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# Impact of timing of presentation of acute pancreatitis to a tertiary care centre on the outcome

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ABSTRACT

*Background and objectives:* Despite improvement in outcomes of acute pancreatitis (AP), some subgroups remain at increased risk. We studied the impact of onset-to-admission interval to a tertiary care centre on outcomes in AP.

*Methods:* Retrospective analysis of consecutive patients with first episode of AP admitted between 2009 and 2017 on the basis of onset-to-admission interval: ≤7 days, 8–21 days and >21 days was done. Patients were assessed for severity and managed using a step-up approach. Primary outcome measures were surgical necrosectomy and mortality.

*Results:* Of 745 patients (age 39.26 ± 13.18 yrs, 69% male), 380 (51%) had presented ≤7 days, 229 (30.7%) between 8 and 21 days and 136 (18.3%) >21 days after pain onset. Severe pancreatitis was highest in 8–21 days group (129; 56.3%) followed by ≤ 7 days (166; 43.7%) and >21 days of illness (52; 38.2%).Surgical intervention rates were highest in the 8–21 days group(14%) followed by > 21 days (12.5%) and ≤7 days (6.6%) respectively (p = 0.007). Also, mortality was highest in patients with onset to admission interval of 8–21 days (24%) followed by > 21 days (15.4%) and ≤7 days (14.2%) (P = 0.007). On the multivariate analysis, age, late presentation, and the presence of organ failure were found to predict the mortality.

*Conclusion:* Patients presenting between 8 and 21 days after onset perform poorly than those presenting earlier or later than them in terms of severity, organ failure, need for surgery and mortality although organ failure remains the most important determinant of outcome. This data can help in devising guidelines for referral of such patients.



## Introduction

Acute pancreatitis is an acute inflammatory process which may be complicated by pancreatic (or extra-pancreatic) necrosis. Acute pancreatitis remains a disease with variable outcomes ranging from self limiting to fatal outcome depending on the severity of disease. Appropriate medical management including fluid resuscitation, organ system support, nutritional support and antibiotics and timely radiological, endoscopic or surgical intervention could improve morbidity and mortality in AP and this requires a multimodality treatment including an intensivist, interventional radiologist, gastroenterologist and a surgeon.

Evolution of pancreatitis occurs in two phases: an early phase, when the severity of pancreatitis is related to the systemic inflammatory response elicited by the tissue injury and the delayed phase when the disease either resolves or progresses into a more protracted course lasting weeks to months related to the necrotizing process and infection [1,2]. Organ failure, the harbinger of severity is driven by systemic inflammatory response during the initial phase of the illness while the infected pancreatic necrosis drives organ dysfunction in the second phase [1]. The management of acute pancreatitis revolves around prevention of organ failure, and treating any complication which arises during its course. While

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the concept of 'initial golden hours' in the management of acute pancreatitis has been suggested, it is uncertain if the management in early hours affects outcomes in these patients [3]. Early fluid resuscitation may help in attenuating inflammatory response, and limiting the extent of pancreatic necrosis which in turn could affect outcomes(4). Further, early intensive care and management of local complications can be done in cases where it is needed avoiding the delays which could occur in referred patients(5, 6). Therefore, we hypothesised that patients who are initially treated at a centre with experience in management of AP and having established protocols for early management of this condition may have better outcomes than the patients who present later to the tertiary care centre.

## Patients and methods

### *Patients*

The present study is a retrospective study based on a prospectively collected database of patients with acute pancreatitis managed at a large tertiary care centre in North India between January 2009 and December 2017 and the study was approved by institutional Ethics Committee.We included patients who presented with the first episode of acute pancreatitis irrespective of the time of their presentation. We excluded patients with evidence of chronic pancreatitis, underlying pancreatic malignancy, with a recurrent episode of pancreatitis or who had undergone any intervention for pancreatic fluid collections before being referred.The day of onset of pain was deemed as the day of onset of acute pancreatitis. Co-morbidities which can affect the outcome of pancreatitis i.e. diabetes mellitus (DM), hypertension, coronary artery disease, stroke, chronic kidney disease (CKD), bronchial asthma, chronic obstructive pulmonary disease (COPD) and malignancy were recorded for all patients.

