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Severity and outcome of a first episode of idiopathic acute pancreatitis is not more severe than pancreatitis of other etiologies

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ABSTRACT

Background: With respect to severity and outcome of an index episode of idiopathic acute pancreatitis the current literature reports conflicting retrospective results. One reason might be the retrospective study design precluding in depth analysis resulting in mixed etiologies and combination of index episode versus recurrent idiopathic acute pancreatitis.
Methods: In this retrospective monocentric cohort study, we retrieved all patients with a first acute pancreatitis episode treated between 2005 and 2021 at the LMU University Hospital from our clinical information system based on the respective ICD-10 codes. In an initial sample of 1390 presumed idiopathic pancreatitis patients we identified 68 confirmed idiopathic acute pancreatitis patients and compared those to 75 first-time alcohol-induced acute pancreatitis patients and 390 first-time biliary-induced acute pancreatitis patients. Clinical outcome (severity, SIRS, mortality, and re-admission rate) was set as outcome measures. Multinomial logistic regression analysis was performed.
Results: In alcohol-induced acute pancreatitis moderate and severe courses occur significantly more often when compared to idiopathic acute pancreatitis (17.33 % vs. 10.29 %; multinomial logistic regression $p = 0.0021$). There were no significant differences in mortality between first-time alcoholic, idiopathic and biliary pancreatitis ($p = 0.6328$). Patients with idiopathic acute pancreatitis had significantly more hospital readmissions (within 30 days) compared to alcohol-induced pancreatitis patients ($p = 0.0284$).
Conclusion: In the context of a first episode of acute pancreatitis, idiopathic acute pancreatitis remains a challenging diagnosis posing an increased risk of recurrence, but not an increased risk for a more severe disease course.

1. Introduction

Most patients with acute pancreatitis suffer from a single episode without recurrence or chronification [1]. The main causes of acute pancreatitis are alcohol and gallstones. The third largest group (between 15 and 25 %) is idiopathic acute pancreatitis [2,3] (IAP). As the third most common cause of pancreatitis, IAP is therefore both clinically and socioeconomically highly relevant, but was often difficult to assess in terms of pancreatitis outcome due to varying definitions of the term "idiopathic" in previous studies [4–6].The proportion of actual idiopathic acute pancreatitis had been significantly overestimated in the pre-endosonography era were patients with EUS detected biliary etiology have been missed and misclassified as idiopathic pancreatitis patients [7]. Due to the lack of uniform diagnostics in the context of pancreatitis etiology work-up and often ambiguous IAP inclusion and exclusion criteria (related to extended/repeated imaging such as CT, MRI, EUS, transabdominal ultrasound) as well as an unclear differentiation from the cohort of idiopathic recurrent acute pancreatitis/early chronic pancreatitis, the risk of adverse outcome in the third largest

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Abbreviations

ALT	Alanine aminotransferase
AP	Acute pancreatitis
AST	Aspartate aminotransferase
BMI	Body mass index
CBD	Common bile duct
CP	Chronic pancreatitis
CRP	C reactive protein
EUS	Endosonography
ERCP	Endoscopic retrograde cholangiopancreatography
HDU	High dependency unit
ICU	Intensive care unit
IPMN	Intraductal papillary mucinous neoplasm
IAP	Idiopathic acute pancreatitis
IRAP	Idiopathic recurrent acute pancreatitis
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
RAC	Revised Atlanta Classification

pancreatitis etiology group is so far unknown [4,8]. Studies from the pre-EUS era indicated that IAP tended to have a more severe course than pancreatitis of other etiologies (persistent organ failure: IAP 16.4 % versus biliary pancreatitis 2.8 % versus alcohol-induced pancreatitis 4.1 %; mortality rates: IAP 9.8 % versus biliary pancreatitis 1.4 % versus alcohol-induced pancreatitis 0.8 %) [8,9].These data were put into perspective by studies in which the cohort of idiopathic pancreatitis adjusted for age, ethnicity and gender showed a lower risk of mortality compared to alcohol-induced pancreatitis [10]. Using a more granular stratification, an American cohort of 338 idiopathic acute pancreatitis patients was shown to have less severe pancreatitis courses compared to a 540 non-idiopathic AP cohort, in contrast to the older study data (shorter hospital stay; 4.98 vs 5.99 days, $P = 0.011$; fewer extrapancreatic complications; 15.4 % vs 25.2 %, $p = 0.001$), but there was no difference between the groups in terms of severity assessment according to the revised Atlanta Classification ($p = 0.161$). However, in that cohort 61.5 % of the IAP and 42.8 % of the non-IAP cohort already had a history of AP, which compromises significance [11]. In summary, there is currently no data that compares outcomes of a first episode of IAP to the outcome of the first episode of pancreatitis of other etiologies. In this study we present a retrospective monocentric cohort assessing outcome of a first episode of idiopathic acute pancreatitis.

