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Original Article

A diagnostic analysis of ultrasound elastography and contrast-enhanced ultrasound in focal liver lesions

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Abstract: Objective: To compare the diagnostic value of ultrasound elastography (UE) and contrast-enhanced ultrasound (CEUS) in focal liver lesions. Methods: Eighty-nine patients with focal liver lesions were included as subjects. All were examined by both UE and CEUS prior to the operation or puncture. The diagnostic accuracy of UE and CEUS was compared with puncture biopsy or postoperative pathological diagnosis results which served as gold standards. Results: Through the pathological diagnosis, the research subjects consisted of 42 patients with benign lesions and 55 patients with malignant lesions. The Kappa coefficient of the UE diagnosis for the focal liver lesions and the pathological diagnosis was 0.57 ($P<0.05$); the sensitivity, specificity and accuracy of the UE diagnosis for the malignant focal liver lesions were 76.36%, 80.95%, and 78.35%, respectively. The Kappa coefficient of the CEUS diagnosis for the focal liver lesions and pathological diagnosis was 0.81 ($P<0.05$); the sensitivity, specificity and accuracy of the CEUS diagnosis for the malignant focal liver lesions were 92.73%, 88.10%, and 90.72%, respectively. The analysis of the receiver operating characteristic (ROC) curve indicated that the area under the curve, the sensitivity, specificity, and accuracy of the diagnosis of UE combined with CEUS for malignant focal liver lesions were 0.90, 100%, 80.95% and 91.75%, respectively. Conclusion: UE can objectively reflect changes in the stiffness of focal liver lesions. CEUS reveals the changes of blood supply within the lesions in terms of microcirculation. Both methods have good diagnostic value. The combined application of UE and CEUS can improve diagnostic accuracy for focal liver lesions.

Keywords: Ultrasound elastography, contrast-enhanced ultrasound, focal liver lesions, diagnostic accuracy, differentiation of malignant and benign lesions

Introduction

Focal liver lesions (FLLs) are the most common liver pathological diagnosis in the clinic. Various contrast-enhanced diagnostic methods, such as computed tomography and magnetic resonance imaging, require the injection of contrast agents; thus, they contribute to greater costs and time and the potential for allergic reactions [1]. Ultrasound is the first line of liver examination because of its low cost, easy use, and lack of exposure to radiation. However, conventional ultrasound still has significant limitations in the differential diagnosis of some atypical FLLs [2].

Contrast-enhanced ultrasound (CEUS) is a real-time detection technology with a high resolution. It uses an enhanced backscattering echo with a microbubble contrast agent, significantly improving the resolution, sensitivity, and specificity of the ultrasound diagnosis [3]. The development of microbubble contrast agents has changed ultrasound, especially in the detection of FLLs. The microbubble contrast agent has no nephrotoxicity and can be completely filled in the blood vessels, enabling the clear display of small blood vessels. Small malignant tumors show no blood vessels on color Doppler ultrasound, which is especially true and valuable for small malignant tumors [4]. The tissue stiffness is closely related to the biological characteristics of the lesions, and an increase in elasticity or stiffness is found in malignant lesions [5]. Ultrasound elastography (UE) is an imaging method that does not require contrast agents and can be used to assess tissue stiffness and

heteroplasy and can be implemented on most advanced ultrasound devices, which has important reference value for the diagnosis of diseases [6]. The detection of FLLs is often used as part of the screening of patients with cancer or cirrhosis, and the identification of imaging features is important for the further management of lesions. This study aims to investigate the diagnostic value of UE and CEUS in different types of FLLs.

Materials and methods

Participants

A total of 89 patients, including 61 males and 28 females, who were treated for FLL at the PKU Care Lu'an Hospital between April 2016 and October 2018 were recruited for the study. The study protocol was approved by the Ethics Committee of the PKU Care Lu'an Hospital. Informed consents were obtained from all patients. They all received both UE and CEUS. The inclusion criteria were as follows: 1) the patients were aged 18 to 80 years; 2) the patients had no severe cardiopulmonary disease; 3) the patients were not pregnant or lactating; 4) the patients had no treatment prior to ultrasound examination; 5) after the ultrasound examination, the lesions were confirmed by puncture biopsy or a surgical pathological diagnosis.

