Emerging Noninvasive Biomarkers for Portal Hypertension: The Role of Right Liver Lobe Diameter/Albumin Ratio and APRI in Predicting Esophageal Varices and Bleeding Risk

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Abstract

Background: Portal hypertension is a major consequence of liver cirrhosis and is strongly associated with the development of esophageal varices (EV) and variceal hemorrhage, which remain important causes of morbidity and mortality in cirrhotic patients. Early detection and risk stratification of EV are essential for preventing life-threatening bleeding episodes and improving clinical outcomes. Although upper gastrointestinal endoscopy is considered the gold standard for diagnosing and grading esophageal varices, its invasive nature, cost, limited accessibility, and patient discomfort have prompted increasing interest in reliable noninvasive alternatives. Among the emerging noninvasive biomarkers, the right liver lobe diameter-to-albumin ratio (RLLD/Alb ratio) and the aspartate aminotransferase-to-platelet ratio index (APRI) have shown promising utility in evaluating portal hypertension and predicting variceal risk.

This review aims to comprehensively evaluate the clinical role of RLLD/Alb ratio and APRI in predicting esophageal varices and variceal bleeding risk among cirrhotic patients. In addition, the review discusses the pathophysiological basis, diagnostic performance, advantages, limitations, and comparative value of these biomarkers relative to other noninvasive approaches used in portal hypertension assessment.

Progressive hepatic fibrosis and portal hypertension produce structural, functional, and hematological alterations that form the basis for both RLLD/Alb ratio and APRI assessment. The RLLD/Alb ratio reflects hepatic morphological changes and declining synthetic function, while APRI integrates hepatocellular injury and thrombocytopenia associated with hypersplenism and advanced fibrosis. Multiple studies have demonstrated significant correlations between elevated values of these indices and the presence, severity, and bleeding risk of esophageal varices. Their diagnostic utility appears particularly valuable in resource-limited settings because both markers are inexpensive, easily obtainable, and reproducible. Furthermore, combining these biomarkers with other clinical or imaging parameters may improve predictive accuracy and reduce unnecessary endoscopic procedures.

Conclusion: RLLD/Alb ratio and APRI represent promising noninvasive tools for predicting esophageal varices and variceal bleeding in cirrhotic patients. Although they cannot currently replace endoscopic evaluation as the definitive diagnostic standard, their integration into multiparametric screening strategies may enhance risk stratification and optimize clinical management. Further large-scale prospective studies are required to establish standardized cutoff values and validate their role within modern portal hypertension screening algorithms.

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Keywords: Portal Hypertension, Esophageal Varices, APRI Score

Introduction

Liver cirrhosis represents the terminal stage of chronic liver disease and constitutes a major global health burden associated with significant morbidity and mortality. Progressive hepatic fibrosis and architectural distortion ultimately result in portal hypertension, hepatic insufficiency, and multiple life-threatening complications. Among these complications, esophageal varices (EV) and variceal hemorrhage are considered the most clinically significant consequences of portal hypertension due to their direct association with increased mortality, recurrent hospitalization, and deterioration in quality of life. Despite substantial advances in hepatology and endoscopic therapy, acute variceal bleeding continues to carry considerable mortality rates, particularly in patients with decompensated cirrhosis and advanced hepatic dysfunction. Early identification of patients at high risk for EV and variceal bleeding therefore remains a fundamental component in the management of cirrhotic patients. [1,2]

Portal hypertension develops primarily as a consequence of increased intrahepatic vascular resistance combined with progressive splanchnic vasodilatation and hyperdynamic circulation. Elevated portal venous pressure promotes the formation of portosystemic collateral vessels, particularly within the distal esophagus and proximal stomach. The prevalence of esophageal varices increases with the severity and duration of cirrhosis, with approximately 50% of compensated cirrhotic patients and up to 85% of decompensated patients developing EV during the course of their disease. Furthermore, the risk of first variceal bleeding is closely linked to variceal size, portal pressure, red wale signs, and the severity of underlying hepatic dysfunction. Because variceal bleeding is associated with high rates of rebleeding and death, current clinical guidelines strongly recommend routine surveillance and prophylactic interventions in high-risk patients. [3,4]

