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Contrast-enhanced ultrasound may distinguish gallbladder adenoma from cholesterol polyps: a prospective case–control study

Xiang Fei,[1] Wen-Ping Lu,[2] Yu-Kun Luo,[1] Jian-Hon Xu,[1] Yan-Mi Li,[1] Huai-Yin Shi,[3] Zi-Yu Jiao,[1] Hong-tian Li[4]

[1]Ultrasound Department, PLA General Hospital, NO.28 Fu Xiang Road, Beijing 100853, China
[2]Surgery Department, PLA General Hospital, NO.28 Fu Xiang Road, Beijing 100853, China
[3]Pathology Department, PLA General Hospital, NO.28 Fu Xiang Road, Beijing 100853, China
[4]Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing 100191, China

Abstract

Purpose: The aim of this study was to find the independent risk factors related with gallbladder (GB) adenoma compared to cholesterol polyp by contrast-enhanced ultrasound (CEUS).
Materials and methods: Between January 2010 and September 2014, a total of 122 consecutive patients undergoing cholecystectomy for GB polypoid lesions were enrolled. Before cholecystectomy, each patient underwent conventional US and CEUS examination and all image features were documented. The patients were divided into adenoma group and cholesterol polyp group according to the pathological findings. All the image features between two groups were statistically compared.
Results: There were differences in patient age, lesion size, echogenicity, and vascularity of lesion between two groups ($P < 0.05$). There were differences in stalk width and enhancement intensity between the two groups ($P < 0.05$). Multiple logistic regression analysis proved that enhancement intensity, stalk of lesion, and vascularity were the independent risk factors related with GB adenoma ($P < 0.05$).
Conclusions: CEUS could offer useful information to distinguish adenoma from cholesterol polyp. The treatment algorithm for gallbladder polyp lesions would likely benefit from CEUS as a routine imaging investigation, especially in cases where the polyp is larger than 1 cm.

Key words: Gallbladder adenoma—Gallbladder polyp—Contrast-enhanced ultrasound

Correspondence to: Wen-Ping Lu; *email:* lvwenping301@126.com

Gallbladder polyp lesions (GPL) are relatively common, with a reported prevalence of 5–7% in healthy subjects [1]. However, GPL defines a wide spectrum of pathological findings, which include neoplastic polyps such as adenomas and non-neoplastic polyps such as cholesterol polyps, inflammatory polyps, or adenomyomatous hyperplasia [2]. Gallbladder (GB) adenoma is the most common neoplastic polyp of the gallbladder, while cholesterol polyps are the most frequently identified non-neoplastic GPL [3]. Several previous studies reported that the incidence cholesterol polyp was 46–70% in operative specimens and that of adenoma in operative specimens was 0.15–0.5% [3–5] Cholesterol polyps are benign lesions without the potential for progression to malignancy [6, 7]. However, GB adenomas have been suggested as a premalignant lesion [8]. As such, there are significant differences in the management of patients with GB adenoma or cholesterol polyps. Most notably, cholecystectomy is indicated for patients with adenoma, while serial ultrasonographic follow-up is appropriate for patients with cholesterol polyp.

At present, the diameter of a GPL is an important discriminator for a management plan [3, 9]. For small polyps (<10 mm), observation with follow-up by ultrasound every 3–6 months is appropriate, but patients with large polyps (>10 mm) are typically referred for laparoscopic cholecystectomy as long as they are good surgical candidates [3, 9]. Unfortunately, GPLs >10 mm in diameter are not always neoplastic lesions [2, 10]. Furthermore, evidence suggests that the lesion size alone is not sufficient to predict the histological nature of polyps detected by ultrasound [2, 10]. In which case, it is inappropriate to offer cholecystectomy to every patient with a GPL larger than 10 mm. Furthermore, the ultrasound-based diagnosis of GPL histology is inaccurate [10–12]. Therefore, a treatment algorithm based solely on GPL size may have significant limitations. As such, Kit et al. argue that the use of such an algorithm for GPLs <10 mm not only causes patient anxiety, but also carries with it significant economic cost due to repeat ultrasonographic follow-up [6].

Regarding cholecystectomy, previous studies report up to a 20% incidence of persistent abdominal pain [13, 14] and a reported incidence of major bile duct injury ranges from 0.25% to 0.74%, and that of minor bile duct injury from 0.28% to 1.7% during the laparoscopic cholecystectomy [14]. Unnecessary laparoscopic cholecystectomy for GPLs of benign pathology >10 mm risks surgical complications without providing any benefit to patients. The aforementioned arguments imply that distinguishing adenomas from cholesterol polyps is critical prior to determining the appropriate treatment.

