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Liver elasticity assessment after biliary drainage in patients with extrahepatic cholestasis by shear wave sono-elastography (SWE)

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Abstract

Background: Extrahepatic cholestasis that is caused by benign and malignant diseases has been reported to influence liver elasticity, independent of liver fibrosis. Shear wave sono-elastography is a novel noninvasive ultrasound-based tool to assess liver stiffness that is indirectly measured by the propagation velocity of ultrasound waves within the liver parenchyma. The aim of our study is to explore the impact of extrahepatic cholestasis on liver elasticity assessed by sono-elastography.

Methods: This is the prospective cohort study of 80 patients with obstructive jaundice. Liver elasticity was measured before biliary drainage (day 0), with measures repeated 2 days (day 2) and seven days (day 7) after biliary drainage. Then, correlation with serum bilirubin and serum liver enzymes values was done.

Results: The studied patients with extrahepatic cholestasis (38 males and 42 females with mean age ± SD of 45.8 ± 14.6 years) referred to our department for biliary drainage. All underwent liver elasticity measurement by real-time shear wave sono-elastography before biliary drainage with the highest value of mean elasticity (± SD) 8.44 kPa (± 3.02) and then repeated on day 2 with mean elasticity 6.82 kPa (± 2.77), followed by maximum improvement of liver stiffness on day 7 with mean elasticity 4.8 kPa (± 1.80), coincided with improvement of cholestatic laboratory levels.

Conclusions: This study confirmed improvement of liver stiffness, measured by sono-elastography, after biliary drainage in patients with extrahepatic biliary obstruction.

Keywords: Biliary drainage, Extrahepatic cholestasis, Liver elasticity, Shear wave sono-elastography

Background

Extrahepatic cholestasis has been known to be caused by various pancreaticobiliary diseases. Several studies [1–4] have reported that biliary obstruction causes cholestatic injury to the liver cells with cellular apoptosis and necrosis. As well, cholestasis has been reported to be closely associated with changes in liver elasticity, independent of liver fibrosis.

Liver biopsy is the criterion standard for evaluating and grading liver stiffness. However, as an invasive procedure, it associated with a variety of complications [5, 6]. Given this situation, a noninvasive method has rapidly emerged as alternative to liver biopsy, such as ultrasound-based elastography to monitor disease progression [7].

Ultrasound elastography is an easy imaging modality, allowing quantitative assessment of tissue stiffness. Shear wave sono-elastography (SWE) is widely used to estimate liver stiffness currently, allowing detailed monitoring of

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the liver elasticity by measuring the shear wave velocity in an area of liver parenchyma [8–10].

Two-dimensional shear wave sono-elastography is a real-time technique using the grayscale imaging mode for assessing morphologic hepatic changes and avoiding vessels within the examining area. It evaluates the liver elasticity at least one hundred times the proportion of the liver that a biopsy does [11–13].

The aim of our prospective study was to evaluate the changes in liver elasticity, before and after biliary drainage, in patients with extrahepatic biliary obstruction using 2D-SWE in relation to serum cholestasis markers.

Methods

Patients selection

In this prospective cohort study, after obtaining the approval of local ethics committee, we evaluated patients diagnosed as obstructive jaundice by ultrasound elastography to assess the liver stiffness, referred to the diagnostic and interventional radiology department in the National Liver Institute between April 2019 and September 2020 for biliary drainage. Written informed consent was obtained from all patients.

The selected patients with confirmed diagnosis of biliary obstruction based on imaging examination, total serum bilirubin level >2 mg/dl and clinical indications for biliary drainage. We excluded patients with liver cirrhosis, liver tumors, marked ascites, comatosed patients and contraindications to biliary drainage as bleeding disorders. All patients were subjected to routine history taking, physical examination, imaging assessment, laboratory investigations including liver biochemical tests (total bilirubin, direct bilirubin, SGOT, SGPT, GGT and ALK) and renal function tests (serum creatinine and urea).

Sono-elastography technique

The examination was performed using Philips Healthcare ultrasound (Bothell, WA; ElastPQ, software version 6.3.2.2) with the C5-1 curvilinear probe.

