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Impact of ceftazidime/avibactam combined dynamic nutritional support on intestinal barrier function in sepsis patients: A focus on barrier protection mechanisms

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Abstract: **Background**: Studies have confirmed that the progression of sepsis is closely related to intestinal barrier dysfunction, including intestinal mucosa ischemia and hypoxia, flora imbalance and epithelial cell apoptosis. Therefore, protecting the intestinal barrier function has become a key link in the comprehensive treatment of sepsis. **Objectives**: This study evaluated the impact of a novel β-lactamase inhibitor compound preparation (ceftazidime/avibactam) on intestinal barrier function in sepsis patients. **Methods**: The study included 108 sepsis patients (January 2022–August 2025) and grouped them as an observation group (54 cases, ceftazidime/avibactam+dynamic nutritional support) and a control group (54 cases, Ceftazidime/Sulbactam+dynamic nutritional support). Of the outcome measures assessed, the 28-day all-cause mortality was primary, while ICU length of stay, mechanical ventilation time, antibiotic course, intestinal barrier function markers (DAO, LBP, Claudin-1) and inflammatory cytokines (IL-6, TNF-α) were secondary. **Results**: The results indicated lower 28-day all-cause mortality in the observation group vs the control group, along with shorter ICU length of stay, mechanical ventilation time and time to negative blood culture conversion ($P<0.05$). Concerning post-treatment intestinal barrier function, DAO, LBP and FC were lower while claudin-1 was higher in the observation group compared to the control group ($P<0.05$). Analysis of inflammatory factors also showed greater reductions in IL-1β, IL-6 and TNF-α in the observation group post-treatment ($P<0.05$). **Conclusion**: Ceftazidime/Avibactam plus dynamic nutritional support is instrumental in improving the intestinal barrier function of sepsis patients and alleviating inflammatory reactions, thus enhancing life safety.

Keywords: Avibactam; Ceftazidime; Intestinal barrier dysfunction; Inflammatory cytokines; Sepsis

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INTRODUCTION

Sepsis is a systemic inflammatory storm triggered by the dysregulated immune response of the host to infection (Srzic *et al*., 2022). The global annual incidence is approximately 50 million cases, with a mortality rate reaching 15%-30% (Watson *et al*., 2024). Studies have established a close correlation between sepsis progression and intestinal barrier dysfunction, including intestinal mucosal ischemia and hypoxia, intestinal flora imbalances and intestinal epithelial cell apoptosis. These disturbances can lead to the translocation of endotoxins and bacteria, further activating the systemic inflammatory response and forming a vicious cycle of "infection—intestinal injury—infection exacerbation" (Yan *et al*., 2024; Zhang *et al*., 2022). Therefore, protecting the intestinal barrier function has become a key link in the comprehensive treatment of sepsis.

Currently, early anti-infection, organ support and metabolic regulation are the core of sepsis treatment (Liu *et al*., 2022). Novel β-lactamase inhibitor compound preparations (e.g., ceftazidime/avibactam) have become the preferred choice for severe infections due to their ability to cover multiple drug-resistant gram-negative bacteria that produce extended-spectrum beta-lactamases (ESBLs) and AmpC enzymes (Matesanz and Mensa, 2021). Nutritional support care has also been proven to improve intestinal barrier function by providing energy substrate, modulating intestinal microecology and maintaining intestinal epithelial metabolism (Cha *et al*., 2022). Yet, research in this field has primarily been confined to the study of individual interventions. A study by a group of researchers, for example, pointed out that antibiotics, though effective in infection control, may aggravate intestinal flora disorders (Tumbarello *et al*., 2021). It is reported that the limitations of conventional nutritional support typically involve ignoring individual metabolic differences and lacking sufficient pertinence for intestinal mucosal repair (Bo *et al*., 2023). It remains a clinical question whether their combination produces a synergistic effect—inhibiting pathogens while simultaneously repairing the intestinal barrier, thereby improving patient outcomes. This study innovatively proposed a joint intervention model of "ceftazidime/avibactam anti-infection+dynamic nutritional support". Unlike conventional nutritional support, dynamic nutritional support is implemented to allow for

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individualized, dynamic adjustment of the nutritional plan, taking into account the patient's inflammatory markers, intestinal function, metabolic state and intestinal barrier function markers. This design breaks through the limitation of "disconnect between antibiotics and nutritional support", pioneering the research into the influence of their combination on intestinal barrier repair and clinical outcomes in sepsis patients. Should the combined intervention prove effective in boosting intestinal barrier function, decreasing infection recurrence and reducing 28-day mortality, this study will offer evidence-based support for the "anti-infection-intestinal barrier protection" dual-track strategy in sepsis treatment and refine clinical pathways. Meanwhile, by quantifying the precise intervention value of nutritional support, we can promote the transformation of critical care to "goal-oriented and dynamic adjustment" strategies, ultimately improving the overall level of medical care for sepsis patients.

