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Original Contribution

Value of Micro Flow Imaging in the Prediction of Adenomatous Polyps

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Objective: The aim of this study was to assess the value of micro flow imaging (MFI) in distinguishing adenomatous polyps from cholesterol polyps.
Methods: A total of 143 patients who underwent cholecystectomy for gallbladder polyps were retrospectively analyzed. B-mode ultrasound (BUS), color Doppler flow imaging (CDFI), MFI and contrast-enhanced ultrasound (CEUS) were performed before cholecystectomy. The weighted kappa consistency test was used to evaluate the agreement of vascular morphology among CDFI, MFI and CEUS. Ultrasound image characteristics, including BUS, CDFI and MFI images, were compared between adenomatous polyps and cholesterol polyps. The independent risk factors for adenomatous polyps were selected. The diagnostic performance of MFI combined with BUS in determining adenomatous polyps was compared with CDFI combined with BUS.
Results: Of the 143 patients, 113 cases were cholesterol polyps, and 30 cases were adenomatous polyps. The vascular morphology of gallbladder polyps was more clearly depicted by MFI than CDFI, and it had better agreement with CEUS. Differences in maximum size, height/width ratio, hyperechoic spot and vascular intensity on CDFI and MFI images were significant between adenomatous polyps and cholesterol polyps ($p < 0.05$). The maximum size, height/width ratio, and vascular intensity on MFI images were independent risk factors for adenomatous polyps. For MFI combined with BUS, sensitivity, specificity and accuracy were 90.00%, 94.69% and 93.70%, respectively. Area under the receiver operating characteristic curve (AUC) of MFI combined with BUS was significantly higher than that of CDFI combined with BUS (AUC = 0.923 vs. 0.784).
Conclusion: Compared with CDFI combined with BUS, MFI combined with BUS had higher diagnostic performance in determining adenomatous polyps.

Introduction

Polyps are one of the most common gallbladder diseases, with an incidence rate of 4%–7% in healthy adults [1,2]. Cholesterol polyps are the most common non-neoplastic polyps and only require follow-up. However, neoplastic polyps are malignant (*e.g.*, gallbladder carcinomas) or have malignant potential (*e.g.*, adenomatous polyps), which is an indication for cholecystectomy [3]. Therefore, to determine appropriate treatment, it is very important to assess the non-neoplastic or neoplastic nature represented by ultrasound (US) characteristics of gallbladder polyps. Maximum size is the most commonly used indicator to distinguish the nature of gallbladder polyps. At present, guidelines of the Chinese Committee of Biliary Surgeons, the European Society of Gastrointestinal and Abdominal Radiology and the Japanese Society of Hepato-Biliary-Pancreatic Surgery recommend that gallbladder polyps with a maximum size of 1.0 cm or more are neoplastic polyps, which need cholecystectomy [4–6]. However, many studies have found that some non-neoplastic polyps are larger than 1.0 cm in size, and some neoplastic polyps are smaller than 1.0 cm [7–9]. Therefore, misestimation of the severity of gallbladder polyps based only on maximum size may lead to unnecessary cholecystectomy or treatment delay.

The vascular character of gallbladder polyps is another important predictor for distinguishing neoplastic polyps from non-neoplastic polyps, as neoplastic polyps usually have rich vascularity [10]. Color Doppler flow imaging (CDFI) has been widely used to evaluate the vascularity and differential diagnosis of gallbladder polyps [7,10,11]. However, due to thin blood vessels and slow blood flow, CDFI is often unable to accurately detect the vascularity of gallbladder polyps, which hinders its ability to perform accurate differential diagnosis of gallbladder polyps [12,13]. Contrast-enhanced ultrasound (CEUS) is a pure blood pool imaging technique, which can accurately assess the vascular features of gallbladder polyps and significantly improve the accuracy of differential diagnosis of gallbladder polyps. As the most common neoplastic polyps, adenomatous polyps exhibit mainly branch-like vascularity, and most cholesterol polyps exhibit dotted vascularity on CEUS [14,15]. However, CEUS has some disadvantages, such as the need for intravenous injections, long examination time, high cost and some contraindications (including being under 18 y of age, allergic to the contrast agent,

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pregnant or lactating, or having unstable cardiac function). Therefore, a novel imaging technique that can be used to accurately evaluate the vascular features of gallbladder polyps is required.

Micro flow imaging (MFI) is a novel technology utilizing principles of power Doppler and additional processing algorithms to improve flow sensitivity and spatial resolution. MFI analyzes Doppler signals by incorporating a novel spatial-temporal filter to separate tissue clutter from small vessels with low-speed blood flow. MFI can detect blood vessels with a diameter as low as 0.1 mm and blood flow with a velocity of 1 cm/s without the use of contrast agents [16–18]. It has been reported that MFI can accurately reveal the microvessels of lesions, such as liver cancer and metastatic lymph nodes, and improve the accuracy of differential diagnosis of benign versus malignant lesions [16,18,19]. Our previous study found that MFI could assess the vascular morphology of a gallbladder polyp [20], but the quantitative analysis of vascular intensity on MFI images and the value of MFI in improving B-mode ultrasound (BUS) in distinguishing adenomatous polyps from cholesterol polyps have not been explored.

In this study, we compared vascular features of gallbladder polyps using CDFI, MFI and CEUS, quantitatively analyzed the vascular intensity on both CDFI and MFI images, and evaluated the diagnostic benefits of adding MFI to improve the accuracy of BUS in determining adenomatous polyps and cholesterol polyps.

