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Response and outcome from fluid resuscitation in acute pancreatitis: a prospective cohort study

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Abstract

Background: Intravenous (IV) fluid resuscitation remains the cornerstone for early management of acute pancreatitis (AP), but many questions remain unanswered, including how to determine whether patients will benefit from additional fluids. The aim was to investigate the utility of serum biomarkers of responsiveness IV fluid resuscitation in patients with AP and systemic inflammatory response syndrome (SIRS).

Methods: Eligible adult patients had abdominal pain for <36 h and ≥2 SIRS criteria. Mean arterial pressure (>65 mmHg) and urine output (>0.5 ml/kg/h) were used to assess responsiveness at 2 and 6–8 h after initiation of IV fluids. Comparison was made between responsive and refractory patients at time points for fluid volume, biomarkers and outcomes.

Results: At 2 h 19 patients responded to fluids (Group 1) while 4 were refractory (Group 2); at 6–8 h 14 responded (Group 3) and 9 were refractory (Group 4). No demographic differences between patient groups, but Group 4 had worse prognostic features than Group 3. Refractory patients received significantly more fluid (Group 4 mean 7082 ml vs. Group 3 5022 mL, $P < 0.001$) in first 24 h and had worse outcome. No significant differences in biomarkers between the groups.

Conclusions: The serum biomarkers did not discriminate between fluid responsive and refractory patients. Refractory patients at 6–8 h had more severe disease on admission, did not benefit from additional fluids and had a worse outcome. New approaches to guide fluid resuscitation in patients with AP are required.

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Introduction

Acute pancreatitis (AP) is a common acute gastrointestinal disease that is increasing globally, and when severe is associated with a high morbidity, mortality and economic burden.[1] About half of the deaths in patients with AP are due to early persistent organ failure (POF).[2] The early management of severe AP remains largely supportive because there are no effective pharmacological treatments despite multiple clinical trials.[3] The cornerstone of

the early management of AP remains fluid resuscitation[4,5] which can improve clinical outcomes.[6] But many questions remain about the best type of fluid, the rate of fluid administration and the best way to guide and monitor the response to fluid resuscitation.[7]

The goal of fluid resuscitation is to correct hypovolemia and improve organ perfusion through increased stroke volume and cardiac output.[8] Both too much and too little resuscitation fluid are associated with a worse outcomes.[9] Uncorrected hypovolemia results in compensatory reflex vasoconstriction of the splanchnic bed, sacrificing blood flow to maintain perfusion of other organs, increasing the risk of pancreatic, intestine and other organ injury.[10] On the other hand, excessive fluid resuscitation increases tissue oedema and impairs cardiac and lung function, increasing the risk of organ failure.[11] Determining the response to fluid resuscitation and whether a patient requires additional fluid is thus a critical clinical question. The cardiac response to fluid resuscitation depends on the relationship between the ventricular end-diastolic volume ('preload') and the contractility of the heart, depicted in the Frank-Starling curve.[12] If patients are hypovolemic, fluid resuscitation will increase preload, stroke volume and cardiac output, providing normal contractility allows the heart to respond to this increased filling pressure. Should preload already be optimal, additional fluids will not improve cardiac output, and may be harmful.

Several different approaches are recommended to determine whether a patient will benefit from additional fluids or not. For intensive care patients, invasive measurement of parameters such as stroke volume and pulse pressure variations has been recommended.[9,12] Whereas for ward patients, non-invasive measurement of parameters including heart rate, mean arterial pressure (MAP), urine output (UO) and haematocrit have been advocated.[13] These are the most frequently used measurements for 'goal-directed' fluid resuscitation,[9,14] where a positive response to a fluid bolus is detected by a decrease in heart rate, increase in MAP and/or increase in UO.[13] When patients respond to a fluid bolus (or an increased rate of fluid resuscitation) it is common practice to give more fluid, on the basis that they are 'fluid responsive', still hypovolemic and likely to benefit from more fluid. When patients do not respond to a fluid bolus (or an increased rate of fluid resuscitation) it is also common practice to administer more fluid, on the basis that might still by hypovolemic. It is difficult to make the distinction between patients with persisting hypovolemia who will respond to additional fluid and patients who are fluid refractory and will not respond and/or be harmed by additional fluid.

Given the aim of resuscitation is to restore normal end-organ perfusion,[15] biomarkers of organ perfusion might have utility in distinguishing fluid responsive and fluid refractory patients, in combination with clinical assessment or on their own.[16] Improved biomarkers of the response to fluid resuscitation that reflect end-organ perfusion might also assist in the design and conduct of future studies seeking to determine optimal and personalised fluid resuscitation protocols. The aim of this pilot study was to test organ-specific serum biomarkers as potential guides to fluid resuscitation using a standardised protocol during the first 24 h after admission and in patients with AP and systemic inflammatory response syndrome (SIRS).

