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Time to onset of organ failure determines outcomes in acute severe pancreatitis- a prospective post HOC analysis

Abstract

Introduction: High mortality rates in severe acute pancreatitis (SAP) have been attributed for quite some time to number and severity of organ failure (OF), rather than on their period of onset. We investigated whether rapidity of onset of organ failure determines the outcomes in SAP.

Patients and methods: We performed a post hoc analysis from a prospectively maintained database of 331(66.1%) of 501 consecutive patients (mean age 41.3 ± 15.2 years, 69.5% males) of acute pancreatitis over a three-year period, who fulfilled revised Atlanta criteria for SAP. Patients were divided into early severe acute pancreatitis (ESAP: 115, 34.7 %) and late severe acute pancreatitis (LSAP: 216, 65.3 %) if OF developed within or after 7 days of disease onset. ESAP was subdivided into fulminant (FAP: 49 of 115, 42.6%) and sub-fulminant (SFAP: 66, 57.4%) groups with onset of organ failure within 72 hours and 72 hours to 7 days of disease respectively.

Results: Within the overall mortality rate of 27% (89 of 331) in SAP, significantly higher deaths occurred in ESAP group (49.6%, 57/115) compared to LSAP (15.7%, 34/216, $p< 0.05$). Within ESAP, it was significantly higher in those with FAP (63.3%, 31/49) than those with SFAP (39.4%, 26/66). Respiratory failure accounted for 50.9% (29/57) of deaths in ESAP, but only in 20.6% (7/34) in LSAP ($p<0.01$). Sepsis, on the other hand, accounted for only 31.6% (18/57) in ESAP but 70.6% (24/34) in LSAP ($p<0.01$).

Conclusion: Our observation suggests that the time of onset of organ failure in SAP is an important determinant of death, mortality being higher in those with a fulminant (SFAP) or rapid course (ESAP) than those where the disease progresses slowly (LSAP).

Keywords: Pancreas, pancreatitis, severity, mortality, pancreatic necrosis, outcome, Early acute severe Pancreatitis, Fulminant Acute Pancreatitis, Subacute Severe Pancreatitis, Late Severe Acute Pancreatitis

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Introduction

The Atlanta classification proposed in 1993 defines acute pancreatitis (AP) as an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems.[1] It is broadly divided into mild and severe acute pancreatitis. Severe acute pancreatitis (SAP) is associated with organ failure and/or local complications, such as necrosis, abscess, or pseudocyst. Mild acute pancreatitis (MAP) is associated with minimal organ dysfunction and an uneventful recovery, and it lacks the described features of severe acute pancreatitis. A multidisciplinary approach is warranted in the management of SAP, involving gastroenterologists, intensivists, interventional radiologists, surgeons, nephrologists and others.[2,3] Various authors have looked at mortality rates in SAP and factors affecting the same.[4-7] These studies regard organ failure as the major determinant of mortality, and those patients who develop multiple organ failures tend to have a worse prognosis.

Most classifications, severity gradings and predictors of outcome have studied the presence of organ failures and local complications to predict severity and mortality. There are several limitations to these criteria, one being that the timing of onset of organ failure was not considered in most. Hence some authors have recently proposed new classification systems for AP based on timing of onset of organ failure.[8-10] The basic assumption is that the earlier the onset of organ failure in a patient with severe AP, the worse the prognosis. The utility of the new classification needs to be tested in large patient populations to confirm or refute the proposed advantages. In this study, we studied whether the time of onset of organ failure was important in predicting mortality in a cohort of patients with severe acute pancreatitis presenting to a tertiary care institute in north India. We applied the proposed new classification in a post hoc manner to a large group of consecutive patients of SAP in a prospective database and looked at its relation to the outcome.

Materials and methods

Data collection

We undertook a post hoc analysis of data from a prospectively maintained database of patients admitted to the department of Gastroenterology at a tertiary care hospital in north India over a three-year period. Case records of all patients admitted with a diagnosis of severe acute pancreatitis were reviewed. Clinical details including demographic data, aetiology, presence of organ failures, and outline of management were recorded as per proforma. Patients with acute on chronic pancreatitis were excluded from the study. Clinical features, blood parameters and imaging, either computerised tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), were used to diagnose underlying chronic pancreatitis wherever suspected.

