REVIEW ARTICLE

Journal of MedVerse Research & Practice
ISSN: 3107-4278

Nutritional Deficiencies in Hepatorenal Syndrome Secondary to Liver Cirrhosis

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Submission Date: 23.07.2025	Accepted Date: 20.08.2025	Published Date: 31.08.2025

Abstract

Malnutrition represents a frequent and clinically significant complication in patients with liver cirrhosis, and its impact becomes more profound when hepatorenal syndrome develops. This narrative review aims to examine the intricate association between nutritional deficiencies, cirrhosis, and hepatorenal syndrome, emphasizing contributing mechanisms, clinical consequences, and implications for patient care. Evidence indicates that malnutrition is highly prevalent in cirrhotic individuals, especially in those progressing to hepatorenal syndrome. Distinct features include sarcopenia, protein-energy wasting, and deficiencies of essential micronutrients. These alterations compromise immune competence, increase vulnerability to infections, and negatively influence hepatic and renal function. Furthermore, systemic inflammation associated with cirrhosis and renal dysfunction accelerates catabolic activity, thereby aggravating malnutrition. Such nutritional impairments are closely linked with reduced tolerance to therapeutic interventions, heightened complication rates, and increased mortality. Although targeted nutritional interventions in hepatorenal syndrome remain challenging, early recognition and proactive management of malnutrition are vital to optimize outcomes. Integrating nutritional support into standard care may improve survival and quality of life in this high-risk population.

Keywords: Liver cirrhosis, Hepatorenal syndrome, Malnutrition, Sarcopenia, Nutritional support, Micronutrient deficiency, Patient outcomes

Introduction

Cirrhosis is not only associated with progressive hepatic dysfunction but also with profound nutritional disturbances that negatively influence overall prognosis. One of the most serious complications in this setting is hepatorenal syndrome (HRS), a unique form of renal impairment that develops in patients with advanced liver disease and is strongly linked to increased morbidity and mortality [1]. The reported incidence of HRS among cirrhotic patients varies widely, ranging between 0.7% and 17.5%, with an estimated prevalence of 7% to 45% in different populations [2,3]. HRS is more frequently observed in men than in women and is particularly common in individuals with advanced stages of cirrhosis [4]. Its occurrence is often associated with ascites and is notably higher in hospitalized patients, especially those admitted to intensive or critical care units [5]. The underlying pathogenesis of HRS is multifactorial and not yet fully understood. It is generally attributed to a complex interplay of hepatocellular dysfunction, systemic and intrahepatic inflammation, portal hypertension, and alterations in neurohormonal systems such as the renin–angiotensin–aldosterone axis [6,7]. Clinically, HRS is classified into two forms: Type 1 HRS, which is acute, severe, and rapidly progressive, and Type 2 HRS, which presents more gradually with a chronic course.

Diagnosis of HRS is based on characteristic clinical and biochemical criteria. These include the presence of ascites, a serum creatinine concentration exceeding 2 mg/dL, and the absence of alternative causes of acute kidney injury [8]. Laboratory features often supporting the diagnosis are elevated serum bilirubin (> 2 mg/dL), persistently high serum creatinine (> 2 mg/dL), and very low urinary sodium concentrations (< 10 mmol/L) [9,10]. Importantly, diagnosis requires the careful exclusion of other etiologies of renal impairment while confirming these specific markers.

Risk factors predisposing to HRS include advanced age, bacterial infections, and the presence of refractory ascites. The prognosis of HRS remains extremely poor, with mortality rates approaching 80% in untreated cases. Among fatal outcomes, sepsis is the leading contributor, followed by cardiovascular complications and end-stage hepatic failure [11].

Pathophysiology

The development of hepatorenal syndrome (HRS) reflects a complex interaction between circulatory disturbances, hepatic dysfunction, and systemic inflammation. The hallmark mechanism is severe renal vasoconstriction occurring in the background of marked splanchnic and systemic arterial vasodilation, which together result in profound renal hypoperfusion [12]. Portal hypertension plays a central role in initiating these hemodynamic changes. Increased intrahepatic resistance leads to splanchnic vasodilation mediated by nitric oxide, carbon monoxide, and other vasodilatory substances. This causes a reduction in effective arterial blood volume, which in turn activates compensatory neurohormonal mechanisms, including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and vasopressin secretion [13]. These systems attempt to preserve circulatory integrity but result in progressive renal vasoconstriction and sodium retention.

