Chapter 38
Steatosis Assessment with Controlled Attenuation Parameter (CAP) in Various Diseases

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The Role of Steatosis in Liver Disease

Liver steatosis is the accumulation of lipid droplets, mainly triglycerides, in the hepatocytes. It can be defined histologically, which necessitates a liver biopsy, by the presence of fat droplets in ≥5% of hepatocytes; or radiologically/chemically by the wet mass of the liver parenchyma consisting of ≥5% lipid mass [1]. Steatosis represents imbalanced hepatic lipid metabolism due to liver injury in a variety of chronic and acute liver diseases, including drug-induced liver injury, alcoholic liver disease (ALD), and chronic viral hepatitis B and C (HBV, HCV). In particular, liver steatosis is the hallmark of non-alcoholic fatty liver disease (NAFLD) which is, by definition, lipid accumulation in the liver, in the absence of excess alcoholic consumption and other known causes of chronic liver disease [2]. Being able to easily assess steatosis is therefore crucial for diagnosing NAFLD. The high prevalence of NAFLD in the western world and the fact that NAFLD is the fastest growing chronic liver disease is one reason for the focus on finding noninvasive methods for diagnosing and grading steatosis in patients at risk of NAFLD. Beyond NAFLD, noninvasive modalities that can diagnose and quantify steatosis may be used for screening, follow-up, and assessment of efficacy of intervention in other chronic liver diseases where liver fat accumulation is an indicator of hepatocyte dysfunction [3].

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Ultrasonography, Serum Markers, Computed Tomography, and Magnetic Resonance Imaging as Noninvasive Markers of Steatosis

The gold standard for evaluation of fatty liver is still liver biopsy despite the method's imperfections [2, 4]. Liver biopsy is subject to sampling error, and to intra- and inter-observer variation [5]. A biopsy is further an invasive procedure, time consuming, and only available in specialist centers. Ultrasound (US) has been, and is still, the most common tool to diagnose liver steatosis, due to its wide availability and low cost. However, US has low sensitivity for mild steatosis, since bright liver echo pattern (BLEP) with or without attenuation of the US beam can only adequately detect a hepatic lipid content above 20% [6, 7]. Bright liver echo pattern is a diffuse increase in liver echogenicity, when compared to the right renal cortex, while US beam attenuation is blurring of the deep liver vein margins and loss of definition of the diaphragm. A meta-analysis on 49 studies showed an AUROC of 0.93 of BLEP with or without attenuation for the diagnosis of moderate-severe steatosis [8]. In addition to the low sensitivity, BLEP's main limitations are observer variability and false positives due to a hyperechoic liver parenchyma in liver disease patients with fibrosis or inflammation [9]. Additionally, US quality is vastly impaired by large skin-capsule distance in obese patients. Novel post-processing computerized analyses of US images such as the hepatorenal sonographic index [10] have shown excellent accuracy for diagnosing ≥S1 steatosis with an AUROC of 0.99, 100% sensitivity, and 91% specificity. Other studies have verified these results [11, 12].

Several serum-based biomarkers for steatosis have been developed and validated against ultrasound, MRS, or liver biopsy (Table 38.1) [13, 14]. However, the serum markers for steatosis are not routinely used, probably because of wide access to ultrasound imaging that have similar or better accuracy which work as point-of-care and therefore outplay the serum markers.

Computed tomography (CT) has the advantage that the whole liver is evaluated but it uses ionizing radiation and its sensitivity is low when steatosis is <30% [15]. Therefore, CT is not routinely used for steatosis assessment, but steatosis may be described as an incidental finding after CT for other indications.

In contrast, magnetic resonance imaging (MRI) based techniques quantify liver fat with excellent sensitivity, especially MR spectroscopy (MRS) and MRI with proton-density-fat-fraction (PDFF) [16–18]. MRI-PDFF and MRS accurately differentiate moderate/severe steatosis (≥S2) from mild/no hepatic steatosis with similar accuracy between techniques, and closely correlated to histological steatosis score [17]. Despite the superior diagnostic accuracy, the MRI modalities are currently restricted to tertiary clinics and research due to cost and demands for specialist equipment and trained personnel.