CEUS examination

The instrument used for the determination of the lesion area was a Philips Color Doppler Ultrasound IU22. The instrument was set at ultrasound contrast mode. Then, SonoVue, an ultrasound contrast agent provided as a lyophilized powder, was dissolved in 5 mL of normal saline and mixed well to prepare a contrast agent with a concentration of 5 mg/mL. A bolus of 2.4 mL of contrast agent was injected into the cubital vein with a large-diameter needle within 3 s. At the same time, the contrast timer was started, continuously recording, and the lesion was kept in the field of view. In order to obtain the time-intensity curve, the performance and degree of enhancement of the lesion were observed for at least 5 min. For multiple FLLs or screening for additional suspected lesions, the entire liver needs to be scanned. Combined with time-intensity curve, two physicians made an analysis and diagnosis by visual observation in the perfusion mode [7].

UE examination

The elastography function was initiated using a Siemens S2000 Color Doppler Ultrasound Scanner. Elastography scores were classified into 5 grades according to the lesions' color flow pattern, referring to the *European Liver Contrast Imaging Guide* (2012 Edition) [8]. One point: no deformation of the lesion as well as surrounding tissues, green in the whole or most of the lesions; 2 points: generally free of deformation, green around the lesion, and blue in a small part of the center; 3 points: slight deformation, almost the same proportion of green and blue in the lesion; 4 points: deformation in most parts of the lesions, no change in small parts; blue in the whole lesion, and green in a very small part of the center; 5 points: general deformation; blue in the whole lesion and its surroundings, and green or no green in a very small part of the center. The criteria of the differentiation of benign and malignant are as follows. Elastography score ≤ 2 shows a benign lesion and elastography score ≥ 3 shows a malignant lesion.

Statistical analysis

SPSS software version 17.0 was used for the statistical analysis. The measurement data were presented as the mean ± standard deviation. The diagnostic value was evaluated using the receiver operating characteristic (ROC) curve, and the sensitivity, specificity, accuracy, positive likelihood ratio, negative likelihood ratio, area under curve (AUC) and its 95% confidence interval in both diagnostic methods were calculated. The statistical significance level was $\alpha=0.05$, and the correction test level was compared among the three groups, $\alpha/3=0.017$ shows the corrected test level by pairwise comparison among the three groups.

Results

General information

In this study, the patients aged from 21.8 to 75.3 years with an average age of 56.3 years. The diameters of the lesions ranged from 1.2 cm to 13.0 cm, and the depths ranged from 1.3 cm-10.0 cm. Forty-nine patients (55 lesions)

Table 1. General information on lesions

	Diagnostic result	Number of lesions	Average diameter of lesions (cm)	Diagnosis basis
Benign lesions	Hepatic hemangioma	28	5.0±1.7	Pathological outcome
	Focal nodular hyperplasia	5	3.1±0.5	Pathological outcome
	Others	9	2.6±1.7	Pathological outcome
Malignant lesions	Hepatocellular carcinoma	48	4.7±2.2	Pathological outcome
	Intrahepatic cholangiocarcinoma	3	3.6±0.3	Pathological outcome
	Liver metastases	4	3.0±1.5	Clinical and pathological outcome

had malignant lesions, including 43 patients (48 lesions) with hepatocellular carcinoma, 3 patients (3 lesions) with intrahepatic cholangiocarcinoma, and 3 patients (4 lesions) with liver metastases. Forty patients (42 lesions) had benign lesions, including 28 patients (28 lesions) with hepatic hemangioma, 2 patients (2 lesions) with inflammatory pseudotumor of the liver, 4 patients (5 lesions) with focal nodular hyperplasia, 3 patients (4 lesions) with adenomatous hyperplasia of the liver and 3 patients (3 lesions) with focal fatty change. See **Table 1**.

