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Original Article

Effect of octreotide combined with ulinastatin on the creatinine-to-albumin ratio and systemic immune-inflammation index in patients with severe acute pancreatitis

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Abstract: Objective: To evaluate the effects of combined octreotide and ulinastatin therapy on the serum creatinine-to-albumin ratio (CAR) and systemic immune-inflammation index (SII) in patients with severe acute pancreatitis (SAP), and to investigate its impact on inflammatory markers, organ function, and clinical outcomes. Methods: This single-center, retrospective cohort study included 240 SAP patients admitted to Northwest University Affiliated Xi'an No. 3 Hospital between October 2021 and April 2023. The control group (n=112) received octreotide 0.1 mg subcutaneously every 8 hours, while the observation group (n=128) received ulinastatin 100,000 U intravenously once daily for 7-14 days. Primary outcomes included 28-day mortality, Intensive care unit (ICU) stay, hospital stay, and 1-year recurrence. Secondary outcomes included CAR, SII, creatinine (Cr), serum amylase, albumin (Alb), C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6), measured on days 1, 3, 7, and 14. Complications and adverse events were recorded based on standardized criteria. Results: From days 1 to 14, the observation group exhibited larger reductions in CAR and SII, lower Cr, CRP, PCT, and IL-6, and higher Alb (all $P<0.05$). Combined therapy reduced the 28-day mortality ($P=0.038$), 1-year recurrence ($P=0.016$), and the overall complication rate ($P=0.003$). Day-14 CAR and SII effectively predicted 28-day mortality and 1-year recurrence with an area under the curve greater than 0.7. Conclusions: The addition of ulinastatin to octreotide therapy in SAP significantly reduces inflammation and organ injury, improving short-term survival and decreasing mid-term recurrence. CAR and SII are promising prognostic biomarkers.

Keywords: Severe acute pancreatitis, octreotide, ulinastatin, serum creatinine-to-albumin ratio, systemic immune-inflammation index, inflammatory markers, prognosis

Introduction

Acute pancreatitis (AP) is a common and potentially life-threatening digestive disorder, characterized by autodigestive inflammation of the pancreas. A meta-analysis spanning 1961 to 2016 reported a global AP incidence increase of 3.07% per year [1]. Although most patients with mild AP experience a short clinical course and favorable prognosis, approximately 20-30% progress to severe acute pancreatitis (SAP). SAP is characterized by pancreatic necrosis, systemic inflammatory response, and multiple organ dysfunction, with a mortality rate of 15-20% [2, 3]. Its pathogenesis involves premature activation of pancreatic enzymes, excessive release of inflammatory mediators, and a cascade of oxidative stress reactions, culminating in systemic inflammatory response syndrome (SIRS) and organ failure [4, 5]. Despite advances in supportive care, such as aggressive fluid resuscitation and continuous renal replacement therapy, effectively controlling excessive inflammation and preventing organ injury remains a major clinical challenge [6, 7]. Consequently, multi-targeted pharmacotherapy

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aimed at modulating inflammation and preserving organ function has become a key focus of research.

Octreotide, a synthetic somatostatin analogue, reduces pancreatic injury by inhibiting enzyme secretion, decreasing vascular permeability, and modulating immune cell activity [8]. Clinical studies have shown that octreotide significantly lowers serum amylase (AMY) and C-reactive protein (CRP) levels in SAP patients and alleviates intra-abdominal hypertension [9]. Ulinastatin, a broad-spectrum protease inhibitor, directly suppresses trypsin and elastase activity and exerts anti-inflammatory effects by blocking the nuclear factor-κB (NF-κB) pathway, reducing the release of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). It also provides antioxidant benefits and improves microcirculation [10, 11]. However, high-quality evidence on the combined use of these agents in SAP is lacking.

The creatinine-to-albumin ratio (CAR) and the systemic immune-inflammation index (SII) have recently emerged as composite prognostic markers in critically ill patients. CAR combines renal function and nutritional status, sensitively reflecting organ impairment in SAP. SII, calculated from neutrophil, lymphocyte, and platelet counts, provides a comprehensive measure of systemic inflammation and immune dysregulation. To date, most studies have focused on the effects of single agents on traditional inflammatory markers (e.g., CRP, IL-6), with few investigating the dynamic changes and clinical implications of novel biomarkers such as CAR and SII under combination therapy.

This study aims to evaluate the effects of octreotide combined with ulinastatin on CAR and SII in SAP patients and to assess the regimen's efficacy in controlling inflammation, preserving organ function, and improving short-term outcomes.

Materials and methods

Study design

This was a single-center retrospective cohort study that included 232 SAP patients admitted to Northwest University Affiliated Xi'an No. 3 Hospital and Xianyang First People's Hospital between October 2021 and April 2023.

Grouping and interventions: Patients were divided into a control group and an observation group. The control group received conventional treatment, including octreotide, while the observation group received conventional treatment plus octreotide and ulinastatin. All patients received standardized comprehensive SAP treatment, which included fluid resuscitation, fasting with gastrointestinal decompression, antibiotic infection control, analgesia, acid suppression, and nutritional support. The control group received octreotide (0.1 mg, subcutaneously every 8 hours, purchased from Zhejiang Zhenyuan Pharmaceutical Co., Ltd., Lot No. 210116) until symptoms improved. The observation group received additional ulinastatin (100,000 U, intravenous infusion, once daily, purchased from Guangdong Techpool Pharmaceutical Co., Ltd., Lot No. 200637) for 7-14 days, with adjustments made according to clinical condition.

Data sources: Baseline data (demographics, medical history, laboratory and imaging data), treatment process records (medications, vital signs, complications), and outcome data (hospital stay, mortality, recurrence) were extracted from the hospital's electronic medical record system (EMR), laboratory information system (LIS), and picture archiving and communication system (PACS).

