Liver, Pancreas and Biliary Tract

Evaluation of three "beyond Baveno VI" criteria to safely spare endoscopies in compensated advanced chronic liver disease

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ABSTRACT

Background: Liver stiffness measurement (LSM) <20 kPa and platelet count >150,000/mm³ exclude varices needing treatment (VNT) in viral compensated advanced chronic liver disease (cACLD), saving-up to 20–25% endoscopies (Baveno VI criteria). Refinements of such criteria to further reduce endoscopies and an approach without LSM (Platelet 150/MELD 6) were later proposed.
Aims: To assess LSM 25/platelet 125, LSM 25/platelet 110 (Expanded-Baveno VI) and Platelet 150/MELD 6 accuracy versus Baveno VI criteria, and the impact of platelet count variability on criteria accuracy in all-etiologies cACLD.
Methods: cACLD patients undergoing screening endoscopy with laboratory data within 6 months and LSM within one year.
Results: Of 442 patients, 31% had varices (7% with VNT). Baveno VI criteria had 100% sensitivity (Se) and negative predictive value (NPV) and spared 19.5% endoscopies. "LSM 25/platelet 125" and "Expanded-Baveno VI" criteria maintained such accuracy, sparing 15% and 24% more endoscopies, respectively (p < 0.001). Platelet 150/MELD 6 was less accurate, misclassifying 10% VNT. Platelet count variability exceeded 8% and one VNT patient was misclassified with both "Expanded-Baveno VI" and "LSM 25/platelet 125" criteria considering the previous platelet count.
Conclusions: Both "Expanded-Baveno VI" and "LSM 25/platelet 125" criteria are accurate in cACLD, but the former are more advantageous. Platelet 150/MELD 6 proved inadequate.

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1. Introduction

Non-invasive tools developed for the assessment of hepatic fibrosis enable early identification of asymptomatic patients with advanced fibrosis/compensated cirrhosis at risk of developing portal hypertension. At the Baveno VI consensus meeting, the term "compensated Advanced Chronic Liver Disease" (cACLD) was approved to name this population. In such patients Liver Stiffness Measurement (LSM) with Transient Elastography (TE) value $\geq$ 10 kPa is suggestive of cACLD [1].

Less than 10% of cACLD subjects have clinically significant portal hypertension (CSPH) with varices needing treatment (VNT) [2], but identifying them is crucial, since bleeding prophylaxis is mandatory. Conversely, performing (and repeating at scheduled intervals) screening endoscopy in most cACLD patients without VNT or without varices has a substantial impact on the patients quality of life as well as health care costs.

Early studies aimed at non-invasively identifying cirrhotic patients with varices by combining serological markers achieved unreliable results [3–8], however the implementation of LSM

by TE and the appraisal of its role for the prediction of CSPH [9–11], renewed the interest on non-invasive tools to identify cirrhotic patients with VNT [12,13]. The Baveno VI Consensus [1] states that cACLD patients of viral aetiology with both LSM <20 kPa (two measurements on different days in fasting conditions) and platelet count >$150 \times 10^3/mm^3$ can safely avoid screening endoscopy. External validation proved this strategy to be safe, since few patients (<5%) with VNT are missed. Unfortunately few endoscopies can be spared with these cutoffs, since as many as 40% [14–19] of cACLD patients without varices still qualify for an unneeded endoscopy [16]. For this reason, attempts to refine the Baveno VI criteria, aimed at sparing more endoscopies without losing accuracy in identifying patients with VNT, have been made. A preliminary study from our group, using LSM <25 kPa and platelet count > $125 \times 10^3/mm^3$ as criteria to avoid endoscopy, attained 100% sensitivity (Se) and Negative Predictive Value (NPV) and saved 44% unnecessary endoscopies [20]. Augustin et al., evaluated LSM <25 kPa, and platelet count threshold at >$110 \times 10^3/mm^3$ and were able to save 40% endoscopies with a <5% risk of not identifying patients with VNT [21]. Both studies validated the proposed criteria also in a limited number of non-viral cACLD. Finally, given the limits of accuracy/reliability of TE [22] and its lack of availability worldwide, Jangouk et al. proposed an approach exclusively based on laboratory parameters, the "Platelet 150/MELD 6" criterion [23]. According to it, cACLD patients with platelet count >$150 \times 10^3/mm^3$ or MELD score 6 could avoid screening endoscopy with a very low chance of failure to identify patients with VNT and up to 42% of endoscopies saved. Primary aim of our study was to compare the accuracy and the effectiveness of these three criteria (LSM 25/platelet 125; LSM 25/platelet 110; Platelet 150/MELD 6) with the original Baveno VI criteria, in a large cohort of cACLD patients of any aetiology. Secondary aim was to measure platelet count variability in two consecutive blood samples (the closest to screening endoscopy, used to validate the criteria, and the most recent previous one, 1–6 months before) in a large subset of the cACLD cohort and to assess whether such variability could lead to misclassifying cACLD patients with VNT.