Characteristics of CEUS and UE

The typical characteristics of the patients' lesions researched by CEUS are shown in **Table 2**. The UE score of the benign lesions was 1.71±0.81, and the score of the malignant lesions was 3.84±1.29. The difference of UE scores between the benign and malignant lesions was statistically significant ($z=10.35$, $P<0.01$). See **Table 3**. The CEUS and UE manifestations of primary liver cancer and hepatic cysts are shown in **Figures 1** and **2**, respectively.

Diagnostic values of UE and CEUS

According to the evaluation criteria for benign and malignant lesions, the classification results by UE and CEUS are shown in **Table 4**. According to the statistical analysis, the specificity, sensitivity, positive likelihood ratio, and negative likelihood ratio of the UE and CEUS diagnoses are shown in **Table 5**. The accuracies of the UE and CEUS were 78.35% and 90.72%, respectively. The Kappa coefficients of the UE and CEUS diagnoses and the pathological diagnoses for the FLLs were 0.57 and 0.81. The AUC of UE and CEUS were 0.79 (95% CI: 0.70, 0.87) and 0.90 (95% CI: 0.84, 0.96), respectively, and there was a significant difference ($\chi^2=8.07$, $P<0.01$). The sensitivity, specificity, and accuracy of the combined diagnoses of UE and CEUS were 100%, 80.95%, and 91.75%, respectively. The Kappa coefficient of the combined diagnosis and the pathological diagnosis for FLLs was 0.92, and the AUC was 0.90 (95% CI: 0.84, 0.96), the AUC of the combined diagnosis was significantly higher than that of the UE ($\chi^2=16.71$, $P<0.01$). There was no significant difference in the AUC and CEUS of the combined diagnosis ($\chi^2=0.0006$, $P=0.98$) (**Figure 3**).

Discussion

Many lesions, especially tumors and fibrosis, can cause changes in tissue stiffness, and traditional imaging techniques do not provide information about the mechanical properties of tissues [9]. A high degree of cirrhosis indicates advanced liver fibrosis because of the association between cirrhosis and the stages of liver fibrosis. Liver stiffness is closely related to liver cancer risk. Patients with cirrhosis have high liver stiffness, which is an important clinical indicator for high-risk patients with liver cancer [10]. In recent years, various non-invasive ultrasound methods have been developed to study tissue elastography. Elastography performed through ultrasound equipment is the most common method for measuring liver stiffness. UE is mainly used for the evaluation of liver fibrosis in chronic liver disease, and other applications include prediction of cirrhosis-related complications, monitoring of antiviral therapy for chronic viral liver disease, and determination of the characteristics of liver tumors [11, 12]. There are several advantages of transient elastography scanning. 1) It is non-invasive and painless. 2) It provides measurement results within 30 seconds. 3) Its results are highly repeatable. 4) The width of the measurement area is 1/500 of the total liver mass, and the

Table 2. Characteristics of contrast-enhanced ultrasound

	Number of lesions	Characteristics
Inflammatory pseudotumor of the liver	2	Marked hypoenhancement or enhancement in relation to the surrounding liver parenchyma of nonenhancement center in arterial phase. Hyperenhancement or isoenhancement in surrounding liver parenchyma in portal-venous phase, and isoenhancement in surrounding liver parenchyma in delayed phase.
Focal nodular hyperplasia	5	Uniform hyperenhancement or progressive enhancement from the center to the periphery, like radial enhancement, in arterial phase. Central low-enhanced and high-enhanced lesions in portal-venous phase; hypo-, hyper- or iso- enhanced lesions in delayed phase with contrast agent dropping out from the central part.
Focal fatty change	3	Isoenhancement in arterial, portal-venous and delayed phases.
Adenomatous hyperplasia of the liver	4	Rapid and completely uniform high-enhancement in arterial phase. Isoenhancement in portal-venous phase, or in hyperenhanced portal-venous and delayed phases the contrast agents at the central part dropping out; isoenhancement or slight hyperenhancement in surrounding liver parenchyma.
Hepatocellular carcinoma	48	Rapid development, diffuse, uniform, heterogeneous or chaotic over-enhancement in arterial phase, which was significantly faster than the surrounding liver tissues. Contrast agents in portal-venous and delayed phases disappeared fast and the lesions are hypoenhanced.
Intrahepatic cholangiocarcinoma	3	Slightly higher irregular enhancement around the liver tissues in arterial phase. Contrast agents in the portal-venous phase rapidly drop out, it showed low enhancement. Low enhancement in delayed phase.
Hepatic hemangioma	28	The lesion enhanced slowly from the periphery to the center in the end of arterial phase or the beginning of portal-venous phase. And the blood supply was often completely or incompletely filled during the delayed phase, showing a typical enhancement mode of “slow-in and slow-out”.
Liver metastases	4	Irregular enhancement in arterial phase mainly lies in the periphery. In most patients, contrast agents were rapidly removed during the portal-venous and delayed phases, and it showed low enhancement.

