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Baveno VI criteria as a prognostic factor for clinical complications in patients with compensated cirrhosis

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ABSTRACT

Background: Combination of liver stiffness measurement and platelets count is a tool to safely rule out varices needing treatment (VNT) in patients with compensated advanced chronic liver disease (cACLD). **Aims:** to evaluate 4-year liver-related complications and survival in low-risk patients according to Baveno VI criteria.

Methods: we conducted a monocentric retrospective analysis of prospectively collected data of all consecutive patients, with cirrhosis (LSM ≥ 12.5 kPa) and without previous complication, evaluated between 2012 and 2015. Liver-related complications and survival were compared between 2 groups of patients: favourable (LSM < 20 kPa and platelet count $> 150.000/\text{mm}^3$) and unfavourable Baveno VI status patients (LSM ≥ 20 kPa or platelet count $\leq 150.000/\text{mm}^3$).

Results: 455 patients with cACLD were analysed. Two hundred patients had favourable Baveno VI criteria, 3.6% with VNT. The 4-year probability of being free of acute decompensation was higher in low-risk patients ($94.4 \pm 1.8\%$ vs. $85.7\% \pm 2.6\%$, $p = 0.018$). Unfavourable Baveno status was independently associated with acute decompensation. The probability of being free of HCC was significantly higher in low-risk patients ($94.2 \pm 1.8\%$ vs. $87.6 \pm 2.4\%$, $p = 0.048$). Liver-related mortality was not different between the 2 groups ($p = 0.56$).

Conclusion: The Baveno VI criteria could predict clinical outcome in cACLD.

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1. Introduction

Advanced chronic liver disease is a serious condition with a high risk of mortality due to acute decompensations mostly associated with portal hypertension (PHT) [1]. The occurrence of a portal hypertension-related complication is an important turning point in the natural history of cirrhosis. The mortality rate at 2 years ranges

from 2% for patients with compensated cirrhosis to more than 50% when the disease is decompensated [2]. All clinical events, such as ascites, hepatic encephalopathy (HE) or variceal bleeding (VB) are associated with a poor prognosis [3–5].

Until 2015, international recommendations included systematic upper endoscopy screening for VNT (varices needing treatment) in all patients with cirrhosis [1,3,6–8]. However, the majority of endoscopies were futile, since VNT were diagnosed in less than 30% of these patients. Several non-invasive methods have been developed in order to better identify patients requiring endoscopic screening [9–15]. In 2015, compensated advanced chronic liver disease (cACLD) was defined during the Baveno VI consensus meeting, i.e. patients with chronic liver disease and a liver stiffness measurement (LSM) > 10 kPa. More, the Baveno VI guidelines recommend using LSM and platelets count to rule out VNT [16]. They state that endoscopy may be avoided in low-risk patients defined by a LSM < 20 kPa and a platelets count $> 150.000/\text{mm}^3$ (favourable Baveno VI status). These criteria have been validated in more than 3000 patients with a percentage of spared endoscopies of at least 20%

Abbreviations: PHT, Portal hypertension; HE, Hepatic Encephalopathy; VB, Variceal Bleeding; VNT, Varices Needing Treatment; cACLD, compensated Advanced Chronic Liver Disease; LSM, Liver Stiffness Measurement; HVPG, Hepatic Venous Pressure Gradient; HCC, Hepatocellular Carcinoma; TE, Transient elastography; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; CHC, Chronic Hepatitis C; CHB, Chronic Hepatitis B; NASH, Non Alcoholic Steatohepatitis; SVR, sustained viral response; INR, International Normalized Ratio; BMI, Body Mass Index; MELD, Model for End-Stage Liver Disease; CI, Confidence Interval; PSVD, Porto-Sinusoidal Vascular Disease; cccDNA, covalently closed circular DNA; MAFLD, Metabolic Associated Fatty Liver Disease.

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[17–22], and less than 5% of missed VNT. Thereafter, new criteria with more restrictive thresholds of platelet count ($< 110.000/\text{mm}^3$ and $\text{LSM} > 25 \text{ kPa}$ (Expanded-Baveno VI) were validated in numerous cohorts and could lead to safely avoid more endoscopies than initial recommendations with a minimal risk of missing VNT [20,23–26].

Longitudinal studies evaluating further risk of acute decompensation according to the Baveno VI status are lacking. In patients with cACLD, hepatic venous pressure gradient measurement (HVPG) is considered as the gold standard technique to assess clinically significant portal hypertension and to predict further decompensation [16]. However, its availability and invasiveness restrict its use in common practice [27,28]. Individualized prediction of endpoints such as clinical decompensation and death by non-invasive diagnostic methods and development of risk algorithms similar to these used in cardiovascular medicine (e.g., Framingham risk score [29] might be beneficial in the future in compensated cirrhosis [8].

The aims of this study were to describe clinical outcomes and survival in patients, with cACLD and without history of acute decompensation, at low risk according to Baveno VI criteria, especially regarding further development of VB, HE, ascites, and hepatocellular carcinoma (HCC). We also aimed to evaluate similar outcomes according to the Expanded-Baveno VI criteria.

2. Patients and methods

2.1. Patients selection

A retrospective analysis of prospectively collected data was conducted in our Fibrosis Unit, in Pitié-Salpêtrière hospital, Paris, France. The Local Ethical Committee approved this analysis and all participants signed an informed consent regarding enrolment in the study. We analysed all data obtained in consecutive patients evaluated cACLD between January 2012 and December 2015. LSM and blood analysis were performed for these patients on the same day. Inclusion criteria were: Age ≥ 18 , reliable $\text{LSM} \geq 12.5 \text{ kPa}$. Exclusion criteria were: patients with previous history of acute decompensation (ascites, VB, EH, portal vein thrombosis, jaundice) or HCC.

2.2. Variables and measurement

LSM was evaluated by TE-M and/or TE-XL probes (Echosens, Paris, France) according to the instructions and training provided by the manufacturer. All the operators were experienced with more than a hundred exams done. TE result used for further analysis was the median of 10 valid measures. TE reliability/reliability of TE was ensured when the following criteria were met: (i) 10 successful measurements; (ii) an interquartile range lower than 30% of the median value; and (iii) a success rate of more than 60%. As well, we investigated demographic factors regarding age, gender, background history, liver disease aetiologies, body mass index and laboratory results including platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, prothrombin time, INR, and creatinine. We used platelets count and laboratory results obtained from blood samples collected on the same day as TE or, otherwise, the closest to the time of TE. Portal hypertension endoscopic screening was achieved at the discretion of physicians but relied on the French recommendations. We only considered upper endoscopies performed within the 3 months after inclusion.

