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Original Research Article

SERUM CHOLINESTERASE AS A PROGNOSTIC BIOMARKER IN CHRONIC LIVER DISEASE: A CROSS-SECTIONAL OBSERVATIONAL STUDY FROM EASTERN INDIA

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ABSTRACT

Background: Chronic Liver Disease (CLD) is a progressive and debilitating condition with high morbidity and mortality, particularly in India. Reliable, cost-effective biomarkers are essential to predict prognosis and guide treatment. Serum cholinesterase, synthesized in the liver, may reflect hepatic synthetic function better than conventional liver tests. The objective is to evaluate serum cholinesterase as a prognostic marker in CLD by correlating it with conventional liver function parameters, prognostic scores (Child-Pugh, MELD-Na), duration of hospital stay, and clinical outcomes.

Materials and Methods: This hospital-based cross-sectional study was conducted in the Department of General Medicine, PGIMER & Capital Hospital, Bhubaneswar, from May 2023 to February 2025. A total of 140 CLD patients were enrolled. Serum cholinesterase levels were estimated and correlated with serum albumin, bilirubin, INR, Child-Pugh and MELD-Na scores, duration of hospital stay, and patient outcomes using appropriate statistical methods.

Results: Most participants were male (87.9%) and aged between 41–50 years (49.3%). Alcohol was the leading etiology (82.9%). Serum cholinesterase showed a significant positive correlation with albumin ($p<0.01$) and a negative correlation with bilirubin and INR ($p<0.01$). It was significantly lower in patients with Child-Pugh Class C and higher MELD-Na scores. Patients with lower cholinesterase had significantly longer hospital stays and higher mortality or referral rates ($p<0.001$).

Conclusion: Serum cholinesterase is a promising, inexpensive, and accessible biomarker that correlates well with disease severity and prognosis in CLD. It may serve as a reliable adjunct to traditional scoring systems for early identification of patients at risk of poor outcomes, particularly in resource-limited settings.

Keywords: Chronic Liver Disease, Serum Cholinesterase, Prognostic Marker, Child-Pugh Score, MELD-Na, Liver Function Tests

INTRODUCTION

Chronic liver disease (CLD) refers to the progressive deterioration of hepatic function lasting more than six months, leading to significant morbidity and mortality globally. It involves sustained hepatic inflammation, destruction, and regeneration of liver parenchyma, eventually culminating in fibrosis and cirrhosis, which is characterized by architectural distortion, regenerative nodules, and portal hypertension.[1] India bears a substantial share of this global burden, with an estimated 270,036 deaths and 9.6 million disability-adjusted life years (DALYs)

annually attributed to liver cirrhosis and other chronic liver diseases.[2]

The clinical assessment of CLD severity and prognosis is commonly performed using liver function tests—such as serum bilirubin, serum albumin, and international normalized ratio (INR)—along with prognostic scoring systems like the Child–Turcotte–Pugh (CTP) score and the Model for End-Stage Liver Disease (MELD) score.[3] However, these indicators can be influenced by confounding factors including nutritional status, infections, and systemic inflammation, potentially limiting their prognostic accuracy in certain clinical settings.[3]

Serum cholinesterase (ChE), also known as pseudocholinesterase or butyrylcholinesterase, is a non-specific esterase synthesized almost exclusively by hepatocytes. Unlike other liver enzymes, serum cholinesterase levels have been observed to correlate directly with hepatic synthetic function.[4] Its production significantly decreases in advanced liver disease, suggesting it may serve as a more specific marker of hepatic function.[5] Earlier studies have shown that ChE levels fall in liver damage induced by toxins such as carbon tetrachloride and rise with hepatic recovery.[6,7] Importantly, serum cholinesterase is not influenced by age, sex, diet, or muscle mass, making it a potentially reliable and objective biomarker.[8]

The clinical interest in serum cholinesterase dates back to early 20th-century work by McArdle and others, who identified decreased levels in various liver conditions.[5,6,9] More recent evidence indicates its prognostic value in patients with cirrhosis, as low serum ChE is associated with worse outcomes, higher MELD scores, and longer hospital stays.[10,11] Additionally, improvement in ChE levels has been documented post-liver transplantation, affirming its hepatic origin and relevance in monitoring disease progression and therapeutic response.[12]

Given its simplicity, low cost, and potential utility, serum cholinesterase could serve as an important adjunct to conventional tests in assessing liver function. In resource-limited settings, where access to advanced diagnostics may be restricted, this biomarker could offer practical advantages for routine patient evaluation and monitoring.

