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Adrenal Insufficiency in Liver Cirrhosis: Mechanisms, Diagnosis, and Therapeutic Perspectives

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ABSTRACT

Background: Adrenal insufficiency (AI) is increasingly recognized as a clinically significant complication in patients with liver cirrhosis, particularly in those with advanced disease or acute-on-chronic liver failure (ACLF). The interplay between hepatic dysfunction and adrenal impairment is multifaceted, involving complex pathophysiological processes such as impaired steroidogenesis, altered binding protein levels, systemic inflammation, and hemodynamic disturbances. AI may contribute to the poor prognosis and high mortality seen in decompensated cirrhosis by exacerbating circulatory dysfunction, increasing susceptibility to infections, and impairing the body's response to stress. However, the true prevalence of AI in cirrhotic patients is subject to debate, largely due to inconsistencies in diagnostic criteria, the impact of liver dysfunction on cortisol-binding proteins, and methodological variability in adrenal function testing. The aim of this review is to provide a comprehensive synthesis of current knowledge regarding the relationship between adrenal insufficiency and liver cirrhosis. This includes a discussion of the epidemiology and risk factors of AI in cirrhosis, an exploration of the underlying mechanisms linking the two conditions, and an examination of the clinical significance of AI in this patient population. We further evaluate current diagnostic approaches, highlighting the challenges inherent in accurately assessing adrenal function in cirrhotic patients. In addition, the review discusses therapeutic strategies, summarizing available evidence for corticosteroid supplementation and its potential benefits and risks in the context of cirrhosis, especially in those with septic shock or ACLF.

Conclusion: Despite growing interest, significant gaps remain in our understanding of adrenal insufficiency in liver cirrhosis. There is a pressing need for standardized diagnostic criteria, more robust outcome data, and clinical trials to define optimal management. By elucidating the complex interactions between liver dysfunction and adrenal impairment, this review aims to support clinicians in identifying and managing adrenal insufficiency in cirrhotic patients, ultimately improving patient outcomes and informing future research directions.

Keywords*:* Adrenal Insufficiency, Liver Cirrhosis, Mechanisms, Diagnosis, Therapeutic Perspectives

INTRODUCTION

Liver cirrhosis represents the end stage of chronic liver diseases, characterized by diffuse hepatic fibrosis, distortion of the hepatic architecture, and the formation of regenerative nodules. It is associated with a broad spectrum of complications, including portal hypertension, hepatic encephalopathy, and increased susceptibility to infections. Over recent decades, it has become increasingly evident that cirrhosis exerts profound effects on multiple organ systems, extending beyond the liver itself. One such extrahepatic complication is adrenal insufficiency (AI), which refers to the inadequate production of corticosteroids necessary for stress adaptation and homeostasis [1].

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The clinical significance of AI in cirrhotic patients is an area of growing interest. AI has been identified with surprising frequency among those with advanced liver disease, particularly in cases of decompensated cirrhosis and acute-on-chronic liver failure (ACLF). The presence of AI in this population has been linked to poor outcomes, such as increased risk of circulatory dysfunction, impaired immune responses, and elevated mortality rates. However, the pathophysiological relationship between cirrhosis and AI remains complex and not fully understood, with multiple factors such as altered cholesterol metabolism, systemic inflammation, and impaired adrenal reserve contributing to its development[2].

Despite its recognized importance, the diagnosis of AI in liver cirrhosis remains controversial. The gold standard tests for adrenal function may not be directly applicable in the setting of hepatic dysfunction, largely due to alterations in cortisol-binding globulin and other confounding factors inherent to liver disease. This diagnostic uncertainty contributes to wide variations in reported prevalence rates and presents a major obstacle to clinical management and research[3].

The aim of this review is to provide a comprehensive overview of adrenal insufficiency in the context of liver cirrhosis. We will discuss the current understanding of the epidemiology, underlying mechanisms, diagnostic challenges, and therapeutic approaches. Additionally, we will identify existing research gaps and propose directions for future investigation. By clarifying the relationship between AI and liver cirrhosis, this review seeks to improve clinical awareness and inform better patient management in this vulnerable population[4].