2.3. Baveno VI status

Patients were classified in 2 groups: unfavourable Baveno VI status, i.e. patients with $\text{LSM} \geq 20 \text{ kPa}$ or platelets count ≤ 150.000

$/\text{mm}^3$; favourable Baveno VI status, i.e. patients with $\text{LSM} < 20 \text{ kPa}$ and platelets count $> 150.000/\text{mm}^3$. Patients fulfilled the Expanded-Baveno VI criteria when platelet count $> 110.000/\text{mm}^3$ and $\text{LSM} < 25 \text{ kPa}$, as previously described [24]. A worsening of Baveno VI status was defined as the occurrence of either platelet count $\leq 150.000 /\text{mm}^3$ or $\text{LSM} > 20 \text{ kPa}$ at any time during follow up in patients with initially favourable Baveno VI status.

2.4. Follow up

The duration of follow-up was calculated from the date when liver fibrosis was assessed (baseline) to death, liver transplantation or liver-related complications. This interval was censored at the time of last follow-up. If several liver-related complications occurred, the first one was taken into account. Liver-related complications were defined as VB, clinical HE, ascites or HCC. Clinical data were collected from medical records. At the time of complication, a worsening of Baveno VI status was defined by the occurrence of either platelet count $\leq 150.000 /\text{mm}^3$ or $\text{LSM} > 20 \text{ kPa}$ for patients initially classified in the favourable Baveno VI status group. For patients with chronic hepatitis C (CHC) or with chronic hepatitis B (CHB) a sustained viral response (SVR) was considered as achieved when respectively: HCV RNA levels by polymerase chain reaction ($< 12 \text{ IU/L}$) the end of the 12 weeks untreated follow-up period and when HBV DNA levels were undetectable. For patients with chronic alcoholic consumption, alcoholic withdrawal was defined as a complete and permanent cessation of alcoholic consumption as mentioned on patients' file.

2.5. Definition of clinical outcomes and endpoints

Acute decompensation was defined by occurrence of a portal hypertension-related complication (ascites, HE and/or VB) in the included patients during the follow-up period.

Primary endpoint was 4-year acute decompensation according to Baveno VI status. Secondary endpoints were 4-year HCC occurrence and survival according to Baveno VI status and expanded Baveno VI criteria.

3. Statistical analyses

Data were presented by means and standard deviations/median and interquartile ranges for normally/non normally distributed continuous variables, frequencies and percentages for categorical data. Characteristics of patients were compared using chi-2 (for categorical variables) and independent-samples t/Wilcoxon test (for normally/non normally distributed continuous variables). Survival rates were calculated using the Kaplan–Meier method, and compared using the log-rank test. Hazard Ratios (HR) and 95% CI were calculated using Cox regression analysis. Univariate regression models used all available variables. Multivariate regression models included selected variables associated with the outcome in the univariate analysis and proportional hazards assumption were checked based on smoothed plots of Schoenfeld residuals. All statistical analyses were performed using R software version 3.5.1. A p value < 0.05 was considered as significant.

4. Results

4.1. Patients' characteristics

During the study period, 1094 patients with $\text{LSM} \geq 12.5 \text{ kPa}$ were evaluated. Among them, 639 patients with a history of previous acute decompensation or HCC were excluded. 455 patients met inclusion criteria and were analysed in the study (Fig. 1). At inclusion, 255 had an unfavourable Baveno VI status and 200 a

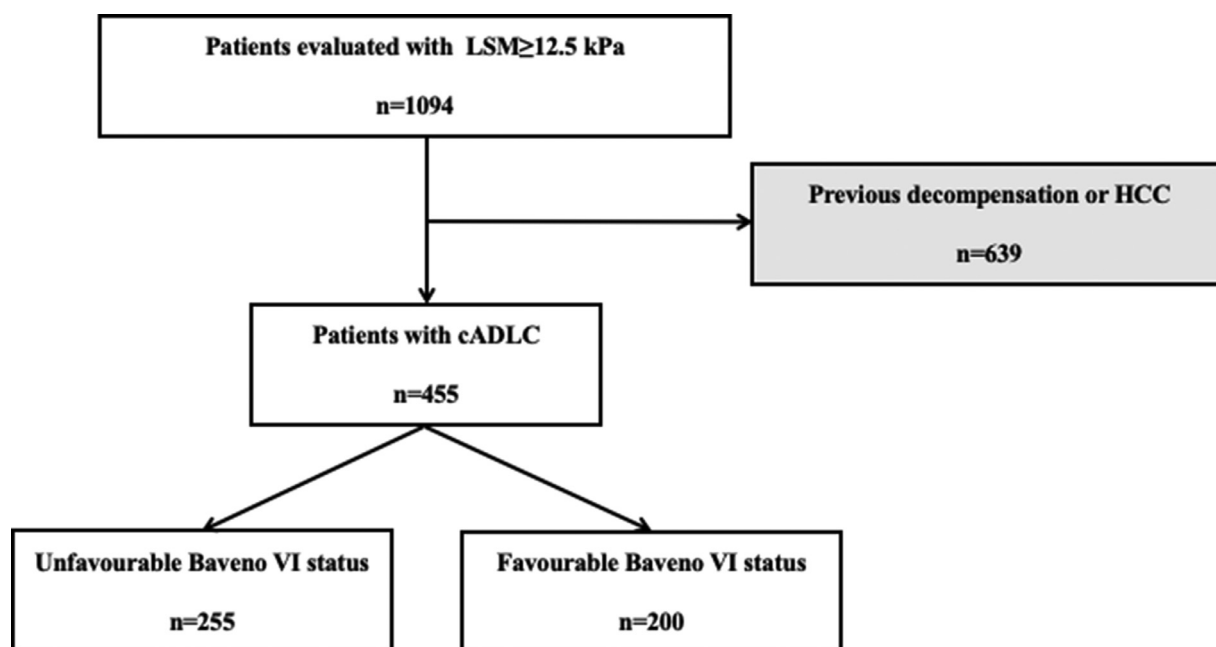


Fig. 1. Flow chart of patients included in our study. 1094 patients with $LSM \geq 12.5$ kPa were evaluated. 639 patients with a history of previous decompensation or HCC were excluded. 455 patients were included: 255 had an unfavourable Baveno VI status and 200 a favourable Baveno VI status.

favourable Baveno VI status. The main characteristics of the patients, according to Baveno VI status, are depicted in Table 1. Of the included patients, chronic hepatitis C (CHC)-related liver disease accounted for 42.5% of cases (of which, 68.4% with metabolic features and 4.1% with chronic hepatitis B (CHB)) followed by non-alcoholic steatohepatitis (NASH) (24.8%), alcoholic-related chronic liver disease (16.9%) and CHB-related liver disease (10.1%). Patients with unfavourable Baveno VI criteria were more prone to be infected with hepatitis C virus, and had a significantly lower albumin, prothrombin time (PT), and platelet count; bilirubin and LSM were significantly higher. An upper endoscopy was performed for 297 patients: 192/255 (75.3%) patients with unfavourable Baveno VI status and 105/200 (52.5%) patients with favourable Baveno VI status. Overall, VNT were diagnosed in 52/297 patients (17.5%). Among them, 4 patients were in the favourable Baveno VI group and 48 patients in the unfavourable Baveno VI group ($p < 0.001$, Fig. 2). The percentage of missed VNT was 4/105 (3.8%).

