Albumin as a Marker of Ascites: The Role of Proteomics in Uncovering Novel Diagnostic Biomarkers

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Liver cirrhosis is a progressive and often irreversible condition that represents a leading cause of morbidity and mortality worldwide. One of the most common and severe complications is the development of ascites, a condition which not only signals hepatic decompensation, but also portends a poor prognosis and increased risk of hospitalization and mortality. Traditional diagnostic tools, such as the serum-ascites albumin gradient (SAAG), are widely used to differentiate between various causes of ascites (whether it is as a result of liver damage or other unknown causes). However, these albumin-based markers can be limited in sensitivity and may not fully capture the complexity of pathophysiological changes occurring in cirrhosis and its associated complications.

In recent years, advances in omics technologies, particularly proteomics, have opened new avenues for identifying disease-specific biomarkers that reflect underlying molecular dysfunction. Proteomics – the comprehensive study of protein expression, modifications, and interactions has emerged as a valuable tool for discovering novel biomarkers that may enable earlier and more accurate diagnosis, better prognostic stratification, and personalized therapeutic monitoring in cirrhotic patients. Biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have shown promise in detecting acute kidney injury in patients with cirrhosis, even before traditional clinical indicators become apparent. Their application in ascites-related pathophysiology could enhance clinical vigilance and facilitate pre-emptive interventions.

This review synthesizes current diagnostic approaches for ascites, evaluates their limitations, and explores the transformative potential of proteomics approaches in augmenting the clinical management of cirrhosis and its complications. We highlight key studies that support the use of proteomic profiling for identifying early renal dysfunction and systemic inflammatory responses in cirrhotic patients. Additionally, we propose a framework for integrating these emerging biomarkers into existing diagnostic algorithms, thereby improving accuracy and clinical relevance. Ultimately, combining proteomic insights with conventional diagnostics offers a powerful strategy to improve early detection, optimize therapeutic interventions, and reduce the overall burden of cirrhosis-related complications such as ascites.

Introduction

Liver diseases pose a major global health burden, accounting for nearly 2 million deaths each year.1 Liver cirrhosis is the eleventh leading cause of mortality worldwide, highlighting the critical need for improved prevention and treatment strategies.[1] Liver cirrhosis can be defined as irreversible liver scarring which can be caused by a number of factors such as excessive drinking, hepatitis B and C viruses, and fatty liver.[1] Liver cirrhosis can progress from an asymptomatic compensated stage where the body functions adequately even with liver scarring to a decompensated stage, where liver function is significantly impaired usually resulting in complications like ascites.[2] This progression of liver cirrhosis to the decompensated stage can lead to clinical portal hypertension (PHT), a condition characterized by increased blood pressure in the portal vein system[3] (Figure 1). The most common sign of decompensated cirrhosis is ascites, a condition marked by the accumulation of fluid in the peritoneal cavity.[3]

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Ascites signals a poor prognosis and significantly worsens patient outcomes. It is associated with symptoms such as abdominal discomfort, dyspnea, and loss of appetite, and increases the risk of severe complications like spontaneous bacterial peritonitis (SBP), a potentially life-threatening infection of ascitic fluid that develops in approximately 25% of individuals with cirrhosis and ascites.[3–5] Evaluating the burden of ascites is essential, as it contributes to frequent hospitalizations, prolonged stays, and a poor quality of life, while placing considerable strain on healthcare systems. However, the burden of ascites needs to be evaluated from the context of liver cirrhosis, which is the underlying cause.[6] It was reported by Hudson et al. that between 2013 and 2015, the cost of management of liver disease in England, UK in over thirteen thousand individuals in their final year of life was an average of £21,113 (CAD $39329.72) per patient.[7] Similarly, Fagan et al. found that 41 patients requiring paracentesis (a medical procedure used to relieve ascites) reported 127 hospital admissions, over 1000 bed-days, and 733 imaging procedures. Notably, 80.3% of admissions were for ascites management, with 41.2% being unplanned.[6] These findings underscore the limitations of current diagnostic and monitoring strategies, which rely heavily on albumin-based markers like the serum-ascites albumin gradient (SAAG). These markers may lack sensitivity for early disease detection, highlighting the need for more predictive approaches.

