

# Effects of Fluid Resuscitation on Organ Failure and Mortality in Patients with Acute Pancreatitis and Systemic Inflammatory Response Syndrome: A Retrospective Cohort Study

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## ARTICLE INFO

Received: 📅 November 11, 2019

Published: 📅 November 15, 2019

**Citation:** Lili Liu, Chao Wang, Tiancheng Luo, Lei Li. Effects of Fluid Resuscitation on Organ Failure and Mortality in Patients with Acute Pancreatitis and Systemic Inflammatory Response Syndrome: A Retrospective Cohort Study. Biomed J Sci & Tech Res 22(5)-2019. BJSTR. MS.ID.003825.

**Keywords:** Acute pancreatitis; Intensive care; Fluid resuscitation; Organ failure; Systemic inflammatory response syndrome

**Abbreviations:** AP: Acute Pancreatitis; DM: Diabetes Mellitus; ICU: Intensive Care Unit; MIMIC: Multi-Parameter Intelligent Monitoring in Intensive Care; SIRS: Systemic Inflammatory Response Syndrome; CI: Confidence Interval; OR: Odds Ratio; aOR: Adjusted Odds Ratio

## ABSTRACT

**Background:** Acute pancreatitis (AP), often presenting with systemic inflammatory response syndrome (SIRS), is a common gastroenterological condition requiring emergent intensive care. Severe cases of AP with SIRS and associated organ failure have high morbidity and mortality. Early, aggressive hydration is the recommended treatment. We investigated the influence of fluid resuscitation on organ failure, in-hospital mortality and 30-day mortality in patients with acute pancreatitis and SIRS.

**Methods:** Data of 317 patients from the MIMIC III 2002-2012 database who were diagnosed with AP, aged >20 years and had an ICU stay >48 hours were included in the analytic sample. Fluid input, urinary output and cumulative fluid resuscitation were measured at 12-hour intervals. Demographics (age, gender, race/ethnicity) and SIRS clinical manifestations (pulse, respiration, temperature and WBC) were analyzed. Endpoints were organ failure, in-hospital mortality and 30-day mortality.

**Results:** Odds of organ failure increased significantly with increased fluid input at 0-12 hours and 36-48 hours (adjusted odds ratio [aOR] = 1.125, 95% confidence interval [CI] = 1.019-1.243; aOR = 1.207, 95% CI = 1.0002-1.457), and with increased fluid balance at 0-12 hours and 36-48 hours (aOR = 1.103, 95% CI = 1.004-1.210; aOR = 1.180, 95% CI = 1.009-1.380, respectively). Odds of in-hospital mortality increased significantly with increased fluid input at 24-36 hours (aOR = 1.205, 95% CI = 1.058-1.373) and increased fluid balance at 24-36 hours (aOR = 1.196, 95% CI = 1.049-1.364). Odds of 30-day mortality increased significantly with increased fluid input at 24-36 hours (aOR = 1.175, 95% CI = 1.028-1.343) and increased fluid balance at 24-36 hours (aOR = 1.188, 95% CI = 1.038-1.359).

**Conclusion:** In fluid resuscitation for ICU patients with AP and SIRS, amounts of early fluid input (first 12 hours) or cumulative fluid resuscitation within 48 hours are associated with organ failure. Amounts of fluid input from 24 to 36 hours or cumulative resuscitation after 36-48 hours are associated with in-hospital mortality, and fluid balance has similar effects. Fluid output has no association with organ failure or mortality in this patient population.

## Introduction

Acute pancreatitis (AP), or inflammation of the pancreas, is a common gastrointestinal condition sometimes associated with systemic inflammatory response syndrome (SIRS), and

usually requiring emergent hospitalization [1]. The international classification system introduced by Dellinger et al. [2] describes acuity ranging from mild acute pancreatitis to severe to critical

acute pancreatitis characterized by the presence or absence of local (pancreatic necrosis) and systemic (organ failure) markers of severity. Severe and critical AP are common causes of ICU admissions [3], and have high morbidity and mortality [4,5]. The incidence of AP in Europe is 100 in 100,000 population [6], and over 270,000 ICU admissions in the United States are attributed to AP annually, while global incidence of AP continues to rise [7]. Diagnosis of AP is made based on sudden-onset abdominal pain that may radiate to the back and vomiting, with confirmation provided by markedly elevated (three times normal) levels of serum amylase or lipase [1,8].

