Original paper

Exploring new noninvasive parameters to predict oesophageal varices in patients with NAFLD-associated compensated liver cirrhosis

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Gastroenterology Rev
DOI: https://doi.org/10.5114/pg.2024.139210

Key words: portal hypertension, endoscopy, accuracy.

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Abstract

Introduction: Nonalcoholic fatty liver disease is a leading cause of liver cirrhosis and portal hypertension, which can be complicated by oesophageal varices and variceal bleeding. Screening for oesophageal varices is essential for initiating bleeding prophylaxis. Several noninvasive parameters for predicting oesophageal varices have been suggested (e.g., Baveno VI, expanded Baveno VI, and platelet count/spleen diameter ratio), although with variable efficacy in patients with nonalcoholic fatty liver disease.

Aim: This study aimed to compare the non-invasive predictors of oesophageal varices.

Material and methods: We retrospectively analyzed the medical records of patients with nonalcoholic fatty liver disease-related compensated liver disease who underwent screening endoscopy at a tertiary care unit in United Arab Emirates. The accuracy of the established (Baveno VI and expanded Baveno VI) and newly devised (platelet count)/(spleen diameter) + liver stiffness × (40 – albumin) noninvasive parameters in predicting oesophageal varices and the presence of large oesophageal varices was assessed in our population.

Results: We found that the (platelet count)/(spleen diameter) + liver stiffness × (40 – albumin) formula had a higher accuracy than both Baveno VI (p = 0.030) and expanded Baveno VI criteria (p = 0.050) in predicting the presence of oesophageal varices. The (platelet count)/(spleen diameter) + liver stiffness × (40 – albumin) formula was associated with a higher number of spared endoscopies than Baveno VI (n = 16, 21.9%) and expanded Baveno VI (n = 9, 12.3%) criteria.

Conclusions: The new formula could provide superior predictive value than the currently practiced noninvasive predictors of oesophageal varices. However, large-scale studies are warranted to confirm its predictive performance in patients with nonalcoholic fatty liver and other etiologies of chronic liver disease.

Introduction

Cirrhosis, which results from chronic liver inflammation and subsequent fibrosis, and affects the liver architecture, is a global problem that promotes the formation of regenerative nodules; this can ultimately lead to portal hypertension and organ failure [1]. Nonalcoholic fatty liver disease (NAFLD) is probably the most common cause of chronic liver disease worldwide, with a prevalence of up to 30% in the general population. This condition is defined based on fat infiltration into the liver in the absence of known causes of hepatic steatosis, such as excess alcohol consumption, chronic viral hepatitis, autoimmune hepatitis, or medications [2]. NAFLD-related cirrhosis has recently become the leading indication for liver transplantation in Europe, surpassing chronic viral hepatitis [3].

In patients with cirrhosis, oesophageal varices (OV) are one of the main complications associated with portal hypertension, whose development marks an important transition stage and identifies a subset of patients

at risk of decompensation due to variceal bleeding [4, 5]. Approximately 90% of patients with portal hypertension may develop OV at any time during their lifetime, and approximately 33% of these OV may bleed [6]. Despite advancements in the medical and endoscopic treatment of variceal haemorrhage over the last 2 decades, the mortality of patients with variceal bleeding remains approximately 25% after a bleeding episode [7]. Thus, early identification of OV, which allows physicians to establish timely prophylactic measures for preventing first bleeding, represents an essential part of the diagnostic workup of patients with cirrhosis [8].