4.2. Development of portal hypertension-related complications according to Baveno VI status

Mean follow-up was 3.6 ± 1.3 years. Thirty-seven patients experienced an acute decompensation as previously defined. Among them, 9 patients (4.5%) displayed a favourable Baveno VI status and 28 (11.0%) an unfavourable status. The probability of being free from any portal hypertension-related complications was statistically higher in the group of patients with favourable Baveno VI status ($94.4 \pm 1.8\%$) as compared with the group of patients with unfavourable Baveno VI status ($85.7 \pm 2.6\%$) ($p = 0.018$) (Fig. 3A). The Supplementary Table 1 shows that similar trends were observed whatever the portal hypertension-related complication was. A worsening of Baveno VI status was observed for the 9 patients with an initially favourable status. Overall, at the time of acute decompensation, all the patients had an unfavourable status.

4.3. Development of HCC according to Baveno VI status

During the follow-up period, HCC occurred in 35 patients, including 25 with unfavourable Baveno VI criteria at inclusion and

10 patients in the favourable Baveno group. The probability of being free of HCC occurrence was higher in patients with favourable Baveno VI status ($94.2 \pm 1.8\%$ vs. 87.6 ± 2.4 , $p = 0.048$) (Fig. 3B).

4.4. Survival according Baveno VI status

Twelve patients died: 8 patients died in the unfavourable Baveno VI status group and 4 in the favourable Baveno IV status group. Liver disease was the cause of death for 7 patients in the unfavourable Baveno VI status group and for 3 patients in the favourable Baveno VI status group. The 4-year actuarial survival probability was $97.3 \pm 1.3\%$ in favourable Baveno VI status group vs. $95.8 \pm 1.5\%$ in unfavourable Baveno VI status group ($p = 0.5$) (Fig. 3C). Liver-related mortality was not different between the 2 groups ($p = 0.564$).

4.5. Portal hypertension-related complications, HCC occurrence and survival according to Expanded-Baveno VI status

296 patients were considered at low risk and 159 at high risk according to Expanded-Baveno VI criteria. Among the 37 patients who developed an acute decompensation, 22 patients were at high risk at inclusion. The probability of being free from portal hypertension-related complications was significantly higher in patients at low risk ($93.6 \pm 1.6\%$ vs. $81.7 \pm 3.7\%$, $p < 0.001$) (Fig. 4A). Regarding $LSM > 25$ kPa criteria specifically, the probability of being free from PHT-related complications was statistically higher in the group of patients with $LSM < 25$ kPa ($92.7 \pm 1.6\%$) as compared with patients with $LSM \geq 25$ kPa ($79.3 \pm 4.6\%$) ($p < 0.001$) (Supplementary figure 1). Among the 35 patients who developed a HCC during follow-up, 14 were at high risk according Expanded-Baveno VI criteria. There was no difference considering the probability of being free of HCC occurrence ($91.7 \pm 1.7\%$ for low-risk patients vs. $88.2 \pm 3.1\%$ for high-risk patients, $p = 0.31$) (Fig. 4B) or 4-year overall survival probability of $96.3 \pm 1.3\%$ for low-risk patients vs. $96.9 \pm 1.5\%$ for high-risk patients, $p = 0.79$) (Fig. 4C).

Table 1
Patients' characteristics at inclusion according to Baveno IV status.

Characteristics at inclusion	Total n = 455	Favourable Baveno VI status Platelet count > 150 G/L and LSM < 20 kPa n = 200	Unfavourable Baveno VI status Platelet count ≤ 150 or LSM ≥ 20 n = 255	p
Age, years	57.7 [50.4–64.9]	57.5 [48.8–64.9]	57.9 [51.0–64.8]	0.294
Female gender, n (%)	129 (28.4)	59 (29.5)	70 (27.5)	0.707
Aetiology of cirrhosis, n				0.004
CHC, n (%)	193 (42.5)	66 (33.0)	127 (49.4)	
Including patients with:				
- metabolic features*	132/193 (68.4)			
- VHB coinfection	8/193 (4.1)			
- chronic alcoholism	1/193 (0.1)			
NASH, n (%)	113 (24.8)	65 (32.3)	48 (18.8)	
Alcohol, n (%)	77 (16.9)	30 (15.0)	47 (18.4)	
CHB, n (%)	46 (10.1)	25 (12.0)	21 (8.2)	
Other, n (%)	26 (5.7)	14 (7.0)	12 (4.7)	
Viral suppression, n (%)	196 (82.0)	83 (91.2)	113 (76.3)	0.070
HIV infection, n (%)	17 (7.8)	7 (6.0)	10 (10.0)	0.398
BMI (kg/m ²)	26.4 [23.4–31.2]	27.1 [23.6–32.1]	25.8 [23.3–30.1]	0.042
Obesity, BMI ≥ 30 kg/m ² , n (%)	134 (30.7)	70 (36.5)	64 (26.1)	0.026
Diabetes, n (%)	138 (30.3)	61 (30.5)	77 (30.2)	1.000
Glucose mmol/L	5.5 [4.9–6.7]	5.6 [4.9–6.8]	5.5 [4.9–6.7]	0.820
Total cholesterol mmol/L	4.3 [3.6–5.0]	4.3 [3.7–5.2]	4.2 [3.5–4.8]	0.053
GGT IU/L	91.0 [49.5–214.0]	94.0 [51.7–244.2]	87.0 [49.0–173.5]	0.189
AST IU/L	51.0 [35.0–78.5]	53.5 [34.0–85.2]	49.0 [37.0–71.5]	0.416
ALT IU/L	51.0 [32.0–90.5]	52.5 [32.7–101.2]	51.0 [31.0–82.5]	0.205
Total bilirubin μmol/L	10.0 [8.0–15.0]	9.0 [7.0–13.0]	12.0 [8.0–16.5]	<0.001
Serum albumin g/L	41.1 [38.5–44.1]	43.0 [39.1–45.0]	41.0 [37.7–43.0]	<0.001
PT (%)	89.0 [80.0–97.25]	93.0 [86.7–100.0]	87.0 [76.0–95.0]	<0.001
MELD score	7.0 [7.0–9.0]	7.0 [7.0–9.0]	7.0 [7.0–9.0]	0.173
FIB-4 index**	2.6 [1.7–4.1]	1.92 [1.5–2.6]	3.4 [2.3–5.2]	<0.001
Platelets count (G/L)	168.0 [119.5–213.0]	202.0 [176.7–241.0]	130.0 [88.5–169.5]	<0.001
LSM, kPa	17.3 [14.1–24.4]	14.3 [13.6–16.5]	22.3 [18.0–30.1]	<0.001

Data are expressed as median [IQR] and n (%).

