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Review Article

Non-invasive tools for compensated advanced chronic liver disease and portal hypertension after Baveno VII – an update

Daniel Segna[a], Yuly P. Mendoza[a], Naomi F. Lange[a,b], Susana G. Rodrigues[a], Annalisa Berzigotti[a,*]

[a] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, BHH D115, Bern 3010, Switzerland
[b] Graduate School for Health Sciences (GHS), University of Bern, Switzerland

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ABSTRACT

Non-invasive tests (NITs) and liver stiffness measurement (LSM) in particular, have entered clinical practice over 20 years ago as point-of-care tests to diagnose liver fibrosis in patients with compensated chronic liver disease. Since then, NITs use has evolved thanks to a large number of studies in all major etiologies of liver disease, and they have become important tools to stratify the risk of portal hypertension and liver-related events. The Baveno VII consensus workshop provided several novel recommendations regarding the use of well-established and novel NITs in the specific setting of portal hypertension screening, diagnosis and follow-up. The Baveno VII expert panels paid special attention to summarizing the existing data into simple clinical rules able to guide clinicians in their practice. The "rule of five" for LSM is a tool to stratify the risk of liver-related events, and LSM alone or in combination with platelet count, can be used now to rule-in and rule-out compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension, as well as to rule-out high-risk varices. Use of NITs in obese subjects with non-alcoholic fatty liver disease (NAFLD) and patients with viral hepatitis C that has been successfully treated, require specific knowledge. This review will update the reader on these aspects.

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1. Introduction

The introduction of non-invasive tests (NITs) has been a key advance for staging liver fibrosis. In addition, NITs currently provide prognostic value beyond the stage of fibrosis. Portal hypertension (PH) plays a pivotal role in the progression from the compensated to the decompensated stage of chronic liver disease (CLD) and consequently holds strong prognostic value to predict clinical decompensation [1]. The gold-standard method to assess and stage portal hypertension in compensated advanced chronic liver disease (cACLD) is the measurement of hepatic venous pressure gradient (HVPG) [2,3]. HVPG is considered normal from 1 to 5 mmHg; mild or pre-clinical sinusoidal PH is defined by an increase in HVPG from 6 to 9 mmHg [4]; and once the HVPG exceeds 10 mmHg PH is defined as "Clinically Significant Portal Hypertension (CSPH)". Patients with CSPH may develop esophageal varices [5], clinical decompensation (ascites, variceal bleeding, hepatic encephalopathy) [6,7], postsurgical decompensation [8], and are at a higher risk of hepatocellular carcinoma (HCC) [9]. Therefore, it is important to detect CSPH from both a prognostic and a therapeutic point of view [1,6,10]. In the recent Baveno VII Consensus Workshop, thanks to the data from the PREDESCI randomized controlled trial [11], the paradigm of treatment of portal hypertension has shifted from a bleeding-centric view (prevention of bleeding and rebleeding) to a much more comprehensive view. According to the new consensus, portal hypertension should be treated early, namely as soon as it can be proven, in order to avoid decompensation [12]. This makes the use of NITs to be used as surrogates of HVPG to assess the presence of CSPH in patients with compensated ACLD very attractive. This has been the subject of several studies over the last 10 years, leading to refined concepts on NITs use, and to the development of novel tools. In the recent Baveno VII consensus workshop, one of the sessions was devoted to assessment of PH, and the Panel on NITs extensively reviewed the literature and generated new recommendations, which will be discussed in the present review.

2. Non-invasive tools for cACLD

The term advanced chronic liver disease, ACLD refers to patients with late stages of chronic liver disease (CLD) [13] and substitutes

* Corresponding author.
E-mail address: annalisa.berzigotti@insel.ch (A. Berzigotti).

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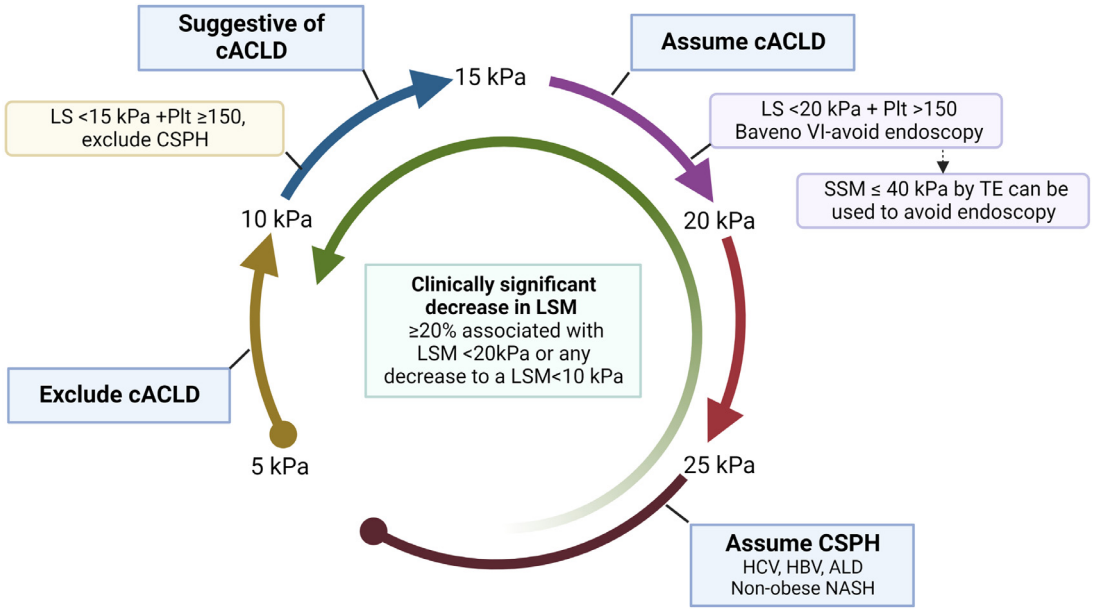

