

Supplementary Appendix

This appendix has been provided by the authors to provide the readers with additional information about the study.

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SUPPLEMENTARY METHODS

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).

DEFINITIONS

Acute pancreatitis

The definition of acute pancreatitis was based on: Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus[1].

The diagnosis of acute pancreatitis requires two of the following three features: (1) Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography and less commonly magnetic resonance imaging or transabdominal ultrasonography.

To classify acute pancreatitis (AP) as biliary etiology, the presence of gallstones must be demonstrated by imaging test.

Calculous acute cholecystitis

The definition of acute cholecystitis was based on: the Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis[2].

The criteria to diagnose acute cholecystitis are divided into three categories: local signs of inflammation, systemic signs of inflammation, and imaging findings. A suspected diagnosis requires the presence of at least one item from category A and one item from category B. A definite diagnosis requires the presence of at least one item from category A, one item from category B, and imaging findings (category C).

A. Local signs of inflammation: (1) Murphy's sign; and (2) Presence of a mass, pain, or tenderness in the right upper quadrant of the abdomen.

B. Systemic signs of inflammation: (1) Fever; (2) Elevated C-reactive protein; and (3) Elevated white blood cells in the blood.

C. Imaging findings characteristic of acute cholecystitis and presence of gallstones

Acute calculous cholangitis

The definition of acute calculous cholangitis was based on: the Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis[3].

The criteria are divided into three categories: (1) Systemic inflammation; (2) Cholestasis; and (3) Imaging. A suspected diagnosis requires the presence of at least one item from category A and one item from either category B or category C. A definite diagnosis requires the presence of at least one item from category A, one item from category B, and one item from category C.

A. Systemic inflammation: (1) Fever and/or shaking chills; and (2) Laboratory data: evidence of inflammatory response such as elevated levels of inflammatory markers like C-reactive protein or an increased white blood cell count.

B. Cholestasis: (1) Jaundice: Total bilirubin ≥ 2 (mg/dl); and (2) Laboratory data: abnormal liver function tests such as elevated levels of bilirubin, liver enzymes or alkaline phosphatase.

C. Imaging: (1) Biliary dilatation; and (2) Presence of gallstones

Symptomatic choledocholithiasis

We define symptomatic choledocholithiasis as the symptomatology secondary to the presence of a common duct stone confirmed by imaging tests, and in the absence of criteria for acute cholangitis or acute pancreatitis[4].

Biliary colic

Defined as the typical biliary pain: epigastric with radiation to the right upper quadrant, intense, of short duration (< 6 hours), occasionally accompanied by nausea or vomiting, in a patient with visualized cholelithiasis on imaging tests and in the absence of criteria for choledocholithiasis or other SGD[4].

Any combination (comb)

If a patient presented criteria of several diseases at the same time, the case was labeled under the any combination group, thus forming a miscellaneous group with patients who could have a combination of acute pancreatitis, acute cholecystitis, acute cholangitis and/or choledocholithiasis.

DATA COLLECTED

The following data were collected: (1) Demographics: Age, gender; (2) Habits: Tobacco, and alcohol use; and (3) Comorbidity: Charlson comorbidity index (takes into account the presence of myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes with and without chronic complications, hemiplegia or paraplegia, renal disease, any non metastatic solid tumor, metastatic solid tumor, leukemia, lymphoma, AIDS)[5].

Type and characteristics of gallstone symptomatic disease that cause index admission and recurrences: (1) AP; (2) Calculous acute cholecystitis (ACC); (3) Acute calculous cholangitis (ACL); (4) Symptomatic choledocholithiasis (SC); (5) Biliary colic (BC); and (6) Combi.

Severity index was calculated according to the Atlanta classification for AP[1].

Mild acute pancreatitis: (1) Characterized by the absence of organ failure; and (2) The absence of local or systemic complications.

Moderately severe acute pancreatitis: Characterized by the presence of transient (< 48 hours) organ failure or local or systemic complications in the absence of persistent organ failure.

Severe acute pancreatitis: characterized by persistent (> 48 hours) organ failure.

Severity index was calculated according to the Tokyo classification for ACC[2].

Grade III (severe) acute cholecystitis: ACC associated with dysfunction of any one of the following organs/systems: (1) Cardiovascular dysfunction: hypotension requiring treatment with dopamine $\geq 5 \mu\text{g}/\text{kg}$ per min, or any dose of norepinephrine; (2) Neurological dysfunction: decreased level of consciousness; (3) Respiratory dysfunction: $\text{PaO}_2/\text{FiO}_2$ ratio < 300; (4) Renal dysfunction: oliguria, creatinine > 2.0 mg/dl; (5) Hepatic dysfunction: PT-INR >1.5; and (6) Hematological dysfunction: platelet count < 100000/ mm^3 .

Grade II (moderate) acute cholecystitis: ACC associated with any one of the following conditions: (1) Elevated WBC count (> 18000/ mm^3); (2) Palpable tender mass in the right upper abdominal quadrant; (3) Duration of complaints > 72 hours; and (4) Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).

Grade I (mild) acute cholecystitis “ACC that does not meet the criteria of “Grade III” or “Grade II” acute cholecystitis.