Table 38.1 Algorithms combining clinical information with serum blood tests for diagnosing liver steatosis

	Score components							
Scores	Sex	BMI	DM	ALT	AST/ ALT ratio	GGT	TG	Other
Fatty liver index (FLI)		x				x	x	Waist circumference
Hepatic steatosis index (HSI)		x	x		x			
Index of NASH (ION)	x			x			x	Waist-to-hip ratio, HOMA
Lipid accumulation product (LAP)	x						x	Waist circumference
NAFLD-liver fat score (NAFLD-LFS)			x		x			MetS and insulin
SteatoTest™	x	x		x		x	x	Age, A2M, ApoA1, haptoglobin, bilirubin, cholesterol, glucose

™=patented, all other scores are non-patented
A2M a2-macroglobulin, *ALT* alanine transaminase, *AST* aspartate transaminase, *ApoA1* apolipoprotein A-1, *BMI* body mass index, *DM* diabetes mellitus, *GGT* gamma-glutamyl transferase, *MetS* metabolic syndrome, *TG* triglycerides

Controlled Attenuation Parameter Is a Novel Ultrasound Technique for Diagnosing Steatosis in Liver Disease Patients

Transient elastography with the FibroScan device has revolutionized our ability to diagnose liver fibrosis in patients with chronic liver disease of various etiologies [19]. Controlled attenuation parameter was added to the FibroScan software in 2010 [20]. With CAP, it is possible to obtain a measure of liver parenchyma attenuation (in dB/m) in parallel with the liver stiffness measurement. An additional advantage is CAP's continuous nature, which increases resolution more than the ultrasound steatosis staging from 0 to 3.

Initially, CAP measurements relied on the FibroScan M-probe, which was a disadvantage due to the high failure rate in patients with central obesity or BMI >30 kg/m^2. In a prospective study with 5323 CAP examinations using the M-probe, 7.7% of measurements failed [21]. Fortunately, CAP for the XL-probe was made available from 2015, which substantially reduced the failure rate [22]. In a 2018 study utilizing both the M- and XL-probes, failure rate was down to 3.2% in 992 NAFLD patients [23]. Whether probe type should be considered, when interpreting CAP values, is however still debated: In a study with 992 NAFLD patients, Vuppalanchi

et al. [23] found that CAP values obtained in the same patient with the XL-probe were on average 16 dB/m higher compared with the M-probe, adjusted for BMI and histological steatosis severity [23]. However, in a recent study by Eddowes and colleagues of similar size, probe type was not a predictor of either false positives or false negatives [24].

Eight studies from 2010 to 2016 investigated the overall performance of CAP to diagnose liver steatosis, using liver biopsy as gold standard [20, 25–31]. In these studies, CAP had sensitivities ranging from 64 to 91% for detecting any steatosis (≥S1) and specificities ranging from 64 to 94%. Similarly, studies reported a broad range of optimal cutoff values for any steatosis, from 214 to 289 dB/m. Cutoffs for ≥S2 and ≥S3 also varied. The between-study heterogeneity indicates substantial spectrum bias, probably due to patient selection. Consequently, an individual-patient data meta-analysis including data from 2735 patients from 19 studies with different etiologies tried to establish common CAP cutoff values for the M-probe (they excluded studies where subjects had BMI above 30 kg/m^2 or a skin to liver capsule distance above 2.5 cm) [32]. The steatosis distribution was 51%/27%/16%/6% for S0/S1/S2/S3. Optimal cutoff for diagnosing any steatosis (≥S1) was 248 dB/m (AUROC 0.82, sensitivity 69%), moderate steatosis (≥S2) was 268 dB/m (AUROC 0.87, sensitivity 77%) and severe steatosis (=S3) was 280 dB/m (AUROC 0.88, sensitivity 88%).

