ORIGINAL ARTICLE

Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis

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ABSTRACT

Objective In patients with pancreatitis, early persisting organ failure is believed to be the most important cause of mortality. This study investigates the relation between the timing (onset and duration) of organ failure and mortality and its association with infected pancreatic necrosis in patients with necrotising pancreatitis.

Design We performed a post hoc analysis of a prospective database of 639 patients with necrotising pancreatitis from 21 hospitals. We evaluated the onset, duration and type of organ failure (ie, respiratory, cardiovascular and renal failure) and its association with mortality and infected pancreatic necrosis.

Results In total, 240 of 639 (38%) patients with necrotising pancreatitis developed organ failure. Persistent organ failure (ie, any type or combination) started in the first week in 51% of patients with 42% mortality, in 13% during the second week with 46% mortality and in 36% after the second week with 29% mortality. Mortality in patients with persistent multiple organ failure lasting <1 week, 1–2 weeks, 2–3 weeks or longer than 3 weeks was 43%, 38%, 46% and 52%, respectively (p=0.68). Mortality was higher in patients with organ failure alone than in patients with organ failure and infected pancreatic necrosis (44% vs 29%, p=0.04). However, when excluding patients with very early mortality (within 10 days of admission), patients with organ failure with or without infected pancreatic necrosis had similar mortality rates (28% vs 34%, p=0.33).

Conclusion In patients with necrotising pancreatitis, early persistent organ failure is not associated with increased mortality when compared with persistent organ failure which develops further on during the disease course. Furthermore, no association was found between the duration of organ failure and mortality.

Significance of this study

What is already known on this subject?
- In patients with necrotising pancreatitis, early persisting organ failure is believed to be the most important cause of mortality.

What are the new findings?
- This is the first study to provide detailed insight into the association between onset, duration and type of organ failure with mortality in patients with necrotising pancreatitis.
- In contrast to previous studies, we found no association between the onset of organ failure and mortality. Also, no association was found between the duration of organ failure, infected pancreatic necrosis and mortality.

How might it impact on clinical practice in the foreseeable future?
- The lack of a direct association between duration of organ failure and the risk of mortality may influence decision making in the intensive care unit when treating patients with necrotising pancreatitis.
- The lack of an association between the onset of organ failure and mortality challenges the concept of a biphasic disease course in acute pancreatitis.
- The lack of increased mortality rates in patients with organ failure and infected pancreatic necrosis compared with patients without infected pancreatic necrosis, challenges the supposed impact of infected pancreatic necrosis on outcome.

INTRODUCTION

Organ failure is the most important determinant for outcome in acute pancreatitis with a mortality rate around 30%.[1–3] Approximately 45% of patients with necrotising pancreatitis develop organ failure with prolonged intensive care unit (ICU) admission and a complicated disease course, most often requiring multiple invasive interventions.[4 5] Consequently, organ failure in necrotising pancreatitis leads to considerable utilisation of healthcare resources and costs.[6]

In the early phase after the onset of pancreatitis, the release of inflammatory chemokines and cytokines during the systemic inflammatory response syndrome (SIRS) contributes to the development of organ dysfunction.[7] Organ failure that lasts <48 hours, that is, transient organ failure, is associated with low mortality and low risk of complications. On the contrary, persisting organ failure, that is, lasting >48 hours, is associated with very high mortality rates.[8–10] Organ failure is a dynamic process which is not limited to the first week and may develop at any stage of the disease. In the early phase, conditions inducing pancreatitis and

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mediators of SIRS play an important role in the development of organ failure. Further on in the disease course, general after several weeks, infection of pancreatic necrosis may be accompanied by sepsis and lead to organ failure. Conversely, infected pancreatic necrosis or other infections such as pneumonia may also occur early in the disease course, thus it can be difficult to determine whether organ failure is caused by SIRS or sepsis.[1 11]

Three organ systems are considered most important in the assessment of organ failure in acute pancreatitis—the cardiovascular, respiratory and renal system.[1] Although numerous studies have reported the general impact of organ failure, the impact of specific characteristics and dynamics of organ failure (such as onset, duration and type of failing organ systems) are largely unknown. These earlier studies lack robust, prospective and detailed data sets with specified analyses. First, only data on admission or only daily assessment during the first week were reported precluding any time-related analysis.[8 9 12–17] In daily practice, the disease course is often protracted and the development of organ failure or that of infected pancreatic necrosis is not limited to the first week. Second, various definitions for organ failure are used.[14 15 17 18] Third, many studies were single-centre studies,[9 12–17 19–25] included fewer than 100 patients with organ failure[9 13–15 17 19–23 25–27] and were performed in tertiary referral centres with >40% of patients transferred from other hospitals during different phases of the disease which may limit the data regarding organ failure in the early phase.[20 26 28] Finally, when analysing the impact of organ failure and infected pancreatic necrosis on mortality, the onset and duration of organ failure in relation to infected pancreatic necrosis is important. Previous studies claimed a relationship between the onset and duration of organ failure on mortality in necrotising pancreatitis, although the exact timing of the onset of organ failure was often not reported.[9 15 22] These limitations seriously hamper pooling of these studies and prohibit meaningful extrapolation of the reported outcomes to other centres.

Improved knowledge about the details of organ failure in acute pancreatitis will help to better estimate the prognosis of patients who suffer from organ failure, especially when end-of-life decisions need to be discussed after a prolonged period of organ failure. Furthermore, an improved insight into the details and outcome of organ failure may provide a base for differential and new treatment strategies in severe acute pancreatitis.

