Compensated Advanced Chronic Liver Disease (cACLD)

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From Baveno VI to Baveno VII

Important new concepts were introduced by Baveno VI consensus guidelines in 2015 regarding the extended use of noninvasive tests, especially transient elastography (TE), for the management of patients in the advanced stages of chronic liver disease (CLD) [1]. The new term "compensated advanced chronic liver disease" (cACLD) was introduced; indications about diagnosing clinically significant portal hypertension (CSPH) were provided, and new noninvasive criteria for avoiding screening endoscopies for varices were developed.

The reasons for the introduction of the cACLD term were several but originated in a progressive change in clinical practice when managing CLD patients, due to the appearance of liver stiffness measurement (LSM) by elastography, and more specifically transient elastography (TE) [2]. The widespread use of TE allowed the early detection of CLD patients with advanced disease at risk of developing CSPH, and consequently, liver-related events during follow-up. This fact has been paralleled by a progressive reduction in the use of liver biopsy for staging purposes in CLD. Therefore, the term cACLD was an attempt to denominate a new clinical scenario derived from the extensive use of TE as an important staging method for CLD, also reflecting that, in the absence of a liver biopsy, it was not possible to distinguish between severe fibrosis and cirrhosis. Because of the clinical implications of this new entity, it was advised that suspected cACLD patients should be referred to a liver disease specialist.

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Based on a very pragmatical and empirical approach, at the Baveno VI conference, it was decided to use a dual TE cutoff approach to maximize the selection of two groups of patients with very different risks of developing CSPH, and consequently liver-related outcomes. Obviously, the proposed cutoffs were derived from the extensive literature reflecting the relationship between different TE cutoffs and liver fibrosis stages in different etiologies of CLD. Consequently, LSM <10 kPa was proposed as a safe cutoff for excluding (ruling out) cACLD, selecting a population of CLD patients with a low prevalence of severe fibrosis/cirrhosis and portal hypertension, and a low risk of developing CSPH and liver-related events, while LSM >15 kPa was highly suggestive (ruling in) of cACLD, selecting CLD patients with a high prevalence of severe fibrosis/cirrhosis and portal hypertension, and at risk of developing CSPH and liver-related events.

Since the publication of the guidelines in 2015, many studies have used the term cACLD; until September 2021, there have been 79 publications indexed in PubMed with the term "cACLD" or "compensated advanced chronic liver disease," 27 of them published in 2020. In a significant proportion, the main topic of the studies where the term was used was the validation of noninvasive criteria to avoid screening endoscopy for varices.

As explained in a previous chapter, in the present consensus workshop, a panelist's survey showed that most (85%) experts believe that the cACLD concept is clinically useful and most of them use it in their clinical practice. Likewise, 76% believe that the cutoff points established in Baveno VI (10 kPa and 15 kPa) for ruling-out and ruling-in are accurate. Despite this, 83% consider that the cutoffs are dependent on the etiology of liver disease.

From Histological Staging to a Noninvasive Clinical Staging of Chronic Liver Disease

Liver histology has been the reference tool for staging CLD through the identification of the degree of liver fibrosis. Liver fibrosis correlates with patient outcomes represented by the development of liver-related events during follow-up. However, the limitations of liver biopsy are widely known (complications, invasiveness, sampling error, etc.); additional drawbacks are the low reliability of liver biopsy evaluation [2], inadequacy for repeated measures, and lack of linearity and granularity in the information provided. On top of that, modern personalized medicine is moving to the use of biomarkers, patients do not like liver biopsies, and their voice and patient centrality are to be increasingly considered. Finally, other current issues like the Covid-19 pandemic will push to find alternatives to invasive procedures.

LSM by elastography possesses many of the desired theoretical properties of a good biomarker and almost none of the limitations and drawbacks of liver biopsy. One of the conceptual problems in hepatology is that we tend to refer and validate every new tool to what we consider a "gold standard," and in that case liver biopsy. However, pretending that a new biomarker is a perfect diagnostic tool of an imperfect standard is probably unrealistic.

