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ORIGINAL ARTICLE

Performance of Controlled Attenuation Parameter in Patients with Advanced Chronic Liver Disease and Portal Hypertension

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Abstract

Background Liver stiffness (LS) measured by vibration-controlled transient elastography (VCTE) is influenced by liver fibrosis and hepatic perfusion pressure. VCTE-based controlled attenuation parameter (CAP) is a noninvasive marker for hepatic steatosis (HS).

Aims To investigate the diagnostic performance of CAP in patients with advanced chronic liver disease (ACLD)/portal hypertension (PHT: hepatic venous pressure gradient (HVPG) ≥ 6 mmHg).

Methods Eighty-eight patients with LS ≥ 10 kPa and/or HVPG ≥ 6 mmHg who underwent simultaneous liver biopsy, CAP, and HVPG measurement were included. HS was histologically graded according to the modified Brunt classification.

Results Patient characteristics: Mean MELD:11 (standard derivation [SD] ± 4), median HVPG:16 (interquartile range [IQR]10–19) mmHg, median LS:27.4 (IQR 16.2–48.9) kPa, and mean CAP:221 (SD ± 75) dB/m. According to histology, 47 (53.4%) patients had no HS (S0), 28 (31.8%) had S1, 11 (12.5%) had S2, and 2 (2.3%) had S3. The area under the receiver operating characteristic curve (AUROC) of CAP for diagnosing any HS (S0 vs. ≥ S1) was 0.692 (95% confidence interval [95% CI] 0.582–0.802) in the overall cohort, 0.830 (95% CI 0.637–1.0) in patients with HVPG < 10 mmHg, and 0.629 (95% CI 0.497–0.761) in patients with clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg; $n = 69$). Using the established cutoff for any HS (248 dB/m), the sensitivity/specificity of CAP was only 48.8%/76.6%, respectively. In contrast, the AUROC and sensitivity/specificity (cutoff 268 dB/m) for diagnosing HS ≥ S2 were 0.842 (95% CI 0.747–0.936) and 84.6%/81.3%, respectively. CAP correlated with the percentage of steatotic hepatocytes (Spearman's $\rho = 0.402$; $p \leq 0.001$) and showed a weak correlation with liver stiffness ($\rho = 0.225$; $p = 0.035$).

Conclusions The diagnostic performance of CAP for any HS seems to be limited in patients with ACLD, if CSPH is present.

Keywords CAP · Transient elastography · VCTE · Portal hypertension · CSPH · Cirrhosis

Abbreviations

LS	Liver stiffness
VCTE	Vibration-controlled transient elastography
CAP	Controlled attenuation parameter
ACLD	Advanced chronic liver disease
PHT	Portal hypertension
HS	Hepatic steatosis

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SD	Standard deviation
IQR	Interquartile range
AUROC	Area under receiver operating characteristic curve
CI	Confidence interval
CSPH	Clinically significant portal hypertension
HVPG	Hepatic venous pressure gradient
PNPLA3	Patatin-like phospholipase domain containing 3
BMI	Body mass index
NAFLD	Nonalcoholic fatty liver disease
ALD	Alcoholic liver disease
PPV	Positive predictive value
NPV	Negative predictive value

Introduction

Portal hypertension (PHT: hepatic venous pressure gradient [HVPG] ≥ 6 mmHg), in particular clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg), plays a critical role in the development of complications of advanced chronic liver disease (ACLD) and thereby significantly contributes to morbidity and mortality in these patients [1–3].

Due to the increasing prevalence of obesity and the metabolic syndrome, hepatic steatosis (HS) is a common finding in patients with ACLD [4]. Although liver biopsy is still considered the gold standard for the assessing of hepatic fibrosis and steatosis, its role has been questioned due to the risk of severe complications and considerable sampling variability [5, 6]. Moreover, since liver biopsy is an invasive procedure, it is not suitable for the longitudinal follow-up of patients [7]. Vibration-controlled transient elastography (VCTE) equipped with controlled attenuation parameter (CAP) is a noninvasive alternative for evaluating HS. VCTE was initially developed for assessing liver fibrosis by measuring liver stiffness (LS), with the recent addition of the CAP module being designed to noninvasively evaluate HS [8, 9]. The diagnostic accuracy of CAP has been investigated in biopsy-controlled studies showing good results in differentiating between no (S0) and any hepatic HS(≥ S1), while the diagnostic accuracy for discriminating specific grades of HS is limited [10–13].

There is an ongoing debate on whether HS, as assessed by CAP, influences LS and vice versa [14–17]. The latest meta-analysis by Karlas and colleagues [17] suggested a potential impact of CAP on LS, with slightly increased LS values in patients with high CAP.

Importantly, information on the influence of liver fibrosis and portal hypertension on CAP is scarce. Wong et al. [11] found a lower accuracy in detecting HS ≥ S2 in patients with advanced liver fibrosis (F3/F4). Moreover, Petta and coworkers [15] reported not only an independent association between CAP and LS, but also significantly elevated CAP values in patients with HS S1/S2 and LS > 10.1 kPa (vs. HS S1/S2 and LS ≤ 10.1 kPa). In addition, the authors observed a higher false positive rate for the diagnosis of HS S3 in patients with LS > 10.1 kPa. These data hint toward an interaction of LS and CAP which may compromise the diagnostic performance of VCTE-based measurements in ACLD/PHT. Indeed, CAP has mostly been validated in cohorts comprising a limited number of patients with liver fibrosis (F3/F4) [10, 11, 15]. Importantly, none of these studies specifically addressed patients with ACLD/PHT. Thus, we aimed to investigate the diagnostic performance of CAP for HS in our cohort of thoroughly characterized patients with ACLD/PHT.