The objective of this article is to examine the clinical impact of ascites, to explore the potential of proteomic approaches to enhance early detection, and to discuss the use of novel biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). These markers could offer earlier insights into disease progression and therapeutic response with an aim to improve diagnostic precision and patient outcomes.

Clinical Relevance of Ascites

As noted above, ascites is a common and clinically significant complication of liver cirrhosis.[3,4] However, the symptoms of ascites are quite common and non-specific, necessitating a thorough differential diagnosis to rule out other systemic diseases such as peripheral edema in heart failure which presents similarly.[8,9] Therefore, it is imperative to have a structured diagnostic approach to determine its etiology in order to guide effective management. One of the most effective ways to achieve this is through a physical examination and percussion of the abdomen, with shifting dullness being a hallmark clinical sign of ascitic fluid buildup.[4] Ascitic fluid accumulation is a key manifestation of decompensated liver disease but may also arise from malignancy, infection, or nephrotic syndrome. Ascitic fluid analysis is essential to determine disease etiology and remains a cornerstone of diagnostic evaluation, with biomarkers offering promise for precision diagnostics.

The initial diagnostic workup for patients presenting with ascites includes a comprehensive biochemical assessment, comprising serum creatinine, albumin, and liver function tests to evaluate renal and hepatic status.[8,9] Once obtained, ascitic fluid is evaluated using parameters such as total protein concentration, cell counts, and albumin-creatinine ratio, to classify the fluid as either transudative (fluid buildup as a result of systemic conditions like hypertension) or exudative (fluid buildup as a result of conditions like inflammation).[8]

A reduction in serum albumin, a hepatic-synthesized protein crucial for maintaining oncotic pressure, is frequently observed in advanced cirrhosis, as reflected by its lowered concentration in ascitic fluid.4,10 This loss contributes significantly to fluid leakage into the peritoneal cavity and the development of ascites in up to 85% of cases, while the remaining 15% are attributable to non-hepatic causes such as nephrotic syndrome or congestive heart failure[4] (Figure 1). A pivotal diagnostic marker in the ascitic fluid is the serum-ascites albumin gradient (SAAG), calculated by subtracting the ascitic albumin concentration from serum albumin.[8] A SAAG ≥1.1 g/dL is indicative of portal hypertension and transudative ascites, most commonly associated with cirrhosis. In contrast, a SAAG <1.1 g/dL suggests exudative ascites, often linked to malignancy, infection, or peritoneal inflammation[4,8] (Figure 1).

Visual inspection of ascitic fluid can provide immediate diagnostic clues: clear or straw-colored fluid typically reflects cirrhotic ascites; cloudy fluid may indicate SBP; and chylous or bloody fluid suggests malignancy or tuberculosis.8 Biochemical analysis further aids differentiation through parameters such as glucose, lactate dehydrogenase, white cell count, and amylase.[4,8]

While ascites is not curable,[4] it is manageable through a tiered approach. Lifestyle modifications (e.g., sodium and fluid restriction), pharmacological therapies (e.g.,

