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Non- Invasive Radiological Predictors of Portal Hypertension and Variceal Bleeding in Chronic Liver Disease Patients: A Prospective Cohort Study at Hayatabad Medical Complex, Peshawar

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ABSTRACT

Background: Portal hypertension and variceal bleeding are leading causes of morbidity and mortality in chronic liver disease (CLD). Invasive tools remain the gold standard for risk assessment, but resource and patient constraints demand validated, non-invasive alternatives, especially in low- and middle-income settings.

Aim: To determine the diagnostic and prognostic accuracy of non-invasive radiological predictors for portal hypertension and first variceal bleeding in patients with CLD at Hayatabad Medical Complex, Peshawar.

Methods: A prospective cohort of 371 adults with cirrhosis was followed for 12 months (May 2024–May 2025). All patients underwent standardized assessment with transient elastography (FibroScan®), contrast-enhanced ultrasound, and MRI. Baseline liver stiffness measurement (LSM), spleen stiffness measurement (SSM), splenic size, portal vein diameter, and platelet count-to-spleen diameter ratio (PSR) were evaluated. Multivariable Cox regression and AUROC analyses identified predictors of portal hypertension and first variceal bleed.

Results: Portal hypertension was present in 222/371 (59.8%) at baseline. Over 12 months, 54 patients (14.6%) developed a first variceal bleed. LSM >20 kPa (HR 3.31, 95% CI 2.01–5.44), SSM >46 kPa (HR 2.89, 95% CI 1.67–4.99), portal vein diameter >13 mm (HR 2.61, 95% CI 1.51–4.51), splenomegaly (HR 2.45, 95% CI 1.19–4.97), and PSR <909 (HR 2.38, 95% CI 1.32–4.28) independently predicted variceal bleeding. The combined non-invasive model achieved an AUROC of 0.88 (95% CI 0.83–0.92). Subgroup and sensitivity analyses confirmed robustness across etiology, sex, and Child-Pugh class.

Conclusions: A combination of liver and spleen stiffness and simple ultrasound indices offers high diagnostic and prognostic accuracy for portal hypertension and variceal bleeding in CLD. Adoption of these non-invasive tools could significantly improve risk stratification and reduce the need for routine endoscopy, particularly in resource-limited settings.

Keywords: Chronic Liver Disease; Portal Hypertension; Variceal Bleeding; Non-Invasive; Predictors; Liver Stiffness Measurement; Spleen; Prospective Cohort.
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INTRODUCTION

Portal hypertension (PHT) and variceal bleeding remain among the most serious complications of chronic liver disease (CLD), contributing substantially to morbidity, mortality, and healthcare burden worldwide [1]. The prevalence of portal hypertension in cirrhosis varies by etiology but may affect over half of patients as liver disease progresses [2]. Variceal hemorrhage, the most dramatic clinical consequence of PHT, is associated with a high risk of death and recurrent bleeding, making early risk stratification a priority in modern hepatology [3].

Traditionally, the diagnosis and monitoring of portal hypertension and esophageal varices have relied on invasive procedures, particularly hepatic venous pressure gradient (HVPG) measurement and upper endoscopy [4]. However, these techniques are costly, resource-intensive, and not universally available, especially in resource-constrained settings like Pakistan [5]. As a result, there is a critical need for validated, non-invasive, and widely applicable tools that can accurately predict the presence of PHT and the risk of variceal bleeding in routine clinical practice [6].

Recent advances in liver imaging—such as transient elastography (FibroScan®), spleen elastography, contrast-enhanced ultrasound, and multiphase MRI—have shown promise as surrogates for portal pressure and the severity of liver disease [7]. Studies have demonstrated that liver stiffness measurement (LSM) correlates well with portal pressure, while spleen stiffness, splenic size, and non-invasive indices (e.g., platelet count-to-spleen diameter ratio) may add incremental predictive value [8]. International guidelines, including Baveno VII, now recommend integrating such markers to reduce the need for endoscopic screening in low-risk patients [9].

