

# Relationship between serum glutamine levels and mortality in sepsis patients: A single-center study in Indonesia

Enola GA. Sihite<sup>1\*</sup>, Franciscus Ginting<sup>2,3</sup> and Lenni Sihotang<sup>2,3</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; <sup>2</sup>Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; <sup>3</sup>Center for Tropical and Infectious Diseases (PETRI), Medan, Indonesia

\*Corresponding author: enolagraciasihite@yahoo.co.id

## Abstract

Glutamine is a conditionally essential amino acid that plays a critical role in immune function, intestinal integrity, and metabolic homeostasis. Alterations in serum glutamine levels have been observed in critically ill patients, including those with sepsis. The aim of this study was to examine the association between serum glutamine levels and in-hospital mortality among sepsis patients. A retrospective cross-sectional study was conducted from April to June 2025 at a tertiary university hospital in Indonesia, including 36 adult patients diagnosed with sepsis. Serum glutamine levels were measured within the first 24 hours of admission. Median serum glutamine levels were significantly lower in non-survivors compared with survivors (2.53 vs 4.96 ng/mL;  $p=0.001$ ). Serum glutamine levels were also negatively correlated with disease severity as assessed by the Sequential Organ Failure Assessment (SOFA) score ( $r=-0.447$ ,  $p=0.006$ ). Lower serum glutamine levels were associated with increased in-hospital mortality and greater organ dysfunction among sepsis patients. These findings suggest that serum glutamine reflects metabolic stress and disease severity rather than serving as a standalone prognostic biomarker.

**Keywords:** Sepsis, glutamine, mortality, biomarker, SOFA score

## Introduction

One out of every five fatalities occurs as a result of sepsis, which is defined as a potentially fatal malfunction of an organ due to an uncontrolled immune response to infection [1]. This condition affects almost 11 million people every year. The worldwide impact of sepsis is still high, even if critical care has come a long way. This is especially true in low- and middle-income nations, where improper antibiotic use and delays in diagnosis are major causes of bad results [2,3].

There is a complicated relationship between inflammation, oxidative stress, and immunological dysregulation in the pathogenesis of sepsis [4]. Since glutamine is the principal fuel for rapidly proliferating immune cells and enterocytes, it has garnered a lot of attention among metabolic substrates [5,6]. Sepsis is associated with a decrease in plasma glutamine levels because endogenous glutamine synthesis is unable to keep up with the increased demand [7]. Systemic inflammation is worsened, intestinal barrier integrity is compromised, and immune cell proliferation is impaired due to this depletion [8]. According to previous research, both low and high glutamine levels are linked to higher mortality in critically sick patients [9,10].

The evidence for glutamine supplementation in critical illness remains equivocal, despite several studies investigating this issue. Contrary to findings in some meta-analyses, certain studies have found that high-dose glutamine improves immune function and decreases infection rates, including the REDucing Deaths due to OXidative Stress (REDOXS) study, whereas others



have reported opposing outcomes [11-14]. Given these ongoing debates, evaluating endogenous serum glutamine as a prognostic biomarker in sepsis may be of clinical relevance. Nevertheless, data from Indonesian populations is still limited. Accordingly, the aim of this study was to determine whether blood glutamine levels are associated with mortality among sepsis patients hospitalized at a university hospital in Medan.

## Methods

### Study design and setting

A cross-sectional retrospective study was conducted from April to June 2025 at Haji Adam Malik Medan Hospital in Indonesia. The study utilized routinely collected inpatient data from internal medicine and critical care wards. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

### Study population and case definition

Adult patients ( $\geq 18$  years) admitted during the study period were included using a total sampling approach, whereby all eligible patients meeting the inclusion criteria were consecutively screened and enrolled. Sepsis was defined according to the Sepsis-3 criteria, namely suspected or confirmed infection accompanied by an acute increase of  $\geq 2$  points in the Sequential Organ Failure Assessment (SOFA) score from baseline. Baseline SOFA score was assumed to be zero in patients without documented pre-existing organ dysfunction, in accordance with Sepsis-3 recommendations.

Patients were excluded if they had incomplete or missing medical records, an absence of serum glutamine measurement within the first 24 hours of admission, prior glutamine supplementation or parenteral nutrition before blood sampling, or transfer from another hospital with unavailable baseline clinical data. Additional exclusion criteria included pregnancy, active malignancy receiving chemotherapy, end-stage liver disease, end-stage renal disease requiring dialysis, known inborn errors of amino acid metabolism, or immunosuppressive therapy (including high-dose corticosteroids or cytotoxic agents), as these conditions may independently alter glutamine metabolism. Patients with do-not-resuscitate (DNR) status at admission were also excluded to reduce bias related to treatment limitation.

