Validation of Baveno VI Criteria for Screening and Surveillance of Esophageal Varices in Patients With Compensated Cirrhosis and a Sustained Response to Antiviral Therapy

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Short title: Screening and surveillance of EV in patients with viral cirrhosis

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Grant Support : ANRS (France REcherche Nord & sud Sida-Hiv Hépatites).

Abbreviations: EV: esophageal varices; VNT: varices needing treatment; SVR: sustained virological response; HCV: hepatitis C virus; PCR: qualitative polymerase chain reaction; HBV: hepatitis B virus; PHT: portal hypertension; Plt: platelet count; LS: liver stiffness; DAAs: direct-acting antiviral agents; BB: beta-blockers; HVPG: hepatic venous pressure gradient

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ACKNOWLEDGMENTS

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Funding/Support: This study was sponsored by the ANRS (France REcherche Nord & sud Sida-hiv Hépatites: FRENSH). .

Role of the Sponsor: The funding sponsor had no role in the design and conduct of the study; the collection, management, analysis, interpretation of the data, and the preparation, review, or approval of the manuscript.

Disclosures: Dr. Thabut has received honoraria from Abbvie, Bristol-Myers Squibb, Gilead, MSD and Gore. Dr Bureau has received honoraria from Abbvie, Gilead and Gore. Dr. Nahon has received honoraria from Abbvie, Bayer, Bristol-Myers Squibb and Gilead. He consults for Abbvie and Bristol-Myers Squibb. Dr. Zarski consults and is on the speakers' bureau for Gilead, Bristol-Myers Squibb, Janssen, Siemens and MSD. He consults for AbbVie. Dr Cales consults for Echosens. Dr. Pol consults for and has received grants from Bristol-Myers Squibb, Gilead, Roche, and MSD. He consults for Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, AbbVie, Roche and MSD. Dr. Alric consults for and has received grants from Bristol-Myers Squibb, MSD and Gilead. He has received grants from Roche and Janssen. Dr. Bourliere consults for and advises AbbVie, MSD, Janssen, Bristol-Myers Squibb,Roche and Gilead. Dr. Di Martino consults for and advises Gilead and MSD. He advises Janssen and Bristol-Myers Squibb. Dr Bacq was speaker for Roche, Bristol-Myers Squibb and Gilead. Dr Roudot-Thoraval has received honoraria from Roche, Gilead, AbbVie, Bristol-Meyers Squibb and MSD and advises Gilead and AbbVie.

Conflicts of interest: none to declare

Author contributions: Drs. Nahon and Roudot-Thoraval had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Study concept and design: Thabut, Bureau, Nahon, Bourcier, Roudot-Thoraval.
Acquisition of data: Nahon, Bourcier, Layese, Marcellin, Guyader, Pol, Larrey, De Lédinghen, Ouzan, Zoulim, Roulot, Tran, Bronowicki, Zarski, Riachi, Calès, Péron, Alric, Bourlière, Mathurin, Blanc, Abergel, Serfaty, Mallat, Grangé, Attali, Bacq, Wartelle, Dao, Thabut, Pilette, Silvain, Christidis, Capron, Bernard-Chabert, Zucman, Di Martino, Roudot-Thoraval, Maryam Hammouche, Karima Ben Belkacem.
Analysis and interpretation of the data: Nahon, Layese, Thabut, Bureau, Audureau, Roudot-Thoraval.
Drafting of the manuscript: Thabut, Bureau, Nahon, Bourcier, Layese, Audureau, Roudot-Thoraval.
Critical revision of the manuscript for important intellectual content: Nahon, Bourcier, Layese, Cagnot, Audureau, Roudot-Thoraval.
Statistical analysis: Layese, Audureau, Roudot-Thoraval
Obtained funding: Prof Jean-Claude Trinchet
Administrative, technical and material support: Nahon, Bourcier, Cagnot, Layese, Roudot-Thoraval.
Study supervision: Thabut, Bureau, Nahon, Bourcier, Layese, Roudot-Thoraval

Role of the Sponsor: The funding sponsor had no role in the design and conduct of the study, the collection, management, analysis or interpretation of the data, and the preparation, review or approval of the manuscript.

Electronic word count: 7000 Tables: 3, Figures: 4, Supplementary Tables: 15, Supplementary Figures: 6; References: 34.

Acknowledgement: This work is dedicated to the memory of Professor Jean-Claude Trinchet.

ABSTRACT

Background & Aims: Management of patients with cirrhosis includes endoscopic screening and surveillance to detect esophageal varices (EV) and prevent bleeding. However, the Baveno VI guidelines recommend avoiding endoscopies for patients with liver stiffness measurements below 20 kPa and platelet counts above 150,000 (favorable Baveno VI status) and endoscopic assessment of patients with higher levels of liver stiffness and platelet counts (unfavorable Baveno VI status). We aimed to validate the Baveno VI guidelines, evaluating outcomes of patients in the ANRS-CO12 CirVir cohort with compensated cirrhosis associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, with or without a sustained response to antiviral therapy.

Methods: We performed an ancillary study using data from 891 patients in the ANRS CO12 CirVir cohort, treated at 35 centers in France, with HCV or HBV infection and biopsy-proven cirrhosis, Child-Pugh A scores, no previous complications, and no hepatocellular carcinoma who underwent an endoscopic procedure and had interpretable liver stiffness measurements and platelet counts. Progression of portal hypertension (PHT) was defined as the onset of varices needing treatment (VNT) or PHT-related bleeding. An sustained response to antiviral therapy was defined as undetectable level of HCV RNA by PCR assay (<50 IU/mL) 12 weeks after the end of treatment (SVR) or an undetectable level of HBV DNA. The primary aims were to validate the Baveno VI guidelines for screening and surveillance of EV in patients with compensated cirrhosis and to study the effects of an SVR on the progression of PHT.

Results: Two hundred patients achieved an SVR (22.4%) (94 patients with HCV infection, 98 patients with HBV infection, and 8 patients with both); 80 of these patients had favorable Baveno VI status and none had VNT. Progression of PHT was studied in 548 patients; during a follow-up period of 61.2 months (interquartile range, 39.5–80.6 months), 105 of these patients (19.1%) had progression of PHT. Lack of an SVR and grade 1 EV were independently associated with progression of PHT. At the time of PHT progression, all patients had unfavorable Baveno VI status. Achieving favorable Baveno VI status after an SVR was associated with the absence of PHT progression. Favorable Baveno VI status and SVR were independently associated with survival.

Conclusions: In an analysis of data from a large cohort of patients with HBV- or HCV-associated cirrhosis in France, we validated the Baveno VI guidelines on screening and surveillance of PHT—even for patients who achieved a sustained response to antiviral therapy.