Ethical approval: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the ethical guidelines for medical research involving human participants. It was approved by the Medical Ethics Review Committee of Xianyang First People's Hospital.

Patient selection

Inclusion criteria: (1) Aged ≥18 years; (2) Diagnosed with SAP, meeting the following diagnostic criteria: persistent organ failure (respiratory, circulatory, or renal failure lasting more than 48 hours); enhanced computed tomography (CT) showing pancreatic necrosis of ≥30% or a CT severity index (CTSI) of ≥4 points; AMY rising to >500 U/dl a few hours after onset and urinary amylase rising 24 hours after onset [12]; an acute physiology and

chronic health evaluation (APACHE) II score of ≥8 points or a sequential organ failure assessment (SOFA) score of ≥5 points [13]; (3) Received at least 72 hours of standardized treatment after admission, with complete clinical data (including baseline and laboratory indicators on days 1, 3, 7, and 14 post-treatment).

Exclusion criteria: (1) Comorbid malignancies, immunodeficiency diseases, chronic organ failure (e.g., end-stage renal disease), or pregnancy; (2) Death within 24 hours of admission, voluntary discharge, or transfer; (3) Missing key data.

Final sample size: Initially, 232 cases were included. After data cleaning, 4 cases from the control group were excluded due to missing key data, resulting in 112 cases in the control group and 128 cases in the observation group.

Study variables and outcome definitions

Primary outcomes: (1) 28-day all-cause mortality: Defined as death from any cause within 28 days of admission, confirmed by medical records, death certificates, or family follow-up via telephone. (2) Hospital stay: Calculated as the number of days from hospital admission to discharge, excluding delays due to non-medical reasons (e.g., social issues). (3) ICU stay: Defined as the number of days from ICU admission to ICU discharge. ICU admission criteria followed the hospital's standard protocol (e.g., need for mechanical ventilation, vasopressor support, or close monitoring of organ failure). (4) 1-year recurrence rate: Defined as rehospitalization for acute pancreatitis (meeting the 2012 Atlanta Classification criteria) in surviving patients, confirmed by review of medical records or telephone follow-up at 12 months post-discharge.

Secondary outcomes: (1) Dynamic changes in laboratory indicators: Detected at baseline and on days 1, 3, 7, and 14 post-treatment.

Inflammatory indicators: C-reactive protein (CRP) was measured by immunoturbidimetry using a kit from Siemens Healthineers Diagnostics Products (Shanghai) Co., Ltd. (Lot No. 211423); procalcitonin (PCT) was measured by chemiluminescence using a kit from Zhejiang Yilikang Biotechnology Co., Ltd. (Lot No. 203365); and interleukin-6 (IL-6) was measured by ELISA using a kit from Shanghai Jianglai Biotechnology Co., Ltd. (Lot No. 803461).

Organ function indicators: Creatinine (Cr), albumin (Alb), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR).

Composite indicators: creatinine/albumin ratio (CAR), systemic immune-inflammation index (SII), calculated as platelet × neutrophil/lymphocyte.

(2) Complications and adverse reactions: Complications included pancreatic necrosis (CT showing non-enhancing area ≥30%), septic shock (Sepsis 3.0 criteria) [14], hypotension unresponsive to fluid resuscitation, with lactate >2 mmol/L, Acute Respiratory Distress Syndrome (ARDS) (Berlin definition, hypoxemia, Partial pressure of arterial oxygen/Fraction of inspired oxygen (PaO_2/FiO_2) ≤300 mmHg, chest imaging showing bilateral infiltrates), acute kidney injury (AKI) Kidney Disease: Improving Global Outcomes (KDIGO criteria, an increase in Cr of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days), etc., determined based on medical records and imaging/laboratory results.

Adverse drug reactions (e.g., nausea/vomiting, rash, liver function abnormalities) were recorded according to NCI-CTCAE 5.0 criteria [15].

(3) Baseline variables: Age, gender, body mass index (BMI), etiology (biliary, alcohol, hyperlipidemia), comorbidities (hypertension, diabetes, coronary heart disease), and disease severity scores (APACHE II, SOFA, CTSI).

Statistical analysis

Statistical analyses were conducted using SPSS 26.0 and GraphPad Prism 9.0, with measurement data are expressed as mean ± standard deviation ($\bar{x} \pm sd$), and group comparisons used independent sample t-tests. Enumeration data are expressed as count (%), with group comparisons using chi-square tests or Fisher's exact test. Repeated measurement data at multiple time points were analyzed by repeated measures ANOVA, and post hoc comparisons were performed using the Bonferroni correction. Pearson's correlation coefficient was used for correlation analysis to

Table 1. Comparison of baseline characteristics

Variable	Control (n=112)	Observation (n=128)	χ^2/t	P
Age (years)	47.32±6.87	47.12±7.26	0.224	0.823
Sex (male), n (%)	62 (55.36)	75 (58.59)	0.255	0.613
Disease duration (h)	13.96±3.62	14.57±3.29	1.350	0.178
BMI (kg/m^2)	24.41±3.45	24.56±3.11	0.348	0.728
Etiology, n (%)			0.846	0.839
Biliary	62 (55.36)	70 (54.69)		
Alcoholic	34 (30.36)	42 (32.81)		
Hypertriglyceridemia	10 (8.93)	12 (9.38)		
Other	6 (5.36)	4 (3.13)		
Hypertension history, n (%)	34 (30.36)	40 (31.25)	0.022	0.881
Diabetes history, n (%)	18 (16.07)	22 (17.19)	0.054	0.817
Coronary artery disease history, n (%)	7 (6.25)	11 (8.59)	0.473	0.492
APACHE II score	12.44±3.06	13.14±3.34	1.700	0.090
SOFA score	5.62±1.79	5.92±1.88	1.253	0.211
CTSI score	8.12±1.57	8.41±1.99	1.220	0.224
BUN (mmol/L)	6.48±2.28	6.65±2.43	0.559	0.576
eGFR (mL/min/1.73 m^2)	79.63±22.03	81.35±20.66	0.622	0.535

Note: APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, CTSI: Computed Tomography Severity Index, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate.

evaluate the association between CAR, SII, inflammatory indicators, and prognosis. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the predictive efficacy of day 14 CAR and SII for 28-day mortality and 1-year recurrence, calculating the area under the curve (AUC). P<0.05 was considered statistically significant.