Materials and Methods

Patients and Definitions

All patients with ACLD undergoing liver biopsy with HVPG and CAP measurement between 2014 and 2017 were included in this retrospective analysis. ACLD was diagnosed by VCTE (LS ≥ 10 kPa) or HVPG measurement (HVPG ≥ 6 mmHg) [1, 2]. Exclusion criteria were: (I) congestive heart failure, (II) hepatocellular carcinoma, (III) liver transplantation, (IV) ongoing antiviral treatment, (V) acute liver failure, (VI) non-cirrhotic portal hypertension, (VII) insufficient liver biopsy specimen, or (VIII) missing data. Transaminase levels were not used as exclusion criterion since inflammation does not seem to influence CAP [10, 11, 15]. Patient characteristics including clinical and laboratory parameters as well as information on the patatin-like phospholipase domain containing 3 (PNPLA3) rs738409 $C > G$ p.I148M variant were extracted from electronic patient records.

HVPG Measurement

HVPG measurements were performed according to a standardized procedure if there were clinical findings suggestive of portal hypertension [18]. In brief, free (FHVP) and wedged hepatic vein pressure (WHVP) tracings were obtained using a 7 French balloon catheter (Pejcl Medizintechnik, Baden, Austria) [19]. HVPG was calculated as the difference between the FHVP and the WHVP and reported as the mean of three measurements [18].

Liver Biopsy

Liver specimens were obtained either by transjugular liver biopsy after the measurement of HVPG using either an aspiration (16G, Cook Medical, Bloomington, USA) or a

Tru-Cut needle (18G, Cook Medical, Bloomington, USA), or by percutaneous liver biopsy using a Menghini needle (16G, B. Braun, Melsungen, Germany). Histological slides were read by pathologists specialized in liver histopathology and blinded to CAP data. Fibrosis was graded according to the Batts–Ludwig or METAVIR system [20, 21]. HS was semiquantitatively assessed and graded according to the modified Brunt system as S0 (lipid accumulation in < 5% of hepatocytes), S1 (lipid accumulation in 5–33% of hepatocytes), S2 (lipid accumulation in 34–66% of hepatocytes), or S3 (lipid accumulation in > 66% of hepatocytes) [22].

Liver Stiffness and CAP Measurements

LS and CAP measurements were performed simultaneously using FibroScan® (Echosens, Paris, France) and by experienced operators, as previously described [18]. Both M and XL probes were used according to the recommendation of the device. Reliability of LS measurement was defined in accordance with previously established criteria [23]. We applied the following cutoffs for HS derived from a meta-analysis by Karlas et al. [10]: any HS (≥ S1) > 248 dB/m, moderate HS (≥ S2) > 268 dB/m, and severe HS (≥ S3) > 280 dB/m.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., New York, USA). Comparisons of continuous variables were performed using Student's *t* test or Mann–Whitney *U* test, as applicable. Group comparison of more than two groups was done using one-way analysis of variance with Fisher's least significance difference for post hoc comparisons. Areas under the receiver operating characteristic curve (AUROC) were calculated to investigate the diagnostic accuracy of CAP for the detection of HS in different subgroups of patients. Pearson's and Spearman's correlation coefficients were calculated to assess parameters associated with CAP values. Simple and multiple linear regression analysis was used to determine factors independently associated with CAP values. A two-sided *p* value ≤ 0.05 was considered as statistically significant.

Results

Patient Characteristics (Table 1)

In total, 157 patients underwent liver biopsy, CAP, and HVPG measurement during the study period. After applying the inclusion and exclusion criteria, 88 patients were considered for this retrospective analysis (Supplementary Figure-S1). In general, CAP measurements were performed on the same day and by the same physician who performed the HVPG measurement/transjugular liver biopsy. However, in two patients, subsequent percutaneous liver biopsies performed on the following day were included, since insufficient specimens were obtained via the transjugular route. Finally, liver biopsy specimens were obtained via transjugular route in 86 patients (97.7%), using an aspiration needle in 72 cases and both a Tru-Cut and aspiration needle in 14 cases, or percutaneous liver biopsy using a Menghini needle in two cases (2.3%). Mean age was 54 ± 14 years; the majority of patients were male ($n = 49$, 55.7%) with a mean BMI of 25.4 ± 5.8 kg/m^2. A considerable proportion of patients (43.2%) had a BMI ≥ 25 kg/m^2, while 22.7% had a BMI ≥ 30 kg/m^2. The underlying cause of liver disease was viral hepatitis in 22 patients (25.0%), nonalcoholic fatty liver disease (NAFLD) in 22 patients (25.0%), and alcoholic liver disease (ALD) in 13 patients (14.8%). Twenty-three patients (26.1%) suffered from other etiologies of liver disease, such as autoimmune hepatitis s($n = 8$), α1-antitrypsin deficiency ($n = 3$), primary biliary cholangitis ($n = 3$), or other rare causes of liver disease ($n = 9$). The etiology of liver disease remained cryptogenic in eight patients (9.1%).

