Research paper

Cite as: Dong Y, Wang W-P, Ignee A, Zuo D, Qiu Y-J, Zhang Q, Lu X-Y, Chen S, Dietrich CF: The diagnostic value of Doppler Resistive Index in the differential diagnosis of focal liver lesions. J Ultrason 2023; 23: e45–e52. doi: 10.15557/JoU.2023.0010.

Submitted: 09.10.2022
Accepted: 03.01.2023
Published: 28.04.2023

The diagnostic value of Doppler Resistive Index in the differential diagnosis of focal liver lesions

Yi Dong[1], Wen-Ping Wang[2], Andre Ignee[3], Dan Zuo[2], Yi-Jie Qiu[2], Qi Zhang[2], Xiu-Yun Lu[2], Sheng Chen[2], Christoph Frank Dietrich[4]

[1] *Department of Ultrasound, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China*

[2] *Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai, China*

[3] *Department of Gastroenterology and Rheumatology, Julius-Spital Würzburg, Germany*

[4] *Department General Internal Medicine, Hirslanden Clinics Beau-Site, Salem and Permancence, Bern, Switzerland*

Corresponding author: Christoph Frank Dietrich; e-mail: c.f.dietrich@googlemail.com

DOI: 10.15557/JoU.2023.0010

Keywords
B-mode ultrasound (BMUS); focal liver lesion (FLL); resistance index (RI); hepatocellular carcinoma (HCC); focal nodular hyperplasia (FNH)

Abstract

Aim: To investigate the diagnostic value of resistance index (RI) in differentiating focal liver lesions. **Patients and methods:** In this retrospective study, a total of 576 patients with histologically confirmed focal liver lesions were included. Each patient underwent B-mode ultrasound examination and color Doppler ultrasound examination. The RI values of different focal liver lesions were recorded and compared. **Results:** The mean RI value of benign lesions was significantly lower than that of malignant lesions (0.54 ± 0.10 *vs.* 0.71 ± 0.12) (p <0.05). In malignant lesions, the RI value of intrahepatic cholangiocarcinoma was significantly lower than that of hepatocellular carcinoma lesions. Furthermore, in hepatocellular carcinoma lesions, the RI of large lesions (group 4: >10 cm) was significantly lower than that of small lesions (group 1: ≤2 cm, group 2: 2–5 cm) (p <0.05). Taken RI of 0.615 as a cutoff value to differentiate malignant and benign lesions, the sensitivity, specificity, positive predictive value and negative predictive value were 82.80%, 81.00%, 81.34% and 82.48%, respectively. **Conclusion:** Color Doppler ultrasound examination is a valuable imaging method in detecting blood flow signal within liver lesions. The RI parameter should be helpful in differentiating malignant and benign liver tumors.

Introduction

Liver cancer is one of the most frequent causes of cancer related death worldwide, with hepatocellular carcinoma (HCC) accounting for about 90% of malignant liver tumors[1–3]. Treatment varies in different pathological types of focal liver lesions (FLLs). For malignant lesions, surgical resection, chemotherapy, radiotherapy or targeted therapy are recommended methods[4,5]. However, for most benign lesions, conservative treatment is first considered[6]. Thus, correct preoperative diagnosis plays an important role in clinical decision making for FLLs. With the advantages of noninvasiveness, real-time nature and no radiation exposure, ultrasound (US) is now used as the first-line imaging modality for detecting and diagnosing hepatic lesions[7]. The resistance index (RI) of spectral Doppler imaging (SDI) in ultrasound examination could reflect the resistance of distal vessels, which may be helpful in the differential diagnosis of FLLs[8–11]. The purpose of this study was to assess the value of RI in the differential diagnosis of different FLLs.

Patients and methods

This retrospective study was approved by the ethical board of our institution. Informed consent was waived.

Patients

From January, 2018 to June, 2021, a total of 576 patients met the criteria and were retrospectively included. Inclusion criteria were as follows: (1) Patients with FLLs detectable on B-mode ultrasound (BMUS), (2) arterial blood flow signals detectable within lesion or

peritumoral area, (3) obtainable surgery/biopsy and histopathological diagnosis of FLLs. No exclusion criteria were defined.

Ultrasound examination

Ultrasound equipment included Siemens ACUSON Sequoia (Siemens Medical Solutions, Munich, Germany), Siemens ACUSON Oxana 2 (Siemens Medical Solutions, Munich, Germany), Aloka Arietta V70 (Hitachi Aloka Medical Systems, Tokyo, Japan) and Mindray Resona 7s (Shenzhen Mindray Bio-Medical Electronic Co., Shenzhen, China). All ultrasound examinations were performed by ultrasound radiologists with at least 10-year liver scan experience.

All patients fasted for at least 8 hours before ultrasound examinations. US examinations were performed in the supine position. A full liver BMUS was performed to locate and characterize the lesion. Using color Doppler mode, the distribution of vascularity within a lesion was detected. If blood flow signals were detected within a lesion, spectral Doppler would then be performed to measure the RI value (difference of peak-systolic and end-diastolic velocity divided by peak-systolic velocity of blood flow). The most obvious artery in CDFI was selected for RI measurement. The RI measurements were performed with the same protocol for all lesions. For multiple lesions, only the largest ones were selected to detect color flow signals and measure RI values.

Statistical analysis

The analysis software was SPSS version 20.0. Kolmogorov-Smirnov test was performed on continuous data to determine normal distributions. Levene test was performed to detect the homogeneity of variance. One-way ANOVA test and independent sample *T* test were used to detect the mean difference in RI for different pathological liver lesions.

Results

Clinical features

From January, 2018 to June, 2021, a total of 576 (173 females, 403 males, age range 20 - 85 years, mean age: 54.82 ± 13.83 years) patients were followed up. Single lesions were detected in 476 patients (82.6%) and multiple lesions were detected in 100 patients ($n \geq 2$). All the lesions were confirmed by surgery or biopsy and pathological diagnosis.