2. Methods

2.1. Selection criteria - idiopathic acute pancreatitis

Patients were identified retrospectively from the LMU University Hospital Munich discharge records. All patients who had been hospitalised for acute pancreatitis during the period 2005–2021 were considered eligible. For screening, the following ICD-10 codes were used: K85.0, K85.00, K85.01(idiopathic acute pancreatitis), K85.8-, K85.80, K85.81 (other acute pancreatitis), K85.9-, K85.90, K85.91(acute pancreatitis unspecified). A total of 1390 patients were identified and assessed for the diagnostic criteria of idiopathic acute pancreatitis (Fig. 1). First, all patients were re-evaluated on an individual case level to determine whether the criteria of revised Atlanta classification for acute pancreatitis were met and whether etiology was with certainty reported [12]. This included: recent and past medical history (previous episodes of acute pancreatitis, gallstone disease, alcohol consumption (five or more units of alcohol consumed within 24 h before the onset of pain/symptoms of acute pancreatitis [13,14]) and medication, laboratory parameters recorded during the pancreatitis-associated hospital stay (hypertriglyceridaemia, hypercalcaemia, IgG4, liver function tests) and transabdominal ultrasound performed during the admission for acute pancreatitis. Only patients with no definitive etiology were assessed for second-level imaging (EUS, MRI, CT) and further analyzed in the presumed IAP cohort. Our IAP selection process followed the algorithm of the Dutch Pancreatitis Study Group, classifying patients as presumed IAP in case of negative standard work-up and as confirmed IAP in case of negative findings with respect to etiology on extended imaging (CT, MRI or EUS without evidence of pancreatitis etiology). Finally, 68 idiopathic acute pancreatitis patients were recruited in our analysis (drop-out rate between presumed ($n = 1390$) and confirmed IAP ($n = 68$): 95.1 %) [15]. In 22 patients, a possible pancreatitis driver mutation was found through genetic testing (genes sequenced: *PRSS1, SPINK-1* and *CTRC*), however with respect to international consensus we only excluded the patients with a PRSS1 mutation from the idiopathic cohort ($n = 9$). The other 13 patients with genetic pancreatitis susceptibility were excluded as each had other possible underlying etiologies or did not fulfil the criterion as a first episode of IAP. As only the cohort of single and not recurrent idiopathic pancreatitis was studied, the absence of testing for genetic pancreatitis was not a general IAP exclusion criterion [2].A total of 128 patients were excluded from the IAP cohort due to pancreatobiliary anatomical anomalies, some of which could not be precisely quantified (sphincter oddi dysfunction and juxtapapillary diverticula ($n = 59$), pancreas divisum ($n = 13$), unclear pancreatic duct stenoses ($n = 53$), papillary adenomas ($n = 3$)). 57 patients suffered from idiopathic recurrent acute pancreatitis [2]. 31 patients were excluded because acute pancreatitis occurred in the context of a gastrointestinal infection. 22 patients with confirmed autoimmune pancreatitis according to ICDC criteria were also excluded [16]. Of the final 68 confirmed IAP patients included, 53 % had IgG4 serum levels determined. All values remained within the normal range; in addition, no image morphological criteria were found in any of the patients that would suggest an underlying autoimmune pancreatitis. A detailed list of the IAP patient selection can be found in Fig. 1.

2.2. Selection criteria - biliary and alcohol pancreatitis cohort

All patients of the same period with alcohol- or biliary-induced acute pancreatitis were used for comparison. After ICD-10-based patient screening, 601 patients with presumed biliary acute pancreatitis (K85.10, K85.11) and 390 patients with presumed alcohol-induced pancreatitis (K85.2-, K85.20, K85.21) were identified. The diagnosis of acute biliary pancreatitis was made in case of evidence of gallstones, microlithiasis or sludge inside the gallbladder or common bile duct (CBD), in case of CBD dilatation or ALT elevation above two times the upper limit of normal [17,18]. A CBD width of more than 8 mm in patients younger than or equal to 75 years and more than 10 mm in patients older than 75 years was used as the threshold for CBD dilatation, analogous to the APEC trial [19]. 390 patients with biliary acute pancreatitis were included in the final evaluation (dropout rate 35.1 %). Of 390 presumed alcohol-induced acute pancreatitis patients, 75 patients were included in the final evaluation (dropout rate 80.8 %). 55 patients had recurrent alcohol-induced acute pancreatitis and 66 had chronic alcohol-induced pancreatitis. A detailed list of the exclusion criteria for biliary and alcohol-induced pancreatitis can also be found in Fig. 1.This retrospective pancreatitis cohort study was conducted according to the criteria of the STROBE guideline [20].The primary

