Journal of the Formosan Medical Association 123 (2024) 1037–1044

Contents lists available at ScienceDirect

Journal of the Formosan Medical Association

journal homepage: www.jfma-online.com

Original Article

Impact of glucose-containing fluid on acute pancreatitis outcomes: A multicenter retrospective analysis

Hsing-Chien Wu [a,b,e,1], Kuo-Liong Chien [b,c,d,1], Chieh-Chang Chen [d,e], Yu-Jen Fang [e,f], Wen-Hao Hu [g], Min-Horn Tsai [g], Wei-Chih Liao [e,h,*]

[a] Department of Medicine, National Taiwan University Cancer Center, National Taiwan University Hospital, Taipei, Taiwan
[b] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[c] Population Health Research Center, National Taiwan University, Taiwan
[d] Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
[e] Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan
[f] Department of Internal Medicine, National Taiwan University Hospital, Yun-Lin Branch, Yunlin, Taiwan
[g] Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu, Taiwan
[h] Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

ARTICLE INFO

Keywords:
Acute pancreatitis
Fluid resuscitation
Glucose-containing fluid
Organ failure

ABSTRACT

Introduction: Fluid resuscitation reduces mortality and morbidity in acute pancreatitis (AP); however, whether glucose-containing fluids negatively impact AP remains uncertain. We aimed to examine the association between glucose-containing fluids and AP outcomes.

Methods: This multicenter retrospective cohort study included patients diagnosed with AP between January 2015 and December 2018. Glucose density was defined as total glucose content divided by total fluid volume (g/dl) on day 1, and was considered high if the level exceeded the median. Endpoints were early organ failure (OF), including cardiovascular, renal, or respiratory system failure within 7 days; 30-day OF; ICU admission; and AP-related 90-day mortality. Logistic regression models, restricted cubic spline curves, and Cox proportional hazards models were used for statistical analysis.

Results: From the database, 1,146 patients with AP were included. Early OF occurred in 8.8% of patients within 7 days. The high glucose-density group (>5 g/dl) had increased risk of early OF (9.7% vs. 8.2%; adjusted odds ratio [aOR], 1.69; 95% confidence interval [CI], 1.03–2.80; $P = 0.039$), respiratory failure (8.0% vs. 6.2%; aOR, 1.88; 95% CI, 1.09–3.24; $P = 0.024$), cardiovascular failure (3.4% vs. 2.4%; aOR, 3.59; 95% CI, 1.28–10.0; $P = 0.015$), and ICU admission (6.8% vs. 5.8%; aOR, 2.06; 95% CI, 1.08–3.94; $P = 0.029$), with a dose-response effect observed for cardiovascular failure and ICU admission. A significant increase 30-day OF risk (adjusted hazard ratio [aHR], 1.70; 95% CI, 1.19–2.45) was also noted.

Conclusion: Excess glucose-containing fluid was associated with increased risks of overall, respiratory, and cardiovascular OF and ICU admission in AP.

1. Introduction

Acute pancreatitis (AP) is characterized by a mortality rate of 0.5%–2.5%, with increasing incidence from 1961 to 2016 [1,2]. In AP, organ failure (OF) within the first week, involving the cardiovascular, renal, or respiratory systems, is critically important [3]. Early onset of OF significantly influences disease severity, and AP-associated mortality rates. Patients are classified as having severe AP if they experience persistent OF (lasting >48 h) or moderately-severe AP if they experience transient OF (lasting <48 h); these categories correlate with mortality rates of approximately 40% and 10%, respectively. Conversely, patients without OF have a mortality rate of only 2% [4]. Despite the current standard of care, a substantial proportion (14.1%) of patients with AP experience OF [5], highlighting the urgent need for effective strategies to reduce the risk and severity of AP-associated OF [3].

Early OF within the first 1–2 weeks of AP accounts for 42–46% of

* Corresponding author. Internal Medicine, National Taiwan University College of Medicine, No. 7, Chung-Shan South Road, Taipei, 10002, Taiwan.
E-mail address: davidntuh@ntuh.gov.tw (W.-C. Liao).
[1] Hsing-Chien Wu, MD, MS, and Kuo-Liong Chien, MD, PhD contributed equally to this work.

https://doi.org/10.1016/j.jfma.2024.05.022
Received 24 November 2023; Received in revised form 11 February 2024; Accepted 31 May 2024
Available online 22 June 2024