Pathological diagnosis

According to pathological diagnosis, there were 458 malignant lesions and 118 benign lesions. Among all the malignant lesions, there were 347 pathologically confirmed HCC lesions, 51 metastatic lesions, 44 intrahepatic cholangiocarcinoma (ICC) lesions, 5 mixed hepatocellular cholangiocarcinoma lesions, 4 sarcomatoid carcinoma lesions, 3 epithelioid cell malignant lesions, 1 B-cell lymphoma of mucosa-associated lymphoid tissue lesion, 1 sarcoma lesion, 1 multiple plasmacytoma lesion and 1 neuroendocrine carcinoma lesion. Among all the benign lesions, there were 52 focal nodular hyperplasia (FNH) lesions, 16 angiomyolipomas lesion, 23 hemangioma lesions, 9 hepatocellular adenoma lesions, 5 inflammatory lesions, 3 lymphoid tissue lesion, 2 necrotic lesions, 2 pseudolymphoma lesions, 1 accessory spleen lesion, 1 lipoma lesion, 1 paraganglioma lesion, 1 papilloma lesion, 1 hyperplasia tissue lesion and 1 neuroendocrine tumor lesion.

B-mode ultrasound features and color Doppler image features

Most of malignant FLLs were hypoechoic (69.87 %, $n = 320$) lesions; 6.77 % ($n = 31$) lesions were isoechoic and 23.36% ($n = 107$) lesions were hyperechoic. Among the 118 benign lesions, hypoechogenicity was detected in 62.71 % ($n = 74$), isoechogenicity was detected in 11.41% ($n = 17$) and hyperechogenicity was detected in 22.88 % of lesions ($n = 27$).

Color blood flow signals were detected in 576 lesions, but only 432 (75%) lesions allowed RI measurement. In malignant lesions, intralesional signals were obtained in 80.57%, perilesional signals in 12.66% and both intralesional and perilesional signals in 6.77% of lesions. In benign lesions, intralesional signals were obtained in 78.81%, perilesional signals in 11.86% and both intralesional and perilesional arterial signals in 9.32% of lesions.

Comparison of resistance index between benign and malignant lesions

While comparing the RI values of benign and malignant lesions, the mean RI of benign lesions was significantly lower than that of malignant lesions (0.54 ± 0.09 *vs*. 0.72 ± 0.12) ($p < 0.05$) (Tab. 1, Fig. 1, Fig. 2, Fig. 3). In malignant FLLs, the RI value of intrahepatic cholangiocarcinoma was significantly lower than that of HCC (Fig. 1, Fig. 4, Fig. 5, Fig. 6, Fig. 7, Fig. 8). However, while comparing RI

Tab. 1. RIs for different focal liver lesions

Pathological diagnosis	Proportion *n*/all (%)	RI (range)	RI (mean ± SD)
Malignant lesions	332/458 (72.5%)	0.43–1.00	0.71 ± 0.12
Hepatocellular carcinoma	254/347 (73.2%)	0.43–1.00	0.72 ± 0.12
Liver metastasis	30/51 (58.82%)	0.52–1.00	0.70 ± 0.10
Intrahepatic cholangiocarcinoma	35/44 (79.5%)	0.51–1.00	0.68 ± 0.10
Mixed hepatocellular Cholangiocarcinoma	3/5 (60%)	0.68–0.82	0.73 ± 0.08
Sarcomatoid carcinoma	3/4 (72.5%)	0.69–0.72	0.71 ± 0.02
Epithelioid cell tumor	3/3 (100%)	0.45–0.59	0.51 ± 0.07
Benign lesions	100/118 (84.7%)	0.35 – 0.84	0.54 ± 0.10
Focal nodular hyperplasia	48/52 (92.3%)	0.40–0.69	0.54 ± 0.08
Angiomyolipoma	15/16 (93.8%)	0.35–0.72	0.51 ± 0.09
Hemangioma	14/23 (60.9%)	0.35–0.66	0.51 ± 0.09
Hepatocellular adenoma	8/9 (88.9%)	0.42–0.66	0.51 ± 0.08
Inflammatory pseudotumors	4/5 (80%)	0.58–0.84	0.68 ± 0.12

values of other malignant lesions and benign lesions, no significant difference was observed (Tab. 1. Fig. 1, Fig. 3, Fig. 9).

Taking RI = 0.615 as a cutoff value to differentiate malignant and benign lesions (RI >0.615: malignant; RI <0.615: benign), the sensitivity, specificity, positive predictive value and negative predictive value were 82.80%, 81.00%, 81.34% and 82.48%, respectively.

Comparison of resistance index of hepatocellular carcinoma lesions

All the HCC lesions were classified into 4 groups (group 1: ≤2 cm, group 2: 2–5 cm, group 3: 5–10 cm, group 4: >10 cm). We found that the RI values of large lesions (group 4: >10 cm) were significantly lower than those of small lesions (group 1: ≤2 cm, group 2: 2–5 cm). However, no significant difference was observed in other groups (Tab. 2, Fig. 5, Fig. 6, Fig. 7, Fig. 8).

Resistance index of hepatocellular carcinoma in different liver background

Based on the differences in liver background, all the HCC lesions were classified into 3 groups (group 1: normal background, group 2: fatty liver background, group 3: cirrhosis background). We found that the RIs of HCC in normal liver background were significantly lower than those of cirrhosis liver background. However, no significant difference was observed in other groups (Tab. 3).

Comparison of resistance index of focal nodular hyperplasia lesions

All the FNH lesions were classified into 4 groups (group 1: ≤2 cm, group 2: 2–5 cm, group 3: 5–10 cm, group 4: >10 cm). A comparison of RI values in different groups showed no significant differences (Tab. 4).