Key words: portal hypertension; elastometry; esophagus; variceal bleeding

Electronic Word Count: 408 words

Variceal bleeding is one of the principal complications of cirrhosis. Despite major improvements in its management, mortality remains as high as 15% after a first episode of bleeding [1]. Primary prophylaxis of variceal bleeding, using either beta-blocker therapy or band ligation, can reduce the bleeding rate by 50% and should be indicated when patients display esophageal varices (EV) needing treatment (VNT, i.e. large or grade 2 or 3 varices). The management of cirrhotic patients therefore includes endoscopic screening and surveillance so that prophylaxis can be initiated[2]. Prior to 2015, endoscopy was mandatory in all cirrhotic patients at the time of diagnosis, and endoscopic follow-up was indicated each year in patients with grade 1 EV, and every two to three years in patients with no EV[3]. Application of this strategy was cost-effective in the past, when up to 30% of patients displayed VNT at endoscopic screening. However, because of the widespread use of non-invasive methods, cirrhosis is now diagnosed at an earlier and compensated stage [4], so that the number of futile endoscopies has risen[4]. Moreover, as far as viral cirrhosis is concerned, viral suppression, is now achieved in the vast majority of patients. Viral suppression has been shown to be associated with a decrease in portal hypertension (PHT) measured from the hepatic venous pressure gradient in patients treated with interferon [5-7]. However, due to the low rates of SVR (and thus, highly selected patients with SVR), it is unclear whether the results of these studies also apply to current IFN-free therapies. Later, same results were obtained using HCV therapies without interferon [8-12], in monoinfected and also coinfected patients [12]. Viral suppression induced also a reduction in the incidence of EV in small series [13, 14], a reduction in the progression of PHT and even PHT regression in a small series of HBV patients [15], as well as a decrease in PHT-related bleeding [16]. As a consequence, one could speculate that the number of futile endoscopies during follow-up may also be increasing in HCV or HBV cirrhotic patients. Last, adherence to screening and follow-up recommendations has been shown to be far from satisfactory[17].

Because of recent studies showing that patients with normal platelet counts associated with low liver stiffness have a very small risk of displaying VNT [18, 19], the guidelines on the screening and surveillance of EV were recently completely revised at the Baveno VI conference [20]. It was stated that: (1) patients with LS <20kPa and a platelet count >150,000 (a “favorable Baveno VI status”) can no longer undergo endoscopic screening (first recommendation, level of evidence 1b; A); (2) regular LSM and platelet counts should be assessed in this latter subset of patients, and endoscopic screening

performed in the event of modifications to any of these parameters above/below the previous cut-off points for LSM and platelets, respectively (second recommendation, level of evidence 5D); (3) the periodicity of endoscopic surveillance should be lengthened in patients with cirrhosis in whom the causal agent for cirrhosis has been cured and who do not display any other factors for liver comorbidities, and should now be every two years in patients with grade 1 EV, and every three years in patients with no EV (third recommendation, level of evidence 5D) [20]. The first statement has been validated on numerous occasions since its publication in 2015 [16, 21, 22], during retrospective studies and in one meta-analysis [23], but never in a pure population of patients with viral cirrhosis. The follow-up recommendations, including LSM, were stated arbitrarily and have never been validated. Lastly, all previous recommendations, including that concerning follow-up once the etiological agent has been cured, have never been validated in virally suppressed patients, in whom LSM values decrease after SVR, even if this does not necessarily translate into an improvement of fibrosis.

Since 2006, the prospective ANRS CO12 CirVir cohort has included 1822 patients with compensated viral and biopsy-proven cirrhosis recruited in 35 French centers[24]. With the advantage of a definite histological diagnosis of cirrhosis and the prospective analysis of clinical events, the lengthy follow-up of the cohort has been able to accurately report the rates of liver-related and extra-hepatic complications in a competing risk framework [16, 25], which are furthermore dramatically impacted by viral suppression [16].

The aims of this study in the large multicenter CirVir cohort were therefore: (1) to provide an independent, prospective validation of the Baveno VI guidelines regarding the screening and surveillance of EV in patients with compensated viral cirrhosis; (2) to study the influence of viral suppression on the progression of PHT, and (3) to validate the Baveno VI criteria for the screening and surveillance of EV in the subset of virally suppressed cirrhotic patients.

METHODS

Details are provided in supplementary materials.

Patient selection

The present work was an ancillary study derived from the ANRS CO12 CirVir cohort [24]. The patients were recruited in 35 French clinical centers (Exhibit 1), according to the main following selection criteria: a) histologically proven Child-Pugh A cirrhosis; b) HCV antibodies or HBs antigen positive; c) absence of previous complications of cirrhosis; d) an endoscopic procedure performed less than one year before inclusion; e) interpretable LSM within a year of inclusion.

Follow-up

As a member of the CirVir cohort, patients were seen by physicians at least every six months according to the recommendations for the monitoring of cirrhosis, and the usual clinical/biological/Doppler US data were recorded (see details in supplementary materials). Regular endoscopic surveillance was assured at the discretion of the physician but based on the French consensus conference recommendations. PHT progression was defined as the occurrence of grade 2 or 3 EV in patients with no prior EV or grade 1 EV, the occurrence of grade 3 EV in patients with initial grade 2 EV, or the onset of a PHT-related bleeding episode.

Baveno VI status

A worsening of Baveno VI status was defined as the occurrence of either Plt ≤150,000/mm3 or LSM ≥20 kPa at any time during follow-up in patients with an initially favorable VI status. An improvement in Baveno VI status was defined as a rise in the platelet count above 150,000/mm3, together with a decrease of LSM to <20kPa in patients with an initially unfavorable status.

Antiviral therapy and viral replication

The primary efficacy endpoint for HCV and HCV-HBV patients was a sustained virological response (SVR), defined as HCV RNA levels that were undetectable by PCR assay (<50 IU/mL) at the end of a 12-week untreated follow-up period, and undetectable HBV DNA levels in HBV patients.

RESULTS

Inclusion period and characteristics of patients at inclusion

A total of 1,822 cirrhotic patients were included in the CirVir cohort, 151 of whom were subsequently excluded from the analysis after a revision of individual data because of either non-compliance with the inclusion criteria (n=142) or the withdrawal of consent (n=9). The final analyses of the CirVir cohort were therefore performed in 1,671 patients, 545 of whom were excluded: 519 (31.1%) did not undergo endoscopy at inclusion, and 26 (1.6%) had a history of banding for primary prophylaxis prior to inclusion. Among the 1126 remaining patients, 235 were excluded because LSM findings or platelet counts were not available at inclusion in order to accurately assess their initial Baveno VI status. For all these reasons, 891 patients were finally included in the present study (See consort diagram, Supplementary Figure 1). Inclusion characteristics and the occurrence of PHT-related bleeding during follow-up differed slightly between included and excluded patients with respect to age, the etiology of cirrhosis, and the severity of liver disease (determined from platelet counts, liver function tests and EV), with excluded patients displaying less severe liver disease (Supplementary Table 1a). For the analysis, the reference date was December 31, 2015, at which time the median duration of follow-up was 61.2 months [IQR: 39.5 – 80.6]. The characteristics of the 891 patients included are shown in Supplementary Table 1. Sixty patients (6.8%) were taking beta blockers (BB) at inclusion (30 patients with grade 2/3 EV, 13 patients with grade 1 EV and 17 patients with no EV). Viral suppression was observed at inclusion in 200 patients (22.5%) (94 HCV patients, 98 HBV and eight HCV-HBV patients; $p<0.001$). Baseline characteristics did not differ between small and large size centres (i.e. including less than or 14 patients vs more than 14 patients) (Supplementary Table 2). At the end of follow-up, 131 HBV patients (89.1%), 345 HCV patients (48.9%) and 10 HCV-HBV patients (50.0%) had achieved viral suppression ([missing data=19], $p<0.001$).