MATERIALS AND METHODS

Study design

This was a prospective, single-center, open-label, parallel-group comparative study conducted from January 2022 to August 2025.

Sample size calculation

The 28-day all-cause mortality served as the primary outcome measure in this study. Referencing previous research data on intestinal barrier interventions in sepsis, the 28-day mortality rate in the conventional treatment group was about 35%, which was expected to be reduced to 25% in the observation group (HR=0.7) (Almangour *et al*., 2023). Using a two-sided test (α=0.05, β=0.2), calculated with G*Power 3.1, each group required 45 participants. Considering a 10% dropout rate (such as patients refusing to continue or being transferred), each group would need at least 50 participants.

Research participants

Between January 2022 and August 2025, our hospital enrolled 108 individuals with sepsis into this research and all patients received dynamic nutritional support. Among them, 54 cases received ceftazidime/avibactam, which was regarded as the observation group. Another 54 patients (control group), matching the participants enrolled in the observation group for age and gender, were given conventional antibiotics (ceftazidime/sulbactam). Patients' clinical data, shown in table 1, demonstrated no statistical inter-group difference (P>0.05).

Patient selection criteria

Eligibility requirements: Fulfillment of the Third International Consensus Definitions for Sepsis (Srzic *et al*., 2022); Age: 18-80 years old; Estimated length of intensive care unit (ICU) stay ≥72h. *Exclusion criteria*: Pregnant/lactating women; Severe immunodeficiency (HIV CD4+ T cells < 200/μL, terminal malignant tumor, etc.); Serious hepatic and renal insufficiency; Use of other specialized nutritional support or intestinal barrier-protective agents within 72 hours before admission; Allergies to target antibiotics; Hospital referral or treatment abandonment during the study period.

Intervention and treatment

Nutritional support care

All patients received dynamic nutritional support: 1) Enteral nutrition (EN) was initiated within 24 hours after admission. Short peptide EN preparations (low FODMAP formula, 1.0 kcal/mL) were prioritized, with an initial infusion rate of 10 ml/h. Patient tolerance (by monitoring abdominal distension, vomiting and gastric residual volume [GRV]) was evaluated every 8 hours, with gradual escalation to the target energy intake of 30-35 kcal/kg/d. 2) After EN initiation, glutamine (50ml/d, containing 30g of glutamine, added to the EN solution) and Bifid Triple Viable Capsules (2g/day, taken with warm water) were added simultaneously for 7 consecutive days. 3) Abdominal distension, diarrhea (Bristol Stool Scale) and GRV were recorded daily. Serum prealbumin and transferrin were measured every 3 days. Weekly fecal calprotectin detection was performed to evaluate intestinal inflammation. Intra-abdominal pressure (IAP) was controlled below 12mmHg to reduce intestinal mucosal ischemia. 4) Individualized cognitive behavioral therapy (CBT) was carried out 2-3 times a week by professional psychotherapists, focusing on correcting cognitive biases of the disease and relieving stress reactions through relaxation training (such as deep breathing and mindfulness meditation). 5) Controlling ICU environmental stimuli (e.g., reducing alarm volume and adjusting light cycle), combined with music therapy (playing relaxing music for 30 minutes per day) to improve sleep quality. For mechanically ventilated patients, pictorial communication boards or electronic devices were used to assist in expressing needs and reducing the sense of helplessness. 6) "Sepsis rehabilitation class" was set up to explain disease knowledge, drug management and early warning symptoms (such as increased abdominal distension and decreased urine volume) once a week and train family members to master basic nursing skills (such as nasogastric tube maintenance). Patient support groups were established to invite convalescent patients to share their experiences and enhance their confidence in treatment.

