Contrast-enhanced ultrasound pattern of hepatocellular carcinoma in noncirrhotic liver – results from the prospective multicentre DEGUM CEUS HCC study

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Objectives Contrast-enhanced ultrasound (CEUS) has a high diagnostic accuracy for the noninvasive diagnosis of hepatocellular carcinoma (HCC) in cirrhosis. However, as HCC in noncirrhosis becomes an emerging clinical concern, our study aimed to assess the diagnostic value of CEUS and the CEUS algorithms CEUS LI-RADS and ESCULAP in noncirrhotic liver in a prospective multicentre real-life setting.
Methods High-risk patients for HCC with focal liver lesions upon B-mode ultrasound were recruited prospectively in a multicentre real-life approach to undergo standardized CEUS. Diagnostic accuracies of CEUS and the CEUS algorithms were assessed for the sub-collective of noncirrhotic patients. Histology, MRI and CT served as the reference standard.
Results In total 47/517 patients were noncirrhotic. The reference standard of the lesions showed 30 HCCs (63.8%), four intrahepatic cholangiocellular carcinomas (iCCAs), two other malignancies and 11 benign lesions. HCCs in noncirrhosis showed a tendency towards larger tumor size and better differentiation. A typical CEUS pattern of arterial phase hyperenhancement and late-onset (>60 s), mild washout occurred in 22/30 HCCs (73.3%). Very late onset of washout > 4–6 min was not seen in noncirrhotic liver. The CEUS algorithm ESCULAP showed a perfect sensitivity (100 vs. 68% with CEUS LI-RADS), whereas CEUS LI-RADS had a superior specificity (83 vs. 53%). The positive predictive value was high with both algorithms.
Conclusion The CEUS patterns of HCCs in noncirrhotic liver resembled those in cirrhosis. Our findings suggest that although designed for the application in cirrhosis only, the diagnostic accuracies of the CEUS algorithms in noncirrhotic liver seem comparable to the findings in cirrhosis. Eur J Gastroenterol Hepatol XXX: XXXX–XXXX

Background

Hepatocellular carcinoma (HCC) occurs mostly in the cirrhotic liver, although there are other risk factors such as chronic hepatitis B infection, chronic hepatitis C infection with advanced fibrosis, and, with increasing incidence, nonalcoholic steatohepatitis (NASH) predisposing to the development of HCC. According to current HCC guidelines, noninvasive diagnosis of HCC by means of contrast-enhanced imaging [contrast-enhanced ultrasound (CEUS); MRI; computed tomography (CT)] is possible if the enhancement pattern of arterial phase hyperenhancement (APHE), followed by late-onset (≥ 60 s) washout of mild intensity is present in a nodule ≥10 mm in size [1,2]. However, this noninvasive diagnosis is limited to cirrhotic liver only, as the high a-priori risk for a nodule to be an HCC has to be taken into account. Yet, so far, there is little prospective evidence on the characteristics of HCC in the noncirrhotic liver. Thus, we initiated a prospective multicentre real-life study in order to assess the characteristics of HCC in the cirrhotic and noncirrhotic liver in direct comparison.

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Materials and methods

Study design

The study design of the prospective multicentre Deutsche Gesellschaft für Ultraschall in der Medizin CEUS HCC (DEGUM CEUS HCC) study has been described in detail recently [3–5]. Briefly, high-risk patients for HCC according to national guidelines (chronic hepatitis B infection, chronic hepatitis C infection with advanced fibrosis, NASH and history of prior HCC [6]) with focal liver lesions were recruited prospectively in a real-life approach. Inclusion criteria were the presence of a focal liver lesion visible upon B-mode ultrasound, patients' informed consent to participate in the study and the availability of a reference

standard (histology or, in case this was not feasible, MRI or CT, or both MRI and CT). Exclusion criteria were age <18 years, a history of systemic treatment for HCC, and contraindications for the use of contrast agents. Clinical and imaging data were entered via password-protected online entry forms. All participants provided written informed consent for the anonymized evaluation of data.

The local ethics committee approved the study (ethics vote 16_17B). The study was registered as a clinical trial (NIH NCT03405909) and funded by the German Society for Ultrasound in Medicine (DEGUM). The study design of this sub-analysis is shown in Fig. 1.

Standardized contrast-enhanced ultrasound

CEUS examinations followed a standardized protocol [3,7]. Briefly, the contrast enhancement of the index lesion relative to the surrounding liver parenchyma was recorded at the following time points: arterial phase (arrival of the first microbubbles until the maximum enhancement was reached in the lesion); early portal venous phase, at 60 s; late phase, at 3 min; very late phase, after 4–6 min in the case of no contrast washout at 3 min (otherwise, this last examination point could be omitted). In the case of contrast washout, examiners had to classify both the onset (early, ≤60 s; late, 3 min; very late, 4–6 min) and extent of washout (mild versus marked).