Severity index was calculated according to the Tokyo classification for ACL[3].

Grade III (severe) acute cholangitis “ACL that is associated with the onset of dysfunction at least in any one of the following organs/systems: (1) Cardiovascular dysfunction: hypotension requiring dopamine $\geq 5 \mu\text{g}/\text{kg}$ per min,

or any dose of norepinephrine; (2) Neurological dysfunction: disturbance of consciousness; (3) Respiratory dysfunction: PaO₂/FiO₂ ratio < 300; (4) Renal dysfunction: oliguria, serum creatinine > 2.0 mg/dl; (5) Hepatic dysfunction: PT-INR >1.5; and (6) Hematological dysfunction: platelet count < 100000/mm³.

Grade II (moderate) acute cholangitis: ACL associated with any two of the following conditions: (1) Abnormal WBC count (> 12000/mm³, < 4000/mm³); (2) High fever (≥ 39 °C); (3) Age (≥ 75 years old); (4) Hyperbilirubinemia (total bilirubin ≥5 mg/dl); and (5) Hypoalbuminemia (< STD × 0.7).

Grade I (mild) acute cholangitis: ACL that does not meet the criteria of "Grade III" or "Grade II" ACL at initial diagnosis. (1) Presence of: acute renal dysfunction (Creatinine ≥ 19mg/dL), acute respiratory dysfunction (PaO₂/FiO₂ < 300 or tracheal intubation), or acute cardiovascular dysfunction (systolic pressure < 90 mmHg despite the use of fluidotherapy)[1]; (2) Blood and bile cultures; (3) ICU admission and length of stay; (4) Presence of fluid or necrotic pancreatic, peripancreatic or pericholecystic collection and liver abscess[1]; (5) Use of complementary exams [transabdominal ultrasonography, computed axial tomography (CT), magnetic resonance imaging (RMI), endoscopic ultrasound (EUS)]; (6) Characteristics of cholelithiasis: absence, microlithiasis/biliary sludge, unique cholelithiasis, multiple cholelithiasis, or indeterminate; (7) Characteristics of the biliary tract in the most reliable complementary test (being RMI or EUS the most reliable followed by CT and transabdominal ultrasound): non dilated, isolated extra-hepatic dilatation, isolated intra-hepatic dilatation, both intra and extra-hepatic dilatation or dilated but not determined which tract; (8) Diameter of the dilated biliary tract; (9) Presence of duodenal diverticula or pancreas divisum (considered only when CT, MRI, EUS, or ERCP were performed, otherwise patient count as invalid); (10) ERCP: performance of sphincterotomy, Wirsung cannulation, placing Wirsung stent, successful ERCP with regards to eliminating all choledocholithiasis in the same ERCP, placing biliary sent, and presence of complications; (11) PTHC: placing biliary stent, successful PTHC with regards to eliminating all choledocholithiasis in the same PTHC, and presence of complications; (12) Cholecystostomy: the way to perform it