Upper gastrointestinal endoscopy remains the gold standard for the diagnosis and grading of esophageal varices. However, routine endoscopic screening for all cirrhotic patients is limited by several important drawbacks including invasiveness, patient discomfort, limited availability, procedural cost, and dependence on experienced endoscopists. These limitations become particularly problematic in low-resource healthcare settings and in regions with high prevalence of chronic liver disease. In addition, many cirrhotic patients undergoing screening endoscopy are ultimately found to have either no varices or low-risk varices that do not require immediate therapeutic intervention. Consequently, there has been increasing interest in developing reliable noninvasive methods capable of identifying patients at high risk for clinically significant portal hypertension and variceal formation while reducing unnecessary endoscopic procedures. [5,6]

Over the last two decades, multiple noninvasive biomarkers and predictive models have been investigated as alternatives to routine endoscopic screening. These include serum fibrosis markers, platelet-based indices, radiological measurements, elastography techniques, and combined scoring systems. Among these markers, the right liver lobe diameter-to-albumin ratio (RLLD/Alb ratio) and the aspartate aminotransferase-to-platelet ratio index (APRI) have attracted growing attention due to their simplicity, accessibility, and potential diagnostic utility. Both parameters are inexpensive, reproducible, and based on routinely available laboratory and ultrasonographic assessments, making them particularly appealing in daily clinical practice. Their utility derives from the close relationship between hepatic structural alterations, synthetic dysfunction, thrombocytopenia, and progressive portal hypertension in cirrhotic patients. [7,8]

The RLLD/Alb ratio was initially proposed as a noninvasive marker for hepatic fibrosis and cirrhosis, combining ultrasonographic measurement of right hepatic lobe size with serum albumin concentration. Enlargement of the liver in early cirrhosis followed by progressive architectural distortion, together with declining hepatic synthetic function reflected by hypoalbuminemia, may contribute to the predictive value of this ratio. Several studies have subsequently demonstrated significant correlations between elevated RLLD/Alb ratios and the presence as well as severity of esophageal varices. Moreover, the

ratio has shown promise in identifying patients with clinically significant portal hypertension and high-risk varices requiring prophylactic management. [9,10]

Similarly, APRI has emerged as an important indirect marker of hepatic fibrosis and portal hypertension. Initially developed for assessing fibrosis severity in chronic hepatitis C infection, APRI incorporates serum aspartate aminotransferase (AST) levels and platelet count, both of which are profoundly affected by progressive hepatic fibrosis and splenic sequestration secondary to portal hypertension. Increasing evidence suggests that APRI may also predict the presence and grade of esophageal varices, as well as the risk of variceal bleeding, across different etiologies of cirrhosis. Because APRI is simple to calculate and requires no specialized equipment, it represents a potentially valuable tool for widespread screening and risk stratification. [11,12]

Although numerous studies have explored the role of individual noninvasive markers in predicting portal hypertension-related complications, the combined diagnostic significance of RLLD/Alb ratio and APRI remains insufficiently clarified. Furthermore, variability in study design, patient populations, etiologies of cirrhosis, and proposed cutoff values has limited the universal applicability of these markers in clinical practice. Current international guidelines continue to rely heavily on endoscopy and elastography-based strategies, while the precise role of combined biochemical and ultrasonographic indices remains an evolving area of investigation. Consequently, further synthesis of available evidence is required to better define the clinical utility, limitations, and future potential of these noninvasive biomarkers. [13,14]

This review aims to comprehensively evaluate the emerging role of the right liver lobe diameter-to-albumin ratio and APRI in predicting esophageal varices and variceal bleeding risk among cirrhotic patients. Additionally, the review discusses the pathophysiological basis of these markers, their diagnostic performance, comparative value relative to other noninvasive tools, and their potential integration into modern strategies for portal hypertension risk stratification and screening. [15]

Portal Hypertension and Pathogenesis of Esophageal Varices

Portal hypertension represents the principal hemodynamic abnormality underlying most complications of liver cirrhosis and is defined as a pathological increase in portal venous pressure. Under normal physiological conditions, the hepatic venous pressure gradient (HVPG) ranges between 1 and 5 mmHg. Clinically significant portal hypertension typically develops when HVPG exceeds 10 mmHg, while values above 12 mmHg are strongly associated with the development and rupture of esophageal varices. The pathogenesis of portal hypertension is multifactorial and involves both structural and dynamic alterations within the hepatic and splanchnic circulation. Progressive hepatic fibrosis, regenerative nodule formation, sinusoidal capillarization, and distortion of hepatic vascular architecture collectively increase resistance to portal blood flow. Concurrently, endothelial dysfunction and impaired intrahepatic vasodilatation further exacerbate portal pressure elevation. These mechanisms form the basis for the development of portosystemic collateral circulation and subsequent variceal formation in cirrhotic patients. [16,17]