Methods

Participants

All procedures performed in this study involving human participants were approved by the Ethics Committees of Chinese PLA general hospital. The requirement for obtaining informed consent was waived because the study was retrospective. From January 2021 to November 2021, 189 consecutive patients with gallbladder polyps were included in the study. Patients' inclusion criteria were as follows: (i) gallbladder polyps on abdominal BUS, (ii) gallbladder polyp ≥0.6 cm in the largest dimension, (iii) US examination performed within 3 wk of cholecystectomy and (iv) gallbladder polyps confirmed by surgical pathological finding. Exclusion criteria were as follows: (i) patients who were not suitable for CEUS examination, such as being under 18 y of age, being allergic to contrast agent or lactating (n = 3); (ii) patients who had a malignant abdominal tumor (n = 7); (iii) patients with a pathological finding that confirmed non-cholesterol polyps and non-adenomatous polyps (n = 32); and (iv) US images of gallbladder polyps that were not of sufficient image quality (n = 4). The remaining 143 patients were enrolled in our study and all underwent BUS, CDFI, MFI and CEUS examination before cholecystectomy (Fig. 1).

US equipment system and scanning protocol

A PHILIPS EPIQ7 US system with C5-1 probe (Philips Healthcare, Bothell, WA, USA) was used. Two physicians with 7–15 y of experience in abdominal US performed all BUS, CDFI, MFI and CEUS examinations. All patients fasted more than 8 h before the US scan. Patients were in supine or left lateral position during the US scan. For patients with multiple gallbladder polyps, the largest polyp was selected for evaluation. Each gallbladder polyp was clearly visualized by optimizing the depth, zoom and focus on BUS images. The BUS setting parameters were: frequency, 2.3–3.5 MHz; gain, 55%; dynamic range, 55 dB. After obtaining BUS images, CDFI and MFI were performed. The CDFI setting parameters were: frequency, 2.3–3.5 MHz; gain, 50%; wall filter, 30–35 Hz; velocity scale, 7.7 cm/s. The MFI setting parameters were: frequency, 2.3–3.5 MHz; gain, 50%; wall filter, 50 Hz; velocity scale, 3.4 cm/s. The US contrast agent used was SonoVue (Bracco, Milan, Italy) with a dosage of 0.02 mL/kg per patient in CEUS. At the same time of injecting contrast agent, the system timer was activated, and the CEUS dynamic images were collected. The CEUS setting parameters were: frequency, 2.3–3.5 MHz; mechanical index, 0.06; gain, 40%–50%.

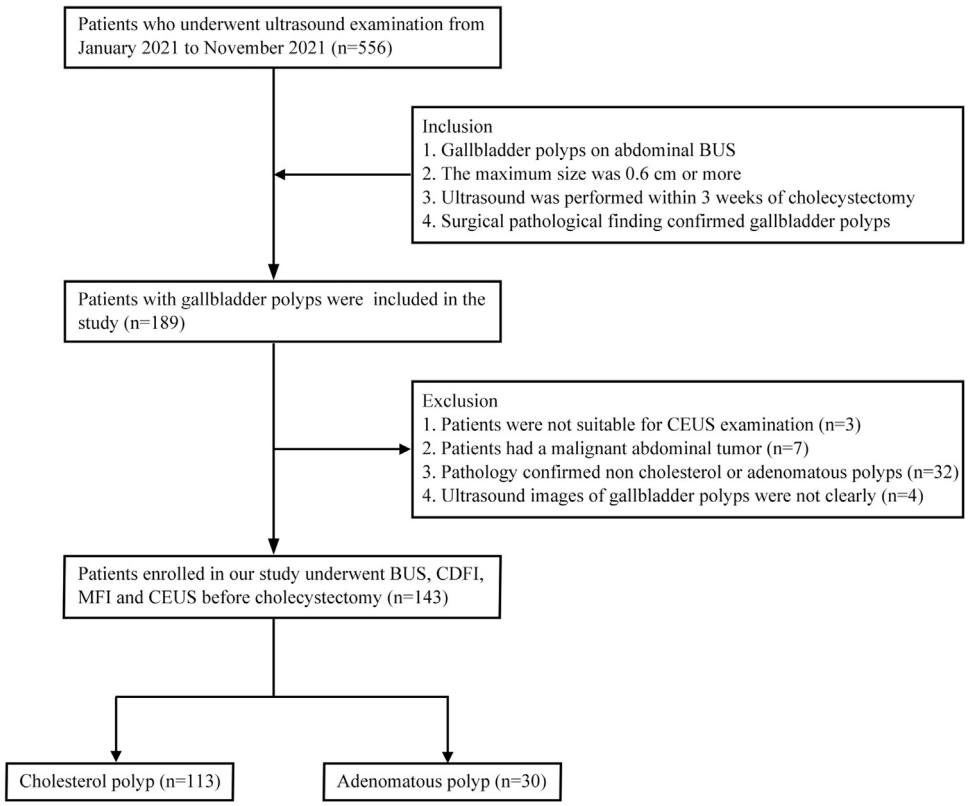

Figure 1. Flowchart study sample. BUS, B-mode ultrasound; CEUS, contrast-enhanced ultrasound; CDFI, color Doppler flow imaging; MFI, micro flow imaging.