At inclusion, the distribution of EV was as follows: no EV: 671 (75.3%); grade 1 EV: 148 (16.6%) and grade 2/3 EV: 72 patients (8.1%). PHT gastropathy was seen in 204 patients (23.0%) and gastric varices in 17 (1.9%). The characteristics of patients as a function of EV grade are shown in Supplementary Table 3. All patients underwent an abdominal ultrasound at inclusion in order to

exclude HCC; the different ultrasound parameters as a function of EV grade are shown in Supplementary Table 4. Only spleen size differed significantly as a function of the grade of EV.

LSM was performed within 3.2 months of inclusion [IQR: 0.7 – 6.9]: 390 patients (65.3%) had LSM<20 kPa, and 264 (29.7%) a platelet count >150,000/mm3. Overall, 221 patients (24.8%) had a favorable Baveno VI status (Plt >150,000/mm3 and LSM <20 kPa) at inclusion. The initial characteristics of patients as a function of Baveno VI status are shown in Table 1. Patients with an initially favorable Baveno VI status were more frequently male, infected with HBV, displaying a significantly lower BMI and with viral suppression at inclusion. As expected, liver function test findings differed significantly between the two groups; patients with a favorable Baveno VI status suffered from less pronounced liver disease (determined from ALT, AST, GGT, bilirubin and albumin levels).

Presence and grade of EV as a function of initial Baveno VI status

The distribution of varices in the 221 patients who had a favorable Baveno VI status at inclusion was: no EV: 205 (92.8%), grade 1 EV: 13 (5.9%) and grade 2/3 EV: 3 (1.3%). Among the 670 patients with an unfavorable Baveno VI status at inclusion, the distribution of varices was: no EV: 466 (69.6%), grade 1 EV: 135 (20.1%) and grade 2/3 EV: 69 (10.3%) (Table 1). The distribution of varices thus differed significantly between the two groups of patients ($p<0.001$) (Figure 1a); among those with a favorable Baveno VI status at inclusion, only three (1.3%) displayed VNT. All had HCV cirrhosis; none of them was an active drinker and none displayed viral suppression. One of the three had a high BMI of 28.1 and arterial hypertension, while the other two did not exhibit any comorbidities (see Supplementary Table 5 for details). None of them was taking BB.

Considering the 200 patients who exhibited viral suppression at inclusion, the distribution of varices was as follows: no EV: 205 (84.0%), grade 1 EV: 21 (10.5%) and grade 2/3 EV: 11 (5.4%). Eighty patients (40%) had a favorable Baveno VI status. The distribution of varices differed significantly as a function of Baveno VI status ($p=0.004$) (Figure 1b), and among the 80 patients with a favorable status, none had VNT.

Progression of PHT during follow-up

During follow-up, a further 343 patients were excluded from the longitudinal analyses: 328 because they had neither undergone a follow-up endoscopy nor experienced PHT-related bleeding, and 15 because they completed a follow-up endoscopy but had a previous history of banding for primary prophylaxis. The progression of PHT was therefore studied in the remaining 548 patients (see Supplementary Figure 1). Baseline characteristics of patients were not different between the patients excluded and included in the follow-up study, except for higher creatinine levels and lower PT in included patients, and a slightly higher proportion of patients who had past or ongoing antiviral therapy (Supplementary Table 1b). Among them at endpoint, 284 (81 HBV patients, 197 HCV patients and 6 HCV-HBV patients) achieved viral suppression. Overall, 105 patients displayed a progression of PHT during follow-up: 88 patients developed grade 2 or 3 EV and 17 patients experienced a PHT-related bleeding episode. The factors associated with the progression of PHT under univariate analysis are shown in Supplementary Table 5. Initial grade 2 or 3 EV, the use of beta-blockers, HCV etiology, the presence of diabetes or arterial hypertension, no viral suppression achieved and an initially unfavorable Baveno VI status, as well as more severe liver disease, a low platelet count and high LSM were all significantly associated with the progression of PHT (Supplementary Table 6). Among the 88 patients in whom varices progressed, six experienced subsequent PHT-related bleeding during follow-up. The incidence of PHT-related bleeding was dependent on the initial EV grade (Supplementary Figure 2a), and was significantly higher in the patients included in the follow-up study (Supplementary Figure 2b).

Progression of PHT as a function of viral suppression and initial EV grade

The progression of PHT at 1, 3 and 5 years concerned 1.8 %, 4.1% and 4.1% of patients with no EV at inclusion in whom viral suppression was achieved, 0%, 15.7% and 15.7% of patients with grade 1 EV at inclusion in whom viral suppression was achieved, 2.2%, 7.7% and 14.2% of patients with no EV at inclusion in whom viral suppression was not achieved and 2.7%, 31.7% and 52.6% of patients with grade 1 EV at inclusion in whom viral suppression was not achieved ($p<0.001$). The cumulative probabilities of PHT progression according to endoscopic findings at inclusion and the achievement of

viral suppression are shown in Figure 2, Supplementary Figure 3 and Supplementary Figure 4. When adjusting for the initial EV grade (no EV vs grade 1 EV vs grade 2/3 EV), an absence of viral suppression remained significantly associated with PHT progression (Supplementary Table 7). Sensitivity analyses showed that the same factors were associated with progression of PHT when excluding patients with grade 2/3 EV at admission (Supplementary Table 8).

Progression of PHT as a function of initial Baveno VI status

PHT progression rates at 1, 3 and 5 years reached 0%, 0.8% and 2.5%, respectively, in the 136 patients with an initially favorable Baveno VI status who were included in the follow-up study, vs 3.9%, 15.9% and 24.3%, respectively, among the 412 patients with an initially unfavorable Baveno VI status ($p<0.001$) (Supplementary Figure 5).

Progression of PHT according to a worsening of Baveno VI status during follow-up

LSM findings were available and interpretable during follow-up in 374/548 patients (68.2%), and in 113/136 patients (83.1%) with an initially favorable Baveno VI status. The number of LSM and platelet determinations performed reached 2 [IQR: 1 – 4] and 9 [IQR: 6 – 12], respectively, (and 3 [IQR: 2 – 5] and 11 [IQR: 7.5 – 13] respectively among the 113/136 patients with an initially favorable Baveno VI status). Overall, 122 patients with initially favorable Baveno VI status underwent at least one LSM or plt count measurement during follow-up and the evolution of their Baveno VI status could be assessed. The median delay between LSM measurements was 13.4 months [IQR: 11.2 – 24.1] in the 331 patients (43/78 did not have LSM assessment at baseline but their Baveno status was known as they had low platelets count), and 13.7 months [IQR: 11.4 – 27.0] among the 113/136 patients with an initially favorable Baveno VI status.

A worsening of Baveno VI status was observed in 66 patients with an initially favorable status within a median period of 12.2 months [IQR: 6.7 – 37.0]. Factors independently associated with such a worsening during follow-up were AST > ULN (HR=3.15 [95% CI: 1.78; 5.59], $p<0.001$) and an absence of viral suppression (HR=3.45 [95% CI: 1.75; 6.67], $p<0.001$).

There was a trend towards a greater progression of PHT at 1, 3 and 5 years in patients whose Baveno VI status worsened than among whose status did not worsen (cumulative incidence at 1, 3, 5 years: 1.6%, 3.6% and 3.6% vs 0%, 1.2% and 1.2%, p=0.15; Supplementary Figure 6). This finding remained true when just the 122 patients who underwent several LSM measurements during follow-up were considered. All four patients with an initially favorable Baveno VI status who experienced a progression of PHT had an unfavorable Baveno VI status at the time of progression.