Liver cirrhosis is a chronic, progressive condition marked by widespread fibrosis, the formation of regenerative nodules, and the loss of normal hepatic architecture. It results from prolonged hepatic injury due to various etiologies, including chronic viral hepatitis (such as hepatitis B and C), excessive alcohol consumption, nonalcoholic fatty liver disease (NAFLD), and autoimmune liver disorders. The natural history of cirrhosis is characterized by an initial compensated phase, which is often asymptomatic, followed by a decompensated stage marked by the development of clinical complications such as ascites, variceal bleeding, hepatic encephalopathy, and jaundice[5].

At the core of cirrhosis pathogenesis is the activation of hepatic stellate cells, leading to excessive deposition of extracellular matrix components and architectural distortion. Portal hypertension, defined as increased pressure within the portal venous system, arises from increased resistance to portal blood flow due to both structural changes (fibrosis and nodules) and dynamic components such as sinusoidal endothelial dysfunction. This elevated portal pressure is central to the development of complications, including variceal formation and splenomegaly[6].

Systemic consequences of cirrhosis extend far beyond the liver itself. Cirrhotic patients often develop a hyperdynamic circulatory state, characterized by increased cardiac output, reduced systemic vascular resistance, and arterial hypotension. Splanchnic vasodilation and activation of neurohumoral systems,

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including the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, contribute to sodium and water retention, leading to ascites and hepatorenal syndrome. Additionally, cirrhosis is associated with immune dysfunction, which increases the risk of bacterial infections and systemic inflammation[7].

From a metabolic standpoint, cirrhosis impairs the liver's synthetic, metabolic, and detoxification functions. Hypoalbuminemia, coagulopathy due to decreased clotting factor production, and disturbances in glucose and lipid metabolism are hallmark features. The reduction in hepatic metabolism of hormones, drugs, and toxins further complicates patient management and increases susceptibility to adverse effects and drug toxicity[8].

In summary, liver cirrhosis is a complex, multisystem disease with widespread effects on hemodynamics, metabolism, immunity, and hormonal balance. Its intricate pathophysiology underlies many extrahepatic complications, including the development of adrenal insufficiency, which is increasingly recognized as a significant contributor to morbidity and mortality in this population[9].

Epidemiology of Adrenal Insufficiency in Cirrhosis

The prevalence of adrenal insufficiency (AI) among patients with liver cirrhosis varies widely in the literature, reflecting differences in diagnostic criteria, patient populations, and severity of liver disease. Studies have reported rates of AI ranging from 10% to over 60%, with higher prevalence observed in those with advanced disease, acute decompensation, or acute-on-chronic liver failure (ACLF)[10]. In stable, compensated cirrhosis, the occurrence of AI appears to be relatively low, but it increases substantially in the setting of sepsis, critical illness, or hepatic decompensation.

One of the largest studies to date, conducted by Fernandez et al., found that the prevalence of AI in cirrhotic patients admitted to intensive care units (ICUs) with septic shock was as high as 68%. Other prospective studies in patients with ACLF have reported similarly elevated rates, suggesting a strong association between the severity of liver dysfunction and the likelihood of developing AI[11]. This relationship is particularly notable among patients with Child-Pugh class C cirrhosis, hypoalbuminemia, and those requiring vasopressor support for hemodynamic instability.

The true epidemiology of AI in cirrhosis is confounded by methodological heterogeneity, particularly regarding the tests used for diagnosis and the cut-off values for defining adrenal dysfunction. The most commonly employed tests include the standard-dose (250 μg) and low-dose (1 μg) short Synacthen (cosyntropin) tests, as well as basal serum cortisol measurements. However, interpretation of these tests is complicated by alterations in cortisol-binding globulin and total serum cortisol levels in cirrhotic patients, which may lead to either over- or underestimation of adrenal dysfunction[12].

