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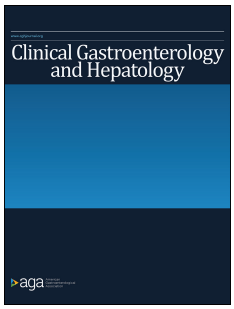

Non-invasive assessment of portal hypertension in patients with primary biliary cholangitis is affected by severity of cholestasis

Vincenza Calvaruso, Ciro Celsa, Laura Cristoferi, Miki Scaravaglio, Rachel Smith, Senamjit Kaur, Gabriele Di Maria, Luigi Capodicasa, Grazia Pennisi, Alessio Gerussi, Eugenia Nofit, Federica Malinverno, Pietro Lampertico, Nora Cazzagon, Marco Marzioni, Umberto Vespasiani-Gentilucci, Francesca Colapietro, Pietro Andreone, Ana Lleo De Nalda, Cristina Rigamonti, Mauro Viganò, Edoardo Giovanni Giannini, Maurizio Russello, Ester Vanni, Federica Cerini, Alessia Orlandini, Maurizia Brunetto, Grazia Anna Niro, Giovanni Vettori, Antonino Castellaneta, Vincenzo Cardinale, Domenico Alvaro, Andrea Mega, Valeria Pace Palitti, Valentina Cossiga, Filomena Morisco, Federico Bellanti, Leonardo Baiocchi, Luca Fabris, Marcello Persico, Elisabetta Degasperi, Sara Labanca, Emanuela Bonaiuto, Francesco Pezzato, Alessandro Federico, Salvatore Petta, Vito Di Marco, George F. Mells, Emma Culver, Pietro Invernizzi, Calogero Cammà, Marco Carbone

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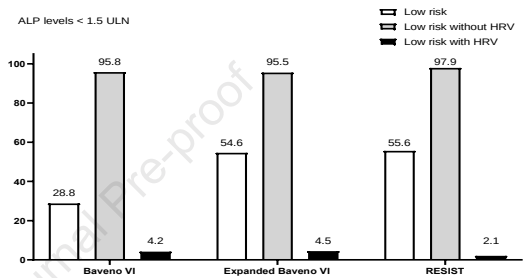
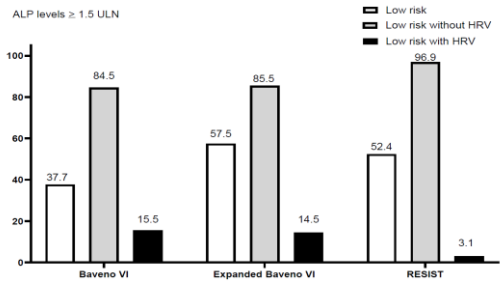
Non-invasive assessment of portal hypertension in patients with primary biliary cholangitis is affected by severity of cholestasis

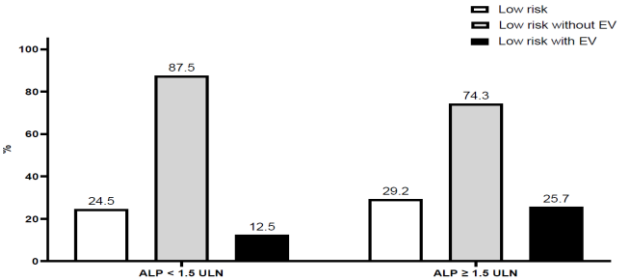
293 patients with primary biliary cholangitis

Risk stratification for high-risk esophageal varices (HRV) by RESIST, Baveno VI and Expanded Baveno VI criteria



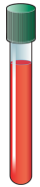


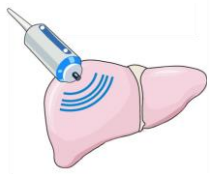
Ruling-out CSPH by Baveno VII criteria

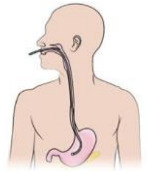


RESIST outperforms stiffness-based criteria

Non-invasive tests perform worse when alkaline phosphatase is higher than 1.5 ULN







Clinical Gastroenterology and Hepatology

Non-invasive assessment of portal hypertension in patients with primary biliary cholangitis is affected by severity of cholestasis

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Tables: 3

Supplementary figures: 3

Supplementary tables: 6

Running head: non-invasive tests for portal hypertension in primary biliary cholangitis

List of abbreviations: PBC: Primary Biliary Cholangitis, HCV: Hepatitis C virus, RESIST: Rete Sicilia Selezione Terapia; PH: portal hypertension, TE: transient elastography, EGD: esophagogastroduodenoscopy; EV: esophageal varices; HRV: high-risk varices; HCC: Hepatocellular Carcinoma; AUROC: area under the receiver operating characteristic; DCA:Decision Curve Analysis; cACLD: compensated advanced chronic liver disease; LSM: liver stiffness measurement; HVPG: hepatic venous pressure gradient

Conflict of interest: Vincenza Calvaruso: advisory board and speaking for Abbvie, Advanz, Echosens, Gilead, Roche, Ipsen. Ciro Celsa: speaking fees from Eisai, MSD and AstraZeneca; travel support from Roche. Laura Cristoferi: speaking fees from Advanz; consulting fees from Ipsen; travel grant from Ipsen. Alessio Gerussi: consulting fees from Ipsen and CAMP4 therapeutics; speaking fees from Advanz. Cristina Rigamonti: speaker and travel grants for Advanz Pharma, Roche. Mauro Viganò: speaking and teaching fees from Advanz Pharma. Edoardo G. Giannini: advisory board for AstraZeneca, Roche; speaking for AstraZeneca, Eisai, Roche. Nora Cazzagon: speaker and or travel grant for Advanz, Orphalan, IPSEN, Albireo. Umberto Vespasiani-Gentilucci: speaker and or grant from Advanz, Alfa-Sigma, IPSEN, Astra-Zeneca, Novo Nordisk. Ana Lleo De Nalda: consulting fees from Advanz Pharma, AlfaSigma, Takeda, Ipsen, and GSK, and speaker fees from Gilead, GSK, AbbVie, MSD, Advanz Pharma, AlfaSigma, GSK, and Incyte. Vito Di Marco: research support from Abbvie, Gilead, MSD, Intercept; advisory boards for Abbvie, MSD. Emma L Culver: advisory board for Advanz, Ipsen, Moderna, Dr Falk Pharma, Horizon Therapeutics, Amgen, Zenus Biopharma, Sanofi; consulting for Advanz, Mirum, Gilead; educational grants from Intercept, Dr Falk Pharma, GSK, Albireo, Horizon; research funding from Jansen. Calogero Cammà: advisory board for MSD/Merck, speaking fees from Eisai, Ipsen, Roche, AstraZeneca. Marco Carbone: advisory board

for Advanz, Ipsen, Cymabay, Moderna; consulted for Echosens, Ipsen, Advanz, Ipsen, Albireo, Perspectum, Mayoly Spindler, GSK. Received grants from genetics spa.

The other authors have no disclosures to declare.