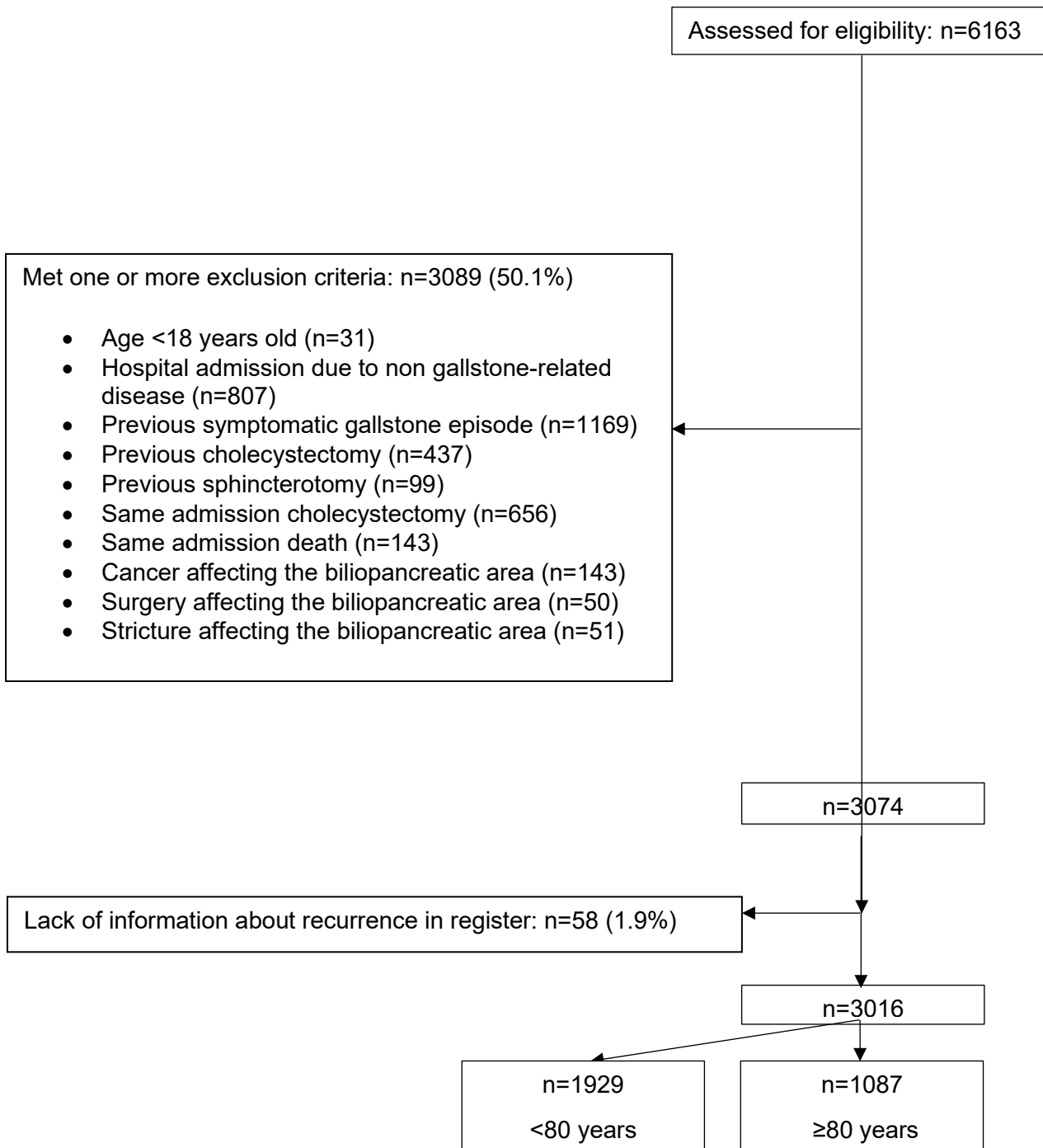
(percutaneous, EUS guided), and presence of complications; (13) Commencement of treatment with Ursodeoxycholic acid at discharge; (14) Length of hospital stay (days); (15) Measurement of analytic parameters at three different moments during hospital admission: at admission (first 24 hours), at discharge (in the last 48 hours of the admission), and the highest value of the parameter during admission. The following parameters were collected: aspartate transaminase (U/L), alanine transaminase (U/L), gamma-glutamyl transferase (U/L), alkaline phosphatase (U/L), bilirubin (mg/dl), leukocytes (/mm³), neutrophils (/mm³), lymphocytes (/mm³), hematocrit (%), urea (mg/dl), and C-reactive protein (mg/L). The pathological cut-off value for each parameter was: Aspartate transaminase: 35U/L, alanine transaminase: 35U/L, gamma-glutamyl transferase: 78 U/L, alkaline phosphatase: 150U/L, bilirubin: 1,2 mg/dl, leucocytes: 11000/mm³, neutrophils: 8500/mm³, lymphocytes: 4500/mm³, hematocrit: 47% for females and 51% for males, urea: 54mg/dl, and C-reactive protein: 5mg/L.

Presence and recount of recurrences and their characteristics: date, type of SGD, severity, and need for hospital admission. Mortality and date during follow-up. Cholecystectomy and date during follow-up. The end of follow-up was considered when the patient was cholecystectomized or died. In other cases, the last clinic visit without being cholecystectomized was considered.

PARTICIPANTS

We excluded 838 patients who did not satisfy the inclusion criteria (age \geq 18 years old ($n = 31$) and hospital admission between 2018-2020 due to first SGD episode ($n = 807$)). We further excluded 2251 individuals who satisfied one or more exclusion criteria (previous SGD episode ($n = 1169$), previous cholecystectomy ($n = 437$), previous sphincterotomy ($n = 99$), same admission cholecystectomy ($n = 656$), same admission death ($n = 143$), cancer affecting the biliopancreatic area ($n = 143$), surgery affecting the biliopancreatic area ($n = 50$) and benign stricture that affects the biliopancreatic area ($n = 51$)). Finally, 58 patients were excluded due to lack of important data in their register leaving 3016 patients as the final study

sample. Of these, 1929 (64%) were aged < 80 years and 1087 (36%) were aged ≥ 80 years.



Supplementary Figure 1 Flowchart showing patient screening for eligibility and subsequent exclusions leading to the final study population.

Supplementary Table 1 Charlson Comorbidity Index by age group, *n* (%)

	< 80 years (n = 1929)	≥ 80 years (n = 1087)	P value
Myocardial infarction			< 0.001
No	1781 (92.3)	954 (87.8)	
Yes	148 (7.7)	133 (12.2)	
Congestive heart failure			< 0.001
No	1825 (94.6)	912 (83.9)	
Yes	104 (5.4)	175 (16.1)	
Peripheral vascular disease			0.002
No	1847 (95.7)	1012 (93.1)	
Yes	82 (4.3)	75 (6.9)	
Cerebrovascular disease			< 0.001
No	1827 (94.7)	891 (82.0)	
Yes	102 (5.3)	196 (18.0)	
Dementia			< 0.001
No	1878 (97.4)	866 (79.7)	
Yes	51 (2.6)	221 (20.3)	
Chronic pulmonary disease			< 0.001
No	1713 (88.8)	910 (83.7)	
Yes	216 (11.2)	177 (16.3)	
Rheumatologic disease			0.513
No	1870 (96.9)	1049 (96.59)	
Yes	59 (3.1)	38 (3.5)	
Peptic ulcer disease			0.019
No	1856 (96.2)	1026 (94.4)	
Yes	73 (3.8)	61 (5.6)	
Liver disease			< 0.001
No	1823 (94.5)	1065 (98.1)	
Mild	66 (3.4)	17 (1.6)	
Moderate or severe	40 (2.1)	4 (0.4)	
Diabetes			< 0.001