Discussion

The type and distribution of blood flow signals were correlated with the histology of FLLs. Previously, the presence of both intra- and peritumoral arterial flow was strongly suggestive of malignancy, while the presence of intralesional venous flow was remarkably suggestive of benignancy. Intratumoral flow could be detected in 73.9% of malignant lesions and in 25% of benign lesions[12]. Although arterial flow signal was more frequently detected in malignant lesions, there were some typical color flow signs specific for benign FLLs[11,13]. Central feeding artery is a typical sign of FNH lesion and the spoke-wheel sign has a high diagnostic value[14,15]. However, in the present study we focused on RI values rather than CDS-architecture.

RI represents the resistance of distal vessels[16,17]. Combining the ultrasound features and the RI parameter would be more helpful in the differential diagnosis of benign and malignant liver tumors[8,12]. In 2014, Nahar *et al*. measured the RI of liver tumors in 50 consecutive patients and found that the RI of malignant lesions was significantly higher than that of benign lesions, but no significant difference between the RI of HCCs and metastatic liver tumors was

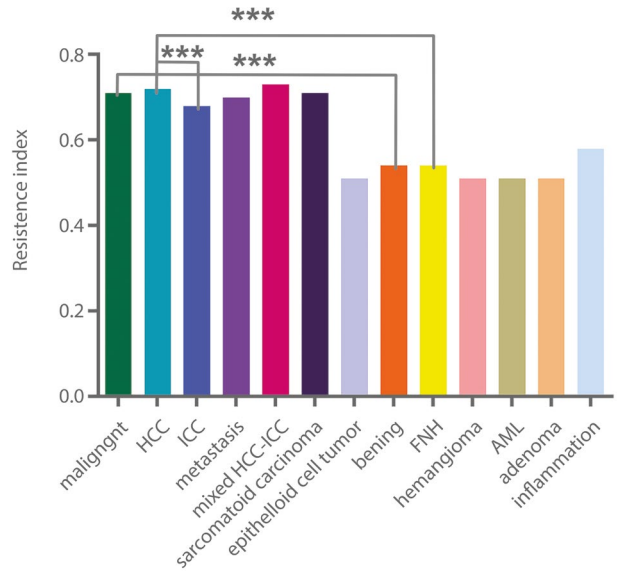

Fig. 1. *The histogram of resistance index (RI) value of different focal liver lesions*

Tab. 2. Comparison of resistance index in hepatocellular carcinoma (HCC)

Group	Number	Size of HCC (cm)	RI (mean ± SD)
1*	63	< 2	0.73 ± 0.12
2#	113	2–5	0.75 ± 0.12
3	63	5–10	0.70 ± 0.11
4*,#	15	>10	0.61 ± 0.13

* Group 1, 4: Significant difference (p <0.05)
# Group 2, 4: Significant difference (p <0.05)

observed[12]. In our study, we observed similar results. However, the RI values of HCC and hemangioma in our study were higher than in previous studies. Besides, Nahar *et al*. and Wang *et al*. evaluated the diagnostic efficiency of RI in differentiating malignant and benign liver lesions[8,12]. Taking RI = 0.6 as cutoff value, when RI was <0.6 for benign liver tumors and ≥0.6 for malignant tumors, they calculated sensitivity of 89.14%, specificity of 66.7%, accuracy of 85.71%, positive predictive value of 97.62 % and negative predictive value of 28.57 % in differentiating benign and malignant tumors[12]. In our study, we took RI = 0.615 as a cutoff value to differentiate malignant and benign liver lesions, and the specificity was significantly higher than in the previous study. Due to their heterogeneous contents, inflammatory pseudotumors of the liver have various blood flow patterns, sometimes with less peritumor flow signals and higher RI. In our results, among all benign lesions, the inflammatory lesions showed much higher RI.

In our study, we evaluated the RI values of HCC lesions with different size. We found that RIs in large FLLs were lower than those of small lesions. The reasons may be correlated with pathological features, such as histological pattern, pseudocapsular growth type, and absence of necrotic areas. As the lesion grows, the formation of arteriovenous shunt and the destruction of pseudocapsules may reduce the resistance of vessels within HCC lesions.