In the case of insufficient contrast enhancement in the late phase, examiners were instructed to apply a second contrast bolus with subsequent assessment of the late phase only to avoid disruption of the microbubbles.

In the case of more than one lesion in a patient, the best accessible lesion was chosen as a target lesion for CEUS and further analysis.

Statistical analysis

Data were exported from the online entry forms using Microsoft Excel. Quantitative variables were expressed as a mean and range. Categorical variables were expressed as frequencies. Due to the differences in sample size between cirrhotic and noncirrhotic patient groups, the analysis was limited to descriptive statistics only.

Results

Patient and tumor characteristics

In total 517 consecutive patients were recruited prospectively; 90.9% had liver cirrhosis according to patient's history, clinical data and findings from imaging or histology. Totally 10 of the 47 noncirrhotic patients presented for HCC surveillance due to a known risk factor (chronic hepatitis B infection, $n=2$; chronic hepatitis C infection with advanced fibrosis, $n=2$; histologically proven NASH, $n=5$; history of prior fibrolamellar HCC, $n=1$). In the other cases, no risk factor was known beforehand, but B-mode ultrasound showed steatosis in 15 patients (31.9%), and uncharacteristic parenchymal changes in six patients (12.8%). In combination with other risk factors (such as diabetes and metabolic syndrome or a history of critical alcohol abuse), these patients were regarded as risk patients by the examiner.

In 16 patients (34%), the liver parenchyma was described as normal upon B-mode ultrasound. In these patients, the following risk factors were identified: histological findings of the liver parenchyma revealed advanced steatosis/steatohepatitis in seven patients and fibrotic changes of the liver parenchyma in eight patients. In one of these patients, a B-mode ultrasound revealed diffuse tumor infiltration, so that a valid assessment of normal parenchyma was not possible.

Most patients in the cirrhotic group had compensated liver cirrhosis (CHILD A, 71.2%; CHILD B, 24.3% and CHILD C, 4.5%). Nine of the cirrhotic patients (2.6%) had a transjugular intrahepatic portosystemic stent shunt.

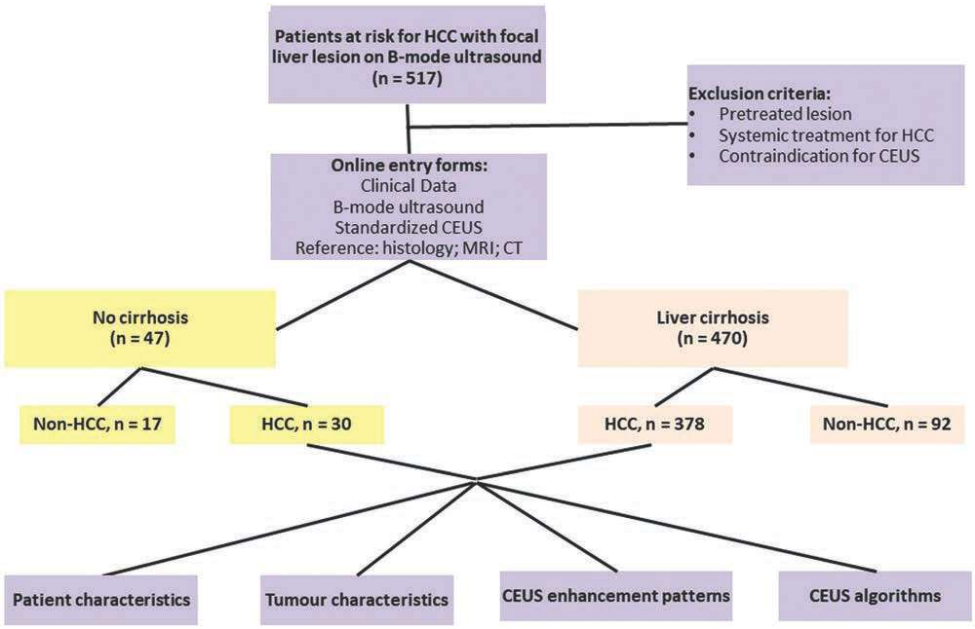

Fig.1. Study design.

Patient characteristics of HCC patients are shown in Table 1. Noncirrhotic patients were significantly older at the time of the first diagnosis of HCC compared with cirrhotic patients and more often showed a better Eastern Cooperative Oncology Group performance state. The other patients' characteristics did not differ between HCC patients with and without cirrhosis.

Histological findings were available in 77.4% of lesions in cirrhotic liver versus 66% in the noncirrhotic liver. For the other lesions in noncirrhotic liver, MRI served as a reference in nine cases (19.1%) and CT in seven cases (14.9%).