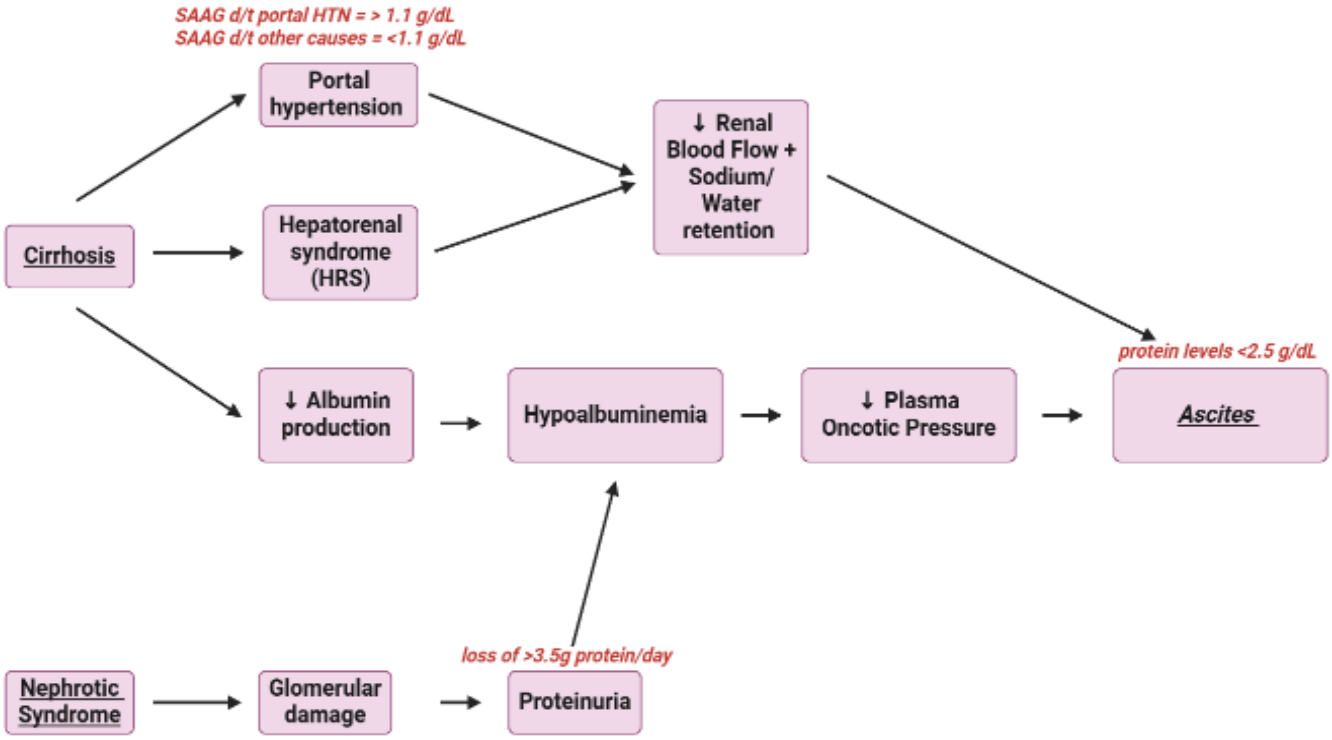

Figure 1. Pathophysiology showing the development of Ascites through Cirrhosis and Nephrotic Syndrome.

diuretics, albumin infusions, antibiotics for SBP), and interventional procedures such as large-volume paracentesis or trans-jugular intrahepatic portosystemic shunt may be employed.[4] Nevertheless, the need for more sensitive and specific molecular biomarkers remains a pressing clinical challenge to reduce diagnostic uncertainty and streamline management.

Despite their clinical utility, conventional methods for assessing ascites, including ultrasound imaging and SAAG calculations, have notable limitations. Ultrasonography, while non-invasive and widely accessible, is operator-dependent and cannot reliably differentiate between benign and malignant ascites.[11] Similarly, SAAG is primarily effective in distinguishing portal hypertension-related ascites but may yield inconclusive results in mixed etiologies or malignancy-associated ascites, where hypoalbuminemia due to systemic inflammation or cancer-related cachexia complicates interpretation.[5,9,12] Routine biochemical assays also lack specificity and fail to detect early molecular alterations that precede clinical symptoms or fluid accumulation, limiting their utility for timely and accurate diagnosis.[13] These diagnostic shortcomings can result in delayed interventions, inappropriate management strategies, and increased healthcare burden. Advances in multi-omics technologies, particularly proteomics can offer promising solutions to these diagnostic gaps. Proteomics plays a crucial role in understanding cellular processes, disease mechanisms, and treatment responses. By contrasting the protein expression profiles of healthy individuals with those afflicted by disease, or by comparing pre- and post-treatment states, proteomics can pinpoint proteins expressed differentially. Such proteins hold promise as potential biomarkers for disease diagnosis, prognosis, and therapeutic efficacy. Moreover, integrating these high-dimensional data sets with machine learning algorithms may significantly enhance diagnostic accuracy, enabling early detection, better risk stratification, and personalized treatment planning. As precision medicine continues to evolve, incorporating these novel diagnostic modalities could transform the clinical landscape of ascites management.