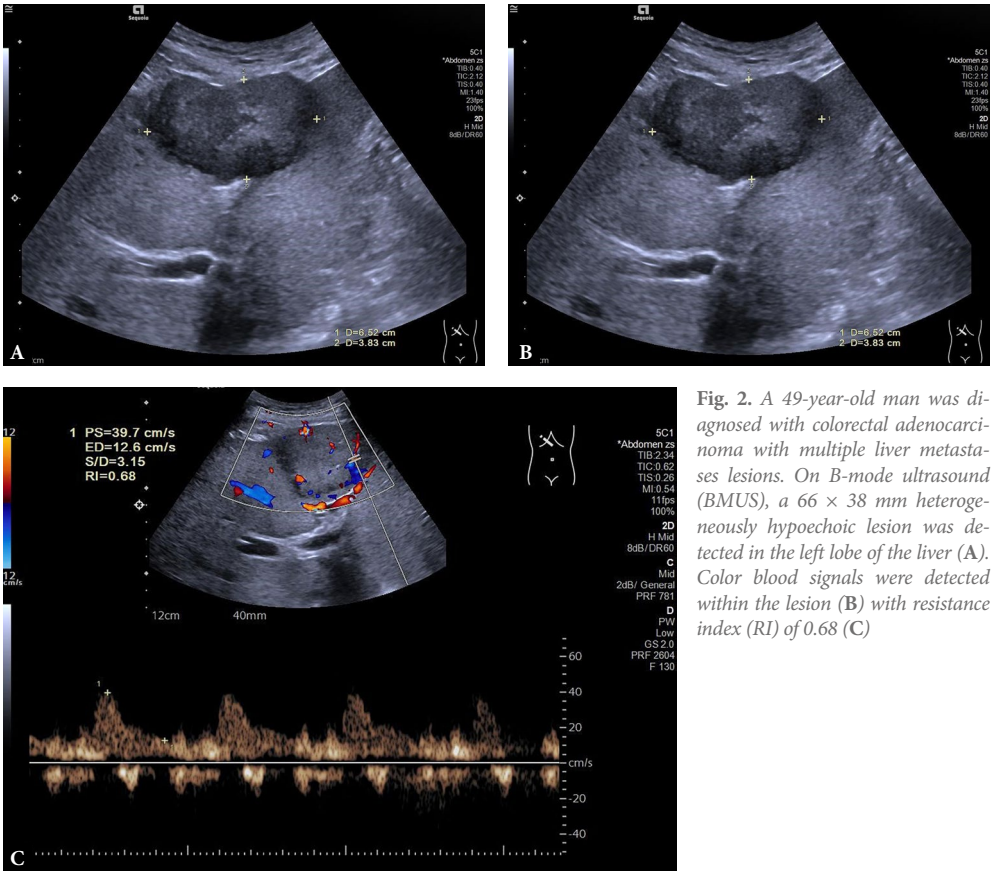

Fig. 2. *A 49-year-old man was diagnosed with colorectal adenocarcinoma with multiple liver metastases lesions. On B-mode ultrasound (BMUS), a 66 × 38 mm heterogeneously hypoechoic lesion was detected in the left lobe of the liver (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.68 (***C***)*

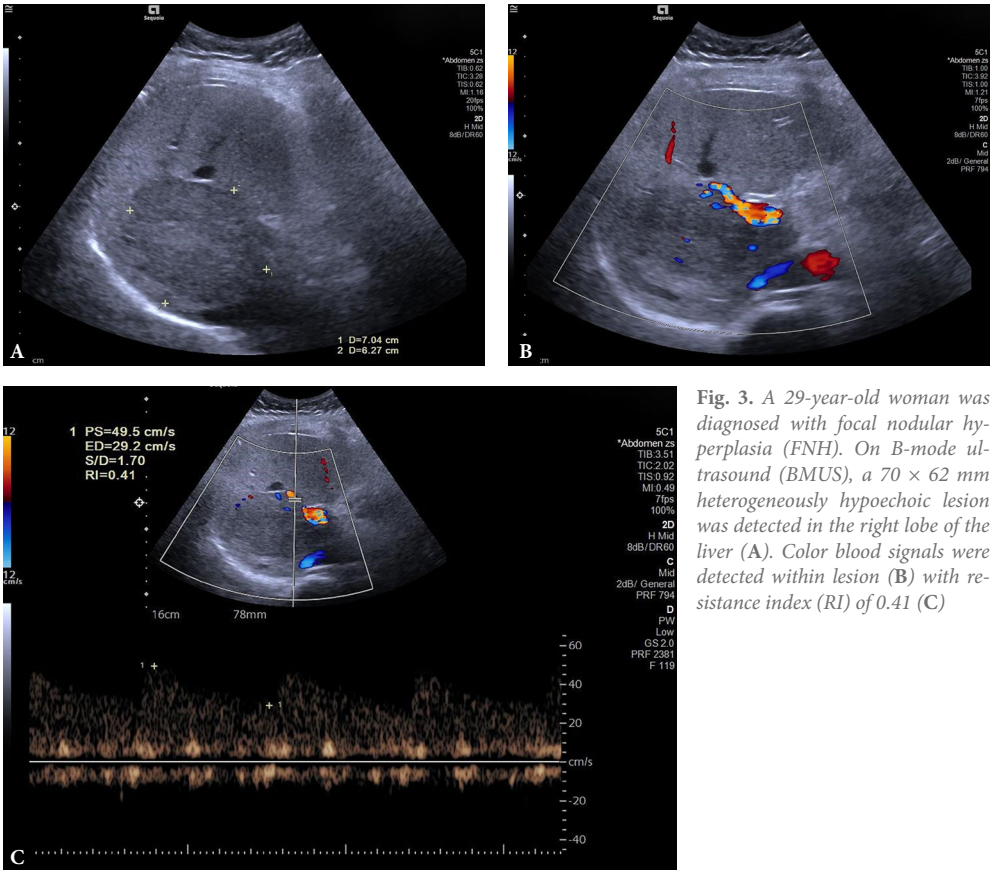

Fig. 3. *A 29-year-old woman was diagnosed with focal nodular hyperplasia (FNH). On B-mode ultrasound (BMUS), a 70 × 62 mm heterogeneously hypoechoic lesion was detected in the right lobe of the liver (***A***). Color blood signals were detected within lesion (***B***) with resistance index (RI) of 0.41 (***C***)*