However, 30 of the 47 lesions in the noncirrhotic liver were HCCs (63.8%), four were intrahepatic cholangiocellular carcinomas (iCCAs) and two were other malignancies. The other lesion entities were: haemangioma, $n=3$; focal nodular hyperplasia (FNH), $n=2$; adenoma, $n=1$; others, $n=5$. The distribution of tumor entities in cirrhotic and noncirrhotic liver is shown in Fig. 2. Expectedly, the prevalence of HCC was lower in the noncirrhotic liver (63.8 vs. 80.4% in cirrhosis, $P=0.013$), with, however, a relatively higher prevalence of intrahepatic cholangiocellular carcinoma (iCCA; $P=0.282$).

In the group of noncirrhotic patients, the liver parenchyma was described as normal in 20 patients (42.6%). In total 40.4% had steatosis, and in 17%, uncharacteristic parenchymal changes were described. The mean lesion size was 58 mm (range, 10–150 mm), with most lesions (40.4%) between 2 and 5 cm in size and 12.8% less than 2 cm in size. Most lesions in the noncirrhotic liver were solitary (72.3%). In three cases (6.4%), diffuse infiltration of the liver was seen, and in two cases (4.3%) a macro-invasion of the liver vessels. Two patients (4.3%) had portal vein thrombosis, one of them with an enhancing tumor thrombus upon CEUS. A second contrast bolus was applied in eight patients (17%). As to the lesion echogenicity, most lesions were hypoechoic (55.3%). In total 31.9% were isoechoic, and the remaining 12.8% were hyperechoic.

Characteristics of hepatocellular carcinomas in noncirrhotic liver

The tumor characteristics of HCCs in the noncirrhotic liver compared to cirrhosis are shown in Table 2 and Figs. 3–4. HCCs in the noncirrhotic liver were more often located in deeper parts (>5 cm from the liver capsule).

Table 1. Patient characteristics of hepatocellular carcinoma patients in cirrhotic and noncirrhotic liver ($n=408$)

	Cirrhosis ($n=378$)	Noncirrhosis ($n=30$)	*P* value
Age (mean; range)	67.3 (18–88)	73.4 (44–86)	0.002051
Male	324 (85.7)	25 (83.3)	0.7863
Female	54 (14.3)	5 (16.7)	
ECOG performance status			0.02618
ECOG 0	229 (60.6)	23 (76.7)	
ECOG 1–2	140 (37)	5 (16.7)	
ECOG 3–4	9 (2.4)	2 (6.7)	
Diabetes	141 (37.3)	11 (36.7)	1
Extrahepatic malignancy	50 (13.2)	4 (13.3)	1

ECOG, Eastern Cooperative Oncology Group.

Lesion echogenicity did not differ between the cirrhotic and noncirrhotic liver, with the majority of HCCs (>50%) showing a hypoechoic appearance upon B-mode ultrasound.

As can be seen from Fig. 3, HCCs in the noncirrhotic liver were significantly larger than those in cirrhosis ($P=0.015$).

Although the proportion of well-differentiated HCCs was higher in the noncirrhotic liver, this did not reach statistical significance (Fig. 4).

Contrast-enhanced ultrasound patterns of hepatocellular carcinomas in cirrhotic and non-cirrhotic liver

The CEUS patterns of HCCs in the cirrhotic and noncirrhotic liver are shown in Figs. 5 and 6. Briefly, all but three HCCs (90%) in noncirrhotic liver displayed APHE; two showed isoenhancement in the arterial phase and one showed hypoenhancement. APHE without subsequent washout (hyper-iso pattern) was seen in two HCCs in the noncirrhotic liver (6.7%). The typical HCC pattern of APHE followed by late-onset (>60 s), mild washout occurred in 22/30 HCCs (73.3%). There was no case of very late washout with onset >4–6 min. However, three HCCs (10%) displayed early washout before ≤60 s, which was of mild intensity in all cases. Washout of marked intensity was noted in six HCCs (Fig. 6).

Onset and intensity of washout did not differ between HCCs in the cirrhotic and non-cirrhotic liver ($P=0.13$).

A typical CEUS example of an HCC in the noncirrhotic liver is shown in Fig. 7.

Contrast-enhanced ultrasound patterns in non-hepatocellular carcinoma lesions in noncirrhotic liver

However, 10/17 non-HCC lesions in the noncirrhotic liver showed APHE (58.8%). Early washout with onset ≤60 s was seen in two lesions: one histologically proven iCCA, and one FNH (diagnosis by CT). Washout was described as mild in both cases. None of the lesions showed very late onset of washout after > 4–6 min. The typical HCC pattern of APHE followed by late-onset (>60 s), mild washout occurred in six non-HCC lesions. In two of the lesions with APHE, no washout was observed. Histological findings were available in four lesions (FNH, $n=2$; adenoma, $n=1$; uncharacteristic changes with no signs of malignancy, re-biopsy recommended, $n=1$). The other two cases were diagnosed by MRI as iCCA and lesion of uncertain origin, respectively.

