Acute pancreatitis: from treatment to prevention

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CHAPTER 7

Gallstones as a cause in presumed acute alcoholic pancreatitis: *observational multicentre study*

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ABSTRACT

Background: Data on the incidence and clinical relevance of gallstones in patients with suspected acute alcoholic pancreatitis are lacking and are essential to minimize the risk of recurrent acute pancreatitis. The aim of this study was to assess the incidence of gallstones and the associated rate of recurrent acute pancreatitis in patients with presumed acute alcoholic pancreatitis.

Methods: Between 2008 and 2019, 23 hospitals prospectively enrolled patients with acute pancreatitis. Those diagnosed with their first episode of presumed acute alcoholic pancreatitis were included in this study. The term gallstones was used to describe the presence of cholelithiasis or biliary sludge found during imaging. The primary outcome was pancreatitis recurrence during 3 years of follow-up.

Results: A total of 334 patients were eligible for inclusion, of whom 316 patients were included in the follow-up analysis. Gallstone evaluation, either during the index admission or during follow-up, was performed for 306 of 334 patients (91.6%). Gallstones were detected in 54 patients (17.6%) with a median time to detection of 6 (IQR 0-42) weeks. During follow-up, recurrent acute pancreatitis occurred in 121 of 316 patients (38.3%), with a significantly higher incidence rate for patients with gallstones compared with patients without gallstones (59% versus 34.2% respectively; $p<0.001$), while more patients with gallstones had stopped drinking alcohol at the time of their first recurrence (41% versus 24% respectively; $p=0.020$). Cholecystectomy was performed for 19 patients with gallstones (36%). The recurrence rate was lower for patients in the cholecystectomy group compared with patients who did receive inadequate or no treatment (5/19 versus 19/34 respectively; $p=0.038$).

Conclusions: Gallstones were found in almost one in every five patients diagnosed with acute alcoholic pancreatitis. Gallstones were associated with a higher rate of recurrent pancreatitis, while undergoing cholecystectomy was associated with a reduction in this rate.

INTRODUCTION

The incidence of acute pancreatitis continues to rise, with an average annual increase of 3.67% in the USA (1). Biliary disease and alcohol are the most common causes (2, 3). Identification of the underlying aetiology is important to guide targeted interventions; cholecystectomy can prevent recurrent biliary events in patients with biliary pancreatitis (4), while alcohol cessation support can reduce the risk of recurrent acute pancreatitis (5). Yet, the precise alcohol threshold that defines alcoholic aetiology is unclear and likely varies between patients (6). Previous studies have used different definitions, with thresholds ranging from more than 3 or 4 units per day (7, 8) to more than 4 units in the 24h before onset (9). As a result, the diagnosis often depends on ruling out other potential causes. Current guidelines recommend a comprehensive evaluation that includes a personal and family history, laboratory tests, and a transabdominal ultrasonography (TUS) (10). If TUS shows cholelithiasis, biliary sludge, or dilated bile duct(s), biliary disease is generally considered the most likely cause (11), at least for those who are not excessive drinkers.

Distinguishing between biliary and alcoholic aetiologies can be challenging. First, the lack of clear criteria for alcoholic pancreatitis may lead clinicians to rely on subjective interpretations of excessive alcohol consumption. This approach may bypass TUS, as recommended by the guidelines (10), potentially leading to the misdiagnosis of patients with biliary aetiology as having alcoholic pancreatitis alone. Second, the diagnostic accuracy of TUS in detecting sludge is limited, especially in the acute phase (12, 13). Therefore, patients with suspected idiopathic acute pancreatitis often undergo TUS for a second time and, if necessary, endoscopic ultrasonography (EUS) (9, 14). Conversely, for patients labelled as having alcoholic pancreatitis, the diagnostic work-up may stop after a single (possibly suboptimal) TUS at the time of diagnosis. This scenario exposes patients to potential recurrent biliary events, including acute pancreatitis. Finally, even if a biliary aetiology is identified, it may go untreated because alcohol is considered the primary trigger of pancreatitis. This again raises the risk of future biliary complications.