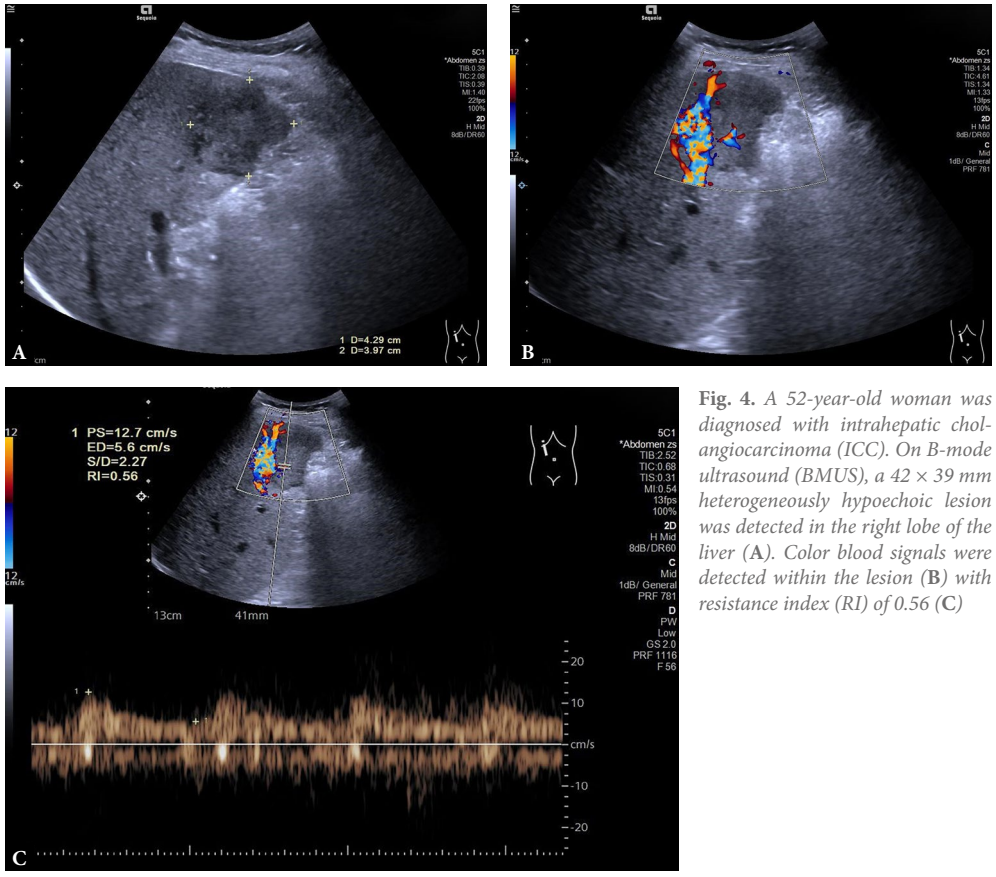

Fig. 4. *A 52-year-old woman was diagnosed with intrahepatic cholangiocarcinoma (ICC). On B-mode ultrasound (BMUS), a 42 × 39 mm heterogeneously hypoechoic lesion was detected in the right lobe of the liver (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.56 (***C***)*

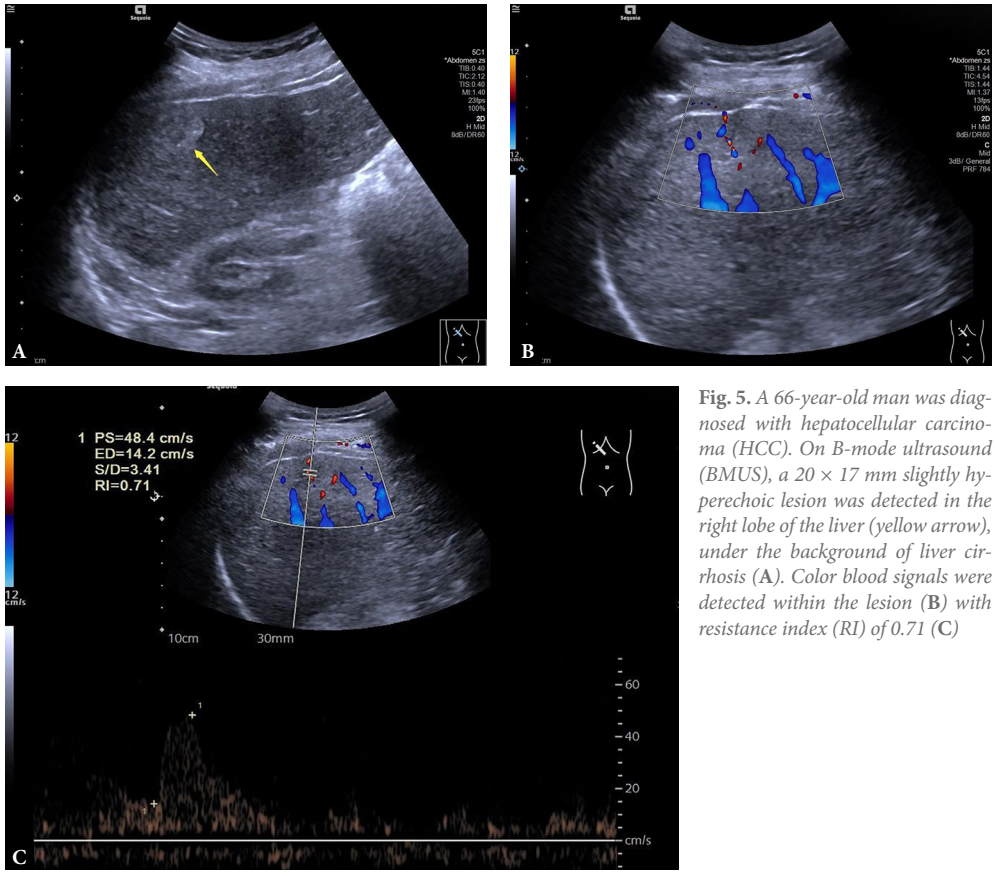

Fig. 5. *A 66-year-old man was diagnosed with hepatocellular carcinoma (HCC). On B-mode ultrasound (BMUS), a 20 × 17 mm slightly hyperechoic lesion was detected in the right lobe of the liver (yellow arrow), under the background of liver cirrhosis (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.71 (***C***)*

