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Effect and safety of sivelestat on acute severe pancreatitis with systemic inflammatory response syndrome: a retrospective study

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The study was to explore the efficacy and safety of sivelestat (SV) in the treatment of severe acute pancreatitis (SAP) with systemic inflammatory response syndrome (SIRS). A total of 102 SAP patients diagnosed and treated in the Emergency Intensive Care Unit of the First Affiliated Hospital of Zhengzhou University from January 2021 to August 2024 were selected. The changes of disease outcome, hospital stays and mortality were compared between the two groups. A total of 102 patients were recruited to control group ($n = 56$) or SV group ($n = 46$) according to whether SV was applied or not. There was no significant difference in baseline data at admission between the two groups. After 1 week of treatment, all the indexes in both groups improved. The duration of ventilator use ($p = 0.0400$) and ICU stays ($p = 0.0495$) in SV group was shorter than that in control group, but there was no significant difference in mortality between the two groups. Although SV did not reduce the mortality of patients with SAP, it reduced the length of ventilator use and ICU stay.

Keywords Sivelestat, Severe acute pancreatitis, Systemic inflammatory response syndrome

Severe acute pancreatitis (SAP) is a cascade inflammatory disease caused by local lesions of the pancreas, with acute onset, severe illness and high mortality[1]. SAP is a common critical illness in clinical emergencies, and the persistence of systemic inflammatory response syndrome (SIRS) and organ dysfunction are important determinants of the severity of the condition. Inhibiting inflammatory response and protecting organ function are very important to improve the prognosis of patients. Sivelestat (SV) is a selective human neutrophil elastase inhibitor (HNEI) for the treatment of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) with SIRS[2–4]. The present study found that SV may also play an important role in ameliorating SAP and its associated lung and kidney damage[5–8]. The Chinese experts' consensus on clinical application of Sivelestat Sodium, published in 2022, recommended that SV should be considered for early use in patients with acute pancreatitis (AP) combined with SIRS based on standard treatment[9]. But high-quality clinical evidence is lacking.

Our study retrospectively analyzed 102 patients with SAP, aiming to explore the efficacy and safety of SV in the treatment of SAP combined with SIRS, and to provide a certain basis for clinical treatment.

Methods

Study design and participants

A total of 102 SAP patients diagnosed and treated in the Emergency Intensive Care Unit of the First Affiliated Hospital of Zhengzhou University from January 2021 to August 2024 were selected, including 69 males and 33 females, aged 18–72 years, who were all admitted within 72 h after onset. The inclusion and exclusion criteria and study process were shown in Fig. 1. The study did not affect patients' treatment. Data from all patients was used for study purposes only. This study has been approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University and all methods were performed in accordance with the guidelines and regulations. Informed consent was obtained from all study participants or their legal guardians.

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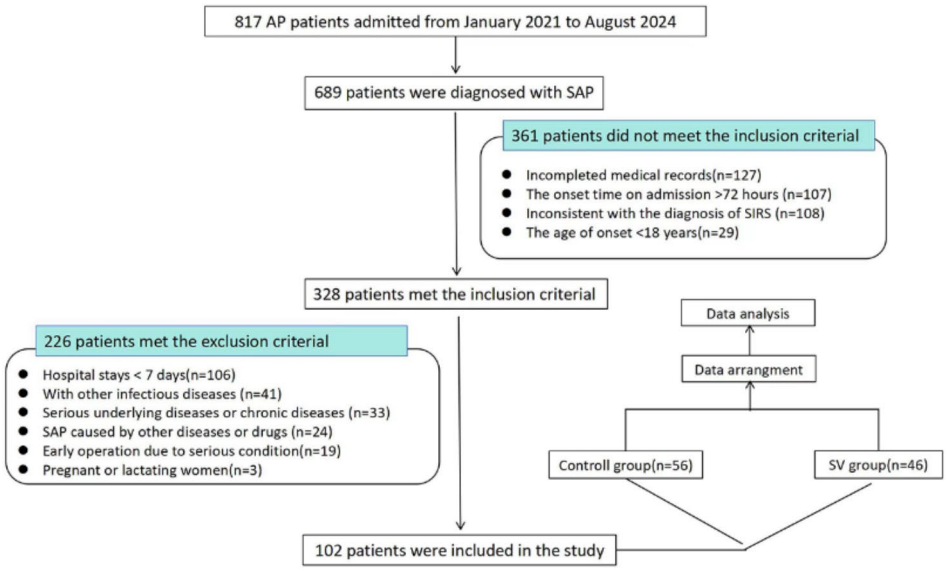

Fig. 1. Flow chart of the study. AP, acute pancreatitis; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; SV, sivelestat.

