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Noninvasive Assessment of Portal Hypertension in Patients With Primary Biliary Cholangitis Is Affected by Severity of Cholestasis

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Abbreviations used in this paper: **ALP, alkaline phosphatase; AUROC, area under the receiver operating characteristic; BVI, Baveno VI; BVII, Baveno VII; cACLD, compensated advanced chronic liver disease; ChLD, cholestatic autoimmune liver disease; CI, confidence interval; CSPH, clinically significant portal hypertension; DCA, Decision Curve Analysis; EBL, endoscopic band ligation; EBVI, Expanded Baveno VI; EGD, esophagogastroduodenoscopy; EVs, esophageal varices; FNR, false-negative rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRVs, high-risk varices; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; NIT, noninvasive test; NSBB, nonselective beta blocker; PBC, primary biliary cholangitis; PH, portal hypertension; PLT, platelet; RESIST, Rete Sicilia Selezione Terapia; SVR, sustained virologic response; TE, transient elastography; UDCA, ursodeoxycholic acid; UK, United Kingdom; ULN, upper limit of normal.**

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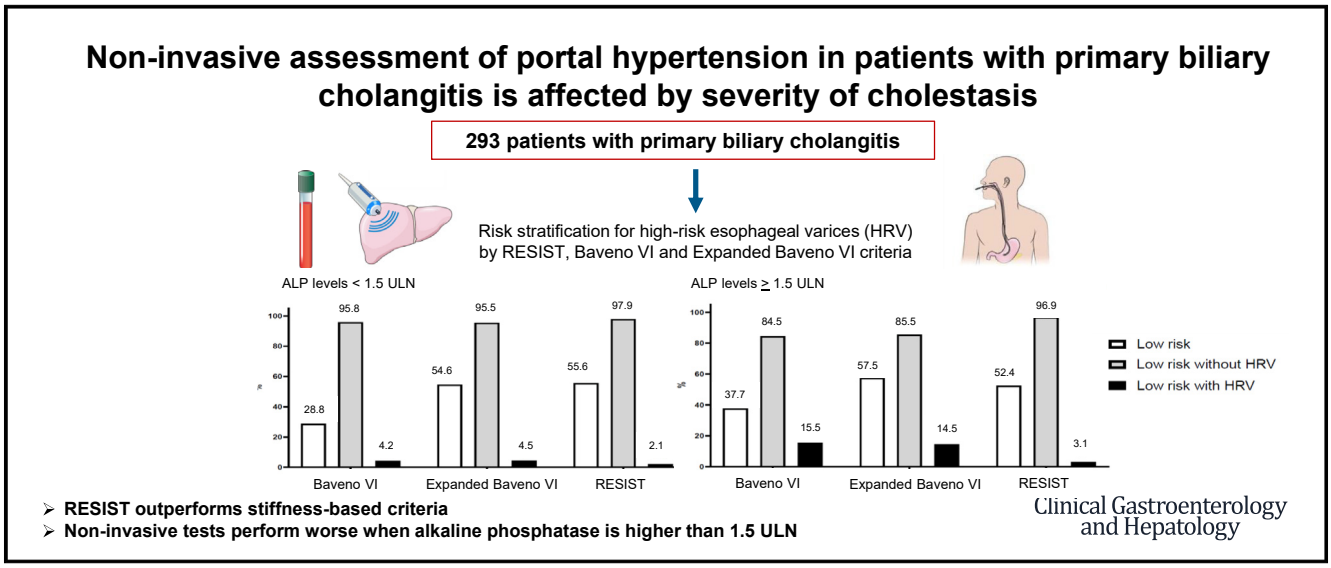

BACKGROUND & AIMS: **Noninvasive tests (NITs) for ruling-out clinical significant portal hypertension (CSPH) and high-risk varices (HRVs) in patients with primary biliary cholangitis (PBC) and compensated advanced chronic liver disease (cACLD) are lacking. We evaluated NITs in these patients and the influence of cholestasis on their performance.**

METHODS: **Consecutive patients from the "Italian PBC registry" and 2 United Kingdom large-volume PBC referral centers with upper endoscopy within 6 months from biochemical evaluation and transient elastography were included. Rete Sicilia Selezione Terapia (RESIST), Baveno VI (BVI), and Expanded Baveno VI (EBVI) criteria for ruling out HRV were assessed according to alkaline phosphatase (ALP) levels (< or ≥1.5 × upper limit of normal). Decision curve analysis was performed. Prevalence of any sized esophageal varices among patients fitting Baveno VII (BVII) criteria was also calculated.**

RESULTS: **The final cohort consisted of 293 patients with cACLD. RESIST criteria were associated with the lowest rate of missed HRV (2.5% vs 9.8% for BVI and 8.9% for EBVI). In patients with ALP levels ≥1.5 × upper limit of normal, BVI and EBVI missed a higher rate of HRV (15.5% and 14.5%, respectively) than RESIST (3.1%). Decision curve analysis demonstrated the highest net benefit of RESIST criteria for ruling out HRV, regardless of ALP levels. Among 75 patients classified as low risk of CSPH according to BVII, 14 (18.7%) showed esophageal varices.**

CONCLUSIONS: **Biochemical-based RESIST criteria demonstrate the highest net benefit compared with elastography-based criteria for ruling out HRV. The severity of cholestasis affects NITs performance to rule out HRV and CSPH in patients with PBC and cACLD.**

Keywords: Esophageal Varices; Liver Stiffness; Noninvasive Tests; Portal Hypertension; Primary Biliary Cholangitis.

The progression of portal hypertension represents a key driver toward the development of esophageal varices (EVs) and it increases the risk of liver decompensation, including variceal bleeding, in patients with compensated advanced chronic liver disease (cACLD).[1,2] The presence of clinically significant portal hypertension (CSPH) is determined either by hepatic vein pressure gradient (HVPG) ≥10 mmHg or by clinical manifestations of portal hypertension. Although the concept of CSPH is HVPG-driven, noninvasive tests (NITs) are sufficiently accurate to identify CSPH in clinical practice. Elastography-based criteria, such as Baveno VI (BVI) and Expanded Baveno VI (EBVI) criteria, have been extensively validated to identify patients that could safely avoid esophagogastroduodenoscopy (EGD) surveillance for medium/large varices, defined as high-risk varices (HRVs).[3–7]

These criteria have been widely validated in patients with viral[8] and metabolic etiology of liver disease.[9] More recently, the new Baveno VII (BVII) consensus[10] has focused on the noninvasive rule out of CSPH, suggesting that those with liver stiffness by transient elastography (TE) lower than 15 kPa and platelet (PLT) count higher than 150.000/mmc have a very low risk of CSPH.[11]

However, the relatively low prevalence of cholestatic autoimmune liver diseases (ChLDs) has made it difficult to evaluate the performance of elastography-based criteria in this setting, and only a limited number of patients with ChLDs have been included in their validation studies.[11,12] The few experiences that have been reported[13,14] showed the applicability of BVI criteria, but they demonstrated that the use of expanded criteria in patients with primary biliary cholangitis (PBC) resulted in a false-negative rate (FNR) higher than 5%.[13] Moreover, these criteria are limited by the use of TE, a tool that may not be available in nonreferral centers and in low-resource countries. For all these reasons, studies evaluating the diagnostic performance of NITs to rule-out HRV in cholestatic disorders are urgently needed.[15]

We previously demonstrated that biochemical-based criteria, including only PLT count and serum albumin (Rete Sicilia Selezione Terapia [RESIST] criteria) showed a similar accuracy to that of elasography-based criteria for predicting the presence of HRV[16–19] in patients with hepatitis C virus (HCV) infection, both before and after sustained virologic response (SVR) by direct-acting antiviral agents. Similarly to elastography-based criteria, this score has also been validated in different etiologies,[17] but whether these findings can be extrapolated to ChLDs remains to be established.