US image analysis

The BUS, CDFI, MFI and CEUS image features were independently evaluated by the two physicians, who were not familiar with the patient's clinical information and pathological finding. Intraclass correlation coefficients or κ coefficients were used to evaluate interobserver agreement between the two physicians. The maximum size (largest diameter at any plane), height and width of gallbladder polyps were measured on BUS images, and the ratio of height to width was calculated. The echogenicity (hyperechoic, isoechoic or hypoechoic

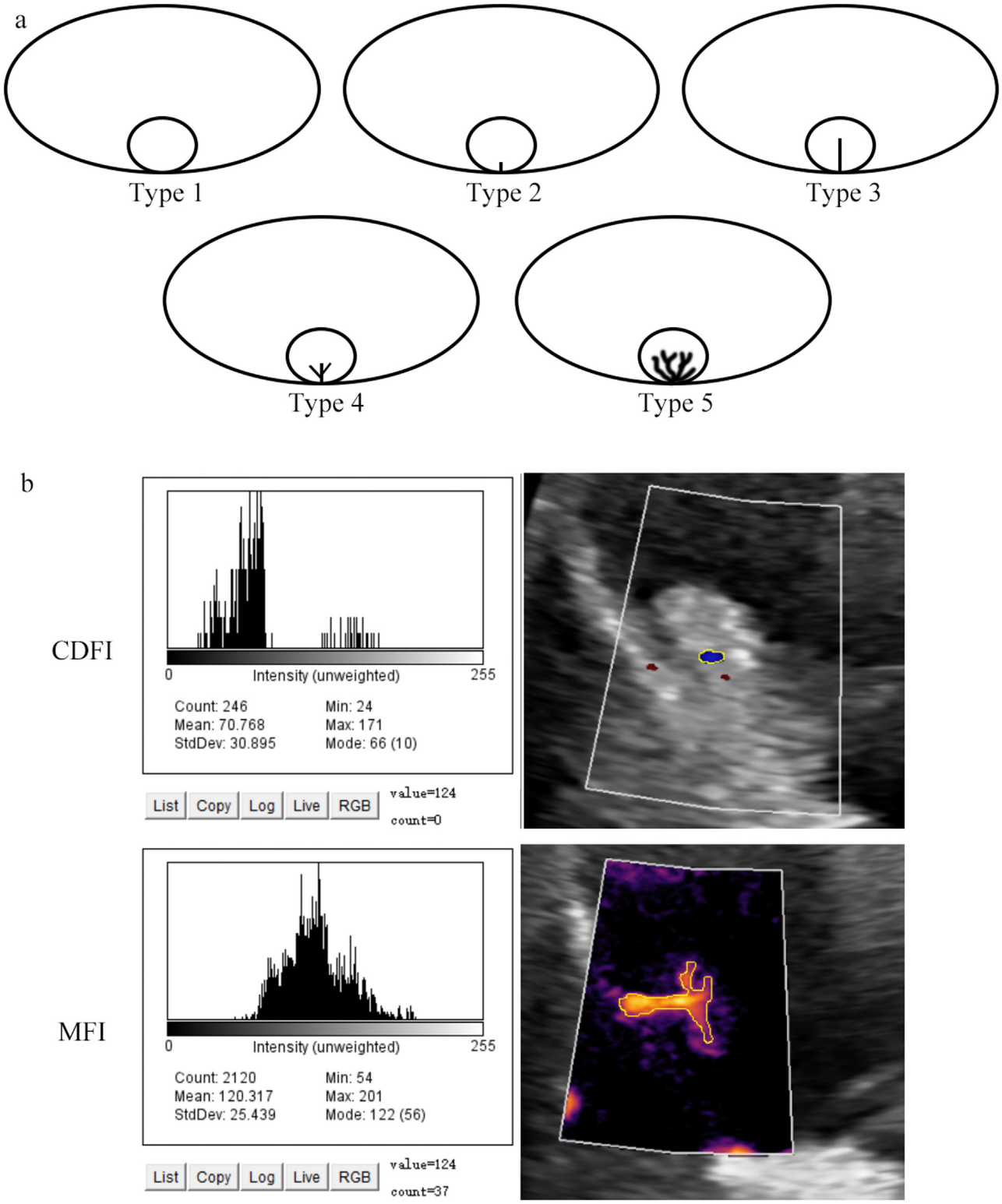

Figure 2. Vascularity analysis. (a) Schematic diagram of vascular morphology of gallbladder polyps. Type 1 indicates absent vascularity; Type 2 indicates dotted vascularity; Type 3 indicates single vascularity; Type 4 indicates branch-like vascularity; and Type 5 indicates irregular vascularity. (b) Example of quantification of vascular intensity on CDFI and MFI. CDFI, color Doppler flow imaging; MFI, micro flow imaging.

compared to the gallbladder wall), number (single or multiple), hyperechoic spot (1–5 mm in size) of gallbladder polyps and gallstone were evaluated on BUS images [21]. The vascular morphology of each gallbladder polyp on CDFI and MFI images was documented and classified as Type 1 to Type 5: Type 1, absent vascularity; Type 2, dotted vascularity; Type 3, single vascularity; Type 4, branch-like vascularity; Type 5, irregular vascularity (Fig. 2a). The vascular morphology of gallbladder polyps (dotted, single, branch-like and irregular vascularity) on CEUS images was also evaluated [14,15]. The vascular intensity of gallbladder polyps on both CDFI and MFI images was assessed by Image J software (National Institutes of Health, Bethesda, MD, USA). The region of interest (ROI) of per gallbladder polyp blood flow was set manually, followed by derivation of quantitative measurements of vascular intensity within the ROI using the histogram (Fig. 2b). The measurement was repeated three times per gallbladder polyp, and the average intensity was recorded.

