewed. The lactate concentration on admission was assessed using a cut-off value of 2.0 mmol/L and then a new cut-off value was determined by maximizing the Youden index. Multivariate logistic regression was employed to verify whether a higher lactate concentration compared with the cutoff value was an independent risk factor for postoperative mortality after 30 days or at 1 year. Results: A total of 1,004 patients were enrolled. There were differences in the incidence of postoperative complications (28.6% *vs.* 21.9%, *P*=0.022), length of stay (13.56±8.66 *vs.* 12.47±7.81 days, *P*=0.047), 30-day mortality (10.8% *vs.* 1.3%, *P*<0.001), 1-year mortality (23.3% *vs.* 11.8%, *P*<0.001) and survival time (23.92±16.58 *vs.* 28.81±16.54 months, *P*<0.001) between the ≥2.0 mmol/L (n=315) and <2 mmol/L (n=689) groups. Serum lactate concentration was a good predictor of 30-day mortality (AUC=0.829, *P*<0.001) with a cutoff value of lactate =2.35 mmol/L (sensitivity =0.744, specificity =0.834). Multivariate analysis revealed that a serum lactate concentration ≥2.35 mmol/L at admission was an independent risk factor for 30-day (OR=9.93, *P*<0.001) and 1-year (OR=2.23, *P*<0.001) mortality. Conclusion: The admission lactate concentration (≥2.35 mmol/L) following hip fracture derived by this study was a significant predictor of mortality 30 days after surgery, which might help physicians to stratify the risk for these patients.

Keywords: Hip fracture, elderly, lactate concentration, 30-day mortality, predictor

Introduction

The number of elderly people is gradually increasing with aging of the population and as a result, the number of hip fractures is increasing year by year [1]. According to statistics, there were 1.6 million elderly hip fracture patients worldwide in 2000 and this number will reach about 2.1 million by 2050 [2]. Patients with hip fracture are generally characterized by older age, multiple comorbidities and poor prognosis, which adds a significant burden to society and their families [3]. The 1-year mortality rate of elderly hip fracture patients is from 20 to 40% [4], and even among survivors, nearly half of the patients will have dysfunctions. If one can predict the mortality risk in elderly hip fracture patients then early targeted therapy can be initiated in a timely manner [5], which is likely to improve patient prognosis. At present, a large number of studies on the mortality of hip fractures mainly focus on the clinical characteristics [5, 6], but few studies have considered the predictive value of pre-operative biochemical indicators [7, 8]. Thus, there is a lack of simple and effective indicators for early warning of mortality after hip fracture surgery in elderly patients [9].

Although hip fractures in elderly patients are mostly caused by low-energy injuries, the impact on the body often exceeds our expectations. Our previous studies [10, 11] have confirmed that hip fractures in elderly patients are physiologically similar to those seen in young patients with multiple injuries. Hyperlactatemia

resulting from anaerobic respiration is generally considered to be a sign of a poor health condition with various etiologies [12]. In the clinic, the lactate concentration is a convenient routine detection index at low cost, and has been applied in the outcome prediction of acute and critical patients with multiple traumas in ICU [13]. In addition, western scholars have carried out studies on the association between lactate concentration and mortality in postoperative patients with hip fractures, but due to the limitations of the number of cases and the study design, there is still no unequivocal conclusion [14-16]. In China, people are also deeply affected by the population aging, and the number of hip fractures is gradually increasing. The postoperative mortality and risk factors for hip fracture may be different from those in other regions [17, 18], but rates are still considerably high. If the lactate level on admission is predictive of the postoperative mortality risk, then patients with high-risk can be targeted and treated early to improve their outcomes.

The present study retrospectively analyzed data obtained from elderly patients admitted to our hospital with hip fractures from Jan. 2012 to Dec. 2016. The aims were to establish unequivocally whether the serum lactate concentrations on admission of these patients could predict postoperative mortality at 30 days and 1 year and to provide a definitive cutoff lactate concentration.

Materials and methods

Study population

Inclusion criteria: (1) Age ≥60 years; (2) Patients who could walk before the injury (walking independently or with the aid of a Zimmer frame, walking stick, etc.); (3) Unilateral hip fracture (intertrochanteric fracture or femoral neck fracture); (4) Low energy injury (falls at or below body height); (5) Patients who were admitted to the hospital on day 1 after the injury.

