



## Original Research Article

# ASSESSMENT OF NUTRITIONAL STATUS OF LIVER CIRRHOTIC PATIENTS BY VISCERAL PROTEINS (ALBUMIN, PREALBUMIN AND TRANSFERRIN) AND THEIR CORRELATION WITH SEVERITY OF THE DISEASE

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Received : 06/01/2025  
Received in revised form : 02/03/2025  
Accepted : 18/03/2025

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DOI: 10.70034/ijmedph.2025.1.313

Source of Support: Nil,  
Conflict of Interest: None declared

**Int J Med Pub Health**  
2025; 15 (1); 1669-1675

### ABSTRACT

The objective of the study was to evaluate the nutritional status of liver cirrhosis patients by the Visceral Proteins (Albumin, Prealbumin and Transferrin) as assessment method of the nutritional status, and their correlation with severity of Liver cirrhosis according to Child Pugh classification. One hundred fifty cirrhotic subjects of either sex ranging in age from 20–70 years were included in the study, and the results were compared with 50 age- and sex-matched healthy control subjects. All cirrhotic subjects were assessed for severity of disease as mild (Child A), moderate (Child B), and severe (Child C) as per Child-Pugh classification. Visceral Proteins (Albumin, Prealbumin and Transferrin) were used for assessment of Nutritional Status, measured in all the subjects. Serum Albumin, Prealbumin and Transferrin were significantly decreased in Cirrhotic Subjects as compared to the healthy Controls. Enrolled 150 Cirrhotic patients were further segregated into three groups Child A, B & C according to the severity of their liver disease as assessed by the Child-Pugh classification. The concentration of Serum Albumin, Prealbumin and Transferrin were decreased with advancement of liver disease and the difference among Child Pugh groups was statistically significant. When further Child Pugh groups were compared a statistically significant difference was found within the groups (Child A-B, A-C and B-C) for Albumin, Prealbumin and Transferrin. There was significant negative correlation between Albumin, Prealbumin, and Transferrin with Child –Pugh Score. Among the various Visceral Proteins (Albumin, Prealbumin, Transferrin) used for nutritional assessment, the prevalence of malnutrition assessed in cirrhotic patients was highest with prealbumin. Hence prealbumin is a better tool for assessment of nutritional status in cirrhotic patient. Evaluation of the nutritional status of these patients should be a part of the routine outpatient clinic checkup, regardless of the etiology of the disease, so that appropriate nutritional intervention can be done to prevent progression of the disease process. However, one single parameter does not serve as the only and best parameter to diagnose malnourished patients or patients with risk for malnutrition.

**Keywords:** Chronic Liver Disease, Protein calorie malnutrition, Child Pugh Turcotte Score, Prealbumin, Transferrin

## INTRODUCTION

Chronic liver disease occurs throughout the world irrespective of age, sex, region or race. Chronic liver disease involves a process of continuous inflammation and regeneration that eventually result in permanent fibrosis and cirrhosis. Although it is difficult to assess, experts estimate that over 844 million people world-wide have Chronic liver disease and this with mortality rate of approximately 2 million death per year. Of those affected by chronic liver disease, approximately 20% with compensated cirrhosis and 65-95 % with decompensated cirrhosis have protein calorie malnutrition.<sup>[1]</sup> Malnutrition in chronic liver disease (CLD) arises from a combination of factors, including impaired absorption and/or digestion, increased metabolic demands, anorexia, and reduced oral intake. The long-term functional impairments caused by cirrhosis lead to nutritional deficiencies with widespread effects on the body. These deficiencies, along with the various mechanisms through which they manifest, make management and support increasingly complicated.<sup>[2,3]</sup> Patients with CLD often experience significant malnutrition, which not only reflects the severity of the disease and its prognosis but also serves as an independent predictor of mortality.<sup>[4]</sup> Cirrhotic patient with associated malnutrition have higher rate of hepatic encephalopathy, infections, ascites and variceal bleeding.<sup>[5]</sup> Multiple studies have documented increase complication and overall length of hospital stay in malnourished patients.<sup>[6]</sup> The diagnosis of the nutritional status and the treatment of malnutrition in Cirrhotic patients can contribute to reduction in the frequency and/or severity of these Complications.<sup>[7]</sup> As Nutritional Status correlates with outcome of patients with liver disease hence, it is important to accurately assess nutritional status and provide timely nutritional support. This task is challenging, due to the complications of altered rates of protein metabolism and presence of ascites and edema. Nutritional assessment is the first step in the treatment of malnutrition. Specific data are obtained to create a metabolic and nutritional profile of the patient. The goals of Nutritional assessment are identification of patients who have, or are at risk of developing malnutrition; to quantify a patient's degree of malnutrition; and to monitor the adequacy of nutrition therapy. Nutritional assessments using anthropometric, visceral, and immunologic measurements were performed to determine the prevalence, characteristics, and clinical importance of nutrition disorders in patients with liver cirrhosis.<sup>[8]</sup> Visceral protein levels are used as indicators of prognosis, severity of injury, and nutritional status in hospitalized patients. Hepatic protein is a term commonly used to refer to Albumin, Prealbumin (transthyretin) and Transferrin. These are three among a much larger group of proteins that are synthesized in the liver.