Results

Baseline characteristics

As shown in **Table 1**, there were no significant differences between the groups in terms of age, sex distribution, duration of symptoms, BMI, etiology, history of hypertension, diabetes, or coronary artery disease, APACHE II score, SOFA score, CTSI score, BUN, or eGFR (all P>0.05). These results indicate that the two cohorts were comparable at baseline.

Dynamic changes in laboratory parameters

Table 2 presents the changes in CAR, SII, and inflammatory indicators before and after treatment in both groups. Prior to treatment, no significant differences were observed in any laboratory parameters (including Cr, AMY, Alb, CAR, SII, CRP, PCT, and IL-6) between the two groups (all P>0.05), indicating comparable baseline characteristics. Over the course of treatment, the observation group demonstrated superior improvement in multiple outcomes compared to the control group (all P<0.05). Specifically, the observation group showed significantly lower levels of Cr and AMY on days 3, 7, and 14 relative to the control group (all P<0.05). Alb levels increased steadily from day 1 onward in the observation group, with statistically significant differences observed at all measured time points (all P<0.05). CAR decreased markedly as early as day 1 and remained significantly lower at all subsequent assessments (all P<0.05). Similarly, SII was significantly reduced in the observation group on days 1, 3, 7, and 14 (all P<0.05). CRP levels declined continuously from day 1 to day 14, and were significantly lower in the observation group throughout this period (all P<0.05). Significant intergroup differences in PCT were observed at every time point (all P<0.05), and IL-6 levels were also significantly reduced in the observation group at all post-treatment measurements (all P<0.05).

Complications and adverse events

As summarized in **Table 3**, the incidence rates of individual complications-including pancreat-

Table 2. Laboratory parameters at baseline and post-treatment

Marker	Time Point	Control (n=112)	Observation (n=128)	t	P
Cr (μmol/L)					
Before treatment	Baseline	128.04±45.39	126.24±42.45	0.315	0.753
After treatment	Day 1	122.53±45.57	117.97±40.66	0.813	0.417
	Day 3	129.72±43.39	116.58±42.21	2.371	0.019
	Day 7	108.47±33.59	98.17±34.38	2.345	0.020
	Day 14	89.79±27.11	74.20±25.00	4.608	<0.001
AMY (U/L)					
Before treatment	Baseline	682.79±129.25	701.97±143.07	1.084	0.280
After treatment	Day 1	574.07±172.41	615.90±170.74	1.885	0.061
	Day 3	482.02±108.91	546.29±157.34	3.628	<0.001
	Day 7	312.58±114.52	377.72±118.65	4.313	<0.001
	Day 14	192.72±85.28	286.69±102.98	7.634	<0.001
Alb (g/L)					
Before treatment	Baseline	28.39±4.15	29.08±3.93	1.307	0.193
After treatment	Day 1	29.13±3.96	31.11±3.70	3.978	<0.001
	Day 3	29.68±3.92	32.51±3.48	5.877	<0.001
	Day 7	31.71±3.87	36.23±3.19	9.798	<0.001
	Day 14	35.02±3.43	38.23±2.85	7.795	<0.001
CAR					
Before treatment	Baseline	4.59±1.75	4.46±1.77	0.593	0.554
After treatment	Day 1	4.31±1.63	3.85±1.44	2.305	0.022
	Day 3	4.47±1.73	3.62±1.35	4.237	<0.001
	Day 7	3.48±1.18	2.74±1.02	5.201	<0.001
	Day 14	2.59±0.84	1.95±0.69	6.349	<0.001
SII					
Before treatment	Baseline	1195.28±185.89	1155.55±164.99	1.740	0.083
After treatment	Day 1	1166.90±198.22	1104.79±232.08	2.236	0.026
	Day 3	1057.72±239.70	972.98±209.33	2.898	0.004
	Day 7	913.03±129.11	849.08±112.16	4.068	<0.001
	Day 14	836.68±115.50	773.40±114.66	4.249	<0.001
CRP (mg/L)					
Before treatment	Baseline	145.51±48.01	134.95±53.63	1.610	0.109
After treatment	Day 1	128.07±45.65	115.09±44.53	2.223	0.027
	Day 3	114.33±49.00	94.11±38.76	3.509	<0.001
	Day 7	87.08±31.79	55.36±26.29	8.352	<0.001
	Day 14	45.25±22.30	29.51±13.78	6.467	<0.001
PCT (ng/mL)					
Before treatment	Baseline	8.21±3.35	8.54±2.96	0.815	0.416
After treatment	Day 1	7.57±2.81	6.74±2.69	2.336	0.020
	Day 3	6.44±2.69	4.79±2.07	5.272	<0.001
	Day 7	3.83±1.43	2.34±1.15	8.799	<0.001
	Day 14	2.00±0.85	1.34±0.54	6.977	<0.001
IL-6 (pg/mL)					
Before treatment	Baseline	180.79±43.44	175.42±51.69	0.873	0.383
After treatment	Day 1	171.16±38.14	155.18±34.09	3.404	<0.001
	Day 3	150.97±40.66	119.36±35.46	6.377	<0.001
	Day 7	108.28±30.78	74.00±26.70	9.152	<0.001
	Day 14	70.64±21.13	45.39±14.56	10.627	<0.001

Note: Cr: Creatinine, AMY: Serum Amylase, Alb: Albumin, CAR: Creatinine-to-Albumin Ratio, SII: Systemic Immune-Inflammation Index, CRP: C-Reactive Protein, PCT: Procalcitonin, IL-6: Interleukin-6.