Progression of PHT among patients with viral suppression

Among the 284 patients who achieved viral suppression at inclusion or during follow-up, a progression of PHT occurred in 14 patients (4.9%), 8/246 (3.3%) without EV, 4/27 (14.8%) with grade 1 EV and 2/11 (18.2%) with grade 2/3 EV at inclusion (log-rank test: p=0.005). Factors associated with PHT progression in these patients were their initial EV grade, beta-blocker treatment, a low platelet count and a high LSM, and more severe liver disease at inclusion (Supplementary Table 9). It should also be noted that even if viral suppression was obtained, patients with initial grade 1 EV still experienced a not inconsiderable progression of their PHT (15.7% at 3 and 5 years), whereas it was negligible in patients without EV (Figure 2). When adjusting for the initial EV grade (no EV vs grade 1 EV vs grade 2/3 EV), the use of beta blockers, a low platelet count, a high LSM and more severe liver disease remained significantly associated with PHT progression (Supplementary Table 10). Sensitivity analyses showed that the same factors were associated with progression of PHT when excluding patients with grade 2/3 EV at admission (Supplementary Table 11).

PHT progression in virally suppressed patients as a function of Baveno VI status at the time of viral suppression

A Baveno VI status at the time of viral suppression was available in 228/284 (80.2%) patients. Overall, 64/228 patients (28.1%) had a favorable Baveno VI status, and their progression of PHT at 1, 3 and 5 years was null, vs 3.4%, 8.1% and 8.1% among the 164/228 patients (71.9%) with an unfavorable Baveno VI status (p=0.007) (Figure 3).

PHT progression in patients with HCV as a function of an improvement in Baveno VI status after achieving an SVR

Variations in LSM values differed significantly in patients with HCV depending on whether an SVR had been achieved or not (considering the inclusion and last LSM determinations: LSM delta of -2.0 [IQR: -6.3 – 0.3] in SVR patients, vs 0.7 [IQR: -4.3 – 6.8] in non-SVR patients, $p<0.001$; data available for 252 patients). Among the 76 SVR patients, the median LSM was 13.4 [IQR: 8.8 – 18.9] at inclusion, vs 8.9 [IQR: 6.3 – 15.3] at the last measurement. When considering only the 44 patients in whom an SVR occurred during follow-up and in whom an LSM determination was available after SVR, the median LSM was 14.4 [IQR: 9.3 – 19.5] at inclusion, vs 9.3 [IQR: 6.4 – 17.8] at the last measurement. Among these patients, 58 had an unfavorable Baveno VI status at inclusion which subsequently became favorable in 17 (29.3%) of them. None of these patients displayed any progression of PHT, and five (8.6%) whose Baveno VI status remained unfavorable during follow-up.

Factors associated with a progression of PHT under multivariate analysis

Factors associated with PHT progression during follow-up under multivariate analysis are shown in Table 2 and 3. An initially unfavorable Baveno VI status, grade 1 EV at inclusion, GGT, creatinine and bilirubin not within the normal range, a low PT level, diabetes, and an absence of viral suppression at endpoint were independently associated with PHT progression in the final multivariate model (Table 2). Considering the patients who experienced viral suppression, only GGT levels, prothrombin time and initial EV grade remained independently associated with a progression of PHT (Table 3). The same factors were retrieved in sensitivity analyses when excluding patients with grade 2/3 EV at admission (Supplementary Table 12a and 12b).

Survival

Out of the total of 891 patients, 111 (12.5%) died during follow-up. The principal causes of death as a function of virological status and initial Baveno VI status are shown in Supplementary Tables 13a and 13b. Overall survival at 1, 3 and 5 years reached 99.3%, 99.3% and 98.3%, respectively, among the

patients with an initially favorable Baveno VI status in whom viral suppression was obtained at inclusion or during follow-up, vs 100%, 97.0% and 92.7% among the patients with an initially favorable Baveno VI status in whom viral suppression was not obtained, vs 99.3%, 97.5% and 97.5% among the patients with an initially unfavorable Baveno VI status in whom viral suppression was obtained at inclusion or during follow-up, vs 98.4%, 92.0% and 81.6% among the patients with an initially unfavorable Baveno VI status in whom viral suppression was not obtained ($p<0.001$) (Figure 4). An older age, the initial EV grade, the initial Baveno VI status, whether viral suppression was achieved or not, the platelet count, baseline LSM, the severity of liver disease, as well as arterial hypertension, any history of cardiovascular events or a past history of malignancy were significantly associated with overall survival under univariate analysis (Supplementary Table 14). After adjusting for the initial EV grade, all these factors remained significantly associated with overall survival. Under multivariate analysis, age, an absence of viral suppression, an initially unfavorable Baveno VI status, past excessive alcohol consumption, low albumin levels and elevated GGT levels remained independently associated with poorer overall survival (Supplementary Table 15). The results were similar after adjusting to the initial grade of EV.

DISCUSSION

With this study, we were able to validate the Baveno VI guidelines for the screening of EV in a large prospective cohort of patients with biopsy-proven B or C viral cirrhosis, even in the event of viral suppression. Moreover, the lengthy follow-up of the CirVir cohort and sequential assessment of PHT-related parameters enabled us to show that viral suppression and an absence of EV at screening were the key drivers determining an absence of PHT progression. Lastly, we were able to validate the clinical value of the Baveno VI criteria in terms of the follow-up of these patients, even in the event of viral suppression.

Since they were published in 2015, the Baveno VI criteria for the screening of PHT have been validated several times in the context of different series of patients with various etiologies of cirrhosis [21, 22, 26] and in one meta-analysis [23]. These series did not focus on patients with viral cirrhosis who achieved viral suppression, and the originality of our study resides in this point, as far as the validation of the criteria for screening is concerned. This is an important issue, as the vast majority of patients with viral cirrhosis will now exhibit a control of viral replication in the case of HBV, or viral eradication in HCV patients. The Baveno VI criteria include LSM values which generally decrease after SVR[27], although this is probably not a reflection of a rapid reduction in PHT, as was shown recently in a population of patients with relatively severe cirrhosis who were cured of HCV using DAAs[8]. In this latter study, 78% of patients still displayed clinically significant PHT (HVPG higher than 10 mmHg) after SVR. It should also be noted that LSM values remained higher than 20 kPa and the platelet count lower than 150,000/mm3 in all these patients, so the validity of the Baveno VI criteria was not called into question in this situation.

We have provided the first longitudinal validation of the Baveno VI criteria in terms of the long-term surveillance of EV. Although the recommendations for screening were based on strong evidence, the surveillance of EV was more arbitrarily determined and reliant on the views of experts. First, significantly fewer patients with a favorable Baveno VI status displayed a progression of PHT, which is reassuring in terms of the ability of the criteria to select a low-risk group. However, the issue of

when physicians should order an upper endoscopy was still unresolved. The suggestion to look for a rise in LSM values and/or a fall in the platelet count was intuitive and based solely on subjective clinical experience rather than scientific data.

There was only a trend in a decrease in PHT progression in patients in whom Baveno VI status remained favorable (p=0.15) : however, in our series of 136 patients in whom sequential LSM assessments were performed, out of the 548 included in the follow-up study, only four patients in the favorable Baveno VI status group experienced a progression of PHT and all four saw a worsening of their Baveno VI status. Although one should remain cautious because of this small sample, it is tempting to speculate that the recommendation to monitor changes to LSM and platelet counts might provide accurate data in clinical routine practice.

