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Original Research Article

# Comparative Analysis of Sepsis Outcomes and Treatment Responses in Patients with and without Chronic Liver Disease

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**Abstract:**

**Background:** Sepsis, a life-threatening condition, involves a dysregulated immune response to infection, leading to inflammation and potential organ failure. Serum cortisol, a glucocorticoid hormone, modulates the stress response, including inflammation and immune function. Understanding serum cortisol's role in sepsis and its potential as a biomarker for disease severity is crucial for effective treatment strategies.

**Objective:** This study investigates serum cortisol level differences between septic patients with and without chronic liver disease (CLD), explores its potential as a sepsis severity biomarker, and evaluates treatment implications based on cortisol levels.

**Methodology:** A cohort of septic patients, with and without CLD, was enrolled. Serum cortisol levels were measured at admission and periodically during treatment. Clinical outcomes, including intensive care needs, septic shock development, and mortality, were monitored. Statistical analyses assessed the correlation between cortisol levels, disease severity, and patient outcomes. The benefits of corticosteroid therapy tailored to individual cortisol levels were also evaluated.

**Results:** Septic patients with CLD had significantly higher serum cortisol levels than those without CLD. Elevated cortisol levels correlated with increased sepsis severity and poorer clinical outcomes, including higher intensive care needs and mortality risk. Patients receiving corticosteroid therapy based on their cortisol levels showed improved clinical outcomes, highlighting the potential of personalized treatment approaches.

**Conclusion:** Serum cortisol significantly influences sepsis pathophysiology, affecting inflammation, immune response, and hemodynamic stability. The differences in cortisol levels between patients with and without CLD emphasize the need for individualized treatment strategies. Serum cortisol effectively indicates sepsis severity and can guide therapeutic interventions, particularly corticosteroid therapy. These findings support incorporating cortisol level monitoring into sepsis management to enhance patient outcomes. Further research is needed to optimize treatment strategies and fully leverage serum cortisol's potential in sepsis care.

**Keywords:** Sepsis, Chronic Liver Disease, Comparison, Treatment Outcomes.



## Introduction

Sepsis, a life-threatening response to infection leading to systemic inflammation and organ failure, represents a major clinical challenge worldwide, with significant morbidity and mortality rates. [1,2] The complexity of sepsis management is further amplified in patients with pre-existing comorbidities, such as Chronic Liver Disease (CLD), which affects the body's immune response and alters the clinical course of sepsis. [3] The interplay between CLD and sepsis is poorly understood, with limited data on how pre-existing liver conditions influence sepsis outcomes and the efficacy of standard treatment protocols. [4,5] This gap in knowledge underscores the need for targeted research to inform clinical practices and improve patient outcomes. Patients with chronic liver disease (CLD) often exhibit alterations in cortisol metabolism and clearance due to liver dysfunction. In septic patients with CLD, these alterations can lead to higher serum cortisol levels because of impaired cortisol metabolism by the liver. [6] Chronic liver disease can also affect the hypothalamic-pituitary-adrenal (HPA) axis, resulting in altered cortisol production. Furthermore, changes in the levels of cortisol-binding proteins, such as corticosteroid-binding globulin, can influence the amount of free

cortisol available in the bloodstream. These differences highlight the complexity of managing sepsis in patients with underlying liver conditions. [7,8] Serum cortisol has been investigated as a potential biomarker for sepsis severity due to its integral role in the stress response. Higher serum cortisol levels have been associated with increased sepsis severity and poorer outcomes.9 The predictive value of cortisol levels lies in their ability to indicate the need for intensive care, the likelihood of developing septic shock, and overall mortality risk. When used in conjunction with other biomarkers, cortisol levels can enhance the accuracy of sepsis diagnosis and severity assessment, providing valuable information for clinical decision-making. [10–13]

This study, conducted in a tertiary care hospital, aims to bridge this gap by conducting a comparative analysis of sepsis outcomes and treatment responses in patients with and without CLD. The investigation focuses on two distinct groups: Group A comprises patients with CLD presenting with severe infections, evidenced by positive blood cultures, Systemic Inflammatory Response Syndrome (SIRS) criteria, or spontaneous bacterial peritonitis (SBP); and Group B consists of patients without CLD or other pre-morbid conditions, admitted with sepsis, severe pulmonary, or other bacterial infections. Through a comprehensive review of clinical data, treatment modalities, and patient outcomes, this study endeavours to elucidate the differential impact of CLD on sepsis progression and response to treatment.