Table 3. Complications and adverse events

	Control (n=112)	Observation (n=128)	χ^2/t	P
Complications, n (%)				
Pancreatic necrosis	20 (17.86)	14 (10.94)	2.352	0.125
Septic shock	16 (14.29)	12 (9.38)	1.398	0.237
ARDS	13 (11.61)	11 (8.59)	0.603	0.438
AKI	11 (9.82)	8 (6.25)	1.045	0.307
MOF	6 (5.36)	4 (3.13)	0.745	0.388
IAH	8 (7.14)	7 (5.47)	0.286	0.593
Gastrointestinal bleeding	5 (4.46)	3 (2.34)	0.834	0.361
Pancreatic fistula	7 (6.25)	4 (3.13)	1.334	0.248
Total complications	59 (52.68)	43 (33.59)	8.903	0.003
Adverse events, n (%)				
Nausea/vomiting	16 (12.50)	20 (15.63)	0.479	0.489
Rash/pruritus	3 (2.68)	6 (4.69)	0.668	0.414
Hepatic dysfunction	9 (8.04)	7 (5.47)	0.633	0.426
Headache/dizziness	6 (5.36)	4 (3.13)	0.745	0.388
Constipation/diarrhea	5 (4.46)	7 (5.47)	0.127	0.722
Total adverse events	28 (25.00)	36 (28.13)	0.498	0.480

Note: ARDS: Acute respiratory distress syndrome, AKI: acute kidney injury, MOF: multiple organ failure, IAH: intra-abdominal hypertension.

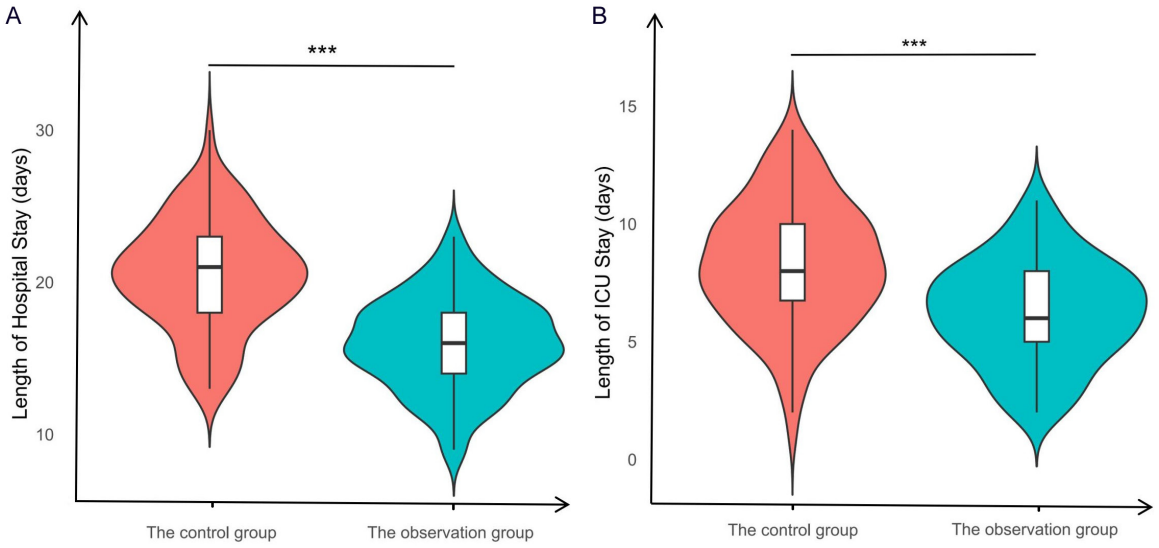

Figure 1. Comparison of hospital stay and ICU stay between the two groups. A. Comparison of hospital stay between the two groups. B. Comparison of ICU stay between the two groups. Note: ***P<0.001, ICU: Intensive Care Unit.

ic necrosis, septic shock, ARDS, AKI, multi-organ failure, intra-abdominal hypertension, gastrointestinal bleeding, and pancreatic fistula-did not differ significantly between groups (all P>0.05). However, the overall complication rate was significantly lower in the observation group compared to the control group (33.6% vs. 52.7%; P=0.003). In contrast, the incidence of adverse events (nausea/vomiting, rash/pruritus, hepatic dysfunction, headache/dizziness, constipation/diarrhea) and the overall adverse event rate showed no significant differences between groups (all P>0.05).

Comparison of hospitalization outcomes

As illustrated in **Figure 1** and **Table 4**, the observation group had significantly shorter total hos-

Table 4. Comparison of prognostic outcomes

	Control (n=112)	Observation (n=128)	χ^2	P
28-day mortality, n (%)	16 (11.61)	8 (6.25)	4.286	0.038
1-year recurrence, n (%)	24 (21.43)	13 (10.16)	5.821	0.016

pital and ICU stays compared to the control group (both P<0.001). Furthermore, the 28-day mortality rate (P=0.038) and the 1-year recurrence rate (P=0.016) were both lower in the observation group, highlighting the superior short- and mid-term outcomes associated with combined octreotide and ulinastatin therapy.

Correlation of day-14 CAR and SII with inflammatory markers

Figure 2 illustrates the correlation analyses between Day-14 CAR, SII, and major inflammatory markers (CRP, PCT, IL-6). In both groups, CAR exhibited significant positive correlations with SII, CRP, PCT, and IL-6 (all P<0.001). Likewise, SII was positively correlated with CRP, PCT, and IL-6 (all P<0.001), highlighting the strong association between systemic immune-inflammatory status and circulating inflammatory mediators.