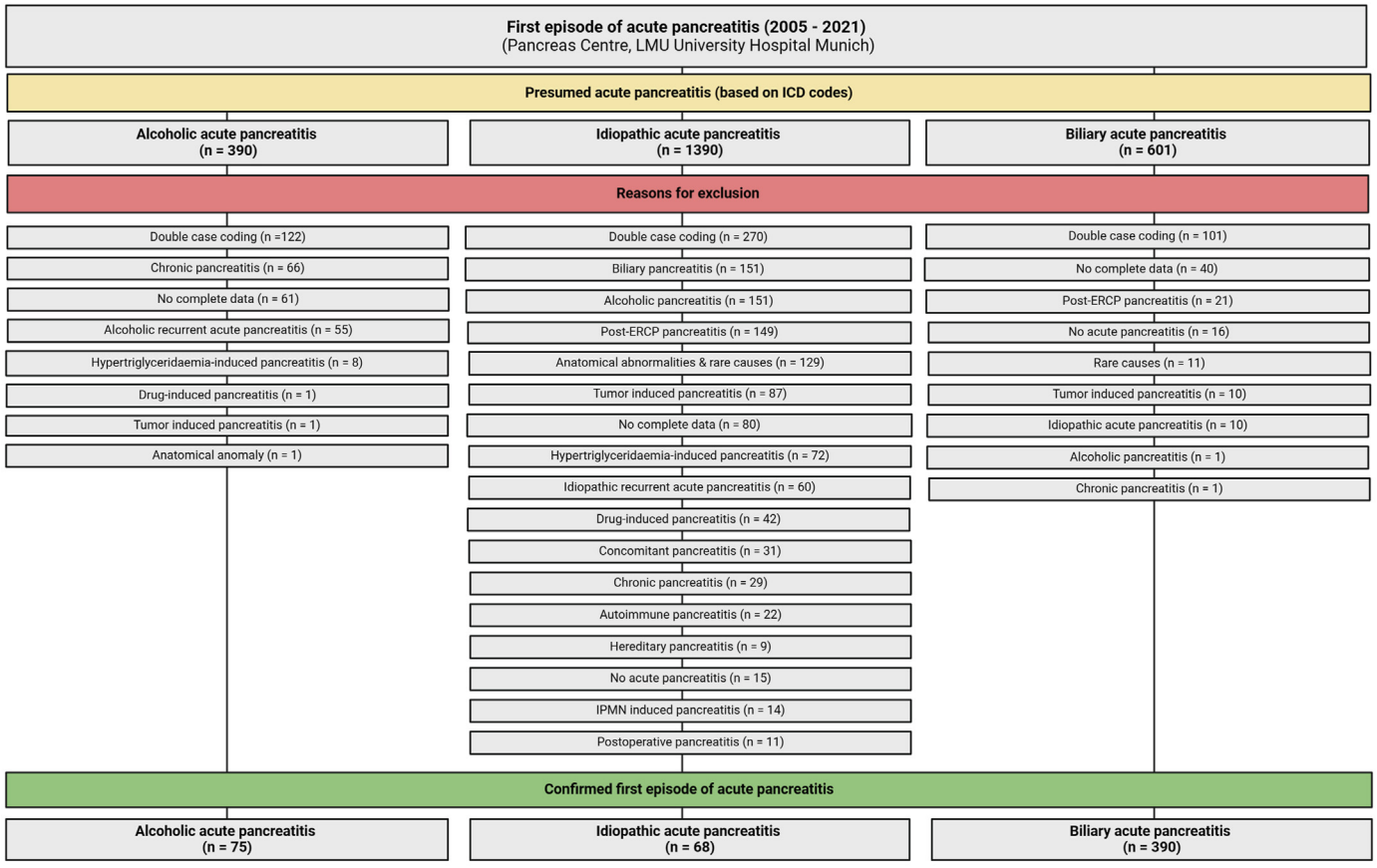

Fig. 1. Consort-Diagramm.
Flow chart of screened and finally included patients at the LMU University Hospital in Munich (Department of Medicine II). The study period examined covered the period 01.01.2005–31.12.2021. Figure created via BioRender.

study outcome was severity of acute pancreatitis (analogous to the revised Atlanta classification) [13], SIRS at hospital admission or during hospitalisation, length of hospital stay, need for IMC or ICU treatment, and readmission rate and mortality compared between the IAP and biliary and alcohol-induced pancreatitis cohorts. As secondary outcome parameters, inflammatory markers and liver values on the day of admission, day 3 and day 7 of hospitalisation were compared between the groups.

2.3. Statistical analysis

The primary outcome was severity of acute pancreatitis based on the revised Atlanta Classification. Secondary outcomes were SIRS at the time of hospital admission, SIRS during hospitalisation, length of hospital stay, need for admission to high dependency or intensive care units, mortality and re-admission rate. The statistical analysis was performed using Kruskal-Wallis test followed by Dunn's multiple comparison test and Bonferroni correction by considering ($\alpha = 0.05$) and adjusted p value = 0.016 for continuous variables and the Chi2 test for categorical variables. A p-value <0.05 was considered statistically significant. A multinomial logistic regression model was used to calculate odds ratio for association of severity of pancreatitis with the etiology which was adjusted for confounding variables. In our model, the idiopathic acute pancreatitis group was used as the baseline group and compared with the alcohol- and biliary-induced acute pancreatitis cohorts. Moderate and severe acute pancreatitis [12] were used as dependent variables, and etiology, age and sex as independent variables. Multinomial logistic regression was performed using R (R-4.0.4) and R-studio (version 1.3.9.59). No unique code was developed for this study. The R scripts or functions are available on request.

