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ORIGINAL ARTICLE

Differences between the outcome of recurrent acute pancreatitis and acute pancreatitis

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Abstract

Background and aim: Overall, a handful of studies are available on the outcomes of recurrent acute pancreatitis (RAP), in comparison to the first episode of acute pancreatitis (AP). We aimed to provide a more complete and updated picture of RAP and how it is different from the initial episode of AP.
Methods: Consecutive patients admitted with an episode of AP over 8 years were divided into two groups on the basis of prior episodes: AP and RAP. Primary outcome measures were for surgical necrosectomy and mortality.
Results: Of the 724 patients (age 39.22 ± 13.25 years, 68% male) with an episode of pancreatitis, 632 (87.3%) had presented with a first episode (AP) and 92 (12.7%) with at least one prior episode (RAP). The incidence of severe pancreatitis was significantly less in RAP patients (10.9%) in comparison to AP patients (48.6%). The requirement of surgical intervention and mortality were less in patients with RAP (1.1 and 2.2%, respectively) compared to patients with AP (9.3 and 18%, respectively). The mean number of episodes per RAP patients was 2.97 ± 1.66 (range 2–10), and 64.1% had only two episodes. Regarding the etiology of RAP patients, biliary etiology (32.6%) and alcohol (30.4%) were the two most frequent factors, and no etiology could be identified in 19.6%.
Conclusion: Patients with RAP had milder disease course and lesser mortality when compared to the initial episode of AP. Appropriate evaluation and dealing with etiological factors at the initial episode of AP can prevent a majority of RAP.

Introduction

Acute pancreatitis (AP) remains a disease of variable outcome, from self-limiting to fatal depending on the severity of disease. Repeat episodes of pancreatitis can occur in 10–30% of patients who survive the first episode of pancreatitis.[1–4] The wide variation in the incidence of recurrent acute pancreatitis (RAP) is due to variability in the definition of RAP used in different studies. Etiology of RAP can be established in 70–90% patients, with gallstones and alcohol being the two most common culprits.[5,6] The other patients are often labeled as idiopathic (IRAP), in whom initial evaluation fails to reveal an etiology. The extent of the evaluation impacts the frequency with which an etiology can be found and how often the label idiopathic can be applied.[5,7,8] In comparison with patients with an initial episode of AP, RAP patients have a milder disease at presentation and, as a result, a lower mortality rate.[1,3,4,6] Considering the increasing incidence of AP across the globe, the potential burden of RAP is immense.[9] However, a majority of etiological factors of RAP are treatable and are expected to be present in the first episode itself. Hence, recurrent episodes can be prevented by eliminating the etiological factors in the first episode.

Overall, a handful of studies are available on outcomes of RAP, in comparison with the first episode of AP. With variable results of reported studies and scanty data from south Asia, we

undertook this study to provide a more complete and updated picture of RAP in Indian patients and see how they behave differently from patients presenting with an initial episode of AP.

Patients and methods

Patients. We retrospectively studied patients with AP admitted to our tertiary teaching hospital in north India between 2010 and 2017, and the study was approved by the institutional Ethics Committee. We categorized patients who had at least one prior episode of AP during the study period, either evaluated at our center or other centers, and those who had proper documentation of a prior episode available for review as RAP and compared them with AP patients who presented with the first episode of pancreatitis. We excluded patients with evidence of chronic pancreatitis (CP) and underlying pancreatic malignancy. The mean follow-up period of RAP patients was 12.8 ± 5.7 months (range 4–19 months), and patients who were diagnosed with CP on follow up were excluded from the study.