Relevant definitions and standards

Acute kidney injury(AKI): Serum creatinine (Scr) increased ≥ 26.4μM/L, or ≥ 50% from baseline within 48 h, and/or urine volume < 0.5mL / (kg· h) for six hours[10]. AKI recovery: Serum creatinine returned to a standard Risk level below risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) classification within seven days of onset of AKI, or within 1.5 times the baseline Scr level, or without renal replacement therapy[11,12]. The diagnostic criteria for SIRS were two or more of the following clinical manifestations[13]: (1) Heart rates > 90 beats/min; (2) Body temperature < 36 ℃ or > 38 ℃; (3) White blood cells (WBC) count $< 4 \times 10^9$/L or $> 12 \times 10^9$/L; (4) Breaths > 20 times/min or arterial carbon dioxide pressure < 30 mmHg. Absence of bowel sounds: Abdominal auscultation lasted 3–5 min without hearing bowel sounds.

Intervention and follow-up

The control group received fasting, gastrointestinal decompression, fluid rehydration, spasmolysis, anti-inflammatory, inhibition of gastric acid and pancreatic fluid secretion, electrolyte balance and other symptomatic treatments. SV treatment group was additionally injected with SV 4.8 mg/kg/d by intravenous micropump on the basis of conventional symptomatic treatment.

After selecting the enrolled patients, we reviewed their medical records and examination results and collected patients' data. The changes of clinical indexes (such as breaths, heart rates, urine volume per hour, oxygenation index, etc.) and serological indexes (serum amylase, lipase, Scr, blood urea nitrogen (BUN), IL-6, IL-10, TNF-α, procalcitonin (PCT) and white blood cells (WBC)) were observed in each group upon admission and one week after treatment. The duration of ventilator usage and continuous renal replacement therapy (CRRT) use, the length of intensive Care Unit (ICU) stay and the number of patients died were recorded.

Statistical analysis

All clinical data were statistically analyzed using GraphPad Prism 10.4.0 software. When comparing measurement data, normality test was carried out first. Measurement data conformed to normal distribution were presented as the means ± SD. If the variance was homogenous, the independent sample t test was used; if not, the mann-whitney test was used. Unpaired t test was used for inter-group comparison, and paired t test was used for intra-group comparison before and after treatment. Data with skewed distribution were expressed as the median (quartile) [M (QL, QU)] and tested for non-parametric rank sum. The counting data were expressed as m/n (%), and the $\chi 2$ test, adjusted $\chi 2$ test or Fisher exact test were used for comparison between groups. $p < 0.05$ indicated a statistically significant difference.

Results

Participant characteristics

A total of 102 patients with SAP were included in this study, including 56 in the control group and 46 in the SV group. There were no significant differences in gender, age, acute physiology and chronic health evaluation II (APACHE II), CT severity index (CTSI) and clinical and laboratory indicators between the two groups at admission (Table 1). The mean breath rates of both groups were greater than 20 times/min ($p < 0.05$), heart rates of three quarters digits greater than 100 beats/min ($p < 0.05$) (Fig. 2). The baseline data of the two groups of patients at admission were basically similar and comparable.