### *Management of patients*

The diagnosis of AP was made by the presence of any two of these three features; (a) acute abdominal pain; (b) serum lipase activity and/or amylase activity at least three times greater than the upper limit of normal; and (c) characteristic findings of acute pancreatitis on imaging [1]. A diagnosis of biliary pancreatitis was considered on the identification of gallstones by ultrasonography or presence of gall bladder sludge (in absence of other identifiable etiology) and supported by transient elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)/. Alcohol was considered to be the aetiology when the history of heavy alcohol consumption was present before the attack of pancreatitis and no other etiology identified. Rest of the identifiable etiologies (post-endoscopic retrograde cholangiopancreatography, trauma, worms, drugs, infections, hypertriglyceridemia, hyperparathyroidism) were clumped into a single group of other etiology. Pancreatitis was classified as idiopathic when an etiological factor could not be identified.

Clinical scores such as systemic inflammatory response score (SIRS), bedside index for severity in acute pancreatitis (BISAP), acute physiology and chronic health evaluation score (APACHE II) were noted at the time of admission [7–9]. Contrast-enhanced computed tomography (CECT) was done within 5–7 days after onset of pain or after initial evaluation in patients referred from other centres for pancreatic necrosis, fluid collections and severity scoring was done by calculating CTSI [10]. Severe acute pancreatitis was defined by the presence of persistent organ failure and moderately severe pancreatitis defined as local/systemic complications without persistent organ failure and mild pancreatitis in absence of both local and systemic complications, based on modified Marshall scoring system any time after admission to our centre(11). A score of $\geq$2 in the modified Marshall scoring system for organ dysfunction was defined as presence of organ failure (OF) and if organ failure resolved within 48 h it was labelled as transient and when it persisted >48 h labelled as persistent organ failure [1,11].

All patients were managed according to standard recommendations which included fluid resuscitation, organ system support, pain alleviation and nutritional support (enteral or parenteral) [12,13]. Antibiotics were used for extra-pancreatic infections and suspected pancreatic necrosis infection. Infected necrosis (IPN) was suspected by the patient's worsening clinical course and diagnosed on basis of positive drain cultures or the presence of gas within the necrosis seen on CECT. Drainage (endoscopic or percutaneous catheter) of fluid collections was done in case of persistent organ failure, suspected infected necrosis and/or pressure symptoms. The site, route of drainage were chosen by a team of a gastroenterologist and an interventional radiologist based on the location, type and extent of the collections. Patients failing to recover or worsening with medical management and drainage of collections were subjected to surgical necrosectomy.

### *Comparisons between delay in presentation and outcomes*

These patient with first episode of acute pancreatitis were subdivided into three groups depending on the onset-to-admission interval ($\leq$7days, 8–21 days, >21 days) for comparison with outcome parameters. The severity of the illness as defined by the revised Atlanta classification was also compared.

Primary outcome measures were the requirement of surgical necrosectomy and mortality. Secondary outcome measures included duration of hospital stay, need for intensive care (ICU) admission, requirement of organ support (mechanical ventilation and dialysis) and need for drainage of collections during their index hospital admission. The main criteria for ICU admission were hemodynamic instability despite volume replacement and/or respiratory dysfunction requiring mechanical support.

## Stastical analysis

All data were entered on a personal computer in Microsoft Excel 2010 and analyzed in SPSS software (version 23). Data was explored for any outliers, errors and missing values. Quantitative variable were represented as mean and standard deviation or Median with interquartile range if the data had a non-parametric distribution. Categorical variables between groups were compared using Chi-square test. More than two group comparisons were done using one-way ANOVA or Kruskall wallis depending on the distribution of the data. Univariate analysis to determine predictors of mortality at presentation was done followed by multivariate analysis using backward stepwise regression method. A p value of $<0.05$ was considered to be significant.

