Original Article

Association between serum lactate levels and enteral feeding intolerance in septic patients treated with vasopressors: a retrospective cohort study

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Background: To assess the association between serum lactate levels and intolerance to enteral nutrition (EN) in septic patients treated with vasopressors.

Methods: This retrospective study was conducted between January 1, 2015 and May 1, 2018 in an intensive care unit (ICU). Patients with sepsis who were given EN and treated with vasopressors were included. EmpowerStats software and R (version 3.3.2) was used to examine the association between serum lactate levels and intolerance to EN.

Results: Among the 132 septic patients (age, 60.6±18.1 years) enrolled, 35 (26.5%) patients suffered intolerance to EN. Multiple logistic regression analysis demonstrated that an elevated lactate level was an independent risk factor for EN intolerance [odds ratio (OR): 2.7; 95% confidence interval (CI): 1.6–4.4; P<0.001]. The area under the receiver operating characteristic (ROC) curve for serum lactate levels was 0.764 (95% CI: 0.664–0.864). Stratified analysis suggested that age was the most prominent interactive factor for serum lactate levels in EN intolerance. Serum lactate levels were closely correlated to EN intolerance in elderly patients (age ≥65 years) (OR: 9.5; 95% CI: 2.1–42.4; P=0.0261 for interaction), while no such association was identified in younger patients (age <65 years; OR: 1.7; 95% CI: 1.0–2.9; P=0.052).

Conclusions: Serum lactate levels were associated with an increased risk of EN intolerance in patients with sepsis, especially in elderly individuals. An elevated serum lactate level may be an early predictor of EN intolerance in elderly septic patients treated with vasopressors. However, further studies are called for to verify these findings.

Keywords: Serum lactate level; enteral nutrition (EN); intolerance; sepsis

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Introduction

In patients with sepsis, enteral nutrition (EN) feeding can preserve the function of the intestinal barrier, promote the recovery of gastrointestinal function, and play a role in metabolic conditioning and support. Early EN plays a key role in reducing the incidence of infection, resulting in shorter length of hospital stay, decreased hospitalisation costs, and lower mortality (1-3). Nutritional guidelines recommend that EN support is started within 24 to 48 hours of admission to the intensive care unit (ICU) to improve the prognosis of critically ill patients (4-6). However, septic patients often suffer from hemodynamic instability, which results in gastrointestinal dysfunction and the inability to tolerate EN, leading to reflux aspiration and increasing the fatality rate and length of ICU stay (7).

Lavrentieva *et al.* (8) showed that approximately 35% of septic patients develop feeding intolerance during EN. Early EN in septic patients may increase the risk of digestive complications compared with early isocaloric parenteral nutrition (9). The guidelines of 2016 Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) for critical nutrition in American adults (10) recommend delaying EN for patients with hemodynamic instability until adequate resuscitation or hemodynamic stability has been achieved. EN can be carefully initiated or reinitiated for patients who have been treated with a reduced dosage of vasoactive drugs. Therefore, the early prediction of EN feeding intolerance is of particularly importance for septic patients who are treated with vasopressors (11).

The pathogenesis of intestinal nutritional intolerance has yet to be fully explored. Possible mechanisms underlying intolerance to EN feeding include gastrointestinal nerve and smooth muscle injuries, inflammation, surgery, opioid use, electrolyte disturbance, and hyperglycemia (8,12). However, studies on the relevant risk factors are still controversial (7,12). Arabi *et al.* (13) suggested that when EN is carried out for severe patients treated with vasopressors, attention must be paid to the occurrence of lactic acidosis, which may be an important indicator of parenteral ischemia.

Serum lactate can serve as a biomarker in the assessment of mortality risk in sepsis patients (14,15), due to the association between hyperlactic acidemia and organ failure (16). Lactate level was found to be significantly correlated with microcirculation perfusion in shock patients (17), and an elevated lactate level may be an indicator of intestinal perfusion in septic patients (18). However, no study to date has confirmed the relationship between serum lactate levels and EN feeding intolerance in patients with sepsis. Therefore, in the present study, we hypothesized that serum lactate levels in septic patients treated with vasopressors were associated with intolerance to EN. We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6317).