The aim of this study is to assess the impact of the different characteristics and dynamics of organ failure on mortality and assess its association with infected pancreatic necrosis.

METHODS

Patients and study design

This was a prospective multicentre cohort study in 21 Dutch hospitals in patients with necrotising pancreatitis in the period 2004–2008. The protocol of this study was described previously.[5 29] In summary, patients with acute pancreatitis were registered on admission and screened for eligibility in the PRObiotics in PAncreatitis TRIAl (PROPATRIA) and PAncreatitis, Necrosectomy versus sTEp up appRoach (PANTER) trials.[30 31] Irrespective whether or not patients were included in these trials, patients with pancreatic necrosis or extrapancreatic necrosis were included in the present study. Antibiotics were administered only if there was suspected or proven infection, that is, prophylactic antibiotic therapy was not prescribed. Invasive interventions were generally performed only in case of (suspected) infected necrosis and, if possible, postponed beyond 4 weeks of disease onset. The decision to intervene was left at the discretion of the physician and no routine fine-needle aspiration was performed. The physician was supported in this decision by the multidisciplinary expert panel.[32]

The present study is an analysis of all patients with organ failure in this prospective database of 639 patients with necrotising pancreatitis (see online supplementary material 2). These data have not been analysed previously. We investigated the onset, duration and type of organ failure in necrotising pancreatitis. The association between the characteristics of organ failure and mortality was studied. Finally, the association between organ failure and infected pancreatic necrosis was analysed.

Data collection

Data on patients' demographics and laboratory investigations during the first 3 days of hospital admission were prospectively collected. In addition, during hospital stay, data regarding onset, duration and type of organ failure (ie, respiratory, cardiovascular and renal failure) were registered daily. The following data were also recorded: age, sex, prognostic scores (Acute Physiology and Chronic Health Evaluation (APACHE)-II Score, Modified Glasgow Score, C reactive protein) at hospital admission, CT severity index, hospital and ICU stay and invasive interventions (ie, percutaneous drainage or surgical debridement). Contrast-enhanced CT (CECT) was routinely performed 7–10 days after admission in patients included in the PROPATRIA trial. In all other patients, CECT was performed in case of clinical deterioration at the discretion of the treating physician. The presence of extrapancreatic necrosis and extent of parenchymal necrosis was based on the highest CT severity index of all CECTs performed during admission. In case of a transferred patient, data were retrieved from the centre of primary hospital admission.

Definitions

Organ failure was defined as failure of the respiratory, cardiovascular or renal system (see online supplementary material 1). Persistent organ failure was defined as organ failure lasting >48 hours (ie, present on more than two consecutive days). Multiple organ failure was defined as failure of two or more organ systems. If patients suffered from intermittent episodes of organ failure, the longest continuous episode of failure of either the respiratory, cardiovascular or renal system was used to study the relation with mortality. Based on the duration of the longest episode, patients were designated having persistent or transient organ failure. Subsequently, a distinction was made between single and multiple organ failure. For example, a patient who suffered from *persistent single* organ failure but only *transient multiple* organ failure, was included in the group of patients with *persistent single* organ failure. A patient who suffered from *persistent single* organ failure and *persistent multiple* organ failure was included in the group of patients with *persistent multiple* organ failure. Patients with early fulminant pancreatitis who died within 48 hours after onset of organ failure and hence were not able to develop organ failure lasting >48 hours (ie, persistent organ failure), were included in the group of patients with persistent organ failure. The prevalence of organ failure represents the total number of organ systems failing per day divided by the number of patients alive; the incidence represents the number of new-onset organs failing divided by the number of patients alive per day. Necrotising pancreatitis was defined as either pancreatic parenchymal necrosis with or without extrapancreatic necrosis, or extrapancreatic necrosis alone.[1] Infected pancreatic necrosis was defined as a positive culture of pancreatic or extrapancreatic necrotic tissue obtained by fine-needle

aspiration or from the first intervention, or the presence of gas in the necrotic collections on CECT.

Statistical analysis

Normal data are presented as mean±SD or as median with IQR. Differences in continuous variables between patients with and without organ failure were tested with the Mann-Whitney U test. Proportions were compared using the χ^2 test or by linear-by-linear χ^2 association test in case of ordinal categorical variables. A multivariable logistic regression analysis, adjusted for age, sex, American Society of Anesthesiologists (ASA, coded as categories) classification and CT severity index, was performed to assess the association between onset of organ failure and mortality. The association between organ failure, infected pancreatic necrosis and mortality was studied and also included in the multivariable model to study whether the risk for mortality was independent of these covariates. Results are presented as unadjusted and adjusted ORs with 95% CIs. As explorative analysis, a sensitivity analysis was performed without patients with mortality occurring within 10 days after admission. A time to event model was used for analyses focusing on the timing (ie, onset) of organ failure in relation with mortality. Results of this Cox regression model are presented as unadjusted and adjusted HRs with 95% CIs. The proportional hazards assumption in the Cox regression model was assessed by including interaction effects of follow-up time and covariates in a Cox regression with time-dependent covariates. A two-sided $p<0.05$ was considered statistically significant and analyses were performed with IBM SPSS Statistics V.24.0.