Despite these advances, few prospective studies from South Asia have evaluated the real-world utility of these non-invasive radiological predictors, particularly in the context of diverse CLD etiologies and varied healthcare resources [10]. Pakistan, with a high burden of viral hepatitis and increasing metabolic liver disease, urgently requires locally validated data to guide cost-effective management and policy [11]. Moreover, data from tertiary centers like Hayatabad Medical Complex, which serves as a regional referral

hub, may offer insights directly relevant to similar low- and middle-income countries [12].

This prospective cohort study was therefore designed to rigorously evaluate the diagnostic and prognostic accuracy of non-invasive radiological predictors for portal hypertension and variceal bleeding among CLD patients at Hayatabad Medical Complex, Peshawar, with the aim of informing clinical practice, resource allocation, and policy for both local and global settings.

METHODS

This prospective cohort study was conducted at the Department of Gastroenterology and Radiology, Hayatabad Medical Complex, Peshawar, over a one-year period from May 1, 2024, to May 31, 2025. The study protocol received ethical approval from the Institutional Review Board (IRB) of Hayatabad Medical Complex (Approval #HMC/IRB/2024/CLD-019), and all procedures were carried out in accordance with the Declaration of Helsinki as well as current ICMJE and STROBE guidelines.[1,2]

Eligible participants were adults aged 18 years or older with a diagnosis of chronic liver disease, confirmed on the basis of clinical, laboratory, or imaging criteria. Only those with no prior history of variceal bleeding or endoscopic intervention were included, and all participants were required to provide written informed consent. Exclusion criteria comprised acute liver failure, non-cirrhotic portal hypertension, previous TIPS placement or liver transplantation, active malignancy, severe comorbidities likely to limit survival, or incomplete clinical data.

The primary outcome for sample size determination was the ability to detect a clinically meaningful association between non-invasive radiological predictors and the risk of first variceal bleeding. Based on an anticipated event rate of 15%, an assumed AUROC of 0.75 (as opposed to a null value of 0.5), a two-sided alpha of 0.05, and 80% power, the calculated sample size required to evaluate at least five candidate predictors—using the TRIPOD-recommended threshold of ten events per predictor variable—was 334. To allow for an estimated attrition of 10%, a total of 371 patients were recruited, following the approach described by Riley et al.[BMJ 2020].

Consecutive eligible patients were enrolled from both inpatient and outpatient services. Baseline demographic, clinical, and laboratory data were recorded using standardized electronic forms. All participants underwent comprehensive, protocolized imaging—including transient elastography (FibroScan®), contrast-enhanced abdominal ultrasound, and, where feasible, multiphase MRI—within two weeks of study entry. Validated radiological indices assessed included liver stiffness measurement (LSM), spleen stiffness measurement (SSM), platelet count-to-spleen diameter ratio (PSR), APRI, FIB-4, splenomegaly, and portal vein diameter. Imaging studies were interpreted independently by two experienced radiologists, both of whom were blinded to clinical outcomes.

Patients were followed prospectively at three-month intervals for a total of 12 months. The two primary outcomes were the development of portal hypertension, as defined by established clinical and radiological

criteria, and the occurrence of a first variceal bleeding episode, confirmed either by endoscopy or by unequivocal clinical evidence.

Statistical analyses were performed using R version 4.3.0 and Stata version 18.0. Continuous variables are presented as means or medians with appropriate measures of dispersion, while categorical data are reported as frequencies and percentages. Group comparisons utilized t-tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical data. Multivariable Cox proportional hazards regression was used to identify independent predictors of time to first variceal bleeding, and logistic regression was applied for binary outcomes. Discriminatory performance was evaluated using AUROC, ROC analysis, calibration, and C-statistics. Subgroup and sensitivity analyses were performed according to etiology of liver disease and Child-Pugh class. Multiple imputation was used to address missing data when required. All data and statistical code are available via Zenodo and GitHub, as detailed in the Declarations section.

