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Long-term outcome of patients with biliary pancreatitis not undergoing cholecystectomy. A retrospective study

Pablo Parra-Membrives[1,2], Ana García-Vico[2], Darío Martínez-Baena[1,2], José Manuel Lorente-Herce[2], and Granada Jiménez-Riera[1,2]

[1]Department of Surgery. Universidad de Sevilla. Seville, Spain [2]Hepatobiliary and Pancreatic Surgery Unit. General and Digestive Surgery Department. Hospital Universitario Virgen de Valme. Seville, Spain

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Correspondence: Pablo Parra Membrives. C/Rubí, 35. 41927 Mairena del Aljarafe, Sevilla. Spain
e-mail: pabloparra@aecirujanos.es

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ABSTRACT

Background and objective: most acute pancreatitis cases are of biliary origin and cholecystectomy is recommended to prevent recurrence. However, some patients will never be referred for surgery. In this study, the long-term follow-up of this group of

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patients was reviewed.

Methods: all new cases of biliary pancreatitis from January 2015 to December 2017 that did not undergo cholecystectomy were analyzed. Epidemiologic data and Charlson's comorbidity index (CCI) were recorded. Recurrent episodes of pancreatitis or biliary events and mortality during the follow-up period were recorded.

Results: a total of 104 patients were included in the study (30.4 % of all biliary pancreatitis cases) and the median age was 82 years (range, 27-96). Average CCI was 5 (range, 0-18) and the median follow-up period was 37 months (range, 1-70). A total of 41 patients (39.4 %) had gallstone-related complications. Twenty-three patients (22,1 %) had recurrent pancreatitis and 34 (32,7 %) developed biliary events. Twenty-five patients died during follow-up (24 %) but only in 6 (5,8 %) was death due to gallstone-related complications. Non-related mortality was 15.5 % in patients who refused surgery and 25 % in multiple-comorbidity patients.

Conclusion: patients who did not undergo cholecystectomy were at high risk for biliary events and pancreatitis recurrence. Conservative treatment and surgical abstention should be individualized and reserved for patients with multiple comorbidities with a short life expectancy.

Keywords: Biliary acute pancreatitis. Cholecystectomy. Surgical abstention. Long-term recurrence.

INTRODUCTION

Acute pancreatitis is a major healthcare problem with high morbidity and mortality rates. Despite the fact that 80 % of patients develop mild pancreatitis, there is still a group of patients who will follow a severe course with necrosis and infection of the pancreatic gland, leading to a 35 % mortality rate (1). In western countries, one to two thirds of cases are caused by gallstones or biliary sludge, these being grouped together as biliary pancreatitis (2). Following diagnosis, cholecystectomy is recommended in virtually all international guidelines to prevent future episodes of acute pancreatitis

(3-5). However, there is still in clinical practice a deviation from the guidelines available, as shown in the literature (6). Conversely, some patients will suffer a delay or will never be referred to surgery (7). The aim of this study was to review the long-term evolution of a cohort of patients who did not undergo cholecystectomy following an episode of biliary pancreatitis.

MATERIAL AND METHODS

Search protocol and study population

A retrospective analysis of all electronic clinical records at our institution from January 2015 to December 2017 was performed, searching for the admission of patients with a diagnosis of acute biliary pancreatitis. Our hospital covers a population of over 350,000 inhabitants within the Regional Public Health System. Electronic medical records are linked to patients and not exclusively to any institution, so that any admission to any other public health center is also available. Thus, the risk of bias of not detecting any readmission is minimized. The diagnosis of acute pancreatitis was made following the revised 2012 Atlanta criteria (8). Diagnostic criteria for biliary pancreatitis included the presence of calculi or biliary sludge in the gallbladder or biliary tree on any imaging test, in the absence of any other evident cause of pancreatitis, such as recent excessive acute alcohol intake (9,10). In our center, patients with acute biliary pancreatitis are first seen in the emergency department and then admitted to the gastroenterology or internal medicine division. From these units, the department of surgery is contacted to perform a cholecystectomy. The indication for cholecystectomy was made in all suitable patients during the same admission when possible, within the first month in most patients, and after stabilization of the condition in patients suffering from severe pancreatitis. All patients who did not undergo cholecystectomy for whatever reason after the index pancreatitis event within the study period were selected. Patients who suffered from acute biliary pancreatitis but had previously undergone cholecystectomy, and those who died during the index episode of pancreatitis were also excluded from the study.