Methods

Study design, registration and ethics

This prospective cohort study was designed to evaluate serum biomarkers between patient groups that were responsive or refractory to a tightly managed fluid resuscitation protocol and the study following the STROBE guideline for observational studies.[17] The current study protocol was approved by the local Institutional Review Board (No. 247) and by the Health and Disability Ethics Committee in New Zealand (12/NTA/39). This trial was registered in Chinese Clinical Trial Registry (ChiCTR-OPN-15006741, http://www.chictr.org.cn). All included patients were informed and provided consent prior to study participation.

Patients and settings

Consecutive patients admitted with the diagnosis of AP[18] to the Emergency Department of West China Hospital, Sichuan University, in Chengdu between 24th January and 23rd June 2015 and who met the inclusion criteria were recruited. Eligible patients were 18–70 years old, had abdominal pain for <36 h before admission and had ≥2 criteria of SIRS.[19] The exclusion criteria are listed in Supplementary Methods.

Fluid resuscitation

The details of the management of AP patients are described in Supplementary Methods. The initial fluid resuscitation protocol, commenced in the Department of Integrated Traditional Chinese and Western Medicine (<2 h after hospital admission), was a continuous infusion of either dextrose saline or normal saline solution[20] with or without a bolus infusion of lactated Ringer's solution.[21]

Response to fluid resuscitation

Fluid responsiveness was determined at 2 h (checkpoint 1) and 6–8 h (checkpoint 2) after starting fluid resuscitation using a standardised clinical assessment (MAP and UO) and based on International Association of Pancreatology and American Pancreatic Association (IAP/APA) guidelines (Supplementary Methods).[4] The fluid resuscitation flowchart and fluid responsiveness checkpoints are shown in Fig. 1. Patients were considered to be *clinically responsive to fluid resuscitation* if their UO was >0.5 ml/kg/h and/or their MAP was >65 mmHg. Patients were considered to be *clinically refractory to fluid resuscitation* if their UO was <0.5 ml/kg/h and/or they had hypotension (MAP <65 mmHg). The detailed fluid

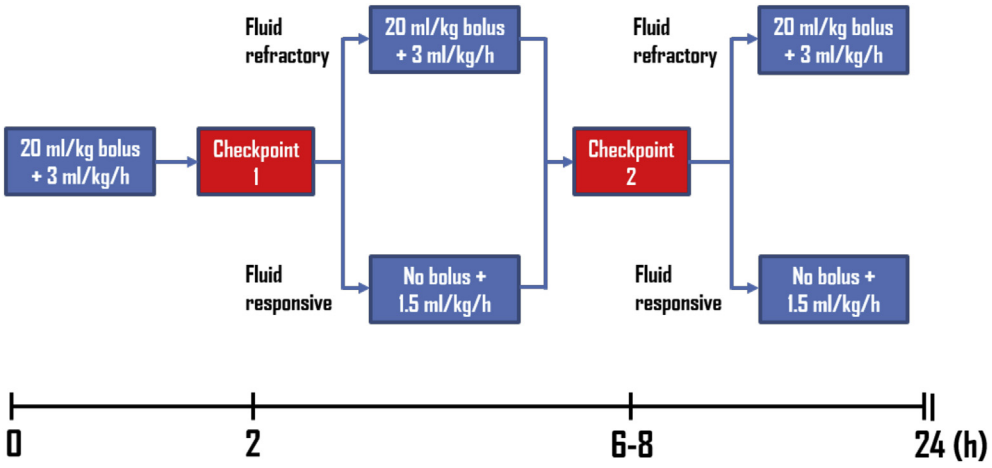

Figure 1 The fluid resuscitation protocol and time points for checking fluid responsiveness

resuscitation protocol is given in Supplementary Methods. Patients were divided into groups based on the clinical assessment of response to fluid resuscitation at the two checkpoints: Group 1 - fluid responsive at 2 h; Group 2 - fluid refractory at 2 h; Group 3 - fluid responsive at 6–8 h; and Group 4 - fluid refractory at 6–8 h.