Fig. 1. Use of NITs according to the rule of five to rule-in and rule-out cACLD, CSPH and high-risk varices. Abbreviations. ALD, alcohol-related liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; NASH, non-alcoholic steatohepatitis.

the use of the term "cirrhosis" which is a histology-driven concept [14]. In the Baveno VI consensus workshop on portal hypertension in 2015, the term "compensated advanced chronic liver disease" (cACLD) was promoted based on NITs [10], allowing the early identification of advanced liver disease at an asymptomatic stage. This term aimed at covering the full spectrum of patients with severe liver fibrosis (bridging fibrosis) on histology and those with compensated cirrhosis [10,13]. In the Baveno VII consensus conference in 2021, the emphasis of the definition shifted from histological diagnosis to an even more pragmatic application, using the prognostic value of NITs to define cACLD, allowing accurate risk stratification regardless of the histological stage [12]. Accordingly, patients having liver stiffness measurement (LSM) by transient elastography (TE) >15 kPa are considered at high likelihood of cACLD in all etiologies; LSM values between 10 and 15 kPa are suggestive of cACLD, and LSM <10 kPa rules-out cACLD in the absence of other clinical/imaging signs [12]. The rationale of this definition comes from a thorough review of the most recent evidence that showed that CLD patients with LSM <10 kPa by TE have a very low 3-year risk (≤1%) of liver-related events (LRE), and the 3-year risk of LRE increases substantially between five to ten times with LSM >15 kPa, irrespective of CLD etiology [12,15–18].

In addition, the Baveno VII consensus encouraged using LSM irrespective of the technique for prognostication and monitoring [18]. Meta-analyses regarding the accuracy of point shear wave elastography (pSWE) and two dimensional shear wave elastography (2D-SWE) for liver fibrosis staging in comparison to liver biopsy, including mixed etiologies, showed that these techniques had accuracy similar to TE for advanced fibrosis detection with AUROCs >0.90 [19,20], and recent large multicenter study confirm the prognostic value of 2D-SWE [21]. Nonetheless, TE remains the technique for which the largest amount of evidence is available. As a prognostic indicator, the use of *rule-of-five* for the cut-off of LSM by TE (10-15-20-25 kPa) was recommended to estimate quickly and at the bedside the risk of decompensation and liver related-death regardless of the ACLD etiology (Fig. 1) [18,22]. In monitoring, LSM may be repeated every year in patients with cACLD and a *clinically significant decrease* in LSM was defined as any decrease to a LSM <10 kPa or decrease in LSM of ≥20% accompanied by LSM <20 kPa [12]. This definition is based on recent longitudinal studies showing a minimal risk of LRE in patients with follow-up LSM <10 kPa, while the risk of LRE and mortality remains high in patients with LSM >20 kPa [17,23,24]. Moreover, a study showed a significant reduction in the rate of LRE in patients with a decrease of LSM compared to patients with stable and increasing of LSM (3.8% vs. 6.2% vs. 14.4%) [17].

3. Non-invasive tools for clinically significant portal hypertension (CSPH) and varices

Simple laboratory tests and imaging tests have a limited sensitivity to rule-in and rule-out CSPH; among signs of CSPH on imaging (ultrasound, computerized tomography, magnetic resonance imaging), the presence of porto-systemic collaterals deserves to be mentioned since: (a) they are pathognomonic of CSPH in cACLD, and (b) they hold a negative prognostic significance [25]. LSM emerged as a significant advance to stratify the risk of CSPH, having a much higher accuracy than other existing NITs. The reliability of LSM by TE to identify the presence of CSPH has been assessed in patients with cACLD due to different etiologies, showing a correlation coefficient ranging between 0.55–0.82 [26]. In 2015, the Baveno VI consensus stated that a LSM >20–25 kPa can be used to identify the presence of CSPH in cACLD patients with untreated hepatitis C (HCV) or hepatitis B (HBV) [10]. Subsequently, several studies and two meta-analyses confirmed the good performance of these cut-offs for diagnosing CSPH in patients with cACLD owing to different causes [22,26–30]. Then, the recent Baveno VII consensus recommend LSM ≤15 kPa plus platelets ≥150 × 10/L to rule-out CSPH in the majority of etiologies and LSM ≥25 kPa was the best cutoff to rule in CSPH (specificity and positive predictive value >90%) in alcoholic liver disease, chronic hepatitis B, chronic hepatitis C, and non-obese patients with non-alcoholic steatohepatitis (NASH). However, in obese patients with NASH, the positive predictive value was lower (62.8%) [22]. The ANTICIPATE NASH model, including LSM by TE, platelet count and body mass index (BMI), can be used in patients with NASH cACLD and obesity to predict the risk of CSPH, although more validation is required [22]. In patients with intermediate values of LSM between 15 and 25 kPa ("gray zone"), the ANTICIPATE study has provided a model to predict CSPH based on LSM and platelet count, which might be used

as an additional tool to further improve risk stratification for CSPH according to the Baveno VII consensus [12].

