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Nonlinear Association Between Calculated Globulin Levels and 28-Day Mortality in Patients with Sepsis: A Retrospective Cohort Study

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Background: Sepsis remains a significant global health challenge, causing approximately 11 million deaths annually. The calculated globulin (CG) level, which is derived from total protein and albumin levels, plays crucial roles in the immune response and inflammation. However, the relationship between the CG level and sepsis mortality remains unexplored.

Methods: This retrospective cohort study analyzed sepsis patients from the eICU Collaborative Research Database. The primary outcome was 28-day ICU mortality. The relationship between the CG level and mortality was examined via generalized additive models with penalized splines and two piecewise linear regression models. Confounders were adjusted in multivariate analyzes.

Results: The overall 28-day ICU mortality was 10.0% among 9110 sepsis patients (mean age 65.3 ± 15.9 years, 48.7% male). An L-shaped relationship was observed between CG level and mortality, with a threshold of 2.9 g/dL (95% CI: 2.8–2.9). This pattern revealed that mortality risk decreased sharply as globulin levels increased to 2.9 g/dL and then plateaued thereafter. Below this threshold, each 1 g/dL increase in the CG was associated with a significantly reduced mortality risk (adjusted OR = 0.51, 95% CI: 0.40–0.64, P < 0.0001). Above 2.9 g/dL, no significant association was observed (OR = 1.04, 95% CI: 0.90–1.19; P = 0.622). These findings remained robust in sensitivity analyzes using hospital mortality as the outcome.

Conclusion: This study revealed an L-shaped relationship between CG level and sepsis mortality, with lower CG levels independently associated with increased mortality risk. This finding provides a simple and cost-effective indicator for risk stratification in sepsis patients, facilitating early identification of high-risk individuals and informing clinical decision-making.

Keywords: sepsis, globulins, mortality, intensive care units

Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a significant global health challenge. It affects millions of patients annually and contributes to nearly 11 million deaths worldwide (approximately 20% of all deaths worldwide).[1] Despite advances in critical care medicine, sepsis mortality remains substantial, with hospital mortality rates of 17% for sepsis and 26% for severe sepsis reported over the past decade.[2] In addition to mortality, sepsis survivors often experience long-term complications, including physical impairment,[3] cognitive decline,[4] and decreased quality of life, which further contribute to their substantial socioeconomic burden.

Inflammatory biomarkers play crucial roles in the diagnosis, risk stratification, disease progression monitoring, and therapeutic regimen adjustment of sepsis. These markers include nonspecific inflammatory and acute-phase markers (such as leukocyte count and C-reactive protein [CRP]), as well as biomarkers with high specificity and sensitivity, such as procalcitonin (PCT) and antigen D-related human leukocyte antigen (HLA-DR).[5] Among these biomarkers, globulin, a major component of serum proteins, has gained increasing attention because of its role in the immune response and inflammation. Globulin is involved in various physiological processes, including immune system function[6,7] and

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complement activation.[8] Previous studies have demonstrated associations between globulin levels and clinical outcomes across various diseases.[9,10] In peritoneal dialysis patients, elevated globulin levels (≥ 2.8 g/dL) are significantly associated with increased risks of all-cause and cardiovascular mortality.[9] Similarly, in hemodialysis patients, those with globulin concentrations > 3.8 g/dL presented increased risks of all-cause and infection-related mortality.[10]

Research on globulin in sepsis has focused primarily on exogenous immunoglobulin (IVIG) therapy. Large-scale clinical trials, including the SBITS study (n = 653), revealed only moderate improvements in morbidity and organ dysfunction with IVIG treatment,[11] whereas systematic reviews failed to confirm mortality benefits.[12] Despite these investigations, the relationship between endogenous globulin levels and sepsis outcomes remains inadequately explored.

The identification of widely accessible and cost-effective prognostic indicators is a primary clinical objective, with routine hematological parameters potentially offering solutions to this need. The calculated globulin (CG), which is derived by subtracting albumin from total protein (CG = total protein - albumin), is a promising candidate that has previously demonstrated utility as a reliable screening marker for the early diagnosis of primary antibody deficiency (PAD) in the adult population.[13] Compared with direct measurement methods, CG offers significant advantages: it can be obtained from routine biochemical tests without additional blood sampling or specialized testing, making it economical, convenient, and widely accessible. Studies have demonstrated that low CG levels (< 16 g/L) are closely associated with immune dysfunction, with approximately 47% of such patients developing secondary antibody deficiency due to hematological malignancies.[14] In addition to detecting primary immunodeficiency disorders (such as common variable immunodeficiency, CVID), CG screening has proven effective in identifying new cases of light chain and nonsecretory multiple myeloma (accounting for 2.2% of screened patients).[14] In patients with thymic epithelial tumors, low CG levels (< 2.0 g/dL) were significantly associated with an increased risk of serious infections (PR = 6.18, 95% CI: 3.12–12.23).[15] Furthermore, in HIV/HCV-coinfected patients, alterations in CG levels demonstrated prognostic significance, with their predictive value being more pronounced in patients with HCV coinfection than in those with HIV monoinfection.[16] These findings highlight the potential of the CG level as an economical and clinically valuable biomarker across various disease states.

Significant advances have been made in understanding the immunopathophysiology of sepsis. Saxena et al[17] reported that monocyte distribution width (MDW), an emerging marker reflecting immune activation, demonstrated promising diagnostic performance for sepsis with sensitivity reaching 84% and a specificity of 68%. Furthermore, sepsis response signature (SRS) classification on the basis of immune gene expression profiles stratifies patients into prognostic subgroups, with SRS1 associated with immunosuppression and increased mortality.[17] This transcriptomic characterization of SRS1 patients provides a theoretical foundation for targeted immunomodulatory therapeutic strategies.

Despite extensive research on the role of the immune system in sepsis, studies specifically investigating the relationship between CG levels and sepsis mortality remain scarce. Given that CG reflects both inflammatory and immune status and can be readily obtained from routine tests, exploring its relationship with sepsis outcomes may have important clinical significance.

Systems biology approaches have recently provided novel tools for deciphering the complex pathophysiology of sepsis. Among these methods, metabolomics has emerged as a powerful technique for characterizing systemic metabolic alterations during sepsis and septic shock.[18] As sepsis involves complex and dynamic metabolic changes, metabolomics offers unique insights by directly reflecting the phenotypic state of cells and tissues, capturing posttranscriptional and posttranslational modifications that may remain undetected at the gene or protein level. Multiple investigations have revealed significant metabolic disturbances in sepsis patients, including abnormalities in ketone bodies, amino acid metabolism, tricarboxylic acid cycle intermediates, and lipid metabolism.[19] Longitudinal metabolomic analyzes have demonstrated potential for tracking disease progression, evaluating treatment response, and predicting clinical outcomes by identifying specific "metabolic signatures" associated with patient recovery or deterioration.[20] Researchers have identified specific metabolites, including acylcarnitines, glycerophospholipids, branched-chain amino acids, and fatty acids, as potential biomarkers with diagnostic and prognostic utility in sepsis.[18,19] Although our current investigation focused on CG levels as potential prognostic markers, the integration of proteomics and metabolomics approaches represents a promising frontier in sepsis research, potentially facilitating more personalized therapeutic strategies based on specific metabolic phenotypes.

Building upon this foundation in biomarker research, the present study aims to investigate the association between CG levels and mortality among patients with sepsis via the multicenter eICU Collaborative Research Database, which contains data from multiple hospitals across the United States.

