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Prognostic Significance of Controlled Attenuation Parameter in Patients With Compensated Advanced Chronic Liver Disease

Cristina Margini, Giuseppe Murgia, Guido Stirnimann, Andrea De Gottardi, Nasser Semmo, Stefania Casu, Jaime Bosch, Jean-François Dufour, and Annalisa Berzigotti

Obesity and steatosis have been associated with liver disease progression in patients with compensated advanced chronic liver disease (cACLD) (liver stiffness measurement [LSM] $\geq$ 10 kPa). The controlled attenuation parameter (CAP) estimates steatosis during LSM by transient elastography. We aimed to evaluate whether CAP is associated with the development of clinically relevant events in cACLD. Consecutive patients with cACLD and CAP measurements observed between September 2013 and September 2015 were retrospectively studied. Classical decompensation and severe bacterial infections on follow-up were recorded. A predefined CAP cut-off for steatosis was used (220 dB/m; 90% sensitivity). The association among LSM, CAP, and events was assessed by univariate and multivariate Cox regression. Among the 193 patients (viral etiology = 58%; median Child score = 5; LSM = 15.1 kPa; CAP = 255 ± 62 dB/m) who were followed up in median for 18 months, 18 developed clinically relevant events (11 liver decompensation, 7 severe bacterial infections). Patients developing events had higher LSM (median: 30.8 versus 14.3 kPa, $P < 0.001$) and showed trends for higher CAP (275 ± 46 versus 252 ± 63 dB/m, $P = 0.07$), lower platelet count (134 ± 74 versus 167 ± 74 G/L, $P = 0.07$), and worse liver function versus patients remaining compensated. Body mass index was similar in the two groups. All events were more frequent in patients with CAP being greater than or equal to 220 dB/m (12.9% versus 1.6% in CAP < 220; $P = 0.013$), and 10 of 11 episodes of liver decompensation occurred in patients with CAP being greater than or equal to 220 dB/m. Following multivariate analysis, LSM and CAP greater than or equal to 220 dB/m remained independently associated with clinical events in the whole population and in patients with clinically significant portal hypertension. *Conclusion:* The CAP being greater than or equal to 220 dB/m is associated with increased risk of clinical decompensation and bacterial infections independent of LSM in patients with cACLD and allows refining the noninvasive risk stratification in this population. (*Hepatology Communications* 2018;2:929-940)

The natural history of advanced chronic liver disease (ACLD) is characterized by a long, asymptomatic compensated phase in which the median survival is around 12 years.[1] Once clinical decompensation occurs, the expected median survival dramatically drops to a median of 2 years.[1] Therefore, the goal of therapy in patients with compensated ACLD (cACLD) is to prevent clinical

Abbreviations: ACLD, advanced chronic liver disease; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CSPH, clinically significant portal hypertension; DAA, direct antiviral agent; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; NIT, noninvasive tool.

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decompensation.[2,3] More recently, it has been shown that bacterial infections should be considered as clinically relevant events in patients with liver disease, as they worsen prognosis independent of the clinical stage.[4]

Because the risk of developing clinical decompensation in cACLD is largely variable, risk stratification is a major need to individualize care.[2] Clinically significant portal hypertension (CSPH), measured by its invasive surrogate hepatic venous pressure gradient ($\geq$ 10 mmHg),[5] and liver function, estimated by serum albumin and the Model for End-Stage Liver Disease (MELD) score, are among the most consistent variables associated with prognosis in cACLD[1] and independently predicted the first clinical decompensation in patients with histologically proven compensated cirrhosis included in a long-term randomized controlled trial of timolol versus placebo for preprimary prophylaxis of gastroesophageal varices.[6]

The availability of noninvasive tools (NITs), particularly the liver stiffness measurement (LSM) by using transient elastography, greatly simplifies the identification of cACLD, leading to a much higher proportion of patients being diagnosed in this early stage of the disease.[3]

According to the recommendations of the Baveno VI consensus conference, LSM greater than or equal to 10 kPa should be used to suspect cACLD (cut-off with >90% sensitivity) and LSM greater than or equal to 15 kPa is diagnostic of cACLD (cut-off with >90% specificity).[2] In addition, because a LSM greater than or equal to 21 kPa yields a specificity of greater than 90% for CSPH,[7] and this cut-off is as accurate as the invasive finding of CSPH to predict first clinical decompensation,[8] the Baveno VI recommendations supporting the use of LSM in the initial risk stratification of patients diagnosed with cACLD.[2,7]

Obesity has been proposed as an additional unfavorable prognostic factor in compensated patients with ACLD, but data in this regard are still limited. In the timolol study cohort, body mass index (BMI) was strongly associated with the risk of clinical decompensation independent of portal hypertension and albumin[9]; and in cACLD due to chronic hepatitis C (HALT-C study), the BMI predicted the progression of fibrosis on histology and the onset of clinical events.[10] In the latter study, when the presence of liver steatosis on histology was analyzed together with BMI on a multivariate analysis, only liver steatosis remained independently associated with the clinical endpoints,[10] suggesting that accurate information on the presence or absence of liver steatosis could improve the prognostic stratification of cACLD.