RESULTS

Organ failure occurred in 240 of 639 patients (38%) with necrotising pancreatitis. A total of 1186 patients with acute pancreatitis were assessed for eligibility (see online supplementary material 2). Table 1 presents the characteristics of patients with and without organ failure. At baseline, diabetes mellitus was present in 20 of 240 patients with organ failure (8%) compared

Table 1 Characteristics of patients with or without organ failure

Characteristic	All patients (n=639)	Organ failure n=240 (38%)	No organ failure n=399 (62%)	P values
Age (years)	58 (45–70)	61 (50–71)	56 (43–70)	0.003*
Male sex, no. (%)	398 (62)	158 (66)	240 (60)	0.15†
ASA class on admission (%)				<0.001‡
I	202 (32)	59 (25)	143 (36)	
II	347 (54)	131 (55)	216 (54)	
III	90 (14)	50 (21)	40 (10)	
Pre-existent chronic disease, no. (%)	28 (4)	20 (8)	8 (2)	<0.01†
Pre-existent diabetes mellitus, no. (%)	52 (8)	20 (8)	32 (8)	0.89†
Dialysis prior to admission, no. (%)	9 (1)	4 (2)	5 (1)	0.67†
Body mass index (kg/m^2)§	27 (25–31)	27.1 (25–31.1)	26.8 (25–30.7)	0.59*
Aetiology (%)				0.91†
Gallstones	304 (48)	114 (48)	190 (48)	
Alcohol abuse	150 (24)	54 (23)	96 (24)	
Other	63 (10)	26 (11)	37 (9)	
Unknown	122 (19)	46 (19)	76 (19)	
Predicted severity				
APACHE II score¶	8 (5–11)	9 (6–13)	7 (4–10)	<0.001*
Modified Glasgow Score¶	3 (2–5)	4 (3–5)	3 (2–4)	<0.001*
Highest C reactive protein 48 hours after admission**	291 (±130)	284 (±134)	295 (±127)	0.24*
CT severity index	4 (4–8)	6 (4–10)	4 (4–6)	<0.001*
Pancreatic parenchymal necrosis, no. (%)	324 (51)	163 (68)	161 (40)	<0.001†
Extent of pancreatic necrosis, no. (%)				<0.001†
<50%	530 (83)	170 (71)	360 (90)	
>50%	109 (17)	70 (29)	39 (10)	
Extrapancreatic necrosis alone, no. (%)	315 (49)	77 (32)	238 (60)	<0.001†
Hospital stay in days	28 (14–66)	64 (31–106)	19 (12–38)	<0.001*
ICU stays in days	3 (0–22)	22 (9–42)	0 (0–0)	<0.001*
Infected pancreatic necrosis, no. (%)	202 (32)	132 (55)	70 (18)	<0.001†
Any intervention (eg, catheter drainage, necrosectomy), no. (%)	242 (38)	177 (74)	65 (16)	<0.001†
Timing intervention (catheter drainage or necrosectomy), days after admission	29 (21–41)	27 (25–31)	38 (23–56)	0.003*
Transferred from other hospital, no. (%)	156 (24)	95 (40)	61 (15)	<0.001†

Continuous variables are reported as mean±SD or median (IQR).
*Mann-Whitney U test.
†χ^2 test.
‡Linear-by-linear χ^2 association test.
§51% missing data.
¶<1% missing data.
**7% missing data.
ASA, American Society of Anesthesiologists; ICU, intensive care unit.

with 32 of 399 patients without organ failure (8%) (p=0.89). Four out of 240 patients with organ failure (2%) had dialysis before admission compared with 5 of 399 patients without organ failure (1%) (p=0.67). Chronic disease was present in 20 out of 240 patients with organ failure (8%) compared with 8 out of 399 patients without organ failure (2%) (p<0.01). Patients with organ failure had a higher percentage of pancreatic parenchymal necrosis, a prolonged hospital and ICU stay, were older, more often developed infected pancreatic necrosis and more often needed an intervention. Overall mortality in the 639 patients with necrotising pancreatitis was 15% (n=93); mortality was 35% in patients with organ failure compared with 2% in patients without organ failure. In patients with transient organ failure, the mortality was 10% as compared with a mortality rate of 38% for patients with persistent organ failure.

Type and combination of organ failure and impact on mortality

Figure 1A,B represent the prevalence and incidence of respiratory, cardiovascular and renal failure during hospital admission in 240 patients with organ failure. The prevalence and incidence of organ failures peaked during the first week. In total, 221 patients (92%) experienced respiratory failure with 37% mortality, followed by cardiovascular failure in 197 patients (82%) with 40% mortality, and renal failure in 106 patients (44%) with 47% mortality. Table 2 lists mortality rates in different subgroups of patients according to type and combinations of organ failure. Transient organ failure occurred in only 21 of 240 patients (9%) with organ failure and was associated with 10% mortality. In 219 patients with persistent organ failure (91%), mortality was 38%. Of these 219 patients, 166 patients (76%) had multiple organ failure with 43% mortality. Failure of the respiratory and cardiovascular system occurred most often (90 patients), followed by failure of the respiratory and renal system (21 patients) with similar mortality rates of approximately 35%. In total, 52 patients had simultaneous failure of all three systems with 63% mortality.