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Authors contributions: V.C. (analysis and interpretation of data; drafting of the manuscript; statistical analysis, critical revision of the manuscript for important intellectual content), Ci.C. (analysis and interpretation of data; drafting of the manuscript; statistical analysis, critical revision of the manuscript for important intellectual content), GDM (statistical analysis), LC. (acquisition of data), GP. (acquisition of data). V.DM. (study concept and design; analysis and interpretation of data; drafting of the manuscript; study supervision). Ca.C. (study concept and design; analysis and interpretation of data; statistical analysis; critical revision of the manuscript for important intellectual content), ELC and SK (data collection, analysis and interpretation, critical revision of the manuscript). PI and M.C. founded and coordinate the Italian PBC Registry. All the other authors participated in the acquisition and interpretation of data and they all approved the final version of the manuscript.

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

Abstract

Background&aims: Non-invasive tests (NITs) for ruling-out clinical significant portal hypertension (CSPH) and high-risk varices (HRV) 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 two UK large-volume PBC referral centres with upper endoscopy within 6 months from biochemical evaluation and transient elastography were included. RESIST, Baveno-VI (BVI) and Expanded Baveno-VI (EBVI) criteria for ruling-out HRV were assessed according to alkaline phosphatase levels (ALP)(<or≥1.5 ULN). Decision curve analysis (DCA) 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 times ULN, BVI and EBVI missed a higher rate of HRV (15.5% and 14.5%, respectively) than RESIST (3.1%). DCA demonstrated the highest net benefit of RESIST criteria for ruling out HRV, regardless 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 to 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.

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Keywords: primary biliary cholangitis; esophageal varices; portal hypertension; non-invasive tests; liver stiffness.

Introduction

The progression of portal hypertension represents a key driver toward the development of esophageal varices(EV) 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, non-invasive tests(NITs) are sufficiently accurate to identify CSPH in clinical practice. Elastography-based criteria, such as Baveno VI and Expanded Baveno VI criteria, have been extensively validated to identify patients that could safely avoid esophagogastroduodenoscopy(EGD) surveillance for medium/large varices, defined as high-risk varices(HRV)[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 consensus[10] has focused on the non-invasive 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 Baveno VI 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 non-referral centres and in low-resources countries. For all these reasons, studies evaluating the diagnostic performance of non-invasive tests(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 HCV infection, both before and after sustained virologic response(SVR) by direct-acting antiviral agents. Similarly to elastography-based criteria, also this score has 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:

- to assess the diagnostic performance of elastography-based NITs and RESIST criteria for predicting the presence of HRV in patients with PBC and cACLD.
- to evaluate the influence of the severity of cholestasis on the performance of all NITs
- to evaluate the performance of Baveno VII criteria to rule out CSPH in patients with PBC and cACLD

Patients and methods

Patient selection

Consecutive PBC patients with cACLD (suggested by liver stiffness higher than 10 kPa or highly suggested by liver stiffness higher than 15 kPa) and/or platelet 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 1 January 2010 and 31 December 2023 at 33 Italian centers involved in the *Italian PBC registry*[20, 21] and in two large volume *UK PBC tertiary referral centers* were accrued in this cross-sectional study. The study flow-chart is showed in **Supplementary Figure S1.**

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 non-selective beta-blockers(NSBB) or endoscopic band ligation(EBL) of EV; portal thrombosis; splenectomy; liver transplantation; hepatocellular carcinoma(HCC).

Outcomes definitions

At the time of EGD, each patient was risk stratified for HRV according to elastography-based criteria (Baveno VI[BVI] and Expanded Baveno VI[EBVI])(**Supplementary Table S1**) and RESIST criteria.

Patients were classified as RESIST-In(low risk of HRV) if they had PLT count$\geq$120x10^9/L and serum albumin$\geq$3.6 g/dL or RESIST-Out(high risk of HRV) if PLT count<120X10^9/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 Baveno VII(BVII) criteria to rule out CSPH(PLT$\geq$150x10^9/L and LSM$\leq$15 kPa) was reported in the whole cohort and after stratification according to ALP levels.

LSM by TE was performed by FibroScan®(EchoSens, Paris, France). Patients were fasted for at least 6 hours before the procedure and LSM 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 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±12.5 years and 257 (87.7%) were female. ALP levels were higher than 1.5 times ULN in 124 (42.3%) patients. Most of patients (205, 70.0%) had Child-Pugh score 5 and mean MELD score was 6.5±1.3.

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

Diagnostic performance of NITs for the prediction of HRV

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

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 HRV(2.5%, 95%CI 0.1-4.9%) compared to elastography-based criteria, that 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 HRV compared to the strategy of perfoming endoscopy in all patients. RESIST criteria correctly spared the highest number of EGD(60.3%, 95%CI 54.3-66.3), with the lowest false positive rate(39.7%, 95%CI 33.7-45.7%) compared to BVI and EBVI criteria, showing the highest discriminating ability for the prediction of HRV(AUROC 0.75, 95% CI 0.69-0.80).

Impact of ALP levels on the diagnostic performance of NITs for the prediction of HRV

The comparison of baseline characteristics between patients with ALP levels lower and higher than 1.5 ULN is showed in **Supplementary Table S2.** Patients with ALP levels higher than 1.5 ULN were more likely to have Child-Pugh class A6, while prevalence of EV, liver stiffness, platelet count and albumin levels were not significantly different between the two groups.

In patients with ALP <1.5 ULN(n=169), the rate of missed HRV 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%]. 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 S3**).

Conversely, in patients with ALP≥1.5 ULN(n=124), all NITs performed worse, with a rate of HRV 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 a false negative rate ranging from 11.1%(95%CI 1.3-40.1%) for RESIST to 55.6%(95%CI 26.6-100%) for EBVI(**Supplementary Table S4**). 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 S4**).

Decision curve analysis(DCA)

Net benefit for ruling out HRV at 5% and 10% threshold probabilities of missing HRV of RESIST and elastography-based criteria is showed 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 S2**) and RESIST criteria showed the best net benefit in patients with ALP≥1.5(**Supplementary Figure S3**).

Overall assessment of Baveno VII criteria to rule out CSPH

Overall, 14 out 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 EV were present in 5 out of 40 patients(12.5%, 95%CI 4.1-29.1%) with ALP<1.5 ULN classified as low-risk and in 9 out 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 S5.**

Supplementary Table S6 reports the comparison of baseline characteristics of patients classified as low risk of CSPH with and without any-sized EV.

Discussion

In this multicentre 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 HRV, potentially leading to a simplification of surveillance programs; 3)Finally, Baveno VII 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 EV 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 Baveno VI, Expanded Baveno VI and RESIST[3, 4, 16] for the prediction of HRV in an international cohort of PBC patients with a larger sample size compared to 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 oesophageal varices, rather than HRV. 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 platelet 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 unnecessaries EGD.