The aims of this multicenter study were: (1) to assess the diagnostic performance of elastography-based NITs and RESIST criteria for predicting the presence of HRV in patients with PBC and cACLD; (2) to evaluate the influence of the severity of cholestasis on the performance of all NITs; and (3) to evaluate the performance of BVII criteria to rule out CSPH in patients with PBC and cACLD.

What You Need to Know

Background

Noninvasive tests (NITs) to rule out high-risk varices and clinically significant portal hypertension in patients with primary biliary cholangitis (PBC) and compensated advanced chronic liver disease are lacking.

Findings

Biochemical-based RESIST criteria outperformed elastography-based criteria for ruling out high-risk varices in patients with PBC. All NITs performed worse in patients with alkaline phosphatase $>1.5 \times$ upper limit of normal. Baveno VII criteria missed with any-size varices in about 19% of patients, and they performed worse in patients with alkaline phosphatase $>1.5 \times$ upper limit of normal.

Implications for patient care

RESIST criteria can help simplify screening for high-risk varices in patients with PBC. However, caution is needed when using NITs in patients with uncontrolled cholestasis.

Patients and Methods

Patient Selection

Consecutive patients with PBC with cACLD (suggested by liver stiffness higher than 10 kPa or highly suggested by liver stiffness higher than 15 kPa) and/or PLT count lower than 150,000/mmc and/or compensated cirrhosis (established by histological diagnosis) who had an EGD for evaluation of endoscopic signs of portal hypertension seen between January 1, 2010, and December 31, 2023, at 33 Italian centers involved in the Italian PBC registry[20,21] and in 2 large-volume United Kingdom (UK) PBC tertiary referral centers were accrued in this cross-sectional study. The study flow-chart is shown in Supplementary Figure 1.

All included patients underwent clinical examination, biochemical evaluation (PLT count, albumin, bilirubin, creatinine, international normalized ratio [INR], alkaline phosphatase [ALP]), and liver stiffness measurement (LSM) by TE within 6 months from index EGD. Child-Pugh and Model for End-Stage Liver Disease (MELD) score were calculated. Biochemical examination was performed in the same day of LSM. Data on treatment with ursodeoxycholic acid (UDCA) and its duration were also collected. Exclusion criteria were: Child-Pugh class B or C; lack of EGD; lack of biochemical assessment; history of treatment with nonselective beta blockers (NSBBs) or endoscopic band ligation (EBL) of EV; portal thrombosis; splenectomy; liver transplantation; and hepatocellular carcinoma (HCC).

Outcome Definitions

At the time of EGD, each patient was risk stratified for HRV according to elastography-based criteria (BVI and EBVI) (Supplementary Table 1) and RESIST criteria.

Patients were classified as RESIST-In (low risk of HRV) if they had PLT count $\geq 120 \times 10^9$/L and serum albumin ≥ 3.6 g/dL or RESIST-Out (high risk of HRV) if PLT count $<120 \times 10^9$/L or serum albumin <3.6 g/dL.

As pre-planned subgroup analysis, we assessed the diagnostic performance of NITs after stratification according to ALP levels below or above 1.50 times the upper limit of normal (ULN).[22]

The prevalence of any-sized EV according to BVII criteria to rule out CSPH (PLT $\geq$150 $\times$ 10^9/L and LSM $\leq$15 kPa) was reported in the whole cohort and after stratification according to ALP levels.

LSM by TE was performed by FibroScan (EchoSens). Patients were fasted for at least 6 hours before the procedure, and LSMs were performed according to standard procedures.

The presence and the size of EV were defined using the North Italian Endoscopic Club criteria.[23]

The study was approved by the University of Milan-Bicocca research ethics committee (Study name: PBC322), coordinator of the Italian National Registry, and by the Research and Development Department of each collaborating hospital. The study was registered as a local audit at Oxford University Hospitals NHS Trust (6446).

Statistical Analysis

For RESIST, BVI, and EBVI criteria, sensitivity, specificity, and positive/negative likelihood ratios were calculated, as well as the number of HRV identified/missed, the number of patients misclassified as high risk, and the number of correctly spared endoscopies. Discriminating ability of NITs for the prediction of the development of HRV was assessed by the area under the receiver operating characteristic curve (AUROC).

Decision curve analysis (DCA) was performed for identifying threshold probabilities at which use of NITs will translate into maximum net benefit of detecting HRV.[24,25] DCA evaluated the net benefit of prediction models in comparison with default strategies of performing upper endoscopy in all patients or none, allowing an assessment of overall yield of prediction rules. In this particular setting, net benefit can be expressed as the number of endoscopies correctly avoided at different threshold probabilities of missing HRV. Further details of DCA are described in the Supplementary Materials.

All data were analyzed using Rstudio. DCA was implemented in R using code derived from Zhang et al.[26] In addition to the base packages in R, tidyverse, survival, survminer, boot, reshape2, and readxl packages were used.

Results

Cohort Characteristics

Baseline characteristics of 293 included patients are shown in Table 1. Mean age was 56 $\pm$ 12.5 years, and 257 (87.7%) were female. ALP levels were higher than 1.5 times ULN in 124 patients (42.3%). Most of the patients (205; 70.0%) had Child-Pugh score 5, and the mean MELD score was 6.5 $\pm$ 1.3.

At the time of index EGD, EVs were absent in 170 patients (58.0%), whereas 87 patients (29.7%) had low-risk varices and 36 (12.3%) had HRVs.

Table 1. Demographic and Clinical Characteristics of 293 Patients With PBC and cACLD

	Whole cohort (N = 293)
Age, *years*	56.2 $\pm$ 12.5
Female sex	257 (87.7)
ALP $\times$ ULN	2.2 $\pm$ 7.3
ALP $\geq$1.50 $\times$ ULN	124 (42.3)
PLT, *10^9/L*	168 $\pm$ 87
Albumin, *g/dL*	3.8 $\pm$ 0.5
Bilirubin, *mg/dL*	0.9 $\pm$ 0.6
INR	1.1 $\pm$ 0.2
Creatinine, *mg/dL*	0.8 $\pm$ 0.2
Child-Pugh score	
5	205 (70.0)
6	88 (30.0)
MELD score	6.5 $\pm$ 1.3
No EVs	170 (58.0)
F1	87 (29.7)
F2	27 (9.2)
F3	9 (3.1)
LSM by TE, *kPA*[a]	18.2 $\pm$ 12.4
UDCA treatment duration longer than 6 months	181 (61.8)

Note: Data are presented as number (%) or mean $\pm$ standard deviation.
ALP, alkaline phosphatase; cACLD, compensated advanced chronic liver disease; EVs, esophageal varices; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cholangitis; PLT, platelet; TE, transient elastography; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[a]Available in 283 patients (96.6%).

Diagnostic Performance of NITs for the Prediction of HRV

At the time of index EGD, all patients were stratified according to RESIST criteria, whereas stratification according to BVI and EBVI was available in 283 patients (96.6%).

Patients classified as low-risk were 54.3% with RESIST, 55.8% with EBVI, and 32.5% with BVI. Patients classified as low-risk by RESIST had the lower proportion of missed HRVs (2.5%; 95% confidence interval [CI], 0.1%–4.9%) compared with elastography-based criteria, which missed HRV in more than 5% of patients classified as low-risk (Figure 1, *panel A*).

Table 2 shows the diagnostic performance of NITs for the prediction of HRVs compared with the strategy of perfoming endoscopy in all patients. RESIST criteria correctly spared the highest number of EGDs (60.3%; 95% CI, 54.3%–66.3%), with the lowest false-positive rate (39.7%; 95% CI, 33.7%–45.7%) compared with BVI and EBVI criteria, showing the highest discriminating ability for the prediction of HRVs (AUROC, 0.75; 95% CI, 0.69–0.80).

