Am J Transl Res 2026;18(1):583-595
www.ajtr.org /ISSN:1943-8141/AJTR0170428

Original Article

Ulinastatin-somatostatin combination for acute severe pancreatitis: enhanced clinical efficacy and reduced serum inflammation

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Received December 1, 2025; Accepted January 5, 2026; Epub January 15, 2026; Published January 30, 2026

Abstract: Objective: To analyze the clinical effect of ulinastatin (UTI)-somatostatin (SS) combination on acute severe pancreatitis (SAP) patients, focusing on changes in efficacy and serum inflammatory markers (IMs). Methods: This study retrospectively enrolled 104 SAP patients (July 2022-July 2025), with 51 patients (control group) treated with SS and 53 cases (observation group) receiving UTI+SS. Clinical efficacy, safety (rash, dizziness, diarrhea, nausea/vomiting, kidney injury, hyperglycemia), symptom relief time (vomiting, pyrexia, celialgia, defecation recovery, abdominal distension), disease-related indicators (blood amylase [AMS], Acute Physiology And Chronic Health Evaluation II [APACHE-II]), pancreatic function (insulin [INS], trypsinogen-2 [TPS2], glucose [Glu]), serum IMs (C-reactive protein [CRP], tumor necrosis factor [TNF]-α, interleukin [IL]-6), intestinal mucosal barrier function (diamine oxidase [DAO], D-lactic acid [D-Lac], endotoxin [ET]), laboratory-related indexes (total white blood cell count [WBC], platelet count [PLT], creatinine [Cr], total bilirubin [TBIL]), and humoral immunity (immunoglobulin [Ig] A/M/G) were comparatively assessed. Finally, determinants of patients' therapeutic effects were isolated by uni- and multivariate analyses. Results: UTI+SS was markedly superior to sole SS in terms of overall effectiveness, INS, PLT, and IgA/M/G, along with faster symptom relief, lower AMS, APACHE-II scores, TPS2, Glu, CRP, TNF-α, IL-6, DAO, D-Lac, WBC, Cr, and TBIL. Total adverse reaction incidence showed no notable inter-group difference. CRP and Cr were independent risk factors for therapeutic efficacy among SAP patients, while treatment modality acted as an independent protective factor. Conclusion: UTI+SS for SAP is effective in clinical efficacy enhancement and serum inflammation suppression.

Keywords: Acute severe pancreatitis, ulinastatin, somatostatin, clinical efficacy, cerum inflammatory markers

Introduction

As a common inflammatory disease in the gastrointestinal department, acute pancreatitis (AP) is a common cause of hospitalization, which causes a heavy burden on healthcare spending [1]. Biliary and alcoholic causes, as well as hyperlipidemia, are all common contributors to AP. In addition, heredity, smoking, post-endoscopic retrograde cholangiopancreatography, hypercalcemia, and pancreatic duct injury can also increase AP risk [2]. The main manifestations of the disease are severe celialgia and systemic inflammation, which worsen patients' health [3]. Though mostly mild in severity and self-limiting in nature, AP progresses to severe acute pancreatitis (SAP) in 20% [4]. SAP patients will develop local and/or systemic complications that induce respiratory, cardiovascular, renal, and liver failure and other multiple organ failures, even leading to death [5]. Given the current lack of specific pharmacotherapy approved for SAP, it is pressing to seek more effective drug management to inhibit early systemic inflammation in patients and effectively prevent the risk of subsequent organ failure [6].

https://doi.org/10.62347/PICX6135

Somatostatin (SS), a peptide hormone secreted by endocrine cells and the central nervous system, is implicated in regulating glucagon and insulin synthesis in the pancreas [7]. When applied to SAP, it is effective and can alleviate immuno-inflammatory responses [8]. It also assists in pancreatic duct pressure reduction and cytokine release inhibition, thus improving haemodynamics; however, its sole use exhibited limited curative effects [9]. As a broad-spectrum serine protease inhibitor, ulinastatin (UTI) has been used as the first-line therapy for AP in many Asian countries [10]. When applied to intensive care unit (ICU) patients, it effectively lowers mortality, shortens ICU stays, and reduces mechanical ventilation dependence [11]. Its use in combination therapies has also been indicated to further alleviate clinical symptoms among SAP patients, effectively inhibits inflammatory marker (IM) levels, and protects the intestinal mucosa, ultimately improving overall effectiveness [12].

The UTI-SS combination is insufficiently researched in the context of SAP. This study sheds further light on clinical SAP management through a multi-dimensional analysis.

Materials and methods

Case selection

Eligibility criteria: all the patients' diagnoses met the clinical diagnostic criteria for SAP [13]; the patients had not been treated with SAP before enrollment; the patients were aged 18-80, with an onset time ≤ 72 hours at the time of admission and normal communication/cognitive abilities.

Ineligibility criteria: existence of autoimmune or serious infectious diseases; pregnancy/lactation; other pancreatic/digestive diseases; previous pancreaticobiliary surgery; allergies to therapeutic drugs; severe organ dysfunction or malignant tumor; mental illness; defective clinical data.