Despite its promise, serum cholinesterase remains underutilized in clinical hepatology, especially in the Indian context. There is a need for further clinical evidence validating its diagnostic and prognostic relevance in chronic liver disease. To address this gap, the present study was conducted in a tertiary care hospital in eastern India to evaluate serum cholinesterase levels among patients with CLD and correlate them with traditional biochemical parameters, established scoring systems (Child-Pugh, MELD-Na), duration of hospitalization, and clinical outcomes.

Primary Objectives:

1. To determine the correlation of serum cholinesterase with liver function test parameters such as serum bilirubin, albumin, and INR.
2. To assess its correlation with prognostic scores—Child-Pugh and MELD-Na.
3. To evaluate the relationship between serum cholinesterase and clinical outcomes, including hospital stay duration and patient outcome (discharge, referral, or death).

Secondary Objective:

- To describe the demographic and etiological profile of patients with chronic liver disease in the study setting.

MATERIALS AND METHODS

Study Design and Setting: This was a hospital-based cross-sectional observational study conducted at the Department of General Medicine, PGIMER & Capital Hospital, Bhubaneswar, Odisha, India. The study duration spanned from May 2023 to February 2025.

Sample Size and Sampling: The sample size was estimated using the Raosoft online calculator, assuming a 10.1% prevalence of chronic liver disease (CLD) in the population, with a 5% margin of error and a 95% confidence level. Based on this, a minimum of 140 participants were required and included in the study.

Sample size calculation formula:

$$n = \frac{Z^2 \times p(1-p)}{e^2}$$

where
$Z = 1.96$ (Z-score for 95% CI),
$p = 0.101$ (prevalence),
$e = 0.05$ (margin of error),
resulting in $n \approx 140$.

Inclusion Criteria

- All old and newly diagnosed patients of chronic liver disease attending the outpatient department (OPD) or admitted to the inpatient department (IPD) of General Medicine.

Exclusion Criteria

Patients with the following conditions were excluded:

- Organophosphate or carbamate poisoning
- Exposure to succinylcholine, morphine, or codeine
- Pregnant women and users of oral contraceptives or warfarin
- Chronic malnutrition, nephrotic syndrome, or diabetic kidney disease
- Congenital liver diseases and post-liver transplant cases
- Patients who received blood or albumin transfusions within the previous four weeks

Ethical Considerations

All patients were enrolled after obtaining written informed consent. The study protocol adhered to the Declaration of Helsinki and institutional ethical guidelines.

Data Collection: A pre-designed proforma was used to collect demographic, clinical, and laboratory data. Sources included direct clinical history, physical examination, laboratory and radiological records, and bed-head tickets.

Study Variables

Demographic variables:

- Age, gender, and residential district

Clinical variables:

- History and duration of alcohol use
- Presence of icterus, splenomegaly, ascites, gastrointestinal bleed, hepatic encephalopathy
- Ascites grading (mild/moderate/severe)
- Encephalopathy grading (1–4)
- Dialysis within the past week
- Duration of hospital stay
- Clinical outcome (discharged/referred/deceased)

Laboratory variables:

- Serum cholinesterase (ChE)
- Liver enzymes: SGOT, SGPT, ALP
- Serum bilirubin
- Serum albumin
- Prothrombin time (PT) and INR
- Urea, creatinine, serum sodium
- Viral markers: HBsAg and anti-HCV

Laboratory Methods

Blood Collection: Venous blood (5 ml) was collected aseptically and processed within 2 hours. Serum was separated and analyzed using the VITROS 5600 Autoanalyzer.