The above-mentioned recommendations are in agreement with the EASL clinical practice guidelines, namely that LSM should be used to diagnose CSPH in patients with cACLD [31]. This has an important implication for clinical practice regarding to the use of nonselective beta-blockers (NSBBs) in patients with CSPH, which have been recently recommended since the findings of the PREDESCI study. This study provided evidence that the clinical decompensation was significantly lower with NSBB use versus placebo (from 27% to 17% over a median follow-up of 37 months: hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.26–0.97) in patients with cACLD and CSPH with no or small varices. The main impact was a reduction in the incidence of ascites from 20% to 9% with the use of NSBB [11]. Therefore, this data prompted researchers in Baveno VII to refine the recommendations. It is now suggested that in cACLD patients with NITs indicating presence of CSPH, independently of the presence of varices, treatment with NSBBs (preferably carvedilol as it is more effective at reducing HVPG) should be considered in order to prevent first clinical decompensation [12].

Regarding NITs for predictions of varices, a milestone recommendation of the previous Baveno Consensus (Baveno VI) regarded the use of NITs to rule-out high-risk varices, so allowing safely avoiding endoscopy. The simple combination of. platelet count $>150 \times 10^9$/L and LSM <20 kPa, could be applied to identify patients with cACLD and a very low risk (<5%) of high-risk varices, [10]. Following the publication of these "Baveno VI Criteria", a large number of studies validated this clinical rule in various etiologies. Some proposed to further refine the use of simple NITs by modeling them to better estimate individual risks, e.g. with the support of nomograms, and some additional ones suggested to expand them by increasing the LSM threshold and/or decreasing the platelet count threshold [32]. In a very recent meta-analysis of 28 studies, the Baveno VI criteria were fully validated; they displayed a pooled 99% negative predictive value for ruling out high-risk varices. Furthermore, a suboptimal performance was displayed when only 16 studies assessing the expanded Baveno VI criteria, which misclassified a significant number of patients, not fulfilling the required safety cut-off (<5% of missed high-risk varices) [33]. Therefore, the classical Baveno VI criteria remain the standard for identifying ACLD patients with very low probability of high-risk varices and who do not need screening gastroscopy. As the paradigm has shifted, and NSBB treatment is indicated for all patients with cACLD and CSPH, the Baveno VI criteria may only remain relevant in the subgroup of patients with contraindications or intolerance to NSBB, in whom endoscopy will be needed not only for screening, but also for potential therapy of high-risk varices in primary prophylaxis.

4. Spleen stiffness

Spleen stiffness measurement (SSM) has been recently proven as a more direct surrogate of PH as compared to LSM. SSM reflects augmented intrasplenic congestion and pressure due to splenic outflow obstruction, enlargement and hyperactivation of the splenic lymphoid tissue, as well as enhanced angiogenesis and fibrogenesis consequent to PH [34]. SSM is a sensitive NIT for CSPH, because while LSM mostly takes into account the fixed component of intrahepatic resistance, SSM likely additionally reproduces the increased portal flow associated with hyperdynamic splanchnic circulation [35]. In line with this hypothesis, it has been noted that SSM is increased in prehepatic causes of PH such as portal vein thrombosis [36], as well as in liver diseases with a presinusoidal component, such as cholestatic liver diseases, and possibly, as recently suggested, to non-alcoholic liver disease (NAFLD) [37].

Data from the last decade has demonstrated that SSM has an excellent discriminative capacity for high-risk gastroesophageal varices [38] and CSPH [39], and, contrarily to LSM, it might potentially guide and monitor treatment response [40,41]. A meta-analysis of 16 studies has shown that sensitivity and specificity of SSM was superior to LSM to diagnose oesophageal varices (SSM Sens 0.88, Spec 0.78 vs. LSM Sens 0.83, Spec 0.66) [38]. Regarding CSPH, in a meta-analysis of nine studies, spleen US elastography correlated well with HVPG, detecting CSPH with a sensitivity and specificity of 0.88 and 0.92 [39]. In HCV patients treated with direct-acting antivirals, SSM is a direct marker of persistent CSPH [42]. As for TE, studies showed that cut-off values above 50 kPa for SSM were associated with CSPH [39,43–45]. Lower thresholds of ≤41–46 kPa were able to rule out CSPH and high-risk varices [46,47]. In addition, SSM holds prognostic information, e.g. it may outperform LSM to predict patients who will develop a first variceal bleeding, and predicts a first clinical decompensation with better accuracy than LSM [43,48,49].

Some studies have underlined the beneficial use of SSM in addition to the Baveno VI criteria to further decrease the proportion of patients safely skipping screening endoscopy [50]. In a study including a prospective external validation cohort, Colecchia et al. showed that the combination of Baveno VI criteria and SSM ≤46 kPa model would have safely spared 37.4% of endoscopies, compared to 16.5% when using the Baveno VI criteria alone [46]. In patients with HBV cirrhosis suppressed with antivirals, spared endoscopies jumped from 37% to 61.6% by adding 50 Hz SSM to Baveno VI criteria [51].

One of major limitations of SSM by TE, until recently, was that it is only applicable in about 70% of cases. The high failure rate is linked to absence of splenomegaly. Additionally, SSM by TE using the liver 50 Hz module currently reaches a maximum of 75 kPa. Broadening the range to 150 kPa with appropriate software modifications has been suggested and tested [52]. In fact, a dedicated SSM probe (100 Hz) has been developed and found to have a better accuracy in detecting high-risk varices [47,53]. The novel 100 Hz spleen specific module was compared to the standard non-spleen specific 50 Hz module by TE. The 100 Hz SSM in combination with the Baveno VI criteria showed the best performance, sparing 38.1% of endoscopies, as compared to 26.5% of SSM 50 Hz + Baveno VI criteria and 8.1% of Baveno VI criteria alone [47].

In light of the growing evidence of SSM in CSPH and high-risk varices detection, the Baveno VII consensus has highlighted the role of SSM in CSPH cACLD due to viral hepatitis (untreated HCV; untreated and treated HBV). SSM can be now used routinely to rule-out and rule-in CSPH (SSM <21 kPa and SSM >50 kPa, respectively) [54].