Correlation of day-14 CAR and SII with hospitalization duration

As shown in **Figure 3**, Day-14 CAR and SII were positively correlated with both total hospital stay and ICU stay across groups (all P<0.001). These findings suggest that elevated systemic immune-inflammatory burden and markers of organ dysfunction are closely linked to prolonged hospitalization.

Predictive value of day-14 CAR and SII for 28-day mortality

Figure 4 presents the ROC curves of Day-14 CAR and SII for predicting 28-day mortality in each group. Both markers achieved AUC values greater than 0.7, indicating good discriminative performance for early mortality risk.

Predictive value of day-14 CAR and SII for 1-year recurrence

As shown in **Figure 5**, ROC analyses of Day-14 CAR and SII for predicting 1-year recurrence yielded AUC values greater than 0.7 in both groups, demonstrating favorable discriminatory ability for long-term relapse risk.

Discussion

SAP carries high mortality, largely due to an excessive inflammatory response that leads to multiple organ dysfunction. Despite advances in fluid resuscitation and organ support techniques, SAP-related mortality remains substantial [16]. The pathogenesis of SAP involves premature activation of pancreatic enzymes, unchecked systemic inflammation, and subsequent organ failure. Therefore, early inhibition of the inflammatory cascade and preservation of organ function are critical therapeutic goals [17, 18]. In this retrospective cohort study, we evaluated whether adding ulinastatin to octreotide-based therapy could modulate two composite biomarkers, CAR and SII, and improve clinical outcomes in SAP patients.

Our results indicate that combined octreotide and ulinastatin therapy resulted in a rapid and sustained decline in CAR, starting on day 1, reflecting both decreased serum Cr and improved Alb levels. The rise in Alb may suggest attenuation of catabolic metabolism, potentially via inhibition of proteolysis by pancreatic enzymes, thus improving nutritional status [19]. Previous studies have linked elevated CAR with an increased risk of AKI, underscoring its value as a marker of renal recovery in SAP [20]. Notably, a recent retrospective study demonstrated that the serum albumin-to-creatinine ratio (sACR) is independently associated with in-hospital mortality in SAP, and that lower sACR predicts higher early mortality risk [21].

Mechanistically, octreotide, a somatostatin analogue, reduces pancreatic autodigestion by inhibiting enzyme secretion, lowers microvascular permeability, dampens inflammatory mediator release, and modulates T-cell and monocyte-macrophage activity [22]. Zhao et al. [23] further showed that octreotide can inhibit pyroptosis and mitigate pancreatic injury by

