ORIGINAL ARTICLE

Screening and surveillance of oesophageal varices in patients with HCV-positive liver cirrhosis successfully treated by direct-acting antiviral agents

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Abstract

Background & Aims: limited evidence is available to guide hepatologists regarding endoscopic surveillance of oesophageal varices (EV) in Hepatitis C Virus (HCV)-positive cirrhotic patients achieving a sustained virologic response. To address these issues, we conducted a long-term prospective study on 427 HCV-positive cirrhotic patients successfully treated by Direct Antiviral Agents (DAAs).

Methods: Patients were divided into two groups according to their baseline Baveno VI status: Group 1 (92, 21.5%, favourable Baveno VI status) and Group 2 (335, 78.5%, unfavourable Baveno VI status). Each patient underwent baseline endoscopy and was endoscopically monitored for a median follow-up of 65.2 months according to Baveno VI recommendations.

Results: About 4.3% of Group 1 patients showed baseline EV compared with 30.1% of Group 2 patients ($p < .0001$). No patients belonging to Group 1 without baseline EV developed EV at follow-up endoscopy compared with 6.5% in Group 2 patients ($p = .02$); 69/107 (64.5%) patients with baseline EV showed small varices. During the endoscopic follow-up, EV disappeared/improved in 36 (33.6%), were stable in 39 (36.4%) and worsened in 32 (29.9%) patients, all belonging to Group 2 ($p = .001$). Improvement in Baveno VI status was observed in 118/335 (35.2%, $p < .0001$) of Group 2 patients and among those without pre-therapy EV, none developed EV throughout the follow-up.

Conclusions: HCV-positive cirrhotic patients cured by DAAs showing baseline favourable Baveno VI status and no worsening during follow-up can safely avoid endoscopic screening and surveillance. Patients having unfavourable Baveno VI status without baseline EV who improve their status may suspend further endoscopic surveillance.

1 | INTRODUCTION

Hepatitis C Virus (HCV)-positive cirrhotic patients achieving a sustained virologic response (SVR) by Direct-Acting Antiviral Agents (DAAs) show a progressive decrease in portal pressure during follow-up reducing the risk of variceal bleeding.[1] However, clinically significant portal hypertension (CSPH) may persist in a significant proportion of them.[2–6] This observation has an important clinical impact by influencing our policy of screening and surveillance of oesophageal varices (EV) in cured patients. Current guidelines[7–9] recommend the use of non-invasive techniques such as transient elastography (TE) and platelet count to reduce endoscopic screening: patients showing a liver stiffness measurement (LSM) <20 kPa and platelet count >150.000/mm^3 can safely avoid endoscopy having a very low risk (<5%) of varices needing treatment (VNT).[10,11] According to the Baveno VI Consensus Workshop, these patients—defined as Baveno VI status favourable—can be safely followed up by yearly repetition of TE and platelet count.[7] However, data supporting this recommendation are still scarce.[12–14]

What it is still matter of debate is the optimal timing for surveillance endoscopy in cured patients showing unfavourable pre-therapy Baveno VI status. According to the international guidelines,[7,9] in compensated patients without comorbidities and no baseline EV or small varices prior to therapy, endoscopy should be repeated at 3- and 2-year intervals respectively. However, the strength of recommendation and level of evidence are very low. A recent clinical practice update-expert review[15] by the American Gastroenterological Association (AGA) suggests follow-up endoscopy after 2–3 years in patients with no EV on prior screening examination and no further surveillance if EV are not found; patients with small EV at baseline should undergo follow-up endoscopy after 2–3 years and no further surveillance if EV unchanged or smaller.

In order to individuate the optimal type, frequency and length of EV surveillance in relation to the clinical status of the patients, we conducted a long-term prospective study on HCV-positive patients with compensated cirrhosis successfully treated by DAAs aiming at monitoring the course of EV according to the Baveno VI criteria[7] as well as the impact on portal hypertension (PH) exerted by changes of Baveno VI status.

2 | PATIENTS AND METHODS

This prospective cohort study included all consecutive patients with Child A-B HCV cirrhosis treated by DAAs according to the European Association for the Study of the Liver (EASL) guidelines[16] in the

Lay Summary

- Non-invasive criteria suggested by the Baveno VI and the Baveno VI expanded guidelines avoid screening endoscopies in a significant subset of cirrhotic patients, but their application on long-term variceal surveillance in patients achieving sustained virologic response (SVR) by direct-acting antiviral agents (DAA) is largely unknown.
- Whether further endoscopic surveillance is required in cirrhotics obtaining SVR with no oesophageal varices (EV) on prior screening examination and which is the optimal endoscopic timing in patients with pre-therapy EV is still debated.
- In this study, we showed that patients having persisting favourable Baveno VI status may not undergo endoscopic surveillance, while patients with unfavourable Baveno VI status and no baseline EV who improve their status may suspend further endoscopic surveillance.
- Patients with pre-therapy unfavourable Baveno VI status and small VE should maintain follow-up endoscopy at 2-year interval.