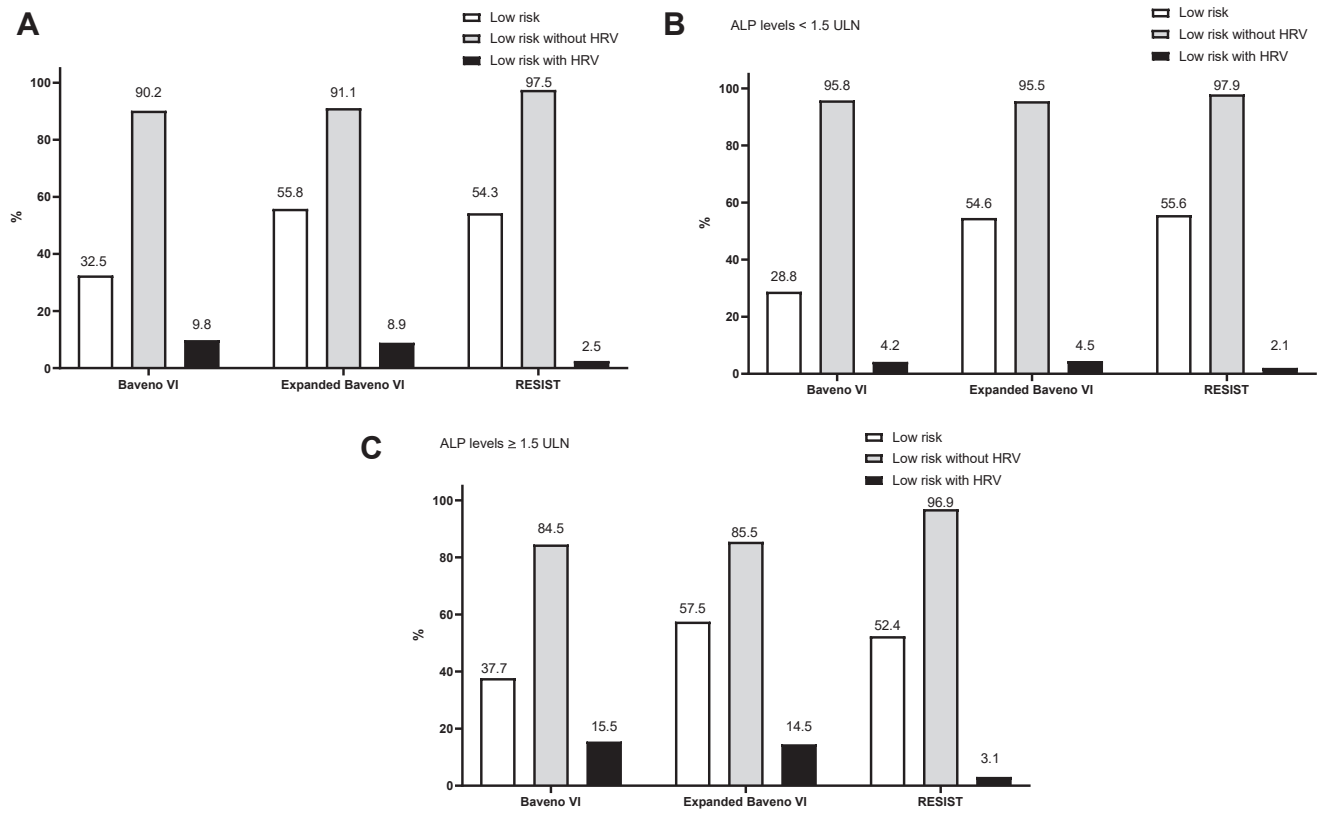

Figure 1. Risk stratification for the presence of HRVs according to BVI, EBVI, BVII, and RESIST criteria in patients with PBC and cACLD. *Panel A*, whole cohort. *Panel B*, ALP <1.5 × ULN. *Panel C*, ALP >1.5 × ULN.

Impact of ALP Levels on the Diagnostic Performance of NITs for the Prediction of HRVs

The comparison of baseline characteristics between patients with ALP levels lower and higher than 1.5 × ULN is shown in Supplementary Table 2. Patients with ALP levels higher than 1.5 × ULN were more likely to have Child-Pugh class A6, whereas the prevalence of EVs, liver stiffness, PLT count, and albumin levels were not significantly different between the 2 groups.

In patients with ALP <1.5 × ULN (n = 169), the rate of missed HRVs was lower than 5% for all the NITs (RESIST: 2.1%; 95% CI, 0.2%–7.7%; BVI: 4.2%; 95% CI, 0.5%–15.4%; and EBVI: 4.5%; 95% CI, 1.2%–11.5%) (Figure 1, *panel B*). RESIST performed better in terms of correctly spared endoscopies (60.9%; 95% CI, 49.1%–74.7%) and AUROC (0.75; 95% CI, 0.68–0.81) (Supplementary Table 3).

Conversely, in patients with ALP ≥1.5 × ULN (n = 124), all NITs performed worse, with a rate of HRVs among those classified as low-risk ranging from 3.1% (95% CI, 0.4%–11.1%) for RESIST to 15.5% (95% CI, 6.2%–32.2%) for BVI (Figure 1, *panel C*), resulting in an FNR ranging from 11.1% (95% CI, 1.3%–40.1%) for RESIST to 55.6% (95% CI, 26.6%–100%) for EBVI (Supplementary Table 4). RESIST criteria were associated with the highest proportion of correctly spared endoscopies (59.4%; 95% CI, 45.7%–76.0%) and the highest AUROC (0.74; 95% CI, 0.65–0.82) (Supplementary Table 4).

Decision Curve Analysis

The net benefit for ruling out HRV at 5% and 10% threshold probabilities of missing HRVs of RESIST and elastography-based criteria is shown in Table 3. At both the risk thresholds, RESIST outperformed all the elastography-based criteria (Figure 2). All the NITs were associated with a higher net benefit in patients with ALP levels <1.5 × ULN (Supplementary Figure 2), and RESIST criteria showed the best net benefit in patients with ALP ≥1.5 × ULN (Supplementary Figure 3).

Overall Assessment of Baveno VII Criteria to Rule Out CSPH

Overall, 14 of 75 (18.7%; 95% CI, 10.2%–31.3%) patients classified as having low risk of CSPH according to BVII (PLT ≥150 and TE ≤15 kPa) had any-sized EV at EGD.

According to ALP levels, any-sized EVs were present in 5 of 40 patients (12.5%; 95% CI, 4.1%–29.1%) with ALP <1.5 × ULN classified as low-risk and in 9 of 35 patients (25.7%; 95% CI, 11.8%–48.8%) with ALP ≥1.5 × ULN (Figure 3). Further details on the diagnostic performance of BVII in the overall cohort and according to ALP levels is reported in Supplementary Table 5.

Supplementary Table 6 reports the comparison of baseline characteristics of patients classified as low risk of CSPH with and without any-sized EVs.