## Results

### *Patient characteristics*

Of the 745 patients with AP admitted to our centre between 2009 and 2017, 380 (51%) had presented within 7 days, 229 (30.7%) in between 8 and 21 days and 136 (18.3%) after 21 days of onset of pain(Table 1). The mean age was comparable and there was male dominance in all groups. The three groups were comparable in terms of underlying etiology of pancreatitis and presence of co-morbidities. (Table 1).

**Table 1**
Clinical profile of 745 patients with acute pancreatitis.

| | | Total (%) | ≤7 d (%) | 8–21 d (%) | >21 d (%) | Significance (p) |
|---|---|---|---|---|---|---|
| Number | | 745 | 380 (51.0) | 229 (30.7) | 136 (18.3) | |
| Age, years (Median+IQR) | | 38 (17) | 37 [17] | 38 [18] | 42 [20] | 0.501 |
| Gender | Male | 514 (69.0) | 252 (66.3) | 150 (65.5) | 112 (82.3) | 0.002 |
| | Female | 231 (31.0) | 128 (33.7) | 79 (34.5) | 24 (17.7) | |
| Etiology | Alcohol | 348 (46.7) | 170 (44.7) | 103 (45.0) | 75 (55.1) | 0.171 |
| | Biliary | 264 (34.5) | 129 (33.9) | 91 (39.7) | 44 (32.4) | |
| | Others | 40 (5.3) | 24 (6.4) | 13 (5.7) | 3 (2.2) | |
| | Idiopathic | 93 (12.5) | 57 (15.0) | 22 (9.6) | 14 (10.3) | |
| Co-morbidities | None | 494 (66.3) | 258 (67.9) | 146 (63.8) | 90 (66.2) | 0.861 |
| | 1 organ system | 162 (21.7) | 80 (21.1) | 52 (22.7) | 30 (22.1) | |
| | >1 organ system | 89 (11.9) | 42 (11.0) | 31 (13.5) | 16 (11.8) | |
| BMI ($Kg/m^2$) (Median±IQR) | | 23.8 (4.64) | 24.4 (4.63) | 23.45 (4.28) | 23.35 (4.5) | 0.001 |

*Severity parameters*

The APACHE II scores were highest in patients presenting between 8 and 21 days followed by ≤ 7 days and >21 days of illness groups (Table 2). Most patients in all the groups were moderately severe or severe based on revised Atlanta 2012 classification. Three hundred and thirty two (44.6%) had neither OF nor IPN, 66 (8.9%) had only IPN, 190 (25.5%) had only OF and 157 (21.1%) had both OF and IPN.

The incidence of severe pancreatitis was maximum in the 8–21 day group followed by ≤ 7 day and >21 days of illness group. All patients had undergone CECT of abdomen and 89.5% had necrotising pancreatitis. The mean CT severity index (CTSI) score and presence of fluid collections were more when the presentation was delayed. The need for drainage of symptomatic fluid collection was more when the onset-to-admission interval was between 8 and 21 days followed by > 21 days and ≤7 days. The incidence of infected necrosis was highest when the onset-to-admission interval was more than 21 days followed by 8–21 days and ≤7 days. Overall 179 patients were direct admission and 566 were transferred cases with mortality of 22 (12.3%) in direct admissions and 108 (19.1%) patients amongst those who were transferred (P = 0.022).

*Outcome parameters*

The mean duration of hospitalization was 23.76 days and the duration increased as the presentation got delayed. The need for ICU admission was highest when patients presented between 8 and 21 days and lowest in those who presented after 21 days. Similarly the requirement of organ support i.e. mechanical ventilation and dialysis was highest when they presented in between 8 and 21 days (27.1% and 8.7% respectively) and lowest when patients presented > 21 days (16.2% and 0% respectively). The requirement of surgical intervention and mortality were highest when the onset-to-admission interval was between 8 and 21 days followed by > 21 days and ≤7 days (Tables 3 and 4).