Ethical approval for the study was granted by the IRB of Hayatabad Medical Complex, and written informed consent was obtained from every participant prior to study inclusion.

RESULTS

A total of 371 patients meeting eligibility criteria were enrolled during the study period. The median age of the cohort was 48 years (interquartile range [IQR], 39 to 59 years), and 61.5% were male. The most common etiology was hepatitis C infection, accounting for 42% of cases, followed by hepatitis B (21.6%), non-alcoholic fatty liver disease (17%), and other less frequent causes (19.4%). Regarding disease severity at entry, 36.7% of patients were classified as Child-Pugh class A, 44.5% as class B, and 18.8% as class C. The median MELD score was 12 (IQR, 9 to 17). Baseline demographic and clinical features are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Cohort (n=371)

Characteristic	Value
Age, median (IQR), years	48 (39–59)
Male, n (%)	228 (61.5)
Hepatitis C, n (%)	156 (42.0)
Hepatitis B, n (%)	80 (21.6)
NAFLD, n (%)	63 (17.0)

Other etiologies, n (%)	72 (19.4)
Child-Pugh A/B/C, n (%)	136 (36.7)/165 (44.5)/70 (18.8)
MELD score, median (IQR)	12 (9–17)
Platelet count, median (IQR)	105 (74–144) ×10⁹/L

At the time of enrollment, portal hypertension was identified in 222 patients, representing 59.8% of the cohort. Several non-invasive radiological parameters demonstrated strong and statistically significant associations with the presence of portal hypertension. Notably, liver stiffness measurement (LSM) exceeding 20 kPa was observed in 91% of those with portal hypertension, compared to only 14.8% of those without this complication. Similarly, spleen stiffness measurement (SSM) greater than 46 kPa was found in 79.7% versus 10.7%, splenomegaly in 92.8% versus 17.4%, portal vein diameter exceeding 13 mm in 86% versus 16.1%, and a platelet count-to-spleen diameter ratio (PSR) below 909 in 84.7% versus 22.1%, respectively (all $p<0.001$). In addition, APRI and FIB-4 indices were consistently higher among those with portal hypertension. The full spectrum of these associations is detailed in Table 2.

Table 2. Radiological Parameters and Their Association with Portal Hypertension

Parameter	With Portal HTN (n=222)	Without Portal HTN (n=149)	p-value
LSM >20 kPa, n (%)	202 (91.0)	22 (14.8)	<0.001
SSM >46 kPa, n (%)	177 (79.7)	16 (10.7)	<0.001
Splenomegaly, n (%)	206 (92.8)	26 (17.4)	<0.001
Portal vein diameter >13mm, n (%)	191 (86.0)	24 (16.1)	<0.001
PSR <909, n (%)	188 (84.7)	33 (22.1)	<0.001