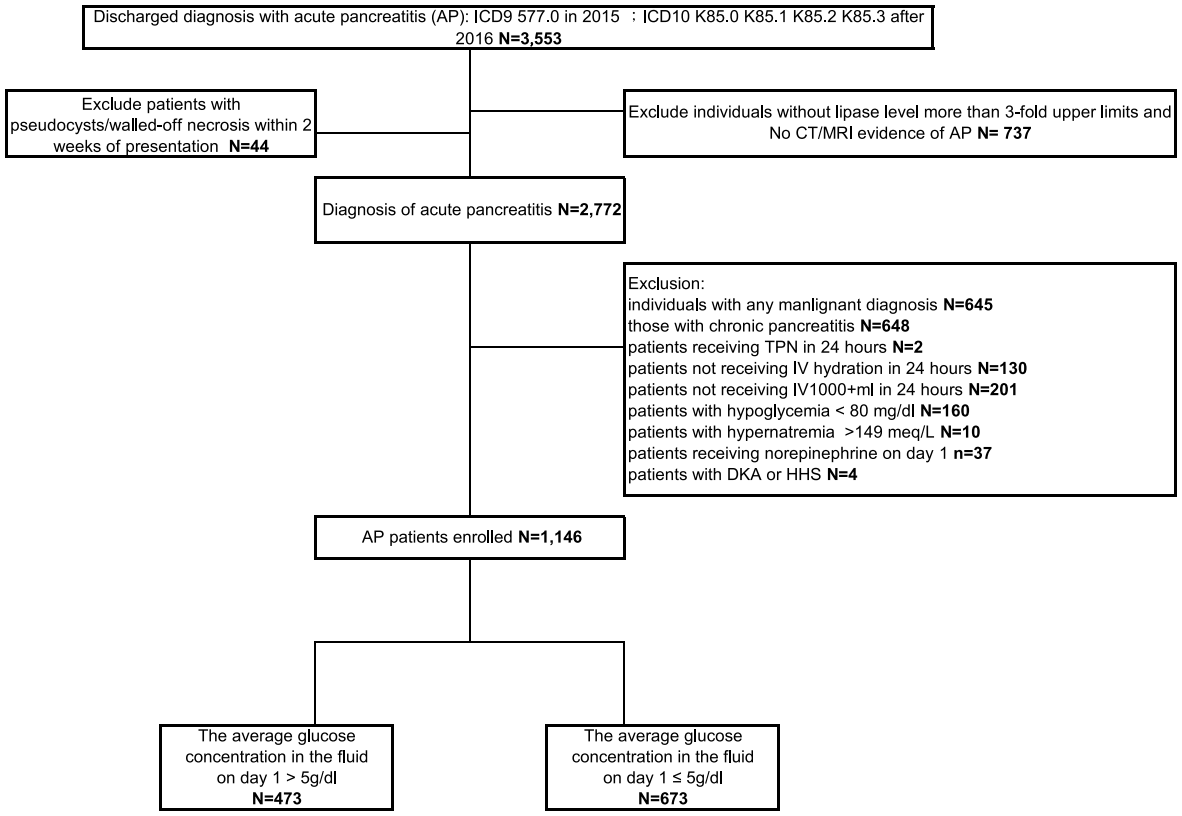

Fig. 1. Flowchart of Patients Included in the Multicenter Retrospective Cohort. From January 2015 to December 2018, all patients with a diagnosis of acute pancreatitis (AP) upon discharge were included in this study. Those who developed late local complications (i.e., pseudocysts, wall-off necrosis) within 2 weeks of presentation or did not meet the radiologic nor laboratory criteria of AP were excluded. Patients were also excluded if they had malignant disease, chronic pancreatitis, hypoglycemia, hypernatremia, diabetic ketoacidosis, hyperglycemic hyperosmolar status, received total parenteral nutrition (TPN) on day 1, received norepinephrine (diluted in glucose solution) on day 1, did not receive intravenous fluid therapy in 24 h, or received less than 1000 ml fluid in 24 h. The included patients were categorized into two groups based on the average glucose concentration in the fluid (defined as glucose density) on day 1, using 5 g/dl as the cut-off. AP, acute pancreatitis; CT, computed tomography; DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar status; ICD, International Classification of Disease; IV, intravenous fluid; TPN, total parenteral nutrition.

mortality and is associated with hypovolemic status and hypoperfusion of vital organs. Given the strong association between the amount of fluid resuscitation and OF [6,7], fluid therapy is key in the initial stages of AP. The choice of intravenous fluid for resuscitation includes isotonic crystalloids, such as normal saline, and balanced fluids like lactated Ringer's and Hartmann's solution. However, glucose-containing balanced fluids, which are occasionally used as maintenance fluids in real-world settings, bring additional considerations to fluid selection. It should be noted that glucose-containing fluids (e.g., Bfluid®, TAITA injections ["OTSUKA"], and Dextrose [glucose]-saline) may demonstrate comparatively limited capacity to improve intravascular tonicity [8], potentially decreasing the effectiveness of fluid resuscitation. Since inadequate fluid resuscitation can result in OF and morbidity [9], the impact of administering glucose-containing fluids (on day 1) in early stages of AP warrants further investigation.

Our objective was to compare early OF, persistent OF, ICU admission, and mortality between two groups receiving either high or low concentrations of glucose-containing fluids on day 1. We focused on examining the association between the use of glucose-containing fluids and early OF.

2. Materials and methods

2.1. Study design, database, and case definition

This multicenter retrospective cohort study used data from the Integrative Medical Database, National Taiwan University Hospital (NTUH-iMD) to identify occurrences of AP. The NTUH-iMD is a consolidated repository for electronic medical records and administrative data sourced from the National Taiwan University Hospital (NTUH) and its affiliated branches across northern and western Taiwan [10,11]. Established in 2013, this comprehensive database has been diligently curated, aligning with the stipulations of the Health Insurance Portability and Accountability Act (HIPAA). Importantly, all individuals in the database are subjected to deidentification protocols.

Study eligibility was determined based on discharge diagnoses coded under International Classification of Diseases (ICD-10) categories K85.0, K85.1, K85.2, K85.3, K85.8, K85.9, and B25.2, as well as ICD-9 codes 577.0 and 072.3. The study covered the period from January 2015 to December 2018 and included a tertiary medical center (NTUH), two secondary referral centers (NTUH Hsing-Chu branch and NTUH Yun-Lin branch), and one community hospital (NTUH Jing-Shan branch). Only the initial occurrence of AP was considered for patients who experienced recurrent AP episodes during the study timeframe. The point at which signs of AP were observed on cross-sectional imaging or when the lipase level exceeded three times the upper threshold of the normal range was assigned as the index date. The study was approved by the Research Committee of the National Taiwan University Hospital (approval number: 202009074RIND) and performed in accordance with the Declaration of Helsinki and its later amendments. Because all electronic data were de-identified in the academic hospital database, the requirement for individual informed consent was waived in accordance with Taiwan's Human Subject Research Act.

Table 1
Baseline demographics.