Certain risk factors for the development of AI in cirrhosis have been identified. These include advanced liver disease, the presence of sepsis or systemic inflammatory response syndrome (SIRS), renal dysfunction, and the use of medications such as etomidate or antifungals that may impair adrenal

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steroidogenesis. Additionally, male gender, older age, and hypoalbuminemia have been associated with an increased risk of AI in this population[13].

In summary, while adrenal insufficiency is an increasingly recognized complication of advanced liver disease, its true prevalence remains difficult to ascertain due to the lack of standardized diagnostic criteria and variability in study populations. Nonetheless, clinicians should maintain a high index of suspicion for AI in cirrhotic patients, particularly those with critical illness, hemodynamic instability, or acute decompensation[14].

Pathophysiological Mechanisms Linking Liver Cirrhosis and Adrenal Insufficiency

The mechanisms underlying adrenal insufficiency (AI) in patients with liver cirrhosis are multifactorial and reflect the complex interplay between hepatic, adrenal, and systemic processes. One of the central contributors is the reduction in hepatic synthesis of cholesterol, the primary substrate for adrenal steroidogenesis. In cirrhosis, both total and high-density lipoprotein cholesterol levels are typically diminished, limiting the availability of precursors required for cortisol production by the adrenal cortex[15].

Systemic inflammation and cytokine activation are also pivotal in the development of AI in cirrhotic patients. Elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), have been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis and directly impair adrenal steroidogenesis. These cytokines can inhibit adrenocorticotropic hormone (ACTH) release and reduce adrenal responsiveness, particularly in the setting of sepsis or acute-on-chronic liver failure (ACLF)[16].

Another important mechanism is the alteration of cortisol-binding proteins, most notably cortisol-binding globulin (CBG) and albumin, both of which are synthesized in the liver. In cirrhosis, decreased synthesis of CBG and albumin leads to a reduction in total serum cortisol, even when free (biologically active) cortisol may remain normal. This alteration complicates the assessment of adrenal function, as standard assays typically measure total cortisol, potentially underestimating adrenal reserve[17].

Hemodynamic instability, a hallmark of advanced cirrhosis, further contributes to AI. The hyperdynamic circulatory state, characterized by systemic vasodilation and reduced effective arterial blood volume, may impair adrenal perfusion and predispose to adrenal hypoperfusion and ischemic injury. In addition, the use of vasopressors, often necessary in the management of septic shock or hepatorenal syndrome, may reduce adrenal blood flow and exacerbate adrenal dysfunction[18].

Medications commonly used in cirrhotic patients, such as azole antifungals, etomidate, and certain opioids, may also interfere with adrenal steroidogenesis or HPA axis function. Furthermore, acute or chronic infections, a frequent complication in cirrhosis, can overwhelm adrenal reserve and precipitate relative adrenal insufficiency, particularly in critically ill patients[19].

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Collectively, these mechanisms illustrate the intricate and multifaceted nature of adrenal dysfunction in cirrhosis, highlighting the need for a nuanced understanding of the pathophysiology to inform effective diagnosis and management.

Clinical Manifestations and Impact on Outcomes

The clinical manifestations of adrenal insufficiency (AI) in patients with liver cirrhosis are often subtle and can overlap with the symptoms of hepatic dysfunction, making the diagnosis particularly challenging. Common features of AI, such as fatigue, hypotension, nausea, vomiting, abdominal pain, and electrolyte disturbances, are frequently present in cirrhotic patients, irrespective of adrenal status. This clinical overlap necessitates a high index of suspicion for AI, particularly in those with unexplained or refractory hemodynamic instability, persistent hyponatremia, or increased vasopressor requirements[20].

A hallmark feature of AI in cirrhosis is the presence of hemodynamic instability, which may manifest as hypotension resistant to fluid resuscitation or vasopressor therapy. This reflects the critical role of endogenous corticosteroids in maintaining vascular tone and modulating the response to catecholamines. In the context of sepsis or acute-on-chronic liver failure (ACLF), the inability to mount an adequate adrenal response can precipitate shock, multiorgan failure, and a rapid decline in clinical status[21].

