

Synchronous Organ Failure and Infected Pancreatic Necrosis Define Genuine Critical Acute Pancreatitis

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Research

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Abstract

Background: The determinant-based classification (DBC) of acute pancreatitis (AP) was proposed in 2012. One of the highlights of the DBC was critical acute pancreatitis (CAP), which was supposed to be strongly associated with the highest risk of adverse outcomes. However, the definition of CAP needs to be further clarified.

Methods: A prospective cohort with consecutive patients of infected pancreatic necrosis (IPN) at a tertiary hospital was analyzed. Patients were assigned to IPN alone, Metachronous-CAP (MCAP) and Synchronous-CAP group (SCAP) according to presence or absence of organ failure (OF) and the crosstalk between OF and IPN. Clinical interventions and outcomes were compared among groups.

Results: A total of 248 IPN patients were enrolled and the overall mortality was 25.8%. Compared with MCAP, patients with SCAP were associated with higher mortality (45/68, 66.2% vs. 5/50, 10.0%; OR= 17.6, 95% CI, 6.2-50.4; $P < 0.001$) and morbidity (28/68, 41.2% vs. 9/50, 18.0%; $P = 0.013$), longer duration of OF (median 35.5 days vs. 12.0 days, $P < 0.001$), longer ICU length of stay (LOS) (median 28.0 days vs. 16.0 days, $P = 0.001$), longer hospital LOS (median 67.0 days vs. 60.0 days, $P < 0.001$) as well as earlier requirement for surgical interventions. The IPN alone and MCAP had comparable mortality (10.8% vs. 10.0%, $P = 0.88$), morbidity and hospital LOS, except that MCAP patients were characterized with longer duration of OF and ICU LOS ($P < 0.05$).

Conclusions: SCAP, characterized with synchronous persistent OF and IPN, was associated with higher mortality and morbidity and should be defined as genuine CAP.

Introduction

Acute pancreatitis (AP) is a heterogeneous disease with increasing incidence [1]. The clinical course of AP ranges from uneventful and self-limiting course to that with high morbidity and mortality [2]. Owing to the advancement in understanding the pathophysiology and natural history of AP, the determinant-based classification (DBC) of AP was proposed by international groups of experts through a multidisciplinary consultative process in 2012 [3]. Prospective validation of DBC has been published by comparing the performance of stratifying outcomes with the Revised Atlanta Classification (RAC) and the Atlanta classification (AC) in a range of clinical settings [4–7]. One of the highlights of the DBC classification is a newly-defined category called critical acute pancreatitis (CAP), which includes patients characterized by the presence of both persistent organ failure (POF) and infected pancreatic necrosis (IPN) and has been supposed to be the most ominous severity category of AP [8, 9]. Prospective observation studies from different centers reported that CAP accounts for only 2.2–6.6% of AP, while the mortality was as high as 17.7–87.5% [4–9]. Although both POF and IPN occur in CAP patients, a considerable portion of cases had already recovered from early organ failure and then came to IPN in the late phase, which was named Metachronous-CAP (MCAP). The prognosis of MCAP seemed comparable with DBC “severe” category. The rest portion of CAP was called Synchronous-CAP (SCAP), in which organ failure persisted until the pancreatic necrosis got infected. SCAP seemed to have the most fulminant course, leading to an

extremely high rate of death and significant medical burden. Therefore, we suppose that the critical category based on DBC should be further modified and propose that the SCAP, not the MCAP, is the genuine “critical” AP.

Herein, we attempt to validate the hypothesis through an evidence-based approach. The present study is undertaken in a prospectively maintained database of the patients with IPN to identify the most lethal subgroup of AP at a large tertiary hospital, with a specific focus on the clinical outcomes to determine whether CAP requires further stratification in a tertiary referral setting.

