

Liver, Pancreas and Biliary Tract

Lower rate of pancreatobiliary complications after sludge and microlithiasis pancreatitis compared to gallstone pancreatitis



Simon Sirtl^a, Bianca Teodorescu^{a,b,c,d}, Leonard Gilberg^e, Arlett Schäfer^a, Georg Beyer^a, Anna Arnau^{f,g,h}, Pablo López-Guillénⁱ, Samuel J. Martínez-Domínguez^{j,k}, Daniel Abad Baroja^{k,l}, Daniel Oyón^{m,n}, Lara M. Ruiz-Belmonte^j, Javier Tejedor-Tejada^o, Raul Zapater^p, Noelia Martín-Vicente^m, Pedro José Fernández-Esparcia^q, Ana Belén Julián Gomara^l, Violeta Sastre Lozano^r, Juan José Manzanares García^r, Irene Chivato Martín-Falquina^s, Laura Andrés Pascual^s, Nuria Torres Monclus^t, Natividad Zaragoza Velasco^t, Eukene Rojo^{u,v}, Berta Lapeña-Muñoz^w, Virginia Flores^x, Arantxa Díaz Gómez^x, Pablo Cañamares-Orbís^{k,y}, Isabel Vinzo Abizanda^z, Natalia Marcos Carrasco^p, Laura Pardo Grau^{aa}, Guillermo García-Rayado^{j,k}, Judith Millastre Bocos^{j,k}, Ana Garcia Garcia de Paredes^{p,ab,ac,ad}, María Vaamonde Lorenzo^{ae}, Arantzazu Izagirre Arostegi^{ae}, Edgard Efrén Lozada-Hernández^{af}, José Antonio Velarde-Ruiz Velasco^{ag}, Michal Žorniak^{a,ah}, Enrique de-Madaria^{ai,aj}, Julia Mayerle^{a,*}, Raúl Velamazán^{j,k}

^a Department of Medicine II, LMU University Hospital, Munich, Germany

^b Chair of Translational Cancer Research and Institute of Experimental Cancer Therapy, Klinikum rechts der Isar, School of Medicine, Technische Universität München, Munich, Germany

^c Center for Translational Cancer Research (TranslaTUM), School of Medicine, Technical University of Munich, Munich, Germany

^d German Cancer Consortium (DKTK), partner site Munich, a partnership between DKFZ and LMU University Hospital Munich (LMU Klinikum), Germany

^e Department of Medicine II, Technical University of Munich, School of Medicine, University Hospital rechts der Isar, Munich, Germany

^f Research and Innovation Unit, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain

^g Central Catalonia Chronicity Research Group (C3RG), Centre for Health and Social Care Research (CESS), University of Vic-Central University of Catalonia (UVIC-UCC), Vic, Spain

^h Faculty of Medicine, University of Vic-Central University of Catalonia (UVIC-UCC), Vic, Spain

ⁱ Department of Gastroenterology, Hospital Universitario de Torrevieja, Alicante, Spain

^j Department of Gastroenterology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

^k IIS (Instituto de Investigación Sanitaria) Aragón, Zaragoza, Spain

^l Department of Gastroenterology, Hospital Universitario Miguel Servet, Zaragoza, Spain

^m Department of Gastroenterology, Hospital de Galdakao, Bizkaia, Spain

ⁿ Instituto de Investigación Sanitaria Biocruces, Bizkaia, Spain

^o Department of Gastroenterology, Hospital Universitario Río Hortega, Valladolid, Spain

^p Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Madrid, Spain

^q Universidad Miguel Hernández, Elche, Spain

^r Department of Gastroenterology, Hospital Universitario Santa Lucía, Cartagena, Spain

^s Department of Gastroenterology, Hospital Universitario de Burgos, Burgos, Spain

^t Department of Gastroenterology, Hospital Universitario Arnau de Vilanova, Lleida, Spain

^u Department of Gastroenterology, Hospital Universitario de La Princesa, Madrid, Spain

^v IIS (Instituto de Investigación Sanitaria)-Princesa, Madrid, Spain

^w Department of Gastroenterology, Hospital Universitario San Pedro, Logroño, Spain

^x Department of Gastroenterology, Hospital Universitario Gregorio Marañón, Madrid, Spain

^y Gastroenterology, Hepatology and Nutrition Unit, Hospital Universitario San Jorge, Huesca, Spain

^z Specialist in Family and Community Medicine, Hospital Universitario San Jorge, Huesca, Spain

^{aa} Department of Gastroenterology, Hospital Universitario Josep Trueta, Girona, Spain

Abbreviations: ALT, Alanine aminotransferase; AP, Acute pancreatitis; AST, Aspartate aminotransferase; CBD, Common bile duct; EUS, Endosonography; ERCP, Endoscopic retrograde cholangiopancreatography; ES, Endoscopic sphincterotomy; ICU, Intensive care unit; IAP, Idiopathic acute pancreatitis; MRCP, Magnetic resonance cholangiopancreatography; MRI, Magnetic resonance imaging; RAC, Revised Atlanta Classification.

* Corresponding author at: Department of Medicine II, University Hospital LMU Munich, Marchioninistr. 15, 81377 Munich, Germany.

E-mail address: julia.mayerle@med.uni-muenchen.de (J. Mayerle).

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^{ab} Universidad de Alcalá, Madrid, Spain^{ac} IRYCIS (Instituto Ramón y Cajal de Investigación Sanitaria), Madrid, Spain^{ad} Centro de Investigación Biomedica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd) Instituto de Salud Carlos III, Madrid, Spain^{ae} Department of Gastroenterology, Hospital Universitario Donostia, Donostia, Spain^{af} Department of Surgery, Hospital Regional de Alta Especialidad Del Bajío-IMSS Bienestar, León, Mexico^{ag} Department of Gastroenterology, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico^{ah} Endoscopy Department, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice, Poland^{ai} Department of Gastroenterology, Hospital General Universitario Dr. Balmis, Alicante, Spain^{aj} ISABIAL (Instituto de Investigación Sanitaria y Biomédica de Alicante), Alicante, Spain

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ABSTRACT

Background and Aims: Cholecystectomy is recommended to prevent recurrence of biliary pancreatitis, but supporting evidence is limited for sludge- and microlithiasis-induced acute pancreatitis (AP). This study aimed to compare relapse patterns and risk factors between patients with sludge/microlithiasis-induced AP and gallstone-induced AP.

Methods: This analysis included 789 patients from the international, multicenter Relapstone cohort (Spain: 16 centers; Mexico: 2 centers), hospitalized between January 2018 and April 2020 with first-time biliary AP and no cholecystectomy during admission. Patients with sludge/microlithiasis-induced AP ($n = 274$) were compared to those with gallstone-induced AP ($n = 515$) regarding pancreatobiliary complications. Multivariate analysis was used to assess relapse risk factors.