CAP in Non-alcoholic Fatty Liver Disease

Controlled attenuation parameter in patients suspected of NAFLD is of particular interest, as a noninvasive tool which affordably can identify and monitor people at risk for NAFLD.

Fifteen studies to date have examined the performance of CAP for diagnosing steatosis (Table 38.2).

From the evidence so far, CAP does not seem to reliably diagnose severe steatosis (≥S3), as AUROCs are consistently below 0.80. However, on average CAP has good accuracy for diagnosing any steatosis (≥S1), with AUROCs in the large studies above 0.85, except in the American multicenter study by Siddiqui and colleagues [33]. However, cutoffs vary highly, which limits generalizability of results. Additionally, sensitivities and specificities for the optimal cutoffs are well below 90% for ≥S1 across studies. This means that from the existing evidence, it is not possible to derive universal cutoffs that can reliably rule-out any steatosis (cutoff with sensitivity above 90% would result in 10% false positive classifications) or rule-in any steatosis (specificity above 90% would result in 10% false negatives).

The vast majority of existing studies on NAFLD have analyzed CAP in secondary and tertiary settings with a high prevalence of steatosis. It is therefore not yet clear how CAP performs in primary care settings where the prevalence of steatosis is much lower.

Table 38.2 Studies evaluating CAP performance with liver biopsy as reference in people with NAFLD

Authors	Year	NAFLD patients	Distribution of steatosis (%)	Probe	Mean ± SD or median (IQR) CAP (dB/m)	Optimal cutoff value (dB/m)	AUROC (95% CI)	Se (%)	Sp (%)
Friedrich-Rust [51]	2012	46	S0 = 1 (2)	M					
			S1 = 11 (24)		S1 = 241 ± 71				
			S2 = 13 (28)		S2 = 298 ± 30	≥S2 = 245	0.78 (0.58–0.99)	97	67
			S3 = 21 (46)		S3 = 314 ± 39	≥S3 = 301	0.72 (0.57–0.86)	76	68
Kumar [52]	2013	63	S0 = 0 (0)	–					
			S1 = 26 (41)		S1 = 213 (100–324)				
			S2 = 30 (48)		S2 = 248 (117–359)	≥S2 = 258	0.79	78	73
			S3 = 7 (11)		S3 = 291 (266–373)	≥S3 = 283	0.76	71	68
Chan [53]	2014	101	S0 = 3 (3)	M					
		+60C	S1 = 33 (33)		S1 = 305 (276–430)	≥S1 = 263	0.97	92	94
			S2 = 51 (51)		S2 = 320 (305–346)	≥S2 = 263	0.86	97	68
			S3 = 14 (14)		S3 = 324 (291–351)	≥S3 = 281	0.75	100	53
Karlas [54]	2014	46	S0 = 0 (0)	M					
		+15C	S1 = 18 (36)		S1 = 253 ± 43	≥S1 = 233	0.93 (0.86–1.00)	93	87
			S2 = 20 (40)		S2 = 321 ± 42	≥S2 = 268	0.94 (0.88–0.99)	97	81
			S3 = 12 (24)		S3 = 335 ± 43	≥S3 = 301	0.82 (0.70–0.93)	82	76

(continued)

Table 38.2 (continued)

