Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Appendix

Study collaborators

This study was performed by the ERICA (int**ER**national league aga**I**nst biliary-pancreati**C** dise**A**ses) consortium. The following members of ERICA were study collaborators:

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Inclusion criteria

A. Patients 18 years or older

B. Diagnosis of acute pancreatitis according to the revised Atlanta classification [1], which requires two of the following three criteria: (A) typical abdominal pain, (B) increase in serum amylase or lipase levels higher than three times the upper limit of normality, and (C) signs of acute pancreatitis in imaging

Exclusion criteria

A. Uncontrolled arterial hypertension (systolic blood pressure >180 and/or diastolic blood pressure >100 mmHg)

B. New York Heart Association class II heart failure (slight limitation of physical activity; fatigue, palpitations, or dyspnea with ordinal physical activity) or worse, or ejection fraction <50% in the last echocardiography

C. Decompensated cirrhosis (Child's class B or C)

D. Hyper or hyponatremia (<135 or >145 mEq/L)

E. Hyperkalemia (>5 mEq/L)

F. Hypercalcemia (albumin or protein-corrected calcium >10.5 mg/dL)

G. Baseline kidney failure (basal glomerular filtration rate <60 mL/min per 1.73 m^2)

H. Clinical signs or symptoms of volume overload or heart failure at recruitment (dyspnea, peripheral edema, pulmonary rales, or evidently increased jugular ingurgitation at 45º)

I. Shock or respiratory failure according to the revised Atlanta classification at recruitment (non-fluid-responding systolic blood pressure <90 mmHg, PaO_2/FIO_2 ≤300)

J. Time from pain onset to arrival to emergency room >24 h

K. Time from confirmation of pancreatitis to randomization >8 h

L. Severe comorbidity associated with an estimated life expectancy <1 year

M. Confirmed chronic pancreatitis [in case of recurrent alcoholic pancreatitis a recent (<6 months) computed tomography (CT) scan/magnetic resonance imaging (MRI) or endoscopic ultrasound is needed to rule out chronic pancreatitis]

Main outcome (includes the definition of severity, local complications, exacerbation of comorbidity, and organ failure)

The main outcome was defined as meeting after recruitment and during hospitalization any of the revised Atlanta classification criteria [1] for moderately severe or severe acute pancreatitis.

Severity

Mild: no local or systemic complications, no organ failure

Moderately severe: presence or local and/or systemic complications and/or transient organ failure

Severe: presence of persistent organ failure

Definitions used to determine severity [1]

Local complications, any of the following: acute peripancreatic fluid collections, pancreatic necrosis, peripancreatic fat necrosis. Necrotizing pancreatitis was defined by the presence of pancreatic and/or peripancreatic fat necrosis

Systemic complications: exacerbation of a preexisting coexisting condition, such as coronary artery disease or chronic lung disease, precipitated by acute pancreatitis *

Organ failure, any of the following: kidney failure (creatinine ≥1.9 mg/dL), cardiovascular failure (systolic blood pressure <90 mmHg despite fluid resuscitation), respiratory failure ($PaO_2/FIO_2 \leq 300$)

Transient organ failure: organ failure lasting ≤48 hours

Persistent organ failure: organ failure lasting >48 hours

* Only 1 patient in the aggressive arm of treatment was classified as having moderately severe or severe pancreatitis based solely on the presence of systemic complications.

Definition of invasive treatment

Any of the following: thoracocentesis due to pancreatitis-induced pleural effusion, percutaneous and/or endoscopic drainage of pancreatic or peripancreatic fluid collections or necrosis, endoscopic or surgical necrosectomy, endoscopic retrograde cholangiopancreatography due to A) ruptured common bile duct, B) jaundice caused by compression of the common bile duct, or C) main pancreatic duct leakage.

Definition of hypovolemia

Hypovolemia was defined by the presence of one criterion or more:

A. Baseline creatinine >1.1 mg/dL or blood urea nitrogen (BUN) >20 mg/dL, equivalent to urea >43 mg/dL
B. Hematocrit >44%
C. Increase in creatinine and/or BUN and/or urea from the previous value
D. Urine output <0.75 mL/kg/h
E. Systolic blood pressure <90 mmHg without other explanation than hypovolemia
F. Signs and/or symptoms of dehydration (intense thirst, dehydrated oral mucosa, decreased skin turgor–skin pinch)

Definition of fluid overload

Fluid overload was defined by the presence of at least two of the following three criteria (adapted from Sharma et al. [2]):

Criterion 1. Hemodynamic or imaging evidence (at least one):

A. Non-invasive diagnostic evidence of heart failure (i.e., echocardiographic)
B. Radiographic evidence of pulmonary congestion
C. Invasive cardiac catheterization suggesting evidence of heart failure [i.e., pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) >18 mmHg, right arterial pressure (or central venous pressure) >12 mmHg, or cardiac index <2.2 L/min per m2]

Criterion 2. Heart failure symptoms:

A. Dyspnea

Criterion 3. Heart failure signs (at least one):

A. Peripheral edema
B. Pulmonary rales
C. Increased jugular venous pressure, hepatojugular reflux, or both

The presence of only one criterion was called "suspicion of fluid overload", for example the presence of dyspnea or pulmonary rales.