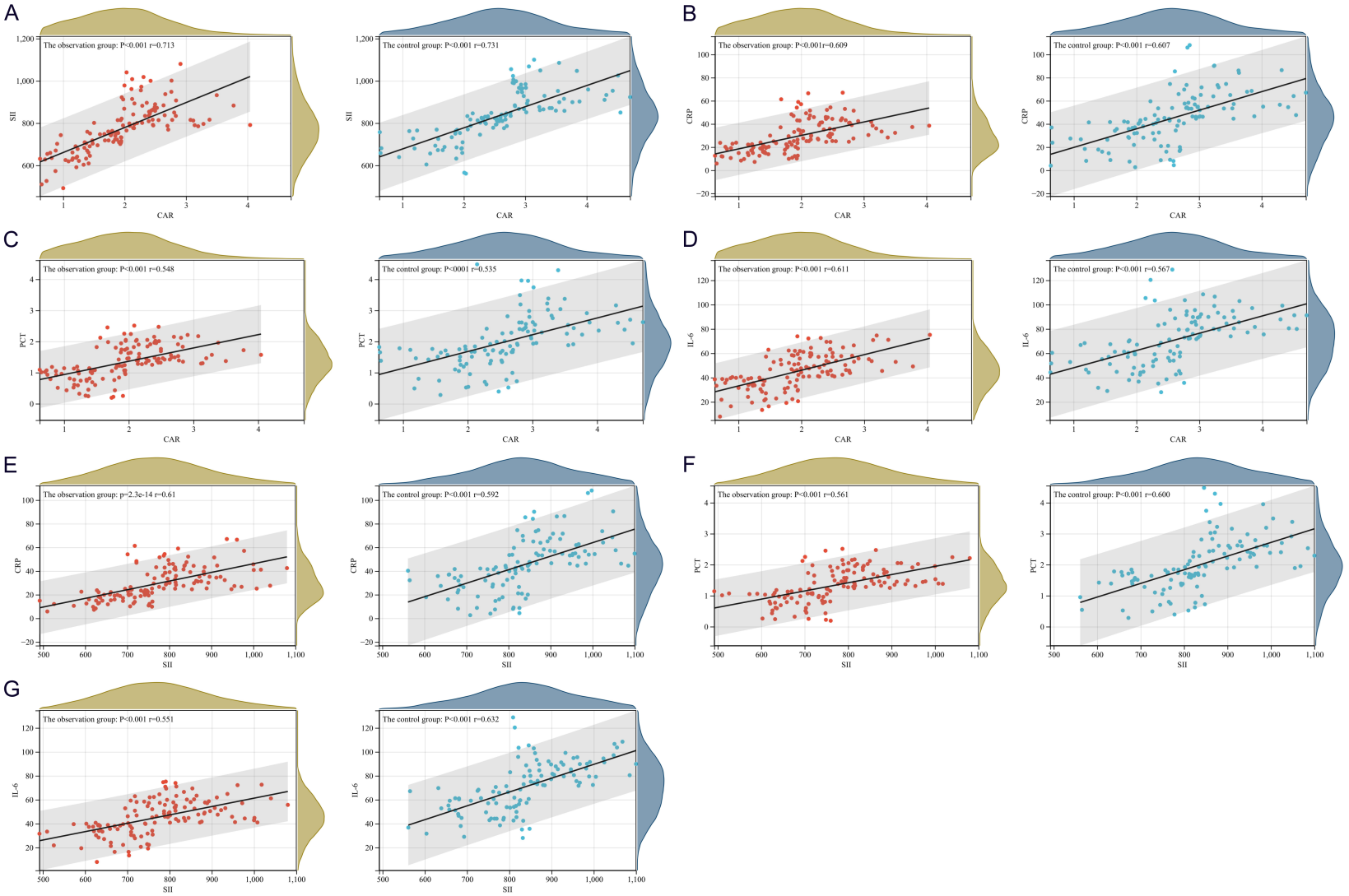

Figure 2. Correlation analysis diagrams of CAR, SII and various inflammatory indicators on day 14 in different groups. A. Correlation between CAR and SII in the control group and the observation group. B. Correlation between CAR and CRP in the control group and the observation group. C. Correlation between CAR and PCT in the control group and the observation group. D. Correlation between CAR and IL-6 in the control group and the observation group. E. Correlation between SII and CRP in the control group and the observation group. F. Correlation between SII and PCT in the control group and the observation group. G. Correlation between SII and IL-6 in the control group and the observation group. Note: SII: Systemic Immune Inflammation Index, CAR: Creatinine-to-Albumin Ratio, CRP: C-Reactive Protein, PCT: Procalcitonin, IL-6: Interleukin-6.

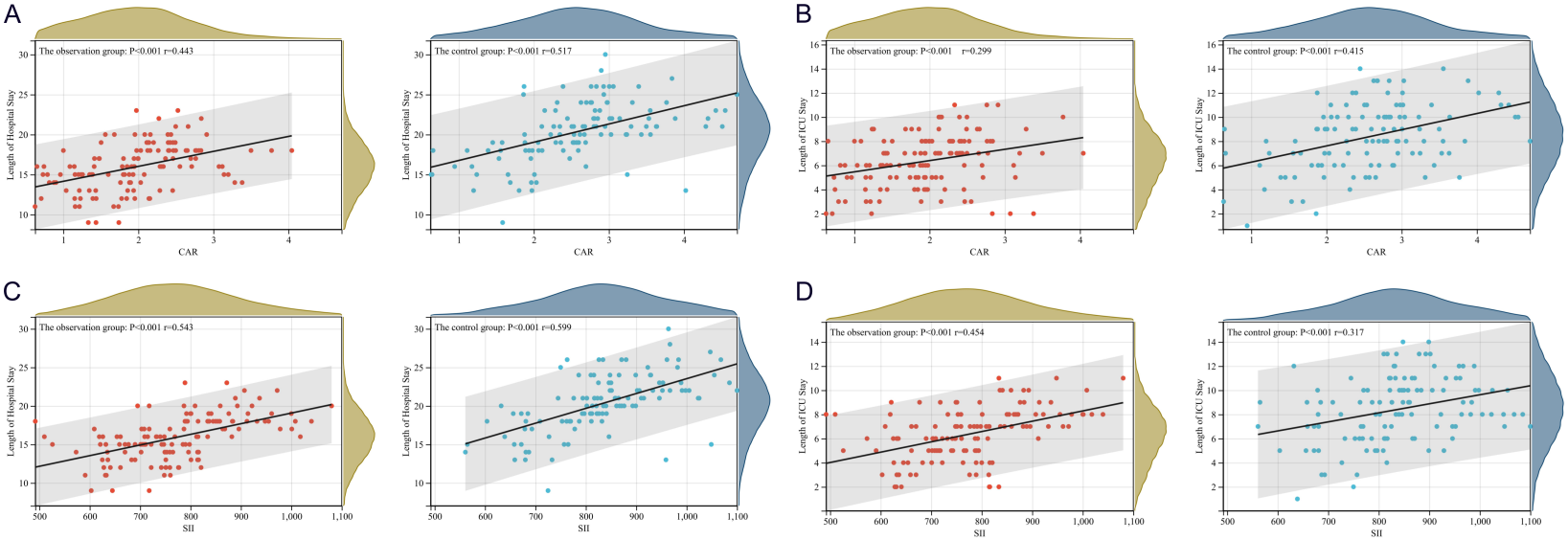

Figure 3. Correlation of CAR and SII with hospital stay and ICU stay on day 14. A. Correlation between CAR and hospital stay in the control group and the observation group. B. Correlation between CAR and ICU stay in the control group and the observation group. C. Correlation between SII and hospital stay in the control group and the observation group. D. Correlation between SII and ICU stay in the control group and the observation group. Note: SII: Systemic Immune Inflammation, CAR: Creatinine-to-Albumin Ratio, ICU: Intensive Care Unit.