Exclusion criteria: (1) Age <60 years; (2) Patients who were unable to take care of themselves before the injury; (3) Multiple injuries; (4) Pathological fractures; (5) Endangered patients (American Society of Anesthesiologists (ASA) grade V); (6) High-energy injuries; (7) Patients who refused follow-ups; (8) Patients with incomplete data; (9) Patients who were admitted >1 day after the injury.

The ethics committee of our hospital gave approval for the study protocols (No. 201709086). Written informed consent was obtained from all patients included in the study.

Measurement of lactate concentrations

A 4 mL specimen of arterial blood was withdrawn from each patient in a quiet morning resting state 24 h after admission and placed in a heparin containing tube, which was centrifuged at 4,000 r/min for 10 min. The upper serum was separated and placed in a blood gas analyzer (Siemens, RAPIDPOINT 500, Germany) to measure the serum lactate concentration. The lactate concentration cutoff value of 2.0 mmol/L was chosen according to a previous study and this lactate concentration was also used to diagnose hyperlactemia in our clinical practice. Thus, patients were assigned into 2 groups, namely, those with ≥2.0 mmol/L and those with <2.0 mmol/L serum lactate concentrations.

Treatment and follow-up

After admission, the patients completed all examinations as soon as possible, including chest X-rays, electrocardiogram, lower limb vein ultrasound, routine blood biochemical tests, liver and kidney function tests, and blood electrolyte concentrations. In addition, surgeons arranged corresponding examination items for the patients according to their comorbidities. It was important that surgical treatment was carried out with a minimal delay. If the general condition of a patient was poor, relevant departments assisted in diagnosis and treatment. After the patient's condition stabilized, they underwent surgery.

Anesthetists developed personalized anesthesia plans (including intraspinal anesthesia, general anesthesia, and nerve block anesthesia) according to the patient's condition. Garden I and II patients with fractures of the femoral neck were treated with cannulated screws while Garden III and IV patients were given total hip or semi-hip replacements. Extramedullary fixation was selected for AO type A1 intertrochanteric fractures and intramedullary fixation

was selected for A2 and A3 intertrochanteric fractures. Low-molecular-weight heparin anticoagulant therapy was routinely administered during hospitalization and antibiotics were used to prevent incision infections within 24 h of surgery. Patients were encouraged to engage in early functional exercises and weight bearing if the pain could be tolerated, with the exception of patients who had femoral neck fractures that were treated with cannulated screws.

After discharge, a resident followed up the patients once a month and made careful records of their condition. The follow-up content mainly included postoperative survival status. Follow-up personnel were not involved in data collection or the analysis of the study data.

Statistical analysis

All analyses were carried out using SPSS software (ver. 21.0). Measurements are expressed as mean ± standard deviation (SD). If data sets were normally distributed, a two independent samples *t*-test was employed. If not, a U test was used. Enumeration data are expressed as numbers (percentages) after analysis by a chi-squared test. The comorbidities, lengths of stay in hospital and the 30-day and 1-year postoperative mortality of patients in the 2 groups were compared. The survival time of the 2 groups was compared using a Kaplan-Meier survival curve. Receiver-operating characteristic (ROC) curves were constructed to assess the best serum lactate concentration cutoff related to 30-day and 1-year mortality after surgery. The Youden's index for each ROC-analysis was used to determine the value for which sensitivity and specificity was maximal. We evaluated the area under the ROC curve (AUC) for sensitivity and specificity of this cutoff value. Multivariate and univariate logistic regression models were employed to verify whether a lactate concentration greater than the cutoff value was an independent risk factor for mortality at 30 days and 1 year. Data are given together with the appropriate 95% confidence intervals (CIs). Two-tailed *P*-values <0.05 were considered to represent significant findings.