Enhanced computed tomography may be performed if biochemical tests are inconclusive, or if indications of local complications or another acute abdominal condition such as gastrointestinal tract perforation are noted [9]. Many ICU admissions for acute pancreatitis and SIRS are associated with significant morbidity in the early stages, which may lead to prolonged hospitalization or death, particularly when other organ systems are affected [3,10]. Guidelines of the 2012 International Association of Pancreatology/American Pancreatic Association (IAP/APA) [8] and the American College of Gastroenterology [9] advise that aggressive hydration should be provided to all patients with organ failure and/or SIRS except when precluded by cardiovascular and/or renal comorbidities. Early aggressive intravenous hydration with Ringer's lactate is reported to be most beneficial within the first 12-24 hours [1,7], serving to restore fluid balance (circulating volume) and output, although further benefits may not be realized [9].

Studies have shown that fewer patients receiving fluid resuscitation developed SIRS and that C-reactive protein (CRP) levels were also lower, indicating reduced inflammation, but patient outcomes remained similar [10,11]. Fluid therapy is a complex process with noted risks due to possible volume overload, and continuous monitoring is essential to assess patient response [3]. Because excessive fluid administration may lead to organ failure, abdominal compartment syndrome, sepsis, need for intubation, and in-hospital mortality, the type, rate, and amount of fluids is critical during the initial 12-24 hours in ICU and throughout 72-hour cumulative fluid resuscitation [12,13]. Mole et al. [14] suggest that fluid prescriptions must be individualized based on patients' specific physiological derangement. Other authors suggest that optimization of fluid resuscitation in treating AP needs further study and consensus [13,15]. However, consensus is still lacking on specific types of fluid therapy, administration rates, amounts of fluid used, and desired end points [16].

The Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC) III database is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (Cambridge, MA, USA). The MIMIC III database encompasses a diverse and exceptionally large population of ICU patients and has been used to support a diverse range of analytic studies [17]. It is freely accessible to researchers and we determined

that it would provide an ideal data source for the present study. Our hypothesis was that fluid resuscitation used to resolve the complex clinical dilemma of AP, with or without SIRS, was likely associated with organ failure and mortality. Therefore, this study aimed to examine the influence of fluid resuscitation (fluid input, fluid output, and fluid balance) on the occurrence of organ failure, in-hospital mortality and 30-day mortality in patients with acute pancreatitis with or without SIRS.

## Methods

### Data Source

The present study obtained all patient data from the Medical Information Mart for Intensive Care III (MIMIC-III) 2002-2012. MIMIC-III is a large, freely accessible database that includes de-identified health-related data collected from over 40,000 patients admitted to critical care units of Beth Israel Deaconess Medical Center (BIDMC), Boston, MA, USA, between 2001 and May 2012. The MIMIC database website (<https://mimic.physionet.org/about/mimic/>) states that the BIDMC Department of Medicine is supported by grants (R01-EB001659, 2003-2013; R01-EB0117205, 2014-2018) from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH). This research database is a joint venture managed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT). Use of the MIMIC is approved by the Institutional Review Boards of BIDMC and MIT and use of the database is granted to investigators for research purposes.

### Study Population

We screened the MIMIC III database of 46,520 ICU patients for patients older than 20 years who were diagnosed with acute pancreatitis and had stayed in ICU more than 48 hours. For patients with more than one ICU stay, only the first ICU stay was eligible for inclusion. Patients who were pregnant, diagnosed with renal failure or had undergone dialysis, had non-systemic inflammatory response syndrome and were diagnosed with heart failure, diabetes mellitus (DM), or pancreatic cancer were excluded. Finally, the data of 317 ICU patients who met the inclusion criteria were included for analysis.

### Study Design

We conducted a retrospective cohort study to evaluate the associations between fluid resuscitation performed within 24 to 48 hours of ICU admission, and the occurrence of SIRS and patients' length of stay in ICU. The study endpoints were organ failure, in-hospital mortality and 30-day mortality. Demographic data included in the analysis were subjects' age, gender and race/ethnicity (categorized by MIMIC as white, black and others). Variables of SIRS clinical manifestations included for analysis were pulse >90 beats per minute, respirations >20 per minute, temperature <96.8oF or >100.4oF, and white blood cell (WBC) count >12000 cells/mm<sup>3</sup>.

## Fluid Resuscitation

The volume and type of fluid input and output were recorded at 12, 24, 36, and 48 hours after ICU admission. Fluid balance (FB) was calculated as fluid intake minus fluid output and dichotomized into two groups based on the median. Percentages of colloids, nutrition, hypertonic crystalloid and non-hypertonic crystalloids in total fluid input were used to define types of fluid input. All evaluations were performed to compare the effects of volume and types of fluid resuscitation within 12, 24, 36 and 48 hours.