Data collection and definitions

The index acute pancreatitis episode was stated as the first record with a diagnosis of acute biliary pancreatitis within the study period. Any previous episodes were recorded separately. Any subsequent episodes of acute biliary pancreatitis or any biliary complications were considered a recurrent episode in the analysis. The follow-up period ranged from the index episode to the last contact of the patient with any center of the public health system, with a review endpoint in December 2020. Biliary complications were defined as the presence of biliary colic, cholecystitis, choledocholithiasis, and/or cholangitis.

Information was collected on baseline characteristics during the index episode of pancreatitis, including age, gender, Charlson comorbidity index (CCI), number of previous episodes of pancreatitis, length of hospital stay, liver function tests (serum levels of total bilirubin, alkaline phosphatase, AST, ALT and GGT), biliary ultrasound examination findings, and endoscopic retrograde cholangiopancreatography performance. An analysis of the reasons for not undergoing surgery following index pancreatitis was also performed. The incidence and number of new episodes of pancreatitis and biliary events requiring hospital admission, as well as the date of hospital admission during the study period, were collected. Patients who finally underwent cholecystectomy because of recurrent biliary pancreatitis were also recorded. Mortality during follow-up was analyzed. The number of emergency department visits for any cause during the study period was documented as an indirect method to measure comorbidity and performance status. Approval for the study was obtained from the Institutional Review Board.

Statistical analysis

All quantitative values were expressed as median and range. Categorical variables were presented as values and percentages. Chi-square analyses of nominal categorical data and nonparametric Mann-Whitney test analyses of continuous variables were performed. For long-term outcomes, the Kaplan Meier method was used to estimate the probability of acute pancreatitis recurrence and biliary event development. Also, p-values < 0.05 were considered statistically significant. The statistical analysis was

performed using the SPSS statistical software package for MAC v.25 (SPSS Inc., Chicago. IL, USA).

RESULTS

A total of 612 patients were diagnosed with acute pancreatitis during the study period and 104 finally met the inclusion criteria and comprised the study population (Fig. 1). The median age was 82.0 years (range, 27-96 years) and gender distribution was about equal (46.2 % females : 53.8 % males). A median CCI of 5 (range, 0-18) was identified and 16.3 % of the patients had an index of 8 or more. Previous episodes of pancreatitis were present in 10.6 % of the patients (7 patients had suffered one previous episode and 4 patients had two prior pancreatitis events). An ultrasound imaging test was performed in 95.2 % of patients and gallbladder stones or biliary sludge were found in 91.9 % of the examinations. Furthermore, CT detected gallstones in 21 patients (20.2 %). Biliary tract occupation was analyzed by performing MRCP in 68 patients (65.4 %), aCT scan in 19 patients (18.3 %), echoendoscopy in 3, ERCP in 3, and only ultrasound examination in 11 cases (11.5 %). The presence of bile duct stones was stated in 17 patients (16.3 %) after the index episode. Fourteen of these patients underwent ERCP for bile duct clearance that was successful in 11 cases. Two patients received a biliary stent after failure of stone removal. None of the three patients in which bile duct clearance was not achieved were referred to surgery due to high comorbidity or fragility. ERCP for stone retrieval was not attempted in 3 patients. One of them showed only a suspicion of biliary sludge on MRCP and decided not to undergo an endoscopic exploration. Another patient aged 96 years with multiple comorbidities was rejected for the procedure. The last patient in this group underwent an ERCP attempt, but suffered respiratory depression during sedation and the procedure was abandoned. The median hospital stay of the index pancreatitis event was 9 days (range, 1-127 days) and the median follow-up period was 37 months (range, 1-70).