Results

A total of 1,004 elderly patients with hip fractures from Jan. 2012 to Dec. 2016 were included in the study. The mean age of patients was 80.01±8.14 years, with the male/female ratio of 329/675. There were 584 cases of intertrochanteric fractures and 420 cases of femoral neck fractures. Preoperative comorbidities included hypertension 590 (58.8%), stroke 359 (35.8%), diabetes 272 (27.1%), coronary heart disease 266 (26.5%), dementia 79 (7.9%) and renal insufficiency 57 (5.7%). After admission, 229 (22.8%) patients with hip fractures chose an early operation. The proportion of spinal anesthesia, general anesthesia and nerve block anesthesia were 47.2% (474), 31.9% (320) and 20.9% (210), respectively. The main methods of internal fixation included 505 (50.3%) cases of proximal femoral nail, 268 (26.7%) cases of cannulated screws, 155 (15.4%) cases of hip replacement and 76 (7.6%) cases of Dynamic Hip Screw (DHS). The average stay in hospital for all patients was 12.78±8.07 days.

Demographic and clinical characteristics of the patients in lactate <2.0 mmol/L and ≥2.0 mmol/L groups

The average lactate concentration of all patients was 1.84±0.84 mmol/L. There were 315 patients (31.4%) in the ≥2.0 mmol/L group, with an average age of 80.93±8.26 years, and 107 (34.0%) males with a mean lactate concentration of 2.83±0.88 mmol/L. There were 689 patients in the <2.0 mmol/L group, with an average age of 79.59±8.05 years, and 222 (32.2%) males with an average lactate concentration of 1.41±0.37 mmol/L. The ≥2.0 mmol/L lactate group had older ages (P=0.016) and higher lactate concentrations (P<0.001) compared to those of the <2.0 mmol/L group, but no gender difference between the 2 groups was found (**Table 1**).

Postoperative hip fracture complications occurred in 241 (24.0%) patients, including delirium (129/241, 53.5%), pulmonary infection (73/241, 30.3%), venous embolism (42/241, 17.4%) and cardiac dysfunction (29/241, 12.0%). There were 142 complications in 90 patients (28.6%, 90/315) in the lactate ≥2.0 mmol/L group, and 180 complications in 151 patients (21.9%, 151/689) in the lactate <2.0 mmol/L group. The rate of occurrence of postoperative complications was significantly different (P=0.022) between the 2 groups (**Table 1**).

Table 1. Comparison of the demographic and clinical data of elderly hip fracture patients classified by lactate concentrations <2.0 mmol/L and ≥2.0 mmol/L

Variable	Lactate <2.0 mmol/L (n=689)	Lactate ≥2.0 mmol/L (n=315)	*P*-value
Age (years)	79.59±8.05	80.93±8.26	0.016
Gender			0.584
Male	222 (32.2)	107 (34.0)	
Female	467 (67.8)	208 (66.0)	
Plasma lactate (mmol/L)	1.41±0.37	2.83±0.88	<0.001
Postoperative complications	151 (21.9)	90 (28.6)	0.022
Delirium	74	55	0.003
Pulmonary infection	43	30	0.063
Venous embolism	14	28	0.780
Cardiac insufficiency	18	11	0.440
Myocardial infarction	12	9	0.252
Arrhythmia	7	5	0.645
Gastrointestinal hemorrhage	6	1	0.569
Cholecystitis	5	1	0.736
Poor wound healing	1	2	0.486
Length of hospital stay (days)	12.47±7.81	13.56±8.66	0.047

Note: Data are expressed as the mean ± SD or as the number of patients (n (%)).

In terms of the average length of stay in hospital, patients had significantly longer stays in the ≥2.0 mmol/L concentration group than those in the <2.0 mmol/L group (13.56±8.66 *vs.* 12.47±7.81, *P*=0.047) (**Table 1**).

Comparison of postoperative mortality and the survival time between lactate <2.0 mmol/L and lactate ≥2.0 mmol/L concentration groups

From the perspective of postoperative mortality, both the 30-day (10.8% *vs.* 1.3%, *P*<0.001) and 1-year (23.3% *vs.* 11.8%, *P*<0.001) mortality rates in the lactate concentration ≥2.0 mmol/L group were higher than those in the <2.0 mmol/L group (**Figure 1A**).

From the Kaplan-Meier survivorship curves, the average survival time (23.92±16.58 months *vs.* 28.81±16.54 months, *P*<0.001) of patients in the lactate concentration ≥2.0 mmol/L group was shorter than that in the lactate concentration <2.0 mmol/L group (**Figure 1B**).