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 Baveno and Expanded Baveno VI. 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 Baveno and Expanded Baveno VI, achieving the lowest risk of 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 non-invasive 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 HRV 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 HRV could be better due to the low probability of having HRV. By contrast, the longer is the time from diagnosis, the higher is 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 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 HRV 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 (i.e. patients wrongly classified as low-risk of HRV according to NITs, but having HRV at EGD). DCA incorporates information on the clinical consequences of performing or not 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 HRV was overall lower in patients with ALP levels higher than 1.5 ULN compared to those with ALP levels lower than 1.5 ULN and that RESIST criteria showed an overall higher net benefit for ruling out HRV compared to elastography-based criteria, suggesting that they could represent the more suitable NIT for HRV risk stratification, regardless of ALP levels.

Our results are plausible since 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 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] analysed 86 PBC patients 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 semi-quantitative 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 hospital to perform liver stiffness measurement. In this line, the use of a biochemical, rather than elastography-based, criteria could be helpful outside of tertiary care centres 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 Baveno VII consensus is mainly focused on the prediction of decompensation through ruling out or ruling in the presence of clinically significant portal hypertension (CSPH)[10], we evaluated the diagnostic performance of NITs for HRV, given that, according to the "rule of five", Baveno VI criteria for ruling out HRV are still considered useful for clinical practice, particularly for patients who are not receiving non selective beta-blockers and for sparing unnecessary endoscopies.

The development of NITs to early predict the presence of CSPH, rather than HRV, remains an unsolved medical need in patients with PBC. In this study, we were also able to assess the ability of Baveno VII criteria to rule out CSPH indicated by diagnosis of any-sized EV[10], demonstrating a high rate of false negative results. About one in five patients classified as low-risk according to Baveno VII criteria showed varices at EGD, indicating CSPH. Again, the existence of a presinusoidal component of portal hypertension in patients with PBC, that could not be accurately detected by LSM- TE[28] is a possible explanation for this finding. LSM may be subject to inter-operator 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 NIT 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 factor that may reduce the performance of NIT for rule in and rule out CSPH. These results indicate a significant undertreatment of CSPH in PBC patients, especially in consideration of recent studies[30], which demonstrated a decreased risk for decompensation and mortality in CSPH- patients treated with NSBBs

Our study suffers from 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 HRV in patients without HRV at the time of diagnosis and treatment start. Second, although Baveno VI suggested 5% as an acceptable risk of missing HRV 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 HRV. 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 PBC patients enrolled in different settings. The high variability in criteria for indicating EGD 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 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 HVPG. These data are overall scarce in the literature, due to the low prevalence of patients with cholestatic disorders included in studies reporting HVPG. 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, that is not reflected by HVPG. Therefore, further studies are needed to define the patients who need to be treated with NSBB.

In conclusion, we demonstrated that NITs for portal hypertension have a suboptimal performance with high rate of false negative both for HRV 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 ULN. The biochemical-based RESIST criteria are the most NIT for predicting HRV 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 Baveno VII criteria in ruling out CSPH.

Figure Legend.

Figure 1. Risk stratification for the presence of high-risk varices(HRV) according to Baveno VI, Expanded Baveno VI, Baveno VII and RESIST criteria in patients with primary biliary cholangitis and compensated advanced chronic liver disease. Panel A: whole cohort. Panel B: ALP <1.5 ULN. Panel C: ALP>1.5 ULN.

Figure 2. Decision curve analysis of Baveno VI, Expanded Baveno VI and RESIST criteria for ruling out high-risk varices(HRV) at different threshold probabilities of missing HRV

Figure 3. Risk stratification for the presence of any-sized esophageal varices(EV) according to Baveno VII criteria, according to alkaline phosphate levels(lower or higher than 1.5 time the upper limit of normal).

References

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-31.
2. D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563-576.
3. de Franchis R, Baveno Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
4. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66:1980-1988.
5. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J Hepatol 2016;65:899-905.
6. Augustin S, Pons M, Genesca J. Validating the Baveno VI recommendations for screening varices. J Hepatol 2017;66:459-460.
7. Cardenas A, Mendez-Bocanegra A. Report of the Baveno VI Consensus Workshop. Ann Hepatol 2016;15:289-90.
8. Thabut D, Bureau C, Layese R, et al. Validation of Baveno VI Criteria for Screening and Surveillance of Esophageal Varices in Patients With Compensated Cirrhosis and a Sustained Response to Antiviral Therapy. Gastroenterology 2019;156:997-1009 e5.
9. Petta S, Sebastiani G, Bugianesi E, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. J Hepatol 2018;69:878-885.
10. de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76:959-974.
11. Pons M, Augustin S, Scheiner B, et al. Noninvasive Diagnosis of Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease. Am J Gastroenterol 2021;116:723-732.
12. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology 2016;64:2173-2184.
13. Moctezuma-Velazquez C, Saffioti F, Tasayco-Huaman S, et al. Non-Invasive Prediction of High-Risk Varices in Patients with Primary Biliary Cholangitis and Primary Sclerosing Cholangitis. Am J Gastroenterol 2019;114:446-452.
14. Pariente A, Chazouilleres O, Causse X, et al. Baveno-VI-Guided Prediction of Esogastric Varices in Primary Biliary Cholangitis. Am J Gastroenterol 2019;114:361-362.
15. Panel AE. Position paper of the Italian Association for the Study of the Liver (AISF): Management and treatment of primary biliary cholangitis. Dig Liver Dis 2024.
16. Calvaruso V, Cacciola I, Licata A, et al. Is Transient Elastography Needed for Noninvasive Assessment of High-Risk Varices? The REAL Experience. Am J Gastroenterol 2019;114:1275-1282.
17. Sharma S, Agarwal S, Gunjan D, et al. Deciding Among Noninvasive Tools for Predicting Varices Needing Treatment in Chronic Liver Disease: An Analysis of Asian Cohort. Am J Gastroenterol 2020;115:1650-1656.
18. Duan Z, Li L, Li J, et al. Validation of the Combined Model Based on Platelet Count and Albumin to Rule out High-Risk Varices in Liver Cirrhosis. Biomed Res Int 2020;2020:5783748.
19. Calvaruso V, Celsa C, D'Ambrosio R, et al. RESIST-HCV Criteria to Monitor Progression of Low-Risk Esophageal Varices in Patients With Compensated Cirrhosis After HCV Eradication: The SIMPLE Study: SIMPLE: Scoring Index to Monitor Progression of Low-risk Esophageal varices. Am J Gastroenterol 2022;117:1816-1824.
20. D'Amato D, De Vincentis A, Malinverno F, et al. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. JHEP Rep 2021;3:100248.
21. De Vincentis A, D'Amato D, Cristoferi L, et al. Predictors of serious adverse events and non-response in cirrhotic patients with primary biliary cholangitis treated with obeticholic acid. Liver Int 2022;42:2453-2465.