Cholinesterase Assay Principle: The kinetic, rate-based enzymatic assay uses butyrylthiocholine iodide as substrate. Hydrolysis by cholinesterase yields thiocholine, which reacts with DTNB to form a colored product measured at 412 nm. The rate of increase in absorbance correlates with cholinesterase activity.

Other Assays:

- SGOT/SGPT were measured via rate-based enzymatic reactions using NADH oxidation.
- Bilirubin was assessed via diazo reaction.
- Albumin was estimated using bromocresol green dye binding.
- INR and PT were determined using citrated plasma on the same analyzer.

Clinical Scoring

Child-Pugh Score and MELD-Na Score were calculated using the online MDCalc tool based on:

- Bilirubin, albumin, INR
- Ascites severity
- Encephalopathy grade
- Serum sodium and creatinine (for MELD-Na)

Radiological Assessment: Ultrasonography was used to assess liver echotexture, presence and grade of ascites, and splenomegaly.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 26.0.

- Descriptive statistics: Frequencies, percentages, means ± SD, medians with interquartile ranges
- Comparison of groups:
  - Mann–Whitney U test (for two groups)
  - Kruskal–Wallis H test (for >2 groups)
- Correlation:
  - Spearman's rho correlation was used to assess association between cholinesterase and other continuous variables
- Graphical tools:
  - Box-and-whisker plots for group comparisons
  - Scatter plots for correlation
  - Bar and pie charts for visualizing categorical data

A p-value <0.05 was considered statistically significant.

RESULTS

Study Population Characteristics: A total of 140 patients with chronic liver disease (CLD) were included in the study. The mean age was 45.6 ± 8.7 years. The majority (49.3%) belonged to the 41–50 year age group, followed by 30% in the 31–40 year range. A substantial male predominance was observed, with 123 males (87.9%) and 17 females (12.1%).

Alcohol was the most common etiology, accounting for 82.9% (116/140) of cases, either alone or in combination with viral hepatitis. Hepatitis B alone accounted for 10% of cases, while hepatitis B and C co-infection with alcohol was noted in 8.6%.

Geographical and Clinical Profile: Most patients were from Khordha (29.3%), followed by Nayagarh (23.6%), and Puri (17.1%) districts in Odisha. Clinical manifestations included ascites in 92.1%, splenomegaly in 35%, icterus in 31.4%, and gastrointestinal bleeding in 20%. Hepatic encephalopathy was observed in 8.6% of patients, with most presenting in grade III.

Table 1: Demographic, Etiological, and Clinical Characteristics of CLD Patients (N = 140).

Characteristic	Category	Frequency (%)
Age Group (years)	31–40 / 41–50 / 51–60 / >60	30 / 49.3 / 14.3 / 6.4
Gender	Male / Female	87.9 / 12.1
Geographic Origin	Khordha / Nayagarh / Puri / Others	29.3 / 23.6 / 17.1
Etiology	Alcohol / Non-alcohol / HBV / HCV	82.9 / 17.1 / 10.0 / 2.9
Alcohol Use Duration	≤10 years / >10 years	11 / 89
Clinical Signs	Ascites / Icterus / Splenomegaly / GI Bleed	92.1 / 31.4 / 35.0 / 20.0
Hepatic Encephalopathy	Present (Grade I–III) / Absent	8.6 / 91.4

Liver Function and Prognostic Markers

Laboratory data revealed significant impairment in synthetic and excretory liver function:

- Serum bilirubin >3 mg/dL was present in 45% of patients.
- Serum albumin <2.8 g/dL in 58.6% of patients.
- INR >2.3 was noted in 28.6% of cases.

According to Child-Pugh classification, 67.9% were in class C and 32.1% in class B. No patients were in class A. Based on MELD-Na scores, 35.7% scored 20–29, and 31.4% had scores between 30–39, indicating severe disease.

Table 2: Liver Function Parameters and Prognostic Scores.