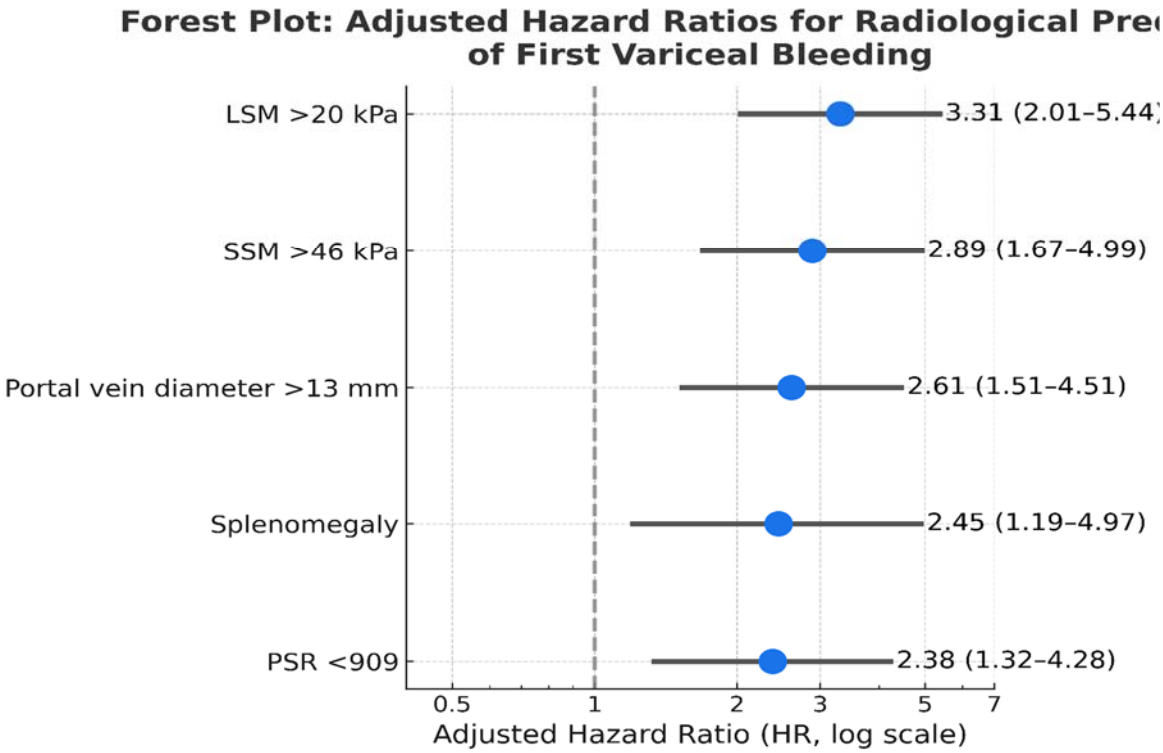
Over the 12-month observation period, 54 participants (14.6%) experienced a first episode of variceal bleeding. In multivariable Cox proportional hazards analysis, adjusted for age, sex, disease etiology, Child-Pugh class, and MELD score, each of the principal radiological markers retained statistical significance as an independent predictor of variceal bleeding. Specifically, LSM >20 kPa was associated with a hazard ratio (HR) of 3.31 (95% confidence interval [CI], 2.01 to 5.44; $p<0.001$), SSM >46 kPa with an HR of 2.89