3. Results

3.1. Population characteristics

The alcohol-induced pancreatitis cohort had a significantly higher proportion of male patients compared to the idiopathic and biliary pancreatitis cohorts (63/75 (84 %) vs. 39/68 (57.35 %) vs. 191/390 (48. 97 %); $p < 0.0001$), while the biliary pancreatitis cohort was of significantly older age (median 65.5 years vs. 55 years (idiopathic AP) versus 50 years (alcohol-induced AP); $p < 0.0001$). No significant difference was found for BMI ($p = 0.8616$). With regard to the consumption of alcohol 88.23 % (60/68) of the idiopathic pancreatitis patients reported no history of alcohol consumption coinciding with the episode of acute pancreatitis. In addition to the alcohol-related pancreatitis cohort, a history of alcohol consumption was determined in 3.33 % (13/390; $p < 0.0001$) of patients with biliary AP, however, not coinciding with the onset of pancreatitis. The highest proportion of active tobacco use was found in the alcohol-induced pancreatitis cohort with 60 % (45/75), compared to 14.7 % (10/68) in the IAP and 0.51 % (2/391) in the biliary AP cohort ($p < 0.0001$). The majority of pancreatitis patients presented to the emergency department for treatment within the first 24 h of pain onset (IAP cohort 91.17 % versus alcohol-induced pancreatitis cohort 88 % (66/75) versus

biliary AP cohort 83 % (324/390)). 73.58 % (287/390) of patients with biliary pancreatitis received pancreatitis-associated endoscopic intervention, the majority consisting of a diagnostic endosonography (45.12 %; 176/390) and/or ERCP (50.76 %; 198/390). The IAP cohort received endoscopic intervention in 41.17 % (28/68), and the alcohol-induced acute pancreatitis cohort received endoscopic intervention in only 26.66 % of cases (72 % of which were EGDs). Almost all patients from the three cohorts received transabdominal ultrasound (IAP: 59/68 (86.76 %), alcohol-induced AP: 63/75 (84 %), biliary AP 326/390 (83.58 %). The rate of cross-sectional imaging (CT and MRI) was highest in the IAP cohort with 85.29 % (CT 42/68 (61.76 %), MRI 16/68 (23.52 %). The rate of endosonography performed was highest in the biliary AP group with 45.12 % (176/390), followed by the IAP cohort with 19.11 % (13/68). A detailed list of all comorbidities and co-medications at the time of hospitalisation for pancreatitis can be found in Table 1.

3.2. Pancreatitis severity

The primary outcome parameters of acute pancreatitis according to the revised Atlanta classification did not differ between the three cohorts ($p = 0.0869$; Table 2). In the multinomial logistic regression analysis, age was shown to be a risk factor for moderate ($p = 0.0021$) or severe pancreatitis ($p < 0.0001$), independent of the underlying etiology (Table 4). In the intergroup comparison, the IAP cohort showed significantly more mild courses compared to the alcohol-induced and biliary AP cohorts (IAP: 69.11 % (47/68), alcohol-induced AP 52 % (39/75), biliary AP cohort 52.3 % (204/390); $p = 0.0334$). Significantly more moderate AP courses were seen in the biliary AP cohort compared to the IAP cohort (33.84 % (132/390) vs. 20.58 % (14/68); $p = 0.0304$). The highest proportion of severe pancreatitis courses was seen in the alcohol-induced pancreatitis cohort, but with no statistically significant difference from the IAP or biliary AP cohorts (17.33 % (13/75) vs. 10.29 % (7/68) vs. 11.53 % (45/390); $p = 0.1642$). In multinomial logistic regression analysis, alcohol-induced pancreatitis had significantly more severe courses compared with the IAP cohort ($p = 0.0217$; 95 % CI 1.2026–10.3208; Table 4) in a direct comparison of the two groups. A significantly higher proportion of biliary pancreatitis patients had already developed SIRS at the time of admission ($p = 0.0296$) compared to alcohol-induced pancreatitis ($p = 0.04$) but not to IAP ($p = 0.089$; intergroup comparison). There was no significant difference in the rate of SIRS developed during hospitalisation between the three groups (IAP 14.7 % (10/68) vs. alcohol-induced AP 22.66 % (17/75) vs. biliary AP 14.87 % (58/390); $p = 0.0781$). Significance in the difference was found in the respective length of hospital stay due to pancreatitis (length in days (mean) ± SD; IAP 11.04 ± 14.28 vs. alcohol-induced AP 10.24 ± 10.06 vs. biliary AP 12.74 ± 13.17; $p = 0.0007$). The biliary pancreatitis cohort had significantly more patient transfers to a high dependency unit (HDU) compared with the idiopathic and alcohol-induced AP cohorts ($p = 0.0465$; biliary AP 13.07 % (51/390) vs. IAP 4.4 % (3/68), $p = 0.049$), but without more patient transfers to an intensive care unit (ICU, $p = 0.9404$). The respective cohort-specific HDU/ICU transfer reasons are listed in Table 2. The high rate of "other" HDU/ICU transfer reasons in the biliary AP cohort also subsumes transfers for monitoring for predicted moderate to severe course, due to SIRS at hospital admission. The 30-day hospital readmission rate was significantly higher in the IAP cohort (7.35 % (5/68)) and the biliary AP cohort (8.97 % (35/390)) compared with no 30-day readmission in the alcohol-induced AP cohort (0 % (0/75); $p = 0.0284$). Differences in 90-day mortality were not detected between the three pancreatitis cohorts ($p = 0.06328$). Already on the day of admission, CRP levels and the leukocyte count in the alcohol-induced cohort were significantly increased compared to the other cohorts ($p = 0.018$ and $p = 0.0031$). During the course of the disease on day 3 the alcohol-induced pancreatitis cohort showed significantly higher CRP levels compared with the IAP and biliary cohorts (18.9 ± 11.9 mg/dl ($n = 55$) vs. 13.2 ± 11.3 ($n = 51$) vs. 13.3 ± 15.9 ($n = 363$); $p = 0.0007$). The cohort of biliary AP showed highest levels of transaminases and bilirubin on the day of admission ($p < 0.0001$). All laboratory values of the three AP etiology groups can be found in Table 3.