Another novelty in the Baveno VI guidelines concerned the method adopted to monitor EVs when the etiological agent of cirrhosis is controlled and no other causes or liver comorbidities can be found. Surveillance has been reduced, with the delay between endoscopies increasing from one to two years in patients with grade 1 EV and from two years to three in those without any. This recommendation was based on several studies which had shown a reduction in PHT after a viral cure affecting HVPG [8-11, 28], the incidence of varices [13, 14], and more recently the progression of PHT in a small series of HBV cirrhotic patients [15]. Underlying this point is a fear of delaying upper endoscopies in asymptomatic patients who have been cured of their viral disease; both they and their physicians may be reluctant to undertake an invasive exploration that will be futile in the majority of cases. The idea of focusing endoscopies in a higher-risk group is therefore understandable, although it was not evidenced-based at the time of Baveno VI conference. To our knowledge, we have now provided the most wide-ranging description of PHT progression in a prospective series of patients with viral cirrhosis, with a long follow-up, where a significant proportion of patients had experienced viral suppression. We were able to show that viral suppression was independently associated with an absence of PHT progression; more interestingly, we were able to highlight the fact that even after viral suppression, PHT progression could occur in patients who were already displaying grade 1 EV beforehand. These two findings are consistent with those obtained by Di Marco et al., who stressed the fact that if a certain degree of PHT is present, liver decompensation will occur even once the causal agent has been

cured[29]. This argues in favor of treating all patients for HCV or HBV as rapidly as possible, particularly in cases of overt cirrhosis. Moreover, we were able to validate the periodicity of endoscopies proposed by the Baveno VI conference as PHT progression in virally suppressed patients reached 4.1% at three years in patients with no EV at screening, and 10.1% at two years in patients with grade 1 EV.

Alongside an analysis of events in the low-risk group of patients with favorable Baveno VI status, another important and original point concerned virally suppressed patients i.e. those with an unfavorable Baveno VI status before viral suppression who experience a reduction in LSM and/or a rise in the platelet count after viral suppression, thus inducing a change from an unfavorable to favorable Baveno VI status. As stated previously, whether these modifications could translate into a reduction in PHT is still under debate. We can nevertheless hypothesize from the study by Lens et al.[8] that a cut-off point of 20 kPa for LSM is very low, and allows the selection of a subgroup of patients with a very small probability of displaying significant PHT. If expanding the Baveno VI criteria might be useful in order to avoid more endoscopies, there may be doubts that this will be a reliable strategy in the particular situation of more severe compensated patients whose Baveno VI status only becomes favorable after viral suppression[30]. We observed that a favorable Baveno VI status, measured after viral suppression in 64 patients, was associated with a complete absence of PHT progression. More importantly, in the 17 patients whose Baveno VI status became favorable after viral suppression, no progression of PHT was observed, even though they had belonged to the high-risk group before their HCV was cured. Of course, because of the small number of patients involved, it is essential to confirm this finding.

The main pitfall of this work concerned its design as a prospective cohort study. The physicians were asked to follow French guidelines[31] regarding the screening and surveillance of PHT, which had not been modified before the Baveno VI conference. However, it remained a real-life study and its protocol did not focus on PHT. All patients included had biopsy-proven cirrhosis, which is different to the current context of use of Baveno VI criteria and to the context from where the criteria were derived, i.e. all-comers identified as having cirrhosis (or at least compensated advanced chronic liver disease) based on liver stiffness, which may differ from those pre-selected for biopsy. However, as far

as a high sensitivity is required to rule-out screening or follow-up endoscopies, we believe that our results would be transferable to less severe patients.

Moreover, the annual sequential assessment of LSM was not recommended at the time. Overall, 31% of patients included in this cohort underwent endoscopic screening for EV at inclusion within the periods required for inclusion in our study, and 63% were subject to endoscopic surveillance. Although far from perfect, this proportion was higher than expected. This was probably a beneficial effect of the French Consensus Conference on PHT which took place in Paris in 2003[31]. Baseline characteristics of patients were not different between the patients included and excluded in the follow-up study, except for higher creatinine levels and lower PT in included patients, and a slightly higher proportion of patients who had past or ongoing antiviral therapy. This probably suggests that included patients displayed a slightly more severe liver disease, which is reassuring when considering the low percentage of PHT progression after viral suppression. Regarding outcomes, as far as bleeding from PHT was concerned, outcome was different between the 2 groups, patients included in the follow-up experiencing more bleeding during follow-up. This again argues in favor of a more severe subset of patients, who were more strictly followed-up. In our opinion, this suggests that progression of PHT could have been overestimated in this study, where patients all underwent liver biopsy, and the more severe were followed-up. This strengthens our findings of a very low progression of PHT in patients exhibiting viral suppression and favorable Baveno VI status, and in our opinion, does not question the transferability of those results into a less severe population.

When the periodicity of EV surveillance was considered, the median period elapsing between endoscopies was 32.1 months [IQR: 23.2 – 39.6] in patients with no EV and 22.1 months [IQR: 14.2 – 31.6] in patients with grade 1 EV. Although longer than recommended, these figures enable us to be confident regarding our results on PHT progression. However, we cannot exclude an underestimation of PHT progression, either because one third of patients did not undergo endoscopic surveillance, or because the delay between endoscopies was slightly more important than recommended. On the other hand, there is probably a high inter-observer variability in differentiating grade 2 and 3 varices. The reproducibility in this study might have been even lower, since endoscopies were performed in clinical routine. This is why we also performed sensitivity analyses excluding grade 2 and 3 varices, where we

found the same predictive factors of PHT progression. On the other hand, we could have overestimated the progression of PHT in patients with hepatic decompensation, as the median delay between endoscopies was significantly lower in the 74 who had an endoscopy realized after decompensation (25.7 months [IQR: 14.7 – 37.2] vs 32.0 months [IQR: 21.1 – 41.2], p=0.029). Regarding LSM, the study was designed in 2004, and the physicians did not have specific recommendations on which probe to use (M or XL, as far as 55% of patients were overweighted). There was no mention of the interpretability of LSM measurements. This also constitutes a bias of the study which has to be acknowledged.

We are convinced that reducing surveillance in selected patients will enable the restriction of endoscopies to those who require close surveillance and avoid non-compliance with the guidelines due to too many futile explorations. Looking at our results, overall, only 10.1% of virally suppressed patients with grade 1 varices at baseline developed portal hypertension progression within 2 years, which was mostly due to the growth of varices. Thus, it would require about 9.9 upper GI endoscopies (or even more) to diagnose one patient in whom varices progressed and needed/required treatment. The NNT for beta blockers in primary prophylaxis in patients with medium to large varices is 6 [32, 33] Thus, it might require more than 59.4 upper GI endoscopies (and BB treatment) to prevent one episode of variceal bleeding. These numbers substantially worsen if looking at patients without varices at baseline, who are at considerably lower risk according to the results of your study. This highlights the need for non-invasive criteria to reduce the number of futile upper GI endoscopies and underlines the importance of studies validating these criteria in the setting of viral suppression/eradication.

Although viral suppression is a key factor in ensuring an absence of PHT progression, other factors such as metabolic syndrome and alcohol consumption will of course impact the natural history of PHT[34]. This was stated in the guidelines such that no co-factors should be present in a patient whose surveillance is to be reduced.