Study variables

Clinical data were prospectively recorded and blood samples taken at recruitment, checkpoint 1, checkpoint 2 and 24 h after the start of the fluid resuscitation (Supplementary Methods). Demographics included age, gender, aetiology, body mass index and American Society of Anaesthesiologists (ASA) co-morbidity severity class. The routine clinical severity scores[22] SIRS, Bedside Index for Severity in Acute Pancreatitis (BISAP), Acute Physiology and Chronic Health Examination II (APACHE II) and Sequential Organ Failure Assessment (SOFA) were calculated from all data obtained in the first 24 h, to obtain values on admission and when most elevated.

Serum biomarkers

Five serum biomarkers were selected on the basis of potential to reflect an organ-specific response to fluid resuscitation and on the basis of the published literature (Supplementary Table 1). These were haematocrit, blood urea nitrogen (BUN), brain natriuretic peptide (BNP), neutrophil gelatinase-associated lipocalin (NGAL) and intestinal fatty acid-binding protein (I-FABP).

Outcome measures

Definitions of outcome measures are presented in Supplementary Methods. The primary endpoint was incidence of POF. Secondary outcomes included intensive care, pancreatic necrosis, necrosectomy, infections, mortality and length of hospital stay, with followed up for 3 months.

Statistical analysis

The study was designed to identify two subgroups of patients, those that were fluid responsive and those that were fluid refractory, based on MAP and UO. Fluid responsiveness as selected as the endpoint. The literature indicates that approximately 50% of acute critically ill patients can be expected to be fluid refractory.[16] If a candidate biomarker did not discriminate between the two patient groups in this pilot study, it would not have utility in tailoring fluid resuscitation to the individual patient. If a candidate biomarker did discriminate between the two patient groups in this pilot study there would need to be validation in a prospective randomised controlled trial.

Quantitative data with normal distribution are expressed as mean ± standard deviation (SD) otherwise as median and interquartile range (IQR) or range. Comparisons were only made between Groups 1 and 2 and between Groups 3 and 4, and not between the other groups. Comparative analysis for normally distributed data was by student *t*-test, otherwise the Mann–Whitney *U* test was used. Qualitative data were presented as number and percentage and compared between groups using Chi-square test or Fisher's test. The changes in concentration of serum biomarkers at different time points were expressed as absolute difference and percentage change. A $P < 0.050$ was considered statistically significant. Statistical analyses were performed using SPSS® 19.0 (IBM, Armonk, New York, USA).

Results

A total of 23 patients were recruited from 547 consecutive patients admitted with AP during the 5-month study period. The patient selection process and group assignment are shown in Fig. 2. Baseline characteristics of these patients are shown in Supplementary Table 2. The mean symptom duration prior to hospital admission was 25 (±8 SD) hours and the mean delay