Methods

Patient identification and definitions

A total of 248 patients with IPN were prospectively and consecutively enrolled at Xiangya Hospital of Central South University (a tertiary referral center with an average of 600 admissions with AP annually) from January 2010 to December 2020. The prospectively maintained Xiangya-IPN cohort included clinical, radiological, microbiological and follow-up data, which has been introduced and published previously [8, 10, 11]. Patients transferred from other hospitals were included in the cohort, medical records from other hospitals were obtained at the time of enrollment, and pertinent data elements were abstracted. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Xiangya Hospital and written informed consent was obtained from all patients or their representatives for publication of data. We followed the STROBE statement for the reporting of data [12].

The diagnosis, classification and definitions associated with AP were based on the DBC [3] and American Gastroenterological Association (AGA) guideline [13], and were also described in our previous studies [8, 10]. Briefly, IPN was defined as the presence of gas bubbles within (peri)pancreatic necrosis on computed tomography or a positive culture of (peri)pancreatic necrotic fluid obtained during the first drainage or necrosectomy. The criteria for organ failure (OF) defined for three organ systems (respiratory, cardiovascular, or renal) based on the worst measurement over a 24-h period. POF was defined as OF in the same organ system for 48 h or more. Failure of at least two organ systems on the same day was named multiple OF. Multi-drug resistant organisms (MDROs) were defined as microorganisms that are resistant to two or more classes of antimicrobial agents [14]. CAP was characterized by the presence of IPN and POF during the course of disease. To further clarify CAP, we separated it into Metachronous-CAP (MCAP) and Synchronous-CAP group (SCAP). MCAP defined patients who had already recovered from early OF and then came to IPN in the late phase. SCAP described patients whose OF persisted until the pancreatic necrosis got infected. The difference in time course between the two groups was shown in Figure 1.

Standardized management protocol

All patients received standard treatment according to the latest international guidelines [1, 2, 13, 15]. After admission, all patients were assessed by the multidisciplinary team, including pancreatic surgeons, ICU physicians, gastroenterology physicians and radiologists. Patients with organ failure were treated with organ-specific support as needed, including mechanical ventilation, continuous renal replacement therapy, vasoactive agents, and others. Principles for the intervention of IPN in this cohort were introduced in our previous publications [8, 11]. Briefly, a step-up approach consisting of percutaneous catheter drainage (PCD) or endoscopic drainage was generally the first-line approach. If drainage did not achieve clinical improvement, subsequent minimally invasive or open pancreatic necrosectomy (OPN) would be performed to control the infection.

Clinical outcomes

Primary outcomes included mortality, major morbidity (hemorrhage, intestinal leakage and pancreatic fistula), intensive care unit (ICU) admission, ICU length of stay (LOS), duration of OF, overall hospital LOS, time from onset to first intervention (percutaneous, endoscopic and surgical drainage/necrosectomy) and times needed for interventions. These outcomes have been previously reported in validation studies to classify AP severity [4, 6, 9, 16]. In this study, inter-Groups were compared for their ability to stratify severity in accordance with clinical outcomes.

Statistical analysis

Categorical variables were described using frequencies and percentages. Continuous variables were summarized using median and interquartile range depending on the distribution. Chi-square test or Fisher exact test was used to compare the distribution of categorical variables, and Student *t*-test or Mann-Whitney *U*-test for continuous variables. All tests were bilateral, and *P*-values < 0.05 were considered statistically significant. The SPSS (22.0) was used for all analyses.

Results

Patient characteristics

A total of 248 patients with IPN were enrolled in the analysis (74.2% males; median age 48 years). The most common etiology was biliary (n = 107, 43.1%), followed by hyperlipidemia (n = 102, 41.1%), others (n = 33, 13.4%), and alcoholic (n = 6, 2.4%). According to DBC categories, 52.4% (n = 130) of patients were classified as severe (IPN without OF), and 47.6% (n = 118) as critical category. The median duration of OF, ICU LOS, and hospital LOS were 17 days, 13 days and 57.5 days, respectively, and overall mortality was 25.8% (64/248). Demographics, etiologies, local, major complications, interventions and clinical outcomes are summarized in Table 1.

