

A study on serum GRP78: A novel endoplasmic reticulum stress marker for the diagnosis of sepsis

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ABSTRACT:

Background: Sepsis is the life-threatening organ dysfunction caused by dysregulated host response to infection and is a leading cause of mortality in critically ill patients, despite aggressive treatment and infection prevention measures. Current biomarkers like Procalcitonin and C-reactive protein primarily reflect systemic inflammation rather than the intracellular stress mechanisms, such as Endoplasmic Reticulum (ER) stress, which contribute to organ injury. **Objectives:** The primary objective of the study was to evaluate the diagnostic efficacy of Glucose- Regulated Protein 78 (GRP78), a master chaperone of the ER stress response, as a novel biomarker for sepsis. The study also aimed to associate GRP78 level with the clinical severity of sepsis as determined by qSOFA scores. **Methodology:** A cross-sectional hospital-based study was conducted involving 100 adult participants: 50 patients with a clinical diagnosis of sepsis (Group I) and non-septic infected controls (Group II). Sepsis severity was assessed using the quick Sequential Organ Failure Assessment (qSOFA) score. Serum GRP78 levels were measured using a quantitative enzyme-linked immunosorbent assay (ELISA). Statistical analysis included independent sample t-tests and Receiver Operating Characteristic (ROC) curve analysis. **Results:** Serum GRP78 levels were significantly elevated in septic patients (47.55 ± 18.39 ng/mL) compared to the control group (1.04 ± 0.46 ng/mL; $p < 0.001$). ROC analysis for GRP78 demonstrated an area under the curve (AUC) of 0.776, with a specificity of 68.0% and a sensitivity of 48.9% at a cutoff of 54.13 ng/mL. A positive correlation ($r = 0.235$) was observed between GRP78 levels and the clinical severity of sepsis. **Conclusion:** Serum GRP78 is significantly upregulated in sepsis, reflecting the activation of ER stress pathways during systemic infection. While its diagnostic sensitivity is moderate, GRP78 serves as a valuable novel adjunct biomarker for the early diagnosis and risk stratification of septic patients in clinical settings.

Keywords: Sepsis, Endoplasmic Reticulum Stress, Biomarker, Glucose-Regulated Protein 78 (GRP78), quick Sequential Organ Failure Assessment (qSOFA)

INTRODUCTION:

Sepsis is a major global health burden and remains one of the leading causes of morbidity and mortality in hospitalized patients, particularly in critical care settings. It is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. Despite advances in antimicrobial therapy and supportive care, early recognition of sepsis remains challenging due to its heterogeneous clinical presentation and rapid progression. Delayed diagnosis

is associated with increased mortality, emphasizing the need for timely and accurate diagnostic tools.

The diagnosis of sepsis is primarily clinical and supported by laboratory markers of infection and inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), lactate dehydrogenase (LDH), and procalcitonin [2,3]. While these biomarkers are widely used, they mainly reflect systemic inflammatory responses and may lack specificity for sepsis. Furthermore, they do not adequately represent the

underlying cellular stress mechanisms that contribute to immune dysregulation, endothelial injury, and multiorgan dysfunction seen in sepsis. This limitation highlights the importance of identifying novel biomarkers that capture fundamental pathophysiological processes.

Endoplasmic reticulum (ER) stress has emerged as an important contributor to the pathogenesis of sepsis. The ER plays a critical role in protein folding, calcium homeostasis, and cellular signaling. During conditions such as infection, hypoxia, and oxidative stress, accumulation of misfolded or unfolded proteins activates the unfolded protein response (UPR), a protective mechanism aimed at restoring ER function. However, sustained or excessive ER stress can lead to apoptosis, amplified inflammatory signaling, and organ dysfunction, all of which are characteristic features of sepsis [4].