2. Patients and methods

2.1. Study cohort

This retrospective analysis included all cACLD patients of any etiology referred for endoscopy screening from February 2010 to January 2016 to the outpatient "A. M. e A. Migliavacca" Center for Liver Disease of the Hepatology Division, Internal Medicine Department of Pathophysiology and Transplantation and "San Giuseppe" Hospital Liver Unit. Patients were eligible for the study if they had laboratory tests performed within 6 months and LSM >10 kPa performed within one year prior to endoscopy. All viral-related cACLD patients were still viremic. None of the patients was taking non selective beta blockers. Exclusion criteria were unreliable TE results, current hepatocellular carcinoma or other neoplasm, portal vein thrombosis, splenectomy and any IFN-based antiviral treatment within one year (because of the possible IFN-related decrease of platelet count) (Fig. 1).

2.2. Endoscopy and transient elastography

Esophageal varices were classified as low risk if small (F1) and without red signs, whereas all other varices (medium/large varices or small varices with red signs and gastric varices) were classified as VNT, according to current guidelines [24]. LSM by TE (FibroScan; Echosens, Paris, France) was performed in fasting state, according to the standard procedure [25]. TE was valid if at least ten suc-
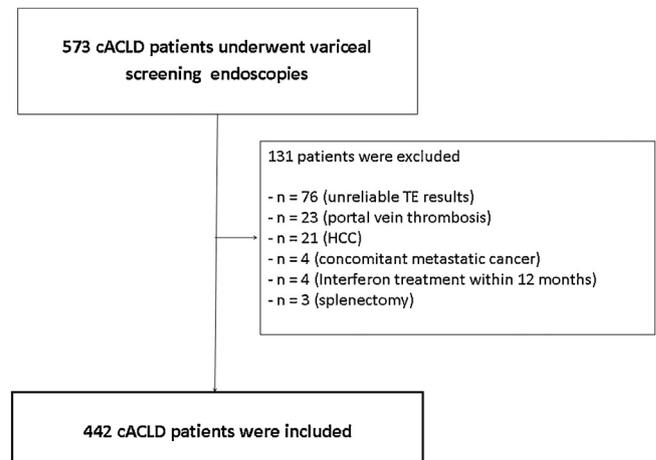

Fig. 1. Patients disposition.

cessful measurements were performed with interquartile range (IQR) lower than 30% and success rate higher than 60%, and was deemed unreliable in other cases [26]. The XL probe, available in both centres, was utilized in obese patients.

2.3. Blood samples collection for platelet count variability assessment

Blood samples were drawn in fasting state and handled according to standard hospital procedures. The index blood samples, collected for assessing the proposed criteria, were the closest to screening endoscopy (median 2 months before, range 0.5–6 months). For a subgroup of patients, the previous closest blood samples available (median 103 days before, range 8–185) in the same clinical situation were used to evaluate platelet count variability and its influence on the accuracy of the criteria.

2.4. Statistical analysis

Demographic and laboratory data were reported as median (range) for continuous parameters and as number and percentage for categorical parameters. Sensitivity (Se), specificity (Sp), positive and negative predictive value (PPV; NPV) to rule out VNT were assessed for each new proposed criterion and for the original Baveno VI criteria. Mc Nemar test was used to compare the number of patients incorrectly classified as well as the number of endoscopies spared by the three new criteria.