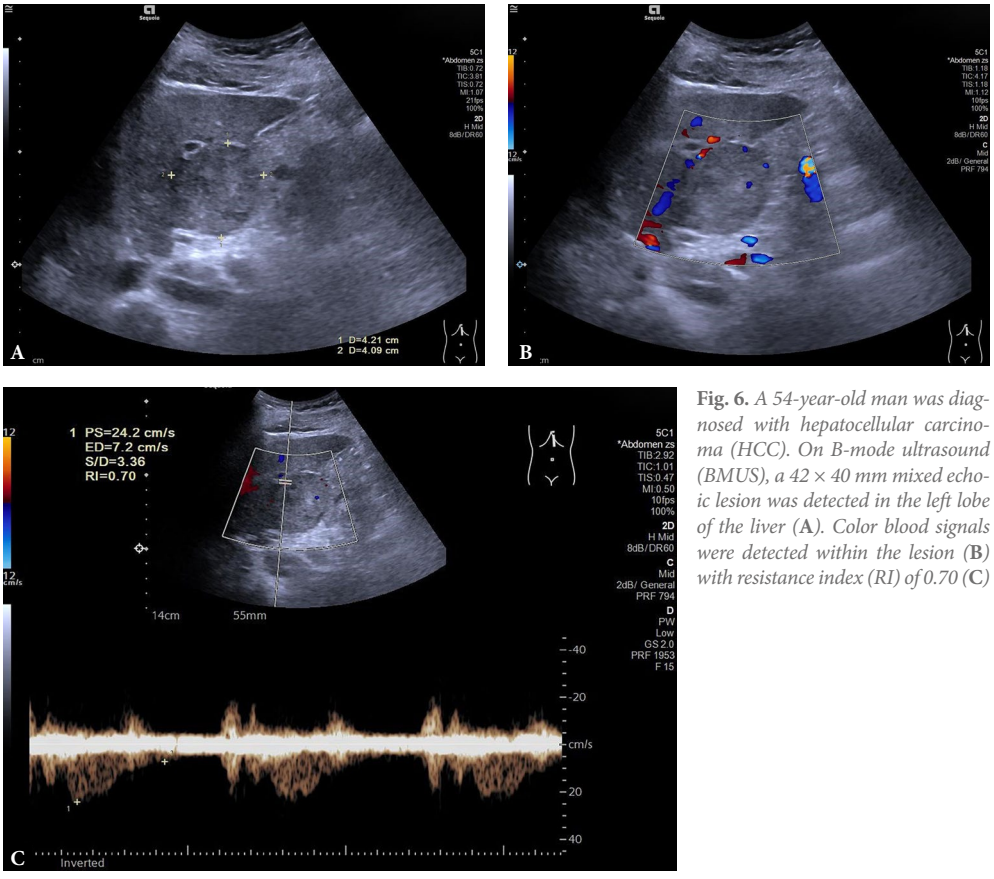

Fig. 6. *A 54-year-old man was diagnosed with hepatocellular carcinoma (HCC). On B-mode ultrasound (BMUS), a 42 × 40 mm mixed echoic lesion was detected in the left lobe of the liver (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.70 (***C***)*

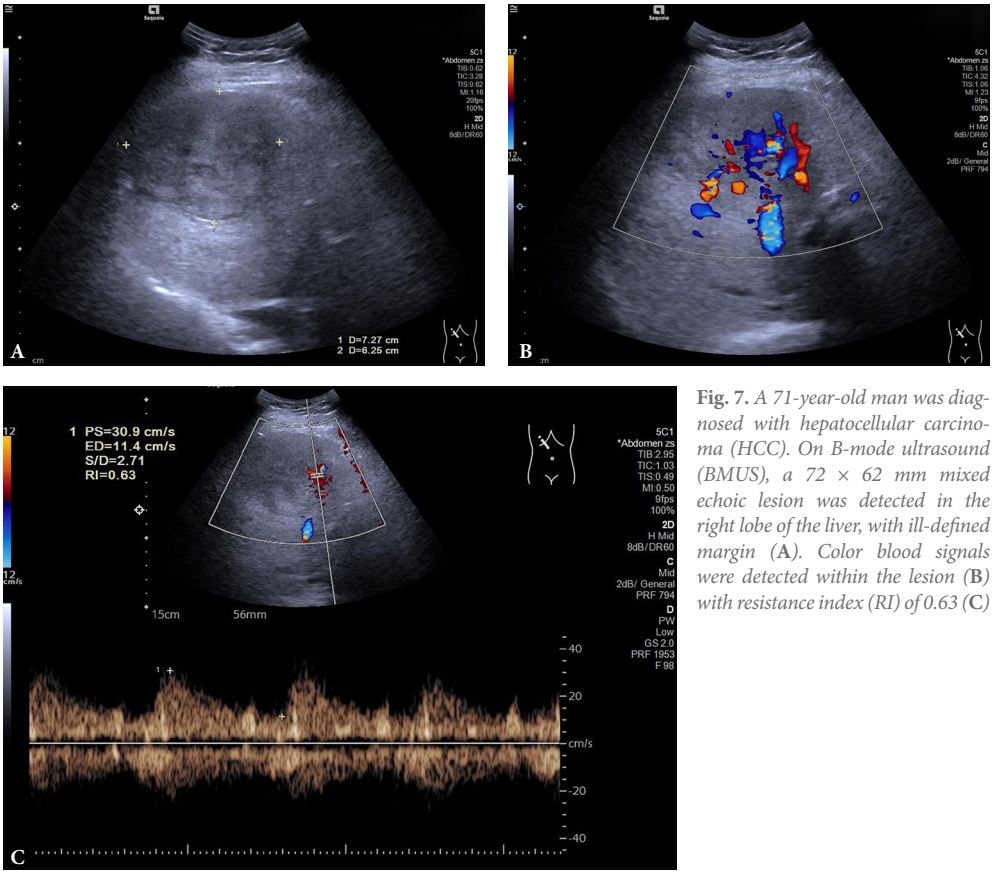

Fig. 7. *A 71-year-old man was diagnosed with hepatocellular carcinoma (HCC). On B-mode ultrasound (BMUS), a 72 × 62 mm mixed echoic lesion was detected in the right lobe of the liver, with ill-defined margin (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.63 (***C***)*