Medication regimen

On this basis, the control group was given ceftazidime/sulbactam. The specific regimen was 3.0 grams per dose, dissolved in 100 mL of normal saline for intravenous infusion once every 8 hours. Each infusion was required to last for 30 minutes or more. For the observation group, patients received Ceftazidime/Avibactam instead. Its administration details included 2.5 grams per dose dissolved in 100 mL of normal saline, intravenous infusion every 8 hours and an infusion time of ≥ 30 minutes. Both

groups had a treatment course of 7 to 14 days, which was adjusted based on blood culture results and clinical symptoms. Antibiotic dosing followed FDA-approved recommendations and previous pharmacokinetic studies in critically ill patients (Wetzel *et al*., 2021).

Endpoints

1) ICU length of stay, mechanical ventilation time, total length of hospital stays, time to negative blood culture conversion, duration of antibiotic therapy and the incidence of ICU-acquired infection (ventilator-associated pneumonia, catheter-related bloodstream infection, etc.) were counted. Patients underwent a 28-day follow-up to record their 28-day all-cause mortality. 2) Pre- and post-treatment venous blood was collected from fasting patients for ELISA measurements of diamine oxidase (DAO), lipopolysaccharide-binding protein (LBP), fecal calprotectin (FC), claudin-1, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), superoxide dismutase (SOD) and malondialdehyde (MDA), with all kits purchased from Beijing Solarbio Science and Technology Co., Ltd.. The detection process was in strict accordance with the kit instructions. 3) Fecal samples were collected before and after treatment to determine FC levels with ELISA. 4) The adverse events during the treatment course were counted. Liver function tests (ALT, AST), renal function (creatinine, eGFR) and neurological symptoms were monitored twice weekly to detect potential hepatotoxicity, nephrotoxicity, or neurotoxicity.

Statistical analysis

This study used SPSS 31.0 for statistical analysis. Comparisons of count data [n(%)] were performed using the chi-square test. For normally distributed measurement data ($\bar{\chi}\pm s$), comparisons were conducted using independent sample t-tests and paired t-tests; non-normally distributed data were analyzed with Mann-Whitney U tests and Wilcoxon rank-sum tests. A $P<0.05$ denotes that the detected difference is statistically significant.

RESULTS

Comparison of clinical outcomes

The observation group showed shorter durations of ICU stay and mechanical ventilation than the control group ($P<0.05$), though no significant difference was identified in the total length of hospital stay ($P>0.05$). The comparison of 28-day all-cause mortality also revealed a lower rate in the observation group ($P<0.05$, Table 2).

Comparative analysis of antibiotic efficacy and drug resistance index

In comparison with the control group, the time to negative blood culture conversion and duration of antibiotic therapy were shortened in the observation group ($P<0.05$). However, the two groups were not markedly different in the incidence of ICU-acquired infection ($P>0.05$, Table 3).

Comparison of intestinal barrier function

According to the detection results of intestinal barrier function markers, DAO, LBP and FC decreased in both cohorts after treatment, while claudin-1 increased ($P<0.05$). The inter-group comparison revealed lower DAO, LBP and FC, as well as higher claudin-1, in the observation group compared to the control group ($P<0.05$, Fig. 1).

Comparison of inflammatory and stress responses

Both therapies led to a reduction in IL-1β, IL-6, TNF-α and MDA, along with a rise in SOD ($P<0.05$). Though SOD and MDA were similar between groups ($P>0.05$), IL-1β, IL-6 and TNF-α were lower in the observation group vs. the control group ($P<0.05$, Fig. 2).

Comparative safety analysis

Finally, the adverse events patients experienced during treatment were analyzed. The total incidence rate was 35.19% in the observation group and 27.78% in the control group, with no significant inter-group difference found ($P>0.05$, Table 4).

DISCUSSION

Sepsis is the leading cause of ICU deaths, with its core pathological mechanism lying in the vicious circle of "infection–intestinal barrier damage–systemic inflammation" (Martin-Loeches et al., 2024). This study validates the multi-dimensional protective effect of ceftazidime/avibactam combined with dynamic nutritional support on the intestinal barrier, which is expected to become a key breakthrough in optimizing the clinical pathway for sepsis and to promote the transformation of critical care toward "precision and dynamic" approaches.