Table 2. Diagnostic performance of NITs for the prediction of HRVs in 293 patients with PBC and cACLD

	Number of endoscopies performed	Number of endoscopies saved	HRV identified (true positive)	HRV missed (false negative)	Misclassified as HRV (false positive)	Correctly spared endoscopies (true negative)	False negative/ number of patients avoiding endoscopies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUROC (95% CI)
EGD in all patients	293 (100)	0 (0)	36 (100)	0 (0)	257 (100)	0 (0)	-	-	-	-	-	-
Baveno VI criteria[a]	191 (67.5)	92 (32.5)	27 (75.0)	9 (25.0)	164 (66.4)	83 (33.6)	9.8%	75.0 (57.8-87.9)	33.6 (27.7-39.9)	1.13	0.74	0.543 (0.483-0.602)
Expanded Baveno VI Criteria[a]	125 (44.2)	158 (55.8)	22 (61.1)	14 (38.9)	103 (41.7)	144 (58.3)	8.9%	61.1 (43.5-76.9)	58.3 (51.9-64.5)	1.47	0.67	0.597 (0.537-0.655)
RESIST criteria	134 (45.7)	159 (54.3)	32 (88.9)	4 (11.1)	102 (39.7)	155 (60.3)	2.5%	88.9 (73.9-96.9)	60.3 (54.0-66.3)	2.24	0.18	0.746 (0.692-0.795)
Ideal strategy	36 (12.3)	257 (87.7)	36 (100)	0 (0)	0 (0)	257 (100)	-	-	-	-		-

Note: Percentage of HRVs identified and missed are calculated by using patients with HRV as denominator (n = 36). All patients with HRVs were evaluable for all the noninvasive criteria.
AUROC, area under the receiver operating characteristic; BVI, Baveno VI; cACLD, compensated advanced chronic liver disease; CI, confidence interval; EBVI, Expanded Baveno VI; EGD, esophagogastroduodenoscopy; HRVs, high-risk varices; NIT, noninvasive test; RESIST, Rete Sicilia Selezione Terapia.
[a]BVI and EBVI criteria were evaluable in 283 patients (96.6%).

Table 3. DCA reporting net benefit for ruling out HRVs at threshold probabilities of 5%, 7.5%, and 10% of different NITs in patients with PBC and cACLD

	Number of EGDs avoided per 100 patients (training cohort)		
Criteria	Threshold probability 5%	Threshold probability 7.5%	Threshold probability 10%
RESIST	27	35	40
BVI	0	0	1
EBVI	0	0	6

Note: Net benefit represents the number of EGDs avoided per 100 patients compared with the strategy to perform EGDs in all patients at different threshold probabilities of missing HRV.
BVI, Baveno VI; cACLD, compensated advanced chronic liver disease; EBVI, Expanded Baveno VI; EGD, esophagogastroduodenoscopy; HRV, high-risk varices; NIT, noninvasive test; PBC, primary biliary cholangitis; RESIST, Rete Sicilia Selezione Terapia.

Discussion

In this multicenter study, we demonstrated that: (1) diagnostic performance of all NITs to rule out HRV was better in patients with adequate biochemical response to treatment, with RESIST criteria being the most accurate independently from ALP levels; (2) the net benefit of RESIST criteria was better than elastography-based criteria, avoiding the highest number of unnecessary endoscopies, at an acceptable risk of missing HRVs, potentially leading to a simplification of surveillance programs; and (3) finally, BVII criteria to rule out CSPH demonstrated a high rate of false negative in our cohort of patients with PBC with a higher risk of missing EVs in patients with high ALP levels. To the best of our knowledge, these results have been obtained in the largest cohort of patients with PBC to date.

We assessed the diagnostic performance of BVI, EBVI, and RESIST[3,4,16] for the prediction of HRVs in an international cohort of patients with PBC with a larger sample size compared with previous experience.[13,14] Although inclusion criteria were similar, differently from previously published studies, we were able to differentiate the performance of NITs according to the severity of cholestasis,[13,14] showing a lower performance of NITs in patients with ALP levels higher than 1.5 × ULN. Moreover, it should be considered that some of the studies[14] assessed the diagnostic performance of NITs only for any-sized EVs, rather than HRVs. In patients with ALP levels lower than 1.5 × ULN, we confirmed good performance of elastography-based criteria. In these patients, RESIST criteria, a simple biochemical-based prediction rule including PLT count and albumin levels, emerged as an accurate and validated tool able to rule out the presence of HRV. We found that the application of these criteria would lead to correctly spare about 60% of unnecessary EGDs.

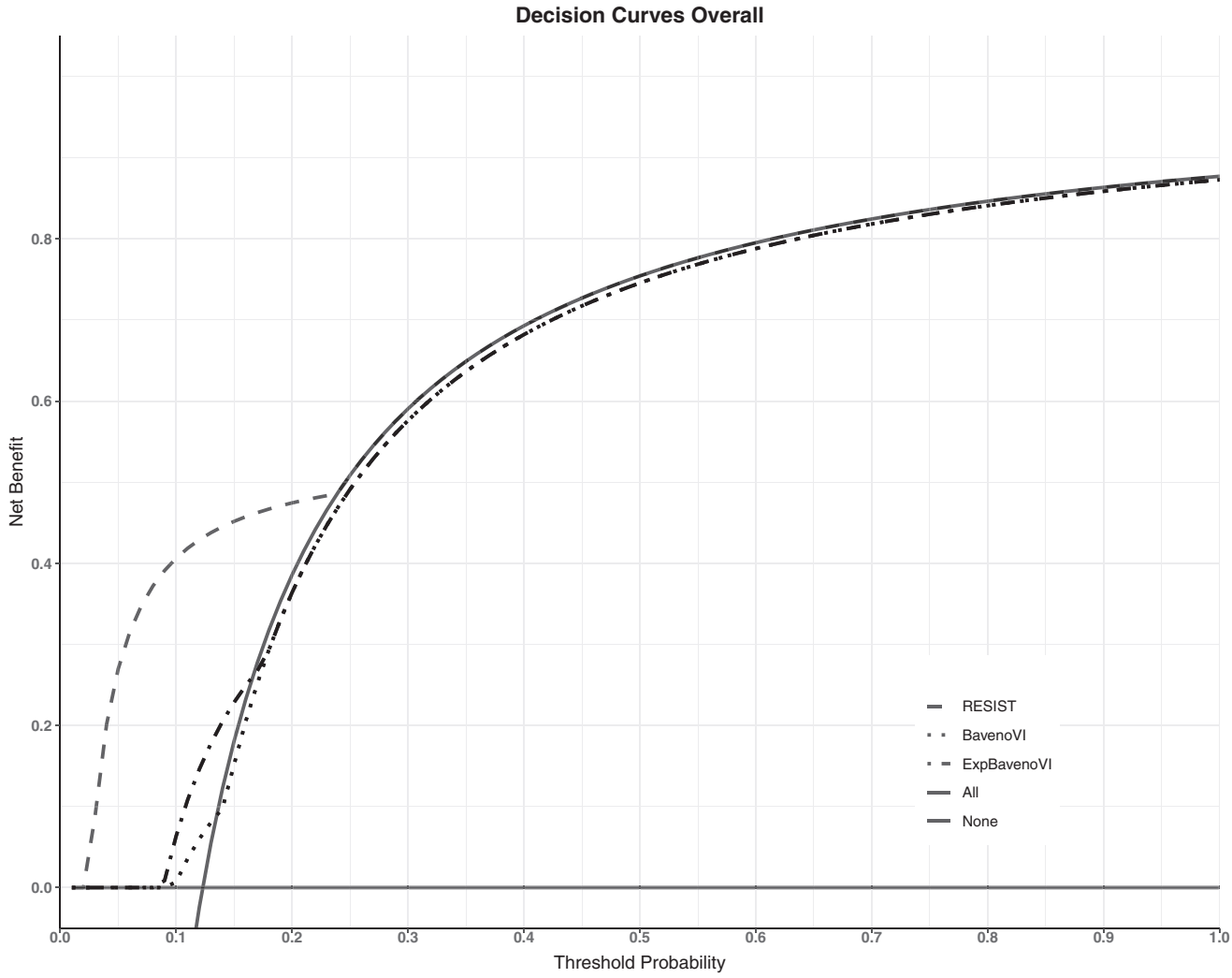

Figure 2. DCA of BVI, EBVI, and RESIST criteria for ruling out HRVs at different threshold probabilities of missing HRVs.