The patients were in fasting condition and examined in a supine or slight (30-degree) left lateral decubitus position with the right arm elevated to make the intercostal space wider and were asked to suspend their breath in intermediate expiration for 5–10 s during each measurement. Optimize the B-mode image for the best acoustic window to provide the best results.

All liver elasticity measurements were obtained from the right lobe with an intercostal approach, by using point shear wave elastography with acoustic radiation force impulse (ARFI) technology. The transducer was perpendicular on the liver capsule and the ROI placed in the right hepatic lobe at a depth of minimum 1 cm below the liver capsule, best at 4–5 cm from the transducer. A ROI of 0.5 × 1 cm was used. Shear wave velocity (SWV) was measured in a pre-defined ROI while performing B-mode ultrasonography.

Data interpretation

Multiple measurements of liver elasticity were obtained in the same location by a consultant radiologist with 5 years of experience. The mean of ten valid acquisitions was considered representative for liver stiffness measurement and expressed in kilopascals (kPa). Liver elasticity values in healthy people have been reported to be less than 4.5 kPa (1.22 m/s). During examination, the stiffer the tissue was recorded with the higher the shear wave velocity.

Liver elasticity was assessed before biliary drainage (day 0), with measures repeated after 2 days (day 2) and 7 days (day 7) following successful biliary drainage. The results were recorded and considered to be reliable when there was a significant decrease in liver stiffness after biliary drainage.

The following serum markers: total bilirubin, direct bilirubin, SGOT, SGPT, ALK phosphatase and GGT, were estimated before biliary drainage and repeated on day 2 and day 7 post-biliary drainage. Then, the laboratory data were recorded to be correlated with the elastographic data.

Statistical analysis

Data were collected and tabulated using SPSS (Statistical Package for Social Science, version 26; Inc., Chicago. IL), employing descriptive statistics (quantitative data were shown as mean, SD and range; qualitative data were expressed as frequency and percent) and analytical statistics (chi-square test, Student's t test, ANOVA test). P value was considered statistically significant when it is less than 0.05.

Results

Study population

Eighty patients (38 males, 47.5% and 42 females, 52.5%) with extrahepatic cholestasis and meeting the clinical criteria for biliary drainage were enrolled into this study. Mean (± SD) age was 45.8 (± 14.6) years.

Within our patients, 46 out of 80 (57.5%) had malignant biliary obstruction, while 34 (42.5%) had non-malignant biliary obstruction. Biliary drainage in our patients was done as following 44 patients (55%) underwent endoscopic retrograde cholangiopancreatography (ERCP), 22 (27.5%) underwent external percutaneous transhepatic biliary drainage (PTBD), and 14 (17.5%) underwent internal PTBD. Table 1 summarizes the demographics and etiology of biliary obstruction in our studied patients.

Table 1 Patient demographics and clinical characteristics

Parameters	No (%)
Age	
Mean ± SD	45.8 ± 14.6
Median (IQR)	45.0 (22)
Min–max	14–70
Gender	
Male	38 (47.5)
Female	42 (52.5)
Nature of obstructive jaundice	
Non-malignant	34 (42.5)
Malignant	46 (57.5)
Causes of biliary obstruction	
Ampullary mass	6 (7.50)
Choledocholithiasis	30 (37.5)
Duodenal mass	4 (5.0)
Gastric carcinoma	2 (2.5)
Lymphoma	2 (2.5)
Multiple porta hepatis lymph nodes	4 (5.0)
Pancreatic carcinoma	28 (35.0)
Post-operative CBD stricture	2 (2.5)
Post-traumatic biliary stricture	2 (2.5)
Type of biliary drainage	
External PTBD	22 (27.5)
Internal PTBD	14 (17.5)
ERCP	44 (55.0)

Changes in liver stiffness and serum cholestasis markers

The liver elasticity values measured by SWE significantly reduced after biliary drainage (Fig. 1) together with cholestatic laboratory markers (Table 2). *Before biliary drainage*, the mean of liver stiffness was 8.44 kPa, mean of total bilirubin was 12.01 Mg/dl and direct bilirubin was 7.79 Mg/dl that significantly decreased on day 7 after drainage as follows: hepatic stiffness (4.8 kPa), T-Bil (3.09 Mg/dl) and D-Bil (1.81 Mg/dl) with p values of < 0.001.