Shorter ICU stay and mechanical ventilation durations were observed in the observation group compared to the control group, consistent with previous studies (Gupta *et al*., 2024; Wu *et al*., 2024). Meanwhile, the duration of antibiotic therapy was also shortened in the observation group and the 28-day mortality was lower, suggesting that the novel antibiotic combination may reduce the risk of secondary infection by clearing pathogens faster. These findings are supported by the research of Hsu *et al*., which noted a shortened course of treatment, associated with reduced mortality, in patients with carbapenem-resistant Enterobacteriaceae infections treated by ceftazidime/avibactam (Hsu *et al*., 2024). The possible reason is that this study actively regulates intestinal microecology through dynamic nutritional support (probiotics+glutamine), forming a double protection mechanism that offsets the risk of some equipment-related infections (Ohta *et al*., 2021). The subsequent intestinal barrier function comparison indicated superior repair efficacy in the observation group after treatment, confirming the direct protection of new nutrients on intestinal mucosal metabolism.

Table 1: Comparison of baseline data between the two groups

		Control (n=54)	Observation (n=54)	95%CI	t or χ^2	P
Age		66.59±4.80	65.96±6.02	-2.706 to 1.447	0.601	0.549
Gender	*Male/female*	34 (62.96%)/20 (37.04%)	29 (53.70%)/25 (46.30%)	0.684 to 3.229	0.952	0.329
Vasopressor use	*Yes/no*	26 (48.15%)/28 (51.85%)	30 (55.56%)/24 (44.44%)	0.348 to 1.558	0.593	0.441
SOFA score		5.19±2.12	5.06±2.00	-0.917 to 0.657	0.327	0.745
APACHE II		20.35±6.36	19.65±5.65	-3.000 to 1.592	0.608	0.545
Lactate (mmol/L)		4.09±0.76	3.88±0.80	-0.504 to 0.093	1.367	0.175
Admission time (h)		15.28±5.17	14.56±4.80	-2.626 to 1.181	0.752	0.454
Source of infection	*Skin and soft tissue*	8 (14.81%)	6 (11.11%)	-	0.520	0.972
	Pulmonary	29 (53.70%)	31 (57.41%)			
	Urinary tract	7 (12.96%)	6 (11.11%)			
	Intestinal	5 (9.26%)	6 (11.11%)			
	Bloodstream	5 (9.26%)	5 (9.26%)			

Table 2: Recovery of patients in the two groups

Groups (54 cases in each group)	Length of ICU stay (d)	Duration of mechanical ventilation (d)	Length of stay (d)	All-cause mortality
Control	11.13±2.69	7.15±1.84	26.43±3.28	16 (29.63%)
Observation	8.78±2.47	6.13±1.35	25.70±2.83	7 (12.96%)
95%CI	-3.336 to -1.368	-1.633 to -0.404	-1.891 to 0.447	1.116 to 7.126
t or χ^2	4.737	3.286	1.225	4.475
P	<0.001	0.001	0.223	0.034

Table 3: Treatment effects in the two groups of patients

Groups (54 cases in each group)	Time to negative blood culture (d)	Duration of antibiotic use (d)	ICU-acquired infection
Control	5.80±1.69	6.30±2.25	7 (12.96%)
Observation	5.09±1.39	5.56±1.46	4 (7.41%)
95%CI	-1.294 to -0.114	-1.464 to -0.018	0.534 to 5.948
t or χ^2	2.365	2.031	Fisher's exact
P	0.020	0.045	0.527