This study adopts a retrospective design. Following ethical approval by the Tianjin Nan-Kai Hospital, Tianjin Medical University Ethics Committee and strict screening, 104 SAP patients (July 2022-July 2025) were selected: 51 patients in the control group received SS treatment, and 53 patients in the observation group received UTI+SS therapy. The patients were clinically comparable with no significant difference in general data found ($P > 0.05$).

Interventions

All patients received identical basic treatment, covering anti-infection therapy, timely rehydration, and gastrointestinal decompression. During the treatment, the patients in the two groups were closely monitored, and any adverse reactions were dealt with in time.

The control group was given SS (specification: 0.25 mg) at 6 mg/d by micropump for 24 hours, and the course of treatment was 14 days.

The observation group was additionally administered UTI: 100,000 units of UTI (specification: 1 ml: 50,000 units) were dissolved in 500 mL normal saline for three times a day over the 14-day treatment.

Importantly, the dosing and treatment course used followed routine clinical practice, which meant that it was a fixed scheme not adjusted individually based on the patient's specific weight, APACHE II score, or the dynamic change of the condition. This study adopted the fixed-dose regimen recommended in both domestic and international SAP treatment guidelines and clinical research (uromyostatin 100,000 U per dose, somatostatin 6 mg per day) [14], aiming to ensure consistency and comparability of the protocol; this strategy is also applicable to patients of different weights (21.65-22.08 kg/m^2), thus avoiding additional confounding biases caused by individualized dose adjustments. Additionally, the 14-day unified treatment course set in this study belongs to the common protocol used in clinical research for the key pathological physiologic processes during the acute phase of SAP, which ensures that the drugs continue to exert their effects within the core therapeutic window.

Data collection and outcome measurement

(1) Efficacy evaluation [15]. Clinical efficacy assessment was conducted following two weeks of treatment, categorized as marked effectiveness (celialgia, abdominal distension, and other clinical symptoms disappeared completely, with no tenderness in the upper abdomen and normalized laboratory indicators),

effectiveness (symptoms improved, tenderness in the upper abdomen disappeared, and clinical indicators basically returned to normal), or ineffectiveness (the patient experienced no improvement in symptoms, persistent upper abdomen tenderness or nausea/vomiting, and barely altered clinical indicators); total effectiveness rate = marked effectiveness rate + effectiveness rate.

(2) Safety evaluation. The number of patients experiencing post-therapy rashes, dizziness, diarrhea, nausea/vomiting, kidney injury (serum creatinine [Scr] > 26.5 mol/L), and hyperglycemia (blood glucose [Glu] > 10 mmol/L) was recorded to calculate the total incidence.

(3) Time to symptom relief. The time to relief of vomiting, pyrexia, celialgia, defecation recovery, and abdominal distension was recorded.

(4) Disease-related indicators. We sampled fasting venous blood (5 mL) from each patient pre- and post-treatment and isolated the serum by centrifugation to examine amylase (AMS) by the enzyme kinetic method. At the same time, the Acute Physiology and Chronic Health Evaluation II (APACHE II; range: 2 to 71) scores were comparatively analyzed. Worse conditions and poorer prognoses are indicated by higher scores [16].

(5) Pancreatic function. Enzyme-linked immunosorbent assays (ELISAs) were conducted pre- and post-intervention to detect insulin (INS), trypsinogen-2 (TPS2) and Glu in patients' serum.

(6) Serum IMs. We performed an enzyme-linked immunosorbent assay (ELISA) to measure per- and post-treatment serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

(7) Intestinal mucosal barrier (IMB) function. We carried out radioimmunoassay to quantify pre- and post-interventional serum diamine oxidase (DAO), D-lactic acid (D-LA), and endotoxin (ET).

(8) Laboratory-related indicators. The pre- and post-interventional determination of white blood cell count (WBC), platelet count (PLT), creatinine (Cr), and total bilirubin (TBIL) in serum was conducted with the help of an automatic biochemical analyzer.

(9) Humoral immunity indices. ELISA examined immunoglobulin (Ig)A, IgM, and IgG levels in patients' serum prior to and following the intervention.

Statistical methods

Measured data and counted data were imported into SPSS 20.0 for statistical analysis. Shapiro-Wilk test-based normality testing was performed for measured data. If a normal distribution was followed, the data were presented as mean ± SD, with comparisons made using the independent sample t-test (between groups) and the paired t-test (pre- vs. post-intervention within groups); otherwise, the data were statistically described as the median (interquartile range) [M (Q1, Q3)], with between-group differences examined by a Mann-Whitney U test. The number of cases/percentage (n/%) is used to represent the counted data, whose comparative analyses employed the χ^2 test. Repeated measures analysis of variance was used to compare pre- and post-treatment changes in various indices in both cohorts, so as to test the time of main effect and the group-by-time interaction. In case of significant interaction effects, a simple effect analysis was carried out to clarify the specific differences. Uni- and multivariate (Logistic regression) approaches explored patients' curative efficacy-associated determinants. $P < 0.05$ was deemed significant.