Additionally, in those patients with fluid overload, acute respiratory distress syndrome (ARDS) had to be ruled out. The exclusion of ARDS was defined by at least one of two criteria:

A. Prompt response to diuretics and/or decrease in fluid resuscitation volume rate and/or hemodialysis/ hemofiltration
B. Absence of ARDS criteria

Definition of acute respiratory distress syndrome

The patient had to meet all the following four criteria (based on the modified Berlin definition [3])

A. Onset within 1 week of the pancreatitis onset
B. Bilateral opacities not fully explained by effusions, lobar collapse, or nodules
C. Respiratory failure not fully explained by cardiac failure or fluid overload needs objective assessment (i.e., echocardiography) to exclude hydrostatic edema if no risk factor is present
D. $PaO_2/FIO_2 \leq 300$

Definition of systemic inflammatory response syndrome

Systemic inflammatory response syndrome was defined by 2 or more of the following criteria:

A. Leukocyte count <4.000 or >12.000/mm^3
B. Heart rate>90/min
C. Respiratory rate>20/min or pCO_2<32 mmHg
D. Temperature (Celsius) <36ºC or >38º

Severity of fluid overload

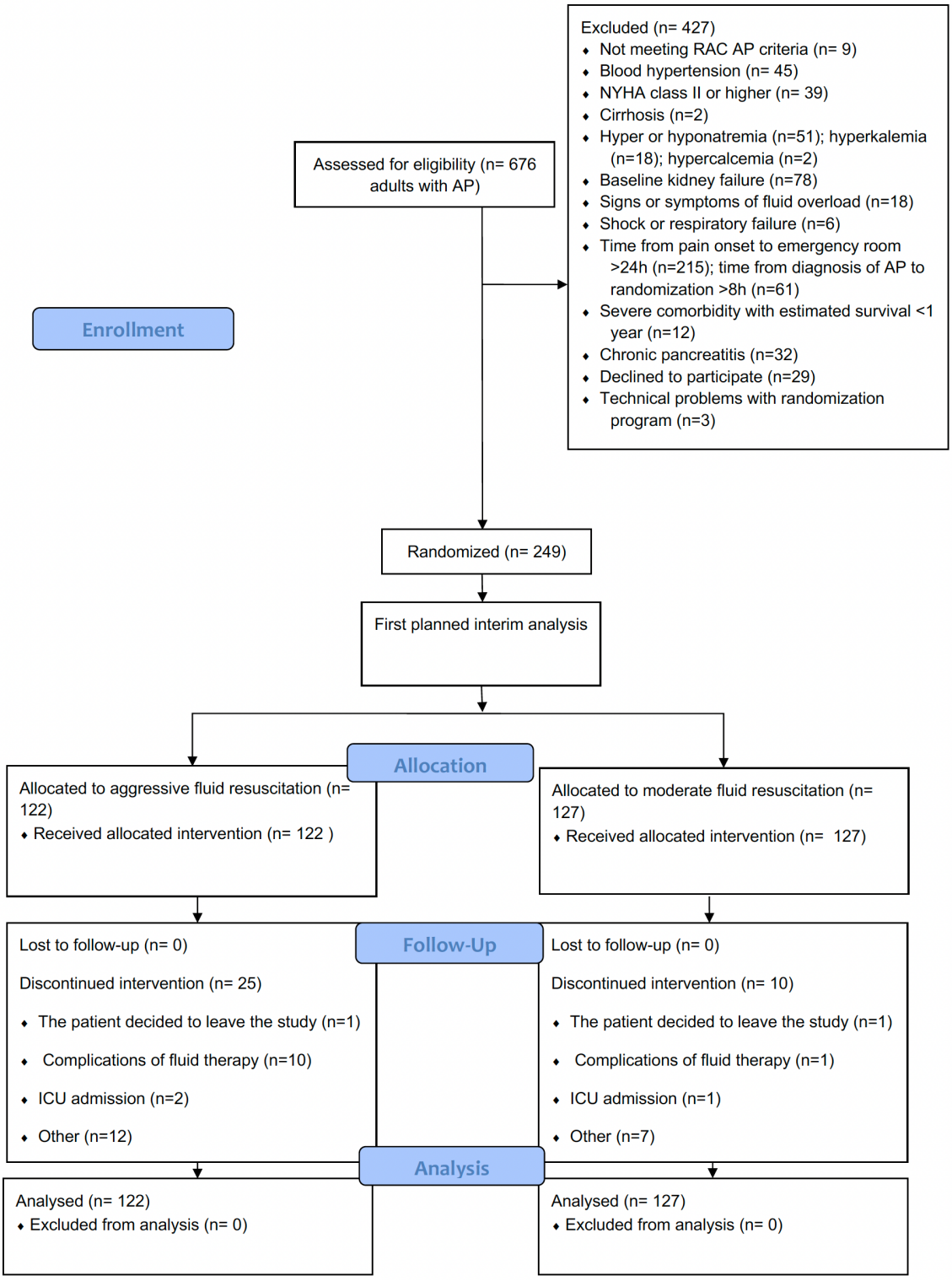
A. Mild: patients respond to medical treatment or decrease in volume infusion rate, and the PaO_2/FIO_2 never decreases <300
B. Moderate: patients respond to medical treatment or decrease in volume infusion rate and have at least one measurement with PaO_2/FIO_2 <300
C. Severe: patients require invasive or non-invasive mechanical ventilation, and/or hemofiltration, or expire due to overload