Gastrohepatologic Clinic of Molinette Hospital, Turin, Italy, from 1 January 2015 to 31 December 2016. Inclusion criteria were as follows: >18 years; positive HCV-RNA by polymerase chain reaction (PCR); liver cirrhosis assessed by TE and aspartate aminotransferase (AST) to platelet ratio (APRI) score. Exclusion criteria were as follows: lack of written informed consent, TE not feasible or unreliable measurement, patients on waiting list for orthotopic liver transplant (OLT), post-OLT patients, past or current history of hepatocellular carcinoma (HCC), past or current episodes of ascites and/or encephalopathy, prophylactic banding of EV, previous episodes of variceal bleeding treated by endoscopic banding, concomitant liver diseases such as haemochromatosis, Wilson's disease, drug-related liver disease, autoimmune hepatitis, HBsAg carriership, human immunodeficiency virus (HIV) infection, primary biliary cholangitis and alpha-1-antitrypsin deficiency. Out of 596 consecutive patients considered for treatment with DAAs, 478 (80.2%) fulfilled the above-mentioned criteria and agreed to participate; 15 out of 478 recruited patients (3.1%) did not achieve SVR and were excluded from the study. Out of 463 sustained responders, 36 (7.8%) were lost to follow-up. Therefore, the final analysis was performed in 427 cirrhotic patients with SVR. Patients' flow is reported in Figure 1.

At baseline, a complete medical history and physical examination was undertaken and the following data were obtained from each patient: age, gender, ethnicity, smoking habits, alcohol intake, body mass index (BMI), waist circumference (WC), duration of HCV infection and relevant comorbidities The following data on laboratory parameters were also recorded to define baseline characteristics: complete blood count, routine liver biochemistry (alanine aminotransferase [ALT] and AST, total bilirubin, albumin, alkaline phosphatase [APH], gamma glutamyltranspeptidase [GGT]) international normalized ratio [INR]), creatinine, fasting plasma glucose [FPG], total cholesterol and HDL, triglycerides, HCV genotype and viral load [AmpliPrep®/ COBAS Taqman® HCV test, Roche Diagnostics, Basel, Switzerland]).

The severity of liver fibrosis was determined within 3 months prior to inclusion into the study by non-invasive (AST to platelet ratio [APRI] and TE) methods. Cut-offs used to diagnose cirrhosis were >1.5 for APRI test and ≥14 kPa for TE. The reliability criteria for LSM were as follows: 10 valid measurements achieved with a success number ≥60% and an interquartile range-to-median ratio ≤30%. A minimum of 3 h fasting was required. Abdominal ultrasound (US) was performed in each patient at baseline in order to exclude HCC.

Patients were stratified according to the Child-Turcotte-Pugh classification and Model for End-Stage Liver Disease [MELD]; LSM and platelet count were obtained in each patient within 3 months before starting treatment in order to establish the Baveno VI status.[7]
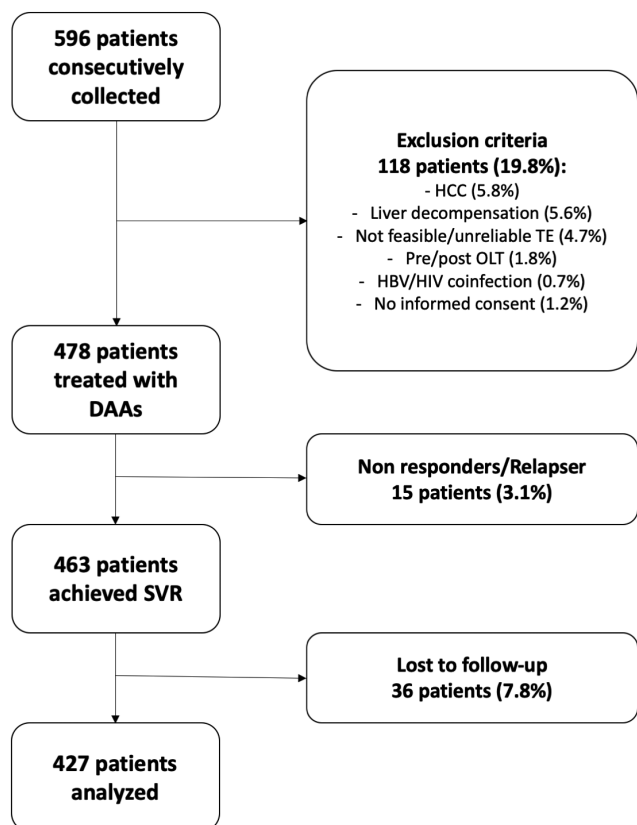

FIGURE 1 Flow of the recruited patients. DAAs, direct-acting antiviral agents; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; OLT, orthotopic liver transplantation; TE, transient elastography

2.1 | Follow-up

When the study was approved, upper endoscopy was still mandatory in cirrhotic patients to assess the presence and grading of oesophageal/gastric varices. For this reason, all patients underwent oesophagogastroduodenoscopy within 3 months before starting therapy; patients with F2/F3 EV were given Non-Selective Beta-Blockers (NSBB). If intolerant or not responding to NSBB, patients underwent prophylactic banding of EV and were excluded from the study. In order to validate the surveillance timing suggested by Baveno VI Consensus Workshop in a population composed by HCV-positive compensated cirrhotics successfully treated by DAAs, we recommended the following endoscopic approach: 1) surveillance endoscopy at 3-year intervals in patients with no varices at baseline endoscopy 2) surveillance endoscopy at 2-year intervals in patients with small varices (F1) at baseline endoscopy. Cirrhotic patients with large varices (F2/F3) on NSBB prophylaxis were planned to undergo yearly endoscopy. Variceal worsening (or PH progression) was defined as the occurrence of EV in patients with no prior EV or large EV in previous carriers of small EV, the occurrence of grade 3 EV in patients with baseline grade 2 EV, or the onset of variceal bleeding.

Control visits were planned at 6-month intervals after achieving SVR and patients were followed until OLT, death or until the end of June 2021. Patients were also censored at the moment of HCC occurrence. Mortality was registered as liver related or non-liver related. At each control visit, medical history and physical examination were performed; liver function tests, platelet determination, HCV-RNA assessment and liver US were recorded as well as the occurrence of liver-related events [LRE] (ascites, variceal bleeding, hepatic encephalopathy and HCC).