Methods

Data collection and treatment

Patients

The institutional ethics committee of the General Hospital of the People's Liberation Army approved this single-centre retrospective cohort study (S2017-055-02). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the research, the requirement for informed consent was waived. Consecutive septic patients aged ≥18 years old who were treated with vasopressors (noradrenaline, dopamine, or epinephrine) and were admitted to the hospital's ICU between January 1, 2015, and May 1, 2018, were enrolled. The exclusion criteria were as follows: EN time ≤1 hour; existing intestinal obstruction; acute pancreatitis, peritonitis, or ischemic colitis; or incomplete or missing data.

Survey data

Patient demographic and clinical data

The following demographic and clinical data were collected for each patient from electronic medical record: sex and age; diagnosis; Acute Physiology and Chronic Health Evaluation (APACHE II) score; Sequential Organ Failure Assessment (SOFA) score; acute gastrointestinal injury (AGI) score; length of hospital stay, length of ICU stay, mechanical ventilation and bedside blood filtration; mean arterial pressure; and blood lactic acid and creatinine levels. For each patient, the gastrointestinal function, position of the nutrient canal, gastric residual volume, amount of vomitus, amount of feces, and frequency of defecation were also recorded. Clinical information and EN tolerance were collected by two assessment groups separately.

Definitions

The patients were divided into the tolerance group and the intolerance group on the basis of the assessment of EN

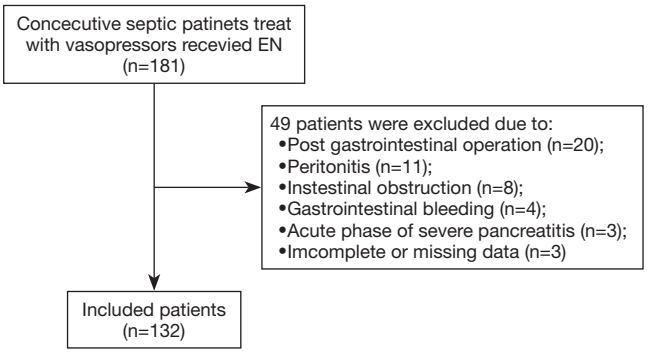

Figure 1 Flow diagram of participants including. EN, enteral nutrition.

tolerance. EN intolerance (19) is defined as a patient having gastric residue >250 mL, vomiting, positivity in abdominal plain film or abdominal computed tomography (CT) imaging, and intestinal ischemia, or perforation.

Statistical analysis

Statistical analyses were performed with EmpowerStats 2.17.8 (http://www.empowerstats.com/cn/) and R-project (version 3.3.2). Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were performed using the independent samples *t*-test. Categorical variables were analyzed using the odds ratio (OR) and chi-square (χ^2) test. Multiple logistic regression analysis was performed with adjustment for possible baseline data imbalances. Curve fitting, an interaction test, and covariate screening were conducted, and the effects of each model were compared. In the stratified analysis, each continuous variable was divided into three groups: low, middle, and high. The receiver operating characteristic (ROC) curve was draw, and the area under the curve (AUC) was used to determine the optimal cutoff for serum lactate level in the prediction of feeding intolerance. A two-tailed P value of <0.05 was considered to be statistically significant. Intended sample size was not estimated for this retrospective cohort study.

Results

This study enrolled 132 patients with sepsis (*Figure 1*). The EN tolerance and EN intolerance groups comprised 97 and 35 patients, respectively. A general comparison of baseline data including the sex, age, and APACHE II, SOFA, and AGI scores of the patients revealed no statistical differences between the intolerance and tolerance groups. No significant difference was observed between the groups in the proportion of abdominal diseases or the proportion of feeding after pylorus. However, the mechanical ventilation ratio of the EN intolerance group was significantly higher than that of the tolerance group (P=0.018) (*Table 1*).

