Nutrition 63–64 (2019) 1–8

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Association of intestinal permeability with a NUTRIC score in critically ill patients

Ghazaleh Eslamian [a], Seyed Hossein Ardehali [b], Zahra Vahdat Shariatpanahi [c,*]

[a] Student Research Committee, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Anesthesiology and Critical Care, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received 24 October 2018
Received in revised form 12 December 2018
Accepted 17 January 2019

Keywords:
Nutrition status
Zonulin
Endotoxin
Glutamine deficiency
NUTRIC
ICU

ABSTRACT

Objectives: The aim of this study was to investigate the association of intestinal permeability with the Nutrition Risk in Critically Ill (NUTRIC) score and the modified NUTRIC score (mNUTRIC) in intensive care unit (ICU) hospitalized patients.
Methods: One hundred and fifty ICU hospitalized adult patients admitted between October 2017 and April 2018 who stayed for >24 h in the general ICU were enrolled in the study. Nutrition status was estimated using the NUTRIC score, an ICU-specific nutrition risk assessment tool. The NUTRIC score was calculated using the exact same thresholds and point system as developed previously. Admission plasma endotoxin and zonulin concentrations were measured to assess intestinal permeability.
Results: Median plasma endotoxin and zonulin increased with increasing mNUTRIC and NUTRIC categories in the overall study population and in the glutamine-deficient subgroup. Multivariate binary logistic regression analyses showed a significant association between the plasma endotoxin (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.8–3.52) and zonulin (OR, 1.11; 95% CI, 1.03–1.20) levels with NUTRIC category in the overall population and the glutamine-deficient subgroup. Similar results were obtained when using mNUTRIC.
Conclusions: Results from the present study provided evidence that higher plasma endotoxin and zonulin levels are associated with a progressively higher NUTRIC score in critically ill patients.

Introduction

Management and monitoring of the nutritional aspects of critically ill patients reveal several challenges [1]. Malnutrition is a prevalent condition and potentially costly problem in critically ill patients admitted to the intensive care unit (ICU) [2]. Malnutrition can occur in 13% to 78% of acute care patients, depending on the population studied and the screening tool employed. This issue is associated with increased mortality and morbidity [3]. In critically ill patients, accurate assessment of nutrition is imperative to categorize nutritional status, identify nutritional problems, and to monitor nutrition support adequacy [4]. Nutrition Risk in Critically Ill (NUTRIC) score is the first nutritional assessment tool used in ICU clinical practice [5]. This scoring tool may be helpful in identifying critically ill patients, who are at risk for adverse events because of their nutrition status, by linking starvation, inflammation, and clinical outcomes [5].

The early and adequate administration of nutrition support may play a vital role in preserving the intestinal barrier and preventing intestinal atrophy, bacterial translocation, and sepsis [6]. Bacterial translocation and gut-derived sepsis can be involved in the pathogenesis of systemic infectious complications and multiple organ deficiency syndrome [7]. Glutamine deficiency leads to villus atrophy, decreased expression of tight junction proteins in several conditions, and increased bacterial translocation and intestinal permeability [8].

This study was financially supported by the Shahid Beheshti University of Medical Sciences, Tehran, Iran. GE conceptualized and designed the study, wrote the manuscript, and collected and analyzed the data. HA conceptualized and designed the study, collected and interpreted the data, provided professional comments, and critically revised the manuscript for intellectual content and data accuracy. ZS conceptualized and designed the study, wrote the manuscript, interpreted the data, provided professional comments, and was responsible for final content. All of the authors read and approved the final manuscript for submission. The authors have no conflicts of interest to declare.
* Corresponding author: Tel.: +98 212 236 0658; Fax: +98 212 236 0657.
E-mail address: Nutritiondata@yahoo.com (Z. Vahdat Shariatpanahi).

https://doi.org/10.1016/j.nut.2019.01.010
0899-9007/

It has been shown that glutamine is reduced in critically ill patients [9]. Thus, intestinal permeability is an important determinant in the outcome of ICU hospitalized patients [10–12]. There is currently a large array of tests to assess intestinal permeability. Zonulin, a physiologic modulator of intercellular tight gap junctions, has been represented as a marker of intestinal permeability. This marker binds the epidermal growth factor and protease-activated receptors in the epithelium [13]. Zonulin plays an important role in protection against microorganism colonization of the proximal intestine; therefore, it is involved in intestinal innate immunity [14]. Elevated levels of serum zonulin have been described in ICU hospitalized patients with sepsis [15]. Another clinical marker of intestinal permeability is endotoxin, lipopolysaccharide (LPS) constituents of the outer membrane of gram-negative bacteria [16]. Malfunction of the intestinal mucosal barrier results in the passage of endotoxin into the systemic circulation [17]. Endotoxemia has been reported in critically ill patients as a potent trigger of the sepsis cascade [18].

There is much debate around whether an independent association exists between increased intestinal permeability and nutrition status in some patients [19–21]. We hypothesized that critically ill patients with high nutritional risk may have increased circulating levels of zonulin and endotoxin. However, our current understanding is still limited in critically ill patients. We, therefore, undertook the present study to assess the association between levels of admission plasma zonulin and endotoxin with a NUTRIC score in the critically ill patients and in subgroups stratified by the absence or presence of glutamine deficiency according to the plasma levels of glutamine.

Methods

Study design and participants

In this observational study, data were collected between October 2017 and April 2018 from the mixed ICU of a university-affiliated hospital. Patients were enrolled within 24 h of admission to the ICU. Patients who were ≥18 y of age and admitted to the ICU for >24 h were included in the study. Exclusion criteria were dying or being discharged within 24 h of ICU admission and patients who were transferred from other ICUs. For patients who were readmitted to the ICU, only data from their first admission was collected. Eligible patients or their legal representatives signed an informed consent. The study was approved by the related ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Baseline characteristics and clinical measurements

Investigators blinded to the clinical outcomes collected all data prospectively. Data on baseline demographic characteristics and past medical history, including a detailed list of comorbidities and medications were collected. Acute Physiology and Chronic Health Evaluation Scores (APACHE II) [22] and Sequential Organ Failure Assessment (SOFA) [23] scores were determined over the first 24 h after admission to the ICU.