In the absence of available literature, the aim of this study was to assess the incidence of gallstones and the associated rate of recurrent acute pancreatitis in a large prospective nationwide cohort of patients with presumed acute alcoholic pancreatitis.

METHODS

This study was performed according to the principles of the Declaration of Helsinki and the STROBE guideline (available as Supplementary material) (15). This study was not pre-registered in an independent, institutional registry.

Study design and population

This study is a post-hoc analysis of the Dutch Pancreatitis Study Group's prospective nationwide registry of acute pancreatitis (PWN-CORE). For this study, all patients from 23 hospitals between 2008 and 2019 were screened for eligibility. Acute pancreatitis was defined according to the revised Atlanta classification (16).

Eligible patients were adults with a first episode of 'presumed' alcoholic pancreatitis, diagnosed when the treating physician considered alcohol as the most likely cause, and no treatment was initiated for other aetiological factors. Patients were excluded if they had chronic pancreatitis according to the M-ANNHEIM criteria at the time of the first diagnosis of acute pancreatitis (17), if they had a previous episode of acute pancreatitis for which data could not be retrieved, or if data were incomplete. PWN-CORE was approved by a medical ethics committee (W19.088). Written informed consent was obtained from each participant.

Data collection

Clinical data, including patient characteristics and results of laboratory and imaging tests, were prospectively collected at the time of initial hospitalization using a standardized case record form. Follow-up data on imaging, and readmissions and outpatient hospital visits for recurrent pancreatitis, biliary complications, and biliary interventions were collected retrospectively from medical records and evaluated until 3 years after the initial admission. Only initial admission data were used for patients who were lost to follow-up. Data were imported into data management software by two researchers (N.J.S. and F.E.M.d.R.). Any discrepancies were resolved by discussion with the involvement of an expert (R.C.V.) until consensus was reached.

Outcomes

The primary outcome was the rate of recurrent acute pancreatitis according to the revised Atlanta classification during the 3 years after the initial admission (16). This follow-up interval was chosen because it was not considered feasible to link the initial episode of pancreatitis to subsequent gallstone detection and possible recurrence beyond this interval. Secondary outcomes included biliary events, biliary interventions, adherence to guidelines for performing the standard diagnostic work-up (10), and diagnostic yield of additional imaging after an initial negative TUS result.

Definitions

Alcohol consumption, as reported immediately upon hospital admission, was converted into standard units per week (1 standard unit equals 10 g) for regular drinkers using an online calculation tool (18). Those who occasionally consumed more than 4 (for women) or 5 (for men) standard units were classified as binge drinkers (19). The term gallstones was used to describe the presence of cholelithiasis or biliary sludge found during the following imaging tests: transabdominal TUS, EUS, magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreaticography (MRCP) (14, 20-22). Biliary events included acute cholecystitis, cholangitis, obstructive choledocholithiasis requiring endoscopic retrograde cholangiopancreaticography, and biliary colic. Acute cholecystitis and cholangitis were defined according to the Tokyo classification (23, 24). Biliary colic was defined according to the Rome IV criteria (25). A complete standard diagnostic work-up was defined as serum calcium and triglycerides tests, and imaging with TUS according to the International Association of Pancreatology/American Pancreatic Association guidelines during the index admission (10). Personal and family histories (that is drug use, genetic mutations, etc.) were not included in this study due to the challenges of the retrospective design. All definitions are listed in Table S1.

Statistical analysis

All analyses were performed using SPSS® (IBM, Armonk, NY, USA). Categorical variables are presented as n (%) and continuous variables are presented as mean (s.d.) or median (interquartile range (IQR)). Statistical comparisons between patients with and without gallstones were made using the chi-squared test or Fisher's exact test for categorical data and Student's t-test or the Mann-Whitney U test for continuous data. Other pre-specified subgroup analyses were attempted based on history of cholecystectomy and initial TUS results. The diagnostic yield for each imaging modality is presented as % (95% CI). Missing data were not imputed. $P<0.050$ was considered statistically significant.

