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Characterization of long-term prognosis in acute pancreatitis: An explorative analysis

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ABSTRACT

Background/objectives: Severity classification systems of acute pancreatitis (AP) assess inpatient morbidity and mortality without predicting outpatient course of AP. To provide appropriate outpatient care, determinants of long-term prognosis must also be identified. The aim of this study was to define clinical groups that carry long-term prognostic significance in AP.
Methods: A retrospective study that included patients admitted with AP was conducted. Determinants of long-term prognosis were extracted: These included Revised Atlanta and Determinant Based Classification (RAC), Charlson Comorbidity Index (CCI), Modified CT Severity Index (MCTSI), etiology, and local complications (LCs). Seven surrogates of morbidity up to 1 year after discharge were also collected and subsequently imputed into a clustering algorithm. The algorithm was set to produce three categories and multinomial regression analysis was performed.
Results: 281 patients were included. The incidences of morbidity endpoints were similar among the 3 RAC categories. Three clusters were identified that carried long-term prognostic significance. Each cluster was given a name to reflect prognosis. The limited AP had the best prognosis and included patients without LCs with a low co-morbidity burden. The brittle AP had a low co-morbidity burden and high MCTSI (LCs 94%). It ran a very morbid course but had excellent survival. The high-risk AP had the worst prognosis with the highest mortality rate (28%). They had a high co-morbidity burden without local complications.
Conclusion: Categories that carry long-term prognostic significance in AP have been developed. This study could help formulate appropriate follow-up and ultimately improve AP outcomes.

Introduction

The last decade has seen a major advancement in categorizing AP into meaningful prognostic categories [1–7]. This advancement culminated in the development of the Revised Atlanta Classification (RAC) and Determinant Based Classification (DBC), which categorize severity of pancreatitis to accurately reflect inpatient morbidity and mortality [4,5,8]. However, the characterization of post-discharge clinical course and its determinants has not yet been fully clarified [3,9]. Recent studies report a deteriorated quality of life and increased incidence of diabetes following an episode of AP. Other studies have identified risk factors for 30-day readmission in

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this population [9–26]. Some of these studies are restricted to patients with acute necrotizing pancreatitis [21,26]. Given that AP has an annual financial burden of over 2 billion dollars and a high recurrence rate, multiple studies stress the importance of close outpatient follow up for patients with AP [2,27]. But unfortunately, there is no clear guidance on which patients should be followed [22–25]. In the face of the increasing emphasis on cost-efficient care, identification of AP patients who require intensive outpatient care coordination is extremely important [28]. We hypothesized that RAC is not a valid system to signify post-discharge morbidity and mortality and a categorization system that convey long-term prognostic implications will help identify patients that require close follow-up and tailor outpatient management [22]. Our aim was to explore determinants of long-term morbidity and mortality and develop a classification system to reflect long-term prognosis.

Methods

Study design

A retrospective cohort study was carried out at a tertiary referral center. Consecutive patients who were admitted to University Hospitals Cleveland Medical Center with AP between January 2010 and January 2015 were identified by searching the billing database with the discharge ICD-9 diagnosis of AP. The diagnosis of AP was verified based on the American College of Gastroenterology Guidelines (ACG) [5]. Patients were excluded if they were younger than 18 years of age, had missing data in the electronic medical record, or did not undergo a CT scan during the admission. Exclusion of patients who did not undergo a CT was done to ensure a correct classification of in-hospital severity. Patients who were transferred from an outside hospital were included only if the hospital record was connected to the electronic medical record of University Hospitals. Patients admitted with recurrent pancreatitis without relevant data on the initial or sentinel episode were also excluded (Fig. 3). Demographic data including age, sex, body mass index, smoking history as well as etiology of sentinel episode of AP were collected. Burden of comorbid condition was measured using Charlson Comorbidity Index (CCI) [29]. The modified CT severity index (MCTSI) was used to grade radiologic severity of AP by a radiologist blinded to clinical outcomes [30–32]. The Revised Atlanta Classification was used to assess severity [4]. The infectious status of local complications (LCs) was recorded and it was defined as a positive culture sampled from a local complication or presence of gas within a collection that had not been intervened on [4,5]. Because morbidity is an arbitrary outcome that is difficult to measure, several surrogates of morbidity that carry clinical significance were chosen *a priori*. These included emergency department visits and hospitalizations related/unrelated to AP, length of hospital stay from additional admissions, need for invasive intervention, and unplanned 30-day readmissions. Elective admissions were not counted. In-hospital and 12-month mortality rate were also collected.