The controlled attenuation parameter (CAP) is a recently developed quantitative, objective NIT for liver steatosis assessment, which measures the attenuation of ultrasound waves transmitted at a known frequency in the liver parenchyma.[11] The CAP values are obtained simultaneously to LSM using the same device,[11-13] and the estimation of liver fat through this method is reliable.[14-18] The CAP values of 215 to 238 dB/m hold a high sensitivity for the detection of steatosis in patients with chronic liver disease of different etiologies,[14-18] and in one study CAP and proton magnetic resonance spectroscopy showed comparable accuracy for the detection of hepatic steatosis in patients.[14]

In the present study we hypothesized that CAP, using a cut-off with high sensitivity for the detection of steatosis, might be used as a noninvasive predictor of prognosis in patients with cACLD, and could improve the risk stratification for clinically relevant events and clinical decompensation provided by LSM in this population.

ARTICLE INFORMATION:

From the Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Annalisa Berzigotti, M.D., Ph.D.
Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital
University of Bern
MEM F807, Murtenstrasse 35
CH - 3010 Bern, Switzerland
E-mail: annalisa.berzigotti@insel.ch
Tel. +41-31-632-87-27

Materials and Methods

STUDY DESIGN AND POPULATION

This is an observational, retrospective, single-center cohort study. The Cantonal Ethical Committee of Bern approved the present study (EK BE 2017-00501).

All consecutive patients with chronic liver disease who underwent an LSM by transient elastography between September 2013 and September 2015 in our outpatient clinic (Hepatology Department, University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland) were screened as potential candidates for inclusion in the study.

Patients were enrolled if they fulfilled the following inclusion criteria: clinically compensated (no presence or history of ascites, bleeding, jaundice, hepatic encephalopathy, or sepsis); LSM greater than or equal to 10 kPa, which is compatible with advanced chronic liver disease[2]; available concomitant CAP measurement (age $\geq$ 18 years); available clinical data at baseline; and at least 6 months of follow-up. Exclusion criteria included all of the following: unreliable LSM defined by interquartile range/median greater than or equal to 0.30[19] and previous or ongoing decompensation of liver disease defined as ascites, bleeding from portal hypertensive sources, jaundice, hepatic encephalopathy, severe bacterial infections leading to hospitalization, and hepato-renal syndrome. Patients with previous liver transplantation, vascular liver disease, hepatocellular carcinoma (HCC) beyond the Milano criteria (alanine aminotransferase $>$ 300 U/L),[19] or denial of the use of personal health–related data were also excluded.

A flowchart illustrating the selection process is provided in Fig. 1.

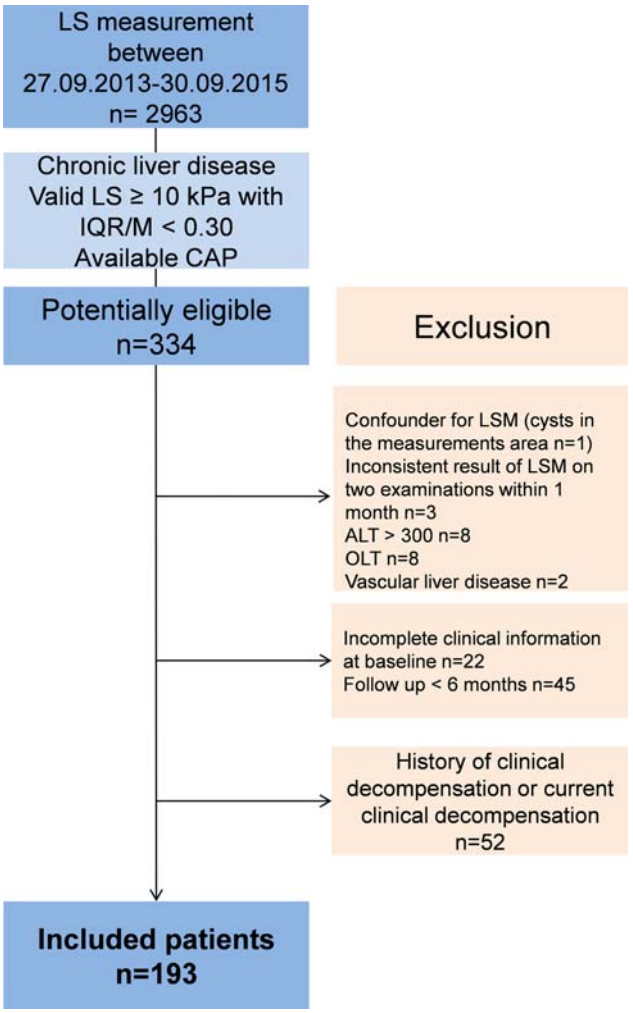

FIG. 1. Flowchart of the inclusion and exclusion process; 193 patients were included.

LIVER STIFFNESS MEASUREMENT AND CONTROLLED ATTENUATION PARAMETER ASSESSMENT

Transient elastography (Fibroscan 502 Touch; Echosens, Paris, France) provided with M probe was used to assess LSM and CAP. The CAP was available only on M probe during the inclusion period. Measurements were performed in fasting conditions during a routine visit at our outpatient facility.

