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Original Article

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Serum Serotonin and Noninvasive Portal Hypertension Indices in Relation to Esophageal Variceal Severity in Cirrhosis: An Exploratory Cross-Sectional Study

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Abstract

Background: Esophageal varices are a life-threatening consequence of portal hypertension in liver cirrhosis, and upper gastrointestinal endoscopy, the reference standard for detecting them, is invasive and resource-intensive. Serum serotonin, over 90% of which is stored in circulating platelets, has been proposed as a candidate biochemical correlate of portal hypertensive and fibrotic change, but its relationship to variceal severity alongside established noninvasive indices has not been well characterized. This study aimed to determine the association of serum serotonin, Child-Pugh class, portal vein diameter, and platelet count to spleen diameter ratio (PSR) with endoscopically graded esophageal variceal severity in patients with liver cirrhosis, and to explore the diagnostic performance of these markers for identifying high-grade varices.

Methods: In this exploratory cross-sectional study, 140 participants were enrolled into five prespecified groups of fixed size: non-hepatic controls (n = 40), cirrhosis without varices (n = 40), and grade 1 (n = 20), grade 2 (n = 20), and grade 3 (n = 20) esophageal varices confirmed endoscopically. Serum serotonin was measured by enzyme-linked immunosorbent assay (ELISA). Group comparisons used one-way ANOVA or the Kruskal-Wallis test according to the normality of model residuals, and the chi-square or Fisher-Freeman-Halton exact test for categorical variables. Spearman correlation and multivariable ordinal logistic regression identified independent predictors of variceal grade among the 60 participants with varices, and receiver operating characteristic (ROC) analysis assessed diagnostic performance for grade 2/3 varices among the 99 cirrhotic participants with complete data, with bootstrap correction of cutoff-based estimates for optimism and pairwise DeLong comparison of AUCs; a Firth-penalized model was fitted as a sensitivity analysis.

Results: Serum serotonin rose progressively across groups, from 30.0 ± 5.6 ng/mL in controls to 106.5 ± 5.2 ng/mL in grade 3 varices ($F = 347.575$, $P < 0.001$), and was, together with portal vein diameter, an independent predictor of variceal grade after adjustment (adjusted odds ratio (OR) of 7.48 per 10 ng/mL, $P = 0.0009$; portal vein diameter adjusted OR of 1.70 per 0.1 mm, $P = 0.0002$; exploratory model,

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n = 59). Apparent areas under the curve (AUCs) for grade 2/3 varices were 0.944 (95% confidence interval (CI), 0.895–0.980) for serotonin, 0.923 (0.864–0.974) for portal vein diameter, 0.764 for PSR, and 0.746 for Child-Pugh class; serotonin and portal vein diameter did not differ significantly (DeLong P = 0.553), whereas each exceeded PSR and Child-Pugh class (all P ≤ 0.004). Both associations persisted in the penalized model, and optimism correction changed the accuracy estimates only slightly.

Conclusions: In this exploratory study, serum serotonin tracked with esophageal variceal severity and, alongside portal vein diameter, was independently associated with variceal grade, with discrimination comparable to that of portal vein diameter. Because the sample was enriched by design and cutoffs were derived and tested in the same cohort, these findings are hypothesis-generating and require validation in unselected surveillance cohorts before clinical use.

Keywords: Liver cirrhosis; Esophageal and gastric varices; Serotonin; Child-Pugh score; Portal hypertension; Platelet count to spleen diameter ratio

Introduction

Liver cirrhosis is the common histological endpoint of chronic liver injury and remains a major contributor to global mortality, with cirrhosis-related deaths continuing to rise across most regions over recent decades [1, 2]. Portal hypertension, the principal hemodynamic consequence, drives the formation of portosystemic collaterals, of which esophageal varices are the most clinically important. Once formed, varices can enlarge over time and eventually rupture, and variceal hemorrhage remains one of the leading causes of death in decompensated cirrhosis, carrying substantial short-term mortality despite advances in endoscopic and pharmacological therapy over the past two decades. Roughly half of patients already have esophageal varices at the time cirrhosis is first diagnosed, and this proportion rises further as hepatic decompensation progresses, making reliable identification of at-risk patients a recurring surveillance need rather than a single assessment at diagnosis.

Upper gastrointestinal endoscopy remains the reference standard for detecting and grading esophageal varices, and current international consensus continues to recommend endoscopic assessment in patients at elevated risk of variceal hemorrhage [3]. Endoscopy is nonetheless invasive, requires sedation and dedicated resources, and is poorly tolerated by some patients, particularly where repeated surveillance is required over many years. These practical limitations have sustained a long-standing effort to identify noninvasive clinical, biochemical, and ultrasonographic parameters capable of triaging patients toward, or safely away from, endoscopic assessment.

The Child-Pugh classification, derived from serum bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy, was originally developed to stratify surgical risk in cirrhosis and remains one of the most widely used prognostic tools in chronic liver disease [4, 5]; it correlates broadly with the severity of portal hypertensive complications, although it reflects hepatic synthetic reserve rather than variceal anatomy directly. Portal vein diameter, measured by abdominal ultrasound, offers a simple surrogate of portal hypertensive hemodynamics that has been associated with the presence of varices [6], although its measurement is influenced by respiratory phase, hydration status, and operator technique. Thrombocytopenia secondary to hypersplenism is a further downstream consequence of portal hypertension, and the platelet count to spleen diameter ratio (PSR), which combines both effects into a single index, has been evaluated across several cohorts as a correlate of variceal presence and severity [7–9], although its diagnostic accuracy varies with the population studied and the cutoff selected. None of these three indices was developed with the others in mind, and although each has been validated individually, their relative and combined performance when measured together in the same patients, alongside a candidate biochemical marker, has rarely been reported.

Serotonin (5-hydroxytryptamine) is synthesized largely outside the liver but is taken up and stored almost entirely within circulating platelets, from which it is released on platelet activation to influence vascular tone, hepatic microcirculation, and liver regeneration [10, 11]. Platelet-derived serotonin modulates hepatic stellate cell activation and fibrogenic signaling [12], and blockade of hepatic serotonin-receptor signaling has attenuated fibrosis in experimental models [13], raising the possibility that circulating serotonin concentration tracks the severity of the portal hypertensive and fibrotic processes that underlie variceal formation. Whether serum serotonin adds discriminative information beyond Child-Pugh class, portal vein diameter, and PSR, rather than simply mirroring them, has not been well characterized in a single cohort.

Acute variceal hemorrhage is also an important precipitant of hepatic encephalopathy, a complication that can require urgent neurological and airway assessment in patients with advanced cirrhosis [14], which reinforces the practical value of identifying patients with high-grade varices before bleeding occurs rather than after. This study therefore examined the association of serum serotonin, Child-Pugh class, portal vein diameter, and PSR with endoscopically graded esophageal variceal severity in a cohort spanning non-hepatic controls, cirrhosis without varices, and grade 1 to grade 3 varices, and explored the diagnostic performance of these four markers, individually, for identifying high-grade varices. The diagnostic analyses were designed as exploratory and hypothesis-generating, not as a validation of any marker or cutoff.