3. Results

3.1. Study cohort and patient characteristics

Main demographic and clinical features of the study cohort are shown in Table 1. Four hundred and forty-two patients, fulfilling the diagnostic criteria of cACLD (Child–Pugh score A without any previous episode of decompensation, LSM ≥10 kPa) were included; a small subgroup of patients had histological diagnosis of cirrhosis (n = 84, 18%), whereas in most patients cACLD diagnosis was based only on LSM. Prevalent aetiology was viral cACLD (351 patients, 79%). Other aetiologies included metabolic cirrhosis (65 patients, 15%) and alcoholic cirrhosis (26 patients, 6%). Patients were mainly males (n = 284, 64%) with a median age of 60 years. The median time interval between upper GI endoscopy and laboratory data or LSM was 2 months (range 0–6 months) and 3 months (range 0–12 months), respectively. LSM was performed with the XL probe in 33 obese patients (7%). Out of 138 (31%) patients with

Table 1
Baseline characteristics of the 442 included patients.

Variables	n = 442
Age, yr[a]	60 (20–85)
Male, n	284 (64%)
Aetiology, n	
HCV	304 (69%)
HBV	47 (10%)
NASH	65 (15%)
Alcohol	26 (6%)
BMI, kg/m^{2}[a]	25.4 (15.9–42)
ALT (U/l)[a]	71 (6–411)
Bilirubin (mg/dl)[a]	0.8 (0.2–2)
Albumin (g/dl)[a]	4.2 (3.3–5.3)
INR	1.1 (0.9–1.5)
Creatinine (mg/dl)[a]	0.8 (0.4–2.4)
Platelet count, $\times 10^{3}/mm^{3}$	122 (39–347)
MELD[a]	8 (6–12)
TE, kPa[a]	19.8 (10–75)
Esophageal varices	138 (31%)
Varices not needing treatment (F1 RCS−)	107 (24%)
Varices needing treatment (F1 RCS+, F2/3 RCS+/−; GOV2)	31 (7%)

[a] Median (range).

varices, 31 (7%) had VNT: 29 patients had esophageal VNT (small varices with red signs or medium/large esophageal varices) and 2 patients had gastroesophageal varices type 2 (GOV2).

3.2. Baveno VI criteria performance

The Baveno VI criteria identified all 31 patients with VNT. Of these, 18 had both LSM $\geq$20 kPa and platelet count $\leq 150 \times 10^{3}/mm^{3}$, 10 had only platelet count $\leq 150 \times 10^{3}/mm^{3}$ and 3 had only LSM $\geq$20 kPa. However, the Baveno VI criteria would have avoided only 86 endoscopies (19.5%) (73 without varices, 13 with low-risk varices) and 325 patients either with low risk varices (n = 94) or without varices (n = 231) would have received an endoscopy. Therefore, in our cohort, Baveno VI criteria had 100% Se and NPV, but low Sp (21%) and PPV (8.7%) (Table 2). The criteria proved accurate in any cACLD aetiology.

3.3. "LSM 25/platelet 125" criteria performance

By assuming LSM <25 kPa and platelet count >$125 \times 10^{3}/mm^{3}$ as criteria to avoid endoscopy, all 31 patients with VNT would have been correctly classified (100% Se and NPV). Of these, 14 had both LSM $\geq$25 kPa and platelet count $\leq 125 \times 10^{3}/mm^{3}$, 13 had only platelet count $\leq 125 \times 10^{3}/mm^{3}$ and 4 had only LSM $\geq$25 kPa. One hundred and fifty-four endoscopies would have been avoided (34.8%), an increase of 15.3% compared to the Baveno VI criteria (p < 0.001) (Table 2). Two hundred and fifty-seven cACLD patients, either with low risk varices (n = 82) or without varices (n = 175) would have still undergone endoscopy (Sp 37%, PPV 10.8%).

3.4. Expanded Baveno VI criteria performance

According to the "Expanded Baveno VI" criteria (LSM <25 kPa and platelet count >$110 \times 10^{3}/mm^{3}$) all 31 patients with VNT would have been correctly classified (100% Se and NPV). Of these, 13 had both LSM $\geq$25 kPa and platelet count $\leq 110 \times 10^{3}/mm^{3}$, 13 had only platelet count $\leq 110 \times 10^{3}/mm^{3}$ and 5 had only LSM $\geq$25 kPa. One hundred and ninety-three endoscopies would have been avoided (43.7%) as compared to 154 (34.8%) and 86 (19.5%) with the previously analysed classifications (p < 0.001 vs Baveno VI criteria; p < 0.001 vs LSM 25/platelet 125 criteria).

Two hundred and eighteen cACLD patients without VNT (53%), either with low risk varices (n = 73) or without varices (n = 145) would have still undergone endoscopy.