More than 90% of all endoscopic procedures were performed by a pool of experienced endoscopists (A.M., W.D.V., C.G., S.C., C.D.A., M.B., E.R., M.P., A.M, T.S..) working in our Endoscopy Unit and adopting the Beppu's classification of EV.[17] All of them were blinded to the study design. For the aims of the study, EV were defined as 1) no EV 2) small EV corresponding to grade 1 EV no needing treatment 3) large EV corresponding to grade 2/3 EV needing treatment.

In order to check for worsening/improvement of their Baveno VI status, all patients underwent at least 1 LSM by TE during follow-up at the time of repetition of endoscopy, at variance with the Baveno VI recommendations suggesting yearly TE; the number of LSM reached 2 (IQR: 1–3) and the median delay between measurements were 24.8 months (IQR: 12.4–36.6). Platelet count was obtained during the 6-month control visits planned throughout the follow-up (number: 10 [IQR: 8–12]).

An improvement in Baveno VI status was defined as an increase in the platelet count above 150.000/mm^3 and a decrease of LSM to <20 kPa in cirrhotics with a baseline unfavourable status. A worsening of Baveno VI status was defined as the occurrence of either platelet count ≤150.000/mm^3 or LSM ≥20 kPa during follow-up in patients with a baseline favourable Baveno VI status.

The study was performed in accordance with the principles of the 1975 Declaration of Helsinki and approved by our local ethics

committee (Comitato Etico Interaziendale Città della Salute e della Scienza di Torino, Turin, Italy); written informed consent was obtained from all patients.

2.2 | Statistical analysis

Continuous variables were reported as median (Inter Quartile Range [IQR] and 95% confidence interval [CI]) or geometric mean according to the data distribution. Normality was checked by the D'Agostino–Pearson test. Categorical variables were reported as number and percentage. Comparison of continuous variables between independent groups was performed by the Mann–Whitney test or independent samples t-test according to data distribution; comparison between paired measurements was performed by the Wilcoxon test or paired samples t-test according to data distribution. Regarding the dichotomous categorical variable, a chi-squared test or McNemar test was performed for unpaired or paired analysis respectively. The association between variables was assessed by Cox proportional-hazards regression; the

strength of association was reported as hazards ratio (H.R.) and 95% CI, accordingly. The rate of favourable and unfavourable Baveno VI status patients free from varices has been presented by using Kaplan–Meier curves and the statistical differences were tested by the Mantel-Cox method. Patients not developing EV were censored at the last visit or at the moment of OLT, HCC occurrence or at the date of death.

All statistical analyses were performed using MedCalc® v.18.9.1 (MedCalc Software Ltd., Ostend, Belgium), and a p value ≤.05 was considered statistically significant.

3 | RESULTS

Baseline characteristics of patients were not different between the 36 patients lost to follow-up and the remaining patients. Neither viral late relapse nor re-infection was observed during the follow-up among the 427 included patients and the cohort had a median follow-up of 65.2 (IQR: 39.2–76.9) months at 30 June 2021, starting from the SVR achievement.

TABLE 1 Baseline epidemiological and clinical characteristics of 427 patients included

	Favourable Baveno VI status[a] N = 92 (21.5%) Group 1	Unfavourable Baveno VI status[b] N = 335 (78.5%) Group 2	p
Age (years), median [IQR]	60 [52–69.5]	61 [54–71]	.31
Males, n (%)	55 (59.8%)	199 (59.4%)	.99
Females, n (%)	37 (40.2%)	136 (40.6%)	
Ethnicity			
Caucasian, n (%)	87 (94.6%)	331 (98.8%)	.02
African, n (%)	5 (5.4%)	4 (1.2%)	
BMI, median [IQR]	24.9 [23.0–28.5]	24.9 [23.0–27.5]	.67
Abnormal waist circumference, n (%)	40 (43.5%)	128 (38.2%)	.36
Obese patients, n (%)	10 (10.9%)	34 (10.1%)	.84
Smoking status			
Never, n (%)	80 (87.0%)	307 (91.6%)	.172
Past or current smokers, n (%)	12 (13.0%)	28 (8.4%)	
Alcohol intake			
No, n (%)	87 (94.6%)	328 (97.9%)	
Yes, n (%)	5 (5.4%)	7 (2.1%)	.09
Diabetes, n (%)	13 (14.1)	65 (19.4)	.25
Metabolic syndrome, n (%)	24 (26.1%)	83 (24.8%)	.80
Arterial hypertension, n (%)	38 (41.3%)	137 (37.9%)	.55
Cardiovascular diseases, n (%)	18 (19.6%)	58 (17.3%)	.62
Kidney diseases, n (%)	6 (6.5%)	8 (2.4%)	.05
Previous NHL, n (%)	9 (9.8%)	46 (13.7%)	.31
Previous non-haematological neoplasia, n (%)	3 (3.3%)	7 (2.1%)	.51
Use of NSBB at inclusion, n (%)	1 (1.1)	36 (10.8)	.003
Sofosbuvir-based treatment, n (%)	64 (69.5)	279 (82.0)	.09

Abbreviations: BMI, body mass index; IQR, inter quartile range; NHL, Non-Hodgkin's Lymphoma; NSBB, non-selective beta-blockers (propranolol or nadolol); TE, transient elastography.

[a]Platelet count >150.000/mm^3 and TE < 20 KPa.

[b]Platelet count ≤150.000/mm^3 and/or TE≥20 KPa.