Materials and Methods

Study design, setting, and ethical considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki [15] and with the ethical standards of the responsible institution on human subjects and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for observational studies [16]. Ethical approval was obtained from the Institutional Review Board (IRB) of

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the Faculty of Medicine, Al-Azhar University, Cairo, Egypt (IRB: AZFM-IRB/2026/07/0087) prior to data collection, and written informed consent was obtained from each participant before enrollment. Participant identifiers were replaced with study codes before analysis, and confidentiality was maintained throughout data handling and reporting.

Study population

A total of 140 adults were enrolled: patients with an established diagnosis of liver cirrhosis undergoing upper gastrointestinal endoscopy, and age- and sex-comparable adults without liver disease who underwent upper gastrointestinal endoscopy for other indications and served as non-hepatic controls. Participants were assigned to one of five groups on the basis of clinical status and endoscopic findings: non-hepatic controls (n = 40); cirrhosis without esophageal varices (n = 40); and cirrhosis with grade 1 (n = 20), grade 2 (n = 20), or grade 3 (n = 20) esophageal varices, graded according to a standard three-tier endoscopic classification of variceal size [17]. Participants were excluded if they had non-cirrhotic portal hypertension, a prior portosystemic shunt or definitive variceal eradication procedure, a hematological disorder independently causing thrombocytopenia or splenomegaly, or incomplete data for the primary predictors or the outcome. Patients with hepatocellular carcinoma or another gastrointestinal malignancy, portal or splenic vein thrombosis, neuropsychiatric disorders, or known carcinoid syndrome, and those taking nonsteroidal anti-inflammatory drugs or selective serotonin reuptake inhibitors, were also excluded because these conditions and drugs can alter circulating serotonin or portal hemodynamics. This five-group design was chosen deliberately so that each candidate marker could be evaluated across the full spectrum of disease, from the absence of cirrhosis, through cirrhosis without portal hypertensive complications, to progressively more severe varices, rather than only across the narrower range of a single cirrhotic population. Non-hepatic controls were included to characterize the range of serum serotonin in the absence of liver disease and were excluded from all regression and diagnostic analyses, which were restricted to participants with cirrhosis.

Participants were recruited from adults (older than 18 years) presenting for upper gastrointestinal endoscopy to the endoscopy units of the Department of Hepatology, Gastroenterology and Infectious Diseases, Al-Azhar University Hospitals, Cairo, Egypt. Eligible patients were enrolled and, after endoscopy, allocated to the corresponding stratum; enrollment into each stratum closed once its prespecified target size (40 without varices, 20 for each variceal grade, and 40 non-hepatic controls) had been reached. Because this stratified (quota) design fixed the number of participants in each variceal grade, the case mix differs from that of an unselected population undergoing variceal surveillance, in which absent or small varices predominate; this was taken into account in the analysis and interpretation of diagnostic performance. Serum serotonin data from this cohort were previously reported in part [18], in an analysis of serotonin in relation to the presence of varices; the present study addresses different questions, namely the joint evaluation of serotonin with Child-Pugh class, portal vein diameter, and PSR, multivariable ordinal modeling, and paired ROC comparison, using the verified participant-level dataset.

Clinical, laboratory, and serotonin assessment

Demographic and clinical data, including duration of liver disease, jaundice, ascites, gastrointestinal bleeding, peripheral edema, and clinically detected splenomegaly, were extracted using a standardized form. Platelet count, prothrombin time, international normalized ratio (INR), total and direct bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase, albumin, and total protein were measured using standard laboratory methods. Serum serotonin concentration was measured using a Human Serotonin enzyme-linked immunosorbent assay (ELISA) kit (Catalogue No. E1128Hu; BT LAB/Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's instructions, with optical density read at 450 nm and concentration derived from the kit's calibration curve. Because circulating serotonin is closely tied to platelet handling, blood collection and processing followed a standardized protocol intended to limit pre-analytical variability from platelet degranulation. A 10-mL venous blood sample was obtained from each participant: 2 mL was collected into ethylenediaminetetraacetic acid for the complete blood count, 2 mL into sodium citrate for coagulation studies, and 6 mL into a plain tube without anticoagulant, which was centrifuged at 4,000 revolutions per minute for 10 min; the separated serum was stored frozen at −20 °C until batch analysis. In the serotonin assay, 40 µL of serum, 10 µL of biotinylated anti-serotonin antibody, and 50 µL of streptavidin-horseradish peroxidase were incubated for 60 min at 37 °C; after five washes, substrate solutions A and B were added, and the mixture was incubated for 10 min at 37 °C in the dark. The reaction was stopped, and optical density was read at 450 nm within 10 min. Concentrations were derived from a standard curve fitted by regression to the kit standards. Assay precision was not re-verified in-house; the manufacturer-stated intra-assay and inter-assay coefficients of variation are < 8% and < 10%, respectively. Because serum was stored for batch analysis, serotonin results were not available to the endoscopists or sonographers at the time of their assessments. Because serum rather than platelet-poor plasma was analyzed, the measured concentration predominantly reflects platelet-stored serotonin released during clotting [10].

Endoscopic assessment

Upper gastrointestinal endoscopy was performed in all participants, including the non-hepatic controls, using a Pentax EG34-i10 video gastroscope (Pentax Medical, Tokyo, Japan), and was the reference standard for the presence and grade of esophageal varices. Varices were graded by size as small (grade 1), medium (grade 2), or large (grade 3) using the standard three-tier classification [17]. Grading was recorded by the performing endoscopist at the time of the procedure, without

knowledge of serum serotonin results, which were generated later; an independent second reading of the endoscopic findings was not documented, so inter-observer agreement could not be assessed.

Ultrasonographic assessment and derived indices

Abdominal ultrasound was used to record liver size and echogenicity, portal vein diameter, splenic vein diameter, spleen diameter, and the presence and grade of ascites. Child-Pugh class (A, B, or C) was obtained from the clinical dataset and analyzed as an ordinal variable. Because the individual component scores, including encephalopathy grade, were not available as discrete variables, the numerical Child-Pugh score could not be independently reconstructed and Child-Pugh class was therefore analyzed as an ordinal variable rather than as a continuous score [4, 5]. PSR was calculated for each participant individually as platelet count ($\times 10^9$/L) divided by spleen diameter (cm), multiplied by 100, which is equivalent to the conventional ratio of platelet count (per mm^3) to spleen diameter (mm).

