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RAPID COMMUNICATION

Timing of mortality in severe acute pancreatitis: Experience from 643 patients

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Abstract

AIM: To determine the timing of mortality after onset of severe acute pancreatitis (SAP) and the course of the disease in a large series of patients.

METHODS: From July 1996 to June 2005, all patients diagnosed with acute pancreatitis at Chang Gung Memorial Hospital, Taipei, Taiwan were retrospectively studied. Three thousand two hundred and fifty episodes of acute pancreatitis were recorded in 2248 patients (1431 males and 817 females; median age, 55.6 years; range, 18-97 years). Mortality was divided into two groups: early death (≤ 14 d after admission), and late death (> 14 d after admission). The clinical features of patients in these two groups were compared.

RESULTS: Although the overall mortality rate of acute pancreatitis was 3.8% (123/3250), mortality rate of SAP was as high as 16.3% (105/643). Of those 105 SAP mortalities, 44 (41.9%) deaths occurred within the first 14 d after admission and 61 (58.1%) occurred after14 d. Incidence of early death did not significantly differ from that of late death. The co-morbidities did not contribute to the timing of death. Early deaths mainly resulted from multiple organ failure. Late deaths were mainly caused by secondary complication of infected necrosis. Intra-abdominal bleeding significantly caused higher mortality in late death.

CONCLUSION: Approximately half (42%) of SAP deaths occur within 14 d and most were due to multiple organ failure. The late deaths of SAP were mostly due to infected necrosis.

Key words: Severe acute pancreatitis; Mortality; Multiple organ failure

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INTRODUCTION

Acute pancreatitis is a common disorder ranging in severity from mild disease to multiple organ failure (MOF) and sepsis. Severe acute pancreatitis (SAP) has a 20% mortality rate[1,2]. SAP reveals its progresses into two phases. The early phase refers to the first 7 to 14 d after onset of acute pancreatitis complicated with systemic inflammatory response syndrome (SIRS) and MOF due to release of large amount of cytokine[3,4]. In the late phase (14 to 28 d after onset of acute pancreatitis), the disease may be complicated by infection of pancreatic necrosis and secondary MOF[5]. Although two peak mortality rates are observed in the course of SAP[6], death occurs primarily in the early or late phase remains unclear. The causes of death in early and late phase of SAP varied in several reports[3,7-14]. This study analyzes the time of death in a large series of patients with SAP and compares clinical features of early and late mortality to fully clarify this disease entity.

MATERIALS AND METHODS

Subjects

Medical charts and computerized records for all patients with acute pancreatitis treated at the Division of General Surgery of Chang Gung Memorial Hospital from July 1996 to June 2005 were retrospectively reviewed. During this period, 3250 episodes of acute pancreatitis were recorded in 2248 patients (1431 males and 817 females; median age, 55.6 years; range, 18-97 years). Acute pancreatitis was diagnosed if clinical features and imaging studies revealed elevated serum amylase and lipase (at least three times higher than the normal level). The definition of severe acute pancreatitis (SAP) was based on the Atlanta classification[5].

Methods

The following general characteristics were recorded: demographic data, etiological factors, early prognostic signs (Ranson's and Acute Physiology and Chronic Health

Table 1 Characteristics of severe acute pancreatitis patients with early (≤ 14 d after admission) and late death (>14 d after admission)

	Early death (n = 44)	Late death (n = 61)	P value
Age, yr (range)	54.7 (34-93)	56.3 (30-84)	0.904
Gender			0.147
Females	32 (72.7%)	36 (59.0%)	
Males	12 (27.3%)	25 (41.0%)	
Etiology			
Biliary	13 (29.5%)	32 (52.5%)	0.019
Alcoholic	13 (29.5%)	11 (18.0%)	0.166
Idiopathic	12 (27.3%)	7 (27.9%)	0.946
Other	6 (13.7%)	1 (1.6%)	
Ranson's score	3.9 (1-9)	4.1 (1-8)	0.676
APACHE-II score	22.4 (9-31)	24.5(11-32)	0.732
BMI, (Kg/m^2)	24.5 (18-39)	23.6 (19-48)	0.814
Comorbidity			0.557
No comorbidity	9 (20.5%)	9 (32.1%)	
1-2 organ systems	22 (50.0%)	22 (50.0%)	
3-4 organ systems	8 (18.2%)	17 (27.9%)	
> 4 organ systems	5 (11.3%)	4 (6.6%)	

BMI: Body mass index.