Although gray-scale ultrasound has been widely used in detecting and diagnosing gallbladder disease, distinguishing neoplastic lesions from non-neoplastic lesions by ultrasound alone is difficult [3], posing a challenge to selecting patients with GPL for surgery or follow-up [6]. Since the introduction of color Doppler sonography in the mid-1980s, it has been reported to be useful in evaluation of gallbladder malignant lesions. It has been reported to be useful for the evaluation nature of neoplastic lesions, but it is not sufficient for obtaining accurate blood flow information on gallbladder lesions [15], meanwhile, this technique suffers from a number of inherent limitations, such as blooming or overpainting artifacts [16] which can contribute to affect the accuracy of diagnosis.

Recently, some physicians regarded that the growth rate of GPL may help to detect the neoplastic lesion from non-neoplastic GPL. However, the data on multivariate analysis proved that the growth rate was not related to the nature of a GPL [17]. Consequently, a new ultrasound imaging technique is required.

In recent years, a new technique of contrast-enhanced ultrasound (CEUS) has been widely used in liver, kidney, pancreas, and spleen, and it has been accepted in clinical practice [18]. CEUS allows visualization of the blood perfusion of lesion because microbubbles of 1–10 μm in diameter for sonography are purely intravascular, which can pass through the pulmonary circulation and subsequently enhance vascular end-organs, and remain in the vessel until it dissolves [19–21]. When microbubbles are exposed to ultrasound, they will increase the US backscatter and, therefore, are useful in the enhancement of echogenicity for the assessment of blood flow, which can help to show microcirculation of organs and lesion. Recently, CEUS has been used to study GPL, however, the value of CEUS in distinguishing the nature of GPL is not currently known [22–24]. In addition, such studies focused on the differentiation between gallbladder carcinoma and benign GPL, with few performing evaluation of cholesterol polyps and polyp-like adenoma features by both US and CEUS.

This study aimed to investigate value of CEUS in distinguishing polyp-like adenoma from cholesterol polyps, to determine independent risk factors linked to GB adenoma and thereby offer guidance for the treatment of gallbladder adenoma and cholesterol polyps.

Materials and methods

Patient

Between January 2010 and September 2014, a total of 122 consecutive patients undergoing cholecystectomy for GB polypoid lesions were prospectively enrolled. In our center, the size of GPL, gallstones, and abdominal symptoms are the indicators for surgery, if the patients enrolled in this study without these indicators were not good candidates for surgery and the pathological findings of GPL could not be obtained. So, the patients were excluded if they had one of the following: diameter of the largest GPL lesion <6 mm, diameter of the largest GPL lesion 7–10 mm without GB stone or symptoms (episodes of biliary colic, frequent vague gastric discomfort and dyspepsia without any abnormality in gastroduodenoscopy, right upper quadrant discomfort), age <18. All patients were treated surgically, and the diagnosis was confirmed by histopathologic evaluation.

The study and corresponding informed consents were approved by the Ethics Committees of PLA general hospital and written informed consent was obtained from each patient before enrollment.

Equipment and examination

A PHILIPS IU22 system providing phase-inversion harmonic (PIH) software and equipped with C5-1 probes at a frequency of 3–5 MHz was used throughout the study.

SonoVue contrast agent (Bracco SpA, Milan, Italy), a suspension of stabilized sulfur hexafluoride microbubbles in saline was used throughout. It was supplied as a lyophilized product in a septum-sealed vial and was reconstituted by injecting 5.0 mL of saline through the septum, followed by hand agitation. The concentration of bubbles ranged from 1 to 5×10^8 microbubbles/mL, with 90% of the microbubbles smaller than 8 μm in diameter. The dose of contrast agent was 0.02 mL/kg per patient.

Before cholecystectomy, each patient underwent conventional US and CEUS examination. At the fundamental frequency, the sizes of lesions were measured. Simultaneously, the echoic features and blood flow within lesions were observed and recorded by color Doppler flow imaging. When two or more polyps were detected, the size of the larger polyp was used for analysis. With the probe at the largest section of the lesion, using pulse inversion imaging (MI <0.1) and microvessel imaging technique, a bolus of SonoVue was injected intravenously followed by a 5 mL saline flush to ensure no residual contrast agent remained in the intravenous catheter. CEUS lasted for at least 3 min and the examination was recorded using the ultrasound equipment. To prevent interoperator variability, all contrast-enhanced US scanning were performed by the same operator using the same examination protocol.

Features of US and CEUS images

The following US features of GPL were recorded: echogenicity (hyperechoic, non-hyperechoic; compared to liver echogenicity), location (bottom, body, neck), and GPL vascularity. The vascularity was classified as absent or present and the number of GPL was classified as single or multiple.

The follows CEUS features of GPL were recorded: (1) the vascular phase of the gallbladder. According to previous literature [25], the vascular phase is divided into arterial and venous (late) phases. In our study, the two phases can be defined as following: arterial phase (10–30 s after bolus injection), venous phase (31–180 s after injection), which was same with Xie study [25]. (2) According to the vascular morphology within lesions during the arterial phase, the vascular types were classified as: 1. homogeneous dotted, 2. single vessel, 3. branch-like vessels, 4. tortuous or irregular vessels. (3) The enhancement intensity, during the arterial phase, was evaluated as hyper-, iso-, hypo-, or non-enhancing compared to the adjacent GB wall. (4) The enhancement pattern was classified as homogeneous or heterogeneous. (5) The GB wall under the GPL was divided into intact or disrupted. Disruption was defined as a discontinuity of the gallbladder wall. (6) During the arterial phase, the size of GPL stalk width was documented.