Data verification

Before analysis, the dataset was checked for completeness and internal consistency. One record, from a participant with grade 3 varices, contained a non-numeric entry for serum serotonin and was treated as missing for serotonin-dependent analyses only, without substitution; the complete-case number of participants analyzed is reported alongside each result. One spleen diameter value was recorded with an implausible decimal placement (1,372 cm) and was corrected to the value consistent with that same participant's independently recorded PSR (13.72 cm); no other values were altered, and no missing data were imputed or calculated in place of an absent measurement anywhere in the dataset. Group-level PSR was reported throughout as the mean of each participant's individually calculated ratio, since the ratio of the group-mean platelet count to the group-mean spleen diameter is a mathematically distinct quantity and was not used.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range (IQR)) according to distribution and were compared across the five study groups using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test; the choice of test for each variable was determined by the Shapiro–Wilk normality of the residuals from a group-wise linear model, rather than applied uniformly across all variables. Categorical variables were presented as n (%) and compared using the chi-square test, or the Fisher-Freeman-Halton exact test where more than 20% of expected cell counts were below 5. Among the 60 participants with grade 1–3 varices, the univariable association between each predictor and ordinal variceal grade was assessed using Spearman rank correlation, and independent predictors were identified using a multivariable ordinal (proportional-odds) logistic regression model [19], with serum serotonin (per 10 ng/mL), Child-Pugh class (coded ordinally as A = 1, B = 2, and C = 3), portal vein diameter (per 0.1 mm, because its range among participants with varices was narrow), PSR (per 100-unit decrease), age, and sex entered as covariates; platelet count and spleen diameter were not entered alongside PSR because of their direct mathematical overlap with it. Because the model estimated six parameters from 59 participants distributed across three outcome categories, which is below commonly recommended sample-size criteria for multivariable modeling [20], it was regarded as exploratory, and no variable selection was performed. To assess the stability of the estimates, the model was refitted by Firth-type penalized maximum likelihood, which reduces small-sample bias and yields finite estimates under quasi-separation [21]; a parsimonious model containing only serum serotonin and portal vein diameter was also fitted, and the full model was refitted in 1,000 bootstrap resamples to examine the consistency of the direction of each association. Diagnostic performance for identifying grade 2 or 3 varices was assessed, as an exploratory analysis, by receiver operating characteristic (ROC) analysis among the 99 cirrhotic participants with a complete serotonin measurement, with cutoffs selected by the Youden index [22] and 95% confidence intervals (CIs) for the area under the curve (AUC) obtained by stratified bootstrap resampling. Because the optimal cutoffs were derived and evaluated in the same sample, apparent sensitivity and specificity were corrected for optimism by bootstrap internal validation (1,000 stratified resamples, re-deriving the Youden cutoff in each resample and applying it to the original sample) [23] and were also estimated by leave-one-out cross-validation; the AUC of the exploratory combined model was corrected for optimism in the same way. External validation was not possible within this study. Ninety-five percent CIs for sensitivity and specificity were calculated by the Wilson score method, and positive and negative likelihood ratios, which do not depend on prevalence, were derived from them. Because predictive values depend on the prevalence of high-grade varices, which was fixed at 39.4% by the stratified design, they were additionally recalculated by Bayes' theorem at illustrative prevalences of 10% and 25%. The AUCs of the individual markers were compared pairwise using DeLong's nonparametric test for correlated ROC curves [24]. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. Analyses were performed in Python (SciPy, statsmodels, and scikit-learn).

Results

Baseline demographic and clinical characteristics

Of the 140 participants, 40 were non-hepatic controls, 40 had cirrhosis without varices, and 60 had cirrhosis with grade 1 (n = 20), grade 2 (n = 20), or grade 3 (n = 20) esophageal varices (Table 1). Age did not differ significantly across the five groups (H = 9.120, P = 0.058), and the proportion of

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Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort

Characteristic	Control (n = 40)	Cirrhosis w/o EV (n = 40)	Grade 1 EV (n = 20)	Grade 2 EV (n = 20)	Grade 3 EV (n = 20)	Statistic, P value
Age, years, median (IQR)	50 (43–61)	48 (43–65)	50 (42–60)	60 (49–64)	58 (54–61)	H = 9.120; P = 0.058
Male sex, n (%)	30 (75.0)	28 (70.0)	12 (60.0)	12 (60.0)	13 (65.0)	χ^2 = 2.227; P = 0.694
Duration of liver disease, years, median (IQR)[a]	—	9 (8–10)	9 (8–13)	10 (8–12)	13 (12–14)	H = 26.589; P < 0.001
Jaundice, n (%)[a]	—	4 (10.0)	2 (10.0)	5 (25.0)	10 (50.0)	χ^2 = 14.708; P = 0.002
Ascites, n (%)[a]	—	3 (7.5)	1 (5.0)	3 (15.0)	6 (30.0)	FFH P = 0.068
Gastrointestinal bleeding, n (%)[a]	—	0 (0.0)	7 (35.0)	9 (45.0)	15 (75.0)	χ^2 = 38.055; P < 0.001
Lower-limb edema, n (%)[a]	—	5 (12.5)	2 (10.0)	5 (25.0)	11 (55.0)	χ^2 = 16.008; P = 0.001
Splenomegaly (clinical), n (%)[a]	—	10 (25.0)	11 (55.0)	16 (80.0)	19 (95.0)	χ^2 = 32.630; P < 0.001

Values are median (IQR), n (%), or as stated. [a]Not applicable to controls, who had no cirrhosis or hepatic decompensation; percentages and statistics for these rows are computed across the four cirrhotic groups only (n = 100). FFH: Fisher–Freeman–Halton exact test; H: Kruskal–Wallis statistic; χ^2: chi-square statistic; EV: esophageal varices.

male participants was similar across all groups (χ^2 = 2.227, P = 0.694). Among the four cirrhotic groups, duration of liver disease was longer with increasing variceal grade (H = 26.589, P < 0.001). Jaundice, gastrointestinal bleeding, peripheral edema, and clinically detected splenomegaly were each more frequent with higher variceal grade (all P ≤ 0.002), while ascites showed a similar but nonsignificant trend across groups (Fisher–Freeman–Halton exact P = 0.068). No participant was excluded after enrollment, so the five group sizes reported here (40, 40, 20, 20, and 20) represent the full analyzed cohort for every baseline variable in Table 1.

Biochemical and hematological profile

Platelet count fell progressively from controls to grade 3 varices (295.1 ± 30.4 to 118.3 ± 41.8 × 10^9/L, F = 38.746, P < 0.001), and prothrombin time, INR, both bilirubin fractions, ALT, AST, and total protein each differed significantly across the five groups (all P < 0.001), while alkaline phosphatase did not (H = 6.023, P = 0.197) (Table 2). Serum albumin declined progressively with worsening disease, from 4.15 ± 0.12 g/dL in controls to 2.37 ± 0.20 g/dL in grade 3 varices (F = 659.734, P < 0.001). Serum serotonin rose progressively across the five groups, from 30.0 ± 5.6 ng/mL in controls, through 60.0 ± 9.8 ng/mL in cirrhosis without varices, to 106.5 ± 5.2 ng/mL in grade 3 varices (F = 347.575, P < 0.001) (Fig. 1), with minimal overlap between the control and highest-grade distributions.