Evaluation Ⅱ score)[6] at 48 h after admission, body mass index (BMI) and presence or lack of necrosis. Necrosis was deemed to be present upon observation of aseptic or infected necrosis. The aforementioned factors were compared between early and late deaths. Instances of comorbidity and cause of death were recorded. Pancreatic necrosis was defined by the character of abnormalities on contrast-enhanced computerized tomography scan[3,5] or the findings of surgical operation. Infection was considered present when necrotic tissue obtained from percutaneous fine-needle aspiration or surgical specimen was positive for bacteria culture.

Early deaths were defined as deaths occurring within 14 d after admission, and late deaths were defined as deaths occurring more than 14 d after admission. Comorbidity was defined as presentation of a pre-existing disease before SAP which became an active problem. Chronic obstructive pulmonary disease, cardiac insufficiency (New York Heart Association; NYHA class Ⅲ or Ⅳ), renal insufficiency, liver cirrhosis, diabetes mellitus, and malignant disease diagnosed within three years before the current episode (immunological disease or chronic immunosuppressive medication) were included.

All patients received treatment from the same physicians throughout the study. However, treatments varied in duration. In cases of biliary pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy was performed. Several patients received intravenous continuous infusion of antiproteases (gabexate mesilate). Antibiotics were routinely administered for infected pancreatitis. Surgery was performed upon infection of necrotic tissue. However, in rare cases, hemorrhage, pancreatic ascites, perforation, pseudocyst rupture or its rapid increase in size were indications of surgery.

Table 2 Pancreatic necrosis and causes of death in severe acute pancreatitis patients with early and late mortality n (%)

Pathology and cause of death	Early deaths (n = 44)	Late deaths (n = 61)	P value
Pathology			
Edematous	2 (4.5)	3 (4.9)	0.95
Sterile necrosis	21 (42.7)	14 (23.0)	0.008
Infected necrosis	6 (13.6)	31 (50.8)	< 0.0001
Necrosis without microbiological data	15 (34.2)	13 (21.3)	0.144
Cause of death			
MOF	40 (90.9)	9 (14.8)	< 0.0001
Infected necrosis	0 (0.0)	14 (23.0)	0.001
Infected necrosis + MOF	1 (2.3)	22 (36.1)	< 0.0001
Intra-abdominal bleeding	1 (2.3)	12 (19.7)	0.008
Heart failure	2 (4.5)	2 (3.3)	0.738
Cerebral stroke	0 (0.0)	2 (3.3)	0.225

MOF: Multi-organ failure.

Statistical analysis

All data were presented as percentage of patients or mean ± SD. Numerical data were compared using independent two-sample t tests. Nominal data were compared using χ^2 test, Mann-Whitney U-test, and Mantel-Haenszel linear-by-linear association when appropriate. All statistical analyses were performed using the SPSS computer software package (Version 11.0, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The present study included 3250 episodes of acute pancreatitis observed in 2248 patients at our facility. Presence of SAP was observed in 643 (19.8%) patients based on characteristics of pancreatic necrosis. The other 2607 (80.2%) episodes were mild forms of acute pancreatitis. Although the overall mortality rate of acute pancreatitis was 3.8% (123/3250), mortality rate of SAP was as high as 16.3% (105/643) All deaths involved patients experiencing their first episode of pancreatitis. With equal distribution, of those 105 SAP mortalities, 44 (41.9%) patients died within 14 d of admission, and 61 (58.1%) died after 14 d of admission. The two groups did not differ in gender, age, Ranson's and APACHE Ⅱ score, BMI, or co-morbidity. However, early death significantly differed from late death in etiology (Table 1). Higher percentage of biliary pancreatitis patients developed more late deaths than early deaths. Forty-two of the 44 (95.5%) patients with early mortality had necrotizing pancreatitis. Similarly, 58 of the 61 (96.2%) patients with late mortality presented necrotizing pancreatitis. A significantly higher ($P < 0.0001$) number of patients died from infected necrosis in the late death group (Table 2). On the other hand, sterile necrosis occurred more frequently in early deaths than late deaths ($P = 0.008$). Forty of the 44 (90.9%) patients suffered early deaths related to MOF (Table 2). Late deaths occurred post-operatively in 37 patients with infected necrosis (23 also presented MOF). A higher incidence of