On the other hand, we demonstrated that the performance of the elastography-based criteria was highly unsatisfactory in patients with ALP levels higher than 1.5 × ULN, showing that the risk of missing HRV was higher than 15% for both BVI and EBVI. However, also in this setting, including both treatment-naïve patients who have been found to have cACLD at the time of PBC diagnosis and previously treated patients with inadequate response to UDCA, we have observed that RESIST criteria outperformed BVI and EBVI, achieving the lowest risk of

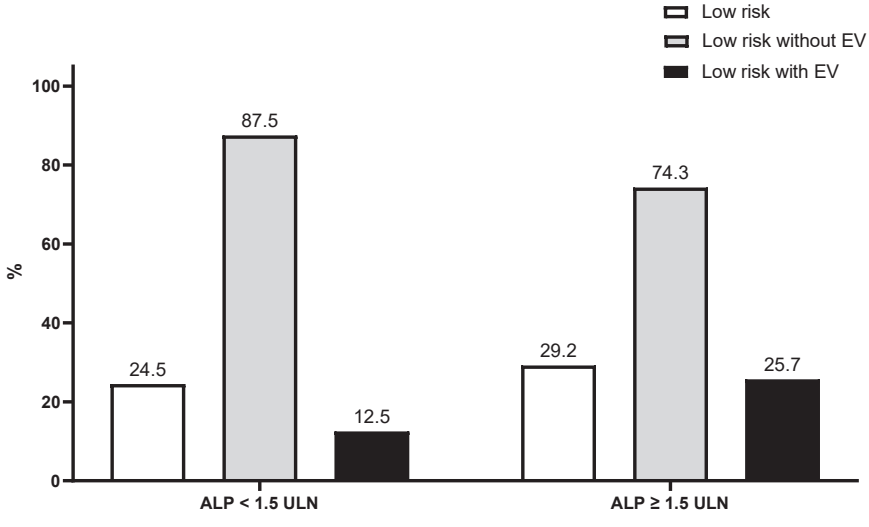

Figure 3. Risk stratification for the presence of any-sized EVs according to BVII criteria, according to ALP levels (lower or higher than 1.5 × ULN).

missing HRV (3.1%) and allowing for a safe reduction of up to 60% of unnecessary endoscopies, similarly to patients with ALP levels lower than 1.5 × ULN.

Therefore, the diagnostic performance of all noninvasive criteria to rule out HRV was superior in patients with ALP levels lower than 1.5 × ULN, demonstrating that the use of elastography-based algorithms may be related to an unacceptable miss rate of HRVs in patients with PBC and advanced liver disease without an adequate response to anticholestatic drugs.

The definition of cACLD includes a wide spectrum of severity of liver disease, including patients with less advanced liver disease without CSPH. In these patients, the performance of NITs for ruling out HRVs could be better due to the low probability of having HRVs. By contrast, the longer the time from diagnosis, the higher the disease severity and then the probability of having HRV. However, Baveno consensus does not consider that performance of NITs could change over time during the disease course. NITs for ruling out HRV should be accurate across the full spectrum of cACLD, ranging from patients with liver stiffness higher than 10 kPa without CSPH to Child-Pugh A patients with signs of CSPH. The individual application of NIT results in clinical practice to stratify the risk for HRVs remains a debated topic, particularly in the setting of PBC etiology. Conventional metrics, such as AUROC, focus only on the accuracy of the test, but it does not take into account the case where a false-negative results may be more harmful than a false-positive result or vice versa.[24,25] In this setting, it appears reasonable to prefer tests that maximize sensitivity over specificity in order to avoid false-negative results (ie, patients wrongly classified as low-risk of HRVs according to NITs, but having HRVs at EGD). DCA incorporates information on the clinical consequences of performing or not performing a diagnostic test, and it represents an appropriate methodology to compare the net benefit of different tests at different threshold probabilities of missing the disease of interest.[24,25]

Our DCA confirmed that the net benefit of all NITs across a wide range of threshold probabilities of missing HRVs was overall lower in patients with ALP levels higher than 1.5 × ULN compared with those with ALP levels lower than 1.5 × ULN and that RESIST criteria showed an overall higher net benefit for ruling out HRVs compared with elastography-based criteria, suggesting that they could represent the more suitable NIT for HRV risk stratification, regardless of ALP levels.

Our results are plausible because it is already known that portal hypertension is common in PBC, and it may be present at the early stages of the disease. Navasa et al demonstrated that portal hypertension in PBC is initially of the presinusoidal type, and then as the disease progresses, it is joined by a sinusoidal component.[27] This presinusoidal component of portal hypertension largely described in patients with PBC might not be properly detected by LSM-TE.[28] In a recent study, Warnes et al[29] analyzed 86 patients with PBC with HVPG measurement and liver biopsy, demonstrating that 82% of patients with pre-cirrhotic PBC had portal hypertension, and in 34%, this was >12 mmHg. In this study, portal pressure correlated significantly with a semiquantitative grading of cholestasis, interface hepatitis, and portal tract and sinusoidal fibrosis.

A relevant clinical benefit associated with the use of RESIST criteria is that they are simple, reliable, and repeatable, and there is no need for patient access to the hospital to perform liver stiffness measurement. In this line, the use of biochemical, rather than elastography-based, criteria could be helpful outside of tertiary care centers to better identify patients needing endoscopic tests for portal hypertension, or in low-income countries with limited health resources. All in all, the routine use in clinical practice of RESIST criteria may have a relevant impact on improving patients' compliance, by simplifying the management of portal hypertension and improving the cost-effectiveness of screening programs, by reducing direct and indirect costs.

Although BVII consensus is mainly focused on the prediction of decompensation through ruling out or ruling in the presence of CSPH,[10] we evaluated the diagnostic performance of NITs for HRV, given that, according to the "rule of five," BVI criteria for ruling out HRVs are still considered useful for clinical practice, particularly for patients who are not receiving nonselective beta-blockers and for sparing unnecessary endoscopies.

The development of NITs to early predict the presence of CSPH, rather than HRVs, remains an unsolved medical need in patients with PBC. In this study, we were also able to assess the ability of BVII criteria to rule out CSPH indicated by diagnosis of any-sized EV,[10] demonstrating a high rate of false-negative results. About 1 in 5 patients classified as low-risk according to BVII criteria showed varices at EGD, indicating CSPH. Again, the existence of a presinusoidal component of portal hypertension in patients with PBC, which could not be accurately detected by LSM- TE,[28] is a possible explanation for this finding. LSM may be subject to interoperator variability and to measurement errors that can influence the results, differently from biochemical values such as albumin and platelet, that have a higher measurement standardization and repeatability. Unfortunately, the lack of data on liver biopsy hampered the confirmation of this hypothesis in our study. Similarly to HRV, the rate of false-negative results reaches up to 26% in patients with high ALP levels, suggesting again that the severity of cholestasis affects the performances of NITs for portal hypertension in patients with PBC. To the best of our knowledge, this is the first study evaluating the role of the severity of cholestasis as a factor that may reduce the performance of NITs for ruling in and ruling out CSPH. These results indicate a significant undertreatment of CSPH in patients with PBC, especially in consideration of recent studies[30] that demonstrated a decreased risk for decompensation and mortality in patients with CSPH treated with NSBBs.

Our study has some limitations. First, the cross-sectional design does not allow extrapolating

conclusions about the prognostic role of NITs in predicting evolutionary events during follow-up, like the development of HRVs in patients without HRVs at the time of diagnosis and treatment start. Second, although BVI suggested 5% as an acceptable risk of missing HRVs for NITs, this threshold remains subjective, and it could change in different clinical settings. However, DCA confirmed the robustness of our results across a wide range of different threshold probabilities of missing HRVs. Third, although RESIST criteria were externally validated in patients with viral etiologies of liver disease for the identification of HRV in cross-sectional studies, they suffer from the lack of further external validation for predicting the progression to HRV in patients with PBC enrolled in different settings. The high variability in criteria for indicating EGDs in real-world clinical practice may affect the reliability of the findings from cross-sectional studies, and properly designed prospective studies are needed to improve the accuracy of the results. Moreover, it should be considered that the reproducibility of endoscopy-based diagnosis and grading of varices as an indicator of CSPH could be unsatisfactory.[31] However, all patients were managed and scoped in tertiary hepatological referral centers with high expertise in the evaluation of endoscopic signs of portal hypertension. Finally, unfortunately, we have no available data on HVPGs. These data are overall scarce in the literature, due to the low prevalence of patients with cholestatic disorders included in studies reporting HVPGs. Moreover, it should be noted that evaluating criteria for ruling-in or ruling-out CSPH based on the reference standard HVPG is complicated by the presence of a presinusoidal portal hypertension component in PBC, which is not reflected by HVPGs. Therefore, further studies are needed to define the patients who need to be treated with NSBBs.