Concerning the hepatic enzymes (SGPT, SGOT), our study showed improvement of liver enzymes accompanying post-drainage decrease in liver elasticity. The mean of SGPT and SGOT levels diminished from 235.03, 167.73 U/L before biliary drainage to 116.3, 90.64 U/L, respectively. Also, we measured ALK and GGT that essentially improved at the follow-up assessment compared to standard level before biliary drainage (Fig. 2).

Over follow-up, there was a decrease in the percentage of our patients who had moderate and severe liver stiffness on day 7 after biliary drainage from that before drainage as shown in Table 3.

Discussion

The main message of this study is that liver elasticity assessed by sono-elastography is significantly elevated in patients with extrahepatic cholestasis with a considerable increase in SWV values. We show that in the studied group as with effective biliary drainage, even after a short time interval of 7 days, the high liver elasticity declines predominantly (Figs. 3, 4, 5). These agreed with several studies as Pfeifer et al. [1], Yashima et al. [3], and Uzunkaya et al. [14] that observed similar findings on liver elasticity measurements by sono-elastography.

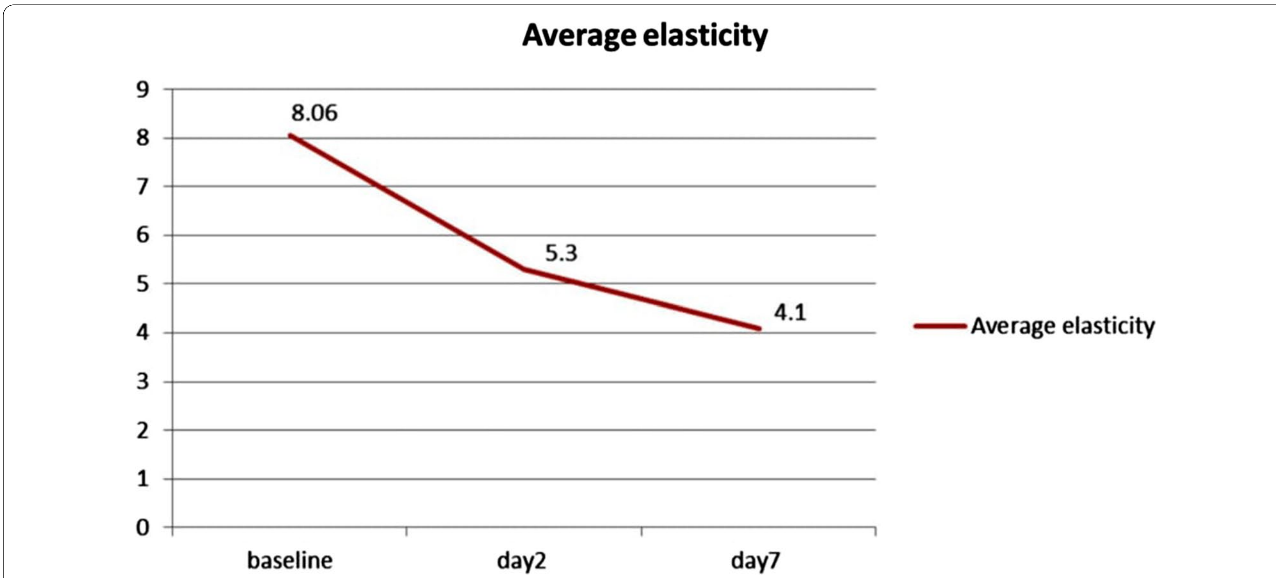

Fig. 1 Changes in the average liver elasticity over baseline (day 0), (day 2) and (day 7)