Variable	Control group ($n=56$)	SV group ($n=46$)	P value
Sex (male/female)	39/17	30/16	*0.6746*
Age (years)	42(32,57)	39(32,49)	*0.2465*
APACHE II score	8(6,11)	8(5,13)	*0.5760*
CTSI	6(5,8)	6(5,7)	*0.9195*
Heart rates(/min)	108 ± 21	116 ± 26	*0.1303*
Body temperature (℃)	36.9(36.6,37.5)	36.9(36.7,37.9)	*0.7536*
Breath rates(/min)	22(18,27)	23(18,30)	*0.8083*
Serum lipase (IU/ml)	470.7(251.0,706.5)	596.2(373.5,914.6)	*0.1147*
Serum amylase (IU/ml)	429.5(156.3,828.0)	594.0(364.8,1047.0)	*0.0706*
WBC count ($\times 10^9$/L)	14.84(11.19,18.88)	14.52(10.17,18.49)	*0.7570*
PCT (ng/L)	1.965(0.875,6.765)	4.355(1.227,8.740)	*0.0679*
IL-6 (pg/ml)	100.50(67.76,254.60)	173.40(63.21,282.10)	*0.3845*
IL-10 (pg/ml)	4.79(3.13,7.61)	5.21(3.75,10.44)	*0.1754*
TNF-α (pg/ml)	2.89(1.49,4.67)	2.86(2.09,4.38)	*0.6675*
Urine volume (ml/h)	90(44,110)	77(21,122)	*0.4946*
Scr (μmol/L)	82.0(59.3,191.8)	99.0(73.8,150.0)	*0.0973*
BUN (mmol/L)	6.20(4.15,9.32)	6.05(4.91,11.0)	*0.5721*
Proportion of AKI patients	21/56(37.50%)	22/46(47.83%)	*0.4710*
Oxygenation index	244 ± 73	233 ± 86	*0.4921*
Proportion of patients without bowel sounds	23/56(41.07%)	24/46(52.17%)	*0.3197*

Table 1. Baseline characteristics of patients. APACHE II, acute physiology and chronic health evaluation II; CTSI, CT severity index; WBC, white blood cell; PCT, procalcitonin; Scr, serum creatinine; BUN, blood urea nitrogen; AKI, acute kidney injury. Measurement data conformed to normal distribution are presented as the means ± SD, and the skewness distribution with median (quartile). Counting data is expressed as m/n (%). $P<0.05$ indicates a statistically significant difference. Significant values are in italics.

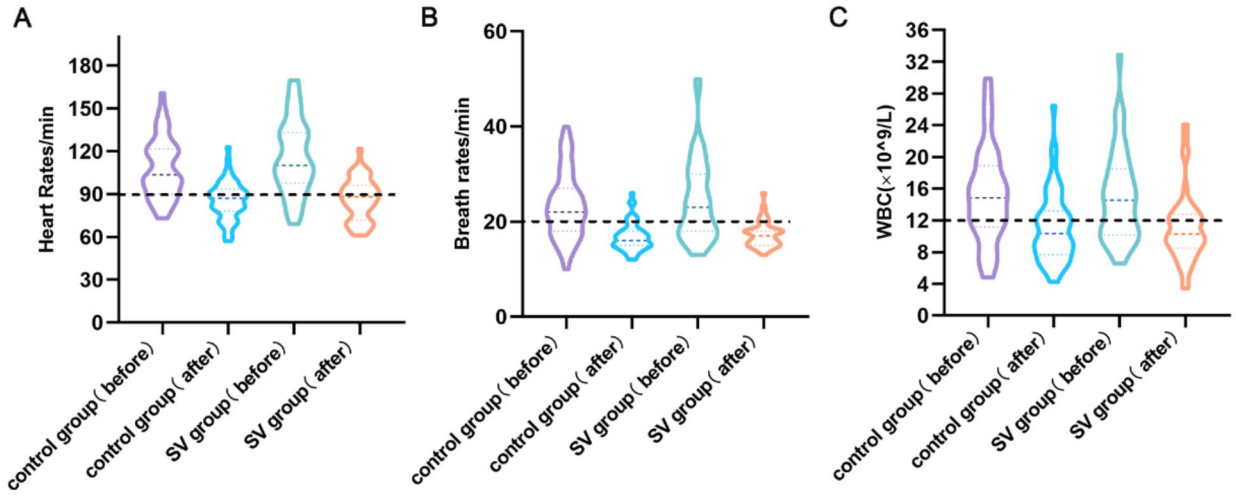

Fig. 2. Heart rates (**A**), breath rates (**B**), blood WBC (**C**) level and their changes at admission (before) and one week after treatment (after) in both groups. WBC, white blood cell.

The characteristics of the two groups before and after treatment

After one week of treatment, the heart rates, breaths, serum amylase, serum lipase, IL-6, IL-8, TNF-α, WBC, PCT of the two groups were significantly decreased compared with that before treatment (Table 2), indicating that pancreatitis and SIRS were improved. After treatment, urine volume per hour in both groups increased significantly, Scr and BUN decreased, suggesting improved renal function (Table 2). Oxygenation index was also higher than before treatment, indicating respiratory function improved (Table 2). The results showed that the treatment was effective in both groups.

