



Commentary

Beyond Baveno VI: How far are we?

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Variceal bleeding is a major complication in patients with cirrhosis, with still a high mortality rate despite improvements in therapy and management. Gastroesophageal varices can develop when hepatic venous pressure gradient (HVPG) is ≥ 10 mmHg. The risk of variceal bleeding is directly related with variceal size. Patients with medium and large varices have the highest risk of bleeding. Also, the presence of small varices with red wale marks or the presence of any-size varices in patients with Child-Pugh class C have been associated with a high risk of bleeding.

Beta-blockers have demonstrated in multiple randomized controlled trials to be effective in preventing first variceal bleeding in patients with high risk varices (medium-large varices or small with red signs), also called varices needing treatment (VNT). For this reason, until 2015, Baveno Consensus had recommended surveillance with an esophagogastroduodenoscopy (EGD) in all cirrhotic patients to detect VNT and start primary prophylaxis with beta-blockers.

During the last decade, the extensive use of non-invasive methods, based on ultrasound elastography, have allowed to diagnose patients at very early phases of cirrhosis who are at risk of developing portal hypertension, but in whom VNT have a very low prevalence. Therefore, the recommended surveillance in these patients increases the number of unnecessary EGD. These compensated patients identified as having severe fibrosis or cirrhosis by elastography have been named with the term compensated advanced chronic liver disease (cACLD) [1].

In order to reduce the number of unnecessary EGD there has been an exhaustive research in detecting varices by non-invasive methods. Some early studies demonstrated that just with a simple

combination of liver stiffness measurement (LSM) by transient elastography and platelet count, using different cut-offs in each study, VNT could be safely rule out (high negative predictive value) [2–4]. Consequently, in 2015, Baveno VI consensus proposed that cACLD patients with LSM < 20 kPa and platelet count $> 150 \times 10^9/L$ could safely avoid screening EGD, as the risk of having VNT is $< 5\%$ [1].

Since Baveno VI publication, many studies have tried to validate the criteria for avoiding screening EGD as shown in table 1A [5–18]. Most of the studies have included mixed cACLD populations being, initially, hepatitis C the main etiology in most of them. More recently, these criteria have been also assessed in some specific populations such non-alcoholic steatohepatitis (NASH) [14] and cholestatic diseases [12], where LSM performance can be influenced by obesity or cholestasis, respectively. As described in the table, VNT prevalence is $< 15\%$ in most series, indicating this low prevalence that patients included are cACLD and not decompensated cirrhotic patients. Applying Baveno VI criteria, approximately 25–30% EGD can be spared with a very low risk of missing VNT ($< 2\%$), that is a very low false negative rate (FNR). However, still around 40% of EGD are unnecessary.

Other classification criteria have been studied to improve results, increasing the number of spared EGD without exceeding the accepted $< 5\%$ FNR. In that sense, Augustin et al. proposed less conservative criteria (“Expanded Baveno VI criteria”: LSM < 25 kPa + platelet count $> 110 \times 10^9/L$) achieving an increase in the number of EGD spared with a FNR $< 5\%$ [5]. These criteria have been also explored in other series as shown in Table 1.

The study of Tosetti, et al. published in this issue of Digestive and Liver Disease aimed to compare the accuracy of some “beyond Baveno VI” criteria (LSM < 25 kPa + platelet count $> 110 \times 10^9/L$; LSM < 25 kPa + platelet count $> 125 \times 10^9/L$; platelet count $> 150 \times 10^9/L$ + MELD 6) [17]. For this purpose, they developed a retrospective study including 442 cACLD patients of any etiology referred for screening EGD in two centers from Italy. Patients included had blood tests and LSM performed by transient elastog-

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Table 1
Summary of fully reported studies evaluating the performance of Baveno VI and expanded Baveno VI criteria for avoiding screening endoscopy for varices. A) All patients included in each study. B) Studies in which etiology was analyzed separately.