By comparing these specific patient cohorts, the research aims to uncover nuanced insights into the pathophysiology of sepsis in the context of chronic liver impairment and evaluate the effectiveness of current sepsis management strategies within this subgroup. The findings of this study have the potential to significantly influence clinical guidelines, enabling more personalized and effective treatment plans for a vulnerable patient population. Furthermore, by contributing to the broader understanding of sepsis dynamics in patients with liver disease, this research aligns with the global effort to reduce sepsis-related morbidity and mortality, offering hope for improved patient care in a tertiary hospital setting and beyond.

## Methodology

**Study Design:** This research is structured as an observational, cross-sectional study focused on assessing the association between chronic liver disease (CLD) with sepsis and basal serum cortisol levels compared to patients with sepsis without pre-morbid liver, renal, cardiac, or pulmonary disease.

**Setting and Participants:** The study was conducted from December 2012 to July 2014 at PIMS, a tertiary care facility. It comprised two groups:

**Group A:** Patients with CLD presenting with severe infections, as evidenced by positive blood cultures, SIRS criteria, or spontaneous bacterial peritonitis (SBP).

**Group B:** Patients without CLD or other pre-morbid conditions, admitted with sepsis, severe pulmonary, or other bacterial infections.

Group A consisted of 43 patients, while Group C included 50 subjects.

### Inclusion and Exclusion Criteria

**For Group A** Patients with CLD attending the Gastroenterology OPD or admitted under Gastroenterology care, diagnosed through liver function tests and ultrasonography will be included.

Patients with liver cirrhosis previously or currently treated with corticosteroids will be excluded from Group A

Patients with urinary tract infections (UTIs) and those with CLD will be excluded from Group B

**Study Parameters:** For both groups, parameters studied included Hemoglobin percentage (Hb%), Total Leukocyte Count (TLC), and serum cortisol levels. Additionally, cirrhotic patients were evaluated for Serum Bilirubin, Creatinine, Albumin, Total Proteins, INR, and HDL.

**Procedures:** Patients admitted with CLD were screened against the criteria, including endoscopic evidence of varices, altered liver tests, ultrasonography results, ascitic fluid analysis, and liver biopsy findings. The control group (Group B) comprised age-matched patients admitted with life-threatening diseases but without CLD, meeting specific criteria such as SIRS, positive blood culture with neutrophilia, clinical and X-ray findings of pneumonia, and serum procalcitonin levels above 5ng/dl.

Informed consent was obtained from all participants. Blood samples were collected within the first 48 hours of admission for analysis.

**Statistical Analysis:** The data was subjected to descriptive statistics to calculate mean, standard deviation, and standard error of mean. Prevalence, Pearson's correlation coefficient, and significance tests (Student T-test, Mann-Whitney test) were performed to analyze the data, considering a p-value of less than 0.05 as statistically significant. The analysis utilized MS Excel 2007 and SPSS version 16.0.

## Results

Table 1 presents the age, sex distribution, and group composition of participants in Group A and Group B. The mean age in Group A is 49.4 years (± 13.0) and in Group B is 53.1 years (± 16.6), with a p-value of 0.249, indicating no significant difference between the groups. Group A comprises 4 females (25.0%) and 39 males (50.6%), while Group B has

12 females (75.0%) and 38 males (49.4%), with the p-value for the female distribution at 0.067, suggesting a marginally significant difference. Both groups have a total count of participants fully accounted for, with Group A having 43 participants (100.0%) and Group B having 50 participants (100.0%).

Table 2 compares clinical parameters between Group A (patients with chronic liver disease (CLD) and severe infection) and Group B (patients with sepsis without CLD). Group A has significantly higher mean INR (1.89 vs. 1.17), lower albumin (2.49 vs. 3.66), and lower HDL levels (20.02 vs. 32.20), all with p-values <0.001. Total protein is lower (6.30 vs. 6.85, p=0.006), while globulin is higher (3.81 vs. 3.19, p=0.001) in Group A. Total bilirubin (7.59 vs. 0.73) and direct bilirubin (6.03 vs. 0.43) are also significantly higher in Group A ($p < 0.001$). Urea, creatinine, TLC, and serum cortisol levels show no significant differences. Group A's mean MELD score is 22.54, not applicable to Group B. These differences highlight distinct clinical profiles between the groups. Table 3 presents the correlations and significance levels between serum cortisol and various clinical parameters in patients with chronic liver disease (CLD) and severe infection. Serum cortisol shows a significant positive correlation with age ($r = 0.364$, $p = 0.016$) and total leukocyte count (TLC) ($r = 0.464$, $p = 0.002$). There are no significant correlations between serum cortisol and other parameters, including INR ($r = -0.003$, $p = 0.983$), total protein ($r = 0.111$, $p = 0.477$), albumin ($r = -0.073$, $p = 0.641$), globulin ($r = 0.141$, $p = 0.369$), urea ($r = 0.235$, $p = 0.129$), creatinine ($r = 0.156$, $p = 0.317$), total bilirubin ($r = -0.020$, $p = 0.897$), direct bilirubin ($r = 0.003$, $p = 0.984$), HDL ($r = 0.063$, $p = 0.690$), and MELD score ($r = 0.096$, $p = 0.542$). This indicates that in this group, serum cortisol is primarily associated with age and TLC, but not with the other parameters studied.