Variable	Control group ($n=56$)		P值	SV group ($n=46$)		*P* value
	Before	After 1 week of treatment		Before	After 1 week of treatment	
Heart rates(/min)	108 ± 21	85 ± 13	*< 0.0001*	116 ± 26	86 ± 14	*< 0.0001*
Body temperature (℃)	36.9(36.6,37.5)	36.8(36.7,37.2)	*0.6874*	36.9(36.7,37.9)	36.9(36.7,37.2)	*0.3196*
Breath rates(/min)	22(18,27)	16(15,18)	*< 0.0001*	23(18,30)	17(15,18)	*< 0.0001*
Serum lipase (IU/ml)	470.7(251.0,706.5)	58.6(30.1,90.8)	*< 0.0001*	596.2(373.5,914.6)	51.3(31.2,84.4)	*< 0.0001*
Serum amylase (IU/ml)	429.5(156.3,828.0)	41.5(28.3,68.0)	*< 0.0001*	594.0(364.8,1047.0)	44.5(31.0,72.0)	*< 0.0001*
WBC count ($\times 10^9$/L)	14.84(11.19,18.88)	10.33(7.70,13.23)	*0.0016*	14.52(10.17,18.49)	10.27(8.50,12.77)	*0.0138*
PCT (ng/L)	1.965(0.875,6.765)	0.785(0.328,1.749)	*< 0.0001*	4.355(1.227,8.740)	0.984(0.363,2.487)	*< 0.0001*
IL-6 (pg/ml)	100.50(67.76,254.60)	48.01(21.37,101.4)	*< 0.0001*	173.40(63.21,282.10)	36.87(19.06,82.28)	*< 0.0001*
IL-10 (pg/ml)	4.79(3.13,7.61)	2.63(1.60,4.72)	*< 0.0001*	5.21(3.75,10.44)	2.62(1.55,4.78)	*< 0.0001*
TNF-α (pg/ml)	2.89(1.49,4.67)	1.78(1.15,2.76)	*0.0053*	2.86(2.09,4.38)	1.52(1.06,2.55)	*< 0.0001*
Urine volume (ml/h)	90(44,110)	107(84,160)	*0.0008*	77(21,122)	120(81,151)	*< 0.0001*
Scr (μmol/L)	82.0(59.3,191.8)	65.5(51.0,89.0)	*< 0.0001*	99.0(73.8,150.0)	79.0(58.8,97.5)	*< 0.0001*
BUN (mmol/L)	6.20(4.15,9.32)	3.66(2.78,5.29)	*< 0.0001*	6.05(4.91,11.00)	3.85(3.143,6.00)	*< 0.0001*
Oxygenation index	244 ± 73	287 ± 72	*0.0011*	233 ± 86	290 ± 91	*< 0.0001*

Table 2. Comparison of the characteristics of the two groups before and after treatment. CTSI, CT severity index; WBC, white blood cell; PCT, procalcitonin; Scr, serum creatinine; BUN, blood urea nitrogen. Measurement data conformed to normal distribution are presented as the means ± SD, and the skewness distribution with median (quartile). Counting data is expressed as m/n (%). $P < 0.05$ indicates a statistically significant difference. Significant values are in italics.

The characteristics between the two groups after one week of treatment

We found no significant differences in blood pressure, heart rates, breaths, serum lipase, serum amylase, IL-6, IL-10, TNF-α, urine volume per hour, Scr, BUN and oxygenation index in SV group after one week of treatment compared with the control group. The proportion of patients with restored renal function (*77.27% vs. 42.86%*,$p=0.0305$) and bowel sounds (*62.50% vs. 30.43%*,$p=0.0415$) were both higher (Table 3). It was suggested that SV treatment may be more beneficial to the recovery of AKI and intestinal function in SAP patients. However, no significant advantage was seen in the improvement of pancreatic inflammation.

The comparison of treatment course and outcome between two groups

There were no statistically significant differences in CRRT and ventilator utilization rate between the two groups during treatment, and there were no statistically significant differences in final mortality (Table 4). However, the duration of ventilator use in SV group was shorter than that in control group (*10(7,16) vs. 7(6,10)*,$p=0.0400$), and as was the length of ICU stay (*13(7,19) vs. 9(7,13)*,$p=0.0495$) (Table 4).