No	1540 (79.8)	796 (73.2)	
Without chronic complications	334 (17.3)	255 (23.5)	
With chronic complications	55 (2.9)	36 (3.3)	
Hemiplegia or paraplegia			0.678
No	1913 (99.2)	1080 (99.4)	
Yes	15 (0.8)	7 (0.6)	
Chronic renal disease			< 0.001
No	1820 (94.3)	864 (79.5)	
Yes	109 (5.7)	223 (20.5)	
Solid tumor			< 0.001
No	1744 (90.4)	928 (85.4)	
Any not metastatic	168 (8.7)	151 (13.9)	
Metastatic solid tumor	17 (0.9)	8 (0.7)	
Leukemia			0.922
No	1916 (99.3)	1080 (99.4)	
Yes	13 (0.7)	7 (0.6)	
Lymphoma			0.223
No	1913 (99.2)	1073 (98.7)	
Yes	16 (0.8)	14 (1.3)	
Acquired immunodeficiency syndrome			1.000
No	1928 (99.9)	1086 (99.9)	
Yes	1 (0.1)	1 (0.1)	

Supplementary Table 2 Symptomatic gallstone disease diagnostic approach and therapeutics by age group (< 80 vs ≥ 80 years), n (%), median (25th percentile-75th percentile)

Initial diagnostic approach			
Transabdominal ultrasonography (yes)	1776 (92.2)	1005 (92.5)	0.773
Computed axial tomography (yes)	702 (36.4)	394 (36.2)	0.920

Magnetic resonance imaging (yes)	539 (28.0)	207 (19.0)	< 0.001
Endoscopic Ultrasound (yes)	291(15.1)	109 (10.0)	< 0.001
Therapeutics			
ERCP index admission (yes)	481 (24.9)	338 (31.1)	< 0.001
Sphincterotomy (yes)	457 (95.0)	322 (95.3)	0.867
Wirsung cannulation (yes)	104 (21.6)	52 (15.4)	0.025
Wirsung stent (yes)	67 (13.9)	40 (11.8)	0.381
Successful ERCP (yes)	392 (83.1)	279 (82.8)	0.783
Biliary stent (yes)	83 (17.3)	59 (17.5)	0.941
ERCP complications (yes)	79 (16.4)	49 (15.5)	0.455
Percutaneous transhepatic cholangiography (yes)	4 (0.2)	4 (0.4)	0.470
Cholecystostomy (yes)	99 (5.1)	144 (13.3)	< 0.001
Type of cholecystostomy			< 0.001
Endoscopic	5 (0.3)	24 (2.2)	
Percutaneous	91 (4.7)	114 (10.5)	
Both	3 (0.2)	6 (0.6)	
Complications (yes)	5 (5.1)	6 (4.2)	0.761
Elective Cholecystectomy (yes)	1329 (68.1)	243 (22.4)	< 0.001
Time to cholecystectomy (months)	4.3 [2.2-6.8]	4.6 (2.4-8.0)	0.034
< 3 months	478 (36.5)	73 (30.2)	
3-6 months	407 (31.0)	70 (28.9)	
> 6 months	426 (32.5)	99 (40.9)	0.032
Type of cholecystectomy			< 0.001
Laparoscopic	1200 (90.6)	197 (81.4)	
Open after laparoscopic	64 (4.8)	19 (7.9)	
Open	60 (4.5)	26 (10.7)	
Complications (yes)	78 (5.9)	21 (8.6)	0.103

ERCP: Endoscopic retrograde cholangiopancreatography.

Supplementary Table 3 Analytical parameters at the index admission by age group (< 80 vs ≥ 80 years)