Despite published evidence, review articles, and editorials that serum levels of these proteins are affected more significantly by factors other than nutritional intake, hepatic proteins continue to be used to evaluate nutritional status, including the presence of malnutrition. Serum hepatic protein status can help identify patients who are likely to become malnourished even if they are adequately nourished at the point of hospital admission. This has been referred to as the “inextricable relationship between nutritional status and severity of illness”.<sup>[9]</sup> When properly evaluated, serum hepatic protein levels assist the clinician in identifying patients who are the most morbid and, thus, those at risk for developing serious nutritional deficits. A patient with a decreased Albumin, Prealbumin and Transferrin level is less likely to meet energy and nutrient requirements voluntarily and therefore will probably require aggressive medical nutrition therapies. Such patients are also likely to be clinically unstable and therefore require frequent monitoring for adjustments in nutritional interventions.<sup>[10]</sup> Evaluation of nutritional status in liver cirrhosis patient is aimed to know the patient's risk factor, to know the effects of this disease development on nutritional status and to monitor therapeutic recovery and for nutritional intervention. Until now, there is no consensus that has been agreed to evaluate the nutritional status of patient with chronic liver disease. Given the prognostic further insight into the assessment and therapy of these patient is essential to appropriate management.

## MATERIALS AND METHODS

The present cross-sectional hospital-based study was conducted in the Department of Biochemistry, in association with Department of Gastroenterology SMS Medical College & attached Hospitals, Jaipur, Rajasthan, India.

### Subject Selection

One hundred fifty cirrhotic subjects of either sex attending Outpatient Department (OPD) or admitted in wards of the Department of Gastroenterology SMS Medical College & attached Hospitals, Jaipur, Rajasthan, ranging in age from 20– 70 years (mean  $\pm$  SD 43.04 $\pm$ 8.51 years) were included in the study. Patients with hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, upper gastrointestinal bleeding, hepatocellular carcinoma, and sepsis (need hospitalization) and patient on albumin and diuretic and malabsorption were excluded from the study. The results were compared with 50 age- (mean  $\pm$  SD 43.14 $\pm$ 9.3 years) and sex matched healthy control subjects, and it was ensured by routine examination that all the subjects were in good health and there were no signs and symptoms or no positive history of cirrhosis and had no evidence of malnutrition and comorbid condition that lead to micronutrient malnutrition. Local institutional ethics committee approval was sought

before commencement of the study. Informed written consent was obtained from all recruited subjects prior to participation.

### Clinical Criteria for Diagnosis

Thorough clinical and symptomatic examination of all the patients was done under the guidance of the treating gastroenterologist. Cirrhosis was diagnosed on the basis of combination of clinical features, blood profile, and radiological imaging. Clinical features were those of portal hypertension, i.e., ascites and/or gastrointestinal varices. Blood profile included evidence of thrombocytopenia and/or

coagulopathy. Radiological features, either with trans-abdominal ultrasound or computerized tomography, had to demonstrate a small shrunken liver with or without splenomegaly and intra-abdominal varices.<sup>[11,12]</sup> To assess severity of disease, cirrhotic subjects (n= 150) were further segregated according to Child-Pugh classification: Child A, mild; Child B, moderate; and Child C, severe, indicating degree of hepatic reserve and function. Child-Pugh-Turcotte (CPT) classification.<sup>[13,14]</sup>

Points	1	2	3
Encephalopathy	Absent	Medically controlled	Poorly controlled
Ascites	Absent	Controlled medically	Poorly controlled
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	<3.5	2.8-3.5	<2.8
PT/INR	<1.7	1.7-2.2	>2.2

Interpretation: class A: 5–6 points, class B: 7–9 points, class C: 10–15 points

Fasting blood sample was drawn of each subject in plain, EDTA, and PT vials and following investigations were done: serum glucose, urea, creatinine, AST, ALT, ALP, bilirubin, total protein, albumin, A/G ratio, cholesterol, triglyceride on fully automated analyser Randox Imola. Prealbumin (Transthyretin) by Quantitative immunoturbidimetric method and Transferrin by Immunoturbidimetric end-point Method. CBC was performed on Five Part XT 1800 I Sysmex and PT/INR was assessed on semi autoanalyzer (Coagulation Analyzer SPR 123).

