Worldwide Variations in Demographics, Management, and Outcomes of Acute Pancreatitis

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Short Title: Geographic Variations in Acute Pancreatitis

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Abbreviations:

AGA: American gastroenterological association

AP: acute pancreatitis

APPRENTICE: acute pancreatitis patient registry to examine novel therapies in clinical experience

BMI: body mass index

CI: confidence interval

DUA: data use agreements

ERCP: endoscopic retrograde cholangiopancreatography

ICU: intensive care unit

IQR: interquartile range

IRB: institutional review board

RAC: revised Atlanta classification

REDCap: Research Electronic Data Capture

LOS: length of stay

SIRS: systemic inflammatory response syndrome

TPN: total parenteral nutrition

Abstract:

Background & Aims: Few studies have compared regional differences in acute pancreatitis. We analyzed data from an international registry of patients with acute pancreatitis to evaluate geographic variations in patient characteristics, management, and outcomes.

Methods: We collected data from the APPRENTICE registry of patients with acute pancreatitis, which obtains information from patients in Europe (6 centers), India (3 centers), Latin America (5 centers), and North America (8 centers) using standardized questionnaires. Our final analysis included 1,612 patients with acute pancreatitis (median age, 49 years; 53% male, 62% white) enrolled from August 2015 through January 2018.

Results: Biliary (45%) and alcoholic acute pancreatitis (21%) were the most common etiologies. Based on the revised Atlanta classification, 65% of patients developed mild disease, 23% moderate, and 12% severe. The mean age of patients in Europe (58 years) was older than mean age for all 4 regions (46 years) and a higher proportion of patients in Europe had comorbid conditions (73% vs 50% overall). The predominant etiology of acute pancreatitis in Latin America was biliary (78%), whereas alcohol-associated pancreatitis accounted for the highest proportion of acute pancreatitis cases in India (45%). Pain was managed with opioid analgesics in 93% of patients in North America versus 27% of patients in the other 3 regions. Cholecystectomies were performed at the time of hospital admission for most patients in Latin America (60% vs 15% overall). A higher proportion of European patients with severe acute pancreatitis died during the original hospital stay (44%) compared with the other 3 regions (15%).

Conclusions: We found significant variation in demographics, etiologies, management practices, and outcomes of acute pancreatitis worldwide.

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KEY WORDS: pancreas; inflammation, drug, treatment

Introduction

Acute pancreatitis (AP) is a global leading cause of gastrointestinal-related hospital admissions [1]. The incidence of AP has been reported to be increasing in the United States and Europe [2, 3]. Approximately 20% of people affected develop severe disease resulting in relatively high morbidity and mortality [4]. Over the last decade, multiple advances have occurred in management of AP such as the development of the revised Atlanta classification of disease severity (RAC), introduction of early goal-directed intravenous fluid resuscitation, and implementation of a minimally invasive step-up approach in subjects with symptomatic necrotic pancreatic collections [5-7]. Possibly as a consequence of these developments, case fatality of AP may have decreased however, estimates tend to vary among different countries [8, 9].

Large, multicenter studies in AP from national registries have been recently published. However, these have been confined to national bounds, with the majority being in North America and Europe [10-13]. Results from these studies have revealed heterogeneity in patient characteristics such as demographics, etiology, and risk factors of severe disease. For instance, a large Spanish study from 2018 revealed an AP mortality rate of 4.2% compared to 1% from recent reports in the United States [13, 14]. Inconsistent severity definitions and methodology hinder the combination and comparison of data from different regions. Furthermore, it is unclear whether recent advances in management of AP have gained traction throughout different areas of the world.

Lack of prospective, multi-national data in AP prompted investigators around the world to create a multi-center collaboration referred as Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE)[15]. This study's aim was to evaluate the geographic differences in patient characteristics, management, and outcomes of AP across four different geographic areas using APPRENTICE data.

Methods

Study Population

APPRENTICE is a prospective, multicenter, international consortium studying clinical characteristics of AP patients across the world[15]. The University of Pittsburgh served as the coordinating center. Ethical committee approvals were obtained from local institutional review boards (IRB) at all participating centers. University of Pittsburgh's IRB approved this study and acted as an umbrella IRB for incoming centers (PRO15040389). The study was registered in clinicaltrials.gov (NCT03075618). Details on design and methodology of APPRENTICE have been previously published[15]. Adults (≥18 years old) admitted with the diagnosis of AP, willing to participate in the study, and enrolled within 2 weeks of presentation were eligible for inclusion. Patients with a history of organ transplantation, trauma induced AP, chronic pancreatitis, and pancreatic cancer were excluded. Enrollment occurred between October 2015 and January 2018. Site investigators were responsible for identifying eligible hospital admitted patients through different screening mechanisms. In total, data from 22 sites, which reached a set minimum number of enrollment (≥ 15 patients/center), were included for statistical analysis (Table 1, Figure 1).

Data collection

Study questionnaires were carefully designed by recognized experts in the field (appendix table 1). A well-established, secure, web-based, electronic data collection software (Research Electronic Data Capture, REDCap) was used[16]. A test period of 3 months was initially undertaken with the goal to assess applicability and quality of the questionnaires. Multiple online sessions with study personnel (site investigators, coordinators) were conducted prior to, and

during the enrollment phase in order to ensure the uniformity of data collection, answer questions, and address technical issues. De-identified data was collected prospectively at different hospitalization time points: admission, day 1, day 2, day 3, day 7, and discharge. Data quality was routinely monitored by a dedicated statistician at the coordinating site. Definition of different collected variables are outlined in appendix table 2.

The primary clinical outcomes of interest included RAC severity, LOS, and in-hospital mortality. Additional outcomes included AP etiology, fluid volume in the first 24 hours of admission, fluid type, analgesic use, feeding methods, and ERCP, or cholecystectomy rates in cases of biliary pancreatitis. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical analysis

Statistical analysis was performed by expert biostatisticians (X.G., G.T.) at the coordinating center. Continuous variables were summarized by median and interquartile range (IQR). Categorical variables were presented with proportions of study subjects. Preliminary comparisons of outcome variables among various geographic areas, were performed using the Fisher's exact test for categorical values, and the nonparametric Kruskal-Wallis test was used for continuous variables (Tables 2-5). These were used as global tests that compared patient characteristic and clinical outcomes of interest through all four regions. Significance was defined as a p-value equal to or less than 0.05; no adjustment for multiple testing was made in these exploratory analyses.

Subsequently, we focused on the primary clinical outcomes and multivariate regression models were applied to assess whether LOS, severity, and mortality differ among the four geographic

areas, adjusting for other patient characteristics. The geographic regions were coded by three dummy variables, with North America as the reference region. For multivariable analysis, a linear regression was used to evaluate LOS differences among geographic areas, and logistic regression was used to assess differences in severity (severe AP vs. others) and mortality (severe patients) among different regions. Such differences in outcomes between a region (Europe, India, or Latin America) and North America were presented as odds ratios in the case of severity and mortality, or as associated model coefficients in the case of LOS (Appendix Tables 3-5).

Multivariable models were run including the following covariates: age, gender, body mass index (BMI), Charlson Comorbidity Index, etiology, transfer status, cholecystectomy during the same admission, narcotic use, and severity (only for LOS). The covariates of age, BMI, Charlson Comorbidity Index, and etiology were constantly kept in the model for more accurate prediction, while the remaining covariates dropped when not significant. The likelihood ratio test was used to compare the nested model with region and the adjusted variables as covariates and the sub-model with only the adjusted variables as covariates. All analyses were performed in R (Version 3.5.1, R Foundation).

Study participants:

In total, 1,680 AP patients were enrolled between August 2015 and January 2018; 68 were omitted from the analysis yielding a final number of 1,612 subjects. Exclusion of the above subjects was related to removal of sites with <15 subjects enrolled from the analysis (13 patients), as part of the predetermined study criteria, or due to missing RAC data (55 patients; Table 1, Figure 1).

Results

Baseline Characteristics and Etiology

Out of the 1,612 patients, median age was 49 (IQR, 34-64), and 47% were females. Biliary (45%) and alcoholic (21%) were the most common pancreatitis etiologies (Table 2). Based on RAC, 65% were classified as developing mild disease, 23% as moderately severe, and 12% as severe disease. Median LOS was 8 days (IQR, 5-13, Table 4). Overall, 45 patients died (2.8%) during their hospitalization (Table 5).

Age, gender, ethnicity, and race distributions differed significantly by geographic areas. Patients from Indian sites were mostly males (75%), younger in age (39 years, IQR: 30-50) with alcohol being the predominant etiology (45% vs. 14% in remaining geographic areas, p <0.001). Latin American patients were mostly young (median age 43, IQR 29-59), females (67%) with the majority of AP linked to biliary etiology (78% vs. 37%, p<0.001). In contrast, European and North American subjects had a relatively equal gender distribution, with an overall older age [58, (IQR 45-74) and 52 (IQR 37-65) respectively, p <0.001]. Post ERCP pancreatitis was significantly more common in North American sites (19% vs 2.8% in remaining geographic areas, p<0.001) (Table 2). These differences were mostly driven by two North American sites with 50 out of 90 and 22 out of 62 enrolled patients classified as post ERCP pancreatitis, respectively.

Management

Data on patient management is presented in table 3. The amount of intravenous fluids administered over the first 24 hours was relatively similar between India, Latin America and North America (ranged between 3-3.2 liters); however, was significantly lower in Europe (2.5 liters, p<0.001). Lactated Ringers (LR) and normal saline were the two main types of

intravenous fluids administered in all regions except Latin America. LR was the dominant type of fluid in India (92%) in contrast to Latin America, where it was rarely used (7%, p <0.001). The major types of fluids given in Latin America were normal saline (61%) and Hartman's (32%); a balanced solution similar to LR, which is not widely available in this region.

The utilization of analgesics was markedly variable across the world. In Europe, non-steroidal anti-inflammatory medications (NSAIDs) comprised the mainstay of pain management (68%). Indian sites, however, used tramadol in 91% of their patients, while Latin American centers frequently used opioids (59%), NSAIDs (48%), and tramadol (34%). In contrast, opioid analgesics constituted the cornerstone of analgesia in North America at 93% of subjects in contrast to 27% in the remaining regions (p<0.001). Furthermore, 64% of subjects in North America were discharged on opioid analgesics compared to 2.7% in other geographic areas (p<0.001).