Methods

Data Source and Ethics

This retrospective cohort study analyzed data from the eICU Collaborative Research Database (eICU-CRD),[21] a comprehensive critical care database maintained by the Massachusetts Institute of Technology's Laboratory for Computational Physiology. The database comprises detailed clinical records from intensive care units across more than 200 hospitals throughout the United States between 2014 and 2015. We obtained access to the database after completing the required Collaborative Institutional Training Initiative (CITI) program and receiving certification from the PhysioNet Review Board (certification ID: 67403327).

In accordance with the official regulatory framework of the eICU-CRD database (https://eicu-crd.mit.edu/about/acknowledgments/), the utilization of these data for research purposes does not necessitate additional institutional review board approval. Exemption from informed consent requirements was granted owing to the retrospective design of this investigation and the comprehensive deidentification of all patient information, which adheres to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provisions—a compliance status formally certified by Privacert (Cambridge, MA; Certificate No. 1031219–2).

This investigation was conducted in strict adherence to the ethical principles delineated in the Declaration of Helsinki. Furthermore, the methodology and findings were documented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure transparent and standardized reporting of observational research.

Study Population

From the eICU-CRD database, we identified 23,136 adult patients with sepsis on ICU admission. Sepsis was diagnosed on the basis of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), which requires a suspected or documented infection along with an acute increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more.[22] The infection status was determined via International Classification of Diseases, Ninth Revision (ICD-9) coding, whereas SOFA scores were calculated via physiological parameters from the Acute Physiology and Chronic Health Evaluation (APACHE) IV dataset.[23] CG was determined by subtracting the serum albumin level from the total protein level (CG = total protein – albumin). All biochemical parameters were obtained from routine laboratory tests performed at the time of patient admission. We applied several exclusion criteria to ensure data quality and consistency: 1) subsequent ICU admissions for the same patient were excluded, retaining only the first admission (n = 3,610); 2) patients with ICU stays shorter than 24 hours (n = 4,254); 3) patients younger than 18 years (n = 10); 4) patients with missing ICU outcome data (n = 2); and 5) patients with missing or erroneous CG measurements (n = 6,150). Patients with ICU stays of less than 24 hours were excluded from our analysis as this brief observation period often yields incomplete laboratory data and insufficient clinical monitoring points for meaningful trend analysis. Additionally, the pathophysiological processes in sepsis typically evolve over days, and a minimum 24-hour observation period allows for more reliable assessment of the relationships between biomarkers and clinical outcomes. This exclusion criterion is also consistent with established practices in critical care research. After applying these criteria, 9,110 patients were included in the final analysis (Figure 1).

Data Collection

We extracted clinical data from multiple tables within the eICU-CRD database, focusing on measurements obtained during the first 24 hours of ICU admission. Demographic information (age, sex, ethnicity, admission weight) and hospital discharge year were obtained from the patient table. From the ApacheApsVar table, we collected vital signs (temperature, respiratory rate, heart rate, and mean arterial pressure), therapeutic interventions (mechanical ventilation, dialysis,

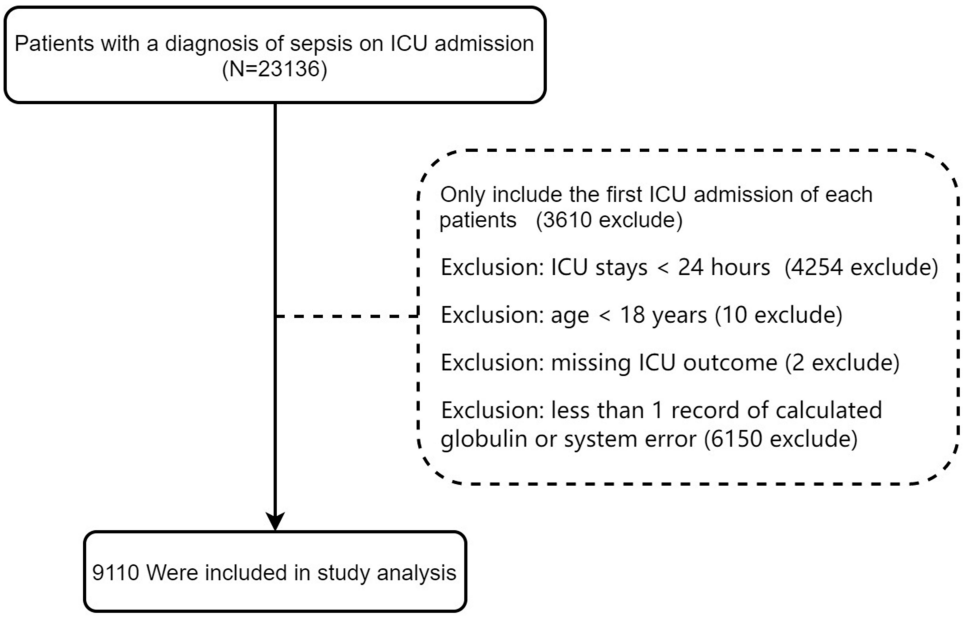

Figure 1 Flow chart of study population.
Abbreviation: ICU, intensive care unit.

vasopressor use, and intubation status), and disease severity scores, including the Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation IV (APACHE IV), Glasgow Coma Scale (GCS), and Acute Physiology Score III (APS III) scores. Laboratory measurements, including blood PH, complete blood count, lactate, cholesterol, triglycerides, glucose, creatinine, liver enzymes, blood urea nitrogen, total protein and albumin were extracted from the laboratory table. Comorbidities, including AIDS, hepatic failure, leukemia, metastatic cancer, immunosuppression, and cirrhosis, were collected from the ApachePredVar table, while the site of infection was determined from the AdmissionDx table.

Outcomes

The primary outcome of our study was all-cause ICU mortality within 28 days after admission to the ICU. In the supplemental analysis, we also analyzed 28-day hospital mortality after admission.

Statistical Analysis

Continuous variables are presented as the means ± standard deviations or medians (interquartile ranges), and categorical variables are expressed as numbers and percentages. The study population was stratified into equal tertiles on the basis of CG levels. Differences across CG tertiles were compared via one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables (Table 1).

To explore the relationship between the CG level and mortality, we used a generalized additive model (GAM) to identify potential nonlinear patterns (Figure 2). The association between the CG level and 28-day mortality was then estimated via logistic regression models, with the results presented as odds ratios (ORs) and 95% confidence intervals (CIs) (Table 2). Both unadjusted and adjusted models were constructed. Confounders were selected on the basis of their clinical relevance and association with outcomes, referencing variables that underwent rigorous screening in studies such as Chang et al.[24] In this study, confounders were selected on the basis of their association with the outcomes of interest or changes in effect estimates of more than 10%, while also considering clinical importance. All the variables considered in our study are presented in Table 1, which describes the baseline characteristics of the study population. The adjusted models included age, gender, ethnicity, admission weight, mechanical ventilation use, vital signs (temperature,

Table 1 Baseline Characteristics and 28-Day Mortality According to the Tertiles of Calculated Globulin (n=9110)