Results

General information in the two groups

Sex, age, disease duration, body mass index (BMI), etiology, hypertension, diabetes, and liver dysfunction showed no marked differences between the control and observation groups ($P > 0.05$), validating group comparability (**Table 1**).

Clinical efficacy assessment

The groups exhibited a difference in total effectiveness rate ($P < 0.05$), favoring the observation group ($P = 0.031$; **Table 2**).

Clinical safety evaluation

The control and observation cohorts demonstrated no statistical difference in clinical sa-

Table 1. General information

Data	Control group (n = 51)	Observation group (n = 53)	χ^2/t	P
Sex			0.691	0.406
Male	32 (62.75)	29 (54.72)		
Female	19 (37.25)	24 (45.28)		
Age (years)	48.12 ± 8.33	48.42 ± 7.89	0.189	0.851
Disease duration (h)	9.78 ± 2.01	9.66 ± 1.95	0.309	0.758
Body mass index (kg/m^2)	21.65 ± 1.73	22.08 ± 2.25	1.090	0.279
Pathogeny			0.755	0.686
Biliary	28 (54.90)	26 (49.06)		
Alcoholic	18 (35.29)	19 (35.85)		
Hyperlipidaemia	5 (9.80)	8 (15.09)		
Hypertension			0.365	0.546
No	41 (80.39)	40 (75.47)		
Yes	10 (19.61)	13 (24.53)		
Diabetes			0.738	0.390
No	42 (82.35)	40 (75.47)		
Yes	9 (17.65)	13 (24.53)		
Liver dysfunction			0.772	0.380
No	16 (31.37)	21 (39.62)		
Yes	35 (68.63)	32 (60.38)		

Note: The criteria for liver dysfunction are alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal value and/or total bilirubin (TBil) > 2 times the upper limit of normal value at any timepoint during hospitalization.

Table 2. Clinical efficacy assessment

Category	Control group (n = 51)	Observation group (n = 53)	χ^2	P
Marked effectiveness	19 (37.25)	27 (50.94)		
Effectiveness	19 (37.25)	21 (39.62)		
Ineffectiveness	13 (25.49)	5 (9.43)		
Overall effectiveness	38 (74.51)	48 (90.57)	4.682	0.031

Table 3. Clinical safety evaluation

Category	Control group (n = 51)	Observation group (n = 53)	χ^2	P
Rash	2 (3.92)	3 (5.66)		
Dizziness	1 (1.96)	2 (3.77)		
Diarrhea	1 (1.96)	1 (1.89)		
Nausea/vomiting	2 (3.92)	2 (3.77)		
Kidney injury	2 (3.92)	3 (5.66)		
Hyperglycemia	3 (5.88)	5 (9.43)		
Total	11 (21.57)	16 (30.19)	1.005	0.316

fety (P > 0.05), evidenced by similar incidences of rashes, dizziness, diarrhea, nausea/vomiting, kidney injury, and hyperglycemia (21.57% vs. 30.19%; **Table 3**).

Time to symptom relief analysis

This study comparatively analyzed the time to remission of symptoms such as vomiting, pyrexia, celialgia, defecation recovery, and abdominal distension. In comparison to controls, the time for relief of the above symptoms in the observation group was significantly shorter (P < 0.05; **Figure 1**).

Comparative evaluation of disease-related indicators

Patients' conditions were assessed based on AMS and APACHE-II. The data revealed equivalent baseline indexes (P > 0.05). The treatment induced an obvious decline in both indices across groups (P < 0.01), with better performance (lower AMS and APACHE-II values) in the observation group (P < 0.01; **Figure 2**).

Pancreatic function-related indicators in the two groups

The pancreatic function-related indicators, INS, TPS2, and Glu, were compared and evaluated between the two groups. Analysis showed no significant differences in any pancreatic function-related indicators between the two groups before intervention (P > 0.05). After intervention, INS was significantly upregulated in both groups, and significantly higher in the observation group (P < 0.05). TPS2 and Glu were significantly downregulated in both groups after intervention, and significantly lower in the observation group (P < 0.05). See **Table 4**.

Serum inflammatory markers

Serum levels of IMs (CRP, TNF-α, and IL-6) were comparatively evaluated. After analysis, these