Recently, a novel scoring tool, the NUTRIC score, was developed and validated to assess the nutritional risk in ICU patients [5]. Thus, the NUTRIC score was used with the following variables: age, a number of comorbidities, days from hospital to ICU admission, serum interleukin (IL)-6, APACHE II, and SOFA scores at admission. The NUTRIC score ranges from 0 to 10; a score ≥6 indicates a high nutritional risk. The modified NUTRIC score (mNUTRIC) was also calculated without IL-6 levels to compare NUTRIC versus mNUTRIC in relation to the intestinal permeability. The mNUTRIC score ranges from 0 to 9, where a score ≥5 also indicates a high nutritional risk [5]. NUTRIC and mNUTRIC scores were determined over the first 24 h after admission at the ICU by a single investigator who was blinded to the intestinal permeability results.

Venous blood samples were taken within 24 h of the ICU admission. Blood samples were collected in EDTA-containing tubes and plasma was separated by centrifugation at 3000 g for 10 min at 4°C within 30 min from the donation. Obtained plasma and serum samples were snap-frozen and stored in small aliquots at −80°C to prevent repeated freezing and thawing until the determination of laboratory data.

Serum IL-6, as an index of hypercytokinemia, was measured using a commercially available human IL-6 enzyme-linked immunosorbent assay (ELISA) kit (Bender Medsystems, Burlingame, CA, USA). Plasma concentrations of endotoxin were measured by a commercially available quantitative chromogenic endpoint Limulus Amebocyte Lysate QCL-1000 kit (Lonza, Walkersville, MD, USA). The plasma zonulin level was analyzed by ELISA (Immundiagnostik, Bensheim, Germany). The glutamine concentration in plasma was measured using high-performance liquid chromatography, as described previously [24]. All assays were performed as recommended by the manufacturers. Tests were carried out in duplicates.

Statistical analyses

The collected data were statistically analyzed with SPSS version 20 (Chicago, IL, USA). Descriptive statistics were used to characterize and summarize the study population. Data were shown as frequencies and percentages or the median with interquartile range (IQR), as most of the continuous variables were highly skewed and not normally distributed [25]. χ^2 or Fisher exact tests were used to check differences in the distribution of categorical variables. In addition, the Mann–Whitney test was used to assess differences in the distribution of continuous non-normal variables between subgroup [25]. The NUTRIC score was analyzed as a categorical variable using two score categories: low nutritional risk (<6) and high nutritional risk (≥6) [5]. The mNUTRIC score was also analyzed as a categorical variable using the following score categories: low nutritional risk (<5) and high nutritional risk (≥5) [5]. Mann–Whitney test was conducted to compare variables across the two NUTRIC or mNUTRIC categories for continuous explanatory variables. Multivariate analyses were conducted using a binary logistic regression model to explore the potential association of higher nutritional risk category with increasing zonulin and endotoxin levels. Analyses were conducted in the overall population and in subgroups stratified by the plasma glutamine level (deficient: <420 μmol/L and normal: ≥420 μmol/L levels).

Results

In all, 150 patients fulfilled the study eligibility criteria (Fig. 1). Demographic and clinical characteristics of the 150 patients are listed in Table 1, overall and by the plasma glutamine level. The

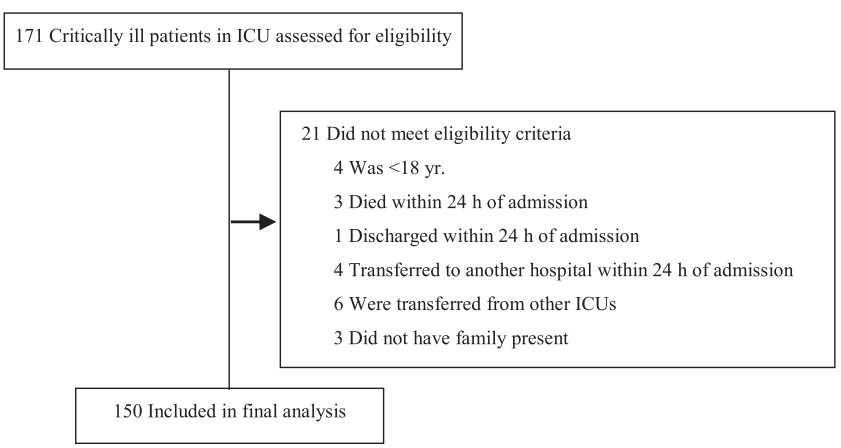

Fig. 1. Flow chart of selection of participants.

Table 1
Baseline demographic and clinical characteristics of the overall population and stratified by the glutamine levels