Glucose-Regulated Protein 78 (GRP78), also known as Binding Immunoglobulin Protein (BiP), is a key ER chaperone and master regulator of the UPR. Under physiological conditions, GRP78 assists in protein folding and maintains ER homeostasis by regulating stress sensors. In pathological states such as systemic infection and inflammation, GRP78 expression is markedly upregulated and may translocate to the cell surface or be released into the circulation [5,6]. Emerging evidence suggests that elevated GRP78 levels are associated with immune dysregulation, altered endothelial function, and enhanced pathogen–host interactions, implicating GRP78 in the progression of sepsis.

Recent clinical and experimental studies have reported significantly higher GRP78 levels in patients with sepsis compared with non-septic controls, supporting its potential role as a biomarker of ER stress-mediated inflammation [7,8]. However, the diagnostic accuracy of GRP78 and its relationship with clinical severity scores such as the quick Sequential Organ Failure Assessment (qSOFA) score remain incompletely defined. Further evaluation is required to determine whether GRP78 can serve as a reliable adjunct to existing clinical and laboratory parameters.

The present study was designed to evaluate serum GRP78 levels in patients with sepsis and compare them with levels in non-septic infected individuals. Additionally, we aimed to assess the diagnostic utility of GRP78 and examine its correlation with sepsis severity as determined by the qSOFA score. By investigating GRP78 as a marker of ER stress in sepsis, this study seeks to contribute to the identification of novel adjunctive biomarkers for early diagnosis and risk stratification in clinical practice.

MATERIALS AND METHODS:

Study Design and Setting: This cross-sectional, hospital-based study was conducted at a superspeciality hospital located in Southern India. The study population comprised 100 adult patients admitted to the 17 bedded

Medical Intensive Care Unit (MICU). Participants were divided into two cohort: Group I (n = 50) included patients with a clinical diagnosis of sepsis and Group II (n = 50) consisted of non-septic patients serving as controls.

Clinical Evaluation and Inclusion Criteria: Sepsis was diagnosed and its severity assessed using quick Sequential Organ Failure Assessment (qSOFA) score. Supplementary laboratory parameters, including Total Leukocyte Count (TLC), C - reactive protein (CRP), and Procalcitonin (PCT), were measured to stratify disease severity. Exclusion criteria included patients with incomplete laboratory data or samples exhibiting hemolysis.

Sample Collection and Processing: Venous blood samples were collected in EDTA vacutainers for plasma and plain tubes for serum separation. Samples clotted at room temperature for 10–20 minutes before centrifugation at 2000–3000 RPM for 20 minutes. The serum was aliquoted into sterile Eppendorf tubes and stored at -20°C until analysis.

Measurement of GRP-78 Levels: Serum Glucose-Regulated Protein 78 (GRP-78) levels were quantified using a commercial ELISA kit (Human GRP-78 ELISA Kit, Bioassay Technology Laboratory, Zhejiang, China) according to the manufacturer's instructions. The assay featured a measurement range of 0.5–100 ng/mL and a sensitivity of 0.23 ng/mL. Concentrations were determined by interpolating optical density values against a standard curve.

Sample Size and Statistical Considerations: As no identical studies were available in the Indian context, sample size calculation was based on Li et al.. the calculation used a Mean serum GRP-78 of 208.79 ± 21.76 ng/mL in sepsis patients and 190.5 ± 46.87 ng/mL in controls, with an expected mean difference of 18.29 ng/mL. Assuming a 95% confidence interval, 90% statistical power, and a pooled standard deviation of 200, the required sample size was 45 patients per group. The present study included 50 patients per group, meeting the estimated requirement.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki, and institutional ethical approval was obtained before study initiation. The use of anonymised leftover samples ensured patient confidentiality and minimized ethical concerns related to direct sample collection.

Statistical Analysis: Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized baseline data as percentages and continuous variables as mean $\pm$ standard deviation (SD). Comparative analysis utilized independent sample t-test to compare GRP-78 levels and other parameters between groups. Diagnostic utility was evaluated via Receiver Operating Characteristic (ROC) curves to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A p-value <0.01 was considered statistically significant.