4. Discussion

In previous studies, idiopathic acute pancreatitis was associated with an astonishing mortality of 9.6 %–16.5 % [5,6,8]. In a multicentre retrospective Chinese study in which only cases of severe acute pancreatitis were evaluated, the patients with idiopathic etiology had the highest mortality rates (82/498 (16. 5 %) compared to 28/178 (15.7 %) in alcohol-induced pancreatitis and 103/1160 (8.9 %) in biliary origin; $p < 0.05$) [6]. Even in studies without preselection for severity, significantly higher mortality rates were reported in case of an idiopathic/unclear etiology compared to other etiologies (13 % vs. 4–6 %) [5]. More recent studies refute this notion to a certain extent: especially for mild or moderate acute pancreatitis no difference in mortality between IAP and non-IAP cohorts was found (inpatient mortality, n (%): Non-IAP ($n = 540$): 4 (0.74) vs. IAP ($n = 338$): 4 (1.19); $p = 0.492$) [11]. Our mortality rate also remained below 3 % across all three etiology groups, with no significant difference between IAP and non-IAP cohorts (IAP: 2/68 (2.94 %); Alcoholic: 2/75 (2.66 %); Biliary: 6/390 (1.53 %); $p = 0.6328$). The fact that LMU University Hospital is a tertiary reference centre must be taken into account as an association between mortality and hospital volume has been demonstrated [21]. Our results are consistent with data from US showing no association between IAP and pancreatitis severity ($p = 0.0869$) [11]. In line with the higher rates of necrotising alcohol-induced acute pancreatitis described in the literature, in our cohort alcoholic etiology showed significantly higher CRP levels on day 3 and leukocyte counts already on the day of hospital admission, as well as a significantly higher rate of severe pancreatitis compared with the IAP cohort alone [22].The 30-day readmission rates in our cohort were significantly higher in the IAP (5/68 (7.35 %)) and biliary AP cohorts (35/390 (8.97 %)) than in the alcohol-induced pancreatitis cohort (0/75 (0 %)), which is consistent with the recent literature [23]. One could speculate, that the reason for early readmissions lies in the unknown and therefor untreated cause of pancreatitis in case of IAP and in recurrent biliary events in case of biliary AP, as cholecystectomy during index admission is still not fully implemented at all. In summary, in our retrospective cohort study there is no evidence that a first episode of idiopathic acute pancreatitis poses a risk factor for increased severity compared to alcoholic and biliary pancreatitis.

4.1. Strengths and limitations

This is a retrospective single center study conducted at a tertiary referral center, relying on available medical records of patients. Therefore missing values such as BMI or need for opioids could not be analyzed for all patients included in the analysis. Due to the lack of predictive power of various scoring systems (BISAP, RANSON, APACHE-II) with regard to the severity of pancreatitis, only SIRS on the day of admission and during the course of hospitalisation was used as a scoring system [24,25]. The fact that our institution is a tertiary referral center serving large parts of Southeast Germany introduces the possibility of referral bias. Furthermore, only

Table 1
Baseline characteristics.