Statistical analysis

Clustering analysis is a statistical method that is used to organize a given heterogeneous dataset into a pre-determined number of homogenous groups. This grouping is guided by domain knowledge aided by key statistical descriptive summaries and preselected surrogates. The K-medoids clustering analysis algorithm was used in this study [33,34]. To mirror the 3 categories of severity proposed by RAC, the algorithm was set to produce three groups with each patient in the cohort assigned only one cluster. These groups were constructed optimally such that the total within cluster variation, summed over all clusters, was the least that could be obtained using this dataset. Seven surrogates of long-term morbidity, mortality data, as well as variables that were clinically judged to be candidates for determinants of long-term morbidity and mortality were imputed into the algorithm. Candidate variables included determinants of in-hospital severity as defined by RAC, CCI, MCTSI, etiology, and a list of all possible local complications (i.e. acute fluid collection, acute necrotic collection, pseudocyst, walled off pancreatic necrosis (WOPN), infected local complications). The cluster variation was defined using squared Euclidian distance. Since the K-medoids clustering algorithm requires an initial random assignment of patients to a cluster, the algorithm was run several times using different random configurations and we selected the iteration that lead to the least sum of variables within a cluster distance. Because the above variables were measured using different units, they were scaled to avoid giving any variables undue influence on the clustering algorithm. All analyses were done using R 3.3. [R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/]. Multinomial regression was also conducted to identify and describe statistically significant variables.

Results

Five hundred and seventy-four patients with AP were admitted during the study period, of which, 318 patients had a CT-scan on admission. Two hundred and eighty-one were included in the cluster analysis and the remaining were excluded due to missing data (Fig. 3). The 3 RAC severity categories resulted in similar post-discharge clinical course, as reflected by comparable morbidity and mortality endpoints especially between the moderately severe and severe categories (Table 1). The clustering algorithm produced three groups, each with a distinct prognostic course. The 3 groups were labeled to reflect their respective clinical course: limited AP ($n = 166$), brittle AP ($n = 68$) and high-risk AP ($n = 47$).

Multinomial regression analysis

After candidate variables that are significantly associated with a cluster were identified, variables that retained significant association with a cluster group are shown in Tables 2 and 3.

Limited AP group

In all eight surrogates of morbidity, patients in this category had the most favorable course when compared with the other two categories. Only 4% in the group developed local complications. Limited AP patients had very low average MCTSI score of 1.85 and comorbidity burden (mean CCI score 2.64 vs CCI of high-risk = 6.19, p-value <0.001). As expected, most patients in this category experienced mild AP (MAP) (81.9%) and only 1.2% experienced severe AP (SAP) (Tables 2 and 3). Alcohol was attributed as the etiology in 41% of the group (vs 19.1% for the high risk AP group and 47.1% for the brittle AP, p-value <0.001). Although more readmissions might be expected due to alcohol recidivism, we observed a very low unplanned 30-day readmission rate (8.4% vs 42.6% for high risk AP and 35.3% for brittle AP, p-value <0.001). This group also had the lowest mean number of admissions in a year following discharge (Tables 2, 3, and 4) (Fig. 1).