The following previously published cut-offs of LSM were predefined for the analysis: LSM $\geq$ 15 kPa: definite cACLD[2]; LSM $<$ 13.6 kPa: unlikely clinically significant portal hypertension (sensitivity 90%); LSM $\geq$ 21 kPa: high likelihood of clinically significant portal hypertension (specificity 90%).[7]

As for CAP, because the presence of any steatosis was associated with a worse prognosis in a previous report using histological data,[10] to avoid false-negative results we selected two previously published cut-offs with sensitivity close to 90%, namely, 220 and 235 dB/m, which we used to discriminate patients without steatosis versus those with likely liver steatosis.[14-18]

Demographic, Clinical, and Laboratory Data

We collected the demographic, clinical, and laboratory data paired to LSM and CAP measurement. Clinical data included etiology of liver disease, BMI,

presence of diabetes, arterial hypertension and dyslipidemia, and ongoing medication for each of these conditions. For patients who underwent screening/surveillance endoscopy, data on the presence of gastroesophageal varices and ongoing primary prophylaxis with nonselective beta-blockers were collected. Laboratory data included aspartate aminotransferase/alanine aminotransferase, gamma-glutamyltransferase (GGT), alkaline phosphatase, creatinine, bilirubin, albumin, glucose, sodium, potassium, platelet count, and international normalized ratio (INR). Bipolar diameter of the spleen on imaging obtained within 3 months of inclusion (ultrasound or computed tomography scan) was also collected.

According to the World Health Organization recommendations, BMI was categorized as < 18 kg/m^2: underweight; 18-24.99 kg/m^2: normal weight; 25-29.9 kg/m^2: overweight; ≥ 30 kg/m2: obese.

In patients on oral anticoagulants, INR was not used and MELD was not calculated.

Clinical Decompensation of Liver Disease and Severe Bacterial Infections in the Follow-up

Patients were followed up every 6 months until February 2017 or until death or liver transplantation. The status of patients lost to follow-up was censored to the date of the last follow-up available. A minimal follow-up of 6 months was required and patients not meeting this criterion were excluded. Clinical decompensation was defined as the occurrence of one of the following: ascites, bleeding from gastroesophageal varices, jaundice, hepatic encephalopathy, or hepato-renal syndrome. Severe bacterial infections requiring hospitalization were considered as relevant clinical events and were recorded.[8] Liver transplantation and death were also recorded, and the date of each event was entered in the database.

Statistical Analysis

The Kolmogorov–Smirnov test was used to test whether variables were normally distributed. A *P* value greater than 0.05 was required to assume a normal distribution. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as numbers or percentages. Chi-square, Student *t*, and Mann-Whitney U tests were used according to variable characteristics. Pearson's test was used for correlations. Comparisons among the three groups were performed using the Kruskal-Wallis test and one-way analysis of variance. Patients undergoing liver transplantation were censored at the time of transplant. Variables with over 30% missing values were not used for the analysis. Risk factors for all clinical events and for clinical decompensation were assessed by univariate Cox logistic regression analysis. Variables with *P* less than 0.10 in patients developing events versus remaining compensated were included in a Cox's multivariate stepwise regression analysis to analyze the independent effect of each variable on the outcome; by default, variables were included in the final step of the model if *P* was greater than 0.10. One variable for every five events was included in the multivariate model.[20] Kaplan-Meier's curves were constructed and compared with the log-rank test. Data were analyzed using PAWS statistics version 23 (SPSS Inc., Chicago, IL). All authors had access to the study data and reviewed and approved the final manuscript.

Results

BASELINE CHARACTERISTICS

Among the 334 patients initially considered, 193 fully compensated patients were included in the study (Fig. 1) and were followed up for a median of 18 months (range 6-40). The main clinical and biochemical characteristics on inclusion are presented in Table 1. Three patients were receiving oral anticoagulants for non-liver-related conditions.

As shown, the median Child and MELD scores were low, as expected in a population of well-compensated patients.

Regarding the 98 patients with liver disease due to chronic hepatitis C virus (HCV) (alone in 90 cases, HCV + hepatitis B virus [HBV] in 2, HCV + alcohol in 6), 12 were HCV-RNA negative on inclusion (spontaneous clearance of the virus in 2; sustained virological response after antiviral drugs in 10). A total of 86 patients were HCV-RNA positive on inclusion; among them, 72 (84%) were successfully treated with direct antiviral agents (DAAs) during the follow-up.

Seventeen patients had liver disease due to HBV (HBV alone in 15, HCV + HBV in 2); among these patients, 10 were under anti-HBV antiviral therapy on inclusion.

Twenty-one patients had liver disease due to excessive alcohol consumption. Among them, 8 patients were abstinent on inclusion and one of them had recurrence of alcohol consumption during follow-up.