Table 3. The classification of lesions via ultrasound elastography (n)

	One point	Two points	Three points	Four points	Five points	Total
Inflammatory pseudotumor of the liver	2	0	0	0	0	2
Focal nodular hyperplasia	1	3	1	0	0	5
Focal fatty change	3	0	0	0	0	3
Hepatic hemangioma	12	9	7	0	0	28
Adenomatous hyperplasia of the liver	3	1	0	0	0	4
Hepatocellular carcinoma	1	10	8	7	22	48
Intrahepatic cholangiocarcinoma	0	1	0	5	2	8
Liver metastases	0	1	0	1	2	4

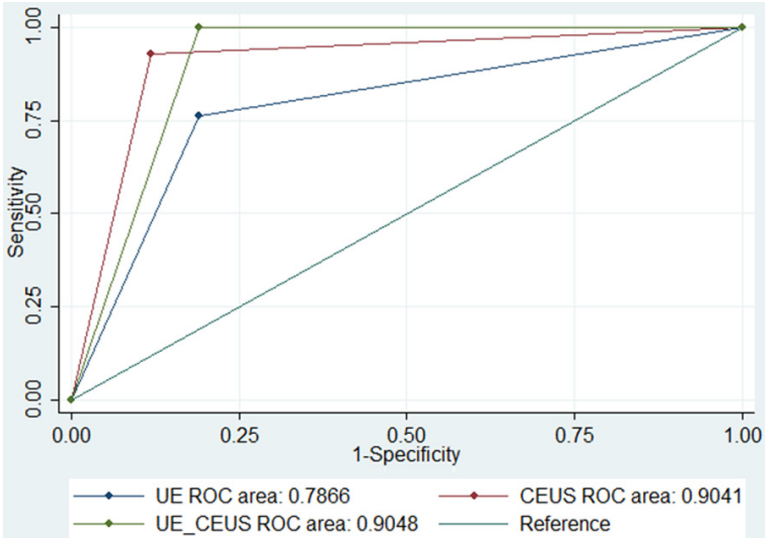

Figure 1. The diagnostic values of ultrasound elastography, contrast-enhanced ultrasound, and their combination. ROC, receiver operating characteristic; UE, ultrasound elastography; CEUS, contrast-enhanced ultrasound.

size of the biopsy specimen is 1/50,000 of the total weight of the liver. 5) It can be safely repeated [10].

Conventional gray-scale ultrasound is a good tool to screen for FLL. However, due to the variability and non-specific manifestations of these lesions, differential diagnosis is difficult with conventional ultrasound alone. In recent years, CEUS has shown excellent efficacy and significant improvement in the detection and characterization of FLL. Previous reports have shown that CEUS identifies FLL with an accuracy of 85%-91%, and presents good consistency in the results [13]. The enhanced mode after the injection of microbubble contrast agents improves the sensitivity of vascular detection and features and is very successful in the diagnosis and differentiation of FLL [14]. Thakur found that malignant lesions showed intratumoral and/or peritumoral vessels in the arterial phase and perfusion defects in the delayed phase; the sensitivity of CEUS for the detection of malignant tumors (100%) was significantly higher than that of conventional ultrasound (81.8%) [15].