RESULTS:

Demographic and Clinical Characteristics: The study analysed 100 participants. The age distribution of group I patients was higher than that of group II patients, and clinical severity, determined by qSOFA scores, showed that 58% of septic patients presented with a score of 3, whereas all the controls had a score of 0 ($p=0.001$), as detailed in Table 1.

Table 1: Comparison of demographic and qSOFA score data between Group I (Sepsis infected) and Group II (Non-sepsis infected controls).

Parameters		Septic patients (cases)	Non-septic patients (controls)	p Value
Number of Patients (n)		50	50	
Age in years (Mean)		53.30 +/- 21.14	44.100 +/- 13.64	0.011 (sig)
Gender	Female %	58	48	0.316
	Male %	42	52	
qSOFA score		1 = 2% 2 = 40% 3 = 58%	0 = 100% 1= nil 2= nil 3= nil	0.001 (vhs)

Clinical Categories of Sepsis: In group I, abdominal sepsis was the most prevalent category (22%), followed by respiratory-related causes (20%) and malignancy-associated sepsis (20%). Other contributors included meningitis (10%), urosepsis (10%), viral sepsis (8%) and sepsis NOS (not otherwise specified) (10%).

Comparison of Serum GRP78 and Procalcitonin (PCT) Levels – Correlation Analysis: The study compared the expression of GRP78 and PCT biomarkers. The data revealed distinct yet complementary roles for these markers in the diagnosis of sepsis. Both markers exhibited a very highly significant elevation in the septic cohort compared to the control group ($p < 0.001$). GRP78 - Septic patients showed a mean value of 47.55 ± 18.39 ng/mL versus 1.037 ± 0.46 ng/mL in controls.

PCT – Septic levels were 13.65 ± 2.96 ng/mL versus 0.56 ± 0.49 ng/mL in controls.

In group I, PCT showed a weak positive correlation with GRP78 ($r = 0.275$) and qSOFA score ($r = 0.252$), while GRP78 also demonstrated a weak positive correlation with qSOFA ($r = 0.235$), indicating a trend toward increasing biomarker levels with greater clinical severity of sepsis, though these correlations were not statistically significant.

In contrast, in group II, PCT exhibited a weak negative correlation with GRP78 ($r = -0.167$), which was not statistically significant. As shown in Table 2, these findings indicate that GRP 78 and PCT are elevated in sepsis and show a positive association with disease severity, supporting the potential role of GRP78 as an adjunct biomarker alongside PCT.

Table 2: Comparison of GRP78 and PCT Levels and their correlation with qSOFA score in group I and group II

Group	Parameter	Mean $\pm$ SD / Correlation	r (Pearson's coefficient)	p value
Group I (Septic patients)	PCT (ng/mL)	13.65 ± 2.96	—	$< 0.001^*$
	GRP78 (ng/mL)	47.55 ± 18.39	—	$< 0.001^*$

	PCT vs GRP78	Correlation	0.275	0.053
	PCT vs qSOFA	Correlation	0.252	0.078
	GRP78 vs qSOFA	Correlation	0.235	0.100
Group II (Non-septic controls)	PCT (ng/mL)	0.56 ± 0.49	—	< 0.001*
	GRP78 (ng/mL)	1.037 ± 0.46	—	< 0.001*
	PCT vs GRP78	Correlation	-0.167	0.248

r = Pearson's correlation coefficient

p = p-value

N = sample size

p < 0.001 = very highly significant (VHS)

qSOFA = Quick Sequential Organ Failure Assessment

Diagnostic Evaluation (ROC Curve analysis):

The distribution of GRP78 levels based on the median value is presented in Table 3. A higher proportion of septic patients showed GRP78 levels above the median compared to controls, supporting its potential diagnostic relevance.

