ORIGINAL ARTICLE

Severe Acute Pancreatitis – Time for a New Stratification

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ABSTRACT

Context Acute pancreatitis is a common surgical emergency. Severe acute pancreatitis has high mortality despite best efforts, and often requires intensive care. **Objectives** We aimed to evaluate the management and outcome of patients admitted with severe acute pancreatitis to our intensive treatment unit and identify their determinants of survival. **Methods** All patients admitted with severe acute pancreatitis to our intensive treatment unit between 2007 and 2010 were retrospectively reviewed. Outcome, clinico-pathological, demographic and radiological information were recorded. **Results** 75 patients were admitted, with an overall mortality of 32%. 51 had complete data for analysis. The median age was 64 years (range 23-95); survivors were younger (median age - 49 years) ($p<0.001$). There was no significant difference between survivors and non-survivors in relation to C-reactive protein ($p=0.898$) or lactate dehydrogenase ($p=0.291$). Antimicrobials did not improve survival ($p=0.70$), although indications and prescription regimes were heterogeneous. Significant determinants of mortality were presence of persistent organ failure or infected pancreatic necrosis ($P=0.002$ & $P=0.003$ respectively). These were used to divide patients into Groups: I – no organ failure or pancreatic necrosis; II – transient organ failure or sterile necrosis; III – persistent Organ Failure or infected pancreatic necrosis; IV – early persistent organ failure ± infected pancreatic necrosis and V – persistent organ failure and infected pancreatic necrosis. All patients who died were in groups III-V, with increasing mortality in higher groups. **Conclusions** Our mortality rate was comparable to the national standard, with higher fatality in older patients. Antimicrobials did not impact on survival, but this requires further evaluation. There appears to be a need to subdivide patients with severe acute pancreatitis to better reflect their outcomes. Our data shows that patients in Groups I-II are likely to do better than group III. Earlier onset of persistent organ failure (Group IV) carries poorer prognosis and combined persistent Organ Failure and infected pancreatic necrosis (Group V) carries the highest mortality. This classification appears to be a better predictor of mortality than Glasgow scoring.

INTRODUCTION

Acute pancreatitis is a common surgical emergency. In the United States of America, it was estimated that acute pancreatitis was the commonest gastrointestinal cause of hospital discharges, accounting for almost 275,000 hospital admissions in 2009 and representing a 30% increase from 2000 [1]. In England, the overall incidence of acute pancreatitis was estimated at 22.4 per 100,000 population with a 3.1% yearly increase and case fatality of 6.7% at 60 days, which was higher for alcoholic than gallstones aetiology [2], although gallstone disease accounts for approximately 50% of cases of acute pancreatitis [3]. The revised Atlanta classification divides acute pancreatitis into three degrees of severity - mild, moderately severe and severe[4]. This definition of severity is based on the degree of organ failure and local or systemic complications [3, 4]. It is therefore important to assess and record the duration of organ failure and also perform a meticulous evaluation of local complications.

Mild acute pancreatitis is defined as acute pancreatitis without organ failure or local/systemic complications. It usually resolves within the initial phase (first 1-2 weeks) with minimal morbidity and very rare mortality [5]. Moderately severe acute pancreatitis encompasses transient organ failure and/or local or systemic complications in the absence of persistent organ failure. The management is guided by the type of local complication, the presence of symptoms and the development of issues related to the local complications e.g. infection of pancreatic and peripancreatic necrosis or bleeding from a pseudoaneurysm. Mortality is significantly less among these patients compared to severe acute pancreatitis and many can be discharged within 2-3 weeks [6].

Severe acute pancreatitis (SAP) is characterised by the presence of persistent organ failure irrespective of the time of development in relation to disease onset (i.e. early or late phase) [7]. Persistence is defined as organ failure lasting for greater than 48 hours [8]. This category of patients

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has prolonged hospitalisation and a higher mortality of around 30%. Older patients are more severely affected than younger patients [9]. The presence of co-morbidities further contributes to the severity of the attack and can worsen the outcome [10, 11]. In the United Kingdom, it has been recommended that severe acute pancreatitis should be recognised within 48hours of admission and should be managed in a high dependency unit (HDU) or intensive treatment unit (ITU) with full monitoring and support systems [3]. Management in, or referral to, a specialist unit is advised for patients with extensive necrosis or with complications requiring specialist interventional radiological, endoscopic or surgical procedures [3].