	Demographics before Matching			Demographics of fluid volume-matched groups		
	Glucose >5g in 100 ml infusion (n = 473)	Glucose ≤5g in 100 ml infusion (n = 673)	*P*	Glucose >5g in 100 ml infusion (n = 473)	Glucose ≤5g in 100 ml infusion (n = 473)	*P*
Age (mean, SD)	59.6 (17.9)	57.3 (17.2)	0.027	59.6(17.9)	58.6(17.2)	0.39
Sex (Women,%)	211 (44.6)	290 (43.1)	0.61	211 (44.6)	212 (44.8)	0.95
BMI (mean, SD)	25.0 (4.1)	25.3 (4.3)	0.23	25.0 (4.1)	25.2 (4.2)	0.38
Smoking (n, %)	112 (23.7)[a]	173 (25.7)[a]	0.73	112 (23.7)[c]	101 (21.3)[c]	0.58
Alcohol (n, %)	92 (19.5)[b]	155 (23.0)[b]	0.31	92 (19.5)[d]	83 (17.5)[d]	0.67
Etiologies of pancreatitis			0.11			0.20
Biliary	175 (37.0)	230 (34.2)		175 (37.0)	170 (35.9)	
Alcoholic	79 (16.7)	121 (18.0)		79 (16.7)	63 (13.3)	
Hypertriglyceridemic	19 (4.0)	49 (7.3)		19 (4.0)	30 (6.3)	
Unknown	200 (42.3)	273 (40.5)		200 (42.3)	210 (44.4)	
CCI (medium, IQR)	0 (0–1)	0 (0–1)	0.65	0 (0–1)	0 (0–1)	0.32
History of diabetes mellitus (n, %)	47 (9.9)	121 (18.0)	<.001	47 (9.9)	96 (20.3)	<.001
24h Fluids (ml, medium, IQR)	2100 (1600–2300)	2400 (1800–3000)	<.001	2100 (1600–2300)	1900 (1600–2450)	0.45
Fluids within 24 h (n, %)			<.001			0.84
< 1700 ml (Q1)	131 (27.7)	123 (18.3)		131 (27.7)	123 (26.0)	
≥ 1700 ml and ≤2700 ml (Q2~Q3)	294 (62.2)	320 (47.6)		294 (62.2)	302 (63.8)	
> 2700 ml (Q4)	48 (10.1)	230 (34.1)		48 (10.1)	48 (10.1)	
Using glucose-containing fluid in initial 1000 ml			<.001			<.001
Not used (n, %)	6 (1.3)	167 (24.8)		6 (1.3)	119 (25.2)	
≥ 400 ml (n, %)	237 (50.1)	448 (66.6)		237 (50.1)	322 (68.1)	
All (n, %)	230 (48.6)	58 (8.6)		230 (48.6)	32 (6.8)	
APACHE II score (medium, IQR)	7 (5–11)	7 (5–11)	0.50	7 (5–11)	7 (5–11)	0.66
Initial Hyperglycemia after diagnosis (1st glucose >200 mg/dl)	83 (17.5)	175 (26.0)	<.001	83 (17.5)	126 (26.6)	<.001
Hematocrit (Hct, %, 95% CI)	40.5 (36.8–44.3)	41.9 (38.0–45.4)	<.001	40.5 (36.8–44.3)	41.6 (37.7–44.9)	0.02
Triglyceride levels			0.17			0.19
<150 mg/dL (n, %)	230 (48.6)	297 (44.1)		230 (48.6)	206 (43.6)	
150–199 mg/dL (n, %)	52 (11.0)	73 (10.9)		52 (11.0)	49 (10.4)	
200–499 mg/dL (n, %)	104 (22.0)	143 (21.2)		104 (22.0)	105 (22.2)	
≥500 mg/dL (n, %)	87 (18.4)	160 (23.8)		87 (18.4)	113 (23.9)	
BUN (mg/dl, medium, IQR)	13.7 (9.0–20.5)	14.0 (9.9–22.2)	0.08	14.0 (9.9–22.2)	14.0 (9.0–21.2)	0.23
CRP (mg/dl, medium, IQR)	8.3 (1.1–12.6)	8.2 (1.0–14.0)	1	5.0 (1.1–12.5)	6.0 (1.2–14.1)	0.34
Treatment sites			0.019			0.46
NTUH (tertiary)(n, %)	188 (39.8)	237 (35.2)		188 (39.8)	186 (39.3)	
NTUH Jinshan (primary)(n, %)	16 (3.3)	16 (2.4)		16 (3.3)	9 (1.9)	
NTUH Yunlin (secondary)(n, %)	151 (31.9)	275 (40.9)		151 (31.9)	164 (34.7)	
NTUH Hsinchu (secondary)(n, %)	118 (25.0)	145 (21.5)		118 (25.0)	114 (24.1)	

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; Hct, hematocrit; IQR, interquartile range; NTUH, National Taiwan University Hospital; Q1–Q4, quartiles 1–4; SD, standard deviation.

[a] Smoking data were unavailable for 10.4% of those receiving high glucose-containing fluid (>5 g per dl) and for 10.1% of those receiving low glucose-containing (≤5 g per dl) fluid.

[b] Alcohol use data were unavailable for 10.2% of those receiving high glucose-containing fluid (>5 g per dl) and for 10.6% of those receiving low glucose-containing (≤5 g per dl) fluid.

[c] Smoking data were unavailable for 10.4% of those receiving high glucose-containing fluid (>5 g per dl) and for 13.5% of those receiving low glucose-containing (≤5 g per dl) fluid.

[d] Alcohol use data were unavailable for 10.2% of those receiving high glucose-containing fluid (>5 g per dl) and for 14.2% of those receiving low glucose-containing (≤5 g per dl) fluid.

2.2. Glucose-containing fluid and glucose density

The fluid administered on day 1 (within 24 h after diagnosis) to patients with AP was identified in the electronic medical record. Total glucose content and total volume of fluid were calculated. Glucose density was defined as total glucose content divided by total volume of fluid (g/dl) on day 1. The glucose density cut-off was determined as the integer (g/dl) level closest to the median. Patients with a glucose density higher than the cut-off were classified as high glucose-density group, while those with a glucose density lower than or equal to the cut-off were classified as the low glucose-density group.

2.3. Comorbidity, Acute Physiology and Chronic Health Evaluation II scores, and laboratory data

Calculation of the Charlson Comorbidity Index (CCI) score was carried out by using diagnosis codes from both outpatient and inpatient electronic medical records that predated the primary admission event [12]. Baseline patient characteristics, including age, gender, smoking, and alcohol consumption status, and body mass index, were extracted. Additionally, laboratory data, including serum glucose, point-of-care glucose, HbA1c, hematocrit levels, serum triglyceride concentrations, blood urea nitrogen values, and C-reactive protein levels, were retrieved. To determine the history of diabetes mellitus, patients were defined as having a history of diabetes if they had a diagnosis of diabetes, an HbA1c level equal to 6.5% or higher, or if they were taking oral glucose-lowering agents. Furthermore, data relevant to the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores as of the index date were extracted from the electronic medical records [13].

2.4. Outcomes

The primary endpoint of this study was early OF, a composite measure inclusive of new-onset failure within 7 days of the index date in the cardiovascular, renal, and respiratory systems, previously devoid of pathological conditions according to the revised Atlanta Classification [3]. To identify events of in the database, the criteria for cardiovascular failure were defined as concurrent records of systolic blood pressure less

Table 2
Glucose density and clinical outcomes in overall and fluid volume-matched analyses.