Image interpretation

Two radiologists were responsible for the interpretation of CEUS images, each of whom has at least 5 years experience of viewing CEUS images. Prior to the interpretation, the radiologists were shown 10 similar examples of CEUS still images to establish a standardized approach regarding the interpretation of vascular type, enhancement intensity, enhancement pattern, and GB wall integrity. Radiologists were blinded to patient identity, final diagnosis, and the results of other imaging investigations. The reviews were performed independently. Agreement between readers was assessed with the multi-reader κ statistics.

Statistics

Statistical analyses were performed using SPSS15.0 for Windows (SPSS Inc., Chicago, IL). Continuous data were expressed as mean (std). Comparisons between categorical data were analyzed by the χ^2 test, Fisher exact test, and one-way ANOVA, respectively. Multiple logistic regression analysis was performed to select independent variables of patients features, US, and CEUS characteristics associated with depend variable. Concordance of agreement between readers was tested by multirater κ statistics. P values <0.05 were considered statistically significant.

Results

57 men and 65 women were included in the study. Patient age was 44.48 ± 10.88 years (range 20–66 years) and 54.02 ± 10.58 years (age range 31–72 years) for patients with cholesterol polyps or adenomas, respectively. There were 81 cases of cholesterol polyps and 41 cases of GB adenoma. The clinical data and US imaging features of the 122 patients with GPL are shown in Table 1.

On standard ultrasonographic examination a significantly higher proportion of cholesterol polyps were <1 cm when compared with adenomas. Furthermore, adenomas were more vascular and a smaller proportions were hyperechogenic. There was no difference in lesion location or number of lesions when comparing patients with cholesterol polyp or adenoma (Table 1).

GB adenomas demonstrated a significantly wider stalk width (Fig. 1) and exhibited more hyper-enhancement frequently when compared to cholesterol polyps (Table 2). However, there were no statistical differences between the two pathologies with regards to vascular type (Figs. 2, 3), enhancement pattern, or GB wall integrity (Fig. 4; Table 2). Interestingly, the irregular vascular type was not detected in this study.

Table 1. Features of GPL on gray-scale ultrasound image

	Cholesterol polyp (81)	Adenoma (41)	P value
Age (years) (mean ± std)	44.48 ± 10.88	54.02 ± 10.58	<0.01
Range (min–max)	(20–66)	(31–72)	
Gender			0.41
F	41	24	
M	40	17	
Size (cm) (mean ± std)	1.06 ± 0.33	1.78 ± 0.78	<0.01
Range (min–max)			
Size <1.0 cm	23	2	0.002
Size ≥1.0 cm	58	39	
Number			0.40
Single	45	26	
Multiple	36	15	
Echogenicity			0.001
Hyperechoic	68	23	
Non-hyper	13	18	
Location			0.23
Bottom	12	11	
Body	44	21	
Neck	25	9	
Vascularity			<0.01
Yes	18	33	

The data from Table 1 proved that there were differences in patient age, size, and vascularity between adenoma group and cholesterol group