Authors	Year	NAFLD patients	Distribution of steatosis (%)	Probe	Mean ± SD or median (IQR) CAP (dB/m)	Optimal cutoff value (dB/m)	AUROC (95% CI)	Se (%)	Sp (%)
Imajo [30]	2016	127	S0 = 0 (0)	M					
		+10C	S1 = 59 (42)		S1 = 263	≥S1 = 236	0.88 (0.80–0.95)	82	91
			S2 = 59 (42)		S2 = 290	≥S2 = 270	0.73 (0.64–0.81)	78	80
			S3 = 24 (17)		S3 = 305	≥S3 = 302	0.70 (0.58–0.83)	64	74
de Ledinghen [55]	2016	261	S0 = 0 (0)	M					
			S1 = 78 (30)		S1 = 264 ± 45				
			S2 = 100 (38)		S2 = 298 ± 48	≥S2 = 310	0.80 (0.73–0.86)	79	71
			S3 = 83 (32)		S3 = 331 ± 37	≥S3 = 311	0.66 (0.59–0.72)	87	47
Lee [56]	2016	183	S0 = 9 (5)	–					
			S1 = 76 (42)		S1 = 265 (173–377)	≥S1 = 247	0.95 (0.93–0.98)	88	100
			S2 = 65 (36)		S2 = 313 (192–350)	≥S2 = 280	0.85 (0.80–0.91)	85	80
			S3 = 33 (18)		S3 = 322 (230–400)	≥S3 = 300	0.73 (0.65–0.81)	73	61

Chan [57]	2017	57	S0 = 1 (2)	M	S1 = 324 (268–350)	≥S1 = 266	0.94 (0.86–0.98)	91	87
		+22C	S1 = 13 (23)		S2 = 321 (299–341)	≥S2 = 266	0.80 (0.69–0.88)	91	87
			S2 = 28 (49)		S3 = 330 (299–344)	≥S3 = 267	0.69 (0.57–0.79)	100	41
			S3 = 15 (26)	XL	S1 = 339 (302–368)	≥S1 = 271	0.97 (0.90–0.99)	95	91
					S2 = 345 (298–389)	≥S2 = 271	0.81 (0.71–0.89)	95	61
					S3 = 345 (305–368)	≥S3 = 304	0.67 (0.56–0.77)	80	55
Park [35]	2017	78	S0 = 9 (9)	M, XL					
			S1 = 49 (48)			≥S1 = 261	0.85 (0.75–0.96)	72	86
			S2 = 29 (28)			≥S2 = 305	0.70 (0.58–0.82)	63	69
			S3 = 16 (16)			≥S3 = 312	0.73 (0.58–0.89)	64	70

(continued)

Table 38.2 (continued)

Authors	Year	NAFLD patients	Distribution of steatosis (%)	Probe	Mean ± SD or median (IQR) CAP (dB/m)	Optimal cutoff value (dB/m)	AUROC (95% CI)	Se (%)	Sp (%)
Naveau [58]	2017	123	S0 = 23 (19)	XL					
			S1 = 29 (24)		S1 = 323 ± 10	≥S1 = 298	0.84 (0.71–0.91)	78	83
			S2 = 25 (20)		S2 = 358 ± 8	≥S2 = 303	0.83 (0.74–0.90)	90	69
			S3 = 46 (37)		S3 = 358 ± 8	≥S3 = 326	0.84 (0.75–0.90)	83	71
Siddiqui [33]	2018	358	S0 = 19 (5)	M, XL					
			S1 = 150 (38)		S1 = 306 (270–338)	≥S1 = 285	0.76 (0.64–0.89)	80	77
			S2 = 119 (30)		S2 = 340 (312–369)	≥S2 = 311	0.70 (0.64–0.75)	77	57
			S3 = 105 (27)		S3 = 340 (311–360)	≥S3 = 306	0.58 (0.51–0.64)	80	40
Garg [59]	2018	76	S0 = 6 (8)	XL					
			S1 = 47 (62)		S1 = 320 (296–345)	≥S1 = 323	0.75 (0.61–0.89)	59	83
			S2 = 19 (25)		S2 = 354 (328–366)	≥S2 = 336	0.74 (0.62–0.86)	74	76
			S3 = 4 (5)		S3 = 362 (361–369)	≥S3 = 357	0.82 (0.73–0.91)	100	78