22. Younossi ZM, Stepanova M, Golabi P, et al. Factors Associated With Potential Progressive Course of Primary Biliary Cholangitis: Data From Real-world US Database. J Clin Gastroenterol 2019;53:693-698.
23. North Italian Endoscopic Club for the S, Treatment of Esophageal V. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-9.
24. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565-74.
25. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. Diagn Progn Res 2019;3:18.
26. Zhang Z, Rousson V, Lee WC, et al. Decision curve analysis: a technical note. Ann Transl Med 2018;6:308.
27. Navasa M, Pares A, Bruguera M, et al. Portal hypertension in primary biliary cirrhosis. Relationship with histological features. J Hepatol 1987;5:292-8.
28. Ali AH, Sinakos E, Silveira MG, et al. Varices in early histological stage primary biliary cirrhosis. J Clin Gastroenterol 2011;45:e66-71.
29. Warnes TW, Roberts SA, Smith A, et al. Portal hypertension in primary biliary cholangitis: prevalence, natural history and histological correlates. Eur J Gastroenterol Hepatol 2021;33:1595-1602.
30. Villanueva C, Albillos A, Genesca J, et al. beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393:1597-1608.
31. Fateen W, Ragunath K, White J, et al. Validation of the AASLD recommendations for classification of oesophageal varices in clinical practice. Liver Int 2020;40:905-912.

Tables

Table 1. Demographic and clinical characteristics of 293 patients with primary biliary cholangitis (PBC) and compensated advanced chronic liver disease (cACLD).

	Whole cohort (N=293)
Age (mean, SD)	56.2±12.5
Sex (Female, %)	257 (87.7)
ALP x ULN (mean, SD)	2.2±7.3
ALP ≥ 1.50 ULN (n, %)	124 (42.3)
PLT (10^9/L) (mean, SD)	168±87
Albumin (g/dL) (mean, SD)	3.8±0.5
Bilirubin (mg/dL) (mean, SD)	0.9±0.6
INR	1.1±0.2
Creatinine (mg/dL)	0.8±0.2
Child-Pugh score 5 6	 205 (70.0) 88 (30.0)
MELD score (mean, SD)	6.5±1.3
No esophageal varices (n, %) F1 F2 F3	170 (58.0) 87 (29.7) 27 (9.2) 9 (3.1)
LSM by TE (kPA)* (mean, SD)	18.2±12.4
UDCA treatment duration longer than 6 months (n,%)	181 (61.8)

*Available in 283 (96.6%) patients.

ULN, upper limit of normal. ALP, alkaline phosphatase. LSM, Liver stiffness measurement. TE, transient elastography.

Table 2. Diagnostic performance of non-invasive tests for the prediction of high-risk varices in 293 patients with primary biliary cholangitis and compensated advanced chronic liver disease.

	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*	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*	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)	-	-	-	-		-

* Baveno VI and Expanded Baveno VI criteria were evaluable in 283 patients (96.6%)

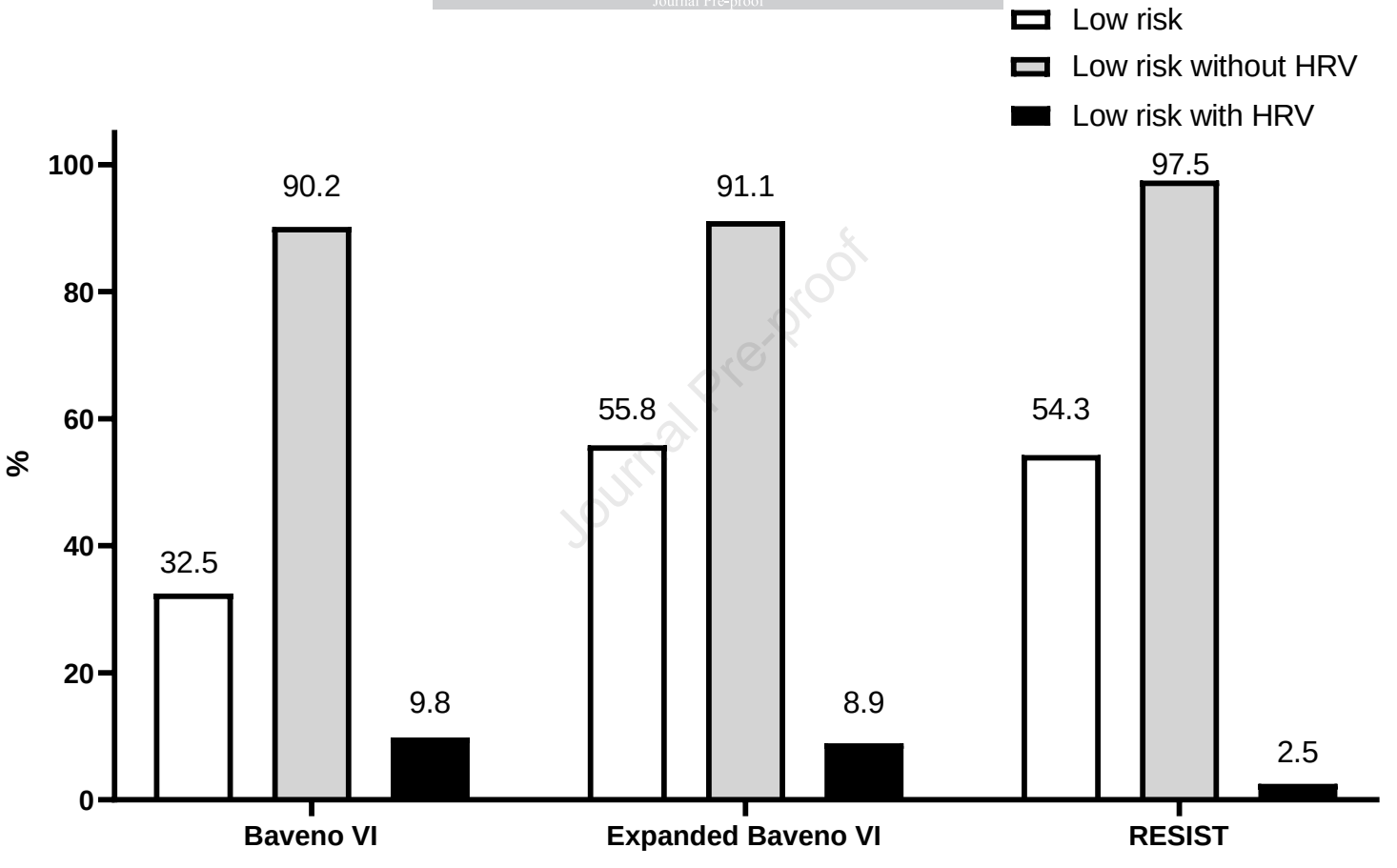
Percentage of HRV identified and missed are calculated by using patients with HRV as denominator (n=36). All patients with HRV were evaluable for all the non-invasive criteria.