European centers had the highest ratio of enteral to parenteral nutrition at 10:1 (32% vs. 3% in subjects with moderate or severe disease); whereas, total parenteral nutrition (TPN) was most commonly administered in India in 27% of patients compared to 20% receiving enteral nutrition (ratio <1:1). The frequency of ERCP among subjects with biliary AP was significantly higher in North America (45% vs. 14% for the remaining sites, p<0.001). With respect to same admission cholecystectomy, considerable variations were noted among patients with mild acute biliary pancreatitis; it was performed in 60% of such patients in Latin America, while in only 15% in India (p<0.001). Moreover, early pancreatic interventions among patients with moderate or severe disease were more frequently performed in India (23% vs. 7% in the remaining regions, p<0.001).

Clinical Outcomes

When comparing the LOS among mild AP, patients in North America were found to stay in the hospital the shortest time (4 days) compared to other regions (7 days; p<0.001). Severe AP developed in 23% of Indian patients compared to 9% in the rest of world (p<0.001, Table 4). ICU admissions were highest in Indian centers at 37.9% (Table 5). In-hospital mortality was found to be the highest in Europe (5.7%), followed by India (3.3%), Latin America (2.3%), and North America (0.6%, p<0.001, Table 5). Among European sites included, in hospital mortality in different countries was distributed as such; Greece: 0%, Spain: 5%, Lithuania: 6.4%, and Romania: 8.6%.

Multivariate Analysis of outcomes:

Based on multivariable regression analyses that adjusted for potential confounders such as age, gender, BMI, Charlson score, etiology, transfer status, and other factors, the odds of severe AP were 11.2 times higher in Europe [95% confidence interval (CI): 5.8-21.6], 7 times higher in India (CI: 3.8-12.8), and 5.6 times higher in Latin America (CI: 2.8-11.1), compared to North America (p<0.001, Appendix Table 3). LOS was 4.3 days longer (CI: 3.5-5.4) in Europe, 1.1 days longer (CI: -0.1-2.3) in India, and 6.4 days longer (CI: 5.2-7.7) in Latin America when compared to North America (p<0.001, Appendix Table 4). The ORs for same-admission mortality among severe AP patients was 10.4 (CI: 2.7-40.5) in Europe, 4.2 (CI: 0.9-18.8) in India, and 8.3 (CI: 1.7-41.3) in Latin America when compared to North America (p<0.001, Appendix Table 5).

Discussion

In this large prospectively collected registry, significant differences in AP patient demographics, etiology, management approaches, severity and clinical outcomes were seen around the world.

Observed differences in etiology and demographics likely reflect a tight interconnection between age, gender, and etiology. In Indian sites, where the most preponderant AP etiology was alcohol, the majority of patients were young males. Previous studies have revealed a high proclivity of alcoholic pancreatitis in young Indian adults with heavy drinking patterns [2, 17-19]. More specifically, a recent study from India published in 2018 reported an average age of 40 years with alcoholic pancreatitis representing 42% of all etiologies [20]. In Latin American sites, females were the predominant gender with biliary etiology being the most common. Latin America is known to have the highest rate of gallstone disease (more common among women) compared to other parts of the world [21, 22]. A study in 2015 emanating from Argentina revealed similar findings, with biliary etiology accounting for 88% of all causes, and 58% of subjects being females[12]. Along the same lines, older age among subjects from Europe is congruent with a study published in 2018 from this region[13].

With regards to AP management, discrepancies in intravenous fluid volume and type administered over the first 24 hours are likely related to differences in accessibility to certain types of fluids, but most importantly, lack of high quality evidence supporting which type and what amount of fluid is optimal, as highlighted in the recent American Gastroenterological Association (AGA) guidelines in 2018 [23-27]. Our findings further support the need for adequately powered, multi-center, randomized controlled trials comparing the efficacy of different fluid resuscitation protocols in AP patients.

The finding of disproportionally higher rate of opioid prescription during hospitalization and at the time of discharge in the North American sites is alarming. Of interest, a meta-analysis comparing NSAIDs versus opioids for pain control in AP subjects revealed no difference in the efficacy between the two treatments [28, 29]. It not entirely clear why such divergences exist

between North American centers compared to the rest of the world. Notably, no clear statements are included in the current societal guidelines addressing optimal strategies for analgesia in AP.

Based on strong evidence, current guidelines recommend limited utilization of urgent ERCP only among biliary AP patients with suspicion of cholangitis or biliary obstruction[23]. Our study showed that the rate of ERCPs performed in patients with biliary AP was much higher in North American sites. Impressive discrepancies have been previously reported in different counties, i.e. 81% in Hungary, 52% in the United States, and 9% in Argentina [10-12]. The discrepancies observed in our study are difficult to explain; they are possibly related to referral bias, local practice patterns, as well as compensation structure differences .

Recent evidence supports same admission cholecystectomy among patients with biliary AP [23, 24]. Our study revealed that the rate of same admission cholecystectomy varied significantly with the highest seen in Latin America and lowest in India. Upon further discussion with site investigators, it appears that AP patients are traditionally admitted under surgical care in Latin America, making performance of inpatient cholecystectomy logistically easier. A recent publication from Latin America confirmed these findings, where 54% of biliary AP subjects underwent same admission cholecystectomy[12]. In contrast, the low rate of same admission cholecystectomy in India could be explained by the high rate of transfers in the participating sites combined with patient preference to undergo this relatively simple operation locally at a later time.

Robust evidence highlights the use of enteral nutrition over TPN, and delaying pancreatic interventions in patients with moderate and severe AP, which is endorsed by current practice guidelines [23 5, 30, 31]. These recommendations were least adhered to in Indian centers, which is possibly accentuated by the higher rate of transfers.

It is clear from the management practices seen in our study that the adherence to current evidence-driven societal guidelines varies significantly between different geographic regions of the world. Only a minority of the above practice patterns could be explained based on availability of resources. Thus, certain aspects of AP management such as the excessive administration of opioid analgesics and performance of ERCP in North American centers, overuse of TPN, and early pancreatic interventions in Indian sites, appear to lag behind the evidence. Additional effort is clearly needed to augment clinical implementation of certain therapeutic approaches supported by strong evidence in AP.

The finding that mild AP patients in North American centers had a shorter LOS compared to other regions is consistent with a recent report showing that the overall LOS of AP in the U.S. has decreased from 6.5 days in 1997 to 4.7 in 2015 [1]. This is likely related to incentive policies that have been applied over the last two decades in the U.S. resulting in shortening inpatient admissions[32].

Our study revealed higher death rate among European sites when compared to other geographic regions. . This observation could potentially be related to older age and higher rate of comorbid conditions seen in the European centers, both of which have been linked to mortality [33]. Notably, this difference persisted after adjustment for pertinent covariates in our multivariate analysis raising the question of other contributing factors. The lower mortality rate in North America seems consistent with recent reports indicating a decreased mortality over the last decade in the U.S, possibly related to improved quality of ICU care, and optimal timing for interventions [14, 34]. Factors pertaining to baseline health and socioeconomic factors could possibly have contributed to these dispcrepancies in mortality.

This study, has several strengths. It is the first of its kind to characterize differences in demographics, etiology, clinical profile, and management patterns and clinical outcomes in AP, by giving a snapshot of subject characteristics across different geographical regions of the world. Prior studies tackling this topic were limited by national bounds and lack of standardized methods for data acquisition. Distinctive attributes, which contribute to this study's strength, include its prospective nature, the large sample size with balanced representation between the different geographic areas with inclusion of at least 300 subjects from each studied region. Another important feature is the relatively recent time of data acquisition over the last 3 years, following the introduction of the RAC thus, accurately reflecting current practices [7, 24]. Moreover, most included sites were large, reputable institutions, with a high degree of expertise relating to pancreatic diseases. Furthermore, data collection was standardized, under rigorous monitoring resulting in a high data completeness rate, and quality. Finally, at the conclusion of the data collection process, in an attempt to better understand regional practice patterns, an additional step was undertaken in obtaining site investigators' input into explaining the observed results.

With regards to the study's limitations, certain parts of the world such as Africa, the Middle East, or East Asia, were not represented. Moreover, the majority of participating sites were academic tertiary care hospitals, which may introduce a bias potentially affecting the generalizability of our results. Especially in North America, major ERCP referral centers were included whose unusual practice mix may not reflect that of the typical large American hospital. Finally, the proportion of subjects enrolled in the study compared to all AP patients hospitalized at each site, varied based on available research resources.

In conclusion, we present a bird's eye view of the variations in clinical characteristics of AP patients across the world by using a large, prospective, international registry. There appears to be remarkable variations in frequency of AP etiologies in different regions. The therapeutic interventions specific to each region are in certain aspects strikingly divergent, and in many occasions lag behind current evidence. Outcomes, such as LOS and mortality, are largely variable. In addition to depicting key features of AP, the results from this study may serve as a reference guide for designing future clinical trials.

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Figure 1 legend: Centers' location and enrollment per center

Table 1: Characteristics of Participating Centers

Center	Geographic Area	Total Enrolled	Estimated # of Beds	Estimated # of AP Admissions/Year	Estimated rate of transfers
LUHS, Kaunas, Lithuania	Europe	109	>1000	100-200	50-75%
University of Medicine, Cluj-Napoca,	Europe	82	101-200	50-100	25-50%
University of Medicine, Bucharest, Romania	Europe	70	>1000	100-200	<25%
Sapienza University, Rome, Italy	Europe	69	301-500	50-100	<25%
Attikon University, Athens, Greece	Europe	59	501-750	50-100	<25%
Investigación, Alicante, Spain	Europe	20	751-1000	100-200	<25%
AIG, Hyderabad, India	India	136	201-300	200-300	>75%
Postgraduate Institute, Chandigarh, India	India	119	>1000	300-500	50-75%
Apollo Gleneagles, Kolkata, India	India	111	501-750	50-100	<25%
UAN, Monterrey, Mexico	Latin	95	301-500	100-200	<25%
Hospital Nacional, Itaugua, Paraguay	Latin	83	301-500	100-200	<25%
Nacional “Posadas”, Buenos Aires, Argentina	Latin	71	301-500	100-200	<25%
Universidad Autónoma, Mexico City, Mexico	Latin	47	201-300	50-100	25-50%
Hospital de Argudos, Buenos Aires, Argentina	Latin	29	301-500	50-100	25-50%
UPMC, Pittsburgh, USA	North	130	751-1000	100-200	50-75%
Johns Hopkins, Baltimore, USA	North	90	>1000	100-200	25-50%
Cleveland Clinic, Cleveland, USA	North	82	>1000	>500	25-50%
EMMC, Bangor, USA	North	81	301-500	100-200	25-50%
Indiana University, Indianapolis, USA	North	62	201-300	200-300	50-75%
AGH, Pittsburgh, USA	North	32	501-750	300-500	25-50%
MUSC, Charleston, USA	North	18	751-1000	200-300	50-75%
Kaiser, Los Angeles, USA	North	17	301-500	100-200	<25%

AP: acute pancreatitis, LUHS: Lithuanian University of Health Sciences, AIG: Asian Institute of Gastroenterology, UPMC: University of Pittsburgh Medical Center, UAN: Universidad Autónoma de Nueva , EMMC: Eastern Maine Medical Center.