Predictive usefulness of lactate concentration on postoperative mortality

Using the ROC analysis, serum lactate was shown to be a good predictor of mortality at 30 days after surgery (AUC=0.829, *P*<0.001), with a cutoff concentration of 2.35 mmol/L (sensitivity =0.744, specificity =0.834, accuracy =0.578) (**Figure 2A**).

The serum lactate concentration could also predict 1-year mortality after hip fracture surgery but the predictive ability was poor (AUC=0.651, *P*<0.001) with a cutoff lactate concentration of 2.35 mmol/L (sensitivity =0.390, specificity =0.846, accuracy =0.236) (**Figure 2B**).

Multivariate analysis of a lactate cutoff concentration of 2.35 mmol/L for mortality at 30 days and 1 year after hip surgery

We conducted multivariate and univariate regression analysis for mortality at 30 days and 1 year. Patients in the ≥2.35 mmol/L group tn admission had a higher 30-day mortality (OR: 9.14, 95% CI: 4.33 to 19.31, *P*<0.001) and 1-year mortality (OR: 2.47, 95% CI: 1.75 to 3.49, *P*<0.001) compared to those with concentrations below the cutoff value.

After adjusting age, gender, fracture type, comorbidities, ASA grade, time to surgery, anesthesia method and surgery method, patients with serum lactate concentrations

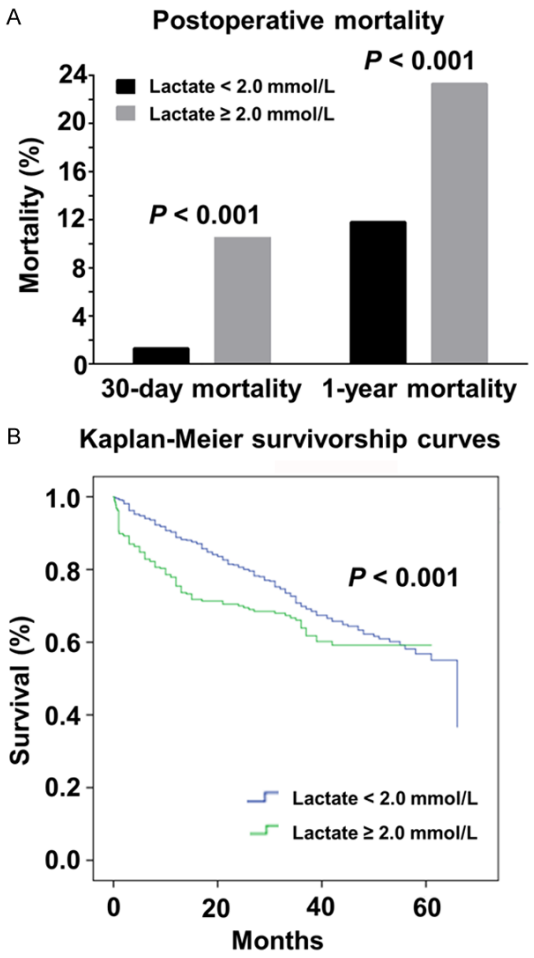

Figure 1. A. 30-day mortality and 1-year mortality; B. Kaplan-Meier survivorship curves of elderly hip fracture patients with lactate concentrations ≥2 mmol/L and those with lactate concentrations <2 mmol/L.

≥2.35 mmol/L at admission was associated with a higher mortality at 30 days (OR: 9.93, 95% CI: 4.52 to 21.83, P<0.001) and 1 year after surgery (OR: 2.23, 95% CI: 1.55 to 3.21, P<0.001) compared to those with lactate concentrations below the cutoff value (**Table 2**).

Discussion

In the present study, 31.4% of elderly patients with hip fractures had lactate concentrations ≥2 mmol/L on the day of admission to the hospital. Compared to patients with normal lactate concentrations, they had a higher postoperative mortality, longer hospital stays and a higher incidence of complications. We propose that a lactate concentration ≥2.35 mmol/L can be used as an indicator to estimate the 30-day mortality risk of elderly patients after hip fracture surgery and might assist clinicians in the early detection of critically ill patients, prediction of outcomes and guidance for treatment.