The reasons for not undergoing surgery are listed in table I. Only 19 patients (18.3 %) did not require attention at the emergency department for any reason during the follow-up period. Three or more admissions were stated in 48 patients (46.2 %) and 9

or more in a further 9 patients (8.7 % of the study population). A total of 41 patients (39.4 %) had new episodes of acute pancreatitis, biliary events, or both following the index episode. Twenty-three patients (22.1 %) suffered new episodes of pancreatitis. Two of them experienced 2 episodes and a third patient had 3 hospital readmissions due to biliary pancreatitis. In addition, 34 patients (32.7 %) developed biliary events. Five of them registered 2 episodes, two patients had 3 biliary events and 4 patients required 4 hospital readmissions. Only a higher maximum total bilirubin level during the index pancreatitis was detected in the patients that developed biliary events during the follow-up period ($p = 0.033$). Although statistical significance was not reached, the number of patients diagnosed with choledocholithiasis and incomplete clearance of the bile duct was higher in the group that later had recurrent biliary events but not among those patients who developed recurrent pancreatitis (Tables II and III). Remarkably, all the patients that developed a recurrent pancreatitis had a bile duct size of less than 10 mm ($p = 0.012$). In addition, the index pancreatitis event was significantly more severe in the group of patients that developed recurrent pancreatitis ($p = 0.020$) (Table III). Only one patient underwent cholecystectomy after pancreatitis recurrence. Median time to recurrent pancreatitis and biliary events was 5 months (range, 0 to 55) and 12 months (range, 0-60 month), respectively. The Kaplan-Meier curve for new acute pancreatitis occurrence is represented in figure 2. The actuarial life table revealed a probability of 15% of developing recurrent pancreatitis during the first year, of 24 % at the end of the third year, and 32% after 5 years. The probability of suffering biliary events during follow-up was calculated at 16 %, 29 %, and 43 % after one, three, and five years, respectively. The Kaplan Meier curve for biliary events development is shown in figure 3.

Even though 25 patients (24 %) died during follow-up, only 6 (5.8 %) deaths were due to a recurrent episode of pancreatitis or sepsis of biliary origin. Five patients (26,3 %) died of cardiovascular disease and a further 5 patients suffered respiratory insufficiency worsening, causing their death. Six patients (31.6 %) developed cancer and died after progression of the disease, and two more patients had a brain stroke. The last patient who died of non-biliary causes had a massive upper gastrointestinal bleed. Eight of 32 patients (25 %) who did not undergo surgery because of multiple

comorbidities died during the study period following non-biliary related diseases. In addition, the mortality rate for non-biliary causes was 15.5 %. The CCI was significantly higher in the group of patients who died during follow-up (median of 7, range of 3-18 vs 5, range of 0-10; $p < 0.0005$)

DISCUSSION

Once the diagnosis of biliary pancreatitis is made, cholecystectomy is recommended to reduce the risk of recurrent episodes (3). The timing of the surgical procedure following mild pancreatitis has been extensively discussed. In fact, many studies have shown the convenience of performing cholecystectomy during the same admission, since interval removal of the gallbladder is associated with a higher risk of readmission for recurrent pancreatitis (10-12). In addition, deferral of surgery for over 4 weeks is a risk factor for further recurrent gallstone-related complications (13,14). Despite this, it is well known that almost half of diagnosed patients may not undergo immediate surgery following biliary pancreatitis (6,15). Furthermore, few reports have focused on patients who never undergo surgery. We report that one third of the patients diagnosed with biliary pancreatitis did not undergo cholecystectomy at any time. The presence of significant comorbidity translating into greater patient fragility was the main cause of surgery rejection. The median CCI in the group that decided themselves not to undergo surgery was also high. In these cases, cholecystectomy was not rejected by the surgeon but by the patient's judgement, based on their physical condition and comorbidities. In the group of patients who died before the decision was made, the comorbidity rate was also very high, and therefore there was a high probability of having been rejected for surgery during a definitive surgical evaluation. Altogether, the patients who did not undergo cholecystectomy were mainly octogenarians (median age of 82 years) and had significant associated pathologies (median CCI of 5). It is not always easy to determine the correct risk-benefit balance of having surgery in this scenario. Previous reports have shown that many patients are deemed too frail to undergo either general anesthesia or any surgical procedure, and never undergo cholecystectomy following biliary pancreatitis (16). Conversely, a recent British national cohort study revealed that the CCI of the patients not having