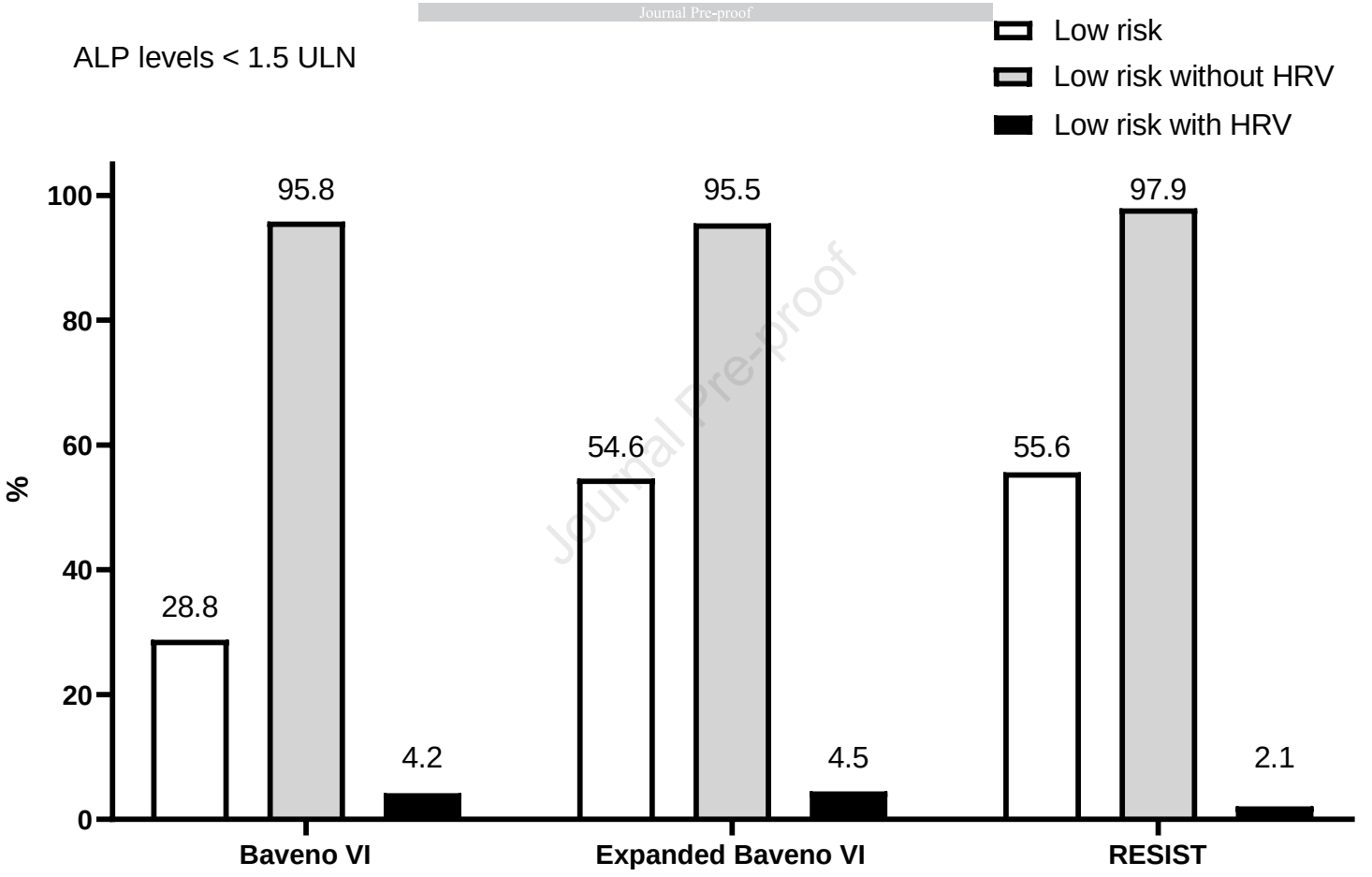
HRV, high-risk varices. EGD, esophagogastroduodenoscopy. AUROC, area under the receiver operating characteristic curve. 95% CI, 95% confidence interval.

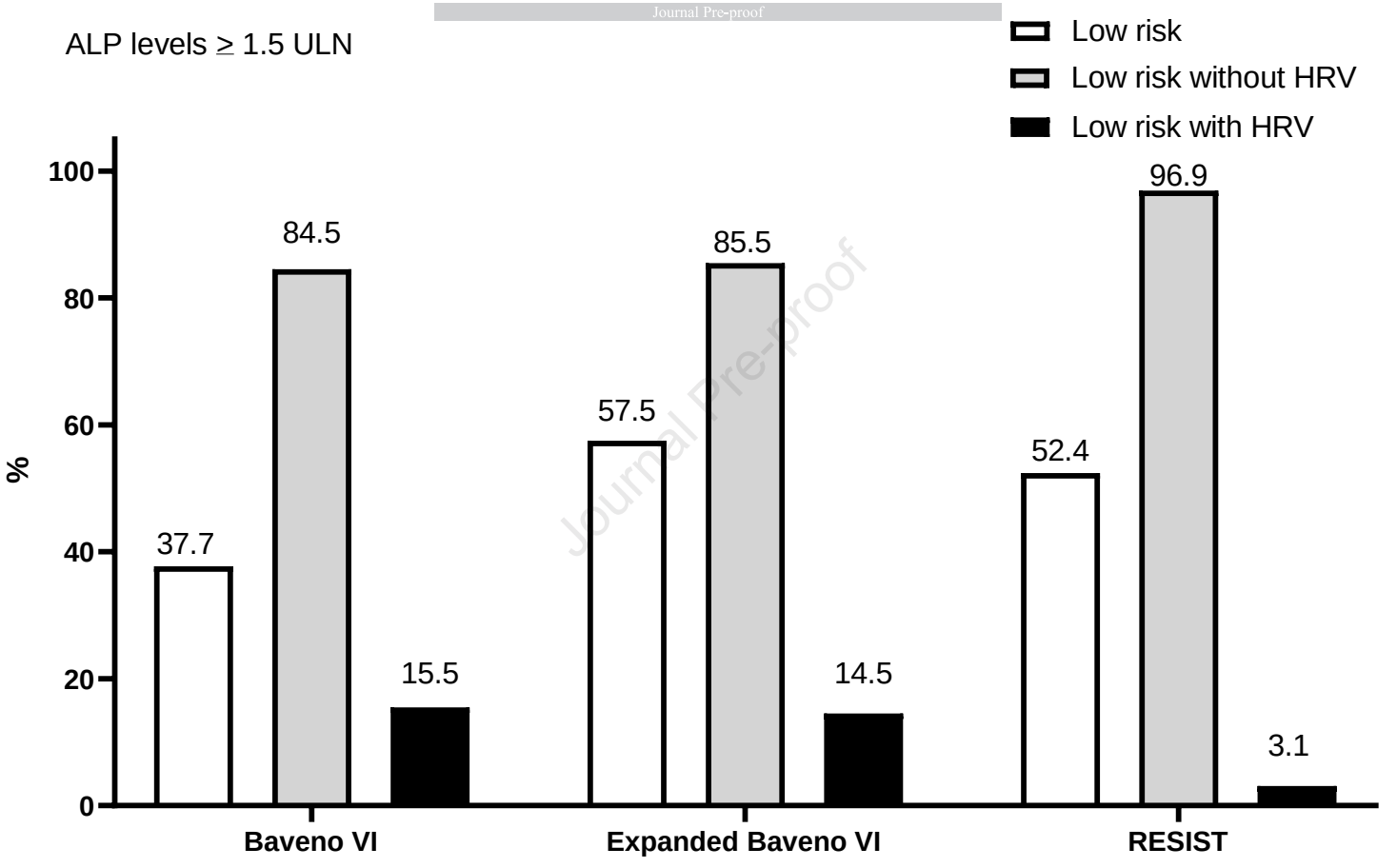
Table 3. Decision curve analysis reporting net benefit for ruling out high-risk varices at threshold probabilities of 5%, 7.5% and 10% of different non-invasive tests in patients with primary biliary cholangitis and compensated advanced chronic liver disease.