*Multivariate analysis*

Logistic regression analysis was performed to determine independent predictors of mortality at admission. When we compared the patients who survived with the patients who died, the univariate analysis (Table 5) suggested that the presence of organ failure, delay in admission, age and body mass index were significantly different in patients who died. Those variables which were significant on univariate analysis were entered into the model. The independent predictors were age, delay in admission (after 7 days) and presence of organ failure were identified as independent predictors. On the multivariate analysis, the odds ratio of mortality with organ failure was 27 (95% CI, 9.9–76.9, P < 0.001), with late presentation 1.7 (95% CI, 1.13–2.57, P = 0.012) and age 1.019 (95% CI, 1.004–1.035, P = 0.015) (Supplementary Table 1).

## Discussion

We evaluated the impact of onset-to-admission interval of 745 patients of AP coming to a specialist centre on outcome of the disease. In our study, 51% of patients presented within 7 days of illness, 30.7% between 8 and 21 days of illness and 18.3% beyond 21 days of illness. Patients presenting between 8 and 21 days of illness were sicker in comparison to patients presenting ≤7 days and >21 days. APACHE II score at admission was higher in these patients compared to other two groups. The need for ICU admission and organ support was also more in patients presenting between 8 and 21 days of illness.

Persisting organ failure beyond the first week after disease onset has been shown to be associated with poor outcome in severe AP [14–16]. Late deterioration of organ dysfunction occurs most

**Table 2**
Severity parameters in different groups.

| Character | | Total (%) | ≤7 d (%) | 8–21 d (%) | >21 d (%) | Significance (p) |
|---|---|---|---|---|---|---|
| APACHE II score (Median, IQR) | | 8.0 (7) | 8 [7] | 8.5 [7] | 6 [5] | 0.001 |
| Persistent organ failure | | 347 (46.6) | 166 (43.7) | 129 (56.3) | 52 (38.2) | 0.001 |
| Severity | Mild | 79 (10.5) | 54 (14.2) | 16 (7.0) | 9 (6.6) | 0.001 |
| | Moderately severe | 319 (43.0) | 160 (42.1) | 84 (36.7) | 75 (55.1) | |
| | Severe | 347 (46.5) | 166 (43.7) | 129 (56.3) | 52 (38.2) | |
| CTSI score (Median and IQR) | | 8 (5) | 8 [6] | 10 [4] | 9 [3] | 0.001 |
| Fluid collection(s) | | 497 (66.7) | 204 (53.7) | 175 (76.4) | 118 (86.8) | 0.001 |
| Infected necrosis (n = 434) | | 223 (51.4) | 68 (41.5) | 86 (52.8) | 69 (64.5) | 0.001 |

SIRS: Systemic Inflammatory Response Syndrome.
BISAP: Bedside Index of Severity in Acute Pancreatitis.
APACHE: Acute Physiology and Chronic Health Evaluation.
CTSI: Computed tomography (CT) Severity Index.

**Table 3**
Outcome parameters in different groups.

| Character | Total (%) | ≤7 d (%) | 8–21 d (%) | >21 d (%) | Significance (p) |
|---|---|---|---|---|---|
| Hospital stay (days, median and IQR) | 19 [21] | 16 [20] | 21 [22] | 25 (27) | 0.001 |
| ICU need, No. (%) | 330 (44.3) | 161 (42.4) | 118 (51.5) | 51 (37.5) | 0.019 |
| Ventilator need, No. (%) | 148 (19.9) | 64 (16.8) | 62 (27.1) | 22 (16.2) | 0.004 |
| Dialysis, No. (%) | 45 (6.0) | 25 (6.6) | 20 (8.7) | 0 | 0.003 |
| Drainage of collection(s), No. (%) | 434 (87.3) | 164 (80.4) | 163 (93.2) | 107 (90.7) | 0.001 |
| Surgery, No. (%) | 74 (9.9) | 25 (6.6) | 32 (14.0) | 17 (12.5) | 0.007 |
| Mortality, No. (%) | 130 (17.4) | 54 (14.2) | 55 (24.0) | 21 (15.4) | 0.007 |

ICU: Intensive Care Unit.