No statistical difference was observed in the length of hospital stay, length of ICU stay, or duration of mechanical ventilation between the two groups. The intolerance group had a significantly higher 28-day mortality rate than the tolerance group (*Table 2*).

The univariable analysis revealed feeding intolerance to be significantly associated with serum lactate levels, mechanical ventilation (MV), and AGI score (*Table 1*). The stratified analysis indicated that age was a significant effect modifier for the relationship between serum lactate levels and intolerance (P=0.0261) (*Table 3*). Covariate screening selected MV and AGI.

In multivariate regression analysis, the dependent variables were mechanical ventilation and EN tolerance, and the independent variables were serum lactate levels, MV, and AGI score. The results indicated that an elevated lactate level was an independent risk factor for EN intolerance [OR: 2.7; 95% confidence interval (CI): 1.6–4.4; P<0.001]. Additionally, smooth curve fitting was conducted after adjustment for all variables together (*Figure 2*).

Figure 3 shows the ROC curve of serum lactate levels in predicting EN intolerance. The AUC for serum lactate was 0.764 (95% CI: 0.664–0.864), with a cutoff value of 2.125 mmol/L. With age as an effect modifier, analysis was performed with the patients stratified into two groups by age: the ≥65 age group and the <65 age group. In the ≥65 age group and the <65 age group, the OR values of association between serum lactate levels and feeding intolerance were 9.5 (95% CI, 2.1–42.4; P=0.003) and 1.8 (95% CI: 1.0–3.1; P=0.053) when adjusted for MV and AGI, respectively (*Figure 4*). The AUC for serum lactate in predicting EN intolerance in patients aged ≥65 was 0.831 (95% CI: 0.667–0.985) (*Figure 5*).

Discussion

This retrospective cohort study found that serum lactate levels are associated with intolerance to enteral feeding among elderly patients with sepsis who undergo treatment with vasopressors. Saturation analysis showed a correlation of the serum lactate levels with EN intolerance when the

Table 1 Baseline characteristics of participants in each group

Characteristics	Tolerance group	Intolerance group	P value
N	97	35	
Gender			0.866
Male	68 (70.1%)	24 (68.6%)	
Female	29 (29.9%)	11 (31.4%)	
Age	61.1±18.3	59.1±17.8	0.593
Hight	168.0±7.4	170±8.9	0.208
Weight	64.9±11.4	67.8±11.2	0.202
BMI	23.4±4.2	23.6±2.3	0.788
Comorbidities			
Hypertension	34	15	0.413
CHD	29	7	0.260
Diabetes	18	3	0.166
CKD	11	3	0.892
Cirrhosis	4	1	0.874
COPD	2	2	0.586
Oncologic	32	13	0.657
Source of sepsis			
Respiratory system	21	9	0.623
Abdominal	28	13	0.364
Urinary system	4	1	0.857
Skin and soft tissues	27	8	0.567
Bloodstream	6	2	0.754
Other	11	2	0.531
MV			0.018*
No	19 (19.6%)	1 (2.9%)	
Yes	78 (80.4%)	34 (97.1%)	
Abdominal diseases			0.935
No	63 (64.9%)	23 (65.7%)	
Yes	34 (35.1%)	12 (34.3%)	
Feeding way			0.681
Jejunal tube	19 (19.6%)	8 (22.9%)	
Gastric tube	78 (80.4%)	27 (77.1%)	
EN total	500.0 (300.0–700.0)#	500.0 (200.0–500.0)#	0.155
EN speed	41.8±36.3	36.7±21.1	0.435
Lactate	1.5±0.8	2.8±2.0	<0.001*
Albumin	31.4±3.9	32.2±7.0	0.400
Hb	106.5±27.3	89.5±13.4	<0.001*
WBC	11.2±6.7	10.5±4.8	0.553
D-dimer	5.7±4.7	5.0±3.8	0.464
SOFA	9.2±3.7	10.7±5.2	0.068
APACHE II	17.7±7.5	19.6±8.4	0.504
AGI			0.335
1	71 (73.2%)	11 (31.4%)	
2	18 (18.6%)	13 (37.1%)	
3	6 (6.2%)	8 (22.9%)	
4	2 (2.1%)	3 (8.6%)	