Table 2 Changes in laboratory data, measured before and after biliary drainage

Studied variable	Baseline (before)	Day 2 (after)	Day 7 (after)	*p* value (Friedman test)
Total bilirubin (Mg/dl)				< 0.001*
Mean ± SD	12.01 ± 5.94	7.26 ± 4.10	3.09 ± 1.47	
Median (IQR)	12.0 (10.8)	6.70 (6.7)	3.0 (2.2)	
Min–max	2.8–23.0	1.6 –16.5	0.8–7.90	
Direct bilirubin (Mg/dl)				< 0.001*
Mean ± SD	7.79 ± 4.43	5.74 ± 3.8	1.81 ± 1.17	
Median (IQR)	8.0 (7.02)	5.0 (5.07)	1.9 (1.5)	
Min–max	1.5–19.0	0.40–15.0	0.20–6.0	
SGOT (U/L)				< 0.001
Mean ± SD	167.73 ± 106.7	131.90 ± 3.75	90.64 ± 4.08	
Median (IQR)	144.5 (136.0)	27.0 (95)	56.0 (79)	
Min–max	45–440	44–390	28–365	
SGPT(U/L)				< 0.001
Mean ± SD	235.03 ± 145.6	159.6 ± 124.2	116.3 ± 1.3	
Median (IQR)	204.5 (212)	115.0 (172)	99 (122)	
Min–max	44–814	44–740	13–544	
ALK (IU/L)				< 0.001
Mean ± SD	447.8 ± 298.5	250.8 ± 198.7	212.6 ± 62.2	
Median (IQR)	355.0 (324)	199.5 (205)	172.0 (119)	
Min–max	166–1626	44–1027	64–821	
GGT(U/L)				< 0.001
Mean±SD	353.5 ± 201.14	302.7 ± 212.7	167.56 ± 01.28	
Median (IQR)	321.0 (170)	255.50 (162)	155.0 (113)	
Min–max	74–972	65–1027	45–545	

*Repeated measure ANOVA test

Our study excluded patients with chronic liver cirrhosis, liver tumors and ascites because these could also affect liver elasticity. Additionally, we measured liver elasticity within a very short time interval following biliary drainage (i.e., day 2 and day 7) to avoid bias of longer or differing experimental period on the estimated values. This is similar to study reported by Kubo et al. [15]; however, the previous research selected a smaller sample of twenty patients with only malignant biliary obstruction and having the clinical criteria for biliary drainage.

Concerning the hepatic enzymes (SGPT, SGOT) as well as GGT and ALK phosphatase, our study showed laboratory improvement with decreased liver elasticity after biliary drainage. However, studies performed by Darweesh et al. [16] that included patients with benign and malignant extrahepatic biliary obstruction and by Trifan et al. [17] that included patients with choledocholithiasis observed that successful biliary drainage led to a significant decline in liver stiffness, which positively correlated with bilirubin and negatively correlated with SGPT and GGT levels.

Increased liver elasticity in patients with extrahepatic biliary obstruction is not because of liver fibrosis, but due to temporarily incrased liver stiffness, especially in early stage of obstruction. Harata et al. [18] revealed that elevated liver elasticity in extrahepatic cholestasis was probably contributed to elevated hydrostatic pressure within the liver parenchyma. Also, Millonig et al. [4] demonstrated that experimental bile duct ligation in pigs for 120 min is associated with remarkable rise in liver elasticity measurements with drop rapidly within 30 min after free bile flow.

There are several limitations to our study. First, this was a single-center research, in which there was some bias in-patient selection and liver elasticity measurements