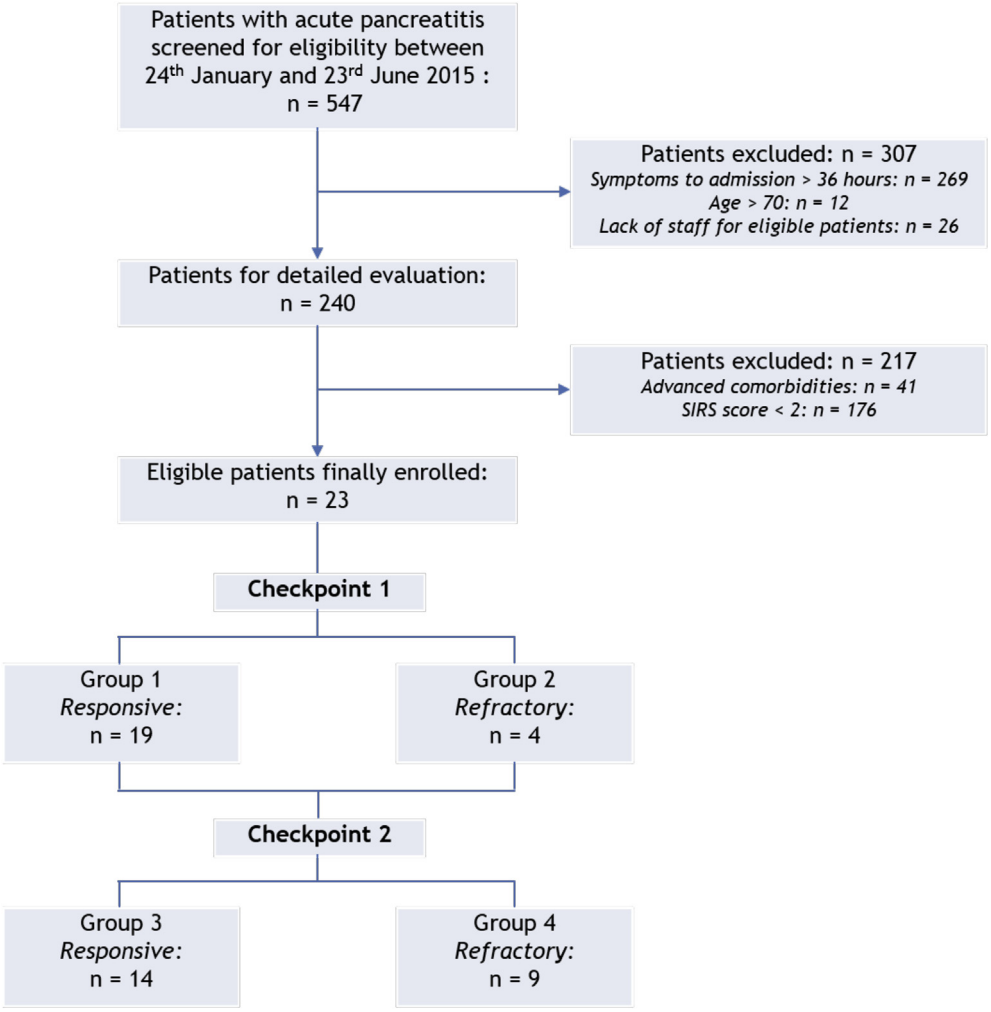

Figure 2 The patient selection process and group allocation for analysis

to the commencement of intravenous resuscitation from admission was 1.4 (±0.5 SD) hours. All the clinical severity scores and many of the laboratory parameters were deranged (Supplementary Table 2). The admission SIRS score was a median 3 (2–3 IQR) and three of the four SIRS criteria were present in all patients.

The fluid responsiveness of the patients and their clinical outcomes are shown in Supplementary Table 3. At the checkpoint 1 (2 h) the 23 patients were divided into 19 patients who were responsive (Group 1) and 4 patients who were refractory (Group 2). At the checkpoint 2 (6–8 h) the 23 patients were divided into 14 patients who were responsive (Groups 3) and 9 patients who were refractory (Group 4). Seven of the responsive patients (Group 1) became refractory (Group 4), and 2 of the refractory patients (Group 2) became responsive (Group 3). There were 12 patients who remained responsive between the two checkpoints, and 2 who remained refractory. Overall, POF occurred in 14/23 of the patients, and it was present on admission in 9/14 and at 3 days in 11/14. All 14 patients with POF had respiratory failure and 6 involved $\geq$2 organs. Four patients died and all were fluid refractory at checkpoint 2. All of these patients died of POF, with one also succumbed with uncontrolled abdominal bleeding after necrosectomy.

The patient characteristics (Table 1) were compared between the two patient groups at the two checkpoints (1 vs. 2 and 3 vs. 4).

A summary of the results for MAP and UO at different time points is shown in Supplementary Table 4. No significant differences were found between the groups for MAP at either time point. Of note, the clinical assessment of whether the patient was responsive or refractory was based on UO in 22 of 23 patients. As expected there was a significant difference for UO between Groups 1 and 2 at the checkpoint 1 ($P < 0.010$) and between Groups 3 and 4 at the checkpoint 2 ($P < 0.010$) and this difference persisted at 24 h ($P = 0.007$).

The prescribed and the actual amounts of fluid delivered are summarised in Table 2. Patients who were assessed as refractory

Table 1 Admission baseline characteristics of the four patient groups at two time points

