SUPPLEMENT

Outline

1. Full search term

2. Literature database

2.1 Research Paper Dataset Summary (Quality Assessment included)

Microlithiasis Legend (Research Paper):

a. Crystal-based
b. Small stones
c. Hyperechoic signal (no acoustic shadowing)
Hyperechoic signal (with or without acoustic shadowing)
Hyperechoic shape (with or without acoustic shadow)
Hyperechoic specks of calcification (with or without posterior acoustic shadowing)
Hyperechoic focus (with or without acoustic shadow)
Hyperechoic circumscript bile duct content (with or without acoustic shadowing)
Hyperechoic spots
Echogenic images (mobile, non-shadowing)
Echogenic material (without acoustic shadowing)

Biliary Sludge Legend (Review + Research Articles)

a. Fluid substance / Fluid-fluid interface / Fluid-fluid level / Calculi / Sediment / Cholesterol monohydrate crystals mixed with bilirubin granules / Calcium bilirubinate granules or cholesterol crystals / Suspension of crystals (usually cholesterol monohydrate) / Multiple nonshadowing calculi, pus, cholesterol crystals / Filling defects or obstruction of the bile ducts with a pluglike appearance / Filing defect in cholangiogram / Non-movable mass-like lesion + absence of internal vascularity / A mixture of particulate matter and bile that occurs when various solutes in bile precipitate / Viscous precipitate containing mucin, cholesterol and calcium bilirubinate

b. Layers in the dependent portion of the gallbladder

c. Low amplitude echoes (No acoustic shadowing/with or without shadowing)

d. Hyperechoic mobile images (no acoustic shadowing) / Hyperechoic specks of calcification
Hyperechoic aggregates / Slightly hyperechoic material
Higher echo levels lesions / Echogenic Lesion / Echogenic foci / Echogenic material
Isoechoic shadow / Presence of echoes in gallbladder (no acoustic shadowing)
Echogenic,mobile debris / Echogenic material inside the gallbladder / Echogenic or flecks of brightly echogenic material / Mobile echoes /Echogenic material / Homogeneous echoes or heterogeneous echoes

e. Size (Yes/No)

2 to 5 mm
< 2 mm

f. Localisation mentioned? Yes/No / Localisation: GB / Localisation: GB + CBD / Localisation: CBD / Localisation: NM

Study	Study type / Population	Date	Total number of patients	Age (mean/ range or SD)	Sex (female)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)	Treatment
1. Allen et al., Am J Surg. 1981	Study type: Prospective Population: Clinical findings and sonograms of all patients in whom sludge was found on routine abdominal sonography a	1977 - 1979	97	NM	NM	97	0	0	US, Bile microscopy	NM	NM	NM	a.Fluid substance b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes f. Localisation: GB	NM
2. Lee et al., Gastroenterology. 1986	Study type: Prospective Population: Upper abdominal pain + abdominal ultrasound + Sludge	1979 - 1982	121	NM	NM	121	0	0	US, Bile microscopy CHE	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	NM
3. Lee et al., Gastroenterology. 1988	Study type: Prospective Population: Sludge + other biliary and pancreatic abnormalities were absent on ultrasound examination	1979 - 1984	96	NM	NM	96	0	0	US, Bile microscopy	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	CHE (6 patients with sludge associated with severe biliary pain)
4. Ohara et al., J Clin Gastroenterol. 1990	Study type: Retrospective Population: Retrospective review of patients with ultrasonographic diagnosis of biliary tract sludge	1979 - 1985	87	NM	NM	87	0	0	US	Bilirubin, AP, AST,	NM	NM	a.Biliary contents b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	CHE (7 patients with sludge)
5. Ros et al., Gastroenterology. 1991	Study type: Prospective Population: 64 consecutive patients convalescing from a recent episode of acute pancreatitis of unknown cause	1979 - 1989	64	62 (18 - 88)	5	10	0	16	US, Bile microscopy, CHE	GGTP, ALT	a.Crystal-based	NM	d.Hyperechoic mobile images (no acoustic shadowing) f. Localisation: NM	CHE, UDCA (for CMC/CBG patients)
6. Buscail et al., Dig Dis Sci. 1992	Study type: Prospective Population: 50 patients with proven stones (Group 1) + 22 patients with suspected microlithiasis (Group 2)	1987 - 1988	72	66	35	0	7	0	US, Bile microscopy, ERCP	AST, ALT, AP, Bilirubin, GGTP	NM	< 3	NM	NM
7. Delchier et al., Hepatology 1986	Study type: Prospective Population; Microscopic bile examination in patients free of stones (Group 1), with proven stones (Group 2) and suspected stones (Group 3)	1985***	79	44	32	7	10	16	US, Bile micro-scopy, Other	AP, ALT	NM	<3	d.Presence of echoes in gallbladder (no acoustic shadowing) f. Localisation: GB	CHE (9 patients of group 3)
8. Lee et al., New England Journal of Medicine 1992	Study type: Prospective Population: Patients with acute idiopathic pancreatitis	1980 - 1988	86	64 (29 – 83)	47	23	0	0	US, Bile microscopy,	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) d.Mobile echoes f. Localisation: GB	CHE, ERCP
9. Murray et al., Gut 1992	Study type: Prospective Population: Incidence of biiary sludge in a prospective study of 36 patients admitted to the intensive care unit for longer than two days.	1991***	36	47 (17 – 80)	10	17	0	0	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) d.. Echogenic material f. Localisation: GB	NM

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10. Maringhini et al., Ann Intern Med. 1993	Study type: Prospective Population: To evaluate the incidence and symptoms of and risk factors for biliary sludge and gallstones during pregnancy	1986 - 1988	272	27	272	42	0	213	US	NM	NM	NM	c.Low amplitude echoes (no acoustic shadowing) d. Homogeneous echoes or heterogeneous echoes e. Size: 2 to 5 mm f. Localisation: NM	NM
11. Toursarkissian et al., South Med J 1995	Study type: Prospective Population: Biliary sludging in critically ill trauma patients	1995***	19	42 (16 – 69)	10	14/19	0	0	US	AST, ALT, AP, Bilirubin,	NM	NM	a.Cholesterol mono-hydrate crystals mixed with bilirubin granules b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: NM	NM
12. Barton et al., AJR Am J Roentgenol 1995	Study type: Retrospective Population: The purpose of this study was to review the imaging findings of biliary sludge occurring after liver transplantation and to determine the relative merits of various imaging procedures (cholangiography, CT, and sonography) for establishing the diagnosis.	1995***	352 patients (400 transplanted livers)	47 (1 – 68)	148	51/400 (transplanted livers)	0	0	US, CT, Other	NM	NM	NM	a. Filling defects or obstruction of the bile ducts with a pluglike appearance seen on cholangiograms or material confined to the lumen of the bile ducts seen on sonograms or CT scans. f.Localisation: CBD	NM
13. Barton et al., AJR Am J Roentgenol 1995	Study type: Retrospective Population: Outcome of several forms of treatment for biliary sludge occurring after liver transplantation	1995***	47	28 (4 – 68)	19	51/400	0	0	Other	NM	NM	NM	a. Filling defects or obstruction of the bile ducts with a pluglike appearance seen on cholangiograms or material confined to the lumen of the bile ducts seen on sonograms or CT scans. f. Localisation: CBD	Other
14. Dill et al., Endoscopy 1995	Study type: Prospective Population: Use of combined EUS + stimulated biliary drainage in the diagnosis of cholecystitis and microlithiasis	1995***	66	NM (Reference to earlier publication)	NM (Reference to earlier publication)	58/66 (biliary sludge or small stones)	58/66 (biliary sludge or small stones)	10 (Patients with biliary pain + possibly sludge evidence but without surgery)	Bile microscopy, EUS	NM	No specific distinction between microlithiasis and sludge (see sludge definition)	NM	a.Biliary Drainage was considered positive if calcium bilirubinate granules or cholesterol crystals were noted microscopically. f.Localisation: GB + CBD	CHE
15. Marotta et al., Can J Gastroenterol	Study type: Retrospective Population: Ultrasound examinations of patients with idiopathic pancreatitis, patients with acute alcohol-associated pancreatitis and a control group were compared. Biliary sludge was found in seven of 21 patients (33%) with idiopathic pancreatitis	1989 - 1992	83 (+ 63 control without age, sex distribution)	53 (20 – 92)	42	10	0	63	US	AST, ALT, AP, Bilirubin, GGTP	NM	NM	a.Fluid-fluid interface b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	CHE
16. Tandon et al, Gut 1997	Study type: Prospective Population: To study prospectively the incidence of gallstones and gall bladder contractility in patients with spinal cord injury	1993 – 1994	73	31	18	14	0	36	US	AST, ALT, AP, Bilirubin, GGTP	NM	NM	b.Layers in the dependent portion of the gallbladder ("gravity dependent") c.Low amplitude echoes (no acoustic shadowing) d. Echogenic material inside the gallbladder f. Localisation: GB	NM

Study	Study type / Population	Date	Total number of patients	Age (mean/ range or SD)	Sex (female)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)	Treatment
17. Sharma et al., Gastroenterology 1997	Study type: Prospective Population; The aim of this study was to determine the abnormalities of gallbladder emptying and bile composition in patients with microlithiasis.	1998***	10	42	4	0	10	10	US, Bile microscopy	NM	a.Crystal-based b.Small stones	< 3	NM	UDCA
18. Grau et al., Int J Pancreatol. 1999	Study type: Retrospective Population: We assessed the diagnostic usefulness of alanine amino-transferase (ALT) and aspartate amino-transferase (AST) for identification of occult microlithiasis in idio-pathic acute pan-creatitis.	1989 - 1996	91	57	33	0	91	0	Bile microscopy, US	AST, ALT	a.Crystal-based	NM	NM	NM
19. Frossard et al., Am J Med. 2000	Study type: Prospective Population: The aim of this study was to evaluate the usefulness of endo-scopic ultra-sonography in the diagnosis of biliary tract pathology or chronic pancreatitis in these patient	1991 – 1995	168	50 (10 – 84)	66	12	NM *Gallstones not discriminated from microlithiasis	0	EUS	NM	c.Hyperechoic signal (no acoustic shadowing	0.5 – 2	c.Low amplitude echoes (no acoustic shadowing) d. Moving echoes f.Localisation: GB	NM
20. Materne et al., Endoscopy 2000	Study type: Prospective Population: The aim of this study was to compare prospectively the diagnostic efficacy of magnetic resonance (MR) imaging and endoscopic ultrasonography (EUS) in extrahepatic biliary obstruct	2000***	50	59 (16 – 90)	27	4	0	0	EUS, MRI	AP, Bilirubin, GGTP	NM	NM	c.Low amplitude echoes (no acoustic shadowing) e.Size: < 2 mm f. Localisation: CBD	ERCP
21. Petroni et al., Eur J Gastroenterol Hepatol 2000	Study type: Prospective Population: To assess risk factors for gallstone recurrence following non-surgical treatment	1987 – 1991	163	47 (18 – 79)	121	9	0	0	US, Other	NM	NM	NM	a.Fluid substance b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	Other
22. Méndez-Sánchez et al. J Nutr. 2001	Study type: Prospective Population: Fish oil (n-3) polyunsaturated fatty acids beneficially affect biliary cholesterol nucleation time in obese women losing weight	2001***	35	38	35	0	0	11	US	NM	NM	NM	a.fluid-fluid level c.Low amplitude echoes (no acoustic shadowing) f. Localisation: NM	UDCA PUFA
23. Tandon et al., Am J Gastro 2001	Study type: Retrospective Population: The aim of this study was to determine the utility of endoscopic ultrasound (EUS) in patients with unexplained acute pancreatitis, and whether endoscopic retrograde cholangio-pancreatography (ERCP) is subsequently needed	2001***	31	49 (19 – 87)	19	5* (no difference between sludge and microlithias is patients made)	5*	0	US, CT, ERCP, EUS, MRI + MRCP Bile microscopy, Other	NM	a.Crystal-based	NM	c.No acoustic shadowing d.Echogenic or flecks of brightly echogenic material f. Gallbladder + CBD	NM

Study	Study type / Population	Date	Total number of patients	Age (mean/ range or SD)	Sex (female)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)	Treatment
24. Kohut et al., World J Gastroenterol. 2002	Study type: Prospective Population: This prospective study was done to investigate the presence and density of CBDM in patients with ABP, when endoscopic retrograde chol-angiopancreatography (ERCP) was done in different periods from the onset of the disease	1993 – 1997	151	54	102	0	118	33	US, Bile microscopy CT, ERCP	AST, ALT, Bilirubin	a.Crystal-based	NM	NM	ERCP
25. Kubota et al., J Gastroenterol Hepatol. 2002	Study type: Prospective Population: We examined the role of biliary intraductal ultrasonography in detecting common bile duct stones that had been overlooked during endoscopic retrograde cholangio-pancreatography.	1997 – 2001	80	61 (30 – 89)	43	37 (only sludge)	NM (*not specified -> Stones < 5 mm)	0	US, ERCP, IDUS	AP, GGTP	NM	NM	c.Low amplitude echoes (no acoustic shadowing) f. Localisation: NM	ERCP
26. Calvo et al. J Clin Gastroenterol. 2002	Study type: Prospective Population: Magnetic resonance cholangiography versus ultrasound in the evaluation of the gallbladder	2002***	80	69	36	13 (sludge = microlithiasis)	13 (sludge = microlithiasis)	0	US, MRCP	NM	b.Small stones	<3	NM	CHE
27. Ierardi et al., Aliment Pharmacol Ther. 2003	Study type: Prospective Population: To verify the impact of second harmonic imaging compared with conventional ultrasonography on the detection of biliary sludge in patients with 'idiopathic' pancreatitis	2000 – 2001	50	51 (46 – 60)	36	41/50 diagnosed via bile microscopy	NM	0	US, Bile microscopy	NM	NM	NM	a.Multiple nonshadowing calculi, pus, cholesterol crystals c.No acoustic shadowing f.Localisation: NM	CHE
28. Rashdan et al., Gastrointest Endosc. 2003	Study type: Retrospective Population: This study examined the frequency at which biliary crystals are found in patients with suspected type II and type III sphincter of Oddi dysfunction	2003***	85	38	66	0	3	0	Bile mcroscopy, ERCP, Other	NM	a.Crystal-based	< 3	NM	ERCP
29. Ponce et al. Eur J Nucl Med Mol Imaging. 2004	Study type: Prospective Population: Quantitative cholescintigraphy and bile abnormalities in patients with acalculous biliary pain	2004***	92	47	83	0	32	NM	Bile microscopy	NM	b. Small stones	<3	NM	CHE
30. Saraswat et al., J Gastroenterol Hepatol. 2004	Study type: Prospective Population: Frequency of microlithiasis and response to treatment in recurrent idiopathic acute pancreatitis (RIAP) and unexplained biliary pain	2004***	70	35 (14 – 58)	42	NM	28	34	Bile microscopy	NM	a.Crystal-based b.Small stones	< 3	NM	ERCP, CHE, UDCA
31. Ko et al., Hepatology 2005	Study type: Prospective Population: This study pro-spectively evaluated the incidence and natural history of pre-gnancy-related gallbladder sludge and stones in the US	2005***	3254	NM	3254	48	NM	3206	US	NM	a.Crystal-based	< 2	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	CHE (postpartum)