The structural component of portal hypertension is primarily driven by chronic hepatic injury leading to activation of hepatic stellate cells and excessive extracellular matrix deposition. Fibrogenesis results in narrowing and compression of the hepatic sinusoids, thereby increasing intrahepatic vascular resistance. In addition, regenerative nodules mechanically disrupt normal vascular pathways and contribute to abnormal blood flow distribution within the cirrhotic liver. However, structural distortion alone does not fully explain the severity of portal hypertension. Dynamic changes including increased hepatic vascular tone mediated by reduced nitric oxide bioavailability, increased endothelin production, and enhanced contractility of activated stellate cells significantly contribute to elevated resistance within the hepatic microcirculation. These dynamic factors may account for approximately 20–30% of the increased intrahepatic resistance observed in cirrhosis. [18,19]

As portal pressure rises, compensatory hemodynamic alterations occur within the splanchnic circulation. Splanchnic vasodilatation, largely mediated by increased nitric oxide synthesis and other vasodilatory mediators, leads to increased portal venous inflow and establishment of a hyperdynamic circulatory

state. This hyperdynamic circulation is characterized by elevated cardiac output, reduced systemic vascular resistance, and increased splanchnic blood flow. Although initially compensatory, these changes further aggravate portal hypertension and contribute to progressive decompensation. The persistent increase in portal blood flow combined with elevated intrahepatic resistance creates sustained pressure overload within the portal venous system, promoting the development of collateral vessels that divert blood from the portal to systemic circulation. [20,21]

Esophageal varices develop as a consequence of portosystemic collateralization, particularly through dilation of the submucosal venous plexus in the distal esophagus and proximal stomach. The left gastric (coronary) vein serves as the principal vascular channel connecting the portal venous system to esophageal collaterals. Progressive elevation of portal pressure causes gradual dilation and elongation of these vessels, eventually resulting in clinically detectable varices. The prevalence and severity of esophageal varices correlate closely with the degree of portal hypertension and progression of liver disease. Small varices may enlarge over time, particularly in patients with ongoing hepatic injury, worsening portal pressure, or advanced hepatic dysfunction. Annual rates of progression from small to large varices have been estimated at approximately 10–15%, emphasizing the importance of regular surveillance and early risk stratification. [22,23]

Variceal rupture and bleeding occur when wall tension within the variceal vessel exceeds its structural capacity. According to Laplace's law, variceal wall tension is directly proportional to transmural pressure and variceal radius while inversely proportional to wall thickness. Large varices exposed to high portal pressures are therefore particularly susceptible to rupture. Endoscopic features such as red wale markings, cherry red spots, and hematocystic spots reflect thinning and increased fragility of the variceal wall and are recognized predictors of imminent bleeding risk. In addition, advanced liver dysfunction contributes to coagulopathy, thrombocytopenia, and impaired vascular integrity, all of which may increase the severity of hemorrhagic episodes once bleeding occurs. [24,25]

Acute variceal bleeding is one of the most severe complications of portal hypertension and remains associated with substantial mortality despite advances in pharmacological, endoscopic, and critical care management. Mortality rates following an initial variceal hemorrhage range from 15% to 25% within six weeks, with higher rates observed among patients with Child-Pugh class C cirrhosis, active bleeding during endoscopy, or renal dysfunction. Furthermore, recurrent bleeding is common and contributes significantly to long-term morbidity and healthcare utilization. Because variceal hemorrhage frequently occurs without preceding symptoms, accurate prediction of high-risk varices before bleeding develops is critically important for implementing prophylactic strategies such as nonselective beta-blockers or endoscopic variceal ligation. [26,27]

The severity of portal hypertension and risk of variceal bleeding are influenced by the underlying etiology of cirrhosis. Viral hepatitis, alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune liver disease, and cholestatic disorders may exhibit differing rates of fibrosis progression and portal pressure elevation. Moreover, inflammatory activity, endothelial dysfunction, and systemic hemodynamic alterations may vary among etiologies, potentially affecting the predictive performance of noninvasive biomarkers. Consequently, understanding the pathophysiological mechanisms underlying portal hypertension is essential for interpreting the clinical utility of markers such as RLLD/albumin ratio and APRI in different patient populations. [28,29]