Considering the dual TE cutoff approach to cACLD, it would be expected that the ruled-in population (LSM >15 kPa) would be enriched with patients with a high prevalence (positive predictive value—PPV) of severe fibrosis/cirrhosis, portal hypertension, and at higher risk of liver outcomes. The other way around would be expected with the population selected by the ruling out criteria (LSM <10 kPa) showing a low prevalence (1-negative-predicted value, NPV) of these features. Between these two populations, we will obviously have a grey zone with patients showing intermediate values of these clinical features.

In order to be clinically sound and scientifically valid, the two proposed cutoffs should be able to identify these high and low-risk populations. Regarding liver histology, it would be desirable that the prevalence of severe fibrosis/cirrhosis in each group reached 90% and 10%, respectively, with intermediate values in the grey zone. However, considering the imperfections of liver biopsy as a reference tool, prevalences of 80% and 20% might be considered acceptable. Far more important than that, these three subgroups of patients should present very different risks of clinical events during follow-up, indicating that subgrouping of CLD patients based on LSM values holds prognostic implications independently of not selecting populations with a 100% and 0% prevalence of severe fibrosis/cirrhosis.

Other relevant issues to be considered concerning the cACLD LSM cutoffs are in relation to practical issues of daily clinical practice; practitioners tend to use what is simple and readily applicable. In that sense, and provided that the scientific value is not lost, the use of the same cutoffs for different etiologies and values with numbers easy to remember are helpful assets.

Finally, changes in the proposed cACLD cutoffs should be balanced against losing important clinical relevance in the identification of the LSM subgroups.

Excluding cACLD (LSM <10 kPa)

Several studies have intended to evaluate the cACLD cutoffs performance by analyzing their ability to detect and exclude severe fibrosis/cirrhosis or portal hypertension. These studies allow us to assess the prevalences of these clinical indicators in the populations selected by the two cACLD cutoffs in the different etiologies of CLD (Table 8.1) [3–9].

As shown in Table 8.1, the prevalence of severe fibrosis/cirrhosis is low in patients with LSM <10 kPa, around 10% in most studies, but ranging between 4% and 20% depending on the etiology of CLD [3–8]. The highest prevalences were observed in hepatitis B patients (16.3%) [5] and obese non-alcoholic fatty liver disease (NAFLD) patients (27%) from the study by Wong et al. [3] using the XL probe of the TE. As seen, other studies with more patients, observed lower prevalences of severe fibrosis/cirrhosis in NAFLD patients with LSM <10 kPa. In the case of NAFLD, it is plausible that a selection bias might exist to obtain histology from patients who are candidates for clinical trials, not adequately reflecting the general population with NAFLD.

Table 8.1 Presence of compensated advanced chronic liver disease (cACLD) clinical features (Fibrosis F3–F4 or hepatic venous pressure gradient-HVPG >5 mmHg) in the three subgroups defined by liver stiffness cutoffs