A								
Study	Etiology	N	VNT	Baveno VI criteria LSM <20 + Plat > 150		N	Expanded Baveno VI criteria LSM <25 + Plat > 110	
				EGD spared ^a	VNT missed ^b		EGD spared ^a	VNT missed ^b
Augustin et al. [5]	Mixed (59% HCV)	925	92 (10%)	198 (21.4%)	3 (1.5%)	925	367 (40%)	6 (1.6%)
Bae et al. [6]	Mixed (59% HBV)	282	55 (19.5%)	78 (27.7%)	3 (3.8%)	282	146 (51.8%)	10 (6.8%)
Colecchia, et al. [7]	Mixed (85% HCV)	498	100 (20.1%)	102 (20.5%)	1 (1%)	498	202 (40.6%)	8 (4%)
Colecchia et al. [7]; Dajti, et al [8]	Mixed (41% HCV)	115	15 (13%)	19 (16.5%)	0	115	34 (29.6%)	2 (6%)
Jangouk et al. [9]	Mixed (71% HCV)	262	31 (11.8%)	57 (21.8%)	0	–	–	–
Llop et al. [10]	Mixed (85% HCV)	161	–	54 (33.5%)	0	–	–	–
Maurice et al. [11]	Mixed (55% HCV)	310	15 (4.8%)	102 (32.9%)	2 (2%)	–	–	–
Moctezuma et al. [12]	65% PBC, 35% PSC	227	28 (12.3%)	82 (36.1%)	0	227	122 (53.7%)	6 (4.9%)
Perazzo et al. [13]	Unknown	97	–	21 (21.6%)	0	–	–	–
Petta, et al. (M ^c) [14]	100% NASH	338	45 (13.3%)	113 (33.4%)	5 (4.4%)	338	183 (54.1%)	8 (4.4%)
Petta et al. (XL ^c) [14]	100% NASH	–	14 (10.1%)	–	–	138	64 (46.4%)	1 (1.6%)
Silva et al. [15]	Mixed (78% HCV)	97	14 (14.4%)	11 (11.3%)	0	–	–	–
Sousa et al. [16]	Mixed (80% HCV)	104	9 (8.7%)	48 (46.2%)	0	–	–	–
Tosetti et al. [17]	Mixed (69% HCV)	442	31 (7%)	86 (19.5%)	0	442	193 (43.7%)	0
Wong et al. [18]	Mixed (Most HBV)	127	11 (8.7%)	105 (82.7%)	1 (1%)	–	–	–
Total	Mixed (46% HCV)	3985	460 (11.5%)	1076 (27%)	15 (1.4%)	2965	1311 (44.2%)	41 (3.1%)

B								
Study ^d	Etiology	N	VNT	Baveno VI criteria LSM <20 + Plat > 150		N	Expanded Baveno VI criteria LSM <25 + Plat > 110	
				EGD spared ^a	VNT missed ^b		EGD spared ^a	VNT missed ^b
5, 6, 16	Hepatitis C	129	–	51 (39.5%)	0	630	262 (41.6%)	4 (1.5%)
5, 6, 16	Hepatitis B	170	–	45 (26.5%)	3 (6.7%)	227	101 (44.5%)	7 (6.9%)
17	Viral	351	–	71 (20.2%)	0	351	156 (44.4%)	0
5, 6, 16, 17	Alcohol	91	–	22 (24.2%)	0	206	83 (40.3%)	2 (2.4%)
5, 6, 14, 17	NASH	420	–	134 (31.9%)	5 (3.7%)	648	334 (51.5%)	11 (3.3%)
12	PBC	147	–	58 (39.5%)	0	147	86 (58.5%)	5 (5.8%)
12	PSC	80	–	24 (30%)	0	80	36 (45%)	1 (2.8%)

N: Number of patients evaluated; VNT: Varices needing treatment; EGD: Esophagogastroduodenoscopy; LSM: Liver stiffness measurement; Plat: platelet count; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

^a Patients within the criteria in which endoscopy could be spared.