### Data collection and clinical variables

Data were retrospectively extracted from medical records using a standardized data abstraction form. Collected variables included age, sex, body mass index (BMI), comorbidity burden assessed using the Charlson Comorbidity Index, source of infection, SOFA score at admission, appropriateness of empirical antibiotic therapy based on local antimicrobial guidelines, length of hospital stay, and in-hospital mortality. Antibiotic appropriateness was evaluated based on concordance between empirical therapy and institutional or national treatment guidelines, considering infection source and culture results when available.

### Laboratory measurements

Serum glutamine concentrations were determined from peripheral venous blood samples collected at hospital admission, within the first 24 hours of sepsis diagnosis, and prior to initiation of nutritional supplementation. Blood samples were drawn into serum separator tubes, allowed to clot at room temperature, and centrifuged at 3,000 rpm for 10 minutes. The resulting serum was analyzed immediately or stored at  $-80$  °C until analysis to prevent amino acid degradation.

Serum glutamine concentrations were measured using a commercially available human glutamine enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, Cat. No. MBS2606017) (MyBioSource, San Diego, CA, USA), employing a double-antibody sandwich technique according to the manufacturer's instructions. The assay utilized horseradish peroxidase-conjugated detection antibodies and tetramethylbenzidine (TMB) substrate, with absorbance measured at 450 nm using a Stat Fax® 3200 microplate reader (Awareness Technology Inc., Palm City, FL, US). Serum glutamine concentrations were expressed in ng/mL. Calibration and internal quality control procedures were performed in accordance with the kit protocol.

## Statistical analysis

The primary outcome was in-hospital all-cause mortality, while secondary outcomes included disease severity as assessed by the SOFA score and its correlation with serum glutamine levels. Only complete cases were included in the analysis, and no data imputation was performed due to the limited sample size and retrospective design. Statistical analyses were conducted using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Data distribution was assessed using graphical inspection and the Shapiro–Wilk test. Continuous variables were summarized as mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR), as appropriate, while categorical variables were expressed as frequencies and percentages.

Comparisons between survivor and non-survivor groups were performed using the Chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Correlations between serum glutamine levels and SOFA score were evaluated using Spearman's rank correlation coefficient. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

### Patient characteristics

The research comprised 36 individuals who had been given a sepsis diagnosis. Male patients predominated, with a mean age of 55 years. With a mean BMI of 19.8 kg/m<sup>2</sup>, the majority of individuals were considered to be of normal weight, with just a small number falling into the underweight or overweight categories. Infections most often occurred in the respiratory system (66.7% of cases), then in the skin and soft tissues, the urinary tract, and the biliary system. The results indicated that most patients had moderate comorbidities, as assessed by the Charlson Comorbidity Index (**Table 1**). In accordance with local prescribing practices, 52.8% of patients in this group were given antibiotics that were not clinically indicated. Inappropriate antibiotic use was not significantly associated with mortality ( $p > 0.05$ ), as presented in **Table 1**. However, challenges in antibiotic stewardship remain, consistent with previous reports from Indonesia [5].

**Table 1. Characteristics of sepsis patients**

Variable	Total (%) n=36	Survive (%) n=26	Non-survive (%) n=10	$p$ -value <sup>a</sup>
Age (years)				
18–34	2 (5.5)	1 (2.7)	1 (2.7)	0.792
35–54	14 (38.8)	12 (33.3)	2 (5.5)	
55–64	12 (33.3)	9 (25)	3 (8.3)	
$\geq 65$ years	8 (22.2)	4 (11.1)	4 (11.1)	
Mean (min-max)	55 (27–84)			
Sex				
Female	17 (47.2)	12 (33.3)	5 (13.8)	0.836
Male	19 (52.8)	14 (38.8)	5 (13.8)	
Body mass index				
Underweight	8 (22.2)	3 (8.3)	5 (13.8)	0.25
Normal	28 (77.8)	23 (63.8)	5 (13.8)	
Overweight	1 (2.7)	1 (2.7)	0	
Type I obesity	0	0	0	
Type II obesity	0	0	0	
Charlson comorbidity index				
Mild	12 (33.3)	9 (25)	3 (8.3)	0.335
Moderate	11 (30.5)	8 (22.2)	3 (8.3)	
Severe	12 (33.3)	8 (22.2)	4 (11.1)	
Source of infection				
Pneumonia	24 (66.7)	14 (38.9)	10 (41.7)	0.170 <sup>b</sup>
Skin infection	10 (27.8)	8 (22.2)	2 (5.6)	0.526 <sup>b</sup>
Urinary tract infection	7 (19.4)	7 (19.4)	0	0.657 <sup>b</sup>
Biliary infection	3 (8.3)	3 (8.3)	0	0.068 <sup>b</sup>
Antibiotic appropriateness				
Appropriate	17 (47.2)	13 (36.1)	4 (11.1)	0.59
Inappropriate	19 (52.8)	13 (36.1)	6 (16.7)	