Sixty-six patients were of Child–Pugh-Score A (75.0%), 14 patients were of Child–Pugh-Score *B* (15.9%), and the remaining eight patients were of Child–Pugh-Score C (9.1%). The mean MELD was 11 (± 4). Importantly, none of the patients included in our analysis had severe ascites [24] at the time of HVPG/CAP measurement. Median HVPG was 16 mmHg (10–19 mmHg) with 84 patients (95.4%) having portal hypertension (HVPG ≥ 6 mmHg). CSPH was present in 69 patients (78.4%) with a mean HVPG of 18.3 mmHg (± 7.8 mmHg) in this subgroup. Median LS and CAP value were 27.4 kPa (16.2–48.9 kPa) and 221 dB/m (± 75 dB/m), respectively. Forty-three patients (56.6%) harbored at least one *PNPLA3 rs738409 G* allele.

According to histological assessment, liver fibrosis stage F1 was present in three patients (3.4%), F2 in six patients (6.8%), F3 in 11 patients (12.5%), and F4/cirrhosis in 56 patients (63.6%). In 12 patients, fibrosis stage could not be reliably assessed by liver histology. Notably, these patients had a median LS of 12.5 kPa (8.3–17.6 kPa). HS S0 was observed in 47 patients (53.4%), S1 in 28 patients (31.8%), S2 in 11 patients (12.5%), and S3 in 2 patients (2.3%).

Comparison of Characteristics According to Histological Steatosis Grade (Table 1)

Direct comparison between patients with (≥ S1, $n = 41$, 46.6%) and without (S0, $n = 47$, 53.4%) any HS in liver histology revealed a statistically significant difference in age (50 ± 15 years vs. 59 ± 12 years, $p = 0.006$), BMI (23.6 ± 5.1 kg/m^2 vs. 27.6 ± 5.9 kg/m^2, $p = 0.001$), CAP (202 ± 73 dB/m vs. 252 ± 70 dB/m, $p = 0.002$), and AP (117

Table 1 Baseline characteristics and comparison of patients with histological hepatic steatosis, or without

Patient characteristics	Overall cohort, $n=88$	No hepatic steatosis, $n=47$	Hepatic steatosis, $n=41$	p value
Age (years)	54 ± 14	50 ± 15	59 ± 12	0.006
Sex, male/female (% male)	49/39 (55.7%)	22/25 (46.8%)	27/14 (65.9%)	0.073
BMI ($kg \times m^{-2}$)	25.4 ± 5.8	23.6 ± 5.1	27.6 ± 5.9	0.001
≥ 25 $kg \times m^{-2}$	38 (43.2%)	13 (27.7%)	25 (61.0%)	0.002
Diabetes	17 (19.3%)	6 (12.8%)	11 (26.8%)	0.084
Etiology				
NAFLD	22 (25.0%)	5 (10.6%)	17 (41.5%)	0.001
ALD	13 (14.8%)	5 (10.6%)	8 (19.5%)	
Viral	22 (25.0%)	11 (23.4%)	11 (26.8%)	
Cryptogenic	8 (9.1%)	7 (14.9%)	7 (17.1%)	
Other	23 (26.1%)	19 (40.4%)	4 (9.8%)	
HVPG (mmHg)	16 (10–19)	16 (10–29)	16 (10–20)	0.583
Liver stiffness (kPa)	27.4 (16.2–48.0)	26.3 (13.5–51.4)	28.8 (17.1–48.0)	0.738
CAP ($dB \times m^{-1}$)	226 ± 75	202 ± 73	252 ± 70	0.002
MELD (points)	11 ± 4	11 ± 4	11 ± 4	0.684
Albumin ($g \times L^{-1}$)	36.7 ± 6.0	36.2 ± 5.8	37.3 ± 6.1	0.416
Bilirubin ($mg \times dL^{-1}$)	1.04 (0.65–1.51)	0.96 (0.64–1.51)	1.04 (0.71–1.58)	0.694
INR	1.31 ± 0.26	1.28 ± 0.26	1.34 ± 0.25	0.291
AP ($U \times L^{-1}$)	101 (69–146)	117 (80–173)	83 (65–115)	0.002
AST ($U \times L^{-1}$)	44 (33–60)	44 (32–63)	42 (35–58)	0.728
ALT ($U \times L^{-1}$)	35 (21–53)	37 (22–62)	33 (20–47)	0.362
GGT ($U \times L^{-1}$)	87 (48–144)	103 (43–210)	82 (51–132)	0.391
PNPLA3 G allele*	43 (56.6%)	21 (53.8%)	22 (59.5%)	0.622
Triglycerides ($mg \times dL^{-1}$)	94.0 ± 41.3	93.3 ± 44.3	94.7 ± 37.9	0.876
Cholesterol ($mg \times dL^{-1}$)	149 ± 51	155 ± 54	142 ± 48	0.261

BMI Body mass index, *NAFLD* nonalcoholic fatty liver disease, *ALD* alcoholic liver disease, *HVPG* hepatic venous pressure gradient, *CAP* controlled attenuation parameter, *MELD* model of end stage liver disease, *INR* international normalized ratio, *AP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyltransferase, *PNPLA*-3 patatin-like phospholipase domain containing three genes

*Information on PNPLA3 genotypes was available in 76 patients (86.4%)

[80–173] vs. 83 [65–115], $p=0.002$), as well as a different distribution of liver disease etiologies ($p=0.028$), with a higher prevalence of patients with NAFLD and ALD. All the other baseline characteristics were comparable between these two groups. Of note, we observed no difference in the severity of liver disease as assessed by HVPG, LS, or MELD score.