Upper gastrointestinal (GI) endoscopy is the gold standard for both identifying and classifying the grade of OV while serving as a therapeutic intervention. However, this procedure is invasive and unpleasant, with questionable cost effectiveness and practicality for universal OV screening [9]. These health care resource-related limitations and the progressively increasing workload on endoscopy units the world over has prompted many researchers to seek parameters that can predict OV noninvasively [9–12]. Recent criteria proposed in Baveno VI suggest that screening endoscopy can be successfully avoided in patients with compensated advanced chronic liver disease (cACLD) who have a liver stiffness (LS) measurement of < 20 kPa on transient elastography and a platelet (PLT) count of > 150 × 10^9/l [11]. The application of an expanded Baveno VI criteria with different PLT count (> 110 × 10^9/l) and LS measurement (< 25 kPa) thresholds can spare even more endoscopies while carrying minimal risk for missing OV that need treatment in only 1.6% of patients fulfilling the criteria and 0.6% of the general population of patients with cACLD [12].

Aim

The current study aimed to compare the efficacy of various noninvasive methods published in the literature, including Baveno VI, expanded Baveno VI, and PLT count/spleen diameter ratio, for the noninvasive prediction of OV requiring treatment in patients with NAFLD-associated cACLD. We also aimed to determine whether a superior prediction tool can be developed using the combination of the abovementioned factors, such as PLT count/(spleen diameter + LS), with and without adjusting for albumin level.

Material and methods

Study design and patients

This retrospective observational analysis evaluated the electronic medical records of all patients diagnosed with NAFLD-related liver fibrosis who visited the Gastroenterology Clinic of Tawam Hospital, United Arab Emirates, and underwent transient elastometry (Fibroscan, Echosense, Paris) between June 2017 and May 2022 (past 5 years). This study was registered with the clinical trial database ClinicalTrials.gov (identifier no. NCT05485714), and ethical approval was obtained from Tawam Human Research Ethics Committee (approval number: MF2058-2022-856).

Patients who fulfilled the following inclusion criteria were included: age ≥ 18 years; either male or female patients without any clinical signs of severe decompensation; Fibroscan-reported LS measurement of ≥ 7 kPa (indicative of fibrosis stage ≥ F2); ultrasound findings showing fatty liver changes confirmed by an experienced ultrasonologist; and stable vital signs (without severe encephalopathy or evidence of hematemesis or melena). Additionally, we only selected patients who underwent upper GI endoscopy and relevant blood tests within 12 months from the Fibroscan LS measurement to avoid interpretation bias due to disease progression. Any patient with active alcohol consumption within the past 6 months; history of excess alcohol consumption within the past 5 years; evidence of other aetiologies for liver cirrhosis, such as infection with hepatitis viruses or other causes (e.g. primary biliary cirrhosis or autoimmune hepatitis); and HIV infection or comorbid liver or biliary diseases were excluded. Patients who had undergone prior endoscopy with evidence of intervention, such as band ligation or sclerotherapy, or any surgery/procedure for portal hypertension were also excluded from this study.

After evaluating the records of 1258 patients, we found that only 986 had completed clinic follow-up and blood tests. From these 986, only the patients who underwent screening endoscopy for OV were identified (n = 73). All data pertaining to presenting illness, documented physical signs, and biochemical workup, including PLT count, albumin, and examinations such as abdominal ultrasound for the presence of ascites and bipolar splenic diameter measurement, as well as data for LS measurement and upper GI endoscopy results, were obtained. OV were categorised into small and large, according to the Baveno recommendations [11]. The expanded Baveno VI criteria, Baveno VI criteria, and PLT count (mm^{-3}) to bipolar spleen diameter (mm) ratio was calculated in all selected patients and compared according to endoscopy results.

Criteria and formulas

OV prediction in patients with cACLD was determined using the Baveno VI criteria, the expanded Baveno VI criteria, and the PLT count (mm^{-3}) to spleen diameter (mm) ratio.

We developed and proposed a new formula that included a combination of previously published predic-

tors like PLT count to spleen diameter ratio and LS: (PLT count/Spleen diameter) + LS. Subsequently, liver function was considered using albumin levels, which were added to this formula: (PLT count/Spleen diameter) + LS × (40 – Albumin) to see if it gave any further predictive value.