Multiple imputation

There were no missing data for baseline characteristics except for 1 patient without a baseline PAN-PROMISE score. There were no missing data for the main outcome and most of the secondary outcomes (Table 2). There were missing data in the secondary outcomes PAN-PROMISE scale at 12, 24, 48 and 72h, c-reactive protein at 48 and 72h and presence of systemic inflammatory response syndrome (SIRS) at 12, 24, 48 and 72h, see details in table 2 of the main manuscript. The presence of missing data was unrelated to the arm of treatment (homogeneous distribution in aggressive/moderate fluid resuscitation). Those variables with missing data were first analyzed as complete cases (see Table 2, main manuscript) and then after multiple imputation for missing data (see supplementary appendix Table S2). We used R version 4.1.2 (see Table S2 for more details) to calculate 5 imputations of missing data to those variables, based on a model containing the following variables: center of origin, age, gender, body mass index, presence of baseline hypovolemia, presence of baseline SIRS, BISAP score at recruitment, Charlson comorbidity score, PAN-PROMISE score at recruitment, baseline urea, baseline hematocrit, baseline creatinine, etiology of pancreatitis, arm of

treatment, development of fluid overload criteria, development of collections, development of necrotizing pancreatitis, infection of necrotizing pancreatitis, presence and type of organ failure, need for intensive care unit admission, hospital stay, mortality and the variables with missing data. Pooled adjusted (center, presence or absence of baseline SIRS and presence or absence of baseline hypovolemia) relative risk was calculated (see Table S2 for more details). For quantitative variables median, interquartile range and standard error of pooled imputed datasets were calculated fitting a quantile regression model with the dependent variable and no covariates, which allowed us to obtain complete data variance estimates to apply Rubin's rules [4] and calculate standard error. Quantile regression models were build using the library Quantreg (Roger Koenker, 2021). Quantreg: Quantile Regression Package version 5.86. R version 4.1.2.

Figure S1. Study flow chart



AP: Acute Pancreatitis. ICU: Intensive Care Unit. NYHA: New York Heart Association. RAC: Revised Atlanta Classification.

Table S1. Representativeness of Study Participants

Disease under investigation	Acute pancreatitis
Special considerations related to	
Sex and gender	Acute pancreatitis incidence is similar in males and females (ratio 1:1). Biliary acute pancreatitis is the most frequent etiology in male and female patients in most countries, but males have increased frequency of alcoholic etiology and according to some studies, slightly worse prognosis
Age	The incidence of acute pancreatitis increases with age
Race or ethnic group	Associations between race or ethnic group have been described with specific etiologies; native Americans have increased risk of gallstones. Currently, there is no robust association between race or ethnic group and prognosis
Geography	Northern countries have increased proportion of alcoholic etiology (USA, northern European countries). Southern countries have increased proportion of biliary etiology
Overall representativeness of this trial	85.5% patients were from Spain, 8.8% from Mexico, 4.8% from India and 0.8% from Italy. Mean age was 57, which is younger than described in the Spanish population (mean age 64 to 66), which is presumably due to the exclusion of patients with certain comorbidities associated with age (heart failure, kidney failure...) 55.7% of patients were female, close to the 1:1 ratio described in the general population of patients. Biologic sex was reported by the participants or close relatives; on the intake survey they were asked about their sex assigned at birth, options were female or male. Race was not recorded. The frequency of biliary etiology was 60.6% and alcohol 12.4%, which is representative of the population of patients with acute pancreatitis in most countries