Given the invasive nature and limited accessibility of direct portal pressure measurement through HVPG, considerable efforts have focused on identifying reliable surrogate markers capable of reflecting clinically significant portal hypertension and variceal risk. The ideal noninvasive marker should correlate strongly with portal pressure, accurately identify high-risk varices, be reproducible, inexpensive, and easily applicable in routine clinical settings. Parameters linked to hepatic synthetic dysfunction, fibrosis severity, splenic congestion, and altered hepatic morphology have therefore gained substantial attention. Within this context, the RLLD/albumin ratio and APRI have emerged as promising tools because they integrate multiple pathophysiological consequences of cirrhosis and portal hypertension into simple and readily obtainable indices. [30,31]

Current Approaches for Screening and Risk Stratification of Esophageal Varices

Early detection and risk stratification of esophageal varices constitute essential components in the management of cirrhotic patients because timely prophylactic interventions can substantially reduce the incidence of first variceal bleeding and associated mortality. Current screening strategies primarily focus on identifying clinically significant portal hypertension and distinguishing patients with high-risk varices who would benefit from pharmacological or endoscopic prophylaxis. Although upper gastrointestinal endoscopy remains the reference standard for diagnosis and grading of esophageal varices, increasing attention has been directed toward noninvasive methods capable of reducing unnecessary invasive procedures while maintaining adequate diagnostic accuracy. The growing burden of chronic liver disease worldwide has further emphasized the need for accessible, reproducible, and cost-effective screening modalities. [32,33]

Upper gastrointestinal endoscopy is considered the gold standard for evaluating esophageal varices because it permits direct visualization, grading, and therapeutic intervention when necessary. Endoscopic examination allows classification of varices according to size, appearance, and presence of high-risk stigmata such as red wale marks or cherry red spots. Current international guidelines recommend that all patients diagnosed with cirrhosis undergo screening endoscopy to evaluate for the presence of varices, followed by periodic surveillance depending on disease severity and initial findings. Patients with compensated cirrhosis and no varices generally undergo repeat endoscopy every two to three years, whereas those with small varices require more frequent monitoring. However, despite its diagnostic utility, endoscopy is invasive, resource-intensive, operator-dependent, and frequently associated with patient discomfort and poor compliance. Furthermore, a substantial proportion of screening endoscopies identify either absent or low-risk varices, raising concerns regarding procedural burden and healthcare costs. [34,35]

Measurement of the hepatic venous pressure gradient (HVPG) represents the gold standard method for direct assessment of portal hypertension severity. HVPG reflects the pressure difference between wedged and free hepatic venous pressure and correlates closely with the risk of decompensation, variceal formation, and bleeding. Clinically significant portal hypertension is defined by HVPG values $\geq$10 mmHg, while values exceeding 12 mmHg are strongly associated with variceal hemorrhage. HVPG is also useful for monitoring therapeutic response to portal pressure-lowering interventions such as nonselective beta-blockers. Nevertheless, HVPG measurement requires specialized expertise, invasive catheterization, fluoroscopic guidance, and limited availability in many healthcare settings. Consequently, its routine use remains largely confined to specialized tertiary centers and research applications. [36,37]

In recent years, transient elastography and other elastography-based techniques have emerged as valuable noninvasive tools for assessing hepatic fibrosis and portal hypertension. Liver stiffness measurement (LSM) correlates with fibrosis severity and portal pressure, particularly in compensated cirrhosis. Several studies have demonstrated that elevated liver stiffness values are associated with increased risk of esophageal varices and clinically significant portal hypertension. In addition, spleen stiffness measurement has shown promising diagnostic performance because splenic congestion directly reflects portal hemodynamic alterations. Elastography offers several advantages including rapid assessment, reproducibility, and noninvasive evaluation. However, its diagnostic accuracy may be influenced by obesity, ascites, acute hepatic inflammation, cholestasis, and operator experience. Moreover, the high cost and limited availability of elastography devices restrict their widespread implementation in resource-limited regions. [38,39]