Statistical analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. All continuous variables were expressed as the mean ± standard deviation. The Mann–Whitney *U* test was used for nonnormally distributed continuous data. The χ^2 test was used for categorical variables. The weighted kappa method was applied to compare percentage differences on CDFI, MFI and CEUS images in terms of vascular morphology of gallbladder polyps. The independent risk factors for adenomatous polyps were selected by binary logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was used to evaluate the

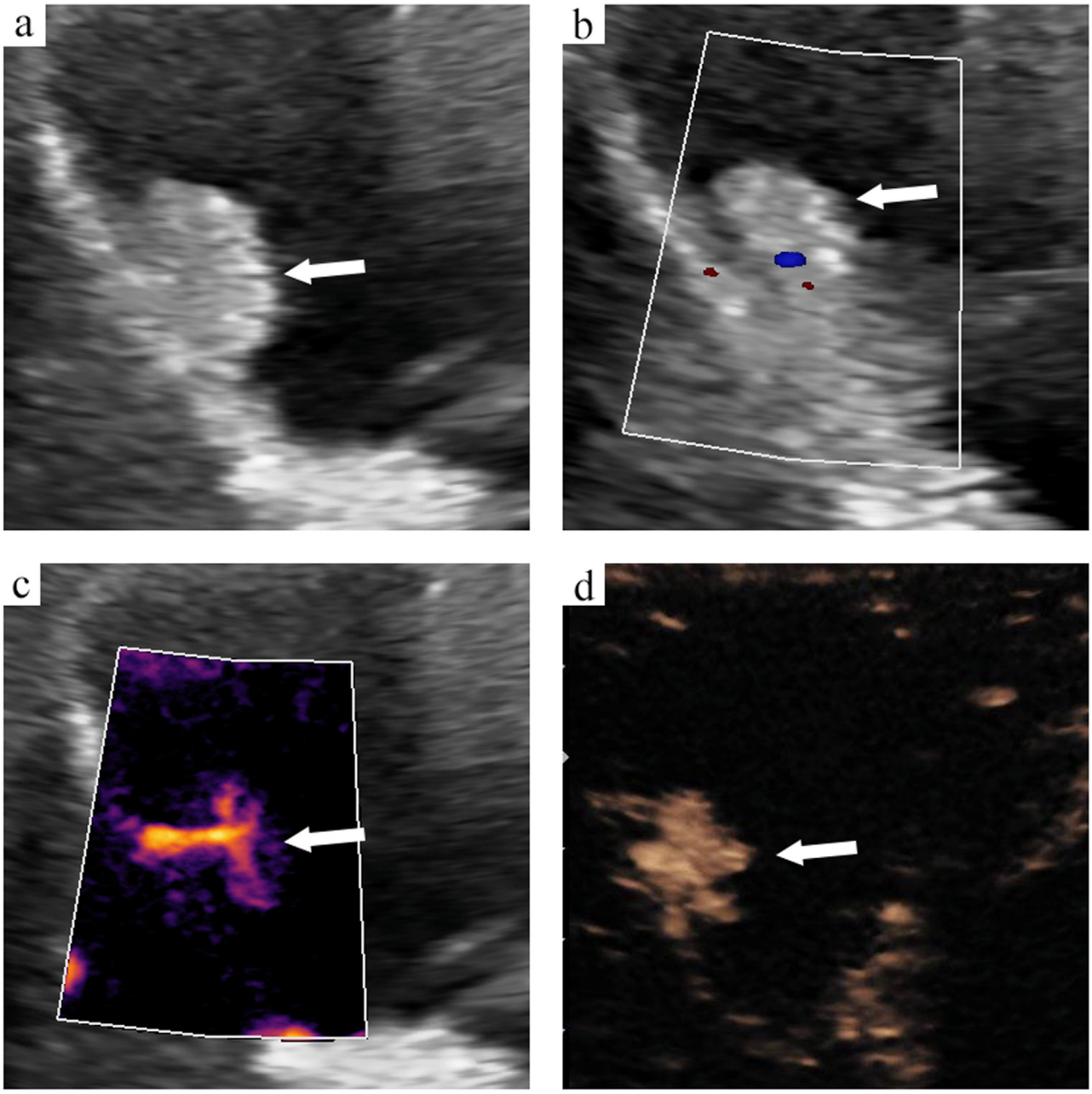

Figure 3. Vascular morphology of adenomatous polyps. (a) An adenomatous polyp with the height/width ratio less than 1.1 on BUS. (b) Dotted vascularity on CDFI (Type 2). (c) Branch-like vascularity on MFI (Type 4). (d) Branch-like vascularity on CEUS (Type 4). The *arrow* indicates the vascular morphology of an adenomatous polyp. BUS, B-mode ultrasound; CDFI, color Doppler flow imaging; MFI, micro flow imaging; CEUS, contrast-enhanced ultrasound.

cutoff value of continuous variables and the sensitivity, specificity and accuracy of CDFI combined with BUS and MFI combined with BUS in the differential diagnosis of gallbladder polyps. The nomogram was performed using R software (version 4.2.2). p values <0.05 indicated statistical significance.

Results

General characteristics of patients with gallbladder polyps

A total of 143 patients with gallbladder polyps were included in this study. Among the 143 gallbladder polyps, 113 were cholesterol polyps, and 30 were adenomatous polyps. There was no significant difference for patients' age and sex between adenomatous polyps and cholesterol polyps ($p > 0.05$).