Regarding treatment of CSPH, in patients who are not candidates for NSBBs fulfilling Baveno VI criteria, a SSM ≤40 kPa by TE can identify those at low probability of high-risk varices, avoiding endoscopy. Areas of further research in this field include the validation of the best cut-off using a 100 Hz specific TE-probe, as well other ultrasound elastography methods, and further validation of SSM in non-viral etiologies [54].

5. Dynamic use of NITs

Invasive procedures such as liver biopsy and HVPG measurements are not suited to frequent use due to their costs and limitations, which limits their utility in the monitoring of cACLD. NITs, on the opposite, are repeatable and are acceptable to the vast majority of patients. NITs are being increasingly tested, not only as diagnostic, but also as prognostic biomarkers [55]. While the prognostic value of a single measurement of NITs, LSM in particular, has been well proven, less data is available on the value of changes

over time (dynamic use of NITs).. A summary of available evidence is highlighted in Table 1 .

Both baseline LSM and an increase in LSM by TE were found to be independent predictors of death, liver decompensation and increase of at least 1 point in Child-Pugh score in a retrospective cohort with cACLD of any etiology (OR 1.12 and 1.02, respectively, both $p < 0.05$) [56]. Interestingly, the combination of baseline LSM $\geq$ 21 kPa and a LSM increase $\geq$10% was associated with a 47-fold risk increase for disease progression in the same study [56].

Furthermore, changes in FIB-4 were associated with an increased risk of future severe liver disease in a population-based Swedish cohort including 40,729 measurements [57]. Increases from low-intermediate to high-risk FIB-4 categories were associated with a substantially increased risk of progression to cirrhosis (adjusted HR 7.99 and 8.64, respectively), and belonging to a high-risk FIB-4 category both at baseline and on follow-up further increased the magnitude of this observation (adjusted HR 17.04; 95% CI 11.67–24.88) [57].

In a multicenter retrospective analysis of 533 patients with cACLD in NAFLD with a median follow-up of 35 months, an increase in LSM of at least 20% was independently associated with a 56–96% relative risk increase of hepatic decompensation, HCC, liver-related and all-cause mortality [17]. In addition, increases in FIB-4, APRI, and NAFLD Fibrosis Score were found to accurately predict progression to advanced liver fibrosis in a retrospective cohort study, as compared to serial liver biopsies [58].

In a nested analysis of 2′154 patients with advanced fibrosis due to NASH from four clinical trials of simtuzumab and selonsertib [59], increases in all NITs (including Enhanced Liver Fibrosis (ELF) score and LSM) were associated with histologic progression to cirrhosis and/or liver-related events in F3 patients. All NITs, but FibroTest, were associated with development of liver-related events in patients showing cirrhosis at baseline. Furthermore, in a prospective cohort study including 142 patients with primary sclerosing cholangitis (PSC), and serial LSM measurements, an increase in LSM was independently associated with a 7 to almost 12-fold increased risk of liver transplant, death, variceal bleeding, hepatic encephalopathy after a median follow-up of 3.4 years among patients with large-duct and any PSC with or without overlap, respectively [60]. Similarly, Corpechot et al. found increases in LSM to be associated with a 30% risk increase in all-cause mortality, liver transplant, or hepatic decompensation in a prospective cohort of 150 patients with primary biliary cholangitis (PBC) [61].

Decreases in LSM below the threshold of 12 kPa after effective antiviral therapy are associated with resolution of CSPH, and the current Baveno VII recommendations take into consideration this data (Fig. 2).

In conclusion, measuring changes in NITs over time (dynamic use), seems to refine the prognostic ability of single measurements in cACLD and may help better stratify the risk of liver-related complications and liver-related and all-cause mortality. Therefore, recent Baveno VII guidelines recommend monitoring LSM every 12 months [12]. Furthermore, a decrease in LSM by $\geq$20% was defined as clinically significant due to a substantially reduced risk of decompensation and liver-related death.