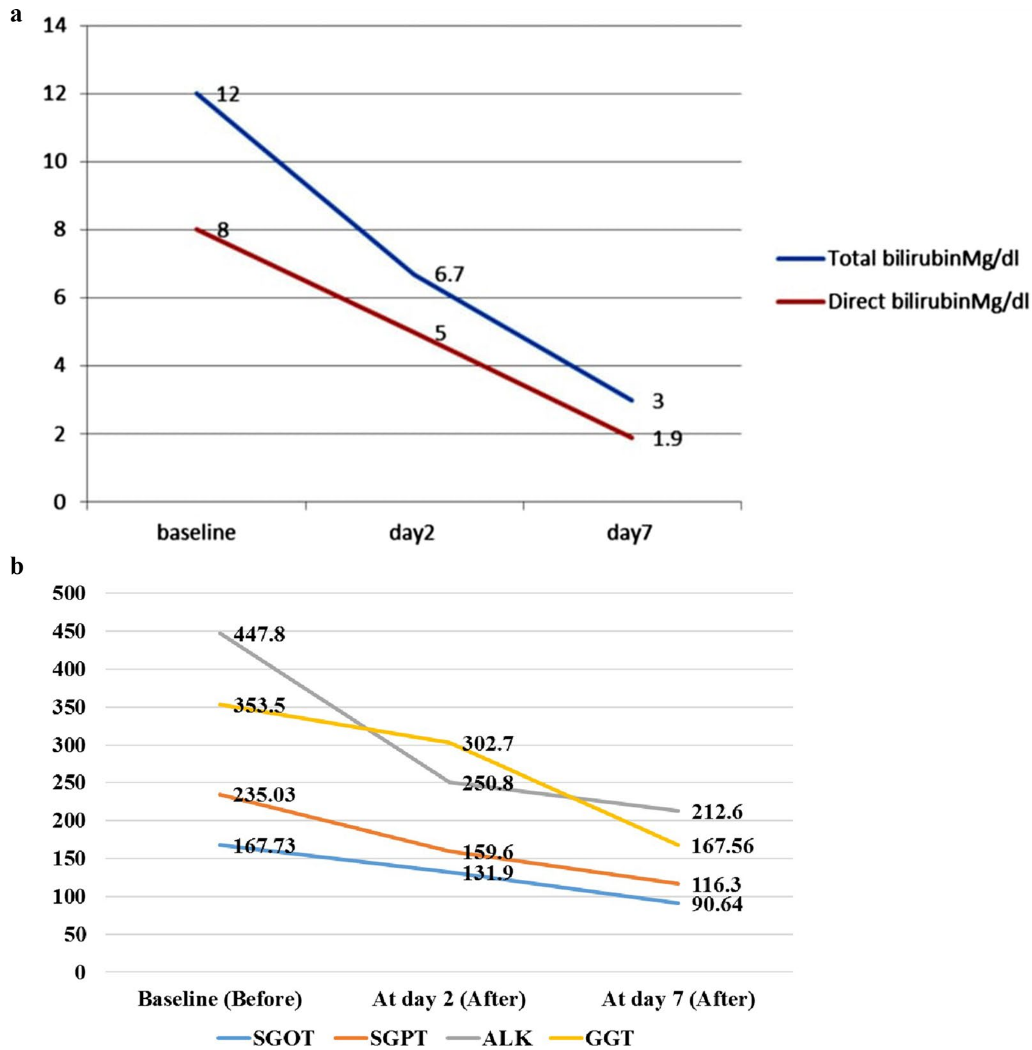

Fig. 2 Changes in the laboratory data over baseline (day 0), (day 2) and (day 7), including **a** bilirubin levels and **b** liver enzymes (SGOT, SGPT) as well as ALK and GGT

were obtained by a non-blinded manipulator. Second, the small sample size may restrain the detection of a higher correlation between liver elasticity values and different laboratory markers. Furthermore, due to its obstacles, liver biopsy was not achieved to exclude secondary hepatic cirrhosis with biliary obstruction. Finally, in our study, correlation between liver elasticity and hepatic functional reserve, which assessed by 99mTc-GSA scintigraphy, was not obtained. So, we recommend that the use of a large cohort survey with hepatic functional reserve correlation should be obtained in the future for superior outcome.

Conclusions

The liver elasticity measurement taken by SWE is an effective noninvasive real-time approach for predicting the changes in liver parenchyma. During research, we observed that liver elasticity is elevated in patients with extrahepatic cholestasis with diminished values after biliary drainage, implying that high liver stiffness values before biliary drainage are not attributable to liver fibrosis or cirrhosis, but to temporarily increased liver elasticity itself. So, our study emphasizes that it is crucial to exclude profound cholestasis when evaluating patients with SWE for liver fibrosis/cirrhosis.