Definition. Until now, there has been no standard definition of RAP that is internationally approved. We defined RAP as two or more episodes of documented AP with at least a 2-month gap between each episode, as suggested by Lee *et al.*[4] and Sajith *et al.*[6] Any episode of pancreatic-type pain in the abdomen within 2 months of the previous episode was considered a continuation or complication of the prior disease process and hence not labeled RAP.[10] The diagnosis of AP was confirmed through the following factors (any two of the three): (i) a consistent abdominal pain, (ii) serum lipase activity and/or amylase activity at least three times greater than the upper limit of normal, and (iii) characteristic findings of AP on imaging.[11]

Evaluation for etiology. Preliminary investigations to identify the etiology of RAP were liver function tests (LFT), fasting levels of triglycerides, serum calcium, parathyroid hormone apart from transabdominal ultrasonography (USG), and contrast-enhanced computed tomography (CECT).[6] When the diagnosis remained elusive after these preliminary investigations, patients underwent the next level of investigations, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and, occasionally, endoscopic retrograde cholangiopancreatography (ERCP).[6] Bile microscopy and genetic testing among patients for RAP was not carried out.

Definition of etiologies. Alcohol-related pancreatitis was defined as the consumption of 50–80 gm/day of alcohol, irrespective of gender, for five or more years or alcoholic binge drinking 1 week before the onset of the disease. Biliary pancreatitis was considered when calculi or sludge in the gallbladder and/or bile duct was visualized on imaging. The other identifiable etiologies of pancreatitis, such as post-ERCP, hypertriglyceridemia, hyperparathyroidism, trauma, worms, drugs, and infections, were clumped into a single group of other etiologies.[7] Pancreatitis was classified as idiopathic (IRAP) when an etiological factor could not be identified.

Severity assessment. Clinical scores, such as the Systemic Inflammatory Response Score (SIRS), Bedside Index for Severity in Acute Pancreatitis (BISAP), and Acute Physiology and Chronic Health Evaluation Score (APACHE II) were noted at the time of admission.[12–14] CECT was performed within 5–7 days after onset of pain or after initial evaluation in patients referred from other centers, and severity scoring was performed by calculating CTSI.[15] Severe AP was defined by the presence of persistent organ failure (OF), moderately severe pancreatitis as local/systemic complications without persistent OF, and mild pancreatitis as the absence of both local and systemic complications.[16] A score of ≥2 in the modified Marshall scoring system for organ dysfunction was defined as the presence of OF, and if OF resolved within 48 h, it was labeled as transient, and when it persisted >48 h, it was labeled as persistent OF.[11,16]

Management. All patients were managed according to standard recommendations, which included fluid resuscitation, organ system support, pain alleviation, and nutritional support (enteral or parenteral).[17,18] Antibiotics were used for extrapancreatic infections and suspected pancreatic necrosis infection. Infected necrosis was suspected by the patient's worsening clinical course and diagnosed based on positive drain cultures or the presence of gas within the necrosis seen on CECT. Drainage (endoscopic or percutaneous catheter) of fluid collections was performed in case of persistent OF, suspected infected necrosis, and/or pressure symptoms. The site and route of drainage was chosen by a team comprising a gastroenterologist and an interventional radiologist based on the location, type, and extent of the collections. Patients failing to recover or worsening with medical management and drainage of collections were subjected to surgical necrosectomy.

Outcome measures. The parameters for the prediction of severity as recorded at the time of presentation were compared between AP and RAP groups. The parameters studied were SIRS, BISAP, and APACHE II scores and the severity of the illness as per revised Atlanta classification. The rate of infected necrosis was also compared between the groups.

Primary outcome measures included the requirement of surgical necrosectomy and mortality. Secondary outcome measures included duration of hospital stay, need for intensive care (ICU) admission, requirement of organ support (mechanical ventilation and dialysis), and need for the drainage of collections during their index hospital admission with pancreatitis.

Statistical analysis

All data were entered on a personal computer using Microsoft Excel 2010 and analyzed using SPSS software (version 23.0, IBM). Quantitative data was expressed as mean and standard deviation (SD). Quantitative variables were compared using Students 't' test or Mann Whitney U test depending on the distribution. Categorical variables were compared using the chi-square test. A p value of < 0.05 was considered to be statistically significant.