Results: Pancreatobiliary complications occurred in 41.7 % of the gallstone cohort versus 32.1 % in the sludge/microlithiasis cohort ($p = 0.01$). Correspondingly, the gallstone AP cohort showed a significantly lower complication-free survival rate (log-rank $p = 0.0022$; median follow-up: 6.1 vs. 8.1 months). In multivariate analysis, older age in the gallstone group was significantly associated with lower relapse risk (HR = 0.54, 95 % CI: 0.39–0.74).

Conclusion: This multicenter study reveals distinct differences in relapse risk between gallstone- and sludge/microlithiasis-induced AP, with gallstone AP showing a higher rate of complications in the absence of cholecystectomy.

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1. Introduction

The prevalence of gallstone disease and gallstone pancreatitis has increased remarkably in recent decades [1,2]. This is due to increased metabolic risk factors, a more standardized global definition of acute pancreatitis, and the increased use of high-resolution imaging techniques such as endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI)/ MRI cholangiopancreatography (MRCP) [3,4]. EUS, in particular, has a high sensitivity in diagnosing gallstones compared to conventional ultrasonography, reclassifying 25 % of pancreatitis considered idiopathic as gallstone-induced [5,6]. A distinction is made between three types of calculi. In addition to classic gallstones, biliary sludge and microlithiasis have increasingly become the focus of attention, especially due to the higher detection rates by EUS [7]. Prospective studies on the pathogenicity of sludge and microlithiasis in acute pancreatitis are still lacking.

In contrast to gallstones, it is known that sludge and possibly also microlithiasis have a high probability of spontaneous resolution [8,9]. In addition to the physicochemical bile composition and interaction, gallbladder hypomotility plays a decisive role in sludge formation [8,10,11]. There are data from various cohorts that suggest that if the specific trigger for sludge formation is eliminated, spontaneous sludge resolution occurs in 30 - 100 % of cases. Typical examples of sludge formation and resolution during the course are pregnant women, patients on total parenteral nutrition, organ transplants, or taking special medications such as ceftriaxone [12–15]. Concerning the assessment of sludge and microlithiasis, many guidelines take a pragmatic approach due to a lack of high-quality data and recommend treatment equivalent to gallstones [16,17]. Data from retrospective studies show that the severity of acute pancreatitis and cholestasis does not differ significantly between sludge, microlithiasis, and gallstone pancreatitis. However, the retrospective study design limits further conclusions and does

not answer whether sludge and microlithiasis in acute pancreatitis should be interpreted as a pancreatitis-related gallbladder hypomotility-induced epiphenomenon [7,18]. Dutch data show that sludge and microlithiasis are also assessed differently from the endoscopist's point of view than gallstones in terms of interventional risk tolerance towards stone extraction. In a video-based study, in contrast to gallstones, sludge and microlithiasis triggered an enormous therapeutic range of 10 - 90 % regarding whether sludge and microlithiasis should be extracted from the common bile duct using ERC and ES [19].

In the case of biliary pancreatitis, there is not only the question of therapeutic intervention in terms of acute treatment, but also the question of how to prevent recurrence. Evidence is lacking for sludge and microlithiasis-induced pancreatobiliary complications after biliary pancreatitis, especially in comparison to gallstone pancreatitis. A lack of differentiation between the three types of calculi and a subsumption of sludge and microlithiasis in either the gallstone pancreatitis cohort or the IAP cohort has so far made calculi-specific risk assessment difficult. Therefore, this multicenter study aimed to describe for the first time pancreatobiliary complication rates after first-time sludge/microlithiasis AP compared to gallstone AP.

2. Methods

2.1. Patient selection

A total of 941 patients with a first episode of biliary pancreatitis from the international multicenter retrospective RELAPSTONE cohort were screened for inclusion in the study [20]. The patients were treated as inpatients for biliary pancreatitis at sixteen Spanish and two Mexican centers between 1 January 2018 and 30 April 2020 (all participating centers are listed at the end of the manuscript). The definition of acute biliary pancreatitis was

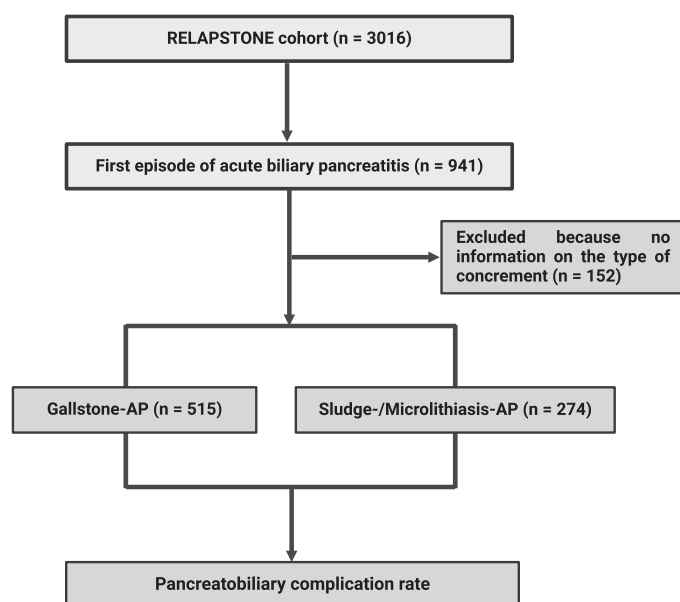


Fig. 1. Relapstone patient selection stratified by underlying concrement type.

based on the revised Atlanta Classification and the mandatory detection of sludge, microlithiasis or gallstones during hospitalization [3]. Patients were classified retrospectively into the gallstone-AP group if imaging revealed gallstones larger than 5 mm with corresponding acoustic shadowing. Those with echogenic calculi ≤ 5 mm accompanied by acoustic shadowing, or with hyperechoic material lacking acoustic shadowing, were assigned to the microlithiasis/sludge AP group. If classification into the sludge/microlithiasis or gallstone group was not possible using transabdominal ultrasound or CT, second-level imaging with EUS or MRI/MRCP was performed to confirm the diagnosis and ensure the most accurate characterization of the concretions. To analyze pancreatobiliary complication rates between the sludge/microlithiasis-induced and gallstone-induced pancreatitis patients, all patients who had undergone cholecystectomy or endoscopic sphincterotomy as part of a previous hospital presentation due to previous pancreatitis or any other pancreatobiliary reason were excluded. Patients with cholecystitis and cholangitis were also excluded, as both diagnoses would have resulted in an indication for surgery or endoscopic retrograde cholangiopancreatography (ERCP), biasing the pancreatobiliary complication. The definitions for cholecystitis and cholangitis are based on the Tokyo Guidelines 2018 [21,22]. Patients who died during the index admission, patients with previous pancreaticobiliary surgery, and patients with biliary, duodenal, or pancreatic cancer were also excluded, as were patients with benign biliary strictures. One hundred fifty-two patients were excluded as the type of calculi could not be extracted from the records. Based on the types of calculi, the biliary pancreatitis cohort ($n = 789$) was stratified into sludge/microlithiasis patients ($n = 274$) and gallstone patients ($n = 515$; Fig. 1). The end of follow-up was defined as cholecystectomy, death of a patient or the last available record on hospital admission until April 30th 2020. A key factor contributing to the methodological analyzability of the cohort was the absence of an active decision-making process regarding surgery. Instead, the observation period for both cohorts was determined by the waiting time for a potential cholecystectomy, rather than being influenced by selection bias from active patient selection. This biliary pancreatitis cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Supplement Table 1) [23]. Data was collected in anonymized form.