	Glucose >5g in 100 ml infusion	Glucose ≤5g in 100 ml infusion	Univariate analysis			Multivariate analysis		
Outcome	*events/total (%)*		OR	95% CI	*P* value	OR	95% CI	*P* value
overall analysis								
Early Organ failure in 7 days								
Organ failure in 7 days	46/473 (9.7)	55/673 (8.2)	1.21	0.80–1.83	0.36	1.69	1.03–2.80	0.039
Respiratory failure	38/473 (8.0)	42/673 (6.2)	1.31	0.83–2.07	0.24	1.88	1.09–3.24	0.024
Cardiovascular failure	16/473 (3.4)	16/673 (2.4)	1.44	0.71–2.90	0.31	3.59	1.28–10.0	0.015
Renal failure	9/473 (1.9)	11/673 (1.6)	1.21	0.80–1.83	0.36	1.17	0.42–3.31	0.76
Persistent organ failure	13/473 (2.8)	16/673 (2.4)	1.16	0.55–2.44	0.70	2.21	0.78–6.24	0.13
ICU admission	32/473 (6.8)	39/673 (5.8)	1.18	0.73–1.91	0.50	2.06	1.08–3.94	0.029
AP related death in 30 days	8/473 (1.7)	1/673 (0.2)	11.6	1.44–92.6	0.021	21.26	1–450.36	0.050
fluid volume-matched analysis								
Early Organ failure in 7 days								
Overall organ failure	46/473 (9.7)	33/473 (7.0)	1.44	0.92–1.45	0.11	1.73	1.02–2.93	0.042
Respiratory failure	38/473 (8.0)	23/473 (4.9)	1.71	1.03–2.83	0.037	2.24	1.25–4.00	0.006
Cardiovascular failure	16/473 (3.4)	8/473 (1.7)	2.04	0.85–4.85	0.11	2.47	0.89–6.80	0.08
Renal failure	9/473 (1.9)	8/473 (1.7)	1.07	0.38–3.04	0.89	1.07	0.38–3.04	0.89
Persistent organ failure	13/473 (2.8)	7/473 (1.5)	1.88	0.74–4.80	0.19	2.60	0.76–8.88	0.13
ICU admission	32/473 (6.8)	20/473 (4.8)	1.64	0.92–2.93	0.09	2.23	1.04–4.76	0.040
AP related death in 30 days	8/473 (1.7)	1/473 (0.2)	8.12	1.01–65.4	0.049	–		

ICU, intensive care unit; CI, confidence interval; OR, odds ratio.

than 90 mmHg (or mean blood pressure less than 65 mmHg) and the administration of intravenous inotropic agents such as norepinephrine or dopamine. The criteria for renal failure included any of the following: creatinine level > 1.9 mg/dl excluding ICD-10 and ICD-9 codes for chronic kidney disease (N18, I13.1, D63.1, 585, 285.21); receipt of renal replacement therapy, including continuous venovenous hemofiltration and sustained low-efficiency daily dialysis; or an ICD-10 diagnosis of acute renal failure (N17, 584). The criteria for respiratory failure were defined as a blood arterial oxygen level less than 60 mmHg, pulse oximeter reading less than 90% on two occasions, or receipt of mechanical ventilation, including endotracheal intubation and noninvasive mechanical intubation. Additionally, the aggravation of pre-existing OF within the same 7-day post-index period was also considered as part of this primary outcome. In cases of multiple OF, the onset of failure in the first affected organ considered the commencement of.

Secondary endpoints included persistent OF, isolated failure of distinct organs (i.e., cardiovascular, respiratory, and renal) within the initial 7 days after onset, OF within 30 days, use of intensive care unit (ICU) services during hospitalization, and mortality linked specifically to AP after diagnosis.

2.5. Statistical analysis

Continuous variables were summarized as mean/standard deviation and median/interquartile range (IQR) for normally and non-normally distributed data, respectively, and compared between groups using the Mann-Whitney *U* test. Categorical variables were presented as counts and percentages and compared using Fisher's exact test. Kaplan-Meier survival curves were used to compare the risk of OF at 30 days and mortality at 90 days between groups with high or low glucose density during fluid resuscitation.

In the univariate, multivariate, and subgroup analyses, odds ratios (ORs) and 95% confidence intervals were calculated using a logistic regression model. Variables including age, sex, APACHE II score, CCI, presence of diabetes mellitus, and total fluid volume within 24 h were included in the univariate logistic and multivariate logistic models. In the fluid volume-matched analysis, a matching algorithm first selected a patient with high glucose density, then matched a patient with low glucose density within a caliper width of 0.25 of the standard deviation of the logit of the 24h fluid volume. The data from the matched groups were further analyzed to estimate the odds ratios in multivariate conditional logistic regression, adjusting for age, sex, APACHE II score, CCI, and the presence of diabetes mellitus. Logistic restricted cubic spline models were used to investigate dose-response associations. These associations were evaluated using the Wald test, which includes a comparison of linear and nonlinear likelihood ratios. To estimate the cause-specific hazards of OF within 30 days and pancreatitis-associated mortality, a Cox proportional hazards model was used, considering death and other causes of death as competing risks. The model was adjusted for age, sex, APACHE II score, CCI, presence of diabetes mellitus, and total fluid volume within 24 h. In the sensitivity analysis, patients with OF on the index date were excluded, and the effect of glucose density on primary and secondary outcomes was examined using univariate and multivariate logistic regression and logistic-restricted cubic spline models. Data analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, North, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

A total of 1,146 patients with a confirmed diagnosis of AP between January 1, 2015, and December 31, 2018, were included in this study. Of these, 673 (58.7%) received fluid resuscitation with a glucose density of less than or equal to 5 g/dL, while 473 (41.3%) received fluid with a high glucose density (Fig. 1). The types of fluids administered are shown in the supplementary material (Supplemental Table S1). Compared to those in the low glucose density group, patients in the high glucose density group were older, had a lower hematocrit level, were less likely to have diabetes mellitus and baseline hyperglycemia, received less fluid on day 1, were less likely to develop hyperglycemia on day 1, and were less likely to receive glucose-containing fluid during the initial infusion. The distribution of patients across the treatment sites also varied between the two groups. After matching by 24h fluid volume, 946 patients were selected for analysis, with 473 patients in the high and 473 patients in the low glucose density groups. This matched cohort showed balanced 24h fluid volumes and treatment site distributions between the two groups (Table 1).