Brittle AP group

The 68 patients in this group had the most morbid course but none died. Ninety-four percent had local complications with a high

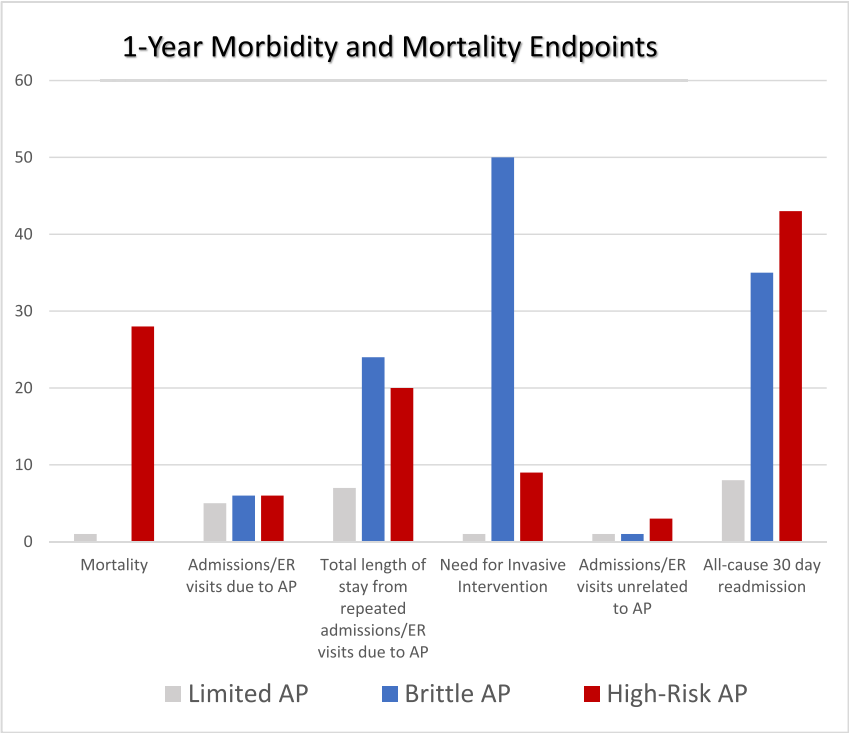

Fig. 1. Admission/ER visit values given in mean per patient; Need for invasive intervention, 30-day readmission and mortality values are in %; Length of stay values given in average number of days per patient.

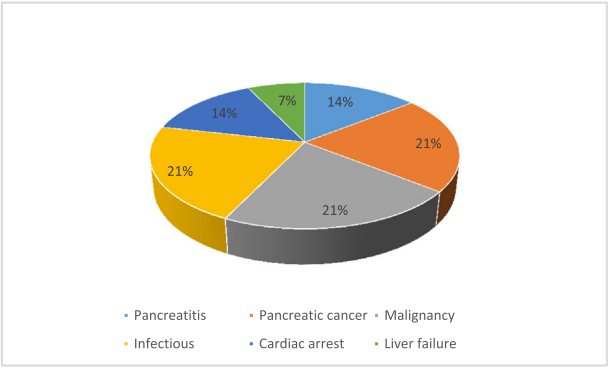

Fig. 2. Cause of death in patients who died 12 months post-discharge.

mean MCSTI of 5.02 (p-value <0.001), but they had the lowest co-morbidity burden (CCI score: 1.78 vs high-risk group CCI score = 6.19, p-value <0.001). All patients who developed extra-pancreatic collections were in this group and 27.9% of this group developed pancreatic necrosis vs 2.1% and 1.2% in high-risk and limited AP groups respectively (p-value <0.001). Over a third of the patients had an unplanned 30-day readmission (35.30% vs 42.60 in high risk group vs 8.40% in limited group, p-value <0.001). The brittle AP group also had the highest average cumulative length of stay over 12 months (23.87 days vs 19.83 days in high-risk group vs 6.72 days in limited group; p-value <0.001). As expected, half of them required an invasive intervention (Tables 2, 3, and 4) (Fig. 1).

High-risk AP group

The high-risk AP group consisted of patients with very few local complications (6.4% had LCs, MCSTI 2.06, p-value <0.001) but carried a significant comorbidity burden (mean CCI score = 6.19, p-value <0.001). The high-risk AP group had the highest mortality rate of 27.7% (p-value <0.001), mostly from causes unrelated to pancreatitis (Fig. 2). This group also had the highest 30-day readmission rate (42.60%, p-value <0.001), highest number of ED visits and admissions unrelated to AP (1.19 visits and 2.21 admissions, p-value <0.001), and a very low number of endoscopic, percutaneous and surgical interventions (8.5%, p-value <0.001) (Tables 2 3, and 4) (Fig. 1).