	Idiopathic	Alcoholic	Billiary	p Value
Patients, N	68	75	390	
Sex, N (%)				
M	39 (57.35 %)	63 (84 %)	191 (48.97 %)	<0.0001
F	29 (42.64 %)	12 (16 %)	199 (51.02 %)	
Age, median (range)	55 (20–88)	50 (21–80)	65.5 (21–101)	<0.0001
BMI (kg/m^2), mean (± SD)	28.36 ± 5.7	27.04 ± 3.4	28.42 ± 6.8	0.8616
Unknown	32/68 (47 %)	10/75 (13.3 %)	81/390 (20.7 %)	
Alcohol consumption				
No	60/68(88.23 %)	0/75(0 %)	132/390(33.84 %)	<0.0001
Yes	1/68(1.47 %)	75/75(100 %)	13/390(3.33 %)	
Unknown	7/68(10.29 %)	0/75(0 %)	245/390(62.82 %)	
Nicotine consumption				
No	44/68(64.70 %)	7/75(9.33 %)	73/390(18.71 %)	<0.0001
Yes	10/68(14.70 %)	45/75(60 %)	2/390(0.51 %)	
Unknown	14/68(20.58 %)	23/75(30.66 %)	315/390(80.76 %)	
Onset of pain before hospital admission				
<24 h	62/68 (91.17 %)	66/75 (88 %)	324/390 (83 %)	
24–48 h	0/68 (0 %)	0/75 (0 %)	2/390(0.512 %)	
48–72 h	0/68 (0 %)	1/75 (1.33 %)	0/390 (0 %)	
Up to 7 days	1/68 (1.47 %)	0/75 (0 %)	0/390 (0 %)	
>7 days	0/68 (0 %)	0/75 (0 %)	0/390 (0 %)	
Unknown	5/68 (7.35 %)	8/75 (10.66 %)	64/390 (16.41 %)	
Endoscopic intervention rate, N (%)				
No	40/68 (58.82 %)	55/75 (73.33 %)	103/390 (26.41 %)	<0.0001
Yes	28/68 (41.17 %)	20/75 (26.66 %)	287/390 (73.58 %)	
Type of endoscopic intervention performed				
EUS	13/68 (19.11 %)	7/75 (9.33 %)	176/390 (45.12 %)	<0.0001
ERCP	1/68 (1.47 %)	0/75 (0 %)	198/390 (50.76 %)	
EGD	20/68 (29.41 %)	18/75 (24 %)	130/390 (33.33 %)	
Abdominal imaging performed				
Ultrasound, N (%)	59/68 (86.76 %)	63/75 (84 %)	326/390 (83.58 %)	
EUS, N (%)	13/68 (19.11 %)	7/75 (9.33 %)	176/390 (45.12 %)	
CT, N (%)	42/68 (61.76 %)	42/75 (56 %)	169/390 (43.33 %)	
MRI, N (%)	16/68 (23.52 %)	12/75 (16 %)	5/390 (1.28 %)	
Comorbidities, N (%)				
None	32/68(47.05 %)	31/75(41.33 %)	117/390(30 %)	
Cholecystectomy prior to AP	11/68(16.17 %)	12/75(16 %)	45/390(11.53 %)	
Gastritis/Reflux	2/68(2.94 %)	12/75(16 %)	34/390(8.71 %)	
Liver disease	7/68(10.29 %)	19/75 (25.33 %)	26/390(6.66 %)	
Cardiac disease	13/68 (19.11 %)	3/75(4 %)	105/390(26.92 %)	
Carcinoma in history/current	3/68 (4.41 %)	0/75(0 %)	50/390(12.82 %)	
Upper GI tract surgery	2/68(2.94 %)	2/75(2.66 %)	14/390(3.58 %)	
Dyslipidemia	7/68(10.29 %)	5/75(6.66 %)	54/390(13.84 %)	
Diabetes mellitus II	9/68 (13.23 %)	5/75(6.66 %)	65/390(16.66 %)	
Arterial hypertension	21/68(30.88 %)	24/75(32 %)	189/390(48.46 %)	
Medication on admission				
Unknown	12/68(17.64 %)	21/75(28 %)	18/390(4.61 %)	
None	25/68(36.76 %)	34/75(45.33 %)	141/390(36.15 %)	
PPI	6/68(8.82 %)	3/75(4 %)	97/390(24.87 %)	
Antihypertensive drugs	20/68(29.41 %)	18/75(24 %)	183/390(46.92 %)	
Lipid lowering drugs	10/68(14.70 %)	5/75(6.66 %)	73/390(18.71 %)	
Diuretics	12/68(17.64 %)	4/75(5.33 %)	55/390(14.10 %)	
Analgesics	3/68 (4.41 %)	1/75(1.33 %)	14/390(3.58 %)	
Pancreatic enzymes	0/68(0 %)	0/75(0 %)	1/390(0.256 %)	
UDCA	0/68(0 %)	0/75 (0 %)	3/390 (0.76 %)	
Immunosuppressant drugs	1/68(1.47 %)	0/75(0 %)	20/390(5.12 %)	

The statistical analysis was performed using Kruskal-Wallis test followed by Dunn's multiple comparison test and Bonferroni correction by considering ($\alpha = 0.05$) and adjusted p value = 0.016 for continuous variables and the Chi2 test for categorical variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA).

readmissions to the LMU University Hospital could be analyzed as data on readmissions to other institutions were incomplete. In contrast to other studies that have looked at the clinical outcome of idiopathic acute pancreatitis, the major strength of this study is, that all patients identified by ICD-screening who were primarily coded as idiopathic were reassessed on an individual case level and matched against the predefined criteria of idiopathic acute pancreatitis [15]. By only including patients with a first episode of acute pancreatitis, the risk for bias was further reduced [4,8,11].