TABLE 1. BASELINE CHARACTERISTICS IN THE OVERALL POPULATION AND IN PATIENTS DEVELOPING OR NOT DEVELOPING CLINICALLY RELEVANT EVENTS

Baseline Characteristics	Overall (n = 193)	Patients Developing Clinically Relevant Events (n = 18)	Patients Remaining Compensated (n = 175)	*P*
Age (years)	56 (20-83)	58 (25-74)	54 (20-83)	0.77
Sex (male) (n [%])	125 (65)	12 (67)	113 (65)	0.79
Etiology (n)				
HCV	90	5	85	
HBV	15	1	14	
HCV + HBV	2	0	2	
Alcohol + HCV	6	1	5	
Alcohol	21	4	17	
Nonalcoholic fatty liver disease	27	3	24	
Cholestatic/autoimmune	20	2	18	
Others	12	2	10	
Nonviral/viral (n)	80/113	11/7	69/106	0.08
HCC at baseline (n)	4	1	3	0.73
BMI (kg/m^2)*	26.5 (16.0-42.8)	27.5 (16.0-38.0)	26.3 (16.9-42.8)	0.66
Overweight (%)	82/183 (44.8)	10/17 (58.8)	72/166 (43.3)	
Obese (%)	39/183 (21.3)	4/17 (23.5)	35/166 (21.0)	
Dyslipidaemia (%)	21	22	21	0.77
Lipid-lowering drug (%)	9	11	9	
Diabetes (%)	18	17	18	0.85
Diabetes therapy (%)	14	17	14	
Arterial hypertension (%)	56	61	55	0.61
Antihypertensive drugs (%)	34	50	33	
Nonselective beta-blockers (n [%])	14 (7.3)	3 (16.7)	11 (6.3)	0.176
Child-Pugh score	5 (5-9)	5 (5-8)	5 (5-9)	0.24
MELD score	7 (6-20)†	7 (6-15)	7 (6-20)†	0.17
Alanine aminotransferase (U/L)	63 (7-296)	44 (15-204)	66 (7-296)	0.20
GGT (U/L)	110 (11-967)	211 (26-967)	96 (11-895)	0.02
Bilirubin (μmol/L)	13 (3-89)	16 (3-66)	13 (4-89)	0.133
Creatinine (μmol/L)	67 (39-463)	62 (48-90)	67 (39-463)	0.60
Albumin (g/L)	38 (23-45)	37 (26-44)	38 (23-45)	0.12
INR	1.04 (1.00-1.68)	1.09 (1.00-1.63)	1.03 (1.00-1.68)	0.01
Platelet count (g/L)	154 (30-456)	114 (36-312)	156 (30-456)	0.07
Spleen size (cm)‡	12.3 (8-24)	13.9 (8-20)	12.0 (8-24)	0.17
LSM (kPa)	15.1 (10-75)	30.8 (11.8-75)	14.3 (10-75)	<0.001
<13.6 kPa (%)	42	3.7	96.2	
≥15.0 kPa (%)	50	77.7	47.5	
≥ 21.0 kPa (%)	33	81.1		
Interquartile range/median	0.16 ± 0.07	0.16 ± 0.08	0.16 ± 0.07	0.93
CAP (dB/m)	255 ± 62	275 ± 46	252 ± 63	0.07
CAP IQR (dB/m)	37 (0-129)	47 (24-109)	36 (0-129)	0.29
CAP ≥ 220 dB/m (n [%])	132 (68.0)	17 (94.4)	115 (65.8)	0.03
CAP ≥ 235 dB/m (n [%])	112 (58.0)	15 (83.3)	97 (55.4)	0.03

Note: Percentages refer to the proportion of the population presenting the condition. Mean ± standard deviation or median and range are given according to the normality of distribution. *P* values were obtained using Cox univariate analysis.
*BMI was available in 183 patients.
†MELD 20 refers to one patient on dialysis.
‡Available in 110 patients.

Of the 13 patients not abstinent on inclusion, 9 became abstinent during follow-up.

The status of varices was known on inclusion in 94 of 193 patients (48.7%), 41 of 94 (44%) patients in whom an endoscopy was available had gastroesophageal varices. Fourteen (7%) patients were on nonselective beta-blockers on inclusion.

Body mass index at baseline was available in 183 of 193 (94.8%) patients. Among them, 44.8% were overweight and 21.3% were obese (Table 1; 13 patients had a BMI > 35 kg/m^2). Two patients (1.1%) were underweight.

The average CAP was 255 ± 62 dB/m; CAP was greater than or equal to 220 dB/m in 132 patients

TABLE 2. COMPARISON OF THE BASELINE CHARACTERISTICS OF PATIENTS WITH CAP < 220 DB/M VERSUS CAP ≥ 220 DB/M

Baseline Characteristics	CAP < 220 dB/m (n = 61)	CAP ≥ 220 dB/m (n = 132)	*P*
Age (years)	55 (20-83)	55 (22-81)	0.96
Sex (male) (n [%])	32 (53)	93 (71)	0.023
Etiology (n)			
HCV	29	61	
HBV	2	13	0.50
HCV + HBV	2	0	
Alcohol + HCV	2	4	
Alcohol	5	16	
NAFLD	3	24	
Cholestatic/autoimmune	12	8	
Others	6	6	
Nonviral/viral (n)	26/35	54/78	0.88
HCC at baseline (n)	1	3	1.0
BMI (kg/m^2)*	24.4 (16.8-38.0)	27.8 (16-42.8)	<0.001
Overweight (%)	19/56 (34)	63/127 (50)	0.05
Obese (%)	3/56 (5)	36/127 (28)	<0.001
Dyslipidaemia (%)	18	23	0.57
Lipid-lowering drug (%)	7	10	
Diabetes (n [%])	9 (15)	26 (20)	0.05
Diabetes therapy (%)	12	15	
Arterial hypertension (%)	49	59	0.21
Anti-hypertensive treatment (%)	31	36	
Child-Pugh score	5 (5-9)	5 (5-8)	0.009
MELD score	7 (6-20)†	7 (6-16)	0.88
ALT (U/L)	57 (10-266)	72 (7-296)	0.23
GGT (U/L)	83 (11-864)	124 (24-967)	0.07
Bilirubin (μmol/L)	14 (4-89)	13 (3-66)	0.51
Creatinine (μmol/L)	63 (39-463)	68 (43-231)	0.33
Albumin (g/L)	36 (23-45)	39 (26-44)	0.01
INR	1.05 (1.0-1.26)	1.03 (1.0-1.68)	0.17
Platelet count (g/L)	154 (30-377)	154 (33-456)	0.91
Spleen size (cm)‡	12.0 (8-24)	12.3 (8-20)	1.0
CAP (dB/m)	187 ± 27	286 ± 47	<0.001
CAP interquartile range (dB/m)	49 (0-129)	39 (0-109)	0.10
LSM (kPa)	14.7 (10-75)	16.1 (10-75).	0.57
Interquartile range/median	0.15 ± 0.07	0.17 ± 0.07	0.89