3.5. Performance of the "Platelet >150,000/MELD score 6" criteria

According to the 'Platelet 150/MELD 6' criteria, three (2 HCV and 1 alcoholic cACLD) of 31 patients with VNT (9.7%) would have been misclassified, skipping a necessary endoscopy (Se 90%, NPV 98%). Overall, 171 endoscopies would have been avoided (38.7%) because of platelet count >150,000 (n = 105) or MELD score 6 (n = 66).

3.6. Criteria accuracy according to cACLD etiology

The Baveno VI criteria, LSM25/platelet125 and Expanded Baveno IV maintained the same accuracy in viral, metabolic and alcoholic cACLD. On the contrary, Platelet 150/MELD 6 criteria proved inadequate since 3 of 31 VNT were missed, one in alcoholic and two in viral cACLD (Table 3).

3.7. Criteria accuracy according to LSM timing and probes

TE-based criteria (Baveno VI criteria, LSM25/platelet125 and Expanded Baveno VI) maintained the highest accuracy (no VNT missed), for different time intervals between LSM and endoscopy (0–3 months n = 238; 3–6 months, n = 83, and 6–12 months, n = 121). The percentage of spared endoscopies was similar in the three time intervals considered for each TE-based criteria (Fig. 2). The three TE-based criteria maintained the highest accuracy also in 33 obese patients with TE assessed by the XL probe.

3.8. Platelet count variability

Platelet count variability was assessed in 191 cACLD patients of the same cohort (13 with VNT). The median time elapsing between the two blood samples collection was 103 days (range 8–185 days). We identified a median variability of $10 \times 10^{3}/mm^{3}$ (8.7%, range 0–85%).

By assuming the $125 \times 10^{3}/mm^{3}$ platelet count threshold, nine patients (4.7%) with higher platelet count at the previous sampling would have avoided endoscopy and none of them would have been rescued by the TE value. Likewise, assuming the $110 \times 10^{3}/mm^{3}$ platelet count threshold, eight patients (4.2%) with higher platelet count at the previous sampling would have avoided endoscopy and none of them would have been rescued by the TE value. One of 13 VNT patients (platelet count $126 \times 10^{3}/mm^{3}$ and LSM 21.3 kPa) would have avoided endoscopy, either by "LSM 25/platelet 125" criteria or by Expanded Baveno VI criteria, if the previous rather than the index platelet count was considered. Conversely, by assuming the $125 \times 10^{3}/mm^{3}$ or the $110 \times 10^{3}/mm^{3}$ platelet count threshold, eight (4.2%) or seven (3.6%) patients with lower platelet count at the previous sampling would have been submitted to an unneeded endoscopy.

4. Discussion

In this study, we compared the accuracy of the original Baveno VI criteria to identify patients who should not undergo upper GI endoscopy for the detection of varices with the "LSM 25/platelet 125" criteria, the "LSM 25/platelet 110" (Expanded Baveno VI criteria) and the "platelet 150/MELD 6" criteria. All these criteria allowed a significant increase in the number of spared endoscopies (34.8%, 43.7% and 38.7%, respectively) as compared to the original Baveno VI criteria (19.5%). However, only the "LSM 25/platelet 125" criteria and the "LSM 25/platelet 110" provided similar accuracy to the original Baveno VI criteria, while the "platelet 150/MELD 6" would have led to the misclassification of almost 10% of patients with VNT that would have skipped endoscopy, higher than the 5% acceptable rate of missed VNT established at the Baveno VI meeting [1] if the preferable formula to calculate the rate of missed

Table 2
Criteria accuracy; endoscopies saved and VNT missed (N = 442; VNT = 31).

Criteria	Se (%)	Sp (%)	PPV (%)	NPV (%)	Saving EGDS n/N (%)	VNT missed/EGDS saved (%)	VNT missed/VNT (%)
Baveno VI (Platelet >150 and LSM <20)	100	21	8.7	100	86/442 (19.5%)	0/86 (0)	0/31 (0)
Expanded Baveno VI (Platelet >110 and LSM <25)	100	47	12.4	100	193/442 (43.7%)	0/193 (0)	0/31 (0)
LSM 25/platelet 125 (Platelet >125 and LSM <25)	100	37	10.8	100	154/442 (34.8%)	0/154 (0)	0/31 (0)
Platelet 150/MELD 6 (Platelet >150 or MELD 6)	90	41	10.3	98	171/442 (38.7%)	3/171 (1.8%)	3/31 (9.7%)

Se: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value. EGDS: esophago-gastric-duodenoscopy; VNT: varices needing treatment.