Statistical analysis

Continuous data were presented as median and interquartile range (IQR), whereas categorical data were presented as absolute values and percentages. Fisher's exact test or Pearson χ^2 test was used to compare the categorical variables according to the sample size. To assess the clinical and biochemical disease activity index, Wilcoxon's test for paired data was applied. We used the Mann-Whitney *U* test to compare between the groups. A *p*-value of < 0.05 in a two-tailed test was considered to indicate statistical significance. Receiver operating characteristic (ROC) curves were constructed to identify optimal cut-off values for predicting the presence of OV and large OV [13]. The Youden index was used to identify the optimal cut-off point for each score. Comparisons of AUCs were carried out using the method proposed by DeLong *et al.* [14].

Results

A total of 73 patients satisfied the inclusion criteria and were included in this study. Their median age was 60 (IQR: 42–67; range: 19–88) years. Among these 73 patients, 41 (56.2%) were male and 48 (65.8%) were born in the Emirates.

Overall, 67 (91.8%) patients had preserved liver function (55 (75.3%) and 12 (16.4%) patients had Child-Pugh classes A5 and A6, respectively), whereas only 5 (6.8%) and 1 (1.4%) patient/s had Child-Pugh classes B and C, respectively. Table I summarises the general characteristics and liver function parameters of patients.

The median spleen diameter was 107 (IQR: 94.2–133) mm, and transient elastometry showed a median LS of 10.2 (IQR: 8.2–16.6) kPa.

Table II details the presence of both OV and large OV in patients stratified according to different criteria based on LS, PLT count, spleen diameter, and liver function. Overall, 18 of 73 (24.7%) patients had OV, among whom 8 had large OV (11.0%).

Area under the receiver operating characteristic curve analysis of Baveno VI for predicting the presence of OV showed an area under the curve (AUC) of 0.83 with 95%CI (95% confidence interval) of 0.71–0.94; sensitivity (Se)/specificity (Sp) of 83.3/81.8; positive predictive value (PPV)/negative predictive value (NPV) of 60.0/93.7; and likelihood ratio of a positive test (LR+)/likelihood ratio of a positive test (LR-) of 4.58/0.2), while the AUC for Baveno VI expanded criteria for predicting the presence of OV was 0.79 (95% CI: 0.65–0.93; Se/Sp, 66.7/90.9; PPV/

Table I. General characteristics of the study population

Characteristics	Data
Age [years]	59 (41–65)
Male sex, *n* (%)	41 (56.2)
Ethnicity, *n* (%):	
Bangladeshi	2 (2.7)
Cameroonian	1 (1.4)
Egyptian	9 (12.3)
Emirati	48 (65.8)
Indian	1 (1.4)
Jordanian	2 (2.7)
Pakistani	1 (1.4)
Sudanese	5 (6.8)
Syrian	3 (4.1)
Yemeni	1 (1.4)
Platelet count [× 10^9/l]	185 (155–241)
Albumin [g/l]	36 (34–38)
International normalised ratio (INR)	1.02 (0.99–1.1)
Bilirubin [µmol/l]	9.3 (6.4–15.9)

Continuous data are presented as median (interquartile range) whereas nominal data are presented as number (% patients).

Table II. The presence of oesophageal varices and large varices stratified according to different noninvasive diagnostic criteria

Criteria	Varices				Large varices			
	TN	FP	TP	FN	TN	FP	TP	FN
Baveno VI criteria	45	10	15	3	47	18	7	1
Expanded Baveno VI	50	5	12	6	54	11	6	2
PLT count/Spleen diameter	43	12	15	3	59	6	6	2
(PLT count/Spleen diameter) + LS	56	9	7	1	56	9	7	1
(PLT count/Spleen diameter) + LS × (40 – Albumin)	49	6	16	2	51	14	8	0

Data are expressed as true negative (TN), false positive (FP), true positive (TP), and false negative (FN).