Parameter	Category	Frequency (%)
Total Bilirubin (mg/dL)	<2 / 2–3 / >3	16.4 / 38.6 / 45.0
Serum Albumin (g/dL)	<2.8 / 2.8–3.5 / >3.5	58.6 / 36.4 / 5.0
INR	<1.7 / 1.7–2.3 / >2.3	32.9 / 38.6 / 28.6
Child-Pugh Class	B / C	32.1 / 67.9
MELD-Na Score	<10 / 10–19 / 20–29 / 30–39	6.4 / 26.5 / 35.7 / 31.4

Serum Cholinesterase Correlation with Prognostic Indicators

Serum cholinesterase showed strong correlations with liver function and disease severity.

- Positive correlation with serum albumin (r = 0.566, p<0.001)
- Negative correlation with:
  - Total bilirubin (r = -0.379, p<0.001)
  - INR (r = -0.760, p<0.001)
  - Child-Pugh Class (r = -0.815, p<0.001)
  - MELD-Na Score (r = -0.801, p<0.001)

Patients with higher MELD-Na and Child-Pugh scores had significantly lower cholinesterase levels. Additionally, lower cholinesterase levels were associated with:

- Longer hospital stay (>3 days; p=0.001)
- Poorer outcomes (death or referral; p<0.001)

Table 3: Correlation of Serum Cholinesterase with Clinical Outcomes

Variable	Cholinesterase (Median, IU/mL)	Correlation (r)	p-value
Serum Albumin	2.20 – 6.68	+0.566	<0.001
Serum Bilirubin	6.48 → 1.93 (as bilirubin ↑)	-0.379	<0.001
INR	6.14 → 1.33 (as INR ↑)	-0.760	<0.001
Child-Pugh B → C	6.48 → 2.65	-0.815	<0.001
MELD-Na (<10 → 30–39)	8.79 → 1.85	-0.801	<0.001
Hospital Stay (≤3 vs >3 days)	3.89 vs 2.12	—	0.001
Outcome (Discharge vs Death)	3.8 vs 1.67	—	<0.001

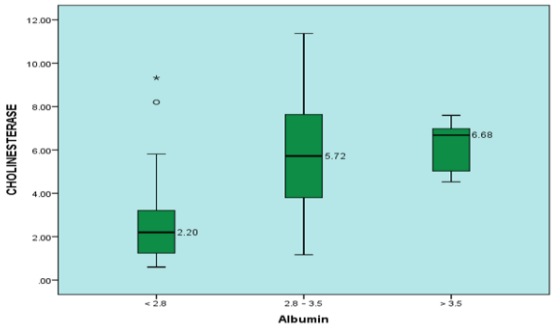

Figure 1: Box and Whisker Plot – Serum Albumin vs Cholinesterase

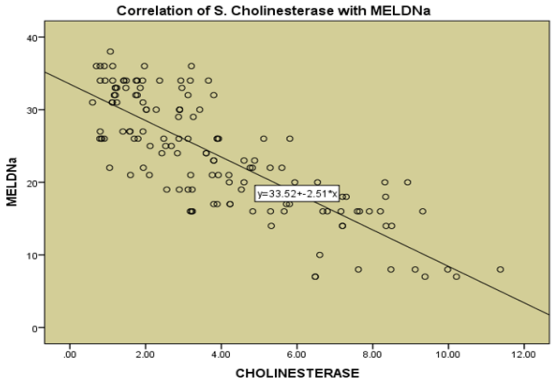

Figure 2. Scatter Plot – MELD-Na Score vs Serum Cholinesterase

DISCUSSION

This study evaluated the prognostic utility of serum cholinesterase (ChE) in patients with chronic liver disease (CLD) and found that lower ChE levels were significantly associated with markers of hepatic dysfunction and poor clinical outcomes. Specifically, ChE showed strong correlations with serum albumin, bilirubin, INR, Child-Pugh class, MELD-Na score, duration of hospital stay, and discharge status.

Demographic and Clinical Profile

The study population was predominantly male (87.9%), with the majority aged between 41 and 50 years. This aligns with earlier Indian studies that found middle-aged males to be disproportionately affected by CLD, largely due to higher rates of alcohol consumption.[13] Alcohol was the leading etiology in our cohort (82.9%), similar to findings by Jagdeesh et al. and other regional reports where alcohol-related liver injury remains the principal driver of cirrhosis in India.[13,14]

The high proportion of patients presenting with ascites (92.1%) and hepatic encephalopathy (8.6%) reflects the predominance of decompensated liver disease in our cohort. Most cases were classified as Child-Pugh class C and MELD-Na ≥20, indicating advanced disease and poor prognosis.

