

# Online Supplementary Material

## ***Supplemental to: Duration of organ failure impacts mortality in acute pancreatitis***

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### **METHODS**

#### **Patient selection**

This study used retrospectively (single centre) and prospectively (multicentre) collected data of patients with acute pancreatitis (AP) and followed the STROBE guidelines<sup>1</sup> for observational studies. The research protocol was approved by the Institutional Review Board of West China Hospital of Sichuan University. Informed patient consent was obtained from patients in prospective cohorts and was waived off in the retrospective cohort due to use of anonymised data. The retrospective cohort database included consecutive patients admitted to West China Hospital of Sichuan University between 1<sup>st</sup> October 2009 and 30<sup>th</sup> September 2013. Eligible patients were identified from electronic Hospital Information System (HIS) by using International Classification of Diseases 10<sup>th</sup> edition (ICD-10) code K85. Prospective cohorts were from West China Hospital (1<sup>st</sup> September 2014, 30<sup>th</sup> December 2015), Royal Liverpool University Hospital (1<sup>st</sup> June 2010 and 30<sup>th</sup> June 2017) and University Hospital of Santiago de Compostela (1<sup>st</sup> June 2013 and 28<sup>th</sup> February 2015) databases including consecutively enrolled patients.

## **Inclusion and exclusion criteria**

AP was diagnosed as defined by revised Atlanta classification<sup>2</sup> and were excluded if: (1) AP was not the first diagnosis; (2) ages <18 years old; (3) time from abdominal pain onset to hospital admission >48 hours; (4) trauma, chronic pancreatitis, pancreatic cancer as aetiologies or pregnancy; (5) advanced co-morbidities (e.g. end stage lung diseases, unstable coronary heart disease or congestive heart failure 3-4, chronic kidney disease stage 4-5, liver cirrhosis with modified Child-Pugh grade 2-3, malignancy or immune deficiency).

## **Data collection**

Retrospective data collection was based on a pre-defined *pro forma* primarily designed by the Liverpool group (WH and RS) and adapted by the Chengdu group (LD, WH and QX); prospective data were collected using similar *pro forma* coordinated by senior authors (WH, QX and RS).

Quality assurance, quality control, standard operating procedures were in place at every step of the study process to ensure proper trainings for researchers. Data collection involved at least two experienced researchers at each centre (Chengdu: NS, LD and TJ; Liverpool: TL and WH; Santiago de Compostela: DdII-G and JED-M). Details to assess onset time, type and duration of organ failure were captured on a daily basis. Demographic data (age, sex and comorbidities), aetiology, admission clinical severity scores, modified computerised tomographic (CT) severity index, treatments in the intensive care settings, surgical interventions and clinical outcomes were also recorded.

## Definitions

Hypertriglyceridemia as an aetiology was defined as admission serum triglyceride level  $\geq 5.65$  mmol/l,<sup>3</sup> biliary origin was diagnosed as confirmation of gallstones using radiological imaging (including abdominal or endoscopic ultrasonography, CT and magnetic resonance cholangiopancreatography)<sup>2 4</sup> while alcoholic excess was considered according to respective centre's own practice. The definitions for outcomes of interest followed Schepers *et al*<sup>5</sup> whenever possible if not otherwise indicated. Organ failure was identified using Sequential Organ Failure Assessment (SOFA) scoring by a score of  $\geq 2$  for individual organs (respiratory, cardiovascular or renal systems) lasting  $< 48$  hours and  $> 48$  hours for transient and persistent organ failure, respectively.<sup>6</sup> In patients with pre-existing chronic kidney disease (stage 1-3), a 2-point reduction of estimated glomerular filtration rate for kidney function was used to assess renal failure, regardless of serum creatinine levels.<sup>7</sup> Local complications were defined as in the revised Atlanta classification.<sup>2</sup> Infected pancreatic necrosis was identified by the presence of gas in necrotic collections on enhanced CT scan, or by microbiological diagnosis of pancreatic infection after sampling/debridement, or by the presence of unresolving sterile necrosis that required debridement and invariably became infected.<sup>8-10</sup> Pancreatic necrosectomy included open, minimally invasive or endoscopic necrosectomy, percutaneous catheter drainage of peripancreatic fluid collection and/or local lavage.<sup>11</sup> Mortality was recorded for the index hospital admission and within 3 months of follow up in prospective cohorts.