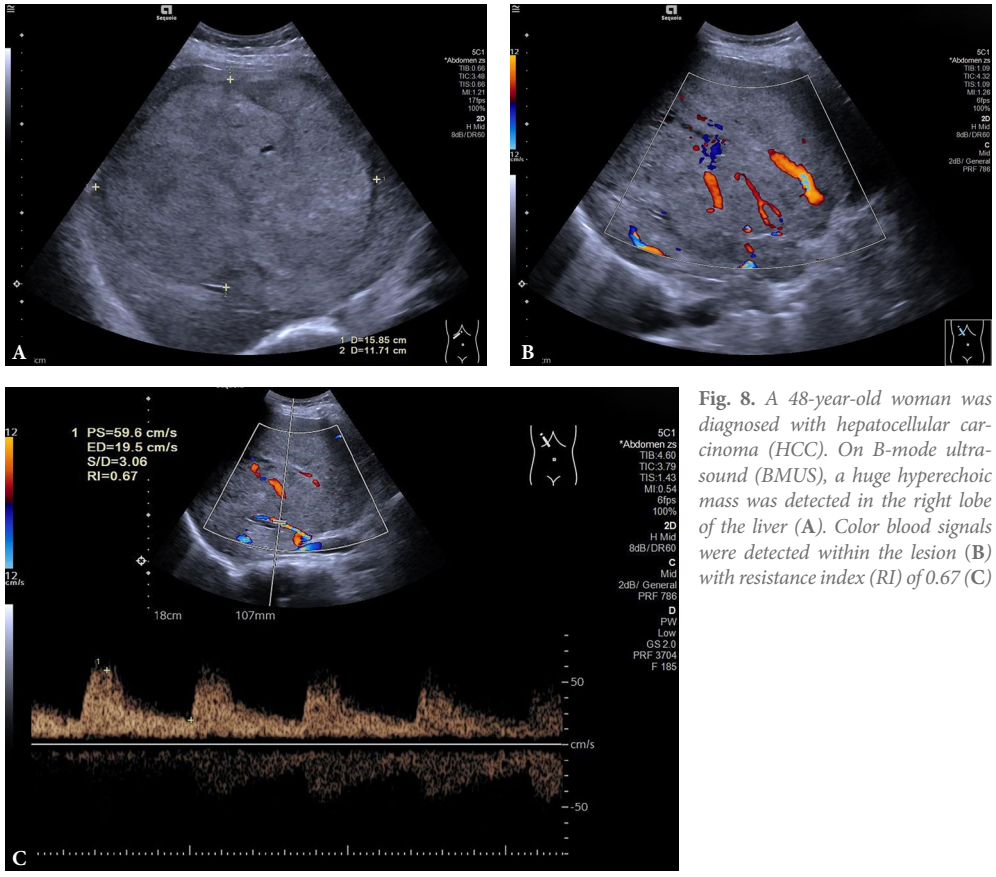

Fig. 8. *A 48-year-old woman was diagnosed with hepatocellular carcinoma (HCC). On B-mode ultrasound (BMUS), a huge hyperechoic mass was detected in the right lobe of the liver (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.67 (***C***)*

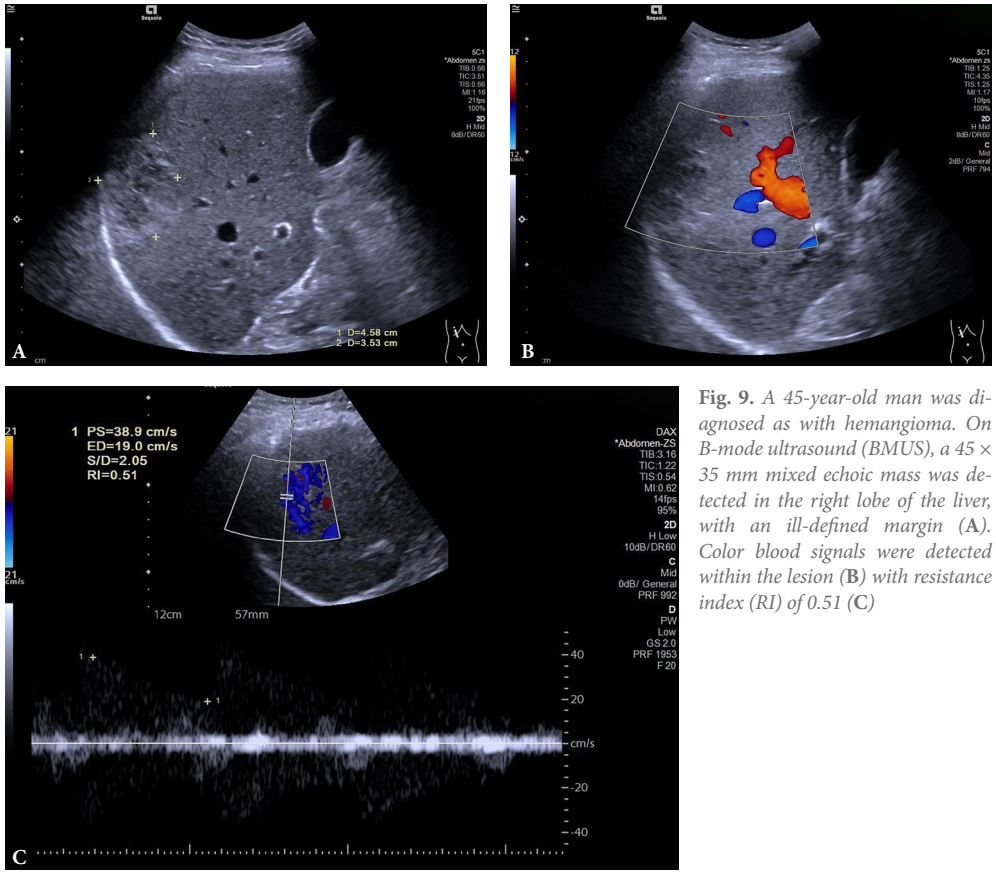

Fig. 9. *A 45-year-old man was diagnosed as with hemangioma. On B-mode ultrasound (BMUS), a 45 × 35 mm mixed echoic mass was detected in the right lobe of the liver, with an ill-defined margin (***A***). Color blood signals were detected within the lesion (***B***) with resistance index (RI) of 0.51 (***C***)*

Tab. 3. Comparison of resistance index in hepatocellular carcinoma in different liver background

Group	Background	Number	RI (mean ± SD)
1*	normal	82	0.69 ± 0.12
2	Fatty liver	16	0.75 ± 0.11
3*	cirrhosis	156	0.73 ± 0.12
* Group 1, 3: Significant difference (p <0.05)			

Tab. 4. Comparison of resistance index in focal nodular hyperplasia lesions (FNH)

Group	Number	Size of FNH (cm)	RI (mean ± SD)
1	3	<2	0.47 ± 0.05
2	28	2–5	0.56 ± 0.07
3	16	5–10	0.54 ± 0.08
4	1	>10	0.49

Limitations

The main limitation is the retrospective nature of this study. Due to the retrospective nature, some of the information may be incomplete. Besides, there may be some factors affecting the RI measurement, such as the localization of the lesion in different liver regions. Further prospective clinical study will be necessary to validate the RI diagnostic criteria in differentiating between benign and malignant FLLs. In the future, besides typical patterns of perfusion, CEUS could be a better imaging method for detecting blood flow in FLL.