Electrolyte disturbances, particularly hyponatremia and hyperkalemia, are common in cirrhotic patients with AI. These abnormalities result from impaired aldosterone and cortisol production, leading to reduced sodium reabsorption and increased potassium retention. While hyponatremia is frequently multifactorial in cirrhosis, persistent or severe cases should prompt consideration of concurrent AI[22].

Importantly, AI in the setting of cirrhosis is associated with increased morbidity and mortality. Studies have demonstrated that cirrhotic patients with AI, especially those admitted to intensive care units with sepsis or shock, experience higher rates of renal dysfunction, prolonged hospital stays, and increased risk of death compared to those with intact adrenal function. The presence of AI has been identified as an independent predictor of poor outcomes in several cohorts, underscoring the clinical significance of timely recognition and management[23].

AI may also contribute to immune dysfunction, impairing the body’s ability to mount an effective response to infections. Corticosteroids are crucial for the modulation of inflammatory and immune responses, and their deficiency can exacerbate systemic inflammation, increase susceptibility to bacterial infections, and contribute to the development of sepsis-related complications[24].

In summary, adrenal insufficiency significantly impacts the clinical course and prognosis of patients with liver cirrhosis, particularly in those with advanced disease or critical illness. Early identification and appropriate management of AI may improve hemodynamic stability, reduce complications, and enhance overall outcomes in this high-risk population[25].

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Diagnosis of Adrenal Insufficiency in Cirrhotic Patients

The diagnosis of adrenal insufficiency (AI) in patients with liver cirrhosis poses substantial challenges due to overlapping clinical features, alterations in cortisol metabolism, and the limitations of standard diagnostic tests. Traditionally, AI is diagnosed using dynamic stimulation tests such as the short Synacthen (cosyntropin) test, which assesses the adrenal response to adrenocorticotropic hormone (ACTH). Both standard-dose (250 μg) and low-dose (1 μg) versions of the test are used, but their interpretation in cirrhotic patients remains controversial[26].

Basal serum cortisol measurements are frequently employed as an initial screening tool for AI. However, total serum cortisol may be misleading in cirrhosis due to reduced synthesis of cortisol-binding globulin (CBG) and albumin, both of which are produced by the liver. These changes can lower total cortisol concentrations despite normal or elevated levels of free (biologically active) cortisol. Consequently, some experts advocate for the measurement of free cortisol or salivary cortisol, which may more accurately reflect adrenal reserve in this population[27].

The diagnostic criteria for AI in cirrhosis are not standardized. Commonly cited thresholds include a basal serum cortisol below 140 nmol/L (5 μg/dL) or a peak serum cortisol after Synacthen stimulation below 500 nmol/L (18 μg/dL). However, these cut-offs are based on studies in non-cirrhotic populations and may not be directly applicable to patients with liver dysfunction. Relative adrenal insufficiency (RAI) is another concept frequently used in critical illness and cirrhosis, defined by a delta cortisol (difference between stimulated and baseline cortisol) of less than 250 nmol/L (9 μg/dL)[28].

Clinical guidelines suggest that the diagnosis of AI in cirrhosis should integrate both clinical suspicion and biochemical assessment. In critically ill cirrhotic patients, especially those with sepsis or refractory shock, a low threshold for testing and potential empirical therapy is often recommended. The utility of corticotropin-releasing hormone (CRH) stimulation tests and insulin-induced hypoglycemia tests is limited in this setting due to safety concerns and lack of validation[29].

Recent research has explored novel biomarkers and dynamic tests for improved assessment of adrenal function in cirrhosis. Free cortisol assays, including equilibrium dialysis and liquid chromatography–tandem mass spectrometry, offer greater specificity but are not widely available in routine practice. Salivary cortisol testing is non-invasive and shows promise but requires further validation in this population[30].