Overall mortality

The most common causes of death were pancreatic cancer, malignancy unrelated to pancreas, and sepsis unrelated to pancreatitis. Pancreatitis and complications related to pancreatitis were only responsible for 14% of overall deaths (Fig. 2).

Discussion

Our analysis revealed 3 categories of AP patients with distinct post-discharge courses which may be useful in the long term care of AP. This is the first study to determine if RAC carried post-discharge prognostic significance. It also explored the potential determinants of post-discharge outcomes of patients after an episode of AP [3–27].

As expected, local complications seem to be an important determinant of post-discharge morbidity. This is illustrated in the brittle AP group which ran the most morbid course, while having the highest rate of LCs (73.5%) at 1 year from discharge. This group had a 35% 30-day readmission rate, the highest average cumulative length of stay over 12 months, an average of nearly 4 hospitalizations per patient from AP, and intervention rate of 50% (Table 4). In addition, it is also worth noting that the mean MCTSI of this group was 5.02 compared with 2.06 for high-risk category and 1.85 for

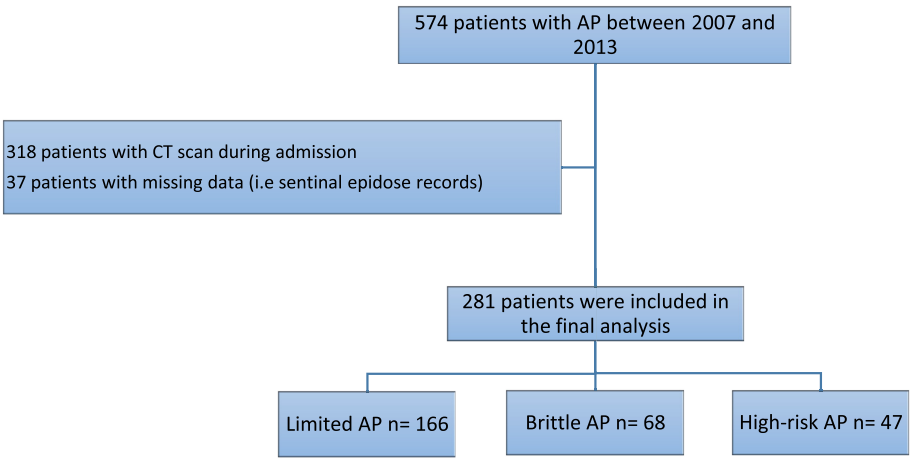

Fig. 3. Flowchart of included patients after applying inclusion and exclusion criteria.

Table 1
Morbidity and mortality outcomes in each of the Revised Atlanta Classification categories.

	Mild AP (N 186)	Moderately Severe AP (N 105)	Severe AP (N 22)
30-day readmission	15.60%	31.4%	31.8%
Number of admissions due to acute pancreatitis (mean)	2.48 (1.40)	3.10 (1.95)	3.00 (1.51)
Number of admissions unrelated to acute pancreatitis (mean)	0.94 (2.21)	0.45 (0.98)	0.60 (1.19)
Cumulative length of stay (mean (sd))	7.60 (9.23)	17.93 (15.66)	36.10 (26.49)
Need for Intervention on local complication	0%	29.3%	40.0%
Mortality	3.2%	5.7%	13.6%

Table 2
Basic demographics of acute pancreatitis in selected cohort.