Concurrently, systemic and intrahepatic inflammation contribute significantly to disease progression. Bacterial translocation from the gut and recurrent infections stimulate pro-inflammatory cytokine release (e.g., TNF-α, IL-6), worsening endothelial dysfunction and amplifying circulatory derangements [14]. This inflammatory milieu further enhances renal vasoconstriction while impairing cardiac function, a phenomenon described as cirrhotic cardiomyopathy, which reduces renal perfusion [15]. HRS is clinically categorized into two main subtypes. Type 1 HRS is characterized by a rapid and severe decline in renal function, often precipitated by infections such as spontaneous bacterial peritonitis, with serum creatinine levels doubling to >2.5 mg/dL within two weeks. In contrast, Type 2 HRS evolves more gradually, presenting with moderate but persistent renal impairment and refractory ascites [16].

Additionally, disturbances in renal tubular function are observed, such as impaired sodium excretion and low urinary sodium levels, even though the renal parenchyma is structurally normal. This functional nature of renal failure in HRS underscores why kidney histology usually appears preserved, despite severe renal dysfunction [17]. In summary, the pathophysiology of HRS involves a cascade of portal hypertension, systemic vasodilation, neurohormonal activation, and inflammatory pathways, ultimately culminating in renal hypoperfusion and failure. These mechanisms explain both the clinical spectrum and the poor prognosis associated with this condition.

Clinical Features

The clinical presentation of hepatorenal syndrome (HRS) is often subtle in its early stages and usually occurs in the setting of advanced cirrhosis with portal hypertension and ascites. Patients frequently have a background of progressive liver failure, which complicates the recognition of renal dysfunction, as many symptoms overlap with those of decompensated cirrhosis [18]. The most common manifestations include progressive oliguria, rising serum creatinine, and low urinary sodium excretion (<10 mmol/L), despite preserved renal parenchymal structure [19]. Ascites is almost universally present and often refractory to

diuretic therapy, serving as a hallmark of type 2 HRS. In type 1 HRS, acute kidney injury progresses rapidly, frequently following an identifiable trigger such as spontaneous bacterial peritonitis, large-volume paracentesis without albumin replacement, gastrointestinal bleeding, or systemic infections [20].

Clinically, patients may also exhibit features of systemic circulatory dysfunction, including hypotension, tachycardia, and signs of poor peripheral perfusion. Laboratory abnormalities often include hyponatremia, low urine output, and elevated blood urea nitrogen (BUN) relative to creatinine, which reflect both impaired renal perfusion and neurohormonal activation [21]. Because structural kidney disease is absent, urine analysis is typically bland, with no significant proteinuria or hematuria. Renal ultrasound usually shows normal morphology, which helps differentiate HRS from other causes of renal failure in cirrhosis such as acute tubular necrosis, glomerulonephritis, or drug-induced nephropathy [22]. An important aspect of clinical presentation is the coexistence of malnutrition and sarcopenia, which further worsens fatigue, muscle weakness, and immune dysfunction. These features, though often under-recognized, significantly contribute to the poor prognosis associated with HRS in cirrhotic patients [23].

Malnutrition in Cirrhosis and Hepatorenal Syndrome

Malnutrition is one of the most frequent and serious complications of chronic liver disease, particularly in patients with cirrhosis complicated by HRS. Studies suggest that between 50–90% of cirrhotic patients experience some degree of nutritional impairment, which worsens with disease progression [24]. In the setting of HRS, the burden of malnutrition is even greater due to combined metabolic, hormonal, and inflammatory disturbances.