## Statistical Analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation (SD) and median value (interquartile range, IQR). Categorical variables are expressed as counts (percentage). Univariate and multivariate logistic regression analyses were performed to examine the impact of fluid resuscitation on organ failure, in-hospital mortality and 30-day mortality. The multivariate regression model of organ failure was adjusted simultaneously for age, gender, race, heart rate, and WBC. The multivariate regression model of in-hospital mortality and 30-day mortality was adjusted simultaneously for age, gender, race, temperature, WBC, and organ failure. All statistical assessments were two-sided and evaluated at the 0.05 level of significance. Statistical analyses were performed by IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, USA).

## Results

A total of 46,520 inpatients were recruited from the Medical Information Mart for Intensive Care III (MIMIC-III) database from which the data of 951 inpatients aged  $\geq 20$  years old and diagnosed with acute pancreatitis were considered eligible for inclusion in the present study. After excluding 288 patients with an ICU stay of less than 48 hours, 6 patients who were missing ICU measurement information, 1 pregnant woman, 11 patients who were on dialysis, 186 patients with heart failure, 134 patients with DM, 1 patient with pancreatic cancer and 7 patients with non-systemic inflammatory response syndrome, the data of a total of 317 patients were included in the analytic sample.

## Subjects Demographic and Clinical Characteristics

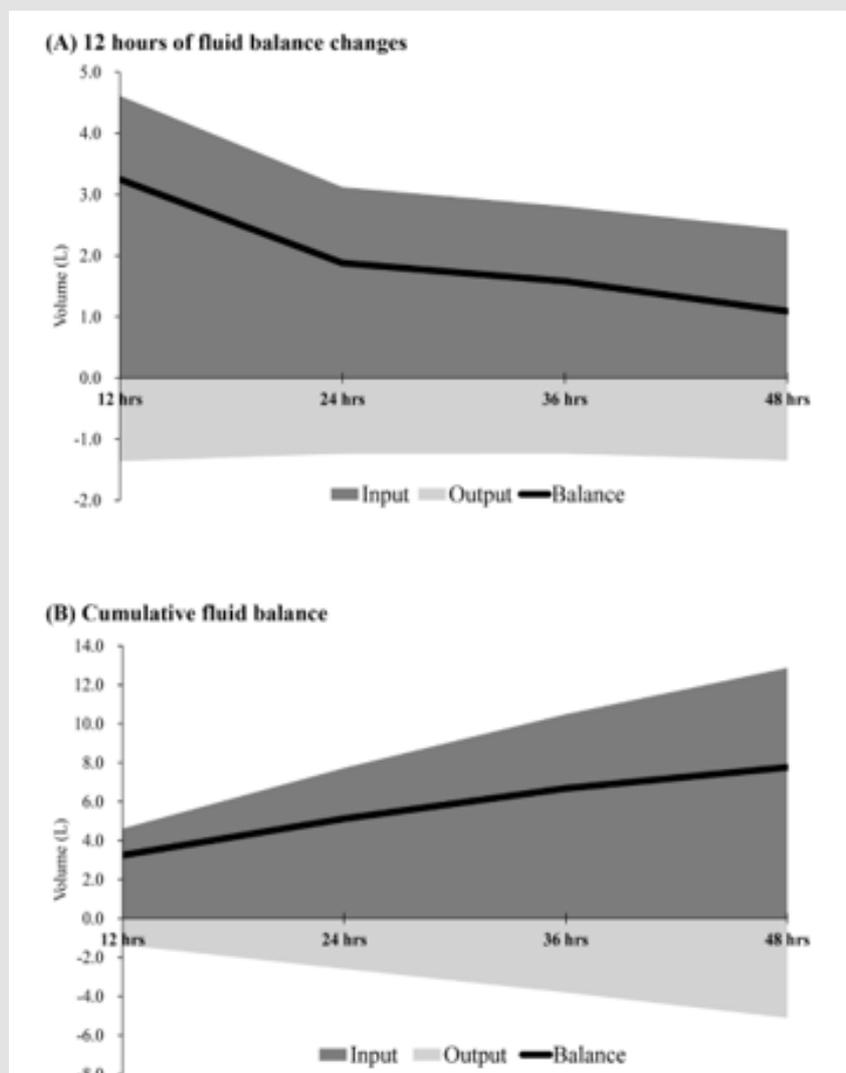
Subjects' characteristics are summarized in Table 1. The mean age of the study population was 60.2 years, made up of 139 females (43.8%) and 178 males (56.2%), in which 74 patients without organ failure (23.3%) and 243 patients with organ failure (76.7%). The mean of length of stay in ICU was 10.6 days. In-hospital mortality of the study population was 14/8% and 30-day mortality was 12.6% (Table 1). At a mean time of 12 hours, the average fluid balance was 3.2 L, with fluid input of 4.6 L and fluid output 1.4 L. Average fluid balance at 24 hours, 36 hours, and 48 hours were 1.9L, 1.6 L, and 1.1L, respectively (Figure 1A). Cumulative fluid balance at 24 hours, 36 hours, and 48 hours were 5.1 L, 6.7 L, and 7.8 L, respectively (Figure 1B).