^b Number of varices needing treatment missed by applying the criteria and percentage as false negative rate. False negative rate calculated as number of varices needing treatment missed/number of patients within the criteria.

^c M refers to patients from Petta, et al. study in which M probe was used and XL refers to patients in which XL probe was used.

^d Studies in which etiology was analyzed separately, validating Baveno VI criteria and/or expanded Baveno VI criteria. N represents the number of patients in whom these criteria were applied.

raphy within six months and 1 year of EGD, respectively. The XL probe, available in both centers, was utilized in obese patients. Viral etiology was the main etiology of the cohort (79%), being 304 hepatitis C patients (69%) and 47 (10%) hepatitis B (HBV). The prevalence of varices was 31%, with 31 patients (7%) having VNT. Using the Baveno VI criteria, 19.5% of EGD could be spared with no VNT missed. Among the others “beyond Baveno” criteria evaluated, the “expanded criteria” (LSM <25 kPa + platelet count >110 × 10⁹/L) was the one in which more EGD were avoided (43.7%) with a risk of 0% of missing VNT, being the best approach in the cohort.

Tosetti, et al. also explored the diagnostic performance of the criteria in the main etiologies of cACLD patients. Baveno VI criteria performed well in the main etiologies (viral, metabolic and alcohol) saving 20%, 14% and 23% of EGD, respectively, without missing any VNT in any group. Again, the “expanded criteria” could save the highest number of EGD (35–44%) without missing any VNT.

Table 1B describes the performance of Baveno VI criteria and expanded criteria among etiologies that have been analyzed separately in some of the published studies [5,6,12,14,16,17]. In short, Baveno VI criteria perform very well in the main etiologies of chronic liver disease saving 20–39% EGD with a FNR <5% (the maximum agreed by consensus). However, in HBV patients, applying the Baveno VI criteria could miss around 6.7% of VNT which is a risk too high to be acceptable. This may be explained by the fact that HBV patients have lower LSM cut-offs for cirrhosis than other etiologies

and probably the LSM cut-off for clinically significant portal hypertension is also lower in HBV than in other etiologies. Therefore, the risk of having VNT in HBV patients with LSM <20 kPa + platelet count >150 × 10⁹/L is higher. The following Baveno consensus will have to address these differences in HBV patients among viral etiology of chronic liver disease. It has to be taken into account that the majority of HBV patients are from a unique Asian cohort [6], and consequently these results need to be further validated in other cohorts. Regarding the applicability of the expanded criteria by etiologies, it seems that these criteria perform well in hepatitis C, NASH, alcoholic liver disease and primary sclerosing cholangitis, but fail in primary biliary cholangitis and HBV patients. The table shows that the expanded criteria save a higher number of EGD than Baveno VI criteria.

As the authors describe, Tosetti's study has some limitations such its retrospective nature and the time interval between procedures (LSM, EGD and platelet count). It needs to be considered that the variability of LSM and platelet counts can influence the applicability of the criteria. Although it is not a real limitation of the study, patients included with hepatitis C were not previously treated, being still viremic. Currently there are successful antiviral therapies for hepatitis C and validation of the Baveno VI criteria in non viremic cohorts is needed. In that sense, recent published data showed that Baveno VI criteria seem safe also in non viremic patients [19].

The main strengths of the study are the large cohort of patients explored and the validation of different previously described criteria with a separate analysis by etiologies.

In conclusion, according to data published so far, Baveno VI criteria are useful to identify cACLD patients in whom EGD can safely be avoided in the main etiologies of chronic liver disease. Expanded Baveno VI criteria increase the number of spared EGD without exceeding the 5% FNR threshold, except in primary biliary cholangitis and possibly HVB patients, although further studies are needed to validate all these criteria in hepatitis B population.

Conflict of interest

None declared.