RESULTS

Between 2008 and 2019, 2447 patients from 23 hospitals were prospectively registered. Of these, 334 were included in the present study (Figure 1). Clinical characteristics are shown in Table 1. A total of 10 patients (3.0%) had previously undergone a cholecystectomy.

Alcohol consumption was self-reported for 295 patients (Table 1). Median liver enzyme levels at admission are shown in Table 1.

During the index admission, serum calcium tests were performed for 290 patients (86.8%) and triglyceride tests were performed for 199 patients (59.6%). Abnormal calcium and triglyceride tests were found for 0 patients and 16 patients (8.0%), respectively. TUS was performed during the index admission for 276 patients (82.6%). The median number of standard alcohol units per week was higher for the group of patients who did not undergo TUS than in those who did undergo TUS (70 versus 35 units per week; respectively; p<0.001) (Table S2). A complete standard diagnostic work-up according to the guidelines was performed for less than half of all patients (156 of 334 patients (46.7%)).

During the 3-year follow-up interval, 19 patients (5.7%) died (of these, 3 patients died during the index admission). A total of 18 patients (5.4%) were lost to follow-up after the index admission (Figure 1), resulting in 316 patients included in the assessment for the follow-up interval.

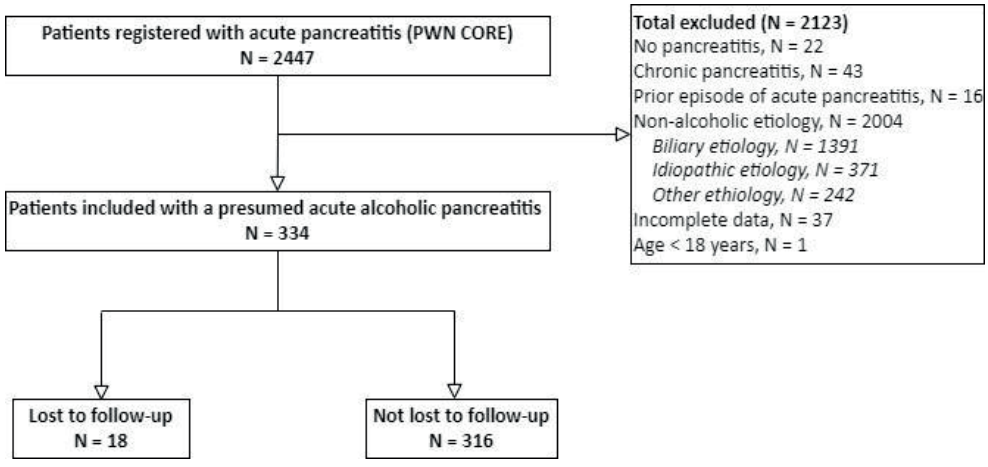

Figure 1. Flowchart

Gallstone detection

During the index admission, 276 out of 334 patients (82.6%) underwent TUS, of whom 18 (6.5%) were found to have gallstones (Table 2). During follow-up, 198 out of 316 patients (62.7%) underwent imaging, including (repeat) TUS for 168 patients (53.2%), MRI/MRCP for 69 patients (21.8%), and EUS for 40 patients (12.7%). These imaging modalities identified gallstones in 47 patients (23.7%). Taking into account overlap, 306 out of 334 patients (91.6%) underwent at least one imaging test for gallstone evaluation, either during the index admission or during follow-up. Gallstones were found in 54 of these 306 patients (17.6%), of whom 1 was lost to follow-up. The median detection time was 6 (IQR 0-42) weeks after the index admission.