Comparison of vascularity between CDFI and MFI

The presence of vascularity on CDFI images was seen in 37.06% of gallbladder polyps, while 90.91% of gallbladder polyps exhibited vascularity on MFI images. The difference between MFI and CDFI in detecting vascularity was statistically significant ($p < 0.05$). Compared with the vascular morphology of gallbladder polyps displayed on CEUS images, the κ coefficient of vascular morphology on CDFI and MFI images was 0.136 and 0.804, respectively. In cholesterol polyps, the κ coefficient of vascular morphology between CDFI and CEUS was only 0.070, while the κ coefficient between MFI and CEUS was 0.752. Moreover, compared

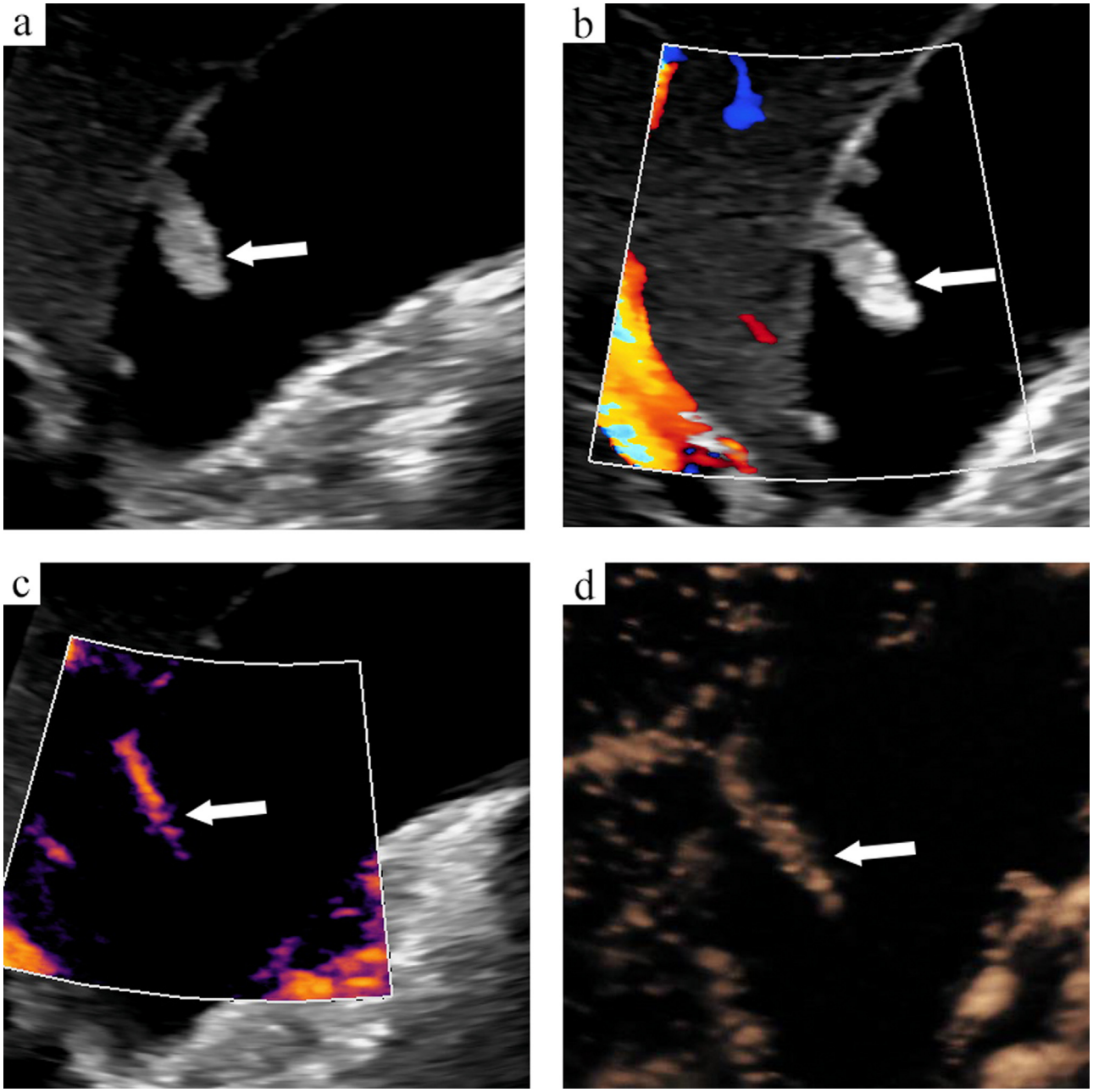

Figure 4. Vascular morphology of cholesterol polyps. (a) A cholesterol polyp with the height/width ratio greater than 1.1 on BUS. (b) Absent vascularity on CDFI (Type 1). (c) Single vascularity on MFI (Type 3). (d) Single vascularity on CEUS (Type 3). The *arrow* indicates the vascular morphology of a cholesterol polyp. BUS, B-mode ultrasound; CDFI, color Doppler flow imaging; CEUS, contrast-enhanced ultrasound; MFI, micro flow imaging.