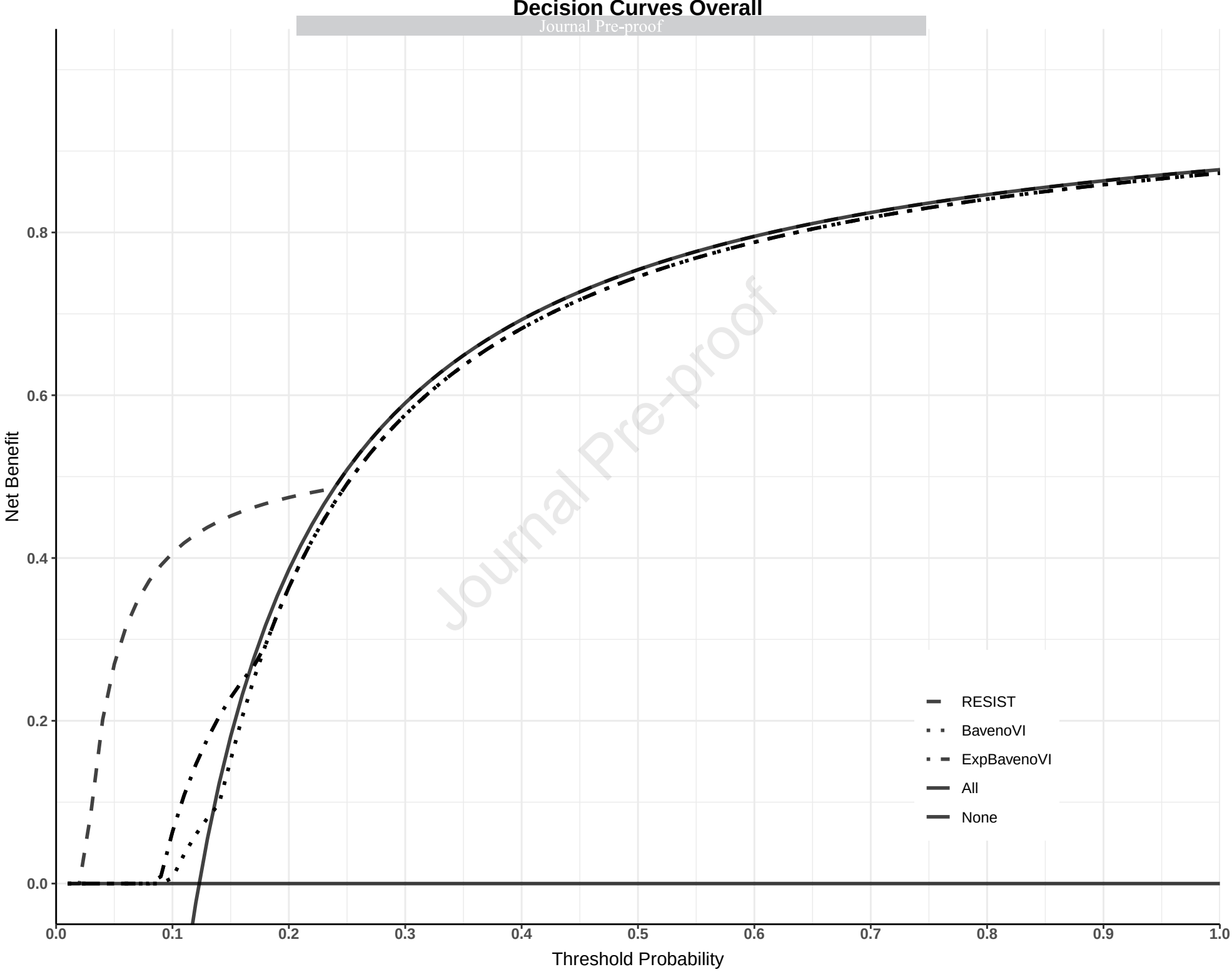
Criteria	Number of EGD avoided per 100 patients (training cohort)		
	Threshold probability 5%	Threshold probability 7.5%	Threshold probability 10%
RESIST	27	35	40
Baveno VI	0	0	1
Expanded Baveno VI	0	0	6

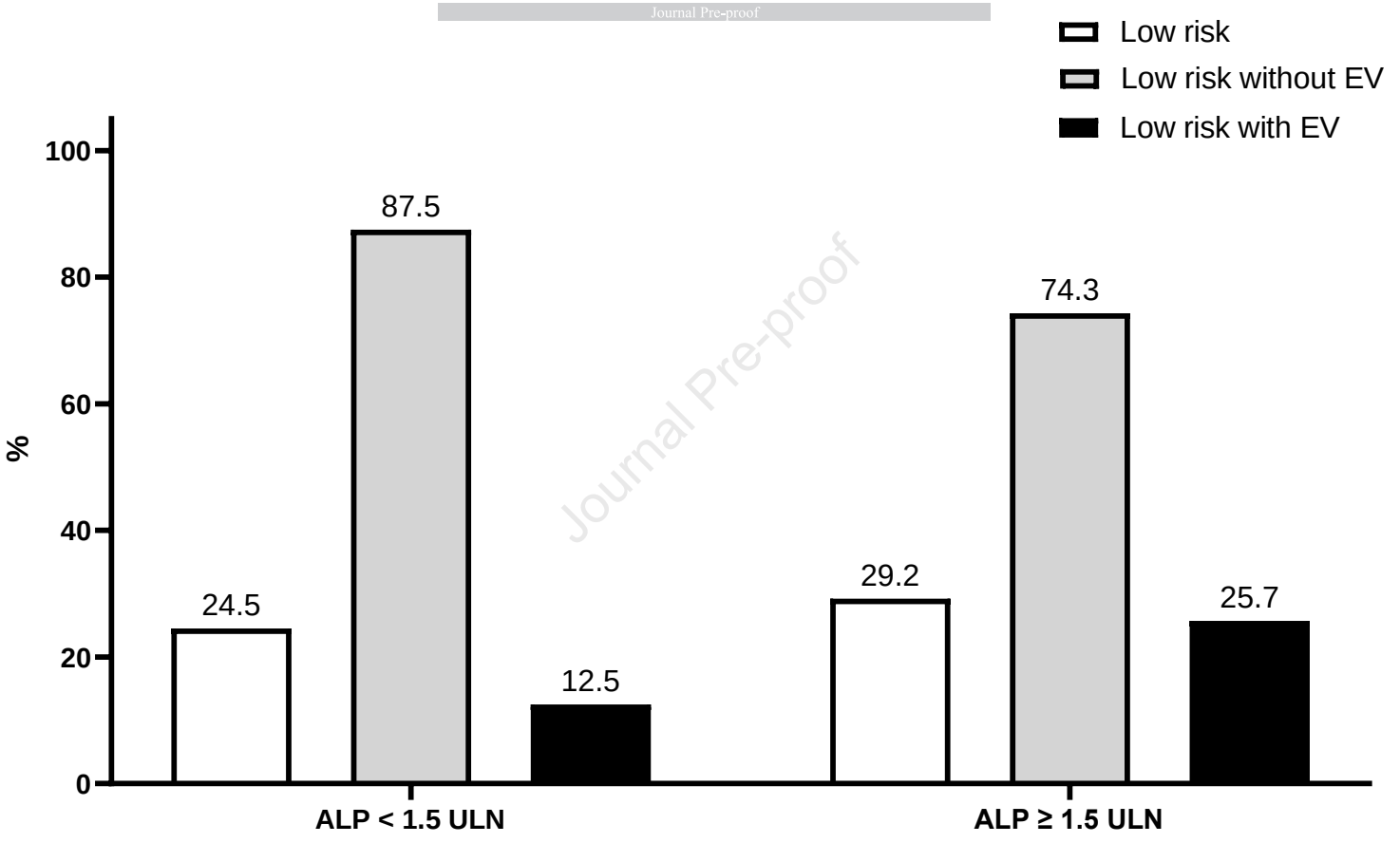
Net benefit represents the number of EGD avoided per 100 patients compared with the strategy to perform EGD in all patients at different threshold probabilities of missing HRV.
HRV, high-risk varices.