*, P<0.05; #, median (Quartile1-Quartile). AGI, acute gastrointestinal abbreviated injury; APACHE, acute physical and chronic health assessment; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney diseases; COPD, chronic obstructive pulmonary disease; EN, enteral nutrition; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

Table 2 The comparison of intolerance and outcomes between two groups

Outcomes	Tolerance group	Intolerance group	P value
N	97	35	
ICU stay (d)	25.0±24.7	23.7±14.7	0.756
Duration of MV	16.2±21.3	17.5±13.5	0.395
28-days mortality			0.042
Non-survival	15 (15.5%)	11 (31.4%)	
Survival	82 (84.5%)	24 (68.6%)	

MV, mechanical ventilation.

serum lactate levels >2.0 mmol/L was an indicator of septic shock. This study shows that a higher serum lactate level is an independent predictor for EN intolerance in septic patients.

Elevated serum lactate levels indicate the presence of hypoxia in tissues and gastrointestinal dysfunction in patients with hemodynamic instability, which further affects their tolerance to EN. In shock patients with mechanical

Table 3 Stratified analysis of characteristics and interaction modifiers

Characteristics	N	Intolerance [OR (95% CI)]	P value	P value of interaction
Age				0.0216*
<65	69	2.0 (1.2, 3.3)	0.0053*	
≥65	63	8.8 (2.5, 31.0)	0.0007*	
APACHE II tertile				0.0716
Low	41	5.1 (1.3, 20.2)	0.0197*	
Middle	46	4.7 (1.7, 13.0)	0.0029*	
High	45	1.5 (0.8, 2.8)	0.2399	
SOFA tertile				0.5888
Low	44	4.3 (1.4, 13.9)	0.0135*	
Middle	32	2.7 (0.8, 9.8)	0.1190	
High	56	2.2	0.0078*	
MV				0.8573
Non-MV	20	1.7 (0.0, 141.7)	0.8252	
MV	112	2.5 (1.5, 4.1)	0.0003*	
Feeding way				0.9345
Jejunal tube	27	2.6 (0.7, 9.3)	0.1328	
Gastric tube	105	2.8 (1.6, 4.8)	0.0003*	
EN total tertile				0.8595
Low	44	2.6 (1.1, 6.3)	0.0313*	
Middle	1	0.0	0.9929	
High	87	2.9 (1.5, 5.5)	0.0010*	
Abdomen disease				0.7677
No	86	2.6 (1.5, 4.6)	0.0008*	
Yes	46	3.1 (1.2, 8.0)	0.0206*	
EN speed tertile				0.5475
Low	30	2.6 (1.0, 7.0)	0.0483*	
Middle	55	4.0 (1.6, 10.2)	0.0036*	
High	47	2.1 (1.1, 4.1)	0.0306*	

*, P<0.05. Continuous variables were divided in to three grade groups as low, middle and high. MV, mechanical ventilation; EN, enteral nutrition.

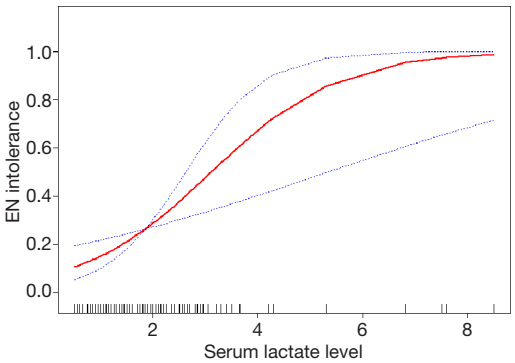

Figure 2 Smooth curve fitting of serum lactate levels and tolerance to enteral nutrition in patients with sepsis. Adjustment variables: age, sex, MV, and AGI. MV, mechanical ventilation; AGI, acute gastrointestinal injury.