Mechanisms of Malnutrition in Cirrhosis with HRS

The development of malnutrition in HRS is multifactorial:

1. Reduced Nutrient Intake – Loss of appetite, altered taste sensation, nausea, and early satiety due to ascites significantly reduce dietary intake. Hospitalized patients with fluid restrictions and frequent paracentesis are particularly vulnerable [25].
2. Altered Metabolism – Cirrhosis induces a hypermetabolic and catabolic state, where glycogen stores are rapidly depleted and muscle protein is broken down to maintain glucose homeostasis. This process accelerates sarcopenia, a hallmark of malnutrition in liver disease [26].
3. Malabsorption and Maldigestion – Portal hypertension leads to edema of the intestinal mucosa, bacterial overgrowth, and impaired bile salt circulation, all of which interfere with nutrient absorption, especially fats and fat-soluble vitamins [27].
4. Neurohormonal and Inflammatory Activation – In HRS, systemic inflammation, activation of the renin–angiotensin–aldosterone system (RAAS), and high circulating cytokines further disrupt protein metabolism and contribute to muscle wasting [28].
5. Frequent Infections – Recurrent bacterial peritonitis and sepsis, common in cirrhotic patients with HRS, enhance catabolic drive, suppress appetite, and increase energy expenditure [29].

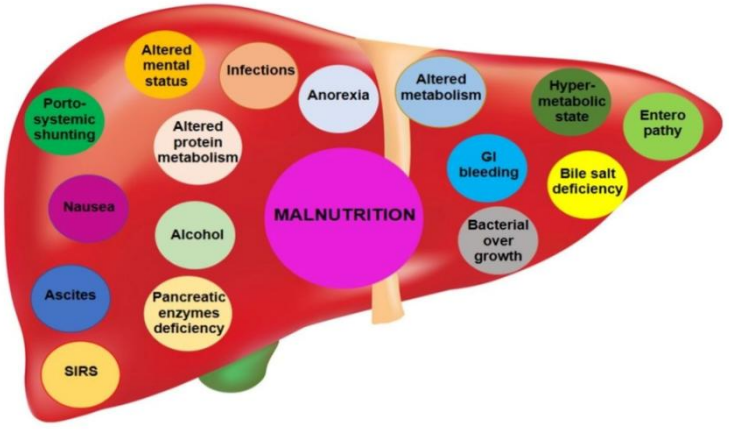

Figure 1: Mechanisms of Malnutrition in Cirrhosis

Clinical Impact of Malnutrition in HRS

Malnutrition and sarcopenia worsen the already poor prognosis of HRS. Patients with cirrhosis and malnutrition have:

•Higher risk of mortality independent of liver disease severity scores.
•Reduced tolerance to infections and invasive procedures due to impaired immunity.
•Poorer response to therapies, including vasoconstrictors and albumin infusion.
•Increased hospital stays and costs, with higher rates of readmission.
•Worsened quality of life, as muscle weakness and fatigue limit daily activity [30].

In fact, malnutrition is now considered an independent predictor of survival in cirrhosis with renal dysfunction. Early identification and nutritional support, therefore, play a crucial role in the management of HRS [31].

Assessment of Malnutrition in Cirrhosis and Hepatorenal Syndrome

Accurate identification of malnutrition is essential in cirrhotic patients, particularly those complicated by hepatorenal syndrome (HRS), since underdiagnosis can delay critical interventions. Traditional methods of nutritional assessment are often unreliable in cirrhosis because of fluid overload, ascites, and peripheral edema, which obscure true body weight and anthropometric indices [32]. Therefore, a multimodal assessment strategy is recommended.

1. Clinical Tools

Subjective Global Assessment (SGA): Widely used for bedside evaluation; incorporates dietary history, weight changes, gastrointestinal symptoms, and physical signs such as muscle and fat wasting. In cirrhosis, modified SGA tools improve accuracy by adjusting for ascites and edema [33]. Royal Free Hospital Global Assessment (RFH-GA): Specifically designed for cirrhotic patients, integrating clinical judgment with objective measures [34].