3.2. Association between glucose density and early OF

Among the 1,146 patients, 101 (8.8%) developed early OF (i.e., OF within 7 days), including 80 (7.0%) patients with respiratory failure, 32 (2.8%) with cardiovascular failure, and 20 (1.8%) with renal failure. Among them, 71 (6.2 %) required ICU admission, 29 (2.5%) had early

Table 3
Subgroup analysis.

Subgroup	Glucose >5g in 100 ml infusion	Glucose ≤5g in 100 ml infusion	Odds Ratio (95% CI)	$P_{interaction}$
	events/total (%)			
All patients	46/473 (9.7)	55/673 (8.2)	1.69 (1.03–2.80)	
Age				0.17
<60	8/237 (3.4)	18/326 (5.0)	1.00 (0.40–2.51)	
≥60	38/236 (16.1)	37/311 (11.9)	2.10 (1.17–3.77)	
Gender				0.17
Female	23/211 (10.9)	22/290 (7.6)	2.47 (1.19–5.11)	
Male	23/262 (8.8)	33/383 (8.6)	1.28 (0.67–2.45)	
History of diabetes mellitus				0.25
Yes	13/46 (28.3)	17/109 (15.6)	2.77 (1.06–7.26)	
No	33/427 (7.7)	38/564 (6.7)	1.46 (0.83–2.57)	
APACHE II score				0.68
<8	3/218 (1.4)	4/283 (1.4)	1.18 (0.26–5.37)	
≥8	43/255 (16.9)	51/390 (13.1)	1.64 (1.02–2.65)	
Serum triglyceride level				0.42
<150	27/230(11.7)	26/297 (8.8)	1.90 (1.01–3.60)	
≥150 and < 200	7/52 (13.5)	5/73 (6.9)	1.62 (0.98–2.69)	
≥200 and < 500	8/104 (7.7)	12/143 (8.4)	1.38 (0.72–2.67)	
≥500	4/87 (4.6)	12/160 (7.5)	1.18 (0.45–3.11)	
Total fluid volume on D1				0.25
<1700	13/131 (9.9)	7/123 (5.7)	2.51 (0.85–7.38)	
≥1700 and ≤ 2700	30/294 (10.2)	21/320 (6.6)	1.70 (0.89–3.24)	
>2700	3/48 (6.3)	27/230 (11.7)	0.99 (0.26–3.69)	

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval.

persistent OF, 143 (12.5%) developed OF within 30 days, and 9 (0.8%) and 20 (1.7%) died of AP within 30 and 90 days, respectively. The median (IQR) length of hospital stay was 6 days (4–10 days) and the mean overall length of stay, including emergency department and ward admissions was 8.9 days. The high glucose-density group had a higher risk of overall OF (9.7% vs. 8.2%; adjusted odds ratio [aOR], 1.69; 95% confidence interval [CI], 1.03–2.80; $P = 0.039$), respiratory failure (8.0% vs. 6.2%; aOR, 1.88; 95% CI, 1.09–3.24; $P = 0.024$), cardiovascular failure (3.4% vs. 2.4%; aOR, 3.59; 95% CI, 1.28–10.0; $P = 0.015$), ICU admission (6.8% vs. 5.8%; aOR, 2.06; 95% CI, 1.08–3.94; $P = 0.029$), and a marginally higher risk of 30-day mortality rate (1.7% vs. 0.2%; aOR, 21.6; 95% CI, 1.0–450.4; $P = 0.05$). Similar results were observed in fluid volume matched analysis for overall OF, respiratory failure, and ICU admission, with borderline significance for cardiovascular failure (Table 2). In the sensitivity analysis, which excluded those with OF on day 1, the high glucose-density group also had a higher risk of renal failure (1.8% vs. 0.6%; aOR, 6.43; 95% CI, 1.08–3.94; $P = 0.029$) (Supplemental Table S2). In the subgroup analysis, the risk associated with high glucose-density on early OF significantly increased in predefined subgroups, including those aged ≥ 60 years (16.1% vs. 11.9%; aOR, 2.10; 95% CI, 1.17–3.77), females (10.9% vs. 7.6%; aOR, 2.47; 95% CI, 1.19–5.11), patients with a history of diabetes mellitus (28.3% vs. 15.6%; aOR, 2.77; 95% CI, 1.06–7.26), those predicted to have severe AP as indicated by an APACHE II score ≥ 8 (16.9% vs. 13.1%; aOR, 1.64; 95% CI, 1.02–2.65), and those with a serum triglyceride level < 200 mg/dl (12.1% vs. 8.4%; aOR, 1.95; 95% CI, 1.06–3.59) (Table 3).

3.3. Dose-response analysis for clinical outcomes by glucose density

In dose-response analysis, the restricted cubic spline curve revealed a significant increased risk for early cardiovascular failure (P for overall = 0.011), and ICU admission (P for overall = 0.013) with increasing glucose density of the total fluid (Fig. 2). Notably, the curve showed an exponential rise in the risk of early cardiovascular failure per unit increase in glucose density (P for non-linear = 0.045). The odds ratio demonstrated a constant escalation from a glucose density of 4 g/dl onwards for early cardiovascular failure (Fig. 2C), persistent OF (Fig. 2E), and ICU admission (Fig. 2F). Additionally, a trend of increased risk was also shown for early respiratory failure within the glucose density range of 0 and 6 g/dl (Fig. 2A). In the sensitivity analysis, the risk of early renal failure from day 2 to day 7 also significantly increased per unit increase in glucose density (P for overall = 0.025), as the risks of cardiovascular and respiratory failures, and ICU admission, continued to be dose-responsive to glucose density (Supplemental Fig. S1).

3.4. Survival analysis for OF and pancreatitis-associated mortality

Kaplan-Meier Analysis revealed an increased risk trend for OF at 30 days (Log-rank $P = 0.12$) and a significantly increased risk for mortality at 90 days in the group with high glucose density (Log-rank $P = 0.045$). In multivariate analysis, the adjusted hazard ratio for the high glucose density group was 1.70 (95% CI, 1.19–2.45; $P = 0.004$) for OF at 30 days and 3.72 (95% CI, 0.82–16.97; $P = 0.09$) for pancreatitis-associated mortality at 90 days (Fig. 3).