2.2. Primary and secondary endpoint

The primary endpoint was the rate of pancreaticobiliary complications in patients with sludge/microlithiasis versus gallstone pancreatitis, measured as complication-free survival rate. The type of pancreaticobiliary complications for each case was recorded as a secondary endpoint. The following were evaluated as pancreaticobiliary complications during follow-up: acute pancreatitis (classified according to RAC), acute cholecystitis, acute cholangitis, symptomatic choledocholithiasis, and biliary colic, always with the need for re-hospitalization.

2.3. Statistical analysis

The Mann-Whitney U test was used for comparison of continuous variables as appropriate. Categorical variables were analyzed using the Chi-squared test. A p -value < 0.05 was considered statistically significant. Missing data were imputed (median values for continuous variables and mode values for categorical variables) for independent variables with $< 5\%$ missing data. Kaplan-Meier survival curves and subsequent statistical analyses were conducted using R (version 4.4.0) and RStudio (version 2023.06.1). Relapse analysis was performed using the “survival” package[24], with the log-rank test employed for bivariate comparisons to evaluate differences in complication-free survival probabilities during the 24 months following the first episode of AP. Multivariate analysis was conducted using the “survivalAnalysis” package[25] to assess the impact of multiple variables on complication-free survival. No custom functions were developed for this study. The R scripts and functions used in the analysis are available upon request.

3. Results

3.1. Population characteristics

The majority of patients with biliary pancreatitis suffered from gallstone-induced pancreatitis ($n = 515/789$, 65.2 %). In both gallstone and the sludge/microlithiasis AP cohorts, the majority of patients were female, $n = 280/515$ (54.3 %) and $n = 146/274$ (53.2 %) respectively. The sludge/microlithiasis AP cohort was significantly older than the gallstone AP cohort: 71.9 years [IQR: 57.80 - 83.62] vs. 68.9 years [IQR: 51.08 - 79.26], $p < 0.001$. 9.5 % of the gallstone AP cohort and 17.14 % of the sludge/microlithiasis AP cohort underwent endosonography during the episode of pancreatitis, while 29.5 % of the gallstone AP and the sludge/microlithiasis cohort underwent MRI. Based on the Charlson comorbidity index, there were no significant differences between the two AP cohorts. In both cohorts, most patients had a low comorbidity score of 0–1 points (gallstone AP: 371/515 (72.0 %) vs. sludge/microlithiasis AP: 189/274 (68.9 %), $p = 0.412$). A detailed list of all comorbidities, stratified by gallstones vs. sludge/microlithiasis AP, can be found in Table 1.

3.2. Outcome of the pancreatitis index episode

No significant difference was found between the two AP cohorts regarding mild and moderate pancreatitis. 76.3 % of the gallstone AP patients and 81.0 % of the sludge/microlithiasis AP patients experienced mild pancreatitis ($p = 0.153$, Table 2). However, the gallstone AP cohort showed a significantly higher rate of severe pancreatitis (7.3 % ($n = 38/515$) vs. 2.5 % ($n = 7/274$), $p = 0.01$). In line with the low number of severe cases, only 12.0 % of gallstone AP patients and 9.4 % of sludge/microlithiasis patients developed acute peripancreatic fluid collection (or pancreatic pseudocyst; $p = 0.33$) and 9.9 % of gallstone AP patients and 8.3 %

Table 1
Baseline characteristics.

	Gallstone-AP	Sludge-/Microlithiasis-AP	p-value
Patients, N	515 (65.27 %)	274 (34.73 %)	
Sex, N (%)			
M	235 (45.63 %)	128 (46.72 %)	0.84
F	280 (54.37 %)	146 (53.28 %)	0.83
Age (median), IQR	68.99 [51.08 - 79.26]	71.96 [57.80 - 83.62]	<0.001
Concrement localisation (%)			
Gallbladder	481 (93.40 %)	274 (100.00 %)	<0.001
Common bile duct	22 (4.27 %)	0	<0.001
Gallbladder + Common bile duct	12 (2.33 %)	0	<0.001
Imaging performed during pancreatitis hospitalisation			
Transabdominal ultrasonography	463 (89.90 %)	257 (93.80 %)	
Endoscopic Ultrasound	49 (9.51 %)	47 (17.15 %)	
Magnetic resonance imaging	152 (29.51 %)	81 (29.56 %)	
Computed axial tomography	234 (45.44 %)	135 (49.27 %)	
Charlson comorbidity index diseases			
Myocardial infarction	33 (6.41 %)	19 (6.93 %)	
Congestive heart failure	22 (4.27 %)	16 (5.84 %)	
Peripheral vascular disease	19 (3.69 %)	13 (4.74 %)	
Cerebrovascular disease	27 (5.24 %)	26 (9.49 %)	
Dementia	24 (4.66 %)	23 (8.40 %)	
Chronic pulmonary disease	59 (11.46 %)	32 (11.68 %)	
Rheumatologic disease	16 (3.11 %)	8 (2.92 %)	
Peptic ulcer disease	17 (3.30 %)	8 (2.92 %)	
Mild liver disease	13 (2.52 %)	8 (2.92 %)	
Moderate or severe liver disease	4 (0.78 %)	2 (0.73 %)	
Diabetes without chronic complications	79 (15.34 %)	50 (18.25 %)	
Diabetes with chronic complications	8 (1.55 %)	6 (2.19 %)	
Hemiplegia or paraplegia	3 (0.58 %)	2 (0.73 %)	
Chronic renal disease	42 (8.15 %)	19 (6.93 %)	
Non-metastatic solid tumor	47 (9.13 %)	22 (8.03 %)	
Metastatic solid tumor	6 (1.17 %)	2 (0.73 %)	
Leukemia	2 (0.39 %)	2 (0.73 %)	
Lymphoma	5 (0.97 %)	3 (1.10 %)	
AIDS	1 (0.20 %)	0 (0 %)	
Charlson comorbidity index			
Low comorbidity (0–1)	371 (72.04 %)	189 (68.98 %)	0.41
Medium comorbidity (2)	101 (19.61 %)	65 (23.72 %)	0.21
High comorbidity (3 or more)	43 (8.35 %)	20 (7.30 %)	0.70

