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Original article

Gallstone pancreatitis vs alcohol-induced pancreatitis: Does aetiology affect the extent of pancreatic necrosis?

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Abstract *Background and aim:* The impact of different aetiologies of acute pancreatitis on the development of pancreatic necrosis (PN) is unclear. This study assessed the extent and progression of pancreatic and peripancreatic necrosis on the computed tomography (CT) scan of patients with gallstone (GP) and alcohol-induced (AIP) pancreatitis and evaluated their impact on disease severity. *Methods:* Patients ≥ 18-year-old with GP, AIP and PN on CT (January 2010 – September 2018), were considered. The radiological extent of PN and clinical outcomes were analysed with a logistic regression model. *Results:* Eighty-one patients, 59 with GP, 22 with AIP, were included. GP had a larger extent of PN when the body and/or tail of the pancreas were involved ($P = 0.009$). Gallstone disease ($P = 0.028$) and higher American Society of Anesthetists scores ($P = 0.043$) were predictors of necrosis diffuse to different areas of the pancreas. Predictors of single/multiple organ failure were GP ($P = 0.040$), necrosis > 50% of the pancreas ($P = 0.002$) with a diffuse pattern ($P = 0.004$). *Conclusions*: Patients with GP had a wider extent of necrosis in the pancreatic body and/or tail. The onset of organ failure can be predicted in subjects with GP and larger amount of PN. (www.actabiomedica.it)

Key words: acute pancreatitis, pancreatic necrosis, gallstones, alcoholic pancreatitis

Introduction

Pancreatic necrosis (PN) develops in up to 20% of patients with acute pancreatitis (AP) and represents a marker of disease severity, with mortality rates of up to 15-30% (1). Tissue necrosis affects the pancreas, the peripancreatic tissues or both (2) and is commonly diagnosed with the computed tomography (CT) scan of the abdomen. The extent of PN varies greatly among patients, as it can involve limited areas of the pancreas or the whole organ.

Gallstones and alcohol abuse account for over 50% of AP (3) and trigger the inflammatory process through different complex mechanisms. While the biliary pathology affects the pancreas via the ductal system (4,5), alcohol comes into contact with the pancreatic cells through the blood circulation (6,7). Several studies had compared the clinical outcomes of GP and AIP (8-13), unfortunately little is known on the patterns of development of PN in the context of the two different aetiologies. This study evaluated the extent and progression of PN on CT scan and the impact on disease severity, in subjects with GP and AIP.

Patients and methods

The research was designed as retrospective observational study and received local board approval. Patients admitted with first onset of GP, AIP and

evidence of PN and peripancreatic necrosis (PPN) on the abdominal CT scan, from January 2010 to September 2018, were included. Alcohol abuse was accepted as the cause of AP in the presence of daily intake of >50 g of pure alcohol, irrespective of drinking duration or alcohol-binge within one week prior to hospital admission (14,15), and when other potential aetiologies of AP were ruled out.

Exclusion criteria were patients' age <18 years, previous admissions with GP and AIP, co-existence of gallstones and history of alcohol abuse, acute on chronic pancreatitis, idiopathic AP, AP caused by aetiologies other than gallstones and alcohol, non-confirmatory evidence of PN on CT scan, PN diagnosed with other imaging modalities.

AP was diagnosed in the presence of at least two out of the three following criteria: clinical presentation, serum amylase >450 IU/L (normal range 0-150 IU/L), radiological imaging (16). The abdominal CT scan was not performed routinely and was considered upon admission, in case of diagnostic uncertainty or if a patient was critically ill or as of day 5, if no clinical and/or biochemical improvement occurred. CT was also performed in case of clinical deterioration, at any time after diagnosis. PN was confirmed on CT scan in the presence of non-contrast enhanced area(s) of the pancreas (17) and its extent was measured as percentage of involved parenchyma, in accordance with the Computed Tomography Severity Index (18). The definition of PPN, acute necrotic collection (ANC) and walled-off pancreatic necrosis (WOPN), conformed to the 2012 Revised Atlanta Classification (19).