Ultrasonographic findings and composite portal hypertension indices

Liver size was normal in controls and shrunken with irregular nodular pattern across the four cirrhotic groups, consistent with progressive parenchymal shrinkage (H = 92.211, P < 0.001) (Table 3, Fig. 2). Portal vein diameter increased progressively with variceal grade, from 10.0 ± 0.7 mm in controls to 15.1 ± 0.4 mm in grade 3 varices (F = 190.412, P < 0.001), as did splenic vein diameter (F = 525.304, P < 0.001) and spleen diameter, from 8.6 cm in controls to a median of 15.3 cm in grade 3 varices (H = 102.260, P < 0.001). PSR fell correspondingly across the same groups, from 3,503.9 ± 482.8 in controls to 829.8 ± 553.0 in grade 3 varices (F = 63.593, P < 0.001). Increased liver echogenicity was near-universal across the cirrhotic groups but absent in controls (χ^2 = 141.472, P < 0.001). Child-Pugh class C became progressively more frequent with increasing variceal grades, from 25.0% of participants with cirrhosis but no varices to 30.0% of grade 1, 60.0% of grade 2, and 70.0% of grade 3 participants.

Predictors of esophageal variceal severity

Among the 60 participants with grade 1–3 varices, serum serotonin (ρ = 0.759, P < 0.001) and portal vein diameter (ρ = 0.754, P < 0.001) showed the strongest univariable correlation with variceal grade, followed by Child-Pugh class (ρ = 0.395, P = 0.002) and PSR (ρ = −0.381, P = 0.003) (Table 4). In the multivariable ordinal logistic regression model (n = 59 with complete serotonin data; likelihood-ratio χ^2 = 77.882, df = 6, P < 0.001; McFadden pseudo-R^2 = 0.601), serum serotonin (adjusted odds ratio (OR) of 7.48 per 10 ng/mL increase; 95% CI, 2.29–24.41; P = 0.0009) and portal vein diameter (adjusted OR of 1.70 per 0.1 mm increase; 95% CI, 1.29–2.23, P = 0.0002; equivalent to 197.1 per 1 mm, 95% CI, 12.7–3059.4) each remained independently and significantly associated with higher variceal grade after mutual adjustment. Child-Pugh class, PSR, age, and sex did not reach independent statistical significance once serotonin and portal vein diameter were accounted for. The very wide CI of the per-millimeter portal vein estimate reflects the narrow range of portal vein diameter among participants with varices (group means 14.0–15.1 mm) and the small sample relative to the number of model parameters; the unpenalized estimates should therefore be regarded as imprecise. In the Firth-penalized model, serotonin (adjusted OR of 5.68 per 10 ng/mL; 95% CI, 2.19–14.70; P = 0.0003) and portal vein diameter (adjusted OR of 1.56 per 0.1 mm; 95% CI, 1.24–1.96; P = 0.0001) remained the only independent predictors, as they did in the parsimonious model containing these two variables

Table 2. Biochemical and Hematological Profile Across Study Groups

Variable	Control	Cirrhosis without EV	Grade 1 EV	Grade 2 EV	Grade 3 EV	Statistic, P value
Platelet count, × 10^9/L, mean ± SD	295.1 ± 30.4	257.6 ± 69.9	201.5 ± 94.9	149.3 ± 67.2	118.3 ± 41.8	F = 38.746; P < 0.001
Prothrombin time, s, median (IQR)	11.0 (11.0–11.2)	22.0 (20.8–23.0)	21.0 (20.0–23.0)	22.0 (20.0–24.0)	24.0 (22.8–25.3)	H = 91.576; P < 0.001
INR, median (IQR)	1.00 (1.00–1.02)	2.00 (1.89–2.09)	1.91 (1.82–2.09)	2.00 (1.82–2.18)	2.18 (2.07–2.30)	H = 91.576; P < 0.001
Total bilirubin, mg/dL, median (IQR)	0.86 (0.79–0.90)	1.53 (1.48–1.58)	1.60 (1.58–1.73)	1.75 (1.70–2.17)	2.60 (1.88–5.10)	H = 107.648; P < 0.001
Direct bilirubin, mg/dL, median (IQR)	0.39 (0.32–0.49)	0.61 (0.53–0.72)	0.67 (0.65–0.74)	0.81 (0.71–1.12)	1.25 (0.79–1.40)	H = 91.459; P < 0.001
ALT, U/L, median (IQR)	21.0 (18.0–24.0)	59.5 (38.8–91.3)	65.0 (56.0–74.5)	78.0 (66.5–88.8)	102.0 (85.0–117.3)	H = 94.478; P < 0.001
AST, U/L, median (IQR)	28.0 (25.0–31.3)	78.0 (52.0–107.3)	78.5 (71.5–86.3)	95.0 (81.3–100.3)	118.5 (98.0–130.0)	H = 93.637; P < 0.001
ALP, U/L, median (IQR)	142.0 (140.0–144.5)	143.0 (133.3–154.0)	143.0 (134.8–154.0)	147.5 (136.3–154.3)	152.5 (138.3–155.0)	H = 6.023; P = 0.197
Albumin, g/dL, mean ± SD	4.15 ± 0.12	3.05 ± 0.15	2.67 ± 0.20	2.59 ± 0.12	2.37 ± 0.20	F = 659.734; P < 0.001
Total protein, g/dL, median (IQR)	6.84 (6.76–6.93)	5.54 (5.43–5.63)	5.40 (5.30–5.45)	5.29 (5.21–5.38)	5.14 (5.04–5.27)	H = 112.478; P < 0.001
Serum serotonin, ng/mL, mean ± SD (n)	30.0 ± 5.6 (40)	60.0 ± 9.8 (40)	79.6 ± 6.9 (20)	91.0 ± 13.2 (20)	106.5 ± 5.2 (19)	F = 347.575; P < 0.001

Values are mean ± SD (compared by one-way ANOVA, F) or median (IQR) (compared by Kruskal–Wallis test, H), according to the Shapiro–Wilk normality of model residuals for each variable. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio. EV: esophageal varices; SD: standard deviation; ANOVA: analysis of variance; IQR: interquartile range.

alone (OR = 4.19; 95% CI, 1.87–9.41; P = 0.0005; and OR = 1.53; 95% CI 1.24–1.89; P = 0.0001, respectively). Across 1,000 bootstrap resamples of the full model, the ORs for serotonin and portal vein diameter exceeded 1 in every resample, although about 5% of resamples produced extreme estimates consistent with quasi-separation; the direction of both associations was therefore robust, whereas their unpenalized magnitude was not.