Study	Etiology	No. of patients	Patient selection	XL probe	cACLD feature	cACLD subgroups		
						<10 kPa	10–15 kPa	>15 kPa
Wong et al. [3]	Non-obese NAFLD	231	All patients	No	F3-F4	21/158 (13.3%)	–	22/24 (91.4%)
	Obese[a] NAFLD	194	=	Yes	=	35/129 (27.1%)	–	25/29 (86.2%)
Piccinni et al. [4]	Mixed[b]	111	≥10 kPa	Yes	=	–	27/47 (58%)	43/64 (67%)
Papatheodoridi et al. [5]	Mixed	5483	All patients	No	=	431/3606 (12.0%)	469/891 (52.6%)	817/986 (82.9%)
	HCV	2864	=	=	=	243/1966 (12.4%)	265/456 (58.1%)	371/442 (83.9%)
	HBV	704	=	=	=	85/522 (16.3%)	59/103 (57.3%)	67/79 (84.8%)
	Alcohol	932	=	=	=	46/515 (8.9%)	52/118 (44.1%)	253/299 (84.6%)
	NAFLD	983	=	=	=	57/602 (9.5%)	93/214 (43.5%)	125/167 (74.9%)
	Non-obese Patients	3530	=	=	=	310/2496 (12.4%)	288/496 (58.1%)	473/538 (87.9%)
	Obese[a] Patients	1056	=	=	=	72/560 (12.9%)	105/242 (43.4%)	189/254 (74.4%)
Ji et al. [6]	MAFLD[c]	220	=	No	=	5/124 (4.0%)	9/57 (15.8%)	22/39 (56.4%)
	Non-obese Patients	174	=	=	=	5/110 (4.6%)	7/35 (20.0%)	16/29 (55.2%)
	Obese[a] Patients	46	=	=	=	0/14 (0%)	2/22 (9.1%)	6/10 (60.0%)
Zhou et al. [7]	NAFLD	830	=	Yes	=	45/582 (7.7%)	74/161 (46.0%)	62/87 (71.3%)
	Non-obese NAFLD	433	=	=	=	30/358 (8.4%)	31/54 (57.4%)	16/21 (76.2%)
	Obese[d] NAFLD	397	=	=	=	15/224 (7.4%)	43/107 (40.2%)	46/66 (69.7%)
Rivera et al. [8]	NAFLD	501	All patients	Yes	=	27/218 (12.4%)	63/161 (39.1%)	91/122 (74.6%)
	Non-obese NAFLD	164	=	=	=	10/86 (11.6%)	22/42 (52.4%)	32/36 (88.9%)
	Obese[a] NAFLD	332	=	=	=	17/131 (13.0%)	40/116 (34.5%)	59/85(69.4%)

(continued)

Table 8.1 (continued)

Study	Etiology	No. of patients	Patient selection	XL probe	cACLD feature	cACLD subgroups		
						<10 kPa	10–15 kPa	>15 kPa
Pons et al. [9]	Mixed	836	≥10 kPa	No	HVPG >5 mmHg	–	130/211 (61.6%)	564/625 (90.2%)
	HCV	358	=	=	=	–	69/90 (76.7%)	253/268 (94.4%)
	HBV	27	=	=	=	–	6/8 (75%)	19/19 (100%)
	Alcohol	203	=	=	=	–	20/24 (83.3%)	176/179 (98.3%)
	NAFLD[c]	248	=	Yes	=	–	35/89 (39.3%)	116/159 (73%)
	Non-obese NAFLD	101	=	=	=	–	14/35 (40%)	55/66 (83.3%)
	Obese[a] NAFLD	133	=	=	=	–	19/53 (35.8%)	54/85 (63.5%)

[a] BMI ≥30 kg/m^2
[b] 36% obese, 64% metabolic component
[c] 129 patients had coexisting chronic liver disease (mainly chronic hepatitis B)
[d] BMI ≥28 kg/m^2
[e] 68.5% with XL probe availability
NAFLD non-alcoholic fatty liver disease, *HCV* hepatitis C virus, *HVB* hepatitis B virus, *MAFLD* metabolic-associated fatty liver disease

In Table 8.2, several studies that have evaluated different liver-related outcomes in the populations selected by the <10 kPa cutoff or similar ruling-out cACLD are described [10–21]. As shown, liver-related events are low in patients with LSM <10 kPa, independently of the etiology; in most studies, cumulative incidence rates at 3 years or event rates are around or below 1%. Data from a collaborative study with 2638 NAFLD patients from France, Hong Kong, Canada, and Spain indicate that the cumulative rate of any liver-related event in 1820 patients with LSM <10 kPa during 3 years of follow-up was 0.1% (unpublished data) (Fig. 8.1). In addition, in the specific population of 365 patients with LSM between ≥8 and <10 kPa, the liver event rate was 0.

Some authors have proposed to lower the cutoff for ruling out cACLD to LSM <7–8 kPa with the aim of increasing the sensitivity to exclude severe fibrosis/cirrhosis, minimizing the false-negative rates [5]. As largely explained, we do not support the concept that cACLD and the TE values that define it should become perfect diagnostic tools for excluding or diagnosing severe fibrosis/cirrhosis, but rather clinically useful rules to categorize CLD patients. By lowering the 10 kPa cutoff, the grey zone increases with patients who are at very low risk of events, and consequently, referrals to hepatologists will increase with such patients. In addition, the transition from normal LSM or absence of fibrosis to possible severe fibrosis will almost disappear.