**Table 1:** Subjects' Demographic and Clinical Characteristics.

Characteristics	Total (n=317)	Organ failure	
		No (n=74)	Yes (n=243)
<b>Demography</b>			
Age (years)			
Mean $\pm$ SD	60.2 $\pm$ 42.2	53.5 $\pm$ 34.2	62.3 $\pm$ 44.2
Median (IQR)	53.1 (41.7-68.2)	50.7 (37.1-62.9)	54.9 (43.0-69.6)
Gender			
Female	139 (43.8)	31(41.9)	108(44.4)
Male	178 (56.2)	43(58.1)	135(55.6)
Race			
White	218 (68.8)	48(64.9)	170(70.0)
Black	22 (6.9)	8(10.8)	14(5.8)
Others (Hispanic/Asian/Middle eastern)	20 (6.3)	4(5.4)	16(6.6)
Unknown	57 (18.0)	14(18.9)	43(17.7)
<b>Clinical manifestations of SIRS</b>			
Temperature			
Normal	274 (86.4)	74(100.0)	200(82.3)
Abnormal	43 (13.6)	0(0.0)	43(17.7)
Heart rate			
Normal	6 (1.9)	2(2.7)	4(1.6)
Abnormal	311 (98.1)	72(97.3)	239(98.4)

Respiratory rate			
Normal	1 (0.3)	0(0.0)	1(0.4)
Abnormal	316 (99.7)	74(100.0)	242(99.6)
White blood cells			
Normal	86 (27.1)	23(31.1)	63(25.9)
Abnormal	231 (72.9)	51(68.9)	180(74.1)
Clinical outcome			
In-Hospital mortality			
Alive	270 (85.2)	73(98.6)	197(81.1)
Death	47 (14.8)	1(1.4)	46(18.9)
30-day Mortality			
Alive	277 (87.4)	72(97.3)	205(84.4)
Death	40 (12.6)	2(2.7)	38(15.6)
Length of ICU (days)			
Mean ± SD	10.6 ± 11.4	3.7 ± 1.8	12.6 ± 12.2
Median (IQR)	6.1 (3.0-13.9)	2.9 (2.5-4.2)	9.0 (4.4-16.3)

Note: Continuous Variables were shown Mean ± SD and Median (IQR); Categorical Variables were Shown Counts (%).



**Figure 1:** (A) Fluid Input, Output and Fluid Balance Changes at 12-Hour Intervals; and (B) Cumulative Fluid Input, Output and Fluid Balance.

### Fluid Resuscitation

Table 2 depicts the results of logistic regression analysis of associations between fluid resuscitation and organ failure, in-hospital mortality and 30-day mortality. Multivariate logistic regression analysis revealed that the odds of organ failure increased significantly in association with increased fluid input at 0-12 hours and 36-48 hours [adjusted odds ratio (aOR) = 1.125, 95% confidence interval (CI) = 1.019-1.243; aOR = 1.207, 95% CI = 1.0002-1.457], and with increased fluid balance at 0-12 hours and

36-48 hours (aOR = 1.103, 95% CI = 1.004-1.210; aOR = 1.180, 95% CI = 1.009-1.380, respectively). The odds of in-hospital mortality increased significantly associated with increased fluid input at 24-36 hours (aOR = 1.205, 95% CI = 1.058-1.373) and with increased fluid balance at 24-36 hours (aOR = 1.196, 95% CI = 1.049-1.364). In addition, the odds of 30-day mortality increased significantly associated with fluid input increases at 24-36 hours (aOR = 1.175, 95% CI = 1.028-1.343) and with fluid balance increases at 24-36 hours (aOR = 1.188, 95% CI = 1.038-1.359) (Table 2).