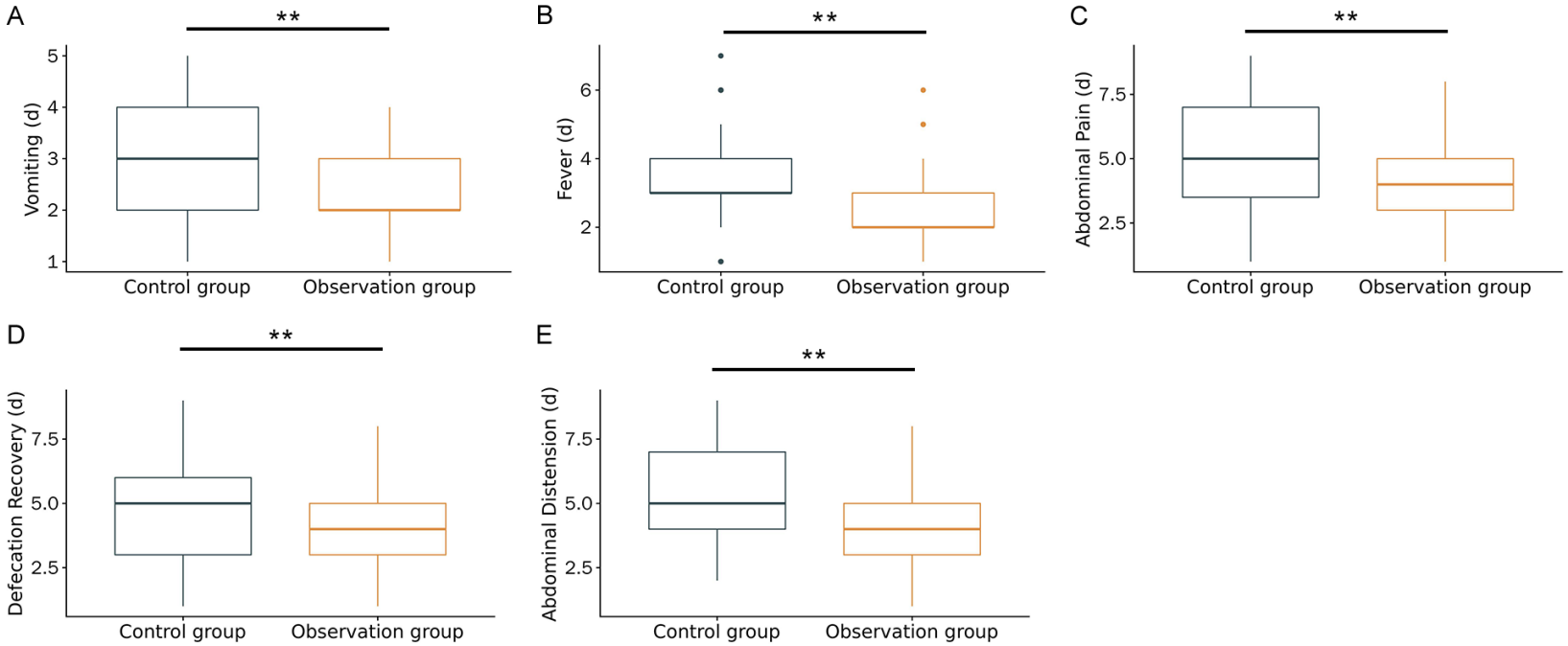

Figure 1. Symptom remission time. A. Vomiting relief time of both groups. B. Time to pyrexia relief across groups. C. Time to celialgia relief. D. Time to defecation recovery. E. Time to abdominal distension relief. Note: **P < 0.01.

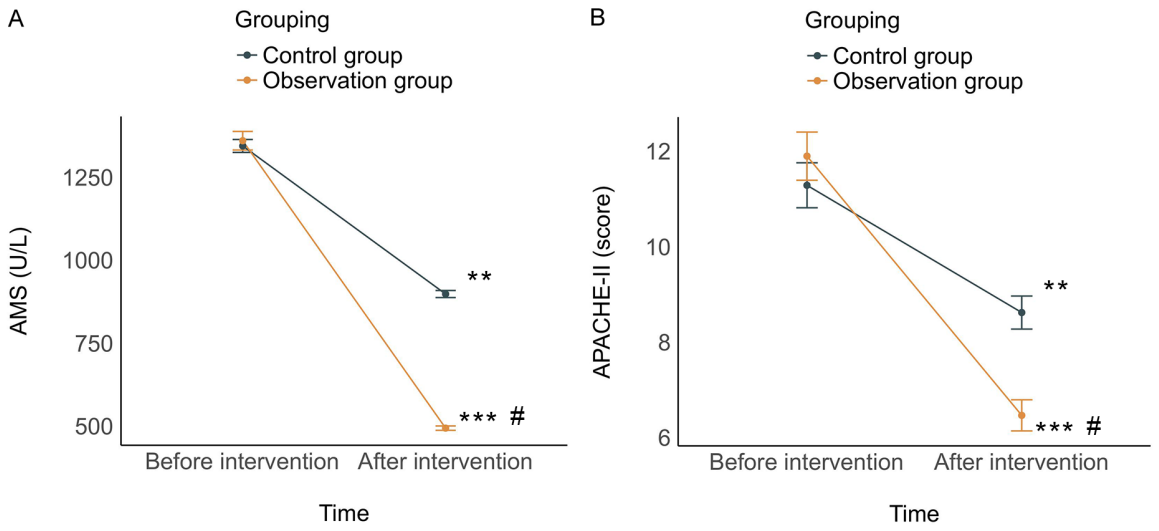

Figure 2. Disease-related indicators. A. AMS pre- and post-intervention. B. Pre- and post-interventional APACHE-II scores. Note: **P < 0.01, ***P < 0.001 vs. pre-intervention; #P < 0.01 vs. control group. AMS, blood amylase; APACHE-II, Acute Physiology and Chronic Health Evaluation II.