Table 1. Clinical characteristics

	N=334
Age in years – mean (SD)	50 (14)
Male sex – no. (%)	275 (82.3%)
BMI – median (IQR) (n=182)	25 (23-28)
Prior cholecystectomy – no. (%)	10 (3.0%)
Self-reported alcohol use per week – no. (%) (n=295)*	
≤21 units	49 (16.6%)
>21 units	188 (63.7%)
Binge drinking	58 (19.7%)
Smoking – no. (%) (n=304)	200 (65.8%)
Liver enzymes at admission – median (IQR)	
Aspartate aminotransferase in U/L (n=324)	39 (25-79)
Alanine aminotransferase in U/L (n=329)	40 (24-72)
Alkaline phosphatase in U/L (n=327)	86 (71-119)
Gamma-glutamyltransferase in U/L (n=330)	113 (52-395)
Bilirubin total in µmol/L (n=329)	14 (9-22)
Standard diagnostic work-up during index-admission	
Calcium testing – no. (%)	290 (86.8%)
Calcium in mmol/L – median (IQR)	2.29 (2.12-2.40)
Calcium >3 mmol/L – no. (%)	0
Triglycerides testing – no. (%)	199 (59.6%)
Triglycerides in mmol/L – median (IQR)	1.53 (0.92-2.80)
Triglycerides >11.2 mmol/L – no. (%)	16 (8.0%)
Transabdominal ultrasound – no. (%)^	276 (82.6%)
Complete standard diagnostic work-up – no. (%)	156 (46.7%)
Severity of acute pancreatitis – no. (%)#	
Mild	207 (62.0%)
Moderate severe	94 (28.1%)
Severe	33 (9.9%)
Mortality – no. (%)	19 (5.7%)
During index admission – no. (%)	3 (0.9%)

*Data are presented as no. (%), mean (SD), or median (IQR). *The cut-off value of 21 units/week was chosen based on the definitions of the Dutch National Institute for Public Health and Environment, which defines excessive alcohol consumption as more that 21 units per week. ^Magnetic resonance cholangiopancreatography was used as the first diagnostic modality in 3 patients. #According to the revised Atlanta classification. Abbreviations: BMI body mass index.*

For the subgroup of patients whose initial TUS during the index admission did not reveal gallstones, the diagnostic yields of subsequent imaging tests are detailed in Table 3. The overall gallstone detection rate was 11.0% (95% CI 7.6-14.4). The individual rates were: 11.5% for repeat TUS, 2.8% for MRI/MRCP, and 23.7% for EUS.

Table 2. Number and yield of imaging tests

Type of test	Patients with imaging test – no. (%)	Patients with gallstones based on imaging test – no. (%)^	Total of imaging tests performed - no	Gallstones demonstrated on first positive imaging– no*
TUS during index admission	276 (82.6%)	18 (6.5%)	276	12 cholecystolithiasis 1 choledocholithiasis 8 sludge in gallbladder 2 sludge in CBD
Imaging tests after index admission	198 (62.7%)	47 (23.7%)	434	37 cholecystolithiasis 2 choledocholithiasis 20 sludge in gallbladder
(Repeat) TUS	168 (53.2%)	40 (23.8%)	300	27 cholecystolithiasis 15 sludge in gallbladder
MRI/MRCP	69 (21.8%)	4 (5.8%)	86	3 cholecystolithiasis 2 sludge in gallbladder
EUS	40 (12.7%)	11 (27.5%)	48	7 cholecystolithiasis 2 choledocholithiasis 3 sludge in gallbladder
Total for all imaging tests	306 (91.6%)	54 (17.6%)	710	49 cholecystolithiasis 3 choledocholithiasis 28 sludge in gallbladder 2 sludge in CBD

*Data are presented as no. (%) or no. ^Multiple positive imaging modalities in one patients were scored as one outcome. *Please not that in several cases multiple biliary findings were observed in a single patient. Abbreviations: Abbreviations: EUS endoscopic ultrasound, CBD common bile duct, MRCP magnetic resonance cholangiopancreatography, MRI magnetic resonance imaging, TUS transabdominal ultrasound.*