In conclusion, we demonstrated that NITs for portal hypertension have a suboptimal performance with high rate of false negatives both for HRVs and for CSPH (indicated by presence of varices of any size) in patients with PBC and cACLD, mostly in those with ALP levels higher than 1.5 $\times$ ULN. The biochemical-based RESIST criteria are the best NIT for predicting HRVs in patients with PBC, helping to simplify HRV screening programs. However, further validation is needed in patients with chronic cholestatic disorders to confirm the effectiveness of the BVII criteria in ruling out CSPH.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.10.020.

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Conflicts of interest
Vincenza Calvaruso reports advisory board and speaking fees for Echosens. Marco Carbone consulted for Echosens. The remaining authors do not have conflicts of interest that are directly relevant to the data presented in the article.

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Data Availability
Data, analytic methods, and study materials will be made available to other researchers upon reasonable request.

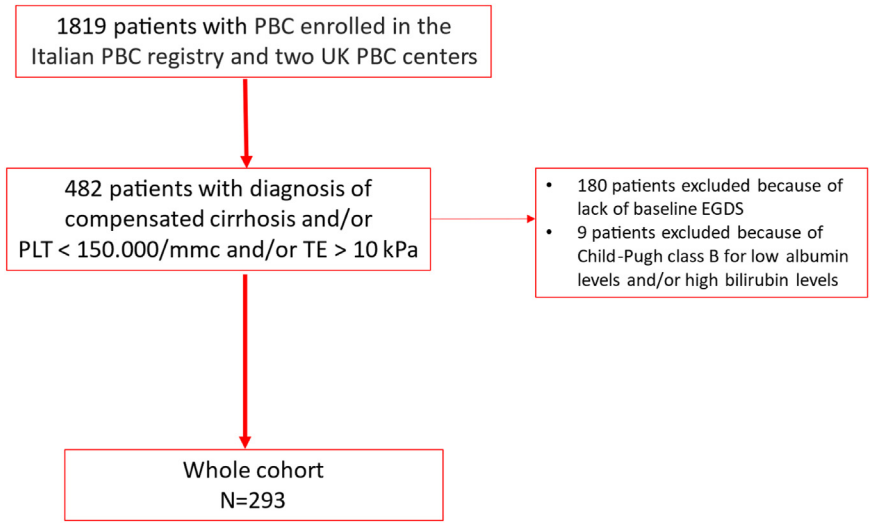
Supplementary Methods

Decision Curve Analysis

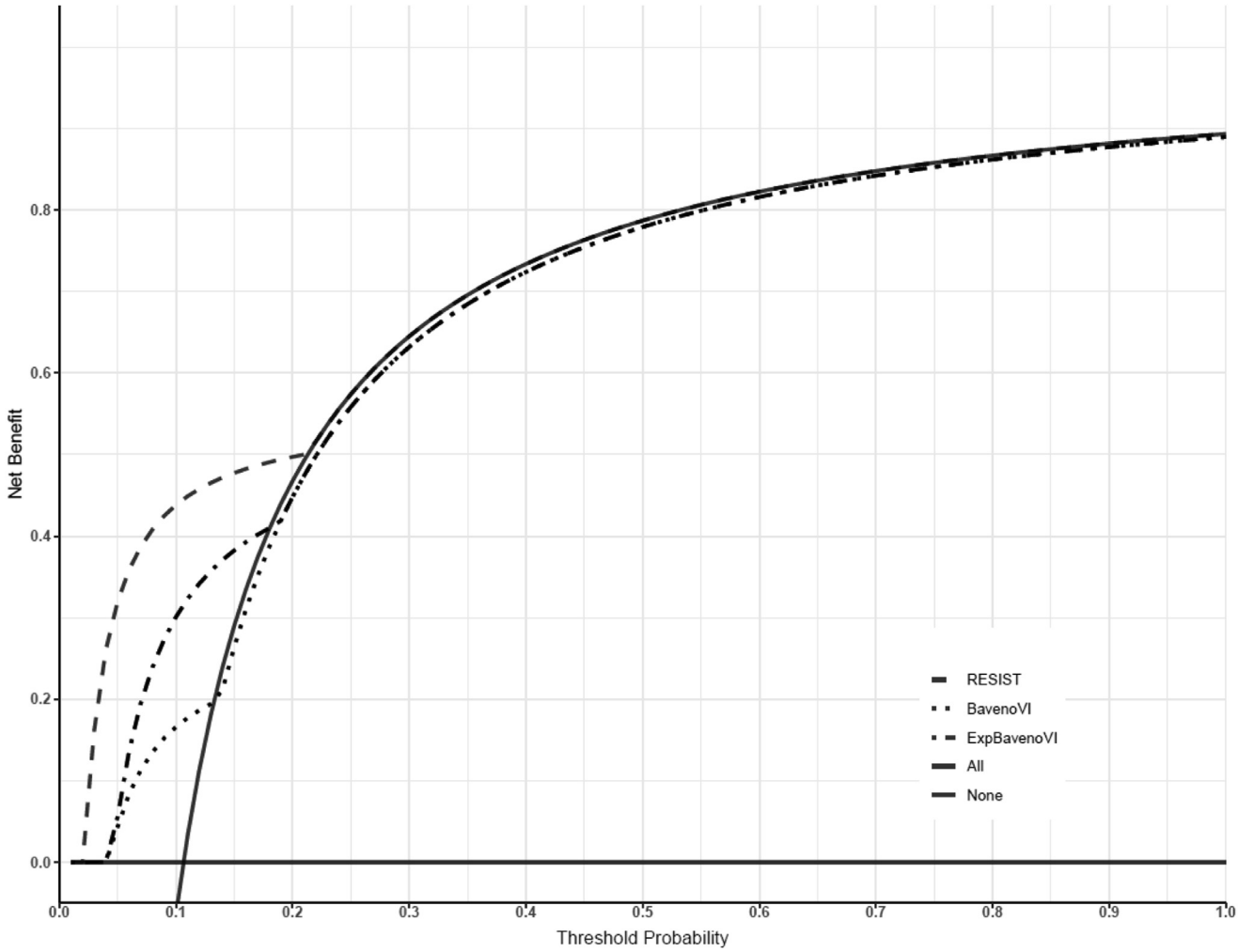
Decision curve analysis (DCA) was performed in training and validation cohorts for identifying threshold probabilities at which use of noninvasive tests (NITs) will translate into maximum net benefit of detecting high-risk varices (HRVs).[23,24] DCA evaluated prediction models in comparison with default strategies of performing upper endoscopy in all patients or none, allowing an assessment of overall yield of prediction rules. Further details of DCA are described in the Supplementary Materials. DCA estimates a "net benefit" for each of prediction rule, defined as

$$\text{net benefit} = \text{sensitivity} \times \text{prevalence} - (1\text{–specificity}) \times (1\text{–prevalence}) \times w$$