Contrast-enhanced ultrasound algorithms in noncirrhotic liver

The application of the standardized CEUS algorithms CEUS LI-RADS and ESCULAP was voluntary so the frequency of their application could give insight into the examiners' readiness to adopt this new tool.

In the collective of noncirrhotic patients, the CEUS algorithms were applied to 31/47 patients (66%); in 22 of these cases, histological findings were available. The frequency of HCCs in the single categories for both algorithms are

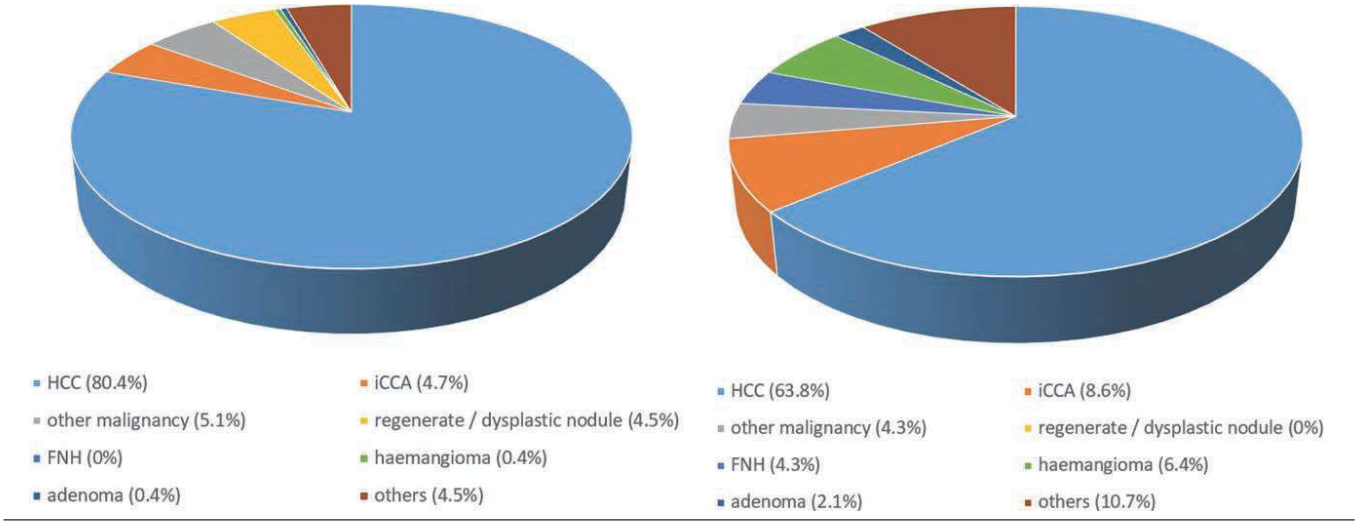

Fig.2. Tumor entities in cirrhotic and noncirrhotic liver.

Table 2. Characteristics of hepatocellular carcinomas in cirrhotic and noncirrhotic liver ($n=410$)

	Cirrhosis ($n=378$)	Noncirrhosis ($n=30$)	P value
Grading (n; %)			
G1	63 (16.7)	8 (26.7)	0.3027
G2	163 (43.1)	10 (33.3)	
G3	48 (12.7)	3 (10)	
n.a.	104 (27.5)	9 (30)	
Size (mm) (mean; range)	55.7 (6–2000)	68 (12–124)	0.01526
≤2 cm	53 (14)	3 (10)	
>2–5 cm	205 (54.2)	9 (30)	
>5–10 cm	92 (24.3)	14 (46.7)	
>10 cm	28 (7.4)	4 (13.3)	
Depth location (cm) (mean; range)	6.6 (2≥15)	5.7 (2≥15)	0.01587
Depth <5 cm	83 (22)	13 (43.3)	
5–9 cm	240 (63.5)	12 (40)	
10–14 cm	52 (13.8)	4 (13.3)	
≥15 cm	3 (0.8)	1 (3.3)	
Echogenicity (n; %)			
Hyperechoic	77 (20.4)	11 (36.7)	0.1081
Isoechoic	87 (23)	4 (13.3)	
Hypoechoic	214 (56.6)	15 (50)	

shown in Tables 3 and 4. Table 5 summarized the diagnostic accuracies of the two CEUS algorithms for the definite diagnosis of HCC (CEUS LI-RADS LR-5, ESCULAP-3) in direct comparison.