* Patients were considered with metabolic features when they had a type 2 diabetes melitus or an atherogenic dyslipidemia (hypercholesterolaemia) or an obesity (defined as a BMI ≥ 30 kg/m²).

** For all patients, Fibrosis-4 (FIB-4) index was calculated using the following formula: (Age x ASAT) / (Plaquettes x √[ALAT]). Abbreviations: CHC = chronic hepatitis C; NASH = Non-alcoholic steatohepatitis; CHB = chronic hepatitis B; HIV = human immunodeficiency virus; BMI = body mass index; GGT = gamma-glutamyl transferase; ALT = alanine aminotransferase; AST: aspartate aminotransferase, PT = prothrombin time; MELD = model for end-stage liver disease; LSM = liver stiffness measurement, IU = international units.

4.6. Factors associated with portal hypertension-related complications

In univariate analysis, independent factors associated with portal hypertension-related complications development were: the absence of CHC, a chronic alcoholism, a lower serum albumin at baseline, a higher serum total bilirubin, a lower PT, a lower platelets count, a higher LSM, an unfavourable Baveno VI or Expanded-Baveno VI status, and the presence of EV at screening upper endoscopy. In multivariate analysis, independent factors associated with further development of portal hypertension-related complications were: the absence of CHC (HR=0.40, 95% CI [0.19–0.83], *p* = 0.014), a low baseline albumin (HR=0.89, 95% CI [0.84–0.93], *p* < 0.001), a high serum total bilirubin rate (HR=1.06, 95% CI [1.03–1.08], *p* < 0.001), a low PT (HR=0.97, 95% CI [0.96–0.99], *p* < 0.001) and an unfavourable Baveno VI (HR=0.46, 95% CI [0.21–0.89], *p* = 0.0235) or Expanded-Baveno VI status (HR=0.37, 95% CI [0.18–0.75], *p* = 0.006) (Table 2 and Supplementary Figure 2).

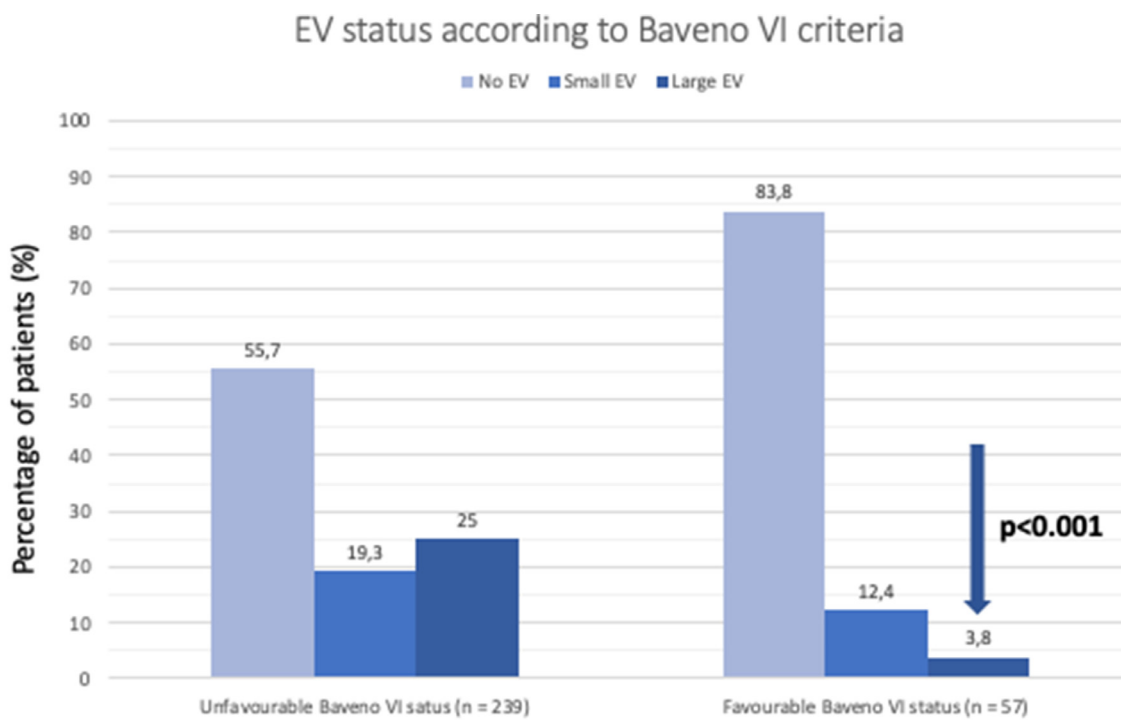
4.7. Factors associated with HCC occurrence

In univariate analysis, factors associated with development of HCC were an older age, a low serum albumin rate, a low PT and a diagnosis of EV at screening upper endoscopy. In multivariate analysis, the only factors that remained associated with development of HCC were an older age and a low serum albumin rate at baseline (Supplementary Table 2). Noteworthy, no patient < 60 years developed HCC in our whole cohort (Supplementary Figure 3).

5. Discussion

In this retrospective study of prospectively collected data, we highlighted that the probability of developing at least one portal hypertension-related complications was statistically lower when patients were initially at low-risk as defined in Baveno VI consensus. Likewise, during the 4-year follow-up, the survival went along the same trend for these patients.