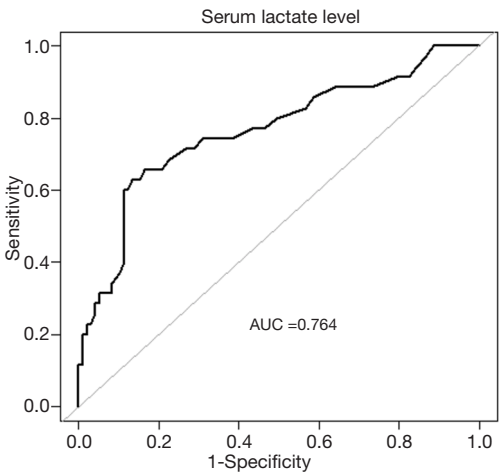

Figure 3 Receiver operating characteristic curve of the relationship between serum lactate levels and tolerance to enteral nutrition in patients with sepsis. AUC, area under the curve.

serum lactate levels are below 2.5 mmol/L. In the present study, 26.5% patients who received EN suffered intolerance, which is similar to the rate reported in a previous study (20). In patients with sepsis, the intestinal blood flow is decreased, the intestinal villi are damaged, the intestinal flora is displaced, and the intestinal tract releases pro-inflammatory response media, resulting in damage to the intestinal mucosa and the deterioration of intestinal function. Various intolerances frequently occur during the course of EN. Patients with sepsis still have persistent hypotension after fluid resuscitation, and vasopressors are required to maintain the mean arterial pressure ≥65 mmHg (21). Moreover, the mortality rate is remarkably increased in patients with a serum lactate level >2.0 mmol/L. The definition of Sepsis 3.0 was validated in a cohort study using a large electronic medical record data set (22), wherein the

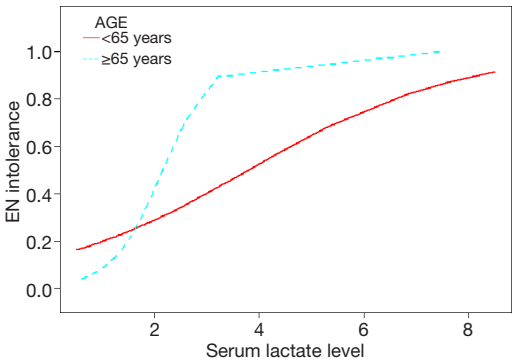

Figure 4 Subgroup smooth curve fitting of serum lactate level and EN tolerance in septic patients stratified by age. Adjustment variables: age, gender, MV, and AGI. EN, enteral nutrition; MV, mechanical ventilation; AGI, acute gastrointestinal injury.

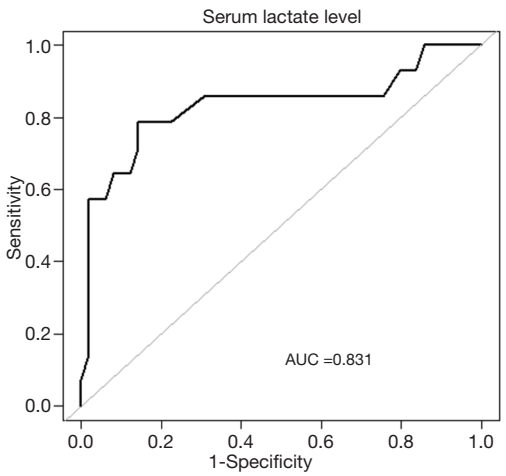

Figure 5 Receiver operating characteristic curve of the relationship between serum lactate level and tolerance to enteral nutrition in septic patients aged ≥65. AUC, area under the curve.

ventilation, no significant differences were found to exist between the serum lactate levels of EN-tolerant and intolerant patients (19); however, the proportion of patients with elevated blood lactate levels was reported to be lower in the EN tolerance group than in the EN intolerance group. Our study showed that the serum lactate levels in the EN intolerance group were higher than those in the EN tolerance group, and multifactor regression analysis revealed that an increase in blood lactic acid was correlated with and was an independent risk factor for EN intolerance. Increased serum lactic acid levels indicate ischemia and hypoxia in tissues, and possibly in the gastrointestinal tract, thereby ischemia and hypoxia may lead to EN intolerance. Shock patients with increased serum lactate may have an increased risk of developing intolerance to EN.