## Statistical analysis

Qualitative data are expressed as number and percentage and compared by  $\chi^2$  test (or Fisher's exact test), while quantitative data are presented as median and

interquartile range (IQR) and compared using Mann–Whitney *U* test (2 groups) or Kruskal–Wallis *H* test (3 groups). Multivariate logistic regression model was used to assess the association between variables and mortality after adjusting age, sex, Charlson comorbidity score and modified CT severity index. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI). A two-sided  $p < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS® 21.0 (IBM, Armonk, New York, USA).

## REFERENCES

1. von Elm E, Altman DG, Egger M, *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
2. 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.
3. Vipperla K, Somerville C, Furlan A, *et al.* Clinical Profile and Natural Course in a Large Cohort of Patients With Hypertriglyceridemia and Pancreatitis. *J Clin Gastroenterol* 2017;51:77-85.
4. van Geenen EJ, van der Peet DL, Bhagirath P, *et al.* Etiology and diagnosis of acute biliary pancreatitis. *Nat Rev Gastroenterol Hepatol* 2010;7:495-502.
5. Schepers NJ, Bakker OJ, Besselink MG, *et al.* Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut* 2018 (gutjnl-2017-3144657).
6. 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.
7. Liu T, Huang W, Szatmary P, *et al.* Accuracy of circulating histones in predicting persistent organ failure and mortality in patients with acute pancreatitis. *Br J Surg* 2017;104:1215-1225.
8. 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.
9. Raraty MG, Halloran CM, Dodd S, *et al.* Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann Surg* 2010;251:787-93.
10. Gomatos IP, Halloran CM, Ghaneh P, *et al.* Outcomes From Minimal Access Retroperitoneal and Open Pancreatic Necrosectomy in 394 Patients With Necrotizing Pancreatitis. *Ann Surg* 2016;263:992-1001.
11. van Grinsven J, van Santvoort HC, Boermeester MA, *et al.* Timing of catheter drainage in infected necrotizing pancreatitis. *Nat Rev Gastroenterol Hepatol* 2016;13:306-12.

## SUPPLEMENTARY FIGURE LEGENDS

**Figure S1.** Characteristics of the dynamic changes of organ failure in patients with severe acute pancreatitis. (A) Prevalence of respiratory, cardiovascular and renal failure in 469 patients with persistent organ failure (POF) in the retrospective cohort and (B) 132 patients with POF in the prospective cohort. Graphs depict the number of patients with individual POF divided by the patients alive on daily basis.

**Figure S2.** Time of persistent organ failure onset in patients with severe acute pancreatitis. (A) Retrospective cohort of 469 patients, (B) Prospective cohort of 132 patients, and (C) A total of 601 with persistent organ failure (POF). Diagrams represent the percentage of POF onset per day 1, day 2, day 3 and  $\geq$ day 4 after admission.