In most patients, liver cancer occurs when they have cirrhosis. Early detection and appropriate treatment strategies are keys to an effective treatment. Most of the malignant lesions are composed of dense tissues, which tend to form adhesions with the surrounding tissues, resulting in a decrease in the mobility of the lump, a decrease in elastography, and an increase in stiffness. UE is one of the most widely used tools for liver cancer monitoring because of its ease of operation, low cost and non-invasiveness [16]. The local blood supply of malignant tumors is rich, and it is highly enhanced in the arterial phase in CEUS, but less enhanced in the portal-venous phase and delayed phase. It is generally characterized by "fast in and fast out". In the arterial phase it often exhibits a uniform diffusion enhancement with little heterogeneous or chaotic peripheral enhancement; if peripheral enhancement occurs, it may be intrahepatic cholangiocarcinoma or metastasis of a malignant tumor [17]. CEUS is superior to conventional ultrasound in sensitivity (96% vs. 66%), specificity (76% vs. 54%), and accuracy (72% vs. 50%) for the diagnosis of malignant tumors. The accuracies of off-site differential diagnosis of CEUS and conventional ultrasound are lower than those of on-site diagnosis. However, the consistency between the on-site and off-site diagnostic results of conventional ultrasound is very low (Kappa=0.29-0.39), while the on-site and off-site diagnostic outcomes were highly consistent in CEUS (Kappa=0.63-0.79) [18].

Benign liver lesions are common in the general population and the incidence is up to 52%. Hemangiomas, located in the periphery of the liver or in large tributaries adjacent to the hepatic vein, are the most common benign liver lesions, whose prevalence rate in the general population is 0.4% to 20%, and they are more commonly found in women [19]. The benign lesions have a slow blood flow, which is characterized by slow filling in the arterial phase and continuous enhancement in the portal-venous phase and the delayed phase, and generally shows "slow in and slow out". Enhancement patterns in the arterial phase are typical for different types of lesions. These characteristic descriptions are particularly essential for the differentiation of FLLs. For example, because