Baseline demographic, anthropometric and clinical characteristics of the cirrhotic patients divided into two groups according to their favourable (Group 1) and unfavourable (Group 2) Baveno VI status are reported in Table 1; biochemical, virological and hepatologic features of both groups are described in Table 2.

As expected, Group 2 patients showed significantly lower liver synthesis values (albumin 4.1 g/dl [IQR:3.8–4.3] vs 4.3 g/dl [IQR: 4.1–4.6], $p = .0002$, total cholesterol 130.0 mg/dl [IQR: 130.0–156.8] vs 149.0 mg/dl [IQR: 130.0–167.5], $p = .001$) and platelet count (93.0 x 10^3/mm^3 [IQR: 61.0–117.5] vs 192 x 10^3/mm^3 [IQR: 164.0–225.0], $p < .0001$); conversely, they showed a higher liver stiffness (21.3 kPa [IQR: 14.8–28.4] vs 14.4 kPa [IQR: 14.1–16.9], <0.0001) as well as more advanced liver disease (MELD 7.0 [IQR: 7.0–9.0] vs 7.0 [IQR: 6.0–7.0], $p < .0001$). A statistically significant difference regarding the presence of EV was also found between the two groups: only 4.3% of Group 1 patients showed baseline EV (three patients with small EV and one patient with F2 EV) compared with 30.1% of Group 2 patients (66 patients with small EV, 37 with large EV, $p < .0001$). The Baveno VI criteria showed a sensitivity of 96.2% (95% CI: 90.7–99.0), a specificity of 27.50% (CI: 22.7–32.7), a positive predictive value (PPV) of 30.7% (CI: 29.1–32.4) and a negative predictive value (NPV) of 95.7% (CI: 89.2–98.3) in predicting baseline EV.

Baseline PH gastropathy was found in 18 (19.5%) Group 1 patients and in 111 (33.1%) Group 2 patients ($p = .002$).

At the end of the follow-up, the overall mortality rate was higher in Group 2 patients (7.7% vs. 3.2%, $p = .37$); 8 (2.3%) patients were referred to OLT, none of them belonged to Group 1. The first hepatic decompensation event (variceal bleeding, ascites and encephalopathy) occurred in 1 out of 92 (1%) Group 1 patient and in 8/335 (2.4%, $p = .08$) Group 2 patients. Overall, 3/92 (3.2%) patients in Group 1 developed HCC during follow-up compared to 44/335 (13.1%) in

TABLE 2 Baseline biochemical, virologic and liver-related characteristics of 427 patients included

	FavourableBaveno VI status[a]N = 92 (21.5%)Group 1	UnfavourableBaveno VI status[b]N = 335 (78.5%)Group 2	p
ALT (IU/mL), median [IQR]	67.0 [44.0–119.0]	70.0 [52.0–113.8]	.46
GGT (IU/mL), median [IQR]	72.0 [35.5–125.0]	60.0 [48.0–98.8]	.67
Albumin (g/dl, median [IQR]	4.3 [4.1–4.6]	4.1 [3.8–4.3]	.0002
Total cholesterol (mg/dl), median [IQR]	149.0 [130.0–167.5]	130.0 [130.0–156.8]	.001
HDL (mg/dl), median [IQR]	40.0 [31.5–50.0]	50.0 [40.0–50.0]	.06
Triglycerides (mg/dl), median [IQR]	95.0 [76.5–114.5]	100.0 [80.0–106.8]	.75
Platelets count (×10^3/mm^3), median [IQR]	192[164.0–225.0]	93.0 [61.0–117.0]	<.0001
Platelets count (×10^3/mm^3), n (%)			
≤150	0 (0)	299 (89.3)	<.0001
>150	92 (100)	36 (10.7)	
Liver stiffness (kPa), median [IQR]	14.4 [14.0–16.9]	21.3 [14.8–28.4]	<.0001
Liver stiffness < 20 kPa (n %)	92 (100)	147 (43.9)	<.0001
Child-Turcotte-Pugh score			
A, n (%)	91 (98.9)	320 (95.5)	.139
B, n (%)	1 (1.1)	15 (4.5)	
MELD score, median [IQR]	7.0 [6.0–7.0]	7.0 [7.0–9.0]	<.0001
MELD <10, n (%)	88 (95.7)	286 (78.4)	
MELD 10–15, n (%)	3 (3.2)	71 (19.4)	.006
MELD >15, n (%)	1 (1.1)	8 (2.2)	
Oesophageal varices			<.0001
No, n (%)	88 (95.7)	232 (69.2)	
Grade 1, n (%)	3 (3.3)	67 (20.0)	
Grade 2 or 3, n (%)	1 (1.0)	36 (10.8)	
Portal hypertensive gastropathy, n (%)	17 (17.9)	141 (42.1)	<.0001

Abbreviations: ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; HDL, High-density lipoprotein; IQR, Inter Quartile Range; kPa, kilopascal; MELD, Model of End-Stage Liver Disease; TE, transient elastography

[a]Platelet count >150.000/mm^3 and TE < 20 KPa.

[b]Platelet count ≤150.000/mm^3 and/or TE≥20 KPa.

Group 2 ($p = .01$). Follow-up was censored, in patients developing HCC; therefore, LRE after HCC development were not recorded.