Variable	Overall (N = 150)	Glutamine level (μmol/L)		
		Deficient <420 (n = 49)	Normal ≥420 (n = 101)	*P*-value
Age, y	64 (50–74)	60 (50–74)	66 (53–73)	0.170*
Sex, n (%)				0.677†
Male	79 (53)	27 (55)	52 (52)	
Female	71 (47)	22 (45)	49 (48)	
Hospital to ICU admission, d	1 (0–1)	1 (0–2)	1 (0–1)	**0.022***
Admission category, n (%)				0.395†
Medical	50 (33)	20 (41)	30 (30)	
Trauma	47 (31)	14 (29)	33 (33)	
Surgical	53 (36)	15 (30)	38 (37)	
Comorbidity n (%)				
Diabetes	29 (19)	11 (22)	18 (18)	0.501†
Hypertension	22 (15)	10 (20)	12 (12)	0.166†
Heart failure	20 (13)	7 (14)	13 (13)	0.811†
Chronic pulmonary disease	20 (13)	6 (12)	14 (14)	0.820†
Neoplasms	24 (16)	10 (20)	14 (14)	0.305†
Chronic kidney disease	4 (3)	1 (2)	3 (3)	0.605‡
Brain stroke or transient ischemic event	7 (5)	3 (6)	4 (4)	0.414‡
Depression, anxiety, or panic disorders	5 (3)	1 (2)	4 (4)	0.472‡
Chronic liver disease	3 (2)	1 (2)	2 (2)	0.698‡
Number of comorbidities	0 (0–1)	1 (0–1)	0 (0–1)	0.545†
Mechanical ventilation, n (%)	28 (19)	9 (18)	18 (18)	0.679‡
APACHE II	24 (19–33)	25 (21–35)	24 (19–30)	0.098*
SOFA score	9 (7–11)	10 (7–11)	8 (7–11)	0.078*
mNUTRIC score	5 (4–5)	5 (4–6)	5 (3–5)	**0.045***
mNUTRIC score class, n (%)				0.375†
Low	69 (46)	20 (41)	49 (48)	
High	81 (54)	29 (59)	52 (52)	
NUTRIC score	5 (4–6)	6 (4–7)	5 (3–6)	**0.015***
NUTRIC score class, n (%)				0.073†
Low	80 (53)	21 (43)	59 (58)	
High	70 (47)	28 (57)	42 (42)	
Serum albumin, g/dL	2.5 (2–3.3)	2.2 (1.8–3)	2.8 (2–3.4)	**0.025***
Serum IL-6, pg/mL	193 (75–448)	332 (103–474)	152 (65–430)	**0.021***
Plasma glutamine, μmol/L	500 (401–630)	370 (202–401)	580 (500–680)	**<0.001***
Plasma zonulin, ng/mL	6.6 (4.3–11.5)	6.8 (3.8-13.4)	6.5 (4.3-9.5)	0.319*
Plasma endotoxin, EU/mL	0.58 (0.33–0.87)	0.69 (0.32–0.90)	0.55 (0.32–0.85)	0.185*

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IL, interleukin; mNUTRIC, modified Nutrition Risk in the Critically Ill; NUTRIC, Nutrition Risk in the Critically Ill; SOFA, Sequential Organ Failure Assessment.
Data are median (P25–P75) unless otherwise stated.
Bold *P*-values indicate statistical significance.
*Mann–Whitney test.
†χ^2 test.
‡Fisher exact test.

median age of participants was 64 y (IQR, 50–74) and 53% were men. Overall, 54% of patients were classified as being at high nutritional risk using the mNUTRIC score algorithm; the proportion was 47% when using the NUTRIC score algorithm. Patients were dichotomized with a cutoff at the plasma glutamine concentration of 420 μmol/L. Of the patients, 32.7% were glutamine deficient (<420 μmol/L). Subgroup analyses showed the severity of disease classification system (APACHE II) and the extent of a participants' organ function or rate of failure (SOFA) were not significantly different between two subgroups of plasma glutamine levels ($P = 0.098$ and $P = 0.114$, respectively). Compared with patients with normal glutamine levels, the glutamine-deficient subgroup had significantly lower serum albumin ($P = 0.025$) and higher levels of serum IL-6 ($P = 0.021$). The proportion of patients at high nutritional risk was not significantly greater in the glutamine-deficient subgroup (59%) than in the patients with normal glutamine levels (52%) using the mNUTRIC score algorithm; the corresponding proportions were 57% versus 42% when using the NUTRIC score algorithm.

Median plasma zonulin increased with increasing mNUTRIC category in the overall study population and in the glutamine-deficient subgroup (Fig. 2; all $P < 0.05$). Similar results were obtained when using NUTRIC (Fig. 3). Median plasma endotoxin increased with increasing mNUTRIC category in the entire study population and also in the glutamine-deficient subgroup (Fig. 4; all $P < 0.05$). Similar results were obtained when using NUTRIC (Fig. 5).

Multivariate analyses using binary logistic regression (mNUTRIC or NUTRIC category: low or high) showed significant associations between increasing zonulin levels and increasing mNUTRIC category or NUTRIC category. Using mNUTRIC, the adjusted odds ratio (OR) was 1.1 (95% confidence interval [CI], 1.02–1.20) in the overall population, 1.13 (1.08–1.28) in the glutamine-deficient subgroup, and 1.07 (0.93–1.19) in patients with normal glutamine levels (Table 2). Using NUTRIC, the corresponding values were 1.11 (1.03–1.20), 1.16 (1.02–1.13), and 1.06 (0.97–1.16; Table 3). The significant positive association of endotoxemia with increasing mNUTRIC category or NUTRIC category in the overall population and in the glutamine-deficient subgroup is demonstrated in Tables 2 and 3, respectively (all $P < 0.05$).

Discussion

This study was designed to determine the association between the levels of zonulin and endotoxin with ICU-specific nutrition