Discussion

Our article presents multicentre prospective real-life data on standardized CEUS in HCCs in patients at risk but without liver cirrhosis. Some patients presented for HCC surveillance with a known risk factor (chronic hepatitis B or hepatitis C infection, NASH, history of prior HCC); in other cases, the examiner assumed a hig h-risk constellation due to a patient's history (for example, known steatosis with uncharacteristic parenchymal changes upon B-mode ultrasound, combined with a history of chronic alcohol abuse, so that beginning cirrhosis seemed plausible), and a risk factor was revealed during the course of the examination.

The tumor characteristics of the HCCs in the noncirrhotic liver did not differ from the findings in cirrhosis, except for a tendency towards larger lesion size and better differentiation in the noncirrhotic patients. This is in accordance with recent studies showing that compared to HCCs in cirrhotic liver; those in noncirrhosis tend to be larger in size and more often well-differentiated [8]. This finding might be explained that the risk of HCC is underrecognized in noncirrhotic patients, leading to the fact that in this patient collective, HCCs are diagnosed as incidental findings and therefore present with the larger size.

Compared with the abundant literary evidence on imaging features of HCC in cirrhosis, a few studies have assessed this issue in noncirrhotic high-risk patients. Concerning CT and MRI, studies suggest that the characteristic imaging features of HCC do not differ between cirrhotic and noncirrhotic liver [9]. However, there is literary evidence suggesting a decreased incidence of washout in CT and MRI in HCCs arising on a background of NASH [10–12]. In our patient collective, washout occurred in 10/12 HCCs in noncirrhotic patients with NASH (83.3%) and therefore with a similar incidence as in cirrhotic patients. However, our subgroup of NASH in noncirrhotic patients was too small to allow for statistically valid conclusions.

The evidence concerning CEUS features of HCC in the noncirrhotic liver is sparse. The first prospective multicentre DEGUM study in 2009 including 1349 focal liver lesions, among these 279 HCCs, reported APHE in 75% of the HCCs and contrast washout in the portal venous phase in 50.8% and in the late phase in 74.6% [13]. With the definition of the characteristic CEUS pattern of HCC as 'irregular chaotic intratumoral vascularity and hyperenhancement in the arterial phase, followed by iso- or hypoenhancement in the late phase', the authors found a diagnostic accuracy of 84.9% for CEUS (247/279 HCCs). However, the study was not designed for HCC high-risk patients. In addition, there was only one examination point in the late phase after 2 min, and no assessment of onset and intensity of washout. In another recent prospective single-center study assessing CEUS as a second-line imaging modality after MRI in 103 focal liver lesions ≥1 cm (among these 79 HCCs) in patients at risk for HCC with 47.6% noncirrhotic patients, Kang et al.