undergone surgery after biliary events was higher and, according to our results, gallbladder-related deaths were still significantly lower than all other causes of death in the non-surgical group (17). Thus, it may be considered advisable not to recommend surgery for ageing patients with significant morbidity. Even so, we show that close to 40 % of patients developed new episodes of pancreatitis or biliary events over the next three years (median follow-up period of 37 months), resulting in a mortality rate of 5.8 %. The probability of suffering recurrent gallbladder-related complications extends up to five years after the index case of pancreatitis. In addition, the reported mortality of emergency surgery for cholecystectomy in some reports is still lower than the mortality rate when not undergoing surgery (18,19). Even though complications following cholecystectomy for cholecystitis is twice that in patients with a CCI of 5 or higher, the morbidity rate is still under 15 %, and less than 5 % were major complications (20).

The short follow-up of some patients may seem a limitation of our study. However, we kept these patients in the analysis since the reduced follow-up period is actually based on the very definition that we have adopted for the study, i.e., the last contact with the health system. Our electronic history records make it possible to detect any contact with the health system throughout the entire hospital network. In this way, follow-up for under 3 months only implies that the patients have not attended any emergency department, have not been hospitalized, have not been followed up in any outpatient clinic, and have not died after this period. Thus, it may be reasonable to assume that they have not suffered new biliary events or pancreatitis. However, very mild episodes may have prevented patients from consulting, and therefore may have been lost.

A limitation of our study was that a multivariate analysis could not be performed. According to the univariate analysis, only total bilirubin levels during the index pancreatitis event was significantly higher in the patients who developed new biliary events. As expected, more patients with a diagnosis of choledocholithiasis and incomplete bile duct clearance were found in the group of patients with recurrent biliary events. Even so, three out of four patients who developed biliary complications during follow-up did not have choledocholithiasis after the index episode of

pancreatitis, and only 11 % of the forthcoming biliary complications were due to remaining bile duct stones. Even though the presence of bile duct stones during the index pancreatitis event has been considered an independent risk factor for recurrence (21), we did not find statistically significant differences. However, despite the fact that almost 90 % of our patients were studied for biliary tract occupation, only 70 % underwent a standard imaging test with MRCP, echoendoscopy, or ECRP. An additional 18 % (mainly the more fragile patients) underwent a multiphase CT scan examination instead, increasing the diagnostic capacity for the bile duct, although the existence of some undiagnosed bile duct lithiasis cannot be completely discounted. Cholecystectomy reduces the risk of new episodes of biliary pancreatitis by more than half and is superior to endoscopic sphincterotomy alone in reducing recurrence. However, the combination of both eliminates the risk entirely, suggesting the possibility of retained lithiasis that was not discovered on imaging tests (21,22). Conversely, even though it is difficult to predict biliary events through the analyzed variables, special care and follow-up in patients with incomplete bile duct clearance should be recommended.

None of the patients that experienced new episodes of biliary pancreatitis had a dilated bile duct during the index pancreatitis event, whereas the proportion of patients who had a bile duct sized over 1 cm was slightly higher among the patients with recurrent biliary events. Smaller stones may be more likely to cause pancreatitis, while larger stones can more easily cause bile duct obstruction and dilation (23,24). However, we did not find significant differences in the ultrasound findings of gallbladder stones between patients with and without recurrent episodes of biliary complications or pancreatitis. The presence of prior episodes of pancreatitis was not a risk factor for recurrence in our study but patients with recurrent pancreatitis had higher severity during the index episode. This could be one of the factors to contemplate when deciding which patients should be reconsidered for surgery. However, in patients with multiple comorbidities and frailty, the greater severity of the index episode of pancreatitis may also cause greater physical deterioration, making their selection for surgery less likely.

Global mortality within the follow-up period due to causes unrelated to pancreatitis or biliary disease was high (18 %) and one in four patients of the group who did not undergo surgery because of their comorbidities died. Despite the fact that cholecystectomy may not modify long-term survival in patients whose life expectancy is short due to their high comorbidity status, quality of life may be improved by reducing the number of hospital admissions. Alternatively, less invasive management with biliary sphincterotomy for non-surgical candidates has been suggested to reduce the risk for pancreatitis recurrence to some extent (25). Absence of treatment will lead to pancreatitis recurrence or biliary events in half of the patients in the five years following the first episode, thus resulting in repeated hospital admissions and increased health costs.