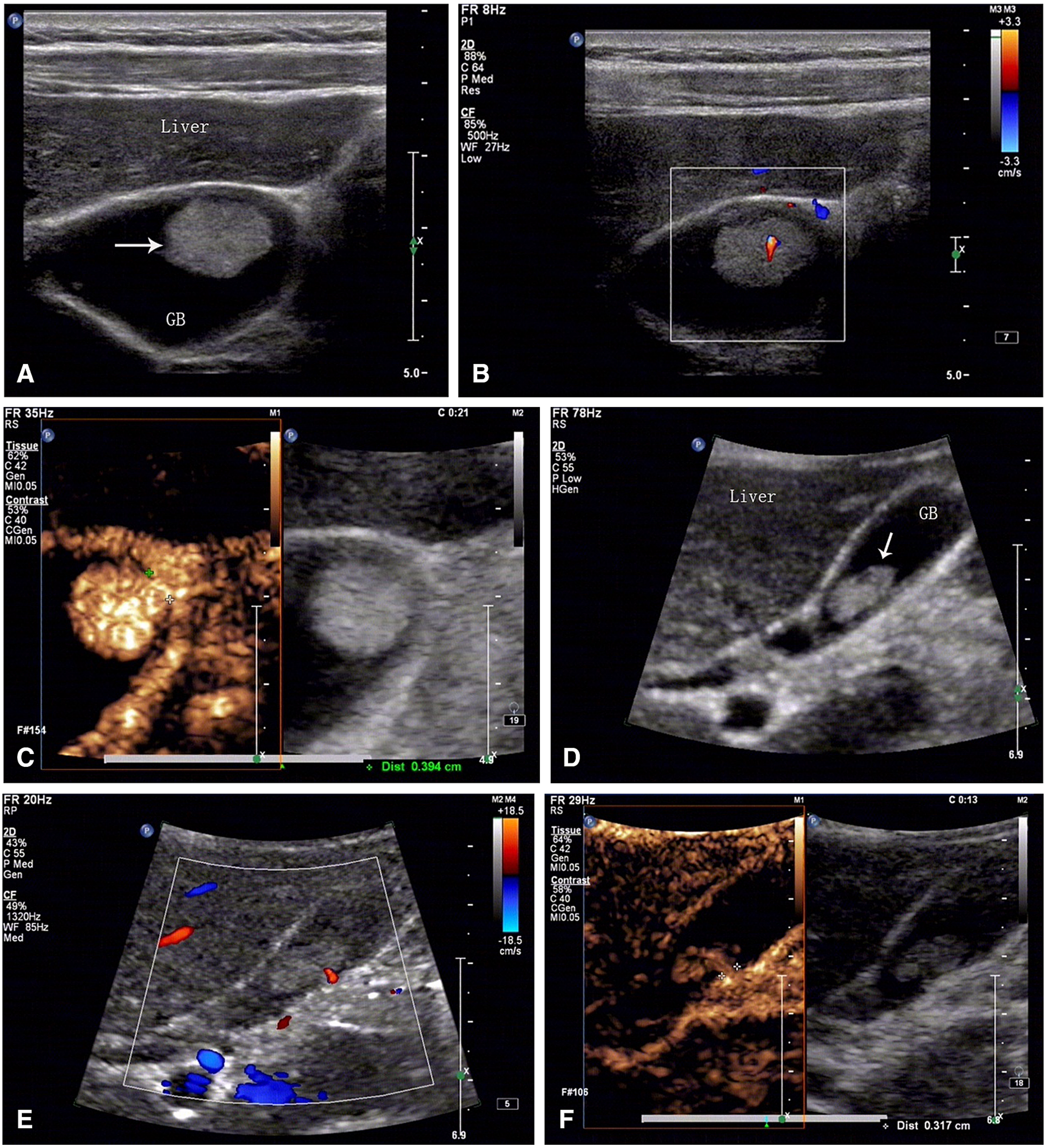

Fig. 1. The stalk width of GB adenoma and cholesterol polyp after enhancement. **A** The hyperechoic polyp (*arrow*) was detected in the gallbladder (GB) and it was pathologically proved GB adenoma after cholecystomy. **B** There was dotted blood flow signal within the lesion by CDFI. **C** After enhancement, the stalk of the lesion could be displayed clearly, and the stalk width was 4 mm. **D** The hyperechoic polyp (*arrow*) could be detected in GB and it was pathologically proved cholesterol poly. **E** There was dotted blood flow signal within the lesion by CDFI. **F** After enhancement, the stalk was displayed clearly, and stalk width was 3 mm. GB, gallbladder.

Independent variables that were significantly different between adenomas and cholesterol polyps were submitted to multiple logistic regression analysis. Enhancement intensity, stalk width, and vascularity were all found to be independent variables associated with the lesion histology (Table 3).

Table 2. Features of GPL on CEUS image

	Cholesterol polyp (81)	Adenoma (41)	*P*
Stalk width	0.23 ± 0.59	0.56 ± 0.48	<0.01
Vascular type I			
Dotted	44	24	
Non-dotted	37	17	
Vascular type II			–
Irregular	0	0	
Non-irregular	81	41	
Vascular type III			0.27
Branch-like	20	14	
Non-branch like	61	27	
Vascular type IV			0.05
Single	17	3	
Non-single	64	38	
Enhancement intensity			<0.01
Hyper-	2	30	
Non-hyper-	79	11	
Enhancement pattern			0.18
Homogeneous	79	37	
Heterogeneous	2	4	
GB wall integrity			–
Intact	81	41	
Destructed	0	0	

According to the CEUS features, there were differences in stalk width and enhancement intensity between two groups