Definitions and management protocols

Acute pancreatitis was diagnosed on the basis of pancreatic type of pain along with serum amylase or lipase elevation to at least 3 times the upper limit of normal with abnormal pancreas on at least one imaging modality; ultrasonography (USG), CT or Magnetic resonance imaging (MRI) scan. All patients with acute pancreatitis were primarily admitted to the department of Gastroenterology. A multidisciplinary approach was adopted in the management of these patients, involving interventional radiologists and surgeons along with the treating gastroenterology team. The revised Atlanta classification[1] was used to classify AP, which mandates the presence of organ failure and/or local complications, such as necrosis, abscess, or pseudocyst to categorise a patient as having severe acute pancreatitis (SAP) Patients with SAP were sub-classified into early severe acute pancreatitis (ESAP) if the development of organ failure occurred within 7 days of onset of pancreatitis. Patients with ESAP were further divided into fulminant (FAP) and sub-fulminant acute pancreatitis (SFAP), depending on the development of organ failures within 72 hours or between 72 hours to 7 days respectively. Patients with SAP who developed organ failure or local complications fulfilling the revised Atlanta criteria for SAP after 7 days were considered to have late severe acute pancreatitis (LSAP).[9]

Presence of pancreatic infection was diagnosed on the basis of cultures from CT guided aspirates or by blood cultures where ever clinically indicated as decided by the treating physician. Antibiotics alone were tried in initial phases for the management of pancreatic infection, followed by attempt at percutaneous drainage or endoscopic drainage depending on the site of infected collection if there was no response. Endoscopic necrosectemy or surgical necrosectomy was reserved for patients who failed medical management and endoscopic/ percutaneous drainage, usually after at least 3 weeks from onset of illness. All patients were followed up till discharge from the hospital.

Data analysis

Statistical analysis was performed using SPSS 15.0 software. Chi-square test was used for categorical data, with a two-tailed p value of less than 0.05 being considered significant.

Results

Baseline parameters

During the study period, 501 patients were admitted to the Gastroenterology department with a diagnosis of acute pancreatitis. The mean age was 41.3 ± 15.2 years, with 69.5% (n=348) being males. Readmissions for various reasons resulted in a mean of 1.5 ± 1.3 admissions per patient with a mean hospital stay of 15.6 ± 17.5 days. Of the 501 patients, 66.1% (n=331) had severe acute pancreatitis, the rest had mild disease as per Atlanta criteria. Biliary pancreatitis was the most common etiology. The distribution of the various etiologies is as summarised in Table 1.

Table 1 Etiology of acute pancreatitis, n=501

Etiology	n=	percentage
Biliary	215	42.9
Alcohol	107	21.4
Recurrent acute	20	4
Other known aetiologies	41	8.2
Idiopathic	118	23.6

Course of SAP

The 331 patients with SAP had a mean duration of hospital stay of 19.9 ± 20.0 days, which was significantly more than those of patients with mild acute pancreatitis (6.3 ± 2.9 days, $p<0.05$). Respiratory complications were seen in 39% of SAP patients (n=129). This included acute lung injury (ALI) in 16.9% (n=56). Acute renal failure occurred in 29.3% of the patients with SAP (n=97), with 15.4% (n=51) needing dialytic support. 85.5% of the patients with SAP (n=283) had evidence of peripancreatic collections which necessitated placement of percutaneous drains in 72 of these patients (25.4%) due to lack of response to conservative management. 33 patients with collections (11.7%) underwent various types of endoscopic procedures to tackle the complications of SAP. This included endoscopic cystogastrostomy in 20 patients, cystoduodenostomy in 2, transpapillary drainage of pseudoscyst in one patient and pancreatic duct stenting in 6 patients. 4 patients with SAP underwent biliary stenting for cholangitis. Due to lack of response to conservative management, percutaneous and/or endoscopic management, 26 patients (9.2%) underwent necrosectemy.

Subgroups

Patients with SAP (n=331) could be divided into two groups, ESAP (n=115, 34.7 %) and LSAP (n= 216, 65.3 %). Of the 115 ESAP patients, 49 (42.6%) could be classified as FAP and 66 (57.4%) were of the SFAP group. The frequency of various organ failures, outcome and causes of death in each of these groups is as summarised in Table 2.

Table 2 Subgroups of severe acute pancreatitis, the frequency of development of organ failures in them, and outcome

	No: of patients	Mortality	ALI	ARDS	ARF	Predominant cause of death		
						Respiratory failure	Sepsis	Bleeding
FAP	49	31	11	30	33	20	11	0
	14.80%	63.30%	22.40%	61.20%	67.20%	49%	22.40%	0%
SFAP	66	26	27	24	36	18	7	1
	19.90%	39.40%	40.90%	36.40%	54.40%	27.30%	10.60%	1.50%
LSAP	216	34	18	19	28	7	24	3
	65.30%	15.70%	8.30%	8.80%	13%	3.20%	11.10%	1.40%
Total	331	91	56	73	97	45	42	4
		27.50%	16.90%	22.10%	29.30%	13.60%	12.70%	1.20%