Figure S1

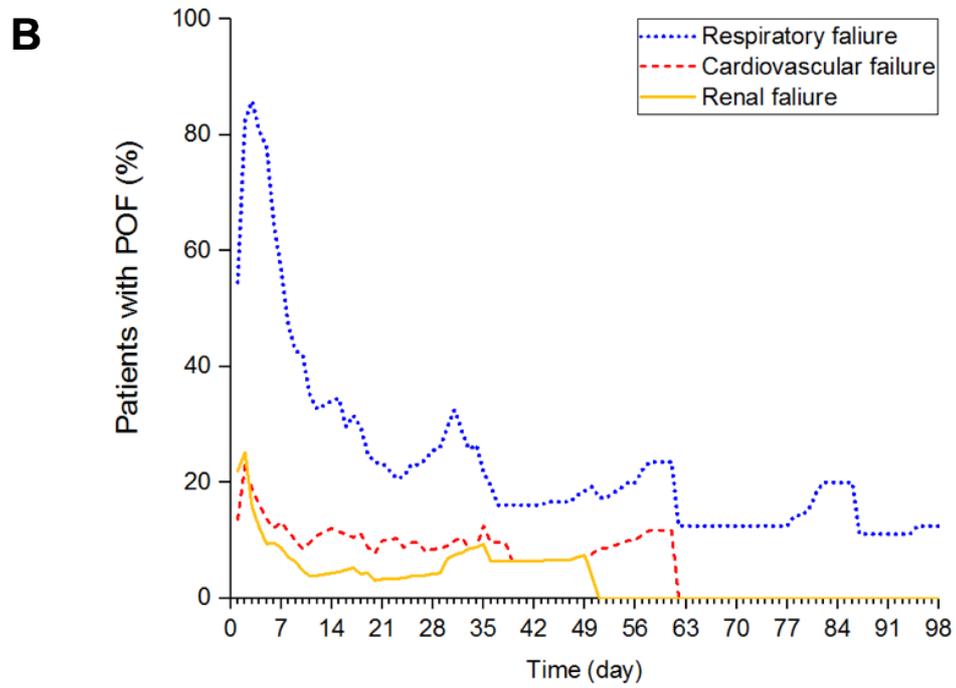