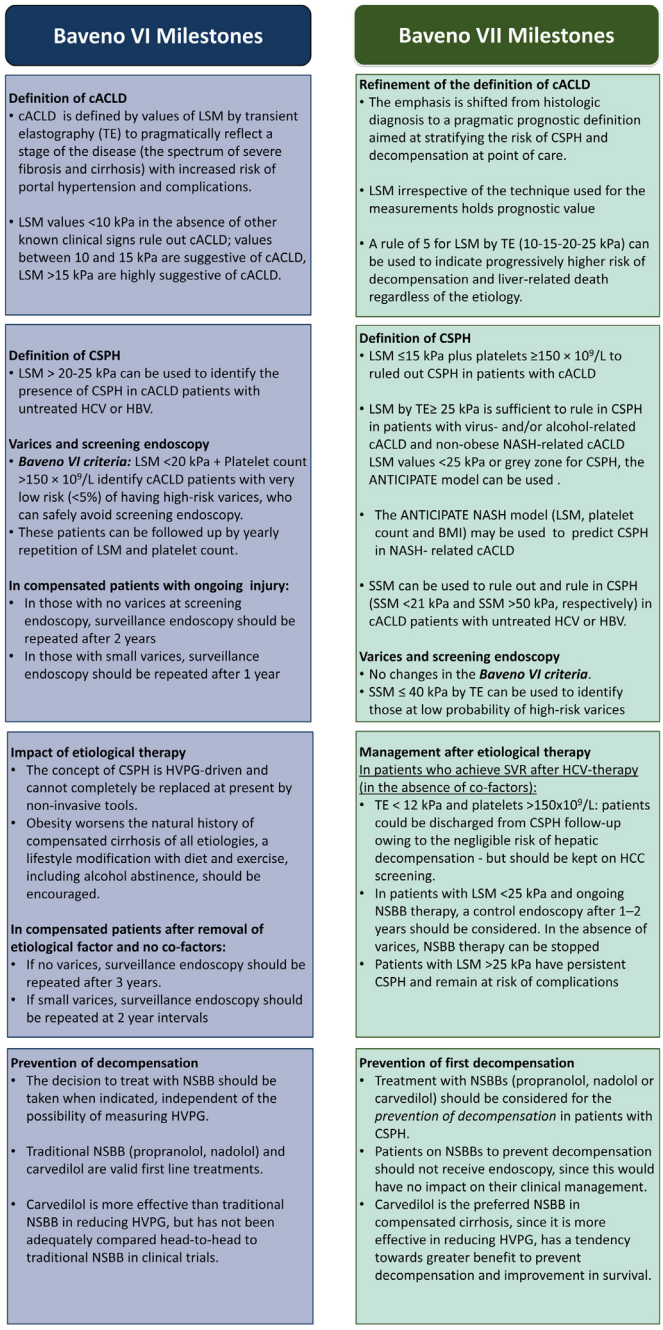

Fig. 2. Comparison of the Baveno VI and VII milestones regarding noninvasive tools for compensated advanced liver disease and portal hypertension. Abbreviations. cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; NASH, non-alcoholic steatohepatitis; NSBB, Nonselective beta-blockers; LSM, Liver stiffness measurement; TE, transient elastography.

6. Etiology specific aspects

6.1. Non-alcoholic steatohepatitis (NASH)

The Baveno VII statement acknowledges that NASH, compared to other etiologies of liver disease, presents important differences with regard to non-invasive diagnostic and prognostic assessment [12].

Notably, the prognostic role of HVPG in the NAFLD population is less clear compared to other etiologies [12]. Presence of CSPH at baseline, defined as an HVPG $\geq$10 mmHg, was found to be associated with a higher rate of liver-related events during a 24 month follow-up period in NASH patients with bridging fibrosis and compensated cirrhosis compared to patients without CSPH (HR, 2.83; 95% CI, 1.33–6.02; $p = 0.007$) [62]. Overall incidence of decompensation across all HVPG strata is higher in advanced liver disease due to NASH compared to hepatitis C [63]. Previous research also indicates that NASH patients show lower overall wedged hepatic venous pressure (WHVP) and HVPG measurements across fibrosis

Table 1
Significance of dynamic changes in non-invasive tests in chronic liver disease.

Author	Year	Study design	Study population	N	Non-invasive tests	Follow-up	Key points
NAFLD							
Pons et al.	2016	Retrospective cohort	Patients with cACLD, with baseline LSM ≥10 kPa, Child-Pugh score 5 and without previous decompensation	94	LSM by TE	43.6 months (median)	Both baseline LSM (OR 1.12, $p < 0.01$) and increase in LSM (OR 1.02, $P < 0.05$) were independent predictors for death, liver decompensation and impairment in at least 1 point in Child-Pugh score during follow-up. High-risk population defined by baseline LSM ≥21 kPa and increase in LSM ≥10% (OR 47.1%, 95% CI: 23–71%).
Hagström et al.	2020	Retrospective analysis of a prospective cohort	Participants with two FIB-4 measurements in a population-based Swedish cohort	40,729	FIB-4	2.4 years (mean)	Increase of 1 unit in FIB-4 associated with elevated risk of severe liver disease (aHR 1.81; 95% CI 1.67–1.96). Transitioning from low or intermediate to a high-risk group during follow-up associated with increased risk of severe liver disease (aHR 7.99 and 8.64, respectively), compared to a consistently low-risk group.
Petta et al.	2021	Multicenter retrospective cohort	NAFLD patients and histologically confirmed F3–F4 fibrosis and/or LSM by TE>10 kPa	533	LSM by TE	35 months (median)	Increase in LSM independently associated with elevated risk of hepatic decompensation (HR, 1.56; 95% CI 1.05–2.51), HCC (HR 1.72, 95% CI 1.01–3.02), overall mortality (HR 1.73, 95% CI 1.11–2.69), and liver-related mortality (HR 1.96, 95% CI 1.10–3.38).
Siddiqui et al.	2019	Retrospective cohort	NAFLD patients with 2 biopsies and accompanying laboratory data	292	FIB-4, NFS, APRI, FIB-4,AST/ALT ratio	2.6 years (median)	Changes in FIB-4 (c-statistics 0.81, 95% CI 0.73–0.81), APRI (0.82, 95% CI 0.74–0.89), and NFS (0.80, 95% CI 0.71–0.88 can detect progression to advanced fibrosis in patients with NAFLD.
Younossi et al.	2021	Nested prospective analysis in 4 randomized controlled trials	Patients with advanced NASH (NASH Clinical Research Network stage F3 or F4) from 4 multinational clinical trials of simtuzumab and selonsertib.	2154	ELF, NFS, FIB-4, LSM by TE, Fibrotest	16 months (median)	Increase in all NIT associated with elevated risk of histologic progression to cirrhosis or liver-related events in the F3 group ($p < 0.01$). Increase in ELF, NFS, FIB-4, and LSM associated with an increased risk of liver-related events in the F4 group ($p < 0.01$).
Cholestatic and Autoimmune liver disease							
Corpechot et al.	2014	Prospective cohort	Patients with PSC with any fibrosis stage	142	LSM by TE	3.9 years (mean)	Increase in LSM independently associated with elevated risk of death, liver transplant, ascites, hepatic encephalopathy, gastrointestinal bleeding related to portal hypertension, cholangiocarcinoma, or HCC (large-duct PSC: HR 7.3, 95% CI 2.9–18.1, overall population including PSC-AIH overlap: HR 11.9,95% CI, 5.2–27.4).
Corpechot et al.	2012	Prospective cohort	Patients with PBC with any fibrosis stage	150	LSM by TE	2.6 years (mean)	Progression of liver stiffness in PBC is predictive of death, liver transplant, or liver decompensation including ascites, variceal bleeding, hepatic encephalopathy, HCC, doubling of total serum bilirubin level above 6 mg/dL, or minimal criteria for liver transplant (HR: 1.3; 95% CI: 1.2–1.5).
Hartl et al.	2018	Prospective cohort	Patients with AIH with any fibrosis stage	125	LSM by TE	2.7 years (mean)	Complete biochemical remission is a reliable predictor of a good prognosis in AIH and leads to fibrosis regression that can be monitored by LSM. Patients in complete biochemical remission of AIH showed a considerable decrease in LSM (7.5%/year; 95% CI 11% to 2.0%; $p < 0.01$), whereas patients without complete biochemical remission no statistically significant change in LSM.
HCV before and after sustained virological response							
Mandorfer et al.	2016	Retrospective cohort	HCV patients with CSPH at baseline prior to DAA therapy	60	LSM by TE	217 days (median)	Excellent diagnostic accuracy for CSPH at a cut-off of 25.3 kPa follow-up LSM (AUROC 0.93, 95% CI 0.90–1.00), at a cut-off of 27.2 kPa or baseline TE (AUROC 0.90, 95% CI 0.82–0.98). Absolute and relative LSM changes from baseline not accurate enough. Optimized baseline and follow-up LSM cut-offs were 18.8 and 12.4 kPa to rule-out CSPH after DAA therapy.
Pons et al.	2020	Prospective cohort	Patients with HCV and cACLD after DAA treatment	572	LSM by TE, albumin (serum)	2.8 years (median)	Baseline LSM ≥20 kPa with no LSM decrease during follow-up associated with increased risk of liver decompensation (HR 39.7; 95% CI 4.4–355.4). Albumin levels at follow-up (HR 0.08, 95% CI 0.02–0.25) and LSM <10 kPa at follow-up (HR 0.33, 95% CI 0.11–0.96) independently associated with a decreased HCC risk.
Vergniol et al.	2014	Prospective cohort	Patients with chronic HCV of any fibrosis stage (44% F2-F4)	1025	LSM by TE, APRI, FIB-4	38 months (median)	LSM/FIB-4 at baseline, change in LSM/FIB-4 and SVR independently predicted survival after DAA treatment.