Runge [36]	2018	55	S0 = 5 (9)	M					
			S1 = 24 (44)			≥S1 = 260	0.77 (0.64–0.88)	90	60
			S2 = 17 (31)			≥S2 = 296	0.78 (0.65–0.88)	92	55
			S3 = 9 (16)			≥S3 = 334	0.79 (0.65–0.88)	79	76
Darweesh [60]	2019	60	S0 = 0 (0)	–					
			S1 = 22 (37)		S1 = 262 (245–299)				
			S2 = 25 (42)		S2 = 323 (278–345)	≥S2 = 297	0.77 (1.01–1.03)	81	85
			S3 = 13 (22)		S3 = 378 (366–400)	≥S3 = 366	0.92 (1.01–1.08)	73	96
Eddowes [24]	2019	380	S0 = 47 (12)	M, XL					
			S1 = 89 (23)			≥S1 = 302	0.87 (0.82–0.92)	80	83
			S2 = 107 (28)			≥S2 = 331	0.77 (0.71–0.82)	70	76
			S3 = 137 (36)			≥S3 = 337	0.70 (0.64–0.75)	72	63

AUROC area under the receiver operating curve, *C* controls without NAFLD without liver biopsy, *CAP* controlled attenuation parameter, *NAFLD* non-alcoholic fatty liver disease, *Se* sensitivity, *Sp* specificity, *95% CI* 95% confidence interval, *IQR* interquartile range, *S1, S2, S3* fat accumulation in 5%–33%, >33%–66%, >66% of hepatocytes

Two studies have suggested quality criteria for the measurement of CAP [18, 34]. A study from Wong and colleagues recommended using an IQR of CAP below 40 dB/m together with 10 valid measurements [34]. Another study from Caussy et al. with 119 MRI-PDFF-proven NAFLD patients recommended using IQR below 30 dB/m and 10 valid measurements [18]. However, both these studies do not take into account an increase in IQR when median CAP increases. Consequently, the quality criteria that use low IQR will be biased towards patients with lower CAP values. Therefore, common quality criteria that can be applied to the full range of CAP measurement from 100 to 400 dB/m are still needed. Three studies have directly compared CAP with MRI-PDFF (Table 38.3). They all show that CAP is significantly inferior to MRI-PDFF in differentiating all steatosis grades [30, 35, 36].

Table 38.3 Studies comparing diagnostic accuracy of CAP versus MRI-PDFF in NAFLD, with liver biopsy as reference

			CAP				MRFI-PDFF			
Author	Year	Steatosis level	Cutoff (dB/m)	AUROC (95% CI)	Se (%)	Sp (%)	Cutoff (%)	AUROC (95% CI)	Se (%)	Sp (%)
Imajo [30]	2016	≥S1	236	0.88 (0.80–0.95)	82	91	5.2	0.98 (0.96–1.00)	90	93
		≥S2	270	0.73 (0.64–0.81)	78	80	11.3	0.90 (0.81–0.98)	79	84
		≥S3	302	0.70 (0.58–0.83)	64	74	17.1	0.79 (0.64–0.95)	74	81
Park [35]	2017	≥S1	261	0.85 (0.75–0.96)	72	86	3.7	0.99 (0.98–1.00)	96	100
		≥S2	305	0.70 (0.58–0.82)	63	69	13.1	0.90 (0.82–0.97)	80	83
		≥S3	312	0.73 (0.58–0.89)	64	70	16.4	0.92 (0.84–0.99)	82	84
Runge [36]	2018	≥S1	260	0.77 (0.64–0.88)	90	60	4.1	0.99 (0.91–1.00)	94	100
		≥S2	296	0.78 (0.65–0.88)	92	55	15.7	0.98 (0.89–0.99)	92	97
		≥S3	334	0.79 (0.65–0.88)	79	76	20.9	0.96 (0.86–0.99)	100	83