### Statistical Analysis

All data were recorded in a database system on a personal computer, and statistical analysis were performed by using SPSS (STATA 12.0 statistical software). All data were expressed as mean  $\pm$ SD. Unpaired student t Test was used for comparison of Cirrhotic patients with healthy Controls. Comparison of parameters among the three groups (patients with Child's class A, B, or C liver disease) were performed using one-way analysis of variance (ANOVA). In order to know the correlation between Visceral Proteins with Child-Pugh classification (Child Score), Pearman correlation test was used. We used the Pearson correlation test to know determine the correlation between within the parameters.  $P < 0.05$  was considered significant.

## RESULTS

150 diagnosed patients of Cirrhosis were compared with 50 healthy Control subjects. Among 50 healthy Control subjects 64% were male and 36% were female and among 150 Cirrhotic patients 66% were Male, 34% were female with male & female ratio was 1.9:1. When the cases were compared on the basis of age, in the Control group the mean age was  $43.14 \pm 9.37$  years, while in Cirrhotics the mean age was  $44.04 \pm 8.57$  years. (Table 1,2 &3).

In our study Visceral Proteins (Albumin, Prealbumin and Transferrin) were used for assessment of nutritional status. Serum Albumin, Prealbumin and Transferrin were statistically highly significantly decreased in Cirrhotic Subjects as Compared to the healthy Controls [Mean  $\pm$  SD of Visceral Proteins in Cirrhotic v/s Control; Albumin ( $2.91 \pm 0.66$  v/s  $4.22 \pm 0.45$  g/dl,  $p < 0.001$ ), Prealbumin ( $11.55 \pm 5.88$  v/s  $28.77 \pm 5.53$  mg/dl,  $p < 0.001$ ), Transferrin ( $154.99 \pm 55.19$  v/s  $266.86 \pm 32.81$  mg/dl,  $p < 0.001$ )] (Table 4).

Further enrolled 150 Cirrhotic patients were segregated into three groups Child A, B & C according to the severity of their liver disease as assessed by the Child-Pugh classification. According to Child Pugh Score out of 150 Cirrhotic patients 51 (34%) belonged to Child A, 50 (33.3%) to Child B and 49 (32.7%) in Child C, category (Table 5). Gender wise distribution of Cirrhotic Subjects in Child Pugh Classes, 62.7% male and 37.3% females were in Child A, 66% male and 34 % female in Child B and in Child C 69.4% male and 30.6% were female (Table 6).

Further Visceral Proteins: Serum Albumin, Prealbumin and Transferrin were compared with severity of Liver cirrhosis. The concentration of Serum Albumin, Prealbumin and Transferrin were decreased with advancement of liver disease and the mean difference among Child Pugh groups was statistically significant ( $p < 0.001$ ) (Table 7). When further Child Pugh groups were compared by Tukey's test a statistically significant ( $p < 0.001$ ) mean difference was found within the groups (Child A-B, A-C and B-C) for Albumin, Prealbumin and Transferrin. (Table 8).

There was significant negative correlation between Albumin ( $r = -0.86$ ;  $p < 0.001$ ), Prealbumin ( $r = -0.83$ ;  $p < 0.001$ ), and Transferrin ( $r = -0.82$ ;  $p < 0.001$ ) with Child –Pugh Score. Although Albumin had significant positive correlation with Prealbumin ( $r = 0.45$ ;  $p < 0.001$ ) and

Transferrin (r=0.48; p<0.001). Prealbumin also had significant positive correlation (r=0.46; p<0.001)

with Transferrin (Table 9, 10 & Figure 1-3).