Table 3: Distribution of GRP78 Levels Based on Median Value in Study Groups

		Group		Total
		Experiment	Control	
> Median	Count	23	16	39
	%	48.9%	32.0%	40.2%
< Median	Count	24	34	58
	%	51.1%	68.0%	59.8%
Total	Count	47	50	97
	%	100.0%	100.0%	100.0%

The diagnostic performance of GRP78 was assessed using ROC analysis (Figure 1). The curve for GRP78 levels greater than the median demonstrated a clear shift toward the upper left quadrant, corresponding to an AUC of 0.776. The optimal cutoff of 54.126 ng/mL was derived from the coordinates of this curve, identifying the point of maximum vertical distance from the diagonal reference line. Furthermore, GRP78 as a biomarker of sepsis showed: Sensitivity=48.9%, Specificity=68%, Positive predictive value=58.9%, Negative predictive value=60.3% and an Accuracy rate=58.8%.

Figure 1: ROC Curve Analysis of Serum GRP78

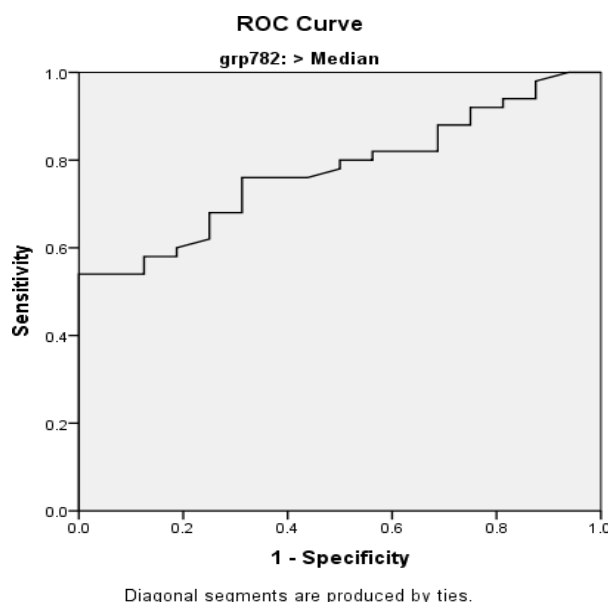


Figure 1 displays the trade-off between sensitivity and specificity. The area under this curve (AUC) represents the probability that the GRP78 tests will correctly classify a randomly chosen pair of septic and non-septic subjects.

DISCUSSION:

Sepsis is a multifaceted clinical condition resulting from an inappropriate host response to infection, culminating in systemic inflammation, organ dysfunction, and significant global mortality [1]. Although biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), lactate dehydrogenase (LDH), and procalcitonin are commonly employed to assist in clinical assessment, they predominantly indicate inflammatory activity and do not adequately reflect the cellular stress mechanisms activated during sepsis [2,3]. In this context, the present study evaluated Glucose-Regulated Protein 78 (GRP78), an endoplasmic reticulum (ER) stress-associated chaperone protein, as a supplementary biomarker for the diagnosis of sepsis.

GRP78, also referred to as Binding Immunoglobulin Protein (BiP), plays a pivotal role in maintaining ER function by regulating the unfolded protein response (UPR) and ensuring proper protein folding under normal physiological conditions [9]. During pathological states such as infection and systemic inflammation, GRP78 expression is markedly increased. Under sustained ER stress, GRP78 may translocate to the cell surface or be released into the circulation, reflecting cellular distress and altered homeostasis. This aberrant expression has been implicated in facilitating pathological signaling processes that may be exploited by invading pathogens [5,6]. Elevated GRP78 levels have therefore been associated with enhanced ER stress and immune dysregulation in inflammatory conditions, supporting its relevance as an indicator of severe systemic stress. In agreement with these mechanistic insights, multiple clinical investigations have reported increased circulating GRP78 levels in patients with sepsis when compared with non-septic controls. A diagnostic cohort