Parameters	Calculated Globulin				*P* value
	Overall n=9110	Tertile 1 0.50–2.70 n=2645	Tertile 2 2.80–3.40 n=3173	Tertile 3 3.50–6.90 n=3292	
Demographics					
Age (years)	65.3 ± 15.9	66.1 ± 16.2	66.3 ± 15.9	63.7 ± 15.6	<0.001
Gender					<0.001
Male	4437 (48.7%)	1357 (51.3%)	1585 (50.0%)	1495 (45.4%)	
Female	4672 (51.3%)	1288 (48.7%)	1588 (50.0%)	1796 (54.6%)	
Ethnicity					<0.001
Caucasian	7007 (76.9%)	2173 (82.2%)	2510 (79.1%)	2324 (70.6%)	
African American	904 (9.9%)	168 (6.4%)	283 (8.9%)	453 (13.8%)	
Hispanic	506 (5.6%)	161 (6.1%)	174 (5.5%)	171 (5.2%)	
Asian	348 (3.8%)	52 (2.0%)	109 (3.4%)	187 (5.7%)	
Native American	100 (1.1%)	12 (0.5%)	27 (0.9%)	61 (1.9%)	
Other/Unknown	245 (2.7%)	79 (3.0%)	70 (2.2%)	96 (2.9%)	
Admission weight (kg)	82.5 ± 27.2	78.4 ± 23.3	82.6 ± 26.5	85.6 ± 30.2	<0.001
Hospital discharge year					0.988
2014	4225 (46.4%)	1226 (46.4%)	1475 (46.5%)	1524 (46.3%)	
2015	4885 (53.6%)	1419 (53.6%)	1698 (53.5%)	1768 (53.7%)	
Vital signs					
Temperature (°C)	36.6 ± 1.3	36.5 ± 1.2	36.5 ± 1.3	36.6 ± 1.3	0.218
Respiratory rate (bpm)	30.3 ± 14.3	30.2 ± 14.5	30.1 ± 14.3	30.6 ± 14.1	0.272
Heart rate (/min)	112.9 ± 28.8	113.8 ± 29.4	111.9 ± 29.5	113.0 ± 27.7	0.043
MAP (mmHg)	56.0 (47.0–112.0)	55.0 (46.0–82.5)	56.0 (47.0–112.8)	57.0 (48.0–116.0)	<0.001
Laboratory data					
PH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	<0.001
WBC (cells×10^9/L)	13.3 (8.8–19.6)	12.7 (7.8–19.1)	13.2 (8.7–19.0)	14.1 (9.6–20.6)	<0.001
RBC (cells×10^{12}/L)	3.5 ± 0.7	3.5 ± 0.8	3.6 ± 0.7	3.5 ± 0.7	<0.001
Platelets (cells×10^9/L)	178.0 (119.0–252.0)	155.0 (101.0–219.0)	180.0 (123.0–248.0)	200.0 (134.0–281.0)	<0.001
Lactate (mmol/L)	1.9 (1.2–3.1)	2.1 (1.2–3.7)	1.8 (1.2–2.9)	1.8 (1.2–2.8)	<0.001
TC (mg/dL)	104.0 (83.2–137.0)	107.0 (87.0–139.0)	105.0 (86.0–136.2)	103.0 (81.0–137.0)	0.650
Triglycerides (mg/dL)	120.0 (79.0–183.0)	114.0 (76.0–180.8)	123.0 (80.5–174.5)	125.0 (79.0–195.0)	0.642
Glucose (mg/dL)	127.0 (101.0–169.0)	124.0 (99.0–164.0)	127.0 (101.0–168.0)	130.0 (102.0–175.0)	<0.001
Scr (mg/dL)	1.4 (0.9–2.4)	1.4 (0.9–2.2)	1.4 (0.9–2.4)	1.4 (0.9–2.6)	0.002
AST (U/L)	36.0 (21.0–78.0)	38.0 (21.0–92.0)	35.0 (20.0–75.0)	36.0 (21.0–71.0)	<0.001
ALT (U/L)	27.0 (16.0–56.0)	29.0 (17.0–70.0)	27.0 (16.0–54.0)	27.0 (16.0–49.2)	<0.001
BUN (mg/dL)	29.0 (17.0–47.0)	27.0 (17.0–44.0)	28.0 (17.0–46.0)	30.9 (18.0–50.0)	<0.001
Total protein (g/dL)	5.7 ± 0.9	4.9 ± 0.7	5.7 ± 0.6	6.4 ± 0.7	<0.001
Albumin (g/dL)	2.5 ± 0.6	2.6 ± 0.6	2.6 ± 0.6	2.3 ± 0.6	<0.001
Site of infection					<0.001
Sepsis, pulmonary	3447 (37.8%)	914 (34.6%)	1191 (37.5%)	1342 (40.8%)	
Sepsis, renal/UTI (including bladder)	2016 (22.1%)	516 (19.5%)	749 (23.6%)	751 (22.8%)	
Sepsis, GI	1322 (14.5%)	514 (19.4%)	460 (14.5%)	348 (10.6%)	
Sepsis, unknown	1027 (11.3%)	358 (13.5%)	350 (11.0%)	319 (9.7%)	
Sepsis, cutaneous/soft tissue	704 (7.7%)	148 (5.6%)	230 (7.2%)	326 (9.9%)	
Sepsis, gynecologic	27 (0.3%)	11 (0.4%)	5 (0.2%)	11 (0.3%)	
Sepsis, other	567 (6.2%)	184 (7.0%)	188 (5.9%)	195 (5.9%)	
Severity of illness					
SOFA score	4.0 (2.0–7.0)	5.0 (3.0–7.0)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.003
APACHE IV score	74.2 ± 26.4	76.6 ± 28.9	73.0 ± 25.2	73.3 ± 25.1	<0.001
GCS score	12.4 ± 3.5	12.3 ± 3.6	12.5 ± 3.5	12.4 ± 3.4	0.201
APS III	60.6 ± 25.0	62.3 ± 27.7	59.1 ± 23.9	60.7 ± 23.6	<0.001

(*Continued*)

Table 1 (Continued).

Parameters	Calculated Globulin				*P* value
	Overall n=9110	Tertile 1 0.50–2.70 n=2645	Tertile 2 2.80–3.40 n=3173	Tertile 3 3.50–6.90 n=3292	
Comorbidities					
AIDS	37 (0.4%)	8 (0.3%)	3 (0.1%)	26 (0.8%)	<0.001
Hepatic failure	248 (2.8%)	63 (2.4%)	79 (2.5%)	106 (3.2%)	0.089
Leukemia	131 (1.5%)	54 (2.1%)	40 (1.3%)	37 (1.1%)	0.008
Metastatic cancer	312 (3.5%)	109 (4.2%)	128 (4.1%)	75 (2.3%)	<0.001
Immunosuppression	526 (5.8%)	237 (9.0%)	167 (5.3%)	122 (3.7%)	<0.001
Cirrhosis	341 (3.8%)	90 (3.4%)	92 (2.9%)	159 (4.9%)	<0.001
Intervention					
Mechanical ventilation					0.007
No	6280 (69.6%)	1828 (69.6%)	2238 (71.5%)	2214 (67.9%)	
Yes	2738 (30.4%)	797 (30.4%)	892 (28.5%)	1049 (32.1%)	
Dialysis					<0.001
No	8543 (94.7%)	2539 (96.7%)	2982 (95.3%)	3022 (92.6%)	
Yes	475 (5.3%)	86 (3.3%)	148 (4.7%)	241 (7.4%)	
Vasopressor use (1st 24 h)					0.110
No	8910 (99.1%)	2584 (98.8%)	3098 (99.2%)	3228 (99.3%)	
Yes	79 (0.9%)	31 (1.2%)	26 (0.8%)	22 (0.7%)	
Intubated					0.006
No	7165 (79.5%)	2031 (77.4%)	2503 (80.0%)	2631 (80.6%)	
Yes	1853 (20.5%)	594 (22.6%)	627 (20.0%)	632 (19.4%)	
ICU 28day mortality					<0.001
No	8198 (90.0%)	2289 (86.5%)	2907 (91.6%)	3002 (91.2%)	
Yes	912 (10.0%)	356 (13.5%)	266 (8.4%)	290 (8.8%)	