Variables	Group 1	Group 2	Group 3	Group 4	1 vs. 2	3 vs. 4
	Responsive at 2 h (n = 19)	Refractory at 2 h (n = 4)	Responsive at 6–8 h (n = 14)	Refractory at 6–8 h (n = 9)	*P*	*P*
Age, years, mean ± SD	47 ± 13	50 ± 10	46 ± 12	50 ± 14	0.903	0.269
Gender, male	10	2	8	4	0.671	0.561
Body mass index, median (IQR)	27 (25–29)	25 (17–30)	26 (24–29)	28 (23–30)	0.465	0.705
ASA class score, median (IQR)	1 (1–2)	2 (1–2)	1 (1–2)	1 (1–1)	0.098	0.450
Time from symptom onset to admission, hours, mean ± SD	25 ± 9	24 ± 4	24 ± 10	27 ± 5	0.745	0.549
Time from admission to enrolment, hours, mean ± SD	1.4 ± 0.6	1.4 ± 0.4	1.3 ± 0.6	1.6 ± 0.5	0.776	0.284
Aetiology						
Biliary	10	1	5	6	0.149	0.344
Hyperlipidaemia	4	3	5	2		
Others	5	0	4	1		
Clinical severity scores, median (IQR)						
SIRS	3 (2–3)	2 (2–3)	3 (2–3)	3 (2–3)	0.073	0.748
BISAP	2 (1–3)	2 (1–4)	2 (1–2)	3 (2–3)	1.0	**0.02**
APACHE II	8 (5–12)	10 (7–19)	6 (4–9)	11 (10–15)	0.416	**0.018**
SOFA	3 (2–4)	3 (2–4)	2 (2–4)	3 (3–4)	0.933	0.09
Routine blood tests (normal ranges), median (IQR)						
pH	7.4 (7.3–7.4)	7.3 (7.2–7.4)	7.4 (7.3–7.4)	7.3 (7.2–7.3)	0.193	**0.009**
PaO_2/FiO_2 mmHg	268 (207–370)	307 (224–350)	319 (204–371)	236 (213–320)	0.935	0.413
Lactate, mmol/L	2.3 (1.4–4.5)	4.5 (2.1–4.9)	1.7 (1.3–4.5)	4.3 (2.3–4.7)	0.209	0.116
Adjusted Ca^{2+}, mmol/L	1.9 (1.7–2.2)	1.7 (1.5–1.9)	2.0 (1.6–2.2)	1.8 (1.7–2.0)	0.123	0.186
Glucose, mmol/L	11 (8–16)	18 (10–27)	11 (8–15)	16 (9–26)	0.292	0.147
Albumin, g/L	37 (33–42)	36 (33–40)	40 (36–43)	35 (32–38)	0.715	**0.035**
BUN, mmol/L	5.7 (4.2–9.8)	7.3 (4.7–10.0)	4.8 (3.5–5.7)	9.3 (7.3–10.1)	0.570	**0.005**
Creatinine, μmol/L	84 (69–105)	86 (56–148)	77 (63–109)	97 (75–114)	0.903	0.207
Haemoglobin, g/L	165 (26)	175 (22)	161 (26)	176 (23)	0.557	0.122
Haematocrit, 40–50%	49 (42–51)	52 (48–57)	47 (42–51)	51 (50–54)	0.095	**0.043**

SD, standard deviation; IQR, interquartile range; ASA, American Society of Anaesthesiologists; SIRS, systemic inflammatory response syndrome; WBC, white blood cell; BISAP, Bedside Index of Severity in Acute Pancreatitis; APACHE II, Acute Physiology and Chronic Health Examination II; SOFA, Sequential Organ Failure Assessment; PaO_2/FiO_2, arterial oxygen partial pressure to fractional inspired oxygen; BUN, blood urea nitrogen
P value in bold indicates that there was significant different at level of 0.05 between the designated two groups.

at checkpoints 1 and 2 (Groups 2 and 4) received significantly more fluid than those who were responsive (Groups 1 and 3), as per protocol.

The absolute values for potential serum biomarkers of fluid responsiveness are shown in Table 3. The only significant differences in the absolute levels of biomarkers, were an elevation of BUN and haematocrit in Group 4 compared with Group 3.

The relative differences and percentage changes of the potential biomarkers are shown in Supplementary Table 5. The response in BUN and haematocrit reflected the increased fluid volumes received by Group 4.

The serum biomarkers were also compared for relative and percentage differences at the two time points in patients that survived and those that died (Supplementary Table 6). The only significant differences in the absolute levels of biomarkers, were an elevation of BUN and haematocrit in Group 4 compared with Group 3.

The clinical outcomes (Table 4) were compared between the two patient groups at the two checkpoints (1 vs. 2 and 3 vs. 4). Patients in Group 4 had a higher incidence of POF (8/9 vs. 6/14), rate of admission to ICU (8/9 vs. 5/14), incidence of infected pancreatic necrosis (7/9 vs. 4/14), higher mortality (4/9 vs. 0/14) and longer hospital stay (56 vs. 18 days) compared with Group 3 (all $P < 0.050$). The necrosectomy and mortality rates were unchanged at 3 months of follow up and there was no documented recurrence of AP.