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32. Mirbargheri et al., J Gastrointest Surg. 2005	Study type: Prospective Population: To investigate the role of endoscopic ultras-onography (EUS) in the diagnosis of microlithiasis in patients with upper abdominal pain and normal TUS	2001 – 2003	35	48 (+/- 13.1)	21	33 (Gallbladder sludge and/or microlithias)	33 (Gallbladder sludge and/or microlithias)	0	US, EUS	AP	c.Hyperechoic specks of calcification, with or without posterior acoustic shadowing	< 3	c.with or without posterior acoustic shadowing d.Hyperechoic specks of calcification, f. Gallbladder + Bile duct	ERCP, CHE
33. Rocca et al., Gastrointest Endosc. 2006	Study type: Prospective Population: This study evaluates a new approach in the management of common bile duct stones, by using an oblique-viewing echoendoscope.	2006***	19	62 (44 – 74)	12	12	0	0	US, EUS, MRCP, ERCP (+ EURCP)	AST, ALT, AP, GGTP	NM	NM	c/d..Hyperechoic aggregates (no acoustic shadowing) e.Size: < 2 mm f. Gallbladder + Bile duct	ERCP, Other
34. Bolukbas et al., J Gastroenterol Hepatol. 2006	Study type: Prospective Population: To define the risk factors in gallstone and sludge formation, and to investigate the incidence of gallstone and biliary sludge formation during pregnancy in a group of healthy pregnant women	2006***	97	25 (19 – 35)	97	7	0	28	US	NM	NM	NM	c.Low amplitude echoes f. Localisation: GB	NM
35. Garg et al., Clin Gastroenterol Hepatol. 2007	Study type: Prospective Population: The aim of the present study was to determine the cause of idiopathic RAP in a long-term follow-up study.	1995 – 2003	75	32 (14 – 67)	15	0	10	0	US, CT, EUS, Bile microscopy, ERCP	NM	a.Crystal-based	< 3	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	ERCP, CHE
36. Inoue et al., Ultrasound Med Biol. 2007	Study type: Prospective Population: We evaluated the usefulness of contrast-enhanced ultra-sonography(US) for detecting and differentiating gallbladder lesions.	2000 – 2005	90	67 (51 – 84)	35	42	0	0	CEUS	NM	NM	NM	b.Layers in the dependent portion of the gallbladder d.Echogenic Lesion f. Localisation: GB	CHE
37. Numata et al., J Ultrasound Med. 2007	Study type: Prospective Population: We evaluated the usefulness of contrast-enhanced harmonic gray scale ultra-sonographic findings for differential diagnosis of gall-bladder diseases.	2002 – 2006	33	62 (26 – 87)	13	12	0	0	CEUS, CT	NM	NM	NM	d. Higher echo levels lesions f. Localisation: GB	NM
38.Okoro et al. Gastrointest Endosc. 2008	Study type: RCT Population: To identify bile microlithiasis in patients with postcholecystectomy pain and to investigate the therapeutic effect of ursodeoxycholi	2001 - 2006	118	NM	10	0	12	6	Bile microscopy	NM	a.Crystal-based	NM	NM	UDCA
39. Bastouly et al., Obes Surg. 2009	Study type: Prospective Population: Early changes in postprandial gallbladder emptying in morbidly obese patients undergoing Roux-en-Y gastric bypass: correlation with the occurrence of biliary sludge and gallstones	2008***	20	39 (28 – 59)	16	13	0	0	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB + CBD	Other

Study	Study type / Population	Date	Total number of patients	Age (mean/ range or SD)	Sex (female)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)	Treatment
40. Kim et al., Dig Dis Sci. 2010	Study type: Prospective Population: We compared the echogenicity seen on IDUS and the findings of bile microscopy (BM) of bile that was collected in the common bile duct (CBD) to determine whether the echogenicity seen on IDUS is real microlithiasis.	2006 – 2007	30	43 (21 – 77)	15	7	14	0	IDUS, ERCP, Bile microscopy	AST, ALT, Bilirubin AP	b.Small stones	< 3	NM	ERCP
41. Elmi et al., Dig Dis Sci. 2010	Study type: Retrospective Population: Biliary sphincter of Oddi dysfunction type I versus occult biliary microlithiasis in post-cholecystectomy patients: are they both part of the same clinical entity?	1997 – 2006	17	51 (+/- 17)	16	0	9	0	ERCP, Other	AST, ALT, Bilirubin AP	b.Small stones	< 3	NM	ERCP
42. Mesotten et al., J Clin Endocrinol Metab. 2009	Study type: Prospective Population: We examined liver dysfunction and biliary sludge prospectively in a large medical long-stay ICU population and hypothesized that tight glycemic control with intensive insulin therapy (IIT) reduces cholestasis and biliary sludge.	2009***	658	63	255	250	0	323	US	AST, ALT, AP, Bilirubin, GGTP	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB	Other
43. Baltas et al., Singapore Med J. 2009	Study type: Prospective Population: Gallstones and biliary sludge in Greek patients with complete high spinal cord injury: an ultra-sonographical evaluation	2004 – 2007	156	35 (19 – 59)	40	15	0	78	US	NM	NM	NM	a.Fluid -fluid level with changes in the patient position b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB + CBD	NM
44. Vila et al., Scand J Gastroenterol. 2010	Study type: Prospective Population: To evaluate the diagnostic yield of endoscopic ultrasonography (EUS) in patients with idiopathic acute pancreatitis (IAP), find factors predictive of a positive EUS finding in these patients and investigate whether these etiological findings are maintained during follow-up.	2004 – 2007	44	61 (23 – 83)	13	1	22	0	EUS, MRCP, CT, Bile microscopy,	NM	a.Crystal-based c.Mobile, non-shadowing echogenic images	NM	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d.Echogenic material f.Localisation: GB + CBD	NM
45. Ardengh et al., Rev Assoc Med Bras (1992). 2010	Study type: Prospective Population: Our objective was to evaluate results from endoscopic ultrasonography (EUS) for diagnosis of gallbladder microlithiasis in patients with unexplained (idiopathic) acute pancreatitis.	2010***	36	47 (20 – 83)	21	0	29	0	EUS	NM	c. Hyperechoic signal with or without acoustic shadowing.	0.5 – 3	NM	ERCP, CHE
46. Ortega et al., Pancreas. 2011	Study type: Prospective Population: Prospective comparison of endoscopic ultra-sonography and MRCP in the etiological diagnosis of "idiopathic" acute pancreatitis	2005 – 2009	49	58 (+/- 17)	25	12 * Cholelithiasis/ biliary sludge	12 * Cholelithiasis/ biliary sludge	0	EUS, MRCP	NM	c. Hyperechoic shape with or without acoustic shadow	NM	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d.Slightly hyperechoic material f.Localisation: GB	ERCP, CHE

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47. Endo et al., Dig Endosc. 2011	Study type: Retrospective Population: The aim of the present study was to elucidate adequate indications for IDUS in cases that undergo endoscopic retrograde cholangio-pancreatography (ERCP) due to suspected bile duct stones	2005 – 2006	213	72 (30 – 94)	99	8	0	0	ERCP, IDUS	NM	NM	NM	c. No acoustic shadowing d.Echogenic foci f.Loacalisation: CBD	ERCP
48. Zhan et al., J Gastroenterol Hepatol. 2011	Study type: Retrospective Population: The aim of the present study was to evaluate the role of EUS in exploring the unknown etiology of mild acute biliary pancreatitis.	2006 – 2009	33	46 (+/- 21)	20	2	NM * stones between 2.2 mm to 5.2 mm in 11 cases	NM	US, EUS, CT, MRCP ERCP	NM	b.Small stones	< 3	d. Isoechoic shadow f. Localisation: NM	ERCP
49. Wang et al. Digestion. 2012	Study type: RCT Population: Effect of urso-deoxycholic acid administration after liver transplantation on serum liver tests and biliary complications	2005 - 2008	112	33	18	10	10	56	MRCP, ERCP	AST ALT AP, GGTP, Bilirubin	NM	NM	a.Filing defect in cholangiogram f. Localisation: NM	UDCA
50. Rana et al., Ann Gastroenterol. 2012	Study type: Retrospective Population: The aim of our study was to retrospectively report our experience with endoscopic ultrasound (EUS) in investigating patients with IAP.	2012*** (three year perod)	40	NM (17 – 72)	14	16	NM	0	US, CT, MRCP, ERCP EUS	AST, ALT, AP, Bilirubin, GGTP	NM	NM	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d.Echogenic material f.Localisation: GB	ERCP, CHE
51. Cheong et al., World J Gastrointest Endosc 2013	Study type: Retrospective Population: To evaluate the efficacy of endoscopic ultrasonography (EUS) in patients with elevated carbohydrate antigen (CA) 19-9 levels of obscure origin.	2007 – 2009	17	51 (28 – 85)	13	16	0	0	CT, EUS	NM	NM	NM	a.Suspension of crystals (usually cholesterol monohydrate) f.Localisation: GB + CBD	UDCA
52. Wong et al., J Clin Gastroenterol. 2013	Study type: Prospective Population: Carbohydrate intake as a risk factor for biliary sludge and stones during pregnancy	2013***	3070	NM	3070	160	0	NM	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB	NM
53. Mathew et al., JPEN J Parenter Enteral Nutr. 2015	Study type: Prospective Population: The aim of this study was to examine the effects of dietary fat and protein intake on incident gallstone disease during pregnancy, a high-risk time for stone formation.	2015***	3070	25 (+/- 4.9)	3070	314	0	0	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB	NM
54. Neri et al., Clin Med Insights Gastroenterol. 2014	Study type: Prospective Population: To define a therapeutic program for mild-moderate acute pancreatitis (AP), often recurrent, which at the end of the diagnostic process remains of undefined etiology	2011 – 2012	64	58 (34 – 83)	39	6	4	0	US, CT, EUS, MRCP,	AST, ALT, Bilirubin, GGTP	b.Small stones	< 3	a. Suspension of cholesterol crystals mixed with mucins and cell detritus f.Localisation: NM	ERCP, CHE

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55. Kim et al., Dig Dis Sci. 2014	Study type: Prospective Population: The aim of this study was to evaluate the accuracy of intraductal ultrasonography (IDUS) for detecting choledocholithiasis in icteric patients with highly suspected common bile duct (CBD) stones without definite stone diagnosis on ERCP.	2006 – 2011	95	55 (+/- 15.5)	44	24	NM	0	ERCP, IDUS	Bilirubin	NM	NM	c. No acoustic shadowing d. Echogenic material f.Localisation: CBD	ERCP
56. Choi et al., Ultrasonography. 2014	Study type: Retrospective Population: To validate the use of harmonic ultrasonography (US) in the detection of gallbladder Microlithiasis	2012 – 2014	55	53 (+/- 12.9)	23	NM	55	0	US	NM	a.Crytal-based b.Small stones	< 3	NM	NM
57. Anderloni et al., World J Gastroenterol. 2015	Study type: Prospective Population: To investigate the clinical usefulness of early endoscopic ultrasonography (EUS) in the management of acute biliary pancreatitis (ABP).	2010 – 2012	71	58 (27 – 89)	38	NM	NM	0	EUS, Other	AST, ALT, AP, Bilirubin, GGTP	NM	NM	c. No acoustic shadowing d.Hyperechoic focus f.Localisation: NM	ERCP
58. Räty et al., Ann Surg. 2015	Study type: RCT Population: The aim of the present trial was to ascertain whether laparoscopic cholecystectomy (LCC) can prevent recurrent attacks of idiopathic acute pancreatitis (IAP).	2009 – 2013	85	57 (17 – 84)	33	NM	NM	46	US, CT, MRCP, Bile microscopy	AST, ALT, AP, Bilirubin, GGTP	b.Small stones	< 3	NM	CHE
59. Hill et al., J Ultrasound Med. 2016	Study type: Retrospective Population: To determine its [sludge] natural history and potential future complications in this setting, we reviewed the imaging and clinical histories of nonhospitalized patients with a diagnosis of sludge on sonography	2011 – 2014	104	48 (13 – 87)	46	104	NM	0	US	AST, ALT	a.Crystal-based	NM	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d. Echogenic,mobile debris f.Localisation: GB	NM
60. Wilcox et al., Am J Gastroenterol. 2016	Study type: Prospective Population: We prospectively evaluated patients with idiopathic pancreatitis over a 10-year period, and clinical information for each episode was reviewed	2003 – 2013	201	53 (17 – 95)	106	NM	20	0	US, EUS, CT, MRCP, ERCP	AST, ALT, AP, Bilirubin, GGTP	b.Small stones c. Echogenic material without acoustic shadowing	< 3	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d.Bright echoes f.Localisation: NM	ERCP, CHE
61. Stevens et al., J Gastrointest Surg. 2016	Study type: Retrospective Population: The aim of this study was to examine the value of prophylactic cholecystectomy following an episode of acute pancreatitis in patients with no history of alcohol abuse and no stones found on ultrasound.	2005 – 2015	195	54 (15 – 93)	95	14	NM	0	US, MRCP	AST, ALT,	b. Small stones	< 3	a. Suspension of cholesterol mono-hydrate crystals or calcium bilirubinate granules f.Localisation: NM	CHE