Notes: Data are expressed as the mean±SD, median (interquartile range), or percentage. Tertiles of calculated globulin were defined by dividing the study population (n=9110) into three equal groups based on CG levels, with ranges (minimum-maximum values) as shown in the table header. Among the 9110 patients, the amount of missing values for the covariates were 1 (0.01%) for gender, 145 (1.59%) for admission weight, 496 (5.44%) for temperature, 117 (1.28%) for respiratory rate, 92 (1.01%) for heart rate, 100 (1.10%) for MAP, 6087 (66.82%) for PH, 2846 (31.24%) for lactate, 8644 (94.88%) for TC, 8377 (91.95%) for triglycerides, 80 (0.88%) for glucose, 44 (0.48%) for Scr, 42 (0.46%) for AST, 122 (1.34%) for ALT, 33 (0.36%) for BUN, 1084 (11.90%) for APACHE IV score, 200 (2.20%) for GCS score continuous, 1084 (11.90%) for APS III, and 92 (1.01%) for comorbidities including AIDS, hepatic failure, leukemia, metastatic cancer, immunosuppression, and cirrhosis.

Abbreviations: MAP, mean arterial pressure; TC, total cholesterol; Scr, serum creatinine; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; UTI, urinary tract infection; GI, gastrointestinal; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology And Chronic Health Evaluation; GCS, Glasgow Coma Scale; APS, Acute Physiology Score; AIDS, Acquired Immunodeficiency Syndrome; ICU, intensive care unit.

respiratory rate, heart rate, MAP), severity scores (SOFA), source of infection, and laboratory parameters (glucose, Scr, RBC count, WBC count).

After identifying nonlinear patterns, we applied a two-piecewise linear regression model to quantify the threshold effect (Table 3). The optimal threshold was determined via a recursive algorithm that selected the inflection point yielding the maximum model likelihood. The 95% CI for the threshold point was calculated via the bootstrap resampling method.[25] A likelihood ratio test was performed to compare the fitness of the one-line linear model with that of the two-piecewise linear model.

To examine the robustness of our findings, we conducted a sensitivity analysis by using 28-day hospital mortality instead of 28-day ICU mortality as the outcome. For missing data, dummy variables were used when more than 1% of the values were missing.[26] For categorical variables with missing values, we created additional categories to represent missing data. For continuous variables with significant missing values, we implemented a two-variable approach: one variable containing the original values (with zeros replacing missing values) and a second indicator variable identifying

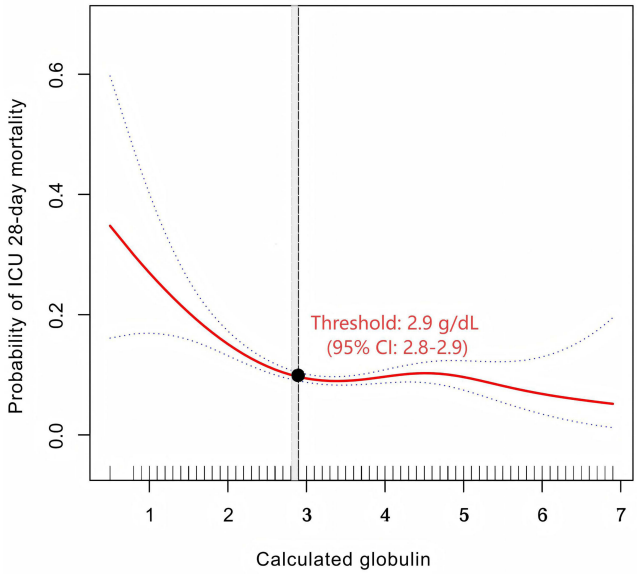

Figure 2 Associations between calculated globulin and 28-day mortality in ICU patients with sepsis (n=9110). A threshold, nonlinear association between calculated globulin and 28-day mortality was found in a generalized additive model (GAM). Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% confidence interval from the fit. The vertical dashed line at 2.9 g/dL indicates the identified threshold point with the light gray shaded area (2.8–2.9 g/dL) representing its 95% confidence interval. The black dot marks the intersection where the relationship changes. Red annotation shows the precise threshold value and confidence interval. Adjusted for age, gender, ethnicity, admission weight, mechanical ventilation use, temperature, respiratory rate, heart rate, MAP, SOFA score, source of infection, glucose, Scr, RBC, and WBC.

Abbreviations: MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; Scr, serum creatinine; RBC, red blood cell; WBC, white blood cell; ICU, intensive care unit.

which observations had missing data. Both variables were included simultaneously in regression models to account for the effect of missingness while utilizing all available information. All the statistical analyzes were performed via EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R software version 4.2.0 (http://www.r-project.org), with P<0.05 considered statistically significant.

Table 2 The Unadjusted Association Between Baseline Variables and 28-Day Mortality (n=9110)

Exposure	Statistics	Odds Ratio (95% CI)	*P* value
Calculated globulin	3.23 ± 0.81	0.75 (0.69, 0.82)	<0.0001
Calculated globulin Tertile			
Low	2645 (29.03%)	Reference	
Middle	3173 (34.83%)	0.59 (0.50, 0.70)	<0.0001
High	3292 (36.14%)	0.62 (0.53, 0.73)	<0.0001
Age (years) Tertile			
Low	2983 (32.74%)	Reference	
Middle	3073 (33.73%)	1.50 (1.26, 1.79)	<0.0001
High	3054 (33.52%)	1.60 (1.34, 1.90)	<0.0001
Site of infection			
Pulmonary	3447 (37.84%)	Reference	
Renal/UTI (including bladder)	2016 (22.13%)	0.45 (0.37, 0.56)	<0.0001
GI	1322 (14.51%)	1.11 (0.92, 1.35)	0.2669
Unknown	1027 (11.27%)	0.99 (0.80, 1.23)	0.9621
Cutaneous/soft tissue	704 (7.73%)	0.50 (0.36, 0.69)	<0.0001
Gynecologic	27 (0.30%)	0.60 (0.14, 2.53)	0.4822
Other	567 (6.22%)	0.70 (0.52, 0.96)	0.0272

(*Continued*)

https://doi.org/10.2147/RMHP.S532501

Table 2 (Continued).