of sludge/microlithiasis patients developed some form of necrotic collection (ANC or WOPN, $p = 0.57$). The length of hospitalization was 6 days in both groups. In the gallstone AP cohort, 2.5 % and in the sludge/microlithiasis AP cohort, 1.1 % required intensive care treatment ($p = 0.28$). In the gallstone AP cohort, significantly higher median values for bilirubin and ALT were observed within the first 48 h after hospital admission compared to the sludge/microlithiasis AP cohort (bilirubin: 1.56 mg/dL vs. 1.01 mg/dL, $p = < 0.001$; ALT: 126.00 U/L vs. 70.00 U/L, $p = < 0.001$). No significant differences in c-reactive protein values were found between the two cohorts in the first 48 h after hospital admission and in the highest measured value. Likewise, no significant difference was found in the number of ERCPs performed (gallstone AP: 50 (9.71 %) vs. sludge/microlithiasis AP: 19 (6.93 %), $p = 0.23$) and the number of ERCP complications (1.36 % vs. 1.10 %, $p = 0.99$). The median follow-up time was significantly longer in the sludge/microlithiasis-AP cohort (8.15 months) than in the gallstone-AP cohort (6.13 months; $p < 0.001$). During follow-up, 339 (65.83 %) patients in the gallstone AP cohort and 154 (56.20 %) patients in the sludge/microlithiasis AP cohort underwent cholecystectomy after a median waiting period of 4.3 and 4.6 months, respectively ($p = 0.41$).

3.3. Pancreatobiliary complication rate

The complication-free survival rate at 6 months was 0.67 [95 % CI: 0.62 – 0.71] for the gallstone AP cohort and 0.75 [95 % CI: 0.69 – 0.81] for the sludge/microlithiasis AP cohort ($p = 0.27$). At 12 months follow-up, the complication-free survival rate was

0.55 for the gallstone AP cohort [95 % CI: 0.49 – 0.61] and 0.73 for the sludge/microlithiasis AP cohort [95 % CI: 0.67 – 0.79], ($p = 0.09$). At 24 months follow-up, the complication-free survival rate was 0.46 for the gallstone AP cohort [95 % CI: 0.39 – 0.53] and 0.59 for the sludge/microlithiasis AP cohort [95 % CI: 0.51 – 0.69], ($p = 0.002$). The gallstone AP cohort showed a significantly lower complication-free survival rate than the sludge/microlithiasis AP cohort (log-rank $p = 0.0022$, Fig. 2). Over the entire follow-up period, the rate of pancreaticobiliary complications was 41.75 % (215/515) in the gallstone AP cohort compared to 32.12 % (88/274) in the sludge/microlithiasis AP cohort ($p = 0.01$, Table 3). The most common complication was a recurrent episode of acute pancreatitis, with a frequency of 24.08 % in the gallstone AP cohort and 20.07 % in the sludge/microlithiasis cohort. The median time to the first pancreaticobiliary complication was 2.22 months in the gallstone AP cohort and 2.3 months in the sludge/microlithiasis cohort ($p = 0.96$). In the gallstone AP cohort, the highest complication rate was observed in patients with severe AP. In contrast, within the sludge/microlithiasis AP cohort, those with severe AP experienced the lowest complication rate at the 24-month follow-up (Supplement Figure 1 & 2). In the multivariate analysis, a Charlson comorbidity index of 2 points (medium) was found to be a prognostic factor for the sludge/microlithiasis AP cohort, which was independently associated with a higher risk of pancreatobiliary complications during follow-up (HR = 2.07, 95 % CI: 1.24 – 3.46). In the gallstone AP cohort, older age was significantly associated with a lower risk of pancreaticobiliary complications (HR = 0.54, 95 % CI: 0.39 – 0.74, Fig. 3), but not in patients with sludge/microlithiasis.

Table 2
Outcome of the pancreatitis index episode.

	Gallstone-AP	Sludge-/Microlithiasis-AP	p Value
RAC (Index-AP)			
Mild	393 (76.31 %)	222 (81.02 %)	0.15
Moderate	84 (16.31 %)	45 (16.42 %)	0.99
Severe	38 (7.38 %)	7 (2.56 %)	0.01
Acute peripancreatic fluid collection (or pancreatic pseudocyst)			
No collection	402 (78.06 %)	225 (82.12 %)	0.21
Liquid collection	62 (12.04 %)	26 (9.48 %)	0.33
Necrotic collection	51 (9.90 %)	23 (8.39 %)	0.57
Location of the necrotic collection			
Intrapancreatic	7 (1.36 %)	5 (1.82 %)	0.84
Extrapancreatic	21 (4.10 %)	4 (1.46 %)	0.07
Both locations	23 (4.47 %)	14 (5.11 %)	0.82
Length of hospital stay (days, median)	6	6	
ICU admission	13 (2.52 %)	3 (1.10 %)	0.28
Length of ICU stay (days, median)	6	7	
CRP (mg/L, median)			
At first 24/48 h of admission	15.00	19.70	0.56
The highest value	129.20	132.20	0.82
At discharge	34.95	42.75	0.02
Bilirubin (mg/dl, median)			
At first 24/48 h of admission	1.56	1.01	< 0.001
The highest value	1.67	1.14	< 0.001
At discharge	0.60	0.52	0.01
ALT (U/L, median)			
At first 24/48 h of admission	126.00	70.00	< 0.001
The highest value	133.50	79.00	< 0.001
At discharge	32.00	28.00	0.01
ERCP			
Performed	50 (9.71 %)	19 (6.93 %)	0.24
All stones removed	36 (7.00 %)	16 (5.84 %)	
Sphincterotomy performed	47 (9.13 %)	17 (6.20 %)	
Wirsung cannulation	16 (3.10 %)	6 (2.19 %)	
Wirsung stent	6 (1.17 %)	6 (2.19 %)	
Biliary stent	5 (0.97 %)	4 (1.46 %)	
ERCP complications	7 (1.36 %)	3 (1.10 %)	0.99
Post ERCP Pancreatitis	3 (0.58 %)	0	
Bleeding	4 (0.78 %)	2 (0.73 %)	
Others	0	1 (0.36 %)	
Median follow-up time (months)	6.13	8.15	< 0.001
Number of cholecystectomies	339 (65.83 %)	154 (56.20 %)	0.01
Median waiting time (months)	4.30	4.60	0.41
<3 months	115	50	
3–6 months	111	48	
>6 months	109	55	
NA	4	1	

Table 3
Pancreatobiliary complication rate stratified by underlying concrement type.