3.1 | EV variations

3.1.1 | No EV at baseline

The incidence of 'de novo' EV according to baseline Baveno VI status is reported in Figure 2. None out of 88 cirrhotics belonging to Group 1 without EV at baseline showed EV at 3-year follow-up endoscopy compared with 15/232 (6.5%, $p = .02$) of Group 2 patients. At the end of follow-up, 50 (16.%) out of 305 EV-free patients 3 years after achieving SVR have repeated a second upper endoscopy and none showed new-onset EV, irrespective of their initial Baveno VI status. The Baveno VI criteria had a sensitivity of 96.7% (CI: 90.9–99.3), a specificity of 26.6% (CI: 22.0–31.7), a PPV of 26.9% (CI: 25.4–28.4) and a NPV of 96.7% (90.6–98.9) in predicting EV occurrence during the follow-up.

Table 3 shows the adjusted HR for variables associated with the occurrence of EV in Group 2 patients. By multivariate analysis and after adjustment for several confounding factors (age, sex, BMI, obesity, diabetes, metabolic syndrome, albumin, AST, ALT, GGT levels, comorbidities, Child-Pugh-Turcotte and MELD staging and liver stiffness), patients who developed EV during follow-up were more frequently diabetic and showed a lower platelet count.

3.1.2 | EV at baseline

Of the 427 patients included in the study, 107 (25%) showed EV at baseline; 4 (3.7%) belonged to Group 1 and 103 (96.3%) to Group 2 ($p < .0001$). During the follow-up, out of 107 patients, 36 (33.6%) improved, 39 (36.4%) remained unchanged and 32 (29.9%) worsened.

In detail, 27/69 (39.1%) patients with pre-therapy F1 EV showed varices disappearance (1/3 of Group 1), in 32 (46.4%) EV remained unchanged (2/3 of Group 1) and in 10 (14.5%) worsened. The finding of endoscopic worsening in these 10 patients occurred at the 2-year scheduled follow-up in 6 (60%) and in 4 (40%) at the second 4-year follow-up; all patients with F1 EV worsening belonged to Group 2 and demonstrated an unfavourable clinical outcome: 3 (33.3%) developed HCC and one patient was referred to OLT.

Among 38 patients with baseline F2/F3 EV, improvement was observed in 9 (23.6%), no changes in 7 (18.4%) and worsening in 22 (57.8%). The only patient with baseline large EV belonging to Group 1 did not show significant EV changes throughout the follow-up.

Overall, variceal worsening was observed only among Group 2 patients (29.9% vs. 0%, $p = .001$).

We were not able to identify independent factors associated with PH progression by using the Cox Proportional Hazards Model (Table 4).

3.2 | Change of Baveno VI status

A worsening in Baveno VI status was found in 7/92 (7.6%, $p = .12$) Group 1 patients within a median period of 20.2 months (IQR: 6.2–44.8) and was determined in all patients by the decrease of the platelet count below the threshold of 150.000/mm^3, only two patients also showing an increase in liver stiffness above 20 kPa by TE measurement. By univariate regression analysis (multiple Cox regression analysis was not feasible owing to the low number of worsened patients), we observed that obesity (HR = 3.85, 95% CI: 1.10–22.50, $p = .04$) was significantly associated with the unfavourable change.

On the other hand, albumin level >4 g/dL was found to be a protective factor (HR = 0.10, 95% CI: 0.01–0.51, $p = .008$). Of those seven patients, one (14.2%) died owing to myocardial infarction
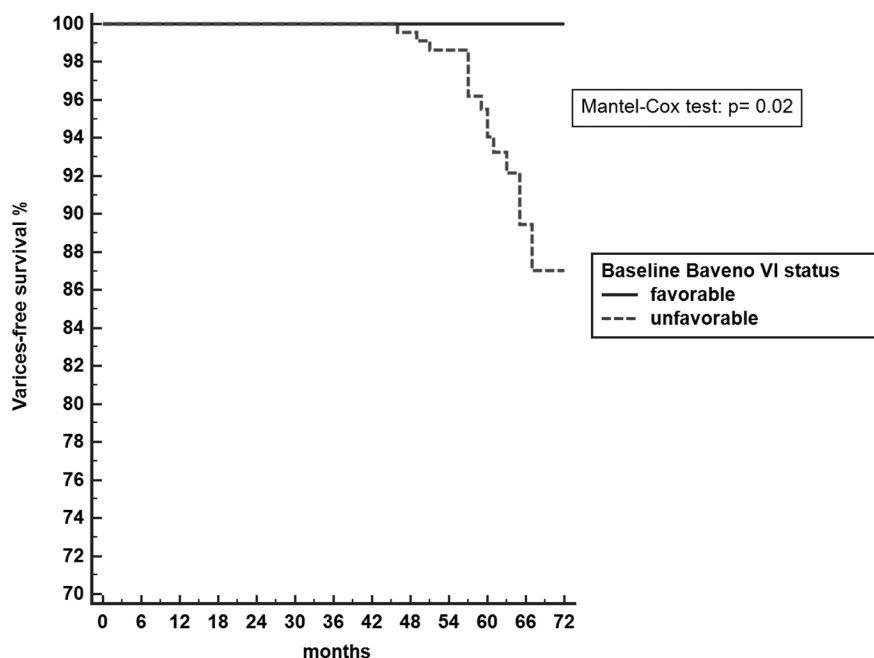

FIGURE 2 The Kaplan–Meier curves showing long-term EV incidence in patients with no baseline EV according to their pre-therapy Baveno VI status