5. Conclusion

In summary, our results suggest that in a first episode of idiopathic acute pancreatitis, severity does not differ from other etiologies. However, identifying the cause of acute pancreatitis early in the course of disease remains important. By attributing the etiology to a potentially reversible cause such as gallstone disease, alcohol or triglyceridemia, patients can be offered a monocausal treatment to alter the course of their current attack and prevent recurrences of pancreatitis. Analogous to our cohort, the prospective PICUS-1 trial from the Netherlands showed that biliary acute

Table 2
Pancreatitis outcome depending on pancreatitis etiology.

	Idiopathic	Alcoholic	Billiary	p Value
RAC, N (%)				0.0869
Mild	47/68 (69.11 %)	39/75 (52 %)	204/390 (52.30 %)	
Moderate	14/68 (20.58 %)	23/75 (30.66 %)	132/390 (33.84 %)	
Severe	7/68 (10.29 %)	13/75 (17.33 %)	45/390 (11.53 %)	
Unknown	0/68 (0 %)	0/75 (0 %)	9/390 (2.30 %)	
SIRS at admission, N (%)	4/68 (5.88 %)	6/75 (8 %)	40/390 (10.25 %)	0.0296
SIRS at hospital stay, N (%)	10/68 (14.70 %)	17/75 (22.66 %)	58/390 (14.87 %)	0.0781
Length of hospital stay (mean ± SD in days)	11.04 ± 14.28	10.24 ± 10.06	12.74 ± 13.17	0.0007
IMC stay, N (%)	3/68 (4.41 %)	5/75 (6.66 %)	51/390 (13.07 %)	0.0465
ICU stay, N (%)	7/68 (10.29 %)	7/75(9.33 %)	35/390(8.97 %)	0.9404
Reason of IMC/ICU stay				
Bleeding	0/68 (0 %)	0/75 (0 %)	4/390 (1.02 %)	
Sepsis	4/68 (5.88 %)	0/75 (0 %)	11/390 (2.82 %)	
Cardiac	1/68 (1.47 %)	3/75 (4 %)	5/390 (1.28 %)	
Pulmonary	1/68 (1.47 %)	1/75 (1.33 %)	2/390 (0.51 %)	
Pain	0/68 (0 %)	0/75 (0 %)	0/390 (0 %)	
Other	3/68 (4.41 %)	4/75 (5.33 %)	61/390 (15.64 %)	
Renal	1/68 (1.47 %)	4/75 (5.33 %)	3/390 (0.76 %)	
Readmission rate, N (%) (within 30 days)				0.0284
No	62/68 (91.17 %)	73/75 (97.33 %)	354/390 (90.76 %)	
Yes	5/68 (7.35 %)	0/75 (0 %)	35/390 (8.97 %)	
Unknown	1/68 (1.47 %)	2/75 (2.66 %)	1/390 (0.25 %)	
Mortality, N (%)	2/68 (2.94 %)	2/75(2.66 %)	6/390 (1.53 %)	0.6328

The statistical analysis was performed using Kruskal-Wallis test followed by Dunn's multiple comparison test and Bonferroni correction by considering ($\alpha = 0.05$) and adjusted p value = 0.016 for continuous variables and the Chi2 test for categorical variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). SIRS ad admission was calculated from the first possible documented data during hospitalisation.

Table 3
Laboratory pattern stratified according to underlying pancreatitis etiology.

	Admission				Day 3				Day 7			
	Idiopathic	Alcoholic	Billiary	P	Idiopathic	Alcoholic	Billiary	P	Idiopathic	Alcoholic	Billiary	P
CRP (Mean±SD)	2.6±3.9	5.1 ±7.5	4.0±6.3	0.0188	13.2 ±11.3	18.9±11.9	13.3±15.9	0.0007	14.2 ±9.5	12.8±8.3	9.9±9.3	0.0235
Lipase (Mean±SD)	2703±39	2332±37	3647±46	0.0027	293.5±419.9	666.9±917.7	514.1±851.8	0.0135	171.5±399.7	361.3±658.6	130.3±186.4	0.0926
Leukocytes (Mean±SD)	11.2 ±4.2	13.3 ±4.6	11.6 ±6.3	0.0031	9.9±4.3	11.3±3.9	10.4±5.6	0.0601	12.2 ±4.7	12.6±5.9	9.629±5.9	0.0004
AST (Mean±SD)	63.4 ±98	97.8 ±105	256.3±249	<0.0001	71.2±106.6	63.9±73.3	97.2 ±97.1	<0.0001	53.4 ±58.8	65.2 ±47.4	47.5 ±36.6	0.0850
ALT (Mean ± SD)	65.3 ±112	65.6±58.8	295.1±434	<0.0001	57.5±83.7	48.4±38.4	181.8±168.8	<0.0001	68.1±91.7	61.9±42.9	86.2±89.7	0.0439
Billirubin (Mean±SD)	1.1 ±1.4	1.1±0.89	3.1 ±2.8	<0.0001	1.3±1.23	1.2 ±0.9	2.2 ±2.2	<0.0001	1.28±0.6	1.02±1.2	1.461±2.4	0.0234