Timing of organ failure and impact on mortality

Figure 2 shows the timing (onset and duration) of persisting organ failure, categorised per organ system. The respiratory system was the first to fail and the longest to persist. The longest episode of persistent organ failure (any type) lasted a median of 7 days (IQR 4–16 days). Overall, a median of 2 episodes of organ failures (IQR 2–3 and range 1–12) occurred. Patients had a median of 19 days (IQR 7–39) of respiratory failure, 7 days (IQR 4–25) of cardiovascular failure and 10 days (IQR 4–23) of renal failure. Table 3 describes the association between the onset and duration of organ failure and mortality. The first episode of persistent organ failure (any type or combination) started in the first week in 51% of patients with 42% mortality, in 13% of patients during the second week with 42% mortality and in 36% of patients after the second week with 29% mortality. Mortality was not related to the onset of persistent multiple organ failure (HR 0.996 (95% CI 0.985 to 1.006), p=0.43). These results persisted after adjusting for age, sex, ASA classification and CT severity index (table 5). When tests were performed to study a random effect for hospital, the results remained similar (data not shown). When considering only patients with pancreatic parenchymal necrosis, we found that mortality was not related to the onset of persistent multiorgan failure (p=0.299), neither was mortality related to the duration of persistent multiple organ failure (p=0.165). Mortality in persistent multiple organ failure lasting <1 week, 1–2 weeks, 2–3 weeks or longer than 3 weeks was 43%, 38%, 46% and 52%, respectively (p=0.68). In other words, after >3 weeks of organ failure, 48% of patients survived. When considering the total number of days of organ failure (any system), mortality was not related to the duration of organ failure (p=0.41, table 4).

Subgroup infected necrosis

Infected necrosis was diagnosed in 132 of 240 patients with organ failure (55%). Of these 132 patients, 50 patients (38%) experienced organ failure in the first week and 82 patients (62%) developed organ failure after the first week. Of all 639 patients with necrotising pancreatitis, 70 patients developed infected pancreatic necrosis without organ failure (11%) with 4% mortality. In the 329 patients with sterile necrosis, mortality was 44% in patients with organ failure compared with 1.5% in patients without organ failure.

In 132 patients with organ failure and infected pancreatic necrosis, the overall mortality was 29%. Surprisingly, 47 of 108 patients (44%) with organ failure but without infected pancreatic necrosis died when compared with 38 of 132 patients (29%) with organ failure and infected pancreatic necrosis (adjusted OR 1.9; 95% CI 1.0 to 3.5, p=0.037). However, when excluding patients with mortality occurring within 10 days after admission, similar mortality rates were observed in patients with infected pancreatic necrosis and organ failure compared with those with organ failure without infected pancreatic necrosis (28% vs 34%, respectively, adjusted OR 1.4, p=0.324). Results did not change after adjusting for age, gender, ASA classification or CT severity index (table 5). When excluding patients with extrapancreatic necrosis, 163 patients had pancreatic necrosis and organ failure and mortality was 55% in patients with organ failure alone compared with 27% in patients with organ failure and infected pancreatic necrosis (adjusted OR 3.6, 95% CI 1.7 to 7.5, p=0.001).

DISCUSSION

This is, to our knowledge, the first study to provide detailed insight into the association between onset, duration and type of organ failure with mortality in patients with necrotising pancreatitis. We found no association between the onset of organ failure and mortality in patients with necrotising pancreatitis. Also, no association was found between the duration of organ failure and mortality. Finally, the combination of organ failure and infected pancreatic necrosis did not increase mortality in this study.

These results are in contrast to previous studies and the current classification systems of acute pancreatitis therefore require careful interpretation and discussion.

Previous studies show conflicting results concerning the time of onset of organ failure after start of pancreatitis and its association with mortality. For example, a higher mortality rate for early organ failure has been shown,[9 10 15 22] while another study reported that a late onset of organ failure was associated with higher mortality,[28] and another study found no difference.[27] Previous studies reporting that organ failure in the first week after onset of pancreatitis is a strong predictor of mortality, assess the presence of organ failure only during the first week after onset of disease.[9 10 15 17] In our study, the presence of organ failure was assessed daily during the entire hospitalisation period. If the first episode of organ failure starts after the first week after onset of pancreatitis, this episode was detected in our dataset and most likely not in the previous studies. Based on our results and analyses, we cannot arrive at any different conclusion