Table S2. Systemic inflammatory response syndrome, PAN-PROMISE scale and serum c-reactive protein according to arm of treatment, multiple imputation method

Endpoint	Pooled adjusted relative risk (95% CI)
Systemic inflammatory response syndrome	
12h	1.04 (0.67 to 1.60)
24h	1.35 (0.78 to 2.35)
48h	1.10 (0.60 to 2.00)
72h	0.70 (0.31 to 1.64)
Persistent	1.62 (0.68 to 3.89)

	Aggressive fluid resuscitation (N=122)			**Moderate fluid resuscitation (N=127)**			
	Median	**IQR**	**SE**	**Median**	**IQR**	**SE**	**Pooled adjusted relative risk (95% CI)†**
PAN-PROMISE score*							
12h	22.0	12.0-34.8	2.0	18.0	9.6-30.5	1.7	1.28 (0.90 to 1.84)
24h	16.5	4.0-26.8	1.9	12.0	5.9-23.0	1.5	1.23 (0.94 to 1.60)
48h	10.0	2.3-23.0	1.6	7.0	1.0-17.0	1.3	1.25 (0.95 to 1.64)
72h	5.0	1.0-16.8	1.3	5.0	0.8-11.8	0.8	1.17 (0.88 to 1.55)
C-Reactive Protein — mg/dL							
48h	8.9	1.6-19.8	1.7	7.3	2.5-17.5	1.3	1.06 (0.73 to 1.53)
72h	5.6	1.6-18.3	1.9	8.2	2.5-18.9	1.6	0.97 (0.65 to 1.44)

Pooled (5 imputation models) adjusted relative risks were calculated using a binomial (link=log) regression model including center, baseline presence of systemic inflammatory response syndrome and baseline

presence of hypovolemia. CI: confidence interval. Persistent: persistent systemic inflammatory response syndrome, lasting more than 48 hours during the first 72h after admission.

PAN-PROMISE score and C-reactive protein: median, interquartile range (IQR) and standard error (SE) of pooled imputed datasets (5 imputation models) were calculated fitting a quantile regression model with the dependent variable and no covariates, which allowed us to obtain complete data variance estimates to apply Rubin's rules [4] and calculate SE. Quantile regression models were build using the library Quantreg (Roger Koenker, 2021). Quantreg: Quantile Regression Package version 5.86. R version 4.1.2.

* PAN-PROMISE score [5] ranges from 0 to 70, with higher scores indicating more severe symptoms; the baseline score was missing for 1 patient in the aggressive fluid resuscitation group.

† Quantitative variables: adjusted relative risk for high (above median) versus low (below median).

Table S3. Volume administration of lactated Ringer's solution according to arm of treatment at different checkpoints

Checkpoint	**Aggressive fluid resuscitation (N=122)**	**Moderate fluid resuscitation (N=127)**
0 to 12 hours	3.4 (2.7-4.5)	1.5 (1.2-2.1)
12 to 24 hours	1.8 (1.3-3.0)	1.5 (1.3-2.1)
24 to 48 hours	2.5 (1.9-3.0)	2.1 (0.4-3.0)
48 to 72 hours	0.0 (0.0-1.7)	0.8 (0.0-1.5)
Cumulative	**Aggressive fluid resuscitation (N=122)**	**Moderate fluid resuscitation (N=127)**
12 hours	3.4 (2.7-4.5)	1.5 (1.2-2.1)
24 hours	5.4 (4.5-6.6)	3.3 (2.6-4.0)
48 hours	7.8 (6.5-9.8)	5.5 (4.0-6.8)
72 hours	8.3 (7.1-10.8)	6.6 (4.1-8.0)

Median volume (interquartile range) — L

Table S4. Efficacy outcomes, subgroup analysis: patients with baseline systemic inflammatory response syndrome