Study	Study type / Population	Date	Total number of patients	Age (mean/ range or SD)	Sex (female)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)	Treatment
62. Kim et al., Radiology. 2017	Study type: Retrospective Population: To evaluate the prevalence of tumefactive sludge of the gallbladder detected at US and to assess whether any clinical and imaging differences exist between benign and malignant tumefactive sludge	2001 – 2015	107	60 (19 – 86)	48	107	NM	0	US	NM	c.Hyperechoic spots	NM	a.Non-movable mass-like lesion + absence of internal vascularity c. No acoustic shadowing f.Localisation: NM	NM
63. Su et al., Transplant Proc. 2018	Study type: Retrospective Population: We retrospectively investigated post-surgical donor gallbladder com-plications in clinical LDLT with gallbladder preservation	2013 – 2015	91	31 (20 – 49)	31	9	0	0	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB	NM
64. Serra et al., J Ultrasound. 2018	Study type: Retrospective Population: The primary objective of this study is to assess the reliability of CEUS in the diagnosis of sludge; the secondary objective is to assess the ability of CEUS to diagnose cancer.	2013 – 2015	43	54 (+/- 12)	26	16	0	23	US (CEUS)	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB	NM
65. Lopes et al., Clin Res Hepatol Gastroenterol 2019	Study type: Prospective Population: This study investigated the role of linear EUS for identification of possible causes for acute pancreatitis when other investigative methods failed	2012 – 2017	35	52 (+/- 17.8)	25	2	8	0	US, EUS	NM	b. Small stones (no acoustic shadowing)	< 5	b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing d. Suspension of echogenic material f.Localisation: GB + CBD	ERCP, CHE
66. Idowu et al. J Ultrason. 2019.	Study type: Cross-sectional Population: Gallbladder diseases in pregnancy: US findings in an indigenous African population	2015-2016	656	31	655/656	2	NM	No	US	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f. Localisation: GB	NM
67. Mitra et al., Indian J Gastroenterol. 2021	Study type: Prospective Population: IAP patients underwent MRCP and EUS at least 4 weeks after an attack of AP	2018 – 2019	31	41 (40 – 49)	17	9 * Gallbladder (GB) Micro-lithiasis/GB sludge/ chole-lithiasis	9 * Gallbladder (GB) Micro-lithiasis/GB sludge/ cholelithiasis	0	MRCP, EUS	NM	c. Hyperechoic focus with or without acoustic shadow	< 3	a./d. Suspension of crystals + Hyperechoic material + b.Layers in the dependent portion of the gallbladder c. No acoustic shadowing f.Localisation: GB	NM
68. Montenegro et al., Gastroenterol Hepatol. 2021	Study type: Retrospective Population: Evaluate the role of EUS in the diagnosis of minilithiasis/biliary sludge in patients with digestive symptoms of probable biliary origin by resolving the symptoms after CHE	2014 – 2018	50	49 (+/- 2.3)	41	50 *microlithiasis/ biliary sludge	50 *microlithiasis/ biliary sludge	0	US, EUS, CT, MRCP,	AST, ALT, AP, Bilirubin, GGTP	b.Small stones	< 3	a.Crystals, Isoechoic and/or hyperechoic focus c. No acoustic shadowing f.Localisation: GB + CBD	NM
69. Quispel et al., Endosc Int Open. 2021	Study type: Prospective Population: To establish the agreement among endosonographers regarding: 1. presence of common bile duct (CBD) stones, microlithiasis and sludge; and 2. the need for subsequent treatment	2021***	Video-fragements	NM	NM	NM	NM	NM	EUS	NM	c. Hyperechoic circumscript bile duct content,with or without acoustic shadowing	< 3	c. No acoustic shadowing d. Echoic, cloud shaped and mobile bile duct content f.Localisation: GB + CBD	ERCP

2.1.1 Overview of fulfilled inclusion criteria / study

Inclusion criteria met	Number of studies (Research Paper Dataset)
5/5	8/69 (11.6 %)
4/5	23/69 (33.3 %)
3/5	32/69 (46.3 %)
2/5	6/69 (8.7 %)

2.2 Review Paper Dataset Summary (No Quality Assessment)

Microlithiasis Legend (Review Paper):

a. Crystal-based

b. Small stones/calculi

c. Precipitates

Viscous precipitate containing mucin, cholesterol and calcium bilirubinate

d. Hyperecho spots with „comet sign"

Biliary Sludge Legend (Review + Research Articles)

a. Fluid substance / Fluid-fluid interface / Fluid-fluid level / Calculi / Sediment / Cholesterol monohydrate crystals mixed with bilirubin granules / Calcium bilirubinate granules or cholesterol crystals / Suspension of crystals (usually cholesterol monohydrate) / Multiple nonshadowing calculi, pus, cholesterol crystals / Filling defects or obstruction of the bile ducts with a pluglike appearance / Filing defect in cholangiogram / Non-movable mass-like lesion + absence of internal vascularity / A mixture of particulate matter and bile that occurs when various solutes in bile precipitate / Viscous precipitate containing mucin, cholesterol and calcium bilirubinate

b. Layers in the dependent portion of the gallbladder

c. Low amplitude echoes (No acoustic shadowing/with or without shadowing)

d. Hyperechoic mobile images (no acoustic shadowing) / Hyperechoic specks of calcification
Hyperechoic aggregates / Slightly hyperechoic material
Higher echo levels lesions / Echogenic Lesion / Echogenic foci / Echogenic material
Isoechoic shadow / Presence of echoes in gallbladder (no acoustic shadowing)
Echogenic,mobile debris / Echogenic material inside the gallbladder / Echogenic or flecks of brightly echogenic material / Mobile echoes /Echogenic material / Homogeneous echoes or heterogeneous echoes

e. Size (Yes/No)

2 to 5 mm
< 2 mm

f. Localisation mentioned? Yes/No
Localisation: GB / Localisation: GB + CBD / Localisation: CBD / Localisation: NM

Study	Study type / Topic	Year	Total number of patients	Age (mean/ range or SD)	Sex (f/m)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microliths (mm)	Sludge (Definition)
1. Angelico et al., J Clin Gastroenterol. 1990	Review Topic: Biliary Sludge – a critical update	1990	NM	NM	NM	NM	NM	NM	US, Bile microscopy	NM	NM	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB + CBD
2. Ko et al., Ann Intern Med 1999	Review Topic: This paper proposes a protocol for the microscopic diagnosis of sludge	1999	NM	NM	NM	NM	NM	NM	Bile microscopy US, EUS .	NM	NM	NM	a.A mixture of particulate matter and bile that occurs when various solutes in bile precipitate b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB + CBD
3. Shaffer et al., Dig Liver Dis. 2003	Review Topic: A calculous biliary pain: new concepts for an old entity	2003	NM	NM	NM	NM	NM	NM	US, EUS	NM	a.Crystal-based	< 3	NM
4. Ko et al. Best Pract Res Clin Gastroenterol. 2003	Review Topic: Gastrointestinal disorders of the critically ill. Biliary sludge and cholecystitis	2003	NM	NM	NM	NM	NM	NM	US	NM	c.Precipitates	NM	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) g.Localisation: GB + CBD
5. Jain et al., Curr Treat Options Gastroenterol. 2004	Review Topic: Biliary Sludge: When Should It Not be Ignored?	2004	NM	NM	NM	NM	NM	NM	US, EUS, Bile microscopy	NM	b.Small stones	< 3	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB + CBD
6. Wilcox et al., Gastrointest Endosc. 2006	Review Topic: Role of endoscopic evaluation in idiopathic pancreatitis	2006	NM	NM	NM	NM	NM	NM	US, EUS, ERCP	NM (*only in context of CBD stones)	b.Small stones	< 3	a. Suspension of crystals (usually cholesterol monohydrate), mucin, glycoproteins, cellular debris,and protein-aceous material within bile. f.Localisation: GB + CBD
7. Jüngst et al., Best Pract Res Clin Gastroenterol. 2006	Review Topic: Gallstone disease: Microlithiasis and Sludge	2006	NM	NM	NM	NM	NM	NM	US, EUS, Bile microscopy	NM	NM	NM	a. Suspension of precipitated 'particulate matter' in bile dispersed in a viscous, mucin-rich liquid phase f.Localisation: GB + CBD
8. Mbongo-Kama et al. Ann Hepatol. 2007	Review Topic: MDR3 mutations associated with intrahepatic and gallbladder cholesterol cholelithiasis:	2007	NM	NM	NM	NM	NM	NM	US, bile microscopy	NM	b. Small stones	<2	a. cholesterol monohydrate crystals constitute first sediment macro-scopically visible (sludge) f.Localisation: GB + CBD
9. Alexakis et al., Pancreatology. 2007	Review Topic: When is pancreatitis considered to be of biliary origin and what are the implications for management?	2007	NM	NM	NM	NM	NM	NM	US, EUS, MRCP,	AST, ALT, Bilirubin	a.Crystal-based b.Small stones	1 – 9	a.A mixture of particulate matter which precipitates from bile, can consist variously of cellular, proteinaceous and bacterial debris and may also contain cholesterol mono-hydrate crystals, calcium bilirubinate and other calcium salts embedded in mucin f.Localisation: GB

Study	Study type / Topic	Year	Total number of patients	Age (mean/ range or SD)	Sex (f/m)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)
10.Canlas et al. World J Gastroenterol. 2007	Review Topic: Role of endoscopic retrograde cholangiopancreatography in acute pancreatitis	2007	NM	NM	NM	NM	NM	NM	EUS, ERCP Bile microscopy	AST ALT, Bilirubin	c. viscous precipitate containing mucin, cholesterol and calcium bilirubinate	NM	a. viscous precipitate containing mucin, cholesterol and calcium bilirubinate which can obstruct the pancreatic duct f.Localisation: GB + CBD
11. Elta et al., World J Gastroenterol. 2008	Review Topic: Sphincter of Oddi dysfunction and bile duct microlithiasis in acute idiopathic pancreatitis	2008	NM	NM	NM	NM	NM	NM	US, EUS, ERCP, MRCP, Other	NM	b.Small stones	1-2	a.Collection of crystals (seen only by microscopic exam), glycoproteins, protein, cellular debris and mucin. f.Localisation: GB
12.Godfrey et al. Postgrad Med J. 2010	Review Topic: Endoscopic ultrasound: a review of current diagnostic and therapeutic applications	2010	NM	NM	NM	NM	NM	NM	EUS	NM	b.Small calculi	<3	NM
13.van Geenen et al. Nat Rev Gastroenterol Hepatol. 2010	Review Topic: Etiology and diagnosis of acute biliary pancreatitis	2010	NM	NM	NM	NM	NM	NM	EUS MRCP	ALT, AP, Bilirubin	b.Small stones	2-5	a.Calculi f.Localisation: GB + CBD
14.Buxbaum et al. Gastroenterol Clin North Am. 2012	Review Topic The role of endoscopic retrograde cholangiopancreatography in patients with pancreatic disease	2012	NM	NM	NM	NM	NM	NM	Microscopy ERCP	NM	b.Small stones	<3	a.Suspension of cellular debris and biliary crystals f.Localisation: GB + CBD
15.Stinton et al. Gut Liver. 2012	Review Topic: Epidemiology of gallbladder disease: cholelithiasis and cancer.	2012	NM	NM	NM	NM	NM	NM	NM	NM	b.Small stones	<1	NM
16. Testoni et al., World J Gastroenterol. 2014	Review Topic: Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment	2014	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP, Bile microscopy	NM	b.Small stones	< 2	NM
17. Şurlin et al., World J Gastroenterol. 2014	Review Topic: Imaging tests for accurate diagnosis of acute biliary pancreatitis	2014	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP, Bile microscopy	NM	a.Crystal-based	NM	NM
18. Smith et al., Am J Med Sci. 2015	Review Topic: Emerging Role of Endoscopic Ultrasound in the Diagnostic Evaluation of Idiopathic Pancreatitis	2015	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP, Bile microscopy	NM	b.Small stones	< 3	NM
19.Macías-Gómez et al., World J Gastrointest Endosc. 2015	Review Topic: Endoscopic management of biliary complications after liver transplantation	2015	NM	NM	NM	NM	NM	NM	NM	NM	b.Small stones	<5	a.Thick collection of mucus, calcium bicarbonate and cholesterol crystals f.Localisation: GB + CBD
20. Wang et al., Eur J Clin Invest. 2017	Review Topic: cholecystokinin secretion, a link between celiac disease and cholesterol gallstone disease	2017	NM	NM	NM	NM	NM	NM	US	NM	NM	NM	a.Precursor of gallstones that consists of solid cholesterol monohydrate crystals, calcium bilirubinate granules, or other calcium salts embedded in strands of mucin gel f.Localisation: GB

Study	Study type / Topic	Year	Total number of patients	Age (mean/ range or SD)	Sex (f/m)	No. of patients (Sludge)	No. of patients (Microlithiasis)	Control	Diagnostics	Lab values	Microliths (Definition)	Microlith (mm)	Sludge (Definition)
21. Jagannath et al., Curr Treat Options Gastroenterol. 2018	Review Topic: Recurrent Acute Pancreatitis: Current Concepts in the Diagnosis and Management	2018	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP, Bile microscopy	NM	b.Small stones	< 3	b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB
22. Wang et al., Liver Res. 2018	Review Topic: Similarities and differences between biliary sludge and microlithiasis: Their clinical and patho-physiological significances	2018	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERPCP, Bile microscopy	Bilirubin	b.Small stones	< 3	a.Amorphous mixture of particulate matter and bile, which occurs when various solutes in bile precipitate. b.Layers in the dependent portion of the gallbladder c. Echogenic (no acoustic shadowing) f.Localisation: GB + CBD
23. Wan et al., Gastrointest Endosc. 2018	Review Topic: Comparison of EUS with magnetic resonance cholangiopancreatography in idiopathic acute pancreatitis: a systematic review and meta-analysis	2018	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP	NM	b.Small stones	< 5	NM
24. Pereira et al., J Gastrointest Surg. 2019	Review Topic: Endoscopic Ultrasound for Routine Assessment in Idiopathic Acute Pancreatitis	2019	1850	NM	NM	NM	NM	NM	EUS Bile microscopy	NM	b.small stones	<3	a.Collection of crystals seen only by microscopic exam f.Localisation: GB + CBD
25. Del Vecchio et al., Clin J Gastroenterol. 2019	Review: Topic: Idiopathic acute pancreatitis: a review on etiology and diagnostic work-up	2019	NM	NM	NM	NM	NM	NM	US, CT, EUS; MRCP, ERCP	AST, ALT, AP	NM	NM	a. Cholesterol monohydrate crystals, calcium bilirubinate granules, calcium carbonate salts or small gallstones (<2 mm) b.Layers in the dependent portion of the gallbladder c.Low amplitude echoes (no acoustic shadowing) f.Localisation: GB
26. Boraschi et al. World J Gastroenterol. 2021	Review Topic: Abdominal and gastrointestinal manifestations in COVID-19 patients	2021	NM	NM	NM	NM	NM	NM	US, CT	NM	d. Hyperecho spots with „comet sign"	NM	a.Sediment b.Layers in the dependent portion of the gallbladder f. Localisation: GB

Regarding the natural occurrence of sludge and microlithiasis in gallbladder and/or common bile duct, the articles mentioning an antomic structure by name were scored as "yes" and then further subdivided into GB, CBD or GB + CBD. In the case of a highly suggestive formulation, such as that sludge and microlithiasis could be detected by bile microscopy, this was taken as evidence of a correlate in gallbladder and common bile duct.