Results

Demographic profile. Of the 724 patients analyzed, 632 (87.3%) presented with first episode (AP) and 92 (12.7%) with a recurrent episode of pancreatitis (RAP). Table 1 shows the demographic and etiological profile of the patients. A majority of the patients in the RAP group were men (73;

Table 1 Demographic profile of acute and recurrent acute pancreatitis patients

Characteristics		Acute pancreatitis (n = 632; 87.3%)	Recurrent acute pancreatitis (n = 92, 12.7%)	Significance (P)
Age, years (mean ± SD)		39.49 ± 13.46	34.57 ± 10.64	0.001
Gender	Male	421 (66.6%)	73 (79.3%)	0.008
	Female	211 (33.4%)	19 (20.7%)	
Etiology	Alcohol	263 (41.6%)	28 (30.4%)	0.001
	Biliary	240 (38%)	30 (32.6%)	
	Others	41 (6.5%)	16 (17.4%)	
	Idiopathic	88 (13.9%)	18 (19.6%)	

79.3%), with a mean age at presentation of 34.57 ± 10.64 years. In comparison, RAP patients presented at a younger age and had more male dominance. Among patients with RAP, biliary etiology was the most frequent etiological factor (30; 32.6%), followed by alcohol abuse (28; 30.4%). Other etiological factors could be identified in 16 (17.4%) patients, and in 18 (19.6%) patients, no cause for a pancreatitis episode could be identified and were thus labeled IRAP. This pattern of etiological factors was significantly different from AP patients, where alcohol was the most frequent etiology (263; 41.6%), and no etiology could be established in 88 (13.9%) patients.

Comparison of severity parameters. Systemic Inflammation Response Syndrome (SIRS), BISAP score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were lower in RAP patients than AP patients (Table 2). All patients had undergone CECT of the abdomen, and the mean CTSI score and the incidence of necrotizing pancreatitis was lower in RAP patients in comparison to AP patients (46.7% *vs* 77.5%, respectively). The incidence of severe pancreatitis was also significantly less in RAP patients (10.9%) in comparison to AP patients (48.6%). Fluid collections were present in 57 (62%) RAP patients and in 573 (90.7%) patients with AP (Table 2).

Comparison of outcome parameters. The mean duration of hospitalization was 10.50 ± 9.54 days for RAP patients and 21.65 ± 16.43 days for AP patients (Table 3). The need for ICU admission was also lower in RAP patients (10; 10.9%) in comparison to AP patients (276; 43.7%). Similarly, the requirement of drainage of fluid collection and surgical necrosectomy was lower in RAP patients (38.6 and 1.1%, respectively) in comparison to AP patients (55.1 and 9.3%, respectively). Of the 92 patients with RAP, 2 (2.2%) died, in comparison to 118 (18%) patients with AP (Table 3). Both the patients with RAP who died had severe necrotizing pancreatitis of biliary etiology.

Etiological distribution of recurrent AP. Table 4 shows the details of the etiology of RAP patients and relation of etiological factors with the number of episodes, type, and severity of pancreatitis. As detailed above, the most frequent etiological factor was biliary etiology followed by alcohol abuse and idiopathic. Among the other etiologies, pancreatic divisum was found in six (6.5%), hyperparathyroidism in five (5.4%), hypertriglyceridemia in three (3.2%) and drugs in two (2.2%) patients. The mean number of episodes per RAP patient was 2.97 ± 1.66 (range 2–10), and a majority of them (59; 64.1%) had only two episodes. However, a higher fraction of IRAP (8/18; 44.5%) patients had ≥4 episodes in comparison to other etiologies. Biliary etiology and alcohol abuse patients had a higher fraction of necrotizing pancreatitis (17/30; 56.7% and 14/28; 50%, respectively) in comparison to IRAP (6/18; 33.3%). Recurrent episodes due to idiopathic etiology had milder disease (10/18; 55.6%) in comparison to biliary etiology (5/30; 16.7%) and alcohol abuse (12/28; 42.9%).