*BMI was available in 183 patients.
†Available in 110 patients.
‡MELD 20 refers to one patient on dialysis.

(68%) and greater than or equal to 235 dB/m in 112 patients (58%). Body mass index and CAP showed a moderate positive correlation (R = 0.323, $P < 0.001$), and CAP increased across the BMI classes (Supporting Table S1). Patients with CAP greater than or equal to 220 dB/m had a higher proportion of male gender, a higher prevalence of diabetes, and higher BMI and GGT as compared with patients with CAP less than 220 dB/m. In addition, they showed higher serum albumin and lower Child-Pugh score (Table 2).

The LSM showed a median of 15.1 kPa (range 10-75). Fifty percent of patients had a definite cACLD according to the Baveno VI criteria (≥15 kPa). As for the predefined threshold for portal hypertension, 33% of the population met the criteria for CSPH (≥21 kPa; n = 64) (Table 1). Patients with an LSM of 13.6 to 20.9 kPa had a lower proportion of obesity and a lower CAP value as compared with patients in the low range and high range of LSM ($P = 0.03$; Kruskal-Wallis test for differences among categories: $P = 0.013$; Supporting Table S2).

Clinical Events During Follow-up

Eighteen patients (9.3%) developed a first relevant clinical event during follow-up. Clinical decompensation of liver disease occurred in 11 patients as follows: ascites (n = 9; in 2 cases associated with bacterial infection), variceal bleeding (n = 1), and hepatic encephalopathy (n = 1). Seven additional patients

developed a severe infection requiring hospitalization (pneumonia in two, urinary tract infection in two, gastrointestinal infection in two, soft tissue infection in one). Regarding the etiology of liver disease, seven relevant clinical events were observed in patients with viral disease (three occurring in patients who achieved a sustained virological response following DAAs after being included in the study), and 11 in nonviral disease (alcohol in four, nonalcoholic steatohepatitis in three, other in four).

Three of the 18 patients (16%) died during follow-up. The cause of death was septic shock in two and HCC in one.

A total of 175 patients remained compensated and without severe bacterial infections. Among them, four (2.3%) died: Two deaths were due to HCC and two were unrelated to liver disease (extrahepatic cancer in one; trauma in one).

As for other liver-related events, four patients were transplanted during the follow-up.

Variables Associated With Clinically Relevant Events (Clinical Decompensation and Severe Bacterial Infections) and Noninvasive Predictors of Clinical Decompensation in cACLD

Table 1 lists the comparison of the baseline clinical parameters in patients who developed decompensation or severe bacterial infections versus patients who remained compensated.

As shown, patients who developed relevant clinical events had a slightly worse liver function (higher INR and lower albumin) and lower platelet count (P = 0.07). Among those patients having endoscopy available (n = 93), 39 had esophageal varices. In the subgroup with endoscopy available, the presence of varices was not associated with the development of clinical events (varices in 57% of those who decompensated versus 39% of those remaining compensated; P = 0.435). Patients developing events in the follow-up featured higher GGT (275 ± 46 versus 252 ± 63, P = 0.07) and CAP values in comparison to patients remaining compensated (proportion with CAP ≥ 220 dB/m: 17 of 18 or 94.4% versus 115 of 175 or 65.8%, P = 0.03). Patients with CAP greater than or equal to 220 dB/m had a significantly higher risk of clinical events as compared with patients with CAP less than 220 dB/m (12.9% versus 1.6%, P = 0.013) (Fig. 2). As for the 11 episodes of first clinical decompensation

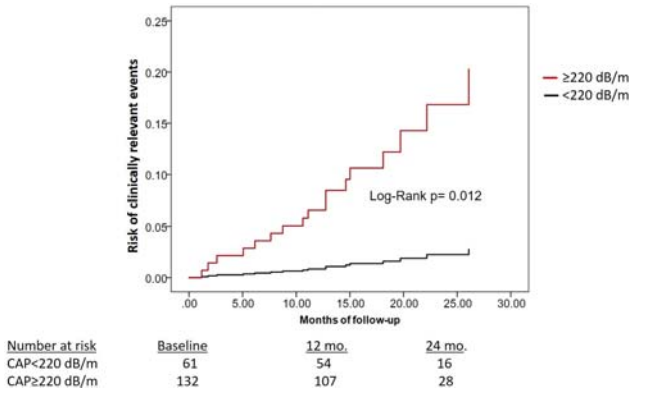

FIG. 2. Risk of developing clinical decompensation in the follow-up according to CAP being less than and greater than or equal to 220 dB/m. As shown, patients with CAP being greater than or equal to 220 dB/m had a significantly higher probability of developing clinical decompensation (log-rank P = 0.012).

of liver disease, 10 occurred in patients with CAP greater than or equal to 220 dB/m (Supporting Fig. S1).