Endpoint	Aggressive fluid resuscitation (N=35)		Moderate fluid resuscitation (N=29)		Relative risk (95% CI)	Adjusted relative risk (95% CI)¶	Missing data**
	no.	%	no.	%			
Moderately Severe or Severe Pancreatitis*	10	28.6%	9	31.0%	0.92 (0.43 to 1.96)	0.72 (0.31 to 1.66)	0
Severe Pancreatitis	6	17.1%	2	6.9%	2.49 (0.54 to 11.40)	1.71 (0.32 to 9.20)	0
Local complications							
Any	10	28.6%	8	27.6%	1.04 (0.47 to 2.28)	0.85 (0.34 to 2.14)	0
Necrosis†	7	20.0%	5	17.2%	1.16 (0.41 to 3.27)	0.97 (0.33 to 2.86)	0
INP	4	11.4%	2	6.9%	1.66 (0.33 to 8.41)	1.60 (0.36 to 7.10)	0
Systemic Inflammatory Response Syndrome‡							
12h	14	40.0%	13	44.8%	0.89 (0.50 to 1.58)	0.78 (0.45 to 1.36)	0
24h	11	33.3%	6	20.7%	1.61 (0.68 to 3.81)	1.18 (0.48 to 2.88)	2
48h	7	21.9%	7	25.0%	0.88 (0.35 to 2.19)	0.69 (0.25 to 1.89)	4
72h	3	9.7%	4	16.7%	0.58 (0.14 to 2.35)	0.74 (0.17 to 3.20)	9
Persistent‡	5	17.2%	5	20.8%	0.83 (0.27 to 2.53)	0.52 (0.14 to 1.87)	11
Other outcomes							
Incidence of invasive treatment‡	8	22.9%	2	6.9%	3.31 (0.76 to 14.40)	2.44 (0.58 to 10.16)	0
Need for nutritional support§	5	14.3%	4	13.8%	1.04 (0.31 to 3.51)	0.93 (0.31 to 2.84)	0
Admitted to ICU	6	17.1%	2	6.9%	2.49 (0.54 to 11.40)	1.64 (0.33 to 8.04)	0
Any organ failure‡	6	17.1%	5	17.2%	0.99 (0.34 to 2.93)	0.63 (0.21 to 1.95)	0
POF‡	6	17.1%	2	6.9%	2.49 (0.54 to 11.40)	1.71 (0.32 to 9.20)	0
Shock‡	4	11.4%	1	3.4%	3.31 (0.39 to 28.04)	2.67 (0.33 to 21.63)	0
Respiratory failure‡	6	17.1%	3	10.3%	1.66 (0.45 to 6.05)	1.12 (0.27 to 4.74)	0
Kidney failure‡	2	5.7%	3	10.3%	0.55 (0.10 to 3.09)	0.59 (0.11 to 3.21)	0
Death	2	5.7%	1	3.4%	1.66 (0.16 to 17.37)	1.00 (0.06 to 15.99)	0
Death, POF or INP	7	20.0%	3	10.3%	1.93 (0.55 to 6.81)	1.41 (0.38 to 5.24)	0
	Median	**IQR**	**Median**	**IQR**			
Length of hospital stay‖	6	4-12	6	4-9	1.22 (0.79 to 1.88)	1.16 (0.75 to 1.78)	0
Days on ICU	0	0-0	0	0-0	Not applicable	Not applicable	0
PAN-PROMISE score‖							
12h	25	18-36	18	12-33	1.51 (0.95 to 2.41)	1.33 (0.79 to 2.25)	1
24h	17	9-27	14	8-27	1.35 (0.83 to 2.20)	1.30 (0.79 to 2.12)	2
48h	10	6-20	8	3-18	1.54 (0.85 to 2.77)	1.33 (0.75 to 2.36)	5
72h	5	2-17	7	2-21	0.86 (0.51 to 1.46)	0.68 (0.38 to 1.22)	10
C-Reactive Protein — mg/dl‖							
48h	13.6	2.0-28.3	27.0	14.8-38.8	0.81 (0.54 to 1.21)	0.76 (0.48 to 1.20)	16
72h	10.0	2.1-18.4	27.8	13.2-39.0	0.69 (0.47 to 1.02)	0.74 (0.49 to 1.12)	20

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; ICU: Intensive Care Unit; INP: infected necrotizing pancreatitis; IQR: interquartile range; POF: persistent organ failure (lasting >48h).

* P-value=0.49 in in binary logistic regression analysis, see below (¶); severity of acute pancreatitis, mild: absence of complications; moderately severe: transient organ failure, local or systemic complications without persistent organ failure; severe: persistent organ failure, see supplementary appendix for more detailed definitions.

† necrotizing pancreatitis defined as pancreatic and/or peripancreatic necrosis.

‡ see definitions in supplementary appendix.
§ need for enteral and/or parenteral nutrition.
‖ Quantitative variables: relative risk and adjusted relative risk for high (above median) versus low (below median).
¶ Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of hypovolemia.
** Complete case analysis in variables with missing data; multiple imputation models were congruent with complete case analysis (data not shown) .