To minimize unnecessary endoscopic screening, international consensus guidelines have proposed noninvasive risk stratification strategies based on elastography and platelet count parameters. The Baveno VI consensus introduced criteria suggesting that patients with compensated advanced chronic liver disease who have liver stiffness measurements below 20 kPa and platelet counts above 150 $\times 10^9$/L can safely avoid screening endoscopy because of the low probability of high-risk varices. Subsequent studies including the expanded Baveno VI criteria attempted to increase the number of spared

endoscopies while maintaining patient safety. Although these criteria demonstrated good negative predictive value, their applicability may vary according to cirrhosis etiology, disease stage, and local patient characteristics. In addition, dependence on elastography remains a limitation in many healthcare systems where access to FibroScan technology is restricted. [40,41]

Several laboratory-based indices have also been investigated as predictors of esophageal varices and portal hypertension. These include platelet count, platelet count-to-spleen diameter ratio, APRI, Fibrosis-4 index (FIB-4), Lok index, AST/ALT ratio, and various composite fibrosis scores. Thrombocytopenia represents one of the earliest hematological manifestations of portal hypertension and primarily results from hypersplenism and reduced thrombopoietin production. Consequently, platelet-based indices have shown moderate utility in predicting varices. The platelet count-to-spleen diameter ratio was among the earliest validated noninvasive markers and demonstrated promising diagnostic performance in several studies. Nevertheless, variability in cutoff values, patient populations, and study methodologies has prevented universal adoption of these indices as standalone screening tools. [42,43]

Radiological imaging modalities including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have also been explored in portal hypertension assessment. Ultrasonography remains widely used because it is inexpensive, safe, and readily available. Sonographic findings such as splenomegaly, portal vein dilatation, collateral circulation, altered liver morphology, and ascites may indirectly suggest portal hypertension. Additionally, Doppler ultrasonography can evaluate portal blood flow velocity and direction. However, conventional ultrasonography lacks sufficient sensitivity and specificity for reliable prediction of variceal grade or bleeding risk when used alone. CT and MRI provide more detailed vascular and anatomical information but are associated with higher costs, radiation exposure in CT, and limited practicality for routine screening. [44,45]

Despite significant advances in noninvasive evaluation, no single biomarker or modality has completely replaced endoscopy for the diagnosis of esophageal varices. Most available tools exhibit variable diagnostic performance across different populations and etiologies of liver disease. Moreover, many noninvasive indices primarily reflect fibrosis severity rather than direct portal hemodynamics. Therefore, combining biochemical, hematological, and imaging parameters may improve predictive accuracy and enhance clinical applicability. Within this evolving landscape, the right liver lobe diameter-to-albumin ratio and APRI have gained increasing interest because they integrate structural hepatic changes, synthetic dysfunction, and hematological alterations associated with progressive portal hypertension. Their simplicity, low cost, and accessibility make them particularly attractive candidates for incorporation into future screening algorithms. [46,47]

The ideal screening strategy for esophageal varices should accurately identify patients at high risk while minimizing unnecessary invasive procedures, healthcare expenditure, and patient burden. Consequently, ongoing research continues to focus on optimizing combinations of noninvasive markers capable of improving diagnostic precision and clinical decision-making. Understanding the strengths and limitations of current screening approaches provides an important framework for evaluating the emerging role of RLLD/albumin ratio and APRI in modern portal hypertension management. [48]

Right Liver Lobe Diameter-to-Albumin Ratio (RLLD/Albumin Ratio)

The right liver lobe diameter-to-albumin ratio (RLLD/Alb ratio) has emerged as a promising noninvasive marker for assessing hepatic fibrosis, portal hypertension, and esophageal varices in cirrhotic patients. This index combines ultrasonographic measurement of the right hepatic lobe with serum albumin concentration, thereby integrating structural hepatic alterations and synthetic liver dysfunction into a single parameter. The rationale behind this ratio is based on the progressive morphological and functional changes that occur during the evolution of chronic liver disease. As fibrosis advances and cirrhosis develops, hepatic architecture undergoes distortion accompanied by alterations in liver size and declining albumin synthesis. These pathophysiological changes are closely associated with worsening portal hypertension and increased risk of variceal formation. Consequently, the RLLD/Alb ratio has gained attention as an inexpensive, simple, and readily available tool for

noninvasive risk stratification in cirrhotic patients. [49,50]