	Gallstone-AP	Median time to relapse	Sludge-/Microlithiasis-AP	Median time to relapse	p
Pancreatobiliary complications	215 (41.75 %)	–	88 (32.12 %)	–	0.01
a. Acute pancreatitis	124 (24.08 %)	2.20 (0.763–5.284)	55 (20.07 %)	2.59 (0.38 - 11.82)	0.23
Severity (RAC)		–		–	0.29
Mild	104 (20.20 %)		46 (16.79 %)		1.00
Moderate	13 (2.52 %)		6 (2.55 %)		1.00
Severe	7 (1.36 %)		3 (1.09 %)		
b. Acute cholecystitis	16 (3.11 %)	2.27 (1.860–2518)	3 (1.09 %)	2.43 (N/A-4.018)	0.13
c. Acute cholangitis	6 (1.17 %)	2.17 (0.583–5.733)	3 (1.09 %)	1.01 (N/A-3.819)	1.00
d. Symptomatic choledocholithiasis	12 (2.33 %)	2.83 (0.394–7.451)	5 (1.82 %)	1.05 (0.25 – 1.47)	0.83
e. Biliary colic	41 (7.96 %)	1.64 (0.560–4.609)	16 (5.84 %)	2.88 (0.67 - 4.23)	0.34
f. Any combination	16 (3.11 %)	3.65 (1.670–7.488)	6 (2.19 %)	1.31 (0.28 – 7.43)	0.60
Median time to first relapse (all; months)		2.22		2.30	0.96

4. Discussion

Our data from a large multicentre cohort demonstrate for the first time a significant difference in the rate of pancreatobiliary complications following AP between sludge/microlithiasis-AP and gallstone-AP. The lower complication rate observed dur-

ing follow-up supports, for the first time, the consideration of the sludge/microlithiasis AP cohort as a distinct clinical entity—one that may warrant a more conservative interventional approach, particularly in patients with elevated perioperative risk. Due to a lack of prospective data to assess the pathophysiological relevance of microlithiasis and sludge, several guidelines have so far taken

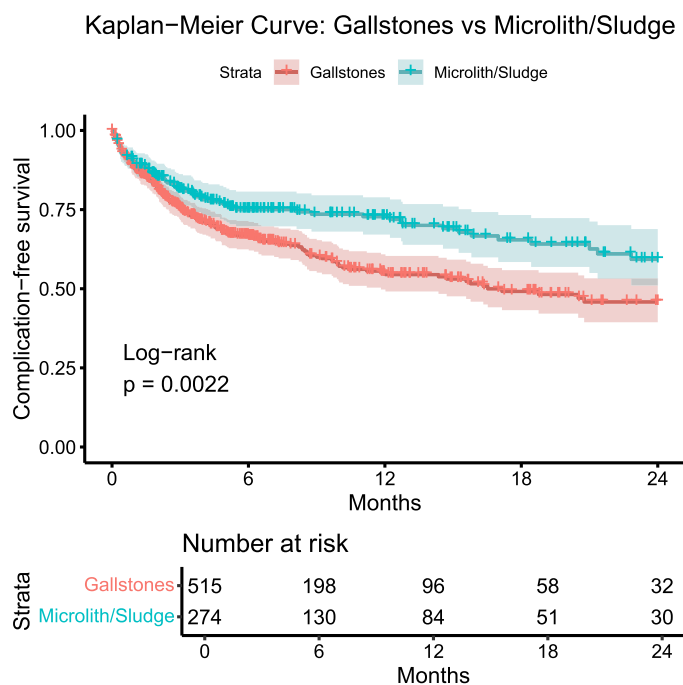


Fig. 2. Complication-free survival rate stratified by underlying concrement type.

the pragmatic approach recommending cholecystectomy if symptoms are in line with microlithiasis or sludge to prevent pancreatitis recurrence [26,27]. The evidence underlying this recommendation is weak and, for example, is based on one single-center study without using EUS to diagnose biliary sludge [28]. Data specifically on the prognostic assessment of sludge and microlithiasis in the context of AP and possible pancreaticobiliary complications in the absence of cholecystectomy or endoscopic sphincterotomy are scarce. The data are missing because cholecystectomy is a highly effective method of preventing recurrences in the case of gallstone AP and appears effective in idiopathic AP cohorts [29–32]. In the latter cohorts, sludge and microlithiasis were often subsumed under this heading without being specifically evaluated as risk factors for pancreatitis recurrence. In addition, there are ethical aspects that prohibit a watch and wait strategy after a first attack of biliary pancreatitis, since effective surgical and endoscopic measures to prevent recurrence are at hand.

As a result, little data has been collected in the past on the ‘natural history’ of sludge and microlithiasis in the context of acute pancreatitis. It is, therefore, also unknown how the spontaneous resolution of sludge and microlithiasis after cured AP compares to the risk of pancreaticobiliary complications if cholecystectomy or ERCP is not performed. Data from the retrospective US National Readmission Database (NRD) from 2010 – 2014 found a 60-day re-hospitalisation rate of 26.8 % (12,040/44,855 patients) for patients with neither a cholecystectomy nor an ERCP after suffering biliary pancreatitis [33]. The cohort was not categorized into gallstones vs. sludge/microlithiasis AP as part of the study. In our study, higher re-hospitalization rates were observed for both gallstone AP (41.75 %) and the sludge/microlithiasis AP with 32.12 %, albeit with a longer median follow-up than the US study.

For patients with symptomatic biliary sludge who did not receive cholecystectomy, a 5-year cumulative biliary event rate of 33.9 % was reported [34]. One possible explanation for the 32.12 % pancreaticobiliary complication rate in the sludge-/microlithiasis AP cohort is the comparatively low number of EUS examinations performed in this cohort (17.15 %). As a result, sludge or microlithi-

asis in the CBD may not have been detected, resulting in an equally low sphincterotomy rate of 6.2 %. The lower rate of cholecystectomies performed in the sludge-/microlithiasis-AP group is possibly an expression of a more cautious recommendation for cholecystectomy as opposed to a possibly more aggressive surgical recommendation in the case of gallstones (56.2 % vs. 65.8 % cholecystectomies performed in the follow-up period). This would be consistent with the reluctant approach of the Dutch endoscopy experts to intervene in the case of sludge, unlike in the case of gallstones, where there was a correspondingly high willingness to perform an ERC [19].