Table 1

Baseline characteristics, complications, interventions and outcomes of IPN cohort

Characteristics	N (%)
Demographic data	
Total no. of patients	248 (100%)
Males	184 (74.2%)
Median age years (IQR)	48 (39–54)
Transfers from other hospitals	107 (43.1%)
CAP patients	118 (47.6%)
Metachronous CAP	50 (20.2%)
Synchronous CAP	68 (27.4%)
Etiology	
Biliary	107 (43.1%)
Hypertriglyceridemia	102 (41.1%)
Alcoholic	6 (2.4%)
Others	33 (13.4%)
Organ failures	
Single OF	53 (21.4%)
Multiple OF	94 (37.9%)
Respiratory failure	132 (53.2%)
Renal failure	92 (37.1%)
Circulatory failure	67 (27.0%)
Infection	
Bloodstream infection	87 (35.1%)
Polymicrobial infection	166 (66.9%)
MDROs infection	153 (61.7%)
Fungal infection	70 (28.2%)
IPN, infected pancreatic necrosis; IQR, interquartile range; CAP, critical acute pancreatitis;	
OF, organ failure; MDROs, multidrug-resistant organisms; PCD, percutaneous catheter drainage	
ICU, intensive care unit; LOS, length of stay.	

Characteristics	N (%)
Interventions	
PCD or endoscopic drainage alone	56 (22.6%)
Surgical operations	192 (77.4%)
Step-up surgical approach	199 (80.2%)
Step-down surgical approach	49 (19.8%)
Major complications	
Hemorrhage	17 (6.9%)
Intestinal leakage	41 (16.5%)
Pancreatic fistula	94 (37.9%)
Outcomes	
Mortality	64 (25.8%)
Times need for interventions, Median (IQR)	3 (2–4)
ICU admission	198 (79.8%)
Duration of OF, median days (IQR)	17.0 (8.0-35.5)
ICU LOS, median days (IQR)	13.0 (3.3–26.0)
Hospital LOS, median days (IQR)	57.5 (43.0–81.0)
IPN, infected pancreatic necrosis; IQR, interquartile range; CAP, critical acute pancreatitis;	
OF, organ failure; MDROs, multidrug-resistant organisms; PCD, percutaneous catheter drainage	
ICU, intensive care unit; LOS, length of stay.	

Comparison between groups

The cohort was divided into three groups, including IPN alone (n = 130), MCAP (n = 50) and SCAP (n = 68) group, based on the presence or absence of organ failure (OF) and the crosstalk between OF and IPN. Baseline characteristics were equally distributed among groups, and overall mortality of patients with CAP and IPN alone were 42.4% (50/118) and 10.8% (14/130). In inter-Group analysis, patients with SCAP were associated with significantly higher mortality (45/68, 66.2% vs. 5/50, 10.0%; OR = 17.6, CI, 6.2–50.4; $P < 0.001$) and morbidity (28/68, 41.2% vs. 9/50, 18.0%; $P = 0.013$), longer duration of OF (median 35.5 days vs. 12.0 days, $P < 0.001$), longer ICU length of stay (LOS) (median 28.0 days vs. 16.0 days, $P = 0.001$), longer hospital LOS (median 67.0 days vs. 60.0 days, $P < 0.001$) as well as need earlier surgical interventions compared with MCAP cases, and SCAP patients were more likely to deteriorate into multiple OF (83.8% vs. 42.0%, $P < 0.001$). In addition, the IPN alone and MCAP group had equivalent performance

for predicting mortality (10.8% vs. 10.0%), morbidity and hospital LOS. However, compared with IPN alone cases, MCAP patients did have a longer duration of OF and ICU LOS, and they also presented more frequently with multiple OF, bloodstream infection and MDROs infection ($P < 0.05$), as shown in Table 2.