The Baveno VI conference introduced simple criteria for the triage of patients with cACLD and selected patients for upper screening gastrointestinal endoscopy. Even if gastroscopy was not systematically performed, in accordance with previously published studies, the probability of missing VNT was estimated of being less than 5% in our cohort. In our longitudinal study, we emphasized the clinical relevance of these criteria not only to rule out VNT but also to identify patients with a better prognosis and at lower risk of developing portal hypertension complications. As a matter of fact, less than 6% of patients with favourable Baveno VI status at baseline developed a portal hypertension-related complication at 4 year. Based on our knowledge, these outcomes have not been previously described. Previous data suggested that LSM alone was independently associated with a clinically significant portal hypertension [30]. More recently, the M10LS20 algorithm, enclosing MELD score with LSM measured by shear wave elastography (SWE), was validated to predict development or worsening of acute decompensation of compensated or decompensated ACLD [31]. In our study, we included only patients with compensated ACLD with



*data available for 57 pts in the favourable Baveno VI group and 239 pts in the unfavourable Baveno VI group

Fig. 2. Histogram of EV status according to Baveno VI criteria. A gastroscopy was performed for 192/255 (75.3%) patients in the unfavourable Baveno VI group and for 105/200 (52.5%) patients in the favourable Baveno VI group. VNT were diagnosed in 4/105 (3.8%) patients with favourable Baveno VI status vs 48/192 (25.0%) patients with unfavourable Baveno VI status.

various aetiologies, diagnosed using non-invasive methods. Of note, all the patients who developed a portal hypertension-related complication had an unfavourable Baveno VI status at the time of the acute decompensation. Indeed, although LSM was not evaluated at the time of acute decompensation because of its diminished reliability in the setting of ascites or variceal bleeding, we observed that all decompensated patients had a platelet count lower than 150.000/mm³. In the light of these outcomes, Baveno VI criteria could represent an easy tool to help physicians for the clinical follow up organization of patients with cACLD and for therapeutic options stratification. These results suggest that monitoring may be simplified in cACLD patients with a favourable Baveno VI status at baseline. Nonetheless, a worsening of Baveno VI status has to be sought by repeating platelet count and LSM measurements during follow-up. Baveno VI criteria could also be used to select patients who could benefit from non-selective beta-blockers whose efficacy has been recently demonstrated in reducing incidence of decompensations in patients with compensated cirrhosis and HPVG superior to 10 mmHg [32]. The relevance of LSM in some aetiologies of liver disease might raise questions. We did not choose to discard HIV patients, for whom a confounding pre-sinusoidal hypertension could develop, or patients with cholestatic disease. Indeed, we only included patients with LSM ≥ 12.5 kPa and Elkrif et al. [37], who recently studied the interest of LSM in patients with porto-sinusoidal vascular disease (PSVD), demonstrated that a LSM < 10 kPa cutoff strongly suggested PSVD as a unique aetiology/cause of PHT in patients with PHT signs. Likewise, Moctezuma-Velazquez et al. [38] conclude in a recent study that Baveno VI criteria could be applied for patients with cACLD due to cholestatic disease to safely rule out VNT.

Last, we found that the probability of being free of HCC development was statistically higher for patients with favourable Baveno VI status. This result is consistent with existing data suggesting that HPVG superior to 10 mmHg is an independent predictive fac-

tor of HCC occurrence [33]. Unfortunately, we did not perform invasive HPVG measurement on patients from our cohort in the purpose of the study. To strongly support the interest of non-invasive methods in the prediction of HCC occurrence, a correlation between non-invasive and invasive HPVG evaluation has to be done. This result has to be qualified for patients with chronic hepatitis B-related liver disease. Though all the patients with CHB who developed HCC had also metabolic features, we may not exclude a role of circular DNA (cccDNA) in HCC occurrence [34]. Moreover, considering the poor prognosis associated with HCC, its screening has to be maintained for all patients with cACLD.

We also attempted to evaluate the Expanded-Baveno VI criteria for the same outcomes. The Expanded-Baveno VI criteria were found to avoid a larger number of futile upper endoscopy than the “classical” Baveno VI did. Our results are in accordance with these findings, suggesting that prognosis was even significantly better in low-risk patients defined according to these criteria, in terms of further development of portal hypertension-related complications. Likewise, considering LSM < 25 kPa cut-off alone, which was proposed as non-invasive marker of HPVG superior to 10 mmHg [24], prognosis was statistically significantly better in patients with LSM measured inferior to 25 kPa. Notably, survival and probability HCC development were not different between patients at low risk and at high risk as defined by Expanded-Baveno VI criteria.

Surprisingly, analysis of factors associated with portal-hypertension related complications indicated that the control of the underlying aetiology of liver disease was not associated with a better prognosis. This result is not in accordance with previously published studies, especially coming from the CirVir cohort (21). This result may be explained by the heterogeneity of our population of patients: we indeed included patients with alcohol-related liver disease, in whom alcohol consumption is very hard to evaluate; more, one quarter of patients were diagnosed with NASH and we arbitrary considered that the underlying