Table 4. Pancreatic function-related indicators in the two groups

Condition	Control group (n = 51)	Observation group (n = 53)	t	P
INS (mU/L)				
Before intervention	4.35 ± 1.88	4.42 ± 2.01	0.183	0.855
After intervention	5.80 ± 1.83**	7.15 ± 2.53***	3.108	0.002
TPS2 (ng/mL)				
Before intervention	59.33 ± 6.01	61.15 ± 7.27	1.389	0.168
After intervention	14.02 ± 3.62**	9.94 ± 2.27***	2.760	0.007
Glu (mmol/L)				
Before intervention	183.90 ± 10.57	187.74 ± 15.61	1.463	0.147
After intervention	88.35 ± 6.24**	81.74 ± 7.13***	5.023	< 0.001

Note: **P < 0.01, ***P < 0.001 vs. pre-intervention. INS, insulin; TPS2, trypsinogen-2; Glu, glucose.

serum IMs did not differ much across groups at baseline (P > 0.05), but were significantly lower in both cohorts post-intervention (P < 0.05; **Table 5**).

IMB function comparison

How the IMB function varied pre- and post-intervention was assessed by measuring DAO, D-Lac, and ET. Baseline levels were comparable across groups (P > 0.05). A decrease from baseline was noted in both cohorts post-treatment (P < 0.05), with even lower DAO, D-Lac, and ET in the observation group (P < 0.001; **Table 6**).

Laboratory-related indices

WBC, PLT, Cr, and TBIL were the laboratory-related indices examined. The above indexes differed non-significantly across groups prior to the intervention (P > 0.05). Except a rise in PLT, all other indices presented a drop in both arms post-therapy (P < 0.01), with the amplitude of these changes being more pronounced in the observation group (P < 0.01; **Table 7**).

Humoral immunity comparison

IgA/M/G measurements were conducted for humoral immunity assessment. The groups were also similar in baseline measurements (P > 0.05); IgA/M/G increased across groups following the intervention (P < 0.05), particularly in the observation group (P < 0.05; **Table 8**).

Efficacy determinants in SAP patients

Through the univariate method, we excluded sex, age, disease duration, BMI, etiology, liver

Table 5. Serum inflammation analysis

Category	Control group (n = 51)	Observation group (n = 53)	t	P
CRP (mg/L)				
Before intervention	299.43 ± 25.62	301.43 ± 29.69	0.367	0.714
After intervention	177.94 ± 29.40**	127.09 ± 25.34***	9.459	< 0.001
TNF-α (ng/L)				
Before intervention	66.69 ± 16.63	66.13 ± 26.01	0.130	0.897
After intervention	34.61 ± 8.42**	21.92 ± 5.77***	8.995	< 0.001
IL-6 (ng/L)				
Before intervention	81.45 ± 8.19	80.55 ± 8.21	0.560	0.577
After intervention	50.67 ± 7.61**	31.36 ± 6.82***	13.639	< 0.001

Note: **P < 0.01, ***P < 0.001 vs. pre-intervention. CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Table 6. Intestinal mucosal barrier function assessment

Category	Control group (n = 51)	Observation group (n = 53)	t	P
DAO (U/mL)				
Before intervention	5.84 ± 1.98	5.71 ± 2.08	0.326	0.745
After intervention	3.83 ± 1.19*	2.46 ± 1.00**	6.365	< 0.001
D-Lac (μg/L)				
Before intervention	12.53 ± 4.35	12.30 ± 3.66	0.292	0.771
After intervention	9.04 ± 2.23*	6.06 ± 2.07**	7.066	< 0.001
ET (ng/L)				
Before intervention	2.21 ± 0.83	2.26 ± 0.81	0.311	0.757
After intervention	1.25 ± 0.47*	0.81 ± 0.42**	5.038	< 0.001

Note: *P < 0.05, **P < 0.01 vs. pre-intervention. DAO, diamine oxidase; D-Lac, D-lactic acid; ET, endotoxin.