In conclusion, we have shown that in the prospective ANRS CO12 CirVir cohort the Baveno VI guidelines regarding the screening and follow-up of EV are valid in patients with compensated viral cirrhosis, even in the event of viral suppression. An upper endoscopy is no longer necessary in the

subgroup of low-risk patients, and viral suppression profoundly modifies the natural course of PHT in cirrhotic patients.

FIGURE LEGENDS

Figure 1- Distribution of varices as a function of initial Baveno VI status. **Figure 1a**: all patients. The distribution of varices in the 221 patients with a favorable Baveno VI status at inclusion was: no EV: 205 (92.8%), grade 1 EV: 13 (5.9%) and grade 2/3 EV: 3 (1.3%). In the 670 patients with an unfavorable Baveno VI status at inclusion, the distribution of varices was: no EV: 466 (69.6%), grade 1 EV: 135 (20.1%) and grade 2/3 EV: 69 (10.3%) ($p<0.001$). The distribution of varices differed significantly between the two groups of patients. **Figure 1b**: 200 patients with viral suppression. The distribution of varices in the 80 patients with a favorable Baveno VI status at inclusion was: no EV: 74 (92.5%), grade 1 EV: 6 (7.5%) and grade 2/3 EV: 0. In the 120 patients with an unfavorable Baveno VI status at inclusion, the distribution of varices was: no EV: 94 (78.3%), grade 1 EV: 15 (12.5%) and grade 2/3 EV: 11 (9.2%) ($p=0.004$).

Figure 2- Progression of PHT as a function of virological response and initial EV grade.

The cumulative progression of PHT at 1, 3 and 5 years was 1.8 %, 4.1% and 4.1% in patients with no EV at inclusion in whom viral suppression was achieved, 0%, 15.7% and 15.7% in patients with grade 1 EV at inclusion in whom viral suppression was achieved, 2.2%, 7.7% and 14.2% in patients with no EV at inclusion in whom viral suppression was not achieved and 2.7%, 31.7% and 52.6% in patients with grade 1 EV at inclusion in whom viral suppression was not achieved ($p<0.001$). Viral suppression and an absence of EV at inclusion were associated with a reduced risk of PHT progression.

Figure 3- Progression of PHT in patients who exhibited viral suppression at inclusion or during follow-up, as a function of Baveno VI status at the time of viral suppression. PHT progression at 1, 3 and 5 years was null in these patients, vs 3.4%, 8.1% and 8.1% in the 164/228 patients (71.9%) with an unfavorable Baveno VI status ($p=0.007$).

Figure 4. Overall survival as a function of viral suppression and initial Baveno VI status.

Overall survival at 1, 3 and 5 years reached 99.3%, 99.3% and 98.3% in the patients with an initially favorable Baveno VI status in whom viral suppression was achieved at inclusion or during follow-up, vs 100%, 97.0% and 92.7% in the patients with an initially favorable Baveno VI status in whom viral suppression was not achieved, vs 99.3%, 97.5% and 97.5% in the patients with an initially unfavorable

Baveno VI status in whom viral suppression was achieved at inclusion or during follow-up, vs 98.4%, 92.0% and 81.6% in the patients with an initially unfavorable Baveno VI status in whom viral suppression was not achieved ($p<0.001$).

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Figure 1A

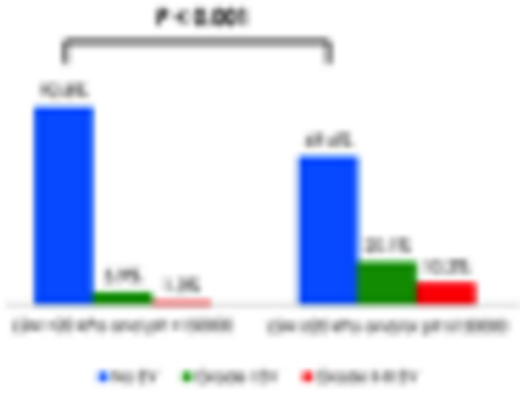
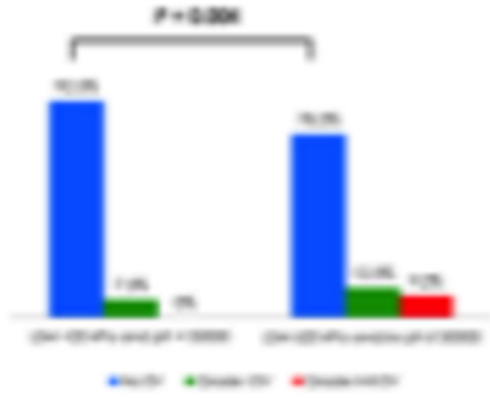
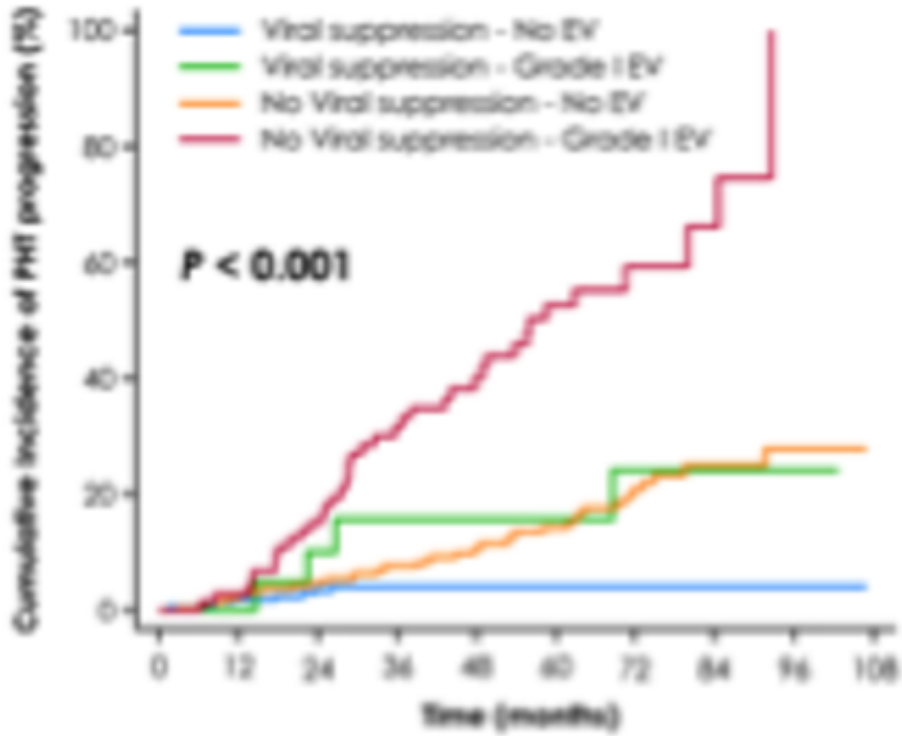