AUROC area under the receiver operating curve, *CAP* controlled attenuation parameter, *MRI-PDFF* magnetic resonance imaging proton-density-fat-fraction, *NAFLD* non-alcoholic fatty liver disease, *Se* sensitivity, *Sp* specificity, *95% CI* 95% confidence interval, *S1, S2, S3* fat accumulation in 5%–33%, >33%–66%, >66% of hepatocytes

CAP in Chronic Viral Hepatitis

Steatosis is a common histological finding in patients with chronic HCV infection. To some extent also in HBV, but liver fat accumulation linked to metabolic comorbidity, alcohol overuse or the viral infection itself seems to play a role in HCV in particular [37]. The prevalence of steatosis is 1.5–3 times higher in HCV patients than in the general population, at 40–86% vs. 25–30% [38, 39]. The presence of steatosis is not only associated with a lower response rate to anti-viral treatment [40], but may also increase fibrosis progression [41, 42] and risk of HCC development [43].

In contrast to HCV, liver steatosis in HBV seems to be comparable to the general population, at approximately 30% [44]. The same meta-analysis found an association between hepatic steatosis in HBV and metabolic comorbidity (obesity, BMI, diabetes), but not viral load.

Seven studies have investigated the use of CAP in chronic viral hepatitis using liver biopsy as diagnostic gold standard (Table 38.4).

Table 38.4 Studies evaluating CAP performance with liver biopsy as reference in people with either HBV or HCV

Authors	Year	Patients	Etiology	Probe	Steatosis prevalence (%)	Optimal cutoff value (dB/m)	AUROC	Se (%)	Sp (%)
Sasso [61]	2012	615	HCV	M	S0 = 55				
					S1 = 31	≥S1 = 222	0.80	76	71
					S2 = 13	≥S2 = 233	0.86	87	74
					S3 = 1	≥S3 = 290	0.88	78	93
Wang [62]	2014	88	HBV	M	S0 = 9				
					S1 = 54	≥S1 = 219	0.71	70	72
					S2 = 28	≥S2 = 230	0.87	83	78
					S3 = 9	≥S3 = 283	0.97	100	97
Ferraioli [63]	2014	115	HBV/ HCV	M	S0 = 29				
	4				S1 = 53	≥S1 = 219	0.76	91	52
					S2 = 14	≥S2 = 296	0.82	60	91
					S3 = 4				
Cardoso [64]	2015	136	HBV	M	S0 = 63				
					S1 = 22		0.82		
					S2 = 12		0.82		
					S3 = 3		0.97		
Mi [65]	2015	340	HBV	M	S0 = 58				
					S1 = 34	≥S1 = 224	0.81	73	76
					S2 = 5	≥S2 = 236	0.90	92	70
					S3 = 2.6	≥S3 = 285	0.97	100	93

(continued)

Table 38.4 (continued)

Authors	Year	Patients	Etiology	Probe	Steatosis prevalence (%)	Optimal cutoff value (dB/m)	AUROC	Se (%)	Sp (%)
Chen [66]	2016	189	HBV	M	S = 49				
					S1 = 32	≥S1 = 222	0.90	89	85
					S2 = 12	≥S2 = 247	0.92	91	93
					S3 = 7	≥S3 = 274	0.94	100	86
Xu [67]	2016	366	HBV	M	S0 = 56				
					S1 = 40	≥S1 = 224	0.78	69	76
					S2 = 2.2	≥S2 = 246	0.93	100	78
					S3 = 1.4	≥S3 = 284	0.99	100	96

Overall, the prevalence of severe steatosis is much lower in HCV and HBV patients compared to NAFLD patients; only in two studies does S3 prevalence exceed 5%. It may be due to these differences that the optimal cutoff values in general are lower than for NAFLD, while the AUROCs are generally higher, particularly moderate (≥S2) and severe (≥S3) steatosis. We speculate that other factors influencing CAP in fatty liver diseases may also diminish the diagnostic accuracy of CAP in NAFLD, compared to chronic viral hepatitis.