Table 3 Liver elasticity changes, measured before and after biliary drainage

Liver elasticity	Baseline		At day 2		At day 7		p value (Friedman test)
Average elasticity							< 0.001
Mean ± SD	8.44 ± 3.02		6.82 ± 2.77		4.80 ± 1.80		
Median (IQR)	8.06 (4.73)		5.30 (4.40)		4.10 (2.0)		
Min–max	3.7–15.7		3.0–14.2		2.2–9.0		
Median elasticity							< 0.001
Mean ± SD	7.83 ± 2.74		6.56 ± 2.66		4.62 ± 1.78		
Median (IQR)	7.60 (4.30)		5.0 (4.70)		4.20 (2.30)		
Min–max	3.2–15.0		3.2–14.0		2.0–8.6		
	No	**(%)**	**No**	**(%)**	**No**	**(%)**	***p* value (Friedman test)**
Staging of liver stiffness							< 0.0001*
Normal	4	5.0	18	22.5	50	62.5	
Normal-mild	10	12.5	28	35.0	14	17.5	
Mild-moderate	52	65.0	32	40.0	16	20.0	
Moderate-severe	14	17.5	2	2.5	0	0.0	

*Maxwell test

Fig. 3 A 34-year-old female patient with calcular biliary obstruction. **a** Ultrasound shows CBD stone. **b** Insertion of plastic stent (arrow) post-clearance of CBD stone by ERCP

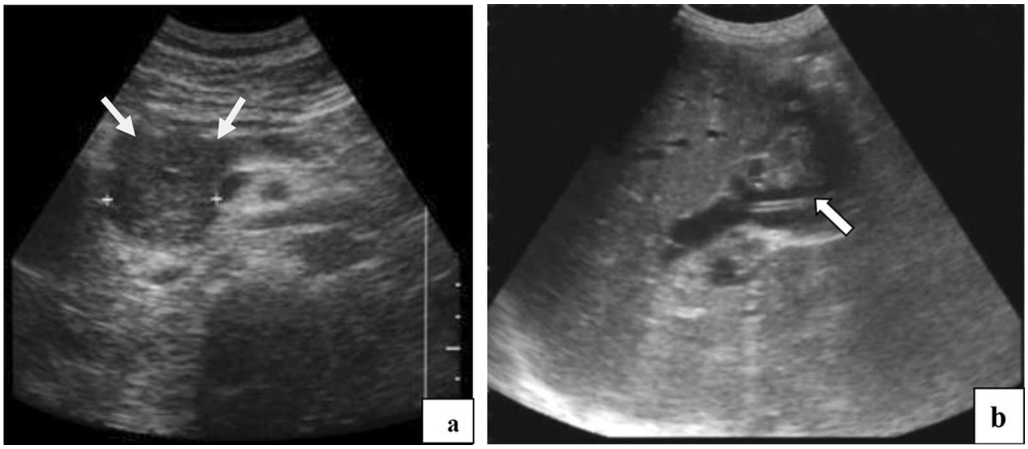

Fig. 4 A 65-year-old male patient with malignant biliary obstruction due to pancreatic neoplasm. **a** Ultrasound shows hypoechoic pancreatic head mass (arrows). **b** Ultrasound shows CBD stent placement (arrow) by ERCP