4. Discussion

The clinical effect of glucose-containing fluid infusion during resuscitation on day 1 has not been previously reported. Here, we demonstrated that fluid infusion within the first 24 h, with an average glucose concentration exceeding 5 g/dL (5%), was associated with early OF in patients receiving more than 1000 ml of fluid resuscitation for AP. In the dose-response analysis, glucose density was associated with an increased risk of early cardiovascular failure and ICU admission. Detrimental effects of high glucose density on 30-day OF and 90-day pancreatitis-associated mortality were also observed.

Glucose-containing fluid is not recommended in the current standard of care during initial management of AP; on the other hand, it is not recommended against. According to the current National Institute for Health and Care Experience (NICE) guideline, a glucose intake of 50–100 g per day in maintenance fluid is suggested after the initial bolus infusion [14]. However, how much glucose-containing fluid is appropriate on day 1, when replenishing fluid deficit with crystalloid fluids is the highest priority, remains unclear. Considering glucose-containing fluid in the analysis, a prospective cohort study that enrolled 247 patients showed that overzealous fluid administration, defined as more than 4.1 litters (third quartile) of normal saline and glucose-containing fluid, may lead to persistent OF, acute fluid collection, respiratory insufficiency, and renal insufficiency [7]. Similar to outcomes of the aforementioned study, our results indicate that respiratory and cardiovascular failure, followed by renal failure may occur after excessive infusion of glucose-containing fluid on day 1. Besides the recommendation of isotonic crystalloid infusion as the fluid of choice in guidelines [15–18], our results suggested that a high average glucose concentration of more than 5 g/dl in the first 24h infusion may have detrimental effects

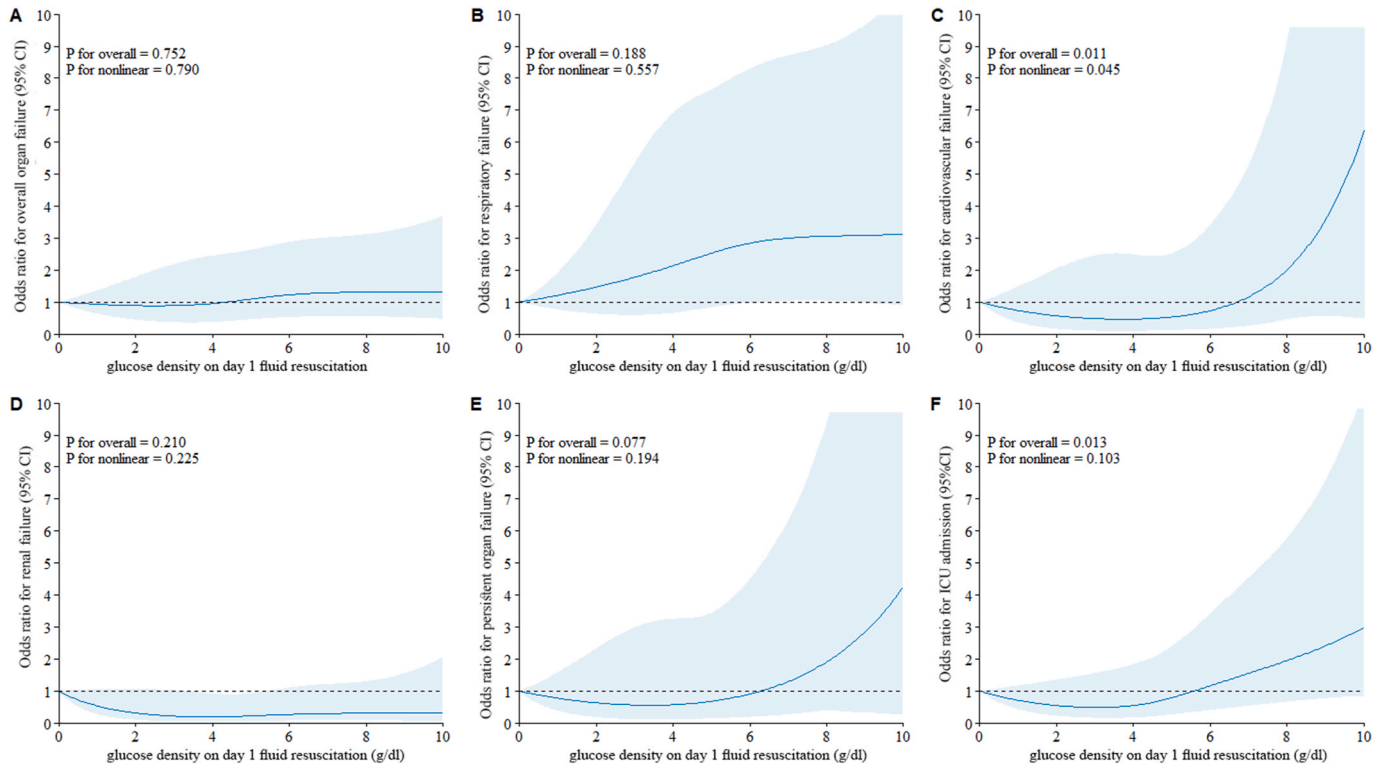

Fig. 2. Dose-response Curve for Organ Failure within 7 days and Intensive Care Unit Admission during Hospitalization according to Glucose Density. Graphics show ORs for glucose density, which was defined as the total parenteral glucose divided by the total volume infused within 24 h of diagnosis. The estimated ORs were adjusted for age, sex, APACHE II score, CCI, history of diabetes mellitus, and total fluid volume within 24 h. A. Outcome of organ failure within seven days of diagnosis; B. Outcome of early respiratory failure within seven days of diagnosis; C. Outcome of early cardiovascular failure within seven days of diagnosis; D. Outcome of early renal failure within seven days of diagnosis; E: Outcome of early persistent organ failure within seven days of diagnosis; F: Outcome of ICU admission. Solid lines indicate ORs, and shadow shape indicate 95% CIs. APACHE II, Acute Physiology and Chronic Health Evaluation; CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio; ICU, intensive care unit.