CAP varied statistically significantly between patients without any HS (S0, 202 ± 73 dB/m), mild HS (S1, 230 ± 67 dB/m), and moderate/severe HS (S2–3, 300 ± 48 dB/m, $p \leq 0.001$, Fig. 1). While the difference between S0 and S2 ($p \leq 0.001$) as well as S1 and S2 ($p=0.003$) attained statistical significance, there was only a trend toward a difference between S0 and S1 ($p=0.095$). The prevalence of the *PNPLA3 rs738409 G* allele was comparable between patients with or without any HS (53.8% vs. 59.5%, $p=0.622$). The same was true for the *G/G* genotype (15.8% vs. 21.6%, $p=0.517$). There was only a numerical trend toward higher CAP values in patients heterozygous or homozygous for the *G* allele (*G/G:* 260 ± 71 dB/m vs. *G/C*: 229 ± 81 dB/m vs. *G/G*: 213 ± 76 dB/m, $p=0.149$).

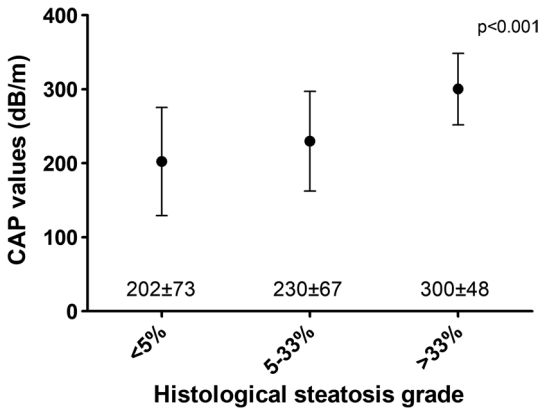

Fig. 1 Comparison of controlled attenuation parameter (CAP) values according to histological steatosis grade

Diagnostic Performance of CAP (Table 2)

Overall, the diagnostic accuracy of CAP for distinguishing between no HS (S0) and any HS (≥S1), as assessed by AUROC, was 0.692 (95% CI 0.582–0.802, Fig. 2A). No improvement was observed when adjusting CAP values according to Karlas et al. (AUROC of 0.675 [95% CI 0.563–0.786], Fig. 2B) [10]. Moreover, we performed subgroup analyses in patients with CPSH ($n=69$), or without ($n=19$). These analyses showed a worse diagnostic performance of CAP in patients with CSPH (AUROC 0.629 [95% CI 0.497–0.761], Fig. 3C), when compared to those without CSPH (AUROC = 0.830 [95% CI 0.637–1.0]. When comparing patients with any HS (≥S1), or without (S0), CAP values were significantly different in both subgroups; however, the difference seemed to be more pronounced in patients without CSPH (175 ± 73 dB/m vs. 258 ± 64 dB/m, $p=0.020$) when compared to patients with CSPH (211 ± 72 dB/m vs. 251 ± 72 dB/m, $p=0.024$, Fig. 3A, B). In a direct comparison of the diagnostic accuracy between patients with cirrhosis (F4) and those without (<F4) in liver histology, AUROC values were 0.607 (95% CI 0.459–0.756, Fig. 3D) and 0.805 (95% CI 0.597–1.0), respectively (Supplementary figure-S2). The etiology-specific AUROC values were 0.600 (95%

Table 2 Diagnostic indices of controlled attenuation parameter (CAP) for diagnosing hepatic steatosis using established cutoffs for hepatic steatosis S1 (> 248 dB/m) and S2 (> 268 dB/m)

	Patient group	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Any steatosis (≥S1) vs. no steatosis (S0)	All patients ($n=88$)	48.8 (32.9–64.9)	76.6 (62.0–87.7)	64.5 (49.8–76.9)	63.2 (55.0–70.6)
	Patients with CSPH ($n=69$)	45.5 (28.1–63.6)	72.2 (54.8–85.8)	60.0 (44.0–74.1)	59.1 (49.9–67.8)
	Patients with cirrhosis ($n=56$)	37.0 (19.4–57.6)	72.4 (52.8–87.3)	55.6 (36.7–72.9)	55.3 (46.1–64.1)
Moderate/severe steatosis (S2–3) vs. no/mild steatosis (S0–1)	All patients ($n=88$)	84.6 (55.6–98.1)	81.3 (70.7–89.4)	44.0 (31.7–57.1)	96.7 (89.5–99.1)
	Patients with CSPH ($n=69$)	80.0 (44.4–97.5)	81.4 (69.1–90.3)	42.1 (28.2–57.4)	96.0 (87.4–98.8)
	Patients with cirrhosis ($n=56$)	75.0 (34.9–96.8)	81.3 (67.8–91.1)	40.0 (24.7–57.6)	95.1 (85.4–98.5)

CI Confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *CSPH* clinically significant portal hypertension