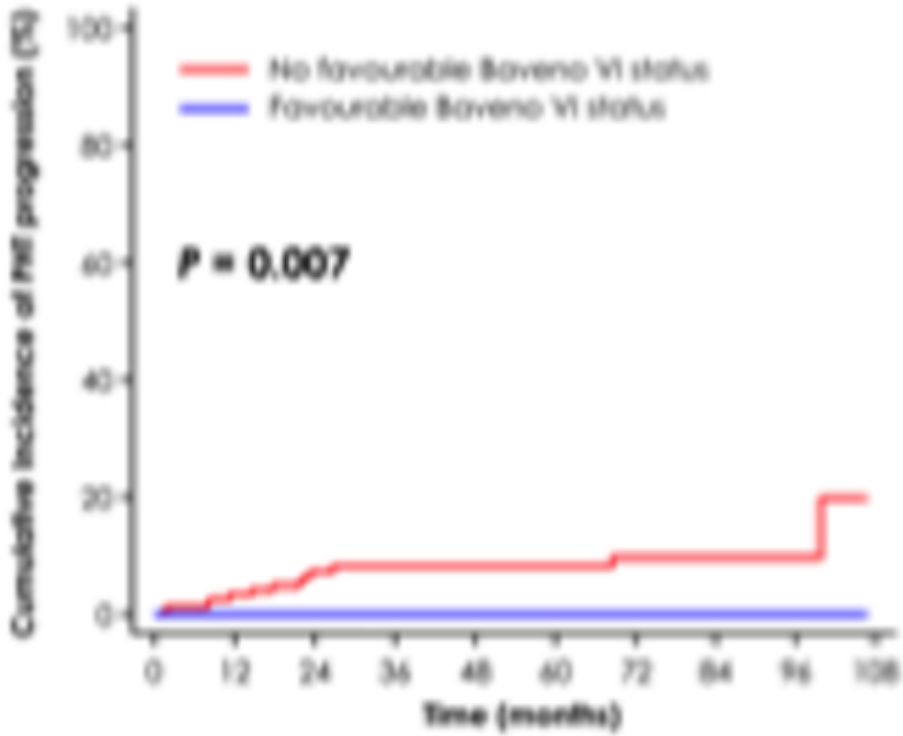
Figure 1B



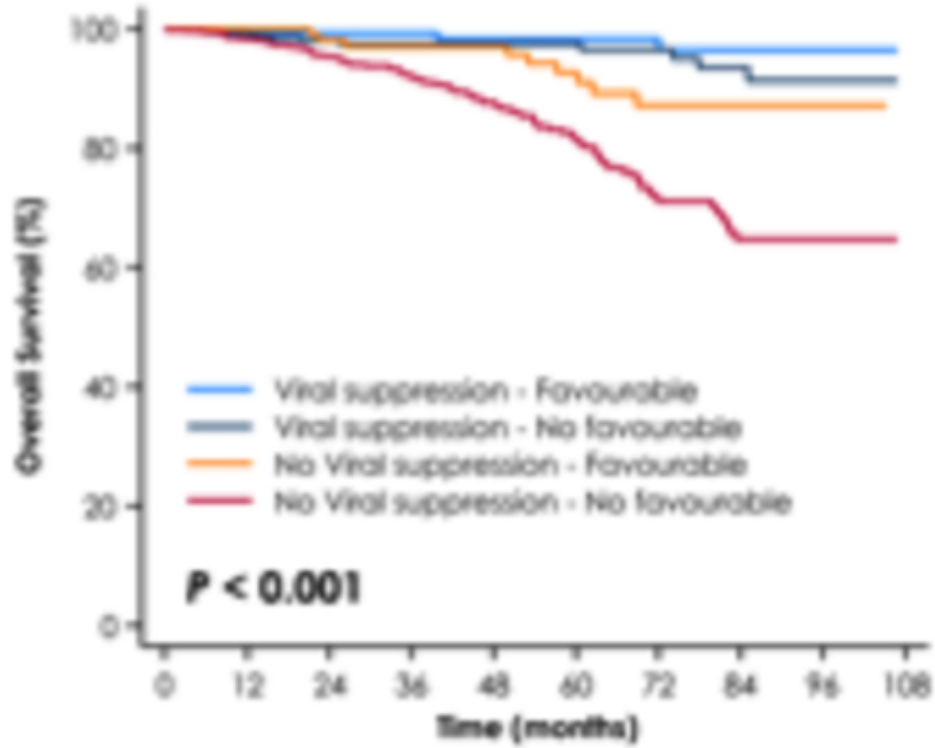


Number at risk (events)

Viral suppression - No EV	244	(4)	201	(3)	170	(1)	151	(0)	133	(0)	114	(0)	95	(0)	58	(0)	34	(0)	5	
Viral suppression - Grade I EV	27	(0)	23	(2)	14	(1)	13	(0)	10	(0)	10	(1)	9	(0)	4	(0)	2	(0)	0	
No Viral suppression - No EV	291	(6)	254	(6)	227	(7)	193	(5)	158	(6)	108	(7)	71	(3)	40	(1)	21	(0)	2	
No Viral suppression - Grade I EV	75	(2)	72	(5)	59	(11)	40	(5)	32	(6)	21	(2)	8	(1)	5	(2)	0	(0)	0	



Number at risk (events)																					
No favourable Baveno VI	164	(5)	135	(5)	112	(1)	98	(0)	84	(0)	72	(1)	55	(0)	32	(0)	14	(1)	2		
Favourable Baveno VI	64	(0)	43	(0)	39	(0)	38	(0)	35	(0)	30	(0)	40	(0)	32	(0)	22	(0)	3		



Number of risk (events)																				
Viral suppression – Favourable Bioviro VI	157	(1)	135	(0)	117	(0)	104	(1)	87	(0)	71	(0)	54	(1)	37	(0)	25	(0)	3
Viral suppression - No favourable Bioviro VI	329	(2)	254	(3)	209	(1)	173	(0)	138	(0)	104	(1)	75	(2)	46	(1)	24	(0)	3
No Viral suppression – Favourable Bioviro VI	126	(0)	114	(2)	99	(1)	88	(0)	74	(2)	53	(2)	36	(0)	18	(0)	7	(0)	1
No Viral suppression - No favourable bioviro VI	513	(8)	442	(13)	382	(12)	302	(13)	240	(14)	163	(16)	94	(7)	58	(0)	23	(0)	2

Table 1: Characteristics of the 891 patients at inclusion as a function of their initial Baveno VI status (univariate analysis)