Discussion

AP is a disease that causes acute inflammation of the pancreas due to the activation of pancreatic enzymes by multiple triggers, which can lead to local damage and systemic inflammatory reactions. Gallstones and heavy alcohol consumption are the two most common causes[14]. According to the severity, AP patients can be divided into three types: mild acute pancreatitis (MAP), moderate severe acute pancreatitis (MASP) and SAP[15]. SAP accounts for a small proportion of AP, but it is often combined with MODS, leading to severe illness and high fatality rate. A retrospective multiple center study found that MAP, MSAP and SAP accounted for 73.4%, 13.5% and 13.1%, but the case fatality rate was 0.3%, 3.1% and 14.3%, respectively[16]. A national multiple center investigation in China found that the overall case fatality rate of acute pancreatitis was up to 4.6%, with 73.9% of deaths occurring within two weeks after admission. In 1743 patients (28.0%) diagnosed with SAP, the in-hospital fatality rate was 15.6%[17]. Although mortality rates have gradually decreased as intensive care has improved, SAP still has a high mortality rate[18,19]. Seeking more effective treatment plan and promoting the rapid recovery of organ injury can shorten the course of disease and hospital stay, but also can reduce the pain of patients and family economic burden.

SV is a highly specific HNEI that acts by inhibiting neutrophil elastase (NE) activity and has beneficial effects on a variety of conditions caused by acute inflammation. It is currently the only drug approved worldwide for the treatment of ALI/ARDS[20–22]. Recent studies have found that the powerful anti-inflammatory ability of SV may also have a better inhibitory effect on the inflammatory response in other organs[23–26].

Blood NE activity was significantly increased in SAP patients, especially those with respiratory failure[27]. Necropsy of patients with acute necrotizing pancreatitis complicated with multiple organ failure showed increased neutrophil infiltration and significantly increased NE expression in necrotic pancreatic tissue[28]. These results suggest that SV as a NE inhibitor may be a potentially effective drug for the treatment of SAP. However, there is a lack of study results on large samples.

Variable	Control group ($n=56$)	SV group ($n=46$)	*P* value
Heart rates(/min)	85 ± 13	86 ± 14	*0.7187*
Body temperature (℃)	36.8(36.7,37.2)	36.9(36.7,37.2)	*0.8525*
Breath rates(/min)	16(15,18)	17(15,18)	*0.2337*
Serum lipase (IU/ml)	58.6(30.1,90.8)	51.3(31.2,84.4)	*0.5607*
Serum amylase (IU/ml)	41.5(28.3,68.0)	44.5(31.0,72.0)	*0.8532*
WBC count ($\times 10^9$/L)	10.33(7.70,13.23)	10.27(8.50,12.77)	*0.9759*
PCT (ng/L)	0.785(0.328,1.749)	0.984(0.363,2.487)	*0.6965*
IL-6 (pg/ml)	48.01(21.37,101.4)	36.87(19.06,82.28)	*0.2366*
IL-10 (pg/ml)	2.63(1.60,4.72)	2.62(1.55,4.78)	*0.9063*
TNF-α (pg/ml)	1.78(1.15,2.76)	1.52(1.06,2.55)	*0.2834*
Urine volume (ml/h)	107(84,160)	120(81,151)	*0.5974*
Scr (μmol/L)	65.5(51.0,89.0)	79.0(58.8,97.5)	*0.0531*
BUN (mmol/L)	3.66(2.78,5.29)	3.85(3.143,6.00)	*0.5813*
Proportion of patients recovering from AKI	9/21(42.86%)	17/22(77.27%)	*0.0305*
The proportion of patients with restored bowel sounds	7/23(30.43%)	15/24(62.50%)	*0.0415*
Oxygenation index	287 ± 72	290 ± 91	*0.8309*

Table 3. Comparison of characteristics between the two groups after one week of treatment. WBC, white blood cell; PCT, procalcitonin; Scr, serum creatinine; BUN, blood urea nitrogen; AKI, acute kidney injury; CRRT, continuous renal replacement therapy. Measurement data conformed to normal distribution are presented as the means ± SD, and the skewness distribution with median (quartile). Counting data is expressed as m/n (%). $P < 0.05$ indicates a statistically significant difference. Significant values are in italics.