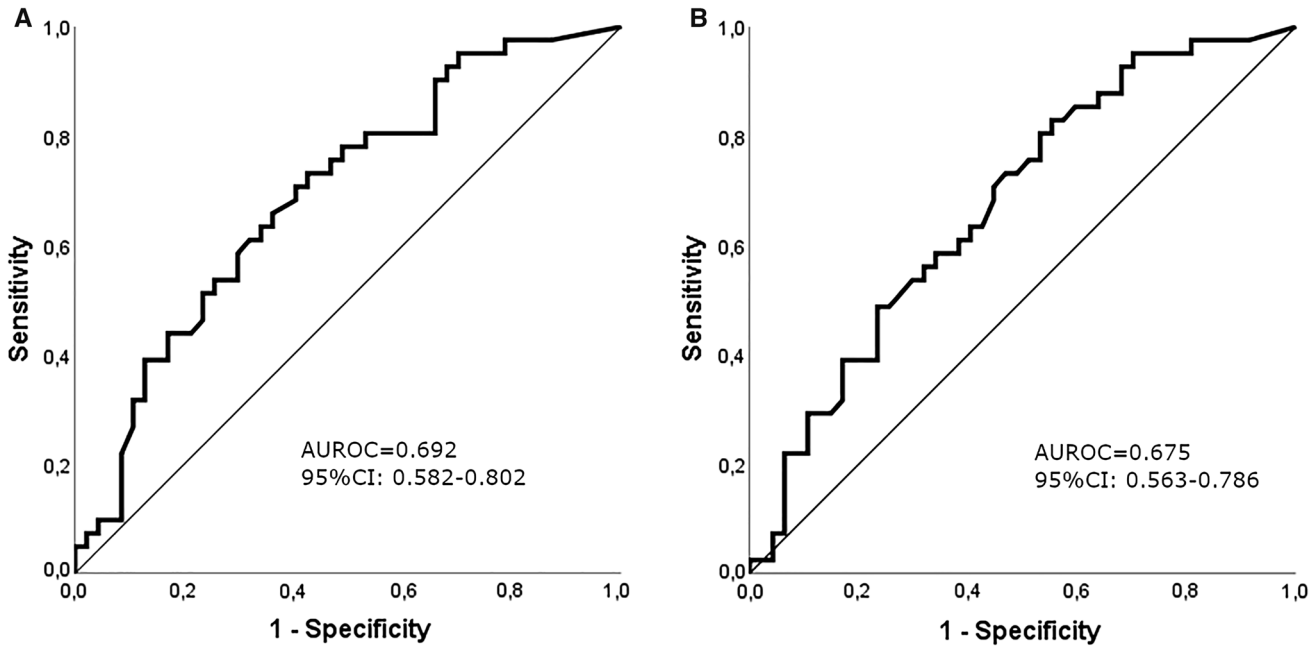

Fig. 2 **A** Area under the receiver operating characteristic curve (AUROC) and 95% confidence interval (95% CI) of controlled attenuation parameter (CAP) for diagnosing any hepatic steatosis. **B** AUROC of CAP adjusted according to Karlas et al.