2. Anthropometric Measures

Mid-Arm Muscle Circumference (MUAC) and Triceps Skinfold Thickness (TSF): Provide estimates of muscle and fat reserves, though values may be skewed in fluid retention. Handgrip Strength (HGS): A practical, reproducible marker of muscle function and sarcopenia; reduced grip strength is strongly associated with mortality in cirrhosis [35].

3. Imaging-Based Assessments

Computed Tomography (CT) or MRI-based Muscle Analysis: Measurement of psoas or skeletal muscle area at the L3 vertebra is considered the gold standard for diagnosing sarcopenia. CT is particularly valuable in transplant candidates, where malnutrition strongly impacts outcomes [36]. Ultrasound Muscle Thickness: Emerging as a non-invasive bedside alternative for assessing muscle mass.

4. Biochemical and Functional Parameters

Serum Albumin and Prealbumin: Although influenced by hepatic synthetic function and inflammation, low levels often correlate with poor nutritional status [37]. Micronutrient Levels: Deficiencies in zinc, magnesium, selenium, vitamin D, and fat-soluble vitamins are frequent in cirrhosis with HRS [38]. Phase Angle (Bioelectrical Impedance Analysis – BIA): Reflects cellular integrity and body composition; reduced phase angle predicts adverse outcomes [39].

5. Composite Scores and Guidelines

Recent consensus guidelines recommend integrating functional measures (HGS, CT muscle analysis) with clinical assessments (SGA, RFH-GA) to improve diagnostic accuracy. The European Society for Clinical Nutrition and Metabolism (ESPEN) emphasizes early screening at diagnosis of cirrhosis and repeated monitoring during decompensations such as HRS [40].

Pathophysiology of Hepatorenal Syndrome and Nutritional Implications

Hepatorenal syndrome (HRS) represents a functional renal failure in advanced cirrhosis, arising from profound circulatory disturbances. The syndrome is primarily characterized by intense renal vasoconstriction and systemic circulatory dysfunction, but nutritional depletion significantly influences its progression and outcomes.

1. Splanchnic Vasodilation and Renal Hypoperfusion

Portal hypertension leads to splanchnic arterial vasodilation, resulting in reduced effective circulating volume. This triggers activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and vasopressin release, collectively causing renal vasoconstriction and sodium–water retention [41]. In malnourished patients, diminished protein stores exacerbate hypoalbuminemia, further lowering oncotic pressure and worsening circulatory collapse.

2. Inflammation and Immune Dysregulation

Cirrhosis is a pro-inflammatory state, amplified during HRS by bacterial translocation, endotoxemia, and systemic inflammatory mediators [42]. Malnutrition, particularly protein-calorie deficiency and micronutrient deficits (zinc, selenium, vitamins A and D), impairs immune competence, heightening susceptibility to infections. Infections are well-established precipitants of HRS, linking malnutrition directly to renal deterioration.

3. Sarcopenia and Muscle Catabolism

Loss of skeletal muscle mass (sarcopenia) is a hallmark of malnutrition in cirrhosis. Muscle tissue normally acts as an ammonia detoxification site via glutamine synthesis; sarcopenia reduces this capacity, worsening hepatic encephalopathy and systemic inflammation [43]. The hypercatabolic state of HRS accelerates muscle breakdown, perpetuating a vicious cycle of malnutrition and disease progression.

4. Mitochondrial Dysfunction and Energy Imbalance

HRS is associated with impaired mitochondrial function in renal tubular cells and hepatocytes, limiting ATP production [44]. Malnutrition further contributes through inadequate energy and substrate supply, compromising cellular repair, and aggravating multi-organ dysfunction.

5. Oxidative Stress and Micronutrient Deficiencies

Oxidative stress plays a central role in hepatocellular and renal injury. Deficiencies of antioxidants such as vitamins C, E, and trace elements (selenium, zinc) reduce defense mechanisms, enhancing oxidative damage in HRS patients [45].

6. Neurohormonal Overactivation and Malnutrition

Persistent RAAS and sympathetic activation lead to catabolic stress, increased protein breakdown, and altered energy metabolism. Malnutrition worsens these adaptive responses, accelerating renal impairment and worsening prognosis [46].