In conclusion, the diagnosis of adrenal insufficiency in cirrhotic patients requires a nuanced approach that accounts for the unique alterations in cortisol metabolism and protein binding associated with liver disease. Standard diagnostic algorithms must be adapted, and there is a need for consensus on optimal testing strategies and cut-off values to guide clinical practice[31].

Diagnostic Challenges and Limitations

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The diagnosis of adrenal insufficiency (AI) in patients with liver cirrhosis is fraught with numerous challenges that complicate both research and clinical management. One of the most significant obstacles is the alteration of cortisol-binding proteins, specifically cortisol-binding globulin (CBG) and albumin, due to impaired hepatic synthesis. As a result, total serum cortisol levels can be deceptively low even when free cortisol, which is biologically active, remains within the normal range. This discrepancy may lead to overdiagnosis of AI if only total cortisol is measured and interpreted using conventional thresholds[32].

Another challenge arises from the use of standard dynamic tests such as the short Synacthen (cosyntropin) test. The appropriateness of both the 250 μg and 1 μg ACTH stimulation tests in cirrhotic patients is debated, as the altered pharmacokinetics and adrenal responsiveness in these individuals may affect the test's reliability. Furthermore, stress-related increases in cortisol production during acute illness may mask adrenal insufficiency, potentially resulting in false-negative results[33].

The lack of universally accepted diagnostic criteria for AI in the context of cirrhosis contributes to substantial variability in reported prevalence and uncertainty in clinical practice. Thresholds for basal and stimulated cortisol levels, as well as the definition of relative adrenal insufficiency (RAI), vary widely between studies. These inconsistencies impede the development of standardized diagnostic algorithms and complicate the interpretation of research findings[34].

Practical considerations further limit the utility of more accurate measures of adrenal function, such as free cortisol assessment via equilibrium dialysis or liquid chromatography–tandem mass spectrometry. These techniques are expensive, time-consuming, and often unavailable in routine clinical settings, particularly in resource-limited environments. Similarly, while salivary cortisol measurement shows promise as a non-invasive tool, its use in cirrhotic patients requires further validation and standardization[35].

Finally, the influence of concurrent medications, infections, and the presence of critical illness can significantly alter adrenal function and cortisol dynamics. Agents such as etomidate, azole antifungals, and opioids can suppress adrenal steroidogenesis, confounding the interpretation of test results. Critical illness-related corticosteroid insufficiency (CIRCI) further blurs the distinction between absolute and relative AI, making clinical decision-making more complex[36].

In summary, the diagnosis of adrenal insufficiency in cirrhotic patients is limited by biological, methodological, and practical challenges. Overcoming these limitations will require the establishment of consensus definitions, validation of alternative testing methods, and greater awareness of the unique factors affecting adrenal function in this population.

Therapeutic Perspectives and Management Strategies

The management of adrenal insufficiency (AI) in patients with liver cirrhosis, especially those with acute decompensation or critical illness, remains an area of evolving clinical practice and ongoing

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debate. The cornerstone of therapy is corticosteroid replacement, typically with hydrocortisone, which aims to restore physiological levels of glucocorticoids and support the body's response to stress. However, the indications, dosing, and duration of therapy in cirrhotic patients are not standardized and require careful consideration of the unique risks and benefits in this population[37].

Several studies have investigated the impact of corticosteroid therapy in cirrhotic patients with septic shock or acute-on-chronic liver failure (ACLF). Evidence suggests that low-dose hydrocortisone may improve hemodynamic stability, reduce the requirement for vasopressors, and shorten the duration of shock. In some cohorts, corticosteroid supplementation has also been associated with improved renal function and reduced inflammatory markers, reflecting the central role of endogenous glucocorticoids in modulating vascular tone and the systemic inflammatory response[38].