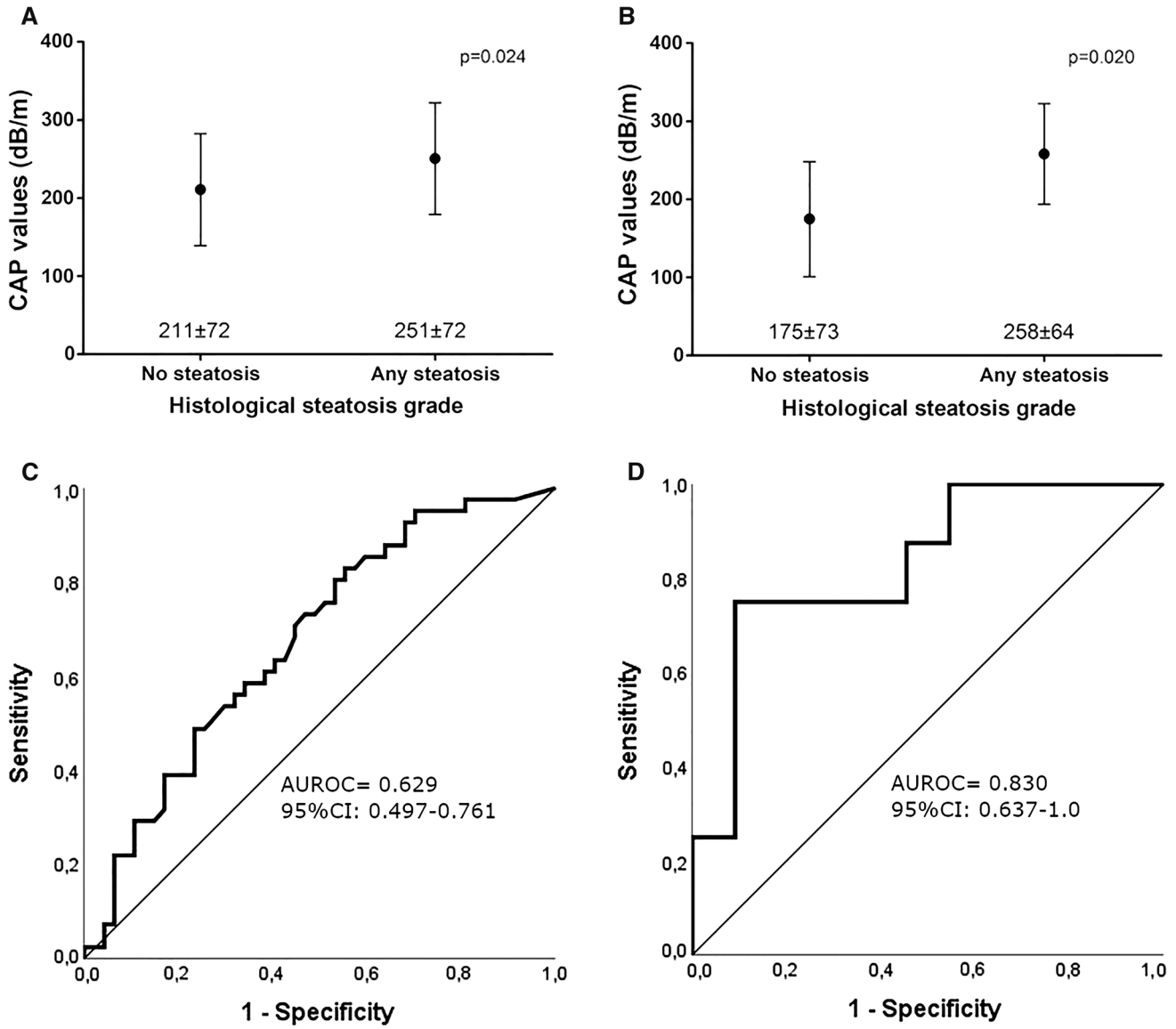

Fig. 3 Comparison of controlled attenuation parameter (CAP) values in between subgroups of patients without clinically significant portal hypertension (CSPH, **A** and **B**). Area under the receiver operating characteristic curve (AUROC) values and 95% confidence intervals (95% CI) of CAP for diagnosing any hepatic steatosis among patients with and without CSPH (**C** and **D**)

CI 0.300–0.900) for NAFLD, 0.650 (95% CI 0.337–0.963) for ALD, and 0.603 (95% CI 0.359–0.848) for viral hepatitis.

In distinguishing S0–1 from ≥ S2, the AUROC of CAP was 0.842 (95% CI 0.747–0.936). Applying the correction proposed by Karlas et al. did not improve the diagnostic performance (AUROC = 0.791 [95% CI 0.675–0.908]) [10]. In a subgroup analysis of patients with and without CSPH, the AUROC values were 0.825 (95% CI 0.702–0.947) and 0.854 (95% CI 0.685–1.0), respectively (Supplementary figure-S3 and S4).

When applying the previously published cutoffs for S1 (> 248 dB/m), S2 (> 268 dB/m), and S3 (> 280 dB/m), identical HS grade was attributed to 42 patients (51.2%) by both CAP and liver histology. For the diagnosis of any HS (≥ S1), overall sensitivity was 48.8%, specificity 76.6%, positive predictive value (PPV) 64.5%, and negative predictive value (NPV) 63.2%. The diagnostic indices were slightly worse in patients with CSPH (sensitivity 45.5%, specificity 72.2%, PPV 60.0%, NPV 59.1%) and cirrhosis (sensitivity 37.0%, specificity 72.4%, PPV 55.6%, NPV 55.3%). For distinguishing between S0–1 and ≥ S2, overall sensitivity was 84.6%, specificity 81.3%, PPV 44.0%, and NPV 96.7%, showing a similar diagnostic performance in the subgroups of patients with CSPH and cirrhosis.

Correlation of CAP with Baseline Characteristics

To investigate the relationship between CAP and baseline characteristics, correlation and linear regression analysis was performed. In correlation/simple linear regression analysis, age (Pearson's $r = 0.274$, unstandardized regression coefficient $B = 1.487$, $p = 0.010$), BMI ($r = 0.497$, $B = 6.475$, $p \leq 0.001$), the presence of diabetes ($r = 0.355$, $B = 67.166$, $p = 0.001$), NAFLD/ALD ($r = 0.323$, $B = 55.132$, $p = 0.002$), LS ($r = 0.234$, $B = 0.798$, $p = 0.028$), and HS grade ($r = 0.430$, $B = 40.946$, $p \leq 0.001$) were significantly associated with CAP values, while HVPG and MELD as well as other baseline characteristics showed no association. However, in multiple linear regression analysis, only BMI ($B = 3.674$, $p = 0.010$) and HS grade ($B = 23.019$, $p = 0.021$) were independently associated with CAP (Supplementary table-S1).

Moreover, CAP correlated significantly with the percentage of steatotic hepatocytes in all subgroup analyses, although a weaker correlation was observed in patients with CSPH (Spearman's $\rho = 0.335$, $p = 0.005$), compared to those without ($\rho = 0.584$, $p = 0.009$), and in patients with cirrhosis in liver histology ($\rho = 0.295$, $p = 0.027$), when compared to patients without ($\rho = 0.574$, $p = 0.008$).

Interestingly, HVPG was neither correlated with CAP ($\rho = 0.054$, $p = 0.653$) or the percentage of steatotic hepatocytes ($\rho = 0.055$, $p = 0.654$), nor with histological HS grade ($\rho = 0.026$, $p = 0.829$). However, we observed a direct correlation of moderate strength between HVPG and LS ($\rho = 0.673$, $p \leq 0.001$). Fifteen patients needed to be excluded from these analyses due to non-selective beta-blocker treatment during HVPG measurement ($n = 13$), the presence of collaterals ($n = 1$), or portal vein thrombosis ($n = 1$) (Supplementary table-S2).