Recurrent acute pancreatitis and biliary events

During follow-up, recurrent acute pancreatitis occurred in 121 of 316 patients (38%). Patients with gallstones (31 of 53 (59%)) were significantly more likely to develop recurrent acute pancreatitis than patients without gallstones (90 of 263 (34.2%)) ($p<0.001$). Self-reported alcohol consumption at admission for the first recurrent episode was available for 114 of the 121 patients with recurrence, of whom 32 (28.1%) reported no longer consuming alcohol (41% versus 24% for patients with and without gallstones respectively $p=0.020$). Subgroup analyses, based on the initial TUS results during the index admission, are presented in Table S3 and show recurrence rates of 53% for patients with an initial positive TUS result, 48% for patients who did not undergo TUS, and 35.0% for patients with an initial negative TUS result. Biliary events after the first episode of pancreatitis were observed in nine patients (3%) (cholangitis, 4 patients; acute cholecystitis, 2 patients; obstructive choledocholithiasis, 2 patients; and colic, 1 patient).

Table 3. Number and yield of additional imaging tests in patients with an initial negative US (n=243)^

Type of test	Patients with diagnostic test – no. (%)	Patients with gallstones based on diagnostic test – no. (%)	Total of diagnostic tests performed – no.	Total times gallstones were demonstrated – no.	Diagnostic yield – percentage (95% CI)
Repeat TUS	128 (52.7%)	21 (16.4%)	218	25	11.5% (6.8-15.2)
MRI/MRCP	56 (23.0%)	2 (3.6%)	71	2	2.8% (-1.0-6.6)
EUS	32 (13.2%)	8 (25.0%)	38	9	23.7% (10.1-37.3)
Total	154 (63.4%)	26 (16.9%)	327	36	11.0% (7.6-14.4)

Data are presented as no. (%), no., or percentage (95% CI). ^A total of 15 patients were excluded as they were lost to follow-up. Abbreviations: EUS endoscopic ultrasound, MRCP magnetic resonance cholangiopancreatography, MRI magnetic resonance imaging, TUS transabdominal ultrasound.

Biliary treatment

During follow-up, 22 of 53 patients with gallstones (42%) underwent biliary intervention. The procedures performed were cholecystectomy with or without biliary endoscopic sphincterotomy (ERCP) (19 patients), biliary endoscopic sphincterotomy alone (1 patient), and percutaneous gallbladder drainage (2 patients). The remaining 31 patients (59%) received no biliary intervention. A single patient underwent an unsuccessful ERCP procedure in which no biliary access could be obtained, one patient's scheduled cholecystectomy was cancelled due to the development of metastatic disease, and another patient did not attend a scheduled appointment at the surgical division to discuss the possibility of elective cholecystectomy.

After receiving appropriate treatment (that is cholecystectomy), 5 of 19 patients developed recurrent acute pancreatitis compared with 19 of 34 patients who received inadequate treatment (that is ERCP or percutaneous gallbladder drainage alone) or no treatment (relative risk 0.47; 95% CI 0.21-1.06; p=0.038).

DISCUSSION

In this first nationwide cohort study, we found that 91.6% of patients with presumed acute alcoholic pancreatitis underwent gallstone evaluation, and 17.6% were found to have gallstones. Patients with gallstones had a nearly twofold increased risk of recurrent acute pancreatitis. In contrast, those patients with gallstones who underwent cholecystectomy had half the risk of recurrence. Cholecystectomy was performed for only 36% of patients.

The main findings are that the risk of pancreatitis recurrence significantly increased from 34.2% to 59% in the presence of gallstones for patients with presumed acute alcoholic pancreatitis, even if more of these patients were alcohol abstinent at the time of recurrence. Although the authors' study group has previously evaluated recurrence rates for patients with biliary pancreatitis and alcoholic pancreatitis (26) (rates of 12% and 24%, respectively), no studies have specifically targeted our study population, making direct comparisons difficult. Based on these results, one could speculate that a significant number of patients diagnosed with alcoholic pancreatitis may indeed have biliary pancreatitis, accompanied by excessive alcohol consumption habits, and may benefit from cholecystectomy. The results of the present study show that the recurrence rate after cholecystectomy is indeed two times lower than after no treatment.