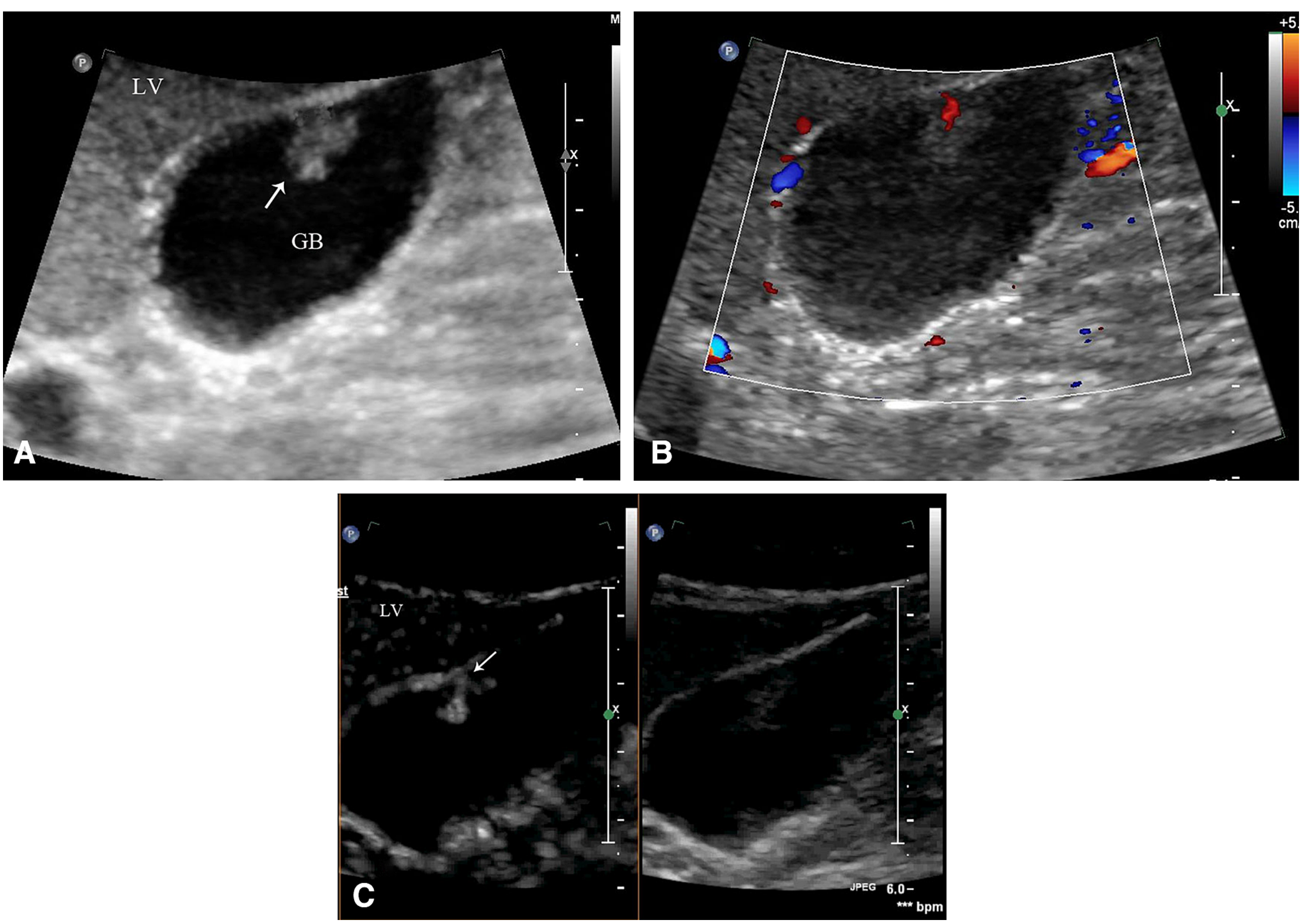

Fig. 2. Vascular type of cholesterol poly after enhancement. **A** There was a hyperechoic polyp lesion (*arrow*) in GB. **B** Blood flow signal could be detected by CDFI. **C** After enhancement, a branch-like vascular type (*arrow*) could be displayed. LV, liver; GB, gallbladder.