Table 2
Comparison of baseline and clinical characteristics and outcomes between three groups.

Variable	CAP			P value ^a	P value ^b
	IPN alone (n = 130)	MCAP (n = 50)	SCAP (n = 68)		
Age, year, median (IQR)	48 (41–54)	43 (34–51)	50 (41–58)	0.063	0.056
Males, n (%)	92 (70.8)	39 (78.0)	53 (78.0)	0.329	0.994
Etiology, n (%)				0.052	0.097
Biliary	62 (47.7)	14 (28.0)	30 (44.1)		
Hypertriglyceridemia	40 (30.8)	28 (56.0)	35 (51.4)		
Alcoholic	3 (2.3)	2 (4.0)	1 (1.5)		
Others	25 (19.2)	6 (12.0)	2 (3.0)		
Organ failures, n (%)					
Multiple OF	16 (12.3)	21 (42.0)	57 (83.8)	< 0.001	< 0.001
Respiratory failure	27 (20.8)	43 (86.0)	62 (91.2)	< 0.001	0.095
Renal failure	8 (6.2)	24 (48.0)	60 (88.2)	< 0.001	0.003
Circulatory failure	15 (11.5)	13 (26.0)	39 (57.4)	0.026	0.006
Infection, n (%)					
Bloodstream infection	26 (20.0)	22 ((44.0)	39 (57.4)	0.001	0.151
Polymicrobial infection	90 (69.2)	35 (70.0)	41 (60.3)	0.658	0.093
MDROs infection	69 (53.1)	35 (70.0)	49 (72.1)	0.039	0.807

IPN, infected pancreatic necrosis; IQR, interquartile range; CAP, critical acute pancreatitis; MCAP, metachronous-CAP; SCAP, synchronous-CAP

OF, organ failure; MDROs, multidrug-resistant organisms; ICU, intensive care unit; LOS, length of stay.

The bold in the table means the P value of these parameters were < 0.05 and considered statistically significant.

^a Group IPN alone vs. MCAP

^b Group MCAP vs. SCAP

Variable	CAP				
	IPN alone (n = 130)	MCAP (n = 50)	SCAP (n = 68)	P value ^a	P value ^b
Fungal infection	37 (28.5)	12 (24.0)	21 (30.9)	0.547	0.41
Interventions and outcomes					
Time from onset to first intervention, median days (IQR)	25.0 (15.0–40.0)	26 (18.0–36.5)	16.0 (10.5–24.7)	0.366	< 0.001
Times need for interventions, Median (IQR)	3 (2–4)	3 (2–4)	4 (2–5)	0.636	0.37
Duration of OF, median days (IQR)	5.0 (3.0–11.3)	12.0 (8.0–17.0)	35.5 (22.3–49.0)	0.001	< 0.001
ICU LOS, median days (IQR)	4.5 (0.0–13.0)	16.0 (12.0–27.3)	28.0 (15.3–43.8)	< 0.001	0.001
Hospital LOS, median days (IQR)	49.0 (28.3–67.8)	60.0 (45.0–81.5)	67.0 (52.0–86.0)	0.058	< 0.001
Major morbidity, n (%)	24 (18.5)	9 (18.0)	28 (41.2)	0.565	0.013
Mortality, n (%)	14 (10.8)	5 (10.0)	45 (66.2)	0.880	< 0.001
IPN, infected pancreatic necrosis; IQR, interquartile range; CAP, critical acute pancreatitis; MCAP, metachronous-CAP; SCAP, synchronous-CAP					
OF, organ failure; MDROs, multidrug-resistant organisms; ICU, intensive care unit; LOS, length of stay.					
The bold in the table means the P value of these parameters were < 0.05 and considered statistically significant.					
^a Group IPN alone vs. MCAP					
^b Group MCAP vs. SCAP					

The SCAP category seemed to identify patients with the highest risk of adverse outcome, while MCAP and IPN alone had comparably favorable prognosis.