BACKGROUND: Non-invasive 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 PBC patients. All NITs performed worse in patients with alkaline phosphatase >1.5x 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 >1.5x upper limit of normal.

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

Non-invasive assessment of portal hypertension in patients with primary biliary cholangitis is affected by severity of cholestasis

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Supplementary Table S1. Elastography-based criteria for ruling out high-risk varices (HRV) and clinically significant portal hypertension (CSPH).

	IN (low risk)	OUT (high risk)	Outcome
RESIST	PLT ≥ 120 X 10^9/L and albumin ≥ 3.6 g/dL	PLT<120 X 109/L and/or albumin < 3.6 g/dL	HRV
Baveno VI	PLT ≥ 150 x 10^9/L and LSM-TE ≤ 20 kPa	PLT<150 x 10^9/L and/or LSM-TE > 20 kPa	HRV
Expanded Baveno VI	PLT ≥ 110 x 10^9/L and LSM-TE ≤ 25 kPa	PLT < 110 x 10^9/L and/or LSM-TE > 25 kPa	HRV
Baveno VII	PLT ≥ 150 x 10^9/L and LSM-TE ≤ 15 kPa	PLT < 150 x 10^9/L and/or LSM-TE > 15 kPa	CSPH

HRV, high-risk varices. CSPH, clinically significant portal hypertension. PLT, platelets. LSM, liver stiffness measurement. TE, transient elastography.

Supplementary Table S2. Comparison of baseline characteristics between patients with alkaline phosphatase levels lower than 1.50 times the upper limit of normal

	>I M9 » -2- »R I K %: . 36&	>I M» -2- »R I K %: . / 1&	m*s^ir b
>db»% b^k)»PA &	22-6π . / +	23-2π . 0+	- -4/ 4
Pbu»%Gbj ^ib)»" &	. 12»%52-5&	. . / »%6- -0&	- -/ 12
>I Mu»R I K»% b^k)»PA &	- -66π - -0	0-5π . - -6	- -+ - .
M Q%- ⁶,I &% b^k)»PA &	. 31π 60	. 40π 45	- -052
>i_r j fk»%d,aI &% b^k)»PA &	0-5π - -1	0-4π - -2	- -+06
?fifor _fk»% d,aI &% b^k)»PA &	- -6π - -2	. -+π - -4	- -+ 4.
IKO	. -+π - -/	. -+π - -/	- -+/ 4
@ob^qfkfkb»% d,aI &	- -5π - -/	- -4π - -/	- -+ - 0
@efia*M-de»p`l ob 2 3	 . / 5»%42-4& 1. »%1-0&	 44»%3/ + & 14»%04-6&	- -+. /
J BI A»p`l ob»% b^k)»PA &	3-4π . -1	3-0π . /	- -+ 5.
Kl »bpl me^db^i»s^of^bp%%)»" & C. » C/ C0»	. - - »%26-/ & 2. »%0- -/ & . 1»%5-/ & 1»%-1 &	4- »%23-2 & 03»%6-+ & . 0»%- -2 & 2»%b-+ &	- -124
I PJ » _v»QB»%%M>& »% b^k)»PA &	. 5-+π . / -5	. 5-2π . / +	- -42.

Supplementary Table S3. Diagnostic performance for the prediction of high-risk varices of non-invasive tests in 169 patients with primary biliary cholangitis, compensated advanced chronic liver disease and alkaline phosphatase levels lower than 1.50 times the upper limit of normal

	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)	-	-	-	-	-	-
Baveno VI criteria*	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)
Expanded Baveno VI Criteria*	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)	-	-	-	-	-	-

* Baveno VI and Expanded Baveno VI were evaluable in 163 (96.4%) patients.

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 non-invasive criteria.

HRV, high-risk varices. EGD, esophagogastroduodenoscopy. AUROC, area under the receiver operating characteristic curve. 95% CI, 95% confidence interval.

Supplementary Table S4. Diagnostic performance for the prediction of high-risk varices of non-invasive tests in 124 patients with primary biliary cholangitis, compensated advanced chronic liver disease and alkaline phosphatase levels higher than 1.50 times the upper limit of normal

	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)	-	-	-	-	-	-
Baveno VI criteria*	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)
Expanded Baveno VI Criteria*	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)	-	-	-	-	-	-

* Baveno VI and Expanded Baveno VI criteria were evaluable in 120 (96.8%) patients.

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 non-invasive criteria.

HRV, high-risk varices. EGD, esophagogastroduodenoscopy. AUROC, area under the receiver operating characteristic curve. 95% CI, 95% confidence interval.

Supplementary Table S5. Diagnostic performance of Baveno VII for predicting any size esophageal varices (EV) in 283 patients with primary biliary cholangitis (PBC) and compensated advanced chronic liver disease (cACLD), according to the alkaline phosphatase levels (lower or higher than 1.5 times the upper limit of normal).

	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 x 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 $\geq$1.5 x 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)

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).

EV, esophageal varices. ALP, alkaline phosphatase. ULN, upper limit of normal. CSPH, clinically significant portal hypertension. AUROC, area under the receiver operating characteristic curve. 95% CI, 95% confidence interval.

Supplementary Table S6. Comparison of baseline characteristics between patients classified as low risk of clinically significant portal hypertension according to Baveno VII criteria with or without any size esophageal varices.