CAP in Alcohol-Related Liver Disease

Simple steatosis is seen in almost all patients who drink excess amounts of alcohol for a sustained period. However, the role of hepatic fat accumulation in ALD is not clear. Many consider alcohol-related fatty liver as relatively benign. However, 7% of patients with biopsy-proven simple steatosis may progress to cirrhosis [45].

The role of CAP for diagnosing and monitoring liver fat in ALD has been scarcely investigated. Only one single-etiology study has assessed the diagnostic accuracy of CAP and CAP changes as an effect of abstinence [46]. In this study, 269 patients received a liver biopsy (steatosis scores S0, S1, S2, S3 = 28%, 35%, 24%, 13%) to address diagnostic accuracy, while 293 patients had dual CAP measurements at the beginning and end of hospital admission for alcohol use, to test the effect of detoxification. CAP diagnostic accuracies were comparable to NAFLD: AUROC ≥S1 = 0.77, ≥S2 = 0.78, and S3 = 0.82. CAP was superior to BLEP by ultrasound, while MRI was not performed. CAP above 290 dB/m ruled-in any steatosis with 88% specificity and 92% positive predictive value. In the 293 patients who were admitted 6 days (IQR 4–6) for detoxification, CAP decreased significantly, except in obese patients with a BMI above 30 kg/m^2. Similarly, the study found that CAP was significantly lower in patients who had abstained from alcohol more than 4 weeks from inclusion, in comparison to ongoing drinkers (253 ± 56 dB/m vs. 284 ± 59 dB/m). The latter is in agreement with another study where low CAP correlated negatively with alcohol use [47].

CAP as a Prognostic Marker

Patients with compensated advanced chronic liver disease and concomitant obesity and steatosis may be at higher risk for progressing to decompensation than normal-weight patients [48]. Therefore, CAP may be a predictive marker of the development of decompensation in patients with compensated advanced chronic liver disease. However, results of two retrospective studies are conflicting. One Swiss study investigated 193 patients for median 18 months (viral etiology = 58%; transient elastography = 15.1 kPa; CAP = 255 ± 62 dB/m; CAP above 220 dB/m sensitivity). They showed a potentially harmful effect of higher CAP, independent of BMI. CAP was 275 ± 46 dB/m in the 18 patients who experienced an event, versus 252 ± 63 dB/m (P = 0.07) in the 175 patients who did not progress. Body mass index was similar in the two groups. All events were more frequent in patients with CAP ≥220 dB/m (12.9% vs. 1.6%; P = 0.013). However, these findings could not be validated in a later study, from Austria, involving 430 patients with compensated (n = 292) or decompensated (n = 138) advanced chronic liver disease [49]. CAP neither predicted of first decompensation (hazard ratio = 0.97; 95% CI 0.91–1.03), nor further hepatic decompensation (hazard ratio = 0.99; 0.94–1.03). Using a CAP cutoff of 248 dB/m for hepatic steatosis, the event rate was similar in patients with hepatic steatosis or without. Consequently, longitudinal data and prospective studies in patients with advanced liver disease are still highly needed to evaluate whether CAP can be used as prognostic marker for liver-related outcomes.

In pre-cirrhotic patients, one large Asian study suggests that CAP holds no prognostic value for predicting short-term liver-related events, hepatocellular carcinoma, non-HCC malignancy, or cardiovascular events. The study followed 4282 patients (median age 57 years; median liver stiffness 6.1 kPa; 41% NAFLD; CAP median 250 dB/m) [50]. During 8540 patient-years of follow-up, there were however few liver-related events: 34 patients developed HCC and 33 decompensations.

The foremost question for the coming years is whether CAP can be used as a surrogate marker for steatosis regression in phase II and III antifibrotic trials, and whether steatosis regression or progression represents any clinical value for patients.

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