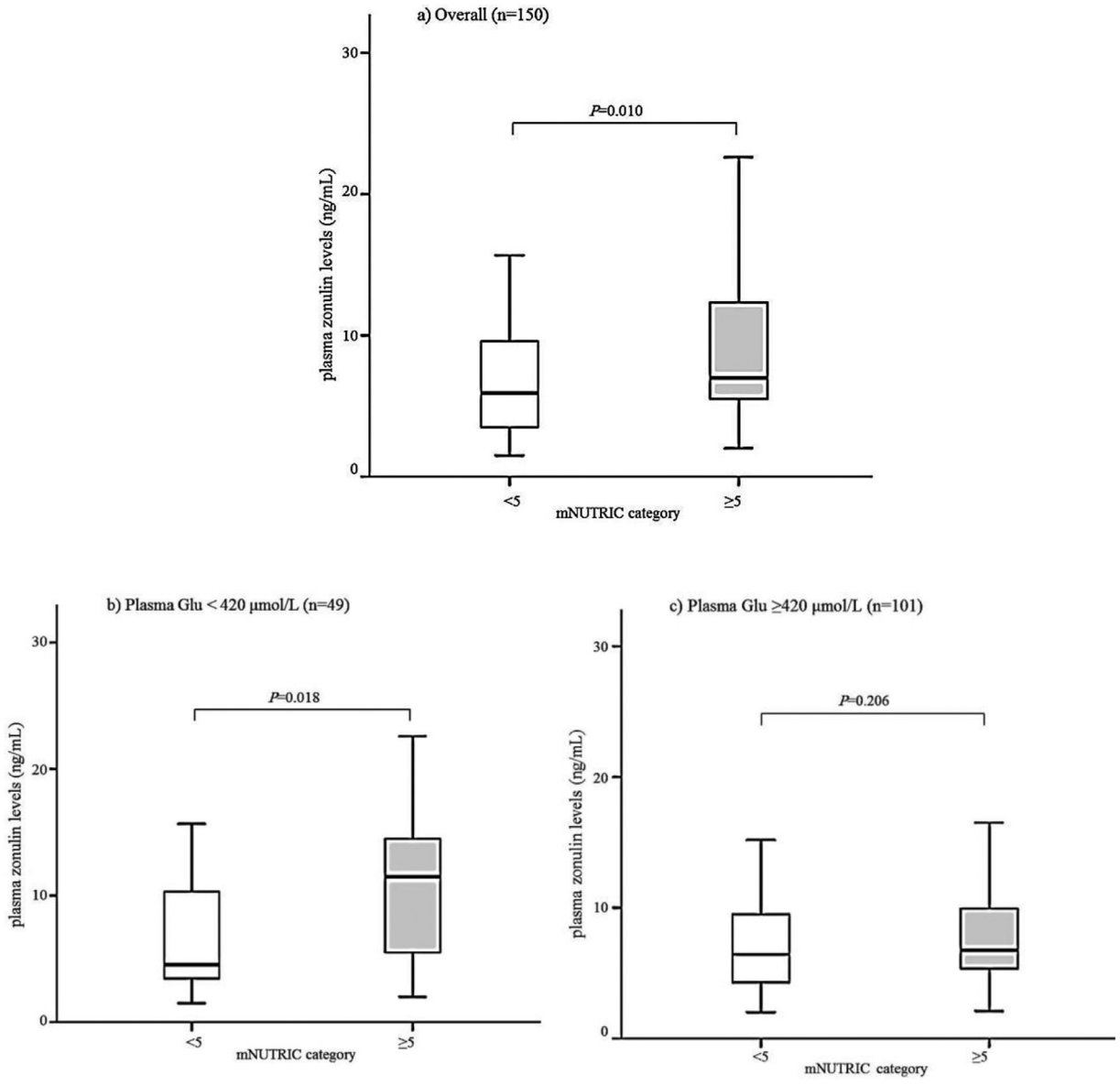

Fig. 2. Median plasma zonulin levels according to the mNUTRIC score category in a) the overall study population, b) patients with pGlu<420 µmol/L, c) patients with pGlu ≥420 µmol/L. P values were calculated using Mann–Whitney U test. Glu, Glutamine; mNUTRIC, Modified Nutrition Risk in Critically ill; pGlu, Plasma Glutamine.

status (NUTRIC score) in critically ill patients. Based on our literature review, the association between intestinal permeability markers and nutrition status was not investigated in the previous studies. Results of the analysis demonstrate a significant positive association between plasma zonulin and endotoxin levels with high scores for the nutrition risk in the ICU patients. The association remained significant when adjusting for potential confounder (serum albumin). Furthermore, the subgroup analysis showed that this association was more pronounced in the subset of patients with glutamine deficiency. However, there was no significant association between intestinal permeability markers and NUTRIC score in patients with normal glutamine levels. These observations support a glutamine's role in the recovery of intestinal barrier function [26].

Previous studies have reported that 30% to 74% of patients who were admitted to the ICU had a glutamine level <420 µmol/L [27–30]. In the present study, about 33% of patients had a glutamine deficiency. Glutamine deprivation leads to cell death in many human cell lines [26]. Enteral administration of glutamine has been proposed as an effective recovery of intestinal barrier function to protect enterocytes from apoptosis by stimulating the intestinal mucosal protein synthesis [8]. Also, glutamine can restore the stress-induced loss of barrier integrity by increasing transepithelial electrical resistance [31]. Today, supplementation of glutamine is a confusing and controversial topic. During the last decades, glutamine supplementation has been recommended for many critically ill patients because available evidence has shown a benefit in reducing mortality and nosocomial infections [32]. However, the results of the REDOXS (Reducing Deaths due to Oxidative Stress) [33] and MetaPlus [34] trials raise concerns about whether high doses of glutamine can result in harm in critically ill patients. It is noteworthy that the majority of patients in these multicenter clinical trials did not have glutamine deficiency at admission. Therefore, further investigations should be performed to assess the