Table 2 Volume of fluids administered to four patient groups between time intervals

Fluid administered[a]	Group 1	Group 2	Group 3	Group 4	1 vs. 2	3 vs. 4
	Responsive at 2 h (n = 19)	Refractory at 2 h (n = 4)	Responsive at 6–8 h (n = 14)	Refractory at 6–8 h (n = 9)	*P*	*P*
Prior to enrollment	376 ± 138	400 ± 122	353 ± 144	422 ± 109	0.128	0.291
During 0 to 2 h						
Prescribed	1807 ± 364	1556 ± 485	1775 ± 406	1745 ± 378	0.248	0.864
Actual	1856 ± 386	1560 ± 487	1779 ± 413	1844 ± 427	0.194	0.721
During 2 to 8 h						
Prescribed	659 ± 198	2745 ± 1451	1040 ± 1110	993 ± 819	**0.002**	0.915
Actual	708 ± 226	2600 ± 1428	1067 ± 1094	989 ± 639	**0.002**	0.847
During 8 to 24 h						
Prescribed	2939 ± 1729	3149 ± 1972	1716 ± 357	4934 ± 947	0.830	<**0.001**
Actual	3315 ± 1668	3046 ± 1557	2174 ± 686	4969 ± 1041	0.771	<**0.001**
During 0 to 24 h						
Prescribed	5404 ± 1915	7450 ± 2776	4530 ± 1483	7673 ± 1593	0.085	<**0.001**
Actual	5879 ± 1927	7205 ± 2208	5022 ± 1483	7802 ± 1427	0.234	<**0.001**

P value in bold indicates that there was significant different at level of 0.05 between the designated two groups.
[a] Values are reported as means ± standard deviation in mL

Table 3 Candidate serum biomarkers of fluid responsiveness for 4 patient groups at 0, 6–8 and 24 h

Time between checkpoints (hours)	Group 1	Group 2	Group 3	Group 4	1 vs. 2	3 vs. 4
	Responsive at 2 h (n = 19)	Refractory at 2 h (n = 4)	Responsive at 6–8 h (n = 14)	Refractory At 6–8 h (n = 9)	*P*	*P*
Haematocrit, %						
0	49 (42–51)	52 (48–57)	47 (42–51)	51 (50–54)	0.095	**0.043**
6-8	46 (42–47)	47 (45–53)	45 (40–47)	47 (46–50)	0.243	**0.030**
24	40 (38–44)	38 (32–44)	41 (39–45)	39 (35–42)	0.371	0.185
BUN, mmol/L						
0	5.6 (4.2–9.8)	7.3 (4.6–9.9)	4.6 (3.5–5.7)	9.3 (7.3–10.1)	0.570	**0.005**
6-8	5.3 (3.5–10.0)	10.4 (5.5–13.8)	4.6 (3.4–6.3)	10.0 (9.4–12.7)	0.156	**0.008**
24	5.1 (3.2–9.3)	10.2 (7.0–13.1)	4.3 (2.8–6.5)	10.0 (8.3–11.9)	0.074	**0.001**
NGAL, ng/mL						
0	397 (323–635)	745 (479–930)	482 (348–649)	367 (304–956)	0.089	0.881
6-8	481 (306–857)	767 (337–1372)	479 (285–732)	713 (311–1533)	0.420	0.233
24	164 (148–777)	441 (143–684)	159 (121–536)	618 (164–789)	0.929	0.062
BNP, pg/mL						
0	83 (60–120)	61 (58–583)	83 (62–139)	67 (57–114)	0.670	0.473
6-8	79 (73–157)	72 (65–374)	111 (76–297)	71 (67–85)	0.477	0.058
24	118 (74–199)	71 (69–628)	175 (69–252)	80 (72–131)	0.449	0.262
I-FABP, ng/mL						
0	3.2 (1.6–6.3)	2.5 (1.2–3.9)	2.1 (1.3–8.0)	3.5 (2.7–4.3)	0.571	0.362
6-8	2.2 (1.8–3.1)	3.0 (2.5–4.5)	2.4 (2.0–3.1)	2.8 (1.8–4.9)	0.156	0.905
24	1.0 (0.7–2.3)	1.0 (0.1–13.6)	1.0 (0.7–1.4)	0.9 (0.1–17.6)	0.777	0.968

BUN, blood urea nitrogen; NGAL, neutrophil gelatinase-associated lipocalin; BNP, brain natriuretic peptide; I-FABP, intestinal fatty acid-binding protein
P value in bold indicates that there was significant different at level of 0.05 between the designated two groups.