	Brittle AP N = 68	High Risk AP N = 47	Limited AP N = 166	p-value
Sex: Male (mean)	40 (58.8%)	19 (40.4%)	87 (52.4%)	0.149
Age (mean (sd))	47.57 (13.67)	60.02 (15.80)	52.20 (16.00)	<0.001
BMI (mean (sd))	27.83 (6.69)	30.27 (11.97)	28.32 (17.29)	0.69
Current smoker	32 (47.1%)	11 (23.9%)	72 (44.2%)	0.094
Etiology				0.048
Alcohol	32 (47.1%)	9 (19.1%)	68 (41.0%)	
Gallstone	18 (26.5%)	13 (27.7%)	35 (21.1%)	
Post-ERCP	0 (0.0%)	1 (2.1%)	3 (1.8%)	
Medications	1 (1.5%)	1 (2.1%)	7 (4.2%)	
Hypertriglycerdemia	5 (7.4%)	1 (2.1%)	7 (4.2%)	
Pancreatic cancer	0 (0.0%)	4 (8.5%)	6 (3.6%)	
Hereditary	1 (1.5%)	0 (0.0%)	1 (0.6%)	
Other	11 (16.2%)	18 (38.3%)	39 (23.5%)	
Charlson Comorbidity Index	1.78 (1.87)	6.19 (3.05)	2.64 (2.17)	<0.001

Table 3
In-hospital severity and specific causes of local complications.

	Brittle AP N = 68	High-Risk AP N = 47	Limited AP N = 166	p-value
Severity				
Mild	10 (14.7%)	24 (51.1%)	136 (81.9%)	<0.001
Moderately Severe	51 (75.0%)	13 (27.7%)	28 (16.9%)	
Transient Organ Failure	8 (11.8%)	6 (12.8%)	14 (8.4%)	0.580
Local complications	64 (94.1%)	3 (6.4%)	7 (4.2%)	<0.001
Comorbid condition flare	0 (0)	13 (27.7%)	9 (5.4%)	<0.001
Severe	7 (10.3%)	10 (21.3%)	2 (1.2%)	<0.001
Modified CT Severity Index (sd)	5.02 (2.74)	2.06 (1.59)	1.85 (1.68)	<0.001
Local complication on presentation				
Pancreatic necrosis	19 (27.9%)	1 (2.1%)	2 (1.2%)	<0.001
Pancreatic fluid collections	43 (63.2%)	0 (0.0%)	0 (0.0%)	<0.001
Extrapancreatic collections	10 (14.7%)	0 (0.0%)	0 (0.0%)	<0.001
None	4 (5.9%)	44 (93.6%)	159 (95.8%)	<0.001
WOPN within 12 months	10 (14.7%)	1 (2.1%)	0 (0.0%)	<0.001

Table 4
Surrogates of morbidity for each category and mortality rate.

	Brittle AP	High-risk AP	Limited AP
30-day readmission	35.30%	42.60%	8.40%
Number of admissions due to acute pancreatitis (mean)	3.79	3.38	2.4
Number of admissions unrelated to acute pancreatitis (mean)	0.32	2.21	0.52
Cumulative length of stay (mean (sd))	23.87 (19.89)	19.83 (17.83)	6.72 (7.78)
Need for Intervention on local complication	50%	8.50%	1.20%
Mortality	0%	27.70%	0.60%

limited category. Additionally, all patients with extra-pancreatic collections belonged to this category. This suggests that, in addition to the presence of LCs, the severity of structural injury to the pancreas is equally an important determinant of long-term clinical course. Large pseudocysts and WOPNs can cause compressive symptoms to surrounding organs and can lead to intractable symptoms of nausea, vomiting and abdominal pain and they often have extra-pancreatic complications that can take months to resolve. This category of patients seems appropriate to target with an intensive outpatient multidisciplinary care coordination when they are discharged. Proportion of patients with endocrine and exocrine pancreatic insufficiency in this study was not measured. However, it is well established that up to 37% develop either pre-diabetes and/or diabetes after an episode of acute pancreatitis [19,20]. Given ease of diagnosis, it seems reasonable to screen all patients after an episode. Exocrine pancreatic insufficiency development is less well characterized and needs further research. While RAC also recognizes the importance of LCs in determining morbidity, development of transient organ failure and exacerbation of a comorbid condition are also recognized to be determinants of inpatient morbidity in RAC. However, transient organ failure did not seem to affect post-discharge morbidity.