Table 2: Comparison of AP patient demographics in different geographic regions.

Variable	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P Value
Age, Median (IQR)	58 (45-74)	39 (30-50)	43 (29-59)	52 (37- 65)	49 (34-64)	<0.001
Gender, Male (%)	203 (49.6)	274 (74.9)	108 (33.5)	258 (50.6)	843 (52.5)	<0.001
Ethnicity, Hispanic or Latino (%)	3 (0.7)	0 (0.0)	303 (97.4)	20 (4.0)	326 (20.6)	<0.001
Race (not Hispanic)						
- Asian Indian (%)	2 (0.5)	361(99.2)	0 (0.0)	6 (1.2)	36 (29.3)	<0.001
- Black or African - American (%)	0 (0.0)	0 (0.0)	0 (0.0)	82 (16.9)	82 (6.5)	
- White (%)	397 (99.3)	0 (0.0)	8 (100.0)	386 (79.4)	791 (62.9)	
- Others (%)	1 (0.3)	3 (0.8)	0 (0.0)	12 (2.5)	16 (1.3)	
CCI >1 (%)	298 (72.9)	132 (36.1)	153 (47.1)	314 (61.3)	897 (55.6)	<0.001
Obesity, BMI ≥ 30 (%)	111 (28.5)	27 (7.4)	86 (27.0)	220 (43.3)	444 (28.0)	<0.001
Etiology						
- Biliary (%)	206 (50.4)	102 (27.9)	249 (78.1)	170 (33.3)	727 (45.3)	<0.001
- Alcohol (%)	78 (19.1)	163 (44.5)	6 (1.9)	89 (17.5)	336 (20.9)	
- Idiopathic (%)	74 (18.1)	77 (21.0)	22 (6.9)	92 (18.0)	265 (16.5)	
- Hypertriglyceride mia (%)	19 (4.6)	7 (1.9)	19 (6.0)	30 (5.9)	75 (4.7)	
- Post-ERCP (%)	13 (3.2)	8 (2.2)	15 (4.7)	97 (19.0)	133 (8.3)	
- Other (%)	19 (4.6)	9 (2.5)	8 (2.5)	32 (6.3)	68 (4.2)	
Current smoking	103 (26.1)	95 (26.0)	38 (11.9)	129 (25.3)	365 (23.0)	<0.001
Current alcohol use	194 (49.1)	166 (45.4)	57 (17.9)	189 (37.1)	606 (38.1)	<0.001
Recurrent AP	95 (23.2)	75 (20.5)	42 (13.2)	185 (36.3)	397 (24.8)	<0.001
Transfers (%)	81 (19.8)	260 (71.0)	35 (11.0)	171 (33.5)	547 (34.1)	<0.001

AP: acute pancreatitis, IQR: inter-quartile range, CCI: charlson comorbidity index, BMI: Body mass index. P values were calculated based on Fisher's exact for categorical variables and Kruskal-Wallis global tests for continuous variables. Overall data completion rate was more than 95% for each of the variables

Table 3: Comparison of AP management practices in different regions.

Variable	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P value
Intravenous fluids						
- Amount, median (IQR)*	2.5 (2.0-3.6)	3.2 (2.0-4.5)	3.0 (2.5-3.8)	3.0 (2.0-4.2)	3.0 (2.0-4.0)	<0.001
- Type of fluid, LR (%)	315 (77.0)	337 (92.3)	24 (7.4)	253 (49.4)	930 (57.7)	<0.001
Inpatient pain management						
- NSAIDs (%)	277 (67.7)	1 (0.3)	155 (47.7)	91 (17.8)	524 (32.5)	<0.001
- Tramadol (%)	184 (45.0)	334 (91.3)	111 (34.2)	40 (7.8)	669 (41.5)	<0.001
- Opioids (%)	41 (11.9)	90 (24.9)	167 (59.0)	454 (92.5)	752 (50.8)	<0.001
Opioids at discharge (%)	1 (0.3)	2 (0.6)	17 (6.2)	314 (64.3)	334 (23.3)	<0.001
Nutritional support						
- Enteral Nutrition (%)**	34 (31.8)	43 (19.9)	15 (15.3)	46 (34.8)	138 (25.0)	<0.001
- TPN (%)**	3 (2.8)	59 (27.3)	4 (4.1)	9 (6.8)	75 (13.6)	<0.001
ERCP (%)¥	29 (14.4)	17 (16.8)	34 (14.1)	76 (44.7)	156 (21.9)	<0.001
Cholecystectomy (%)‡	52 (31.7)	6 (15.0)	101 (59.8)	52 (42.6)	211 (42.6)	<0.001
Early pancreatic intervention (%)**	9 (8.4)	50 (23.1)	5 (5.1)	9 (6.8)	73 (13.2)	<0.001

*LR: Lactated ringers; NSAIDs: Non steroidal Anti-Inflammatory Drugs. P values are based on Fisher's exact for categorical variables and Kruskall-Wallis global tests for continuous one. * Amount in liters within initial 24 hours of admission. ** Among RAC moderately severe or severe patients. ¥ Among Biliary AP patients. ‡ Among RAC mild biliary AP patients.*

Missing data: Narcotics use during hospitalization was missing in 65 patients in Europe, 4 in India, 23 in Latin America and 21 subjects in North America. Overall data completion rate for narcotics during hospitalization was 91.8%.

Narcotics at discharge were missing in 90 patients in Europe, 16 in India, 51 in Latin America and 24 subjects in North America. The overall data completion rate for Narcotics at discharge was 88.8% ; all other variables had overall data completion rate of over 95%.

Table 4: Comparison of AP severity in various regions of the world.

Severity based on RAC	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P Value*
-Mild (%)	296 (73.4)	148 (40.7)	213 (68.5)	374 (73.9)	1031 (65.1)	<0.001
-Mod. severe (%)	59 (14.6)	134 (36.8)	75 (24.1)	94 (18.6)	362 (22.9)	
-Severe (%)	48 (11.9)	82 (22.5)	23 (7.4)	38 (7.5)	191 (12.1)	

RAC: revised Atlanta classification. Data completion rate is more than 95%.

** Fisher's exact test was used as a global test to assess the association between regions and RAC severity.*

Table 5: Comparison of AP LOS, ICU admissions, and in hospital mortality among various regions within each RAC group and among all study participants.

LOS						
LOS per RAC groups	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P Value
-Mild AP, median (IQR)	7 (6-10)	7 (5-9)	10 (6-16)	4 (3-6)	6 (4- 10)	<0.001*
-Mod. severe, median (IQR)	11 (8.5-18)	10 (7- 15)	17 (8.-26)	8.0 (6-12.8)	11 (7- 16)	<0.001*
-Severe, median (IQR)	28 (25- 41)	19 (13-25)	19 (13-25)	20 (13.5-32.5)	20 (14- 31)	<0.001*
-Overall, median (IQR)	8 (6-12)	9 (6- 15)	11 (7-19)	5 (3-8)	8 (5-13)	<0.001**
ICU Admissions						
ICU per RAC groups	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P Value
-Mild AP (%)	2 (0.7)	18 (12.2)	0 (0.0)	9 (2.4)	29 (2.8)	<0.001¥
-Mod. severe (%)	11 (18.6)	54 (40.3)	3 (4.0)	26 (27.7)	93 (25.8)	<0.001¥
-Severe AP (%)	39 (81.2)	66 (80.5)	10 (43.5)	33 (86.8)	148 (77.5)	<0.001¥
-Overall (%)	54 (13.3)	138 (37.9)	13 (4.2)	68 (13.4)	273 (17.2)	<0.001¥¥
In Hospital Morality						
Mortality in various RAC groups	Europe (n=409)	India (n=366)	Latin America (n=325)	North America (n=512)	Total (n=1612)	P Value
-Mild AP (%)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	NA
-Mod. severe (%)	2 (3.4)	1 (0.8)	0 (0.0)	0 (0.0)	3 (0.8)	0.12¶
-Severe AP (%)	21 (43.8)	11 (13.4)	7 (30.4)	3 (7.9)	42 (28.2)	<0.001¶
-Overall (%)	23 (5.7)	12 (3.3)	7 (2.3)	3 (0.6)	45 (2.8)	<0.001¶¶

LOS: length of stay. Mod. severe: moderately severe; ICU: intensive care unit; RAC: revised Atlanta criteria. Data completion rate is more than 95%.