Ultrasonographic assessment of the right liver lobe diameter is typically performed in the midclavicular line during quiet inspiration. Ultrasonography remains one of the most widely utilized imaging modalities in hepatology because it is noninvasive, accessible, cost-effective, and free from ionizing radiation. In cirrhosis, hepatic morphology may vary according to disease stage and etiology. Early disease may be associated with hepatomegaly due to inflammation and fatty infiltration, whereas advanced cirrhosis often results in nodular shrinkage and architectural distortion. Simultaneously, serum albumin concentration progressively declines because of impaired hepatic synthetic capacity, systemic inflammation, malnutrition, and increased catabolism. Combining these two variables into the RLLD/Alb ratio therefore provides a surrogate marker reflecting both structural hepatic remodeling and functional deterioration associated with portal hypertension progression. [51,52]

The RLLD/Alb ratio was initially proposed by Islam and colleagues as a noninvasive marker capable of distinguishing cirrhotic from noncirrhotic patients with chronic hepatitis C infection. Their study demonstrated that the ratio showed favorable diagnostic performance and correlated significantly with the severity of hepatic fibrosis. Subsequent investigations extended the application of this ratio to portal hypertension and esophageal varices prediction. Elevated RLLD/Alb values were found to correlate with increased portal venous pressure, splenomegaly, thrombocytopenia, and severity of liver dysfunction. Because portal hypertension develops as a direct consequence of progressive architectural distortion and fibrosis, the ratio may indirectly reflect the hemodynamic burden associated with advanced cirrhosis. [50,53]

Several clinical studies have evaluated the relationship between RLLD/Alb ratio and the presence of esophageal varices. Alempijevic et al. demonstrated that cirrhotic patients with esophageal varices had significantly higher RLLD/Alb ratios compared with those without varices. The ratio also correlated positively with variceal size and severity of portal hypertension. Importantly, the investigators suggested that the index could serve as a reliable screening tool for identifying patients requiring endoscopic evaluation. Similar findings were subsequently reported in other cohorts involving different etiologies of chronic liver disease, reinforcing the potential utility of this parameter in routine clinical practice. [49,54]

The predictive value of the RLLD/Alb ratio for high-risk varices is particularly important because identification of patients at increased bleeding risk represents the primary objective of variceal screening programs. Large varices, red wale markings, and advanced hepatic dysfunction are recognized predictors of first variceal hemorrhage. Several studies have shown that elevated RLLD/Alb ratios are associated not only with the presence of varices but also with higher variceal grades and bleeding risk. This relationship likely reflects the close association between progressive portal hypertension, worsening hepatic synthetic failure, and development of clinically significant collateral circulation. Therefore, the ratio may provide useful prognostic information beyond simple fibrosis assessment. [55,56]

One of the major advantages of the RLLD/Alb ratio lies in its simplicity and broad applicability. Both ultrasonographic liver measurements and serum albumin testing are routinely available in most healthcare settings, including low-resource regions where access to endoscopy or elastography may be limited. Unlike advanced imaging modalities or invasive pressure measurements, the ratio does not require specialized equipment or highly trained personnel. In addition, it is inexpensive and easily reproducible, making it suitable for repeated monitoring during disease progression. These characteristics enhance its potential role as a practical screening and triaging tool in large populations of cirrhotic patients. [57,58]

Despite these advantages, several limitations affect the universal applicability of the RLLD/Alb ratio. Ultrasonographic liver measurements may exhibit interobserver variability and can be influenced by patient body habitus, obesity, ascites, and operator expertise. Furthermore, liver morphology differs according to cirrhosis etiology and disease stage, potentially affecting the consistency of right lobe measurements across patient populations. Serum albumin levels may also be influenced by factors

unrelated to liver function including malnutrition, nephrotic syndrome, systemic inflammation, and protein-losing enteropathy. Consequently, interpretation of the ratio should always occur within the broader clinical context rather than as an isolated diagnostic parameter. [59,60]

Another important limitation involves the heterogeneity of proposed cutoff values across different studies. Various investigators have reported differing threshold values for predicting esophageal varices and clinically significant portal hypertension, limiting standardization and widespread implementation. Differences in study design, patient selection, sample size, etiology of cirrhosis, and endoscopic grading systems may contribute to these discrepancies. Moreover, most available studies have been conducted in relatively small single-center cohorts, emphasizing the need for larger multicenter validation studies to establish optimal cutoff values and improve generalizability. [61,62]