A dual role for alcohol in the pathophysiology of acute pancreatitis, acting as either a trigger or a modulator, has previously been suggested (6). This is supported by the low lifetime risk of developing acute pancreatitis in the overall population of excessive alcohol consumers (27). However, the potential interaction of alcohol with biliary disease in the development of acute pancreatitis and vice versa remains far from clear. Furthermore, the authors believe that the exact aetiology cannot be determined when a patient presents with both gallstones and excessive alcohol consumption. Future studies should focus on identifying biochemical and clinical markers and combining them in a (machine learning) prediction model to adequately differentiate between these two aetiologies. Meanwhile, it is important to recognize and address both potential aetiologies, with the initial approach being that patients with excessive alcohol consumption undergo the same diagnostic work-up as non-drinkers.

At admission, current guidelines recommend testing for calcium and triglycerides and performing an TUS (10). In the present study, only half of the patients underwent this recommended work-up. Although TUS is both affordable and non-invasive, it was not performed in 17.4% of patients. Notably, a significant difference in alcohol consumption was observed, favouring patients who underwent TUS. This raises concerns about potential alcohol-related stigma in the management of acute pancreatitis, which should be further explored, for example in a qualitative study assessing the stigmatizing attitudes of pancreatologists towards their patients. Such attitudes have been well documented in other diseases often considered to be self-inflicted, such as HIV, obesity, and psychiatric disorders (28-30). The potential influence of stigma on the doctor-patient relationship, and its impact on a patient's quality of life (31) underscores the need to improve the understanding of the pathophysiology and to establish universally accepted diagnostic criteria for acute alcoholic pancreatitis. In the meantime, strict adherence to guidelines for patients suspected of having alcoholic pancreatitis remains critical, especially as the recurrence rate of pancreatitis was sig-

nificantly higher for patients who did not undergo TUS compared with patients with an initially negative TUS result.

Positive TUS findings for gallstones were present for 6.5% of patients during the index admission, suggesting that an initial diagnosis of just alcoholism would be incorrect. However, given the established prevalence of biliary disease in the general population in the USA (32), these findings must be interpreted with caution. Factors known to increase the risk of biliary disease include female sex, older age, and higher BMI (33), while the effect of alcohol remains controversial (34-36). Alcohol has been associated with gallstones because of its role in lipid metabolism, but studies also report that alcohol may increase gallbladder motility and decrease bile lithogenicity, thus protecting against gallstone formation.

Additional imaging was performed for 62.7% of patients with an initial negative TUS result. The overall yield was 11.0%, which may be an underestimate given the relatively low utilization rates of EUS and MRCP, the two modalities with the highest accuracy for detection of gallstones (37, 38). This supports the hypothesis that patients diagnosed with alcoholic pancreatitis may have undetected occult gallstones. However, the inclusion of patients with a high suspicion of gallstones, as indicated by prior diagnostic tests such as repeat TUS, may have influenced the high individual yield of EUS (23.7%). Nevertheless, the repeat TUS showed a notable yield of 11.5%, above the 10% cut-off considered sufficient for routine use of EUS for patients after the first episode of idiopathic acute pancreatitis (9). In the absence of prospective studies, the validity, futility and optimal timing of additional imaging for patients with excessive alcohol consumption and an initial negative TUS result require further investigation before reliable recommendations can be made.

In the present study, only 36% of patients with gallstones underwent a cholecystectomy, while the remaining patients received no or inadequate treatment (that is ERCP or percutaneous gallbladder drainage alone). This suggests that clinicians often consider gallstones in patients with presumed alcoholic pancreatitis as an incidental finding that does not warrant further treatment, which is concerning, as the incidence rate of recurrent acute pancreatitis after cholecystectomy was 5/19 compared with 19/37 for untreated patients. This finding, together with the consistent evidence for the effectiveness of cholecystectomy in preventing recurrence (4, 39), emphasizes that timely cholecystectomy should be considered once gallstones are identified. Nevertheless, the observed recurrence rate after cholecystectomy highlights the importance of broadening the focus beyond the consideration of cholecystectomy alone. Previous studies have shown that alcohol cessation reduces recurrence to almost 0% (40, 41). However, complete alcohol abstinence is notoriously difficult, as the authors have also

observed. In an earlier Finnish trial, additional alcohol reduction efforts were shown to reduce the risk of recurrent acute pancreatitis (5). Recently, the Dutch Pancreatitis Study Group has initiated the multicentre PANDA trial (42). This trial aims to determine the effectiveness of a structured alcohol cessation support programme in reducing the rate of recurrent acute pancreatitis for patients after their first episode of acute alcoholic pancreatitis when compared with the current standard practice.