Only one patient with CAP less than 220 dB/m developed decompensation during follow-up (ascites associated with partial portal vein thrombosis). This patient was obese (BMI 38 kg/m^2), diabetic, and had an LSM of 20.4 kPa.

Diabetes and arterial hypertension were equally represented in patients developing or no clinical events, and BMI was similar in the two groups; the proportion of events in patients with normal BMI, overweight, and obesity was 5% (3 of 60), 12.2% (10 of 82), and 10.2% (4 of 39), respectively (P = 0.31).

The LSM was markedly higher in patients developing clinical events (33.6 ± 19.2 versus 19.8 ± 13.0 kPa in those remaining compensated, P < 0.001), and the highest proportion of clinical events was observed in patients with LSM greater than or equal to 21 kPa (18.8% versus 6.3% in LSM, 13.6-20.9 kPa versus 3.7% in LSM < 13.6 kPa; P = 0.006) (Fig. 3A), who had the highest risk of clinical events over the follow-up (Fig. 3B).

The different multivariate models that were tested are provided in Table 3. As indicated, LSM and CAP greater than or equal to 220 dB/m remained independently associated with the first clinically relevant event in all of the tested models. Similarly, in a sensitivity analysis performed with a CAP cut-off of 235 dB/m, LS and CAP greater than or equal to 235 dB/m remained independently associated with the first

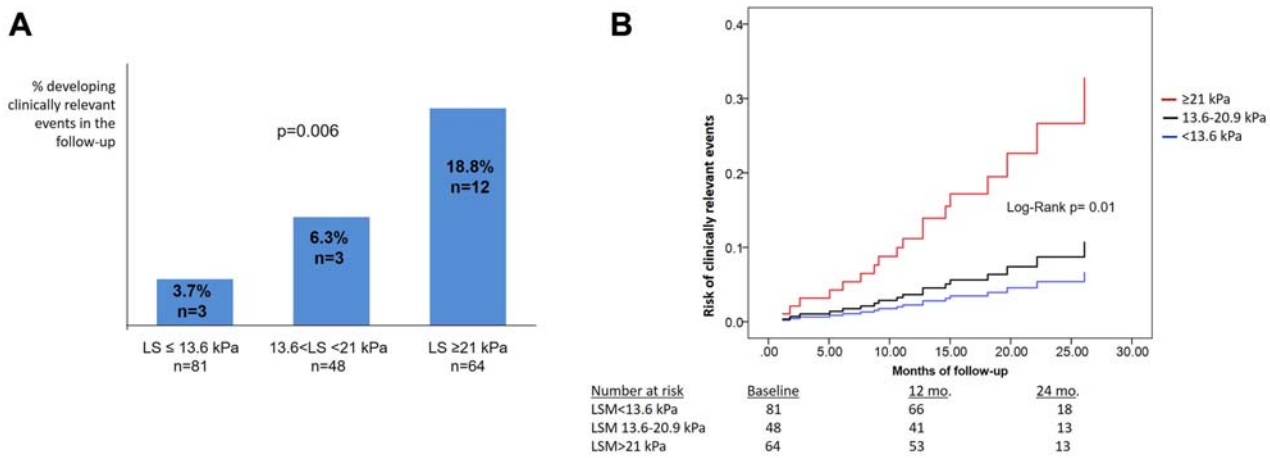

FIG. 3. Clinical decompensation according to LSM. A, Proportion of patients developing decompensation according to previously published LSM cut-offs for portal hypertension. All patients but one (belonging to the group with 13.6-21 kPa) had a CAP greater than or equal to 220 dB/m. B, Risk of developing clinical decompensation over time according to different LSM cut-offs. As shown, the highest risk was observed in patients with a LSM greater than or equal to 21 kPa (log-rank $P = 0.01$).

TABLE 3. COX'S MULTIVARIATE STEPWISE REGRESSION ANALYSIS TO ANALYZE THE INDEPENDENT EFFECT OF SELECTED VARIABLES ON THE RISK OF CLINICALLY RELEVANT EVENTS