Despite not being labeled as cACLD, patients with abnormal TE values but below <10 kPa should be monitored for changes indicating progression to cACLD. Since the risk of liver events in these patients is very low within a 3-year time period, reassessment in 2–3 years seems a reasonable strategy.

Table 8.2 Liver-related events during follow-up in different studies evaluating patients with chronic liver disease selected by a liver stiffness value below 10 kPa or similar values

Study	Etiology	Patients (*n*)	Liver event	Follow-up (months)	LSM cutoff	Event rate
Masuzaki et al. [10]	HCV	866	HCC	36 (mean)	≤10 kPa	CI: 0.4% (3 years) ER: 2/511 (0.4%)
Fung et al. [11]	HBV	528	LRD + HCC	35 (median)	<10 kPa	CI: 0 (3 years) ER: 0/445
Vergniol et al. [12]	HCV	1457	OS	47.3 (median)	≤9.5 kPa	OS: 96% (5 years)
Jung et al. [13]	HBV	1130	HCC	30.7 (median)	≤8 kPa	CI: 1.58% (3 years)
Coperchot et al. [14]	PBC	150	LRE	28 (mean)	≤9.6 kPa	ER: 1/113 (0.8%)
Klibansky et al. [15]	Mixed	400	LRE	28 (median)	<10.5 kPa	ER: 3/224 (1.3%)
Pang et al. [16]	Mixed	2052	LRE	15.6 (median)	<10 kPa	CI: 3.9% (3 years)
Coperchot et al. [17]	PSC	168	LRE	48 (mean)	≤9.9 kPa	ER: 6/112 (5%) OS: 97% (3 years)
Tatsumi et al. [18]	HCV	470	HCC	23 (median)	≤12 kPa	CI: 0 (2 years) ER: 1/363 (0.3%)
Shili-Masmoudi et al. [19]	NAFLD	2245	LRE	27 (median)	≤12 kPa	CI: 0.2% (3 years) OS: 96.5% (3 years)
Rasmussen et al. [20]	ALD	443	LRE[a]	49 (median)	<10 kPa	CI: 1.1% (3 years) ER: 9/303 (3%)
Grgurevic et al. [21]	T2D-78% NAFLD	454	LRE	25 (median)	<9.6 kPa	ER: 0

[a] Including alcoholic hepatitis

HCV hepatitis C virus, *HBV* hepatitis B virus, *PBC* primary biliary cholangitis, *PSC* primary sclerosing cholangitis, *NAFLD* non-alcoholic fatty liver disease, *ALD* alcoholic liver disease, *HCC* hepatocellular carcinoma, *CI* cumulative incidence, *ER* event rate, *LRD* liver-related mortality, *OS* overall survival, *LRE* liver-related events