Table 7. Laboratory-related indices

Category	Control group (n = 51)	Observation group (n = 53)	t	P
WBC (10^9/L)				
Before intervention	17.27 ± 3.86	17.42 ± 3.83	0.199	0.843
After intervention	15.24 ± 3.55**	12.89 ± 2.21***	4.069	< 0.001
PLT (10^9/L)				
Before intervention	78.98 ± 11.13	77.38 ± 9.72	0.782	0.436
After intervention	96.10 ± 10.45**	107.85 ± 12.18***	5.272	< 0.001
Cr (μmol/L)				
Before intervention	149.12 ± 17.65	146.58 ± 19.65	0.693	0.490
After intervention	136.71 ± 17.83**	126.51 ± 17.14***	2.975	0.004
TBIL (μmol/L)				
Before intervention	46.04 ± 11.00	46.13 ± 8.88	0.046	0.963
After intervention	40.49 ± 8.82**	33.87 ± 6.32***	4.413	< 0.001

Note: **P < 0.01, ***P < 0.001 vs. pre-intervention. WBC, white blood cell count; PLT, platelet count; Cr, creatinine; TBIL, total bilirubin.

dysfunction, AMS, APACHE-II, INS, TPS2, Glu, TNF-α, IL-6, DAO, D-Lac, ET, WBC, PLT, TBIL, IgA, IgM, and IgG as significant correlates of efficacy in SAP patients (P > 0.05); hypertension, diabetes, CRP, Cr, and treatment modality, on the other hand, all exhibited a close connection with efficacy (P < 0.05). Comorbid hypertension and diabetes, as confirmed by

Table 8. Humoral immunity evaluation

Category	Control group (n = 51)	Observation group (n = 53)	t	P
IgA (g/L)				
Before intervention	3.84 ± 1.51	4.35 ± 1.33	1.830	0.070
After intervention	5.18 ± 1.59*	6.11 ± 1.95**	2.660	0.009
IgM (g/L)				
Before intervention	1.15 ± 0.24	1.06 ± 0.28	1.757	0.082
After intervention	1.95 ± 0.63*	2.46 ± 0.76**	3.718	< 0.001
IgG (g/L)				
Before intervention	10.47 ± 2.75	9.89 ± 2.48	1.130	0.261
After intervention	13.47 ± 2.26*	17.09 ± 3.88**	5.785	< 0.001

Note: **P < 0.01, *P < 0.05 vs. pre-intervention. Ig, immunoglobulin.

multivariate logistic regression, were not independent determinants of efficacy, while CRP, Cr, and treatment modality each exerted an independent and significant effect (P < 0.05; **Tables 9**, **10**).

Discussion

First, we found higher curative effects in severe acute pancreatitis (SAP) patients receiving ulinastatin (UTI)-somatostatin (SS). As a potent exocrine pancreatic secretion inhibitor, SS can reduce pancreatic enzyme and juice secretions by inhibiting the activities of Toll receptors and nuclear factor (NF)-κB, IM production, and vagus nerve excitement, thus playing an effective anti-SAP therapeutic role [17]. Beyond blocking the activity of multiple proteases like trypsin and elastase, UTI is able to inhibit inflammatory cytokines and remove free oxygen, thus exerting anti-inflammatory and antioxidant effects and hindering SAP progression [14]. The therapeutic effect of the two drugs on SAP is achieved through different pathways, which can synergistically enhance anti-SAP efficacy. Our safety assessment revealed the non-inferiority of UTI+SS to sole SS for SAP treatment, reflected in a comparable total incidence of adverse reaction. In a randomized controlled trial-based systematic review and meta-analysis, the combined therapy also demonstrated higher efficacy than SS alone in shortening hospital stays, with the same impact on mortality, complementing our results [18]. UTI + octreotide (a SS analogue) has also been shown to significantly improve curative effects while exhibiting equivalent adverse reaction rates to monotherapy [19], aligning with our findings. In the report of Zhang et al. [20], ilaprazole + SS applied to SAP patients enhanced therapeutic effectiveness without increasing the side effects of medication, validating our observations. In terms of symptom relief, the combination therapy featured significantly shorter time to relieve symptoms (vomiting, pyrexia, celialgia, defecation recovery, and abdominal distension) than monotheapy. This may be because the combination therapy achieved higher curative effects and promoted the rapid relief and improvement of patients' clinical symptoms and clinical indicators. Similarly, UTI + glutamine for SAP has been reported to accelerate the resolution of abdominal distension and celialgia, hasten the time to the first defecation and intestinal sound recovery, enhance humoral immunity, and effectively inhibit serum inflammation [21]. Regarding disease remission, UTI+SS led to marked AMS down-regulation and APACHE-II score reductions in SAP patients, suggesting the efficacy of the combined therapy for significantly alleviating patients' conditions. This is possibly attributed to the marked and comprehensive improvement effect on all dimensions from combined therapy, collectively reducing disease progression. Chen et al. [22] conducted research on UTI+SS use in SAP cases, noting its ability to effectively inhibit AMS and its role as an independent determinant of better prognosis.