Table 2 Severity parameters of acute and recurrent acute pancreatitis patients

Characteristics		Acute pancreatitis	Recurrent acute pancreatitis	Significance (P)
SIRS (≥2)		481 (76.1%)	30 (32.6%)	0.001
BISAP		1.98 ± 1.03	0.99 ± 1.02	0.001
APACHE		8.51 ± 9.81	6.64 ± 4.10	0.001
CTSI		7.29 ± 2.79	4.99 ± 2.96	0.001
Type of pancreatitis	AIP	142 (22.5%)	49 (53.3%)	0.001
	ANP	490 (77.5%)	43 (46.7%)	
Severity	Mild	59 (9.3%)	35 (38%)	0.001
	Moderately severe	266 (42.1%)	47 (51.1%)	
	Severe	307 (48.6%)	10 (10.9%)	
Fluid collection		573 (90.7%)	57 (62%)	0.001

AIP, acute interstitial pancreatitis; ANP, acute necrotizing pancreatitis; APACHE, acute physiology and chronic health evaluation; BISAP, bedside index of severity in acute pancreatitis; CTSI, computed tomography (CT) severity index; SIRS, systemic inflammatory response syndrome.

Table 3 Comparison of outcomes of acute pancreatitis and recurrent acute pancreatitis

Characteristics	Acute pancreatitis	Recurrent acute pancreatitis	Significance (*P*)
Hospital stay (days)	21.65 ± 16.43	10.50 ± 9.54	0.001
ICU need	276 (43.7%)	10 (10.9%)	0.001
Drainage of fluid collection	316 (55.1%)	22 (38.6%)	0.012
Surgical necrosectomy	59 (9.3%)	1 (1.1%)	0.002
Mortality	114 (18%)	2 (2.2%)	0.001

ICU, intensive care unit.

Discussion

In this study, we have evaluated the frequency, etiological factors, severity parameters, and outcome of patients with RAP and how they differed from patients presenting with the first episode of AP. Of the 724 patients analyzed, 92 (12.7%) had RAP, and 632 (87.3%) had AP. All the severity predicting scores, that is, SIRS, BISAP, and APACHE II, were lower in patients with RAP when compared to AP patients. The days of hospitalization, need for ICU admission, need for drainage of fluid collections, need for surgical necrosectomy, and mortality were also lower in patients with RAP.

There are conflicting data on the frequency of RAP.[1–4] One study from China had reported its incidence to be 10.7%,[1] while other studies from Europe, USA, and China have reported incidence rates of 27%, 28%, and 31.4%, respectively.[2–4] Most of the studies have not clearly defined the diagnostic criteria for RAP. The diagnostic criterion used by us was the same as used by Lee *et al.*[4] and Sajith *et al.*,[6] that is, two or more episodes of documented AP based on revised Atlanta criteria,[11] with at least a 2-month gap between each episode.

Biliary etiology and alcohol were the most common causes of RAP in our study. Studies from China[2] and India[6] have shown that biliary etiology was the most frequent factor among identifiable etiologies, although other studies have reported alcohol being the most common etiology.[1,3,4] The predominance of these two etiologies in our study could be because of: (i) the location our center in the Gangetic plains of northern India with high incidence of gall stone disease and (ii) a high alcohol consumption in the area.[19,20]

Both alcoholic and biliary AP episodes have been associated with subsequent recurrent episodes.[21,22] Pelli *et al.* reported that 260 (46%) of their 562 patients with a first episode of acute alcoholic pancreatitis had recurrence of pancreatitis episodes within 20-year follow up.[21] Hernandez *et al.* reported a recurrence rate of 18.2% in 233 patients with biliary pancreatitis within 3 years.[22]

With the availability of better imaging modalities, the rate of identification of etiological factors of AP has improved.[7] The incidence of IRAP in our study was 19.6%, while other studies have reported it in 10–38% of patients.[1,3,4,6,23] The rate of IRAP varies depending on the extent of evaluation for etiology, and the incidence is expected to fall further in the coming years with the use of better imaging modalities.[6] We have not performed bile microscopy for microlithiasis and genetic studies in patients with IRAP, so our frequency of 19.6% of IRAP could probably decrease even further. We have also not investigated these patients for suspected Sphincter of Oddi Dysfunction (SOD). Our data also show that hyperparathyroidism, hypertriglyceridemia, pancreatic divisum, and drugs are important causes of RAP, whose treatment can prevent future attacks.