Exposure	Statistics	Odds Ratio (95% CI)	*P* value
Gender			
Male	4437 (48.71%)	Reference	
Female	4672 (51.29%)	1.00 (0.87, 1.14)	0.9574
Ethnicity			
Caucasian	7007 (76.92%)	Reference	
African American	904 (9.92%)	0.98 (0.78, 1.24)	0.8615
Hispanic	506 (5.55%)	1.04 (0.77, 1.40)	0.7949
Asian	348 (3.82%)	0.89 (0.61, 1.29)	0.5374
Native American	100 (1.10%)	1.24 (0.67, 2.28)	0.4907
Other/Unknown	245 (2.69%)	1.46 (1.01, 2.12)	0.0440
Hospital discharge year			
2014	4225 (46.38%)	Reference	
2015	4885 (53.62%)	1.04 (0.91, 1.20)	0.5304
Admission weight, kg Tertile			
Low	2977 (33.21%)	Reference	
Middle	2980 (33.24%)	0.80 (0.68, 0.95)	0.0093
High	3008 (33.55%)	0.71 (0.60, 0.85)	<0.0001
Temperature (°C) Tertile			
Low	2651 (30.78%)	Reference	
Middle	2630 (30.53%)	0.55 (0.47, 0.66)	<0.0001
High	3333 (38.69%)	0.50 (0.42, 0.59)	<0.0001
Respiratory rate (bpm) Tertile			
Low	2939 (32.68%)	Reference	
Middle	2782 (30.94%)	1.43 (1.18, 1.73)	0.0002
High	3272 (36.38%)	2.09 (1.75, 2.49)	<0.0001
Heart rate (/min) Tertile			
Low	2975 (32.99%)	Reference	
Middle	2985 (33.10%)	1.40 (1.16, 1.69)	0.0004
High	3058 (33.91%)	2.07 (1.74, 2.47)	<0.0001
MAP (mmHg) Tertile			
Low	2863 (31.78%)	Reference	
Middle	3090 (34.30%)	0.51 (0.43, 0.60)	<0.0001
High	3057 (33.93%)	0.51 (0.43, 0.61)	<0.0001
SOFA score Tertile			
Low	2390 (26.23%)	Reference	
Middle	3289 (36.10%)	1.66 (1.30, 2.13)	<0.0001
High	3431 (37.66%)	5.17 (4.14, 6.46)	<0.0001
APS III Tertile			
Low	2663 (33.18%)	Reference	
Middle	2620 (32.64%)	2.32 (1.78, 3.04)	<0.0001
High	2743 (34.18%)	8.55 (6.73, 10.86)	<0.0001
APACHE IV score Tertile			
Low	2622 (32.67%)	Reference	
Middle	2655 (33.08%)	2.75 (2.07, 3.65)	<0.0001
High	2749 (34.25%)	10.26 (7.93, 13.28)	<0.0001
GCS score Tertile			
Low	2625 (29.46%)	Reference	
Middle	2373 (26.63%)	0.62 (0.52, 0.74)	<0.0001
High	3912 (43.91%)	0.41 (0.34, 0.48)	<0.0001

Notes: Data are expressed as the mean±SD, or percentage.

Abbreviations: MAP, Mean Arterial Pressure; UTI, Urinary Tract Infection; GI, Gastrointestinal; SOFA, Sequential Organ Failure Assessment; APS, Acute Physiology Score; APACHE, Acute Physiology And Chronic Health Evaluation; GCS, Glasgow Coma Scale.

Table 3 Threshold Effect Analysis of Calculated Globulin on ICU 28-Day Mortality

Models	Per-Unit Increase		Per-SD Increase	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model I				
One line effect	0.82 (0.74, 0.90)	<0.0001	0.85 (0.78, 0.92)	<0.0001
Model II				
Turning point (K)	2.9		−0.41	
Calculated globulin < K	0.51 (0.40, 0.64)	<0.0001	0.57 (0.47, 0.69)	<0.0001
Calculated globulin > K	1.04 (0.90, 1.19)	0.622	1.03 (0.92, 1.16)	0.631
P value for LRT test*		<0.001		<0.001
95% CI for turning point	2.8, 2.9		−0.53, −0.41	

Notes: Data were presented as OR (95% CI) P value; Model I, linear analysis; Model II, non-linear analysis. Adjusted for age, gender, ethnicity, admission weight, mechanical ventilation use, temperature, respiratory rate, heart rate, MAP, SOFA score, source of infection, glucose, Scr, RBC, and WBC. *P<0.001 indicates that model II is significantly different from Model I.

Abbreviations: CI, confidence interval; OR, odds ratio; LRT, logarithm likelihood ratio test; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; Scr, serum creatinine; RBC, red blood cell; WBC, white blood cell.

Results

Baseline Characteristics

A total of 9110 patients with sepsis were included in this study. The mean age was 65.3 ± 15.9 years, with 4437 males (48.7%). Patients were stratified into three groups according to their CG levels. Table 1 compares the patients' demographics, vital signs, laboratory results, site of infection, severity of illness, comorbidities, and interventions among the groups. Compared with those in Quartile 1, patients in Quartile 3 were younger (63.7 ± 15.6 vs 66.1 ± 16.2 years) and had higher admission weights (85.6 ± 30.2 vs 78.4 ± 23.3 kg).

28-Day Mortality

The overall 28-day ICU mortality was 10.0%. As CG levels increased, 28-day ICU mortality showed a decreasing trend: the highest mortality was observed in tertile 1 (low CG group) at 13.5% (356/2645), whereas lower rates were observed in tertiles 2 and 3 (8.4% (266/3173) and 8.8% (290/3292), respectively; compared with tertile 1, adjusted ORs were 0.59 (95% CI: 0.50–0.70) and 0.62 (95% CI: 0.53–0.73), both $P < 0.001$).

Unadjusted Associations Between Baseline Variables and 28-Day Mortality

Table 2 presents the univariate logistic regression analysis results. The analysis revealed that CG levels were inversely associated with 28-day ICU mortality (OR = 0.75, 95% CI 0.69–0.82; $P < 0.0001$). Both the middle and high CG groups presented a lower mortality risk than the low CG group did (OR = 0.59, 95% CI 0.50–0.70 and OR = 0.62, 95% CI 0.53–0.73, respectively; both $P < 0.0001$). A high respiratory rate increased mortality risk (OR = 2.09, 95% CI 1.75–2.49; $P < 0.0001$), whereas a high MAP reduced mortality risk (OR = 0.51, 95% CI 0.43–0.61; $P < 0.0001$). High SOFA scores significantly increased mortality risk (OR = 5.17, 95% CI 4.14–6.46; $P < 0.0001$).

Identification of Nonlinear Relationships

We observed an L-shaped relationship between CG levels and 28-day ICU mortality (Figure 1 and Table 3). For CG concentrations < 2.9 g/dL, mortality decreased with increasing CG (adjusted OR 0.51, 95% CI 0.40–0.64, $P < 0.0001$ per 1 g/dL increase). For CG ≥ 2.9 g/dL, no significant association was found (OR 1.04, 95% CI 0.90–1.19, $P = 0.622$ per 1 g/dL increase). Per standard deviation increase, when the CG was < 2.9 g/dL, the mortality OR was 0.57 (95% CI 0.47–0.69, $P < 0.0001$), whereas when the CG was ≥ 2.9 g/dL, the OR was 1.03 (95% CI 0.92–1.16, $P = 0.631$) (Table 3).

A generalized additive model was applied to explore the relationship between the CG levels and 28-day ICU mortality, revealing an L-shaped association (Table 3). The log-likelihood ratio test ($P < 0.001$) confirmed that a two-

piecewise linear regression model fit better than a linear model. The identified threshold turning point was at 2.9 g/dL (95% CI 2.8–2.9).