Serum Cholinesterase as a Prognostic Marker: Our study found a strong positive correlation between serum albumin and serum cholinesterase ($r = 0.566$, $p<0.001$). This is consistent with findings by Ramachandran et al., who reported a similar correlation ($r = 0.67$, $p<0.01$) in patients with cirrhosis.[15] Albumin is a well-established marker of hepatic synthetic function, and ChE—also synthesized in hepatocytes—mirrors its decline in liver disease.[16]

We also observed a significant inverse correlation between ChE and serum bilirubin ($r = -0.379$, $p<0.001$), which mirrors results from earlier studies showing that ChE levels decrease with worsening hepatic excretory function.[15] Similarly, INR, a marker of coagulation capacity, was strongly inversely correlated with ChE ($r = -0.760$, $p<0.001$). These findings further reinforce the idea that ChE reflects hepatic synthetic function and liver reserve.

Serum ChE levels declined markedly across worsening Child-Pugh classes and increasing MELD-Na scores, with strong inverse correlations ($r = -0.815$ and -0.801, respectively; both $p<0.001$). This supports the utility of ChE in disease severity stratification. Similar trends have been reported in studies by Gu et al. and Meng et al., where cholinesterase levels dropped progressively across Child-Pugh A to C categories.[17,18] Ramachandran et al. also demonstrated that a ChE cut-off of 1484 IU/L predicted a high MELD status with 71% sensitivity and 73% specificity.[15]

Association with Hospital Stay and Clinical Outcome: Importantly, patients with longer hospital stays (>3 days) and those who died or required referral had significantly lower ChE levels. This underscores the prognostic value of ChE beyond traditional laboratory markers. Similar associations were reported by Sujatha et al., who found that lower ChE levels were linked with increased hospitalization duration due to advanced liver decompensation.[19] Temel et al. also highlighted the role of ChE in predicting mortality and complications in liver disease.[20]

The significant associations between ChE and both clinical severity and outcomes suggest it could be integrated into existing prognostic models. Given its ease of estimation and low cost, serum ChE may serve as a useful marker in resource-limited settings to triage and monitor patients with CLD.

Comparison with Traditional Biomarkers

While biomarkers like bilirubin and INR are influenced by hemolysis, vitamin K levels, or infections, ChE appears more stable. Cholinesterase synthesis decreases earlier in hepatic dysfunction than albumin due to its shorter half-life (~12 days).[21] This makes it a sensitive indicator, especially when evaluating recovery or subclinical deterioration.

Moreover, unlike ALT, AST, and ALP, which reflect hepatocellular injury, ChE levels provide insight into synthetic functional reserve. This distinction is particularly valuable in cirrhosis, where enzyme levels may be normal or misleading despite advanced disease.

Strengths and Limitations: Strengths of this study include a well-defined cohort, use of standardized measurement techniques, and comprehensive correlation with multiple clinical parameters. This is one of the few Indian studies to evaluate ChE alongside MELD-Na and detailed patient outcomes.

However, the study has limitations. The cross-sectional design limits its ability to evaluate the longitudinal prognostic value of ChE. Additionally, external factors such as renal dysfunction or nutritional status—though excluded to some extent by criteria—may still affect ChE levels. The single-center design may limit generalizability.

Future Directions: Future research should focus on longitudinal validation of serum ChE in larger and diverse populations. Establishing ChE-based cut-off points for clinical decision-making could further enhance its utility. Moreover, integration of ChE into composite prognostic scores (e.g., MELD-ChE) may improve risk prediction and guide transplant referrals.

CONCLUSION

In summary, this study confirms that serum cholinesterase is a reliable, cost-effective biomarker that correlates strongly with liver function, disease severity, and clinical outcomes in chronic liver disease. It offers valuable prognostic insights and may complement existing tools in both high- and low-resource settings.

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