Biomarker	Time	Units	< 80 years (<i>n</i> = 1920)		≥ 80 years (<i>n</i> = 1087)		<i>P</i> value
			<i>n</i>	%	<i>n</i>	%	
			AST (U/L)	At first admission	24/48h of ≤35 U/L	466	
		>35 U/L	1368	74.6%	772	75.8%	
	The worst value	≤35 U/L	349	18.8%	179	17.4%	0.353
		>35 U/L	1512	81.2%	852	82.6%	
	At discharge	≤35 U/L	919	50.2%	598	58.6%	<0.001
		>35 U/L	912	49.8%	423	41.4%	
ALT (U/L)	At first admission	24/48h of ≤35 U/L	424	22.3%	261	24.3%	0.208
		>35 U/L	1479	77.7%	813	75.7%	
	The worst value	≤35 U/L	292	15.2%	189	17.5%	0.106
		>35 U/L	1624	84.8%	891	82.5%	
	At discharge	≤35 U/L	583	30.6%	494	46.0%	<0.001
		>35 U/L	1321	69.4%	580	54.0%	
GGT (U/L)	At first admission	24/48h of ≤78 U/L	383	21.0%	233	22.7%	0.273
		>78 U/L	1445	79.0%	793	77.3%	
	The worst value	≤78 U/L	264	14.2%	144	13.9%	0.817
		>78 U/L	1590	85.8%	890	86.1%	
	At discharge	≤78 U/L	380	20.9%	227	22.3%	0.391
		>78 U/L	1440	79.1%	793	77.7%	
ALP (U/L)	At first admission	24/48h of ≤150 U/L	1019	55.9%	469	46.0%	<0.001
		>150 U/L	803	44.1%	550	54.0%	
	The worst value	≤150 U/L	828	44.8%	358	34.8%	<0.001
		>150 U/L	1021	55.2%	670	65.2%	
	At discharge	≤150 U/L	1083	59.6%	529	52.1%	<0.001
		>150 U/L	733	40.4%	486	47.9%	

Bilirubin (mg/dl)	At first admission	24/48h of	≤1.2 mg/dl	753	39.7%	391	36.6%	0.102
			>1.2 mg/dl	1146	60.3%	677	63.4%	
	The worst value		≤1.2 mg/dl	659	34.5%	353	32.7%	0.320
			>1.2 mg/dl	1249	65.5%	725	67.3%	
	At discharge		≤1.2 mg/dl	1409	74.7%	833	78.1%	0.034
			>1.2 mg/dl	478	25.3%	233	21.9%	
Leucocytes (count/mm ³)	At first admission	24/48h of	≤11000 /mm ³	1024	53.2%	506	46.6%	<0.001
			>11000 /mm ³	900	46.8%	581	53.4%	
	The worst value		≤11000 /mm ³	868	45.1%	420	38.6%	<0.001
			>11000 /mm ³	1056	54.9%	667	61.4%	
	At discharge		≤11000 /mm ³	1674	87.7%	970	89.6%	0.124
			>11000 /mm ³	235	12.3%	113	10.4%	
Neutrophils (count/mm ³)	At first admission	24/48h of	≤8500 /mm ³	967	50.4%	454	41.9%	<0.001
			>8500 /mm ³	951	49.6%	630	58.1%	
	The worst value		≤8500 /mm ³	828	43.2%	365	33.7%	<0.001
			>8500 /mm ³	1088	56.8%	717	66.3%	
	At discharge		≤8500 /mm ³	1734	91.0%	981	90.7%	0.836
			>8500 /mm ³	172	9.0%	100	9.3%	
Lymphocytes (count/mm ³)	At first admission	24/48h of	≤4500 /mm ³	1900	99.1%	1074	99.1%	0.921
			>4500 /mm ³	17	0.9%	10	0.9%	
	The worst value		≤4500 /mm ³	1897	99.0%	1069	98.8%	0.591
			>4500 /mm ³	19	1.0%	13	1.2%	
	At discharge		≤4500 /mm ³	1894	99.5%	1076	99.5%	0.816
			>4500 /mm ³	10	0.5%	5	0.5%	
Hematocrit (%)	At first admission	24/48h of	>47(F) & 51(M)	1835	96.2%	1058	97.8%	0.020
			>47(F) & 51(M)	72	3.8%	24	2.2%	
	The worst value		>47(F) & 51(M)	1822	95.4%	1050	97.1%	

		>47(F) & 51(M)	87	4.6%	31	2.9%	0.023
	At discharge	>47(F) & 51(M)	1880	99.1%	1074	99.5%	
		>47(F) & 51(M)	18	0.9%	5	0.5%	0.146
Urea	At first 24/48h	of ≤54 mg/L	1628	87.0%	612	58.4%	
(mg/L)	admission	>54 mg/L	244	13.0%	436	41.6%	<0.001
	The worst value	≤54 mg/L	1514	81.0%	480	45.8%	
		>54 mg/L	356	19.0%	567	54.2%	<0.001
	At discharge	≤54 mg/L	1738	93.5%	828	79.2%	
		>54 mg/L	120	6.5%	217	20.8%	<0.001
CRP (mg/L)	At first 24/48h	of ≤5 mg/L	388	21.3%	149	13.9%	
	admission	>5 mg/L	1432	78.7%	924	86.1%	<0.001
	The worst value	≤5 mg/L	123	6.8%	21	2.0%	
		>5 mg/L	1676	93.2%	1043	98.0%	<0.001
	At discharge	≤5 mg/L	285	15.9%	76	7.2%	
		>5 mg/L	1510	84.1%	981	92.8%	<0.001

Supplementary Table 4 Number of episodes of recurrences by patient during the follow-up time according age group, *n* (%)

Episodes recurrences	of < 80 years (<i>n</i> = 668)	≥ 80 years (<i>n</i> = 353)	Total recurrences (<i>n</i> = 1021)	<i>P</i> value
1	403 (60.3)	174 (49.3)	577 (56.5)	< 0.001
2	162 (24.3)	117 (33.1)	279 (27.3)	
3	59 (8.8)	28 (7.9)	87 (8.5)	
4	25 (3.7)	25 (7.1)	50 (4.9)	
5	11 (1.6)	3 (0.8)	14 (1.4)	
6	2 (0.3)	3 (0.8)	5 (0.5)	
7	6 (0.9)	1 (0.3)	7 (0.7)	