Diagnostic performance for high-grade varices

Among the 99 cirrhotic participants with a complete serotonin measurement, 39 had grade 2 or 3 varices (Table 5, Fig. 3). The apparent AUC for high-grade varices was 0.944 (95% CI, 0.895–0.980) for serum serotonin, compared with portal vein diameter (AUC 0.923; 95% CI, 0.864–0.974), PSR (AUC 0.764; 95% CI, 0.660–0.861), and Child-Pugh class (AUC 0.746; 95% CI, 0.654–0.830). On DeLong's test, the AUCs of serotonin and portal vein diameter did not differ significantly (difference 0.021; 95% CI, −0.049 to 0.091; P = 0.553), whereas serotonin exceeded both PSR (difference 0.180; 95% CI, 0.093–0.268; P < 0.001) and Child-Pugh class (difference 0.198; 95% CI, 0.112–0.285; P < 0.001); portal vein diameter likewise exceeded PSR (P = 0.004) and Child-Pugh class (P < 0.001), and PSR and Child-Pugh class did not differ (P = 0.687). At its Youden-optimal cutoff of 88.3 ng/mL or higher, serotonin showed an apparent sensitivity of 82.1% (95% CI, 67.3–91.0) and specificity of 96.7% (95% CI, 88.6–99.1), corresponding to a positive likelihood ratio of 24.6 and a negative likelihood ratio of 0.19 (Table 6). Its positive and negative predictive values of 94.1% and 89.2% reflect the 39.4% prevalence of high-grade varices fixed by the study design; at illustrative prevalences of 10% and 25%, the corresponding values would be 73.2% and 98.0%, and 89.1% and 94.2%, respectively (Table 6). After bootstrap optimism correction, the sensitivity and specificity of the serotonin cutoff were 80.1% and 95.9% (leave-one-out cross-validated, 79.5% and 96.7%), and corrections for the other markers were similarly small (Table 6). A *post-hoc* logistic model combining all four markers reached an apparent AUC of 0.984 in this same sample (0.979 after bootstrap optimism correction); because this combined model was neither derived nor tested in an independent cohort, its performance is reported as exploratory only and should not be interpreted as validated diagnostic accuracy. None of the four individual markers reached this level of apparent accuracy alone, which is consistent with each capturing a partially distinct aspect of portal hypertensive pathophysiology; the practical implication is that no single noninvasive test, on the evidence pre-

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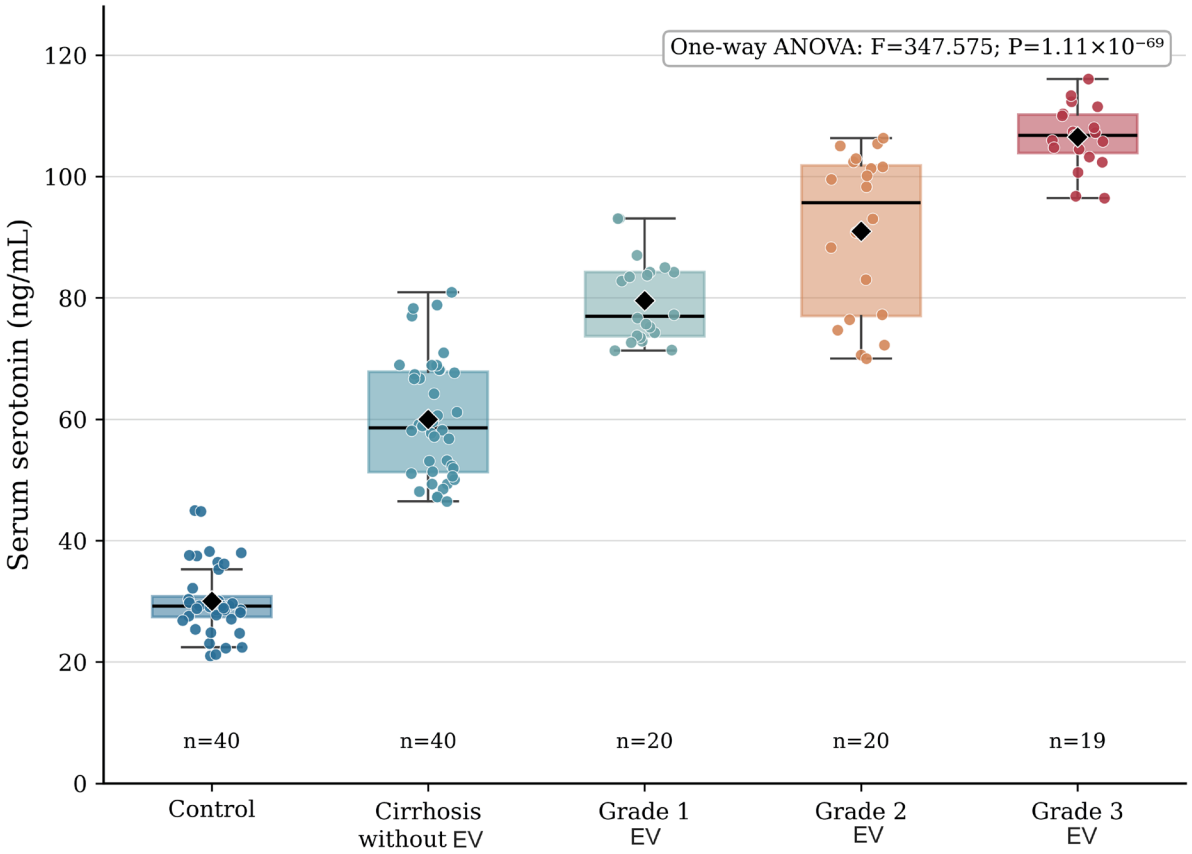


Figure 1. Serum serotonin concentrations across study groups. Box plots show median, interquartile range, and range; diamonds indicate group means; dots represent individual participants (n = 19 in the grade 3 group owing to one non-numeric (missing) serotonin value). ANOVA: analysis of variance; EV: esophageal varices.

Table 3. Ultrasonographic Findings and Composite Portal Hypertension Indices

Variable	Control	Cirrhosis without EV	Grade 1 EV	Grade 2 EV	Grade 3 EV	Statistic, P value
Liver size, cm, median (IQR)	13.68 (13.52–13.87)	10.21 (9.88–10.62)	9.97 (9.81–10.14)	9.89 (9.71–10.01)	9.88 (9.73–10.01)	H = 92.211; P < 0.001
Portal-vein diameter, mm, mean ± SD	10.03 ± 0.69	13.17 ± 1.30	14.04 ± 0.43	14.72 ± 0.33	15.13 ± 0.37	F = 190.412; P < 0.001
Splenic-vein diameter, mm, mean ± SD	6.31 ± 0.68	10.31 ± 0.47	10.24 ± 0.45	11.04 ± 0.35	11.36 ± 0.42	F = 525.304; P < 0.001
Spleen diameter, cm, median (IQR)	8.60 (8.08–8.94)	10.61 (10.12–11.61)	11.91 (10.05–13.24)	13.63 (12.54–14.93)	15.34 (14.82–16.04)	H = 102.260; P < 0.001
PSR[a], mean ± SD	3,503.9 ± 482.8	2,392.4 ± 778.1	1,613.2 ± 970.0	1,355.6 ± 780.8	829.8 ± 553.0	F = 63.593; P < 0.001
Increased liver echogenicity, n (%)	0 (0.0)	36 (90.0)	14 (70.0)	16 (80.0)	14 (70.0)	χ^2 = 141.472; P < 0.001
Child-Pugh class A/B/C, n[b]	—/—/—	20/10/10	9/5/6	2/6/12	1/5/14	χ^2 = 21.556; P = 0.001

Values are mean ± SD, median (IQR), or n (%). PSR was calculated for each participant individually as platelet count (× 109/L) divided by spleen diameter (cm), multiplied by 100. [a]Group means are the mean of each participant's individually calculated ratio, not the ratio of group-mean platelet count to group-mean spleen diameter. [b]Child-Pugh class was not assigned in controls (no cirrhosis); the chi-square test for class distribution was computed across the four cirrhotic groups only. EV: esophageal varices. PSR: platelet count to spleen diameter ratio.