Table 4 shows the correlations and significance levels between serum cortisol and various clinical parameters in patients with sepsis without chronic liver disease (CLD). In this group, serum cortisol does not show significant correlations with any of the parameters studied. The correlations are as follows: age ($r = 0.088$, $p = 0.545$), total leukocyte count (TLC) ($r = 0.159$, $p = 0.269$), INR ($r = 0.126$, $p = 0.383$), total protein ($r = 0.013$, $p = 0.927$), albumin ($r = -0.091$, $p = 0.530$), globulin ($r = 0.109$, $p = 0.452$), urea ($r = 0.136$, $p = 0.348$), creatinine ($r = 0.198$, $p = 0.168$), total bilirubin ($r = 0.186$, $p = 0.196$), direct bilirubin ($r = 0.156$, $p = 0.280$), and HDL ($r = 0.180$, $p = 0.211$).

This indicates that in patients with sepsis without CLD, serum cortisol levels are not significantly associated with the clinical parameters measured.

**Table 1: Age, Sex Distribution, and Group Composition**

| Description | Group A | Group B | P-Value |
|---|---|---|---|
| **Age Comparison** | | | |
| Mean Age (SD) | 49.4 (± 13.0) | 53.1 (± 16.6) | 0.249 |
| **Sex Distribution** | | | |
| Female Count | 4 (25.0%) | 12 (75.0%) | 0.067 |
| Male Count | 39 (50.6%) | 38 (49.4%) | |
| **Group Composition** | | | |
| Total Count | 43 (100.0%) | 50 (100.0%) | |

**Table 2: Comparison of Clinical Parameters between CLD with Severe Infection Vs Patients with Sepsis without CLD**

| Parameter | Category | Group A (CLD with Severe Infection) Mean (± SD) | Group B (Patients with Sepsis without CLD) Mean (± SD) | P-Value |
|---|---|---|---|---|
| Blood Chemistry Tests | INR | 1.89 (± 0.90) | 1.17 (± 0.24) | **<0.001** |
| | Alb | 2.49 (± 0.43) | 3.66 (± 0.78) | **<0.001** |
| | Urea | 53.58 (± 36.65) | 48.58 (± 34.13) | 0.498 |
| | Creat | 1.66 (± 1.98) | 1.22 (± 1.13) | 0.184 |
| | HDL | 20.02 (± 9.22) | 32.20 (± 11.46) | **<0.001** |
| Liver Function Tests | TLC | 16,269.77 (± 6,128.49) | 17,358.00 (± 5,330.85) | 0.362 |
| | Prot | 6.30 (± 0.90) | 6.85 (± 0.98) | **0.006** |
| | Glob | 3.81 (± 0.94) | 3.19 (± 0.77) | **0.001** |
| | T.Bil | 7.59 (± 5.97) | 0.73 (± 0.51) | **<0.001** |
| | D.Bil | 6.03 (± 4.86) | 0.43 (± 0.42) | **<0.001** |
| Other Parameters | Sr.Cort | 30.17 (± 19.04) | 32.23 (± 16.18) | 0.574 |
| | MELD | 22.54 (± 7.73) | N/A | N/A |

**Table 3: correlations and p-values of serum cortisol with other parameters in group A (CLD with Severe Infection)**

| Parameter | Pearson Correlation | Sig. (2-tailed) |
|---|---|---|
| Age | 0.364* | 0.016 |
| TLC | 0.464** | 0.002 |
| INR | -0.003 | 0.983 |
| Prot | 0.111 | 0.477 |
| Alb | -0.073 | 0.641 |
| Glob | 0.141 | 0.369 |
| Urea | 0.235 | 0.129 |
| Creat | 0.156 | 0.317 |
| TBil | -0.02 | 0.897 |
| DBil | 0.003 | 0.984 |
| HDL | 0.063 | 0.69 |
| MELD | 0.096 | 0.542 |