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Table 1 (*continued*)

Author	Year	Study design	Study population	N	Non-invasive tests	Follow-up	Key points
Vutien et al.	2020	Retrospective cohort	HCV patients with at least one liver stiffness before ($n = 492$) or after therapy	124 (longi-tudi-nal)	LSM by TE	27.3 months (median)	Post-treatment LSM >20 kPa, associated with increased risk of decompensated cirrhosis (adjusted HR 3.85, 95% CI 1.29–11.50) and the composite outcome of death, liver transplant, decompensated cirrhosis or HCC (adjusted HR 1.95, 95% CI: 1.07–3.56), compared to ≤12.5 kPa. Increasing or stable LSM post-treatment associated with significant association with death or liver transplant (adjusted HR 7.93, 95% CI 1.59–39.47) and the composite outcome (adjusted HR 4.83, 95% CI 1.12–20.86). No significant associations between pre-treatment liver stiffness and any outcomes on multivariable analysis.
Ravaioli et al.	2018	Retrospective cohort	DAA-cured HCV patients with cirrhosis	139	LSM by TE	15 months (median, after end of DAA)	Decrease in LSM significantly lower in patients with new HCC (−18.0% vs. −28.9% $p < 0.05$) than in controls. Change in LSM < −30% independently associated with HCC development.
Lens et al.	2017	Prospective cohort	DAA-cured HCV patients with cirrhosis and CSPH	226	LSM by TE	Maximum 6 months prior to, follow-up 24 weeks after treatment	1/3 of patients with LSM< 13.6 kPa after SVR with ongoing CSPH. Cut-off at 13.6 kPa is not reliable enough for ruling out CSPH after SVR (Sensitivity 88%, Specificity 54%, positive predicate value 87%, negative predictive value: 57%). Higher baseline HVPG and a lower decrease in LSM after treatment associated with persisting CSPH after SVR. Changes in TE do not correlate with HVPG and
Mauro et al.	2018	Retrospective cohort	HCV-infected liver transplant recipients undergoing antiviral treatment with subsequent SVR 12	84	LSM by TE, ELF	12 months (median)	One year after SVR, LSM and ELF showed an excellent diagnostic accuracy to rule out advanced fibrosis (LSM >10.6 kPa, AUROC 0.90, 95% CI 0.84–0.0.96; ELF >10.83, AUROC 0.88, 95% CI 0.79–0.98) and CSPH (LSM > 11.3 kPa, AUROC 0.88, 95% CI 0.80–0.98). ELF showed a fair diagnostic accuracy at a cut-off > 10.25 for CSPH
Piedade et al.	2021	Retrospective cohort	HCV patients with TE ≥ 10 kPa at baseline and serial measurements before DAA and after SVR	456	LSM by TE	2.3 years (median)	LSM decrease ≥ 20% after SVR decreases the risk of liver-related events or death (HR = 0.45, 95% CI 0.21–1.02)
HBV							
Kim et al.	2013	Prospective cohort	Patients with histologically F3 or F4 fibrosis due to HBV receiving antiviral therapy	103	LSM by TE	6 months	Changes in LSM significantly correlated with liver-related events (ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, HCC and liver–related death). Increased LSM > 11.6 kPa at both baseline and follow-up showed the highest incidence (11.05% per person-year) and those with consistent LSM < 11.6 kPa the lowest incidence (1.22% per person-year)
Ye et al.	2021	Prospective cohort	Treatment-naive HBV patients with decompensated cirrhosis awaiting antiviral treatment at baseline	149	LSM by 2D-SWE	34.8 months	Last follow-up LSM (HR 1.11, 95% CI 1.04–1.18) was the only independent risk factor for the occurrence of liver-related events (spontaneous bacterial peritonitis, variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, and HCC) rather than pre-treatment or dynamic changes in LSM.
Kim et al.	2018	Prospective cohort	Patients with HBV-related advanced fibrosis or cirrhosis	209	LSM by TE	2 years	LSM < 11.6 kPa after two years of antiviral therapy was independently associated with a lower risk of HCC development (HR = 0.49, 95% CI 0.23–0.92)
Liu et al.	2020	Retrospective cohort	Patients with HBV-related HCC awaiting operation	158	LSM by TE	12 months	LSM changes were independent factors associated with overall survival (HR 1.89). LSM changes were independent factors for HCC-free survival (HR 1.52).