** Kruskal-Wallis test was used to assess the association between regions and LOS within different severity groups.*

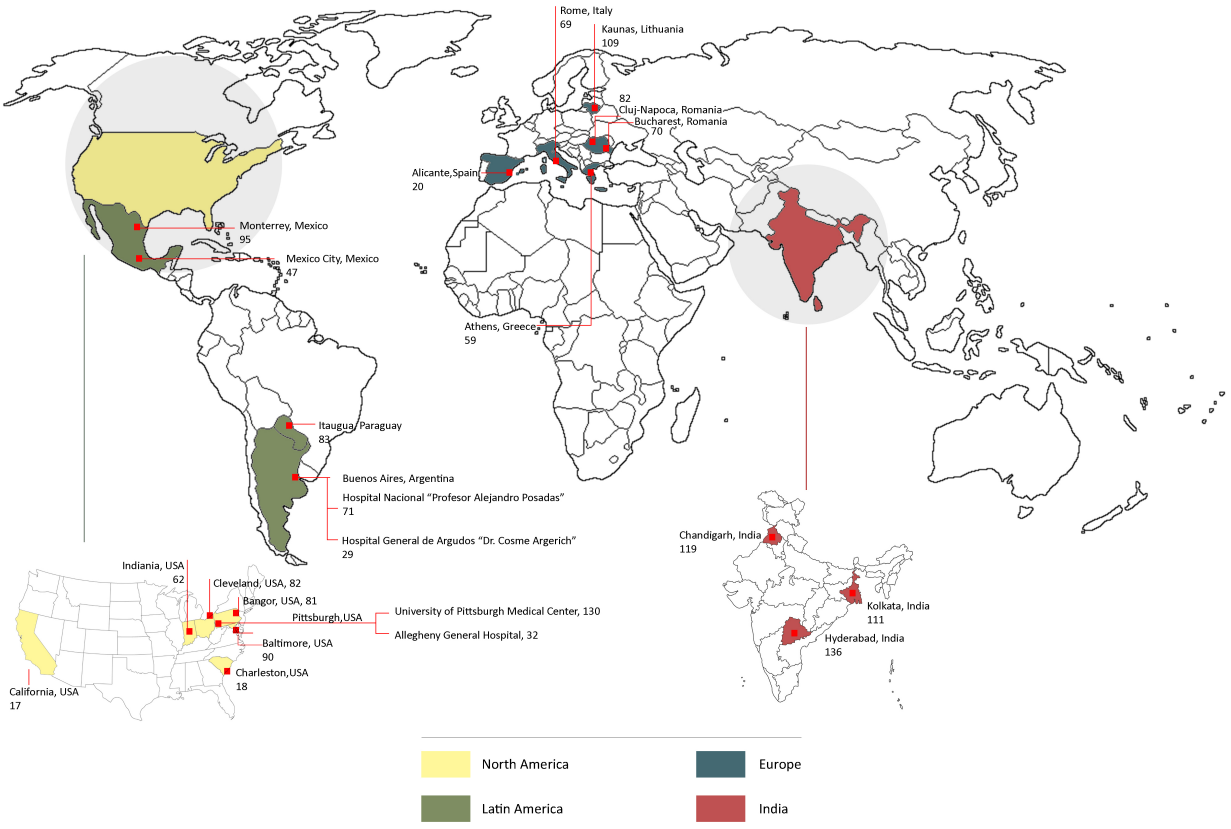
** * Kruskal-Wallis test was also applied for the association between regions and LOS among all participants.*

¥ *Fisher's exact test was used to assess the association between regions and ICU admissions within different severity groups.*

¥¥ *Fisher's exact test was also applied for the association between regions and ICU admissions among all study participants.*

¶ *Fisher's exact test was used to assess the association between region and mortality (assessed in moderately severe and severe groups; no death seen in mild AP group)*

¶¶ *Fisher's exact test was also applied for the association between hospital mortality and regions among all study participants.*


Rome, Italy
69
Kaunas, Lithuania
109
82
Cluj-Napoca, Romania
Bucharest, Romania
70
Alicante,Spain
20
Monterrey, Mexico
95
Mexico City, Mexico
47
Athens, Greece
59
Itaugua, Paraguay
83
Buenos Aires, Argentina
Hospital Nacional "Profesor Alejandro Posadas"
71
Hospital General de Argudos "Dr. Cosme Argerich"
29
Chandigarh, India
119
Kolkata, India
111
Hyderabad, India
136
Indiania, USA
62
Cleveland, USA, 82
Bangor, USA, 81
Pittsburgh,USA
University of Pittsburgh Medical Center, 130
Allegheny General Hospital, 32
Baltimore, USA
90
Charleston,USA
18
California, USA
17
North America
Europe
Latin America
India

Appendix Table 1. Study questionnaire.

(see attached PDF folder)

Appendix table 2: Definitions of collected variables.

Variable	Definition
AP diagnosis	At least 2 out 3 three criteria: 1) upper abdominal pain characteristic of AP 2) serum amylase and/or lipase ≥ 3 times the upper limit of normal 3) imaging findings characteristic of AP
Current smoking	Active smoking within 6 months prior to admission
Current alcohol use	AP preceded by heavy alcohol consumption as determined by site investigators
Alcoholic AP	AP preceded by heavy alcohol consumption as determined by site investigators
Biliary AP	AP with objective evidence of cholelithiasis or choledocholithiasis on imaging, and no other plausible explanation for pancreatitis as determined by site investigators
Hypertriglyceridemia induced AP	AP occurring in setting of a high serum triglyceride level (>500 mg/dL) with exclusion of other causes. Post ERCP AP: development of AP within 24 hours of ERCP
Other cause of AP	AP with the presence of a clear inciting factor, such as a suspected medication.
Idiopathic AP	AP not fitting any of the above mentioned categories
Early pancreatic interventions	Open surgical, minimally invasive, endoscopic, or percutaneous approaches in drainage or debridement, performed within 2 weeks of admission
Organ Failure	Score >1 on the modified Marshal system for cardiovascular, pulmonary, or renal failure
Time of admission	Time of index presentation to hospital; in cases where subjects were transferred from outside hospitals, time of admission referred to the original presentation to the hospital, and total LOS included the duration of stay in both the primary and referral center
Enteral nutrition	Nutrition by means of a feeding tube (nasogastric or nasojejunal)
Parenteral nutrition	Intravenous nutrition (subjects who received both enteral and parenteral nutrition were categorized as having received parenteral nutrition)
Mortality	Death during the same hospitalization
Systemic inflammatory response syndrome	Positive when at least 2 of the following criteria were present: 1) Heart rate >90

	2) Body temperature >38□ or <36□ 3) White blood cell count >12000/mm3 or <4000/ mm3 4) Respiratory rate >20

AP: acute pancreatitis; LOS: length of stay.

Appendix table 3. Multivariate logistic regression model that compares severity of AP (severe AP vs. mild/moderately severe APs) among regions

Variables	OR (95% CI)	p-value
Regions (vs. North America)		<0.001*
Europe	11.2 (5.8,21.6)	<0.01
India	7.0 (3.8,12.8)	<0.01
Latin America	5.6 (2.8,11.1)	<0.01
Age	1.0 (1.0,1.0)	0.28
Gender (Male)	1.9 (1.2,2.8)	<0.01
BMI (>=30)	1.4 (0.9,2.1)	0.13
Charlson score (>1)	0.7 (0.4,1.3)	0.29
Etiology (vs. Biliary)		0.045*
Alcoholic	1.5 (0.9,2.5)	0.11
Post-ERCP	1.2 (0.5,2.8)	0.67
Other	1.0 (0.6,1.7)	0.91
Transfer (Yes)	5.8 (3.7,9.0)	<0.01
Cholecystectomy (Yes)	0.3 (0.1,0.7)	<0.01
Opioid Use (Yes)	5.2 (3.4,8.1)	<0.01

** The likelihood ratio tests were used for the association between severity of AP and factors with more than 2 categories (region and etiology).*

A backward model selection procedure was followed

Appendix table 4. Multivariable linear regression model that compares length of stay (LOS) among regions.

Variable	Beta (95% CI)	p-value
Regions (vs. NA)		<0.001*
EU	4.3 (3.3,-5.4)	<0.01
IND	1.1 (-0.1,-2.3)	0.07
LA	6.4 (5.2,7.7)	<0.01
Age	0.0 (0.0,0.0)	0.79
Gender (Male)	0.2 (-0.6,1.1)	0.94
BMI (>=30)	0.1 (-0.8,1.0)	0.45
Charlson score (>1)	0.1 (-1.2,1.4)	0.57
Etiology (vs Biliary)		0.02*
Alcoholic	0.9 (-0.3,2.2)	0.13
Post-ERCP	0.1 (-1.4,1.6)	0.87
Other	0.3 (-0.8,1.3)	0.59
Transfer (Yes)	2.2 (1.3,3.1)	<0.01
Cholecystectomy (Yes)	4.6 (3.5,5.8)	<0.01
RAC (vs Moderate)		<0.01*
Mild	-5.6 (-6.6,-4.7)	<0.01
Severe	10.6 (9.1,12.0)	<0.01

** The likelihood ratio tests were used for the association between LOS of AP and factors with more than 2 categories (region etiology and severity).*

A backward model selection procedure was followed

Appendix table 5. Multivariable logistic regression that compares mortality in patients with severe AP among regions.

Variables	OR (95% CI)	p-value
Regions (vs NA)		<0.001*
EU	10.4 (2.7,40.5)	0.06
IND	4.2 (0.9,18.8)	<0.01
LA	8.3 (1.7,41.3)	<0.01
Age	1.0 (1.0,1.1)	0.02
Gender (Male)	1.4 (0.6,3.4)	0.46
BMI (>=30)	2.0 (0.8,5.0)	0.13
Charlson score (>1)	1.2 (0.3,4.5)	0.65

** The likelihood ratio test was used for the association between mortality of AP and regions.*

A backward model selection procedure was followed

Demographics

Record ID _____

All variables in brackets should preferably be obtained by interviewing the patient

Patient initials _____
(First name initial, last name initial)

Age _____
(Age in years)

Gender
◯ Female
◯ Male

{Race}
◯ White or Caucasian (not Hispanic)
◯ Hispanic or Latino
◯ Native American
◯ Black or African American
◯ Asian Indian
◯ Asian Oriental
◯ Asian Middle East
◯ Native Hawaiian or Other Pacific Islander
◯ Other

{Weight} (kg) _____
(Patient weight in kilograms)

{Height} (cm) _____
(Patient height in centimeters)

BMI (Body Mass Index) _____

{Waist size} (inches) _____
(The waist size can be estimated based on the patient's pants size. Use the following chart to transform the pants size to waist size in cm.)

waist size chart

Men's Size	Waist
XS	28.5-29
S	29.5-31
M	31.5-34
L	34.5-38
XL	38.5-42
XXL	42.5-43

Women's Size	Waist
XXS	23
XS	24-25
S	26-27
M	28-29.5
L	31-32.5
XL	34-35.5
XXL	37-39

History of Present Illness (Acute Pancreatitis)

{Date and time of Pain Onset}

_____
(Date and time when the characteristic upper abdominal pain of acute pancreatitis started)

{Date and time of initial presentation to the hospital}

_____
(Date and time of initial presentation to emergency room, or direct admission to hospital)

Transfer

◯ Yes
◯ No
(It applies when the patient transfers from the hospital where he/she initially presented to a different hospital (referral center) for further management)

Date and time of admission to referral center

_____

Acute Pancreatitis primary etiology	◯ Gallstones ◯ Alcoholic ◯ Idiopathic ◯ Hypertriglyceridemia-induced ◯ Post-ERCP (Endoscopic Retrograde Cholangiopancreatography) ◯ Other (Select the most prominent etiology. Idiopathic acute pancreatitis is defined as of no clear etiology after laboratory work-up has been completed and other common etiologies have been excluded; Hypertriglyceridemia-induced acute pancreatitis is confirmed when common etiologies have been excluded and serum triglycerides are >500 mg/dL)
Other cause	_____ (Please write the other etiology responsible for causing Acute Pancreatitis)
Is there any secondary etiology?	◯ Yes ◯ No
Acute Pancreatitis secondary etiology	◯ Gallstones ◯ Alcoholic ◯ Idiopathic ◯ Hypertriglyceridemia-induced ◯ Post-ERCP (Endoscopic Retrograde Cholangiopancreatography) ◯ Other
Date and time of ERCP in the case of post-ERCP Acute Pancreatitis	_____ (ERCP stands for Endoscopic Retrograde Cholangiopancreatography)

Medications

{NSAIDS use}	◯ Yes ◯ No (This refers to even single dose of Non Steroidal Anti Inflammatory Drugs (NSAIDS) taken within the last 7 days from the onset of acute pancreatitis. NSAIDS include aspirin, ibuprofen, indomethacin, naproxen, celecoxib, ketorolac, diclofenac, sulindac, etc)
Statin use	◯ Yes ◯ No (This refers to daily use of statin before the onset of acute pancreatitis. Statins include atrovastatin, simvastatin, pravastatin, fluvastatin, etc)
Medications within the last one month	_____ (Please write down the names of medications which were started within the last one month prior to pain onset.)