Most hospitals in the UK currently use the modified Glasgow Scoring System to identify patients with severe pancreatitis and escalate care [12]. There is continued controversy on whether or not a CT scan should be performed on admission except for diagnostic clarification. It is unclear how soon necrosis occurs, but it has been suggested that a scan done at less than a week following the onset of symptoms or during the initial phase (first 1-2 weeks) may grossly underestimate the degree of necrosis [13]. Therefore imaging with contrast enhanced CT (CECT) or MRCP is unlikely to be of benefit in assessment or prognostication in this early phase; and although local complications do develop during this phase they are not proportional to the extent of organ dysfunction, thereby negating them as the predominant determinants of severity during this phase. It has been recommended that a CT scan could be performed in patients with persisting organ failure, new organ failure developing after initial presentation, continuing pain and signs of sepsis. This decision is usually made after approximately one week of hospitalisation [3]. The diagnosis of infected pancreatic necrosis requires the presence of systemic inflammatory response syndrome accompanied by either positive blood culture or fine needle pancreatic aspirate and culture or evidence of free gas on the CECT in the presence of pancreatic necrosis. This is rarely present within the first week of onset.

We performed this study to evaluate the management and mortality rate of patients admitted with SAP to our intensive treatment unit compared with the national standard. We also sought to identify determinants of outcome in this cohort of patients and highlight problems encountered in managing this group of patients and, if possible, provide our recommendations to resolve them.

METHODS

This is a retrospective study of all patients over the age of 18, admitted with SAP to our ITU between 2007 and 2010. They were identified from a prospectively maintained ITU database followed by comprehensive review of case notes. Standard demographics and clinico-pathological data inclusive of age, sex, C-reactive protein (CRP), lactate dehydrogenase (LDH), fluid resuscitation, nutritional supplementation, organ failure, pancreatic necrosis and mortality were recorded. SAP was defined as organ failure >48 h (Atlanta classification), Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 8 and Glasgow score greater than 3 during the initial 48hours after admission.

The patients were stratified into 5 groups based on outcome after the 5 groups **(Table 1)** and the data analysed using SPSS 22.0 (SPSS, Chicago, IL, United States). Ordinal and non-parametric variables were expressed as median with interquartile range (IQR); scale variables were expressed as mean with standard deviation; categorical variables were expressed as frequencies and percentages. The impact of different variables on the outcome was assessed using binary logistic regression analysis.

RESULTS

A total of seventy-five-patients were admitted with SAP to the intensive treatment unit between 2007 and 2010. All cases fulfilled the Atlanta criteria of SAP (and had an APACHE II score >8, and modified Glasgow score >3). There were 23 deaths in total. The median age of patients with SAP was 64 years (range 23-95) with an overall mortality of 32%. Increased age correlated with higher mortality with high statistical significance ($p<0.001$). The median age of patients that survived was 49 years and it was 74 in those that died. Gender was equally distributed between the survivors and non survivors.

Fifty-one-patients had detailed clinical and radiological information available for further analysis. Aetiology of pancreatitis was separated into gallstones, alcohol and not found. There was no significant association between these classifications and mortality ($\chi^2(2.51)=1.587$, $p=0.452$). There was no statistically significant difference between survivors and non-survivors of SAP with parameters such as CRP and LDH (using maximal values in the first 48 hours) ($p=0.898$ & $p=0.291$ respectively).

All but one patient who died were admitted to ITU within 24 hours of presentation. All patients had at least 3L of intravenous fluids within 24 hours of presentation. 29 patients had nutritional supplements started, 9 of whom died (31%); while 17 patients had no documented nutritional supplementation, 9 of whom died (52.9%). Neither of these factors were statistically significant ($\chi^2(1.49)=0.420$, $p=0.517$). 14 patients were not recorded as reviewed by a dietician, of whom 7 died (50%), and again no statistically significant effect was observed ($\chi^2(1.46)=1.470$, $p=0.225$).

Forty three patients received antibiotics. 61% (n=31) of patients were started on antibiotics on admission. Seven patients were confirmed to have pancreatic infections

Table 1. Proposed stratification based on clinical severity of pancreatitis.