**Table 2:** Logistic Regression Analysis of Fluid Resuscitation Associated with Organ Failure, In-Hospital Mortality and 30-Day Mortality.

Organ failure <sup>a</sup>		In-hospital mortality <sup>b</sup>		30-day mortality <sup>b</sup>		
OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	
<b>Fluid Input (L)</b>						
0-12 hours	1.118 (1.017-1.229)	1.118 (1.017-1.229)	1.090 (1.004-1.183)	1.057 (0.967-1.154)	1.057 (0.966-1.156)	1.048 (0.951-1.154)
12-24 hours	1.041 (0.927-1.169)	1.047 (0.926-1.184)	1.053 (0.938-1.184)	1.063 (0.939-1.204)	1.006 (0.878-1.152)	1.006 (0.881-1.165)
24-36 hours	1.056 (0.929-1.201)	1.048 (0.918-1.197)	1.193 (1.056-1.348)	1.205 (1.058-1.373)	1.154 (1.016-1.311)	1.175 (1.028-1.343)
36-48 hours	1.196 (0.999-1.431)	1.207 (1.0002-1.457)	1.159 (1.004-1.338)	1.145 (0.982-1.336)	1.115 (0.955-1.303)	1.112 (0.946-1.308)
<b>Fluid Output (L)</b>						
0-12 hours	1.143 (0.867-1.507)	1.194 (0.895-1.592)	0.752 (0.524-1.079)	0.75 (0.517-1.087)	0.672 (0.445-1.014)	0.716 (0.467-1.099)
12-24 hours	0.931 (0.715-1.212)	0.989 (0.748-1.308)	0.802 (0.552-1.166)	0.912 (0.625-1.330)	0.698 (0.448-1.086)	0.821 (0.531-1.269)
24-36 hours	0.937 (0.733-1.196)	0.98 (0.755-1.271)	0.887 (0.621-1.267)	1.031 (0.734-1.448)	0.729 (0.462-1.149)	0.87 (0.554-1.366)
36-48 hours	0.871 (0.693-1.095)	0.91 (0.718-1.153)	1.069 (0.816-1.400)	1.184 (0.898-1.561)	1.013 (0.746-1.377)	1.138 (0.843-1.535)
<b>Fluid Balance (L)</b>						
0-12 hours	1.101 (1.007-1.205)	1.103 (1.004-1.210)	1.109 (1.022-1.204)	1.076 (0.986-1.175)	1.082 (0.991-1.181)	1.069 (0.972-1.175)
12-24 hours	1.059 (0.943-1.190)	1.055 (0.935-1.189)	1.075 (0.963-1.201)	1.071 (0.949-1.208)	1.045 (0.925-1.180)	1.034 (0.908-1.179)
24-36 hours	1.06 (0.941-1.195)	1.044 (0.923-1.180)	1.2 (1.065-1.353)	1.196 (1.049-1.364)	1.183 (1.044-1.341)	1.188 (1.038-1.359)
36-48 hours	1.197 (1.025-1.397)	1.18 (1.009-1.380)	1.123 (0.980-1.288)	1.083 (0.936-1.253)	1.102 (0.952-1.275)	1.068 (0.913-1.248)

<sup>a</sup>Multivariate logistic regression was simultaneously adjusted for age, gender, race, heart rate and white blood cells. (Temperature and respiratory rate were not put into model adjustments because all organ failure patients have abnormal temperatures and almost all patients have abnormal respiratory rates.)

<sup>b</sup>Multivariate logistic regression was simultaneously adjusted for age, gender, race, temperature and white blood cells. (Heart rate and respiratory rate were not put into model adjustments because heart rate and respiratory rate are normal in survived patients.)

**Cumulative Fluid Resuscitation**

Table 3 depicts the results of multivariate logistic regression analysis of cumulative fluid resuscitation. The odds of organ failure increased significantly in association with increased fluid input at 0-12 hours, 0-24 hours and 0-48 hours (aOR = 1.125, 95% CI = 1.019-1.243; aOR = 1.070, 95% CI = 1.002-1.142; aOR = 1.052, 95% CI = 1.007-1.10, respectively). In addition, the odds of organ failure increased significantly associated with increased fluid balance at 0-12 hours and 0-48 hours (aOR = 1.103, 95% CI = 1.004-1.210; aOR = 1.043, 95% CI = 1.001-1.086, respectively). The odds of in-hospital mortality increased significantly associated with increased fluid input at 0-36 hours and 0-48 hours (aOR = 1.044, 95% CI =