Past Medical History

History of Acute Pancreatitis	◯ First episode ◯ Recurrent episode (at least one episode before)
{Number of prior acute pancreatitis episodes}	_____
Prior cholecystectomy	◯ Yes ◯ No
History of Pre-existing Hypertriglyceridemia	◯ Yes ◯ No (Presence of Hypertriglyceridemia before onset of acute pancreatitis.)
Baseline Triglyceride (TG) level	_____ (TG levels before this episode of acute pancreatitis (if TG level measurements are available from prior admissions or visits))
Preexisting Diabetes Mellitus (DM)	◯ Yes ◯ No (Presence of diabetes mellitus before the onset of acute pancreatitis)
Diabetes Mellitus (DM) type	◯ Type 1 ◯ Type 2 non-insulin dependent/diet controlled ◯ Type 2 non-insulin dependent/on antidiabetics ◯ Type 2 insulin dependent (Type of preexisting diabetes mellitus)
End-organ damage due to Diabetes Mellitus	◯ Yes ◯ No (End organ damage includes retinopathy, neuropathy, or nephropathy)
Congestive Heart Failure (CHF)	◯ Yes ◯ No (Symptomatic congestive heart failure, i.e. NYHA functional class ≥III)
Myocardial infarction	◯ Yes ◯ No (History of medically documented myocardial infarction)
Peripheral artery disease	◯ Yes ◯ No (History of intermittent claudication, peripheral arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aortic aneurysm (>=6cm))
Cerebrovascular disease	◯ Yes ◯ No (History of Transient Ischemic Attack (TIA), or Cerebral Vascular Attack (stroke) with no or minor sequelae)

Dementia	◯ Yes ◯ No (Chronic cognitive deficit, i.e. Mini-Mental Status Exam(MMSE) ≤26)
Chronic pulmonary disease	◯ Yes ◯ No (Symptomatic dyspnea due to chronic respiratory conditions (including asthma))
Connective tissue disorders	◯ Yes ◯ No (Connective tissue disorders include Lupus, Polymyositis, mixed Connective Tissue Disorders, Polymyalgia Rheumatica, moderate to severe Rheumatoid Arthritis)
Peptic Ulcer Disease (PUD)	◯ Yes ◯ No (Patients who have required treatment for peptic ulcer disease)
Liver disease	◯ No ◯ Mild ◯ Moderate to severe (Mild means chronic liver disease with/without compensated cirrhosis. Moderate to severe means decompensated cirrhosis (includes: ascites, portosystemic encephalopathy, or history of variceal bleeding))
Renal disease	◯ No ◯ Mild ◯ Moderate to severe (Mild means Cr >1.5 mg/dL (133 µmol/L) and less than 3 mg/dL (265 µmol/L). Moderate to severe means creatinine > 3 mg/dL (265 µmol/L), history of renal transplantation, history of dialysis or history of uremic syndrome)
Hemiplegia (or paraplegia)	◯ Yes ◯ No (Hemiplegia means impairment in motor function of one side of the body. Papaplegia means impairment in motor function of lower extrimities.)
Solid tumor	◯ Yes ◯ No (Tumors diagnosed within the last 5 years (pancreatic cancers, non-melanomatous skin cancers, and in situ cervical carcinomas are excluded))
Metastasis of solid tumor	◯ Yes ◯ No
Leukemia	◯ Yes ◯ No (Including chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, polycytemia vera)

Lymphoma

◯ Yes
◯ No
(Including Non-Hodgkin, Hodgkin, Waldenstrom macroglobulinemia, Multiple Myeloma)

AIDS (not just positive HIV test)

◯ Yes
◯ No
(Acquired Immune Deficiency Syndrome (AIDS) defined as confirmed positive Human Immunodeficiency Virus (HIV) test plus either CD4 count < 250 or any HIV-related complications)

Social History

{Smoking}

◯ Never (< 100 cigarettes or 5 packs in lifetime)
◯ Active (within the last 6 months)
◯ Former (>6 months without smoking)

{Total years of smoking}

_____
(How many years has the patient smoked in total?)

{Average number of cigarettes per day}

_____
(How many cigarettes on average does/did the patient smoke per day?)

{Alcohol consumption}

◯ Never (< 20 drinks in lifetime)
◯ Active (within the last 6 months)
◯ Former (>6 months without drinking)
(Does the patient drink alcohol?)

{Date/time of last drink}

_____
(When was the last alcoholic drink?)

{Total years of alcohol consumption}

_____

{Average drinking days per week}

_____
(How many days on average does/did the patient drink per week?)

{Average drinks on a drinking day}

_____
(How many drinks on average does/did the patient drink on a drinking day?)

Family History

Family history of Acute Pancreatitis

◯ Yes
◯ No
(Does the patient have any first-degree relatives diagnosed with acute pancreatitis (first-degree relatives include parents, siblings, or children))

Family history of Chronic Pancreatitis

◯ Yes
◯ No
(Does the patient have any first-degree relatives diagnosed with chronic pancreatitis (first-degree relatives include parents, siblings, or children))

Family history of Cystic Fibrosis (CF)	◯ Yes ◯ No (Does the patient have any first-degree relatives diagnosed with cystic fibrosis (first-degree relatives include parents, siblings, or children))

On Admission

Record ID _____

Vital Signs

Temperature on admission (in Celsius, with 1 decimal) _____
(Temperature measured upon presenting to initial hospital (not transferred hospital))

Heart rate on admission (beats/min) _____
(Heart rate recorded upon presenting to initial hospital (not transferred hospital))

Respiratory rate on admission (breaths/min) _____
(Respiratory rate recorded upon presenting to initial hospital (not transferred hospital))

Physical Examination

Pain on admission _____
(On scale of 0-10, what was the worst pain in the last 12 hours from admission?)

Nausea/vomiting on admission
◯ Yes
◯ No
◯ unavailable
(Did the patient have nausea or vomiting in the last 12 hours from admission?)

Rebound tenderness/guarding on admission
◯ Yes
◯ No
◯ unavailable
(Rebound tenderness refers to presence of pain that is more intense when the examiner releases pressure than when palpating the abdomen. Guarding refers to spasm of abdominal wall muscles detected on palpation.)

Altered mental status on admission
◯ Yes
◯ No
(It refers to disorientation, somnolence, lethargy, stupor, or coma)

Pleural effusions assessed within 24 hours
◯ Yes
◯ No
◯ unavailable
(Pleural effusions identified on physical exam, chest X-ray or computed tomography (CT) scan within 24 hours from presentation)

Laboratory Markers

Are the laboratory markers available from the time of admission?

◯ Yes
◯ No
(Are the laboratory markers available from the time of admission to the primary center?)

WBC on admission (x,xxx/micro-liters)

_____
(White blood count measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Hematocrit on admission (%, with 1 decimal)

_____
(Hematocrit measured upon presenting to initial hospital (not the referal hospital in case of transfer))

BUN on admission (mg/dL)

_____
(Blood urea nitrogen measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Creatinine on admission (mg/dL, with 1 decimal)

_____
(Creatinine measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Lipase level on admission

_____
(Lipase measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Lipase Upper Limit of Normal

_____

Admission in this questionnaire refers to the time that the patient presented to the initial center and not the transferred center.

At 24 hours

Record ID _____

Vital Signs

Temperature at 24 hours (in Celsius, with 1 decimal)
_____
(Highest temperature recording between 12-24 hours from admission)

Heart rate at 24 hours (beats/min)
_____
(Highest heart rate recording between 12-24 hours from admission)

Respiratory rate at 24 hours (breaths/min)
_____
(Highest respiratory rate recording between 12-24 hours from admission)

Physical Examinations

Pain at 24 hours
_____
(On scale of 0-10, what was the worst pain between 12-24 hours from admission?)

Nausea/vomiting at 24 hours
◯ Yes
◯ No
(Did the patient have nausea or vomiting between 12-24 hours from admission?)

Laboratory Markers

WBC at 24 hours (x,xxx/microliters)
_____
(Highest white blood count measured between 12-24 hours from admission)

Hematocrit at 24 hours (%, with 1 decimal)
_____
(Highest hematocrit measured between 12-24 hours from admission)

BUN at 24 hours (mg/dL)
_____
(Highest blood urea nitrogen between 12-24 hours from admission)

Creatinine at 24 hours (mg/dL, with 1 decimal)
_____
(Highest creatinine measured between 12-24 hours from admission)

Lipase level at 24 hours
_____
(Lipase measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Lipase Upper Limit of Normal
_____

Intravenous Fluid Therapy

Type of intravenous fluids within first 6 hours of presentation

- ☐ No intravenous fluid
- ☐ Normal saline
- ☐ Lactated Ringers
- ☐ Other
- ☐ Unavailable

(Type of intravenous fluids administered within first 6 hours since patient presentation to initial hospital)

Other Intravenous Fluids

_____

(Please write the name of the other intravenous fluids which were used within 6 hours of admission)

Amount of normal saline within first 6 hours of presentation (in milliliters)

_____

(How much normal saline was administered within first 6 hours since patient presentation to initial hospital ? Add boluses and continuing drips.)