<sup>a</sup>Analyzed using Chi-square

<sup>b</sup>Analyzed using independent t-test

### Serum glutamine and mortality

Serum glutamine levels ranged from 2.03 to 37.53 ng/mL, with a mean of 7.42 ng/mL. These values were markedly lower compared to the typical reference range of 58–131.5 ng/mL. In contrast, serum glutamate levels were higher in survivors compared to non-survivors (**Figure 1**). Serum glutamine levels were significantly associated with in-hospital mortality in patients with sepsis.

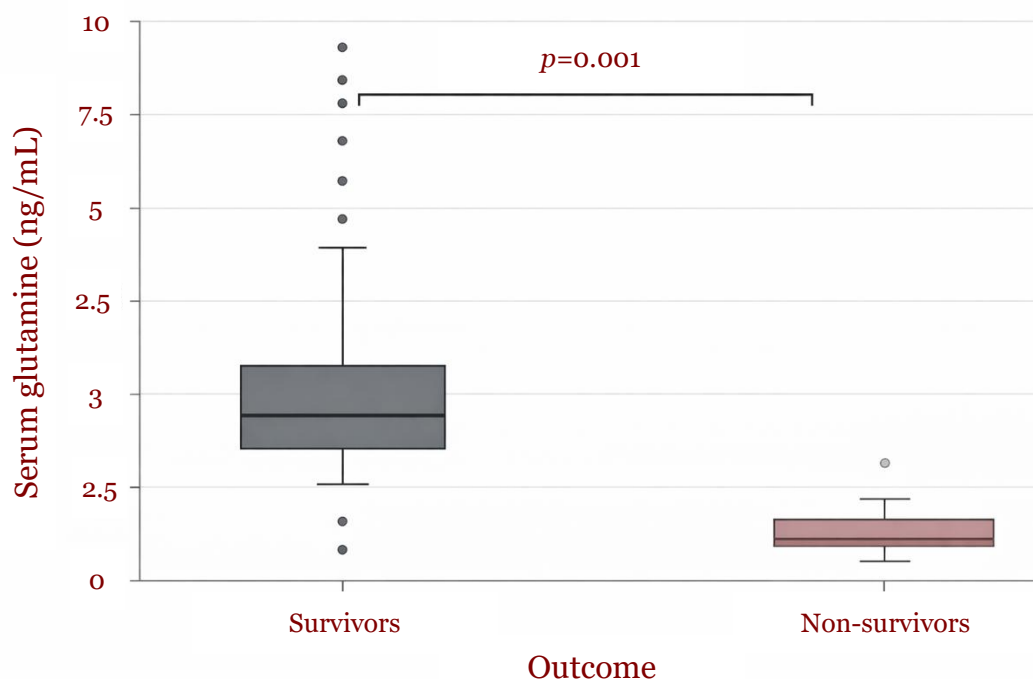


Figure 1. Boxplot of serum glutamine levels in survivors and non-survivors. Median serum glutamine levels were significantly lower in non-survivors compared with survivors (2.53 vs 4.96 ng/mL;  $p=0.001$ ). The boxes represent the interquartile range, the horizontal line indicates the median, whiskers denote  $1.5\times$  interquartile range, and dots represent outliers.

The boxplot demonstrated a wider distribution and a higher median serum glutamine level among survivors compared with non-survivors. Several high-value outliers were observed among survivors, whereas non-survivors exhibited a narrower distribution with generally lower glutamine levels. These findings were consistent with the Mann-Whitney U test, which showed a statistically significant difference between the two groups.

### Serum glutamine levels and SOFA score

Mortality risk increased with higher SOFA scores. Glutamine plays a critical role in maintaining intestinal barrier integrity, serving as the precursor for the antioxidant glutathione, and supporting protein synthesis involved in immune defense. During sepsis, severe hypermetabolism and systemic inflammation increase glutamine intake, leading to reduced circulating levels in the blood. Spearman correlation analysis demonstrated a significant negative association between serum glutamine levels and SOFA scores ( $r=-0.447$ ;  $p=0.006$ ;  $n=36$ ). Thus, lower serum glutamine levels were associated with greater organ dysfunction severity, as reflected by higher SOFA scores.