Omics: The next best thing in ascites care

During Mayo Clinic's Tenth Annual Individualized Medicine Conference, Dr. Farrugia, then president and CEO of Mayo Clinic, said *"The road ahead must be focused on expanding our genomic tools and further integrating individualized medicine. We've only just begun to glimpse what is possible."*[14] This quote has gone on to define a role of omics not only in health research but as an innovative tool to change our

approach to life's challenges. Simply put, omics refers to the comprehensive study of sets of biological molecules with aims to identify, quantify and characterize these molecules.[15,16]

Omics research is driven by various motivations, with one primary goal being to gain a comprehensive understanding of biological systems. For example, a proteomics study on normal human kidney tissues can provide valuable insights into protein to protein interactions, functional pathways, and molecular interactions. Another key objective is to link omics-derived molecular data to clinical outcomes, such as prostate cancer survival, breast cancer recurrence risk, or treatment response. By leveraging these detailed molecular measurements, researchers can develop more precise predictive or prognostic models, leading to omics-based tests that offer greater accuracy than conventional clinical approaches.[15] Many areas of research can be classified as a form of omics, such as genomics (the study of the entire genome of an organism)[16], transcriptomics (the study of the complete set of RNA transcript produced by the genome)[17], epigenomics (the study of reversible chemical modifications to DNA or to the histone proteins that package it, influencing gene expression without altering the underlying DNA sequence)[16], metabolomics (the study of the complete set of metabolites within an organism that are implicated in diverse cellular functions and metabolic pathways)[18], and proteomics (the study of the entire set of proteins expressed by an organism).[19]

Proteomics is an increasingly powerful tool in the identification of novel biomarkers and therapeutic targets, offering critical insights into disease mechanisms, treatment responses, and individual variability.[19] In the setting of cirrhosis and ascites, proteomic profiling holds transformative potential for enhancing diagnostic accuracy and guiding clinical decision-making. High-throughput mass spectrometry-based proteomic analyses have enabled the detection of previously unrecognized proteins in biological fluids, including ascitic fluid, which may not only clarify the etiology of fluid accumulation but also provide early indicators of systemic complications such as renal dysfunction.[19]

Historically, the SAAG has been the cornerstone for differentiating ascites due to portal hypertension from other causes such as malignancy or peritoneal infection.[5,8,9] A SAAG value equal to or greater than 1.1 g/dL is highly suggestive of portal hypertension and has long been the gold standard and employed as a first-line diagnostic criterion to distinguish transudative ascites from exudative causes in cirrhotic patients (Table 1).[10] However, despite its diagnostic utility, the accuracy of SAAG can be compromised in patients with coexisting etiologies or atypical presentations.[10] Several studies have highlighted its limited sensitivity and specificity, especially in populations with heterogeneous disease patterns or overlapping inflammatory and malignant processes.[10,13,20,21] These limitations underscore a critical need for improved biomarkers that offer higher diagnostic precision and prognostic value.

Proteomics has emerged as a leading approach in this regard, facilitating the identification of kidney injury biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), both of which have shown considerable promise in cirrhotic patients with ascites.[22–24] These biomarkers are upregulated in the setting of nephrotic-syndrome induced-ascites (Figure 1), and can be readily quantified in urine, providing a non-invasive method for early detection of renal complications. Importantly, acute kidney injury (AKI), particularly in the form of hepatorenal syndrome (HRS), represents a life-threatening complication of decompensated cirrhosis with ascites, making early recognition essential for timely intervention (Figure 1).[25,26] Allegretti et al. also demonstrated that urinary NGAL levels were significantly elevated in patients with HRS-AKI who developed ascites compared to those with other forms of AKI or no renal impairment, offering both a potential diagnostic and prognostic information.[27] Furthermore, NGAL not only differentiated between AKI subtypes but also improved mortality risk prediction, suggesting its potential role in patient stratification and individualized care.[27,28] Likewise, KIM-1, a transmembrane protein expressed in injured proximal tubular cells, was found to be elevated in patients with HRS, with strong sensitivity and specificity for AKI related to cirrhosis.[23,29] Supporting evidence from diverse clinical contexts reinforces the reliability of these biomarkers in HRS-AKI.[8,13,30] For example, in a study of preterm neonates, Hanna et al. found that urinary NGAL levels were significantly higher in those who developed AKI, underscoring the broader applicability of this biomarker across disease states and age groups.[31]

Incorporating NGAL and KIM-1 into the diagnostic landscape of cirrhotic ascites could offer substantial clinical benefit. While SAAG remains a valuable structural indicator of portal hypertension, NGAL and KIM-1 provide dynamic information about renal stress and injury. Together, these markers offer a more holistic view of disease pathophysiology, capturing both hemodynamic and inflammatory components, and identifying patients at higher risk for adverse outcomes.