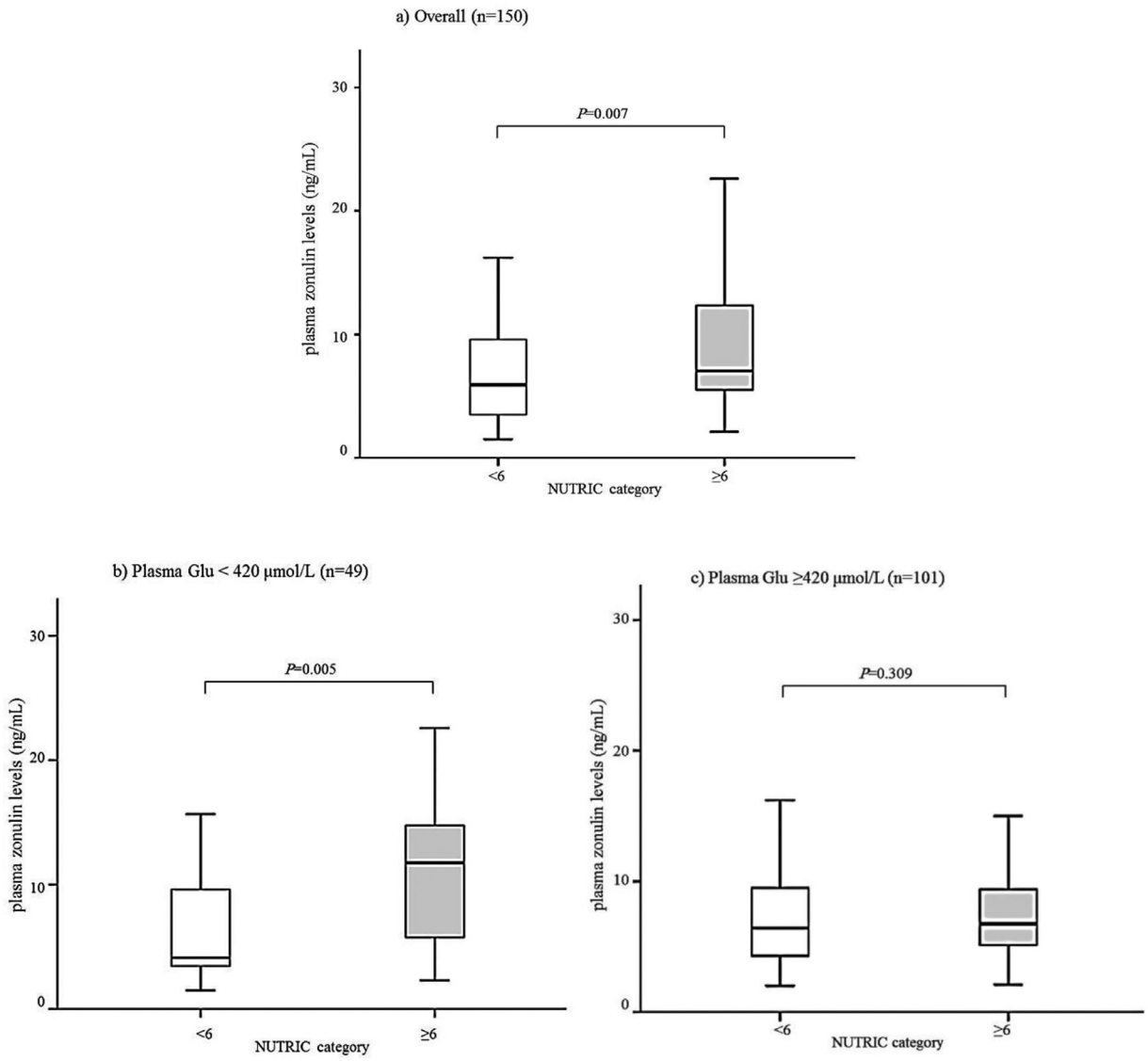

Fig. 3. Median plasma zonulin levels according to the NUTRIC score category in a) the overall study population, b) patients with pGlu<420 μmol/L, c) patients with pGlu ≥420 μmol/L.P values were calculated using Mann–Whitney U test. Glu, Glutamine; NUTRIC, Nutrition Risk in Critically ill; pGlu, Plasma Glutamine.

effects of early glutamine supplementation in critically ill patients with glutamine deficiency to guide the necessity of immediate supplementation in certain patient groups.

Above-normal–range plasma glutamine concentrations are related to high ammonia levels and to the development of hepatic encephalopathy and liver failures [35]. High glutamine levels also have been reported to be associated with advanced stages of chronic kidney disease [36] owing to increased protein catabolism. Intestinal hyperpermeability has been implicated as a potential contributory factor in the development of spontaneous bacterial peritonitis and encephalopathy among patients with liver cirrhosis [37]. However, in the present study, no one had supranormal levels of glutamine on the first day of ICU admission. Thus, this issue did not affect the present results.

The gut is considered to play a pivotal role in pathophysiologic processes of critical illness [11], although specific factors associated with this finding have not been fully elucidated. Previous studies have presented a link between nutritional status and intestinal permeability in both humans [19–21] and animal [38] models. However, knowledge of the nutritional status associated with intestinal permeability is still limited in critically ill patients. The 2016 American Society for Parenteral and Enteral Nutrition (ASPEN) guideline suggests a determination of nutrition risk using the mNUTRIC or NUTRIC score for all patients admitted to the ICU to make a decision about when enteral nutrition (EN) therapy should be initiated [39]. The NUTRIC scoring system is externally validated and may be useful in identifying nutritionally at-risk critically ill patients [5]. In the present study, 47% of patients were classified as being at high nutritional risk based on NUTRIC score, compared with 54% when using mNUTRIC score. The significant association observed between plasma endotoxin and zonulin levels and increased risk for nutrition-associated complications in the current analysis was found both when using the mNUTRIC score and when using NUTRIC score. Moreover, these associations remained significant in the glutamine-deficient subgroup, but not in the patients with normal glutamine levels. The present results suggested the utility of these associations as predictors and ultimately the targets for initiating EN at admission time. Admission