Data collection

Subjects were divided in two groups, GP and AIP. Clinical and radiological data were taken from clinical records and were compared between groups. The distribution of necrosis was arbitrarily categorised into localised and diffuse. Localised PN involved one or more areas to the right (head, uncinate process, neck) or the left (body, tail) of the midline; diffuse necrosis occurred in two or more regions across the midline (i.e., head and tail). ANC was localised in a single area of the retroperitoneum (i.e., pancreatic, peripancreatic, lesser sac, left para-renal) or diffuse to two or more retroperitoneal regions. In case of single or multiple readmissions within 30 days from discharge, the overall length of stay (LoS) was calculated as the sum of each single hospital event. Mortality was considered when occurring during the hospital stay.

Study objectives

Primary objectives were the percentual extent of PN, the proportion of localised and diffuse PN and PPN, the progression of necrosis over time, in the two groups. Secondary objective was the evaluation of patients' characteristics and extent of PN towards the onset of single/multiorgan failure.

Statistical analysis

Statistical analysis was conducted using R version 4.1.3 (R Foundation for Statistical computing, Austria). Means were compared with the Student's t-test, medians with the Mann-Whitney U test; categorical data were evaluated with the Chi-Square and Fisher's exact tests. The multiple logistic regression analysis evaluated predictors of extent and distribution of PN, organ failure and admission to the ICU; results were given as odds ratio (OR) and 95% confidence interval (CI). Two-tailed *P*-values were used and were considered as significant if <0.05.

Results

Sample characteristics

A total of 1573 subjects with AP were identified, of these 1054 had gallstone or alcohol disease. The abdominal CT scan was performed in 313 and confirmed PN in 102. Twenty-one were excluded because of recurrent pancreatitis or acute on chronic pancreatitis, leaving 81 patients in the study – 59 (72.8%) with GP, 22 (27.2%) with AIP (Figure 1).

Patients' characteristics and radiological data are described in Table 1. The mean age of the whole study population was 54.9 (18-92) and there were 31 (38.3%) females. In the GP group, patients were

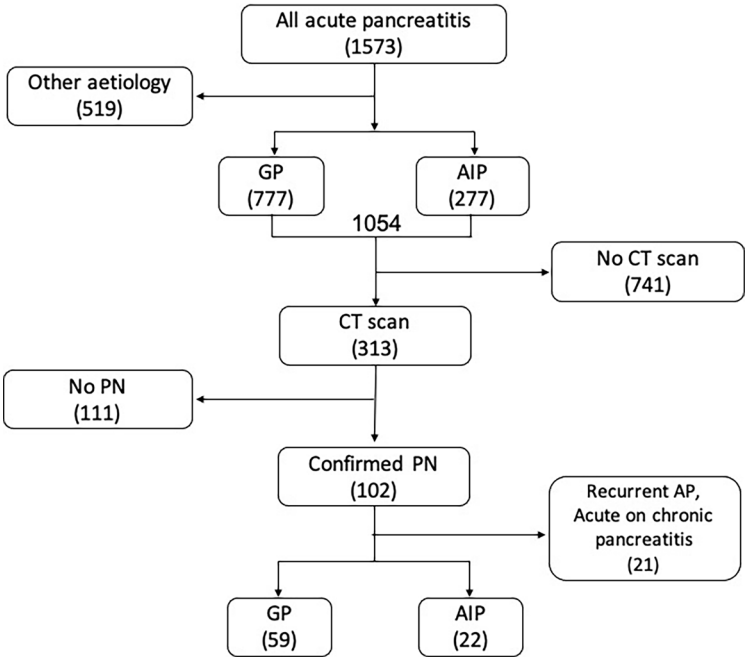

Figure 1. Patients' flow diagram. Abbreviations: The flow diagram shows the inclusion/exclusion criteria and the proportion of gallstone and alcohol-induced pancreatitis in the study population. GP, gallstone pancreatitis. AIP, alcohol-induced pancreatitis. CT, computed tomography. PN, pancreatic necrosis. AP, acute pancreatitis.

older (P = 0.001), the female sex was more represented (P = 0.0009), and the BMI was higher (P = 0.037). Subjects with AIP had higher American Society of Anesthetists (ASA) scores (P = 0.026).