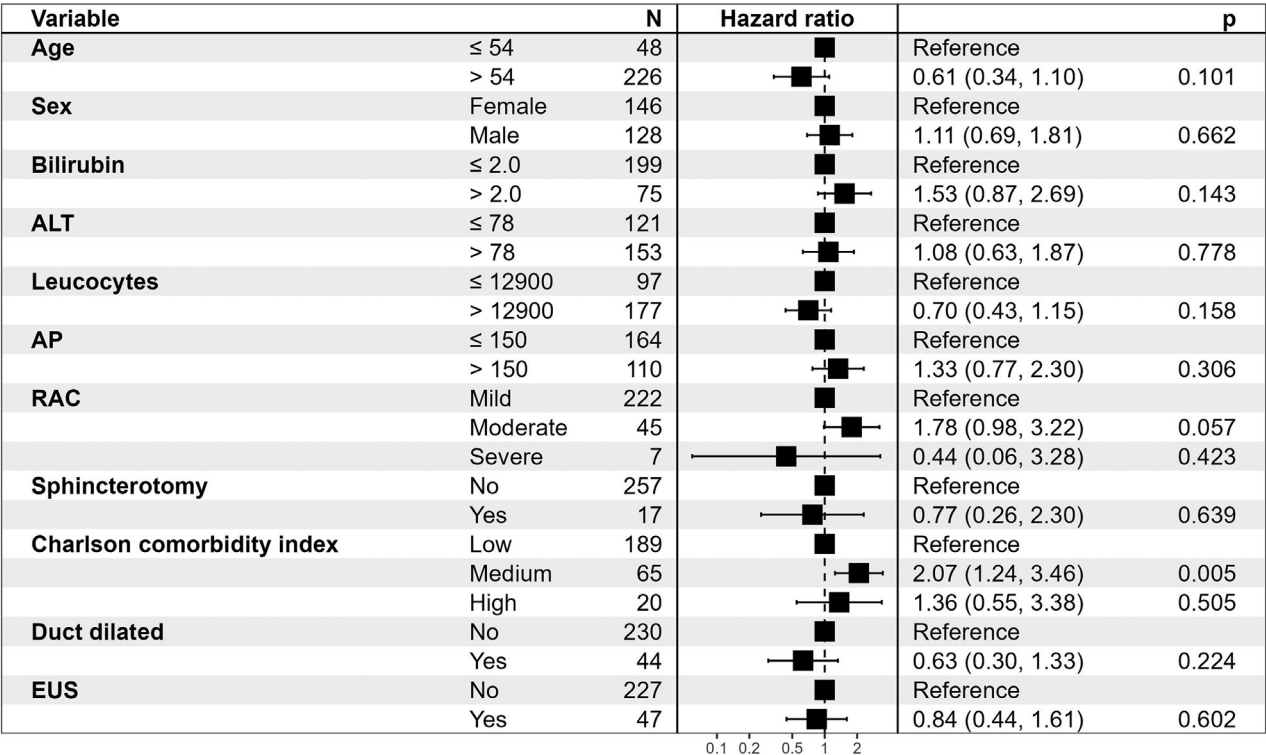
One methodological advantage that arose from the long waiting time for a cholecystectomy in Spain was the fact that the ‘natural course’ of gallstone and sludge/microlithiasis AP could be observed for the first time in the context of our study and that a systematic bias effect could be avoided by avoiding an active medical decision-making process.

For the first time, it could be shown in a large multicenter cohort that even when microlithiasis and sludge are grouped together as one cohort and compared with the classic gallstone AP, the complication rates in the follow-up are significantly lower. This effect would probably be even more pronounced if a pure sludge AP cohort with a higher post-inflammatory resolution probability were considered. Furthermore given that 10.8 % of patients suffer complications within 30 days of cholecystectomy for benign gallbladder disease and that, in an 18-month comparison, laparoscopic cholecystectomy is no better than conservative management for uncomplicated symptomatic gallstone disease, the question arises as to whether patients with sludge and microlithiasis AP should undergo cholecystectomy per se or whether an endoscopic sphincterotomy might be sufficient as an alternative procedure to prevent recurrence [35,36]. In the gallstone AP cohort, age over 54 years was a favorable prognostic factor. It correlated with a lower rate of pancreaticobiliary complications in line with previous data for patients over 70 years of age with symptomatic CBD stones after endoscopic stone removal [37]. However, it remained unclear why a medium Charlson comorbidity index in the sludge/microlithiasis AP cohort could be identified as an independent risk factor for a higher rate of pancreaticobiliary complications. It is possible that the increased disease burden and comorbidities, including pharmacotherapy in this cohort, correlates with the tendency towards increased sludge and microlithiasis formation.

4.1. Strengths and limitations

Due to the retrospective study design, it was impossible to stratify patients in advance based on the newly published consensus definition for sludge and microlithiasis [7]. This and the comparatively low rate of EUS examinations have led to some heterogeneity within the sludge and microlithiasis AP cohort, since the classification as such remained dependent on the examiner. Furthermore, the initial sample size calculation for the trial was based on the rate of pancreaticobiliary complications in symptomatic cholelithiasis, with AP as one cause. Therefore, other possible prognostic factors such as BMI, hypothyroidism or genetic predispositions may not have reached significance in the multivariate analysis. Likewise, due to the selection of the cohort as a first episode of biliary pancreatitis, no analyses could be performed with respect to a corresponding therapeutic effect of UDCA intake in this collective. Owing to the high likelihood of sludge or microlithiasis translocating into the duodenum, concretions were consistently detected only within the gallbladder in the sludge/microlithiasis-associated pancreatitis (AP) cohort. This limitation somewhat restricts the generalizability of the findings to cases involving CBD sludge or microlithiasis. Our study highlights various strengths that expand the pathophysiological understanding of sludge and mi-