### Discussion

This study demonstrates that lower serum glutamine levels at hospital admission are associated with increased in-hospital mortality and greater organ dysfunction among patients with sepsis. Beyond a statistical association, these findings suggest that glutamine depletion reflects the intensity of metabolic stress and immune dysregulation inherent to severe sepsis rather than functioning as a direct determinant of outcome. Sepsis is characterized by a complex interplay of

systemic inflammation, mitochondrial dysfunction, and hypercatabolism, all of which contribute to profound metabolic derangements [1,4,20].

From a clinical perspective, glutamine is a conditionally essential amino acid during critical illness, serving as a primary substrate for immune cells and enterocytes and as a precursor for glutathione synthesis, which is critical for maintaining redox homeostasis [5-7]. During sepsis, inflammatory and catabolic responses markedly increase glutamine utilization, while endogenous production becomes insufficient to meet metabolic demands, leading to reduced circulating levels [7,8]. Consequently, low serum glutamine concentrations may indicate an exhausted metabolic reserve and impaired cellular adaptive capacity, supporting its role as a marker of disease severity rather than a causal driver of mortality [9,10].

Importantly, the present findings should be interpreted within the context of routine sepsis management. Current international guidelines emphasize early source control, timely antimicrobial therapy, hemodynamic resuscitation, and organ support, while metabolic biomarkers such as glutamine are not incorporated into standard therapeutic algorithms [2,15]. Consistent with these recommendations, the present study does not support the use of serum glutamine levels to guide supplementation or treatment decisions. Instead, glutamine measurement may provide complementary information regarding metabolic stress in selected clinical or research settings, particularly where access to advanced biomarkers is limited.

The persistence of observational associations between low glutamine levels and adverse outcomes, despite neutral or harmful results from interventional trials, warrants careful consideration. Large randomized trials, most notably the REDOXS study, and subsequent meta-analyses have demonstrated no mortality benefit—and potential harm—from glutamine supplementation in critically ill patients [11-14]. This apparent contradiction can be reconciled by distinguishing biomarkers of severity from therapeutic targets. While low glutamine levels reliably reflect severe metabolic stress, exogenous glutamine administration may disrupt tightly regulated metabolic pathways during acute critical illness, particularly in patients with established organ failure [14,19]. Thus, glutamine appears to function primarily as an indicator of physiological derangement rather than a substrate whose correction improves outcomes.

The inverse correlation observed between serum glutamine levels and SOFA score further supports this interpretation. The SOFA score reflects cumulative organ dysfunction across multiple systems, and its association with lower glutamine concentrations suggests that glutamine depletion parallels the overall burden of organ failure rather than isolated inflammatory activity [15,17]. This relationship likely reflects the combined effects of acute inflammatory load, sustained catabolism, and impaired metabolic adaptation, positioning glutamine as an integrative marker of disease severity in sepsis.

Contextualization to low- and middle-income settings is particularly relevant for interpreting these findings. In Indonesia and similar settings, patients with sepsis often present later in the disease course, with higher inflammatory burden, a greater prevalence of baseline malnutrition, and limited access to advanced intensive care resources [3,20]. These factors may exacerbate glutamine depletion and strengthen its association with organ dysfunction and mortality compared with high-income settings. Therefore, local data are essential for understanding how metabolic vulnerability influences sepsis outcomes in resource-limited environments.

This study provides institution-based evidence from Indonesia demonstrating that serum glutamine levels are closely linked to organ dysfunction severity and mortality in adult sepsis patients. By confirming an inverse association between glutamine levels and SOFA score, this study reinforces the concept that glutamine acts as a severity-linked metabolic marker rather than a therapeutic target. These findings contribute to the growing body of evidence cautioning against extrapolating observational biomarker associations into supplementation strategies, particularly in heterogeneous and resource-limited clinical settings.

The retrospective observational design of the present study precludes causal inference and limits control over potential confounding factors. Further, the relatively small sample size and single-center setting may reduce statistical power and limit the generalizability of the findings to other populations or healthcare settings. The small number of outcome events also restricted the use of multivariable regression models, raising the possibility of residual confounding. In

addition, serum glutamine levels were measured at a single time point at admission, and serial measurements were not available. Consequently, temporal changes in glutamine levels and their dynamic relationship with disease progression and treatment response could not be evaluated. Finally, unmeasured factors such as nutritional status, prior dietary intake, and metabolic stress response could have influenced serum glutamine concentrations and were not fully accounted for in the analysis.