In sensitivity analyzes using hospital 28-day mortality as the outcome, we observed a similar L-shaped relationship with a turning point at 2.8 g/dL (95% CI 2.6–2.8), confirming the robustness of our primary findings (Figure S1 and Table S1). Additionally, when we conducted analyzes using dummy variables for missing covariate values, the results remained consistent with our primary findings (Table S2), suggesting that our findings were not substantially influenced by missing data. When the included patients were compared with the excluded patients (Table S3), the included patients had greater illness severity (higher SOFA, APACHE IV, and APS III scores; all $P < 0.001$) and longer ICU and hospital stays (both $P < 0.001$). However, 28-day ICU mortality (10.0% vs 10.6%, $P = 0.129$) and hospital mortality (15.8% vs 16.3%, $P = 0.318$) did not differ significantly between the groups, suggesting a limited impact of selection bias on our primary mortality endpoints.

Discussion

This large multicenter retrospective cohort study, which utilized data from the eICU Collaborative Research Database, demonstrated that CG levels were independently associated with 28-day mortality in patients with sepsis. The most striking finding was an L-shaped relationship between the CG concentration and mortality risk, with the risk threshold identified at 2.9 g/dL. To our knowledge, this is the first study to investigate the relationship between CG levels and mortality risk in patients with sepsis, and this nonlinear association remained robust after adjusting for potential confounders.

Several potential mechanisms may explain the relationship between low CG levels and poor outcomes in sepsis patients, although these mechanisms remain hypothetical and require further investigation. Low CG levels could reflect an impaired immune status, as globulins include various immunoglobulins that are thought to play crucial roles in host defense against pathogens. Previous studies have demonstrated that insufficient immunoglobulin levels are associated with increased susceptibility to infections and adverse outcomes in noncritically ill and critically ill patients.[27] Additionally, low globulin levels may indicate poor nutritional status, which is a well-established risk factor for increased mortality in sepsis patients.[28] Furthermore, reduced CG levels might hypothetically represent an inadequate acute phase response, possibly suggesting an impaired ability to mount an appropriate inflammatory response to infection. The threshold effect at 2.9 g/dL suggests that a minimum CG level is necessary for proper immune function. Beyond this threshold, further increases provide limited survival benefits.

Several potential explanatory mechanisms for this phenomenon warrant consideration. First, the plateau in mortality benefit above 2.9 g/dL may represent a physiological “ceiling effect”, wherein sufficient globulin levels have been achieved to maintain essential immune functions, and additional increases confer diminishing returns. This pattern parallels observations of other physiological parameters such as hemoglobin or oxygen saturation, where improvements beyond certain thresholds yield limited clinical benefit.

Second, CG levels exceeding this threshold might reflect immune overactivation, a complex factor in sepsis pathophysiology. While adequate immune responses are crucial for infection control, excessive activation can lead to uncontrolled inflammation and tissue damage. In this context, elevated immunoglobulin levels may indicate dysregulated immune responses rather than enhanced protective functions.

Third, globulin heterogeneity likely contributes to the nonlinear relationship observed. CG encompasses diverse proteins, including various immunoglobulin classes and acute phase proteins, each serving distinct functions in sepsis. In patients with high CG levels, the aggregate value may mask important variations in specific components. Research conducted by Martin-Loeches et al[29] and Donadello et al[30] has demonstrated that in sepsis, the relative balance among different immunoglobulin subclasses provides a more accurate reflection of patients’ immune status and prognosis compared to total immunoglobulin levels alone.

The role of immunoglobulins in sepsis outcomes remains complex and controversial. While examining our findings on endogenous CG, it is important to distinguish between endogenous globulins and exogenous immunoglobulin therapy (IVIG). Endogenous globulins represent a heterogeneous group of proteins produced by the host immune system, including not only immunoglobulins but also acute phase proteins, complement components, and other immune

mediators. These proteins collectively reflect the host's integrated immune response, nutritional status, and overall inflammatory state. In contrast, IVIG consists primarily of standardized IgG antibodies derived from pooled plasma of healthy donors, with a composition that differs substantially from the patient's own globulin profile.

These fundamental functional differences may explain the inconsistent clinical findings. While some studies indicate that low IgG levels are associated with poor outcomes and potential benefits from IVIG therapy in septic patients,[11,31] others have reported contrasting findings.[12] Notably, the ALBIOS trial, involving 956 patients with severe sepsis and septic shock,[32] revealed that elevated levels of IgA and IgG at sepsis onset correlated with increased 90-day mortality, suggesting that elevated specific immunoglobulins might represent dysregulated immune responses. Interestingly, another study focusing on patients with severe sepsis and septic shock reported that higher serum IgG levels were paradoxically associated with increased mortality risk.[33] In contrast, our observation of an L-shaped relationship between the CG level and mortality indicates that low levels may reflect overall impaired immune status and poor nutritional conditions. These seemingly divergent findings demonstrate the complexity of immune responses in sepsis, where both immunosuppression and hyperactive immune states can contribute to adverse outcomes. Furthermore, these findings suggest that immunoglobulin levels may serve as valuable biomarkers for risk stratification in sepsis, although their interpretation requires careful consideration of measurement timing, specific patient populations, and the broader context of immune dysfunction.

Other acute-phase proteins, such as CRP and PCT, demonstrate certain limitations in sepsis diagnosis and monitoring. In a comparative study of intensive care unit patients, PCT was more reliable than CRP in diagnosing septic shock, but both markers exhibited limited predictive value for 30-day all-cause mortality.[34] In neonatal sepsis research, CRP was found to be more reliable for monitoring antibiotic therapy, whereas PCT levels decreased significantly after two days of antibiotic treatment, indicating that CRP and PCT may have distinct clinical uses and limitations in different clinical contexts.[35]

In contrast to these specialized biomarkers, CG offers complementary advantages worth considering. As a derivative parameter from routine laboratory tests, CG requires no additional blood sampling or specialized equipment, making it highly cost-effective and universally available across healthcare settings. While PCT and CRP primarily reflect acute inflammatory responses, CG provides a more comprehensive assessment of both immune function and nutritional status. The clinical applications also differ significantly – PCT and CRP excel in diagnosis and antimicrobial therapy guidance, whereas our findings suggest that the unique value of CG lies in prognostic assessment and risk stratification. The L-shaped relationship between CG and 28-day mortality identified in our study offers nuanced clinical insights beyond what traditional biomarkers typically provide. These distinctions highlight how CG may serve as a valuable supplement to established biomarkers such as PCT and CRP, with each fulfilling different yet complementary roles in the comprehensive management of sepsis patients.

Several protein markers have been extensively studied in sepsis, providing context for understanding the role of CG. The level of serum albumin, the most abundant plasma protein, has been well documented as a predictor of mortality in sepsis patients. Low albumin levels are associated with increased mortality, reflecting both acute inflammatory responses and nutritional status.[36,37] However, as albumin is a negative acute-phase protein whose concentration decreases during inflammation, albumin levels alone may not fully capture the complexity of the septic response. Our investigation complements traditional biomarkers by examining the role of CG in sepsis prognosis, potentially offering additional insights for disease progression assessment and patient risk stratification.

The advantages of the use of the CG level as a prognostic marker deserve comprehensive consideration. Unlike specialized globulins such as group-specific component globulin (Gc-globulin, also known as vitamin D-binding protein) and gelsolin (GSN), which require additional specialized tests,[38] CG can be readily assessed through routine laboratory evaluations. As a biomarker, CG offers unique advantages because of its universal availability and cost-effectiveness across various healthcare settings. While CG represents an aggregate measure encompassing various proteins, including immunoglobulins and complement factors, its prognostic value in sepsis aligns with findings from studies of specific globulins. For example, research has shown that Gc-globulin levels are associated with the severity and prognosis of sepsis.[38] In addition, recent studies have shown that deficiency and depletion of corticosteroid-binding globulin (CBG) are independently associated with increased mortality in patients with sepsis and septic shock,[39,40] which is consistent

with our findings regarding the relationship between CG levels and mortality. Unlike single protein markers that may fluctuate under specific conditions, CG serves as a broader indicator, reflecting both immune function and nutritional state.