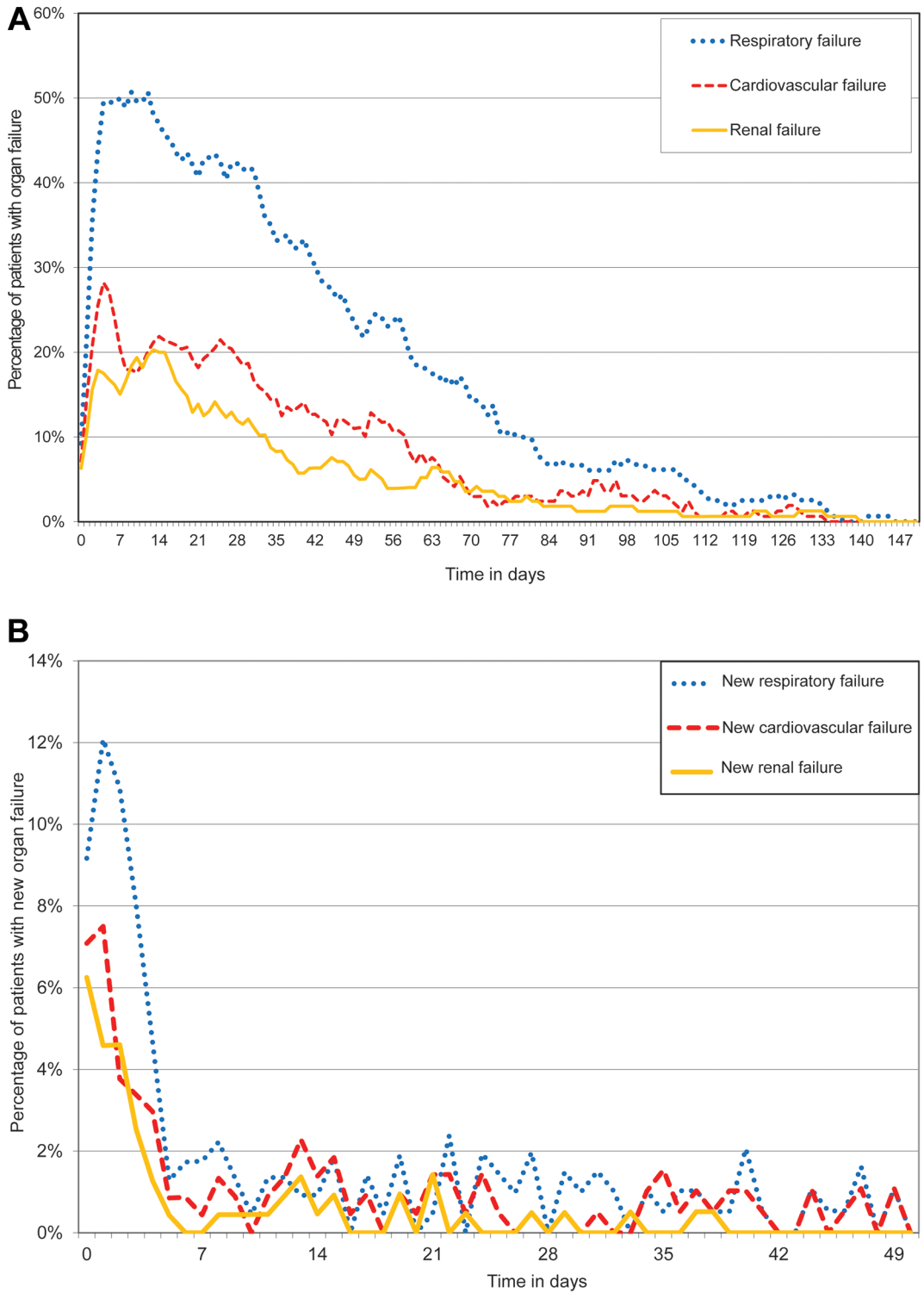

Figure 1 (A) Prevalence of respiratory, cardiovascular and renal failure in 240 patients with organ failure. Graph presents the daily number of patients with organ failure per system divided by the patients alive. (B) Onset (incidence) of pulmonary, cardiovascular and renal failure in 240 patients with organ failure. Graph presents the daily number of patients with *new-onset* organ failure per system divided by the patients alive.

other than the fact that organ failure after onset of pancreatitis has less impact on mortality than previously reported.

In this study, no association was found between the duration of organ failure and mortality. We will try to explain our findings. Documentation of organ failure during long hospital admissions requires prolonged, extensive and accurate data collection. Organ failure is a dynamic process and, for example, a hospital stay of months includes many episodes of different failing organs. These data collection include daily registration of onset, finish and type of organs failing. Studies reporting organ failure as a binomial variable (persistent or transient organ failure, present or absent) instead of accounting for all different episodes of organ failure may lack the statistical power to investigate the association between duration of organ failure and outcome in detail. These differences may explain the difference between this and other studies.

Table 2 Mortality in different subgroups in 240 patients with organ failure

Subgroups	Mortality (%) in transient organ failure	Mortality (%) in persistent organ failure
Single organ failure		
Any organ system	2/15 (13)	11/53 (21)
Cardiovascular	0/6 (0)	2/4 (50)
Respiratory	0/3 (0)	8/46 (17)
Renal	2/6 (30)	1/3 (33)
Multiple organ failure (any two or more organ systems)	0/6 (0)	72/166 (43)
Any two organ systems	0/6 (0)	39/114 (34)
Cardiovascular and respiratory	0/6 (0)	32/90 (36)
Respiratory and renal	–	7/21 (33)
Renal and cardiovascular	–	0/3 (0)
All three organ systems	–	33/52 (63)

All values in parentheses are percentages. Data represent the longest persistent episode of organ failure per system. In case episodes of different organ systems were equal in duration, the organ system involved in the first episode was used.

Table 3 Mortality related to onset and duration of persistent organ failure

	Mortality (%)	
	Single organ failure	Multiple organ failure
Onset of persistent organ failure (first episode after onset)		
Within 48 hours	2/11 (18)	12/20 (60)
First week (>48 hours)	5/20 (25)	28/61 (46)
Second week	0/4 (0)	13/24 (54)
Third or fourth week	2/8 (25)	10/30 (33)
Fifth week or later	2/10 (20)	9/31 (29)
Duration of persistent organ failure (longest episode during hospital stay)		
<48 hours	–	5/5 (100)
48 hours to 1 week	4/22 (18)	29/75 (39)
1–2 weeks	2/11 (18)	15/40 (38)
2–3 weeks	1/12 (8)	6/13 (46)
>3 weeks	4/8 (50)	17/33 (52)

Data represent *onset* of the first episode of persistent organ failure (any organ system) and *duration* of the longest episode of persistent organ failure (any organ system). Patients who died within 48 hours after onset of organ failure are included and were considered to have persistent organ failure.