NPV, 70.6/89.3; LR+/LR-, 7.33/0.37). Moreover, the same criteria for predicting the presence of large OV showed an AUC of 0.80 (95%CI 0.65–0.95; Se/Sp 87.5/72.3; PPV/NPV 28.1/97.9; LR+/- 3.16/0.17) and 0.79 (95%CI 0.61–0.98; Se/Sp 75/83.1; PPV/NPV 35.4/96.4l; LR+/- 4.44/0.3) for Baveno VI and Baveno VI Expanded, respectively.

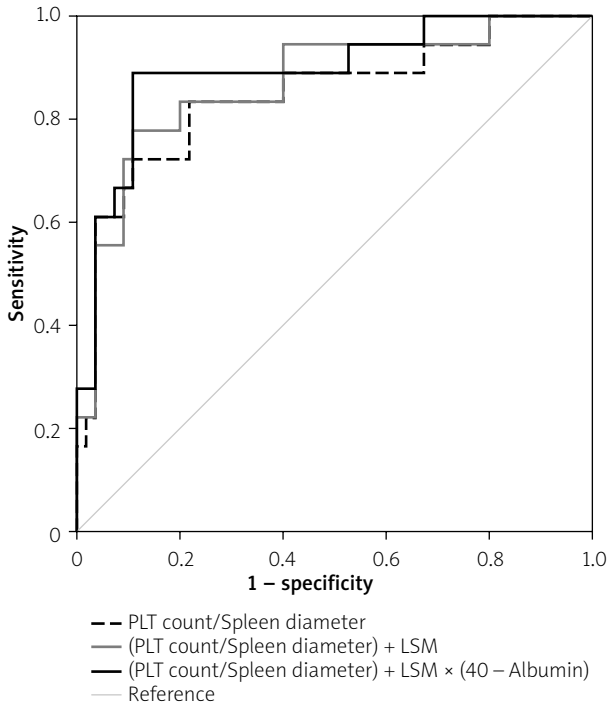
The (PLT count/Spleen diameter) formula had an AUC of 0.84 (0.73–0.96) with a cut-off of ≤ 1472 (Se/Sp 83.3/78.2; PPV/NPV 56/93.5; LR+/- 3.82/0.21) for predicting the presence of all OV and an AUC of 0.94 (0.87–1) with a cut-off of ≤ 933 (Se/Sp 87.5/90.8; PPV/NPV 54/98.3; LR+/- 9.51/0.14) for predicting the presence of large OV (Figures 1 and 2).

The (PLT count/Spleen diameter) + LS formula had an AUC of 0.87 (0.77–0.97) with a cut-off of ≤ 1269 (Se/Sp 83.3/80.0; PPV/NPV 58/93.6; LR+/- 4.17/0.21) for predicting the presence of all OV and an AUC of 0.94 (0.87–1) with a cut-off of ≤ 876 (Se/Sp 87.5/86.2; PPV/NPV 44.0/98.2; LR+/- 6.34/0.15) for predicting the presence of large OV (Figures 1 and 2).

The (PLT count/Spleen diameter) + LS × (40 – Albumin) formula had an AUC of 0.89 (0.80–0.99) with a cut-off of ≤ 572 (Se/Sp 88.9/89.1; PPV/NPV 73/96.1; LR+/- 8.16/0.12) for predicting the presence of all OV and an AUC of 0.94 (0.87–1) with a cut-off of ≤ 501 (Se/Sp 87.5/80.0; PPV/NPV 35.1/98.1; LR+/- 4.38/0.16) for predicting the presence of large OV (Figures 1 and 2).