On the basis of our data analysis, these findings have important implications for clinical practice. The identified CG threshold could serve as a simple and effective tool for risk stratification, where patients with lower CG levels warrant closer monitoring and potentially more aggressive interventions. The L-shaped relationship we observed suggests that careful interpretation of CG values is necessary, particularly when levels fall outside the optimal range. Furthermore, integrating CG measurements with other clinical parameters may increase prognostic accuracy and guide personalized treatment approaches for sepsis patients.

Several important limitations of this study should be noted. First, as a retrospective study, it inherits the inherent limitations of this design, including potential selection bias and the inability to control for all confounding variables. The quality and completeness of medical records may affect data accuracy, and some relevant clinical information might not have been consistently documented. Additionally, our data source (eICU Collaborative Research Database) contains information from 2014–2015, which predates certain important changes in sepsis management guidelines, including the introduction of Sepsis-3 definitions in 2016.[22] The evolution of clinical practice since the data collection period may influence the applicability of our findings to current sepsis management paradigms. While the fundamental physiological relationships we investigated are unlikely to have changed substantially, changes in early recognition, resuscitation strategies, and supportive care could affect the distribution and impact of the parameters we studied. Therefore, our findings may benefit from validation in more contemporary cohorts and may not be fully generalizable to other populations or current clinical practice.

Second, this database study had limitations in terms of data granularity and standardization. The laboratory measurements were not uniformly standardized, and some potentially important clinical variables might not have been captured in the database. Additionally, the database may not fully represent the broader patient population, potentially limiting the generalizability of our findings. While we conducted stratified analyzes for various clinical factors, we did not formally test for interaction effects between CG levels and factors such as age, sex, or underlying diseases. These potential interactions might reveal important differential effects of CG levels across specific patient subgroups and represent an important area for future research.

Third, the timing of blood sampling may have impacted our results due to the dynamic nature of CG levels during sepsis. The samples, which were collected within the first 24 hours of ICU admission, provide only a snapshot of immunological status. CG levels fluctuate throughout sepsis progression in response to disease course, interventions, and individual immune responses. Patients admitted at different stages of sepsis may have variable CG profiles even within the 24-hour collection window. Serial measurements would provide better insights into this biomarker's temporal dynamics and relationship with outcomes. Future studies incorporating longitudinal assessments of CG levels could help elucidate whether specific temporal patterns hold greater prognostic value than single measurements do.

Fourth, missing data represent another limitation of our study. We employed contemporary methods, including dummy variables, to handle missing data and minimize potential bias. Moreover, the lack of information about interventions during initial stabilization would bias toward the null hypothesis, potentially underestimating the true strength of the association between CG levels and mortality.

Finally, despite our efforts to adjust for various confounding factors, residual confounding cannot be completely eliminated. Variations in clinical management, the timing of interventions, and underlying comorbidities might influence the relationship between CG levels and outcomes in ways that could not be fully accounted for through retrospective analysis alone. Specifically, factors such as nutritional status and liver function, which can directly impact globulin production and metabolism, may not have been fully captured in our analysis. The eICU database lacks a comprehensive assessment of nutritional parameters, and while we included some liver function indicators, the complex interplay between hepatic function and CG levels may not be completely represented in our models.

Future research should focus on four key directions: (1) prospective validation studies to overcome the limitations of retrospective analyzes and enable standardized data collection; (2) mechanistic studies to elucidate the underlying pathophysiological pathways linking CG levels to clinical outcomes; (3) interventional studies, including randomized

controlled trials, to evaluate whether therapeutic strategies targeting CG levels could improve patient outcomes; and (4) validation studies across diverse populations to assess the generalizability of our findings in different ethnic groups, healthcare settings, and geographical regions.

Conclusion

This multicenter retrospective study revealed an L-shaped relationship between CG levels and 28-day mortality in sepsis patients, with a significantly increased mortality risk below 2.9 g/dL.

Abbreviations

AIDS, Acquired immunodeficiency syndrome; ALT, Alanine transaminase; ANOVA, Analysis of variance; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; APS III, Acute Physiology Score III; AST, Aspartate transaminase; BUN, Blood urea nitrogen; CBG, Corticosteroid-binding globulin; CG, Calculated globulin; CI, Confidence interval; CRP, C-reactive protein; CVID, Common variable immunodeficiency; eICU-CRD, eICU Collaborative Research Database; GAM, Generalized additive model; GCS, Glasgow Coma Scale; Gc-globulin, Group-specific component globulin; GI, Gastrointestinal; GSN, Gelsolin; HCV, Hepatitis C virus; HIPAA, Health Insurance Portability and Accountability Act; HIV, Human immunodeficiency virus; HLA-DR, Human leukocyte antigen-DR; ICD-9, International Classification of Diseases, Ninth Revision; ICU, Intensive Care Unit; IVIG, Intravenous immunoglobulin; LRT, Logarithm likelihood ratio test; MAP, Mean arterial pressure; MDW, Monocyte distribution width; OR, Odds ratio; PAD, Primary antibody deficiency; PCT, Procalcitonin; RBC, Red blood cell; Scr, Serum creatinine; SOFA, Sequential Organ Failure Assessment; SRS, Sepsis response signature; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TC, Total cholesterol; UTI, Urinary tract infection; WBC, White blood cell.

Data Sharing Statement

The data are fully available at https://eicu-crd.mit.edu/.

Ethics Approval and Consent to Participate

Owing to the retrospective nature of the study and the established security framework, the requirement for informed consent was waived. No additional institutional review board approval was required for the use of this database, as detailed at https://eicu-crd.mit.edu/about/acknowledgments/.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work. Specifically, XGC and XS designed the study. XZ collected the data, and XS and HYY analyzed the data. XS drafted the manuscript. XGC revised the manuscript. All the authors read and approved the final manuscript.