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References

- [1] de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743–52, <http://dx.doi.org/10.1016/j.jhep.2015.05.022>.
- [2] Augustin S, Millán L, González A, Martell M, Gelabert A, Segarra A, et al. Detection of early portal hypertension with routine data and liver stiffness in patients with asymptomatic liver disease: a prospective study. *J Hepatol* 2014;60:561–9, <http://dx.doi.org/10.1016/j.jhep.2013.10.027>.
- [3] Montes Ramirez ML, Pascual-Pareja JF, Sánchez-Conde M, Bernardino De la Serna JI, Zamora Vargas FX, Miralles P, et al. Transient elastography to rule out esophageal varices and portal hypertensive gastropathy in HIV-infected individuals with liver cirrhosis. *AIDS* 2012;26:1807–12, <http://dx.doi.org/10.1097/QAD.0b013e3283573267>.
- [4] Ding NS, Nguyen T, Iser DM, Hong T, Flanagan E, Wong A, et al. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. *Liver Int* 2016;36:240–5, <http://dx.doi.org/10.1111/liv.12916>.
- [5] 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;66:1980–1, <http://dx.doi.org/10.1002/hep.29363>.
- [6] 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, <http://dx.doi.org/10.1111/liv.13732>.
- [7] Colecchia A, Ravaoli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol* 2018;69:308–17, <http://dx.doi.org/10.1016/j.jhep.2018.04.023>.
- [8] Dajti E, Ravaoli F, Colecchia A, Marasco G, Galès P, Festi D. Are the Expanded Baveno VI Criteria really safe to screen compensated cirrhotic patients for high-risk varices? *Dig Liver Dis* 2019;51:456–7, <http://dx.doi.org/10.1016/j.dld.2018.12.013>.
- [9] 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, <http://dx.doi.org/10.1111/liv.13379>.
- [10] 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. *J Gastroenterol Hepatol* 2017;32:1867–72, <http://dx.doi.org/10.1111/jgh.13781>.
- [11] 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, <http://dx.doi.org/10.1016/j.jhep.2016.06.021>.
- [12] Moctezuma-Velazquez C, Saffiotti 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.
- [13] Perazzo H, Fernandes FF, Castro Filho EC, Perez RM. Points to be considered when using transient elastography for diagnosis of portal hypertension according to the Baveno's VI consensus. *J Hepatol* 2015;63:1048–9, <http://dx.doi.org/10.1016/j.jhep.2015.06.036>.
- [14] Petta S, Sebastiani G, Bugianesi E, Viganò M, VW-S Wong, 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, <http://dx.doi.org/10.1016/j.jhep.2018.05.019>.
- [15] Silva MJ, Bernardes C, Pinto J, Loureiro R, Duarte P, Mendes M, et al. Baveno VI recommendation on avoidance of screening endoscopy in cirrhotic patients: are we there yet? *GE - Port J Gastroenterol* 2017;24:79–83, <http://dx.doi.org/10.1159/000452693>.
- [16] Sousa M, Fernandes S, Proença L, Silva AP, Leite S, Silva J, et al. The Baveno VI criteria for predicting esophageal varices: validation in real life practice. *Rev Esp Enferm Dig* 2017;109:704–7, <http://dx.doi.org/10.17235/reed.2017.5052/2017>.
- [17] Tosetti G, Primignani M, La Mura V, D'Ambrosio R, Degasperis E, Mezzina N, et al. Evaluation of three "beyond Baveno VI" criteria to safely spare endoscopies in compensated advanced chronic liver disease. *Dig Liver Dis* 2019. In Press.
- [18] Wong GLH, Kwok R, Hui AJ, Tse Y-K, Ho K-T, Lo AOS, et al. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: a randomized trial. *Liver Int* 2018;38:636–44, <http://dx.doi.org/10.1111/liv.13560>.
- [19] 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, <http://dx.doi.org/10.1053/j.gastro.2018.11.053>, e5.