Characteristics at inclusion	Number of patients	Total n=891	Plat. Count≤150 and/or LSM≥20 n=670 (75.2%)	Plat. Count>150 and LSM<20 n=221 (24.8%)	P–value
Male gender (n, %)	891	601 (67.5)	432 (64.5)	169 (76.5)	**0.001**
Age (years) (median, IQR)	891	53.9 [47.4 – 63.3)	54.1 [47.4 – 63.5]	53.7 [47.6 – 62.1]	0.53
Etiology	891				**<0.001**
HCV (n, %)		772 (81.0)	557 (83.1)	165 (74.7)	
HBV (n, %)		148 (16.6)	94 (14.0)	54 (24.4)	
HCV-HBV (n, %)		21 (2.4)	19 (2.9)	2 (0.9)	
HIV Co-infection (n, %)	882	43 (4.9)	29 (4.4)	14 (6.3)	0.24
Use of beta-blockers at inclusion (n, %)	888	60 (6.8)	53 (8.0)	7 (3.2)	**0.014**
Viral suppression at inclusion (n, %)	891	200 (22.5)	120 (17.9)	80 (36.2)	**<0.001**
Past excessive alcohol consumption (n, %)	852	254 (29.8)	199 (31.3)	55 (25.5)	0.11
Ongoing alcohol consumption (g/day)	833				0.69
0 or <10 (n, %)		765 (91.8)	568 (91.6)	197 (92.5)	
≥10 (n, %)		68 (8.2)	52 (8.4)	16 (7.5)	
BMI (kg/m²) (median, IQR)	797	25.5 [22.7 – 28.3]	25.8 [23.0 – 28.6]	24.6 [22.2 – 27.7]	**<0.001**
BMI (class)	797				**0.006**
<25 (n, %)		355 (44.5)	243 (41.3)	112 (53.6)	
[25 ; 30[(n, %)		312 (39.2)	240 (40.8)	72 (34.4)	
≥ 30 (n, %)		130 (16.3)	105 (17.9)	25 (12.0)	
Diabetes (n, %)	891	159 (17.9)	122 (18.2)	37 (16.7)	0.62
Dyslipidemia (n, %)	891	55 (6.2)	42 (6.3)	13 (5.9)	0.84
Arterial hypertension (n, %)	891	236 (26.5)	188 (28.1)	48 (21.7)	0.06
Past history of CV events (n, %)	891	76 (8.5)	56 (8.4)	20 (9.1)	0.75
Metabolic syndrome (n, %) **	891	144 (16.2)	114 (17.0)	30 (13.6)	0.23
Past history of malignancy (n, %)	891	41 (4.6)	34 (5.1)	7 (3.2)	0.24
Platelet count (10^3/mm^3) (median, IQR)	890	124.5 [92.0 – 162.0]	108.0 [83.0 – 133.0]	194.0 [174.0 – 220.0]	**<0.001**
Platelet count (10^3/mm^3)	890				**<0.001**
≤150 (n, %)		626 (70.3)	626 (93.6)	0	
> 150 (n, %)		264 (29.7)	43 (6.4)	221 (100)	
LSM (median, IQR)	597	15.3 [10.3 – 23.6]	21.1 [14.2 – 28.5]	10.4 [8.1 – 13.4]	**<0.001**
LSM < 20 kPa (n, %)	597	390 (65.3)	169 (45.0	221 (100)	**<0.001**
AST (IU/L) (median, IQR)	891	58.0 [35.0 – 96.0]	67.0 [42.0 – 103.0]	38.0 [29.0 – 63.0]	**<0.001**
ALT (IU/L) (median, IQR)	891	64.0 [35.0 – 112.0]	71.5 [40.0 – 118.0]	44.0 [27.0 – 85.0]	**<0.001**
Creatinine (µmol/L) (median, IQR)	886	73.0 [62.0 – 84.0]	71.0 [61.9 – 82.0]	76.0 [65.0 – 89.6]	**<0.001**
GFR (MDRD) (median, IQR) [b]	886	94.7 [80.0 – 112.0]	96.1 [81.2 – 113.7]	90.8 [78.0 – 104.2]	**0.005**
GGT (IU/L) (median, IQR)	890	88.0 [45.0 – 163.0]	101.0 [53.0 – 179.0]	57.0 [33.0 – 105.0]	**<0.001**
Serum albumin (g/L) (median, IQR)	886	41.5 [38.1 – 44.9]	40.5 [37.6 – 44.0]	43.7 [40.7 – 46.0]	**<0.001**
Total bilirubin (µmol/L) (median, IQR)	890	12.0 [8.0 – 17.0]	12.0 [9.0 – 18.0]	10.0 [8.0 – 13.0]	**<0.001**
Prothrombin time (%) (median, IQR)	874	87.0 [78.0 – 96.0]	86.0 [76.0 – 94.0]	94.0 [86.0 – 100.0]	**<0.001**
Esophageal varices	891				**<0.001**
No (n, %)		671 (75.3)	466 (69.6)	205 (92.8)	
Grade 1 (n, %)		148 (16.6)	135 (20.1)	13 (5.9)	
Grade 2 or 3 (n, %)		72 (8.1)	69 (10.3)	3 (1.3)	
Past or ongoing antiviral treatment (n, %)	888	822 (92.6)	614 (91.8)	208 (95.0)	0.12

BMI: body mass index; SVR: sustained virological response; GFR: glomerular filtration rate; MDRD, modification of diet in renal disease; CV: cardiovascular

[a] PROPANOLOL or NADOLOL intake

[b] GFR = 186.3 × (creatinine (µmol/L) / 88.4)$^{-1.154}$ × age$^{-0.203}$ × k; k = 1 for men and k = 0.742 for women

** defined by the hepatologist

Table 2. Features associated with PHT progression in patients with compensated HCV- or HBV-related cirrhosis according to the Cox proportional hazards model (results of multivariate analyses) applied to the whole population.

Characteristics	HR [95%CI]	P–value
Etiology		**0.045**
HCV	Ref	
HBV	1.52 [0.61 ; 3.80]	0.37
HCV-HBV	4.24 [1.29 ; 13.92]	**0.017**
Viral suppression*	0.28 [0.14 ; 0.58]	**0.001**
Favorable initial Baveno VI status	0.16 [0.06 ; 0.45]	**0.001**
Diabetes	2.35 [1.49 ; 3.71]	**<0.001**
GGT > ULN	5.13 [1.84 ; 14.31]	**0.002**
Creatinine (µmol/L)	1.00 [1.00 ; 1.01]	**0.020**
Total bilirubin > 17µmol/L	1.92 [1.26 ; 2.95]	**0.003**
Prothrombin time ≤ 80%	1.56 [1.03 ; 2.38]	**0.037**
Esophageal varices at inclusion		**<0.001**
No	Ref	
Grade 1	3.11 [2.01 ; 4.82]	**<0.001**
Grade 2 or 3	1.18 [0.58 ; 2.43]	0.65

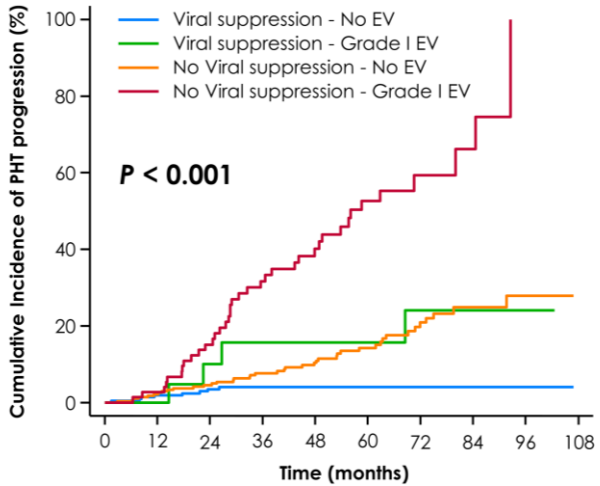
ULN: Upper Limit of Normal
* time-dependent covariate

Table 3. Features associated with PHT progression in patients with compensated HCV- or HBV-related cirrhosis according to the Cox proportional hazards model (results of multivariate analyses) applied to the patients experiencing viral suppression

Characteristics	HR [95%CI]	P–value
GGT > ULN	9.42 [1.18 ; 75.12]	**0.034**
Prothrombin time ≤ 80%	6.72 [1.87 ; 24.14]	**0.003**
Esophageal varices		**0.014**
No	Ref	
Grade 1	7.15 [1.90 ; 26.91]	**0.004**
Grade 2	1.80 [0.35 ; 9.13]	0.48

ULN: Upper Limit of Normal

Progression of Portal Hypertension as a function of virological response and initial EV grade (Prospective CirVir cohort)



N=548

Gastroenterology