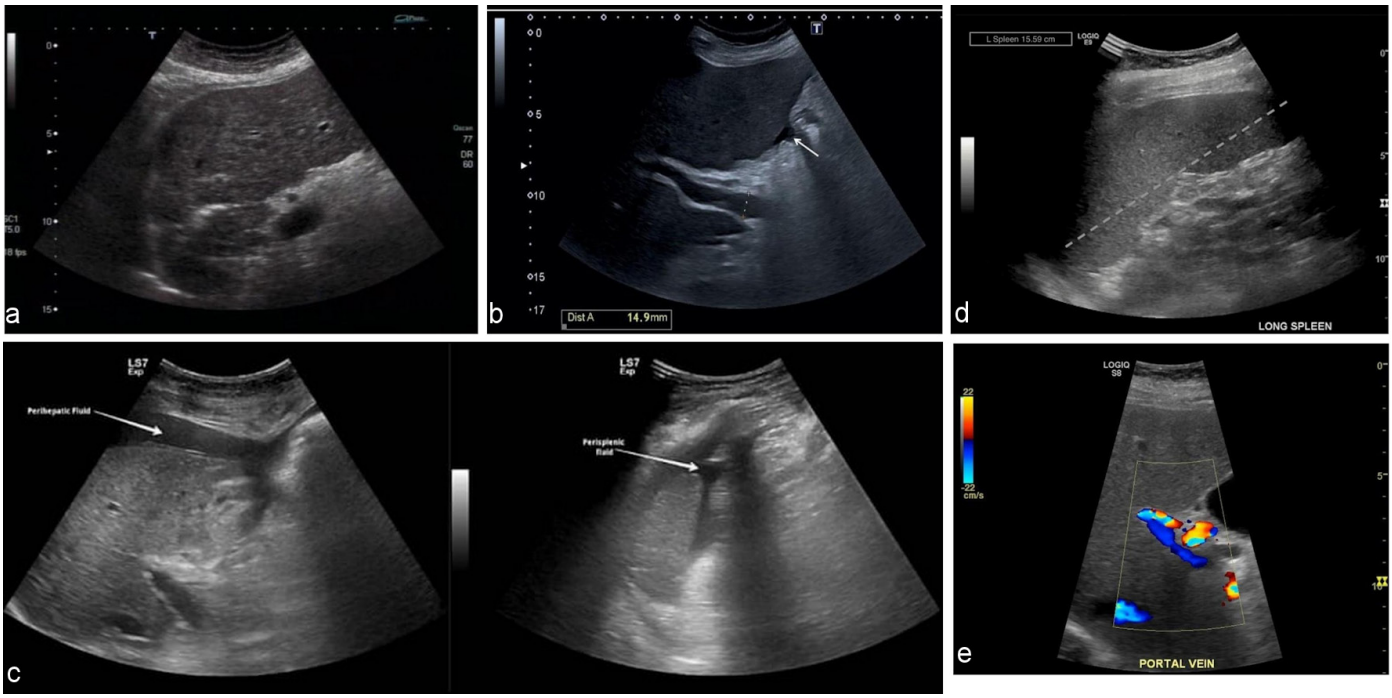


Figure 2. Representative abdominal ultrasound findings of cirrhosis and portal hypertension in the study cohort. (a) Greyscale ultrasound of the liver showing coarse, heterogeneous parenchymal echotexture with an irregular, nodular surface contour, typical of cirrhosis. (b) Greyscale ultrasound with caliper measurement of the main portal vein showing a diameter of 14.9 mm (arrow), exceeding the normal upper limit of 13 mm and consistent with portal hypertension. (c) Greyscale ultrasound demonstrating free perihepatic (left) and perisplenic (right) fluid collections (arrows), consistent with ascites. (d) Greyscale ultrasound of the long axis of the spleen showing splenomegaly, with a measured splenic length of 15.59 cm (dashed line), consistent with portal hypertension. (e) Color Doppler ultrasound of the main portal vein showing preserved hepatopetal flow within a dilated vessel.

sented here, is likely to fully replace endoscopic assessment in an individual patient.

Discussion

In this cross-sectional study of 140 participants spanning the full spectrum from the absence of liver disease to grade 3 esophageal varices, serum serotonin rose progressively with variceal severity and, together with portal vein diameter, remained an independent predictor of variceal grade after adjustment for Child-Pugh class, PSR, age, and sex. Serotonin and portal vein diameter showed similarly high discrimination for high-grade varices, with no significant difference between

Table 4. Univariable Correlation and Multivariable Ordinal Regression Analysis of Predictors of Esophageal Variceal Severity (N = 59–60, Participants With Grade 1–3 Varices)

Predictor	Spearman ρ (univariable)	P value	Adjusted OR (95% CI), multivariable	P value
Serum serotonin, per 10 ng/mL	0.759	< 0.001	7.48 (2.29–24.41)	0.0009
Portal-vein diameter, per 0.1 mm	0.754	< 0.001	1.70 (1.29–2.23)	0.0002
Child-Pugh class, per class	0.395	0.002	0.36 (0.09–1.46)	0.152
PSR, per 100-unit decrease	−0.381	0.003	0.94 (0.84–1.06)	0.323
Age, per 1 year	—	—	1.03 (0.95–1.13)	0.477
Male sex	—	—	0.61 (0.13–2.81)	0.523

Ordinal (proportional-odds) logistic regression model, n = 59 (complete serotonin data); likelihood-ratio χ^2 = 77.882, df = 6, P < 0.001, McFadden pseudo-R^2 = 0.601. Platelet count and spleen diameter were not entered alongside PSR because of direct mathematical overlap. Portal vein diameter is expressed per 0.1-mm increase because of its narrow range among participants with varices; the equivalent estimate per 1-mm increase is 197.1 (95% CI, 12.7–3059.4). Given the number of parameters relative to the sample size, adjusted estimates are exploratory; Firth-penalized estimates were 5.68 (2.19–14.70) for serotonin and 1.56 (1.24–1.96) for portal vein diameter, and in a model containing only these two variables, 4.19 (1.87–9.41) and 1.53 (1.24–1.89), respectively. OR: odds ratio; CI: confidence interval.