1.0004-1.091; aOR = 1.039, 95% CI = 1.002-1.078, respectively). Similarly, the odds of in-hospital mortality increased significantly in association with increased fluid balance at 0-36 hours and 0-48 hours (aOR = 1.049, 95% CI = 1.005-1.096; aOR = 1.039, 95% CI = 1.002-1.078, respectively). However, the odds of 30-day mortality decreased significantly in association with increased fluid output at 0-24 hours and 0-36 hours (OR = 0.776, 95% CI = 0.608-0.991; OR = 0.836, 95% CI = 0.70-0.9996, respectively), and the odds of 30-day mortality increased significantly associated with increased fluid balance at 0-36 hours and 0-48 hours (OR = 1.047, 95% CI = 1.003-1.093; OR = 1.039, 95% CI = 1.002-1.077, respectively). After adjusting for covariates, the results of multivariate logistic regression were no longer significant (Table 3).

**Table 3:** Logistic Regression Analysis of Cumulative Fluid Resuscitation Associated with Organ Failure, In-Hospital Mortality and 30-Day Mortality.

Organ failure <sup>a</sup>		In-hospital mortality <sup>b</sup>		30-day mortality <sup>b</sup>		
OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	
<b>Fluid Input (L)</b>						
0-12 hours	1.118 (1.017-1.229)	1.125 (1.019-1.243)	1.090 (1.004-1.183)	1.057 (0.967-1.154)	1.057 (0.966-1.156)	1.048 (0.951-1.154)
0-24 hours	1.063 (0.9997-1.131)	1.070 (1.002-1.142)	1.053 (0.996-1.113)	1.040 (0.980-1.103)	1.027 (0.966-1.093)	1.025 (0.960-1.094)
0-36 hours	1.046 (0.998-1.097)	1.050 (0.999-1.105)	1.051 (1.009-1.096)	1.044 (1.0004-1.091)	1.033 (0.988-1.080)	1.034 (0.987-1.083)
0-48 hours	1.048 (1.005-1.092)	1.052 (1.007-1.100)	1.045 (1.009-1.082)	1.039 (1.002-1.078)	1.030 (0.993-1.069)	1.030 (0.991-1.071)
<b>Fluid Output (L)</b>						
0-12 hours	1.143 (0.867-1.507)	1.194 (0.895-1.592)	0.752 (0.524-1.079)	0.750 (0.517-1.087)	0.672 (0.445-1.014)	0.716 (0.467-1.099)
0-24 hours	1.026 (0.875-1.203)	1.063 (0.899-1.257)	0.844 (0.682-1.044)	0.872 (0.699-1.087)	0.776 (0.608-0.991)	0.831 (0.645-1.070)
0-36 hours	1.007 (0.901-1.127)	1.035 (0.919-1.165)	0.902 (0.775-1.050)	0.937 (0.798-1.099)	0.836 (0.700-0.9996)	0.885 (0.734-1.067)
0-48 hours	0.998 (0.919-1.084)	1.019 (0.934-1.113)	0.956 (0.856-1.067)	0.990 (0.882-1.111)	0.909 (0.797-1.036)	0.956 (0.836-1.095)
<b>Fluid Balance (L)</b>						
0-12 hours	1.101 (1.007-1.205)	1.103 (1.004-1.210)	1.109 (1.022-1.204)	1.076 (0.986-1.175)	1.082 (0.991-1.181)	1.069 (0.972-1.175)
0-24 hours	1.059 (0.998-1.125)	1.060 (0.996-1.128)	1.065 (1.009-1.124)	1.049 (0.991-1.112)	1.046 (0.987-1.108)	1.038 (0.975-1.105)
0-36 hours	1.044 (0.998-1.094)	1.044 (0.995-1.095)	1.059 (1.017-1.104)	1.049 (1.005-1.096)	1.047 (1.003-1.093)	1.042 (0.996-1.091)
0-48 hours	1.044 (1.004-1.086)	1.043 (1.001-1.086)	1.049 (1.013-1.086)	1.039 (1.002-1.078)	1.039 (1.002-1.077)	1.034 (0.995-1.074)

<sup>a</sup>Multivariate logistic regression was simultaneously adjusted for age, gender, race, heart rate and white blood cells. (Temperature and respiratory rate were not put into model adjustments because all organ failure patients have abnormal temperatures and almost all patients have abnormal respiratory rates.)

<sup>b</sup>Multivariate logistic regression was simultaneously adjusted for age, gender, race, temperature, white blood cells and organ failure. (Heart rate and respiratory rate were not put into model adjustments because heart rate and respiratory rate are normal in survived patients.)