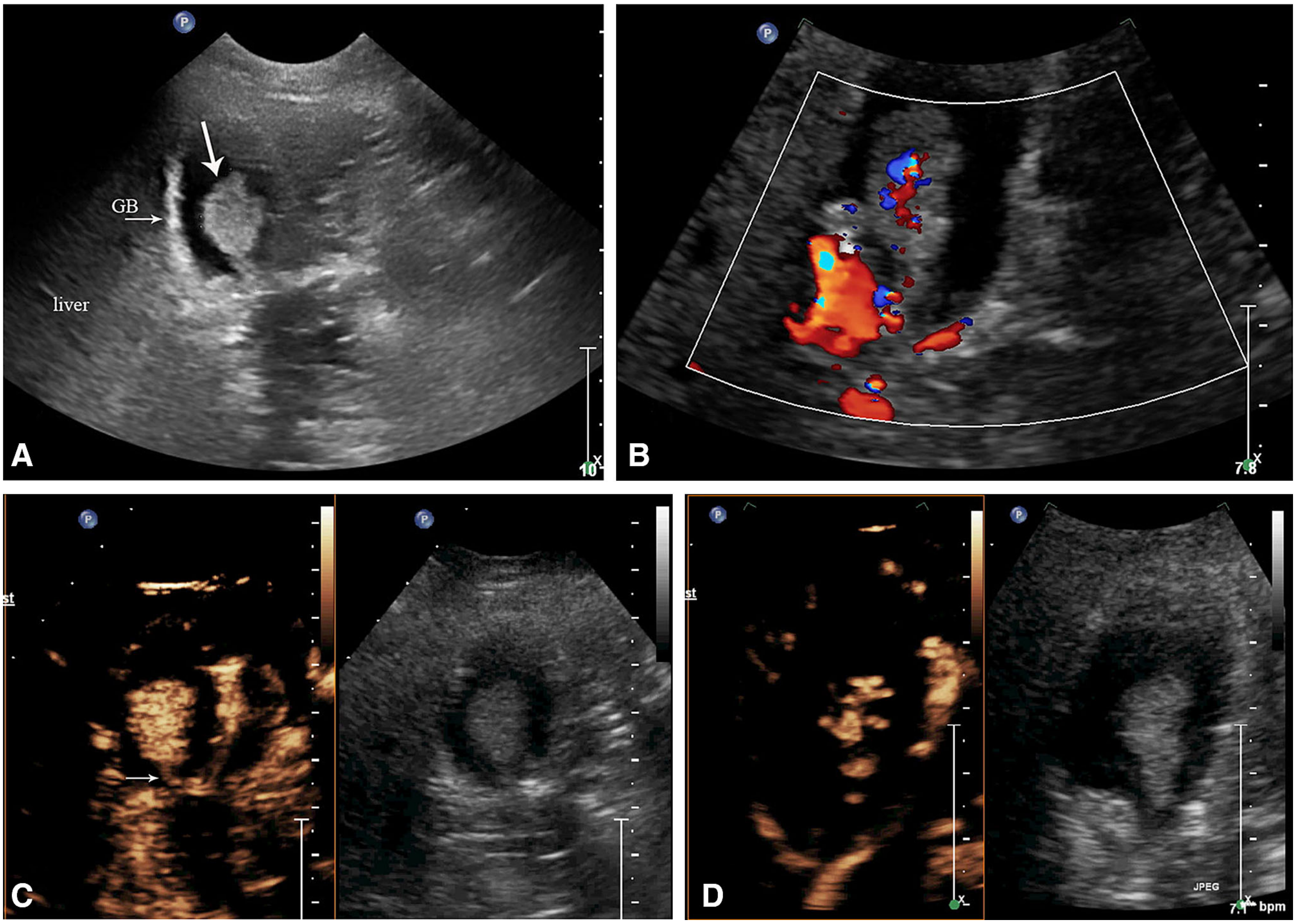

Fig. 3. Vascular type of GB adenoma after enhancement. **A** There was a hyperechoic polyp lesion (*arrow*) in GB. **B** There was blood flow signal within the lesion by CDFI. **C** The stalk (*arrow*) of the lesion could be observed. **D** Branch-like vascular type was displayed after enhancement. GB, gallbladder.

The data in Table 4 indicated that the concordance between the different readers in this study was good.

Discussion

GPLs, which refer to any mucosal mass within the lumen of the gallbladder, are relatively common. GPL includes several different pathological findings, and there is variability in the treatment strategy for patients with GPL. Choosing an appropriate treatment for patients with GPL greatly depends on accurate diagnosis and physicians often make the diagnosis according to information obtained from radiological imaging [3]. Ultrasonography is the most widely used imaging modality for the diagnosis of gallbladder disease, but it is difficult to distinguish adenoma from benign cholesterol polyp on the basis of standard ultrasonographic features [26]. Several studies report that the polyp size larger than 10 mm is not only a useful discriminator but also a risk factor indicating for cholecystectomy in treatment algorithm [3, 9, 27]. In this study, we identified differences in several ultrasonographic features between adenoma and cholesterol polyps, particularly for polyps larger than 10 mm. However, we found that 71.6% of cholesterol polyps were larger than 10 mm, while 4.1% of adenomas were smaller than 10 mm, indicating that it is not possible to categorize cholesterol polyps based on size alone, which is coherent with the previous studies [2, 27]. Furthermore, based on this evidence, it would be inappropriate to perform cholecystectomy for all patients with a lesion size >10 mm, as a high proportion of such patients will have cholesterol polyps rather than adenoma.

Interestingly, 84% of cholesterol polyps appeared to be highly echogenic on standard ultrasonographic examination, with non-hyperechoic cholesterol polyps typically being larger in size [28]. Furthermore, 56.1% of adenomas were hyperechoic, indicating that echogenicity is unlikely to distinguish sufficiently between pathologies. However, this is supported by our finding that echogenicity was not independently associated with the presence of adenoma. We hypothesize that cholesterol