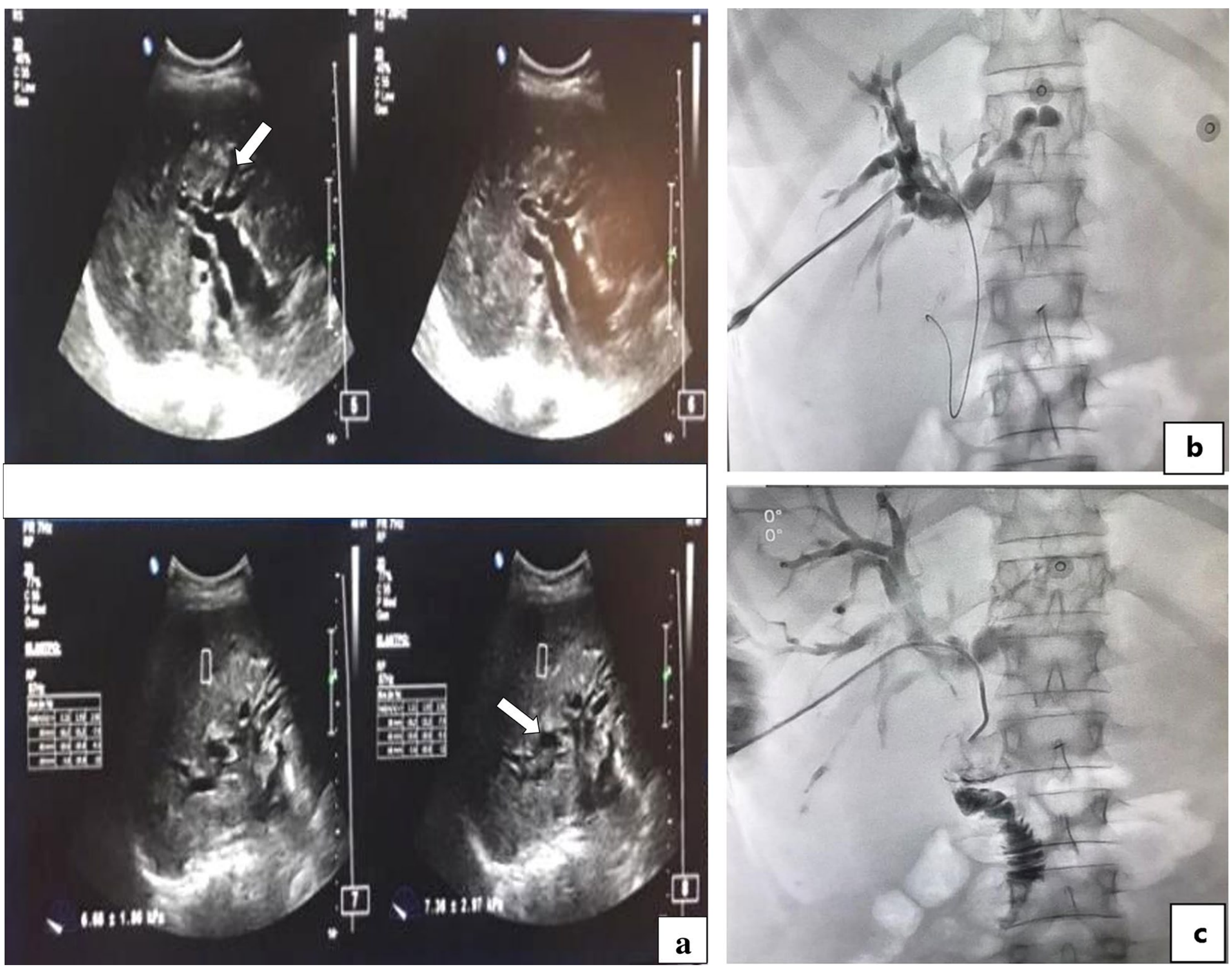

Fig. 5 A 40-year-old female patient with obstructive jaundice due to duodenal mass. **a** Shear wave elastography imaging before biliary drainage with moderate intrahepatic biliary radicles dilatation (IHBRD) (arrows). **b** Percutaneous transhepatic biliary cholangiogram shows biliary radicles dilatation. **c** Cholangiogram shows position of internal–external biliary catheter drainage

Abbreviations
ALK: Alkaline phosphatase; ARFI: Acoustic radiation force impulse; D-BIL: Direct bilirubin; T-BIL: Total bilirubin; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; GB: Gallbladder; GGT: Gamma-glutamyl transferase; kPa: Kilopascal; IHBRD: Intrahepatic biliary radicles dilatation; PTBD: Percutaneous transhepatic biliary drainage; ROI: Region of interest; SD: Standard deviation; SWE: Shear wave elastography; SWV: Shear wave velocity; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; US: Ultrasound; 99mTc-GSA: Technetium-99m galactosyl human serum albumin.

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Author contributions
RAA wrote the research, reported the radiological data and prepared the figures for case demonstration. RFF collected the patients, gathered the data and shared in the writing and follow-up of cases. MSA put the idea of the research and reviewed the research. EMK reviewed the research. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional Review Board (IRB) of National Liver Institute Menoufia University and with the Helsinki Declaration of 1964 and later versions. Committee's reference number is unavailable (NOT applicable). A written informed consent was obtained from the patient.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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