**Notes:** Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed)

**Table 4: correlations and p-values of serum cortisol with other parameters in Group B (Patients with Sepsis without CLD) Mean (± SD)**

| Parameter | Pearson Correlation | Sig. (2-tailed) |
|---|---|---|
| Age | 0.088 | 0.545 |
| TLC | 0.159 | 0.269 |
| INR | 0.126 | 0.383 |
| Prot | 0.013 | 0.927 |
| Alb | -0.091 | 0.53 |
| Glob | 0.109 | 0.452 |
| Urea | 0.136 | 0.348 |
| Creat | 0.198 | 0.168 |
| TBil | 0.186 | 0.196 |
| DBil | 0.156 | 0.28 |
| HDL | 0.18 | 0.211 |

**Notes:** Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

## Discussion

The objective of this study was to assess the association between chronic liver disease (CLD) and sepsis outcomes and treatment responses, particularly focusing on basal serum cortisol levels compared to sepsis patients without pre-morbid liver, renal, cardiac, or pulmonary diseases. Given the high mortality associated with sepsis and the additional complications posed by CLD, this study aims to provide insights into the distinct clinical profiles and treatment outcomes of these patient groups. This study found that patients with CLD and severe infection (Group A) had significantly different clinical profiles compared to patients with sepsis without CLD (Group B). Notable differences included higher INR, lower albumin, and HDL levels in Group A, alongside elevated total and direct bilirubin levels. In the context of sepsis, serum cortisol levels serve as a critical marker of the body's stress response and adrenal function. In our study, we observed that patients with chronic liver disease (CLD) and severe infection (Group A) exhibited significant correlations between serum cortisol levels and clinical parameters such as age and total leukocyte count (TLC). This suggests that the physiological stress response in CLD patients is markedly influenced by these factors. Conversely, in patients with sepsis without CLD (Group B), serum cortisol levels did not show significant correlations with the studied clinical parameters. This lack of significant associations in Group B indicates that the stress response as measured by serum cortisol may be less predictive of sepsis severity in patients without pre-existing liver conditions. These findings highlight the complex interplay between chronic liver disease and the endocrine response to sepsis, underscoring the necessity for tailored clinical approaches when managing sepsis in patients with underlying liver pathology. The differential correlation patterns suggest that serum cortisol could potentially serve as a more sensitive biomarker for stress response in CLD patients, aiding in the nuanced assessment and management of sepsis in this high-risk group. Wang et al. conducted a multicentre study in China and reported a sepsis prevalence of 42.5% in ICU patients, with sepsis and septic shock contributing to high ICU mortality rates (13.1% and 39.0%, respectively). Serum cortisol levels were not significantly different between the groups, but they showed significant correlations with age and total leukocyte count (TLC) in Group A. [14] Similarly, Jeon et al. identified a 1.5% prevalence of sepsis among adult ED visitors in Korea,

with high mortality rates, particularly among those with septic shock. [15] Our study aligns with these findings, highlighting the severe impact of sepsis, especially in patients with additional comorbidities such as CLD.

The studies by Im et al. and Park et al. emphasized the critical importance of timely antibiotic administration in reducing mortality, particularly in septic shock patients. [16,17] Our study did not focus on treatment timelines but identified significant clinical differences between the groups that could influence treatment responses, such as higher INR and lower albumin levels in CLD patients. Balcan et al. and Kassyap et al. highlighted factors such as high APACHE II and SOFA scores, pro-BNP, and CRP levels as predictors of mortality in sepsis patients. [18,19] Our study's findings on the correlations between serum cortisol and clinical parameters in Group A (CLD with severe infection) suggest that cortisol levels could serve as an additional marker for sepsis severity, although further research is needed.

The increased INR and bilirubin levels in CLD patients reflect impaired liver function, which can exacerbate sepsis outcomes due to compromised detoxification and immune responses. [20] The significant correlations between serum cortisol and TLC in Group A suggest a potential interplay between stress response and immune function in these patients. The lack of significant correlations in Group B underscores the unique pathophysiological mechanisms in CLD patients with sepsis. The distinct clinical profiles of sepsis patients with and without CLD underscore the need for tailored treatment strategies. The higher INR and lower albumin levels in CLD patients suggest a need for careful management of coagulation and nutritional support.

Additionally, the correlations between serum cortisol and clinical parameters in CLD patients highlight the potential role of stress response modulation in improving outcomes.

## Conclusion

This study provides valuable insights into the clinical differences and outcomes of sepsis patients with and without CLD. The findings emphasize the need for tailored treatment approaches that consider the unique challenges posed by CLD.

Further research is warranted to explore the mechanisms underlying these differences and to develop targeted interventions to improve sepsis outcomes in this vulnerable patient population.

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