The post-hoc design of the present study has limitations, leading to several drawbacks. First, it must be emphasized that the observed association between gallstones and recurrent pancreatitis and between cholecystectomy and recurrent pancreatitis does not imply causality. For example, it was not possible to account for the possibility of different aetiologies for different attacks. Second, data on continued alcohol use or cessation after the first episode of pancreatitis were collected post hoc and only at the time of recurrent episodes. Therefore, it was not possible to perform a multivariable analysis with alcohol use as a potential confounder to compare the primary outcome for patients with and without gallstones. In addition, the study utilized a pragmatic approach to assessing alcohol use, relying on patient self-reporting and making the following distinction: continued alcohol use? (yes or no). Third, it was not possible to reliably assess data on smoking after the first episode of pancreatitis, a factor that could also influence the primary outcome. Fourth, a diagnosis of acute alcoholic pancreatitis was made based on the discretion of the treating physician and therefore no predefined diagnostic work-up was required, which may have introduced bias. On the other hand, the present study reflects what is happening in current clinical practice. Another limitation is that all of the imaging studies performed were evaluated and not just those that were done to assess the presence of gallstones. Also, patients who did not undergo any imaging were included in the subgroup of patients thought to have no gallstones. Finally, subgroup analyses based on gallbladder status were not possible because only 10 out of the 334 patients had a history of cholecystectomy.

CONCLUSION

Our study found that 17.6% of patients diagnosed with acute alcoholic pancreatitis had gallstones, which were significantly associated with a higher rate of recurrent acute pancreatitis. In addition, we show that gallstone evaluation at initial admission was not consistently performed. The same was true for the performance of cholecystectomy once gallstones were identified. This is of concern, especially since our results also showed an almost significant reduction in recurrent pancreatitis after cholecystectomy. With the ever-increasing burden of acute pancreatitis, we strongly recommend better adherence to guidelines for all patients suspected of having acute alcoholic pancreatitis, including performing an transabdominal ultrasound, and considering cholecystectomy for those diagnosed with gallstones.

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Table S1. Definitions

Baseline	
Acute pancreatitis	When two of the following criteria were met: upper abdominal pain, serum lipase concentration (or amylase) ≥ 3 times higher than the upper limit of normal or features of acute pancreatitis on imaging
(Presumed) alcoholic pancreatitis	Acute pancreatitis was classified as 'presumed' alcoholic if the treating physician considered alcohol as the most probably cause, and no treatment was initiated for other etiological factors.
Binge drinking	The term binge drinking was used for women consuming 4 or more standard units on an occasion or 5 or more standard units on an occasion for men
Outcomes	
Gallstones	Gallstones were defined as the presence of cholelithiasis or biliary sludge on the following imaging techniques: transabdominal ultrasound, endoscopic ultrasound, magnetic resonance imaging, and magnetic resonance cholangiopancreaticography
Biliary events	Acute cholecystitis, biliary colic, cholangitis, or obstructive choledocholithiasis
Acute cholecystitis	An acute inflammation of the gallbladder, diagnosed when one item in A, B, and C is present (according to the Tokyo classification): A) Local signs of inflammation 1) Murphy's sign, or 2) Right upper abdominal quadrant mass, pain or tenderness B) Systemic signs of inflammation 1) Fever or hypothermia 2) Elevated C-reactive protein, or 3) Elevated white blood cell count C) Imaging findings characteristics of acute cholecystitis Note: Acute cholecystitis that occurs in the absence of gallstones (i.e. acalculous cholecystitis) did not meet our criteria for acute cholecystitis
Biliary colic	Intermittent pain located in the epigastrium and/or right upper quadrant lasting at least 30 minutes, severe enough to interrupt daily activities or lead to an emergency department visit, not related to bowel movements, and not relieved by postural change or acid suppression (according to Rome IV criteria)