Table 1
κ coefficient of vascular morphology in different maximum sizes

Maximum size (cm)	Number	κ coefficient for CDFI	κ coefficient for MFI
0.6–1.0	60	0.036 (−0.012 to 0.083)	0.681 (0.520–0.842)
1.1–1.5	66	0.148 (0.036–0.260)	0.786 (0.674–0.898)
≥1.6	17	0.105 (−0.031 to 0.241)	0.926 (0.784–1.068)

CDFI, color Doppler flow imaging; MFI, micro flow imaging.

with CEUS, the κ coefficient of vascular morphology of adenomatous polyps on CDFI and MFI images was 0.107 and 0.683, respectively. MFI offered advantages over CDFI in detecting the vascular morphology of adenomatous polyps and cholesterol polyps (Figs. 3 and 4). MFI was more accurate than CDFI in evaluating the vascular morphology of gallbladder polyps in different maximum size subgroups (Table 1). The κ coefficient of vascular morphology of gallbladder polyps between MFI and CEUS was associated with maximum size. The larger the maximum size, the higher the κ coefficient. However, the κ coefficient of vascular morphology of gallbladder polyps between CDFI and CEUS was highest when maximum size ranged from 1.1 to 1.5 cm. As far as gallbladder polyp vascularity quantification was concerned, vascular intensity on MFI images was significantly higher than that on CDFI images in gallbladder polyps, cholesterol polyps and adenomatous polyps ($p < 0.05$).

US image characteristics

The maximum size of gallbladder polyps ranged from 0.6 to 3.1 cm. Both maximum size and height/width ratio were significantly different between adenomatous polyps and cholesterol polyps ($p < 0.05$) (Table 2). The maximum size of adenomatous polyps was significantly greater than that of cholesterol polyps, while the height/width ratio of adenomatous polyps was significantly less than that of cholesterol polyps. However, the echogenicity, number of polyps and gallstone between adenomatous polyps and cholesterol polyps were not different ($p > 0.05$) (Table 2). The hyperechoic spot could be seen in most cholesterol polyps, while the majority of adenomatous polyps had no hyperechoic spot, and the difference between adenomatous polyps and cholesterol polyps was significant ($p < 0.05$) (Table 2). The vascular intensity of adenomatous polyps on both CDFI and MFI images was significantly greater than that of cholesterol polyps ($p < 0.05$) (Table 2).

Diagnostic performance of MFI combined with BUS

The image features with statistically significant differences between adenomatous polyps and cholesterol polyps were further analyzed. The maximum size, height/width ratio and vascular intensity on MFI images were the independent risk factors for adenomatous polyps (Table 3). Based on the ROC analysis results, the optimal cutoff values for maximum size, height/width ratio and vascular intensity on MFI images for predicting adenomatous polyps were 1.3 cm, 1.1 and 89.5 pixels, respectively (Table 4, Fig. 5). In agreement with most guidelines, which regard a maximum size of greater than 1.0 cm as classifying neoplastic polyps, we defined the maximum sizes of 1.0 and 1.3 cm as cutoff points in the three-way classification. The scoring points for independent risk factors for adenomatous polyps is shown in Figure 6. The diagnostic performance of CDFI combined with BUS versus MFI combined with BUS in distinguishing adenomatous polyps from cholesterol polyps are shown in Table 4 and Figure 7. The sensitivity and negative predictive value between MFI combined with BUS versus CDFI combined with BUS were not different ($p > 0.05$). The specificity, positive predictive value, accuracy and area under ROC curve of MFI combined with BUS were significantly higher than those of CDFI combined with BUS ($p < 0.05$).

Interobserver variability

Interobserver reliability of vascular morphology of gallbladder polyps on CDFI, MFI and CEUS images were 0.705, 0.749 and 0.795, respectively. Intraclass correlation coefficients for maximum size, height/width ratio and vascular intensity on CDFI and MFI images were 0.903, 0.918, 0.905 and 0.927, respectively. Interobserver agreements of echogenicity, number, hyperechoic spot, and gallstone were 0.793, 0.846, 0.703 and 0.727, respectively.

Discussion

The nature of gallbladder polyps determines the treatment method. However, current imaging methods cannot accurately

Table 2
General characteristics and ultrasound image features of gallbladder polyps

Characteristic	Cholesterol polyps (n = 113)	Adenomatous polyps (n = 30)	$z/\chi 2$	p Value
Age (y)	41.91 ± 12.34	44.47 ± 16.52	0.593	0.553
Sex			2.758	0.097
Male	53	9		
Female	60	21		
Maximum size (cm)	1.09 ± 0.27	1.48 ± 0.47	−4.75	<0.001
Height/width ratio	1.63 ± 0.59	0.97 ± 0.76	−5.298	<0.001
Echogenicity			4.148	0.113
Hyperechoic	84	19		
Isoechoic	25	7		
Hypoechoic	4	4		
Number			1.855	0.173
Single	52	18		
Multiple	61	12		
Hyperechoic spot			8.167	0.004
Present	74	11		
Absent	39	19		
Gallstone			1.701	0.243
Present	7	4		
Absent	106	26		
CDFI intensity (pixels)	12.98 ± 22.56	34.00 ± 31.42	−3.588	<0.001
MFI intensity (pixels)	62.94 ± 25.80	112.21 ± 29.98	−7.065	<0.001

CDFI, color Doppler flow imaging; MFI, micro flow imaging.

Table 3
Independent risk factors of adenomatous polyps

Ultrasound parameter	Coefficient	Standard error	Odds ratio	95% CI	*p* Value
Maximum size	4.401	1.651	81.549	3.207–2073.679	0.008
Height/width ratio	−2.046	0.583	0.129	0.041–0.405	<0.001
MFI intensity	0.083	0.018	1.086	1.049–1.125	<0.001

CI, confidence interval; MFI, micro flow imaging.