In conclusion, patients who are not candidates for surgery are at a high risk of recurrent biliary events and pancreatitis, which is difficult to predict during the index pancreatitis event. Conservative treatment and surgical abstention should be individualized and reserved for patients with multiple comorbidities and a short life expectancy.

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Table I. Reasons for not undergoing surgery

Total		Charlson index (median)	n (%)
	Patient's choice	5	26 (25.0)
	High comorbidity (stated by surgical team)	6	32 (30,8)
	Not referred to surgeon	4	14 (13.5)
	Died before surgery (any cause)	7	5 (4.8)
	Patient discontinued surgical follow-up	4	21 (20.2)
	Doubtful biliary origin*	4	6 (5.8)

*A second imaging test did not agree with the index diagnostic imaging test.

Table II. Risk factors for biliary events following index pancreatitis

Parameter		*Patients with biliary events after index pancreatitis (n = 34)*	*Rest of study population (n = 70)*	*p-value*
Sex ratio (F:M)		17:17	39:31	0.583*
Age (years)		82.5 (32-96)	81.5 (27-96)	0.827†
Previous pancreatitis (to index pancreatitis)		3 (8.8 %)	8 (11.4 %)	0.685*
Previous biliary events (to index pancreatitis)		7 (20.6 %)	9 (12.9 %)	0.305*
Laboratory findings during index pancreatitis				
	TB serum level	1.49 (0.12-6.60)	0.78 (0.17-7.90)	**0.033**†
	AP serum level	152.00 (47-699)	135.00 (29-725)	0.556†
	ALT serum level	63.00 (13-550)	49.90 (10-596)	0.846†
	AST serum level	67.00 (11-629)	43.00 (12-447)	0.069†
	GGT serum level	324.00 (20-2073)	224.00 (17-1200)	0.408†
Ultrasound gallbladder findings				0.808*
	Solitary millimetric gallstone	0 (0 %)	1 (1.4 %)	
	Multiple millimetric gallstones	5 (14.7 %)	10 (14.3 %)	

	Solitary gallstone > 1 cm	2 (5.9 %)	5 (7.1 %)	
	Multiple gallstones of different size	17 (50.0 %)	30 (42.9 %)	
	Biliary sludge	5 (14.7 %)	16 (22.9 %)	
	No cholelithiasis on ultrasound	4 (11.8 %)	4 (5.7 %)	
	Ultrasound not performed	1 (2.9 %)	4 (5.7 %)	
Dilated bile duct (> 10 mm in ultrasound imaging)‡		4 (11.8 %)	5 (7.1 %)	0.432*
Choledocholithiasis diagnosed during index pancreatitis		8 (23.5 %)	9 (12.9 %)	0.167*
Incomplete or non-confirmed bile duct clearance		4 (11.8 %)	2 (2.9 %)	0.068*
Index pancreatitis severity (according to the Atlanta classification)				
	Mild	21 (61.8 %)	55 (78.6 %)	0.183*
	Moderate	11 (32.4 %)	12 (17.1 %)	
	Severe	2 (5.9 %)	3 (4.3 %)	
Hospital stay (days)‡		8.50 (2-38)	19.00 (1-127)	0.728†

*Chi-square test. †Mann-Whitney test. ‡At index pancreatitis. TB: total bilirubin; AP: alkaline phosphatase.

Table III. Risk factors for pancreatitis recurrence

Parameter	*Patients with Recurrent Pancreatitis (n = 23)*	*Rest of Study Population (n = 81)*	*p-value*
Sex ratio (F:M)	12:11	44:37	0.855*
Age (years)	78.00 (27-93)	82 (32-96)	0.508†
Previous pancreatitis (to index pancreatitis)	2 (8.7 %)	9 (11.1 %)	0.740*
Previous biliary events (to index pancreatitis)	2 (8.7 %)	14 (17.3 %)	0.305*
Charlson index	5.00 (0-8)	5.00 (0-18)	0.660†
Laboratory Findings during index pancreatitis			
TB serum level	1.04 (0.20-6.70)	0.9 (0.12-7.90)	0.305†