Table 3
Criteria accuracy according to cACLD aetiologies; endoscopies saved and VNT missed.

	Baveno VI		LSM 25/Platelet 125		Expanded Baveno VI		Platelet 150/MELD 6	
	Saving EGDS n/N (%)	VNT missed/ EGDS saved (%)	Saving EGDS n/N (%)	VNT missed/ EGDS saved (%)	Saving EGDS n/N (%)	VNT missed/ EGDS saved (%)	Saving EGDS n/N (%)	VNT missed/ EGDS saved (%)
Viral (N = 351)	71/351 (20)	0/71 (0)	125/351 (36)	0/125 (0)	156/351 (44)	0/156 (0)	136/351 (39)	2/136 (1.5)
Metabolic (N = 65)	9/65 (14)	0/9 (0)	22/65 (34)	0/22 (0)	28/65 (43)	0/28 (0)	25/65 (38)	0/25 (0)
Alcohol (N = 26)	6/26 (23)	0/6 (0)	7/26 (27)	0/7 (0)	9/26 (35)	0/9 (0)	10/26 (38)	1/10 (10)
Differences among groups	p = 0.415	na	p = 0.648	na	p = 0.613	na	p = 0.990	p = 0.193

EGDS: esophago-gastric-duodenoscopy; VNT: varices needing treatment.
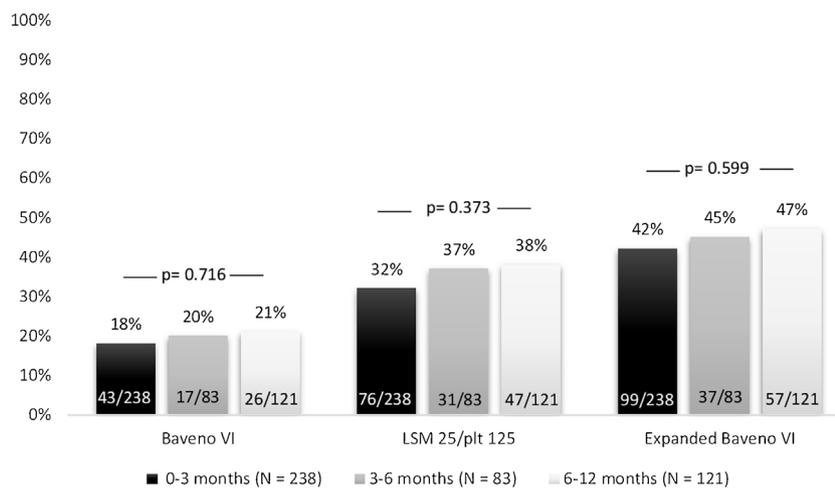
Fig. 2. EGDS saved: LSM-EGDS time intervals (0–3 months; 3–6 months; 6–12 months) in TE-based non invasive criteria (Baveno VI; LSM 25/platelet 125; Expanded Baveno VI).

VNT should be the missed VNT/total VNT ratio rather than the VNT missed/EGDS spared or the VNT missed/whole patient population ratio, as recently pointed out by Calés et al. [27].

Since the purpose of these non-invasive screening tools is to decrease the burden of unnecessary endoscopies while maintaining high accuracy to rule out VNT, we can conclude that the performance of the "platelet 150/MELD 6" criteria proved to be inadequate.

Conversely, both the "LSM 25/platelet 125" criteria and the "LSM 25/platelet 110" maintained the highest accuracy, with the latter sparing significantly more endoscopies than the former.

Although most LSM were performed within 6 months before upper endoscopy, TE-based criteria maintained the highest accuracy, without VNT misclassification, also in those patients (27%) with LSM performed 6–12 months before endoscopy.

In our study LSM proved especially valuable in patients with platelet count beyond the thresholds of Baveno VI criteria, "LSM 25/platelet 125" and "Expanded Baveno VI" criteria, as 3, 4 and 5 of 31 patients with VNT, respectively, were "rescued" to endoscopy by LSM.