The median number of CT scans performed was 2.7 (1-13) and the time from admission to the first CT scan was 2 (0-18) days. Fifty-one (62.9%) subjects underwent multiple cross-sectional imaging studies during their admission.

Extent of PN

The median time from admission to radiological evidence of PN was 3 (0-52), with 4 days in the GP group and 2.5 in AIP (P = 0.025). PN was associated with PPN in 70 (86.4%) patients and was localised in 11 (13.6%). Subjects with GP had larger pancreatic involvement when necrosis developed in the body and/or neck (P = 0.009). On regression analysis, gallstone disease (OR 3.9, 95% CI 1.2 to 12.8, P = 0.028) and ASA scores ≥ 3 (OR 0.39, 95% CI 0.16 to 0.97, P = 0.043) were predictors of diffuse pattern of PN.

ANC developed in 39 (48.1%) patients, WOPN in 12 (14.8%); the median time of diagnosis of WOPN from admission was 46.5 (29-78) days.

Progression of necrosis

Among the 51 subjects who had more than one CT scan, progression of necrosis was observed in 42 (82.4%). The mean progression time was 10 (1-52) days from admission and 8 (1-49) days from initial evidence of necrosis on CT scan, respectively. Sixteen (19.8%) had no necrosis upon the first cross sectional imaging – 15 with GP, 1 with AIP, respectively (p=0.074). Further CT scans showed progression towards PN and PPN (15), ANC (10) and WOPN (3). In those 26 (32.1%) with necrosis seen upon the first CT, PN was isolated in 1 patient, associated with PPN in 16, combined with PPN and ANC in 9; progression

Table 1. Patients' characteristics and radiological findings.

Parameter	Gallstone pancreatitis n=59	Alcoholic pancreatitis n=22	Overall n=81	*P*
Age, mean (range)	62.6 (18-92)	50.9 (25-80)	54.9 (18-92)	**0.001**[*]
Female:Male	27:32	4:18	31:50	**0.0009**[**]
Body Mass Index (%) ≤30 >30	27 (45.8) 32 (54.2)	14 (63.6) 8 (36.4)	41 (50.6) 40 (49.4)	**0.037**[**]
ASA[†] score, median (range)	2 (1-5)	3 (2-4)	3 (1-5)	**0.026**[***]
N. of CT[§] scans, median (range)	2 (1-13)	1.5 (1-6)	2.7 (1-13)	0.057
Evidence of PN[¶] from admission in days, median (range)	4 (0-52)	2.5 (0-9)	3 (0-52)	**0.025**[***]
PN (%) Isolated Associated with PPN[o]	 7 (11.9) 52 (88.1)	 4 (18.2) 18 (81.8)	 11 (13.6) 70 (86.4)	 0.460
Extent of PN[¶] (%) <30% 30-50% >50%	 17 (28.8) 28 (47.5) 14 (23.7)	 12 (54.5) 6 (27.3) 4 (18.2)	 29 (35.8) 34 (41.9) 18 (22.3)	 0.093
Distribution of PN[¶] Right Left Diffuse	 19 (32.2) 14 (23.7) 26 (44.1)	 9 (40.9) 8 (36.4) 5 (22.7)	 28 (34.6) 22 (27.2) 31 (38.2)	 0.202
Right-sided PN[¶] <30% 30-50% >50%	 16 (27.1) 3 (5.2) 0	 8 (36.4) 1 (4.5) 0	 24 (29.6) 4 (4.9) 0	 1.000
Left-sided PN[¶] <30% 30-50% >50%	 1 (1.7) 11 (18.6) 2 (3.4)	 4 (18.2) 1 (4.5) 3 (13.7)	 5 (6.2) 12 (14.8) 5 (6.2)	 **0.009**[**]
Diffuse PN[¶] <30% 30-50% >50%	 0 14 (23.7) 12 (20.3)	 0 4 (18.2) 1 (4.5)	 0 18 (22.2) 13 (16.1)	 0.368
ANC[‡], n. (%)	32 (61.5)	7 (31.8)	39 (41.4)	0.072
Distribution of ANC[‡] (%) Peripancreatic Pararenal – left Lesser sac Diffuse	 7 (11.9) 1 (1.7) 7 (11.9) 17 (28/8)	 0 1 (4.5) 2 (9.1) 4 (18.2)	 7 (8.6) 2 (2.5) 9 (11.1) 21 (25.9)	 0.391
WOPN[^], n. (%)	8 (13.6)	4 (18.2)	12 (14.8)	0.602
Progression of necrosis, n. (%)	35 (59.3)	7 (31.8)	42 (82.4)	0.087

