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Original Article

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 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 (interquartile range 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 treatment or no treatment (5/19 *versus* 19/34 respectively; $P = 0.038$).

Conclusion: 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.

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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 24 h 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 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 for 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 workup may stop after 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 guidelines (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, 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.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 workup[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: TUS, EUS, MRI, and magnetic resonance cholangiopancreatography (MRCP)[14,20–22]. Biliary events included acute cholecystitis, cholangitis, obstructive choledocholithiasis requiring endoscopic retrograde cholangiopancreatography, 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 workup was defined as serum calcium and triglyceride tests and TUS imaging 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 (i.q.r.)). 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% c.i.). Missing data

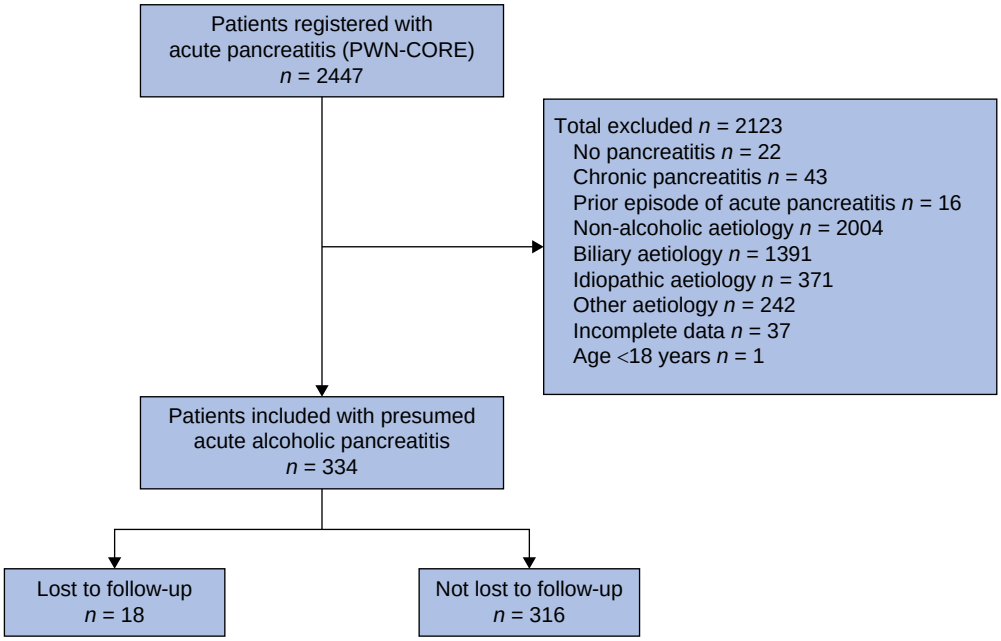

Fig. 1 Flow chart

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 (*Fig. 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, 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 workup 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 (*Fig. 1*), resulting in 316 patients included in the assessment for the follow-up interval.

Gallstone detection

During the index admission, 276 of 334 patients (82.6%) underwent TUS, of whom 18 (6.5%) were found to have gallstones (*Table 2*). During follow-up, 198 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 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

Table 1 Clinical characteristics; *n* = 334

	Value
Age (years), mean(s.d.)	50(14)
Male	275 (82.3)
BMI (kg/m^2), median (i.q.r.) (*n* = 182)	25 (23–28)
Prior cholecystectomy	10 (3.0)
Self-reported alcohol use per week (*n* = 295)*	
≤21 units	49 (16.6)
>21 units	188 (63.7)
Binge drinking	58 (19.7)
Smoking (*n* = 304)	200 (65.8)
Liver enzymes at admission, median (i.q.r.)	
Aspartate aminotransferase (U/l) (*n* = 324)	39 (25–79)
Alanine aminotransferase (U/l) (*n* = 329)	40 (24–72)
Alkaline phosphatase (U/l) (*n* = 327)	86 (71–119)
γ-Glutamyl transferase (U/l) (*n* = 330)	113 (52–395)
Bilirubin total (μmol/l) (*n* = 329)	14 (9–22)
Standard diagnostic workup during index admission	
Calcium testing	290 (86.8)
Calcium (mmol/l), median (i.q.r.)	2.29 (2.12–2.40)
Calcium >3 mmol/l	0
Triglyceride testing	199 (59.6)
Triglycerides (mmol/l), median (i.q.r.)	1.53 (0.92–2.80)
Triglycerides >11.2 mmol/l	16 (8.0)
Transabdominal ultrasonography†	276 (82.6)
Complete standard diagnostic workup	156 (46.7)
Severity of acute pancreatitis‡	
Mild	207 (62.0)
Moderately severe	94 (28.1)
Severe	33 (9.9)
Deaths	19 (5.7)
During the index admission	3 (0.9)

Values are *n* (%) unless otherwise indicated. *The cut-off value of 21 units per week was chosen based on the definitions of the Dutch National Institute for Public Health and Environment, which defines excessive alcohol consumption as more than 21 units per week. †Magnetic resonance cholangiopancreatography was used as the first diagnostic modality for three patients. ‡According to the revised Atlanta classification[16]. i.q.r., interquartile range.