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>I Mu»RI K»%b^k)»PA &	. -5π. -1	. -4π. -θ	/+π. -2	-θ0.
>I M»» -2-»RI K%)»" &	02»%13-4&	/3»%1/-3&	6»%31-θ&	-+12
MI Q%-6,I &%b^k)»PA &	/0. π4/	/04π43	/-2π1/	-+/5
>i_rj fk»%d,aI &%b^k)»PA &	1+π-1	1+π-1	0-5π-2	-+24
?fifor_fk»%d,aI &%b^k)»PA &	--4π-θ	--3π-θ	--5π-1	-+0.
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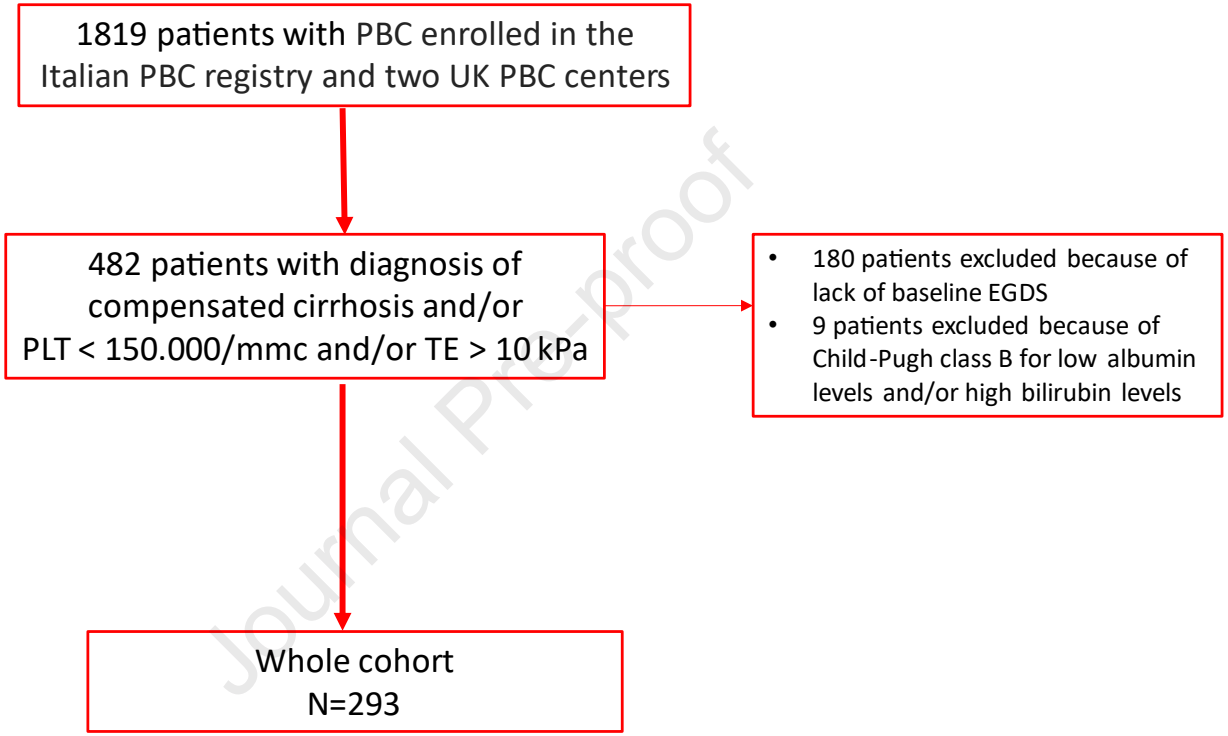

PBC, primary biliary cholangitis. PLT, platelet. TE, transient elastography. EGDS, esophagogastroduodenoscopy. ALP, alkaline phosphatase.

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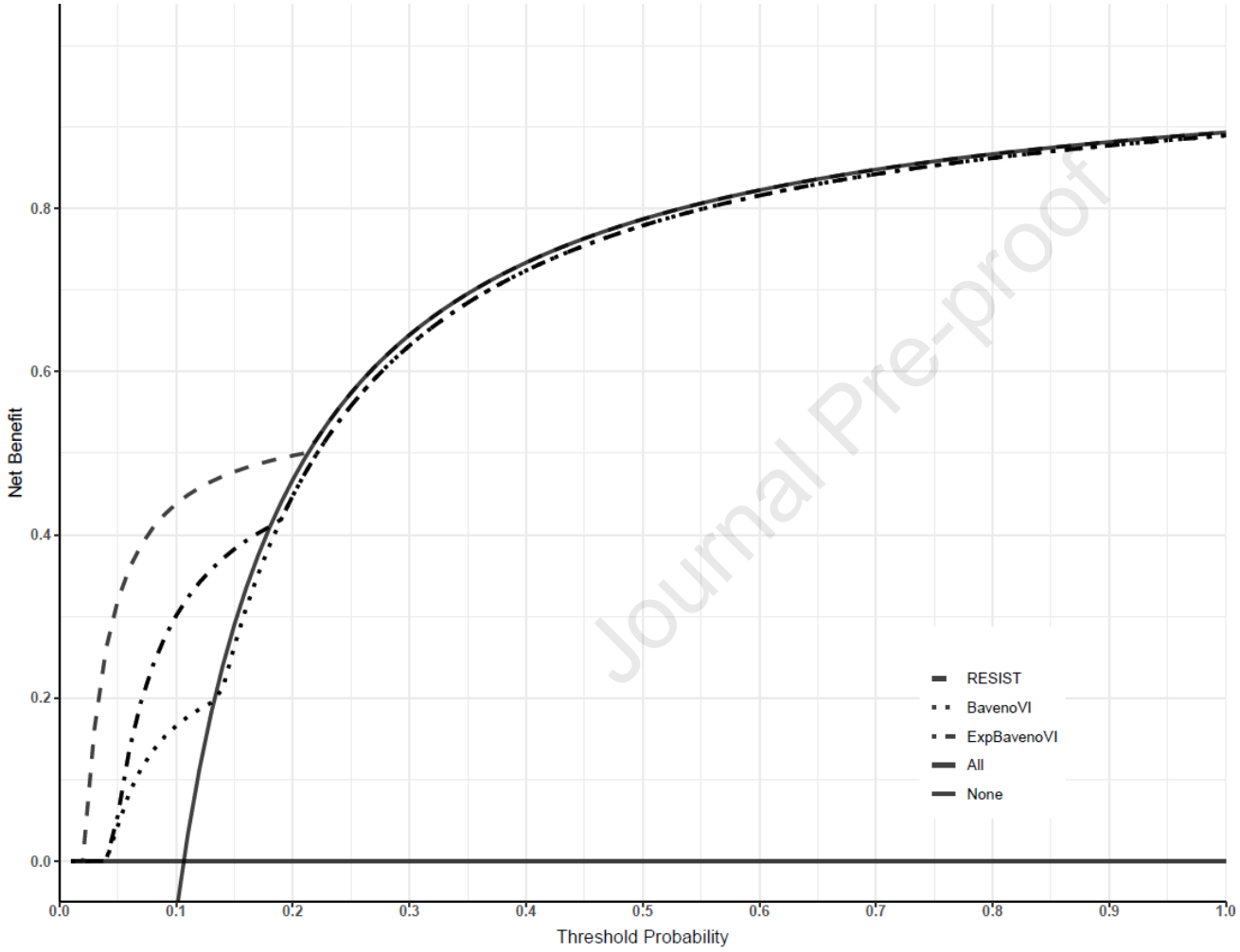

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