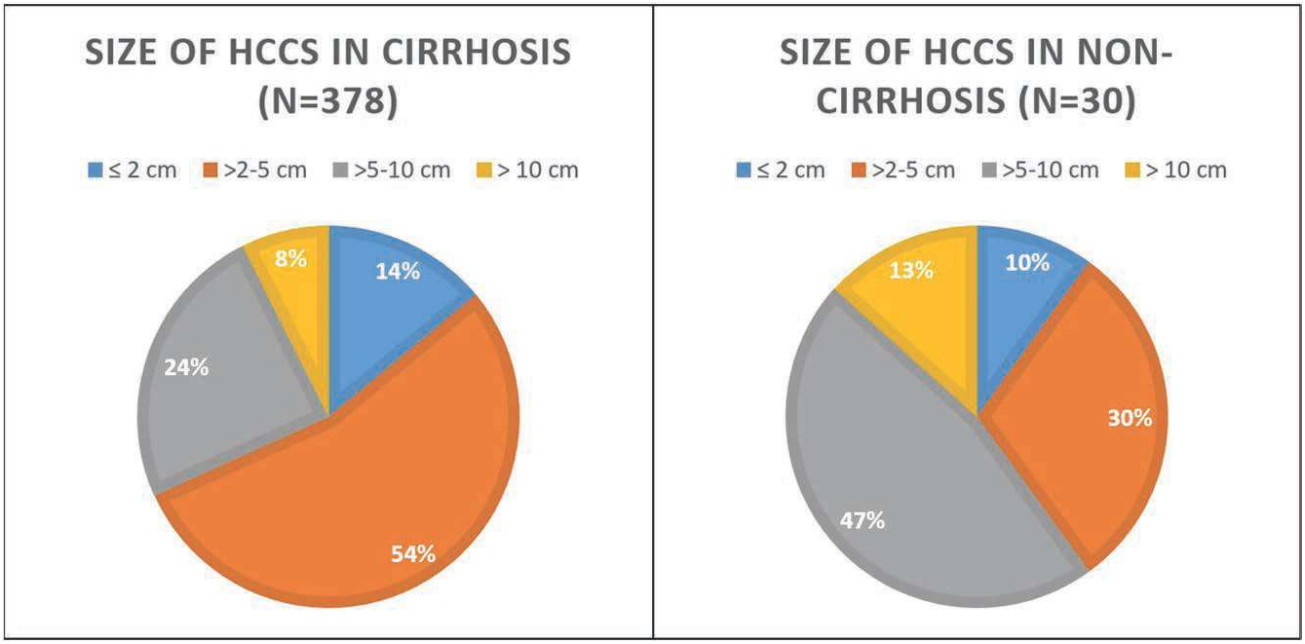

Fig.3. Size of HCCs in cirrhotic and noncirrhotic liver. HCC, hepatocellular carcinoma.

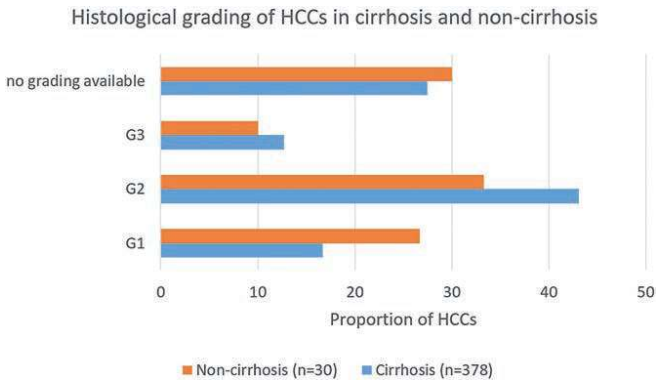

Fig.4. Histological grading of HCCs in cirrhotic and noncirrhotic liver. HCC, hepatocellular carcinoma.

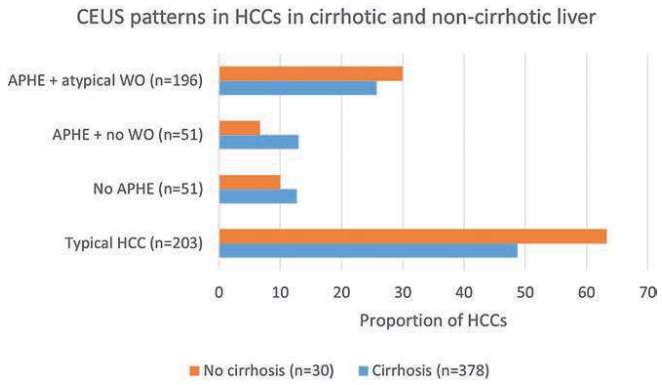

Fig.5. CEUS patterns of HCCs in cirrhotic and noncirrhotic liver. CEUS, contrast-enhanced ultrasound; HCC, hepatocellular carcinoma.

[14] found APHE in 87.3% (63/79 HCCs) and contrast washout in 64.6% of HCCs. However, histological findings were available in 34/79 HCCs only (43%), and the authors did not compare the findings in cirrhotic versus noncirrhotic liver. In addition, the CEUS examination standard differed from the one in our study, because Kang et al. [14] performed continuous scanning for the first 60 s, followed by intermittent scans every 15 s for 5 min after contrast agent administration. Similarly, in a recent retrospective single-center study in China assessing CEUS in 372 histologically proven HCCs ≤30 mm in 346 patients (noncirrhosis, 41.5%), Fan et al. found APHE in 93.3% of HCCs (347/372 HCCs) in total [15]. The authors noted early washout (<60 s) in 25% (93/372) and late washout (>120 s) in 19.1% (71/372) of the HCCs. A later examination point was not assessed; neither did the authors assess the extent of washout. Moreover, they did not differentiate between findings in cirrhotic and noncirrhotic liver.

Accordingly, the CEUS patterns of HCC in the noncirrhotic liver in our study collective strongly resembled those in cirrhosis; the typical HCC pattern of APHE followed by late-onset (>60 s), mild washout was even seen in a slightly higher percentage of HCCs in noncirrhosis. Also, the proportion of HCCs with marked washout was slightly higher in noncirrhosis, whereas very late washout after more than 4–6 min did not occur in noncirrhotic liver.

Originally, the recently developed standardized CEUS algorithm CEUS LI-RADS is designed for application in cirrhotic liver only, whereas ESCULAP can also be applied to other high-risk patients. Our results show that with both algorithms, there were no HCCs misclassified by the lower categories of CEUS LI-RADS LR-1, LR-2 and LR-3 or ESCULAP-1 and ESCULAP-2. However, the CEUS LI-RADS category LR-4 contained 75% HCCs, and the LR-M category 42.9%, whereas no HCC was misclassified as ESCULAP-C. Correspondingly, the ESCULAP algorithm showed a perfect sensitivity of 100% (vs. 68% with CEUS LI-RADS), whereas CEUS LI-RADS had a superior specificity (83 vs. 53%). The positive predictive value was high with both algorithms. These results are in accordance with the recently

published findings from the prospective multicentre DEGUM study: in the sub-collective of 299 cirrhotic patients with histology as the gold standard, the CEUS LI-RADS algorithm yielded a sensitivity of 64% and specificity of 78.9%, vs. 94.2/50.9% with the ESCULAP algorithm [3]. Thus, the diagnostic accuracies of the CEUS algorithms seem comparable in cirrhotic and non-cirrhotic high-risk patients.