Table S5. Safety outcomes, subgroup analysis: patients with baseline systemic inflammatory response syndrome

Endpoint	Aggressive fluid resuscitation (N=35)		Moderate fluid resuscitation (N=29)		Relative risk (95% CI)	Adjusted relative risk (95% CI) †	P-value†
	no.	%	no.	%			
Fluid overload*	11	31.4%	3	10.3%	3.04 (0.94 to 9.87)	2.93 (1.00 to 8.62)	0.0498
Symptoms of FO	10	28.6%	5	17.2%	1.66 (0.64 to 4.30)	1.34 (0.59 to 3.05)	0.537
Signs of FO	11	31.4%	4	13.8%	2.28 (0.81 to 6.40)	2.08 (0.82 to 5.26)	0.238
Hemodynamic-imaging evidence of FO	6	17.1%	3	10.3%	1.66 (0.45 to 6.05)	0.97 (0.23 to 4.09)	0.966

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; FO: Fluid Overload.

* Fluid overload: 2 or more criteria (symptoms, signs and/or hemodynamic-imaging) and absence of acute respiratory distress syndrome, see specific definitions in supplementary appendix. There were no missing data.

† Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of hypovolemia.

Table S6. Efficacy outcomes, subgroup analysis: patients without baseline systemic inflammatory response syndrome

Endpoint	Aggressive fluid resuscitation (N=87)		Moderate fluid resuscitation (N=98)		Relative risk (95% CI)	Adjusted relative risk (95% CI)¶	Missing data**
	no.	%	no.	%			
Moderately Severe or Severe Pancreatitis*	17	19.5%	13	13.3%	1.47 (0.76 to 2.86)	1.80 (0.91 to 3.55)	0
Severe Pancreatitis	2	2.3%	0	0.0%	-	-	0
Local complications							
Any	15	17.2%	13	13.3%	1.30 (0.66 to 2.58)	1.60 (0.80 to 3.19)	0
Necrosis†	10	11.5%	4	4.1%	2.82 (0.92 to 8.66)	3.74 (1.02 to 13.68)	0
INP	1	1.1%	1	1.0%	1.13 (0.07 to 17.74)	1.10 (0.06 to 20.01)	0
Systemic Inflammatory Response Syndrome‡							
12h	13	15.3%	10	10.3%	1.48 (0.69 to 3.21)	1.65 (0.72 to 3.78)	3
24h	11	13.4%	11	11.5%	1.17 (0.54 to 2.56)	1.47 (0.69 to 3.12)	7
48h	11	13.8%	9	9.9%	1.39 (0.61 to 3.18)	1.64 (0.66 to 4.09)	14
72h	6	8.5%	11	13.6%	0.62 (0.24 to 1.60)	0.87 (0.34 to 2.23)	33
Persistent‡	5	7.5%	2	2.5%	2.99 (0.60 to 14.89)	5.44 (0.75 to 39.68)	38
Other outcomes							
Incidence of invasive treatment‡	3	3.4%	3	3.1%	1.13 (0.23 to 5.44)	1.00 (0.23 to 4.38)	0
Need for nutritional support§	2	2.3%	1	1.0%	2.25 (0.21 to 24.42)	2.36 (0.21 to 26.5)	0
Admitted to ICU	2	2.3%	0	0.0%	-	-	0
Any organ failure‡	3	3.4%	0	0.0%	-	-	0
POF‡	2	2.3%	0	0.0%	-	-	0
Shock‡	1	1.1%	0	0.0%	-	-	0
Respiratory failure‡	3	3.4%	0	0.0%	-	-	0
Kidney failure‡	2	2.3%	0	0.0%	-	-	0
Death	2	2.3%	0	0.0%	-	-	0
Death, POF or INP	2	2.3%	1	1.0%	2.25 (0.21 to 24.42)	2.25 (0.19 to 27.00)	0
	Median	**IQR**	**Median**	**IQR**			
Length of hospital stay‖	5	4-7	4	3-7	1.32 (0.93 to 1.87)	1.38 (0.95 to 2.00)	0
Days on ICU	0	0-0	0	0-0			0
PAN-PROMISE score‖							
12h	21	11-35	18	8-31	1.22 (0.90 to 1.67)	1.21 (0.88 to 1.65)	3
24h	17	5-27	12	5-23	1.26 (0.93 to 1.69)	1.29 (0.96 to 1.73)	9
48h	11	4-24	8	2-18	1.22 (0.91 to 1.64)	1.28 (0.98 to 1.69)	16
72h	7	2-20	5	0-13	1.35 (0.97 to 1.87)	1.40 (1.02 to 1.92)	35
C-Reactive Protein — mg/dl‖							
48h	8.0	1.6-19.9	6.7	3.0-15.1	1.16 (0.83 to 1.63)	1.25 (0.86 to 1.82)	23
72h	5.1	1.7-20.4	7.3	2.8-16.8	1.04 (0.72 to 1.50)	1.05 (0.70 to 1.56)	43

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; ICU: Intensive Care Unit; INP: infected necrotizing pancreatitis; IQR: interquartile range; POF: persistent organ failure (lasting >48h).