A. Sludge-/Microlithiasis AP



B. Gallstone-AP

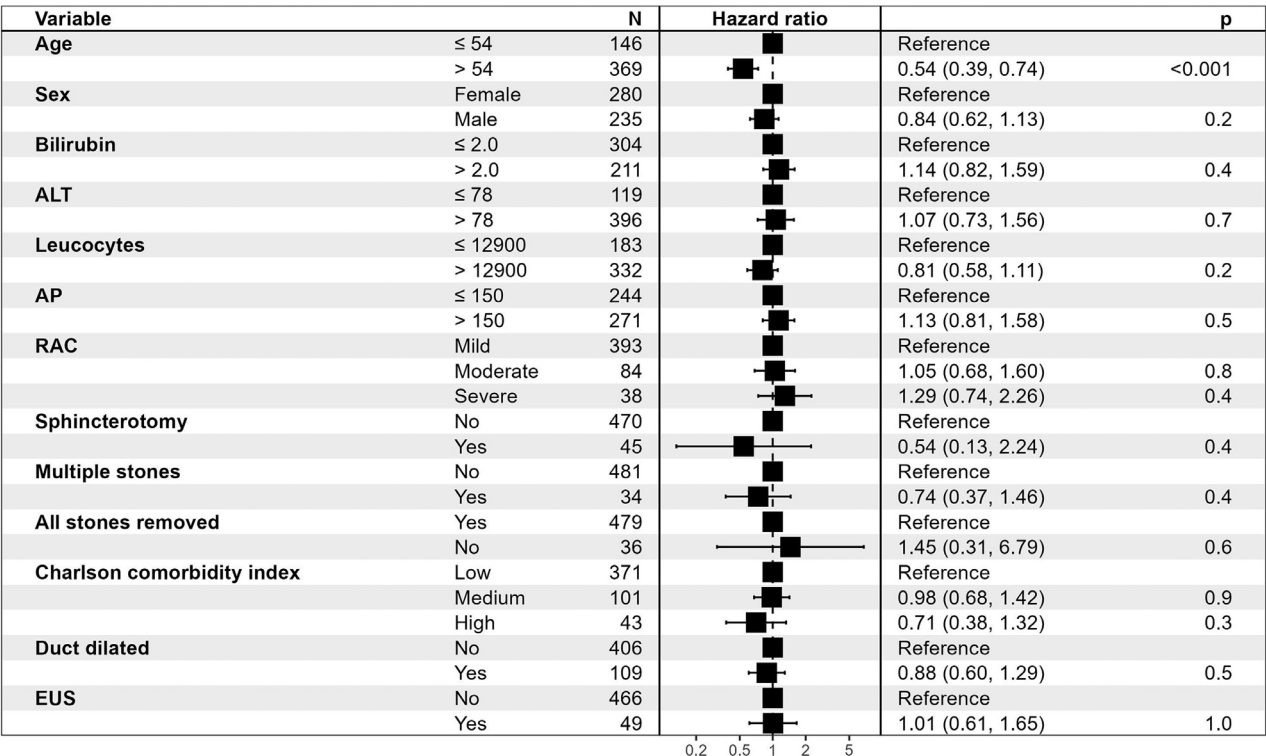


Fig. 3. Multivariate analysis - Identification of independent factors associated with relapse.

colithiasis in the context of acute pancreatitis. For the first time, we show in a large, multicenter cohort that the rates of pancreaticobiliary complications after biliary pancreatitis differ significantly between gallstone AP and sludge/microlithiasis AP patients. This provides the basis for a prospective study design to investigate whether patients with evidence of sludge and microlithiasis in the context of acute pancreatitis should always undergo cholecystectomy, as previously recommended by various guidelines, or whether an endoscopic sphincterotomy $\pm$ choleretics as a treatment option for the prevention of recurrence might be sufficient. Only a prospective trial design can ultimately determine whether sludge detected in the context of AP is merely a consequence of AP-related gallbladder hypomotility, rather than a primary causal factor of the condition. By focusing on the clinically relevant endpoint of pancreatobiliary complication rates during follow-up, such a prospective RCT would enable an initial assessment of whether offering endoscopic sphincterotomy as a non-inferior treatment option for patients with sludge- or microlithiasis-associated AP is ethically and logistically justifiable and feasible. Another strength of the study is the combination of endpoints since, unlike in previous studies, not only the rate of pancreatitis recurrence but also all symptoms associated with cholelithiasis were recorded.

5. Conclusion

Our study shows for the first time in a large multicenter cohort that the rates of pancreaticobiliary complications after acute biliary pancreatitis differ significantly between gallstones and sludge/microlithiasis AP. The rate of complications was significantly lower in patients with sludge and microlithiasis. Therefore, prospective studies are needed to validate these findings and evaluate specific treatment concepts for sludge and microlithiasis in the context of acute pancreatitis.

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Ethical committee

The study was approved by the central Institutional Review Board (CEiM, Dr. Balmis General University Hospital, reference 2020-257) and by the local Institutional Review Boards of collaborating centers.

Participating centers

Patients were recruited at 16 tertiary Spanish centers (University Hospital Lozano Blesa, Zaragoza; University Hospital Miguel Servet, Zaragoza; General University Hospital Dr. Balmis, Alicante; University Hospital Ramon y Cajal, Madrid; University Hospital Gregorio Marañón, Madrid; University Hospital La Princesa, Madrid; University Hospital Son Espases, Palma de Mallorca; University Hospital Santa Lucia, Cartagena; University Hospital Galdakao, Vizcaya; University Hospital San Pedro, Logroño; University Hospital of Donostia, Donostia; University Hospital of Burgos, Burgos; University Hospital Arnau de Vilanova, Lleida; University Hospital San Jorge, Huesca; University Hospital Josep Trueta, Girona; University Hospital Rio Hortega, Valladolid) and 2 tertiary Mexican centers (High Speciality Regional Hospital of Bajío, Leon; Civilian Hospital Fray Antonio Alcalde, Guadalajara).

Conflict of interest

None.

Author contribution

Simon Sirtl: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. **Bianca Teodorescu:** Formal analysis, Investigation, Methodology. **Leonard Gilberg:** Formal analysis, Investigation, Methodology. **Arlett Schäfer:** Investigation, Methodology. **Georg Beyer:** Investigation, Methodology. **Anna Arnau:** Data curation. **Pablo López-Guillén:** Data curation. **Samuel J. Martínez-Domínguez:** Data curation. **Daniel Abad Baroja:** Data curation. **Daniel Oyón:** Data curation. **Lara M. Ruiz-Belmonte:** Data curation. **Javier Tejedor-Tejada:** Data curation. **Raul Zapater:** Data curation. **Noelia Martín-Vicente:** Data curation. **Pedro José Fernández-Esparcia:** Data curation. **Ana Belén Julián Gomara:** Data curation. **Violeta Sastre Lozano:** Data curation. **Juan José Manzanares García:** Data curation. **Irene Chivato Martín-Falquina:** Data curation. **Laura Andrés Pascual:** Data curation. **Nuria Torres Monclus:** Data curation. **Natividad Zaragoza Velasco:** Data curation. **Eukene Rojo:** Data curation. **Berta Lapeña-Muñoz:** Data curation. **Virginia Flores:** Data curation. **Arantxa Díaz Gómez:** Data curation. **Pablo Cañamares-Orbís:** Data curation. **Isabel Vinzo Abizanda:** Data curation. **Natalia Marcos Carrasco:** Data curation. **Laura Pardo Grau:** Data curation. **Guillermo García-Rayado:** Data curation. **Judith Millastre Bocos:** Data curation. **Ana García García de Paredes:** Data curation. **María Vaamonde Lorenzo:** Data curation. **Arantzazu Izagirre Arostegi:** Data curation. **Edgard Efrén Lozada-Hernández:** Data curation. **José Antonio Velarde-Ruiz Velasco:** Data curation. **Michał Żorniak:** Investigation, Methodology. **Enrique de-Madaria:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Julia Mayerle:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Raúl Velamazán:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dld.2025.06.005](https://doi.org/10.1016/j.dld.2025.06.005).