*NM: not mentioned in the article

***Year of publication (or duration of the recruitment period, if indicated)

The mean age has been rounded up from 0.5 and down below

3. Data collection

The following parameters were collected for all studies included: Study type (prospective/retrospective/RCT) and study population investigated, study period (alternatively the year of publication if the study period was not clearly stated), journal of publication, number of study participants included (+ mean age, gender distribution), number of patients with evidence of sludge and/or microlithiasis, number of control patients (in most cases, no control groups were specifically matched to patients with sludge or microlithiasis detection due to thematic study heterogeneity), diagnostic and laboratory tools used, definitions of biliary sludge and/or microlithiasis used, and if mentioned, which therapeutic consequences were in case of detection. Due to a large number of sludge/microlithiasis definitions used, coding was carried out using defined signal words for ease of statistical quantification (see Figures 3 and 4). No attempt was made to obtain undisclosed data by contacting the corresponding authors, but missing data were marked "NM (not mentioned)". An overview of the included studies can be found in Figure 1. The entire data set of the studies examined is given in the supplement.

4. Quality assessment

The quality of the included studies and the risk of bias were assessed by two independent investigators (S.S. and M.Z.) using the QUADAS-2 score, adjusted to the predefined inclusion criteria. One problem in the tool application was that the sludge/microlithiasis characteristics formulated as inclusion criteria or a uniform definition design was not set as study endpoints in most articles, but a definition of the two entities was usually presented as already predefined in the context of the diagnostic work-up (for example, in the context of the search for causes in idiopathic acute pancreatitis). The sole consideration of biliary sludge and/or biliary microlithiasis definition(s) across all studies was thereby rated as equally good or poor in the absence of a universally applicable definition (in the corresponding QUADAS 2 categories 2) index test, 3) reference standard and 4) flow and timing). Regarding patient selection, the risk of bias was assessed depending on whether pre-diagnosed sludge patients were examined in the respective study or whether it was unclear at the beginning whether sludge/microlithiasis would be detectable. It was also assessed whether a (sludge/microlithiasis-specific) control group was examined. The applicability of the respective studies was assessed following the exact criteria to overcome the lack of uniform definitions and the resulting (currently still too large) scope for interpretation (for more information see supplement No.5 and 6).

5. Risk of bias assessment

5.1 Domain 1: Patient Selection

Risk of Bias:

Could the Selection of Patients Have Introduced Bias?

Survey-Manuscript:

It was assessed whether already sludge-diagnosed patients were examined or whether it was not clear at the beginning of the study whether sludge was present. It was also assessed whether a control group was examined (e.g. sonographically a group of patients with sludge detection and a group without sludge detection).

Applicability:

The assessment of the study's applicability was standardised on the basis of the predefined inclusion criteria. Therefore, all studies (since by definition the inclusion criteria were met) are colour-coded with the same colour.

5.2 Domain 2: Index Text

Risk of Bias:

Could the Conduct or Interpretation of the Index Test Have Introduced Bias?

Survey-Manuscript:

As no globally universal sludge/microlithiasis definition is currently used, all studies (that met the inclusion criteria) were colour-coded.

Applicability:

Since the diagnosis of sludge/microlithiasis, especially in ultrasound-based procedures, is currently still subject to (too) great variability (ultrasound device, experience, interpretation of findings), all studies were assessed uniformly in terms of colour ("equally good" or "equally bad").

5.3 Domain 3: Reference Standard

Risk of Bias:

Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?

Survey-Manuscript:

Potential for bias is related to the potential influence of previous knowledge on the interpretation of the reference standard. Since in our case no predefined standard is used for ultrasound or endosonography, there is no bias due

to prior knowledge of a reference value. Of course, this absence itself creates an enormous room for interpretation. All studies were therefore given a uniform colour rating ("equally good" or "equally bad").

Applicability:

Are There Concerns That the Target Condition as Defined by the Reference Standard Does Not Match the Question?

Without a reference standard there can be no different interpretations of a possible threshold. For example, in the (endo-)sonographic diagnosis of microlithiasis, a acoustic shadow is mentioned as a characteristic, but whether this acoustic shadow should still be considered differentiated with regard to different intensity strengths is omitted. All studies were therefore given a uniform colour rating ("equally good" or "equally bad").

5.4 Domain 4: Flow and Timing

Risk of Bias:

Could the Patient Flow Have Introduced Bias?

Survey-Manuscript:

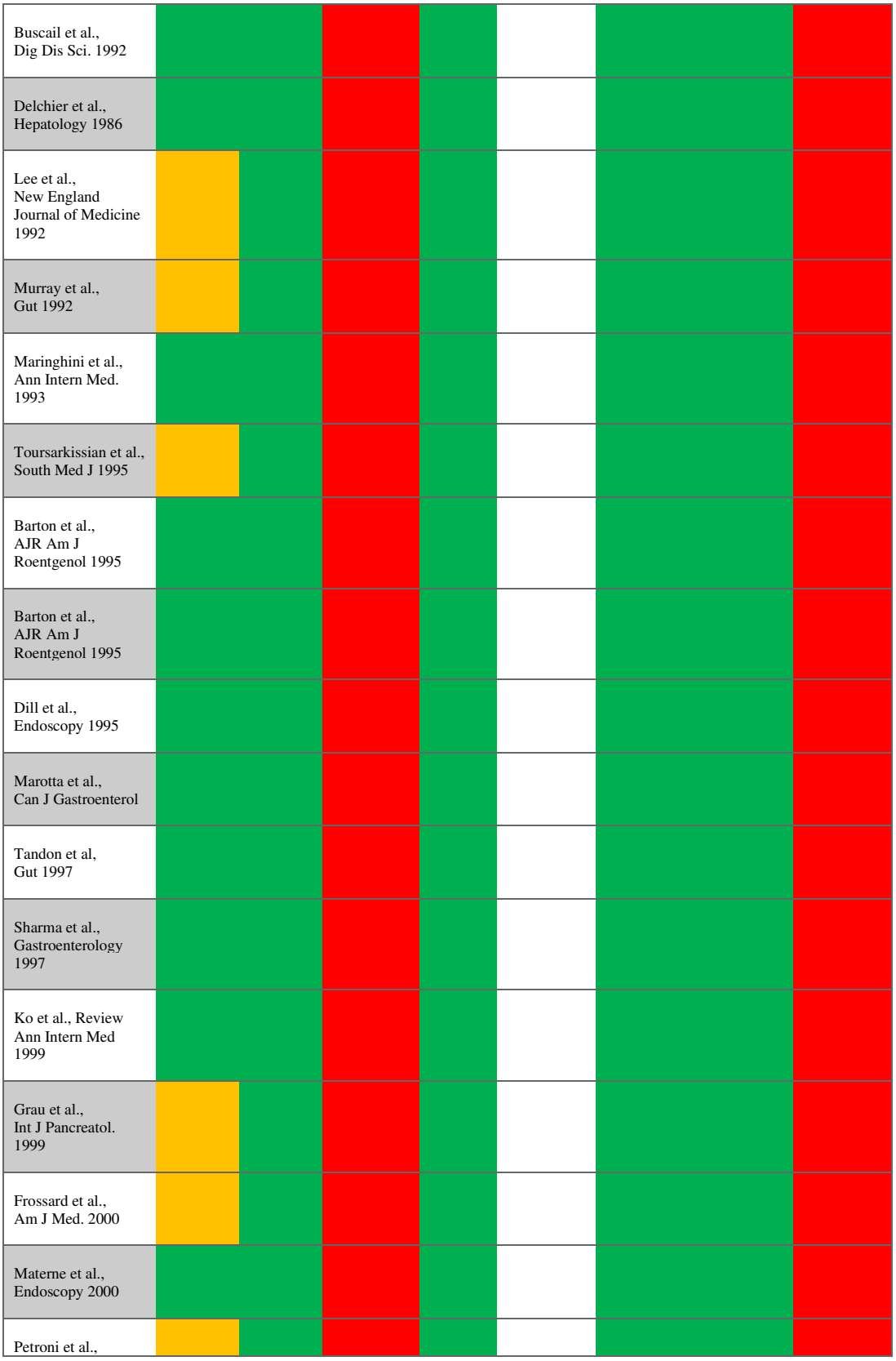
The time interval between index test and reference standard to be investigated for this is omitted due to the lack of (universally) defined index test and reference standard modalities.

5.5 Quadas 2 Tool

Categories:

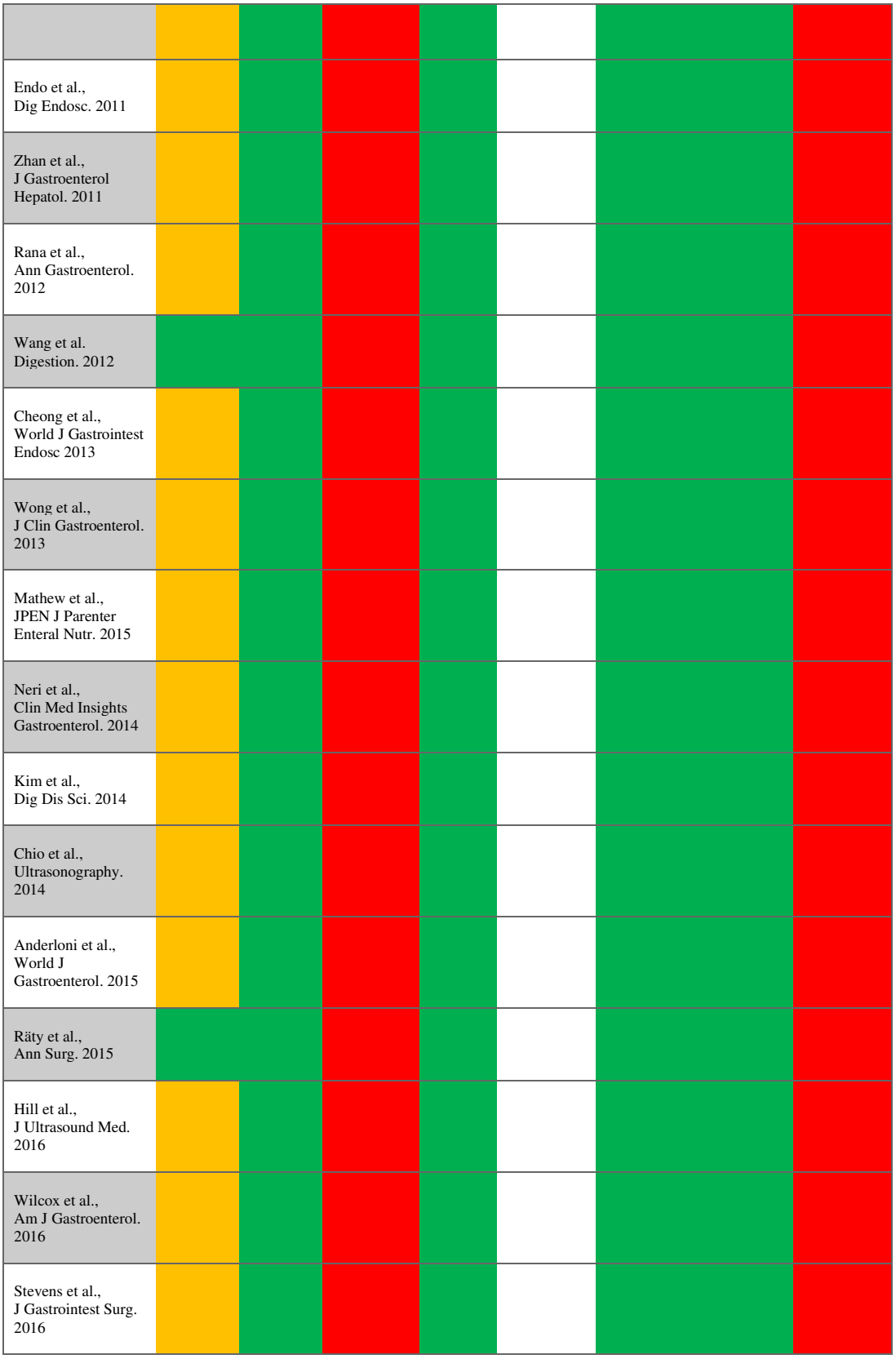
Low/High/Unclear

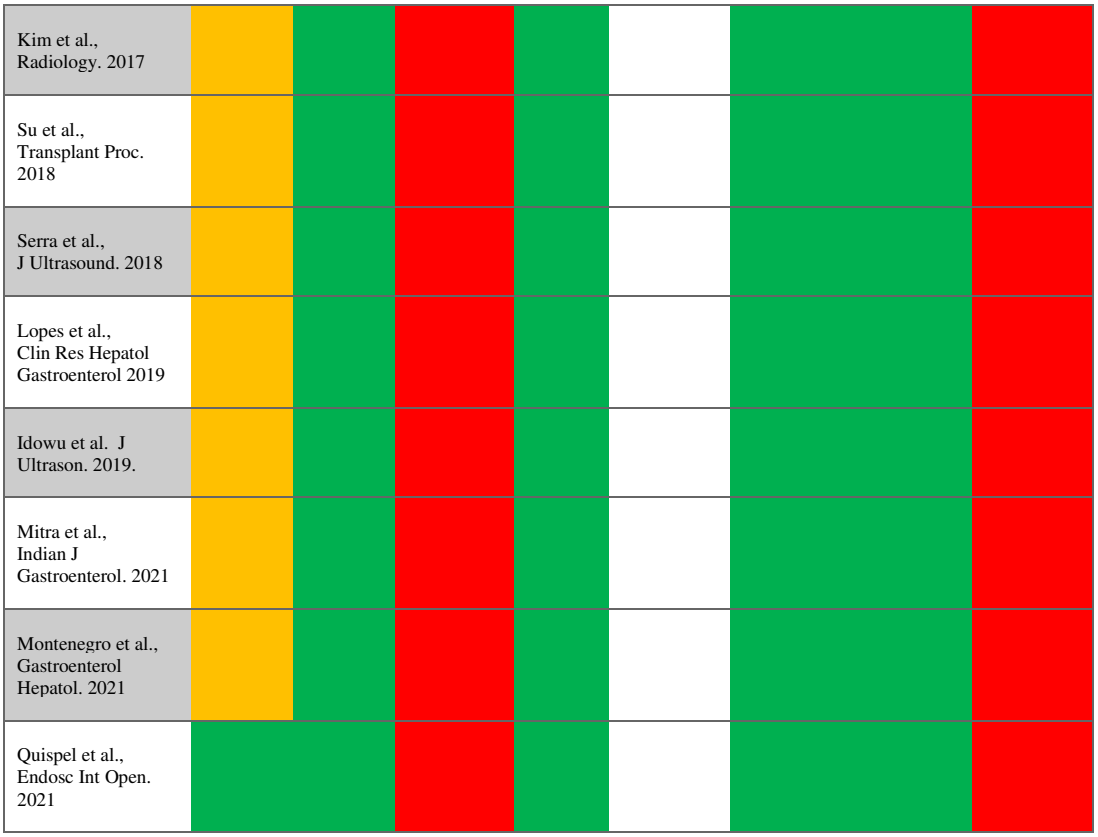
	Risk of Bias					***Applicability***		
Study	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow and Timing**		**Patient Selection**	**Index Test**	**Reference Standard**
Allen et al., Am J Surg. 1981								
Lee et al., Gastroenterology. 1986								
Lee et al., Gastroenterology. 1988								
Ohara et al., J Clin Gastroenterol. 1990								
Ros et al., Gastroenterology. 1991								


Buscail et al., Dig Dis Sci. 1992
Delchier et al., Hepatology 1986
Lee et al., New England Journal of Medicine 1992
Murray et al., Gut 1992
Maringhini et al., Ann Intern Med. 1993
Toursarkissian et al., South Med J 1995
Barton et al., AJR Am J Roentgenol 1995
Barton et al., AJR Am J Roentgenol 1995
Dill et al., Endoscopy 1995
Marotta et al., Can J Gastroenterol
Tandon et al, Gut 1997
Sharma et al., Gastroenterology 1997
Ko et al., Review Ann Intern Med 1999
Grau et al., Int J Pancreatol. 1999
Frossard et al., Am J Med. 2000
Materne et al., Endoscopy 2000
Petroni et al.,


Eur J Gastroenterol Hepatol 2000
Méndez-Sánchez et al. J Nutr. 2001
Tandon et al., Am J Gastro 2001
Calvo et al., J Clin Gastroenterol. 2002
Kohut et al., World J Gastroenterol. 2002
Kubota et al., J Gastroenterol Hepatol. 2002
38. Calvo et al. J Clin Gastroenterol. 2002
Ierardi et al., Aliment Pharmacol Ther. 2003
Rashdan et al., Gastrointest Endosc. 2003
Saraswat et al., J Gastroenterol Hepatol. 2004
Ponce et al. Eur J Nucl Med Mol Imaging. 2004
Ko et al., Hepatology 2005
Mirbargheri et al., J Gastrointest Surg. 2005
Ko et al., Clin Gastroenterol Hepatol. 2005
Rocca et al., Gastrointest Endosc. 2006
Wilcox et al., Gastrointest Endosc. 2006


Bolukbas et al., J Gastroenterol Hepatol. 2006
Garg et al., Clin Gastroenterol Hepatol. 2007
Jüngst et al., Best Pract Res Clin Gastroenterol. 2006
Inoue et al., Ultrasound Med Biol. 2007
Numata et al., J Ultrasound Med. 2007
Alexakis et al., Pancreatology. 2007
Elta et al., World J Gastroenterol. 2008
Okoro et al. Gastrointest Endosc. 2008
Bastouly et al., Obes Surg. 2009
Kim et al., Dig Dis Sci. 2010
Elmi et al., Dig Dis Sci. 2010
Mesotten et al., J Clin Endocrinol Metab. 2009
Baltas et al., Singapore Med J. 2009
Vila et al., Scand J Gastroenterol. 2010
Ardengh et al., Rev Assoc Med Bras (1992). 2010
Ortega et al., Pancreas 2011


Endo et al., Dig Endosc. 2011
Zhan et al., J Gastroenterol Hepatol. 2011
Rana et al., Ann Gastroenterol. 2012
Wang et al. Digestion. 2012
Cheong et al., World J Gastrointest Endosc 2013
Wong et al., J Clin Gastroenterol. 2013
Mathew et al., JPEN J Parenter Enteral Nutr. 2015
Neri et al., Clin Med Insights Gastroenterol. 2014
Kim et al., Dig Dis Sci. 2014
Chio et al., Ultrasonography. 2014
Anderloni et al., World J Gastroenterol. 2015
Räty et al., Ann Surg. 2015
Hill et al., J Ultrasound Med. 2016
Wilcox et al., Am J Gastroenterol. 2016
Stevens et al., J Gastrointest Surg. 2016



6. Studies excluded at full-text screening stage (with brief reasons)

1. Farinon AM, Ricci GL, Sianesi M, Percudani M, Zanella E. Physiopathologic role of microlithiasis in gallstone pancreatitis. Surg Gynecol Obstet. 1987 Mar;164(3):252-6. PMID: 3824114
   Reason: no full text viewable
2. Gafá M, Sarli L, Miselli A, Pietra N, Carreras F, Peracchia A. Sludge and microlithiasis of the biliary tract after total gastrectomy and postoperative total parenteral nutrition. Surg Gynecol Obstet. 1987 Nov;165(5):413-8. PMID: 3118486.
   Reason: no full text viewable
3. Belghiti J, Kleinman P, Cherqui D, Perniceni T, Bernades P, Fékété F. Traitement précoce de la lithiase biliaire au cours des pancréatites biliaires [Early treatment of biliary lithiasis in biliary pancreatitis]. Gastroenterol Clin Biol. 1987 Nov;11(11):786-9. French. PMID: 3322925.
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7. Expert Survey

Besides questions on definition and treatment strategies in the case of sludge and microlithiasis detection a total of 7 case vignettes based on extracted original patient cases (including the first laboratory report from the time of presentation in the central emergency department; slightly modified to protect anonymity) were to be answered, each with a diagnostic and a therapeutic assessment. The patient case vignettes were anonymised and modified in relation to the age stated in the vignette in such a way that it is not possible to trace them back to the individual patient case. The expert selection was based on clinical and scientific merits, scientific expertise through publications in endoscopy/endosonography, or many years/decades of clinical endoscopy experience with clinical and/or scientific visibility. The contact and sending of the participation link was done by mail. We used the LimeSurvey administration interface to create the survey (LimeSurvey version 4.4.12+210308). The created survey was first evaluated in an internal validation round at the Department of Medicine II (LMU University Hospital Munich) before being sent to the expert group. Experts who did not respond to the invitation email, were sent two reminders. The response to the survey was anonymous. The data protection officer of LMU University Hospital Munich approved the survey . The complete survey was available only for invited experts on a protected LMU University Hospital Munich server. Outcomes of the expert survey were presented and discussed at the European Pancreas Congress in Verona, which took place online on June 11th, 2021 during the “Biliary Pancreatitis” panel session. An online voting poll was conducted involving the session participants (Supplement Table 2). The results of the EPC online voting were initially evaluated internally by the author team in conjunction with the results of the systemic literature review. A final definition of the terms: biliary sludge/biliary microlithiasis was agreed upon in a second expert survey round, in which the EUS expert panel was able to evaluate the definition proposals delineated from the literature review, EUS expert panel round 1 and EPC online voting session using a voting link. For the second round of expert voting, we made the results of our literature review available to the experts

Expert profile		Response	Response rate
Speciality	Ganstroenterology	27 / 29	93.1 %
	No information	2 / 29	6.9 %
Years of experience	10 - 20 years	8 / 29	27.6 %
	20 - 30 years	10 / 29	34.5 %
	> 30 years	9 / 29	31.0 %
	No information	2 / 29	6.9 %
Performing Endoscopy	Yes	26 / 29	89.7 %
	No	2 / 29	6.9 %
	No information	1 / 29	3.4 %
EUS experience	Not performig	5 / 29	17.2 %
	< 50 procedures / year	2 / 29	6.9 %
	50 - 100 procedures / year	2 / 29	6.9 %
	> 100 procedures / year	18 / 29	62.1 %
	No information	2 / 29	6.9 %
Type of practice	Private practice	1 / 29	3.4 %
	Academic teaching hospital	26 / 29	89.7 %
	No information	2 / 29	6.9 %
Continent	Europe	21 / 29	72.4 %
	North-America	4 / 29	13.8 %
	Asia	1 / 29	3.4 %
	Africa	1 / 29	3.4 %
	No information	2 / 29	6.9 %

Supplement Table 1. The LMU Microlithiasis Survey Expert Consortium.

30 world-renowned experts in the field of endosonography-assisted diagnosis and therapy were contacted, of whom 25 (83·3 %) returned the survey questionnaire in full. 65·5 % of the experts had more than 20 years, 31·0 % even more than 30 years of professional experience. The highly relevant field of endosonography in biliary sludge/microlithiasis diagnostics was excellently covered by 62·1 % of the experts with more than 100 procedures per year. The majority of the experts surveyed are employed at university hospitals (89·7 %) in European centres (72·4 %).

Microlithiasis Expert-Survey

In clinical practice and literature, there are many definitions of biliary sludge / microlithiasis. This situation is confusing and makes it difficult to compare different studies concerning the clinical manifestations of biliary sludge or microlithiasis (e.g. pancreatitis, upper-abdominal pain, cholestasis).

Analysis of reports published in the last ten years (2010-2020) shows that there is a significant lack of inter-author agreement concerning:

I. Diagnostic imaging differences/similarities between biliary sludge and microlithiasis

II. Clinical manifestations of sludge or microlithiasis concerning its localization (gallbladder, bile ducts)

III. Size cut-off values and imaging features of microliths

Moreover, in nearly **30% of published papers, the terms microlithiasis and biliary sludge are used as synonyms.**

The current study aims to:

- Identify **controversies** in the definition of biliary sludge/microlithiasis, involving recommendations for clinical practice
- Establish an **expert-based survey** on the definition and diagnostic (as well as therapeutic) strategy of biliary sludge/microlithiasis
- Perform a **global survey** among gastroenterologists, surgeons, and endoscopists, which will help to coin **a new, worldwide and clear definition** of this frequent disease and determine what would help research evidence-based therapeutic strategies in the future.

There are 36 questions in this survey.

Next

Responder data.

(This question is mandatory)

Data usage note

Your data will be treated confidentially by us within the offered WEB application framework and will be used exclusively to answer the questions formulated in the introduction to the survey.

Your data will be adequately protected against third parties' access and processed following the provisions of the German Data Protection Act (DSGVO). This information will not be passed on or transmitted to unauthorized third parties. Your data will be deleted at the latest three months after processing for your data's intended purpose or forwarding to the responsible office.

You can revoke your authorization for the purpose-related processing of your data at any time in writing without giving reasons. Your stored data will then be deleted immediately following legal regulations.

The processing of your data within the smartphone application's scope (remote device) is carried out via encrypted access and is only permitted for your data.

"I am aware, and I am informed that my data can be disclosed to third parties on the Internet and can be viewed by anyone without protection!"

Datenverwendungshinweis

Ihre persönlichen Daten werden von uns im Rahmen der angebotenen WEB-Applikation vertraulich behandelt und ausschließlich dazu verwendet, um die in der Einleitung des Surveys formulierten Fragestellungen zu beantworten.

Ihre Angaben werden vor dem Zugriff Dritter angemessen geschützt und nach den Bestimmungen der Datenschutzgrundverordnung (DSGVO) verarbeitet. Eine Weitergabe oder Übermittlung dieser Angaben an nicht berechtigte Dritte erfolgt nicht. Ihre Daten werden spätestens 3 Monate nach zweckgebundener Verarbeitung bzw. Weiterleitung Ihrer Angaben an die zuständige Stelle gelöscht.

Sie können Ihre Genehmigung zur zweckgebundenen Verarbeitung Ihrer Daten jederzeit ohne Angabe von Gründen schriftlich widerrufen. Ihre gespeicherten Daten werden dann unverzüglich im Rahmen gesetzlicher Vorschriften gelöscht.

Die Verarbeitung Ihrer personenbezogenen Daten im Rahmen der Smartphone-Applikation (Private Device) erfolgt über verschlüsselte Zugänge und ist Ihnen nur für Ihre eigenen Daten gestattet.