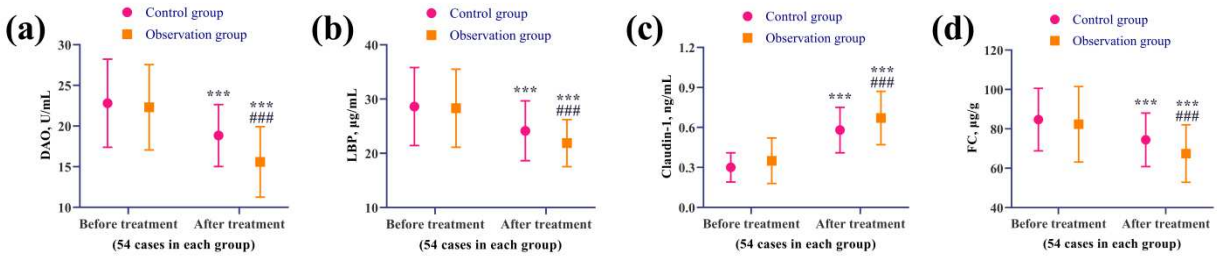

Fig. 1: Comparison of the detection results of markers of intestinal barrier function between the two groups. After treatment, claudin-1 in the observation group was higher than that in the control group; DAO, LBP, and FC were lower than those in the control group. (a) Comparison of DAO; (b) Comparison of LBP; (c) Comparison of claudin-1; (d) Comparison of FC. Note: *** and ### indicate that there are differences in the results of intra-group and inter-group comparisons, respectively (P<0.05).

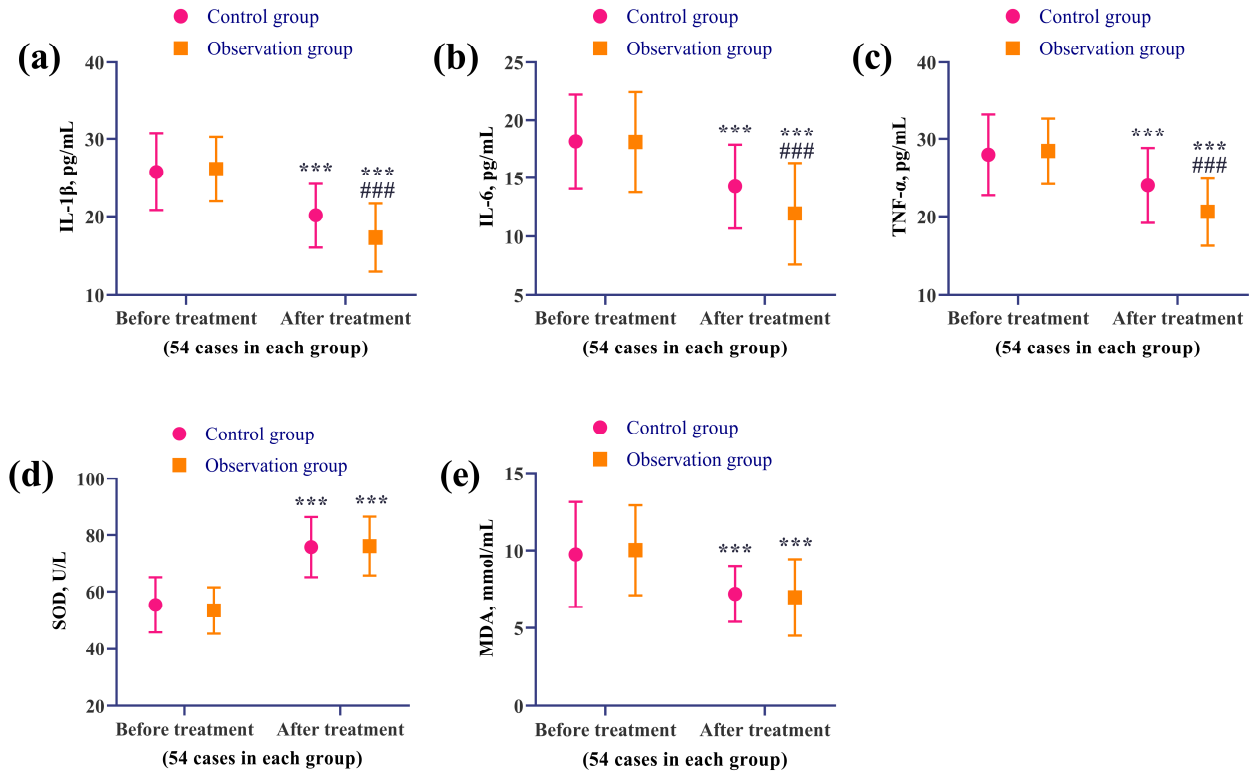

Fig. 2: Detection results of inflammatory factors and stress response markers in both groups of patients. The levels of IL-1β, IL-6 and TNF-α in the observation group after treatment were lower than those in the control group. (a) Comparison of IL-1β; (b) Comparison of IL-6; (c) comparison of TNF-α; (d) comparison of SOD; (e) Comparison of MDA. Note: *** and ### indicate that there are differences in the results of intra-group and inter-group comparisons, respectively ($P<0.05$).