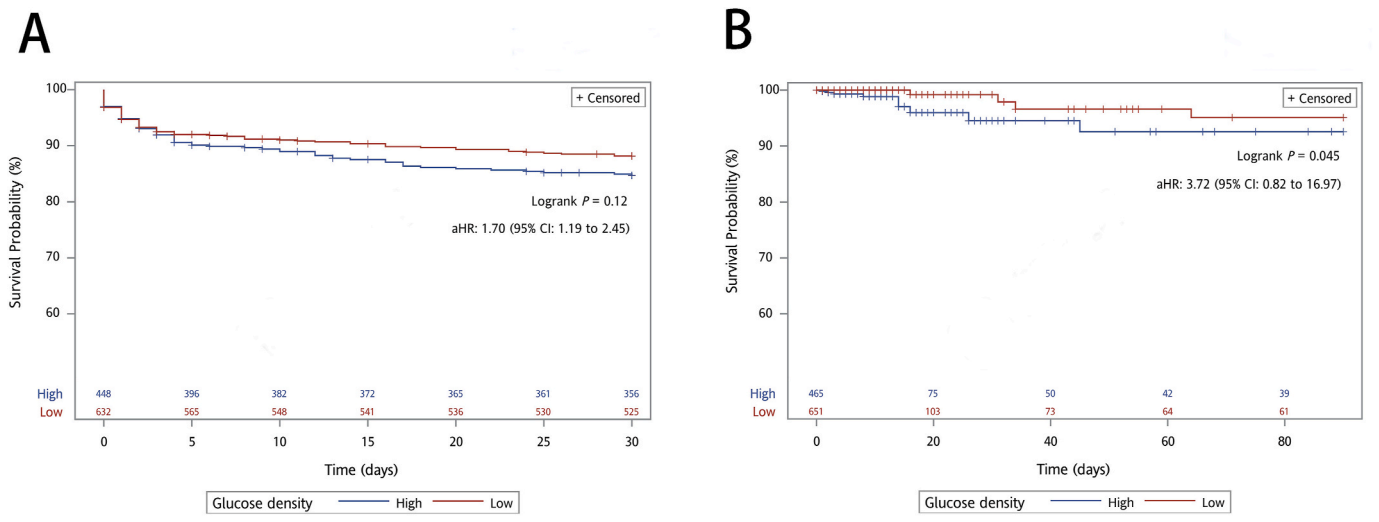

Fig. 3. Kaplan-Meier Curves for Organ Failure in 30 days and Acute Pancreatitis-associated Mortality in 90 Days according to Glucose Density. Graphics show Kaplan-Meier curves for organ failure and acute pancreatitis-associated mortality. High or low glucose density was defined based on the average glucose concentration being >5 g/dl or ≤5 g/dl in the total fluid administered within 24 h of diagnosis. The adjusted hazard ratio was estimated by incorporating age, sex, APACHE II score, CCI, history of diabetes mellitus, and total fluid volume within 24 h in the Cox proportional hazards model. A. Kaplan-Meier Curve of organ failure after 30 days. B. Kaplan-Meier curve for acute pancreatitis-associated mortality after 90 days. APACHE II, Acute Physiology and Chronic Health Evaluation; CCI, Charlson Comorbidity Index.

on patients with AP.

Worldwide, the practice of fluid therapy varies significantly. The Fluid Challenges in Intensive Care study, which focused on the initial 2-h fluid challenge in the ICU, and enrolled 2,213 patients in intensive care, reported highly variable fluid management practices across European countries in terms of types, volume, and decision regarding successive

fluids. Further, it reported that 41.9% of the fluids administered were balanced or glucose-containing fluids [19]. Furthermore, 54% of patients receiving maintenance fluid in the ICU received balanced or glucose-containing fluid [20]. Consistent with studies in critical care, our real-world data showed that fluid replacement in initial stages of AP tends to be liberal, particularly regarding glucose-containing fluids. Notably, most patients (89.9%) with AP in our study received glucose-containing fluids on day 1, a proportion significantly higher than that observed in critically ill patients [19,20]. This could be due to the nature of AP, where most patients experience abdominal pain, and 80% develop vomiting, making them particularly vulnerable to fluid and energy deficits [21]. Thus, physicians tend to administer balanced fluids and parenteral glucose replacement as initial therapy. However, studies on the use of glucose-containing fluids in patients with AP are limited. One study that investigated the association between fluid volume in the initial 24 h and clinical outcomes considered glucose-containing fluid as part of the total volume, while others did not describe the use of glucose-containing fluid [17,18,22]. Our study showed that glucose-containing fluid therapy varies among patients and contributes to the clinical outcomes of AP.

Subgroups vulnerable to fluid with high glucose density (i.e., age $\geq$ 60 years, female, history of diabetes mellitus, predicted severe AP with APACHE II score $\geq$ 8, and serum triglyceride level $<$ 200 mg/dl) were identified in the subgroup analysis. Since age, diabetes mellitus, and APACHE II score $\geq$ 8 are risk factors for severe AP, which can lead to deterioration of microvascular permeability in the splanchnic and pulmonary circulation [23], patients with these risk factors are reasonably more susceptible to inadequate effective crystalloid infusion and interstitial edema resulting from the rapid diffusion of glucose and water. Meanwhile, for those with serum triglyceride levels $>$ 200 mg/dl, fluid with high glucose density was a protective factor, which may be explained by the coadministration of glucose-containing water accompanied by insulin infusion, associated with better clinical outcomes in patients with hypertriglyceridemic AP [24]. More evidence is needed to determine the detrimental effects of high glucose density on vulnerable subgroups, especially female patients with AP.

Crystalloids containing approximately 140 mmol of sodium can transiently increase intravascular volume during fluid resuscitation. However, most glucose-containing balanced fluids in this study had suboptimal effective tonicity. This is because the glucose concentration in intravenous fluid inversely relates to that of sodium, meaning a high glucose density reduces the efficiency of fluid resuscitation. When an intravascular fluid deficit occurs, it leads to the hypoperfusion of target organs such as the heart, intestine, and pancreas, initiating danger-associated molecular patterns [25], that aggravate the systemic inflammatory response and increase the capillary permeability of the damaged organs. This creates a vicious cycle of hypovolemia and inflammation, resulting in OF, morbidity, and mortality.

In the dose-response analysis, cardiovascular failure was the most sensitive to a per-unit increase in glucose density, exhibiting an exponential increase in risk. This suggests a detrimental effect of high-glucose-containing fluids when volume expansion is required for microvascular hyperpermeability. Moreover, because many patients initially presented with an elevated creatinine level in a hypovolemic status, even before fluid challenge, the dose-response relationship for renal failure was not uncovered. However, after excluding those with day 1 renal failure, the risk of new-onset renal failure was found to be proportional to glucose density (Supplemental Fig. S1). Both cardiovascular and renal failures are vulnerable to hypoperfusion and tissue ischemia, which result from inadequate timely volume expansion with crystalloid fluid. This contributes to subsequent ICU admission, the risk of which is also proportional to glucose density. Respiratory failure, vulnerable to fluid overexpansion, is less likely to have a dose-responsive relationship with glucose density and inadequate volume expansion.