Amount of lactated ringers within first 6 hours of presentation (in milliliters)

_____

(How much lactated ringers was administered within first 6 hours since patient presentation to initial hospital ?)

Amount of other intravenous fluids within first 6 hours of presentation (in milliliters)

_____

(How much other intravenous fluids was administered within 6 hours since patient presentation to initial hospital ?)

Type of intravenous fluids within the first 24 hours

- ☐ Normal saline
- ☐ Lactated Ringers
- ☐ Other
- ☐ Unavailable

(Type of intravenous fluids administered during the first 24 hours from admission including the first 6 hours)

Other Intravenous Fluids

_____

(Please write the name of the other intravenous fluids which were used within 24 hours of admission)

Total amount of normal saline within the first 24 hours (in milliliters)

_____

(Includes total amount of normal saline given during the first 24 hours from admission)

Total amount of lactated ringers within the first 24 hours (in milliliters)

_____

(Includes lacted ringers given during the first 24 hours from admission)

Total amount of other intravenous fluids within the first 24 hours (in milliliters)

_____

(Includes other IVFs given during the first 24 hours from admission)

Pain Management

Narcotics (day 1)

◯ Yes
◯ No
◯ unavailable
(Were oral or parenteral narcotics administered?)

Common Narcotics

☐ Morphine (IV, SC)
☐ Morphine (PO)
☐ Fentanyl (IV, SC)
☐ Hydromorphone (PO)
☐ Hydromorphone (IV, SC)
☐ Oxycodone (PO)
☐ Oxymorphine (PO)
☐ Hydrocodone (PO)
☐ Codeine combinations (PO)
☐ Methadone
☐ Meperidine (PO)
☐ Meperidine (SC, IV)
(All doses are in milligrams)

Total amount of Morphine (IV, SC) administered during the first 24 hours of admission _____

Total amount of Morphine (PO) administered during the first 24 hours of admission _____

Total amount of Fentanyl (IV) administered during the first 24 hours of admission _____

Total amount of Hydromorphine (PO) administered during the first 24 hours of admission _____

Total amount of Hydromorphine (IV, SC) administered during the first 24 hours of admission _____

Total amount of Oxycodone (PO) administered during the first 24 hours of admission _____

Total amount of Oxymorphine (PO) administered during the first 24 hours of admission _____

Total amount of Hydrocodone (PO) administered during the first 24 hours of admission _____

Total amount of Codeine combinations (PO) administered during the first 24 hours of admission _____

Total amount of Methadone (PO) administered during the first 24 hours of admission _____

Total amount of Meperidine (PO) administered during the first 24 hours of admission _____

Total amount of Meperidine (IV) administered during the first 24 hours of admission _____

Other types of analgesics

☐ NSAIDS
☐ Tramadol
☐ Epidural Analgesia
☐ Other

At 48 hours

Record ID _____

Vital Signs

Temperature at 48 hours (in Celsius, with 1 decimal) _____
(Highest temperature recording between 36-48 hours from admission)

Heart rate at 48 hours (beats/min) _____
(Highest heart rate recording between 36-48 hours from admission)

Respiratory rate at 48 hours (breaths/min) _____
(Highest respiratory rate recording between 36-48 hours from admission)

Physical Examinations

Pain at 48 hours _____
(On scale of 0-10, what was the worst pain between 36-48 hours from admission)

Nausea/vomiting at 48 hours
◯ Yes
◯ No
(Did the patient have nausea or vomiting between 36-48 hours from admission?)

Laboratory Markers

WBC at 48 hours (x,xxx/microliters) _____
(Highest white blood count measured between 36-48 hours from admission)

Lipase level at 48 hours _____
(Lipase measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Lipase Upper Limit of Normal _____

Pain Management

Narcotics (day 2)
◯ Yes
◯ No
◯ unavailable
(Were oral or parenteral narcotics administered?)

Common Narcotics (day 2)

- ☐ Morphine (IV, SC)
- ☐ Morphine (PO)
- ☐ Fentanyl (IV, SC)
- ☐ Hydromorphone (PO)
- ☐ Hydromorphone (IV, SC)
- ☐ Oxycodone (PO)
- ☐ Oxymorphine (PO)
- ☐ Hydrocodone (PO)
- ☐ Codeine combinations (PO)
- ☐ Methadone
- ☐ Meperidine (PO)
- ☐ Meperidine (SC, IV)

(All doses are in milligrams)

Total amount of Morphine (IV, SC) administered within 25-48 hours from admission _____

Total amount of Morphine (PO) administered within 25-48 hours from admission _____

Total amount of fentanyl (IV) administered within 25-48 hours from admission _____

Total amount of Hydromorphone (PO) administered within 25-48 hours from admission _____

Total amount of Hydromorphone (IV, SC) administered within 25-48 hours from admission _____

Total amount of Oxycodone (PO) administered within 25-48 hours from admission _____

Total amount of Oxymorphine (PO) administered within 25-48 hours from admission _____

Total amount of Hydrocodone (PO) administered within 25-48 hours from admission _____

Total amount of Codeine combinations (PO) administered within 25-48 hours from admission _____

Total amount of Methadone (PO) administered within 25-48 hours from admission _____

Total amount of Meperidine (PO) administered within 25-48 hours from admission _____

Total amount of Meperidine (IV) administered within 25-48 hours from admission _____

Other types of analgesics (day 2)

- ☐ NSAIDS
- ☐ Tramadol
- ☐ Epidural Analgesia
- ☐ Other

At 72 Hours

Record ID _____

Is the patient still in the hospital?
◯ Yes
◯ No

Vital Signs

Temperature at 72 hours (in Celsius, with 1 decimal) _____
(Highest temperature recording between 60-72 hours from admission)

Heart rate at 72 hours (beats/min) _____
(Highest heart rate recording between 60-72 hours from admission)

Respiratory rate at 72 hours (breaths/min) _____
(Highest respiratory rate recording between 60-72 hours from admission)

Physical Examinations

Pain at 72 hours _____
(On scale of 0-10, what was the worst pain between 60-72 hours from admission?)

Nausea/vomiting at 72 hours
◯ Yes
◯ No
(Did the patient have nausea or vomiting between 60-72 hours from admission?)

Laboratory Markers

WBC at 72 hours (x,xxx/microliters) _____
(Highest white blood count measured between 60-72 hours from admission)

Lipase level at 72 hours _____
(Lipase measured upon presenting to initial hospital (not the referal hospital in case of transfer))

Lipase Upper Limit of Normal _____

Pain Management

Narcotics (day 3)

◯ Yes
◯ No
◯ unavailable
(Were oral or parenteral narcotics administered?)

Common Narcotics (day 3)

☐ Morphine (IV, SC)
☐ Morphine (PO)
☐ Fentanyl (IV, SC)
☐ Hydromorphone (PO)
☐ Hydromorphone (IV, SC)
☐ Oxycodone (PO)
☐ Oxymorphine (PO)
☐ Hydrocodone (PO)
☐ Codeine combinations (PO)
☐ Methadone
☐ Meperidine (PO)
☐ Meperidine (SC, IV)
(All doses are in milligrams)

Total amount of Morphine (IV, SC) administered within 49-72 hours from admission _____

Total amount of Morphine (PO) administered within 49-72 hours from admission _____

Total amount of fentanyl (IV) administered within 49-72 hours from admission _____

Total amount of Hydromorphone (PO) administered within 49-72 hours from admission _____

Total amount of Hydromorphone (IV, SC) administered within 49-72 hours from admission _____

Total amount of Oxycodone (PO) administered within 49-72 hours from admission _____

Total amount of Oxymorphine (PO) administered within 49-72 hours from admission _____

Total amount of Hydrocodone (PO) administered within 49-72 hours from admission _____

Total amount of Codeine combinations (PO) administered within 49-72 hours from admission _____

Total amount of Methadone (PO) administered within 49-72 hours from admission _____

Total amount of Meperidine (PO) administered within 49-72 hours from admission _____

Total amount of Meperidine (IV) administered within 49-72 hours from admission _____

Other types of analgesics (day 3)

☐ NSAIDS
☐ Tramadol
☐ Epidural Analgesia
☐ Other

On day 7

Record ID _____

Vital Signs

Is the patient still in the hospital?
◯ Yes
◯ No

Temperature at 7 days (in Celsius,, with 1 decimal)
_____
(Highest temperature recording between 156-168 hours from admission)

Heart rate at 7 days (beats/min)
_____
(Highest heart rate recording between 156-168 hours from admission)

Respiratory rate at 7 days (breaths/min)
_____
(Highest respiratory rate recording between 156-168 hours from admission)

Physical Examinations

Pain at 7 days
_____
(On scale of 0-10, what was the worst pain between 156-168 hours from admission?)

Nausea/vomiting at 7 days
◯ Yes
◯ No
(Did the patient have nausea or vomiting between 156-168 hours from admission?)

Laboratory Markers

WBC at 7 days (x,xxx/microliters)
_____
(Highest white blood count measured between 156-168 hours from admission)

Pain Management

Narcotics (day 7)
◯ Yes
◯ No
◯ unavailable
(Were oral or parenteral narcotics administered?)

Common Narcotics (day 7)

- ☐ Morphine (IV, SC)
- ☐ Morphine (PO)
- ☐ Fentanyl (IV, SC)
- ☐ Hydromorphone (PO)
- ☐ Hydromorphone (IV, SC)
- ☐ Oxycodone (PO)
- ☐ Oxymorphine (PO)
- ☐ Hydrocodone (PO)
- ☐ Codeine combinations (PO)
- ☐ Methadone
- ☐ Meperidine (PO)
- ☐ Meperidine (SC, IV)

(All doses are in milligrams)

Total amount of Morphine (IV, SC) administered during the day 7 of admission _____

Total amount of Morphine (PO) administered during 7th days of admission _____

Total amount of fentanyl (IV) administered during 7th days of admission _____

Total amount of Hydromorphone (PO) administered during 7th days of admission _____

Total amount of Hydromorphone (IV, SC) administered during 7th days of admission _____

Total amount of Oxycodone (PO) administered during 7th days of admission _____

Total amount of Oxymorphine (PO) administered during 7th days of admission _____

Total amount of Hydrocodone (PO) administered during 7th days of admission _____

Total amount of Codeine combinations (PO) administered during 7th days of admission _____

Total amount of Methadone (PO) administered during 7th days of admission _____

Total amount of Meperidine (PO) administered during 7th days of admission _____

Total amount of Meperidine (IV) administered during 7th days of admission _____

Other types of analgesics (day 7

- ☐ NSAIDS
- ☐ Tramadol
- ☐ Epidural Analgesia
- ☐ Other

At discharge

Record ID _____

Laboratory Markers

Discharge date _____
(Date the patient was discharged.)