Discussion

In general, CAP has shown a good diagnostic performance for HS in patients with chronic liver disease [10–13]. However, most patients included in previous studies had either NAFLD or viral hepatitis and the vast majority of patients did not have ACLD/PHT. In the meta-analysis of individual patient data by Karlas and co-workers [10], for instance, median LS was 7.4 kPa, and only 13% of patients had cirrhosis. Thus, the ability of CAP to evaluate HS in patients with more advanced liver disease (i.e., ACLD and PHT) has not been sufficiently studied. This is the first study to investigate the diagnostic performance of CAP for HS in a cohort comprising only patients with ACLD/PHT, including a relevant proportion of patients with CSPH.

Several studies underline the importance of HS for liver fibrosis progression (i.e., progression to ACLD) in nonalcoholic fatty liver disease as well as viral and autoimmune hepatitis [25–34]; however, the impact of HS in patients who have already developed ACLD is less well established. In an analysis of data from the HALT-C trial, the severity of HS modulated the risks of disease progression in patients with bridging fibrosis and cirrhosis due to chronic hepatitis C [35]. Moreover, obesity has been found to increase the risk of hepatic decompensation independently of HVPG in patients with compensated cirrhosis, regardless of etiology. In line with this finding, an intensive life-style intervention (diet and exercise) has been shown to lower HVPG in weight-loss-dependent manner [36]. Accordingly, there is increasing evidence for obesity and associated HS being an important cofactor in patients who have already progressed to ACLD, and thus, it is easily conceivable that there will be considerable research activities in the near future, which highlights the need for noninvasive methods to assess HS in this patient population.

Interestingly, studies investigating the influence of CAP on disease progression (i.e., hepatic decompensation and mortality) in patients with ACLD showed inconsistent results [37–39]. Moreover, we did not observe an association between *PNPLA3* genotype and CAP values in a previous study from our center [40]. Therefore, we hypothesized that the diagnostic performance of CAP for diagnosing HS may be worse in patients with ACLD and CSPH [37].

Indeed, in our study population of ACLD/PHT patients, the AUROC for diagnosis of any HS ($\geq$ S1; 0.692) was considerably lower, when compared to published data (0.77–0.953) from previous studies including mostly patients without advanced liver fibrosis [10, 12, 41–47]. CAP tended to perform even worse in diagnosing any HS ($\geq$ S1) in patients with CSPH (0.629) and/or histologically confirmed cirrhosis (0.607). In contrast, we found a robust diagnostic performance of CAP for identifying patients with HS $\geq$ S2, yielding an AUROC of 0.842 versus 0.78–0.956 as reported in the previous studies, including mostly patients without advanced liver fibrosis [10, 12, 13, 41–44, 46, 47].

Applying the previously published CAP cutoff of 248 dB/m for diagnosing any HS, sensitivity and specificity in our cohort of patients with ACLD/PHT were considerably lower (sensitivity 48.8% and specificity 76.6%) as compared to published sensitivity and specificity values of 68.8–88.0% and 81.0–100%, respectively [10, 43, 44, 47, 48]. Again, indicators of the diagnostic performance were particularly poor in the subgroups of patients with CSPH (sensitivity 45.5% and specificity 72.2%) or histologically confirmed cirrhosis (sensitivity 37.0% and specificity 72.4%). However, the specificity and sensitivity of CAP for diagnosing HS $\geq$ S2 were comparable to those for the previous studies including predominantly patients without ACLD/PHT [10, 43, 44, 47, 48].

In line with the poor diagnostic performance for any HS, CAP values in patients with HS S0 and S1 were comparable, confirming the inability of CAP to reliably discriminate between HS S0 and S1 in our cohort of ACLD/PHT patients. Another explanation for the limited diagnostic value of CAP to discriminate S0 from S1 HS in patients with ACLD/PHT includes the potential influence of liver fibrosis/cirrhosis and/or hemodynamic changes associated with CSPH on CAP measurements. Next to the direct correlation between CAP and LS—which has been previously reported in the literature and was also confirmed in our study [15]—de Ledinghen and colleagues [12] found an association between elevated CAP values and LS > 6 kPa. Moreover, Petta and co-workers [15] reported significantly elevated CAP values in patients with HS S1–2 and LS > 10.1 kPa, when compared to patients with HS S1–2 and LS ≤ 10.1 kPa. Accordingly, we hypothesize that the architectural/hemodynamic changes may affect the ultrasonic attenuation of the liver in ACLD patients and, thus, CAP measurements.

Consequently, the accuracy of CAP for ruling out any HS (NPV for HS ≥ S1) is limited (63.2%) in our overall cohort and further decreases to 59.1%/55.3% in patients with CSPH/cirrhosis, as compared values of 61.5–92.3% reported in the previous studies using similar cutoffs and histological grading systems [43, 44, 46, 47].

In addition, the diagnostic performance of CAP for ruling-in HS ≥ S2 or ≥ S3 is limited with a PPV of 44.0% and 9.5% in the overall cohort, while being 59.0–83.0% and 28.9–44.0% in the literature, respectively [46, 47]. However, since the PPV also depends on the prevalence of the condition, these results have to be interpreted with caution, as the prevalence of HS ≥ S2 or ≥ S3 in our cohort was relatively low (S2 12.5%; S3 2.3%). The low prevalence of HS ≥ S2 or ≥ S3 might be explained by the fact that histological HS frequently regresses with liver fibrosis progression [49, 50].