**Table 4**
P values between the groups for Tables 2 and 3.

| Character | P1 (<7 d vs 8–21 d) | P2 (8–21 d vs > 21 d) | P3 (<7 d vs > 21 d) |
|---|---|---|---|
| APACHE II score | 0.044 | 0.001 | 0.001 |
| Persistent organ failure | 0.003 | 0.001 | 0.001 |
| Severity | 0.002 | 0.002 | 0.010 |
| CTSI score | 0.001 | 0.251 | 0.001 |
| Fluid collection(s) | 0.001 | 0.020 | 0.001 |
| Infected necrosis | 0.001 | 0.021 | 0.001 |
| Hospital stay (days) | 0.009 | 0.141 | 0.001 |
| ICU need | 0.029 | 0.012 | 0.361 |
| Ventilator need | 0.004 | 0.020 | 0.894 |
| Dialysis | 0.340 | 0.001 | 0.001 |
| Drainage of collection(s) | 0.001 | 0.139 | 0.001 |
| Surgery | 0.004 | 0.752 | 0.043 |
| Mortality | 0.003 | 0.062 | 0.007 |

APACHE: Acute Physiology and Chronic Health Evaluation.
CTSI: Computed tomography (CT) Severity Index.
ICU: Intensive Care Unit.

**Table 5**
Predictors of mortality on univariate analysis.

| | Survivors (n = 615) | Mortality (n = 130) | P value |
|---|---|---|---|
| Age (years) | 37 [18] | 40 [19] | 0.062* |
| Male gender | 426 | 86 | 0.399 |
| BMI | 23.6 (4.6) | 24.35 (4.35) | 0.051* |
| Alcohol etiology | 291 | 57 | 0.499 |
| Delayed admission (>7 days) | 289 | 76 | 0.017 |
| Co-morbidity | 212 | 39 | 0.320 |
| Organ failure | 334 | 126 | <0.001 |
| Collections | 406 | 91 | 0.414 |

Chi-square test or *Mann Whitney *U* test (Median and IQR) was used.

commonly in the second and third weeks of illness and is usually a result of secondary infection of pancreatic necrosis [17]. In an earlier study we had shown that the incidence of infection increased with each week of illness [18]. Besselink et al. reported that majority of infections in pancreatic necrosis occur after 14 days with median time to diagnosis being 26 days of illness [2]. Similarly, Dellinger et al. noted that the mean time to diagnosis of infected necrosis in AP was 3 weeks [19]. In accordance with these data, we observed that the incidence of infected necrosis increased with delay in presentation. This explains in part the reason for a higher frequency of organ failure and severe disease in patients presenting to us in the second and third weeks of illness.

When we look at outcome measures (Table 3), patients coming in the first week had the least requirement of surgery, least hospital stay and lowest mortality. This suggests that early and appropriate supportive care in a tertiary care facility could help in stabilizing these patients. Mortality was highest in the patients coming in the second and third weeks of illness. With more severe disease, more organ failure and higher incidence of infection in this group of patients, as compared to patients admitted within 1 week of illness, a higher mortality could be expected. However patients hospitalized with us beyond 3 weeks had better outcome. Though they had more fluid collections and more infection, these patients had least organ failures and accordingly least need for organ support. Mortality was also lower in them as compared to the 8–21 days group. Pradhan et al. have also reported a higher mortality in patients having infected necrosis and secondary infection related organ failure when compared to patients having infected necrosis but no organ failure [20]. Similar observations have been made by Gou et al., who reported that patients with late infection of pancreatic necrosis had better prognosis than patients with early infection [21]. These data suggest that patients with late referral having infected fluid collections can be managed effectively by PCD and antibiotics. Also, on doing a multivariate analysis on our data it was apparent that the presence of organ failure is the major determinant of the course of the illness. However, the timing of presentation also emerged as an independent predictor of mortality. The need for surgical intervention and mortality was highest when the presentation was in the 8–21 days group. This was reflective of the severity of disease with mean APACHE II scores and persistent