Despite these potential benefits, the routine use of corticosteroids in all cirrhotic patients with AI is not universally recommended. Concerns persist regarding the risk of adverse effects, including hyperglycemia, increased susceptibility to infections, gastrointestinal bleeding, and impaired wound healing. The immunosuppressed state inherent to advanced liver disease may exacerbate these risks, particularly with prolonged or high-dose corticosteroid use[39].

In clinical practice, the decision to initiate corticosteroid therapy should be individualized, taking into account the severity of adrenal insufficiency, the presence of hemodynamic instability or shock, and the patient's overall risk profile. Current guidelines from critical care societies recommend considering corticosteroid therapy in cirrhotic patients with refractory septic shock or persistent hypotension despite adequate fluid resuscitation and vasopressor support. Hydrocortisone is the preferred agent, typically administered at a dose of 200–300 mg per day in divided doses or as a continuous infusion, with tapering guided by clinical response[40].

Monitoring and follow-up during corticosteroid therapy are essential to mitigate potential complications. Blood glucose levels, electrolyte balance, signs of infection, and gastrointestinal symptoms should be closely monitored. In patients who recover from critical illness or no longer require vasopressor support, corticosteroids should be tapered and discontinued as soon as clinically feasible to minimize adverse effects[41].

In addition to corticosteroid supplementation, supportive management of underlying cirrhosis, prompt identification and treatment of infections, hemodynamic optimization, and avoidance of medications that impair adrenal function are vital components of care. Multidisciplinary collaboration between hepatologists, intensivists, and endocrinologists is recommended for the management of complex or refractory cases[42].

Ongoing research is needed to refine the indications for corticosteroid therapy, optimize dosing regimens, and identify subgroups of cirrhotic patients most likely to benefit from treatment. Clinical

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trials addressing these questions will be crucial in guiding evidence-based management strategies and improving outcomes in this vulnerable population[43].

Current Guidelines and Controversies

Current clinical guidelines regarding the diagnosis and management of adrenal insufficiency (AI) in liver cirrhosis are largely extrapolated from broader recommendations for critical illness-related corticosteroid insufficiency (CIRCI) and sepsis, as robust, cirrhosis-specific data remain limited. The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) recommend considering corticosteroid therapy in critically ill patients with septic shock who remain hypotensive despite adequate fluid resuscitation and vasopressor support, a group that includes many patients with advanced liver disease[44].

However, several controversies persist in the field. One major area of debate is the definition and diagnostic criteria for AI in cirrhosis. The lack of consensus regarding appropriate thresholds for cortisol levels, the reliability of stimulation tests, and the interpretation of total versus free cortisol in the setting of hypoalbuminemia and reduced cortisol-binding globulin complicate both clinical practice and research. As a result, the prevalence of AI reported in cirrhosis varies widely, and recommendations for screening and diagnosis remain inconsistent across guidelines and expert opinions[45].

Another contentious issue is the indication and timing of corticosteroid therapy in cirrhotic patients. While evidence supports the use of low-dose hydrocortisone in septic shock, the benefits in less severely ill patients or those without shock are uncertain. There is concern that indiscriminate use of corticosteroids may increase the risk of adverse effects, such as infection, hyperglycemia, and gastrointestinal bleeding, particularly in patients with underlying immune dysfunction[46].

Guidelines also diverge regarding the optimal test for assessing adrenal function. Some advocate for the standard-dose Synacthen test, while others suggest using low-dose tests or measuring free cortisol. Practical limitations, cost, and availability further influence local practice patterns. No single diagnostic strategy has been universally accepted, highlighting the need for cirrhosis-specific protocols[47].

International liver societies have yet to issue detailed guidance on the management of AI in cirrhosis. Most recommendations are derived from expert consensus and extrapolation from studies in the general critically ill population. The absence of randomized controlled trials focused specifically on cirrhotic patients contributes to ongoing uncertainty, emphasizing the importance of individualized care and clinical judgment[48].