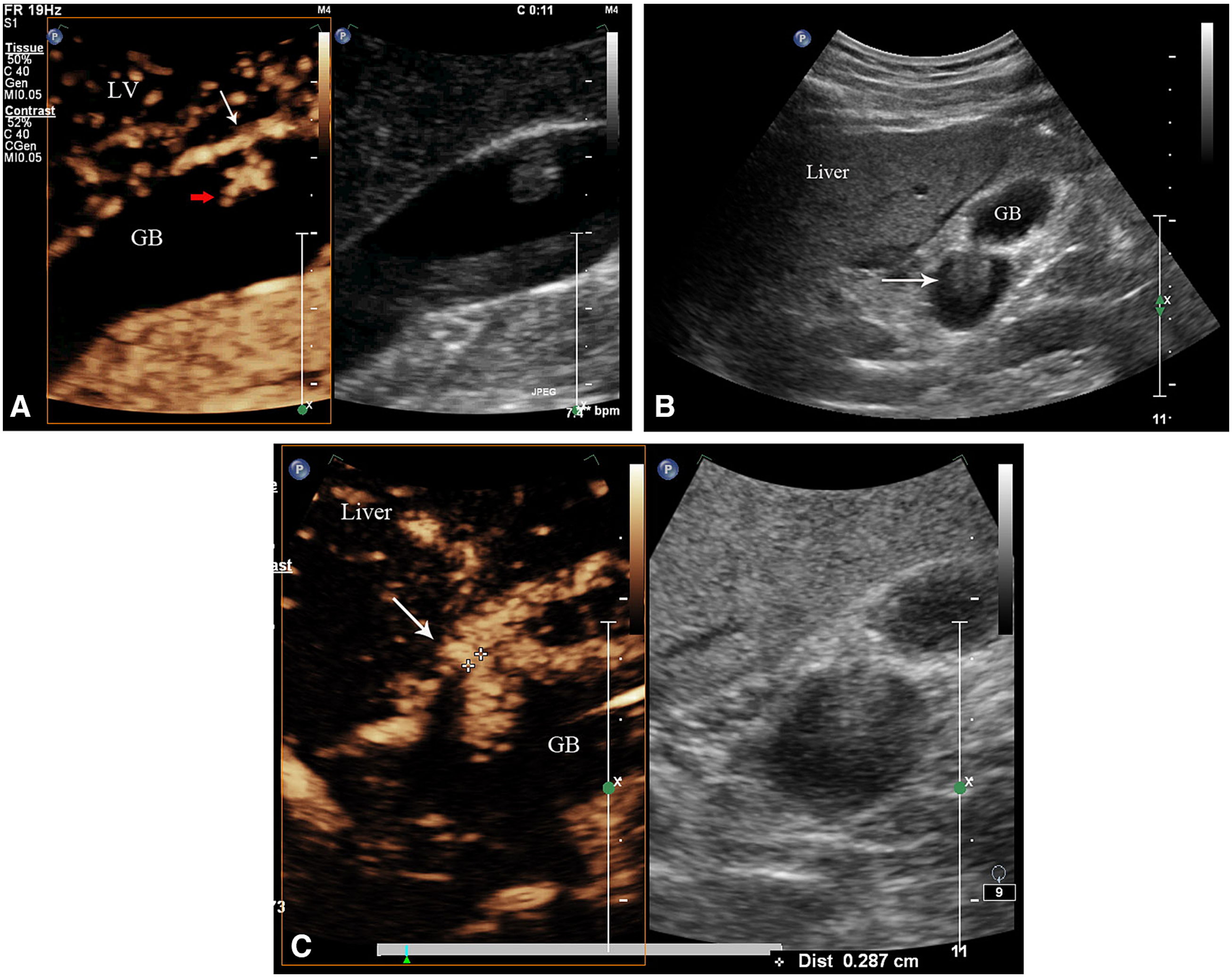

Fig. 4. GB wall integrity after enhancement. **A** During arterial phase, the GB wall (*white arrow*) the cholesterol polyp (*red arrow*) attached to was integrity. **B** The hyperechoic polypoid gallbladder adenoma (*arrow*) could be detected by ultrasound. **C** During arterial phase, the GB wall (*arrow*) the adenoma attached to was integrity. GB, gallbladder; LV, liver.

attached to the surface of some adenomas may result in their increased echogenicity. Consequently, further analysis of ultrasonographic characteristics and risk factors associated with polyp-like adenoma is required.

Recently, CEUS has been widely used for diagnosing pathologies of the liver, kidney, pancreas, and spleen—uses which are now accepted in clinical practice. CEUS has an advantage over gray-scale ultrasound for the evaluation of vascularity as it allows for visualization of the perfusion of lesions, offering useful diagnostic information [19–21]. In our study, we investigated whether the vessel types revealed by CEUS are of value in distinguishing adenoma from cholesterol polyps. Interestingly, the irregular vascular type was not be detected in cholesterol polyps or adenomas, while the dotted, branch-like, and single vessel types were all detected on CEUS imaging for both cholesterol polyps and adenomas. In cholesterol polyps, normal-caliber arteries taper normally and subdivide normally into small vessels. In this case, the examination showed a dotted-, branched-, or single-vessel pattern [29]. In adenoma cases, dotted-, branched-, or single vessel type could also be detected probably because vessels of adenoma may be homogeneously distributed when the lesions are small but that as the lesions increase in size the vascular structure develops branch-like vessels. Therefore, vascular types on CEUS cannot be used to distinguish adenoma from cholesterol polyp according to our data. Inoue et al. report a similar finding, in that the vascular pattern simply reflects size of lesion rather than the nature of GPL [16]. In this study, we found that the majority of adenomas displayed hyper-enhancement, while the majority of cholesterol polyps displayed iso-enhancement during the arterial phase. The microvascular density difference may partly account for the difference in enhancement intensity between cholesterol polyps and GB adenoma. Our data therefore