References

- [1] Unalp-Arida A, Ruhl CE. Increasing gallstone disease prevalence and associations with gallbladder and biliary tract mortality in the US. *Hepatology* 2023;77:1882–95.
- [2] Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. *Gastroenterology* 2022;162:122–34.
- [3] Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
- [4] Lammert F, Gurusamy K, Ko CW, et al. Gallstones. *Nat Rev Dis Primer* 2016;2:16024.
- [5] Umans DS, Rangkuti CK, Serna Weiland CJ, et al. Endoscopic ultrasonography can detect a cause in the majority of patients with idiopathic acute pancreatitis: a systematic review and meta-analysis. *Endoscopy* 2020;52:955–64.
- [6] Umans DS, Timmerhuis HC, Anten M-PGF, et al. Prospective multicentre study of indications for surgery in patients with idiopathic acute pancreatitis following endoscopic ultrasonography (PICUS). *Br J Surg* 2023;110:1877–82.
- [7] Żorniak M, Sirtl S, Beyer G, et al. Consensus definition of sludge and microlithiasis as a possible cause of pancreatitis. *Gut* 2023;72:1919–26.
- [8] Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. *Gastroenterology* 1988;94:170–6.
- [9] Janowitz P, Kratzer W, Zemmler T, et al. Gallbladder sludge: spontaneous course and incidence of complications in patients without stones. *Hepatology* 1994;20:291–4.
- [10] Lee SP. Pathogenesis of biliary sludge. *Hepatology* 1990;12:200S–203S discussion 203S–205S.

- [11] Davis M, Ryan JP. Influence of progesterone on guinea pig gallbladder motility in vitro. *Dig Dis Sci* 1986;31:513–18.
- [12] Maringhini A, Marcenò MP, Lanzarone F, et al. Sludge and stones in gallbladder after pregnancy. Prevalence and risk factors. *J Hepatol* 1987;5:218–23.
- [13] Messing B, Bories C, Kunstlinger F, et al. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? *Gastroenterology* 1983;84:1012–19.
- [14] Jacobson AF, Teefey SA, Lee SP, et al. Frequent occurrence of new hepatobiliary abnormalities after bone marrow transplantation: results of a prospective study using scintigraphy and sonography. *Am J Gastroenterol* 1993;88:1044–9.
- [15] Ettestad PJ, Campbell GL, Welbel SF, et al. Biliary complications in the treatment of unsubstantiated Lyme disease. *J Infect Dis* 1995;171:356–61.
- [16] EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. *J Hepatol* 2016;65:146–81.
- [17] Gutt C, Schläfer S, Lammert F. The treatment of Gallstone disease. *Dtsch Arztebl Int* 2020;117:148–58.
- [18] Sirtl S, Bretthauer K, Ahmad M, et al. Severity of gallstone-, sludge-, or microlithiasis-induced pancreatitis-all of the same? *Pancreas* 2024;53:e633–40.
- [19] Quispel R, Schutz HM, Hallensleben ND, et al. Do endosonographers agree on the presence of bile duct sludge and the subsequent need for intervention? *Endosc Int Open* 2021;9:E911–17.
- [20] Velamazán R, López-Guillén P, Martínez-Domínguez SJ, et al. Symptomatic gallstone disease: recurrence patterns and risk factors for relapse after first admission, the RELAPSTONE study. *United Eur Gastroenterol J* 2024;12:286–98.
- [21] Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepato-Biliary-Pancreat Sci* 2018;25:41–54.
- [22] Kiriya S, Kozaka K, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepato-Biliary-Pancreat Sci* 2018;25:17–30.
- [23] von Elm E, Altman DG, Egger M, et al. The strengthening of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet Lond Engl* 2007;370:1453–7.
- [24] Therneau TM. until 2009 TL (original S->R port and R maintainer, Elizabeth A, et al. *Survival* 2024. <https://cran.r-project.org/web/packages/survival/index.html> [Accessed 22 January 2025].
- [25] Wiesweg M. survivalAnalysis: High-Level Interface for Survival Analysis and Associated Plots; 2022 <https://cran.r-project.org/web/packages/survivalAnalysis/index.html> [Accessed 22 January 2025].
- [26] Ärzteblatt DÄG. Redaktion Deutsches. Behandlung von Gallensteinleiden. Deutsches Ärzteblatt 2020. <https://www.aerzteblatt.de/archiv/212753/Behandlung-von-Gallensteinleiden> [Accessed 14 December 2024].
- [27] EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones *J Hepatol*, [https://www.journal-of-hepatology.eu/article/S0168-8278\(16\)30032-0/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(16)30032-0/fulltext) [Accessed 28 November 2024].
- [28] Lee YS, Kang BK, Hwang IK, et al. Long-term outcomes of symptomatic gallbladder sludge. *J Clin Gastroenterol* 2015;49:594–8.
- [29] Boerma D, Rauws EAJ, Keulemans YCA, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. *Lancet Lond Engl* 2002;360:761–5.
- [30] da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet Lond Engl* 2015;386:1261–8.
- [31] Rätty S, Pulkkinen J, Nordback I, et al. Can laparoscopic cholecystectomy prevent recurrent idiopathic acute pancreatitis?: a prospective randomized multicenter trial. *Ann Surg* 2015;262:736–41.
- [32] Umans DS, Hallensleben ND, Verdonk RC, et al. Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis. *Br J Surg* 2020;107:191–9.
- [33] Qayed E, Shah R, Haddad YK. Endoscopic retrograde cholangiopancreatography decreases all-cause and pancreatitis readmissions in patients with acute gallstone pancreatitis who do not undergo cholecystectomy: a nationwide 5-year analysis. *Pancreas* 2018;47:425–35.
- [34] Lee YS, Kang BK, Hwang IK, et al. Long-term outcomes of symptomatic gallbladder sludge. *J Clin Gastroenterol* 2015;49:594–8.
- [35] CholeS Study Group WMRC. Population-based cohort study of outcomes following cholecystectomy for benign gallbladder diseases. *BMJ* 2016;353:1704–15.
- [36] Ahmed I, Hudson J, Innes K, et al. Effectiveness of conservative management versus laparoscopic cholecystectomy in the prevention of recurrent symptoms and complications in adults with uncomplicated symptomatic gallstone disease (C-GALL trial): pragmatic, multicentre randomised controlled trial. *BMJ* 2023;383:e075383.
- [37] Park BK, Seo JH, Jeon HH, et al. A nationwide population-based study of common bile duct stone recurrence after endoscopic stone removal in Korea. *J Gastroenterol* 2018;53:670–8.