Previous studies also suggested that the influence of organ failure and infected pancreatic necrosis on mortality was similar and that the combination increased mortality.[3 28 33] More recent studies conclude that the influence of organ failure on mortality is stronger than that of infected pancreatic necrosis.[16 24] We also found that the influence of organ failure is stronger than of infected pancreatic necrosis, but in addition, we found that the combination of organ failure and infected pancreatic necrosis did not increase mortality in comparison with organ failure without infected pancreatic necrosis. Moreover, mortality was higher in patients with organ failure alone when compared with patients with organ failure and with infected pancreatic necrosis. These differences may be explained by differences in study design and data collection. In our study, patients with necrotising pancreatitis were prospectively included and data collection started on the day of primary admission after onset of symptoms at the emergency department. Other studies may have included patients that survived this first phase of the disease and inclusion was started after patients were transferred to pancreatic expert centres or inclusion started when patients were admitted at the ICU. This complete registration of patients in our study is relevant as it also includes those patients who succumbed very early in the disease course as a result of fulminant early organ failure. This is a small group of patients with persistent multiple organ failure and without infected pancreatic necrosis but with a 100% mortality rate. This group increases the mortality rate in the group of patients with organ failure but without infected necrosis and thus may explain the lack of difference in mortality between the group of patients with organ failure alone and the group of patients with organ failure and with infected pancreatic necrosis. This is confirmed in a sensitivity analysis. When we analyse the mortality rate in the group of patients that survived the first 10 days of primary admission (arbitrarily chosen), the difference in mortality between patients with and patients without infected pancreatic necrosis was no longer present. But still, mortality in patients with organ failure and infected pancreatic necrosis was not higher than in patients with organ failure alone.

Unfortunately, our data do not support the critical category used in the determinant-based classification.[2] The determinant-based classification contains an additional category including patients with infected pancreatic necrosis and organ failure, named 'critical acute pancreatitis'. The clinical relevance of this category is based on studies suggesting that patients with infected pancreatic necrosis and organ failure are at excessive risk for mortality. Data in our study were obtained from hospitals

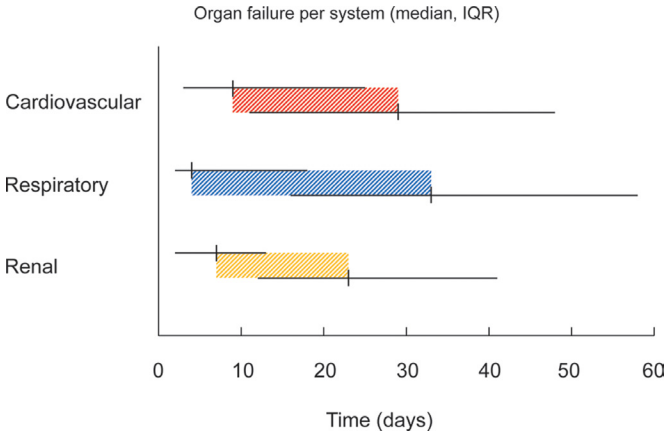

Figure 2 Timing of failure per organ type in 240 patients with organ failure. Data represent the timing of persistent organ failure per system. The solid horizontal lines represent the IQR of the start (upper line) and end day (lower line) of persistent organ failure. The vertical solid line represents the median day the organ failure started and ended. The shaded grey area is constructed between the median start and end day of organ failure and can be interpreted as the median timing of organ failure per system.

Table 4 Mortality related to total (absolute) number of days of organ failure during hospital stay (any type and including different episodes of organ failure)

Total duration of organ failure	Mortality (%)
<48 hours	8/27 (30)
48 hours to 1 week	20/53 (38)
1–2 weeks	11/33 (33)
2–3 weeks	7/31 (23)
>3 weeks	39/96 (41)

Table 5 Unadjusted and adjusted HR, OR and 95% CI in multivariate analysis of risk for mortality

Covariate	Unadjusted HR (95% CI)	P values	Adjusted HR (95% CI)*	P values
Onset of first episode persistent organ failure	0.996 (0.985 to 1.006)	0.427	0.997 (0.987 to 1.007)	0.563
Organ failure alone vs organ failure with infected necrosis	1.9 (1.1 to 3.3)	0.018	1.9 (1.0 to 3.5)	0.037
Organ failure alone vs organ failure with infected necrosis—*considering only mortality after 10* days	1.3 (0.8 to 2.4)	0.325	1.4 (0.7 to 2.7)	0.324
Organ failure with infected necrosis vs infected necrosis alone	9.0 (2.7 to 30.5)	<0.001	17.9 (3.8 to 83.7)	<0.001

*Adjustment for age, sex, American Society of Anesthesiologists classification and CT severity index.

linked to the Dutch Pancreatitis Study Group. These are hospitals and physicians who over the years have developed a considerable multidisciplinary expertise in the treatment of pancreatitis, especially in the minimally invasive treatment of infected pancreatic necrosis. Perhaps this is (part of) the explanation why in our series we did not observe an increased mortality in patients with infected pancreatic necrosis which has been reported by other researchers. The clinical impact of infected pancreatic necrosis may be different worldwide depending on the local healthcare setting. This theory is confirmed by the findings of a recent prospective international study that investigated the association between infected pancreatic necrosis and persistent organ failure in 374 patients in 46 ICUs.[34] In this study, in patients with persistent organ failure but without infected pancreatic necrosis a 41% mortality was found as opposed to a mortality of 59% in those with infected pancreatic necrosis.