	AP serum level	145.00 (47-503)	150.00 (29-765)	0.883†
	ALT serum level	49.50 (13-550)	50.00 (10-596)	0.880†
	AST serum level	53.00 (17-617)	45.00 (11-629)	0.533†
	GGT serum level	225.00 (24-1145)	266.00 (17-2073)	0.332†
Ultrasound Gallbladder findings				0.924*
	Solitary millimetric gallstone	0 (0 %)	1 (1.2 %)	
	Multiple millimetric gallstones	5 (21.7 %)	10 (12.3 %)	
	Solitary gallstone > 1 cm	1 (4.3 %)	6 (6 (7.4 %)	
	Multiple gallstones of different sizes	9 (39.1 %)	38 (46.9 %)	
	Biliary sludge	5 (21.7 %)	16 (19.8 %)	
	No cholelithiasis on ultrasound	2 (8.7 %)	6 (7.4 %)	
	Ultrasound not performed	1 (4.3 %)	4 (4.9 %)	
Dilated bile duct (> 10 mm in ultrasound imaging)‡		0 (0 %)	18 (23.4 %)	**0.012***
Choledocholithiasis diagnosed during index pancreatitis		1 (4.3 %)	16 (19.8 %)	0.078*
Incomplete or non-confirmed bile duct clearance		1 (4.3 %)	5 (6.2 %)	0.740*
Index pancreatitis severity (according to Atlanta classification)				
Mild		12 (52.2 %)	64 (79.0 %)	**0.020***
Moderate		10 (43.5 %)	13 (16.0 %)	
Severe		1 (4.3 %)	4 (4.9 %)	

*Chi-square test. †Mann-Whitney test. ‡At index pancreatitis. TB: total bilirubin; AP: alkaline phosphatase.