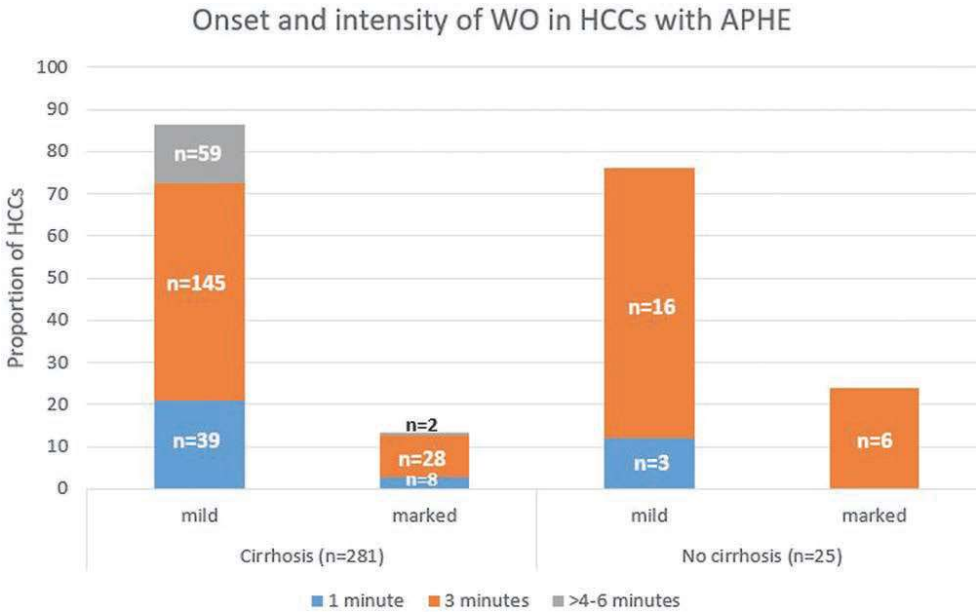

Fig.6. Onset and intensity of washout in HCCs with APHE. APHE, arterial phase hyperenhancement; HCC, hepatocellular carcinoma.