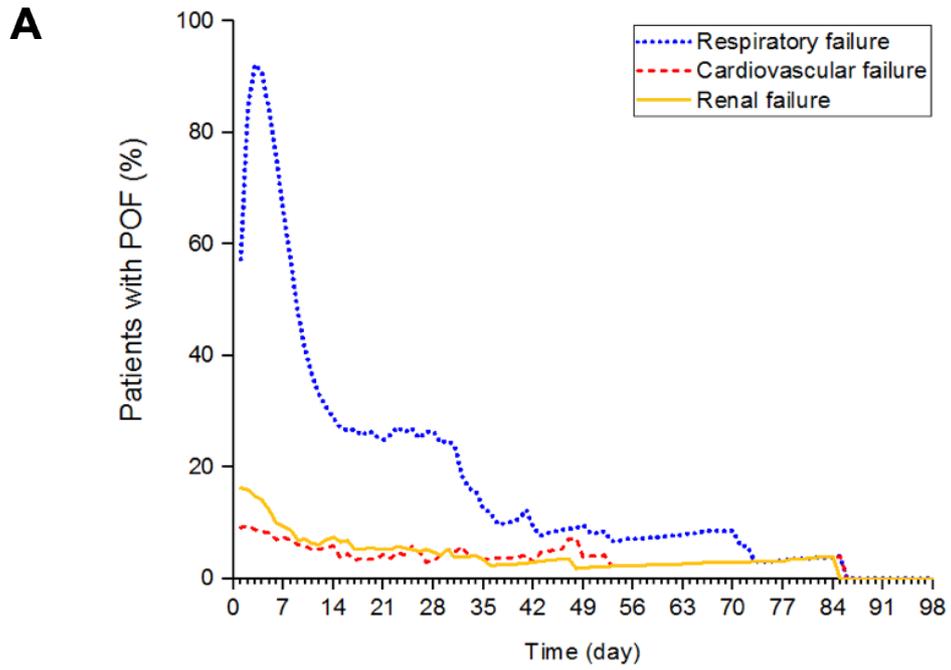
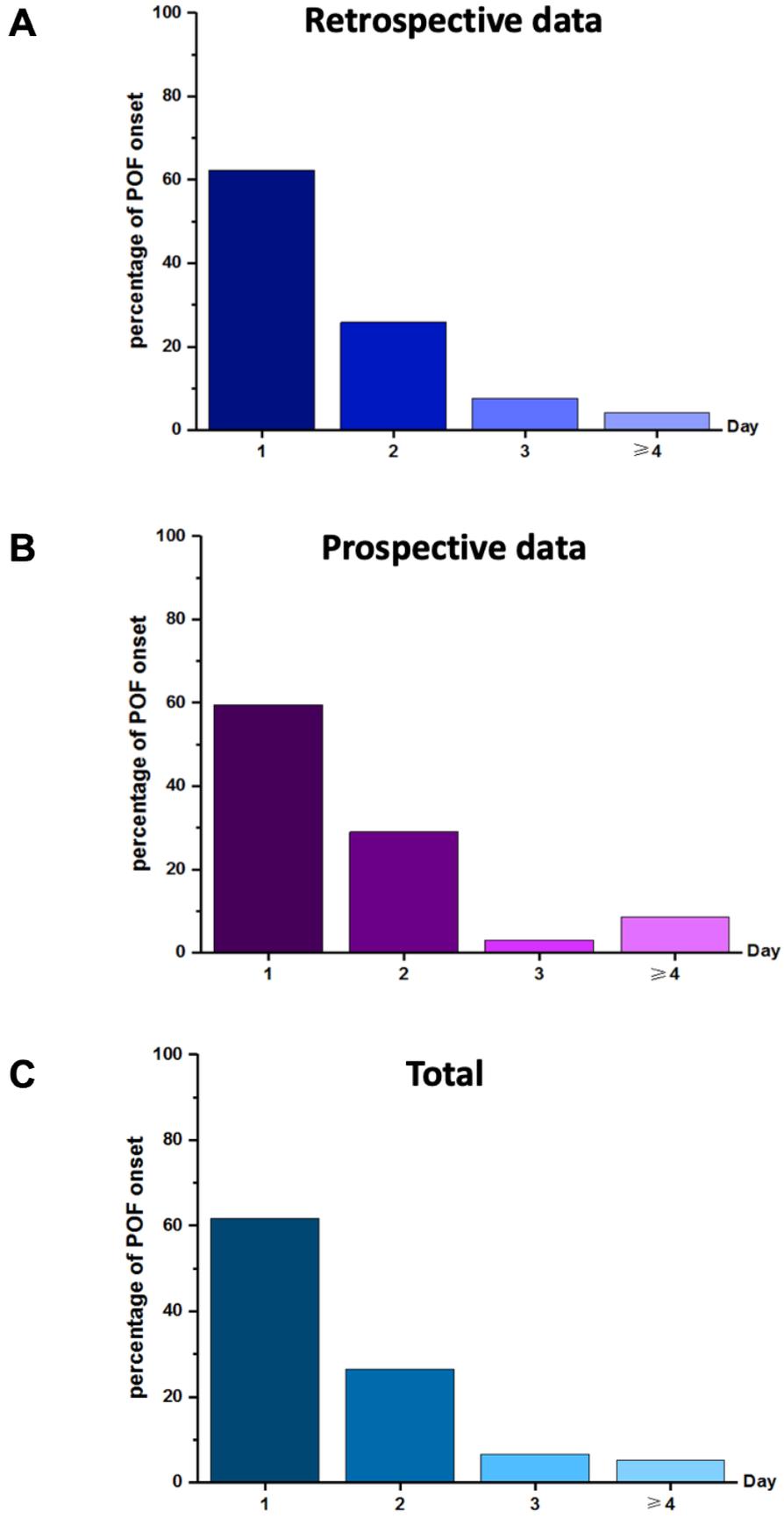