Comparative analyses between RLLD/Alb ratio and other noninvasive predictors have shown variable results. While some studies demonstrated diagnostic accuracy comparable to platelet count/spleen diameter ratio or APRI, others suggested that combining multiple biomarkers may provide superior predictive performance. Integrating RLLD/Alb ratio with laboratory indices, elastography findings, or clinical scoring systems may enhance sensitivity and specificity for identifying high-risk varices. Such combined approaches align with the current trend toward multiparametric risk stratification models in portal hypertension assessment. [63,64]

Overall, the RLLD/Alb ratio represents a promising noninvasive biomarker that reflects both structural and functional consequences of chronic liver disease. Its accessibility, affordability, and association with portal hypertension severity make it an attractive candidate for incorporation into future screening algorithms for esophageal varices and bleeding risk. Nevertheless, additional large-scale prospective studies are required to standardize measurement techniques, validate diagnostic thresholds, and define its precise role relative to emerging elastography-based and composite predictive models. [65]

Aspartate Aminotransferase-to-Platelet Ratio Index (APRI)

The aspartate aminotransferase-to-platelet ratio index (APRI) is one of the most widely studied noninvasive biomarkers for the assessment of hepatic fibrosis and cirrhosis. Initially developed by Wai and colleagues in patients with chronic hepatitis C infection, APRI was designed as a simple laboratory-based index capable of predicting significant fibrosis and cirrhosis without the need for liver biopsy. Over time, its clinical utility expanded beyond fibrosis assessment to include evaluation of portal hypertension, esophageal varices, and variceal bleeding risk. APRI gained substantial attention because it relies on two routinely available laboratory parameters—serum aspartate aminotransferase (AST) level and platelet count—making it inexpensive, reproducible, and easily applicable in daily clinical practice. [66,67]

The APRI score is calculated using the following formula:

APRI=(AST/ULNPlatelet Count (109/L))×100APRI = \left(\frac{AST / ULN}{Platelet\ Count\ (10^9/L)} \right) \times 100APRI=(Platelet Count (109/L)AST/ULN)×100

where AST represents serum aspartate aminotransferase concentration, ULN denotes the upper limit of normal for AST, and platelet count is expressed as $\times 10^9$/L. Elevated AST levels reflect hepatocellular injury and necroinflammatory activity, while thrombocytopenia primarily reflects portal hypertension-induced hypersplenism and reduced thrombopoietin synthesis in advanced liver disease. Therefore, APRI indirectly integrates biochemical and hematological consequences of hepatic fibrosis and portal hypertension into a single predictive index. [66,68]

The pathophysiological basis linking APRI to portal hypertension and esophageal varices derives from progressive hepatic fibrosis and increasing intrahepatic vascular resistance. Chronic hepatic injury leads to hepatocyte necrosis and inflammatory activity, contributing to elevated aminotransferase levels. Simultaneously, worsening fibrosis and portal hypertension result in splenic congestion, hypersplenism, and platelet sequestration, ultimately causing thrombocytopenia. As cirrhosis advances, these processes intensify and become increasingly associated with clinically significant portal hypertension and collateral vessel formation. Consequently, elevated APRI values have been correlated with both fibrosis severity and the presence of esophageal varices in multiple studies involving diverse etiologies of

chronic liver disease. [69,70]

Several investigations have demonstrated the diagnostic utility of APRI in predicting esophageal varices among cirrhotic patients. Sebastiani and colleagues evaluated multiple serum-based noninvasive markers and reported that APRI was significantly associated with the presence of varices and advanced portal hypertension. Similarly, Deng et al. found that APRI showed moderate diagnostic accuracy for identifying esophageal varices and could serve as a useful adjunctive screening tool in cirrhotic patients. Other studies further demonstrated positive correlations between increasing APRI values and variceal grade, suggesting that APRI may also provide prognostic information regarding variceal severity and bleeding risk. [43,64]

The ability of APRI to predict high-risk varices is clinically important because large varices and advanced portal hypertension are strongly associated with first variceal hemorrhage. Several studies have reported significantly higher APRI scores in patients with large varices compared with those with small or absent varices. This association may reflect the close relationship between progressive fibrosis, worsening portal hypertension, and splenic sequestration of platelets. In addition, elevated APRI values have been associated with decompensated cirrhosis, ascites, and impaired hepatic reserve, all of which contribute to increased bleeding susceptibility and poorer clinical outcomes. Therefore, APRI may function not only as a fibrosis marker but also as an indirect indicator of portal hypertension severity and hemorrhagic risk. [71,72]