„Mir ist bewusst und ich bin darüber informiert, dass damit meine persönlichen Daten im Internet gegenüber Dritten offenbart werden können und ggfs. ungeschützt für Jedermann einsehbar sind!“

Choose one of the following answers

- I declare my consent to this / Ich erkläre mich damit einverstanden.

Summary years of experience in medicine:

Choose one of the following answers

- <5 years
- 5-10 years
- 10-20 years
- 20-30 years
- >30 years

What is your specialty:

Choose one of the following answers

- Gastroenterology
- Surgery
- Internal Medicine
- Pediatrics
- Other
-

Are you performing endoscopy?

Choose one of the following answers

- Yes
- No

EUS experience:

Choose one of the following answers

- Not perfroming EUS
- <50 procedures/year
- 50-100 procedures/year
- >100 procedures/year

Type of practice:

Choose one of the following answers

- Private practice
- Community hospital
- Academic teaching hospital

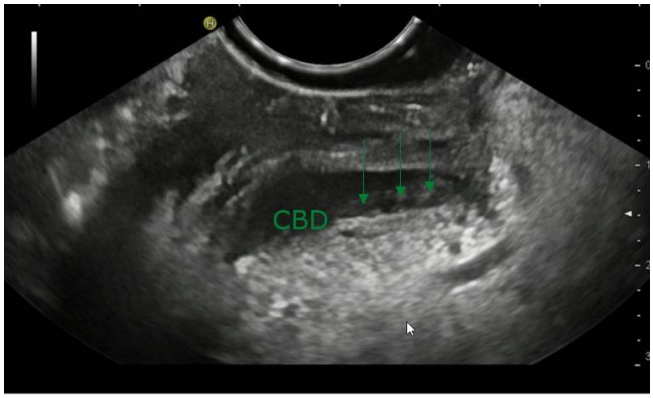
Please write down the country of your professional activity:

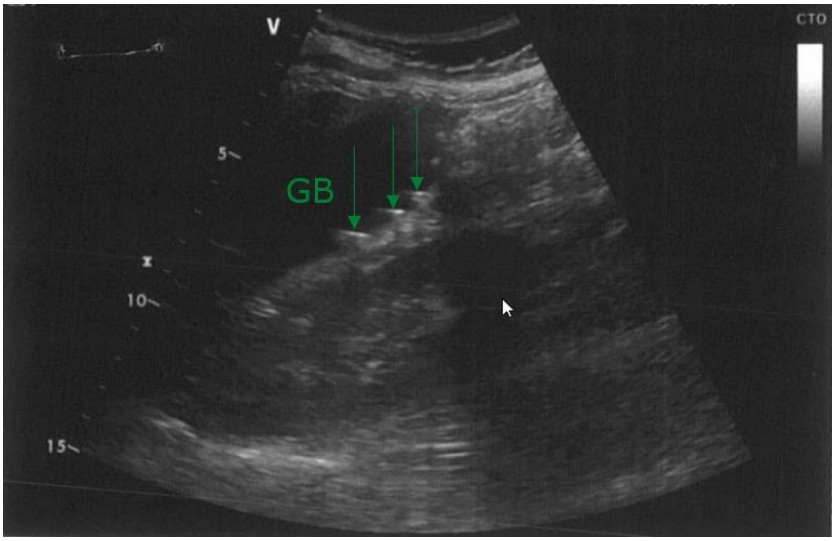
Clinical cases

CASE 1

30 – 40 year old patient, diagnosed in ER – severe abdominal pain, no chronic diseases , no trauma, no alcoholic history, ECOG 0.

Natrium	mmol/l	S	135 - 145	139
Kalium	mmol/l	S	3,5 - 5,1	4,1
Osmolalität	mosm/kg	S	280 - 300	M 291
Glucose	mg/dl	S	60 - 99	107
Harnstoff	mg/dl	S	17 - 49	22
Kreatinin (Jaffé)	mg/dl	S	0,5 - 1,0	0,8
GFR (CKD-EPI)	ml/min	S	>= 90	99
Harnsäure	mg/dl	S	2,3 - 6,1	3,9
Calcium	mmol/l	S	2,05 - 2,65	2,29
Calcium (Alb.-korr.)	mmol/l	S	2,05 - 2,65	2,27
Calcium (Eiw.-korr.)	mmol/l	S	2,05 - 2,65	2,35
Magnesium	mmol/l	S	0,66 - 1,07	0,74
Anorg. Phosphat	mg/dl	S	2,5 - 4,8	2,8
CRP	mg/dl	S	<= 0,5	0,7
Procalcitonin	ng/ml	S	<= 0,1	< 0,1
Eiweiß, gesamt	g/dl	S	6,4 - 8,4	6,8
Albumin	g/dl	S	3,5 - 5,2	4,1
Bilirubin, gesamt	mg/dl	S	<= 1,2	3,5
GOT [AST]	U/l	S	<= 34	84
GPT [ALT]	U/l	S	<= 34	230
Gamma-GT (37°)	U/l	S	<= 39	265
Alkalische Phosphatase	U/l	S	35 - 105	234
Alpha-Amylase	U/l	S	<= 109	2056
Lipase	U/l	S	13 - 60	>7000
LDH (37°)	U/l	S	<= 249	217





Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)

Picture 2 - Linear endoscopic ultrasound, focus on the common bile duct (CBD), arrows are pointed at the area of interest.

Picture 3 - Transabdominal ultrasound examination, focus on the gallbladder, arrows are pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge (both GB and CBD)
- Biliary Microlithiasis (both GB and CBD)
- Biliary Sludge (GB) and Microlithiasis (CBD)
- Biliary Microlithiasis (GB) and Sludge (CBD)
- Gallstone(s) (both GB and CBD)

QUESTION 2: What would be your FIRST CHOICE of treatment:

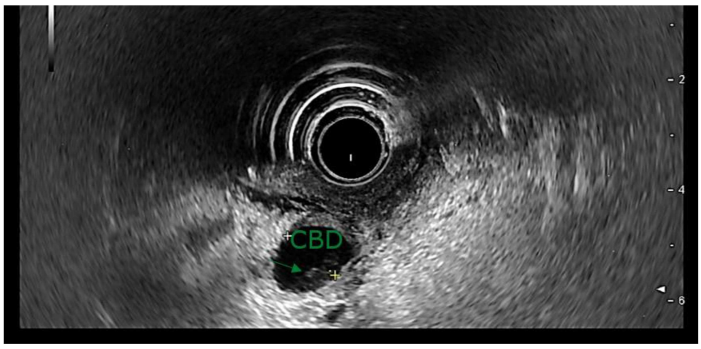
Choose one of the following answers

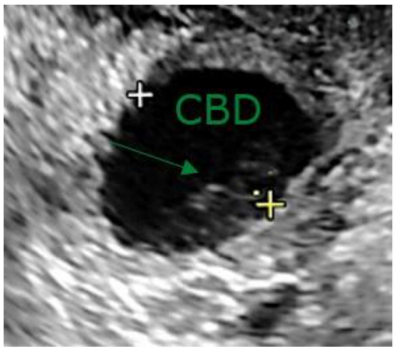
- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

CASE 2

60-70 year old patient, with accidentally detected dilatation of CBD in US (11mm), no focal lesions found on CT, no history of biliary-type pain in the past, no signs of gallstones, no pancreatitis in the past, ECOG 0.

Klinische Chemie					
Natrium	mmol/l	S	135 - 145	143
Kalium	mmol/l	S	3,5 - 5,1	3,8
Kreatinin (Jaffé)	mg/dl	S	0,5 - 1,0	0,3
GFR (CKD-EPI)	ml/min	S	>= 90	113
CRP	mg/dl	S	<= 0,5	2,3
Bilirubin, gesamt	mg/dl	S	<= 1,2	2
GOT [AST]	U/l	S	<= 34	53
GPT [ALT]	U/l	S	<= 34	68
Gamma-GT (37°)	U/l	S	<= 39	110
Hämatologie				
Kleines Blutbild		EB		
Leukozyten	G/l	EB	4,00 - 10,40	13,4
Erythrozyten	T/l	EB	3,96 - 5,16	4,59
Hämoglobin	g/dl	EB	11,5 - 15,4	13,3
Hämatokrit	l/l	EB	0,346 - 0,453	0,412
MCV	fl	EB	80,0 - 95,5	89,8
MCH	pg	EB	26,1 - 32,6	29,0
MCHC	g/dl	EB	31,9 - 35,5	32,3
Thrombozyten	G/l	EB	176 - 391	381
Normoblasten (maschinell)	/100 Leu	EB	<= 1,0	< 0,1
RDW-CV #	%	EB	12,1 - 14,8	14,1
PDW #	fl	EB	10 - 15	10
MPV #	fl	EB	9,2 - 12,5	9,4





Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)

Picture 2 - Radial endoscopic ultrasound examination. Focus on the common bile duct (CBD), the arrow is pointed at the area of interest.

Picture 3 - Magnification of radial endoscopic ultrasound image. Focus on the common bile duct (CBD), the arrow is pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge
- Biliary Microlithiasis
- Biliary Sludge and Microlithiasis
- Gallstone(s)

QUESTION 2: What would be your FIRST CHOICE of treatment:

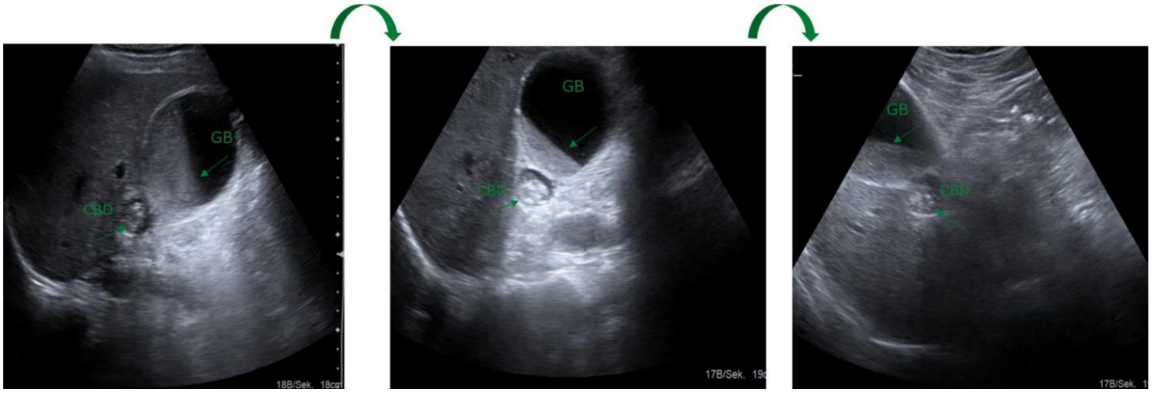
Choose one of the following answers

- ○ Cholecystectomy (preferably laparoscopic)
- ○ ERCP, with sphincterotomy
- ○ Non-invasive (UDCA treatment)
- ○ All of above options are equally of use
- ○ Other therapy option

CASE 3

50-60 year old patient, with relapsing upper-right and middle quadrant abdominal pain, Sporadically vomiting, no history of pancreatitis, ECOG 0.

☐	Natrium	mmol/l	S	135 - 145	139
☐	Kalium	mmol/l	S	3,5 - 5,1	4,2
☐	Kreatinin (Jaffé)	mg/dl	S	0,7 - 1,2	1,0
☐	GFR (CKD-EPI)	ml/min	S	>= 90	84
☐	CRP	mg/dl	S	<= 0,5	0,8
☐	Bilirubin, gesamt	mg/dl	S	<= 1,2	6,2
☐	GOT [AST]	U/l	S	<= 49	106
☐	GPT [ALT]	U/l	S	<= 49	174
☐	GLDH (37°)	U/l	S	<= 6,9	54,3
☐	Gamma-GT (37°)	U/l	S	<= 59	445
☐	Alkalische Phosphatase	U/l	S	40 - 130	98
☐	Alpha-Amylase	U/l	S	<= 109	94
☐	Lipase	U/l	S	13 - 60	37
☐	LDH (37°)	U/l	S	<= 249	200



Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)
Picture 2 - Abdominal ultrasound. Focus on the gallbladder (GB) and common bile duct (CBD). Pictures were taken after subsequent changes of probe and patients positions. Arrow point to the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge (both GB and CBD)
- Biliary Microlithiasis (both GB and CBD)
- Biliary Sludge (GB) and Microlithiasis (CBD)
- Biliary Microlithiasis (GB) and Sludge (CBD)
- Gallstone(s) (both GB and CBD)

QUESTION 2: What would be your FIRST CHOICE of treatment:

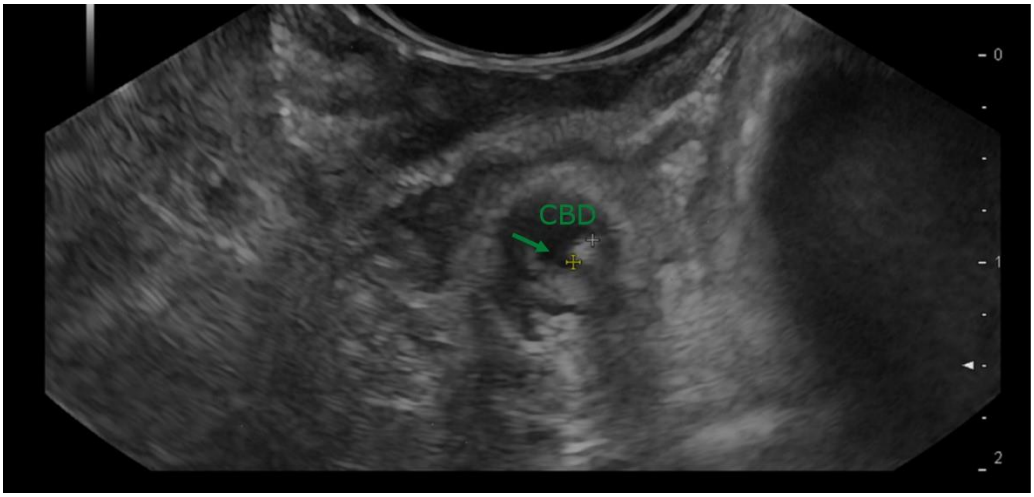
Choose one of the following answers

- Cholecystectomy (preferably laparoscopic)
- ERCP followed by cholecystectomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

CASE 4

60-70 year old patient, with colic upper right quadrant abdominal pain, ECOG 0.