* P-value=0.09 in in binary logistic regression analysis, see below (¶); severity of acute pancreatitis, mild: absence of complications; moderately severe: transient organ failure, local or systemic complications without persistent organ failure; severe: persistent organ failure, see supplementary appendix for more detailed definitions.

† necrotizing pancreatitis defined as pancreatic and/or peripancreatic necrosis.
‡ see definitions in supplementary appendix.
§ need for enteral and/or parenteral nutrition.
‖ Quantitative variables: relative risk and adjusted relative risk for high (above median) versus low (below median).
¶ Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of hypovolemia.
** Complete case analysis in variables with missing data; multiple imputation models were congruent with complete case analysis (data not shown).

Table S7. Safety outcomes, subgroup analysis: patients without baseline systemic inflammatory response syndrome

Endpoint	Aggressive fluid resuscitation (N=87)		Moderate fluid resuscitation (N=98)		Relative risk (95% CI)	Adjusted relative risk (95% CI)†	P-value†
	no.	%	no.	%			
Fluid overload*	14	16.1%	5	5.1%	3.15 (1.18 to 8.40)	2.80 (1.05 to 7.43)	0.033
Symptoms of FO	12	13.8%	5	5.1%	2.70 (0.99 to 7.37)	2.39 (0.86 to 6.58)	0.083
Signs of FO	21	24.1%	10	10.2%	2.37 (1.18 to 4.74)	2.48 (1.22 to 5.06)	0.010
Hemodynamic-imaging evidence of FO	7	8.0%	4	4.1%	1.97 (0.60 to 6.51)	1.64 (0.49 to 5.44)	0.422

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; FO: Fluid Overload.

* Fluid overload: 2 or more criteria (symptoms, signs and/or hemodynamic-imaging) and absence of acute respiratory distress syndrome, see specific definitions in supplementary appendix. There were no missing data.

† Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of hypovolemia.

Table S8. Efficacy outcomes, subgroup analysis: patients with baseline hypovolemia

Endpoint	Aggressive fluid resuscitation (N=64)		Moderate fluid resuscitation (N=65)		Relative risk (95% CI)	Adjusted relative risk (95% CI)¶	Missing data**
	no.	%	no.	%			
Moderately Severe or Severe Pancreatitis*	20	31.3%	17	26.2%	1.19 (0.69 to 2.06)	1.16 (0.65 to 2.08)	0
Severe Pancreatitis	6	9.4%	2	3.1%	3.05 (0.64 to 14.54)	1.71 (0.32 to 9.20)	0
Local complications							
Any	20	31.3%	16	24.6%	1.27 (0.73 to 2.22)	1.28 (0.69 to 2.37)	0
Necrosis†	15	23.4%	8	12.3%	1.90 (0.87 to 4.18)	1.87 (0.79 to 4.40)	0
INP	4	6.3%	3	4.6%	1.35 (0.32 to 5.81)	1.13 (0.28 to 4.51)	0
Systemic Inflammatory Response Syndrome‡							
12h	22	34.4%	19	29.7%	1.16 (0.70 to 1.92)	1.07 (0.63 to 1.80)	1
24h	18	30.0%	14	21.9%	1.37 (0.75 to 2.51)	1.46 (0.79 to 2.68)	5
48h	13	22.0%	15	24.6%	0.90 (0.47 to 1.72)	0.86 (0.41 to 1.78)	9
72h	9	17.0%	11	21.6%	0.79 (0.36 to 1.74)	1.11 (0.49 to 2.52)	25
Persistent‡	9	18.4%	7	13.7%	1.34 (0.54 to 3.31)	1.32 (0.52 to 3.38)	29
Other outcomes							
Incidence of invasive treatment‡	7	10.9%	4	6.2%	1.78 (0.55 to 5.78)	1.14 (0.35 to 3.73)	0
Need for nutritional support§	5	7.8%	5	7.7%	1.02 (0.31 to 3.34)	0.77 (0.26 to 2.30)	0
Admitted to ICU	7	10.9%	2	3.1%	3.55 (0.77 to 16.47)	2.25 (0.52 to 9.79)	0
Any organ failure‡	7	10.9%	5	7.7%	1.42 (0.48 to 4.25)	0.87 (0.31 to 2.41)	0
POF‡	6	9.4%	2	3.1%	3.05 (0.64 to 14.54)	1.71 (0.32 to 9.20)	0
Shock‡	4	6.3%	1	1.5%	4.06 (0.47 to 35.37)	2.67 (0.33 to 21.63)	0
Respiratory failure‡	7	10.9%	3	4.6%	2.37 (0.64 to 8.76)	1.54 (0.41 to 5.74)	0
Kidney failure‡	2	3.1%	3	4.6%	0.68 (0.12 to 3.92)	0.59 (0.11 to 3.21)	0
Death	2	3.1%	1	1.5%	2.03 (0.19 to 21.85)	1.00 (0.06 to 15.99)	0
Death, POF or INP	7	10.9%	4	6.2%	1.78 (0.55 to 5.78)	1.10 (0.32 to 3.80)	0
	Median	IQR	Median	IQR			
Length of hospital stay‖	6	4-10	5	3-8	1.11 (0.79 to 1.57)	1.12 (0.78 to 1.61)	0
Days on ICU	0	0-0	0	0-0	Not applicable	Not applicable	0
PAN-PROMISE score‖							
12h	24	18-35	21	10-34	1.20 (0.88 to 1.63)	1.12 (0.82 to 1.54)	2
24h	21	11-27	18	7-27	1.11 (0.83 to 1.48)	1.10 (0.82 to 1.48)	6
48h	12	5-24	10	4-23	1.14 (0.83 to 1.57)	1.14 (0.85 to 1.54)	11
72h	9	2-20	9	3-21	0.87 (0.62 to 1.20)	0.89 (0.65 to 1.22)	25
C-Reactive Protein — mg/dl‖							
48h	12.6	3.9-26.9	17.0	6.2-27.5	1.00 (0.72 to 1.37)	1.11 (0.79 to 1.57)	20
72h	13.0	2.4-28.5	18.3	5.1-27.9	0.86 (0.61 to 1.19)	0.96 (0.71 to 1.32)	34