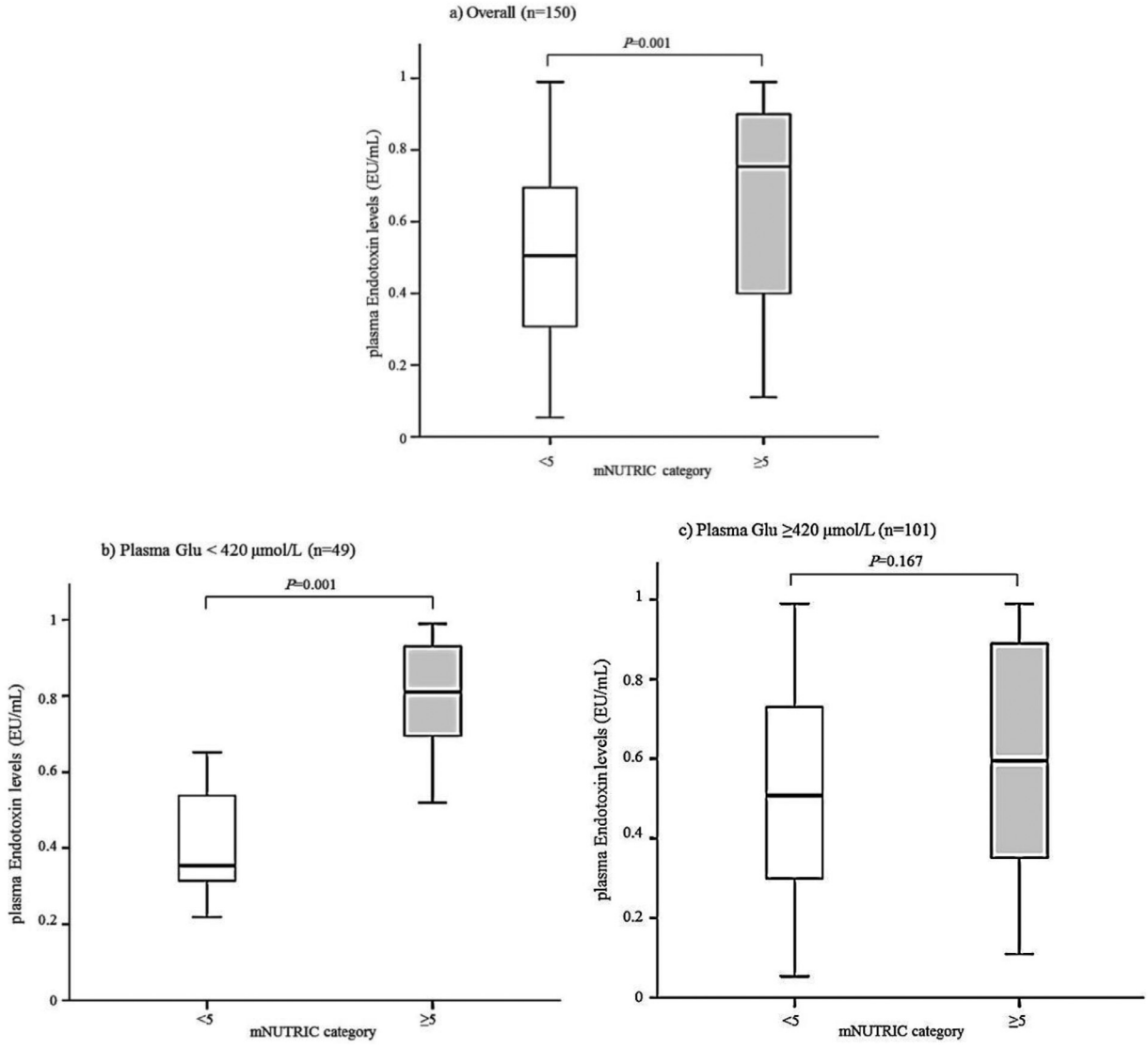

Fig. 4. Median plasma endotoxin levels according to the mNUTRIC score category in a) the overall study population, b) patients with pGlu<420 µmol/L, c) patients with pGlu ≥420 µmol/L. P values were calculated using Mann–Whitney U test. Glu, Glutamine; mNUTRIC, Modified Nutrition Risk in Critically ill; pGlu, Plasma Glutamine.

plasma glutamine levels combined with mNUTRIC and NUTRIC scores should be considered in future studies to show whether this combination could increase the prediction of initiating EN in the ICU. As nutrition status has been shown to affect adverse outcomes in critically ill patients [1], adding nutritional variables could improve the power of mNUTRIC and NUTRIC scores to make a decision about selecting an appropriate time to start feeding to prevent systemic inflammatory response syndrome and multiple organ dysfunction syndrome as well as improving the survival rate in advanced cases.

The main strengths of the present study are the use of standardized procedures to collect data and of a central laboratory for blood analyses. The NUTRIC score is easy to calculate and is based on variables that are mostly easy to assess in the critical care setting, except IL-6 levels that are not commonly measured [40].

A potential limitation of the present study is that NUTRIC score only is applied to the provision of macronutrients and energy and does not identify patients who may benefit more or less from pharmaconutrient supplementation [5]. In this regard, a highly heterogeneous group of critically ill patients makes it difficult to draw more conclusive results. So, more investigations are needed to confirm the results of this study in the specific populations. Furthermore, the study's cross-sectional design does not provide insight into the longitudinal association between plasma endotoxin and zonulin levels and the NUTRIC score. Finally, the possibility that residual confounding factors may explain the association between plasma endotoxin and zonulin levels and the NUTRIC score is not excluded.

Conclusion

Results of this analysis demonstrate that plasma endotoxin and zonulin levels are significantly positively associated with a score for nutritional risk in critically ill patients. A subgroup analysis by plasma glutamine levels showed that higher plasma endotoxin and zonulin levels are associated with a progressively higher NUTRIC score in critically ill patients with glutamine deficiency. However, this association was not significant in patients with normal