☐	Natrium	mmol/l	S	135 - 145	144		138
☐	Kalium	mmol/l	S	3,5 - 5,1	4,6		3,7
☐	Kalium	mmol/l	S	3,5 - 5,0			
☐	Glucose	mg/dl	S	60 - 99			120
☐	Glucose S	mg/dl	S	70 - 115			
☐	Kreatinin (Jaffé)	mg/dl	S	0,5 - 1,0	0,8		0,8
☐	GFR (CKD-EPI)	ml/min	S	>= 90	91		91
☐	CRP	mg/dl	S	<= 0,5	0,3		0,2
☐	Bilirubin, gesamt	mg/dl	S	<= 1,2	0,7		0,7
☐	GOT [AST]	U/l	S	<= 34	55		
☐	GPT [ALT]	U/l	S	<= 34	58		49
☐	Cholinesterase	kU/l	S	3,93 - 10,80	6,70		
☐	Gamma-GT (37°)	U/l	S	<= 39	61		55
☐	Alkalische Phosphatase	U/l	S	35 - 105	69		82
☐	A-Amylase (25°)	U/l		<= 120			
☐	Lipase	U/l	S	13 - 60	25		282
☐	LDH (37°)	U/l	S	<= 249	123		222
☐	Creatinkinase (CK)	U/l	S	<= 169		59	72



Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)

Picture 2 - Linear endoscopic ultrasound. Focus on the common bile duct (CBD). Arrows are pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge
- Biliary Microlithiasis
- Biliary Sludge and Microlithiasis
- Gallstone(s)

QUESTION 2: What would be your FIRST CHOICE of treatment:

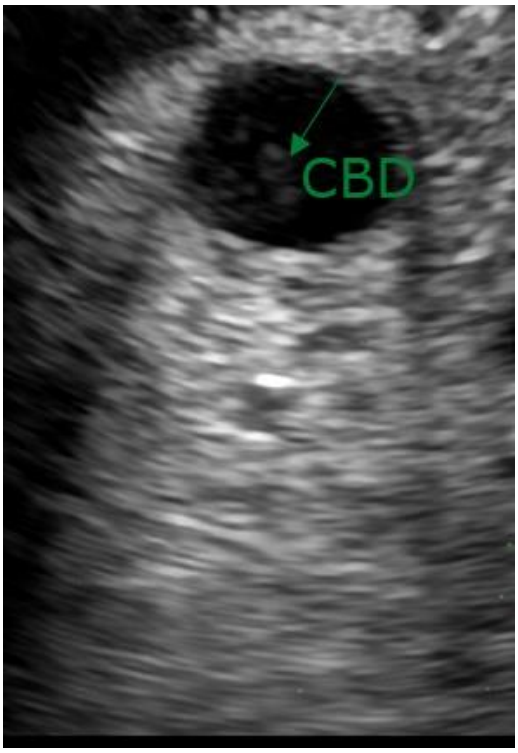
Choose one of the following answers

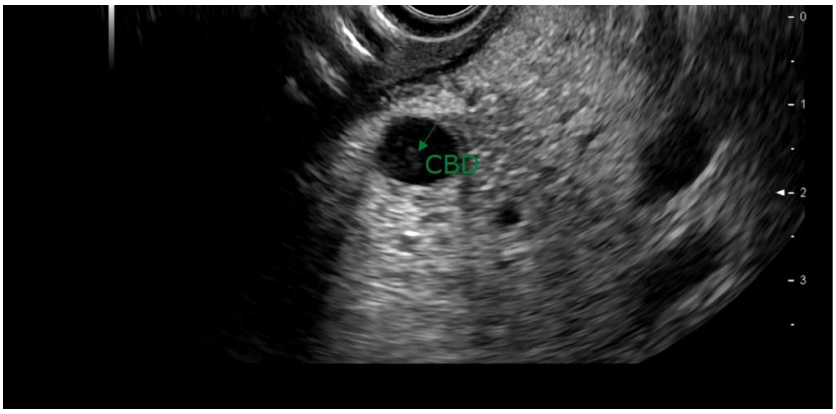
- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

CASE 5

40-50 year old patient, severe abdominal pain, no trauma, no history of alcohol abuse, no history of chronic diseases, ECOG 0.

Natrium	mmol/l	S	135 - 145	137	137	141	138
Kalium	mmol/l	S	3,5 - 5,1	3,8	3,6	4,1	3,8
Kalium	mmol/l	S	3,5 - 5,0				
Glucose	mg/dl	S	60 - 99				106
Harnstoff	mg/dl	S	17 - 49		14		20
Kreatinin (Jaffé)	mg/dl	S	0,5 - 1,0	0,7	0,7	0,9	0,8
GFR (CKD-EPI)	ml/min	S	>= 90	105	102	94	96
Harnsäure	mg/dl	S	2,3 - 6,1				
Calcium	mmol/l	S	2,05 - 2,65				
Calcium	mmol/l	S	2,20 - 2,55		2,26		2,35
Calcium (Alb.-korr.)	mmol/l	S	2,20 - 2,55		2,23		
Magnesium	mmol/l	S	0,66 - 1,07				
Kupfer	µg/dl	S	88 - 201				
Freies Kupfer	µg/dl	S	<= 20				
Freies Kupfer	%	S	<= 10				
Eisen	µg/dl	S	60 - 180				
CRP	mg/dl	S	<= 0,5	4,4	2,4	1,7	1,5
Eiweiß, gesamt	g/dl	S	6,4 - 8,4				
Eiweiß, gesamt	g/dl	S	6,0 - 8,0				
Albumin	g/dl	S	3,5 - 5,2		4,1		
Bilirubin, gesamt	mg/dl	S	<= 1,2	2,9	4,2	4,0	2,9
Bilirubin, direkt	mg/dl	S	<= 0,2	1,4			
GOT [AST]	U/l	S	<= 34		387	604	
GPT [ALT]	U/l	S	<= 34		729	735	717
GLDH (37°)	U/l	S	<= 4,9				
Cholinesterase	kU/l	S	3,93 - 10,80			11,4	
Gamma-GT (37°)	U/l	S	<= 39	267	250	249	238
Alkalische Phosphatase	U/l	S	35 - 105	232	212	194	171
Alpha-Amylase	U/l	S	<= 109				
Lipase	U/l	S	13 - 60	1827		>6000	>6000





Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)

Picture 2 - Linear endoscopic ultrasound. Focus on the common bile duct (CBD). Arrow is pointed at the area of interest.

Picture 3 - Magnification of linear endoscopic ultrasound image. Focus on the common bile duct (CBD), the arrow is pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge
- Biliary Microlithiasis
- Biliary Sludge and Microlithiasis
- Gallstone(s)

QUESTION 2: What would be your FIRST CHOICE of treatment:

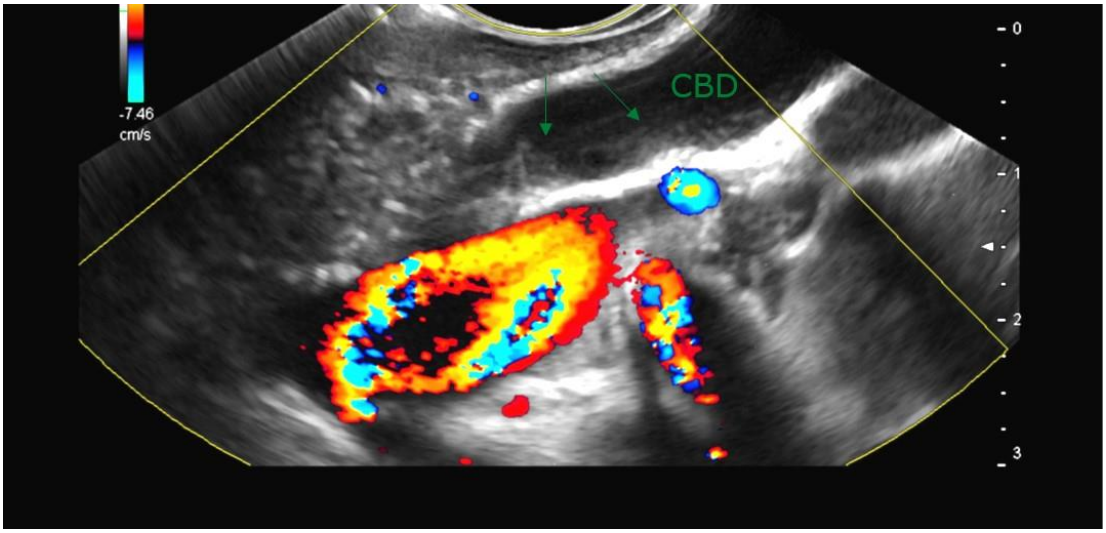
Choose one of the following answers

- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

CASE 6

20 - 30 year old patient with repeating episodes of colic pain in the right upper abdominal quadrant, biochemically and on the abdominal US no other pathologies, ECOG 0.

Klinische Chemie					
Natrium	mmol/l	S	135 - 145	141	139
Kalium	mmol/l	S	3,5 - 5,1	3,8	4,1
Chlorid	mmol/l	S	98 - 107		
Glucose	mg/dl	S	60 - 99		93
Harnstoff	mg/dl	S	17 - 49		26
Kreatinin (Jaffé)	mg/dl	S	0,5 - 1,0	0,8	0,7
GFR (CKD-EPI)	ml/min	S	>= 90	127	136
Calcium	mmol/l	S	2,15 - 2,50		2,47
Calcium (Alb.-korr.)	mmol/l	S	2,15 - 2,50		2,32
Calcium (Eiw.-korr.)	mmol/l	S	2,15 - 2,50		2,48
Magnesium	mmol/l	S	0,66 - 1,07		
Anorg. Phosphat	mg/dl	S	2,5 - 4,8		
CRP	mg/dl	S	<= 0,5	0,6	0,7
Eiweiß, gesamt	g/dl	S	6,4 - 8,4		7,7
Albumin	g/dl	S	3,5 - 5,2		4,6
% Albumin	%	S	55,8 - 66,1		
Bilirubin, gesamt	mg/dl	S	<= 1,2	0,4	0,3
GOT [AST]	U/l	S	<= 34		21
GPT [ALT]	U/l	S	<= 34		11
Gamma-GT (37°)	U/l	S	<= 39	23	26
Alkalische Phosphatase	U/l	S	35 - 105	84	91
Alpha-Amylase	U/l	S	<= 109		
Lipase	U/l	S	13 - 60	23	23
LDH (37°)	U/l	S	<= 249		142



Picture 1 - Biochemical results. (all results and following images come from Klinikum LMU, Munich; Harnstoff - Urea, Harnsaure - Uric acid, Eiweiß gesamt - Total protein, Freies Kupfer - Free coppper, Eisen - Iron)

Picture 2 - Linear endoscopic ultrasound. Focus on the common bile duct (CBD). Arrows are pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge
- Biliary Microlithiasis
- Biliary Sludge and Microlithiasis
- Gallstone(s)

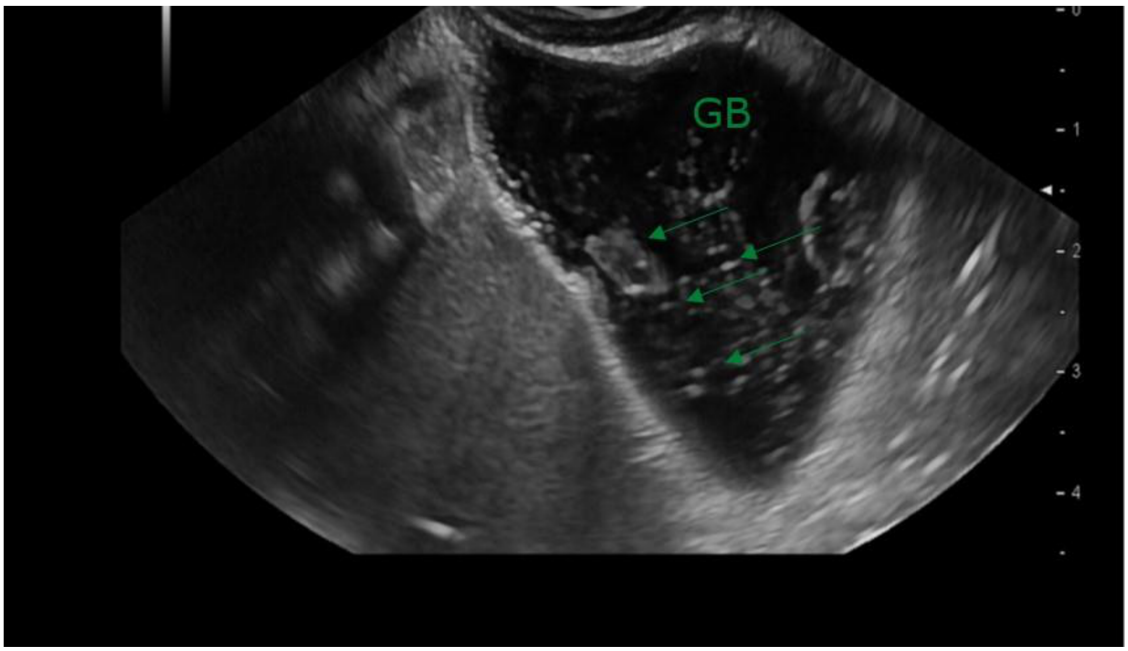
QUESTION 2: What would be your FIRST CHOICE of treatment:

Choose one of the following answers

- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

CASE 7

40 – 50 year old patient with repeated right upper abdominal pain and history of cholestasis; biochemically and on the abdominal US no other pathologies reported, ECOG 0.



Picture 1 - Linear endoscopic ultrasound. Focus on the gallbladder (GB). Arrows are pointed at the area of interest.