Group	Descriptor
I	no organ failure or pancreatic necrosis
II	transient organ failure or sterile necrosis
III	persistent organ failure or infected necrosis
IV	early persistent organ failure
V	persistent organ failure and infected pancreatic necrosis

based on positive culture 4 had chest infections, 2 had urinary tract infection and 1 had Clostridium difficile. The causative organism in all the extra-pancreatic infections was Gram negative bacilli. All but two of the patients with proven pancreatic infection died. The first choice of antibiotics were cefuroxime and metronidazole in 45% of the patients, co-amoxiclav and metronidazole in 12% of cases and tazobactam-piperacillin ± metronidazole in 14% of cases. In 26% of cases, a combination of imipenem ± fluconazole ± gentamicin ± vancomycin was used. The use of antimicrobials did not seem to improve survival ($\chi^2(3.51)=1.818$, p=0.611). In addition, there was no significant association between the timing of antimicrobials (whether started on admission (58.1% survival) or later in the course of the episode (83.3% survival)) and survival ($\chi^2(1.43)=2.432$, p=0.119).

Mann-Whitney U tests showed a statistically significant difference in Glasgow score between those who died (median=4) and survived (median=3) (U=179.5, p=0.016) as well as a difference in Atlanta 2012 score (uniform score of 3 among those who died, maximum and median of 3 with minimum of 1 among those who survived; U=171, p=0.001). Mortality expressed for nominal variables is shown in **Table 2**. Mortality expressed for ordinal and scale variables is shown in **Table 3**.

A proposed stratification system was suggested based on the variables that showed significant results from the bivariate analysis: Persistent organ failure, Organ dysfunction on admission to ITU (as a proxy measure of early persistent organ failure as all but one patient, were admitted to ITU within the first 24 hours of presentation) and Infected necrosis. This showed statistical significance when determining survival (P<0.001). **Table 4** shows the breakdown of survival rate of our cohort with the proposed classification system. To facilitate comparison, **Table 5** shows the breakdown of survival rate with the Glasgow Score.

Logistic Regression models

Logistic regression models were created. With no independent variables included, a prediction success rate of 64.7% was achieved for mortality. Success increased to 70.6% using Glasgow Score. When significant variables from binary analysis were used (Persistent organ failure, Organ dysfunction on admission to ITU, infected necrosis), a success rate of 77.6% was achieved; the proposed stratification system based on these variables achieved 72.5% success. Finally, combining Glasgow Score with the Proposed Classification achieved 77.1% success, with a sensitivity of 66.67% and specificity of 87.88%. The model showed good fit (Hosmer-Lemeshow $\chi2=3.296$, p=0.856). Incorporating APACHE II as an independent variable in the model does not improve the predictive success rate.

DISCUSSION

This is a retrospective analysis detailing the management and outcome of patients with severe acute pancreatitis in the intensive treatment unit. The disease is still characterised by high morbidity and mortality especially when associated with increased age, necrosis or persistent organ failure.

The mortality rate of 32% in our study is similar to that reported in London hospitals [14, 15], but higher than the rate reported from Australia [16] and Spain [17]. It is also higher than the recommended limit of 30% by the UK Working Party on Acute Pancreatitis [3]. The reason for this high mortality in the UK is unclear but one possibility is that British patients have higher co-morbidities, which thus increases their overall mortality [18, 19]. A second possibility is the varying trusts which make up the NHS may not be following best practice, perhaps due to lack of awareness or capacity to deliver the care recommended by the UK working party.

Our study found that the mean age of survivors was significantly lower than that of non-survivors. We therefore agree with the general consensus that older patients have worse prognosis in severe acute pancreatitis. We further analysed specific indices such as CRP and LDH. Our findings showed that, in SAP, these indices have a poor ability to predict survival. Newer markers such as Procalcitonin and Interleukin-8 have been shown to be more accurate in predicting the severity of pancreatitis, presence of sepsis, infected necrosis and clinical outcome [20, 21]. However, these were not routinely performed in our institution and hence we were unable to analyse its effect in the current cohort.

Maximum Glasgow score in the first 48 hours did predict survival, as expected. A Glasgow score of 3 or less on admission is associated with a better survival while a Glasgow score of ≥ 4 at 48 hours indicates a poor prognosis [12]. In our cohort, Glasgow scores were not recorded at the recommended intervals frequently enough at 48hours to enable meaningful analysis. So patients who may have had an initial low score could have advanced or decreased during the the period in question.