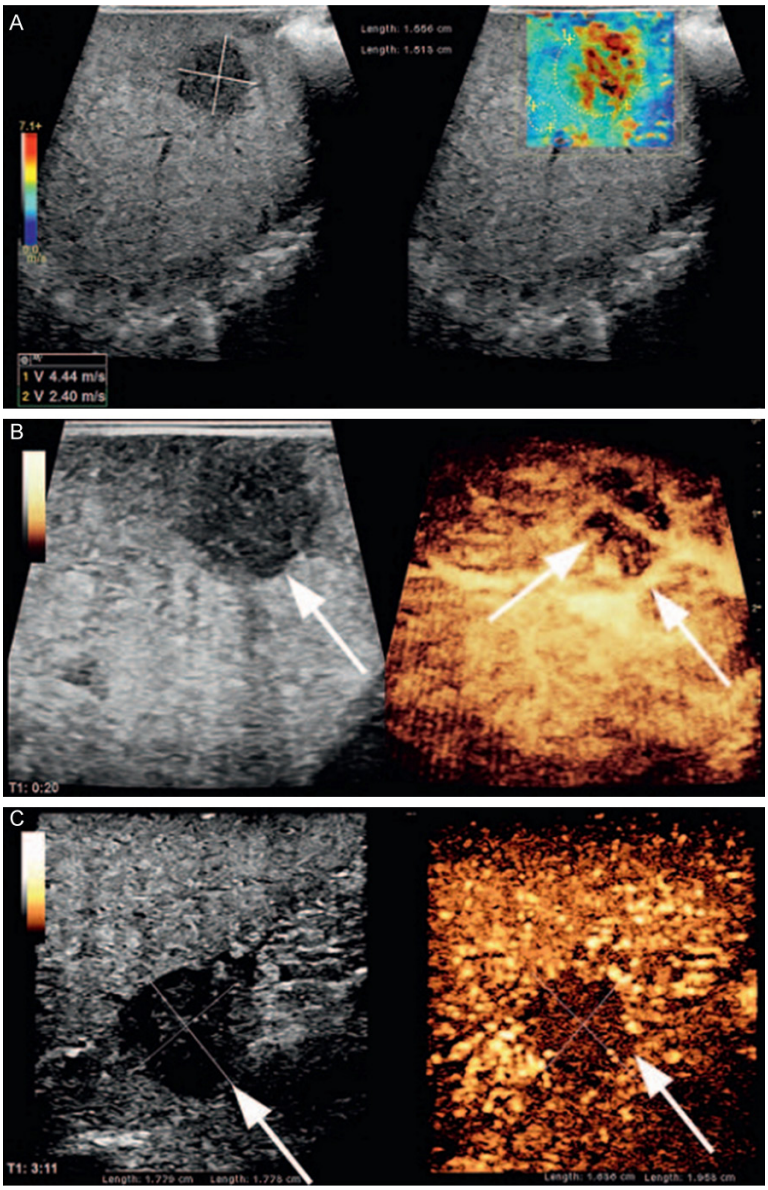

Figure 2. The CEUS and UE manifestations of primary liver cancer. The SWV value of the lesion was 2.4 m/s. A. General deformation, blue around the lesion, and green in a small part of the center. B and C. White arrows showed an excessive heterogeneity at the edge of the lesion of arterial phase via CEUS, suggesting a malignant tumor. SWV, shear wave velocity; UE, ultrasound elastography; CEUS, contrast-enhanced ultrasound.

the blood supply of focal nodular hyperplasia is derived from the central artery, it often exhibits a radial enhancement in the arterial phase [20]. Hahn et al. reported that there were significant differences in the strain ratio and elastography score between benign and malignant lesions in 73 patients (including 40 benign tumors and 33 malignant tumors). The ROC curve was drawn according to the outcome of the pathological examination. The AUC of the strain ratio was 0.700, and ratio of the elastography score was 0.623; the diagnostic performance of the strain ratio was better than that of the elastography score [21].

There are different working principles of CEUS and UE. The former determines the nature of the lesion by recording the dynamic process of blood flow perfusion in the lesion from the arterial phase, portal-venous phase to the delayed phase, while the latter determines the nature of the lesion by the difference in stiffness between the lesion and its surrounding tissue [22]. In this study, in terms of sensitivity, specificity and accuracy for FLL detection, CEUS was better than UE. The effectiveness of CEUS is limited by the same factors as B-mode ultrasound, including obese patients, uncooperative patients, and the difficulty of accessing the lesion due to its depth or location. These limitations can be overcome by patient counseling, improvements in CEUS technology, and an increase in clinician experience [4]. Similarly, transient elastography also has shortcomings. The reproducibility of measurements and even the measurement itself may be affected by ascites, thick subcutaneous fat layers, narrow intercostal space, and severe hepatic atrophy [23]. In order to improve the diagnostic efficiency, the examination and diagnosis of CEUS combined with UE has an accuracy rate of 91.75%, and a higher sensitivity for malignant lesions than separate CEUS and UE examination [24]. The difference between the combined method and CEUS alone is not statistically significant, which may be due to an insufficient sample size. This is

Table 4. Detected number of lesions comparison

Pathological outcome	Number	Contrast-enhanced ultrasound		Ultrasound elastography	
		Benign lesions	Malignant lesions	Benign lesions	Malignant lesions
Benign lesions	42	37	5	34	8
Malignant lesions	55	4	51	13	42

Table 5. The diagnostic efficiency of ultrasound elastography and contrast-enhanced ultrasound (%)

	Specificity	Sensitivity	Negative likelihood ratio	Positive likelihood ratio
Ultrasound elastography	80.95	76.36	0.29	4.01
Contrast-enhanced ultrasound	88.10	92.73	0.08	7.79