## Conclusions

Lower serum glutamine levels at hospital admission were associated with increased in-hospital mortality and greater organ dysfunction among patients with sepsis. These findings support the interpretation of serum glutamine as a marker of metabolic stress and disease severity rather than a standalone prognostic or therapeutic target. Given the retrospective design, small sample size, and single-center setting, causal inferences cannot be drawn, and the results should be interpreted with caution. Larger, multicenter prospective studies incorporating serial measurements are warranted to further elucidate the clinical significance of glutamine dynamics in sepsis.

## Ethics approval

The study protocol was reviewed and approved by the Health Research Ethical Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, on 31 December 2024 (Approval No: 1479/KEPK/USU/2024). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians prior to inclusion. All data were anonymized prior to analysis to ensure confidentiality.

## Acknowledgments

We acknowledged the Department of Internal Medicine of Universitas Sumatera Utara.

## Competing interests

All the authors declare that there are no conflicts of interest.

## Funding

This study received no external funding.

## Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

## Declaration of artificial intelligence use

The authors confirm that ChatGPT was used to assist with language editing and manuscript preparation. All AI-assisted processes were critically reviewed by the authors to ensure the integrity, accuracy, and reliability of the work. All scientific decisions, data interpretation, and final conclusions presented in this article were made solely by the authors.

## How to cite

Sihite EGA, Ginting F, Sihotang L. Relationship between serum glutamine levels and mortality in sepsis patients: A single-center study in Indonesia. *Narra X* 2025; 3 (3): e238 - <http://doi.org/10.52225/narrax.v3i3.238>.

## References

1. Rudd KE, Johnson SC, Agesa KM, *et al*. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395(10219):200–211.

2. Evans L, Rhodes A, Alhazzani W, *et al.* Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021;47(11):1181-1247.
3. Ginting F, Sugianli AK, Barimbing M, *et al.* Appropriateness of diagnosis and antibiotic use in sepsis patients admitted to a tertiary hospital in Indonesia. *Postgrad Med* 2021;133(6):674-679.
4. Chiu C, Legrand M. Epidemiology of sepsis and septic shock. *Curr Opin Anaesthesiol* 2021;34(2):71-76.
5. Cruzat V, Rogero MM, Keane KN, *et al.* Glutamine: Metabolism and immune function. *Nutrients* 2018;10(11):1564.
6. Wernerman J, Christopher KB, Hammarqvist F. Clinical use of glutamine supplementation in critical illness. *Curr Opin Clin Nutr Metab Care* 2019;22(2):138-143.
7. Weitzel LR, Wischmeyer PE. Glutamine in critical illness: The time has come. *Crit Care Clin* 2010;26(3):515-525.
8. Oudemans-van Straaten HM, Bosman RJ, Treskes M, *et al.* Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001;27(1):84-90.
9. Tsujimoto T, Shimizu K, Hata N, *et al.* Both high and low plasma glutamine levels predict mortality in critically ill patients. *Surg Today* 2017;47(11):1331-1338.
10. Mearelli F, Nunnari A, Chitti F, *et al.* Association between glutamine levels and mortality in internal medicine sepsis patients. *J Clin Med* 2025;14(10):3124.
11. Heyland DK, Dhaliwal R, Day AG, *et al.* Randomized trial of glutamine and antioxidants in critically ill patients (REDOXS Study). *N Engl J Med* 2013;368(16):1489-1497.
12. Sun Y, Zhu S, Li S, Liu H. Effect of glutamine supplementation on critically ill patients: A meta-analysis. *Ann Palliat Med* 2021;10(2):1503-1520.
13. Chen QH, Li N, Lin J, *et al.* High-dose glutamine supplementation increases mortality: A meta-analysis of randomized controlled trials. *Clin Nutr* 2022;41(4):872-880.
14. Martensson J, Bellomo R. The rise and fall of glutamine in critical care. *J Parenter Enteral Nutr* 2017;41(5):712-715.
15. Singer M, Deutschman CS, Seymour CW, *et al.* The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315(8):801-810.
16. Rodas PC, Rooyackers O, Norberg A, Wernerman J. Glutamine and glutathione at ICU admission in relation to outcome. *Clin Sci* 2012;122(12):591-597.
17. Blaauw R, Nel DG, Schleicher GK. Plasma glutamine levels and ICU outcome: A prospective observational study. *Nutrients* 2020;12(2):361.
18. Wang J, Zhou J, Bai S. Combination of glutamine and ulinastatin treatments improves sepsis outcomes. *J Inflamm Res* 2020;13:109-115.
19. Mårtensson J, Bellomo R. Glutamine as a biomarker compared with SOFA score in critical illness. *J Parenter Enteral Nutr* 2017;41(5):712-715.
20. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet* 2018;392(10141):75-87