Discussion

This is, to our knowledge, the largest study of a prospective cohort of IPN to specifically evaluate the clinical outcomes of CAP so far. We found that SCAP, characterized with synchronous persistent OF and

IPN, had significantly higher mortality and morbidity than MCAP. These results justified a further classification of CAP. For the first time, we put forward two subgroups of CAP, ie. SCAP and MCAP. According to the results, SCAP defines genuine CAP. These results gave us an update to the current knowledge about stratifications and classifications of AP.

The Atlanta classification (AC) reported in 1992 was the most widely accepted classification system in the past for the severity in AP, which divided AP into two groups: mild and severe [17]. However, due to substantial progress in understanding the pathophysiological and disease-related complications, most experts realized the necessity for revising the above classification system. Thus in 2012, the revised Atlanta classification (RAC) [18] and a novel DBC system were proposed [3]. The development of the DBC involved three steps. First, Petrov and Windsor performed a comprehensive review of available evidence and proposed the new classification [19]. The second phase consisted of a global Web-based survey of pancreatologists with recent clinical publications regarding AP [3]. Finally, an international consensus symposium was held during the 2011 International Association of Pancreatology meeting to further discuss the proposed classification [3]. The DBC was based on the local determinant (pancreatic necrosis) and the systemic determinant (organ failure) which were causally associated with clinical outcomes of AP. As both RAC and DBC systems were adopted, which inevitably raised issues about their validity and practicability. For the past decades, we have witnessed a tremendous effort on the independent external validation of RAC and DBC. By comparing the performance characteristics of each classification system in predicting important clinical outcomes, both RAC and DBC were found to be comparable and superior to AC [4–6, 16, 20]. Although there were still some controversies, DBC has become one of the internationally recognized criteria for AP severity classification, especially in tertiary medical centers. Hence, we focused on DBC classification in this study, especially the most severe category named CAP [3]. The Auckland group [21] performed a meta-analysis of 14 studies comprising 1478 patients demonstrating that both OF and IPN were equivalent determinants of severity with a mortality rate of 30% and 32%, respectively. However, taking them together during the course of AP was associated with even higher mortality (43%). In the multivariate analysis of a Korean study [16], POF was thought of as a continuum, and IPN served as a preceding event pertaining to mortality of late POF, thus concluding that both POF and IPN were independent risk factors for mortality of AP and should be recognized as actual determinants of severity. Among the Spanish [7], Chinese [9], British [6] and Indian [5] cohorts, the mortality of CAP was as high as 54.1%, 57.1%, 87.5% and 87.5%. Also, the death rate of our previous CAP cohort was 31.4% [8]. In that study, 102 CAP patients were enrolled to specifically evaluate the prognostic factors associated with CAP, especially from three aspects, including organ failure, infection, and surgical interventions. Therefore, identifying patients classified as “critical” has definite implications for prognosis and management choices. However, some controversies still exist about whether the critical category makes sense because of its rarity and whether IPN should be recognized as a key determinant of severity. In a Spanish cohort, only 3 of 543 patients (0.6%) were classified as CAP, and mortality among these patients was similar to the severe category. A nationwide multicenter prospective cohort study from the Spain group comprising 1655 AP patients showed that among patients with POF, the presence of infection was solely associated with increased morbidity, but

not mortality, which marked POF as the most significant determinant of severity [7]. More recent studies concluded that the influence of OF on mortality was stronger than that of IPN [22, 23], and in Scheper's study [23], even no association was found between the duration of organ failure and mortality. It was not surprising that these divergences existed because all the studies mentioned above were based on different settings (community hospital or tertiary referral center) and purposes (clinical management or research). In other words, if the results in these studies all held true, we might note that none of the existing classifications were based on uniform study designs and outcomes. A Spanish prospective multicenter study [24] proposed a modified DBC (MDBC) in ICU patients, where the severe category of DBC was separated into two groups: patients with IPN and transient OF and patients with POF but no IPN, and the two distinct subgroups marked with significantly different rates of intervention, morbidity and mortality. Recently, Wu et al. [9] provided further validation for the MDBC proposal to subdivide the DBC "severe" category into two groups in all hospital admissions. Viewing this, during our clinical practice, we noticed that the "critical" category of DBC might also be separated into two groups: the MCAP and SCAP, which might show a significant difference in clinical outcomes.