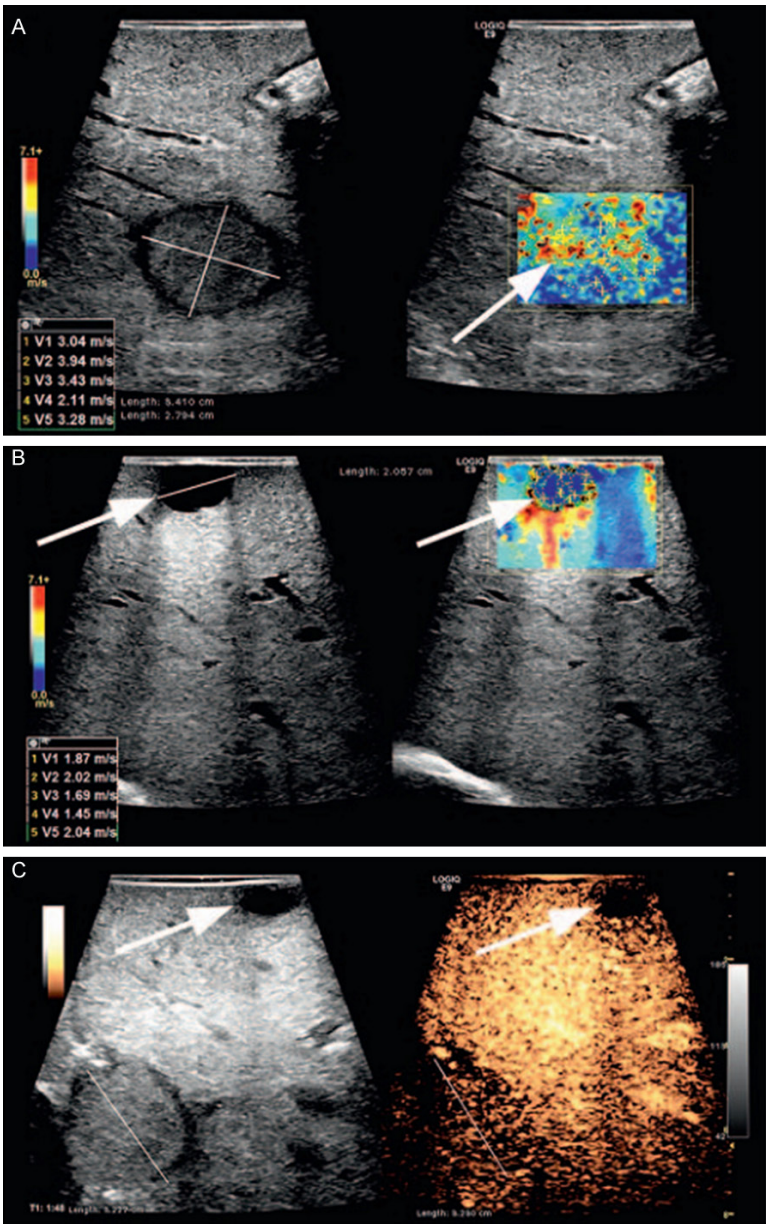

Figure 3. The CEUS and UE manifestations of a hepatic cyst. A and B. No deformation of the lesion as well as surrounding tissues, green in the whole or most of the lesions, and blue in a small part of the center. C. There was no enhancement during the angiography, and there were three echo-free nodules with clear boundaries, suggesting benign lesions. UE, ultrasound elastography; CEUS, contrast-enhanced ultrasound.

consistent with the result in another study that researched the combined diagnosis of CEUS and UE for FLLs, thyroid, breast cancer, and testicular tumors, and the combination of CEUS and UE has a good promotion value for the differentiation of benign and malignant tumors [25, 26].

In summary, UE can objectively reflect the change of stiffness of FLLs. CEUS reveals the changes of blood supply within a lesion in terms of microcirculation. Both methods have a good diagnostic value. The combined application of UE and CEUS can improve the diagnostic accuracy for focal liver lesions.

Disclosure of conflict of interest

None.

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