study involving critically ill patients demonstrated significantly higher serum GRP78 concentrations in individuals with sepsis, with a reported ROC AUC of 0.771, sensitivity of 75.0%, and specificity of 73.1%, indicating moderate diagnostic performance [7]. Similarly, an observational study examining neutrophil ER stress responses found that GRP78 expression was significantly elevated during the early stages of sepsis relative to healthy subjects, highlighting the activation of ER stress pathways within immune cells during disease progression [9]. These observations are consistent with the findings of the present study, which revealed significantly higher mean serum GRP78 levels in septic patients compared to those with non-septic infections.

Despite demonstrating elevated levels in sepsis, GRP78 exhibited only moderate sensitivity and specificity in the present analysis, limiting its utility as a stand-alone diagnostic marker. Nevertheless, its incorporation alongside established clinical tools such as the qSOFA score and conventional inflammatory biomarkers may improve early identification and severity stratification of sepsis. Previous studies suggest that integrating ER stress markers like GRP78 with traditional diagnostic parameters enhances overall diagnostic accuracy [7]. Moreover, experimental models have linked GRP78 to immune dysregulation and organ injury in sepsis, further reinforcing its pathophysiological relevance. Interpretation of GRP78 levels must account for the inherent heterogeneity of sepsis and the potential influence of comorbid conditions, including diabetes mellitus, hypertension, autoimmune diseases, and immunocompromised states, all of which are known to modulate ER stress responses [10]. Such factors may contribute to inter-individual variability in GRP78 expression. Additionally, treatment-related variables,

including antibiotic administration and timing of sample collection, may influence GRP78 dynamics and should be systematically evaluated in future studies.

The present study has certain limitations. The relatively small sample size and single-centre design restrict the generalizability of the findings. Larger, multicenter studies with longitudinal follow-up are required to validate GRP78 as a diagnostic or prognostic biomarker and to establish standardised cutoff values applicable across diverse patient populations.

In summary, the observed elevation of GRP78 in sepsis, supported by both the current findings and existing literature, underscores its potential role as a marker of ER stress in systemic inflammation. Although GRP78 alone may not be sufficient for definitive diagnosis, its use in combination with clinical assessment tools and established biomarkers may enhance early recognition and risk stratification of sepsis. Further research is warranted to confirm these findings and to elucidate the molecular mechanisms linking ER stress to sepsis pathogenesis.

CONCLUSION:

The study demonstrates that serum GRP78 is significantly elevated in patients with sepsis compared to non-septic controls, reflecting profound systematic Endoplasmic Reticulum (ER) stress response. The high degree of statistical significance ($p < 0.001$) suggests that GRP78 is a potent biological indicator of the cellular dysfunction that characterises septic states.

The diagnostic evaluation using ROC curve analysis identified an optimal cut-off of 54.126 ng/mL. At this threshold, GRP78 exhibited a specificity of 68%, indicating its reliability in distinguishing sepsis from other non-septic conditions. While its sensitivity (48.9%) was moderate, the positive correlation with established markers like Procalcitonin (PCT) ($r = 0.275$) and clinical severity scores like qSOFA ($r = 0.235$) suggests that GRP78 provides complementary information regarding the host's cellular health and organ failure risk.

This study concludes that GRP78 serves as a novel and valuable adjunct biomarker. Unlike traditional inflammatory markers that measure the immune response, GRP78 offers a unique window into the intracellular stress pathways. Integrating GRP78 into the standard diagnostic protocol could improve early risk stratification and the clinical management of critically ill patients in the ICU.

CONFLICT OF INTEREST:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of Informed Consent:

All procedures followed the ethical standards of the Institutional Ethics Committee and the 1964 Helsinki Declaration. Informed consent was obtained from all participants or their legal guardians. For this study, anonymized leftover samples were utilized, ensuring strict maintenance of patient privacy and confidentiality.

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