Findings of the current study suggest that baseline comorbidity burden may be the most important determinant of patients' mortality once a patient survives an episode of AP. Patients in the high-risk category were older, and carried strikingly higher burden of comorbidities when compared to brittle AP and limited AP (total CCI score: high risk 6.19 vs brittle 1.78 vs limited 2.64, $p < 0.001$, Table 2). Over 93% of death in the overall cohort occurred in this group. The association between mortality and baseline comorbidities is well established in other diseases and our findings validate the association in patients with AP [6,35,36]. Advanced age is also an established determinant of mortality [35,36].

A third of patients in the high-risk category experienced an exacerbation of one of their comorbid conditions during the hospitalization for AP. Interestingly, although only 8.5% developed LCs, patients in this group experienced similarly high rates of AP related ER visits, AP-related admissions and 30-day unplanned readmissions rates when compared with the LC prevalent brittle AP category. One mechanistic hypothesis could be that, there is interplay between AP and their comorbid conditions. We postulate that AP and patients' comorbid conditions may lead to smoldering symptoms of AP and AP in turn accelerates the progression of comorbid conditions. Supporting this hypothesis, 86% of the deaths were attributable to worsening comorbid condition (Fig. 2). Although there are no studies that specifically address this question in AP, the impact of an acute illness on the progression of comorbid conditions is well demonstrated in the literature [37,38].

While no studies attempted to develop a classification system that carry post-discharge prognostic significance, Umapathy et al. characterized the natural history of acute necrotizing pancreatitis (ANP) following discharge from the hospital for a median follow-up period of 34 months [21]. Age, persistent organ failure, and overt necrosis (>50%) were shown to be predictors of one-year mortality which is similar to our findings. Takeyama et al. found alcoholic AP to have a high recurrence rate and a 41% risk of progression to chronic pancreatitis if they continued to drink at the same level as before the sentinel AP episode [16]. In our cohort, alcoholic AP was similarly distributed among the limited and brittle group (limited 41%, brittle 47%) with extremely different clinical courses. This demonstrates that the alcohol etiology alone may not determine morbidity. This is supported by Gloor et al. and Uhl et al. who both found no relation between etiology and morbidity [17,39].

Findings of the current study are clinically relevant in several ways. It informs the clinicians and patients alike on possible determinants of post-discharge course. For patients who develop local complications, especially with a high MCTSI, efforts should be made to coordinate a smooth transition of care at the time of discharge. The attention needs to be given to prevent unplanned 30-day readmission, as well as future hospitalizations. Patients with advanced age, with a high burden of comorbidities, regardless of in-hospital severity should be very closely monitored post discharge to optimize their comorbid conditions. Communication with specialists who manage their comorbid conditions would be crucial to also arrange follow-up care for their respective conditions.

To our knowledge, this is the first study to develop post-discharge categories of AP that carry prognostic significance. By exhaustively collecting data on patients' inpatient clinical course as well as data on surrogates of morbidity and mortality, we could explore their associations. By using clustering analysis method, what was otherwise a very heterogenous cohort could be categorized into homogeneous groups that carry clinical significance. Because University Hospital System covers over 27 health centers with a standardized charting system that cover a large proportion of northeast Ohio, most of the follow-up data was available for analysis.

There are several limitations of the study. Some patients might have presented to other hospitals that were not captured and thus, were lost to follow up. To overcome this limitation, patients without relevant follow up data or records of sentinel AP episode were excluded from the study. Because the institution is a tertiary referral center, we could have selected for sicker patients, and thereby overestimating the morbidity of post-discharge course of patients with LCs. Additionally, this was an explorative study. As such, concrete definitions of the 3 categories need to be established and, the classification system needs to be validated in a separate cohort. Nevertheless, the findings provide insight into possible determinants of morbidity and mortality. Lastly, recurrent hospitalizations due to behavioral issues were not adjusted for. The morbid course suffered by the brittle AP category may have been attributable to behavioral issues underlying alcoholism instead of local complications.

In summary, three categories carry long-term prognostic significance in AP. Comorbid conditions, and LCs are important long-term morbidity and mortality predictors. The study could help formulate appropriate follow-up care for the identified groups and ultimately improve AP outcomes.

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