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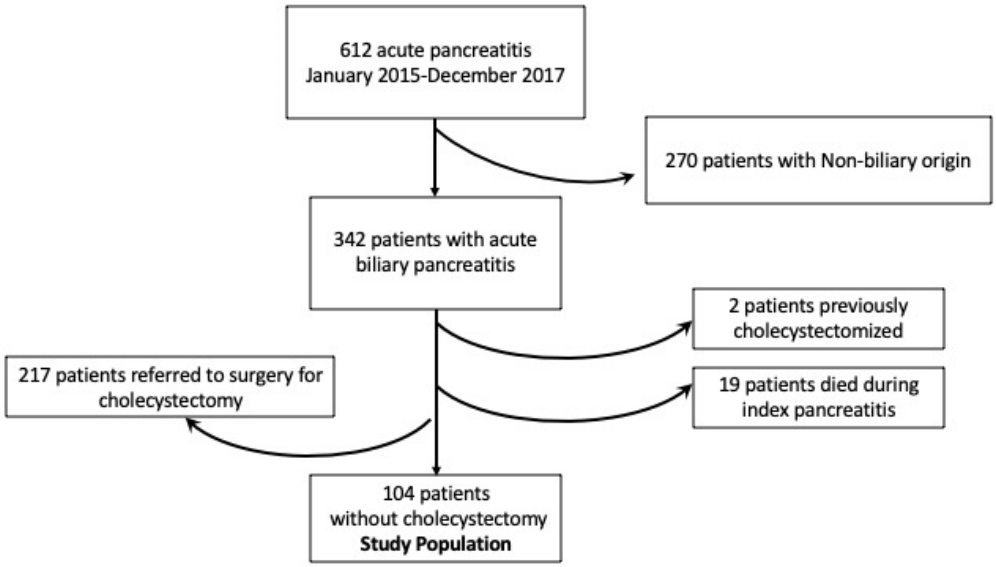
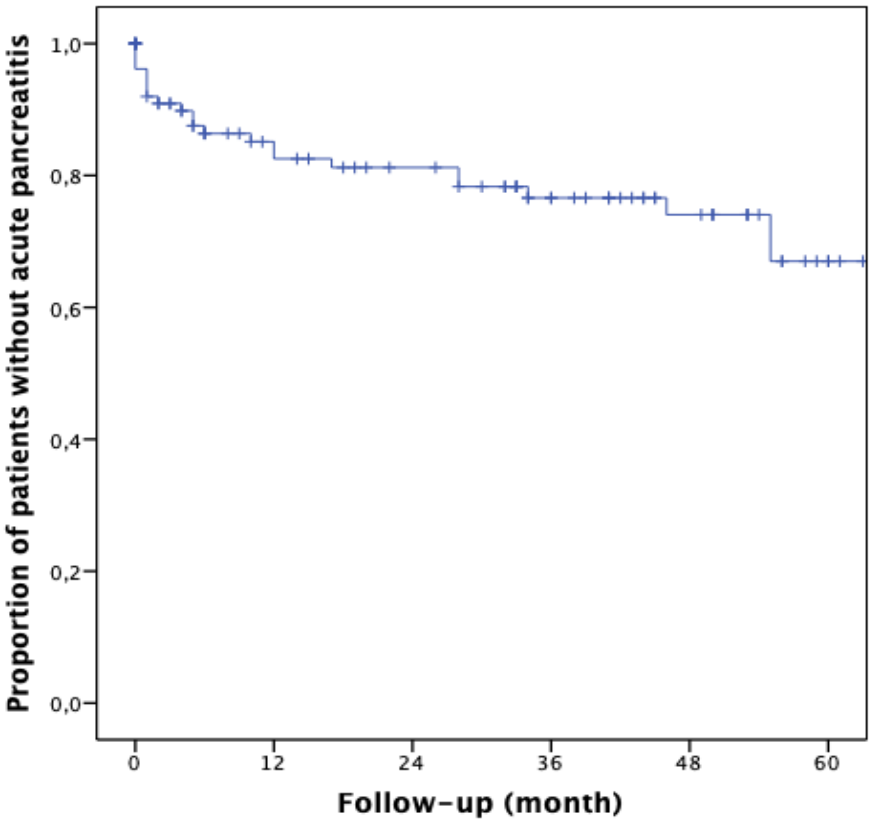
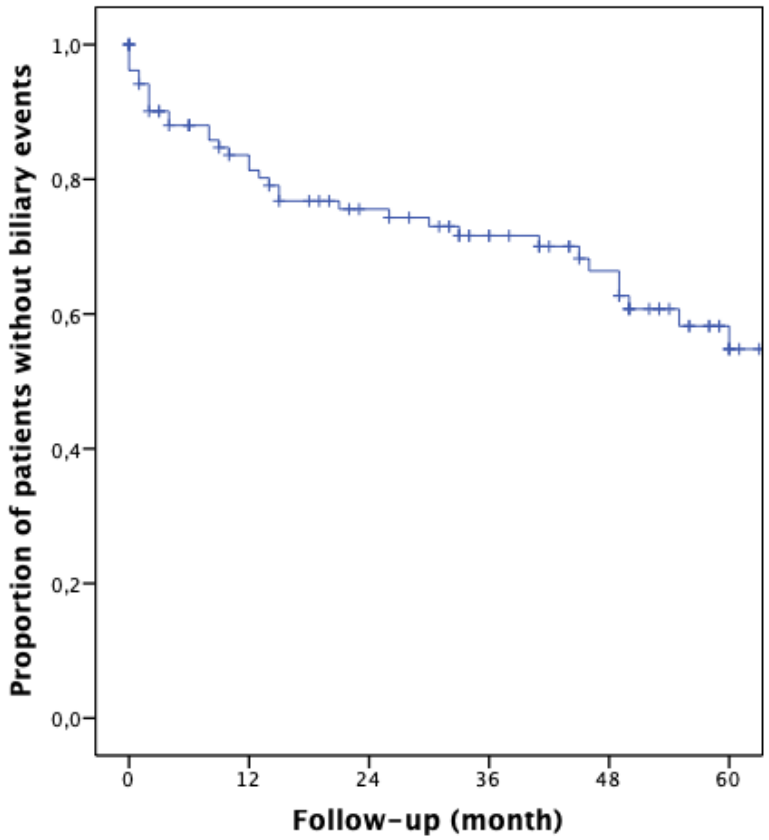


Fig. 1. Flowchart of the study population.



Number at risk	104	92	63	51.5	36.5	23	7.5

Fig. 2. Kaplan-Meier curve of the time to recurrent pancreatitis.



Number at risk	104	97	70.5	55.5	43.5	28.5	9

Fig. 3. Kaplan-Meier curve of the time to biliary events after the index episode of pancreatitis.