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Table 5. Diagnostic Performance (ROC Analysis) of Noninvasive Markers for Identifying Grade 2 or 3 Esophageal Varices

Marker	N	AUC (95% CI)	Cutoff	Sensitivity/specificity, %	PPV/NPV, %
Serum serotonin, ng/mL	99	0.944 (0.895–0.980)	≥ 88.32	82.1/96.7	94.1/89.2
Portal-vein diameter, mm	99	0.923 (0.864–0.974)	≥ 14.41	92.3/90.0	85.7/94.7
PSR	99	0.764 (0.660–0.861)	≤ 948.95	64.1/83.3	71.4/78.1
Child-Pugh class	99	0.746 (0.654–0.830)	≥ 2.00	92.3/48.3	53.7/90.6

Positive cases were grade 2 or 3 varices (n = 39); negative cases were no varices or grade 1 varices (n = 60), among 99 cirrhotic participants with complete serotonin data. Cutoffs were selected by the Youden index. The 95% Cis were obtained by stratified bootstrap resampling (2,000–3,000 replicates). PPV and NPV are shown at the prevalence of high-grade varices in this sample (39.4%), which was fixed by the stratified design; prevalence-independent likelihood ratios and prevalence-adjusted predictive values are given in Table 6. All cutoffs were derived and evaluated in the same sample and are exploratory. Pairwise DeLong comparisons of AUCs: serotonin vs portal vein diameter, P = 0.553; serotonin vs PSR, P < 0.001; serotonin vs Child-Pugh class, P < 0.001; portal vein diameter vs PSR, P = 0.004; portal vein diameter vs Child-Pugh class, P < 0.001; PSR vs Child-Pugh class, P = 0.687. AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value;

them on paired comparison, and in this enriched sample both discriminated significantly better than PSR and Child-Pugh class. These findings are consistent with the hypothesis that platelet-derived serotonin reflects, at least in part, the severity of the portal hypertensive process underlying variceal formation, rather than serving only as an incidental marker of hepatic dysfunction. The graded increase in serum serotonin across variceal grades was not reported in an earlier analysis of this cohort [18]; the per-grade values presented here were derived from the verified participant-level dataset (Table 2).

Because more than 90% of circulating serotonin is stored within platelet dense granules, serum concentration is shaped jointly by platelet turnover, splenic sequestration, and hepatic vascular handling [10]. Platelet-derived serotonin supports liver regeneration in humans [11] and modulates hepatic stellate cell activation, a central step in fibrogenesis [12], and blockade of its receptors has attenuated fibrosis in experimental models [13]. In the context of progressive portal hypertension, increased splenic platelet turnover and altered hepatic serotonin clearance could plausibly raise circulating concentrations in parallel with worsening variceal disease; however, the cross-sectional design of the present study cannot establish this mechanism directly, and the association observed here should be interpreted as correlative rather than causal. A further con-

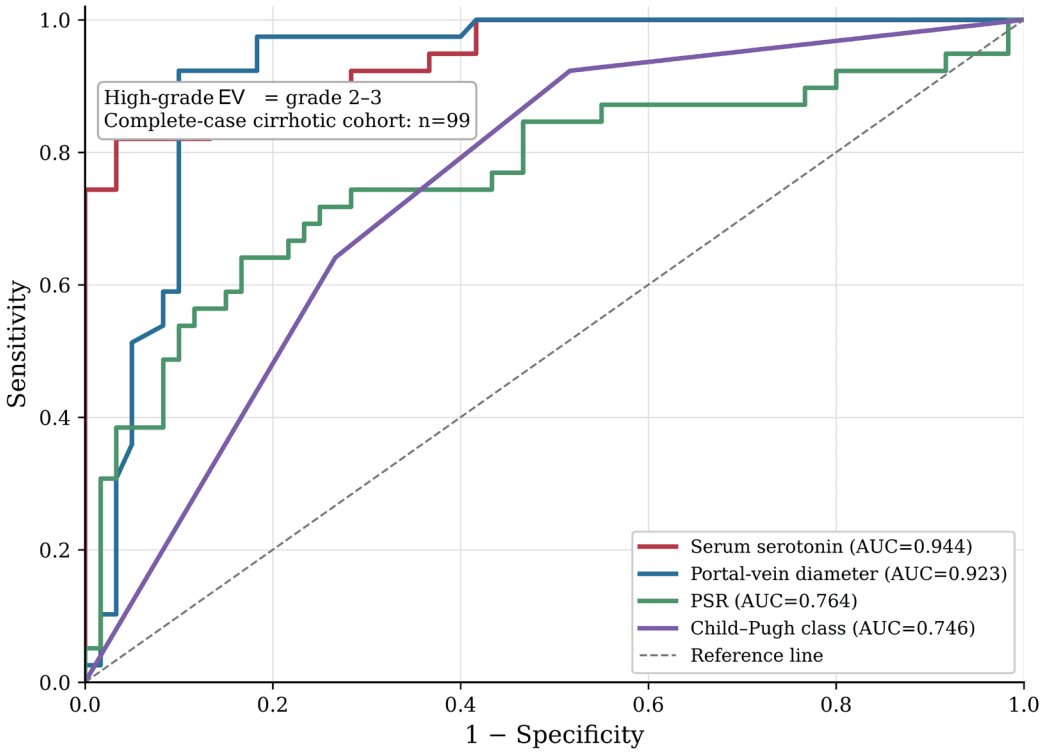


Figure 3. Receiver operating characteristic curves for noninvasive markers of high-grade esophageal varices. The diagonal dashed line represents the line of non-discrimination (AUC = 0.5). EV: esophageal varices; AUC: area under the curve; PSR: platelet count to spleen diameter ratio.

Table 6. Exploratory Accuracy Measures for Identifying Grade 2 or 3 Esophageal Varices: Optimism-Corrected, Prevalence-Independent, and Prevalence-Adjusted Estimates

Marker (cutoff)	Apparent sensitivity, % (95% CI)	Apparent specificity, % (95% CI)	Optimism-corrected sensitivity/specificity, %	LR+/ LR−	PPV/NPV at 10%; 25% prevalence, %
Serum serotonin (≥ 88.32 ng/mL)	82.1 (67.3–91.0)	96.7 (88.6–99.1)	80.1/95.9	24.6/0.19	73.2/98.0; 89.1/94.2
Portal-vein diameter (≥ 14.41 mm)	92.3 (79.7–97.3)	90.0 (79.9–95.3)	90.2/89.1	9.2/0.09	50.6/99.1; 75.5/97.2
PSR (≤≤ 948.95)	64.1 (48.4–77.3)	83.3 (72.0–90.7)	60.2/81.2	3.8/0.43	29.9/95.4; 56.2/87.4
Child-Pugh class (≥ B)	92.3 (79.7–97.3)	48.3 (36.2–60.7)	90.1/47.2	1.8/0.16	16.6/98.3; 37.3/95.0

Positive cases were grade 2 or 3 varices (n = 39) and negative cases were no varices or grade 1 varices (n = 60), among 99 cirrhotic participants with complete serotonin data; the observed prevalence was 39.4%. Confidence intervals for sensitivity and specificity were calculated by the Wilson score method. Optimism-corrected values were obtained by bootstrap internal validation (1,000 stratified resamples), re-deriving the Youden cutoff in each resample and applying it to the original sample. PPV and NPV at 10% and 25% prevalence were calculated by Bayes' theorem from the apparent sensitivity and specificity and are illustrative; they assume that sensitivity and specificity are unchanged in a population with a different case mix, which may not hold (spectrum effect). Cutoffs were derived in this sample and require external validation. LR+: positive likelihood ratio (sensitivity divided by (1 − specificity)); LR−: negative likelihood ratio ((1 − sensitivity) divided by specificity). PSR: platelet count to spleen diameter ratio; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

sideration is that serotonin is metabolized hepatically and renally, so impaired clearance in more advanced liver disease could, in principle, contribute to the rise in circulating concentration independently of platelet biology; distinguishing production, storage-release, and clearance contributions to serum serotonin was outside the scope of this cross-sectional design.