TABLE 3 Association between baseline characteristics and development of EV in patients with unfavourable Baveno VI status and without EV at baseline

| | Hazard ratio (95% CI) | | | |
Characteristics	Univariate	p	Multivariate	p
Age >65 years	1.01 (0.97–1.07)	.46	1.07 (0.98–1.15)	.12
Male gender	0.16 (0.02–1.12)	.70	0.91 (0.25–3.38)	.07
African ethnicity	0.22 (0.03–1.68)	.15	0.23 (0.01–1.99)	.19
Normal waist circumference	0.96 (0.89–1.03)	.21	0.751 (0.55–1.02)	.07
Obesity	1.94 (0.44–8.60)	.39	1.89 (0.12–82.2)	.51
BMI < 25	0.65 (0.23–1.83)	.41	0.74 (0.14–4.02)	.72
Alcohol intake	N.F.		N.F.	
Metabolic syndrome	0.46 (0.10–2.03)	.30	0.40 (0.09–2.76)	.09
Diabetes	1.16 (0.33–4.11)	.82	2.77 (0.88–35.87)	.02
Arterial hypertension	1.49 (0.53–4.19)	.45	10.46 (2.26–86,56	.08
Cardiovascular diseases	0.45 (0.06–3.39)	.44	0.13 (0.006–3.06)	.21
Kidney disease	N.F.		N.F.	
Neuropathy	N.F.		N.F.	
Previous NHL	2.24 (0.71–7.06)	.17	2.09 (0.34–12.85)	.43
Previous non-haematological neoplasia	3.31 (0.43–25.45)	.25	75.59 (0.02–3161.93)	.31
Liver stiffness >25 kPa	1.004 (0.99–1.02)	.55	1.01 (0.99–1.03)	.40
MELD score <10	0.25 (0.08–0.73)	.01	0.12 (0.02–0.88)	.04
Child-Turcotte-Pugh score B	1.47 (0.19–11.35)	.71	N.F.	
ALT > ULN	1.003 (0.996–1.01)	.35	1.01 (0.999–1.02)	.06
AST > ULN	1.002 (0.992–1.01)	.69	0.99 (0.97–1.004)	.13
GGT > ULN	0.999 (0.99–1.004)	.76	0.997 (0.99–1.006)	.48
Platelet count >100000/mm^3	0.18 (0.06–0.58)	.004	0.15 (0.02–0.94)	.04
Albumin >4 g/dl	0.31 (0.11–0.87)	.03	0.45 (0.06–3.19)	.42

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EV, oesophageal varices; GGT, gamma-glutamyl transpeptidase; MELD, model for end-stage liver disease; N.F.: not feasible; NHL, Non-Hodgkin lymphoma; ULN, upper limit of normal.

and one (14.2%) showed recurrent episodes of ascites. One of them (14.2%) showed baseline EV which did not worsen during the endoscopic follow-up; of the remaining six patients without EV at baseline, none developed EV 3 years after the end of therapy.

Of the 335 patients in Group 2, 118 (35.2%, p < .0001)) became Baveno VI status favourable and 15 of them (12.7%) had pre-therapy EV compared to 88/217 (40.5%, p = .02) patients who did not improve their status; of those 15, 5 (33.3%) did not show any significant variceal change, 9 (60%) showed an improvement and 1 (6.6%) a worsening compared to—respectively—31 (35.2%), 24 (27.2%) and 33 (37.5%) of 88 patients with baseline EV and no Baveno VI status variation (p = .01). Out of 118 patients showing an improvement in their clinical status, 103 (87.3%) did not have baseline EV compared with 129/217 (59.4%, p = .03) cirrhotics with no changes: none developed EV throughout the follow-up, while in 15/129 (11.6%, p = .04) patients with persisting unfavourable Baveno VI status, a progression of PH was observed. The independent predictive

factors of improvement were BMI <25 (HR = 2.07, 95% CI: 1.41–3.03, p = .0002)) and platelet count >100000/mm3 (HR = 3.64, 95% CI: 2.16–6.13, p ≤ .0001) (Table 5).

A flow chart showing the suggested timing of endoscopy based on the dynamic of Baveno VI status is reported in Figure 3.

Finally, we looked for the diagnostic ability of Baveno VI criteria analysed at the first post-treatment endoscopy and LSM/platelet count in predicting EV, regardless of baseline variceal and Baveno VI status. Out of 203 (47.5%) patients maintaining or achieving a favourable Baveno VI status, 193 (95.1%) showed no EV, 7 (3.4%) showed F1 EV and 2 (1.5%) showed VNT compared, respectively, with 158 (70.5%), 44 (19.6%) and 22 (9.8%) of patients with unfavourable Baveno VI status. Post-treatment Baveno VI criteria had a sensitivity of 88.0% (95% CI: 68,8–97,5), a specificity of 49.8% (95% CI: 44,8–54,7), a PPV of 9.8 (95% CI: 8,4–11,5) and a NPV of 98.5% (95% CI: 95,8–99,5) in predicting the absence of VNT.