QUESTION 1: How do you phrase the depicted finding in your report:

Choose one of the following answers

- Biliary Sludge
- Biliary Microlithiasis
- Biliary Sludge and Microlithiasis
- Gallstone(s)

QUESTION 2: What would be your FIRST CHOICE of treatment:

Choose one of the following answers

- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use
- Other therapy option

Next

Impressum und Datenschutz

Definitions

Discrete, hyperechoic material inside the gallbladder or the bile duct, without acoustic shadowing, which sediment in the most dependent part of the gallbladder represents microlithiasis:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

Discrete, hyperechoic material inside the gallbladder or the bile duct, without acoustic shadowing, which sediment in the most dependent part of the gallbladder represents biliary sludge:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

The term „biliary sludge“ should be exclusively used if detected in gallbladder:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

The term „biliary sludge“ should be used exclusively if detected in the bile duct:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

The term „biliary sludge“ can be used both to diagnose findings in the bile duct as well as the gallbladder:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

The term „biliary microlithiasis“ should be used exclusively for cases in which solid biliary and cholesterol crystals are detected after bile sample centrifugation and examination by phase-contrast and polarizing light microscopy:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

The term „biliary microlithiasis“ should be used exclusively for cases in which EUS examination of the biliary tree reveals presence of stones less than (in diameter):

Choose one of the following answers

- < 10 mm
- < 5 mm
- < 3 mm
- Any stone visualized by EUS-examination but not causing obstruction of biliary duct

The terms „biliary sludge“ and „biliary microlithiasis“ describe an identical finding because both entities can cause clinically significant pain, cholangitis, and pancreatitis:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

Management

In your personal experience biliary sludge/microlithiasis is a cause of "idiopathic" pancreatitis in (percentage of cases):

Choose one of the following answers

- >75%
- 50-75%
- 10-50%
- <10%

In your personal experience the method of choice for confirming presence of biliary sludge/microlithiasis is:

Choose one of the following answers

- EUS
- MRI
- CT
- Transabdominal ultrasound
- ERCP
- ERCP + microscopic examination of the bile

What would be your FIRST CHOICE of treatment when microlithiasis/sludge is detected during IAP etiology assessment:

Choose one of the following answers

- Cholecystectomy (preferably laparoscopic)
- ERCP, with sphincterotomy
- Non-invasive (UDCA treatment)
- All of above options are equally of use

How often do you use ursodesoxycholic acid in patients with IAP and biliary sludge for prevention of sludge formation:

Choose one of the following answers

- Always
- Only in patients not qualified for surgical or endoscopic intervention
- Never

When EUS is not available, but elevated liver function tests are detected (e.g., ALAT levels >150 U/L within 48 h after onset of symptoms) and other criteria of idiopathic pancreatitis are met, the patient should be referred for cholecystectomy:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

When EUS is not available, but elevated liver function tests are detected (e.g., ALAT levels >150 U/L within 48 h after onset of symptoms) and other criteria of idiopathic pancreatitis are met, the patient should be reffered for ERCP with sphincterotomy:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

When EUS is not available, but elevated liver function tests are detected (e.g., ALAT levels >150 U/L within 48 h after onset of symptoms) and other criteria of idiopathic pancreatitis are met, UDCA therapy should be prescribed:

Choose one of the following answers

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

8. Pancreatitis patient population stratified by underlying biliary entity

Of the initial 601 acute biliary pancreatitis patients retrospectively identified via ICD-10 code who were hospitalised at LMU University Hospital between 2005 and 2021, 101 patients were excluded from the final evaluation due to double recording, 82 patients due to incomplete data sets and 70 patients due to possible additive underlying pancreatitis etiologies (alcohol-induced, autoimmune pancreatitis, anatomical anomaly, idiopathic pancreatitis; Genetic pancreatitis susceptibilities were not found in the collective (as far as could be recorded retrospectively). Of 348 patients with biliary pancreatitis, 171 were excluded due to the occurrence of combined biliary concrementalities, so that 84 gallstone-induced pancreatitis patients, 43 microlithiasis-induced pancreatitis patients and 50 singular sludge-induced pancreatitis patients were finally evaluated. The statistical analysis was performed using the one-way ANOVA (baseline characteristics) and the Chi-Square test (clinical outcome) with an assumed statistical significance at $p < 0.05$.

	Sludge-AP (n = 50)	Microlithiasis-AP (n = 43)	Gallstone-AP (n = 84)	p Value
Sex, N (%)				
M	24 (48 %)	19 (44.18 %)	39 (46.42 %)	
F	26 (52 %)	24(55,81 %)	45 (53.57 %)	
Age, median (range)	66 (26-96)	59 (21-96)	69 (22-101)	0.0058**
BMI (kg/m²)	26.49 ± 5.48	30.83± 7.98	27.32± 6.36	0.0103*
Concrement localisation (%)				
GB	54 %	51.2 %	54.7 %	0.99 (ns)
CBD	28 %	30.2 %	28.6 %	
GB + CBD	18 %	18.6 %	16.7 %	
CBD with in mm (mean ± SD)	7.6 ± 3.2	8.7 ± 3.9	9.7 ± 4.2	0.017*
Comorbidities, N(%)				
None	17 (34 %)	13 (30.23 %)	27 (32.14 %)	
Cholecystectomy	3 (6 %)	4 (9,3 %)	11 (13.09 %)	
Gastritis/Reflux	3 (6 %)	6 (13.95%)	6 (7.14 %)	
Liver disease	4 (8 %)	2 (4.65 %)	11 (13.09 %)	
Cardiac disease	16 (32 %)	11 (25.58 %)	24 (28.57 %)	
Carcinoma in history/current	6 (12 %)	4 (9.3 %)	15 (17.85 %)	
Upper GI tract surgery	3 (6 %)	2 (4.65 %)	2 (2.38 %)	
Dyslipidemia	9 (18 %)	6 (13.95%)	13 (15.47 %)	
Diabetes mellitus II	8 (16 %)	4 (9.3 %)	10 (11.9 %)	
Arterial hypertension	27 (54 %)	19 (44.18 %)	41 (48.8 %)	
Medication on admission				
None	19 (38 %)	15 (34.88 %)	32 (39.09 %)	
PPI	10 (20 %)	12 (27.9 %)	20 (23.8 %)	
Antihypertensive drugs	24 (48 %)	19 (44.18 %)	40 (47.61 %)	
Lipid lowering drugs	12 (24 %)	6 (13.95 %)	16 (19.04 %)	
Diuretics	5 (10 %)	7 (16.27 %)	17 (20.23 %)	
Analgesics	0 (0 %)	2 (4.65 %)	0 (0 %)	
Pancreatic enzymes	0 (0 %)	0 (0 %)	0 (0 %)	
UDCA	1 (2 %)	1 (2.32 %)	1 (1.19 %)	
Immunosuppressant drugs	2 (4 %)	0 (0 %)	6 (7.14 %)	

Supplement Table 2. Baseline characteristics

9. Audience Agreement

The term „biliary sludge“ can be used both to diagnose findings in the bile duct as well as the gallbladder	
Strongly agree	34.5 %
Agree	55.2 %
Neutral	3.5 %
Disagree	6.7 %

Discrete, hyperechoic material inside the gallbladder or the bile duct, without acoustic shadowing, which sediments in the most dependent part of the gallbladder represents biliary sludge	
Strongly agree	35.3 %
Agree	35.3 %
Neutral	23.5 %
Disagree	5.99 %

The term „biliary microlithiasis“ should be used exclusively for cases in which EUS examination of the biliary tree reveals presence of stones > 3 and less than 5 mm (in diameter) with acoustic shadowing:	
Strongly agree	47.9 %
Agree	17.4 %
Neutral	13.0 %
Disagree	17.4 %
Strongly disagree	4.3 %

Supplement Table 3.

Based on the survey expert consensus (biliary sludge) and survey expert consensus/internal review, the three statements were released for online plenary voting at the European Pancreatic Congress 2021 during the session on biliary pancreatitis. 89·7 % agreed that biliary sludge can be named as such in the gallbladder and common bile duct (n = 29). 70·6 % agreed that biliary sludge should be described sonomorphologically as discrete, hyperechoic material inside the gallbladder or the bile duct, without acoustic shadowing, which sediments in the most dependent part of the gallbladder represents biliary sludge (n = 17). 65·3% agreed with the definition that biliary microlithiasis is in a size range between 3 and 5 mm (n = 23).

10. Clinical Case Vignettes

In the clinical case vignette's part, the experts were asked to analyze transabdominal and endosonographic ultrasound images together with a short clinical case description and laboratory values. All cases included real-life scenarios selected among patients who presented themselves in the Emergency Department of LMU University Hospital in Munich-Grosshadern between 2018-2020. In case vignettes 1 and 3, terminology for concrements in the gallbladder and the common bile duct had to be selected, while in case vignettes 2, 4, 5, 6, and 7, terminology for concrements in the gallbladder or the common bile duct had to be given and a therapy recommendation had to be made. The following results were derived from the survey: 1) there is deep disagreement as to the definition of microlithiasis and biliary sludge among experts. 2) in case of microlithiasis with pain endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (SE) is more frequently recommended than cholecystectomy (76·9 % vs. 15·4 % and 88·5 % vs. 0·0 %, respectively p = 0·056). In case of biliary sludge ERCP with sphincterotomy was recommended as the therapeutic approach of choice (p = 0·021). If gallbladder stones were present ERCP with sphincterotomy received only 34·6 % of the votes and thus only slightly more than cholecystectomy with 26·9 %. Noninvasive UDCA therapy was also considered reasonable by 15·4 % of the experts in this case of a 23-year-old patient with a recurrent right upper abdominal colic. In case vignettes 4, the clear recommendation was for ERCP with sphincterotomy (84·6 %), whereas in case vignette 7, 88·5% favored cholecystectomy.

Case Vignettes	Biochemical results	Expert Vote - Sonomorphology		Expert Vote - Treatment	
Case 1		One answer choice allowed		First choice of treatment	
33-year-old woman severe abdominal pain, no chronic diseases, no trauma, no alcohol history	CRP 0,7 mg/dl Lipase > 7000 U/l Amylase 2056 U/l ALT, AST, GGT, Bilirubin ⇑	Biliary Sludge (both GB and CBD): Biliary Microlithiasis (both GB and CBD): Biliary Sludge (GB) and Microlithiasis (CBD): Biliary Microlithiasis (GB) and Sludge (CBD): Gallstone(s) (both GB and CBD):	11.5 % 7.7 % 3.8 % 65.4 % 7.7 %	CHE: ERCP + EPT: UDCA: All equal: Other:	15.4 % 76.9 % 0.0 % 3.8 % 0.0 %
Case 2		CBD			
70-year-old woman, dilatation of CBD in US (11 mm), no focal lesions found on CT, no history of biliary-type pain in the past, no pancreatitis in the past	CRP 2,3 mg/dl Lipase n.c. Amylase n.c. ALT, AST, GGT, Bilirubin ⇑	Biliary Sludge: Biliary Microlithiasis: Biliary Sludge and Microlithiasis: Gallstone(s):	76.9 % 11.5 % 7.7 % 0.0 %	CHE: ERCP + EPT: UDCA: All equal: Other:	7.7 % 69.2 % 11.5 % 0.0 % 7.7 %
Case 3		GB + CBD			
53-year-old man, relapsing upper-right and upper-middle quadrant abdominal pain, sporadically vomiting, no history of pancreatitis,	CRP 0.8 mg/dl Lipase normal Amylase normal ALT, AST, GGT, Bilirubin ⇑	Biliary Sludge (both GB and CBD): Biliary Microlithiasis (both GB and CBD): Biliary Sludge (GB) and Microlithiasis (CBD): Biliary Microlithiasis (GB) and Sludge (CBD): Gallstone(s) (both GB and CBD):	23.1 % 0.0 % 65.4 % 3.8 % 0.0 %	CHE: ERCP + EPT: UDCA: All equal: Other:	0.0 % 88.5 % 0.0 % 0.0 % 3.8 %
Case 4		CBD			
62-year-old male, with colic upper right quadrant abdominal pain	CRP normal Lipase 282 U/l Amylase n.c. ALT, AST, GGT ⇑ Bilirubin normal	Biliary Sludge: Biliary Microlithiasis: Biliary Sludge and Microlithiasis: Gallstone(s):	7.7 % 38.5 % 11.5 % 34.6 %	CHE: ERCP + EPT: UDCA: All equal: Other:	0.0 % 84.6 % 3.8 % 0.0 % 3.8 %
Case 5		CBD			
46-year-old patient, severe abdominal pain, no trauma, no history of alcohol abuse, no history of chronic diseases	CRP 1,5 mg/dl Lipase > 6000 U/l Amylase n.c. ALT, AST, GGT Bilirubin ⇑	Biliary Sludge: Biliary Microlithiasis: Biliary Sludge and Microlithiasis: Gallstone(s):	69.2 % 15.4 % 7.7 % 0.0 %	CHE: ERCP + EPT: UDCA: All equal: Other:	15.4 % 69.2 % 3.8 % 3.8 % 0.0 %
Case 6		CBD			
23-year-old patient with repeating episodes of colic pain in the right upper abdominal quadrant, biochemically and on the abdominal US no other pathologies	CRP 0,7 mg/dl Lipase normal Amylase n.c. ALT, AST, GGT and Bilirubin normal	Biliary Sludge: Biliary Microlithiasis: Biliary Sludge and Microlithiasis: Gallstone(s):	84.6 % 7.7 % 0.0 % 0.0 %	CHE: ERCP + EPT: UDCA: All equal: Other:	26.9 % 34.6 % 15.4 % 3.8 % 11.5 %
Case 7		GB			
44-year-old patient with repeated right upper abdominal pain and history of cholestasis	Biochemically no pathologies reported	Biliary Sludge: Biliary Microlithiasis: Biliary Sludge and Microlithiasis: Gallstone(s):	11.5 % 15.4 % 34.6 % 30.8 %	CHE: ERCP + EPT: UDCA: All equal: Other:	88.5 % 3.8 % 0.0 % 0.0 % 0.0 %

Supplement Table 4. Case vignettes

On the basis of original case vignettes from the LMU hospital (Munich), the experts interviewed were to make definitional and therapeutic decisions on the basis of image-morphological and laboratory-chemical criteria. The laboratory values on presentation of the patients in the emergency room were presented, as well as an (endo)sonographic image with pre-marked concrements for more precise classification.