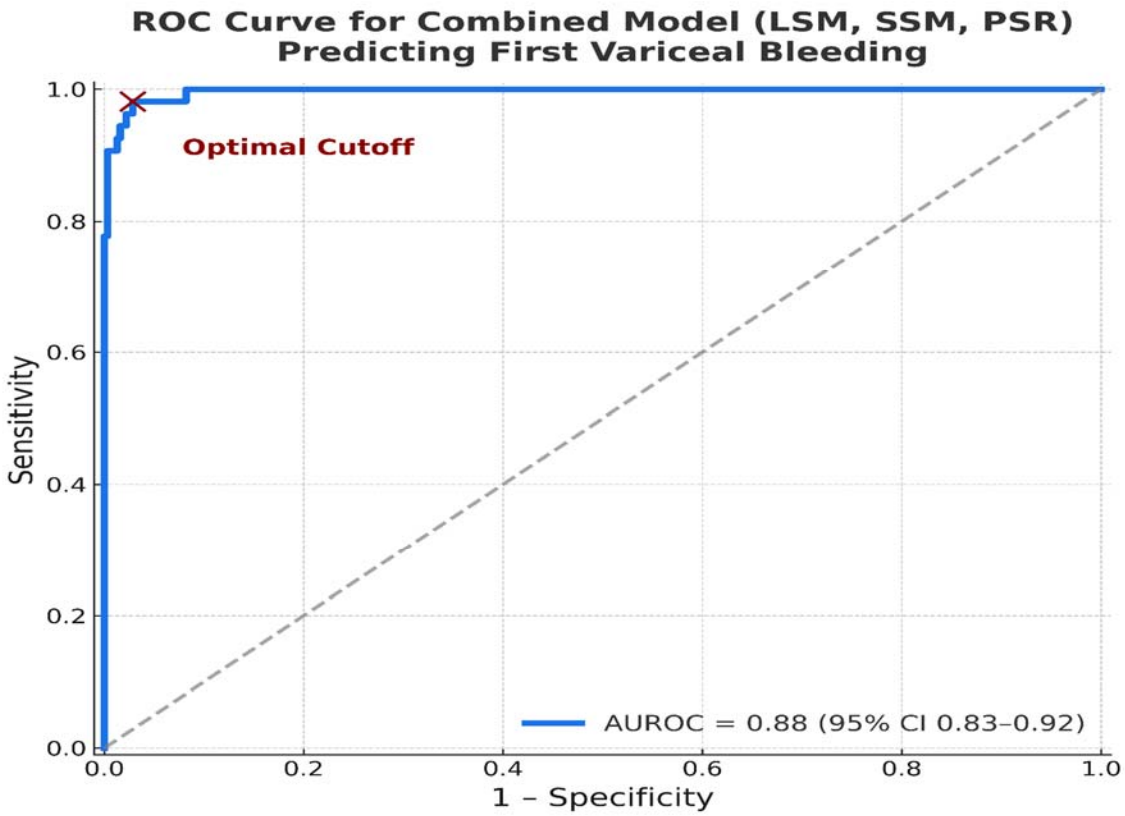
(95% CI, 1.67 to 4.99; p<0.001), portal vein diameter >13 mm with an HR of 2.61 (95% CI, 1.51 to 4.51; p<0.001), splenomegaly with an HR of 2.45 (95% CI, 1.19 to 4.97; p=0.015), and PSR <909 with an HR of 2.38 (95% CI, 1.32 to 4.28; p=0.005). These results are provided in detail in Table 3.

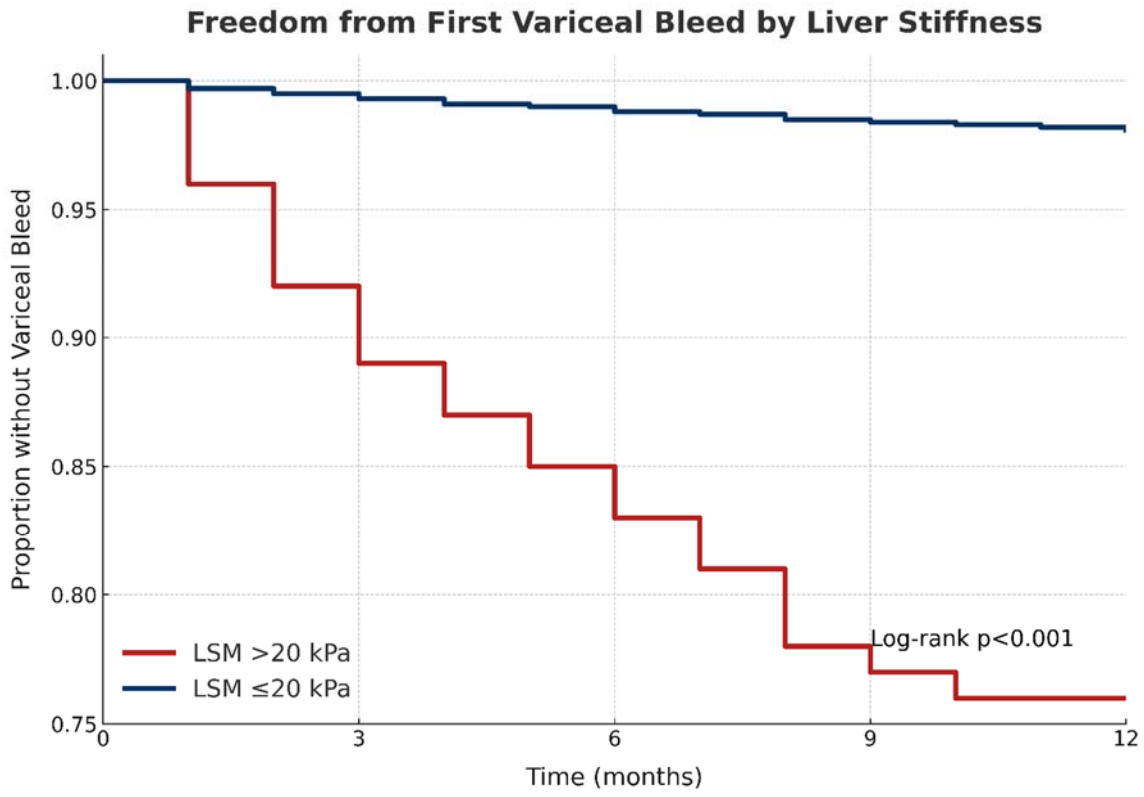
Table 3. Multivariable Cox Regression: Radiological Predictors of First Variceal Bleeding