**Table 1: Distribution of Subjects**

Groups Studied	Number of Subjects
Healthy Controls	50
Cirrhotic Patients	150
Total subjects	200

**Table 2: Distribution of Subjects according to Gender (n=200)**

Groups Studied	Gender of subjects	
	Male n (%)	Female n (%)
Healthy Control (50)	32 (64%)	18 (36%)
Cirrhotic subject (150)	99 (66%)	51 (34%)

**Table 3: Distribution of Subjects according to age (n=200)**

Groups	Age (years) Mean ± SD
Healthy Control (50)	43.14±9.37
Cirrhotic subject (150)	44.04 ± 8.57

**Table 4: Comparison of Visceral Proteins in Controls and Cirrhotic subjects (n=200)**

Parameters	Controls (n=50)	Cirrhotics (n=150)	Unpaired Student t Test	P value
	Mean ± SD (Range)	Mean± SD (Range)		
Albumin (g/dl)	4.22±0.45 (3.5-5.1)	2.91±0.66 (1.5-3.9)	13.049	<0.001***
Prealbumin (mg/dl)	28.77±5.53 (22.42-39.67)	11.55±5.88 (2.44-23.9)	18.195	<0.001***
Transferrin (mg/dl)	266.86±32.81 (214.87-338.76)	154.99±55.19 (52.74-258-45)	13.543	<0.001***

Comparison was done using unpaired student t test) \*(p < 0.05) significant,

\*\* (P < 0.01) very significant, \*\*\* (P<0.001) indicates that groups are responsible for variance in the measured variable and is highly significant & Rest are not significant (p>0.05).

**Table 5: Distribution of Cirrhotic Subjects on the basis of Child-Pugh Score for Severity of Liver Cirrhosis (n =150)**

Cirrhotic Subjects	No: of Subjects
Child-A	51 (34.0%)
Child-B	50 (33.3%)
Child-C	49 (32.7%)

**Table 6: Gender wise distribution of Cirrhotic Subjects (n=150) on the basis of Child Pugh Score**

Child-Pugh Score	No: of Subjects	Gender of subjects	
		Male n (%)	Female n (%)
Child –A	51 (34.0%)	32 (62.7%)	19 (37.3%)
Child-B	50 (33.3%)	33 (66%)	17 (34%)
Child-C	49 (32.7%)	34 (69.4%)	15 (30.6%)

**Table 7: Comparison of Visceral Proteins according to Child Pugh Score for Severity of Disease by (Analysis of variance (ANOVA) of parameters of Child-A, Child-B and Child-C (n=150)**

Parameters	Child-A (n=51)	Child – B (n=50)	Child-C (n=49)	ANOVA	
	Mean±SD (Range)	Mean±SD (Range)	Mean±SD (Range)	F	P (value)
Albumin (g/dl)	3.50±0.26 (3.0-3.9)	3.05±0.46 (1.9-3.6)	2.19±0.37 (1.5-2.8)	159.709	<0.001***
Prealbumin (mg/dl)	17.39±4.13 (9.76-23.9)	10.76±4.39 (4.46-19.93)	6.54±2.74 (2.44-11.89)	102.362	<0.001***
Transferrin (mg/dl)	205.88±31.33 (146.56-258.45)	154.25±45.06 (81.31-227.67)	104.86±32.30 (52.74-204.43)	94.384	<0.001***

Comparison was done using ANOVA (Analysis of variance test) \*(p < 0.05) significant, \*\* (P < 0.01) very significant, \*\*\* (P<0.001) indicates that groups are responsible for variance in the measured variable and is highly significant & Rest are not significant (p>0.05).



**Table 8: Post-Hoc Analysis Tukey's test (n=150)**

Parameters	Groups		
	Child A-Child B (P value)	Child A-Child C (P value)	Child B-Child C (P value)
Albumin	<0.01**	<0.001***	<0.001***
Prealbumin	<0.001***	<0.001***	<0.001***
Transferrin	<0.001***	<0.001***	<0.001***

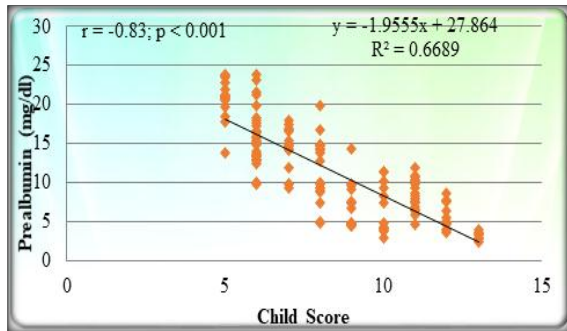
Comparison was done using Tukey's test with in the groups \*(p < 0.05) significant, \*\* (P < 0.01) very significant, \*\*\* (P<0.001) indicates that groups are responsible for variance in the measured variable and is highly significant & Rest not significant (p>0.05).