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; ICU: Intensive Care Unit; INP: infected necrotizing pancreatitis; IQR: interquartile range; POF: persistent organ failure (lasting >48h).

* P-value=0.49 in in binary logistic regression analysis, see below (¶); severity of acute pancreatitis, mild: absence of complications; moderately severe: transient organ failure, local or systemic complications without persistent organ failure; severe: persistent organ failure, see supplementary appendix for more detailed definitions.

† necrotizing pancreatitis defined as pancreatic and/or peripancreatic necrosis.
‡ see definitions in supplementary appendix.
§ need for enteral and/or parenteral nutrition.
‖ Quantitative variables: relative risk and adjusted relative risk for high (above median) versus low (below median).
¶ Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of systemic inflammatory response syndrome.
** Complete case analysis in variables with missing data; multiple imputation models were congruent with complete case analysis (data not shown).

Table S9. Safety outcomes, subgroup analysis: patients with baseline hypovolemia

Endpoint	Aggressive fluid resuscitation (N=64)		Moderate fluid resuscitation (N=65)		Relative risk (95% CI)	Adjusted relative risk (95% CI)†	P-value †
	no.	%	no.	%			
Fluid overload*	19	29.7%	6	9.2%	3.22 (1.37 to 7.53)	2.90 (1.29 to 6.52)	0.009
Symptoms of FO	16	25.0%	8	12.3%	2.03 (0.94 to 4.41)	1.65 (0.81 to 3.38)	0.189
Signs of FO	22	34.4%	9	13.8%	2.48 (1.24 to 4.97)	2.56 (1.29 to 5.09)	0.007
Hemodynamic-imaging evidence of FO	10	15.6%	5	7.7%	2.03 (0.74 to 5.61)	1.42 (0.50 to 4.01)	0.504

The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

CI: confidence intervals; FO: Fluid Overload.

* Fluid overload: 2 or more criteria (symptoms, signs and/or hemodynamic-imaging) and absence of acute respiratory distress syndrome, see specific definitions in supplementary appendix. There were no missing data.

† Adjusted relative risk (95% Confidence Interval): Cochran-Mantel-Haenszel estimates adjusted for variables used for stratified randomization: center and baseline presence of systemic inflammatory response syndrome.

References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
2. Sharma A, Bhatt DL, Calvo G, Brown NJ, Zannad F, Mentz RJ. Heart failure event definitions in drug trials in patients with type 2 diabetes. Lancet Diabetes Endocrinol 2016;4:294-6.
3. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
4. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons; 2004.
5. de-Madaria E, Sanchez-Marin C, Carrillo I, et al. Design and validation of a patient-reported outcome measure scale in acute pancreatitis: the PAN-PROMISE study. Gut 2021;70:139-47.