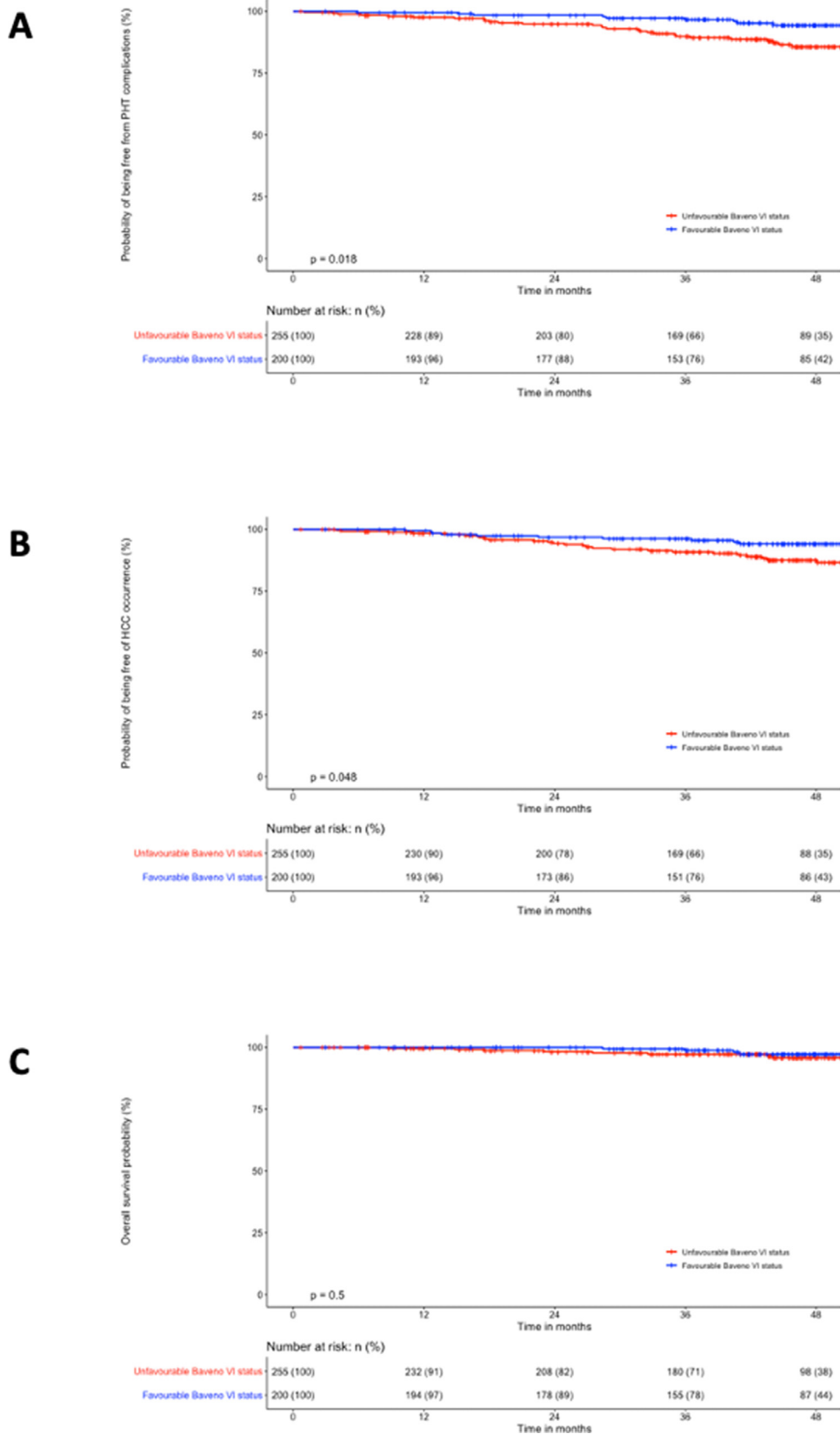


Fig. 3. Kaplan Meier curve of 4-year probability of being free from portal hypertension-related complications (3A) and from HCC occurrence (3B) and survival (3C) according to Baveno VI criteria. (3A) The probability of being free from any portal hypertension-related complications was statistically higher in the group of patients with favourable Baveno VI status as compared with the group of patients with unfavourable Baveno VI status ($94.4 \pm 1.8\%$ vs. $85.7\% \pm 2.6\%$, $p = 0.018$). (3B) The probability of being free of HCC occurrence was statistically higher in patients with favourable Baveno VI status ($94.2 \pm 1.8\%$ vs. $87.6 \pm 2.4\%$, $p = 0.048$). (3C) The 4-year survival was not different between the patients with favourable Baveno VI status and patients with unfavourable Baveno VI status ($97.3 \pm 1.3\%$ vs. $95.8 \pm 1.5\%$, $p = 0.5$).

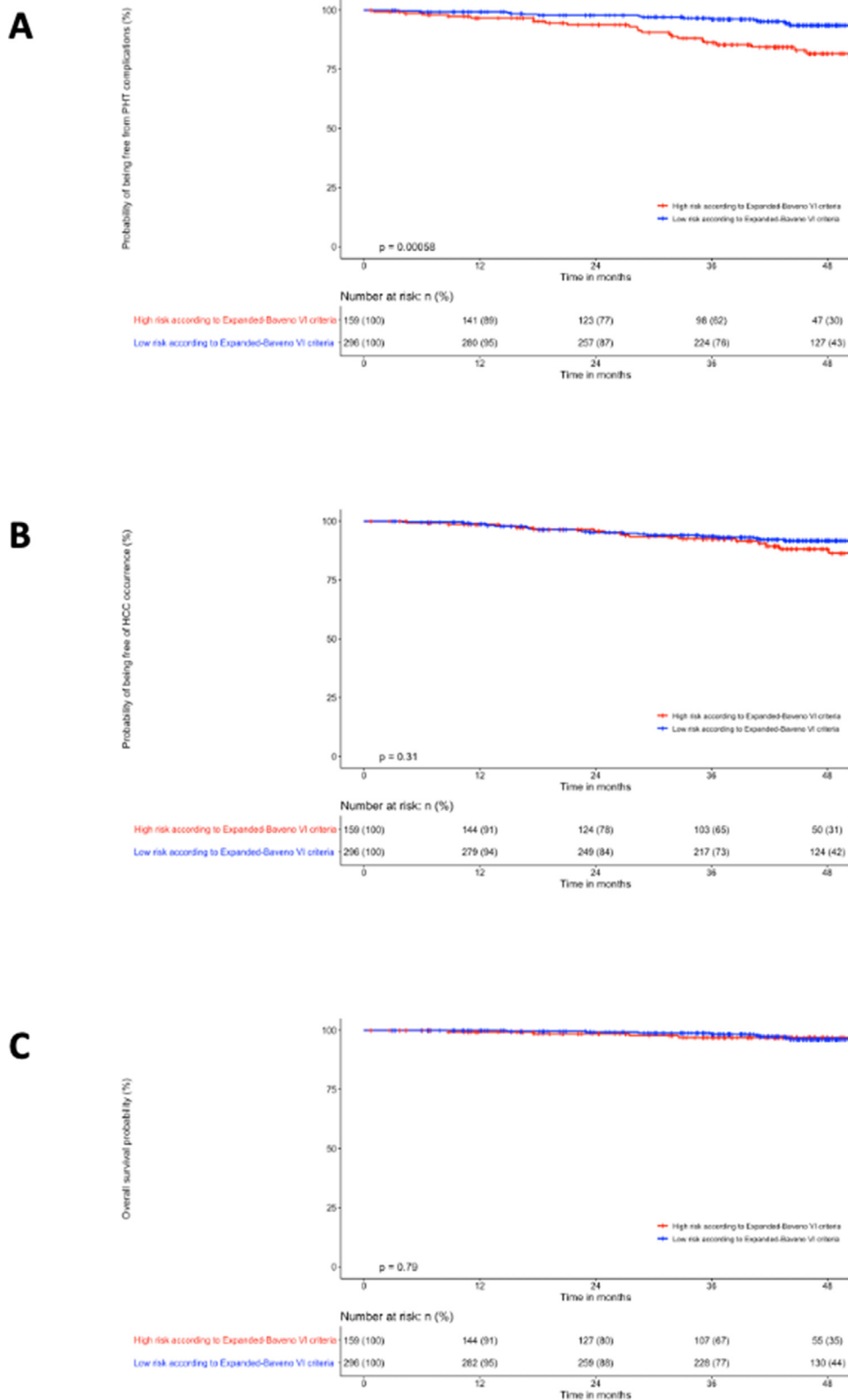


Fig. 4. Kaplan Meier curve of 4-year probability of being free from PHT complications (4A) and from HCC occurrence (4B) and survival (4C) according to expanded Baveno VI criteria. (4A) The probability of being free from any acute decompensation was significantly higher in patients at low risk than in patients at high risk according to expanded Baveno VI criteria ($93.6 \pm 1.6\%$ vs. $81.7 \pm 3.7\%$, $p < 0.001$). There was no significant difference when we interested in the probability of being free of HCC occurrence ($91.7 \pm 1.7\%$ for low-risk patients vs. $88.2 \pm 3.1\%$ for high-risk patients, $p = 0.31$) (4B) and survival ($96.3 \pm 1.3\%$ vs. $96.9 \pm 1.5\%$, $p = 0.79$) (4C) according to expanded Baveno VI criteria.