One of the most important purposes of AP reclassification was to focus on the population with the highest mortality. There was a considerable portion of DBC "critical" cases whose clinical courses were not that bad and might belong to the DBC "severe" category. This provided evidence that CAP could be further modified. Due to the limited number of cases with CAP in previous studies [4–6, 9], it was not easy to analyze the outcomes of CAP, let alone to redefine it. The present study made full use of a large cohort of CAP and found a significant increase in adverse effects in patients with synchronous persistent OF and IPN compared with MCAP. Thus, theoretically, SCAP should define genuine "critical" AP. It was acknowledged that mortality rates in severe pancreatitis were believed to have two peaks, that was, following "early" organ failure and following "late" organ failure due to secondary infection of pancreatic or peripancreatic necrosis [1, 2]. It was also generally considered that IPN developed over time, peaking at approximately three weeks or later after disease onset [1, 2]. With regard to SCAP in this study, the median time from onset to the diagnosis of IPN was only 16 days, which showed early intervention was preferable in this setting. In 2020, the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG) designed a multi-center randomized controlled trial protocol to compare the clinical outcomes of early on-demand drainage (EOD) with the current standard approach among acute necrotizing pancreatitis (ANP) patients complicated by POF [25]. Recently, the preliminary result showed that the EOD approach might have potential clinical benefits [26], which was similar to our conclusion.

Another strength of the present study was that MCAP patients did not have higher mortality compared with those with IPN alone, and this was consistent with a recent multicenter study [23], which found early persistent OF was not associated with increased mortality in patients with necrotizing pancreatitis. The pathophysiology of OF may differ according to whether OF occurs early or late in the disease [22]. In the early phase, the release of inflammatory chemokines and cytokines during the systemic inflammatory response syndrome (SIRS) plays an important role in the development of OF. Fortunately, with the improvement of ICU treatment modality, a majority of severe patients could come through the early OF period. Frequently after several weeks, infection of pancreatic necrosis may be accompanied by sepsis

and leads to the late OF phase. Choi et al. [16] demonstrated that patients with late persistent OF were associated with higher mortality and morbidity than those with early persistent OF. IPN-induced late OF rather than SIRS-induced early OF is the key determinant of prognosis. In other words, MCAP might be regarded as “severe” AP according to DBC, just as IPN alone.

There are still several limitations in this study. One of the limitations is that this cohort was conducted at a tertiary care center, 43% of enrolled patients were transferred from other institutions. This could have resulted in selection bias and potential confounding effects related to heterogeneity in initial treatment during the critical early phase of AP, and the results of the current study are less relevant to community hospital settings. Another limitation is that the prospectively maintained cohort all consist of IPN patients, thus, we can't evaluate the pooled influence of OF on mortality regardless of the presence or absence of IPN, which is also one of the key determinants of DBC [3]. Lastly, the results of the present study, which were derived from a single center, could not be generalized to other hospitals indiscriminately. Further multicenter, prospective original studies would provide more precise data to reduce potential confounding results.

Conclusions

Our present findings suggested that SCAP characterized with synchronous POF and IPN, had the most fulminant course, leading to an extremely high mortality and morbidity and should be defined as genuine CAP. While MCAP defined patients who had already recovered from early OF and then came to IPN in the late phase, had comparably favorable prognosis compared with IPN alone cases.