Table 4 Clinical outcomes of four patient groups during index hospitalisation

Clinical outcomes	Group 1	Group 2	Group 3	Group 4	1 vs. 2	3 vs. 4
	Responsive at 2 h (n = 19)	Refractory at 2 h (n = 4)	Responsive at 6–8 h (n = 14)	Refractory at 6–8 h (n = 9)	*P*	*P*
Persistent organ failure	10	4	6	8	0.127	**0.04**
Pancreatic necrosis	7	4	4	7	0.072	**0.005**
Necrosectomy	6	0	1	5	0.539	**0.018**
Infected pancreatic necrosis	6	0	1	5	0.539	**0.018**
Extrapancreatic infections	4	0	1	7	1	**0.005**
Need intensive care	10	3	5	8	0.412	**0.012**
Length of hospital stay, days, median (IQR)[a]	20 (14–66)	20 (13–24)	18 (11–21)	56 (24–77)	0.654	**0.019**
Mortality	4	0	0	4	1	**0.014**

IQR, interquartile range
P value in bold indicates that there was significant different at level of 0.05 between the designated two groups.
[a] Patients died during the first two weeks of admission were excluded from the analysis

Discussion

This prospective cohort study found that the candidate serum biomarkers did not discriminate between the patient groups that were fluid responsive and fluid refractory as determined by the clinical assessment of UO and MAP at two time points during the first 24 h. This study suggests that this type of clinical assessment, though widely used, is not an acceptable or safe way to determine whether a patient will benefit from additional fluid or not. The standardised protocol for fluid resuscitation used in this study, based on common practice and the IAP/APA guidelines,[4] produced distinct groups of patients in regards to fluid responsiveness and clinical outcome. An important finding from this study is that patients assessed to be refractory at 2 h (checkpoint 1) were able to benefit from additional fluids, but not those assessed to be refractory at 6–8 h (checkpoint 2). This did not reverse with additional fluids and these patients had a worse clinical outcome: increased incidence of systemic and local complications, interventions, mortality and prolonged hospital stay. This worse outcome in these refractory patients is most likely due to more severe disease. While the additional fluid might have had a detrimental effect on outcomes, the size of this effect will only be defined by future randomised controlled trials.

There were 7 patients responsive to fluid at 2 h who subsequently became refractory and 4 of these patients died. It is possible that this was in part because they only received maintenance fluids between the two time points and did not get sufficient fluids. The timing of the checkpoints were arbitrarily determined and it could be argued that 2 h is too soon to make an accurate assessment of whether additional fluid was required. The KDIGO guidelines[23] recommends determining fluid responsiveness, based on UO, over 6 h. The findings of this study appear to support this as the assessment of fluid responsiveness at the second checkpoint (6–8 h) distinguished groups with different clinical outcomes.

As per protocol the volume and rate of fluid resuscitation were higher in the fluid refractory groups. Previous prospective studies have shown that larger volume loads[20] or more rapid haemodilution[24,25] were associated with worse outcomes in predicted moderate to severe AP patients. Other studies with predominantly mild cases of AP have suggested that a more aggressive resuscitation protocol resulted in better clinical outcomes.[6,26–28] Our data show that 7/9 patients with early POF were fluid refractory at either time point, and that additional fluids did not appear to improve outcome.

It is known that giving additional fluid (increasing preload) will not improve stroke volume and cardiac output if the Frank-Starling curve has reached the flat portion or plateau.[16] Other factors that may be responsible for the lack of response to fluid resuscitation and the adverse effect of additional fluids. One of these factors is likely to be tissue oedema secondary to the capillary leak syndrome that characterises acute inflammatory diseases and can impact organ function.[28] It is also known that cytokines[29] and damage-associated molecular pattern molecules (i.e. extracellular histones) can directly injure cardiomyocytes.[30] These cardiac depressant factors could also explain a suboptimal response to increasing preload with additional fluids. This study highlights the importance of identifying patients who are fluid refractory after 6–8 h to institute alternative treatment strategies (e.g. vasopressors) to avoid harmful additional fluids. This study also highlights that UO alone is not a satisfactory guide or goal for fluid resuscitation in these patients. In this study MAP did not prove to be useful because only 1/23 patients were hypotensive (MAP <65 mmHg). This is in contrast with septic shock patients where MAP[31] serves as a key indicator for fluid responsiveness. It is recognised that MAP does not reflect the early and important cardiovascular response to hypotension, where peripheral and splanchnic vasoconstriction increases diastolic pressure, narrowing the pulse pressure (the difference between systolic and diastolic pressures). This means that MAP can

remain unchanged even when there is a reduction in systolic pressure (reflecting a decrease in stroke volume) because of the commensurate increase in diastolic pressure (reflecting an increase in peripheral resistance). These findings underscore the need for relevant and sensitive biomarkers of fluid responsiveness.

The candidate serum biomarkers were selected because they were considered likely to discriminate between responsive and refractory patients. Surprisingly none of the biomarkers (cardiac, renal or intestinal) were significantly different between the patient groups at any of the time points, except for BUN.