Table 2

Univariate and multivariate analyses of independent factors associated with portal hypertension-related complications development.

PHT complications Factors	Univariate analysis (n = 455)			Multivariate analysis			
	HR	95% HR CI	p value	n patients / n events	HR	95% HR CI	p value
Age	1.01	0.98 – 1.039	0.45				
Female gender	0.70	0.34 – 1.44	0.331				
HCV	0.47	0.24 – 0.91	0.024*	388/41	0.45	0.22 – 0.89	0.021*
Chronic alcoholism	2.32	1.02 – 5.32	0.046*				
Serum albumin	0.86	0.82 – 0.91	< 0.001*	351/38	0.88	0.83 – 0.92	< 0.001*
Serum bilirubin	1.06	1.04 – 1.08	< 0.001*	407/36	1.06	1.03 – 1.08	< 0.001*
PT	0.97	0.95 – 0.98	< 0.001*	388/41	0.97	0.96 – 0.99	< 0.001*
Platelets count	0.99	0.99 – 1.00	0.033*				
LSM	1.04	1.02 – 1.06	< 0.001*				
Favourable Baveno VI status	0.45	0.23 – 0.89	< 0.001*	388/41	0.46	0.23 – 0.91	0.025*
Favourable Expanded- Baveno VI status	0.36	0.19 – 0.66	< 0.001*	407/36	0.37	0.18 – 0.75	0.006*
EV at screening upper endoscopy [†]	3.19	1.69 – 6.00	< 0.001*				
cACLD patients with SVR or alcoholic withdrawal [‡]	1.14	0.53 – 2.46	0.740				

[†] this factor takes into account all EV, regardless of their size, diagnosed during the screening gastroscopy.

[‡] data available for 351 patients (including 149 patients who sustained a SVR or with alcoholic withdrawal and 202 patients with a persistent aetiologic factors of cACLD).

* indicates significance, with $p < 0.05$. Abbreviations: HR = hazard ratio; 95% HR CI = 95% HR confidence intervals; HCV = chronic hepatitis C; PT = prothrombin time; LSM = liver stiffness measurement; EV = oesophageal varices.

aetiology of cACLD was not controlled for these patients, as no specific treatment was available at the time of data collection. Moreover, the control of metabolic risk factors has not proven its efficacy in the prevention of liver-related complications. Last, considering the new concept of metabolic associated fatty liver disease (MAFLD), a large part of our patients could have been classified as mixed MAFLD (MAFLD + another cause of cACLD). We categorized patients as NASH in only 25% of cases but found almost 70% of patients in the entire cohort, either with diabetes, dyslipidemia or obesity, suggesting at least an underestimation of this entity. This observation is particularly important for patients with CHC as principal aetiology of cACLD. Even if a large majority of these patients achieved a long-term response to antiviral therapy during follow-up, we noted that 68% of patients with CHC had metabolic features as coexisting risk factors of acute decompensation after SVR. Other limitations should be underlined, the main one being the retrospective nature of the analysis of our data. Thus, exact timepoint of SVR was missing for all patients, not allowing us to pursue analysis of impact of their clinical evolution according to SVR. In the same way, we did not correlate our results to radiological features such as presence of spontaneous portosystemic shunt, another non-invasive marker of clinically significant PHT recently proposed [35]. Furthermore, even though, the 4-year period is long enough for all portal hypertension complications development according to previous longitudinal studies in cirrhotic population [5], the limited number of patients included in our cohort implied a restricted number of clinical events. Therefore, even if we described that the 4-year prognosis was excellent, we were not able to demonstrate any statistical difference regarding mortality for patients classified according to the Baveno VI criteria. This restricted number of events did not allow us to perform complementary analyses on subgroups of patients such as patients with NASH-related or chronic viral-related cACLD.

We only included patients without any history of acute decompensation. The exclusion of patients with history of decompensation may explain the very low rate of further acute decompensation observed. Indeed, though ACLD is a multi-directional disease, previous history of decompensation, even in recompensated patients, remains a major risk factor of acute-on-chronic liver failure [36]. Nonetheless, this population homogeneity is one of the strengths of our study and allowed us to be in the capacity of describing the natural history of compensated cirrhosis in low-risk patients.

In conclusion, we found in this longitudinal study that the Baveno VI criteria could enable us to identify patients with cACLD at low risk of portal hypertension-related complications occurrence. A better description of natural history of compensated cirrhosis diagnosed using non-invasive methods is warranted, including the new concept of MAFLD.

Authorship

Nicolas Asesio: acquisition of data; analysis and interpretation of data; drafting. **Priscila Pollo-Flores:** acquisition of data; analysis and interpretation of data; drafting. **Olivier Caliez:** statistical analysis. **Mona Munteanu:** acquisition of data, critical revision of manuscript. **Thierry Poynard:** critical revision of the manuscript. **Yen Ngo:** acquisition of data. **An Ngo:** acquisition of data. **Dominique Thabut:** study concept and design; analysis and interpretation of data; study supervision. **Marika Rudler:** study concept and design, analysis, interpretation of data, drafting and critical revision of manuscript.

Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.09.004.

References

- [1] de Franchis R, Faculty BV. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;53:762–8. doi:10.1016/j.jhep.2010.06.004.
- [2] 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. doi:10.1016/j.jhep.2005.10.013.
- [3] Garcia-Tsao G. Preventing the development of varices in cirrhosis. *J Clin Gastroenterol* 2007;41 Suppl 3:S300–4. doi:10.1097/MCG.0b013e318157c63d.
- [4] Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver Int* 2012;32:1407–14. doi:10.1111/j.1478-3231.2012.02830.x.