The mean APACHE II scores of 12 and 20 for survivors and non-survivors respectively were statistically significant (P<0.001) and are similar to findings in previous studies in the literature [22, 23]. A combination of Glasgow and APACHE II scores seem to be an accurate predictor of survival in SAP in the critical care setting. However APACHE II is not calculated routinely on admission of the pancreatitic patient until they are moved to the intensive care setting.

Nutritional support has been taken into account in the latest BSG guidelines for management of acute pancreatitis. According to this, although enteral feeding has failed to demonstrate benefit in mild pancreatitis, consideration for this is needed in severe pancreatitis [3]. In the current cohort, based on the documentation available, no significant survival benefit was noted despite nutritional support. We found no difference in the length of stay in the critical care unit between survivors and non-survivors of SAP, which is similar to findings in London [15] and Portugal [24].

Table 2. Mortality expressed for nominal variables.

Determinant		n	Survivors	Deaths	% mortality	χ2	p
Persistent organ failure	Yes	35	19	16	45.7	9.5	0.002
	No	14	14	0	0		
Organ dysfunction on admission to ITU	Yes	37	20	17	45.9	6.696	0.01
	No	14	13	1	7.1		
Pancreatic necrosis	Yes	15	8	7	53.3	1.532	0.216
	No	35	25	10	28.6		
Infected pancreatic necrosis	Yes	9	2	7	77.8	8.637	0.003
	No	42	31	11	26.2		
Persistent organ failure and infected necrosis	Yes	8	2	6	75	6.55	0.01
	No	43	31	12	27.9		
Early organ failure and any necrosis	Yes	11	4	7	63.6	5.52	0.019
	No	39	29	10	25.6		
Nutritional Support	Yes	29	20	9	31	0.42	0.517
	No	20	12	8	40		
Antibiotics on Admission	Yes	31	18	13	41.9	1.527	0.217
	No	20	15	5	25		
Any Antimicrobial Use	None	7	4	3	42.9	1.251	0.535
	Antibiotics	19	14	5	26.3		
	Antibiotics + Antifungals	24	14	10	41.7		

Table 3. Mortality expressed for ordinal variables.

Determinant	Survivors			Deaths				
	N	Median	IQR	N	Median	IQR	U	p
LDH	30	365.5	194	13	311	220	194.5	0.989
Glasgow Score	33	3	1	18	4	2	179.5	0.016
	N	Mean	SD	N	Mean	SD	t	p
CRP	33	285.43	109.01	18	246.68	148.05	1.067	0.291
APACHE 2	50	13.34	5.61	24	18.03	9.1	2.35	0.025

Table 4. Survival rate of our cohort with the proposed classification

Group	n	Survivors	Deaths	% mortality
I (No OF/PN)	9	9	0	0
II (transient OF/sterile PN)	4	4	0	0
III (pOF/IPN)	3	2	1	33.3
IV (early pOF)	27	16	11	40.7
V (OF + IPN)	8	2	6	75

Table 5. Survival rate of our cohort with the Glasgow score.

Score	n	Survivors	Deaths	% mortality
1	2	2	0	0
2	6	5	1	16.7
3	15	11	4	26.7
4	17	11	6	35.3
5	10	4	6	60
6	1	0	1	100

On analysis of the data, it seemed patients could be divided into four groups depending on the presence or absence of organ failure and pancreatic necrosis which could then be further analysed. Patients in groups I and II are almost always likely to survive. However, the presence of infected necrosis or persistent organ failure in SAP (group III) is associated with high mortality. The mortality increases if onset of organ failure is earlier in the disease process The combination of infected necrosis and early persistent organ failure (group V) is highly fatal in SAP, even when managed in the critical care unit. The majority of the patients in our cohort fell into groups III (n=15) and IV (n=27), with 8 patients in group V. All the patients that died were in these three groups, with 75% mortality in group V. Five of the patients in group IV and V underwent necrosectomy while 1 had CT-guided drainage of an infected acute fluid collection.

When looking at the effect of antibiotics by group, all the patients in groups I and II survived whether or not they received antibiotics. The use of antibiotics in management in SAP remains controversial and there is no consensus on its use in any case of acute pancreatitis.. In a review of controlled studies by Wilmer, he concluded that antibiotics may decrease the number of complications from SAP but not the mortality and that there was no place for prophylactic antibiotics in acute mild pancreatitis [25]. A 2012 meta-analysis on the subject concluded that prophylaxis is not indicated for SAP but use should be considered on a patient per patient basis. However, it is difficult with the pooled data to differentiate the effects of different antibiotics as individual trials were either underpowered or methodologically flawed [26]. The UK Working party guidelines suggest that prophylactic antibiotics are only considered in cases where necrosis is

greater than 30% and for a maximum duration of 14 days unless microbiological evidence of sepsis is obtained [4].