Severe acute pancreatitis is thought to run a biphasic course.[1 35 36] The first 2 weeks are characterised and dominated by SIRS, which may cause early organ failure. This early phase is believed to be followed by a state of compensatory anti-immune response syndrome in which patients are susceptible for infections.[37 38] Based on this hypothesis, mortality rates in severe pancreatitis are believed to have two peaks, that is, following 'early' organ failure and following 'late' organ failure and subsequent sepsis. Unfortunately, our data do not support the existence of such a biphasic pattern. Neither an increase in the onset of organ failure nor a second peak in mortality was observed after the early phase of the disease course. The biphasic model is based predominantly on experimental and immunological data and is confirmed in clinical studies that report an increased mortality in patients with persistent organ failure and infected pancreatic necrosis as infected pancreatic necrosis usually occurs after several weeks. Therefore, the biphasic course is also stated in the 2012 Revised Atlanta Classification to describe the typical clinical course of severe pancreatitis. Our findings do not support this part of the Revised Atlanta Classification.

A limitation of our study is that the underlying cause of organ failure could not be specified. For example, when organ failure occurs after open necrosectomy for infected pancreatic necrosis, the cause is obvious (ie, combination of ongoing abdominal sepsis and major surgery). The cause of organ failure, however, is less clear in the early phase where organ failure might be due to severe or persistent SIRS or (pancreatic or extrapancreatic) infection. The exact timing of infected pancreatic necrosis or other extrapancreatic infections such as pneumonia is often impossible to unravel, especially when persisting organ failure is already present. Organ failure caused by SIRS without documented infection and organ failure caused by sepsis may overlap in time and are difficult to distinguish from one another.[11] This is a well-known limitation of studies regarding organ failure and infected necrosis. Furthermore, pre-existent comorbidity plays an important role in determining outcome in patients with necrotising pancreatitis.[39] Vulnerable patients with severe comorbidity may develop organ failure faster compared with those without significant comorbidity. Most likely, organ failure carries a worse outcome in patients with comorbidity compared with those without. An explanation for the lack of higher mortality in patient with organ failure and infected pancreatic necrosis could hypothetically be attributed to a higher percentage of patients with severe comorbidity as these patients may have succumbed from organ failure before developing infected pancreatic necrosis. However, the mean age (58 years), body mass index (27 kg/m^2) and percentage of patients with severe comorbidity are comparable to other studies.[16 24 28 34] For these reasons, we believe that our findings are applicable to other populations worldwide. Our study is underpowered to answer specific research questions, such as the impact of combinations of organ failure on mortality and the impact of transient organ failure. Confirmation of our results and further research is needed. Unfortunately to date, no other study has provided a larger sample, or more detailed data to address these research questions. Another limitation is that patients with organ failure but without necrotising pancreatitis were not included. As organ failure in interstitial pancreatitis is rare (around 1%) and mortality rates are around 3%, we believe that this limitation is of minor importance.[40] Also, patients who died before informed consent was given or before CECT to detect pancreatic necrosis was performed, were not included. Theoretically, these patients would contribute to first mortality peak of the biphasic model. However, as all patients were prospectively registered at hospital admission, we estimate this group to be small. Finally, the definitions of organ failure slightly differ from the definitions proposed in the 2012 Revised Atlanta Classification, which uses the modified Marshall scoring system.[1] The definitions used in our study are more stringent than the modified Marshall scoring system. This may also be the reason why transient organ failure was observed only in 21 of 639 patients (3%) with necrotising pancreatitis with 10% mortality. Compared with previous studies, using the Marshall scoring system, transient organ failure was reported in 16%–24% of patients with (predicted severe) acute pancreatitis with mortality rates from 1% to 3%.[8 10] Although, proposed as a relative simple and easy to use scoring system, the modified Marshall score has two major disadvantages. First, patients with persisting organ failure are sometimes admitted for over 6 months in the hospital. It is cumbersome to calculate the modified Marshall score for three separate organ systems on a daily basis throughout the whole disease course. Likewise, when retrospective cohorts describe the incidence of organ failure with the modified Marshall system one might question the validity of the reported organ failure rates. Second, endotracheal intubation for respiratory failure, the use of vasopressors for persistent hypotension after fluid resuscitation and renal replacement therapy for renal insufficiency are not incorporated in the modified Marshall score. Patients receiving these

supportive therapies may show normal arterial oxygen measurements. Hence, using the Marshall score these patients would be categorised as having moderate severe pancreatitis.

In conclusion, this study challenges several existing dogmas on the impact of organ failure on mortality in necrotising pancreatitis. The lack of an association between duration of organ failure and mortality in patients with necrotising pancreatitis may act as a plea for intensive and prolonged treatment of this group of patients. The lack of an association between the onset of organ failure and mortality challenges the concept of a biphasic disease course. Finally, the lack of increased mortality rates in patients with organ failure and infected pancreatic necrosis, compared with those without infected pancreatic necrosis, challenges the supposed impact of infected pancreatic necrosis on outcome.