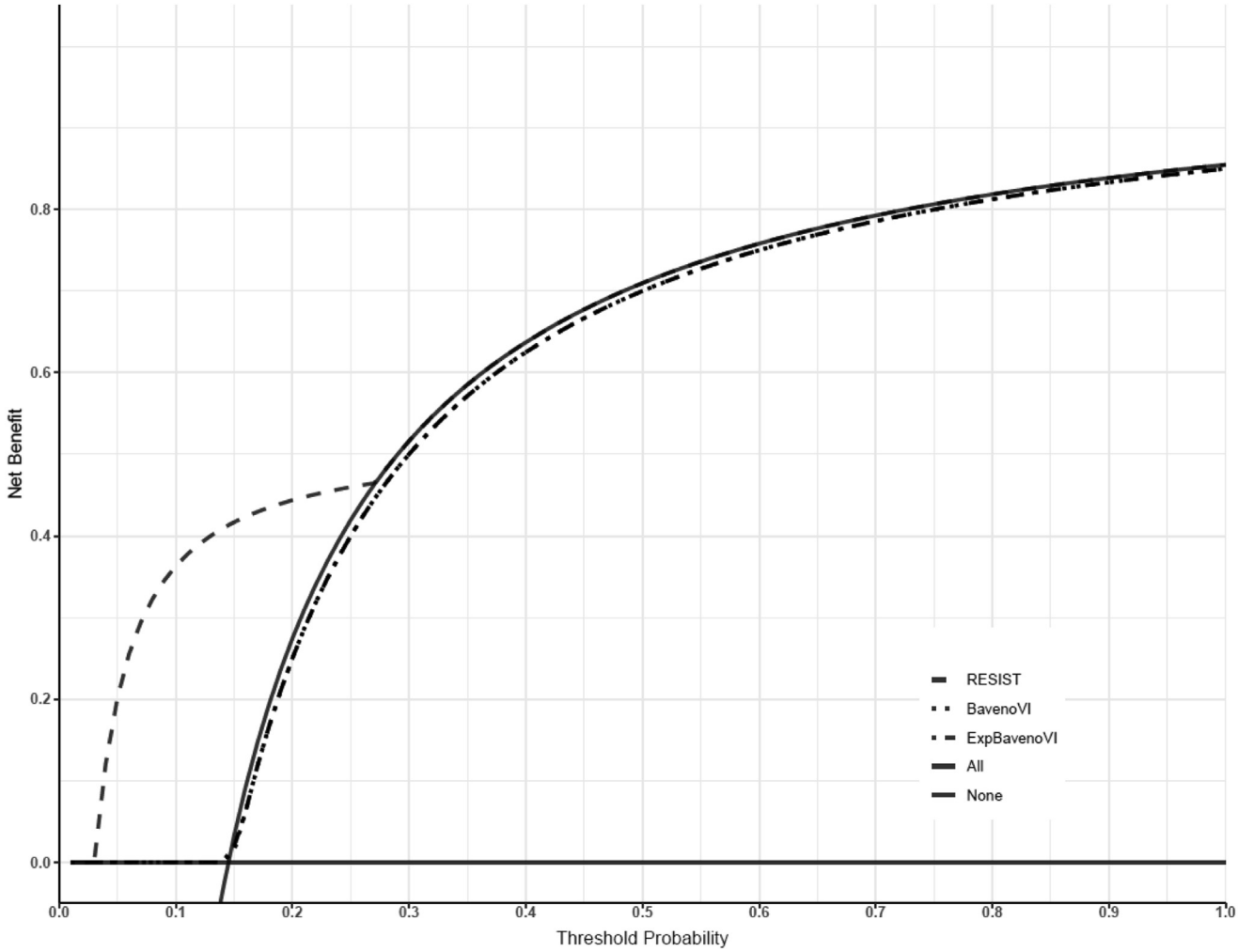
where w is the odds of true diagnosis (ie, HRV in this case) across different threshold probabilities. In this setting, net benefit represents a composite of the benefit gained by performing screening EGD for true HRV (true positive) and risk/discomfort incurred due to EGD in those without HRV (false positive). Threshold probability represents a theoretical risk-level where the expected benefit of treatment is equal to the expected benefit of avoiding treatment (eg, benefit of upper endoscopy equals risk of not performing it). Thus, net benefit is assessed across a range of threshold probabilities to identify the best diagnostic strategy for different risk scenarios.



Supplementary Figure 1. Study flowchart.



Supplementary Figure 2. DCA of elastography-based criteria (BVI and EBVI) and RESIST criteria in patients with PBC and cACLD with ALP levels lower than 1.50 × ULN for ruling out HRVs at different threshold probabilities of missing HRVs.



Supplementary Figure 3. DCA of elastography-based criteria (BVI and EBVI) and RESIST criteria in patients with PBC and cACLD with ALP levels higher than 1.50 × ULN for ruling out HRVs at different threshold probabilities of missing HRVs.

Supplementary Table 1. Elastography-based Criteria for Ruling Out HRVs and CSPH

	IN (low risk)	OUT (high risk)	Outcome
RESIST	PLT $\geq$120 $\times$ 10^9/L and albumin $\geq$3.6 g/dL	PLT <120 $\times$ 10^9/L and/or albumin <3.6 g/dL	HRV
BVI	PLT $\geq$150 $\times$ 10^9/L and LSM-TE $\leq$20 kPa	PLT <150 $\times$ 10^9/L and/or LSM-TE >20 kPa	HRV
EBVI	PLT $\geq$110 $\times$ 10^9/L and LSM-TE $\leq$25 kPa	PLT <110 $\times$ 10^9/L and/or LSM-TE >25 kPa	HRV
BVII	PLT $\geq$150 $\times$ 10^9/L and LSM-TE $\leq$15 kPa	PLT <150 $\times$ 10^9/L and/or LSM-TE >15 kPa	CSPH

BVI, Baveno VI; BVII, Baveno VII; CSPH, clinically significant portal hypertension; EBVI, Expanded Baveno VI; HRV, high-risk varices; LSM, liver stiffness measurement; PLT, platelets; RESIST, Rete Sicilia Selezione Terapia; TE, transient elastography.

Supplementary Table 2. Comparison of Baseline Characteristics Between Patients With ALP Levels Lower and Higher Than 1.50 $\times$ ULN

	ALP <1.50 $\times$ ULN (n = 169)	ALP $\geq$1.50 $\times$ ULN (n = 124)	*P*-value
Age, *years*	55.9 $\pm$ 12.1	56.5 $\pm$ 13.0	.727
Female sex	145 (85.8)	112 (90.3)	.245
ALP $\times$ ULN	0.99 $\pm$ 0.3	3.8 $\pm$ 10.9	.001
PLT, *10^9/L*	164 $\pm$ 93	173 $\pm$ 78	.385
Albumin, *g/dL*	3.8 $\pm$ 0.4	3.7 $\pm$ 0.5	.139
Bilirubin, *mg/dL*	0.9 $\pm$ 0.5	1.0 $\pm$ 0.7	.071
INR	1.1 $\pm$ 0.2	1.0 $\pm$ 0.2	.127
Creatinine, *mg/dL*	0.8 $\pm$ 0.2	0.7 $\pm$ 0.2	.003
Child-Pugh score 5 6	 128 (75.7) 41 (24.3)	 77 (62.1) 47 (37.9)	.012
MELD score	6.7 $\pm$ 1.4	6.3 $\pm$ 1.2	.081
No EVs	100 (59.2)	70 (56.5)	.457
F1	51 (30.2)	36 (29.0)	
F2	14 (8.2)	13 (10.5)	
F3	4 (2.4)	5 (4.0)	
LSM by TE, *kPA*[a]	18.0 $\pm$ 12.8	18.5 $\pm$ 12.0	.751

Note: Data are presented as number (%) or mean $\pm$ standard deviation.
ALP, alkaline phosphatase; EVs, esophageal varices; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; PLT, platelet; TE, transient elastography; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[a]Available in 283 patients (96.6%).