Table 4: Adverse effects in the two groups of patients

Groups (54 cases in each group)	Rash	Deterioration of renal function	Elevated liver enzymes	Glycemic variability	Gastric retention	Total
Control	6 (11.11%)	3 (5.56%)	4 (7.41%)	1 (1.85%)	1 (1.85%)	27.78%
Observation	7 (12.96%)	5 (9.26%)	5 (9.26%)	1 (1.85%)	1 (1.85%)	35.19%
95%CI						0.315 to 1.543
t or χ^2						0.687
P						0.407

This finding echoes the conclusion drawn in an animal experiment: β-lactamase inhibitors reduce intestinal epithelial cell apoptosis by inhibiting bacterial endotoxin release (Castanheira *et al*., 2022). It is worth noting that the greater decrease in fecal FC in the observation group may be related to the selective killing characteristics of new antibiotics on intestinal flora. In contrast to conventional antibiotics, we hypothesize that ceftazidime/avibactam may have a lesser impact on butyrate-producing bacteria compared to conventional antibiotics, based on its narrower antimicrobial spectrum (e.g., Roseburia spp.) (Mekadim *et al*., 2025), a group essential for the preservation of intestinal mucosal barrier integrity. However, this requires validation through microbiome sequencing in future studies.

The difference in inflammatory cytokines suggests that the novel intervention model has a stronger systemic anti-inflammatory effect. This is complementary to the clinical research conclusions of a previous study, where the authors reported that new antibiotics directly inhibit the release of bacterial endotoxins while blocking the inflammatory cascade at the source by modulating the TLR4/NF-κB axis (Naveed *et al*., 2022). Of note, MDA levels showed no significant disparity between the two groups in this study. One possible reason is that the 28-day observation period failed to capture the long-term variations in oxidative stress. Another explanation might be that the antioxidant ingredients (such as vitamin E) in the nutritional support were balanced in both groups, thereby weakening the specific impact of the intervention.

Finally, although there was no significant difference in the incidence of adverse events between the two groups, only one case of diarrhea was reported in the observation group. This aligns with previous research, which reported a reduced incidence of antibiotic-associated diarrhea when broad-spectrum antibiotics are combined with probiotics (Chen *et al*., 2021). The differences in safety observed may be due to: 1) Ceftazidime/avibactam having a stronger inhibitory effect on Clostridium perfringens in the gut; 2) The dynamic nutritional monitoring system more accurately preventing excessive feeding that leads to an overload in the intestinal cavity. Based on the above findings, we propose that in future clinical practice, priority should be given to the combination of ceftazidime/avibactam and dynamic nutritional support when managing three specific groups of ICU patients: those with ESBL or AmpC enzyme-producing gram-negative bacterial infections, sepsis patients with acute gastrointestinal injury (AGI ≥ Grade II) and septic shock patients in need of long-term mechanical ventilation. However, while our sample size of 108 was statistically justified by G*Power, being from a single center makes it difficult to rule out the influence of local pathogen patterns. Meanwhile, due to the limited intervention period, the long-term effect of dynamic nutritional support was not analyzed. In terms of mechanism, there is no basic research on intestinal mucosal permeability or intestinal stem cell proliferation, warranting further investigation.

CONCLUSION

Ceftazidime/avibactam combined with dynamic nutritional support significantly improves the prognosis of sepsis patients through the triple mechanism of "strengthening antibacterial activity–accelerating intestinal mucosal repair–modulating systemic inflammation". The precise anti-infection effect of the new antibiotic combination synergizes with the microecological regulation mediated by nutritional support, providing an innovative solution to break the "infection–intestinal injury" vicious cycle.

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Authors' contributions
Jun Wu: Conceived, designed and supervised the study; Xiaojuan Sha: Wrote and revised the manuscript; Lijuan Sun: Collected and analyzed the data; Xiaojuan Sha and Lijuan Sun: Contributed equally to this work as co-first authors. All authors have read and approved the final submitted manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
The study involving human subjects complied with the Declaration of Helsinki and was approved by the ethical committee of the Nanjing First Hospital (No. KY20230829-03) and all participants provided written informed consent.

Conflict of interest
All the authors declare no conflict of interest.

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