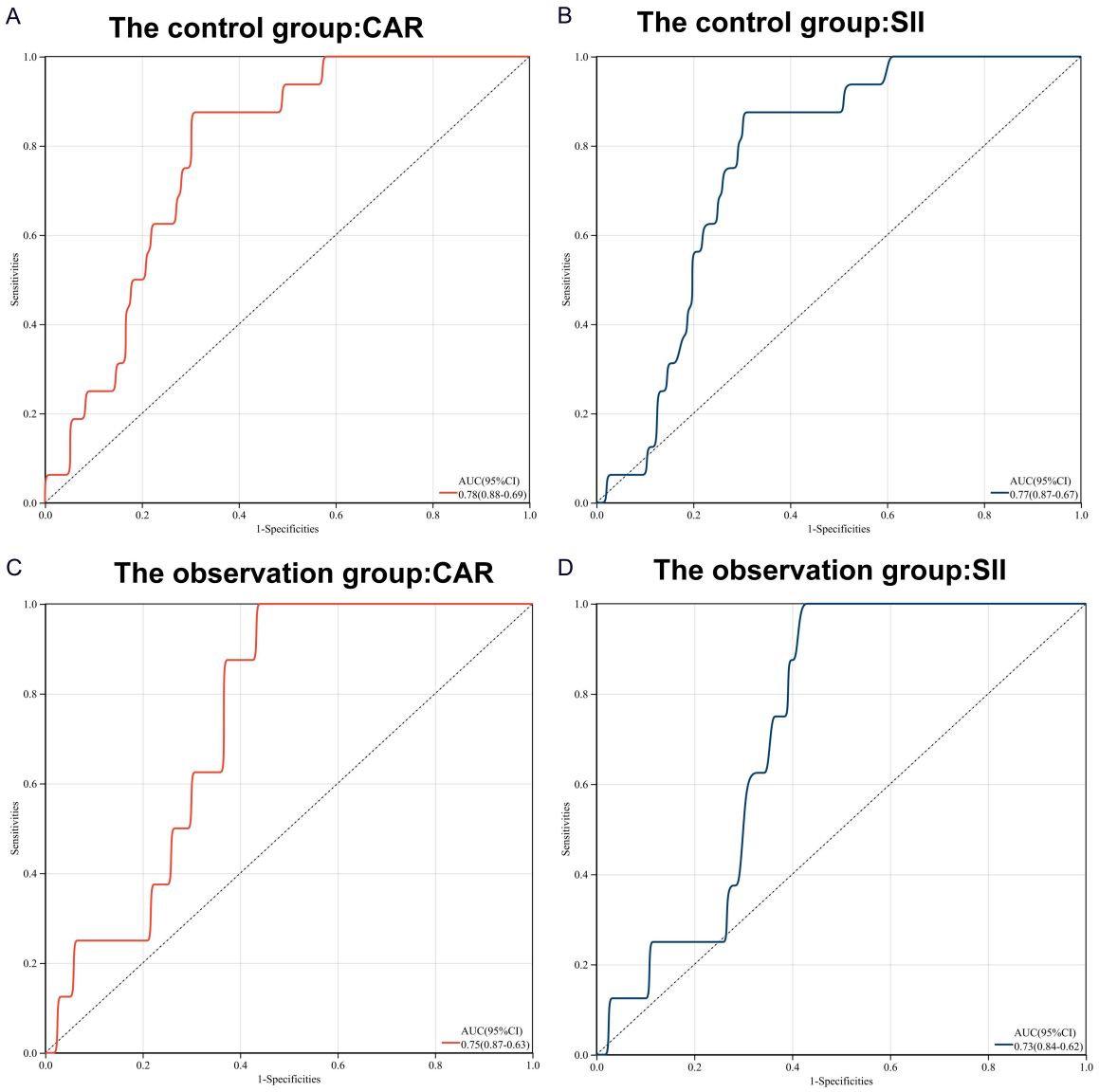

Figure 4. Predictive value of CAR and SII on day 14 for mortality within 28 days. A. ROC curve of CAR on day 14 in the control group for predicting 28-day mortality. B. ROC curve of SII on day 14 in the control group for predicting 28-day mortality. C. ROC curve of CAR on day 14 in the observation group for predicting 28-day mortality. D. ROC curve of SII on day 14 in the observation group for predicting 28-day mortality. Note: SII: Systemic Immune Inflammation Index, CAR: Creatinine-to-Albumin Ratio, ROC: Receiver Operating Characteristic.

restoring gut microbiota balance. Ulinastatin, a broad-spectrum serine protease inhibitor, directly suppresses trypsin and elastase, blocks NF-κB signaling to reduce TNF-α and IL-6 release, improves microcirculation, and mitigates oxidative stress [24]. In a SAP murine model, Liu et al. demonstrated that ulinastatin exerts multi-targeted protection via the ACE2-Ang-(1-7)-Mas axis [25]. Moreover, a recent systematic review and meta-analysis of 30 RCTs confirmed that octreotide combined with ulinastatin significantly increases overall treatment efficacy, shortens hospital stays and symptom resolution times, and reduces inflammatory cytokines (TNF-α, CRP, IL-6, IL-8) without increasing adverse events [26].

In the combination-therapy cohort, SII decreased significantly by day 1 and continued to decrease through day 14. Because SII reflects the balance between inflammatory activation (neutrophils) and immune competence (lymphocytes and platelets), its reduction suggests that ulinastatin mitigates neutrophil-driven