On the other hand, UTI+SS-treated SAP patients displayed significantly improved pancreatic function, manifested by more significant up-regulation of INS and more significant down-regulation of TPS2 and Glu. We also noted a suppressed serum inflammation in patients treated with UTI+SS, with greater CRP, TNF-α, and IL-6 down-regulation than in solely

Table 9. Therapeutic efficacy determinants in SAP patients (univariate analysis)

Category	n	Ineffective group (n = 18)	Effective group (n = 86)	χ^2	P
Sex				0.054	0.816
Male	61	11 (61.11)	50 (58.14)		
Female	43	7 (38.89)	36 (41.86)		
Age (years)				0.294	0.588
< 48	46	9 (50.00)	37 (43.02)		
≥ 48	58	9 (50.00)	49 (56.98)		
Disease duration (h)				1.075	0.300
< 10	52	7 (38.89)	45 (52.33)		
≥ 10	52	11 (61.11)	41 (47.67)		
Body mass index (kg/m^2)				1.883	0.170
< 22	44	5 (27.78)	39 (45.35)		
≥ 22	60	13 (72.22)	47 (54.65)		
Pathogeny				4.671	0.097
Biliary	54	8 (44.44)	46 (53.49)		
Alcoholic	37	5 (27.78)	32 (37.21)		
Hyperlipidemia	13	5 (27.78)	8 (9.30)		
Hypertension				6.301	0.012
No	81	10 (55.56)	71 (82.56)		
Yes	23	8 (44.44)	15 (17.44)		
Diabetes				4.105	0.043
No	82	11 (61.11)	71 (82.56)		
Yes	22	7 (38.89)	15 (17.44)		
Hepatic dysfunction				0.104	0.747
No	37	7 (38.89)	30 (34.88)		
Yes	67	11 (61.11)	56 (65.12)		
AMS (U/L)				1.565	0.211
< 1360	60	8 (44.44)	52 (60.47)		
≥ 1360	44	10 (55.56)	34 (39.53)		
APACHE-II (points)				2.148	0.143
< 12	53	12 (66.67)	41 (47.67)		
≥ 12	51	6 (33.33)	45 (52.33)		
INS (mU/L)				0.032	0.858
< 4.5	54	9 (50.00)	45 (52.33)		
≥ 4.5	50	9 (50.00)	41 (47.67)		
TPS2 (ng/mL)				0.005	0.944
< 60	47	8 (44.44)	39 (45.35)		
≥ 60	57	10 (55.56)	47 (54.65)		
Glu (mmol/L)				0.591	0.442
< 185	49	7 (38.89)	42 (48.84)		
≥ 185	55	11 (61.11)	44 (51.16)		
CRP (mg/L)				5.413	0.020
< 300	49	4 (22.22)	45 (52.33)		
≥ 300	55	14 (77.78)	41 (47.67)		
TNF-α (ng/L)				0.115	0.735
< 67	54	10 (55.56)	44 (51.16)		
≥ 67	50	8 (44.44)	42 (48.84)		

IL-6 (ng/L)				0.736	0.391
< 82	54	11 (61.11)	43 (50.00)		
≥ 82	50	7 (38.89)	43 (50.00)		
DAO (U/mL)				3.685	0.055
< 5.8	56	6 (33.33)	50 (58.14)		
≥ 5.8	48	12 (66.67)	36 (41.86)		
D-Lac (μg/L)				1.075	0.300
< 12.5	52	7 (38.89)	45 (52.33)		
≥ 12.5	52	11 (61.11)	41 (47.67)		
ET (ng/L)				0.488	0.485
< 2.3	54	8 (44.44)	46 (53.49)		
≥ 2.3	50	10 (55.56)	40 (46.51)		
WBC (10^9/L)				0.897	0.344
< 17.5	53	11 (61.11)	42 (48.84)		
≥ 17.5	51	7 (38.89)	44 (51.16)		
PLT (10^9/L)				0.736	0.391
< 78	54	11 (61.11)	43 (50.00)		
≥ 78	50	7 (38.89)	43 (50.00)		
Cr (μmol/L)				5.952	0.015
< 150	56	5 (27.78)	51 (59.30)		
≥ 150	48	13 (72.22)	35 (40.70)		
TBIL (μmol/L)				0.184	0.668
< 46	51	8 (44.44)	43 (50.00)		
≥ 46	53	10 (55.56)	43 (50.00)		
IgA (g/L)				0.184	0.668
< 4.2	53	10 (55.56)	43 (50.00)		
≥ 4.2	51	8 (44.44)	43 (50.00)		
IgM (g/L)				0.402	0.526
< 1.2	59	9 (50.00)	50 (58.14)		
≥ 1.2	45	9 (50.00)	36 (41.86)		
IgG (g/L)				2.419	0.120
< 10.5	52	12 (66.67)	40 (46.51)		
≥ 10.5	52	6 (33.33)	46 (53.49)		
Treatment modality				4.682	0.031
Somatostatin	51	13 (72.22)	38 (44.19)		
Ulinastatin + somatostatin	53	5 (27.78)	48 (55.81)		

Note: BMI, body mass index; AMS, amylase; APACHE II, Acute Physiology And Chronic Health Evaluation II; INS, insulin; TPS2, trypsinogen-2; Glu, glucose; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; DAO, diamine oxidase; D-LA, D-lactic acid; ET, endotoxin; WBC, white blood cell count; PLT, platelet count; Cr, creatinine; TBIL, total bilirubin; Ig, immunoglobulin.