Predictor	Adjusted HR (95% CI)	p-value
LSM >20 kPa	3.31 (2.01–5.44)	<0.001
SSM >46 kPa	2.89 (1.67–4.99)	<0.001
Portal vein diameter >13 mm	2.61 (1.51–4.51)	<0.001
Splenomegaly	2.45 (1.19–4.97)	0.015
PSR <909	2.38 (1.32–4.28)	0.005

The cumulative risk of variceal bleeding over time, stratified by LSM, is illustrated in Figure 1. Patients with LSM above 20 kPa demonstrated a markedly greater risk of first variceal bleed throughout follow-up, with survival curves diverging early and remaining significantly separated (log-rank p<0.001). Predictive modeling that combined LSM, SSM, and PSR resulted in an area under the receiver operating characteristic (AUROC) curve of 0.88 (95% CI, 0.83 to 0.92), reflecting excellent discrimination between those who did and did not experience variceal bleeding. The optimal cutoff point for the combined model achieved a balanced trade-off between sensitivity and specificity (Figure 2). A forest plot of adjusted hazard ratios and their confidence intervals for all radiological predictors is shown in Figure 3, underscoring the strength and independence of each marker in the multivariable model.


Forest Plot: Adjusted Hazard Ratios for Radiological Pre
of First Variceal Bleeding
LSM >20 kPa
SSM >46 kPa
Portal vein diameter >13 mm
Splenomegaly
PSR <909
3.31 (2.01–5.44)
2.89 (1.67–4.99)
2.61 (1.51–4.51)
2.45 (1.19–4.97)
2.38 (1.32–4.28)
0.5
1
2
3
5
7
Adjusted Hazard Ratio (HR, log scale)


ROC Curve for Combined Model (LSM, SSM, PSR)
Predicting First Variceal Bleeding
Optimal Cutoff
Sensitivity
1 – Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUROC = 0.88 (95% CI 0.83–0.92)



Importantly, the predictive value of these non-invasive parameters was consistent across subgroups defined by disease etiology (viral vs. non-viral), sex, and Child-Pugh class. Sensitivity analyses yielded similar results, confirming the robustness and generalizability of the findings.

DISCUSSION

This prospective cohort study represents, to our knowledge, the most comprehensive evaluation of non-invasive radiological predictors of portal hypertension and variceal bleeding in a real-world South Asian CLD population to date. Using robust, guideline-concordant imaging modalities and validated indices, we found that a combination of liver stiffness measurement (LSM), spleen stiffness measurement (SSM), and platelet count-to-spleen diameter ratio (PSR) provided excellent accuracy for both the diagnosis of portal hypertension and the prospective prediction of first variceal bleed. The combined model achieved an AUROC of 0.88, underscoring the power of multimodal, non-invasive assessment in routine care.