## Discussion

The present study examined the influence of fluid resuscitation on the occurrence of organ failure, in-hospital mortality and 30-day mortality in 317 AP patients from the MIMIC III database who had been in the ICU for at least 48 hours. We found mainly that the amount of early fluid input (0-12 hours) or the cumulative fluid resuscitation after 48 hours in ICU is associated with the incidence of organ failure in these patients. The amount of fluid input for 24 to 35 hours and the cumulative fluid resuscitation at 36 or 48 hours in ICU are associated with in-hospital mortality for AP patients. Fluid balance showed similar effects as fluid input. In the AP patient population studied, the amount of early fluid balance (0-12 hr) or the cumulative fluid resuscitation at 48 hours in ICU is also associated with the incidence of organ failure, and for 24 to 36 hours or the cumulative fluid balance at 36 or 48 hours in ICU is associated with in-hospital mortality. However, the fluid output appears to have no association with organ failure or mortality in this patient population.

Severe AP involves inflammation of the pancreas combined with SIRS causing extravasation of fluid into interstitial spaces, which can lead to hypovolaemia, hypoperfusion and organ failure [1,8]. To offset this projected course in the absence of curative therapy, it becomes critical to provide supportive therapy with fluid resuscitation and management of pain in the early acute phase [18]. However, even though early fluid resuscitation is reported to reduce morbidity and mortality in AP patients, the agreement is lacking on fluid type and amounts. Some authors advise first achieving hemodynamic stability by bolusing fluids and then administering 250cc to 500cc of balanced crystalloid solutions in patients without volume depletion and 500cc to 1000cc for those with severe depletion [9]. The IAP/APA guideline based its recommendations for fluid resuscitation on one randomized controlled trial that showed improvements in the CRP levels and SIRS with the use of Ringer's lactate [8], and although other studies use balanced fluids like Plasma-Lyte, the benefits of these fluids have not been confirmed to date [1].

One study showed that patients receiving goal-directed fluid therapy with invasive monitoring had shorter ICU stays, less ventilator support, fewer incidents of compartment syndrome and organ failure, and lower in-hospital mortality [18]. In contrast, a randomized controlled trial with 115 patients found that

rapid, uncontrolled fluid resuscitation within 48 hours (or until hematocrit was <35%) actually resulted in significant increases in the rates of infection, abdominal compartment syndrome, need for mechanical ventilation and mortality [15]. In the present study, the amount of early fluid input (0-12 hours) was associated with an increased incidence of organ failure, primarily in patients with severe disease already accompanied by SIRS. Another investigation of early fluid resuscitation of AP patients reported a reduced incidence of SIRS and organ failure at 72 hours, but this was mainly in patients with interstitial disease and not in severe cases [19]. Those authors concluded that early fluid resuscitation is most beneficial in preventing severe disease in those admitted with less severe AP.

Other authors found that effects of the initial intravenous fluid resuscitation rate in the first 24 hours of admission increased the risk of mortality in patients with severe AP unless the early fluid resuscitation amount was at least one-third of the cumulative fluid resuscitation amount at 72 hours [20]. In other words, aggressive early treatment-more fluid at a faster rate- achieved more favorable outcomes. In the present study, the amount of cumulative fluid resuscitation after 48 hours in ICU was associated with an increased incidence of organ failure, and the amount of fluid input for 24 to 35 hours and the cumulative fluid resuscitation at 36 or 48 hours were associated with in-hospital mortality for AP patients. Among our patient population, the odds of in-hospital mortality increased significantly associated with increased fluid input at 24-36 hours and with increased fluid balance in the same timeframe.

When equal numbers of AP patients in an "early" resuscitation group and a "late" resuscitation group received the same total volume of fluid over 72 hours but the early group received more of that volume in the first 24 hours, the "late" group had a higher rate of in-hospital mortality, with four patients dying of acute renal failure, cardiopulmonary arrest and ventricular tachycardia [20]. However, rates of organ failure, SIRS development and hospital length of stay were the same between the two groups. Results of that study again support the idea of aggressive fluid resuscitation in the first 24 hours after hospital admission, including volume and rate. Accordingly, in the present study, since early fluid resuscitation was associated with organ dysfunction but not with in-hospital or 30-day mortality, we suggest, along with other authors [19], that it was the acute severe status of our AP patients that influenced organ involvement and not the volume or rate of fluid resuscitation.

The present study found no association between fluid output and organ failure or mortality.