Characteristics	Hazard ratio (95% CI)			
	Univariate	p	Multivariate	p
Age >65 years	1.03 (0.995–1.07)	.09	1.06 (0.99–1.11)	.05
Male gender	0.52 (0.24–1.13)	.10	1.61 (0.17–1.37)	.41
Normal waist circumference	1.002 (0.97–1.04)	.93	1.001 (0.94–1.06)	.98
Obesity	0.70 (0.32–1.51)	.36	2.12 (0.56–.02)	.27
BMI <25	0.78 (0.39–1.54)	.47	0.61 (0.56–1.96)	.41
Alcohol intake	N.F.		N.F.	
Metabolic syndrome	1.001 (0.40–2.47)	.99	2.27 (0.28–18.66)	.44
Diabetes	0.96 (0.39–2.36)	.93	1.36 (0.25–7.43)	.72
Arterial hypertension	1.02 (0.49–2.11)	.97	0.79 (0.27–2.34)	.67
Cardiovascular diseases	1.45 (0.59–3.58)	.42	0.64 (0.18–2.24)	.48
Kidney disease	N.F.		N.F.	
Neuropathy	N.F.		N.F.	
Previous NHL	1.53 (0.52–4.47)	.44	2.96 (0.78–11.20)	.11
Previous non-haematological neoplasia	N.F.		N.F.	
Liver stiffness >25 kPa	1.03 (1.006–1.06)	.01	1.04 (0.99–1.08)	.05
MELD score <10	0.24 (0.11–0.50)	.001	0.35 (0.12–1.03)	.06
Child-Turcotte-Pugh score B	2.93 (0.97–8.84)	.06	3.03 (0.48–19.23)	.24
ALT > ULN	0.998 (0.99–1.005)	.58	0.98 (0.96–1.005)	.12
AST > ULN	1.002 (0.99–1.01)	.63	1.03 (0.99–1.06)	.05
GGT > ULN	0.99 (0.99–1.002)	.13	0.99 (0.98–1.007)	.41
Platelet count >100000/mm^3	0.35 (0.13–0.92)	.03	0.36 (0.11–1.21)	.10
Albumin >4 g/dl	0.48 (0.21–1.08)	.08	0.35 (0.15–3.34)	.20

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EV, oesophageal varices; GGT, gamma-glutamyl transpeptidase; MELD, model for end-stage liver disease; N.F.: not feasible; NHL, Non-Hodgkin lymphoma; ULN, upper limit of normal.

TABLE 5 Features associated with Baveno VI status improvement in patients with unfavourable Baveno VI status prior to therapy

Features	Hazard ratio (95% CI)			
	Univariate	p	Multivariate	p
BMI <25	1.86 (1.28–2.71)	.001	2.07 (1.41–3.03)	.0002
MELD score <10	2.31 (1.13–4.74)	.02	1.29 (0.58–2.84)	.53
Pre-therapy EV	0.53 (0.35–0.81)	.003	0.71 (0.46–1.11)	.13
Platelet count >100000/mm^3	3.55 (2.19–5.74)	<.0001	3.64 (2.16–6.13)	<.0001
Albumin >4 g/dl	1.34 (0.90–2.00)	.15	0.70 (0.45–1.09)	.13

Abbreviations: BMI, body mass index; CI, confidence interval; EV, oesophageal varices MELD, model for end-stage liver disease.

4 | DISCUSSION

Since they were published in 2015,[7] the Baveno VI criteria for the screening of EV have been validated by several studies involving cirrhotic patients of different etiologies,[10–12,18–20] while data in cirrhotics who have cleared HCV are still scarce, in particular those regarding the endoscopic follow-up.[12–14]

According to our data, the Baveno VI criteria can safely rule out VNT in HCV-positive cirrhotic patients with SVR, sparing about 21%

screening endoscopies and missing only 1.0% of VNT, confirming what has already been published.

What it is new here is the validation of the Baveno VI guidelines for the endoscopic surveillance in cured patients. The Baveno VI criteria regarding patients with initial favourable status obtaining the removal of the aetiological factor (in this case, recovery from HCV infection) recommend clinical monitoring only (by yearly TE and platelet count); if liver stiffness increases or platelet count declines, these patients should undergo endoscopy.[7] In our study, no patients
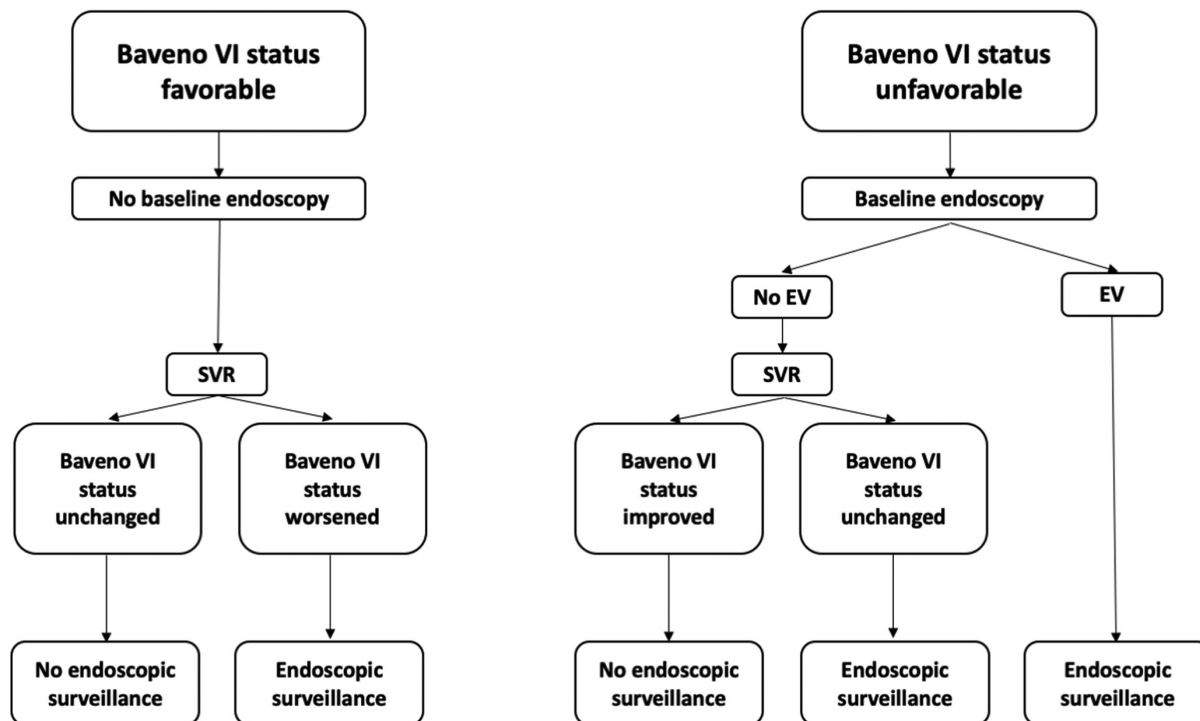
FIGURE 3 Flow chart suggesting need and timing of endoscopy for HCV-positive cirrhotic patients achieving SVR after DAA treatment according to the dynamic of their Baveno VI status. EV, oesophageal varices; SVR, sustained virological response

in Group 1 developed EV during the follow-up, even if showing Baveno VI status worsening.