Table 3 The incidence of early death in severe acute pancreatitis in this study and in the literature

	Total number	Early death (%)
Renner *et al*, 1985[8]	405	60
Wilson *et al*, 1988[15]	126	55.5
Lankisch *et al*, 1996[17]	37	56.7
Isenmann *et al*, 2001[19]	36	55.5
Present study	105	42

hemorrhagic complication from intra-abdominal bleeding was noted in the late death group than in the early death group ($P = 0.008$). Clearly, MOF was more prevalent in the early death group, and death due to infection was more common in late deaths. In addition to the pancreatic pathologic complications, co-morbidities, such as stroke or heart failure, did not significantly differ between the two groups.

DISCUSSION

According to previous studies, the pattern of morbidity and mortality in SAP varied[8-10,12,14-19]. The primary causes of death in SAP remain controversial. A literature review reveals early mortality rates ranging from 0 to 80% (mean value, 53.9%, Table 3). In present study, the early mortality rate was 42%. The cause of the wide range in reported early mortality rates is unclear. Aggressive restoration of multiple organ failure (MOF) may be important to reduce early mortality rate. On the other hand, as shown in this study, the studied populations have consisted of groups of patients from a single department or ward rather than from the entire hospital population. This fact may explain the lower early mortality rate. In addition, time of admission may also be related to variations in SAP early mortality rates[12]. The other explanation is that the early surgical debridement was avoided in this study. It could prevent the frequent conversion of sterile necrosis to infected necrosis which resulted in increased early SAP mortality rate[19].

The present study revealed that approximately half of the deaths (41.9%) occurred within two weeks; the major cause was MOF. Extended pancreatic necrosis, especially the extent of intra-pancreatic parenchyma necrosis, leads to a high incidence of early organ failure[19]. In addition, if early organ failure occurs at the time of admission in SAP, the risk of ongoing and progressive organ failure remains extremely high[20]. According to recent reports, if organ failure worsens in the first week of admission, mortality rate increases significantly[21,22]. In our study, once the disease has been initiated by the pathogenetic mechanism, the course and outcome were not influenced by underlying etiological factors, demographic features, physical features or co-morbidity. Even some reports indicated the importance of co-morbid medical problems in SIRS and MOF in elderly SAP patients, in addition to the effect of infected necrosis[6,14]. The present study revealed no significant differences in age or pre-existing disease. Early prognostic factors, such as Ranson's score and APACHE Ⅱ score, did not differentiate patient risk of early mortality or late mortality in SAP. However, some reports suggest that obesity increases MOF rate and SAP mortality[14,23]. Similar to other studies[9,12,24], BMI values were not associated with differences in early or late death in SAP in the present study.

The present study demonstrated vital role of MOF occurrence in the outcome of SAP. Considering all SAP cases were fatal (105 patients), a high incidence of MOF was observed in this group. Death caused by MOF was observed in 72 (68.6%) patients. In particular, 24 of the 38 patients with infected necrosis suffered at least two organ failures directly related to the fatal outcome. According to previous reports[3-6,25-29], the standard treatment for infected pancreatic necrosis, including antibiotics and surgical resection or drainage procedure, is widely accepted. However, in the present study, the results of MOF management remained poor in SAP cases[6,25,27]. As a result, the goal of therapeutic planning was based on continuous resuscitation and restoration of failed organs. However, McKay *et al*[10] documented that even after intensive treatment, 40% of patients died 3 d after hospital admission.

This study demonstrated that MOF occurred more frequently in the early death group than in the late death group, being the major cause of early death in SAP. However, the incidence of infected necrosis was higher in the late death group than in the early death group. Other causes of death, including stroke or heart disease, were rare and statistically insignificant. Therefore, in the first two weeks of admission, the goals of treatment should be aggressive resuscitation, restoration of failed organ systems and inhibition of MOF progression. In the late phase, controlling infection and preventing infected necrosis is vital. The importance of co-morbidity control is not significant in elderly patients. SAP remains a serious medical problem. Effective control of early MOF and treatment of systemic complications associated with the infected necrosis require innovative strategies.

In conclusion, approximately half (42%) of SAP deaths occur within two weeks and most are due to multiple organ failure. The data revealed the significance of multiple organ failure in the outcome of SAP. The late deaths of SAP are mostly due to infected necrosis.

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