	Exp(B)	95% CI	*P*	Loss if term removed (*P*)
Model 1 Variables Tested: LSM, CAP ≥ 220 dB/m, Viral Etiology				
LS (per kPa)	1.04	1.02-1.07	<0.001	0.002
CAP ≥ 220 dB/m	6.66	0.88-50.5	0.067	0.015
Model 2 Variables Tested: LSM, CAP ≥ 220 dB/m, Albumin				
LS (per kPa)	1.04	1.02-1.06	0.001	0.002
CAP ≥ 220 dB/m	6.31	0.83-47.9	0.075	0.019
Model 3 Variables Tested: LSM, CAP ≥ 220 dB/m, GGT				
LS (per kPa)	1.04	1.02-1.07	<0.001	0.001
CAP ≥ 220 dB/m	6.38	0.84-48.4	0.073	0.018
Model 4 Variables Tested: LSM, CAP ≥ 220 dB/m, INR				
LS (per kPa)	1.05	1.02-1.07	<0.001	0.002
CAP ≥ 220 dB/m	4.73	0.61-36.9	0.138	0.068
Model 5 Variables Tested: LSM, CAP ≥ 220 dB/m, Platelet Count				
LS (per kPa)	1.05	1.02-1.07	<0.001	0.001
CAP ≥ 220 dB/m	6.42	0.85-48.5	0.072	0.017
Model 6 Variables Tested: LSM, CAP ≥ 235 dB/m				
LS (per kPa)	1.04	1.02-1.07	<0.001	0.001
CAP ≥ 235 dB/m	3.03	0.87-10.61	0.083	0.054
Model 7 Variables Tested in Patients With LS ≥ 15 kPa: LSM, CAP ≥ 220 dB/m				
LS (per kPa)	1.04	1.01-1.07	0.018	0.029
CAP ≥ 220 dB/m	4.53	0.58-35.2	0.149	0.076

Abbreviation: CI, confidence interval.

clinically relevant event (Table 3; Supporting Fig. S2). Of note, the results were similar after restricting the analysis to patients with definite cACLD according to the Baveno VI criteria (LSM $\geq$ 15 kPa)[2] (Table 3), in patients with viral and nonviral etiology of ACLD (Supporting Fig. S3), and after excluding the 13 patients with BMI greater than 35 kg/m^2 (data not shown).

CAP as a Tool for Further Risk Stratification in Patients With CSPH Defined by LSM Greater Than or Equal to 21 kPa

Among the 64 patients with LSM greater than or equal to 21 kPa, 12 developed clinically relevant events. None of them had a CAP less than 220 dB/m on inclusion (Fig. 3A). On Cox regression, the probability of developing relevant events over time was higher in patients with CAP greater than or equal to 220 dB/m versus patients with lower CAP ($P = 0.03$) (Supporting Fig. S4). On multivariate analysis, including LS and CAP greater than or equal to 220 dB/m, both variables remained independently associated with the development of relevant events.

Discussion

Risk stratification in patients with cACLD is a crucial need for personalizing medical care.[2] The NITs are easily applicable and provide a quick point-of-care risk stratification that can be promptly integrated into the clinical management. Among NITs, LSM, which provides a quantitative estimation of liver fibrosis, is the best validated to identify cACLD[21] and to further stratify the risk of clinical complications in cACLD.[7]

The major finding of our study is that CAP, a NIT addressing liver fat content and obtained simultaneous to LSM, adds precision to the risk stratification for relevant events and clinical decompensation obtained by LSM alone in European patients with cACLD of different etiologies. Patients with CAP greater than or equal to 220 dB/m in our study had a substantially higher risk of developing clinical decompensation and severe bacterial infections, and this additional predictive value over that of LSM remained true also when the analysis was restricted to the high-risk patients, selected by LSM greater than or equal to 21 kPa, indicating CSPH.

The CAP has been shown to reflect the presence and severity of liver steatosis with high accuracy.[15] Importantly, CAP detects steatosis independent of liver fibrosis stage,[15] and an increase in CAP value is associated with the presence of steatosis even in patients with advanced fibrosis/cirrhosis, in whom steatosis is known to decrease.[22,23] In our cohort, patients with CAP less than 220 had a slightly higher Child-Pugh score and a lower serum albumin as compared with patients with CAP greater than or equal to 220 dB/m, which is in agreement with previous observations showing a lower fat content in patients with more severe liver disease.[22,23] In contrast, although CAP and LSM showed no significant correlation, CAP and BMI were positively and significantly correlated, and patients with higher CAP had higher prevalence of diabetes. These results are in line with several other studies in different scenarios in chronic liver disease linking metabolic risk factors to higher CAP values as a biomarker of steatosis.[13,24]

In our patients, CAP greater than or equal to 220 dB/m was significantly associated with clinically relevant events independent of LSM. In this scenario, our finding confirms the previously reported association between the presence of steatosis and further progression of liver disease in cACLD.[10] The choice of using categorization and the choice of the cut-offs we used depends on the observation that in the HALT-C study cohort,[10] only the presence, but not the severity of liver steatosis, remained associated with the progression of liver disease and clinical events. According to this observation, false-negative results of a steatosis biomarker (i.e., classifying a patient with steatosis as not carrying it) would lead to "missed" high-risk patients, with potentially serious consequences. Therefore, we considered that a sensitive detection of patients with liver steatosis had to be prioritized over specificity in the choice of a CAP cut-off, and because there is still a substantial uncertainty regarding which CAP cut-off should be used, we arbitrarily decided to choose 220 dB/m among those published with high sensitivity,[11,16] and to analyze a second higher cut-off, namely, 235 dB/m[17], to increase a confident interpretation of the results. Our results diverge from those recently published by Liu et al.[25] in an Asiatic population; in their study, CAP showed no prognostic predictive value for liver-related events. We do not have a clear explanation for the observed difference, and we hypothesize that might be inherent to differences in the population included (e.g., severity of the disease, geographic origin).