9	0	1 (0.3)	1 (0.1)
10	0	1 (0.3)	1 (0.1)

Supplementary Table 5 Severity of recurrence episodes, *n* (%)

	< 80 years	≥ 80 years	<i>P</i> value
Severity of acute pancreatitis recurrence			0.195
Mild	169 (86.2)	62 (91.2)	
Moderate	18 (9.2)	6 (8.8)	
Severe	9 (4.6)	0	
Severity of acute cholecystitis recurrence			0.002
Mild	84 (74.3)	57 (54.3)	
Moderate	25 (22.1)	32 (30.5)	
Severe	4 (3.5)	16 (15.2)	
Severity of acute cholangitis recurrence			0.017
Mild	28 (57.1)	15 (30.6)	
Moderate	17 (34.7)	31 (63.3)	
Severe	4 (8.2)	3 (6.1)	

Supplementary Table 6 Recurrence free survival at 3, 6 and 12 months according to demographic and clinical variables in patients aged 80 years and older

	<i>n</i> (%)	S3	S6	S12	<i>P</i> value	Unadjusted-hazard ratio	95%CI
All patients	1087 (100)	0.84	0.77	0.69			
Type of gallstone disease					0.004		
Acute cholangitis	190 (17.5)	0.90	0.84	0.79		1	
Acute pancreatitis	252 (23.2)	0.81	0.75	0.68		1.66	1.16-2.37
Acute cholecystitis	368 (33.9)	0.81	0.73	0.63		1.82	1.30-2.55
Symptomatic choledocholithiasis	94 (8.6)	0.89	0.85	0.78		1.08	0.65-1.80
Biliary colic	63 (5.8)	0.87	0.74	0.53		1.85	1.13-3.02
Multiple diseases	120 (11.0)	0.85	0.82	0.77		1.31	0.84-2.03

Age					0.890		
80-85 years	405 (37.3)	0.83	0.76	0.69		1	
85-90 years	397 (36.5)	0.85	0.79	0.70		0.98	0.78-1.25
90-95 years	222 (20.4)	0.84	0.77	0.68		0.96	0.72-1.30
> 95	63 (5.8)	0.85	0.76	0.69		1.16	0.75-1.79
Gender					0.853		
Women	634 (58.3)	0.84	0.78	0.71		1	
Men	453 (41.7)	0.84	0.76	0.67		1.02	0.83-1.26
Charlson comorbidity index					0.144		
Low (0-1)	470 (43.2)	0.85	0.79	0.71		1	
Medium comorbidity (2)	246 (22.6)	0.82	0.72	0.62		1.27	0.98-1.65
High comorbidity (3)	371 (34.1)	0.84	0.78	0.71		0.99	0.78-1.27
Acute renal dysfunction					0.332		
No	974 (89.6)	0.83	0.77	0.69		1	
Yes	113 (10.4)	0.90	0.82	0.71		0.83	0.58-1.21
Acute respiratory dysfunction	1066				0.749		
No	(98.1)	0.84	0.77	0.61		1	
Yes	21 (1.9)	0.89	0.84	0.77		0.88	0.39-1.96
Acute cardiovascular dysfunction	1053				0.387		
No	(96.9)	0.84	0.77	0.69		1	
Yes	34 (3.1)	0.85	0.81	0.81		0.75	0.39-1.45
Cholelithiasis					0.560		
No multiple cholelithiasis	555 (51.1)	0.85	0.79	0.71		1	
Multiple cholelithiasis	532 (48.9)	0.83	0.76	0.68		1.064	0.86-1.31
Biliary tract dilation					< 0.001		
Not dilatated	641 (59.0)	0.81	0.73	0.63		1	
Dilated	444 (41.0)	0.89	0.83	0.78		0.65	0.52-0.81
Duodenal diverticula					0.143		
No	636 (85.1)	0.83	0.76	0.68		1	
Yes	111 (14.9)	0.91	0.84	0.78		0.76	9.53-1.10
Pancreas divisum					0.650		

No	731 (98.1)	0.84	0.77	0.69	1	
Yes	14 (1.9)	1.00	0.91	0.68	1.21	0.54-2.70
Sphincterotomy					< 0.001	
No	765 (70.4)	0.81	0.73	0.63	1	
Si	322 (29.6)	0.92	0.86	0.83	0.44	0.33-0.58
Cholecystostomy					0.228	
No	942 (86.7)	0.84	0.78	0.70	1	
Si	144 (13.3)	0.83	0.73	0.64	1.20	0.89-1.62
Start of ursodeoxycholic acid at discharge	1026				0.072	
No	(94.4)	0.84	0.77	0.69	1	
Si	61 (5.6)	0.92	0.84	0.79	0.61	0.36-1.04

N = 1087.