Abbreviations: LSM: liver stiffness measurement, 2D-SWE: two-dimensional shear-wave elastography, aHR: adjusted hazard ratio; AIH: autoimmune hepatitis; ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; APRI: aspartate aminotransferase-platelet ratio; AUROC: area under the receiver operating characteristic curve; cACLD: compensated advanced chronic liver disease; CI: confidence interval; CSPH: clinically significant portal hypertension; DAA: direct-acting antiviral agents; ELF: enhanced liver fibrosis test; FIB-4: Fibrosis-4 score; HR: hazard ratio; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HVPG: hepatic venous pressure gradient; LSM: liver stiffness measurement; N: number of patients with baseline and follow-up non-invasive tests; OR: Odds ratio; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NFS: non-alcoholic fatty liver disease fibrosis score; NIT: non-invasive tests; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; SVR: sustained virologic response; TE: liver stiffness by transient elastography (Fibroscan®).

stages, compared to other etiologies (3.4 ± 2.4 vs. 7.5 ± 11 mm Hg/stage; $p = 0.01$) [64]. These findings support the presence of more severe liver disease despite detection of comparatively low HVPG values in NASH-cirrhosis. Conversely, HVPG values in line with presence of CSPH (≥10 mmHg) have been described in individuals with NASH without histological fibrosis [65], although the extent of this phenomenon has been debated [66].

Several mechanisms have been proposed to explain this mismatch between HVPG and prognostic and diagnostic outcomes in NASH [37]. For one, it is hypothesized that HVPG may be less accurate in assessing portal pressure in NASH. In a case-control study of decompensated cirrhotic patients undergoing Transjugular intrahepatic portosystemic shunt (TIPS), WHVP underestimated portal pressure (PP) in the NASH group compared to matched patients with alcohol- or HCV-related cirrhosis [67]. This indicates a possible systematic measurement error and thus decreased accuracy of HVPG for detection of PP in NASH.

Obesity has been proposed to modulate the correlation between NITs and reference standard in the assessment of severity of liver disease [24,68]. In a cohort of patients with different etiologies of cACLD defined according to the Baveno VI criteria (LSM ≥10 kPa), undergoing both LSM by TE and HVPG assessment, overall prevalence of CSPH was found to be markedly lower among obese NASH patients [24]. The predictive ability of LSM to detect CSPH was demonstrated to decrease with increasing BMI [24]. The derived ANTICIPATE-NASH model, including LSM, BMI and platelet count, to predict CSPH in NASH is newly recommended in the Baveno VII statement [12,24]. Taking into consideration, however, that HVPG may not be an ideal reference standard for PP assessment in NASH, further validation of the ANTICIPATE-NASH as a prognostic score may be warranted.

Besides LSM, blood-based markers have demonstrated impaired test performance in sub-populations of NASH. The performance of several blood-based NITs for detection of different fibrosis stages has been shown to vary by degree of obesity [68]. In patients with diabetes mellitus type 2, both routine and patented NITs have been shown to perform less well [69,70].

Overall, risk stratification with commonly used non-invasive tools according to established cut-offs may be less reliable in the NASH population, especially those with obesity and diabetes.

Magnetic resonance elastography is being increasingly used in clinical trials, and has recently proven prognostic value for the prediction of clinical decompensation [71]. Its use in European centers is still limited by its cost and suboptimal availability.

6.2. Chronic hepatitis after removal of the etiologic agent

There is increasing knowledge on the role of NITs in patients who achieved viral suppression (HBV) or cure of the underlying viral infection (HCV) after antiviral therapy, and this topic has been discussed in detail in the Baveno VII consensus.

6.3. Chronic hepatitis C after DAA treatment

Most longitudinal studies agree on a significant decrease in LSM, FIB-4 and APRI after successful DAA treatment in the vast majority of patients achieving sustained virological response (SVR), while the amplitude and definition of predictors and subpopulation at risk for progression of fibrosis, development of liver-related events/death and all-cause mortality is quite heterogeneous [23,24,72–81]. Furthermore, the diagnostic accuracy of LSM, APRI and FIB-4 for ruling out cirrhosis was shown to be poor even three years after DAA therapy [82].