Septic patients may suffer from gastrointestinal dysfunction and EN intolerance due to hemodynamic instability and the application of vasopressors. Therefore, the optimal time for starting EN has not been established. The current guidelines (10) recommend that EN should be delayed for patients with hemodynamic instability until adequate resuscitation or hemodynamic stability has been achieved. Patients who are administered a reduced dosage of vasopressors can carefully start or restart EN. The tolerance rate of shock patients was reported to reach 75% when the equivalent dose of noradrenaline was 12.5 $\mu g \cdot min^{-1}$ (23). Merchan *et al.* (19) showed that the EN tolerance of patients treated with methylepinephrine was 62% when the equivalent dosage was <0.14 $\mu g \cdot kg^{-1} \cdot min^{-1}$. However, their study did not further analyse the factors related to the high occurrence rate of EN intolerance in shock patients.

EN-intolerant patients have a higher mortality rate. This study showed that the blood lactic acid levels and the mortality rate of the EN intolerance group were higher than those of the EN tolerance group. These results may be related to the disease severity of patients, as EN intolerance can also manifest as gastrointestinal failure. Furthermore, tissue hypoxia worsened the condition of the patients. Further studies are needed to determine whether EN intolerance is an independent risk factor for mortality in septic patients.

The findings of the present study suggested that age (≥65) was the significant interaction modifier for the relationship between serum lactate levels and EN intolerance in septic patients. Previous studies have shown that elderly patients have a higher likelihood of experiencing gastric emptying delay combined with increased gastric residue than younger patients, old age is an independent risk factor influencing the prognosis (24). Park *et al.* (25) reported high mortality and poor prognosis among patients with ischemic bowel disease without surgical intestinal resection and nonobstructive ischemic bowel disease. Halm *et al.* (26) showed that advanced age (age >80 years old) is an independent risk factor for the occurrence of EN-related complications in cardiac surgery patients. However, Rai *et al.* (7) believed that despite delayed gastric emptying, early EN should also be started on patients with hemodynamic instability. Age has no effect on the prognosis of gastrointestinal diseases and EN complications. Barone *et al.* (27) showed that age is not an influencing factor

of EN complications, although it is relevant to the rate of comorbidities. Regardless of the high incidence of comorbidities in elderly patients, age is not an indicator that influences the recovery of gastrointestinal function or the prognosis of patients with acute upper gastrointestinal haemorrhage who are treated with endoscopy (25). However, the present study suggested that serum lactate levels were closely correlated with EN intolerance in elderly patients (age ≥65 years), while no such association was observed in the other patients (age <65 years). Therefore, an elevated serum lactate level may be an early predictor of EN intolerance in elderly patients with sepsis who receive treatment with vasopressors. For elderly septic patients who have been treated with vasopressors, serum lactate levels could be a valuable biomarker for informing treatment decision-making.

There are several limitations to this study. Firstly, as a retrospective cohort study, bias could not be avoided. The intolerance group had a higher AGI score and MV rate, which might be confounders. However, the results were confirmed by multiple analysis. Second, the study's single-center nature and small sample size may affect the generalizability of the results. Larger studies using prospective methods are needed in the future.

In conclusion, serum lactate levels were associated with EN intolerance in patients with sepsis, especially in elderly patients. These results indicate that serum lactate levels may be an early biomarker for predicting EN intolerance in septic patients in eldely patients. However, our findings need to be confirmed in further studies.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6317

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-6317

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6317). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The institutional ethics committee of the General Hospital of the People's Liberation Army approved this single-centre retrospective cohort study (No. S2017-055-02). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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