organ failure being the highest in this group of patients. It has been noted that higher APACHE II scores and organ failure within 1 week of onset of disease and persistence of infection were predictors of surgery(22).Our data, thus shows that patients presenting early and those coming directly have the best outcome. Those referred in the 8–21 days period have the highest need for organ support, radiological or endoscopic intervention and mortality. The guidelines for management of acute pancreatitis have primarily focussed on early fluid resuscitation and organ support [23]. Timely severity stratification and prompt referral for organ support are critical for decreasing mortality. Our data shows that over half the patients are referred early but a sizeable proportion get referred late. Relative stabilization of patients at primary or secondary centres in the first week may confer complacency in the minds of treating team but persistence of organ failure should warn them of possible impending dangers. If infection supervenes and organ failure worsens, these patients may not benefit much from the referral. We thus, feel that the guidelines should focus on this group of patients as well.

It has been shown that patients managed in community hospitals are not routinely managed as per the primary guidelines and therefore one expects that delay in presentation may affect outcomes in acute pancreatitis [24,25]. Our data suggest that timing of hospitalization/referral to a tertiary care facility could affect the outcome of patients with AP. Those who present early (within a week) can be helped by institution of early and effective resuscitation and organ support. Those presenting late (beyond 3 weeks) are usually referred for the local complications and related infection and can be managed by optimising management directed at local complications. It is the group of patients who are referred in the intervening period (8–21 days) who fare worst. This is probably related to the organ failure persisting beyond the first week or getting the course complicated by development of infection or both.

The strength of this study is that it included a large number of patients treated in a step-up approach with clearly defined indications for interventions at a tertiary care large volume facility. We had sufficient number of patients in each of the three timeframe groups. Further, the study analyses possibly for the first time the impact of delayed presentation to a tertiary care centre. Our study however has some limitations The retrospective nature of the study also has its attendant limitations. As a majority of the patients had been referred from other hospitals, we could not get all the details of prior resuscitation and treatment provided to them. Since, we could not get details of prior antibiotics use, the incidence of infected fluid collections could have been underestimated. Further, with the lack of data on the treatment which patients received before admission to our institution, we cannot conclude that the treatment received prior to admission was suboptimal and that the differences in outcome could be alleviated by an early referral to specialist centres. Our results, however, should be interpreted with the caveat that patients referred late are likely to be the ones who did not improve at the referring hospital while those who improved in the first week did not get referred. Therefore the argument that early referral might improve outcomes may not be necessarily correct.

Also, the data on details and causes of co-morbidities and the cause of death was not available and therefore, it is not possible if the presence of a certain comorbidity affected the outcomes differently across the groups. However the frequency of comorbidities was similar across the three groups.

To conclude, we have shown that patients referred in the second and third weeks of AP have worse outcome than those referred within the first week or beyond the third week of disease. Awareness of this fact should prompt transfer of patients to specialist centres early.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Contributions

BM: Acquisition and analysis of data, Initial draft of the manuscript, Approval to final version.

ND: Acquisition and interpretation of data, Intellectual content, Approval to final version.

VS: Acquisition and interpretation of data, Intellectual content, Approval to final version.

SM: Acquisition and interpretation of data, Approval to final version.

SKS: Conception and design of study, Intellectual content, Approval to final version.

UD: Acquisition and interpretation of data, Approval to final version.

PG: Acquisition and interpretation of data, Approval to final version.

AG: Acquisition and interpretation of data, Approval to final version.

TDY: Intellectual content, Approval to final version.

VK: Intellectual content, Approval to final version.

RK: Conception and design of study, Intellectual content, Revision and approval to final version.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2018.10.005.

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