In the present study, LSM was the strongest predictor of clinical events in the follow-up. Patients with LSM greater than or equal to 21 kPa experienced most of the events, therefore confirming the results obtained by Robic et al.[8] and reinforcing that patients with LSM over this value should be considered at very high risk, likely because of the presence of CSPH at baseline. In addition, we observed that LSM (treated as a continuous variable) maintains a strong predictive value for clinical events beyond the cut-off used to identify the presence of CSPH. This reinforces the concept that continuous models of risk could be used to improve personalization of care.[26]

Contrary to what was observed in a previous study,[9] in this cohort BMI was not associated with higher risk of clinical decompensation. We postulate two possible explanations for this discrepancy. The most likely is that this was due to the fact that when conducting the study CAP was available only on M probe, which made our results only applicable to patients with a skin-to-capsule distance appropriate for this probe. The lack of CAP values using the XL probe is a clear limitation of our study, as most patients with obesity and most patients with BMI greater than or equal to 35 kg/m^2 exceed the limits of the M probe[27,28]; therefore, obesity is underrepresented in our cohort. However, despite the lack of predictive value of BMI, CAP greater than or equal to 220 dB/m remained associated with a higher risk of decompensation in our cohort, which suggests that this NIT could help in refining the prognosis even in patients with relatively low BMI. Further studies using the XL probe will clarify whether our results can be extrapolated to obese patients with cACLD.

Another possible explanation might be that the current definition of cACLD includes a spectrum of advanced fibrosis and cirrhosis[2,29]; consequently, the population included in the present study might be at an earlier stage, on average, as compared with that included in the Timolol study cohort.[9,30] Therefore, the interaction among obesity, steatosis, fibrosis, and prognosis might not be identical and requires further investigation. We consider, however, that this is less likely, as the association between CAP and prognosis was confirmed when the analysis was restricted to patients with an LSM greater than or equal to 21 kPa, who have cirrhosis and CSPH (a more advanced population than that of the Timolol study).

Our study has several limitations. First, it is a retrospective study, which implies the risk of an inclusion bias. However, to minimize this, we included consecutive patients strictly defined according to *pre hoc* rules. Second, in this cohort, no histological confirmation of fibrosis at the time of LSM/CAP assessment was available, and we cannot provide data to support whether the identification of cACLD was correct. However, the rate of clinical events observed in the follow-up is in agreement with that expected in cACLD[31]; furthermore, we were able to confirm the predictive value of CAP independent of LSM in the subgroup of patients who have LSM greater than or equal to 15 kPa. These patients have a definite cACLD according to the Baveno VI consensus conference,[2,32] and most importantly, a LSM greater than or equal to 21 kPa, indicating that they very likely have CSPH.[7] Because liver biopsy was not available in the study population, we cannot confirm whether the CAP-increased values genuinely mirror steatosis or whether the increases are due to unknown factors in cACLD; in any case, the CAP prognostic ability remains tied to whatever components might contribute to it. Interestingly, the CAP prognostic ability was maintained both in viral and nonviral etiologies, and several of our patients (similar to those reported in other contemporary series) showed co-causes of liver disease (e.g., viral + metabolic, alcoholic + metabolic). Therefore, we do not think that the inclusion of different etiologies should be regarded as a major limitation.

Finally, the number of events and clinical decompensation occurring in the follow-up is low. This is inherent to the selection of the population of the study, which consisted of many patients in an early stage of cACLD. This also explains why in a relevant proportion of the included patients an endoscopic screening for esophageal varices was not available at inclusion, as it was not deemed to be necessary by the physician in charge of the patient. In contrast, our patients received state-of-the-art treatment for the cause of liver disease, including DAAs for HCV in most patients with HCV-related cACLD, and this may have contributed to decreasing the risk of decompensation.

However, the fact that even in these circumstances CAP was independently associated with the risk of relevant clinical events adds further value for the use of this parameter in risk stratification in clinical practice. Severe bacterial infections leading to hospitalization accounted for a significant proportion of events and were considered as clinically relevant events. This was decided *pre hoc* in the design of the study due to the increasingly recognized negative effect of infections as worsening events in the natural history of cirrhosis, regardless of its stage,[4,33] similar to the work

published by Robic et al.[8] Importantly, even after restricting the events to classical decompensating events, CAP greater than or equal to 220 dB/m maintained a negative prognostic significance, as observed in 10 of 11 patients who decompensated (Supporting Fig. S4).

The results of a recent study suggested that liver stiffness changes over time provide additional prognostic information in patients with cACLD[31] Future studies are required to address the potential implications of longitudinal liver stiffness and CAP changes, and their interaction for the prognostic stratification in this scenario.

In conclusion, in European patients with cACLD diagnosed noninvasively by means of LSM, using CAP with a cut-off of 220 dB/m improves the noninvasive prediction of clinically relevant events (clinical decompensation and severe bacterial infections), indicating that it represents a simple and effective tool in combination with LSM with no additional cost in this scenario. The LSM is a strong predictor of clinically relevant events in patients with cACLD, and its predictive value exceeds the simple identification of the CSPH stage, providing additional evidence for further studies to address the personalization of management according to individualized risk assessment based on this parameter.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1201/full.