Abbreviations: [†]American Society of Anesthetists. [§]Computed tomography. [¶]Pancreatic necrosis. [o]Peri-pancreatic necrosis. [‡]Acute necrotic collection. [^]Walled-off pancreatic necrosis. [*]Student's t-test. [**]Chi-square test. [***]Mann-Whitney U test.

of necrosis consisted of enlarging PPN (3), new onset or enlarging ANC (22), WOPN (3), acute fluid pancreatic collection (3).

Clinical outcomes

Clinical data are described in Table 2. Higher rates of severe disease were observed in subjects with GP (P = 0.040) and in those with extent of PN >50% (P = 0.007). Overall, single or multiorgan failure developed in 40 (49.4%) patients; predictors of organ failure were gallstones disease (OR 0.29, 95% CI 0.09 to 0.95, P = 0.040), PN > 50% (OR 9.3, 95% CI 2.30 to 37.4, P = 0.002) and diffuse pattern of necrosis (OR 0.25, 95% CI 0.09 to 0.64, P = 0.004). Admission to the intensive care unit was required in 29 (35.8%) subjects and PN >50% was predictor of that (OR 7.83, 95% CI 2.45 to 25.02, P = 0.0005). In-hospital death occurred in 10 patients (12.3%), 8 with GP, 2 with AIP, respectively (P = 0.587). Causes of death were multiorgan failure (5), respiratory failure (2) and sepsis (3), respectively. The median time from admission to death was 29.5 (3-67) days. Death within 2 weeks from admission occurred in 4 subjects, at day 3 and 10 (two patients) respectively. The overall median hospital stay was 15 days (range 1-256), it was longer among subjects with GP – 19 vs 13.5 days (P = 0.052).

Conclusions

In this study, we assessed extent and progression of pancreatic and extra-pancreatic necrosis in subjects with GP and AIP and evaluated the impact of necrosis on disease severity. The two groups were not homogeneous, reflecting the epidemiology of the respective aetiologies; in fact, while gallstones are more prevalent in old female adults and are associated with higher BMI (20), alcohol abuse per se is associated with higher ASA scores and leads to long-term ill health (21). PN necrosis was detected earlier in patients with AIP; we could hypothesize that this group presented late to hospital, when the damage to the pancreatic and extra-pancreatic tissues was at a more advanced stage. In both groups, the association of PN and PPN was the most common finding, while isolated PN was observed in 13.6% of cases. In other series (22) isolated PN accounted for up to 5% of the radiological findings. Perhaps, our figures were overestimated, in fact, the differentiation of necrosis from fatty infiltration or oedema of the pancreas can be challenging (23) and when PN is less than 30%, the false-negative rates on CT are up to 21% (24). Moreover, in those subjects with isolated PN who underwent a single CT it was not possible to evaluate if necrosis had progressed to the peripancreatic tissues.