PSR and portal vein diameter both moved in the expected direction with variceal severity, consistent with previous studies [7–9], but PSR did not remain an independent predictor once serotonin and portal vein diameter were included in the multivariable model, and its univariable correlation with grade was weaker than that of either serotonin or portal vein diameter. This pattern is compatible with PSR capturing much of the same underlying hypersplenism and portal-pressure information that is already reflected, separately, in spleen diameter and platelet count, rather than adding independent discriminative value once those pathways are represented by a direct anatomical measurement. Portal vein diameter, despite its relative simplicity, performed strongly in this cohort, though ultrasonographic measurement is more operator-dependent than a laboratory assay, a difference that should temper any direct comparison of the two markers' apparent accuracy.

If replicated in independent, unselected surveillance cohorts, a noninvasive assessment anchored on serum serotonin and portal vein diameter could help identify patients most likely to have high-grade varices before endoscopy is performed, consistent with the broader shift toward risk-stratified, rather than universal, endoscopic screening reflected in current consensus and practice guidance [3, 17]. Because acute variceal hemorrhage is an important precipitant of hepatic encephalopathy and can necessitate urgent escalation of care in decompensated cirrhosis [14], earlier noninvasive identification of patients at highest risk could support more timely surveillance and prophylactic treatment, potentially reducing both the burden of unnecessary endoscopy among low-risk patients and the risk of delayed diagnosis among those at genuine risk of bleeding. Any such pathway would need to be validated against hard clinical endpoints, such as incident variceal hemorrhage on follow-up, rather than against endoscopic grade alone, before it could reasonably influence surveillance intervals in practice.

Strengths of this study include the simultaneous evaluation of a novel biochemical marker alongside three established noninvasive indices within the same cohort, endoscopic confirmation of the primary outcome in every participant, a five-group design spanning the full disease spectrum from non-hepatic controls to grade 3 varices, and a statistically prespecified, distribution-driven choice of test for each variable rather than a single default method applied uniformly across a heterogeneous set of clinical and laboratory measures.

This study also has several limitations. Its cross-sectional design cannot establish whether serotonin elevation precedes or follows variceal progression, and a longitudinal cohort with serial endoscopic and biochemical assessment would be needed to test this directly [25]. Participants were recruited into strata of prespecified size, so the distribution of variceal grades was fixed by design and enriched for high-grade varices relative to an unselected surveillance population; together with the comparison of clearly separated disease categories, this spectrum effect is likely to have inflated the apparent discriminative performance of all four markers [26]. The modest per-group sample sizes, particularly for the multivariable model (n = 59), limit precision and generalizability, and the wide CI around the portal vein diameter OR reflect this constraint. The multivariable model estimated six parameters from 59 participants, fewer than commonly recommended for multivariable modeling [20]; although the two principal associations persisted in penalized and parsimonious models and were directionally consistent across bootstrap resamples, their magnitude remains imprecise and should be confirmed in larger cohorts. Serum serotonin is sensitive to pre-analytical handling and platelet degranulation, and although a standardized collection protocol was followed, some residual measurement variability cannot be excluded; moreover, serum rather than platelet-poor plasma serotonin was measured and values were not normalized to platelet count, so the contributions of platelet serotonin content and free circulating serotonin could not be separated. Serum was stored at −20 °C rather than −80 °C, the interval between collection and centrifugation and the number of freeze-thaw cycles were not recorded, and assay precision was not re-verified in-house. Blinding of

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the laboratory staff to group allocation was not documented, and variceal grading relied on the real-time assessment of the performing endoscopist without a documented independent second reading. The optimal cutoffs were derived in the same sample; bootstrap optimism correction and cross-validation reduced the apparent estimates only modestly, but internal validation cannot substitute for external validation, and predictive values depend on the prevalence fixed by the design. Finally, because the exploratory model combining all four markers was developed and evaluated in the same sample, its apparent AUC of 0.984 should not be interpreted as validated external diagnostic performance, and this figure is not presented as a clinical decision threshold.

Conclusions

In this cohort spanning non-hepatic controls, cirrhosis without varices, and grade 1 to grade 3 esophageal varices, serum serotonin increased progressively with variceal severity and, together with portal vein diameter, was independently associated with higher variceal grade after adjustment for Child-Pugh class, PSR, age, and sex. Serotonin discriminated grade 2 or 3 varices as well as portal vein diameter, with no significant difference between the two, and better than PSR and Child-Pugh class; however, these diagnostic estimates are exploratory, were obtained in a sample enriched by design, and require external validation. These findings support serum serotonin as a biologically plausible, measurable correlate of variceal severity that may complement, rather than replace, established noninvasive indices when risk-stratifying patients with cirrhosis. Prospective, multicenter studies using pre-analytically standardized serotonin assays and, ideally, longitudinal endoscopic follow-up are needed before serum serotonin, alone or in combination with portal vein diameter, can be recommended as a tool to guide the timing and frequency of endoscopic variceal surveillance.

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Conflict of Interest

The authors declared no conflict of interest relevant to the content of the manuscript.

Informed Consent

Written informed consent was obtained from each participant before enrollment.

Author Contributions

AMF and AME contributed equally to this work and shared first authorship. AMF and AME conceived and designed the study, performed the upper gastrointestinal endoscopies and variceal grading, and wrote the first draft of the manuscript. AAk supervised the laboratory work, including the serum serotonin ELISA and routine laboratory investigations, and contributed to the data analysis and interpretation. ASEE performed and interpreted the abdominal ultrasound and Doppler examinations. AEE, FSM, NRM, OMAE, AAMA, AAb, MAM, IAMIB, and AAr recruited patients, carried out the clinical assessment and Child-Pugh scoring, and collected the data. SASA performed the statistical analysis and contributed to the interpretation of the data. SMEN supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

AI Use Declaration

During the preparation of this manuscript, the authors used AI to assist with language editing and with formatting the manuscript, tables, and references according to the journal's author guidelines. The tool was not used to generate data, perform or interpret statistical analyses, or draw scientific conclusions. The authors reviewed and edited all output and took full responsibility for the content, citations, analyses, interpretations, and conclusions of this publication. No AI tool is listed as an author.

Abbreviations

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANOVA: analysis of variance; AST: aspartate aminotransferase; AUC: area under the receiver operating characteristic curve; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; FFH: Fisher–Freeman–Halton; INR: international normalized ratio; IQR: interquartile range; IRB: institutional review board; LR+/LR−: positive/negative likelihood ratio; NPV: negative predictive value; OR: odds ratio; EV: esophageal varices; PPV: positive predictive value; PSR: platelet count to spleen diameter ratio; ROC: receiver operating characteristic; SD: standard deviation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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