Data are in number of patients in each group with their percentages in brackets. Abbreviations used –FAP, fulminant acute pancreatitis; SFAP, sub- fulminant acute pancreatitis; LSAP, late severe acute pancreatitis; ALI, Acute lung injury; ARDS, Acute respiratory distress syndrome; ARF, Acute renal failure

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Mortality rates

The mortality rate for AP in our study was 18.2 % (n=91). There was no mortality in the mild acute pancreatitis group, while that for SAP was 27.5% (n=91). Mortality rates were significantly higher in the ESAP group (57/115, 49.6%) compared to LSAP (34/216, 15.7%, p<0.05). Likewise, the mortality rates were significantly higher in the FAP group (31/49, 63.3%) compared to the SFAP group (26/66, 39.4%, p=0.009).

Causes of mortality

Among the 91 patients who died, sepsis was the predominant cause leading to mortality in 51 (56 %) while respiratory failure led to death in 36 (39.6%). Uncontrollable bleeding was the immediate cause of death in 4 patients (4.4%). The mean duration from onset of illness to death in these patients was 26.5 ± 24.4 days. Respiratory failure was the chief factor responsible for death in accounted for 50.9% (29/57) of deaths in ESAP. However, only 20.6% (7/34) of deaths in LSAP could be attributed to respiratory failure. (p<0.01). On the other hand, sepsis accounted for 70.6% (24/34) of all deaths in LSAP compared to only 31.6% (18/57) in ESAP (p<0.01). In patients who eventually developed ARDS, the mortality rates were similar whether it developed early (ESAP) or late (LSAP) (14/19, 73.3% Vs 45/54, 83.3%, p=0.274). The same pattern was observed for patients with ALI (4/18, 22.2% Vs 8/38, 21.1%, p=0.589) and for patients with ARF (17/28, 60.7%, Vs 42/69, 60.9%, p=0.582)

Discussion

Our study reports mortality rates of 18.2% for acute pancreatitis in the current era from a tertiary care institution in a developing country. We found significantly higher mortality rates for early severe acute pancreatitis compared to late severe and for fulminant acute pancreatitis compared to sub-fulminant. We found that respiratory failure is the chief factor leading to mortality in ESAP whereas it is sepsis which predominates in LSAP deaths. Demographic parameters in our study are similar to that from other centres.[10-14] We noted a preponderance of biliary pancreatitis, which is the norm in a geographical area with a high frequency of gallstones. In general, majority of cases of AP are mild and do not need specialised care. The fact that majority of cases of AP are severe in our series is quite expected since our data is from a tertiary care set up. Frequency of organ failures was also similar to other experiences.[15,16]

Several authors have looked at the adverse prognostic factors in patients with SAP. The presence of respiratory failure, renal failure, infected necrosis, the extent of necrosis, etc have all been associated with high mortality.[3, 4,6] These factors are taken into account when the Atlanta criteria are applied in classifying patients with AP. However, several authors have now brought out limitations of Atlanta criteria and proposed newer classification systems to prognosticate an individual patient with AP.[8-11,16,17] These observations are based on factors like time of onset of organ failure, presence of transient or persistent organ failure, and inclusion of a new group of moderately severe acute pancreatitis. One of the newer classification systems of SAP is based on the timing of onset of organ failure and our study has applied this classification to a retrospective cohort of patients.[8-10] Our study is well in concordance with other data and shows significantly higher mortality rates for ESAP compared to LSAP and FAP compared to SFAP. Our data further justifies this classification system. These subgroups help in prognostication in a particular patient with SAP i.e.: earlier the onset of organ failure, worse the prognosis.

In ESAP, systemic inflammatory response syndrome (SIRS) with its cytokine activations is responsible for high frequency of respiratory complications like ARDS and ALI, and these were the most important causes of mortality in this group of patients.[18] With the progression of the disease, sepsis sets in and results in a fresh set of complications even in ESAP patients who survived the initial insults. In LSAP however, the major factor behind mortality is sepsis, mostly secondary to infected necrosis and infected collections. Hence, we observe that the two groups- ESAP and LSAP have different prognosis, the mechanisms leading to complications and mortality are different in them. Advances in intensive care have reduced mortality rates in SAP.[21,22] However, our study from a developing country reports higher mortality rates. The need for predicting the prognosis in a particular patient becomes more important in such a resource poor setting. Hence such newer classifications based on timing of organ failures which are simple and relevant in prognostication in an individual patient would be helpful in-patient management.

In short, we found that death rates in SAP are high even in the current era and the timing and rapidity of onset of organ failure is helpful in predicting the risk of mortality. Early onset of organ failure leads to increased mortality especially from respiratory failure, while late onset organ failure has a better prognosis and sepsis is the major factor responsible for mortality in this group.

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