Table 2. Clinical outcomes.

Parameter	Gallstone pancreatitis n=59	Alcoholic pancreatitis n=22	Overall n=81	*P*
Atlanta classification *Mild* *Moderate* *Severe*	 26 11 22	 15 0 7	 41 11 29	**0.040**[*]
Organ failure (%)	33 (55.9)	7 (31.8)	40 (49.4)	0.054
ICU[†] admission (%)	18 (22.2)	7 (31.8)	25 (30.9)	0.909
Reason for ICU[†] admission	Multiorgan failure (12); respiratory failure (6)	Multiorgan failure (2); respiratory failure (3); sepsis (1), bleeding (1)		-
ICU[†] stay in days, median (range)	11 (3-52)	9 (2-31)	9 (2-52)	0.263
Mortality (%)	8 (9.9)	2 (9.1)	10 (12.3)	0.587
Hospital stay in days, median (range)	19 (4-256)	13.5 (1-79)	15 (1-256)	0.052

Abbreviations: [†]Intensive care unit. [*]Fisher's exact test.

Overall, the extent and distribution of PN did not differ between groups, however subjects with gallstone disease had larger pancreatic involvement when necrosis was localised to the body and/or the tail. Gallstones were also predictors of diffuse PN. In GP, the reflux of bile acids involves the whole main pancreatic duct, with the potential to affect wider areas of the pancreatic parenchyma (25) such as the body and tail, which represent two thirds of the organ on CT scan (26). In contrast, in AIP the injury to the pancreatic cells occurs in spots, as fibrosis develops in the interlobular spaces, thus resulting in a more localised extension of necrosis (27-29). Moreover, high alcohol intake is associated with an impaired immune response (30), hence it would be interesting to hypothesize that the curbed inflammatory process in patients with AIP might account for a more limited extent of PN. Indeed, such hypotheses cannot be confuted nor accepted without histopathological confirmation.

Progression of tissue necrosis consisted mainly on the development or enlargement of ANC. In spite of that, the proportion of WOPN was relatively low. One possible reason to explain such a finding is that not all the subjects with ANC received further radiological follow-up after discharge, particularly if there were no clinical concerns; in such circumstances, it was not be possible to detect WOPN. The pattern of progression of necrosis did not differ between groups. Perhaps, this would corroborate the findings of Uhl et al (31) who suggest that once the initial injury to the pancreas occurs and tissue necrosis develops, further progression of PPN, ANC, WOPN, ensues irrespective of the aetiology. Gallstone disease and extended PN were predictors of organ failure. Although the older age of patients with GP could in part explain such a correlation (32), we feel that the increased extent of necrosis observed in this group may account for that, as the relationship between amount of PN and disease severity had been largely demonstrated (33-37).

Limitations of this study are the small sample, the retrospective, single-institutional design, and the lack of description of duration and severity of alcohol abuse. The quantification of alcohol consumption could have allowed for the stratification of the extent of PN, onset of organ failure and admission to the ICU, based on the amount of alcohol intake. Moreover, the study did not take into account patients with isolated PPN, which occurs in up to 30% of cases and is associated with better outcomes than combined PN and PPN (38-40). Finally, we selected patients with confirmed PN and PPN only. Perhaps, we could have missed subjects with less extensive necrosis due to the fact that the CT was performed on the basis of clinical indication.

Within these limitations, the authors conclude that in this comparison between GP and AIP, subjects with gallstone disease had a wider extent of necrosis in the pancreatic body and/or tail. The onset of organ failure can be predicted in subjects with GP and larger amount of necrosis.

Ethic Committee: Royal Devon University Healthcare NHS Foundation Trust – Eastern Services, reference number 23-5835.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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