Figure S2



**Supplementary Table 1A.** Baseline characteristics and clinical outcomes of retrospective cohort

	<b>Total n=2145</b>	<b>MAP n=958</b>	<b>MSAP n=718</b>	<b>SAP n=469</b>	<b>p value†</b>
Age, years*	45 (38-55)	44 (37-53)	45 (38-56)	46 (39-59)	0.001‡
Male sex	1420 (66.2)	665 (69.4)	457 (63.6)	298 (63.5)	0.018§
Pre-existing comorbidity					
Pulmonary	56 (2.6)	19 (2.0)	19 (2.6)	18 (3.8)	0.119
Cardiovascular	368 (17.2)	142 (14.8)	115 (16.0)	111 (23.7)	<0.001‡
Liver	983 (45.8)	466 (48.6)	324 (45.1)	193 (41.5)	0.026//
Diabetes	420 (19.6)	168 (17.5)	161 (22.4)	91 (19.4)	0.044¶
Aetiology					
Biliary	650 (30.3)	295 (30.8)	228 (31.8)	127 (27.1)	0.209
Hyperlipidaemia	657 (30.6)	280 (29.2)	206 (28.7)	171 (36.5)	0.008‡
Alcohol excess	106 (4.9)	35 (3.7)	42 (5.8)	29 (6.2)	0.045§
Mixed	165 (7.7)	49 (5.1)	59 (8.2)	57 (12.2)	<0.001**
Unknown or others	567 (26.4)	299 (31.2)	183 (25.5)	85 (18.1)	<0.001**
Time to admission, hours*	20 (10-28)	16 (10-26)	24 (12-30)	25 (15-30)	<0.001**
Persistent organ failure	469 (21.9)	0	0	469 (100)	<0.001‡
Respiratory	459 (21.3)	0	0	459 (97.9)	<0.001‡
Cardiovascular	77 (3.6)	0	0	77 (16.4)	<0.001‡
Renal	87 (4.1)	0	0	87 (18.6)	<0.001‡
Need for HDU/ICU	302 (14.1)	2 (0.2)	22 (3.1)	278 (59.3)	<0.001**
Modified CT severity index*‡	8 (2-8)	2 (2-2)	8 (8-8)	8 (8-10)	<0.001**
Acute necrotic collection	297 (13.8)	0	143 (19.9)	154 (32.8)	<0.001**
Acute peripancreatic fluid collection	686 (32.0)	0	414 (57.7)	272 (58.0)	<0.001§
Infection					
Infected pancreatic necrosis	57 (2.7)	0	4 (0.6)	53 (11.3)	<0.001**
Bacteraemia	80 (3.7)	5 (0.5)	6 (0.8)	69 (14.7)	<0.001‡
Lung	168 (7.8)	12 (1.3)	23 (3.2)	133 (28.4)	<0.001**

Necrosectomy	69 (3.2)	0	8 (1.1)	61 (13.0)	<0.001**
Mortality	92 (4.3)	0	0	92 (19.6)	<0.001‡
Length of hospital stay, days*	10 (7-16)	8 (6-11)	12 (9-16)	18 (13-29)	<0.001**

Values in parentheses are percentages unless indicated otherwise. MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; HDU, Highly Dependence Unit; ICU, Intensive Care Unit; CT, computerised tomography.

\*values are median (IQR).

†p value indicates  $\chi^2$  or Fisher's exact test for qualitative data and Kruskal–Wallis *H* test for quantitative data.

‡p<0.05, SAP versus MAP or MSAP.

§p<0.05, MAP versus MSAP or SAP.

//p<0.05, MAP versus SAP.

¶p<0.05, MAP versus MSAP.

\*\*p<0.05, between any two groups.