Despite advances in our understanding of adrenal insufficiency (AI) in the context of liver cirrhosis, several critical research gaps remain that must be addressed to optimize patient care. One of the foremost needs is the development of standardized, cirrhosis-specific diagnostic criteria and protocols for AI. Current diagnostic strategies rely heavily on data derived from non-cirrhotic populations, which

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may not adequately account for the profound alterations in cortisol metabolism, protein binding, and adrenal responsiveness characteristic of advanced liver disease[49].

Future research should prioritize large, prospective studies that assess the utility and accuracy of various diagnostic tests for AI in cirrhotic patients, including dynamic stimulation protocols, free cortisol assays, and salivary cortisol measurements. Establishing validated cut-off values for these tests, tailored to the cirrhotic population, will be essential to reduce diagnostic uncertainty and improve clinical decision-making[50].

Clinical trials are urgently needed to evaluate the efficacy and safety of corticosteroid supplementation in different subsets of cirrhotic patients. While evidence supports the use of corticosteroids in patients with refractory septic shock, the benefits and risks of therapy in those with less severe disease, compensated cirrhosis, or isolated adrenal dysfunction are unclear. Trials should also address optimal dosing regimens, duration of therapy, and criteria for discontinuation to minimize adverse effects while maximizing benefit[51].

Another important area for future investigation is the elucidation of the underlying pathophysiological mechanisms linking liver dysfunction and adrenal insufficiency. Greater understanding of how systemic inflammation, altered cholesterol metabolism, hemodynamic instability, and medications interact to impair adrenal function may reveal novel therapeutic targets and strategies. Biomarker discovery and the integration of genomics, proteomics, and metabolomics could further refine risk stratification and guide personalized management[52].

Additionally, studies should focus on the long-term outcomes of cirrhotic patients with AI, particularly regarding quality of life, incidence of complications, and overall survival. The potential impact of early identification and intervention on these outcomes remains largely unexplored. The role of multidisciplinary collaboration between hepatologists, endocrinologists, and intensivists should also be investigated to determine the most effective models of care delivery for this high-risk population[53], significant opportunities exist to advance the diagnosis and management of adrenal insufficiency in liver cirrhosis. Rigorous, cirrhosis-specific research is needed to fill existing knowledge gaps, inform evidence-based guidelines, and ultimately improve outcomes for affected patients.

Conclusion

Adrenal insufficiency is a significant but often underrecognized complication in patients with liver cirrhosis, particularly those with advanced disease, acute decompensation, or sepsis. The multifaceted interplay between hepatic dysfunction, systemic inflammation, altered cholesterol metabolism, and hemodynamic changes renders cirrhotic patients especially vulnerable to impaired adrenal steroidogenesis and an inadequate stress response. The clinical ramifications are considerable,

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including hemodynamic instability, increased risk of infections, worsened renal function, and higher mortality rates.

Diagnostic challenges remain a major barrier to effective management, given the limitations of standard testing, the impact of altered cortisol-binding proteins, and the absence of universally accepted criteria specific to cirrhosis. While dynamic stimulation tests and total cortisol assays are commonly used, they frequently produce ambiguous results in this setting, emphasizing the need for innovative diagnostic approaches such as free or salivary cortisol measurement.

Therapeutic strategies must be carefully tailored to balance the potential benefits of corticosteroid supplementation with the risks, particularly in immunocompromised individuals. Low-dose hydrocortisone has shown benefit in critically ill cirrhotic patients with refractory septic shock, but its role in less severe cases is still uncertain. Close clinical monitoring and multidisciplinary collaboration are essential for optimal management.

Despite advances in understanding, substantial gaps in knowledge persist, especially regarding diagnosis, treatment indications, and the long-term impact of adrenal insufficiency on outcomes in cirrhosis. Future research focused on cirrhosis-specific diagnostic criteria, clinical trials, and mechanistic studies is needed to inform evidence-based guidelines. Enhanced clinical awareness and ongoing investigation will be key to improving recognition, management, and prognosis for patients with adrenal insufficiency in the setting of liver cirrhosis.

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