Cardiac dysfunction is common phenomena in patients with AP.[32] BNP is a hormone produced by the heart and released in response to changes in pressure inside the heart, as in fluid overload.[33] In this study, there were no significant changes in BNP between patient groups, and it was not elevated in the refractory groups that received more fluid. This is consistent with only one patient developing hypotension. It cannot be discounted that BNP may become elevated in patients with more severe AP and in those with limited cardiac reserve, and may prove to be more helpful in these contexts.

The kidney is particularly vulnerable in hypovolemia and the results for BUN are consistent with the published literature, supporting its role as a prognostic marker in AP.[34] In this study BUN discriminated between groups 3 and 4 even before the 2 h checkpoint, and was the most responsive biomarker to fluid resuscitation. Given that the clinical assessment of fluid responsiveness was based almost entirely on UO, it is not surprising that the BUN results were markedly different between the fluid responsive and refractory groups. These findings are in accordance with study by Wu *et al.*[21] in which BUN has been shown to be have value as a potential guide to fluid therapy. It was on this basis that BUN was recommended in the current guidelines[4] and a recent study has shown that a rise in BUN outperforms all other laboratory markers in predicting POF.[35] NGAL, which is expressed by neutrophils and proximal tubular cells of the kidney, is emerging as a biomarker for early prediction of acute kidney injury in different clinical settings, including severe AP and in this setting the prediction of multiple organ dysfunction syndrome and death.[36] NGAL is sensitive marker, being raised within 2 h of renal hypoperfusion and 2 days ahead of any rise in the serum creatinine.[37] That NGAL proved inferior to BUN as a marker of the response to fluid resuscitation was surprising, and warrants further investigation.

The intestine is also vulnerable to hypovolemia, and compensatory splanchnic vasoconstriction causes mucosal ischemia. I-FABP is a sensitive marker of acute intestinal ischaemia and gut barrier dysfunction in AP,[38] but it has not been studied as a marker of the response to fluid resuscitation. This study revealed very marked changes in serum I-FABP, but the variability was so great that the mean changes rarely reached significance, probably reflecting the over-sensitivity of this measure. It nevertheless warrants further investigation.

The search for biomarkers that reflect the adequacy of tissue perfusion and fluid resuscitation should continue, but is hampered by the absence of any gold standard against which to evaluate them. Recently, an elegant study has shown that passive leg raising test has pooled sensitivity and specificity of 88% and 92%, respectively, in predicting fluid responsiveness[16] Future larger studies need to consider using the response to passive leg raising as a means of evaluating potential biomarkers for fluid responsiveness. New serum biomarkers should reflect critical pathophysiology in AP. An example could be markers of oxidative stress secondary to impaired organ perfusion, as it is known that suboptimal oxygen and glucose supply causes mitochondrial dysfunction, increased oxygen free radicals, reduced ATP production and failed cellular bioenergetics.[39]

There are a number of limitations to this study. The study sample was small because of the narrow inclusion criteria. This was in order avoid recruiting a majority of patients with mild AP and because it was important that recruited patients could improve or deteriorate in response to fluid resuscitation. The rate of intravenous fluid resuscitation, both bolus and maintenance, used in this study were based on current guidelines.[4,5] The study design produced sufficiently distinct patients groups (responsive and refractory) for discrimination. The highly select subgroup limits the generalisability of the results, and this study suggests that it might be preferable to use predicted severity rather than UO to guide fluid resuscitation and determine whether additional fluids are indicated. This is because refractory patients at checkpoint 2 had additional fluids, a worse outcome and more severe disease on admission.

In conclusion, this study highlights the need for better methods to determine whether a patient with AP will benefit from additional resuscitation fluids or not. Giving more fluid to a patient that is fluid refractory resulted in a worse clinical outcome. And while fluid resuscitation remains the cornerstone of the early management of AP[6,21] there is an urgent need to find a better way to guide it.

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Specific author contributions

T.J. and K.J. contributed equally to this work as co-first authors. Concept and design: J.A.W., A.M., V.A., P.J. and adapted by Q.X., W.H., T.J., and X.Y. to be conducted in the West China Hospital under the supervision of Q.X., X.Y. and W.H., who also obtained research funding; acquisition of data: T.J., K.J., L.D., J.G., Y.W., Z.W. N.S. X.Z. and Z.L.; statistical analysis and interpretation of data: T.J., K.J., W.H., X.Y., Q.X. and J.A.W.; drafting and revision of manuscript: J.T., K.J., R.S., W.H., X.Y., Q.X. and J.A.W.

Conflict of interests

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.05.018.