Abbreviations

AP: Acute pancreatitis; CAP: Critical acute pancreatitis; DBC: The determinant-based classification; EOD: Early on-demand drainage; IPN: Infected pancreatic necrosis; LOS: Length of stay; MCAP: Metachronous-CAP; OF: Organ failure; POF: persistent organ failure; SCAP: Synchronous-CAP.

Declarations

Acknowledgements

Not applicable

Authors' contributions

DS and GH designed the study and take overall responsibility for its content. QW, HH, CN and JL conducted the search and the statistical analysis. LC and SZ assessed the study eligibility and quality and interpreted the data. All authors contributed to the manuscript and approved the final version to be considered for publication.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Xiangya Hospital and written informed consent was obtained from all patients or their representatives for publication of data.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

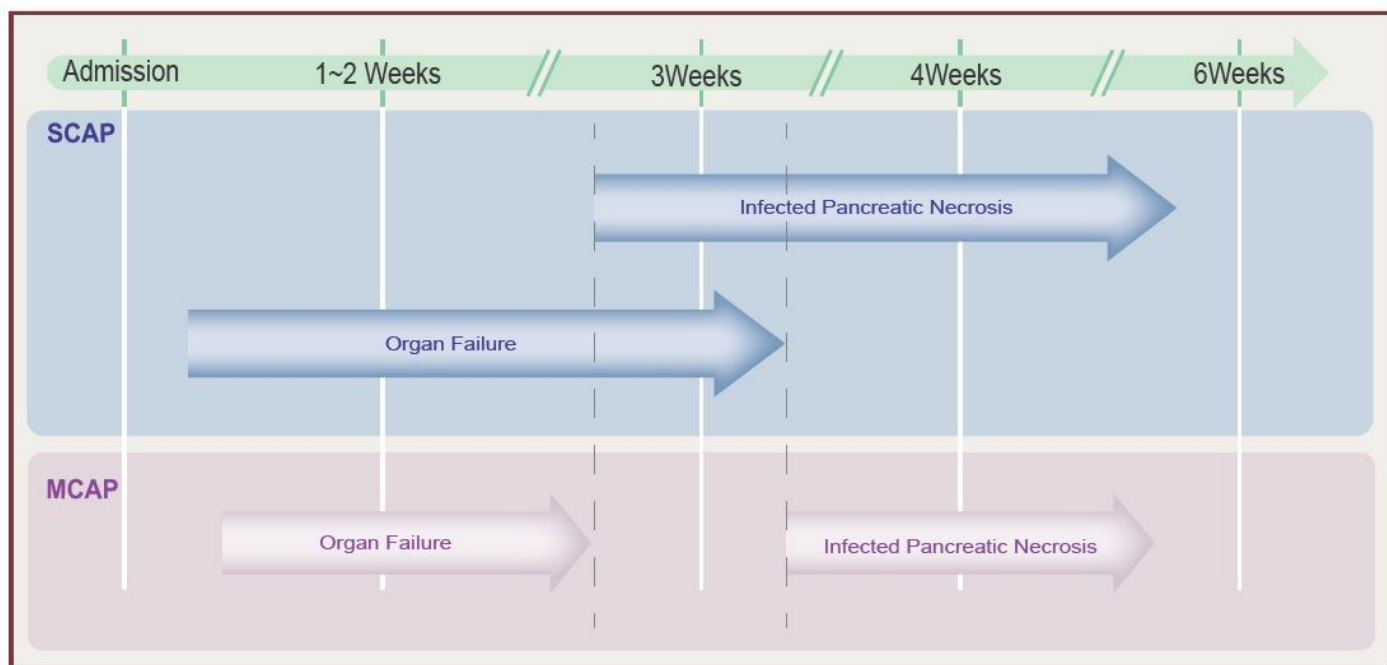


Figure 1

The difference between MCAP and SCAP in time course of organ failure and infected pancreatic necrosis.