Table 2 Number and yield of imaging tests

Type of imaging test	Patients who underwent the imaging test	Patients with gallstones based on the imaging test*	Total no. of imaging tests performed	No. of patients with gallstones demonstrated during the first positive imaging test†
TUS during the index admission	276 (82.6)	18 (6.5)	276	12 cholecystolithiasis 1 choledocholithiasis 8 sludge in gallbladder 2 sludge in CBD
Imaging tests after the 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 (6)	86	3 cholecystolithiasis 2 sludge in gallbladder
EUS	40 (12.7)	11	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

Values are *n* (%) unless otherwise indicated. *Multiple positive imaging modalities for one patient were scored as one outcome. †Please note that for several cases multiple biliary findings were observed for a single patient. TUS, transabdominal ultrasonography; CBD, common bile duct; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasonography.

Table 3 Number and yield of additional imaging tests for patients with an initial negative transabdominal ultrasonography result (*n* = 243)*

Type of diagnostic test	Patients who underwent the diagnostic test	Patients with gallstones based on the diagnostic test	Total no. of diagnostic tests performed	Total no. of times gallstones were demonstrated	Diagnostic yield, % (95% c.i.)
Repeat TUS	128 (52.7)	21 (16.4)	218	25	11.5 (6.8, 15.2)
MRI/MRCP	56 (23.0)	2 (4)	71	2	2.8 (−1.0, 6.6)
EUS	32 (13.2)	8	38	9	23.7 (10.1, 37.3)
Total	154 (63.4)	26 (16.9)	327	36	11.0 (7.6, 14.4)

Values are *n* (%) unless otherwise indicated. *A total of 15 patients were excluded as they were lost to follow-up. TUS, transabdominal ultrasonography; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasonography.

median detection time was 6 (i.q.r. 0–42) weeks after the index admission.

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% c.i. 7.6% to 14.4%). The individual rates were: 11.5% for repeat TUS, 2.8% for MRI/MRCP, and 23.7% for EUS.

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).

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 sphinterotomy 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% c.i. 0.21 to 1.06; $P = 0.038$).

Discussion

In this nationwide cohort study, 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 two-fold 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 workup as non-drinkers.

At admission, current guidelines recommend testing for calcium and triglycerides and performing TUS[10]. In the present study, only half of the patients underwent this recommended workup. Although TUS is both affordable and non-invasive, it was not performed for 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], underscore 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 significantly higher for patients who did not undergo TUS compared with patents with an initial 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, 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 19/34for 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 workup 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 of the 334 patients had a history of cholecystectomy.

In 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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Author contributions

Noor J. Sissingh (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Fleur E. M. de Rijk (Data curation, Resources, Software, Writing—review & editing), Hester C. Timmerhuis (Conceptualization, Data curation, Methodology, Writing—review & editing), Devica S. Umans (Conceptualization, Methodology, Writing—review & editing), Marie-Paule G. F. Anten (Resources, Writing—review & editing), Stefan A. W. Bouwense (Resources, Writing—review & editing), Foke van Delft (Resources, Writing—review & editing), Brechje C. van Eijck (Resources, Writing—review & editing), Willemien G. Erkelens (Resources, Writing—review & editing), Wouter L. Hazen (Resources, Writing—review & editing), Sjoerd D. Kuiken (Resources, Writing—review & editing), Rutger Quispel (Resources, Writing—review & editing), Tessa E. H. Romkens (Resources, Writing—review & editing), Matthijs P. Schwartz (Resources, Writing—review & editing), Tom C. Seerden (Resources, Writing—review & editing), B. W. Marcel Spanier (Resources, Writing—review & editing), Tessa Verlaan (Resources, Writing—review & editing), Frank P. Vleggaar (Resources, Writing—review & editing), Rogier P. Voermans (Resources, Writing—review & editing), Robert C. Verdonk (Conceptualization, Methodology, Resources, Supervision, Visualization, Writing—review & editing), and Jeanin van Hooft (Conceptualization, Methodology, Resources, Supervision, Validation, Visualization, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Data are available upon reasonable request from the corresponding author.

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