**Table 9: Assessment of Nutritional Status of Cirrhotic Subjects on the basis of Various Tools of Nutritional Assessment (n=150)**

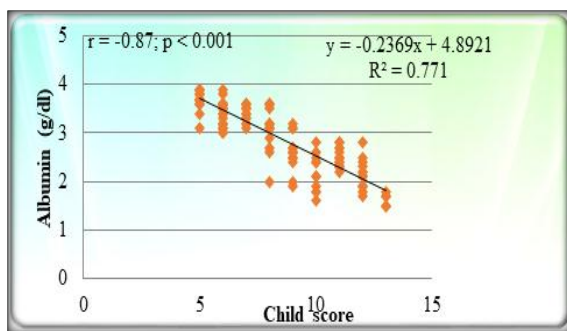
Nutritional Parameters	Nutritional Status	
	Normal n(%)	Malnourished n(%)
Albumin	56 (37.4)	94 (62.6)
Prealbumin	41(27.3)	109 (72.7)
Transferrin	50(33.3)	100 (66.7)

**Table 10: Spearman Correlation (r) of Nutritional Markers with Child Pugh Score**

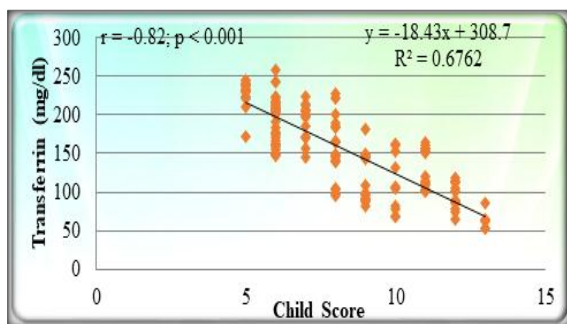
Parameters	R	P value
Albumin	-0.869	<0.001***
Prealbumin	-0.833	<0.001***
Transferrin	-0.822	<0.001***



**Figure 1:**



**Figure 2:**



**Figure 3:**

## DISCUSSION

Cirrhosis of the liver is a growing health problem in India and death from this condition is increasing rapidly among both men and women. Nutritional deficiency is common in patients with end stage liver disease (cirrhosis) and is often associated with a poor prognosis. Malnutrition is a well-known complication in patients with liver cirrhosis, and its presence has important prognostic implications because it is an independent predictor of mortality and is associated with decompensation, complications (ascites, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome) and a poor quality of life.<sup>[1,15]</sup>

The aim of the study was to evaluate the nutritional status of liver cirrhosis patients by the Visceral Proteins (Albumin, Prealbumin and Transferrin) as assessment method of the nutritional status. and their correlation with severity of Liver cirrhosis according to Child Pugh classification.

Yovita H et al,<sup>[16]</sup> & Roongpisuthipong C et al,<sup>[17]</sup> had similar observation that the decreasing levels of Albumin, Prealbumin and Transferrin correlated with different stages of Cirrhosis. Singh N et al,<sup>[7]</sup> observed that Serum protein and visceral protein levels significantly differed between Child-Pugh B and C liver disease. However visceral protein and protein reflects the function of liver, can be affected by the stage of liver disease. Decreasing levels of visceral proteins in grade C patients indicates the low synthesis capacity of the liver with the increasing disease severity. The most often analysed visceral proteins are serum albumin, transferrin, and prealbumin.<sup>[18]</sup> A number of studies have investigated associations between nutritional status and serum hepatic protein levels. Most of the

literature was published prior to the current understanding of the physiology of inflammation. As such, none of the studies addressed the relationship between inflammation and hepatic protein status. Investigators did not measure inflammation, thus missing the most important variable impacting hepatic protein metabolism. Studies in children and adult indicate that the serum albumin level remains essentially unchanged by virtue of decreased turnover (reduced synthesis and catabolism) during protein and energy deprivation. The same is probably true for other hepatically synthesized proteins. Therefore, serum hepatic protein levels are not directly linked to nutritional deprivation. However, there is an indirect relationship with nutritional status that is important for clinicians to appreciate. Inflammation contributes to an increase in net protein loss caused by catabolism. Inflammation also induces anorexia, reducing the probability that a patient will consume adequate nutrients for even normal metabolic requirements. Albumin, Transferrin, and Prealbumin can be viewed as indicators of inflammatory processes that will accelerate nutritional depletion. This is not to say that nutritional interventions will correct aberrations of serum hepatic proteins and the signs and symptoms of severe illness.<sup>[19]</sup>