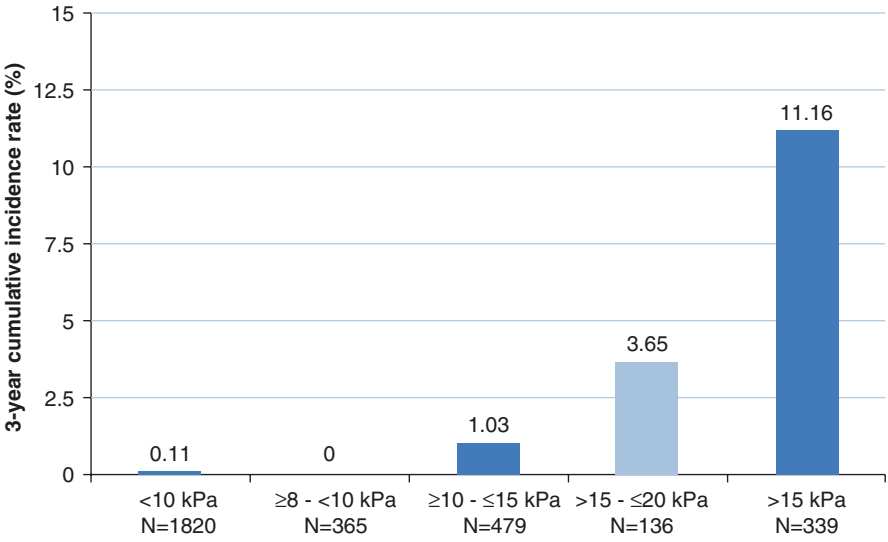

Fig. 8.1 Liver-related events (3-year cumulative incidence rate) in a cohort of 2638 patients with non-alcoholic fatty liver disease distributed in subgroups defined by different liver stiffness cutoffs, including the values that define compensated advanced chronic liver disease (cACLD)

Detecting Highly Suggestive cACLD (LSM >15 kPa)

Similar to what was observed with the ruling out criterium for cACLD, the ruling in criterium for cACLD of >15 kPa selects a population of patients with a prevalence of advanced fibrosis/cirrhosis higher than 80% across the different etiologies of CLD (Table 8.1). In addition, the prevalence of portal hypertension, as defined by a hepatic venous pressure gradient ≥5 mmHg, was higher than 90% in most patients evaluated in one study [9] (Table 8.1). NAFLD patients, especially obese patients, present lower prevalences of advanced fibrosis/cirrhosis or portal hypertension in most studies [5–7, 9]. Although not completely clear, it is possible that obesity might interfere with LSM measurements reducing the rate of NAFLD patients with severe fibrosis/cirrhosis independently of the probe (M or XL) used [22].

There are few studies that have explored the outcomes in the specific population of patients with LS >15 kPa. Rasmussen et al. [20] demonstrated in a cohort of patients with early alcohol-related liver disease that patients with LSM >15 kPa have a higher risk of presenting liver-related events (54% at 4 years of follow-up) compared to those with LSM between 10 and 15 kPa (intermediate risk-21% of events) and those with LSM <10 kPa (3% of events-Table 8.2). Many other studies have not explored specifically the cutoff of 15 kPa but have demonstrated that the prognosis worsens substantially when LSM increases and specially in the range from 15 to 25 kPa; this will be extensively discussed in the next chapter (Outcome

and Prognosis). The risk of developing hepatocellular carcinoma was also higher in those patients with LSM between 15.1 and 20 kPa (cumulative incidence of 19% at 3 years) and intermediate in those with LSM 10.1–15 kPa (11.7% at 3 years) as compared to patients with LSM ≤10 kPa (Table 8.2) in a cohort of patients with chronic hepatitis C [10]. Again, data from the collaborative study from France, Hong Kong, Canada, and Spain indicate that the cumulative rate of any liver-related event in 339 patients with LSM >15 kPa during 3 years of follow-up was 11% (unpublished data) (Fig. 8.1).

It has been proposed to decrease the cutoff for ruling in cACLD to >12 kPa with the aim of decreasing a too high specificity of the >15 kPa cutoff to rule in severe fibrosis/cirrhosis, minimizing the false-negative rates [5]. By lowering the 15 kPa cutoff, the grey zone decreases, but the population of cACLD increases at the expense of a significant reduction in the percentage of patients with severe fibrosis/cirrhosis. This is especially dramatic for NAFLD patients, since in some series the prevalence (PPV) of severe fibrosis/cirrhosis might be decreased to less than 50%. More importantly, the cACLD population would increase at the expense of patients with a minimal rate of liver-related events.

Suggestive cACLD (Grey Zone/LSM ≥10 to <15 kPa)

As expected, patients classified in the grey or intermediate zone (LSM ≥10 to <15 kPa) present intermediate prevalences of the clinical features of cACLD (Table 8.1). The presence of severe fibrosis/cirrhosis is around 50% in many cohorts and portal hypertension (HVPG >5 mmHg) can be detected in 75%–80% of patients. Again, patients with NAFLD show lower prevalences of these clinical features.