**Supplementary Table 1B.** Baseline characteristics and clinical outcomes of prospective cohort

	<b>Total n=939</b>	<b>MAP n=486</b>	<b>MSAP n=321</b>	<b>SAP n=132</b>	<b>p value†</b>
Age, years*	53 (41-66)	54 (40-68)	51 (41-65)	54 (43-64)	0.531
Male sex	506 (53.9)	237 (48.8)	188 (58.6)	81 (61.4)	0.004‡
Charlson comorbidity index*	0 (0-1)	0 (0-1)	0 (0-1)	1 (0-2)	0.371
Aetiology					<0.001‡
Biliary	447 (47.6)	243 (50.0)	146 (45.5)	58 (43.9)	0.30
Alcohol excess	121 (12.9)	70 (14.4)	35 (10.9)	16 (12.1)	0.335
ERCP	24 (2.6)	19 (3.9)	4 (1.2)	1 (0.8)	0.024§
Drug-induced	8 (0.9)	3 (0.6)	4 (1.2)	1 (0.8)	0.631
Hyperlipidaemia	157 (16.7)	46 (9.5)	74 (23.1)	37 (28.0)	<0.001‡
Unknown or others	182 (19.4)	105 (21.6)	58 (18.1)	19 (14.4)	0.136
Time to admission, hours*	11 (6-24)	9 (5-18)	12 (6-24)	24 (10-28)	<0.001//
Persistent organ failure	132 (14.1)	0	0	132 (100)	<0.001¶
Respiratory	127 (13.5)	0	0	127 (96.2)	<0.001¶
Cardiovascular	40 (4.3)	0	0	40 (30.3)	<0.001¶
Renal	28 (3.0)	0	0	28 (21.2)	<0.001¶
Need for HDU/ICU	128 (13.6)	4 (0.8)	17 (5.3)	107 (81.7)	<0.001//
Modified CT severity index*	2 (0-6)	0 (0-0)	6 (4-6)	8 (6-8)	<0.001//
Necrosis	137 (14.6)	0	67 (20.9)	70 (53.0)	<0.001//
Acute peripancreatic fluid collection	224 (23.9)	0	152 (47.4)	72 (54.5)	<0.001‡
Infection					
Infected pancreatic necrosis	32 (3.4)	0	5 (1.9)	27 (20.5)	<0.001//
Bacteraemia	30 (3.2)	4 (0.9)	6 (2.0)	20 (16.7)	<0.001¶
Lung	63 (6.7)	13 (2.7)	14 (4.4)	36 (27.3)	<0.001¶
Necrosectomy	28 (3.0)	0	8 (2.5)	20 (15.2)	<0.001//
Mortality	31 (3.3)	0	1 (0.3)	30 (22.7)	<0.001¶
Length of hospital stay, days*	8 (5-14)	6 (4-9)	11 (7-15)	19 (12-34)	<0.001//

Values in parentheses are percentages unless indicated otherwise. MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; HDU, Highly Dependence Unit; ICU, Intensive Care Unit; CT, computerised tomography.

\*values are median (IQR).

†p value indicates  $\chi^2$  or Fisher's exact test for qualitative data and Kruskal–Wallis  $H$  test for quantitative data.

‡p<0.05, MAP versus MSAP or SAP.

§p<0.05, MAP versus MSAP.

//p<0.05, between any two groups.

¶p<0.05, SAP versus MAP or MSAP.

**Supplementary Table 2.** Mortality in different subgroups of patients with organ failure

<b>Subgroups</b>	<b>Mortality (%) in transient organ failure</b>	<b>Mortality (%) in persistent organ failure</b>
<b>Single organ failure</b>		
Any organ system	1/445 (0.2)	25/453 (5.5)
Respiratory	1/432 (0.2)*	23/444 (5.2)
Cardiovascular	0/7 (0)	2/3 (66.7)
Renal	0/6 (0)	0/6 (0)
<b>Multiple organ failure (any two or more organ systems)</b>		
Any two organ systems	0/9 (0)	35/78 (44.9)
Respiratory and cardiovascular	0/1 (0)	17/39 (43.6)
Respiratory and renal	0/8 (0)	17/36 (47.2)
Renal and cardiovascular	-	1/3 (33.3)
All three organ systems	-	62/70 (88.6)

\*The actual cause for death was unexpected myocardial infarction.

**Supplementary Table 3.** Mortality related to persistent organ failure with or without infected pancreatic necrosis

	<b>Mortality (%) in persistent organ failure</b>		<b>p value</b>
	<b>Without infected pancreatic necrosis</b>	<b>With infected pancreatic necrosis</b>	
Retrospective data	77/416 (18.5)	15/53 (28.3)	0.09
Prospective data	24/105 (22.9)	6/27 (22.2)	0.94
Total	101/521 (19.4)	21/80 (26.3)	0.16

**Supplementary Table 4.** Mortality related to duration of persistent organ failure

<b>Duration of organ failure</b>	<b>Mortality (%)</b>	<b>versus</b>	<b>p value</b>
48 h-1 week	60/326 (18.4)	1-2 week	0.604
		2-3 week	<b>0.050</b>
		>3 week	<b>0.009</b>
1-2 week	26/160 (16.3)	2-3 week	<b>0.033</b>
		>3 week	<b>0.007</b>
2-3 week	16/54 (29.6)	>3 week	0.717
>3 week	20/61 (32.8)	-	-