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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. doi:10.1016/S0140-6736(19)32989-7
2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med*. 2016;193(3):259–272. doi:10.1164/rccm.201504-0781OC
3. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787–1794. doi:10.1001/jama.2010.1553
4. Annane D, Sharshar T. Cognitive decline after sepsis. *Lancet Respir Med*. 2015;3(1):61–69. doi:10.1016/S2213-2600(14)70246-2
5. Marshall JC, Vincent JL, Fink MP, et al. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the fifth toronto sepsis roundtable, Toronto, Ontario, Canada, october 25-26, 2000. *Crit Care Med*. 2003;31(5):1560–1567. doi:10.1097/01.CCM.0000065186.67848.3A
6. Hurwitz SH, Meyer KF. Studies on the blood proteins: i. The serum globulins in bacterial infection and immunity. *J Exp Med*. 1916;24(5):515–546. doi:10.1084/jem.24.5.515
7. Hiss PH, Atkinson JP. serum-globulin and diphtheric antitoxin.-a comparative study of the amount oe globulin in normal and antitoxic sera, and the relation of the globulins to the antitoxic bodies. *J Exp Med*. 1900;5(1):47–66. doi:10.1084/jem.5.1.47
8. Veremeyko T, Barteneva NS, Vorobyev I, Ponomarev ED. The emerging role of immunoglobulins and complement in the stimulation of neuronal activity and repair: not as simple as we thought. *Biomolecules*. 2024;14(10):1323. doi:10.3390/biom14101323
9. Hsieh YP, Tsai SM, Kor CT, Chiu PF. Serum globulin is a novel predictor of mortality in patients undergoing peritoneal dialysis. *Sci Rep*. 2023;13(1):1139. doi:10.1038/s41598-023-27688-z
10. Pai AY, Sy J, Kim J, et al. Association of serum globulin with all-cause mortality in incident hemodialysis patients. *Nephrol Dial Transplant*. 2022;37(10):1993–2003. doi:10.1093/ndt/gfab292
11. Werdan K, Pilz G, Bujdoso O, et al. Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. *Crit Care Med*. 2007;35(12):2693–2701.
12. Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. *Crit Care Med*. 2007;35(12):2686–2692.
13. Jolles S, Borrell R, Zouwail S, et al. Calculated globulin (CG) as a screening test for antibody deficiency. *Clin Exp Immunol*. 2014;177(3):671–678. doi:10.1111/cei.12369
14. Ramasamy I. A single center study investigating clinical outcomes of testing for multiple myeloma and immune deficiency at low globulin levels. *J Blood Med*. 2023;14:345–358. doi:10.2147/JBM.S409234
15. Cui J, Tanvetyanon T. Association between infection and calculated globulin level among patients with thymic epithelial tumor. *J Clin Med*. 2024;13(18):5600. doi:10.3390/jcm13185600
16. Scherzer R, Heymsfield SB, Rimland D, et al. Association of serum albumin and aspartate transaminase with 5-year all-cause mortality in HIV/hepatitis C virus coinfection and HIV monoinfection. *Aids*. 2017;31(1):71–79. doi:10.1097/QAD.0000000000001278
17. Saxena J, Das S, Kumar A, et al. Biomarkers in sepsis. *Clin Chim Acta*. 2024;562(119891):119891. doi:10.1016/j.cca.2024.119891
18. Siddiqui MA, Pandey S, Azim A, Sinha N, Siddiqui MH. Metabolomics: an emerging potential approach to decipher critical illnesses. *Biophys Chem*. 2020;267(106462):106462. doi:10.1016/j.bpc.2020.106462
19. Pandey S, Azim A, Sinha N. Longitudinal NMR based serum metabolomics to track the potential serum biomarkers of septic shock. *Nanotheranostics*. 2023;7(2):142–151. doi:10.7150/ntno.79394
20. Liu Z, Triba MN, Amathieu R, et al. Nuclear magnetic resonance-based serum metabolomic analysis reveals different disease evolution profiles between septic shock survivors and non-survivors. *Crit Care*. 2019;23(1):169. doi:10.1186/s13054-019-2456-z
21. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU collaborative research database, a freely available multi-center database for critical care research. *Sci Data*. 2018;5(180178). doi:10.1038/sdata.2018.178
22. 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. doi:10.1001/jama.2016.0287
23. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34(5):1297–1310. doi:10.1097/01.CCM.0000215112.84523.F0
24. Chang L, Chen X, Lian C. The association between the non-HDL-cholesterol to HDL-cholesterol ratio and 28-day mortality in sepsis patients: a cohort study. *Sci Rep*. 2022;12(1):3476. doi:10.1038/s41598-022-07459-y
25. Lin L, Chen CZ, Yu XD. The analysis of threshold effect using empower stats software. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2013;34(11):1139–1141.
26. Vetter C, Devore EE, Wegrzyn LR, et al. Association between rotating night shift work and risk of coronary Heart disease among women. *JAMA*. 2016;315(16):1726–1734. doi:10.1001/jama.2016.4454
27. Vrettou CS, Vassiliou AG, Kakkas I, et al. Low admission immunoglobulin G levels predict poor outcome in Patients with mild-to-critical COVID-19: a prospective, single-center study. *J Epidemiol Glob Health*. 2021;11(4):338–343. doi:10.1007/s44197-021-00002-8
28. Oh TK, Song IA. Prior evaluation of nutritional status and mortality in patients with sepsis in South Korea. *Nutrients*. 2023;15(24):5040. doi:10.3390/nu15245040
29. Martin-Loeches I, Muriel-Bombín A, Ferrer R, et al. The protective association of endogenous immunoglobulins against sepsis mortality is restricted to patients with moderate organ failure. *Ann Intensive Care*. 2017;7(1):44. doi:10.1186/s13613-017-0268-3
30. Donadello K, Taccone FS. Should we measure immunoglobulin levels in septic patients? *Int Immunopharmacol*. 2012;12(3):540–541. doi:10.1016/j.intimp.2011.12.021
31. Akatsuka M, Masuda Y, Tatsumi H, Sonoda T. Efficacy of intravenous immunoglobulin therapy for patients with sepsis and low immunoglobulin G levels: a single-center retrospective study. *Clin Ther*. 2022;44(2):295–303. doi:10.1016/j.clinthera.2021.12.008
32. Alagna L, Meessen J, Bellani G, et al. Higher levels of IgA and IgG at sepsis onset are associated with higher mortality: results from the Albumin Italian Outcome Sepsis (ALBIOS) trial. *Ann Intensive Care*. 2021;11(1):161. doi:10.1186/s13613-021-00952-z

33. Dietz S, Lautenschläger C, Müller-Werdan U, et al. Serum IgG levels and mortality in patients with severe sepsis and septic shock: the SBITS data. *Med Klin Intensivmed Notfmed*. 2017;112(5):462–470. doi:10.1007/s00063-016-0220-6
34. Schupp T, Weidner K, Rusnak J, et al. C-reactive protein and procalcitonin during course of sepsis and septic shock. *Ir J Med Sci*. 2024;193 (1):457–468. doi:10.1007/s11845-023-03385-8
35. Jimoh AK, Bolaji OB, Adelekan A, et al. Clinical utility of procalcitonin and C-reactive protein in the management of neonatal sepsis in a resource-limited nigerian hospital. *Niger J Clin Pract*. 2023;26(12):1895–1901. doi:10.4103/njcp.njcp_397_23
36. Lee SM, Jo YH, Lee JH, et al. Associations of the serum albumin concentration and sequential organ failure assessment score at discharge with 1-year mortality in sepsis survivors: a retrospective cohort study. *Shock*. 2023;59(4):547–552. doi:10.1097/SHK.0000000000002083
37. Tie X, Zhao Y, Sun T, et al. Associations between serum albumin level trajectories and clinical outcomes in sepsis patients in ICU: insights from longitudinal group trajectory modeling. *Front Nutr*. 2024;11(1433544). doi:10.3389/fnut.2024.1433544
38. Horváth-Szalai Z, Kustán P, Szirmay B, et al. Predictive value of serum gelsolin and Gc globulin in sepsis - a pilot study. *Clin Chem Lab Med*. 2018;56(8):1373–1382. doi:10.1515/cclm-2017-0782
39. Lee JH, Meyer EJ, Nenke MA, Falhammar H, Torpy DJ. Corticosteroid-binding globulin (CBG): spatiotemporal distribution of cortisol in sepsis. *Trends Endocrinol Metab*. 2023;34(3):181–190. doi:10.1016/j.tem.2023.01.002
40. Meyer EJ, Nenke MA, Rankin W, et al. Total and high-affinity corticosteroid-binding globulin depletion in septic shock is associated with mortality. *Clin Endocrinol*. 2019;90(1):232–240. doi:10.1111/cen.13844