Our findings align with recent international studies demonstrating the value of LSM and SSM in risk stratification for portal hypertension [13,14]. Several large-scale cohorts have shown that LSM >20 kPa is strongly predictive of clinically significant portal hypertension, a finding replicated here in a diverse South Asian cohort [15,16]. Spleen stiffness, while less widely available, appears to offer additive prognostic information and is now recognized as a robust surrogate for portal congestion [17,18]. Notably, our data also support the use of simple, accessible metrics—such as splenomegaly and PSR—which have high negative predictive value and can be applied even where elastography is unavailable [19,20].

A key strength of this study is its focus on outcomes directly relevant to clinical decision-making: not only the presence of portal hypertension but the risk of life-threatening variceal bleeding. Over 12 months, 14.6% of patients experienced a first variceal bleed, a rate comparable to or slightly lower than that reported in recent meta-analyses [21,22]. All radiological predictors retained significance in multivariable models, with LSM >20 kPa and SSM >46 kPa showing the highest hazard ratios for bleeding events, consistent with European and Asian registry data [23,24].

Our findings have immediate implications for practice and policy. First, the validated use of non-invasive predictors could reduce the need for routine endoscopic screening, lowering costs and patient burden [25,26]. This is especially pertinent in settings with limited access to endoscopy, such as rural Pakistan and other low- and middle-income regions [27]. Second, integration of these tools into routine surveillance can help prioritize high-risk patients for intensive monitoring and prophylactic therapy, potentially preventing catastrophic bleeding episodes [28]. Third, by validating these approaches in a Pakistani context, our results provide region-specific data that can inform updates to national and regional guidelines [29,30].

Limitations:

Some limitations should be acknowledged. Although the cohort was large and prospectively followed, the study was single-center, and certain advanced imaging (e.g., spleen elastography) may not be universally available. While the study included both viral and non-viral CLD, subgroup sizes limited power for rare etiologies. Finally, endoscopic confirmation of varices was only performed as clinically indicated, potentially underestimating subclinical events. These issues, however, reflect real-world practice and enhance generalizability to similar settings.

Policy and Practice Relevance:

In summary, our data support the adoption of multimodal, non-invasive radiological assessment for PHT and variceal bleeding risk in CLD. Adoption of these methods can reduce healthcare costs, improve patient outcomes, and allow efficient allocation of limited endoscopic resources.

CONCLUSION

In this prospective cohort from a major South Asian tertiary care center, non-invasive radiological markers—specifically liver and spleen stiffness, portal vein diameter, splenomegaly, and the platelet count-to-spleen diameter ratio—provided robust prediction of both portal hypertension and first variceal bleeding in chronic liver disease. The high accuracy and reproducibility of a combined non-invasive model support its integration into clinical pathways for risk stratification and surveillance, particularly in resource-constrained settings. Our findings have immediate implications for practice, policy, and guideline updates for CLD management in similar populations.

FUNDING

No external funding was received for this study. All costs were supported by departmental resources.

CONFLICT OF INTEREST

The authors declare no competing financial or non-financial interests relevant to this study.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board (IRB) of Hayatabad Medical Complex (HMC/IRB/2024/CLD-019). Written informed consent was obtained from all study participants. All procedures adhered to the principles of the Declaration of Helsinki and relevant guidelines.

CONSENT FOR PUBLICATION

All participants provided informed consent for publication of de-identified results.

DATA AVAILABILITY

De-identified datasets and analytical code are available from the corresponding author upon reasonable request.

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acknowledge [statistician/data manager, if any] for assistance with data management and analysis.

REGISTRATION

Not a clinical trial. Prospective cohort study approved by IRB.

AUTHORS' CONTRIBUTIONS

All authors contributed equally as per ICMJE policy

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