Table 4
Diagnostic performance of ultrasound parameters to determine adenomatous gallbladder polyps

Ultrasound parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	AUC
Maximum size	63.33	82.30	48.72	89.42	78.32	0.781
Height/width ratio	76.67	81.42	52.27	92.93	80.42	0.815
MFI intensity	86.67	88.50	65.00	96.11	87.41	0.920
CDFI combined with BUS	83.33	73.45	45.45	94.32	75.52	0.784
MFI combined with BUS	90.00	94.69	81.81	97.27	93.70	0.923

AUC, area under the receiver operating characteristic curve; BUS, B-mode ultrasound; CDFI, color Doppler flow imaging; MFI, micro flow imaging.

evaluate the nature of gallbladder polyps before operation, which may lead to unnecessary cholecystectomy [8,12,22]. Our study found that MFI could more accurately evaluate the vascular features of gallbladder polyps than CDFI, and the vascular intensity on MFI images was a predictor of adenomatous polyps. According to our results, MFI could enhance the diagnostic performance of BUS in distinguishing adenomatous polyps from cholesterol polyps.

Due to the technical limitations of CDFI technology, it is difficult to detect microvessels or low-speed blood flow, which affects the accuracy of differential diagnosis of gallbladder polyps to a certain extent [13]. Compared with CDFI, MFI exhibits better sensitivity in small and/or slow-flow vessels. These characteristics are directly related to MFI's ability to accurately visualize and quantify vascularity differences between adenomatous polyps and cholesterol polyps. Our study found that MFI was superior to CDFI in detecting the presence of vascularity of gallbladder polyps. When CEUS was used as the imaging "gold standard" of vascular morphology evaluation [23], the consistency between MFI and CEUS in displaying the vascular morphology of gallbladder polyps, adenomatous polyps and cholesterol polyps was all near-perfect or substantial, while the consistency between CDFI and CEUS was poor for all gallbladder polyp types. In addition, the consistency between MFI and CEUS in displaying the vascular morphology of gallbladder polyps was better than that of CDFI and CEUS in different maximum size subgroups. Finally, the vascular intensity of gallbladder polyps on CDFI and MFI images was further quantitatively analyzed in our study. The vascular intensity on MFI images was also significantly higher than that on CDFI images in gallbladder polyps, cholesterol polyps and adenomatous polyps. These results indicated that, relative to CDFI, MFI could more accurately demonstrate the vascularity of gallbladder polyps, and the ability of MFI to display vascularity was not affected by the maximum size of gallbladder polyps.

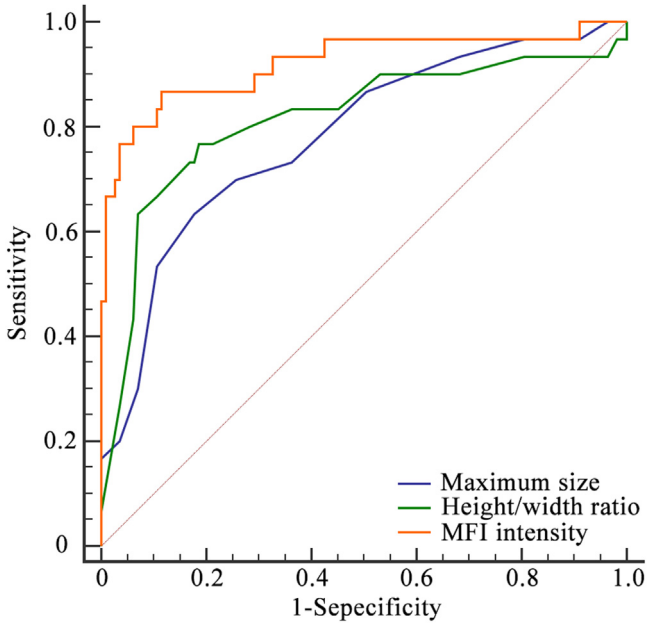

Figure 5. ROC curve analysis of ultrasound image characteristics. The optimal cutoff of maximum size, height/width ratio and vascular intensity on MFI for predicting adenomatous polyps was 1.3 cm, 1.1 and 89.5 pixels, respectively. MFI, micro flow imaging; ROC, receiver operating characteristic.

The vascular intensity of adenomatous polyps on both CDFI and MFI images was higher than that of cholesterol polyps, which meant adenomatous polyps were more vascular than cholesterol polyps [24,25]. Although the vascular intensity was significantly different between adenomatous polyps and cholesterol polyps on both CDFI and MFI images, regression analysis found that only the vascular intensity on MFI images was an independent risk factor for adenomatous polyps. The vascular intensity on MFI images >89.5 pixels indicated adenomatous polyps. The diagnostic performance of MFI combined with BUS was better than that of CDFI combined with BUS, especially regarding specificity, positive predictive value and accuracy. Therefore, MFI could better reveal the vascular features of gallbladder polyps than CDFI and improve the diagnostic performance of BUS in distinguishing adenomatous polyps from cholesterol polyps.