Variable	Control group ($n=56$)	SV group ($n=46$)	*P* value
Proportion of patients treated with CRRT	15/56(26.79%)	14/46(30.43%)	*0.8258*
Proportion of AKI patients treated with CRRT	15/21(71.43%)	14/22(61.64%)	*0.7470*
Days of CRRT	8(7,15)	8(6,11)	*0.3004*
Proportion of patients on ventilators	18/56(32.14%)	15/46(32.61%)	*0.9999*
Days of ventilator use	10(7,16)	7(6,10)	*0.0400*
Mortality ratio	11/56(19.64%)	6/46(13.04%)	*0.4323*
ICU stay	13(7,19)	9(7,13)	*0.0495*

Table 4. The comparison of treatment course and outcome between two groups. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, intensive Care Unit. Measurement data conformed to normal distribution are presented as the means ± SD, and the skewness distribution with median (quartile). Counting data is expressed as m/n (%). $P < 0.05$ indicates a statistically significant difference. Significant values are in italics.

We retrospectively analyzed 71 patients with SAP, 29 of whom received SV in addition to conventional treatment, and the remaining 42 patients received conventional symptomatic supportive treatment. Previous studies have found that IL-6, IL-10 and TNF-α are important biomarkers in the progression of SAP and correlated with disease severity[29–33]. Therefore, these indicators were included in our study to reflect the disease progression of SAP. The results showed that there were no statistically significant differences in heart rates, breath rates, oxygenation index, body temperature, IL-6, IL-8, TNF-α, WBC, PCT, the rate of CRRT and ventilator utilization the two groups after one week of treatment, which were all improved compared with admission. In addition, there was no difference in the mean length of hospital stays and mortality between the two groups. SV showed no significant advantage in the treatment of SAP and SIRS.

The ratio of AKI recovery in SV group was higher than that in control group after one week of treatment, which may be related to the improvement of AKI kidney inflammation by SV. Li et al. found that SV could reduce the iNOS overexpression in the kidney of sepsis rats, inhibit the activation of Akt signaling pathway, and reduce inflammation, thus reducing the AKI caused by sepsis[5]. SV also significantly reduced Scr and urine KIM-1 levels in extracorporeal shock wave lithotripsy (ESWL) treated rats, and inhibited renal tissue inflammation and interstitial damage[34]. These results suggested that SV may play a role in the recovery of kidney injury.

Previous studies have shown that SV could significantly reduce pathological abnormalities of lung and pancreas as well as biochemical abnormalities in rat models with taurochate-induced acute pancreatitis[7,8]. Our

results found that although there was no difference in the proportion of patients using ventilator between the two groups, the SV group had shorter ventilator use and reduced patient suffering.

In addition, we found that bowel sounds seemed to recover better in the SV group after one week treatment. SV might improve intestinal motility in SAP patients. This may attribute to that SV can improve the intestinal microbial and metabolic disorders caused by sepsis[35]. However, this phenomenon is influenced by subjective factors and there is no relevant study at present. The validity of the results needs more data to verify.

Limitation

Our study preliminarily observed the safety and efficacy of SV in SAP combined with SIRS. Due to the small sample size and retrospective analysis, our study had some limitations, which may affect the determination of results. In addition, there are few studies related to SV in AP treatment, and our study lacks sufficient theoretical basis, and a larger sample size randomized controlled study is needed to verify it. Considering the retrospective nature of the study, there is a high potential for selection bias and confounding factors. We plan to address these issues in future iterations of the study through prospective study designs.

Conclusion

SV had a good safety in the treatment of SAP combined with SIRS, which could shorten the time of ventilator use in patients with respiratory failure and promote the recovery of renal function and intestinal function. Although SV did not reduce the mortality of patients with SAP, it reduced the length of ICU stay.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Jiafeng Xie and Ruyi Lei wrote the main manuscript. Zhiqiang Zhu and Changju Zhu decided the research direction. Yulei Gu and Ruyi Lei provided the fundings.Jiafeng Xie, Hui Pei and Luanluan Zhang did data analysis. Jiafeng Xie, Yanhui Huang, Yepeng Zhang, Jingrong Liu and Yanan Zi prepared figures and tables. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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