Supplementary Table 3. Diagnostic Performance for the Prediction of HRVs of NITs in 169 Patients With PBC, cACLD, and ALP levels lower than 1.50 × ULN

	Number of endoscopies performed	Number of endoscopies saved	HRV identified (true positive)	HRV missed (false negative)	Misclassified as HRV (false positive)	Correctly spared endoscopies (true negative)	False negative / number of patients avoiding endoscopies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUROC (95% CI)
EGD in all patients	169 (100)	0 (0)	18 (100)	0 (0)	151 (100)	0 (0)	–	–	–	–	–	–
BVI criteria[a]	116 (71.2)	47 (28.8)	16 (88.9)	2 (11.1)	100 (69.0)	45 (31.0)	4.2%	88.9 (65.3–98.6)	31.0 (23.6–39.2)	1.29	0.36	0.600 (0.520–0.675)
EBVI Criteria[a]	74 (45.4)	89 (54.6)	14 (77.8)	4 (22.2)	60 (41.4)	85 (58.6)	4.5%	77.8 (52.4–93.6)	58.6 (50.2–66.7)	1.88	0.38	0.682 (0.605–0.753)
RESIST criteria	75 (44.4)	94 (55.6)	16 (88.9)	2 (11.1)	59 (39.1)	92 (60.9)	2.1%	88.9 (65.3–98.6)	60.9 (52.7–68.8)	2.27	0.18	0.749 (0.677–0.813)
Ideal strategy	18 (10.7)	151 (89.3)	18 (100)	0 (0)	0 (0)	151 (100)	–	–	–	–	–	–

Note: Percentage of HRV identified and missed are calculated by using patients with HRV as denominator (n = 18). All patients with HRV were evaluable for all the noninvasive criteria.
ALP, alkaline phosphatase; AUROC, area under the receiver operating characteristic; BVI, Baveno VI; cACLD, compensated advanced chronic liver disease; CI, confidence interval; EBVI, Expanded Baveno VI; EGD, esophagogastroduodenoscopy; HRVs, high-risk varices; NIT, noninvasive test; RESIST, Rete Sicilia Selezione Terapia.
[a]BVI and EBVI were evaluable in 163 patients (96.4%).

Supplementary Table 4. Diagnostic Performance for the Prediction of HRVs of NITs in 124 Patients With PBC, cACLD, and ALP levels higher than 1.50 × ULN

	Number of endoscopies performed	Number of endoscopies saved	HRV identified (true positive)	HRV missed (false negative)	Misclassified as HRV (false positive)	Correctly spared endoscopies (true negative)	False negative / number of patients avoiding endoscopies	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC (95% CI)
EGD in all patients	124 (100)	0 (0)	18 (100)	0 (0)	106 (100)	0 (0)	–	–	–	–	–	–
BVI criteria[a]	75 (62.5)	45 (37.7)	11 (61.1)	7 (38.9)	64 (62.7)	38 (37.3)	15.5%	38.9 (17.3–64.3)	62.7 (52.6–72.1)	1.04	0.97	0.508 (0.415–0.601)
EBVI criteria[a]	51 (42.5)	69 (57.5)	8 (44.4)	10 (55.6)	43 (42.2)	59 (57.8)	14.5%	44.4 (21.5–69.2)	57.8 (47.7–67.6)	1.05	0.96	0.511 (0.419–0.604)
RESIST criteria	59 (47.6)	65 (52.4)	16 (88.9)	2 (11.1)	43 (40.6)	63 (59.4)	3.1%	88.9 (65.3–98.6)	59.4 (49.5–68.9)	2.19	0.19	0.742 (0.655–0.816)
Ideal strategy	18 (14.5)	106 (85.5)	18 (100)	0 (0)	0 (0)	106 (100)	–	–	–	–	–	–

Note: Percentage of HRV identified and missed are calculated by using patients with HRV as denominator (n = 18). All patients with HRV were evaluable for all the noninvasive criteria.
ALP, alkaline phosphatase; AUROC, area under the receiver operating characteristic; BVI, Baveno VI; cACLD, compensated advanced chronic liver disease; CI, confidence interval; EBVI, Expanded Baveno VI; EGD, esophagogastroduodenoscopy; HRVs, high-risk varices; NIT, noninvasive test; PBC, primary biliary cholangitis; RESIST, Rete Sicilia Selezione Terapia.
[a]BVI and EBVI criteria were evaluable in 120 patients (96.8%).

Supplementary Table 5. Diagnostic Performance of BVII for Predicting Any Size EVs in 283 Patients With PBC and cACLD, According to the ALP Levels (Lower or Higher Than 1.5 × ULN)

	Patients classified as high risk	Patients classified as low risk	EV identified (true positive)	EV missed (false negative)	Misclassified as EV (false positive)	Correctly excluded EV (true negative)	False negative / patients classified as low risk	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUROC (95% CI)
Whole cohort (n = 283)	208 (73.5)	75 (26.5)	105 (88.2)	14 (11.8)	103 (62.8)	61 (37.2)	18.7%	88.2 (81.0–93.4)	37.2 (29.8–45.1)	1.40	0.32	0.627 (0.568–0.684)
ALP <1.5 × ULN (n = 163; 57.8%)	123 (75.5)	40 (24.5)	62 (92.5)	5 (7.5)	61 (63.5)	35 (36.5)	12.5%	92.5 (83.4–97.5)	36.5 (26.9–46.9)	1.46	0.20	0.645 (0.566–0.718)
ALP ≥1.5 × ULN (n = 120; 42.4%)	85 (70.8)	35 (29.2)	43 (82.7)	9 (17.3)	42 (61.8)	26 (38.2)	25.7%	82.7 (69.7–91.8)	38.2 (26.7–50.8)	1.34	0.45	0.605 (0.511–0.693)

Note: Percentage of any size EV identified and missed are calculated by using patients with EV as denominator (n = 119 in the overall cohort, n = 67 in patients with ALP levels lower than 1.5 × ULN, and n = 52 in patients with ALP levels higher than 1.5 × ULN).

ALP, alkaline phosphatase; AUROC, area under the receiver operating characteristic; BVII, Baveno VII; cACLD, compensated advanced chronic liver disease; CI, confidence interval; EV, esophageal varices; NIT, noninvasive test; PBC, primary biliary cholangitis.

Supplementary Table 6. Comparison of Baseline Characteristics Between Patients Classified as Low Risk of CSPH According to BVII Criteria With or Without Any Size EVs

	Patients classified as low risk of CSPH (N = 75)	EVs absent (n = 61; 81.3%)	EVs present (n = 14; 18.7%)	*P*-value
Age, *years*	55.3 ± 13.1	53.5 ± 12.5	63.1 ± 13.6	.013
Female sex	69 (92.0)	55 (90.2)	14 (100)	.224
ALP × ULN	1.8 ± 1.4	1.7 ± 1.3	2.1 ± 1.5	.331
ALP ≥1.50 × ULN	35 (46.7)	26 (42.6)	9 (64.3)	.145
PLT, 10^9/*L*	231 ± 72	237 ± 76	205 ± 42	.128
Albumin, *g/dL*	4.0 ± 0.4	4.0 ± 0.4	3.8 ± 0.5	.057
Bilirubin, *mg/dL*	0.7 ± 0.3	0.6 ± 0.3	0.8 ± 0.4	.231
INR	1.0 ± 0.3	1.0 ± 0.2	1.1 ± 0.4	.302
Child-Pugh score 5 6	 65 (86.7) 10 (13.3)	 57 (93.4) 4 (6.6)	 8 (57.1) 6 (42.9)	< .001
No EVs	61 (81.3)	61 (100)	0 (0)	< .001
F1	7 (9.3)	0 (0)	7 (50.0)	
F2	7 (9.3)	0 (0)	7 (50.0)	
LSM by TE, *kPA*	9.9 ± 2.9	9.7 ± 3.0	10.8 ± 1.8	.191

Note: Data are presented as number (%) or mean ± standard deviation.
ALP, alkaline phosphatase; BVII, Baveno VII; CSPH, clinically significant portal hypertension; EVs, esophageal varices; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; PLT, platelet; TE, transient elastography; ULN, upper limit of normal.