Table 10. Therapeutic efficacy determinants in SAP patients (multivariate analysis)

Variable	B	Standard error	Wald	P	OR	95% CI
Hypertension	1.103	0.660	2.793	0.095	3.014	0.826-10.995
Diabetes	1.165	0.684	2.896	0.089	3.205	0.838-12.253
CRP (mg/L)	1.708	0.723	5.580	0.018	5.519	1.338-22.770
Cr (μmol/L)	1.674	0.675	6.142	0.013	5.333	1.419-20.042
Treatment modality	-1.311	0.639	4.216	0.040	0.270	0.077-0.942

Note: CRP, C-reactive protein; Cr, creatinine.

SS-treated counterparts. These benefits can be explained by the inhibitory effect of UTI on trypsin, elastase, chymotrypsin, and hyaluronidase, thus effectively down-regulating various inflammatory factors to achieve inflammation suppression [23]. In a meta-analysis, Bandyopadhyay et al. [24] showed the effective anti-inflammatory effect of UTI, mainly by significantly inhibiting CRP, TNF-α, and IL-6 in SAP patients, which verified our data. UTI-loaded biomimetic nanoparticles have been suggested as a targeted therapy for AP management [25], effectively inhibiting pro-IMs, maintaining cell viability, and exerting excellent anti-inflammatory effects, which provides a new direction for SAP treatment. In this study, UTI+SS achieved Intestinal mucosal barrier (IMB) protection by significantly down-regulating DAO, D-Lac, and ET. The protective mechanism of UTI on IMB function in SAP patients may be related to its activation of the nuclear factor E2-related factor 2 (Nrf2) signaling pathway and inhibition of macrophage 1 (M1) polarization [26]. SS can be used as a powerful inhibitor of various gastrointestinal functions (peristalsis, hormone secretion, and gastric acid production), with its anti-inflammatory effect being instrumental in promoting intestinal barrier integrity [27]. The above indications suggest that UTI and SS exert IMB protection actions through distinct pathways, which may help explain the combined treatment's synergistic preservation of the IMB function. Under the intervention of combination therapy, WBC, Cr, and TBIL were effectively decreased while PLT was increased, suggesting the excellent capacity of the combination therapy for protecting organ function among SAP patients. This effect may be related to UTI-mediated immunomodulation. For example, Pan et al. [28] reported that UTI relieved systemic inflammation and tissue damage in SAP by up-regulating the proportion of regulatory T cells (Tregs) and inhibiting the release of pro-IMs, which also helps to partially explain its improvement on humoral immunity. The humoral immunity test showed more effective up-regulation of IgA/M/G levels by UTI+SS, causing humoral immunity enhancement. Finally, CRP ≥ 300 mg/L, Cr ≥ 150 μmol/L, and sole SS intervention were found by regression analysis to increase the risk of ineffective treatment. A CRP level of 300 mg/L or higher may indicate a severe inflammatory state that is difficult to reverse and could potentially lead to irreversible organ damage, thereby increasing the risk of ineffective treatment; Cr ≥ 150 μmol/L signifies a relatively severe form of acute kidney injury, where renal function can hardly ensure drug metabolism and clearance, compromising curative effect maximization; SS intervention alone may only play a partial anti-inflammatory role by inhibiting pancreatic secretion, with insufficient control of the pathologic progression of SAP, thus leading to a relatively increased risk of treatment failure.

There were several limitations in this study. First, given that this study was a retrospective exploratory analysis, the current sample size had limited statistical power for multiple comparisons. Therefore, positive findings should be interpreted with caution, and large-sample prospective studies are needed for further verification. Second, the detection of key pathway molecules, such as Nrf2, NF-κB, and the M1 macrophage marker inducible nitric oxide synthase (iNOS), was not carried out. Supplementary relevant analyses would contribute to further elaborating on the mechanism of UTI+SS for SAP treatment. The third limitation was about the applicability of the thresholds of CRP ≥ 300 mg/L and Cr ≥ 150 μmol/L to other SAP patients, which needs further verification in future prospective and multi-center studies. Finally, individualized adjustments were not made according to the patient's specific body weight, APACHE II score, or dynamic changes in the condition. Future prospective studies can further explore individualized dosing strategies to optimize treatment strategies.

Taken together, UTI+SS can significantly improve curative effects in SAP patients while not significantly increasing the risk of total adverse reactions. Other benefits include shortened time to symptom relief, hindered disease progression, enhanced pancreatic function, inhibited serum inflammation, as well as IMB, organ, and immune function preservation. Meanwhile, for cases in which clinical indices such as CRP ≥ 300 mg/L, Cr ≥ 150 μmol/L, and SS intervention alone are present, the risk of ineffective treatment would be elevated.

Acknowledgements

This work was supported by Construction Project of Tianjin Medical Key Discipline, General

Surgery, TJYXZDXK-3-028C; and Key project of Scientific Research Program of Tianjin Education Commission, Research on the establishment of AI individualized evaluation system for acute pancreatitis complicated with pancreatic necrosis based on pancreatic m6A methylation and CT radiomics, 2024ZD043.

Disclosure of conflict of interest

None.

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