Patients showing baseline unfavourable status having no EV and comorbidities who achieve SVR should undergo surveillance endoscopy at 3-year intervals; in our series, 6.5% of Group 2 patients without EV at baseline developed EV 3 years after obtaining SVR. However, 'de novo' EV were not observed in patients showing improvement in their Baveno VI status indicating a potential consisting number of spared endoscopies. Conversely, EV development was mainly found among patients with metabolic comorbidities such as diabetes.

In patients with small EV at baseline and no comorbidities obtaining SVR, surveillance endoscopy should be repeated at 2-year intervals. In our study, about 65% of patients with pre-therapy F1 EV remained unchanged or worsened throughout the follow-up, confirming previous studies[4–6] which reported persistence of CSPH in the majority of HCV-positive cirrhotic patients despite HCV clearance by DAAs. Improvement in Baveno VI status was not helpful in distinguishing patients who showed variceal amelioration as more than 40% of patients with pre-therapy EV who changed their initial unfavourable status maintained or worsened CSPH. Thus, this finding validates the timing of endoscopic surveillance proposed by current guidelines, even in the specific setting of cured HCV-positive patients. In particular, the necessity of continuing endoscopic surveillance is further stressed by the variceal worsening observed in four patients at the second endoscopic control, 4 years after achieving SVR.

Our data confirm the results of a French multicentre study[12] where 891 cirrhotic patients of different origins with and without

viral suppression were followed up for about 6 years. In the subgroups' analysis, 4.1% of patients without pre-therapy EV and showing viral suppression developed EV in the follow-up compared to 4.6% found in our study, while 14.8% of cured patients with baseline F1 EV showed a worsening in CSPH compared with 14.5% in our series. Similarly to what reported by Thabut et al.,[12] improvement in Baveno VI status had a beneficial impact on the PH progression, but we were able to show that the clinical benefit can be safely translated into a significant reduction of follow-up endoscopies only in patients with pre-therapy unfavourable Baveno VI status and without baseline EV ameliorating their status during the follow-up.

Moreover, we showed that the absence of PH progression in this subgroup of patients is maintained over the long term as no patients without EV at baseline and at 3-year follow-up endoscopy developed EV at 6-year control endoscopy. This finding validates the AGA recommendations[15] which suggest no further surveillance endoscopy if EV are not found on prior screening examination and after 2–3 years. On the other hand, we cannot confirm the AGA conclusions regarding patients with pre-therapy small EV; according to Jacobson et al.,[15] they can safely avoid further surveillance endoscopy if the F1 EV are unchanged or smaller at 2–3 years after SVR achievement. According to our data, a not negligible number of patients with baseline F1 EV developed VNT at 4-year follow-up endoscopy, suggesting to not let our guard down in this particular subgroup of patients. This recommendation is even more stringent if patients with baseline large EV are considered, as about 48% of them showed a worsening in size and

aspect needing band ligation, 28% remained unchanged and only 24% improved.

The strengths of our study are the prospective design with long-term follow-up, the predetermined schedule for surveillance endoscopy and TE, the restricted and homogeneous pool of endoscopists reducing the risk of interobserver variability regarding the EV grading.

A limitation of this study is the relatively high number of excluded patients not complying with the endoscopic follow-up or not fit for TE; for this reason, we have to keep in mind that the Baveno VI criteria cannot be applicable to all patients. Moreover, despite their capacity of ruling out VNT, the Baveno VI criteria allow to safely avoid only about 25% of screening endoscopies. We could obtain a larger number of spared endoscopies, if we adopted the expanded Baveno VI criteria,[8] but their generalized applicability is still matter of debate.[13,18,21]

Finally, at variance with our study design which adopted pre-treatment parameters to stratify the patients, recent studies[22,23] showed that a post-treatment algorithm combining simple serum markers (albumin, von Willebrand/platelet count ratio) with TE enables a reliable risk stratification for the development of hepatic decompensation after SVR. Moreover, other non-invasive tests such as laboratory tests, spleen elastography, magnetic resonance-based techniques and subharmonic-aided pressure estimation (SHAPE)[24] alone or in combination seem promising approaches in evaluating CSPH but are still awaiting validation.

In conclusion, our findings confirm that HCV-positive cirrhotic patients achieving SVR and having persisting favourable Baveno VI status can safely avoid endoscopic screening and surveillance. Patients with unfavourable Baveno VI status and no pre-therapy EV who change their status may suspend endoscopic surveillance. Patients with pre-therapy EV should maintain endoscopic follow-up owing to the persistence of CSPH in the majority of them.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Obtained.

POTENTIAL COMPETING INTERESTS

All authors declare no potential conflicts of interest.

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CONFLICT OF INTEREST

None of the authors have conflicts of interest for the reported study.

ETHICS APPROVAL

Obtained.

PATIENT CONSENT

Obtained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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