SIRS (Systemic inflammatory response syndrome) criteria

SIRS
defined by presence of two or more criteria
Heart rate >90 beats/min
Core temperature <36°C or >38°C
White blood count <4000 or >12000/mm3
Respirations >20/min or PCO2 <32 mm Hg13

SIRS (Systemic inflammatory response syndrome)
◯ Yes
◯ No
(Did the patient develop positive SIRS during hospitalization?)

Date and time of SIRS onset
◯ Admission
◯ Day 1
◯ Day 2
◯ Day 3
◯ After day 3
(When did the patient develop positive SIRS for the first time?)

SIRS duration
◯ Less than 48 hours
◯ More than 48 hours
(How many hours in total did the patient have positive SIRS until resolution or organ failure development?)

Triglyceride measurement
◯ Yes
◯ No
(Are serum Triglyceride (TG) levels available within 48 hours of admission?)

Date and time of Triglyceride measurement _____

Triglyceride level (mg/dL)

_____
(Highest triglyceride level measured within 48 hours of admission)

Management/Narcotics

Total days of narcotics administered

_____
(How many days did the patient receive narcotics (oral or intravenous)?)

Management/ICU

Intensive Care Unit (ICU) admission

◯ Yes
◯ No
(Was the patient admitted to ICU for further care?)

Date and time of intensive care unit (ICU) admission

_____

Death while in Intensive Care Unit (ICU)

◯ Yes
◯ No

Intensive Care Unit (ICU) length of stay (days)

_____
(length of ICU stay in days; when multiple ICU admissions during same hospitalization, record the total length of stay)

Management/Nutrition

Date and time of initial feeding attempt

_____
(Initial feeding attempt includes: oral intake, enteral, or parenteral nutrition)

Type of initial oral feeding

◯ clear liquid
◯ full liquid
◯ soft mechanical
◯ low-fat
◯ regular diet
(Which type of oral diet was tolerated by patient in initial feeding?)

Initial feeding route

◯ Oral
◯ Enteral nutrition- gastric route [Nasogastric (NG) or Percutaneous endoscopic gastrostomy(PEG)]
◯ Enteral nutrition- enteral route [Nasojejunal (NJ) or Percutaneous endoscopic jejunostomy (PEJ)]
◯ Total parenteral nutrition (TPN)
(Which feeding route was attempted initially after acute pancreatitis onset?)

Tolerance of initial feeding attempt

◯ Yes
◯ No
(Did the patient tolerate the initial feeding attempt (for at least 24 hours) ?)

Second feeding attempt
◯ Yes
◯ No
(Was there second and different feeding attempt?)

Route of second feeding attempt
◯ Oral
◯ Enteral nutrition- gastric route [Nasogastric (NG) or Percutaneous endoscopic gastrostomy(PEG)]
◯ Enteral nutrition- enteral route [Nasojejunal (NJ) or Percutaneous endoscopic jejunostomy (PEJ)]
◯ Total parenteral nutrition (TPN)
(Which feeding route was used following initial feeding attempt?)

Date and time of second feeding attempt
_____
(When did the patient start second different feeding following initial attempt?)

Type of second oral feeding
◯ clear liquid
◯ full liquid
◯ soft mechanical
◯ low-fat
◯ regular diet
(Which type of oral diet was tolerated by patient in second feeding?)

Tolerance of second feeding
◯ Yes
◯ No
(Did the patient tolerate the second feeding attempt (for at least 24 hours)?)

Third feeding attempt
◯ Yes
◯ No
(Was there third different feeding attempt?)

Date and time of third feeding
_____
(When did the patient start third different feeding following second attempt?)

Route of third feeding attempt
◯ no
◯ Oral
◯ Enteral nutrition- gastric route [Nasogastric (NG) or Percutaneous endoscopic gastrostomy(PEG)]
◯ Enteral nutrition- enteral route [Nasojejunal (NJ) or Percutaneous endoscopic jejunostomy (PEJ)]
◯ Total parenteral nutrition (TPN)
(What feeding route was used in third feeding attempt?)

Type of third oral feeding
◯ clear liquid
◯ full liquid
◯ soft mechanical
◯ low-fat
◯ regular diet
(Which type of oral diet was tolerated by patient in third feeding?)

Tolerance of third feeding
◯ Yes
◯ No
(Did the patient tolerate the third feeding attempt (for at least 24 hours)?)

Oral tolerance
_____
(When did the patient tolerate oral feeding (for at least 24 hours)?)

Management/Early Intervention

Early pancreatic intervention
◯ Yes
◯ No
(Early intervention on the pancreas or peripancreatic tissues within 2 weeks from presentation (ERCP and cholecystectomy are excluded))

Type of early pancreatic intervention
◯ Drainage only
◯ Drainage and debridement
(Early pancreatic intervention can include only drrainage of necroma, or both drainage and necrosectomy (debridement))

Mode of early pancreatic intervention
☐ Laparotomy
☐ Minimally invasive surgery (laparoscopic, retroperitoneal, etc)
☐ Percutaneous catheter drainage
☐ Endoscopic drainage/debridement

Date of early pancreatic intervention
_____
(The date of intervention on pancreas or perpancreatic tissues within 2 weeks from presentation (ERCP and cholecystectomy are excluded))

ERCP during hospitalization
◯ Yes
◯ No
(ERCP stands for endoscopic retrograde cholangiopancreatography)

Date of first ERCP
_____

ERCP indication
◯ Common bile duct stone
◯ Jaundice without bile duct stone
◯ Pancreatic duct injury
◯ other

Cholecystectomy during hospitalization
◯ Yes
◯ No

Date of cholecystectomy
_____

Complications during hospitalization

Organ Failure (choose more than one if indicated)
☐ no
☐ cardiovascular (systolic blood pressure < 90 mmHg (not fluid responsive), pH< 7.3, or use of inotropes)
☐ respiratory (PaO2 /FiO2< 300, or need for intubation)
☐ renal [(serum creatinine >1.8 mg/dL or >169 µmol/L, or need to hemodialysis), if there is no pre-existing renal failure]
(Organ failure based on modified Marshall score)

Date and time of organ failure onset
_____

System that failed first (choose more than one if indicated)
☐ Cardiovascular
☐ Pulmonary
☐ Renal

Cardiovascular failure duration
◯ Transient (< 48 hours)
◯ Persistent (>=48 hours)
(When systolic blood pressure < 90 mmHg not fluid responsive, pH< 7.3, or use of inotropes)

Respiratory failure duration
◯ Transient (< 48h)
◯ Persistent (>=48h)
(When PaO2/FiO2< 300, or need to intubation)

Renal failure duration
◯ Transient (< 48h)
◯ Persistent (>=48h)
(When serum Cr >1.8 mg/dl or >169μmol/l, or need to hemodialysis. [If there is no pre-existing renal failure])

Total length of Organ Failure
_____
(Total days of organ failure)

Extrapancreatic Infection
◯ Yes
◯ No
(This includes extrapancreatic infections that developed during hospitalization)

Type of extra-pancreatic infection
☐ Respiratory infection
☐ Urinary Tract Infection
☐ Catheter-related bacteremia
☐ Clostridium difficile
☐ Cholangitis
☐ other

Early Radiologic Findings
(Choose the CECT scan closest to 7 days of admission)

Contrast-enhanced computed tomography (CECT) scan
◯ Yes
◯ No
(Was CECT scan performed during hospitalization or follow-up within 1 month?)

Date of CECT
_____
(In cases of more than 1 CECT scans, choose the one closest to day 7)

CECT findings
◯ Normal Pancreas
◯ Interstitial Edematous Pancreatitis
◯ Pancreatic Necrosis

Extent of pancreatic necrosis
◯ < 30%
◯ 30%-50%
◯ >50%
(Percent of total pancreas necrosis)

Peripancreatic Necrosis	◯ no ◯ yes ◯ not recorded in our center (Presence of heterogeneous areas of non-enhancement on CECT scan in the peripancreatic area that contain non-liquefied, ill-defined components, nodular areas of increased peripancreatic fat attenuation with visual density higher than simple fluid and considerably higher than simple stranding)
Infected Necrosis	◯ Yes ◯ No
Diagnostic method of infected necrosis	◯ Culture of surgical specimen ◯ Culture of FNA specimen ◯ Based on imaging ◯ Clinical suspicion only ◯ Other (How infected necrosis was diagnosed?)

Late Radiologic Findings
(Choose the CECT scan closest to 1 month of admission)

Walled-off Necrosis	◯ Yes ◯ No (Walled-off necrosis defines as encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined borders)
Date of walled-off necrosis	_____ (When was the walled-off necrosis identified?)
Largest diameter of walled-off necrosis (centimeters)	_____ (How much is the largest diameter of walled-off necrosis (reported in CECT)?)

Severity classification

Revised Atlanta Classification	◯ mild acute pancreatitis ◯ moderately severe acute pancreatitis ◯ severe acute pancreatitis

Revised Atlanta Classification definitions

Box 3 Grades of severity

- Mild acute pancreatitis
  - No organ failure
  - No local or systemic complications
- Moderately severe acute pancreatitis
  - Organ failure that resolves within 48 h (transient organ failure) and/or
  - Local or systemic complications without persistent organ failure
- Severe acute pancreatitis
  - Persistent organ failure (>48 h)
  - –Single organ failure
  - –Multiple organ failure

Determinant-based Classification

- ◯ mild acute pancreatitis
- ◯ moderate acute pancreatitis
- ◯ severe acute pancreatitis
- ◯ critical acute pancreatitis

Determinat-based Clasiffication definitions

TABLE 1. Determinant-Based Classification of Acute Pancreatitis Severity

	Mild AP	Moderate AP	Severe AP	Critical AP
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	AND	*AND/OR*	*OR*	*AND*
Organ failure	No	Transient	Persistent	Persistent

Clinical outcomes

Mortality in hospital	◯ Yes ◯ No (Patient death during hospitalization)
Cause of Mortality	◯ related to acute pancreatitis ◯ unrelated to acute pancreatitis (Did the patient die during hospitalization due to complications of acute pancreatitis which include organ failure or secondary infection?)
Date of death	_____
Total Hospital Length of Stay (days)	_____ (Total hospital length of stay in days. If patient is transferred add length of stay in both the initial and the referral hospital)

Patient Satisfaction

During this stay at the hospital, how often were you treated with courtesy and respect?	◯ Never (0-10%) ◯ Sometimes (10-50%) ◯ Usually (50-90%) ◯ Always (90-100%) (To be answered before discharge by the patient)
During this stay at the hospital, how often was your pain well controlled?	◯ Never (0-10%) ◯ Sometimes (10-50%) ◯ Usually (50-90%) ◯ Always (90-100%) (To be answered before discharge by the patient)

APPRENTICE
Acute Pancreatitis Patient Registry To Examine Novel Therapies In Clinical Experiences

Specific Aims

- Prospective collection of demographic, clinical, laboratory, and radiologic data in acute pancreatitis patients from several centers throughout the world with central storage of de-identified data at the University of Pittsburgh
- Evaluation of the existing risks, predictive scores, and markers of severe disease and allocation of patients in the two recent severity classifications based on their clinical course
- Evaluation of the current management and outcomes of acute pancreatitis around the world.