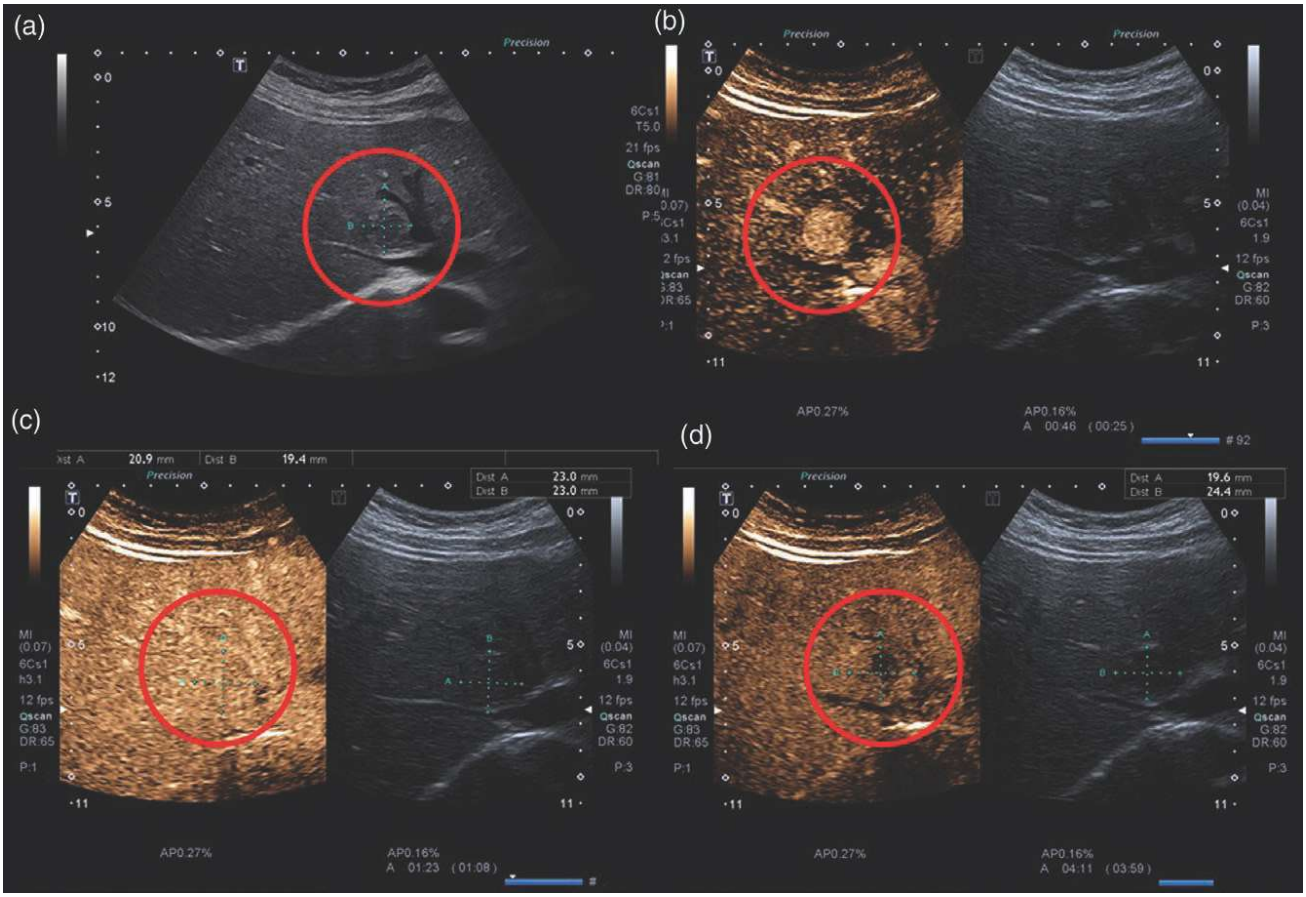

Fig.7. Typical example of an HCC in noncirrhotic liver. HCC in noncirrhotic liver. (a) B-mode ultrasound: isoechoic lesion of 2 cm. (b–d) CEUS. (b) arterial phase hyperenhancement. (c) isoenhancement in the portal venous phase. (d) mild washout in the late phase. . CEUS, contrast-enhanced ultrasound; HCC, hepatocellular carcinoma.

Table 3. Proportion of hepatocellular carcinomas in CEUS LI-RADS categories

LR-1	0/2
LR-2	0/2
LR-3	0/1
LR-4	3/4 = 75%
LR-5	13/15 = 86.7%
LR-M	3/7 = 42.9%
LR-TIV	0

Table 4. Proportion of hepatocellular carcinomas in ESCULAP categories

ESCULAP-1	0/5
ESCULAP-2	0/1
ESCULAP-3	19/24 = 79.2%
ESCU-LAP-C	0/1
ESCU-LAP-V	0

Table 5. Diagnostic accuracies of the contrast-enhanced ultrasound algorithms for the noninvasive diagnosis of hepatocellular carcinoma in noncirrhotic liver in patients with both algorithms available ($n = 31$)

	CEUS LI-RADS LR-5	ESCULAP-3	*P* value
Sensitivity	0.68 (13/19)	1 (19/19)	0.00031
Specificity	83.3 (10/12)	58.3 (7/12)	0.2482
Positive predictive value	0.87 (13/15)	0.79 (19/24)	0.3388
Negative predictive value	0.63 (10/16)	1 (7/7)	0.0334

Nonetheless, the examiner has to bear in mind that especially in unequivocal cases of CEUS patterns in the noncirrhotic liver in high-risk patients, a biopsy is needed for clarification. In particular with the evolvement of new targeted drug therapies for HCC, a biopsy can be expected to gain even further diagnostic and therapeutic strategies in the future.

Limitations of our study are the small sample size of noncirrhotic patients and the lack of availability of histology as the reference standard in all patients. A strength is the prospective multicentre design in a real-life setting and the high proportion of histologically proven lesions. Further research is needed to confirm our findings in noncirrhotic high-risk patients, especially as the rising incidence of metabolic syndrome and fatty liver disease, risk factors for HCC other than cirrhosis will gain further importance.

Conclusion

Our prospective multicentre real-life data suggests that CEUS has a high diagnostic accuracy for the noninvasive diagnosis of HCC in noncirrhotic high-risk patients. CEUS patterns of HCC in noncirrhotic liver strongly resemble those in cirrhosis. However, as very late washout with onset >4–6 min was a feature of HCC in cirrhosis only, this examination point might be dispensable in noncirrhotic liver. Although primarily designed for application in cirrhotic liver, the diagnostic accuracies of the standardized CEUS algorithms CEUS LI-RADS and ESCULAP in noncirrhotic high-risk patients are equal to those in cirrhosis.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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