Conclusion

Color Doppler examination is a valuable ultrasound imaging method for detecting blood flow signals of FLLs. The RI parameter would be helpful in differentiating malignant and benign FLLs.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: YD, WPW, AI, CFD. Writing of manuscript: YD, AI, DZ, XYL, S.C. Analysis and interpretation of data: YD, AI, DZ, YJQ, QZ, XYL, S.C. Final acceptation of manuscript: YD, WPW, AI, DZ, YJQ, QZ, XYL, S.C., CFD. Collection, recording and/or compilation of data: YD, DZ, YJQ, QZ, XYL, S.C. Critical review of manuscript: YD, WPW, CFD.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7–30. doi: 10.3322/caac.21590.
2. Dong Y, Teufel A, Wang WP, Dietrich CF: Current opinion about hepatocellular carcinoma <10 mm. Digestion 2021; 102: 335–341. doi: 10.1159/000507923.
3. Dong Y, Wang WP, Lee WJ, Meloni MF, Clevert DA, Chammas MC *et al.*: Hepatocellular carcinoma in the non-cirrhotic liver. Clin Hemorheol Microcirc 2022; 80: 423–436. doi: 10.3233/ch-211309.
4. Anwanwan D, Singh SK, Singh S, Saikam V, vSingh R: Challenges in liver cancer and possible treatment approaches. Biochim Biophys Acta Rev Cancer 2020; 1873: 188314. doi: 10.1016/j.bbcan.2019.188314.
5. Petrowsky H, Fritsch R, Guckenberger M, De Oliveira ML, Dutkowski P, Clavien PA: Modern therapeutic approaches for the treatment of malignant liver tumours. Nat Rev Gastroenterol Hepatol 2020; 17: 755–772. doi: 10.1038/s41575-020-0314-8.
6. Grazioli L, Ambrosini R, Frittoli B, Grazioli M, Morone M: Primary benign liver lesions. Eur J Radiol 2017; 95: 378–398. doi: 10.1016/j.ejrad.2017.08.028.
7. Dietrich CF, Nolsoe CP, Barr RG, Berzigotti A, Burns PN, Cantisani V *et al.*: Guidelines and Good Clinical Practice Recommendations for Contrast-Enhanced Ultrasound (CEUS) in the Liver-Update 2020 WFUMB in Cooperation with EFSUMB, AFSUMB, AIUM, and FLAUS. Ultrasound Med Biol 2020; 46: 2579–2604. doi: 10.1016/j.ultrasmedbio.2020.04.030.
8. Wang Y, Wang WP, Ding H, Huang BJ, Mao F, Xu ZZ: Resistance index in differential diagnosis of liver lesions by color doppler ultrasonography. World J Gastroenterol 2004; 10: 965–967. doi: 10.3748/wjg.v10.i7.965.
9. Dietrich CF, Jedrzejczyk M, Ignee A: Sonographic assessment of splanchnic arteries and the bowel wall. Eur J Radiol 2007; 64: 202–212. doi: 10.1016/j.ejrad.2007.06.034.
10. Ignee A, Boerner N, Bruening A, Dirks K, von Herbay A, Jenssen C *et al.*: Duplex sonography of the mesenteric vessels – a critical evaluation of inter-observer variability. Z Gastroenterol 2016; 54: 304–311. doi: 10.1055/s-0041-107544.
11. Dietrich CF, Maddalena ME, Cui XW, Schreiber-Dietrich D, Ignee A: Liver tumor characterization – review of the literature. Ultraschall Med 2012; 33 Suppl 1: S3–10. doi: 10.1055/s-0032-1312897.
12. Nahar N, Khan N, Chakraborty RK, Rima SZ, Ara R, Islam SM *et al.*: Color Doppler sonography and resistivity index in the differential diagnosis of hepatic neoplasm. Mymensingh Med J 2014; 23: 35–40.
13. Chiorean L, Cui XW, Tannapfel A, Franke D, Stenzel M, Kosiak W *et al.*: Benign liver tumors in pediatric patients – Review with emphasis on imaging features. World J Gastroenterol 2015; 21: 8541–8561. doi: 10.3748/wjg.v21.i28.8541.
14. Vidili G, Piscaglia F, Ainora ME, Solinas G, Sagrini E, Gianstefani A *et al.*: Focal nodular hyperplasia: new findings at Doppler ultrasonography. Eur Rev Med Pharmacol Sci 2020; 24: 12288–12295. doi: 10.26355/eurrev_202012_24020.
15. Dong Y, Wang WP, Mao F, Zhang Q, Yang D, Tannapfel A *et al.*: Imaging features of fibrolamellar hepatocellular carcinoma with contrast-enhanced ultrasound. Ultraschall Med 2021; 42: 306–313. doi: 10.1055/a-1110-7124.
16. Bernatik T, Seitz K, Blank W, Schuler A, Dietrich CF, Strobel D: Unclear focal liver lesions in contrast-enhanced ultrasonography – lessons to be learned from the DEGUM multicenter study for the characterization of liver tumors. Ultraschall Med 2010; 31: 577–581. doi: 10.1055/s-0029-1245649.
17. Dietrich CF, Schuessler G, Trojan J, Fellbaum C, Ignee A: Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. Br J Radiol 2005; 78: 704–707. doi: 10.1259/bjr/88181612.