Nutritional Management and Interventions in Hepatorenal Syndrome

Nutritional optimization is a cornerstone in managing patients with cirrhosis complicated by HRS, as malnutrition and sarcopenia are strong predictors of morbidity and mortality. The goals of nutritional therapy are to preserve lean body mass, optimize hepatic and renal function, prevent complications, and improve overall survival.

1. Energy Requirements

Patients with cirrhosis and HRS have a hypermetabolic state with increased resting energy expenditure. Current guidelines recommend an intake of 30–35 kcal/kg/day to meet energy demands and prevent catabolism [47]. Caloric needs should be adjusted according to the patient's clinical status, physical activity, and degree of malnutrition.

2. Protein Intake

Contrary to older practices of protein restriction, evidence supports adequate protein intake (1.2–1.5 g/kg/day) to counteract sarcopenia and protein-energy malnutrition [48]. In cases of severe sarcopenia, intake may be increased up to 1.8 g/kg/day, provided there is no overt hepatic encephalopathy. For patients with recurrent encephalopathy, branched-chain amino acid (BCAA) supplementation is preferred as it improves nitrogen balance and reduces neurocognitive complications [49].

3. Meal Pattern and Timing: Frequent small meals and a late-night carbohydrate-rich snack are recommended to minimize fasting-induced catabolism and preserve glycogen reserves [50]. This strategy helps maintain nitrogen balance and prevents muscle protein breakdown.

4. Micronutrient Supplementation

Cirrhotic patients, particularly those with HRS, commonly present with zinc, selenium, magnesium, vitamin D, vitamin A, and folate deficiencies [51]. Supplementation should be individualized based on laboratory monitoring. Zinc is crucial for ammonia detoxification, while vitamin D deficiency worsens bone disease and muscle weakness.

5. Sodium and Fluid Management

HRS patients often require strict sodium restriction (≤2 g/day) to control ascites and edema. Fluid intake is usually adjusted according to serum sodium and renal function. Overly restrictive diets, however, should be avoided as they may further worsen caloric and protein intake [52].

6. Enteral and Parenteral Nutrition

Enteral nutrition is preferred whenever feasible, as it preserves gut integrity, reduces bacterial translocation, and supports immune function. In advanced cases where oral/enteral feeding is not possible, parenteral nutrition may be considered, with careful monitoring of electrolytes and glucose [53].

7. Specialized Nutritional Approaches

BCAA-enriched formulations: beneficial in cirrhotic sarcopenia and encephalopathy. Probiotics and prebiotics: may help reduce bacterial translocation and systemic inflammation. Omega-3 fatty acids: emerging evidence suggests anti-inflammatory and hepatoprotective effects [54].

8. Integration with Medical Therapy

Nutritional therapy should complement pharmacological interventions (albumin infusion, vasoconstrictors such as terlipressin, midodrine, octreotide) and procedural approaches (TIPS, liver transplantation). Optimizing nutritional status improves transplant eligibility, reduces post-operative complications, and enhances recovery [55].

Discussion

Malnutrition in cirrhotic patients with hepatorenal syndrome (HRS) represents a major clinical challenge. The complex interaction between hepatic dysfunction, renal impairment, systemic inflammation, and altered metabolism accelerates muscle wasting and nutrient deficiencies. Several studies have consistently demonstrated that malnutrition and sarcopenia are independent predictors of mortality in cirrhosis, irrespective of the Model for End-Stage Liver Disease (MELD) score, as reported by Montano-Loza et al. [56].

The pathophysiology of malnutrition in HRS is multifactorial. Reduced oral intake due to anorexia, nausea, and dietary restrictions is compounded by impaired digestion and absorption resulting from portal hypertension–related gut changes. Hypermetabolism, increased protein catabolism, and hormonal disturbances further contribute to progressive muscle breakdown, as described by Tsien et al. [57]. Additionally, ascites and fluid retention may obscure true weight loss, leading to underestimation of nutritional deterioration, as emphasized in the ESPEN guidelines by Plauth et al. [58].