Considering the risk associated with the use of exceedingly high glucose-containing fluids in AP, several strengths of this study are noteworthy. Utilizing detailed electronic medical records allowed for precise identification and calculation of total glucose content and volume of fluid infusion, enabling exact glucose density estimates. Moreover, we carefully examined the total fluid volume and excluded patients receiving inadequate fluid resuscitation (less than 1000 ml per day on day 1). This exclusion criteria were applied because individuals receiving less than 1000 ml likely had mild AP and did not have a significant fluid deficit or did not receive appropriate fluid management. Lastly, we examined the dose-response relationship between glucose density and outcomes, revealing a dose-response relationship for cardiovascular failure and ICU admission.

This study faced some limitations. Firstly, the baseline characteristics were quite imbalanced, with an uneven distribution of factors including diabetes mellitus, age, fluid volume, hematocrit level, and treatment sites between the low- and high-glucose fluid groups. Nevertheless, all these factors were adjusted for and balanced in the multivariate and fluid volume-matched models, yielding similar results. Secondly, data on local complications were not available, yet ICU admissions and AP-related mortality were used as proxies, correlating with local infection complications. Thirdly, the study did explore the timing of nutritional intake resumption, although early enteral nutrition has been shown to reduce the risk of subsequent sepsis and complications. Fourthly, a considerable proportion of the patients had an unspecified etiology of AP. However, fluid therapy is so fundamental to the management of AP that its effects should be universal across different etiologies.

In conclusion, the overuse of glucose-containing fluids was associated with an increased risk of respiratory and cardiovascular OF and ICU admission. A dose-response relationship was observed between glucose density and AP outcomes, including early cardiovascular failure and ICU admission. The judicious use of glucose-containing fluids may decrease AP-related morbidity.

Funding

This study received financial support from the Department of Medical Research of the National Taiwan University Hospital and the National Taiwan University Cancer Center (NTUCCS-111-18).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT3.5 in order to revise the grammar of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Acknowledgements

The authors thank the staff of the Department of Medical Research for providing clinical data from the National Taiwan University Hospital-Integrative Medical Database and Mr. Shih-Hsiang Tseng, who helped with this project. We would like to thank Editage *(www.editage.com.twn)* for English language editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2024.05.022.

References

[1] Peery AF, Crockett SD, Murphy CC, Jensen ET, Kim HP, Egberg MD, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2021. Gastroenterology 2022;162:621–44.

[2] Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology 2022;162:122–34.

[3] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.

[4] Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2019;68:1044–51.

[5] Sternby H, Bolado F, Canaval-Zuleta HJ, Marra-López C, Hernando-Alonso AI, Del-Val-Antoñana A, et al. Determinants of severity in acute pancreatitis: a nation-wide multicenter prospective cohort study. Ann Surg 2019;270:348–55.

[6] de-Madaria E, Banks PA, Moya-Hoyo N, Wu BU, Rey-Riveiro M, Acevedo-Piedra NG, et al. Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. Clin Gastroenterol Hepatol 2014;12:997–1002.

[7] de-Madaria E, Soler-Sala G, Sánchez-Payá J, Lopez-Font I, Martínez J, Gómez-Escolar L, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol 2011;106:1843–50.

[8] Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol 2018;14:541–57.

[9] Warndorf MG, Kurtzman JT, Bartel MJ, Cox M, Mackenzie T, Robinson S, et al. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:705–9.

[10] Lee Y-C, Chao Y-T, Lin P-J, Yang Y-Y, Yang Y-C, Chu C-C, et al. Quality assurance of integrative big data for medical research within a multihospital system. J Formos Med Assoc 2022;121:1728–38.

[11] Yang Y-Y, Juan Y-C, Lee Y-C. Medical big data value creation: role of the hospital-based research database. J Formos Med Assoc 2023;122:809–11.

[12] Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288–94.

[13] Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The Apache III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619–36.

[14] National Institute for Health and Care Excellence (NICE). Pancreatitis. NG104 [updated 2020/12/16; accessed 2023/10/21]. Available from: https://www.nice.org.uk/guidance/ng104/chapter/Recommendations#acute-pancreatitis; 2020.

[15] IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1–15.

[16] Takada T, Isaji S, Mayumi T, Yoshida M, Takeyama Y, Itoi T, et al. JPN clinical practice guidelines 2021 with easy-to-understand explanations for the management of acute pancreatitis. J Hepatobiliary Pancreat Sci 2022;29:1057–83.

[17] Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:710–717.e1.

[18] de-Madaria E, Herrera-Marante I, González-Camacho V, Bonjoch L, Quesada-Vázquez N, Almenta-Saavedra I, et al. Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: a triple-blind, randomized, controlled trial. United European Gastroenterol J 2018;6:63–72.

[19] Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med 2015;41:1529–37.

[20] Bihari S, Watts NR, Seppelt I, Thompson K, Myburgh A, Prakash S, Bersten A. Maintenance fluid practices in intensive care units in Australia and New Zealand. Crit Care Resusc 2016;18:89–94.

[21] Johnson CD, Besselink MG, Carter R. Acute pancreatitis. BMJ Br Med J (Clin Res Ed) 2014;349:g4859.

[22] Singh VK, Gardner TB, Papachristou GI, Rey-Riveiro M, Faghih M, Koutroumpakis E, et al. An international multicenter study of early intravenous fluid administration and outcome in acute pancreatitis. United European Gastroenterol J 2017;5:491–8.

[23] Garg PK, Mahapatra SJ. Optimum fluid therapy in acute pancreatitis needs an alchemist. Gastroenterology 2021;160:655–9.

[24] Hoff A, Piechowski K. Treatment of hypertriglyceridemia with aggressive continuous intravenous insulin. J Pharm Pharmaceut Sci 2021;24:336–42.

[25] Hoque R, Malik AF, Gorelick F, Mehal WZ. Sterile inflammatory response in acute pancreatitis. Pancreas 2012;41:353–7.