Though the original Baveno VI statement recommends "two TE measurements on different days in fasting condition", neither the early confirmative studies nor the following refinements of the Baveno VI criteria applied such rule. Indeed, in patients with high LSM discrepant results are common and variability may exceed 20% [28,29]. Repeated LSM were not available in our cohort and indeed are not part of the routine clinical practice, but a high rate of LSM variability is expected for LSM around 25 kPa, which represent the TE threshold of both the "LSM 25/platelet 125" and the "Expanded Baveno VI criteria". In our study, we could analyze platelet count variability in a large number of cACLD patients by considering two consecutive platelet counts within 6 months.

We found a platelet count variability that, in 8% of cases, would have led to misclassifying patients for such parameter, with both platelet count thresholds. However, all patients but one would have been rescued by LSM, thus avoiding misclassification. Since in this study we could not assess LSM variability, no firm conclusion can actually be drawn on how the proposed criteria would work if both LSM and PLT were performed twice before ruling out VNT.

Although both the "LSM 25/platelet 125" criteria and the "LSM 25/platelet 110" maintained the highest accuracy in our cohort, it is reasonable that the greater the grey zone, the higher the risk of misclassification. In this setting, a close re-evaluation of platelet count and the rule of "two TE measurements on different days"

should be kept and endoscopy performed in case a worsening of the platelet count or LSM is observed. Although both "LSM 25/platelet 125" criteria and the "LSM 25/platelet 110" perform better than the original Baveno VI criteria, in terms of spared endoscopies, still as many as 50%–60% endoscopies would be performed in patients without VNT. This highlights the need for further refining of TE measurements, maybe including spleen stiffness as recently suggested [30,31]. However, the chance of marked improvements of the prediction rules of VNT in cACLD cohorts, given the low prevalence of VNT, may be hard to achieve.

We do acknowledge our study has some further limitations: firstly, it is retrospective, which may have led to potential bias in data reporting. The low prevalence of VNT in our cohort, although within the range reported in other studies, clearly impacts on the sensitivity of the algorithms tested. However, since our results are consistent with those found in other cohorts at different prevalence of VNT, our data support the validity of both TE-based criteria, regardless of the retrospective nature of the study.

Secondly, given the composition of our study cohort, our results apply mostly to viremic HCV-related cACLD patients, while they need confirmation in alcoholic and metabolic cACLD, less prevalent in our cohort.

Most studies [14–19] suggested that these criteria are useful in any cACLD etiology although few recent evidence does not seem to confirm the accuracy of the "Expanded Baveno VI" criteria in all-etiology cACLD [32], especially in cACLD patients with chronic cholestatic liver disease [33]. Whether TE thresholds could be optimized also according to the probe type, as recently suggested for non-alcoholic fatty liver disease (NAFLD) compensated cirrhosis patients [34–36], requires confirmation.

Thirdly, and probably more important, HCV infection can now be cured and HBV replication effectively suppressed in nearly all patients; anti-HBV and anti-HCV treatments improve inflammation and, in many cases, cause a steady decrease in liver stiffness [37,38]. Therefore, the LSM threshold identified to select viremic cACLD patients for screening endoscopy is most likely to prove inadequate for HBV suppressed or HCV cured cACLD patients. Clearly this point cannot be answered by the current study due to its design which included only patients with active and untreated viral hepatitis. Further studies are required to assess whether LSM still provides meaningful information in such cACLD patients with sustained viral response and, if so, to identify the adequate LSM threshold.

In conclusion, our study demonstrates the high accuracy of "LSM 25/platelet 125", and validates the "Expanded Baveno VI" criteria in viral untreated cACLD as well as in cACLD patients of non-viral aetiology, whereas it demonstrates that the "platelet 150/MELD 6" criteria are inadequate in such clinical settings. The Expanded Baveno VI "LSM 25/platelet 110" criteria seem the best advantageous approach, but, due to the variability of LSM and platelet count, two assessments on different days may be required at least for patients with LSM and platelet count close to the threshold limits.

Conflict of interest

Mauro Viganò is on the speakers' bureau of Roche and Bristol-Myers Squibb. He is also in the speakers' bureau of and received grants from Gilead. Mariagrazia Rumi is on speaker bureau of AbbVie and received research grants from MSD. Alessio Aghemo has received honoraria, fees and travel grants from Abbvie, Gilead, MSD, Janssen, BMS and research grants from Gilead and AbbVie. Pietro Lampertico advises, is on the speakers' bureau of Bristol-Myers Squibb, Roche, Gilead, GlaxoSmithKline, MSD and Abbvie. The other authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.12.025.

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