Recently, Piccinni et al. [51] observed a good performance of CAP for assessing HS in 124 patients with compensated ACLD showing an AUROC for diagnosing any HS(≥ S1) of 0.827 and 0.864 for HS ≥ S2. Importantly, the median LS of their cohort was considerably lower (16.3 kPa) when compared to our study (27.4 kPa), indicating less-advanced liver disease. Moreover, liver histology revealed that 40.7% of patients had liver fibrosis grade F0–2, and thus, did not have ACLD based on the reference method. This might be explained by the high prevalence of any HS (≥ S1), as diagnosed by CAP (69.4%), as well as a high mean BMI of 27.8 kg/m^2, since both of these factors have previously been found to be associated with an overestimation of liver fibrosis by VCTE [14, 15, 52]. Lastly, the authors did not provide information on HVPG; however, the lower median LS values strongly suggest a substantially lower prevalence of CSPH than in our study. Our study comprised a higher proportion of patients with advanced liver fibrosis (≥ F3; 76.1%) on liver histology, and 63.6% and 78.4% had cirrhosis and CSPH, respectively. Thus, since both of these factors seemed to impair the diagnostic performance of CAP for any HS in our study, the discrepancy between our results and the findings of Piccinni and colleagues [51] is likely explained by differences in patient characteristics.

Our study has some limitations: While stringent inclusion and exclusion criteria resulted in a thoroughly characterized cohort of patients with ACLD/PHT, limited sample size has to be taken into account when interpreting our results. Moreover, in patients with pronounced perihepatic ascites, it is usually not possible to obtain valid liver LS by VCTE. Importantly, there is convincing evidence, from both experimental and clinical studies, that LS provides reliable measurements in phantoms/patients with a thin lamella of water/ascites [52]. Since the presence of severe ascites makes catheterization of the hepatic veins more difficult, patients with severe ascites commonly undergo paracentesis prior to HVPG measurement at our center [37]. In addition, several patients did not have any ascites at the time of HVPG/CAP measurement despite moderate/severe hepatic impairment, since they were on diuretics. Thus, we were able to obtain reliable LS measurements in the Child–Pugh-Score B/C patients included in our analysis. Although there are well-established quality criteria for LS measured by VCTE [23], there are no generally accepted quality criteria for CAP; thus, we abstained from applying quality criteria for CAP, since it would have further compromised sample size [11]. Moreover, the broad use of transjugular liver biopsy usually providing smaller liver specimens, as compared to percutaneous liver biopsy, needs to be acknowledged as a limitation of our study. Finally, the use of both the METAVIR and Batts–Ludwig score for grading liver fibrosis stages may have compromised the discrimination of F2 and F3; however, this did not affect the results of our analyses.

In conclusion, our study provides important information on the diagnostic performance of CAP for HS in patients with ACLD. Our results indicate that either liver biopsy or presumably more accurate noninvasive methods (e.g., MRI-based proton density fat fraction [53]) are required for correctly diagnosing any HS(≥ S1) in patients with ACLD. However, these methods are invasive and/or resource-intensive, which prevents their broad clinical application [54]. The development of accurate and easily accessible noninvasive surrogates of HS is particularly relevant in light of the ongoing screening activities for the increasing number of NASH trials which will also include patients with ACLD [55].

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Author's contribution GS, JS, BS, TR, and MM contributed to the concept of the study, all authors contributed to data collection, GS and MM contributed to statistical analysis, GS, JS, BS, TR, and MM contributed to drafting of the manuscript, and all authors contributed to the revision for important intellectual content. All authors approved the final version of this manuscript.

Compliance with Ethical Standards

Conflict of interest The authors have nothing to disclose regarding the work under consideration for publication. The following authors disclose conflicts of interests outside the submitted work: JS received grant support from Gilead, Eli, and Lilly. BS received travel support from Gilead. PS received speaker fees from Boehringer Ingelheim and travel support from Boehringer Ingelheim and Gilead. MP received speaker fees from Bayer and Bristol-Myers Squibb, travel support from Bayer, and served as advisory board member for Bayer, Bristol-Myers Squibb, and Eisai. AF has served as a speaker and consultant for AbbVie, Gilead, and Intercept and owns a patent on a catheter for the measurement of hepatic venous pressure gradient. MT received speaker fees from Gilead and MSD, travel support from Gilead, grant support from MSD, and honoraria for consulting from AbbVie, Gilead, Janssen, and MSD. TR received speaker fees from Boehringer Ingelheim, Gore, and MSD, travel support from Boehringer Ingelheim, Gilead, MSD, and Gore, grant support from AbbVie, Boehringer Ingelheim, Boston Scientific, Cook Medical, Gilead, Gore, Guerbet, Phenex Pharmaceuticals, Philips, and MSD, and served as a consultant for AbbVie, Bayer, Boehringer Ingelheim, Gilead, and MSD. MM served as a speaker and consultant for AbbVie, Bristol-Myers Squibb, Gilead, Gore, and Janssen. GS, RP, KW, and AFS have nothing to disclose.

Ethical approval This study was approved by the ethics committee of the Medical University of Vienna (No. 1124/2017) and performed in accordance with the ethical guidelines denoted in the Declaration of Helsinki (version 2013). Since this is a retrospective analysis, the requirement of a written informed consent was waived by the ethics committee.

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