Table 3. The independent variables associated with the GB adenoma by multiple logistic regression analysis

	B	95% CI	*P*
Enhancement intensity	4.919	6.507–2876.160	0.002
Stalk of lesion	11.418	137.685–6.006E7	0.001
Vascularity	5.207	3.529–9438.515	0.01
Constant	−9.710		0.000

In Table 3, multiple logistic regression analysis results proved that there were three risk factors related with gallbladder adenoma

Table 4. Concordance between different readers

Features on US and CEUS image	Feature	Value
Echogenicity	Hyper- or non-hyper	0.56
Vascularity	Yes or no	0.74
Vascular type I	Dotted or non-dotted	0.73
Vascular type II	Irregular or non-irregular	–
Vascular type III	Branch or non-branch	0.55
Vascular type	Single or non-single	0.65
Enhancement intensity	Hyper or non-hyper	0.52
Enhancement pattern	Homo- or heterogeneous	0.80
GB wall integrity	Disruption or integrity	–

In Table 4, the data proved that there were concordance between different readers in interpreting US and CEUS images

demonstrate that hyper-enhancement is strongly predictive of the presence of GB adenoma. This is in keeping with a previous report showing that adenomas and even cholesterol polyps are mildly or markedly tumor enhancing when viewed using contrast-enhanced harmonic gray-scale ultrasonography [29].

On gray-scale US imaging a thin, fragile stalk is typical of cholesterol polyps, while GB adenomas are usually stalk [3]. However, it is usually difficult to assess the stalk of a GB lesion due to the low resolution of trans-abdominal US. CEUS is able to overcome such disadvantages of standard US. The enhancing gallbladder wall and stalk of polyps were better visualized during the arterial phase because the cystic artery and gallbladder wall enhance earlier than the adjacent liver parenchyma [26]. In our study, the stalk width of cholesterol polyps was significantly smaller than that of adenomas. Indeed, the stalk width served as an independent indicator of the presence of GB adenoma. Some previous studies reported that stalk width was one of important risk factors to predict the malignancy of GPL [2, 30], but few studies reported stalk width difference between cholesterol polyps and adenomas by CEUS as we did in this study.

The gallbladder wall consists of a mucosa, lamina propria, thin muscular layer, perimuscular connective tissue, and a serosa [31].On gray-scale ultrasound imaging, it is not always possible to identify individual GB wall layers due to the low resolution of transabdominal ultrasound. However, on CEUS image, the normal GB structure displayed as homogeneous enhancement line and the thickness was not larger than 3–4 mm. In this study, all lesions identified demonstrated an intact GB wall and GB wall destructed could not be detected. Therefore, wall integrity was not a discriminator for adenoma or cholesterol polyp. Several previous studies have reported that wall integrity serves as a risk factor for gallbladder cancer [32, 33] but these studies do not report on the relationship between GB wall integrity and the presence of adenoma or cholesterol polyp.

Generally, contrast-enhanced ultrasound provides the advantages of real-time, repeatable, multiplanar imaging without compromising patient safety, or exposing the patient to radiation. CEUS could help to detect vessel type, GPL stalk, enhancement intensity, and GB wall integrity. However, there were limitations in our study. Firstly, the number of adenomas <10 mm was lacking, so the CEUS features of these adenomas are needed in future study. Secondly, the contrast agent harmonic signals were affected due to the existence of harmonic signal from tissue, which could cause the decrease of the signal-to-noise ratio, so the depicting of CEUS features would be affected. But in our study, the image interpreters have at least 5 years experience of viewing CEUS images and they were shown 10 similar examples of CEUS still images to establish a standardized approach before interpretation. Meanwhile, the same US equipment and the scanner were employed in our study. All of these would be help to decrease the side effect due to the low quality of CEUS images.

Conclusions

CEUS could offer useful information to distinguish adenoma from cholesterol polyp. The vascularity, enhancement intensity, and stalk width were independent risk factors associated with GB adenoma. However, lesion size and vessels type on CEUS were not risk factors for predicting adenoma. The treatment algorithm for GPL would likely benefit from CEUS as a routine imaging investigation, especially in cases where the polyp is larger than 1 cm. Considering there were overlaps of CEUS features between cholesterol polyp and GB adenoma, we suggested that the patients with cholesterol polyps diagnosed by CEUS would have ultrasound follow-up every 6 months.

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