Nutritional assessment tools such as the Subjective Global Assessment (SGA), handgrip strength, mid-arm muscle circumference (MUAC), and bioelectrical impedance analysis are increasingly utilized in clinical practice to identify early nutritional decline. The usefulness of handgrip strength and SGA in cirrhotic patients has been demonstrated by Alvares-da-Silva et al. [59]. Importantly, sarcopenia is now recognized as a critical determinant of liver transplant outcomes, with malnourished patients experiencing higher perioperative morbidity and reduced post-transplant survival, as reported by Praktiknjo et al. [60]. Recent evidence also highlights the therapeutic role of targeted nutritional interventions. Supplementation with branched-chain amino acids (BCAAs), omega-3 fatty acids, and late-night carbohydrate intake has been shown to attenuate muscle breakdown and improve energy homeostasis, as demonstrated by Honda et al. [61]. Furthermore, correction of micronutrient deficiencies—including zinc, vitamin D, and selenium—has been associated with reduced hepatic encephalopathy, lower infection rates, and improved frailty indices, as described by Carey et al. [62].

Despite advances in the pharmacological management of HRS, including albumin infusion, vasoconstrictor therapy, and transjugular intrahepatic portosystemic shunt (TIPS), nutritional optimization remains underrecognized and underutilized in routine clinical practice. An integrated, multidisciplinary approach involving hepatologists, nephrologists, dietitians, and transplant teams is essential to improve clinical outcomes in this vulnerable population, as emphasized by Merli et al. [63].

Summary

Hepatorenal syndrome (HRS) is a severe, life-threatening complication of advanced cirrhosis, characterized by functional renal failure due to intense renal vasoconstriction, systemic vasodilation, and neurohormonal dysregulation. It commonly occurs in patients with ascites and carries a very poor prognosis, with mortality rates reaching up to 80% without treatment. Type 1 HRS presents acutely and progresses rapidly, while Type 2 evolves slowly with refractory ascites. The pathogenesis involves portal hypertension, activation of the renin–angiotensin–aldosterone system, systemic inflammation, and circulatory collapse, leading to renal hypoperfusion despite structurally normal kidneys. Malnutrition is highly prevalent in cirrhotic patients, affecting 50–90%, and is particularly severe in those with HRS. Factors contributing to malnutrition include reduced intake, malabsorption, hypermetabolism, hormonal and inflammatory imbalances, and frequent infections. Malnutrition worsens outcomes by reducing treatment response, increasing infection risk, prolonging hospitalization, and elevating mortality. Assessment tools like the Subjective Global Assessment, handgrip strength, mid-arm muscle circumference, and imaging-based sarcopenia evaluation are crucial for early detection.

Nutritional management is a cornerstone of HRS care. Adequate energy intake (30–35 kcal/kg/day) and protein (1.2–1.5 g/kg/day) are essential, along with BCAA supplementation, frequent small meals, and late-night snacks to prevent catabolism. Micronutrient correction (zinc, vitamin D, selenium), sodium restriction, and preference for enteral over parenteral nutrition improve outcomes. Integrating nutritional therapy with medical treatments such as albumin infusion, vasoconstrictors, and TIPS can enhance transplant readiness, reduce complications, and improve survival. A multidisciplinary approach involving hepatology, nephrology, and nutrition teams is vital for optimal patient management.

Conclusion

Malnutrition is a critical but modifiable factor in patients with liver cirrhosis complicated by hepatorenal syndrome. It accelerates disease progression, worsens quality of life, and adversely impacts survival and transplant outcomes. Timely recognition of malnutrition through structured assessments, coupled with individualized nutritional interventions—adequate calories, optimal protein intake, micronutrient repletion, and specialized supplements—can substantially improve prognosis.

Future research should focus on integrating precision nutrition strategies with conventional HRS therapies, thereby offering a holistic approach to management. Until then, clinicians should prioritize nutritional care as an essential component of the therapeutic algorithm for HRS, rather than a supportive measure..

Conflict of Interest: Nil

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