In our study, we did not specifically examine complications from SAP, but the use of antibiotics in the setting of severe attacks did not seem to impact on survival, regardless of the indication. Furthermore, the combination of different types of antibiotics such as carbapenems, quinolones and nitroimidazoles conferred no survival advantage in SAP. Among patients in Groups III, IV and V, antibiotics did not improve survival. It is therefore highly likely that other factors such as age, co-morbidities, extent of pancreatic necrosis and degree of organ failure are more important. We suggest that broad spectrum antibiotics be considered only in the presence of sepsis on admission and this should be reviewed within the first 24 hours following the diagnosis of acute pancreatitis. There should be a clear indication for the use of antibiotics and the choice should be appropriate to the system being treated. Pancreatic and extra-pancreatic infections are strongly associated with increased mortality, in similarity with previous studies [27, 28]. The commonest extra-pancreatic infections was pneumonia, with the causative organism in all cases being Gram negative bacilli. The current literature suggests there may be some benefit from treatment with imipenem in necrosis [29].

We found that patients who were admitted with organ failure early Severe Acute Pancreatitis or eSAP), had a worse prognosis and therefore we created an extra group to accommodate these patients (group IV), as early organ failure appeared to be an independent predictor of mortality. When running a logistic regression model the factors that produced the most accurate prediction of mortality were persistent organ failure, organ dysfunction on admission to ITU and infected necrosis giving a success rate of 77.6%, compared to maximum Glasgow score (70.6%). However when looking at the range of maximum Glasgow scores (within the first 48 hours), patients who died scored anything from 2-6 inclusive, which makes it difficult to narrow down who has a worse prognosis. If the same patients are classified according to the proposed stratification, mortality clearly falls within the last 3 groups. This intuitively makes it easier to make decisions for escalation of care , however some of the parameters won't be available before the end of the first week after admission making such stratification of less use during the first 48 hours of admission.

We therefore propose that patients who would fit the Atlanta criteria for severe acute pancreatitis be further divided into five groups at the earliest possible opportunity i.e. once all the necessary parameters and results of investigations become available which may not be before the end of the third day of admission which provides a more accurate determination of outcome based on pancreatic necrosis and organ failure: *group I* (no OF or PN), *group II* (transient OF or sterile PN), group III (persistent OF or infected PN (IPN), group IV (eOF) and group V (persistent OF and IPN). When this proposed stratification is tested as a model to predict survival in SAP using logistical regression, this showed a higher ability to correctly predict mortality (72.5%) than Glasgow score. Interestingly the combined use of Glasgow and the proposed stratification raised this to 77.1%. More data, both internal and external is needed to further validate this model

CONCLUSIONS

In conclusion, severe acute pancreatitis requiring admission to the critical care unit is associated with significant morbidity and high mortality. Older patients with SAP have a worse prognosis than their younger counterparts. The use of antibiotics did not impact survival in our cohort of patients with SAP and neither did the combination of different types of antibiotics. However, antibiotics should be considered in the presence of sepsis on admission, although this should be reviewed within 24 hours of admission following the diagnosis of acute pancreatitis and the source of sepsis should be identified.

A combination of high Glasgow and APACHE II scores is seems to be a good predictor of mortality in SAP in the critical care setting. It is our view that acute pancreatitis survival and clinical outcome (mortality) in SAP of greater than 3 days duration who needed admission to ITU are probably better represented by stratifying patients into the following 5 groups: I - no OF or PN, II - transient OF or sterile PN, III - persistent OF or IPN, IV - early OF, V - persistent OF and IPN. This is in broad agreement with the consensus study outlining the new international classification of pancreatitis [30] and provides data to support the determinant-based classification of patients diagnosed with severe acute pancreatitis.

This is a retrospective study of a limited cohort of patients and further research both at our unit and other similar units is essential to attempt to validate or refute our findings. With the permission of the local ethics committee, we intend to apply this stratification at our hospital initially as an adjunct alongside the currently practised Modified Glasgow scoring system to test its performance. We aim to prospectively evaluate the proposed stratification and then present our findings in due course.

Competing and conflicting Interests

The authors have no competing or conflicting interests to declare.

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