One of the major strengths of APRI is its exceptional simplicity and accessibility. Unlike elastography or HVPG measurement, APRI requires no specialized equipment, imaging technology, or invasive procedures. Because AST levels and platelet counts are routinely obtained during evaluation of chronic liver disease, APRI can be calculated rapidly and repeatedly without additional cost. This characteristic makes the index particularly valuable in resource-limited settings where advanced diagnostic modalities may not be available. Furthermore, APRI is easily reproducible and suitable for large-scale screening strategies aimed at identifying cirrhotic patients requiring endoscopic surveillance. [73,74]

Despite its advantages, APRI has several important limitations that affect its diagnostic performance in portal hypertension assessment. Serum AST levels may fluctuate due to acute inflammation, alcohol intake, muscle injury, medication effects, or concomitant metabolic disorders, potentially reducing specificity for hepatic fibrosis. Likewise, thrombocytopenia may result from causes unrelated to portal hypertension including bone marrow suppression, viral infections, immune thrombocytopenia, or drug-induced platelet destruction. Consequently, APRI may be less accurate in patients with multifactorial hematological abnormalities or fluctuating hepatic inflammatory activity. [75,76]

Another challenge involves variability in proposed APRI cutoff values for predicting esophageal varices and clinically significant portal hypertension. Different studies have utilized diverse thresholds depending on patient populations, cirrhosis etiologies, and study methodologies. This heterogeneity has limited universal standardization and contributed to inconsistent sensitivity and specificity across studies. In general, APRI demonstrates moderate diagnostic accuracy rather than sufficient precision to independently replace endoscopic screening. Therefore, many investigators advocate combining APRI with other clinical, laboratory, or imaging parameters to improve predictive performance and enhance risk stratification. [77,78]

Comparative studies evaluating APRI alongside other noninvasive markers have yielded variable findings. Some investigations reported comparable diagnostic performance between APRI and platelet count/spleen diameter ratio, while others suggested superiority of elastography-based approaches. Nevertheless, APRI consistently demonstrates value as a low-cost preliminary screening tool, particularly when incorporated into multiparametric predictive models. Combining APRI with ultrasonographic indices such as the RLLD/albumin ratio may improve identification of high-risk varices by integrating biochemical, hematological, and structural hepatic alterations associated with portal hypertension progression. [79,80]

Recent research has also explored the prognostic significance of APRI in predicting clinical outcomes among cirrhotic patients. Elevated APRI values have been associated with increased risk of hepatic

decompensation, mortality, and portal hypertension-related complications. In addition, APRI may help identify patients with compensated advanced chronic liver disease who are more likely to progress toward clinically significant portal hypertension and require closer surveillance. Such findings support the broader role of APRI within modern noninvasive hepatology beyond fibrosis staging alone. [81,82] Overall, APRI remains an attractive and clinically practical noninvasive biomarker for evaluating hepatic fibrosis, portal hypertension, and esophageal varices risk. Although its standalone diagnostic accuracy may be insufficient to completely replace endoscopic screening, its affordability, accessibility, and reproducibility make it highly valuable in routine clinical practice. Future studies focusing on standardized cutoff values, multicenter validation, and integration with complementary biomarkers may further enhance the role of APRI in portal hypertension risk stratification and prediction of variceal bleeding. [83]

Conclusion

Noninvasive biomarkers have become increasingly important in the assessment of portal hypertension and prediction of esophageal varices among cirrhotic patients. Both the right liver lobe diameter-to-albumin ratio and APRI represent simple, inexpensive, and readily accessible tools that reflect key structural, functional, and hematological alterations associated with progressive liver disease. Current evidence suggests that these markers demonstrate useful diagnostic value in identifying patients at increased risk of esophageal varices and variceal bleeding, particularly when used in combination with other clinical and imaging parameters. Although neither marker can currently replace endoscopic evaluation as the gold standard, their incorporation into multiparametric screening strategies may help reduce unnecessary invasive procedures and improve risk stratification, especially in resource-limited settings. Further large-scale prospective studies are required to validate standardized cutoff values and define their precise role within modern portal hypertension management algorithms

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