Maximum size is an important feature in the differential diagnosis of gallbladder polyps [26]. Gallbladder polyps with a maximum size ≥1.0 cm usually require cholecystectomy in clinical practice. In our study, maximum size of adenomatous polyps was larger than that of cholesterol polyps, and maximum size was an independent risk factor of adenomatous polyps, which was consistent with previous studies [22,27]. Some studies have confirmed that maximum size is associated with risk of adenomatous polyps, but they suggest that a maximum size of 1 cm is not a good surgical threshold for cholecystectomy [3,8,28]. The cutoff value of maximum size for predicting adenomatous polyps was 1.3 cm in our study, which was similar to previous reports [29–31]. Considering most guidelines used 1.0 cm as the threshold, we used 1.0

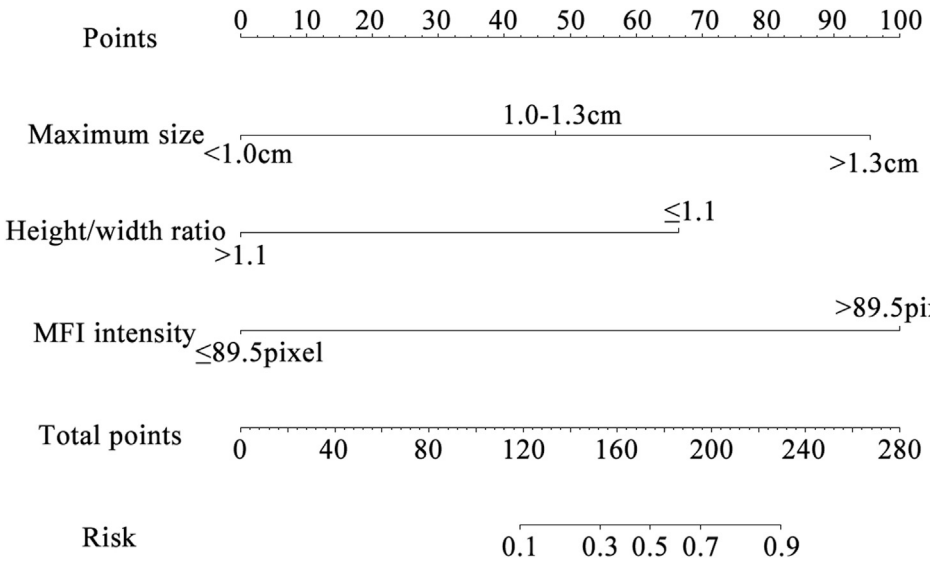

Figure 6. The nomogram was established with maximum size, height/width ratio and vascular intensity on MFI. MFI, micro flow imaging.

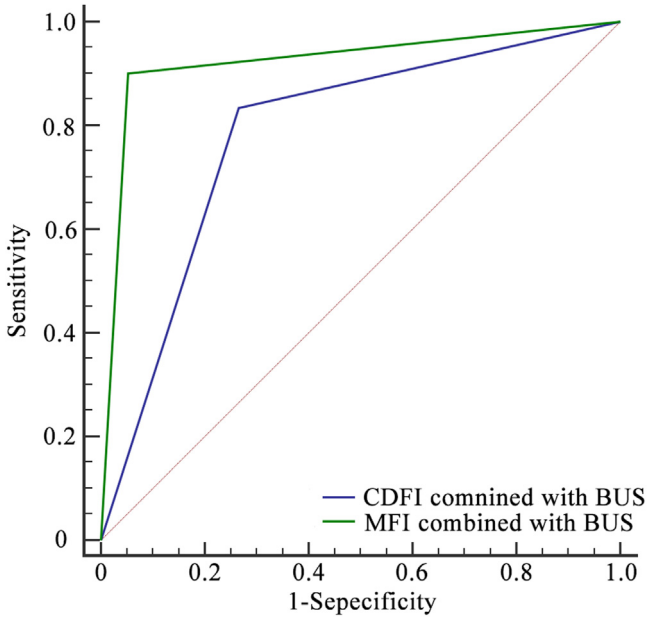

Figure 7. ROC curve analysis of CDFI combined with BUS vs. MFI combined with BUS in distinguishing adenomatous polyps from cholesterol polyps. BUS, B-mode ultrasound; CDFI, color Doppler flow imaging; MFI, micro flow imaging; ROC, receiver operating characteristic.

and 1.3 cm as the cutoff values to diagnose gallbladder polyps, which was more beneficial for the accurate differential diagnosis of adenomatous polyps and cholesterol polyps.

Height/width ratio refers to the ratio of height to width, which could also be used to distinguish adenomatous polyps. A low height/width ratio suggests that gallbladder polyps grow parallel to the gallbladder wall. The cutoff value for differential diagnosis of adenomatous polyps was 1.1, which was similar to previous studies [31,32]. The height/width ratio of adenomatous polyps was usually less than 1.1, while it was greater than 1.1 for cholesterol polyps. Our finding further confirmed that a low height/width ratio was associated with adenomatous polyps. Therefore, height/width ratio could reflect the growth direction and nature of gallbladder polyps.

This study has the following limitations. First, this was a retrospective study of a single institution, with a relatively small sample size. Second, inherent selection biases cannot be avoided, because the study only included patients undergoing cholecystectomy. Finally, the relationship between vascular patterns documented on MFI images and the vascular distribution derived from pathology needs further evaluation.

Conclusions

The evaluation of vascularity is helpful in the differential diagnosis of adenomatous polyps and cholesterol polyps. MFI could better demonstrate the vascular features of gallbladder polyps compared with CDFI and has a higher correlation with CEUS. The vascular intensity on MFI images is a significant predictor of adenomatous polyps. Therefore, MFI combined with BUS could improve the diagnostic performance in distinguishing adenomatous polyps from cholesterol polyps and provide more reliable diagnostic information for patients with gallbladder polyps to determine the proper treatment.

Data availability statement

The data are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no competing interests.

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