Table S1. Definitions (*continued*)

Cholangitis	An inflammation of the bile duct(s), diagnosed when one item in A, B, and C is present (according to the Tokyo classification): A) Systemic inflammation 1) Fever, hypothermia and/or shaking chills 2) Laboratory data: evidence of inflammatory response (abnormal white blood cell counts, increase of serum CRP levels, and other changes indicating inflammation) B) Cholestasis 1) Jaundice 2) Laboratory data: abnormal liver function tests C) Imaging 1) Biliary dilatation 2) Evidence of aetiology on imaging Note: Cholangitis that occurs in the absence of gallstones did not meet our criteria for cholangitis
Obstructive choledocholithiasis	Presence of gallstones or biliary sludge in the common bile duct on imaging, requiring an ERCP, according to the treating physician
Chronic pancreatitis	A chronic inflammation of the pancreatic parenchyma, defined as typical clinical history or chronic pancreatitis (such as recurrent acute pancreatitis or abdominal pain, except for primary painless pancreatitis and one or more of the following (according to the M-ANNHEIM criteria): A) Pancreatic calcifications B) Moderate or marked ductal lesions C) Marked and persistent exocrine insufficiency D) Typical histology
Complete standard diagnostic work-up	Complete standard diagnostic work-up was defined as laboratory testing, including calcium and triglycerides, and imaging using transabdominal ultrasound, MRI or MRCP (according to IAP/APA guidelines). Note: The standard diagnostic work-up did not include the patient's family history of hereditary pancreatitis or associated genetic mutations, as well as their personal history, such as drug use, due to the challenges of collecting this data retrospectively
Positive imaging	Positive imaging is defined as imaging in which proof of gallstones were found. Note: Isolated dilatation of the intrahepatic bile ducts or CBD was not deemed conclusive evidence for establishing a biliary etiology. This is due to the limitations imposed by the post-hoc design of the study, which prevents reliably confirmation of the absence of other factors that could potentially contribute to duct dilatation, such as stenosis, obstruction caused by external compression, or opioid use
Recurrent acute pancreatitis	Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis after complete resolution of all symptoms associated with the previous episode (according to the Revised Atlanta criteria)

Table S2. Self-reported alcohol use in patients with and without transabdominal ultrasound at index admission

Self-reported alcohol use per week	All patients (n=295)*	Patients with TUS (n=246)	Patients without TUS (n=49)	P-value
Units – median (IQR) (n=237)^	42 (28-70)	35 (28-70)	70 (35-112)	**<0.001**
≤ 21 units – no. (%)	49 (16.6%)	43 (17.5%)	6 (12.2%)	0.369
> 21 units – no. (%)	188 (63.7%)	155 (63.0%)	33 (67.3%)	0.564
Binge drinking – no. (%)	58 (19.7%)	48 (19.5%)	10 (20.4%)	0.885

*Data are presented as no. (%), or median (IQR). *The levels of self-reported alcohol use were available in 295/334 patients. ^The 58 patients who met the definition for binge drinking were excluded to calculate the median self-reported alcohol use per week. Abbreviations: TUS transabdominal ultrasound.*

Table S3. Subgroup analyses of recurrent acute pancreatitis

	All patients (n=316)^	**Patients with positive first TUS (n=17)[A]**	**Patients with negative TUS (n=243)[B]**	**Patients with no TUS (n=56)[C]**	**P-value**	
					A vs. B	**B vs. C**
Recurrent acute pancreatitis	121 (38.3%)	9 (52.9%)	85 (35.0%)	27 (48.2%)	0.136	0.065

Data are presented as no. (%). ^A total of 18 patients were excluded as they were lost to follow-up . Abbreviations: TUS transabdominal ultrasound.