The laboratory values were determined on the admission day, day 3 and day 7 of the pancreatitis-related hospital stay. The cohorts of idiopathic, alcohol-induced and biliary-induced pancreatitis were compared using one way ANOVA (mean +SD). A p-value <0.05 was considered statistically significant. CRP admission day (normal range ≤0.5 mg/dl): IAP (n = 68), AAP (n = 75), BAP (n = 390);CRP day 3: IAP (n = 52), AAP (n = 56), BAP (n = 364), CRP day 7: IAP (n = 21), AAP (n = 36), BAP (n = 245); Bilirubin admission day (normal range ≤1.2 mg/dl): IAP (n = 67), AAP (n = 74), BAP (n = 388); Bilirubin day 3: IAP (n = 40), AAP (n = 47), BAP (n = 361); Bilirubin day 7: IAP (n = 16), AAP (n = 26), BAP (n = 229); ALT admission day (normal range ≤49 U/l): IAP (n = 65), AAP (n = 74), BAP (n = 388); ALT day 3: IAP (n = 42), AAP (n = 45), BAP (n = 358); ALT day 7: IAP (n = 16), AAP (n = 26), BAP (n = 224); AST admission day (normal range ≤49 U/l): IAP (n = 58), AAP (n = 58), BAP (n = 339); AST day 3: IAP (n = 37), AAP (n = 41), BAP (n = 350);AST day 7: IAP (n = 16), AAP (n = 24), BAP (n = 213); Lipase admission day (normal range ≤60 U/l): IAP (n = 68), AAP (n = 74), BAP (n = 383); Lipase day 3:IAP (n = 44), AAP (n = 43), BAP (n = 296); Lipase day 7:IAP (n = 15), AAP (n = 23), BAP (n = 170); Leukocytes admission day (normal range 4,00–10,40 G/l): IAP (n = 68), AAP (n = 75), BAP (n = 389); Leukocytes day 3: IAP (n = 50), AAP (n = 54), BAP (n = 367); Leukocytes day 7: IAP (n = 22), AAP (n = 38), BAP (n = 240).

pancreatitis accounts for the largest proportion of identifiable (and treatable) etiologies in patients with supposed idiopathic pancreatitis [26]. Although the identification of IAP patients based on the ICD-10 codes is certainly weaker, the reduction by 95.1 % between the presumed (n = 1390) and confirmed IAP (n = 68) highlights the diagnostic and therapeutic potential of reassessment of the etiology based on the available diagnostics.

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Ethical committee

The study was approved by the Ethics Committee at LMU Munich (Project no. 22–0084 and 22–0073) and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Authors contributions

SS and GB designed the study. SS, EH, KB, MA, MJ, MV, EG, UA, MZ and MK acquired data. SS, MA, DS and UM analyzed, SS, GB and JM interpreted data. SS and GB wrote the manuscript. JM critically revised the manuscript. All authors approved the final version of the manuscript.

Table 4
Multinomial logistic regression model for bias factor calculation.

Severity	Variable	OR	[95 % CI]	p-Value
Moderate	Age (in years)	1.0182	0.0377 – 0.02343	0.0021
Moderate	Gender (male)	1.3251	0.8864 – 1.0908	0.17
Moderate	Etiology Alcoholic	2.0979	0.9359 – 4.7025	0.072
Moderate	Etiology Biliary	1.9482	1.0188 – 3.7254	0.0438
Severe	Age (in years)	1.0538	1.0334 – 1.0745	< 0.0001
Severe	Gender (male)	1.0633	0.5947 – 1.901	0.8361
Severe	Etiology Alcoholic	3.5231	1.2026 – 10.3208	0.0217
Severe	Etiology Biliary	1.0127	0.413 – 2.483	0.978

A multinomial logistic regression model was used to calculate possible bias factors related to the severity of pancreatitis stratified by underlying etiology (Odds ratio (OR), p-Value, 95 % confidence intervals (CI)). In our model, the idiopathic acute pancreatitis group was used as the baseline group and compared with the alcohol- and biliary-induced acute pancreatitis cohorts. Pancreatitis severity moderate and severe acute pancreatitis (analogous to the revised Atlanta Classification [14]) were used as dependent variables, and etiology, age and sex as independent variables. Multinomial logistic regression was performed using R (R-4.0.4) and R-studio (version 1.3.9.59). No unique code was developed for this study. The R scripts or functions used are available on request.

Declaration of competing interest

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2024.08.004.

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