Patients with a recurrent episode of pancreatitis are less sick compared to patients with the first episode of pancreatitis.[1,2,4,6] In our study, the incidence of severe pancreatitis was only 10.9% in RAP patients as compared to 48.6% in patients with a first episode of pancreatitis. Gao *et al.* reported severe pancreatitis in 21% of their 157 patients with RAP,[1] while Lee *et al.* reported that only 2.4% of their patients with RAP had severe pancreatitis as compared to 11.7% of patients with an initial episode of pancreatitis.[4] The possible explanation for lower severity of disease in patients with RAP is due to the loss of acinar cells through the necrosis and fibrosis sequence.[24] Fewer acinar cells will lead to less auto-digestion, necrosis, and inflammatory cascade in subsequent episodes. Fibrosis also has been shown to reduce adipokine levels, which in turn reduces acinar necrosis.[25] As such, recurrent episodes of pancreatitis will lead to parenchymal fibrosis, which in turn may be protective against the inflammatory cascade. Lee *et al.* reported that a prior episode of AP is protective against the development of multisystem OF, with an odds ratio of 7.14 for each prior episode.[4]

Table 4 Etiological division of recurrent acute pancreatitis

		Biliary	Alcohol	Idiopathic	Hyper-parathyroid	Hyper-triglyceridemia	Pancreatic divisum	Drugs
Total		30	28	18	5	3	6	2
No. of episodes of pancreatitis	2	25	18	7	3	3	2	1
	3	2	4	3	1	0	2	0
	≥4	3	6	8	1	0	2	1
Type of pancreatitis	AIP	13	14	12	3	2	4	1
	ANP	17	14	6	2	1	2	1
Severity of pancreatitis	Mild	5	12	10	3	0	4	1
	Moderately severe	19	14	7	1	3	2	1
	Severe	6	2	1	1	0	0	0

AIP, acute interstitial pancreatitis; ANP, acute necrotizing pancreatitis.

We noted that patients with recurrent episodes of pancreatitis were less likely to require ICU care, undergo percutaneous/endoscopic or surgical intervention, and die during index hospitalization. This is reflective of the severity of disease, with mean APACHE II scores, severity of pancreatitis, and fluid collection being lower in this group of patients. The need for ICU admission in our patients with RAP was 10.9% in comparison to 43.7% in patients with AP. Other workers have also reported a lower need for organ support and ICU care in patients with RAP.[1,4] Although there is variation in the frequency of complications like fluid collection and the need for intervention, all studies have reported that RAP patients have a more favorable clinical course and outcome when compared to AP.[1–6] Our mortality of 2.2% is again in accordance with the reported range of 0–5.9%.[3,4,6]

The mean number of episodes per RAP patients was 2.97 ± 1.66, and 64% of them had only two episodes. Other researchers have reported that 54–80% of their patients had only two episodes.[1–4] We observed that 44.5% of our patients with IRAP patients had ≥4 episodes. Literature on this aspect is contradictory; Gullo *et al*. reported that 6.7% of their IRAP patients had ≥4 episodes,[3] while Lee *et al*. observed that 41.9% of their IRAP patients had ≥4 episodes.[4] A higher number of episodes in IRAP patients because of etiology could not be identified, and hence, these patients were not excluded.

The strengths of our study are that we have used clear and strict criteria for the diagnosis of RAP in a large number of patients, and we have directly compared the severity and outcome parameters between patients with RAP and AP. Our study has certain limitations, retrospective nature being one. We did not perform bile microscopy and genetic studies to ascertain the etiology of IRAP nor did we study the contribution of SOD. Furthermore, the follow up and details of treatment of RAP patients after the index hospital admission were not available.

In conclusion, this study demonstrated that RAP had a milder disease course and lower mortality when compared to the initial episode of pancreatitis. Appropriate evaluation and dealing with etiological factors at the initial episode of AP can prevent a majority of RAP.

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