Serum Albumin is of virtually some value in assessment or monitoring of nutritional status but is mentioned here because, surprisingly, there still remain some clinicians who use it as part of their nutritional assessment. The main factor affecting plasma albumin concentration in patients is the rate of transcapillary escape into the interstitial fluid. This transcapillary escape of albumin is markedly increased in disease as part of the systemic inflammatory response syndrome (SIRS), leading to decreased plasma albumin concentrations. It is inevitable that postoperative patients and patients with severe infection will have low plasma albumin concentrations. The more severe the disease, the lower the albumin, and therefore the lower the albumin, the worse the prognosis.<sup>[20]</sup> However, the use of albumin, a visceral protein synthesized by the liver, in these equations is questionable since visceral proteins appear to correlate better with the severity of underlying liver disease rather than with malnutrition status. Albumin levels have been used as a determinant of nutritional status, but they are relatively insensitive to changes in nutrition. Albumin has a relatively large body pool and a half-life of 20 days. Serum albumin concentrations are affected by the patient's state of hydration and renal function.<sup>[21]</sup> Serum prealbumin, another measurable nutritional indicator, is also able to reflect nutritional status objectively. As a precursor for synthesizing albumin, prealbumin is barely influenced by external supplementation.<sup>[22]</sup> With a shorter half-life than serum albumin, serum prealbumin is a precise marker to evaluate the severity of liver disease. Numerous studies have incorporated prealbumin into preoperative

nutritional assessments and have used it for surgical risk stratification.<sup>[23]</sup> As for hepatopancreatobiliary disease, preoperative prealbumin plays a crucial role in predicting postoperative complications, such as for patient undergoing pancreaticoduodenectomy or hepatectomy.<sup>[24,25]</sup> Moreover, preoperative prealbumin combined with disease severity has been reported yield better prediction in patient with liver cirrhosis.<sup>[26]</sup> Devoto et al,<sup>[27]</sup> found that prealbumin levels correlated well with detailed Nutritional Assessment (DNA) tool, which was used as a reference standard for detecting PCM. They concluded that prealbumin is a good screening tool for protein malnutrition. Furthermore, low prealbumin levels as Nutritional Marker have been shown to correlate with higher rates of complications and mortality.

Transferrin (half-life: 8–10 days; <0.1 g/kg body weight) has been identified as markers of nutrition status. However, because Transferrin is involved with iron transport, its levels are influenced by iron status. Tissue distribution the liver is the main site of transferrin synthesis, but other tissues and organs, such as the brain, also produce it. The main role of transferrin is to deliver iron from absorption centres in the duodenum and white blood cell macrophages to all tissues. Transferrin plays a key role where erythropoiesis and active cell division occur.<sup>[28]</sup> The receptor helps maintain iron homeostasis in the cells by controlling iron concentrations. Transthyretin and retinol-binding protein levels seem to be the most sensitive to nutritional intervention. They are also the earliest to rise at the decrease of acute-phase protein levels, therefore representing a good index of the reversing reprioritization of hepatic protein synthesis. An inconsistent relationship was found between visceral protein plasma levels and clinical outcome in intensive care unit patients, probably because of the difficulty in demonstrating clearly a beneficial effect of nutritional supplementation in highly catabolic conditions.<sup>[29]</sup>

## CONCLUSION

The results demonstrate that cirrhotic patients experience significant nutritional deficiencies and these deficiencies worsen as liver function deteriorates, as reflected by the Child-Pugh score. This emphasizes the importance of closely monitoring the nutritional status of cirrhotic patients, as nutritional markers are strongly linked to the severity of liver disease. Prealbumin, due to its higher sensitivity to acute changes in nutritional status compared to albumin and transferrin, proves to be a vital tool for the early detection of malnutrition in these patients. The findings suggest that regular monitoring of prealbumin levels is crucial for timely nutritional interventions, which could potentially enhance outcomes and improve the quality of life for this at-risk population. Including prealbumin assessment in routine nutritional

evaluations could be essential in managing cirrhosis effectively. Furthermore, evaluating the nutritional status of cirrhotic patients should be part of regular outpatient check-ups, irrespective of the underlying cause of the disease, to ensure appropriate nutritional interventions are implemented and disease progression is mitigated.

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