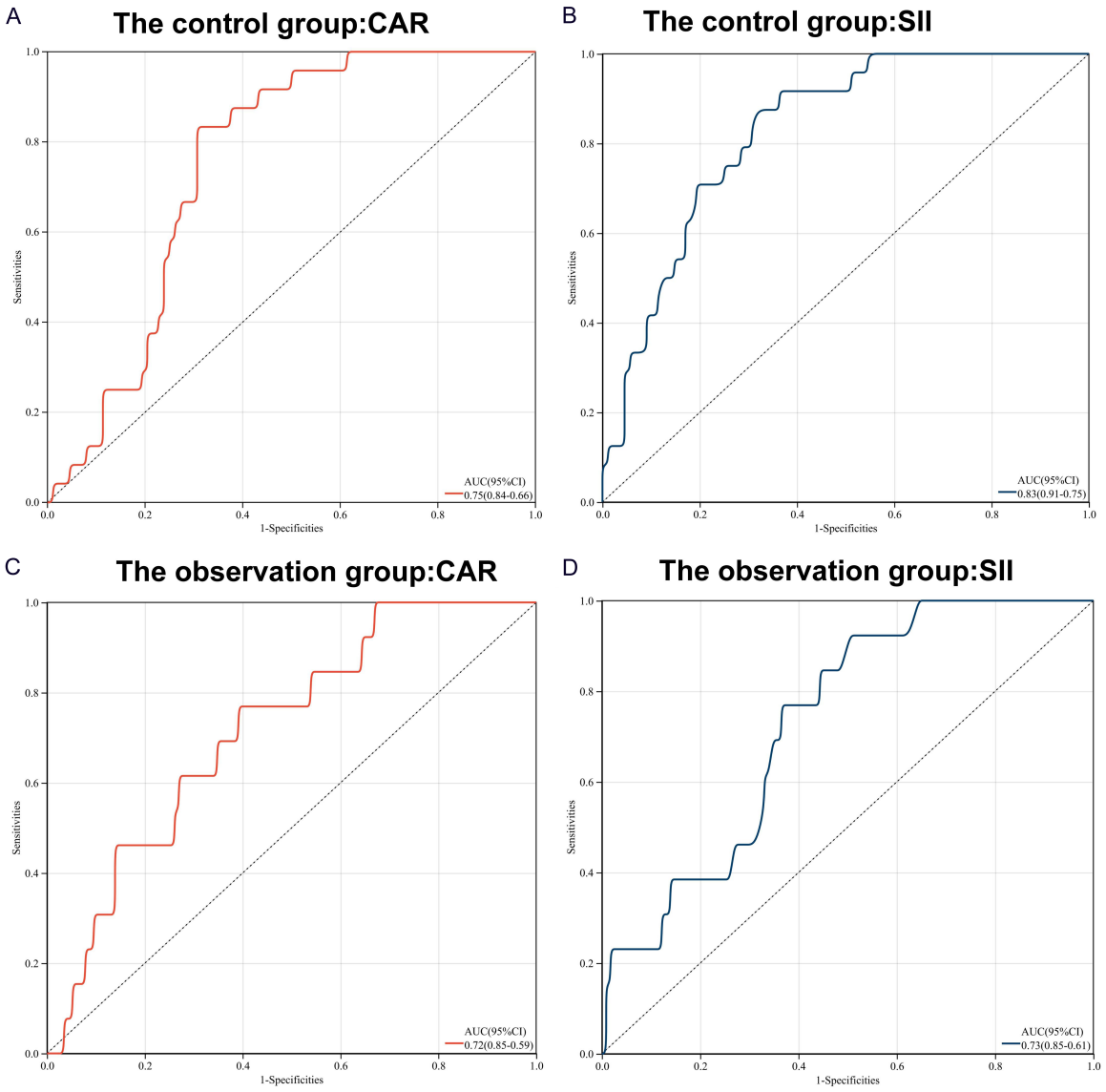

Figure 5. Predictive value of CAR and SII on day 14 for 1-year recurrence. A. ROC curve of CAR on day 14 in the control group for predicting 28-day mortality. B. ROC curve of SII on day 14 in the control group for predicting 28-day mortality. C. ROC curve of CAR on day 14 in the observation group for predicting 28-day mortality. D. ROC curve of SII on day 14 in the observation group for predicting 28-day mortality. Note: SII: Systemic Immune Inflammation Index, CAR: Creatinine-to-Albumin Ratio, ROC: Receiver Operating Characteristic.

cytokine storms, while octreotide helps reverse SAP-associated immunoparalysis through T-cell modulation [27, 28]. Notably, SII has shown high sensitivity for distinguishing mild from severe AP, further supporting its utility as a composite marker of inflammation and immune dysregulation [29]. This aligns with a single-center retrospective study that established inflammation-based models - incorporating SII, CAR, PCT, and CLR - as reliable predictors of SAP, with a model including fatty liver, PCT, and CLR achieving an AUROC of 0.795 [30].

We observed a strong correlation between SII and IL-6 levels, suggesting that SII reliably reflects systemic cytokine activity. Although septic shock and ARDS rates did not differ significantly between groups, the overall complication rate was lower in the observation group, likely due to restored immune-inflammatory balance following SII reduction. A recent

meta-analysis reported that combining ulinastatin with somatostatin analogues significantly reduces the incidence of ARDS, AKI, and multi-organ failure [31].

Importantly, the combination regimen led to significant reductions in 28-day mortality and 1-year recurrence rates, supporting its beneficial effects on both early survival and long-term disease course. We propose a "cascade effect" of inflammation control, leading to endothelial protection, enhanced albumin synthesis, and tissue repair. Yang et al. [32] documented in a randomized trial that ulinastatin plus a somatostatin analogue elevates CD4+ and NK cell counts and improves the CD4+/CD8+ ratio, further supporting the reversal of immune suppression. Comparable adverse event rates between groups underscore the safety of adding ulinastatin to standard therapy.

The innovation of this study lies in its systematic evaluation of the effects of octreotide combined with ulinastatin on serum CAR and SII in SAP patients. These indices integrate organ function (renal function, nutritional status) and systemic immune-inflammatory status, allowing for a more comprehensive assessment of disease severity and treatment response compared to traditional single markers (such as CRP and IL-6). In addition, the study confirms that the combined therapy not only reduces inflammatory markers (CRP, PCT, IL-6) but also improves CAR and SII. Moreover, these two indices are closely correlated with short-term mortality, 1-year recurrence rate, and length of hospital stay, suggesting their potential as prognostic tools for SAP.

This study has several limitations. First, its single-center retrospective design may introduce selection bias; although baseline characteristics were well-matched, multicenter randomized controlled trials are needed to confirm our findings. Second, we did not measure early renal injury markers, such as urinary microalbumin, limiting mechanistic insight into CAR improvement. Future research should include multicenter RCTs to optimize ulinastatin dosing and explore its effects on specific immune-cell subsets.

In summary, the addition of ulinastatin to octreotide therapy in SAP significantly reduces CAR and SII - composite indices of organ function and systemic inflammation - thereby improving short-term mortality and mid-term recurrence. CAR and SII warrant further investigation as prognostic and therapeutic response markers in SAP management.

Disclosure of conflict of interest

None.

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