Another study that used the large MIMIC III database found that, in critically ill AP patients with negative fluid balance, increased fluid intake and increased urine output were both associated with lower risk of hospital mortality [21]. The authors of that study believed that fluid intake was directly responsible for increased urine output in their patient population, and that the association

between urine output and mortality was secondary following an association between fluid intake and mortality. They also suggested that achieving a negative fluid balance in patients who are receiving high fluid intake is a factor most likely related to satisfactory organ function. The degree of AP severity, again, appears to greatly influence outcomes of fluid resuscitation. In patients with severe AP with SIRS and organ failure, the hour-to-hour administration of fluids (fluid resuscitation profiles) are found to vary considerably between those who survive and those who don't [14], and standard measures of judging adequate filling are needed. Although the present study did not consider fluid monitoring parameters in this investigation, it is clear that managing fluids in critically ill patients, whether AP or other diagnoses, is a clinical challenge because of the well-known associations between fluid overload and poor outcomes [3].

As such, monitoring fluid resuscitation in AP is essential. The IAP/APA guideline [8] recommends using specific target measures to monitor fluid resuscitation since no single parameter indicates hydration status; laboratory measures include hematocrit (ideally between 35% and 44%), and blood urea nitrogen (BUN) and creatinine levels (within the normal range); continuous monitoring in the ICU includes heart rate (less than 120/min), mean arterial pressure (between 64-85mmHg) and urinary output (0.5 ml/kg/hour). Newer monitoring methods that focus on the intravascular compartment include cardiac output monitoring and transesophageal Doppler waveform analysis [14]. As monitoring methods for fluid resuscitation in AP improve, it may shed light on the most beneficial amounts and rates of fluid administration from early fluid resuscitation to cumulative fluid resuscitation, helping to refine fluid resuscitation profiles.

### Strengths and Limitations

The present study used data retrieved from MIMIC III, a high-quality database that provides demographic and clinical data from a large, diverse population of ICU patients. The quality of our data analysis and research results benefitted greatly from the high temporal resolution data of MIMIC III, including clinical laboratory results, electronic documentation, and bedside monitoring trends and waveforms. However, this study also has certain limitations, mainly that the data were derived from only one medical center, meaning that the study results cannot be generalized to other populations in other locations. Lifestyle and dietary information, environmental exposure and family medical history are not included in the MIMIC III database and therefore could not be analyzed; we must consider that our results may have been influenced by these factors if they had been included in the analysis. Fluid balance prior to ICU admission was also not included in the analysis since only limited information was included in the database, and this omission could lead to information bias. Also, only in-hospital data during patients' ICU stays were included and no information was provided on medical utilization after discharge. Finally, due to the nature of retrospective research using a secondary database,

only associations between fluid resuscitation and mortality could be inferred. Further prospective studies are needed to investigate the optimization of fluid resuscitation protocols associated with improved outcomes for severe acute pancreatitis.

### Conclusion

In fluid resuscitation for ICU patients with AP and SIRS, amounts of early fluid input (first 12 hours) or cumulative fluid resuscitation within 48 hours are associated with organ failure. Amounts of fluid input from 24 to 36 hours or cumulative resuscitation after 36-48 hours are associated with in-hospital mortality, and fluid balance has similar effects. Fluid output has no association with organ failure or mortality in this patient population. Results of the present study suggest that early fluid resuscitation is essential in severe AP but that the entire hour-to-hour fluid resuscitation profile determines outcomes. Our results also emphasize the need for consensus on a classification system for AP severity, a monitoring protocol for use in nursing units to guide fluid resuscitation and standard recommendations for fluid administration, including fluid type, volume, and rate of administration associated with satisfactory outcomes.

### Declarations

#### Ethical Considerations and Consent to Participate

Use of the MIMIC-III database is approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (BIDMC), Boston, MA, USA, and Massachusetts Institute of Technology and use of the database is granted to investigators for research purposes. Since all patient data in MIMIC III database is de-identified, signed informed consent by patients is not required.

#### Data Availability

The MIMIC-III database is freely accessible. Use of the database by researchers is granted by the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC) for research purposes only.

**Consent for Publication:** Not applicable.

#### Competing Interests

The authors have no conflicts of interest to declare associated with the present study.

#### Funding

None.

#### Author Contributions

[please make a list using authors' initials (e.g., LLC) with project description such as Subject selection; Data analysis; Writing manuscript; Manuscript evaluation; etc.]

#### Acknowledgment

The authors wish to the Philips Healthcare and staff at the Beth Israel Deaconess Medical Center, Boston, for supporting database development.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.22.003825

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