Supplementary Table 7 Recurrence free survival at 3, 6 and 12 months according to analytical parameters in patients aged 80 years and older

Bioma rker	Time	Units	<i>n</i> (%)	S3	S6	S12	<i>P</i> value	Haza rd ratio	95% CI
AST (U/L)	At first admission	≤35 U/L	246 (24.2)	0.81	0.74	0.65	0.119	1	0.65-1.05
		>35 U/L	772 (75.8)	0.85	0.78	0.70			
	The worst value	≤35 U/L	179 (17.4)	0.79	0.73	0.66	0.170	1	0.63-1.08
		>35 U/L	852 (82.6)	0.85	0.78	0.70			
ALT (U/L)	At first admission	≤35 U/L	261 (24.3)	0.83	0.76	0.70	0.733	1	0.75-1.22
		>35 U/L	813 (75.7)	0.84	0.78	0.69			
	The worst value	≤35 U/L	189 (17.5)	0.82	0.77	0.69	0.716	1	0.72-1.25
		>35 U/L	891 (82.5)	0.84	0.77	0.69			

	At discharge	≤35 U/L	494 (46.0)	0.85	0.77	0.68		1	
		>35 U/L	580 (54.0)	0.83	0.77	0.70	0.404	0.92	0.74-1.13
GGT (U/L)	At first 24/48h of admission	≤78 U/L	233 (22.7)	0.85	0.77	0.70		1	
		>78 U/L	793 (77.3)	0.84	0.77	0.69	0.893	0.98	0.76-1.27
	The worst value	≤78 U/L	144 (13.9)	0.85	0.76	0.70		1	
		>78 U/L	890 (86.1)	0.84	0.77	0.69	0.705	0.94	0.70-1.28
	At discharge	≤78 U/L	227 (22.3)	0.84	0.75	0.70		1	
		>78 U/L	793 (77.7)	0.84	0.78	0.69	0.753	0.96	0.75-1.24
ALP (U/L)	At first 24/48h of admission	≤150 U/L	469 (46.0)	0.82	0.75	0.68		1	
		>150 U/L	550 (54.0)	0.86	0.80	0.71	0.342	0.90	0.73-1.11
	The worst value	≤150 U/L	358 (34.8)	0.80	0.72	0.67		1	
		>150 U/L	670 (65.2)	0.86	0.80	0.71	0.034	0.79	0.64-0.98
	At discharge	≤150 U/L	529 (52.1)	0.83	0.75	0.69		1	
		>150 U/L	486 (47.9)	0.86	0.80	0.70	0.353	0.91	0.73-1.12
Bilirub in (mg/d l)	At first 24/48h of admission	≤1.2 mg/dl	391 (36.6)	0.83	0.75	0.66		1	
		>1.2 mg/dl	677 (63.4)	0.85	0.79	0.71	0.083	0.83	0.67-1.03
	The worst value	≤1.2 mg/dl	353 (32.7)	0.83	0.75	0.65		1	
		>1.2 mg/dl	725 (67.3)	0.85	0.78	0.71	0.069	0.82	0.66-1.02
	At discharge	≤1.2 mg/dl	833 (78.1)	0.84	0.77	0.69		1	
		>1.2 mg/dl	233 (21.9)	0.84	0.77	0.71	0.163	0.83	0.64-1.08
Leucoc ytes (count /mm3)	At first 24/48h of admission	≤11000 /mm3	506 (46.6)	0.83	0.76	0.68		1	
		>11000 /mm3	581 (53.4)	0.85	0.78	0.70	0.226	0.88	0.71-1.08
	The worst value	≤11000 /mm3	420 (38.6)	0.82	0.75	0.66		1	
		>11000 /mm3	667 (61.4)	0.86	0.79	0.71	0.027	0.79	0.64-0.97
	At discharge	≤11000 /mm3	970 (89.6)	0.84	0.77	0.68		1	
		>11000 /mm3	113 (10.4)	0.82	0.80	0.77	0.486	0.88	0.60-1.27
Neutro	At first	≤8500 /mm3	454 (41.9)	0.83	0.78	0.70		1	