Conclusion

The integration of proteomic biomarkers such as NGAL and KIM-1 into the clinical evaluation of ascitic patients represents a promising advancement in the management of cirrhosis. Although not yet adopted in standard practice guidelines, these markers have demonstrated strong potential for differentiating ascites etiology, predicting the onset of AKI, and stratifying mortality risk.[13,23–25] Future directions will focus on validating these biomarkers in larger, diverse cohorts and on embedding them within multi-omic frameworks incorporating genomic, transcriptomic, and metabolomic data to advance personalized medicine in liver disease. By bridging the gap between molecular insights and clinical outcomes, proteomics may redefine the diagnostic and therapeutic approach to cirrhotic ascites.

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Table 1. Comparison of Albumin, KIM-1, and NGAL as markers of Ascites.

Marker (Sample collected)	Albumin (Blood Test, SAAG)	Albumin (Urine Test)	Albumin (Ascitic Fluid, SAAG)	KIM-1	NGAL
Sample type	Venous blood sample	Spot urine sample or 24-hour urine collection	Paracentesis (ascitic fluid)	Urine or blood sample	Urine or blood sample
Normal and pathological reference ranges for liver	Normal: >3.4 g/dL - 5.4 g/dL Low: < 2.5 g/dL[32,33]	Normal UACR: <30 mg/g Elevated UACR: >300 mg/g [34]	Normal: SAAG > 1.1 g/dL = Portal HTN SAAG < 1.1 g/dL = Non-cirrhotic ascites [32]	Normal: <1ng/mL Elevated: >1 ng/mL[29]	Normal: <149 ng/mL Elevated: >150 ng/mL[35]
Patient populations with highest changes in these biomarkers	Cirrhosis, nephrotic syndrome, malnutrition, sepsis	Nephrotic syndrome, Chronic kidney disease (CKD), diabetic nephropathy, infections[36]	Cirrhosis, malignancy, infections, heart failure[32]	Acute kidney injury (AKI), CKD, sepsis-associated AKI, HRS-AKI[37]	AKI, CKD, hepatorenal syndrome, sepsis, heart failure[28]
Sensitivity and specificity for detecting ascites	Highly specific (~97%) for cirrhotic ascites[32]	Useful for assessing kidney function and detecting proteinuria, but low sensitivity for diagnosing ascites.	Highly sensitive and specific for ascites for cirrhotic ascites (~97%).[32]	Limited research on direct connection to ascites.	May predict worsening renal function in cirrhosis but not specific to ascites.
Biomarker that can distinguish between cirrhosis-related vs. nephrotic syndrome-related ascites?	Normal: SAAG > 1.1 g/dL = Portal HTN SAAG < 1.1 g/dL = Non-Cirrhotic Ascites.[32]	Helps diagnose nephrotic syndrome but does not classify ascites directly.	Gold standard for ascites classification (cirrhosis vs. nephrotic syndrome)[32]	KIM-1 is elevated in liver or kidney damage but has no direct role in ascites detection.	NGAL is elevated in AKI-related ascites caused by cirrhosis.
How do these biomarkers perform in predicting disease progression?	Low albumin indicates poor prognosis in cirrhosis and nephrotic syndrome or malnutrition.[32]	High proteinuria predicts worsening CKD and nephrotic syndrome.	SAAG levels differentiate between cause of ascites.	Strong early predictors in kidney disease, can predict progression.[29]	Strong early predictors of AKI and HRS in cirrhosis.[28]
Analysis time in clinical setting	Routine lab test/CBC (~hours)	Routine urine test (~hours)	Paracentesis lab analysis ~24 hours	Rapid tests available (~hours)	1 - 4 hours.[28]
External factors that affect their accuracy?	Malnutrition, infection, inflammation[32]	Dehydration, exercise, diabetes, fever or infection, heart failure, hypertension.	Fluid sample contamination and infection	Sepsis, ischemia, inflammation.[37]	Sepsis, systemic inflammation, nephrotoxic drugs.[28]
Costs and feasibility	Low-cost	Cost-effective	Invasive procedure, costly	Moderate costs (ELISA Kits)	Cost-effective[38]