- [5] D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther* 2014;39:1180–93. doi:10.1111/apt.12721.
- [6] de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33:846–52. doi:10.1016/S0168-8278(00)80320-7.
- [7] Kovalak M, Lake J, Mattek N, Eisen G, Lieberman D, Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. *Gastrointest Endosc* 2007;65:82–8. doi:10.1016/j.gie.2006.08.023.
- [8] Berzigotti A. Advances and challenges in cirrhosis and portal hypertension. *BMC Med* 2017;15:200. doi:10.1186/s12916-017-0966-6.
- [9] Thabut D, Trabut J-B, Massard J, Rudler M, Muntenau M, Messous D, et al. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. *Liver Int* 2006;26:271–8. doi:10.1111/j.1478-3231.2005.01227.x.
- [10] Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. *Aliment Pharmacol Ther* 2008;27:1261–8. doi:10.1111/j.1365-2036.2008.03701.x.
- [11] Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. *Hepatology* 2010;51:1445–9. doi:10.1002/hep.23478.
- [12] Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013;144:102–11 e1. doi:10.1053/j.gastro.2012.10.001.
- [13] Poynard T, Ratziu V, Munteanu M. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Ann Intern Med* 2013;159:370–1. doi:10.7326/0003-4819-159-5-201309030-00019.
- [14] Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Non-invasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the “Anticipate” study. *Hepatology* 2016;64:2173–84. doi:10.1002/hep.28824.
- [15] de Franchis R, Krag A. Ruling out esophageal varices in NAFLD cirrhosis: can we do without endoscopy? *J Hepatol*. 2018;69:769–71. doi:10.1016/j.jhep.2018.06.013.
- [16] de Franchis R, Faculty BVI. 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. doi:10.1016/j.jhep.2015.05.022.
- [17] Maurice JB, Brodtkin E, Arnold F, Navaratnam A, Paine H, Khawar S, 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. doi:10.1016/j.jhep.2016.06.021.
- [18] Jangouk P, Turco L, De Oliveira A, Schepis F, Villa E, Garcia-Tsao G. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. *Liver Int* 2017;37:1177–83. doi:10.1111/liv.13379.
- [19] Llop E, Lopez M, de la Revilla J, Fernandez N, Trapero M, Hernandez M, et al. Validation of noninvasive methods to predict the presence of gastroesophageal varices in a cohort of patients with compensated advanced chronic liver disease: validation of noninvasive methods. *J Gastroenterol Hepatol* 2017;32:1867–72. doi:10.1111/jgh.13781.
- [20] Bae J, Sinn DH, Kang W, Gwak G-Y, Choi MS, Paik Y-H, et al. Validation of the Baveno VI and the expanded Baveno VI criteria to identify patients who could avoid screening endoscopy. *Liver Int* 2018;38:1442–8. doi:10.1111/liv.13732.
- [21] Petta S, Sebastiani G, Bugianesi E, Viganò M, Wong VW-S, Berzigotti A, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. *J Hepatol* 2018;69:878–85. doi:10.1016/j.jhep.2018.05.019.
- [22] Thabut D, Bureau C, Layese R, Bourcier V, Hammouche M, Cagnot C, 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. doi:10.1053/j.gastro.2018.11.053.
- [23] Stafylidou M, Paschos P, Katsoula A, Malandris K, Ioakim K, Bekiari E, et al. Performance of Baveno VI and expanded Baveno VI criteria for excluding high-risk varices in patients with chronic liver diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2019;17:1744–55 e11. doi:10.1016/j.cgh.2019.04.062.
- [24] Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology* 2017;66:1980–8. doi:10.1002/hep.29363.
- [25] Nawalerspanya S, Sripongpan P, Chamroonkul N, Kongkamol C, Piratvisuth T. Validation of original, expanded Baveno VI, and stepwise & platelet-MELD criteria to rule out varices needing treatment in compensated cirrhosis from various etiologies. *Ann Hepatol* 2019. doi:10.1016/j.aohep.2019.08.005.
- [26] Gaete MI, Díaz LA, Arenas A, González K, Cattaneo M, Fuster F, et al. Baveno VI and Expanded Baveno VI criteria successfully predicts the absence of high-risk gastro-oesophageal varices in a Chilean cohort. *Liver Int* 2020. doi:10.1111/liv.14373.
- [27] Villanueva C, Graupera I, Aracil C, Alvarado E, Miñana J, Puente Á, et al. A randomized trial to assess whether portal pressure guided therapy to prevent variceal rebleeding improves survival in cirrhosis. *Hepatology* 2017;65:1693–707. doi:10.1002/hep.29056.
- [28] Qi X, Berzigotti A, Cardenas A, Sarin SK. Emerging non-invasive approaches for diagnosis and monitoring of portal hypertension. *Lancet Gastroenterol Hepatol* 2018;3:708–19. doi:10.1016/S2468-1253(18)30232-2.
- [29] Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S49–73. doi:10.1161/01.cir.0000437741.48606.98.
- [30] Wang J-H, Chuah S-K, Lu S-N, Hung C-H, Kuo C-M, Tai W-C, et al. Baseline and serial liver stiffness measurement in prediction of portal hypertension progression for patients with compensated cirrhosis. *Liver Int* 2014;34:1340–8. doi:10.1111/liv.12525.
- [31] Trebicka J, Gu W, de Ledinghen V, Aubé C, Krag A, Praktikno M, et al. Two-dimensional shear wave elastography predicts survival in advanced chronic liver disease. *Gut* 2021. doi:10.1136/gutjnl-2020-323419.
- [32] Villanueva C, Albillos A, Genesca J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2019;393:1597–608. doi:10.1016/S0140-6736(18)31875-0.
- [33] Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol* 2009;50:923–8. doi:10.1016/j.jhep.2009.01.014.
- [34] Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. *Virology* 2015;479–480:672–86. doi:10.1016/j.virol.2015.02.031.
- [35] Praktikno M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, et al. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. *J Hepatol* 2020;72:1140–50. doi:10.1016/j.jhep.2019.12.021.
- [36] Monteiro S, Grandt J, Uschner FE, Kimer N, Madsen JL, Schierwagen R, et al. Differential inflammasome activation predisposes to acute-on-chronic liver failure in human and experimental cirrhosis with and without previous decompensation. *Gut* 2021;70:379–87. doi:10.1136/gutjnl-2019-320170.
- [37] Elkrief L, Lazareth M, Chevret S, Paradis V, Magaz M, Blaise L, et al. Liver stiffness by transient elastography to detect porto-sinusoidal vascular liver disease with portal hypertension. *Hepatology* 2020. doi:10.1002/hep.31688.
- [38] Moctezuma-Velazquez C, Saffioti F, Tasayco-Huaman S, Casu S, Mason A, Roccarina D, et al. Non-invasive prediction of high-risk varices in patients with primary biliary cholangitis and primary sclerosing cholangitis. *Am J Gastroenterol* 2019;114:446–52. doi:10.1038/s41395-018-0265-7.