In terms of liver-related outcomes, in the few studies mentioned above that have specifically evaluated patients in the suggestive cACLD group, intermediate incidences of liver-related events are demonstrated. Again, data from the collaborative study from France, Hong Kong, Canada, and Spain indicate that the cumulative rate of any liver-related event in 479 patients in the grey zone (LSM ≥10 to <15 kPa) during 3 years of follow-up was 1% (unpublished data) (Fig. 8.1). This is 10 times higher than patients with LSM <10 kPa and 10 times lower than patients with LSM >15 kPa. In addition, in the specific subpopulation of 136 patients with LSM between >15 and 20 kPa, the liver event rate increased to 3.6%.

Baveno VI suggested that in the grey zone, invasive procedures such as liver biopsy demonstrating at least severe fibrosis, endoscopy confirming the presence of varices or an HVPG confirming the presence of portal hypertension must be performed to confirm cACLD [1]. Endoscopy should only be indicated if Baveno VI criteria for screening endoscopy are met and performing a liver biopsy or HVPG to these patients is not routinely carried out in many centers. These procedures should probably be individualized considering the risk-benefit of the intervention. What is clear is that monitoring for progression is required.

Other Elastography Techniques

Acoustic radiation force impulse (ARFI) techniques, as TE, use shear-wave elastography (SWE) for the noninvasive assessment of liver fibrosis. ARFI techniques can be divided into point shear wave elastography (pSWE) and multidimensional shear wave elastography (2D-SWE and 3D-SWE) [23, 24]. Although ARFI techniques have been available for almost 10 years and they provide some technological advances compared to TE, their use in daily clinical practice has been rather modest. One of the main limitations of their use is that they use different proprietary algorithms to determine velocity of the shear wave and hence liver stiffness. As a consequence, the cutoffs for fibrosis staging vary across different systems from different vendors. However, in the recent years, the Quantitative Imaging Biomarker Alliance (QIBA) committee of the Radiologic Society of North America has contributed to diminish this variability by developing standardized phantoms that vendors use to harmonize their measurements [25, 26].

Both pSWE and 2D-SWE have been demonstrated to have high accuracy (similar to TE) for fibrosis staging. Moreover, 2D-SWE performed with the Aixplorer machine was shown to have a good concordance with TE. Casinotto, et al. [27] indicated that 2D-SWE values were slightly higher compared to TE in low percentiles and lower in high percentiles, being the best concordance in values between 7 and 9 kPa. Best accuracy cutoff values of 2D-SWE for identifying TE values <10 kPa and >15 kPa were 10 kPa and 14 kPa, respectively.

According to the previous evidence and to classify cACLD patients, the Society of Radiologists in Ultrasound [25] have proposed a vendor-neutral "rule of four" (5, 9, 13, 17 kPa) for the ARFI techniques for viral etiologies and NAFLD, being the cutoff for ruling out <9 kPa (<1.7 m/s) (in the absence of other known clinical signs) and >13 kPa (>2.1 m/s) the cutoff for ruling in cACLD. According to the consensus, those patients with >17 kPa (>2.4 m/s) values are suggestive of having CSPH, but additional tests may be required. The authors have also suggested that cACLD cutoffs may be lower in some NAFLD patients and follow-up or additional tests are needed for those patients with liver stiffness values between 7 and 9 kPa [25].

Magnetic resonance elastography (MRE) has demonstrated a good accuracy for fibrosis staging in the main etiologies of chronic liver disease, especially NAFLD; however, its cost and lack of extended availability have limited its use in clinical practice [28, 29].

Summary

The concept of cACLD with the dual LSM cutoffs identifies two very clinically different populations of CLD patients with high and low prevalence of severe fibrosis/cirrhosis, portal hypertension, and most importantly, liver-related outcomes during follow-up.

A question remains open regards to the use of etiology-dependent cACLD thresholds. This was already an issue when using the cACLD definition regarding

the presence of severe fibrosis/cirrhosis and it was also indicated in the panelist's questionnaire. However, to be able to provide this information, more data on the rate of liver events in the different etiologies is needed, especially in the LSM range of 10–15 kPa. In addition, it would also be helpful to have a clear definition of what it is considered low or high event rate (and at what time frame), what are the different types of liver-related events to consider, and what are the implications of changing the thresholds.

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