Background and Significance

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable clinical course but generally is characterized by sudden onset of upper abdominal pain radiating to the back, nausea, epigastric tenderness and elevation of pancreatic digestive enzymes (e.g. amylase and lipase) in the serum and urine. Currently, AP is the leading cause of GI related admissions in the US hospitals resulting in high physical and financial burden (Gastroenterology 2012;143:1179-87.e1-3). Most cases are mild and self-limited; however, around 20% of AP cases result in local or systemic complications associated with high morbidity and mortality that can reach up to 30% (Gut 2013;62:102-11).

Over the last 2 decades there has been increased interest in evaluating clinical severity of patients with AP. This research has led to the revision of disease definitions and severity classification. Examples of commonly used AP classification systems are Revised Atlanta Classification Group (Gut 2013;62:102-11) and the Determinant Based Classification (Ann Surg 2012;256: 875–880) systems. In addition, available clinical scores and markers at predicting the severity of AP are only moderately accurate (Mounzer R. Gastroenterology 2012).

The management of AP is largely based on expert opinions. Further large randomized controlled trials are needed and novel therapeutic approaches are necessary in order to provide foundations for determining best course of treatment/s, symptom management, and develop novel therapeutic approaches.

Further challenges may be explained by limitations in current studies in which the statistical power is limited because of small patient population and/or because they are conducted in a single center. In order to address these issues, we propose a multi-center, international, collaboration of major AP centers to develop a network of qualified investigators throughout the world and enroll large number of subjects into an online database. The results of this study and development of this database will show the feasibility of developing multicenter, international protocols in AP aiming to identify risks and improve treatment of AP.

Methods:

This is a multi-center, prospective study, which will aim to recruit and follow hospitalized patients with AP. This study is coordinated by the pancreas group at the University of Pittsburgh Medical Center (UPMC) and supported by the Collaborative Alliance for Pancreatic Education and Research community (CAPER). The study will include adults with confirmed diagnosis of AP admitted to the hospital. Each center's research team will determine patient's eligibility to participate in this research study.

This is an observational study, collecting clinical data in patients with AP. Data collection will include: **severity of symptoms, pain, demographics, laboratory markers, radiologic findings, management, hospital course, and outcomes**. Our **primary outcome variables** are presence of **persistent organ failure and pancreatic necrosis** as those two are the main determinants of severity suggested by the two revised severity classifications (Revised Atlanta Classification and Determinant-Based Classification). Based on those two main outcomes we will evaluate existing risks, predictive scores, and markers of severe disease. Furthermore, we will evaluate current management practices in AP patients around the world. **Secondary outcomes** that will be studied include **need for ICU, need for nutritional support, need for intervention, hospital length of stay and mortality**.

De-identified data from each center will be recorded in an **online standardized questionnaire through the REDCap** website. Research coordinators gather data through both direct interview and patients' clinical records. Those variables, which are required to be collected through patient interview, are labeled by brackets in **the questionnaire**. Completion of this **questionnaire takes, on average, 45 minutes**, while **patient interviews are usually less than 30 minutes**. The research coordinator and investigators at each center will be provided with a unique password protected username to access REDCap. They will be responsible for verifying patients' eligibility and data entry.

The questionnaire is designed to gather information about **patient demographics, pancreatic disease history, family history, alcohol use, current medications, clinical characteristics, diagnostic tests, current therapies, hospital course, interventions and disease classification**. Patients will be contacted **within 30-90 days after discharge** from the hospital **to complete a follow-up questionnaire**. **The follow-up questionnaire** will mainly focus on **recurrent attacks of AP, the need to delay intervention, and the potential development of AP-related complications**, i.e.

diabetes mellitus and exocrine pancreatic insufficiency.

Recruitment Procedures:

Recruitment will be accomplished using the Investigators' and co-investigators' own patient population at each center. Every principal investigator and co-investigator have been selected based on their expertise in AP research. **Investigators** will correctly **diagnose the patients with AP and review the inclusion and exclusion criteria according to protocol**. Eligible patients will be approached by study personnel and the study will be explained to them. In the event that the patient is not able to give consent (e.g. intubated and unable to talk) **the patient's proxy** will complete **the consent form**. Patients who are interested in participating in the study will be given a detailed approved consent form that explains the study and informs them of the potential risks and benefits associated with participation in the study. After all of the patients questions and concerns are addressed by the study coordinator and/or investigator and the consent form is signed, the research coordinator and/or investigator will conduct the interview. **This will occur during the patient's hospital stay**. The participant will then be contacted after 30 to 90 days post discharge from hospital.

Power and statistical approach:

We plan to recruit 5,000 cases in one year. For the evaluation of existing predictive scores, z- statistic will be utilized for sample size calculation since both predictive scores and primary outcomes are dichotomous variables. Continuous data will be evaluated for normality of distribution by the Kolmogorov-Smirnov test (or other). Normally distributed data will be presented as mean values ± standard deviation (SD), whereas data that are not normally distributed as median values with interquartile range (IQR). Differences between two groups with continuous data will be assessed using the student-t test for normally distributed data and the Mann-Whitney test for non-normal data distributions. Comparisons of three or more groups of data will be made using one-way analysis of variance (ANOVA) and Kruskal-Wallis (non-parametric ANOVA) tests. Discrete data will be compared by the chi-square or chi-square trend test depending on the number of groups. A two-sided p-value of less than 0.05 will be considered statistically significant.

Patient Identification:

The racial, gender and ethnic characteristics of the proposed subject population reflects the demographics of the approved research center and surrounding communities participating in this study. No exclusion criteria shall be based on race, ethnicity, gender or HIV status.

Inclusion Criteria:

1. The diagnosis of AP based upon presence of **two out of the three** following criteria:

a. Abdominal pain typical to AP

b. Serum amylase or lipase levels more than three times the upper limit of normal

c. Imaging findings suggestive of AP

2. Willingness to participate in the study and ability to sign informed consent by patient or his/her proxy (if unable to speak).

Exclusion criteria:

1. Age under 18 years
2. Unwilling to provide consent by patient or his/her proxy
3. Presence of pancreatic cancer
4. Presence of chronic pancreatitis
5. Occurrence of AP following a multiple trauma episode
6. Having history of organ transplant
7. Presence of any cancer which required chemotherapy or radiation therapy in the past year.

Risks and Benefits:

The possibility that the results of the research study will become generally known is rare and occurs in less than 1% (less than 1 out of 100 people). We developed a process, which is detailed in the Data Safety and Monitoring section, in order to reduce the chances of this from occurring.

There is no direct benefit to the patient for participation in this study. The information obtained from this study may lead to greater knowledge of AP.

Data Safety and Monitoring:

All the data will be collected and stored prospectively on an online database (REDCap) accessible by study personnel at each center. The data will be de-identified and assigned a study code before storage. **REDCap** is an established secure online software used to access the study material (e.g. questioners), enter and save the collected data, and communicate with other sites about the latest news regarding the study. The data will be monitored by the data coordinator at the Pittsburgh Coordinating Site. All data and safety issues will be discussed at regularly scheduled DSM meetings with the PI. 2. **The data will be de-**

identified by each site and the link of study code to study code to identity will be maintained by each site. No identifying information will be entered into the database.

Every center will have access to their own data. Raw data from all centers will be stored centrally in the REDCap coordinating site at the University of Pittsburgh. The data will be accessible by the analysis and publication committee of APPRENTICE with their members including Dr. Papachristou (PI) and additional principal investigators from other geographical areas. All collaborators will be invited to propose research ideas based on their expertise and experience and will have an opportunity to lead one of the projects. The committee will be in charge of assigning projects to individual investigators and setting a time frame for completion. An experienced statistician at the coordinating or leading center based on resources, will have access to the relevant de-identified data so as to complete the statistical analysis for each project.

Cost and Compensation:

There are no costs to the participant or the participants insurance for procedures conducted for research purposes only.

There is no compensation to those patients participating in this study.

Qualifications of Investigators:

PI-Georgios Papachristou, M.D., is an Associate Professor at the Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh. Dr. Papachristou has conducted an extensively important researches focused on AP and continues to do research and clinical studies on AP. He has over 100 publications and many federal and foundation grants.

David C. Whitcomb, M.D., Ph.D., is a Professor of Medicine in the Division of Gastroenterology and Hepatology, Department of Medicine, Cell Biology and Physiology, and Human Genetics, University of Pittsburgh, and Chief of the Division of Gastroenterology and Hepatology.

Dhiraj Yadav, M.D., is an Associate Professor of Medicine in the Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh. He is an expert in epidemiology and alcoholic pancreatitis.

Amir Gougol, M.D., is a research scholar with the University of Pittsburgh, Department of Medicine, Gastroenterology division.

Efstratios Koutroumpakis, M.D., is a research scholar with the University of Pittsburgh, Department of Medicine, Gastroenterology division.

Venkata Akshintala, M.D., is a resident of Internal Medicine at UPMC

Kim Stello is a member of the research staff with the University of Pittsburgh, Department of Medicine, Gastroenterology division.

Danielle Dwyer is a member of the research staff with the University of Pittsburgh, Department of Medicine, Gastroenterology division.
Gregory Owens, BA, CCRP is a research coordinator in the Department of Medicine, Division of Gastroenterology, University of Pittsburgh