The risk of postoperative mortality is determined by a wide range of factors [19], including a delay in surgery [20], type of anesthesia [21], inappropriate medical management [22], postoperative complications (especially cardiovascular complications and infections) and the numbers of healthcare staff [23], in addition to the patients characteristics at admission. Various factors influenced each other, which challenges the prediction of mortality risk after hip fracture surgery [24]. Scoring systems such as Elixhauser, Charlson and POSSUM that mainly report various complications [25, 26] are currently widely used in the clinic. However, a recent study [27] revealed that with different physical states, ages and genders of patients, various risk factors will play different roles, so this kind of scoring system does not accurately reflect the whole-body state. An elevated lactate concentration has previously been linked to increased morbidity and mortality, and has been shown to have prognostic value in a number of situations [28]. Serum lactate has been proven to be a sensitive sign of mortality and morbidity due to hypovolemic shock [29]. In the emergency department, normalization of lactate concentrations has been shown to be an excellent indicator of patients' full resuscitation. Measurement of lactate concentrations at admission also helps identify occult hypoperfusion and shock [30]. These findings suggest that the lactate concentration may be an effective classification and prediction indicator [31].

Serum lactic acid has been identified as a prognostic indicator after major trauma [32]. In a study of 18,304 trauma patients reported by Dezman et al. [33], it was found that a lactate concentration ≥10 mmol/L at admission could predict mortality within 24 h (sensitivity =0.86, specificity =0.73), but the study mainly focused on young people. In addition to patients with multiple injuries, the lactate concentration could also predict mortality in critically ill patients. In an investigation of 14,040 ICU patients, Haas et al. [34] noted that in hospital ICUs with an average death rate of 9.8%, the death rate of 400 ICU patients with severe hyperlactatemia (≥10 mmol/L) of different eti-

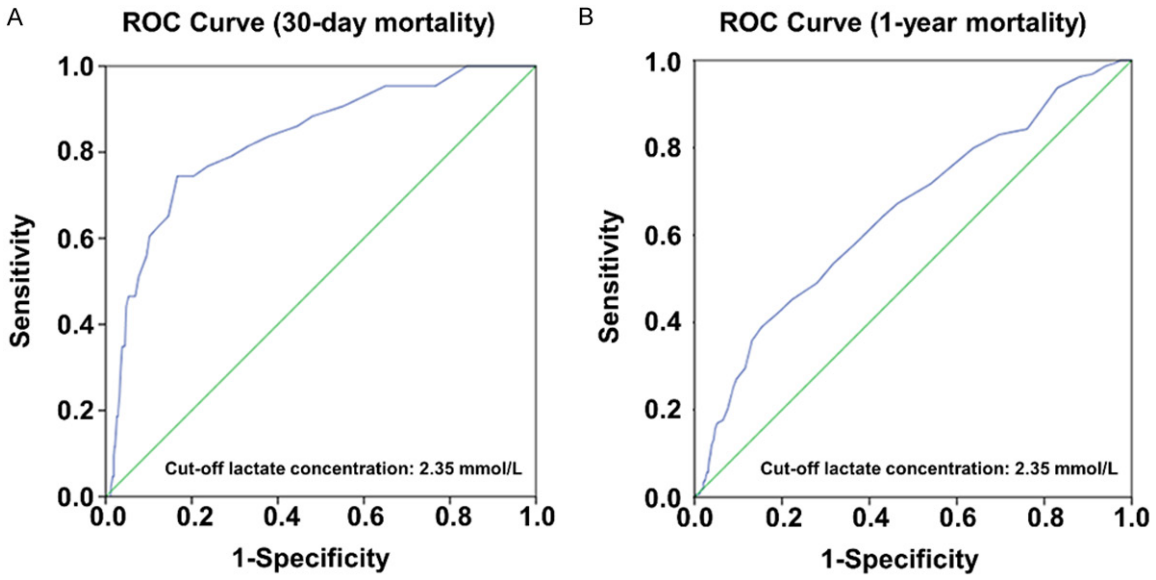

Figure 2. ROC curves of the predictive model of (A) 30-day mortality (AUC: 0.829) and (B) 1-year mortality (AUC: 0.651) in elderly patients with hip fractures.