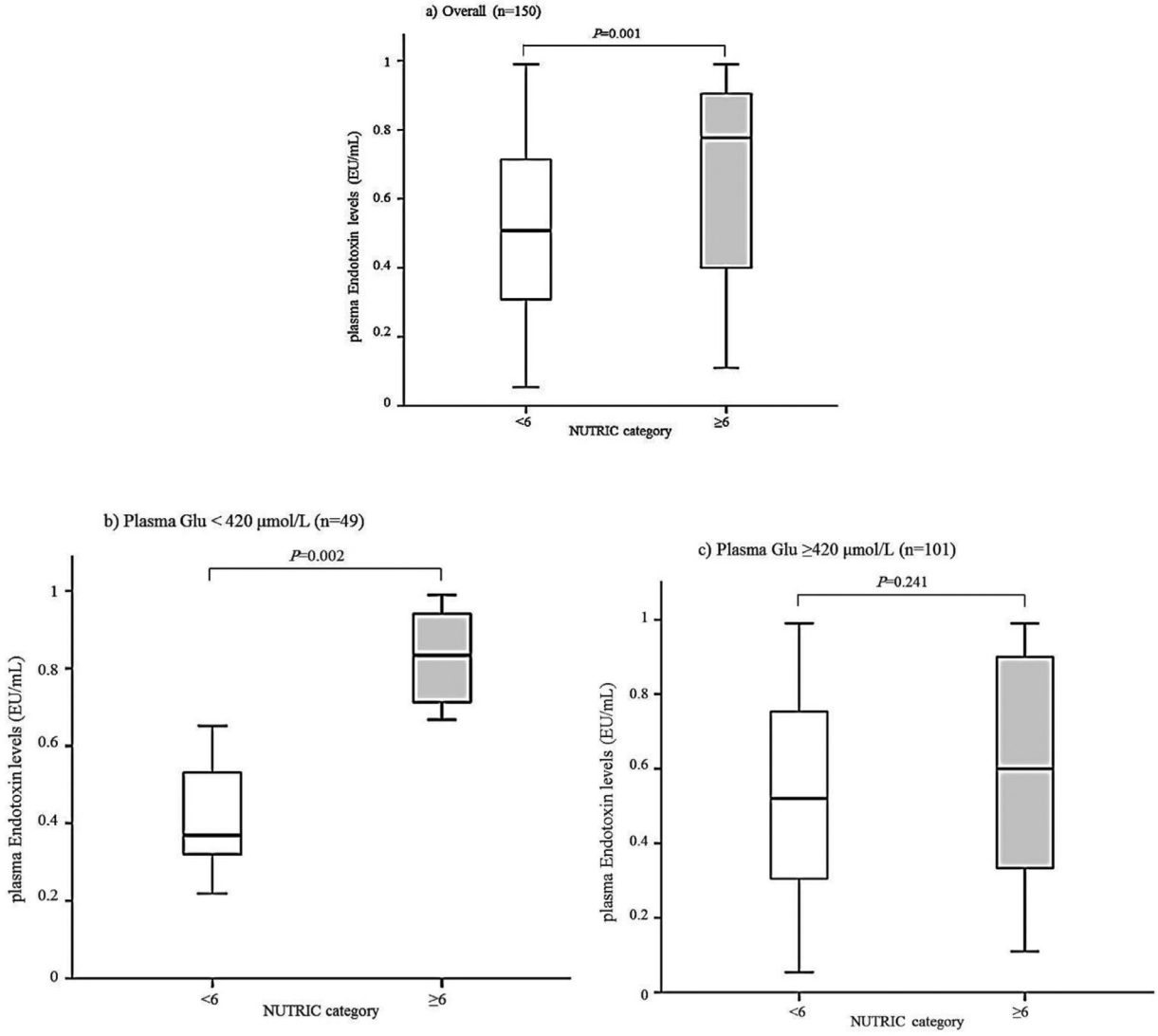

Fig. 5. Median plasma endotoxin levels according to the NUTRIC score category in a) the overall study population, b) patients with pGlu<420 µmol/L, c) patients with pGlu ≥420 µmol/L.P values were calculated using Mann–Whitney U test. Glu, Glutamine; NUTRIC, Nutrition Risk in Critically ill; pGlu, Plasma Glutamine.

glutamine levels. Although causality cannot be inferred from this cross-sectional study, the findings of this study have several important implications for prospective cohort studies to establish causality and model the observed association. The most recent revision of the ASPEN guidelines suggests a determination of nutrition risk for all patients admitted to the ICU for whom volitional intake is anticipated to be inadequate [39]. The present results suggest that clinicians should screen critically ill patients by using the NUTRIC score as a nutrition risk indicator, which may be associated with intestinal permeability.

Table 2
Binary logistic regression analysis to model the association of the plasma zonulin and endotoxin levels with mNUTRIC score in the overall population and stratified by the glutamine levels

	Overall (N = 150)		Glutamine level (µmol/L) Deficient (n = 49) <420		Normal (n = 101) ≥420	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Plasma zonulin						
Crude model	1.11 (1.03–1.19)	0.007	1.14 (1.01–1.29)	0.029	1.08 (0.98–1.18)	0.130
Full model*	1.10 (1.02–1.20)	0.008	1.13 (1.08–1.28)	0.038	1.07 (0.93–1.19)	0.109
Plasma endotoxin						
Crude model	2.34 (1.29–4.25)	0.005	3.74 (1.95–4.98)	0.009	1.55 (0.81–2.99)	0.182
Full model*	2.28 (1.25–4.16)	0.007	3.66 (1.89–4.66)	0.012	1.56 (0.80–3.01)	0.190

mNUTRIC, Modified Nutrition Risk in Critically ill.
*Adjusted for serum albumin.

Table 3
Binary logistic regression analysis to model the association of the plasma zonulin and endotoxin levels with NUTRIC score in the overall population and stratified by the glutamine levels

	Overall (N = 150)		Glutamine level (μmol/L) Deficient (n = 49) <420		Normal (n = 101) ≥420	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Plasma zonulin						
Crude model	1.12 (1.03–1.19)	0.005	1.17 (1.03–1.32)	0.014	1.05 (0.95–1.16)	0.211
Full model*	1.11 (1.03–1.20)	0.006	1.16 (1.02–1.13)	0.024	1.06 (0.97–1.16)	0.195
Plasma endotoxin						
Crude model	2.74 (1.50–3.88)	0.005	3.82 (1.80–4.42)	0.007	1.86 (0.97–3.59)	0.064
Full model*	2.04 (1.18–3.52)	0.015	3.71 (1.77–4.40)	0.010	1.84 (0.96–3.57)	0.067

NUTRIC, Nutrition Risk in Critically ill.
*Adjusted for serum albumin.