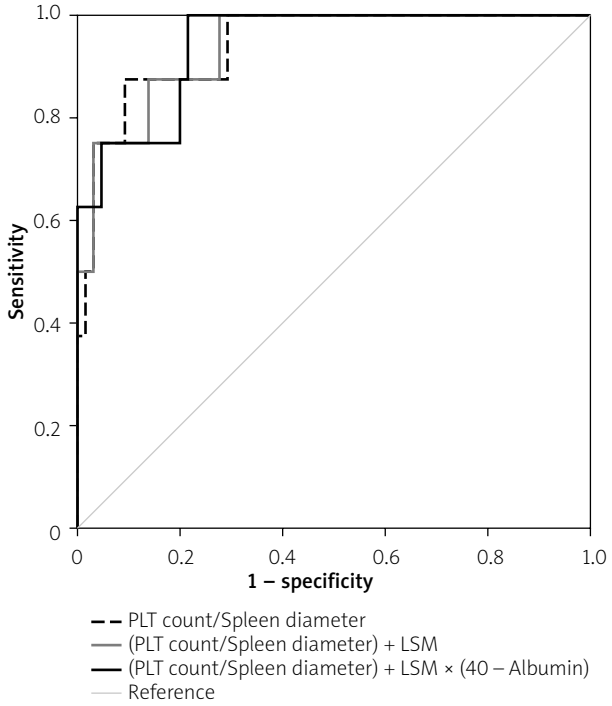
The pairwise comparison among AUCs showed that the (PLT count/Spleen diameter) + LS × (40 – Albumin) formula showed a significantly higher accuracy for predicting the presence of any grade OV other than both Baveno VI and expanded Baveno VI criteria (differences in AUC, 0.07 and 0.11; $p = 0.030$ and $p = 0.050$, respectively). Moreover, Baveno VI and expanded Baveno VI criteria were inferior to the (PLT count/Spleen diameter) (differences in AUC, 0.14 and 0.15; $p = 0.0001$ and $p = 0.010$, respectively), (PLT count/Spleen diameter) + LS (differences in AUC, 0.14 and 0.15; $p = 0.0005$ and $p = 0.006$, respectively), and (PLT count/Spleen diameter) + LS × (40 – Albumin) (differences in AUC, 0.15 and 0.16; $p = 0.0002$ and $p = 0.006$, respectively) formulas in predicting the presence of large OV.

Overall, the numbers of spared endoscopies were 47 (64.4%) and 54 (74.0%) using the Baveno VI and ex-



Score	Area under ROC curve	Cut-off value	Se/Sp	PPV/NPV	LR +/–
PLT count/Spleen diameter	0.84 (0.73–0.96)	1472	83.3/78.2	56/93.5	3.82/0.21
(PLT count/Spleen diameter) + LSM	0.87 (0.77–0.97)	1269	83.3/80	58/93.6	4.17/0.21
(PLT count/Spleen diameter) + LSM × (40 – Albumin)	0.89 (0.80–0.99)	572	88.9/89.1	73/96.1	8.16/0.21

Figure 1. Area under the receiver operating curve analysis of different criteria for predicting the presence of oesophageal varices of any grade in patients with compensated advanced chronic liver disease



Score	Area under ROC curve	Cut-off value	Se/Sp	PPV/NPV	LR +/–
PLT count/Spleen diameter	0.94 (0.87–1)	933	87.5/90.8	54/98.3	9.51/0.14
(PLT count/Spleen diameter) + LSM	0.94 (0.87–1)	876	87.5/86.2	44.0/98.2	6.34/0.15
(PLT count/Spleen diameter) + LSM × (40 – Albumin)	0.94 (0.87–1)	501	87.5/801	35.1/98.1	4.38/0.16

Figure 2. Area under the receiver operating curve analysis of different criteria for predicting the presence of large oesophageal varices in patients with compensated advanced chronic liver disease

panded Baveno VI criteria, respectively, and 59 (80.8%), 60 (82.2%), and 63 (86.3%) using (PLT count/Spleen diameter), (PLT count/Spleen diameter) + LS, and (PLT count/Spleen diameter) + LS × (40 – Albumin) formulas, respectively.