The predictive value of NITs changes for HVPG variations and for clinical outcomes deserves special attention (Table 1).

Dynamic LSM values did not correlate with changes in HVPG in 226 patients with HCV cirrhosis 24 weeks after successful DAA treatment. Importantly, one third of patients, with a reduction in LSM to below 13.6 kPa after SVR, still had CSPH at this time point [75]. In a second retrospective study from a different center, however, in 226 patients with HCV cirrhosis and CSPH assessed by serial HVPG measurements, both follow-up and baseline LSM showed an excellent predictive value for persistent CSPH after SVR. Here again, absolute and relative changes in LSM from baseline were not accurate enough to rule out CSPH [76].

In HCV-infected liver transplant recipients undergoing antiviral treatment, both LSM and ELF at 1 year after SVR12 showed an excellent diagnostic accuracy to rule out advanced fibrosis (TE < 10.6 kPa, ELF < 10.83), but only LSM reliably ruled out CSPH (TE < 11.3 kPa) [77]. Of note, SSM unlike LSM by TE and acoustic radiation force impulse (ARFI) did not significantly decrease in a prospective cohort including 54 patients with HCV-associated cirrhosis after a follow-up of 3 years after treatment [73].

In light of evidence showing that CSPH continues to decrease over time after SVR, and might stabilize only in the medium-long term, the above-mentioned, apparently contradictory data have been re-assessed at the Baveno VII consensus. An individual patient data meta-analysis was recently published [83]. The authors showed that among cACLD patients, the prevalence of CSPH decreased from 80% to 54%, and that the correlation between LSM and HVPG improves after SVR ($r = 0.60$ vs. 0.45 pre-treatment); the correlation between platelet count and HVPG remained unchanged. Combining post-treatment LSM/platelet count yielded a high diagnostic accuracy for post-treatment-CSPH (AUC: 0.884; 95%CI: 0.843–0.926). Post-treatment-LSM<12 kPa & platelet count >150 × 10^9/L excluded CSPH (sensitivity: 99.2%), while LSM ≥ 25 kPa was highly specific for CSPH (93.6%).

The Baveno VII recommendations hence suggest that cured HCV patients with LSM < 12 kPa and platelets >150 × 10^9/L post treatment could be discharged from follow-up for CSPH owing to the negligible risk of high-risk varices and hepatic decompensation [12].

Regarding clinical outcomes, only LSM > 20 kPa after SVR 12 was associated with increased risks for decompensated cirrhosis (adjusted HR 3.85 vs ≤12.5 kPa) and the composite endpoint of the latter, death, need for liver transplant, and HCC (adjusted HR 1.95) after 27.3 months in a retrospective analysis [81]. Moreover, decrease in LSM ≥ 20% after SVR decreased the risk of liver-related events or death in another retrospective cohort from Portugal [84]. Another large prospective study identified LSM/FIB-4 at baseline, changes in LSM/FIB-4 and SVR as independent predictors for survival after DAA treatment [80]. Furthermore, baseline LSM ≥20 kPa with no improvement during follow-up was associated with a 40-fold increased risk of decompensated liver cirrhosis in a prospective cohort study [24].

Finally, prediction scores for risk of CSPH, decompensation, and development of HCC have been proposed for HCV patients with cACLD and SVR [23,72,85] (Fig. 2).

6.4. Suppressed HBV infection following antiviral treatment

Evidence on the role of NIT after adequate HBV suppression has also been accumulating during the last years, which is reflected by recently published guidelines in the field [12,86].

While the association between increased baseline LSM and higher risk for hepatic decompensation has already been investigated previously [87], the dynamic use of NITs and its prognostic accuracy for liver-related events and mortality deserve further investigation in this population (Table 1).

Early LSM changes within 6 months of initiation of antiviral therapy were assessed in a prospective cohort including 103 HBV

patients with cACLD. Using a threshold of 11.6 kPa at baseline and follow-up, the lowest risk for liver-related events was found in patients with consistently low LSM or decreasing LSM during follow-up, whereas the highest risk category was found in serial TE ≥ 11.6 kPa and those who changed from values below to above this threshold after antiviral treatment [88].

Repeated measurements of LSM using 2D-SWE predicted liver-related outcomes in a prospective cohort of 149 patients with decompensated HBV cirrhosis after a follow-up of 34.8 months [89]. There is very scarce data on the correlation of HVPG and LSM in the context of treated HBV, and this is a field for future research.

7. Conclusion

NITs use in the context of cACLD and portal hypertension continues to grow. The use of LSM as a simple tool to trigger NSBB initiation in patients with cACLD could potentially prevent a large number of decompensating events, if widely used. This is an attractive field for clinical research. However, several areas require further work. About 40–50% of patients belong to the "gray zone" of LSM 15–25 kPa, in which a precise estimation of the risk of CSPH is not possible. Whether SSM can be used to reduce the proportion of patients in this indeterminate group is currently matter of research, and pilot data suggest that this might be the case [90]. Further refining NITs in emerging etiologies such as NAFLD in obese subjects and patients with mixed etiologies is urgently needed; while combining unrelated NITs (e.g. FIB-4 and LSM, or LSM and SSM) might reduce misclassification of patients [15], a precise discrimination of patients with and without CSPH is still not achievable. How to exactly account for co-factors of progression of liver disease in the context of patients cured from their primary etiology remains an open field for research. Finally, novel, blood-based markers of CSPH to be used alone or combined to LSM (and SSM) to guide treatment, use of dynamic NIT values, and potential use of SSM to predict treatment response in the emerging etiologies of liver disease remain unmet needs in this field.

Declaration of Competing Interest

None declared.

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