phils (count /mm3)	24/48h admission	of	>8500 /mm3	630 (58.1)	0.85	0.77	0.69	0.846	0.98	0.79-1.21
	The	worst	≤8500 /mm3	365 (33.7)	0.82	0.77	0.68		1	
	value		>8500 /mm3	717 (66.3)	0.85	0.78	0.70	0.326	0.90	0.72-1.11
	At discharge		≤8500 /mm3	981 (90.7)	0.84	0.77	0.69		1	
			>8500 /mm3	100 (9.3)	0.82	0.77	0.73	0.877	1.03	0.71-1.49
Lymp hocyte s (count /mm3)	At 24/48h admission	first of	≤4500 /mm3	1074 (99.1)	0.84	0.77	0.69			
			>4500 /mm3	10 (0.9)	0.77	0.77	0.77	0.789	0.83	0.21-3.32
	The	worst	≤4500 /mm3	1069 (98.8)	0.84	0.77	0.69		1	
	value		>4500 /mm3	13 (1.2)	0.83	0.83	0.83	0.335	0.51	0.13-2.03
	At discharge		≤4500 /mm3	1076 (99.5)	0.84	0.77	0.69		1	
			>4500 /mm3	5 (0.5)	1.00	1.00	1.00	1.00		
Hemat ocrit (%)	At 24/48h admission	first of	≤47(F)& 51(M)	1058 (97.8)	0.84	0.77	0.69		1	
			≤47(F)& 51(M)	24 (2.2)	0.87	0.78	0.66	0.862	1.06	0.53-2.15
	The	worst	≤47(F)& 51(M)	1050 (97.1)	0.84	0.77	0.69		1	
	value		≤47(F)& 51(M)	31 (2.9)	0.90	0.80	0.71	0.857	1.06	0.58-1.93
	At discharge		≤47(F)& 51(M)	1074 (99.5)	0.84	0.77	0.69		1	
			≤47(F)& 51(M)	5 (0.5)	1.00	0.80	8.00	0.853	1.14	0.28-4.58
Urea (mg/L)	At 24/48h admission	first of	≤54 mg/L	612 (58.4)	0.84	0.77	0.70		1	
			>54 mg/L	436 (41.6)	0.84	0.78	0.68	0.996	1.00	0.81-1.24
	The	worst	≤54 mg/L	480 (45.8)	0.83	0.76	0.69		1	
	value		>54 mg/L	567 (54.2)	0.85	0.79	0.69	0.572	0.94	0.76-1.16
	At discharge		≤54 mg/L	828 (79.2)	0.84	0.77	0.69		1	
			>54 mg/L	217 (20.8)	0.84	0.79	0.69	0.982	1.00	0.77-1.30
CRP (mg/L)	At 24/48h admission	first of	≤5 mg/L	149	0.81	0.73	9.63		1	
			>5 mg/L	924	0.85	0.78	0.70	0.077	0.77	0.58-1.03
	The	worst	≤5 mg/L	21	0.95	0.95	0.83		1	

value	>5 mg/L	1043	0.84	0.80	0.69	0.347	1.61	0.60-4.30
At discharge	≤5 mg/L	76	0.79	0.67	0.62		1	
	>5 mg/L	981	0.84	0.78	0.70	0.055	0.69	0.48-1.01

**Supplementary Table 8 Missing values in the cohort aged ≥ 80 years (*n* = 1087),
n (%)**

Variables	Missing values
Age	0 (0.0)
Gender	0 (0.0)
Tobacco	329 (30.3)
Alcohol	368 (33.9)
Charlson Comorbidity Index	0 (0.0)
Type of gallstone disease	0 (0.0)
Severity of acute pancreatitis	0 (0.0)
Severity of acute cholecystitis	0 (0.0)
Severity of acute cholangitis	0 (0.0)
Acute renal dysfunction	0 (0.0)
Acute respiratory dysfunction	0 (0.0)
Acute cardiovascular dysfunction	0 (0.0)
Cholelithiasis	0 (0.0)
Biliary tract dilation	2 (0.0)
Duodenal diverticula	340 (31.3)
Pancreas divisum	342 (31.5)
ICU admission	1 (0.0)
Length of hospital stay (days)	0 (0.0)
Transabdominal ultrasonography	0 (0.0)
Computed axial tomography	0 (0.0)
Magnetic resonance imaging	0 (0.0)
Endoscopic ultrasound	0 (0.0)
ERCP index admission	0 (0.0)
Percutaneous transhepatic cholangiography	0 (0.0)

Cholecystostomy		1 (0.0)
Ursodeoxycholic acid at discharge		0 (0.0)
Elective Cholecystectomy		0 (0.0)
AST (U/L)	At first 24/48h of admission	69 (6.3)
	The worst value	56 (5.2)
	At discharge	66 (6.1)
ALT (U/L)	At first 24/48h of admission	13 (1.2)
	The worst value	7 (0.6)
	At discharge	13 (1.2)
GGT (U/L)	At first 24/48h of admission	61 (5.6)
	The worst value	53 (4.9)
	At discharge	67 (6.2)
ALP (U/L)	At first 24/48h of admission	68 (6.3)
	The worst value	59 (5.4)
	At discharge	72 (6.6)
Bilirubin (mg/dl)	At first 24/48h of admission	19 (1.7)
	The worst value	9 (0.8)
	At discharge	21 (1.9)
Leucocytes (count/mm ³)	At first 24/48h of admission	0 (0.0)
	The worst value	0 (0.0)
	At discharge	0 (0.0)
Neutrophils (count/mm ³)	At first 24/48h of admission	3 (0.3)
	The worst value	5 (0.5)
	At discharge	6 (0.6)
Lymphocytes (count/mm ³)	At first 24/48h of admission	3 (0.3)
	The worst value	5 (0.5)
	At discharge	6 (0.6)
Hematocrit (%)	At first 24/48h of admission	5 (0.5)
	The worst value	6 (0.6)

	At discharge	8 (0.7)
Urea (mg/L)	At first 24/48h of admission	39 (3.6)
	The worst value	40 (3.7)
	At discharge	42 (3.9)
CRP (mg/L)	At first 24/48h of admission	14 (1.3)
	The worst value	23 (2.1)
	At discharge	30 (2.8)

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