Discussion

To date, hepatic venous pressure gradient has been considered the gold standard for the diagnosis of clinically significant portal hypertension (CSPH); however, it is an invasive test that requires an equipped centre and expert staff [5, 15, 16]. Several noninvasive methods have been used to stratify and predict the presence of CSPH and OV development in patients with CLD and safely decrease the need for endoscopy [17]. Moreover, the new Baveno consensus research agenda focuses on the need for validating and refining these noninvasive tools for detecting CSPH in patients with NAFLD-associated cACLD, because the current evidence has no standard recommendations other than well-established aetiologies.

The present study weighed the different combined biochemical and radiological parameters in predicting the presence and severity of OV in patients suffering from NAFLD-associated cACLD. Overall, both the Baveno criteria (i.e. Baveno VI and expanded Baveno VI) and PLT-to-spleen diameter ratio, which also incorporates LS and albumin measurements, were effective in predicting the presence of varices of any size, with an AUC of up to 0.8 on AUROC analysis. Although the PLT count/spleen diameter ratio has been used to predict OV in patients with CLD secondary to infectious aetiologies like chronic hepatitis C and schistosomiasis, it has not been specifically used in patients with NAFLD [16, 17]. In fact, all Baveno criteria and PLT count/spleen diameter ratios, albeit consolidated in CLD, have not been validated in the NAFLD population [11, 12, 18]. Interestingly, our proposed formula appears to be effective in this population of patients, with the addition of LS and albumin measurements seemingly having better accuracy compared to PLT count/spleen diameter ratio alone.

Indeed, when comparing the Baveno VI and expanded Baveno VI criteria with (PLT count/Spleen diameter) + LS × (40 – Albumin), the latter appears to better pre-

dict the presence of any size and large OV. We believe that all parameters included in the proposed formula are commonly available during clinical evaluation and could represent a simple and uncostly tool for stratifying CLD patients in actual clinical practice with a higher accuracy than previously known criteria [18, 19].

Moreover, these formulas could decrease the financial burden of rural care centres with limited financial and logistic resources by reducing the endoscopy costs. In fact, the present findings highlighted that a significant number of endoscopies could be avoided by using all scores proposed. Moreover, several studies have already demonstrated that the application of noninvasive predictive tools, such as the PLT count/spleen diameter ratio, for the detection of OV would offer more cost-effective approach than would the "scope all strategy" [18, 20].

We believe that the incorporation of LS and serum albumin measurements into the previously validated PLT/spleen diameter ratio is of interest and is supported by both clinical and statistical evidence. From a clinical perspective, LS measurements could serve as an additional parameter reflecting liver fibrosis and inflammatory involvement typical of nonalcoholic steatohepatitis pathogenesis and should not be influenced by other causes of thrombocytopaenia or splenomegaly, such as haematological disorders [21]. Moreover, serum albumin levels could provide objective and reliable information on liver function in patients with overall preserved hepatic compensation [22]. From a statistical viewpoint, the (PLT count/Spleen diameter) + LS × (40 – Albumin) formula seems to be the most effective and accurate tool for predicting the presence of varices and large varices based on AUROC analysis.

This study has certain limitations. First, it is a retrospective study with a limited sample size. Moreover, although transient elastography has become a useful technique in actual clinical practice, its reliability in the NAFLD population has not yet been confirmed owing to the variable results caused by several factors, such as liver steatosis, inflammation, obesity, food intake, and cholestasis [23, 24]. However, we could establish a simple formula based on noninvasive tests to increase the negative predictive value of OV presence in patients with NAFLD-associated cACLD. Further larger-scale studies are warranted to confirm the wider applicability of this newly proposed formula.

The presence of CSPH and OV in patients with NAFLD and CLD can be safely assessed using noninvasive tools such as Baveno VI, expanded Baveno VI, and PLT count/spleen diameter ratio. A superior predictive value can be easily achieved by considering LS and serum albumin measurements along with the PLT count/spleen diameter ratio.

Conflict of interest

The authors declare no conflict of interest.

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Received: 22.07.2023
Accepted: 19.01.2024
Online publication: 24.04.2024