Table 2. Univariate logistic regression analysis and multivariate logistic regression analysis of lactate concentrations ≥2.35 mmol/L at 30 days and 1 year for mortality

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
30-day mortality	9.14	4.33-19.31	<0.001	9.93	4.52-21.83	<0.001
1-year mortality	2.47	1.75-3.49	<0.001	2.23	1.55-3.21	<0.001

Note: OR, odds ratio.

ologies was 78.2%. They concluded that hyperlactatemia was significantly associated with death in the ICU [odds ratio 1.35 (95% CI 1.23; 1.49; *P*<0.001)]. Furthermore, Drolz et al. [35] reported that the lactate concentration may reflect the degree of organ failure and a concentration ≥10 mmol/L could predict short-term mortality in patients with cirrhosis (the AUC was 0.702). This evidence strongly indicates that the lactate concentration is closely related to the prognosis of patients with severe multiple injuries and can predict mortality. In elderly patients with a poor cardiovascular reserve, sustaining a hip fracture is likely to be the physiological equivalent of severe multiple injuries in younger patients. As a result, the lactate concentration may be used as a specific indicator in elderly patients to evaluate the degree of physiological injury after a hip fracture and to predict mortality. It is noteworthy that two recent observational studies of elderly patients with hip fractures in the United Kingdom have shown that a lactate concentration ≥3 mmol/L was associated with increased postoperative mortality [14], but the predictive ability was not analyzed. Our study also confirms a similar conclusion and further proposes that a lactate concentration ≥2.35 mmol/L should be used as the cut-off value to predict short-term mortality (sensitivity and specificity reached 0.744 and 0.834, respectively; the AUC was 0.829). Multivariate analysis also showed that the 30-day postoperative mortality of patients with concentrations of lactate ≥2.35 mmol/L was nearly 10 times higher than those with concentrations <2.35 mmol/L.

Due to comorbidities, multidrug usage and reduced physiological reserves, the elderly population may be particularly vulnerable to an underestimated risk. Studies have unveiled that lactic acid is also a predictor of poor prognosis in an elderly population. Venous lactate concentration >2.5 mmol/L in trauma patients over 65 years of age has been linked to higher mortality [36]. Another retrospective study

found an increase in mortality of normal blood pressure trauma patients over 55 years of age when the lactate concentrations were >2.5 mmol/L [37]. In the present study, patients with lactate concentrations ≥2 mmol/L had higher postoperative mortality, shorter survival time, a higher incidence of complications and longer hospital stays, which indicated that the serum lactate concentration was closely related to the adverse outcomes of elderly hip fracture patients. The excessive production of lactate is caused by anaerobic metabolism, which is a sign of insufficient oxygenation of tissues. The increase of lactate may also be caused by an increase in aerobic glycolysis and/or a decrease of metabolism resulting from the stress response of the body. A high lactate concentration after a hip fracture indicates that the patient is in a debilitating state, with severe ischemia and hypoxia in the tissues and organs. If no special treatment is given, slight stress can induce the "domino" effect and systemic multiple organ failure [10, 11].

The present study has revealed that the lactate concentration has a high predictive value for short-term mortality after surgery, but the predictive value for 1-year mortality after surgery was limited. This is probably because the lactate concentration is mainly used to assess short-term ischemia and hypoxia of the body tissues and organs, but over time, the lactate concentration will gradually change and it is therefore difficult to assess the long-term postoperative mortality risk using the lactate concentration at admission alone.

There are a number of limitations in our study: 1) Our study was conducted in a single hospital, with retrospective analysis that inevitably could lead to selection bias, so it needs to be further verified by a larger cohort, multi-center prospective study; 2) The study did not dynamically detect the concentration of lactate, so we were unable to monitor the relationship between lactate concentrations and mortality from time to time; 3) Unmeasured potential confounding factors affecting lactate concentrations cannot be ruled out; 4) The impact of the fracture type and surgery mode on postoperative mortality was not analyzed, and therefore further investigations are required.

Conclusions

The serum lactate concentration was found to be a good prognostic indicator of postoperative mortality at 30 days in elderly hip fracture patients. Patients with a serum lactate cut-off concentration of 2.35 mmol/L were identified as a high-risk population. The lactate concentration at admission revealed a good short-term postoperative mortality prediction ability, which can help physicians and surgeons to stratify the risk for these patients and to construct individualized care plans.

Disclosure of conflict of interest

None.

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