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REFERENCES

1 Banks PA, Bollen TL, Dervenis C, *et al*. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
2 Dellinger EP, Forsmark CE, Layer P, *et al*. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg* 2012;256:875–80.
3 Petrov MS, Shanbhag S, Chakraborty M, *et al*. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010;139:813–20.
4 Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006;101:2379–400.
5 van Santvoort HC, Bakker OJ, Bollen TL, *et al*. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011;141:1254–63.
6 Fagenholz PJ, Fernández-del Castillo C, Harris NS, *et al*. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas* 2007;35:302–7.
7 Agarwal N, Pitchumoni CS. Acute pancreatitis: a multisystem disease. *Gastroenterologist* 1993;1:115–28.
8 Mofidi R, Duff MD, Wigmore SJ, *et al*. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg* 2006;93:738–44.
9 Thandassery RB, Yadav TD, Dutta U, *et al*. Dynamic nature of organ failure in severe acute pancreatitis: the impact of persistent and deteriorating organ failure. *HPB* 2013;15:523–8.
10 Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004;53:1340–4.
11 Besselink MG, van Santvoort HC, Boermeester MA, *et al*. Timing and impact of infections in acute pancreatitis. *Br J Surg* 2009;96:267–73.
12 Halonen KI, Pettilä V, Leppäniemi AK, *et al*. Multiple organ dysfunction associated with severe acute pancreatitis. *Crit Care Med* 2002;30:1274–9.
13 Isenmann R, Rau B, Beger HG. Early severe acute pancreatitis: characteristics of a new subgroup. *Pancreas* 2001;22:274–8.
14 Le Mée J, Paye F, Sauvanet A, *et al*. Incidence and reversibility of organ failure in the course of sterile or infected necrotizing pancreatitis. *Arch Surg* 2001;136:1386–90.
15 Lytras D, Manes K, Triantopoulou C, *et al*. Persistent early organ failure: defining the high-risk group of patients with severe acute pancreatitis? *Pancreas* 2008;36:249–54.
16 Kadiyala V, Suleiman SL, McNabb-Baltar J, *et al*. The Atlanta classification, revised atlanta classification, and determinant-based classification of acute pancreatitis: which is best at stratifying outcomes? *Pancreas* 2016;45:510–5.
17 Buter A, Imrie CW, Carter CR, *et al*. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg* 2002;89:298–302.
18 Tenner S, Sica G, Hughes M, *et al*. Relationship of necrosis to organ failure in severe acute pancreatitis. *Gastroenterology* 1997;113:899–903.
19 Li XY, Wang XB, Liu XF, *et al*. Prevalence and risk factors of organ failure in patients with severe acute pancreatitis. *World J Emerg Med* 2010;1:201–4.
20 Perez A, Whang EE, Brooks DC, *et al*. Is severity of necrotizing pancreatitis increased in extended necrosis and infected necrosis? *Pancreas* 2002;25:229–33.
21 Remes-Troche JM, Uscanga LF, Peláez-Luna M, *et al*. When should we be concerned about pancreatic necrosis? Analysis from a single institution in Mexico City. *World J Surg* 2006;30:2227–33. discussion 34-5.
22 Sharma M, Banerjee D, Garg PK. Characterization of newer subgroups of fulminant and subfulminant pancreatitis associated with a high early mortality. *Am J Gastroenterol* 2007;102:2688–95.
23 Zhu A-J, Shi J-S, Sun X-J. Organ failure associated with severe acute pancreatitis. *World J Gastroenterol* 2003;9:2570–3.
24 Guo Q, Li A, Xia Q, *et al*. The role of organ failure and infection in necrotizing pancreatitis: a prospective study. *Ann Surg* 2014;259:1201–7.
25 Schmidt PN, Roug S, Hansen EF, *et al*. Spectrum of microorganisms in infected walled-off pancreatic necrosis - impact on organ failure and mortality. *Pancreatology* 2014;14:444–9.
26 Wig JD, Bharathy KG, Kochhar R, *et al*. Correlates of organ failure in severe acute pancreatitis. *JOP* 2009;10:271–5.
27 Talukdar R, Bhattacharrya A, Rao B, *et al*. Clinical utility of the revised Atlanta classification of acute pancreatitis in a prospective cohort: have all loose ends been tied? *Pancreatology* 2014;14:257–62.
28 Choi JH, Kim MH, Cho DH, *et al*. Revised Atlanta classification and determinant-based classification: Which one better at stratifying outcomes of patients with acute pancreatitis? *Pancreatology* 2017;17:194–200.
29 Bakker OJ, van Santvoort H, Besselink MG, *et al*. Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? *Gut* 2013;62:1475–80.
30 Besselink MG, van Santvoort HC, Buskens E, *et al*. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;371:651–9.
31 van Santvoort HC, Besselink MG, Bakker OJ, *et al*. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010;362:1491–502.
32 van Grinsven J, van Brunschot S, van Santvoort HC, *et al*. The Value of a 24/7 Online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis. *Gastroenterology* 2017;152:685–8.
33 Werge M, Novovic S, Schmidt PN, *et al*. Infection increases mortality in necrotizing pancreatitis: a systematic review and meta-analysis. *Pancreatology* 2016;16:698–707.
34 Zubia-Olaskoaga F, Maraví-Poma E, Urreta-Barallobre I, *et al*. Comparison between revised atlanta classification and determinant-based classification for acute pancreatitis in intensive care medicine. Why do not use a modified determinant-based classification? *Crit Care Med* 2016;44:910–7.
35 Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). *Ann Intern Med* 1996;125:680–7.
36 Moore FA, Sauaia A, Moore EE, *et al*. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma* 1996;40:501–10. Discussion 10-2.
37 Cobb JP, O'Keefe GE. Injury research in the genomic era. *Lancet* 2004;363:2076–83.
38 Mayerle J, Dummer A, Sendler M, *et al*. Differential roles of inflammatory cells in pancreatitis. *J Gastroenterol Hepatol* 2012;27 Suppl 2(Suppl 2):47–51.
39 Frey C, Zhou H, Harvey D, *et al*. Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. *J Gastrointest Surg* 2007;11:733–42.
40 Singh VK, Bollen TL, Wu BU, *et al*. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol* 2011;9:1098–103.