Acknowledgments

This study is related to the project NO 1397/58552 From Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study. The authors acknowledge the patients who participated in this study and the ICU personnel for their assistance; indeed, without their collaboration the study would not have been possible.

References

[1] Hejazi N, Mazloom Z, Zand F, Rezaianzadeh A, Amini A. Nutritional assessment in critically ill patients. Iran J Med Sci 2016;41:171–9.
[2] Sungurtekin H, Sungurtekin U, Oner O, Okke D. Nutrition assessment in critically ill patients. Nutr Clin Pract 2008;23:635–41.
[3] Kubrak C, Jensen L. Malnutrition in acute care patients: a narrative review. Int J Nurs Stud 2007;44:1036–54.
[4] Prins A. Nutritional assessment of the critically ill patient. South Afr J Clin Nutr 2010;23:11–8.
[5] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 2011;15:R268.
[6] Kathrani A. Nutritional support in the intensive care unit. In Practice 2016;38:18–24.
[7] MacFie J, O'Boyle C, Mitchell C, Buckley P, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut 1999;45:223–8.
[8] Labow BI, Souba WW. Glutamine. World J Surg 2000;24:1503–13.
[9] van Zanten AR, Dhaliwal R, Garrel D, Heyland DK. Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis. Crit Care 2015;19:294.
[10] Rombeau JL, Takala J. Summary of round table conference: Gut dysfunction in critical illness. Intensive Care Med 1997;23:476–9.
[11] Sertaridou E, Papaioannou V, Kolios G, Pneumatikos I. Gut failure in critical care: old school versus new school. Ann Gastroenterol 2015;28:309–22.
[12] Eslamian G, Ardehali SH, Baghestani A-R, Shariatpanahi ZV. Effects of early enteral bovine colostrum supplementation on intestinal permeability in critically ill patients: a randomized, double-blind, placebo-controlled study. Nutrition 2019;60:106–11.
[13] Li C, Gao M, Zhang W, Chen C, Zhou F, Hu Z, et al. Zonulin regulates intestinal permeability and facilitates enteric bacteria permeation in coronary artery disease. Sci Rep 2016;6.
[14] Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev 2011;91:151–75.
[15] Klaus DA, Motal MC, Burger-Klepp U, Marschalek C, Schmidt EM, Lebherz-Eichinger D, et al. Increased plasma zonulin in patients with sepsis. Biochem Med 2013;23:107–11.
[16] Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, et al. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J Infect Dis 2004;190:527–34.
[17] Rietschel ET, Kirikae T, Schade FU, Mamat U, Schmidt G, Loppnow H, et al. Bacterial endotoxin: molecular relationships of structure to activity and function. FASEB J 1994;8:217–25.
[18] Balk RA. Endotoxemia in critically ill patients: why a reliable test could be beneficial. Crit Care 2002;6:289–90.
[19] Liboredo JC, Vilela EG, Ferrari Mde L, Lima AS, Correia MI. Nutrition status and intestinal permeability in patients eligible for liver transplantation. JPEN J Parenter Enteral Nutr 2015;39:163–70.
[20] Souza NC, Simoes BP, Junior AA, Chiarello PG. Changes in intestinal permeability and nutritional status after cytotoxic therapy in patients with cancer. Nutr Cancer 2014;66:576–82.
[21] Norman K, Pirlich M, Schulzke JD, Smoliner C, Lochs H, Valentini L, et al. Increased intestinal permeability in malnourished patients with liver cirrhosis. Eur J Clin Nutr 2012;66:1116–9.
[22] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[23] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.
[24] van Eijk HM, Wijnands KA, Bessems BA, Damink SWO, Dejong CH, Poeze M. High sensitivity measurement of amino acid isotope enrichment using liquid chromatography–mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2012;905:31–6.
[25] Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. Ann Transl Med 2016;4:91.
[26] Rao RK, Samak G. Role of glutamine in protection of intestinal epithelial tight junctions. J Epithel Biol Pharmacol 2012;5:47–54.
[27] Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med 2001;27:84–90.
[28] Rodas PC, Rooyackers O, Hebert C, Norberg A, Wernerman J. Glutamine and glutathione at ICU admission in relation to outcome. Clin Sci 2012;122:591–7.
[29] Buter H, Bakker AJ, Kingma WP, Koopmans M, Boerma EC. Plasma glutamine levels in patients after non-elective or elective ICU admission: an observational study. BMC Anesthesiol 2016;16:15.
[30] Nienaber A, Dolman RC, van Graan AE, Blaauw R. Prevalence of glutamine deficiency in ICU patients: a cross-sectional analytical study. Nutr J 2016;15.
[31] Li N, DeMarco VG, West CM, Neu J. Glutamine supports recovery from loss of transepithelial resistance and increase of permeability induced by media change in Caco-2 cells. J Nutr Biochem 2003;14:401–8.
[32] Avenell A. Glutamine in critical care: current evidence from systematic reviews. Proc Nutr Soc 2006;65:236–41.
[33] Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013;368:1489–97.
[34] van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA 2014;312:514–24.
[35] Helling G, Wahlin S, Smedberg M, Pettersson L, Tjader I, Norberg A, et al. Plasma glutamine concentrations in liver failure. PLoS One 2016;11:e0150440.
[36] Fadel FI, Elshamaa MF, Essam RG, Elghoroury EA, El-Saeed GSM, El-Toukhy SE, et al. Some amino acids levels: glutamine, glutamate, and homocysteine, in plasma of children with chronic kidney disease. Int J Biomed Sci 2014;10:36–42.
[37] Aldersley MA, Howdle PD. Intestinal permeability and liver disease. Eur J Gastroenterol Hepatol 1999;11:401–3.
[38] Rodriguez P, Darmon N, Chappuis P, Candalh C, Blaton MA, Bouchaud C, et al. Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc. Gut 1996;39:416–22.
[39] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40:159–211.
[40] Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr 2016;35:158–62.