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Improvement of health status of sepsis patients undergoing blood purification therapy by using combination of acetylcysteine and frail management

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Abstract: In this study, the efficacy of Fatigue, Resistance, Ambulation, Illness and Loss of weight (FRAIL) management combined with acetylcysteine (AChE) in blood purification therapy for sepsis (SS) patients was investigated. Seventy-eight SS patients undergoing blood purification were randomized to an observation group (FRAIL + AChE, n=42) or a control group (conventional care, n=36). FRAIL score, APACHE II score, vital signs (heart rate, mean arterial pressure, oxygen saturation), inflammatory factors oxidative stress indexes and nutritional proteins were assessed before and after the intervention in both groups. The results of the study showed that after the intervention, the FRAIL score and APACHE II score were reduced more significantly in the observation group ($P<0.05$). In addition, vital signs improved more significantly in the observation group. After the intervention, all inflammatory factors in the observation group were lower than those in the control group, while nutritional proteins were higher than those in the control group ($P<0.05$). In addition, oxidative stress injury was also more favorable in the observation group than in the control group after the intervention. These results suggest that FRAIL management combined with AChE may play a significant role in SS treatment.

Keywords: Acetylcysteine, blood purification therapy, ambulation-fatigue-illness-loss of weight, nutritional status, Sepsis

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INTRODUCTION

The morbidity and mortality of SS remain high, afflicting approximately 48.9 million people and causing 11 million deaths each year (Cecconi *et al.*, 2018). SS is clinically presented with chills, fever, palpitations, shortness of breath, mental state changes, etc. (Srzic *et al.*, 2022). At present, SS is mainly defined as two clinical stages, namely, latent infection stage and acute onset stage (Zhao, 2022). The insidious symptoms at the initial infection stage of SS usually result in the failure of medical staff to identify, diagnose and treat it in time, which leads to the rapid deterioration of SS and circulatory shocks (Kellum *et al.*, 2022). During the acute onset period, patients may experience significant blood pressure drops, limb dampness and coldness, decreased body temperature, inadequate circulatory perfusion, loss of nutritional proteins, organ dysfunction and even failure (Jang *et al.*, 2017). Therefore, timely and early detection of SS in clinical practice, as well as more targeted intervention measures are needed to alleviate disease progression and ensure patients' health and life safety.

Fatigue, Resistance, Ambulation, Illness and Loss of weight (FRAIL) management refers to the evaluation of patients' fatigue, endurance, mobility, disease and body mass based on the F RAIL score and the formulation of targeted and individualized nursing interventions according to patients different problems, so as to more effectively help them improve their prognostic quality and promote their vital sign stability (Dias *et al.*, 2020). FRAIL management has been proven to have excellent clinical application effects in the clinical treatment of cardiovascular diseases, chronic obstructive pulmonary disease, etc., providing more reliable safety guarantees for patient rehabilitation (Yamato *et al.*, 2022; Verduri *et al.*, 2024). In addition, acetylcysteine (AChE), a very common antioxidant in clinical practice, belongs to the commonly used adjuvant drugs in blood purification therapy and its mechanism of action is to bind with electrophilic chemical groups to generate L-cysteine, which induces glutathione (GSH) production, fights against free radicals and attenuates oxidative damage to cells and tissues (Kumar *et al.*, 2023). Meanwhile, due to the small relative molecular mass of AChE active component, it is easy to enter the cell through the cell membrane and its antioxidant effect is extremely significant (Raghu *et al.*, 2021). The use of AChE in SS is now clinically validated (Chertoff, 2018).

However, there is no clinical report to validate the effect of FRAIL management combined with AChE on SS and the application value of their combination remains uncharacterized. Accordingly, this study discusses the improvement effect of FRAIL management combined with AChE on the health status of SS patients undergoing blood purification therapy, so as to provide more reliable safety guidance for future SS treatment.

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MATERIALS AND METHODS

Study population

The sample size required for the study was estimated by G-Power software. With effect size=0.5, α=0.05 and power=0.95, a minimum of 34 study subjects were needed in each group. 78 patients with SS who underwent hemodialysis in Nanjing First Hospital from March 2019 to December 2023 were selected for the study and 42 patients receiving FRAIL management combined with AChE (observation) and the rest 36 patients receiving conventional management (control group). This study has been approved by the Medical Ethics Committee of Nanjing First Hospital (KY20201102-03) and all patients and their families have been informed and signed informed consent. All study participants and the researchers who collected the data were unaware of the subgroups of patients.

Eligibility and exclusion criteria

Inclusion criteria: Patients were clinically diagnosed as SS (Ackerman *et al.*, 2021) and needed continuous blood purification, with complete clinical data. Exclusion criteria: Patients younger than 18, those with severe liver and kidney dysfunction, severe bleeding/anemia, coagulopathy, serious cardio-cerebral complications, end-stage uremia, or malignant tumors, as well as those with poor compliance and inability to cooperate with treatment, were excluded.

Blood purification therapy

All patients were treated with continuous blood purification therapy, heparin anticoagulation for vascular access, dialysis with reverse osmosis water and bicarbonate dialysate, blood flow rate set at 200 mL/min, replacement fluid rate set at 5 L/min, 10-12 h/d and heparin anticoagulation for vascular access for 4 weeks.

FRAIL management

Control group: During the treatment, patients' vital signs, such as body temperature, pulse, blood pressure and electrocardiograph, were strictly monitored. Besides, patients' urine volume, filtrate volume and substitution fluid volume were strictly recorded every day to ensure the maintenance of fluid balance in the body. Timely intervention measures were initiated when the patient's blood pressure dropped. Furthermore, the patency of vascular access was ensured, the filter and pipeline were flushed regularly and the patient's mouth, nasal cavity and skin were closely observed for bleeding points. The dosage of anticoagulant drugs was also controlled. Attention was paid to the occurrence of hyperkalemia or hypokalemia in patients and if so, timely intervention was carried out. Moreover, patients were given adequate nutritional support during treatment. Observation group: FRAIL management was performed in the control group. The patients' underlying diseases, disease course, treatment methods and previous health conditions were evaluated, with attention paid to avoiding guiding words to ensure objectivity during the assessment. According to the evaluation results, a targeted nursing plan was made for each patient. Meanwhile, nurses actively communicated with patients and their families to improve their treatment compliance. Furthermore, the nursing staff provided psychological counseling for patients with emotional abnormalities and encouraged and affirmed patients with family members, so that they were more motivated to cooperate with the treatment, care and related functional exercises. Patients were also given active encouragement and support to improve their mobility. In addition, patients were informed of the treatment progress and precautions to improve their treatment cooperation and accelerate their recovery from the disease. The nurses also patiently listened to patients' inner feelings and needs, actively cared for and comforted them and eliminated their current doubts and other negative emotions. For patients with nutritional deficiencies and low body mass levels, timely recommendations were made for nutritious and easily digestible foods, emphasizing the reasonable combination of different types of food to ensure balanced nutrient intake and improve patient body mass. Nursing staff strengthened their monitoring of patients' conditions, closely observed potential adverse reactions and promptly prepared for interventions. They also helped to enhance the observation ability of patients and their families on disease symptoms, thus effectively preventing the further development of the condition and accelerating patient recovery.

AChE therapy

AChE (Hangzhou Minsheng Pharmaceutical Co., Ltd, H20051788) was given to the observation group patients for intravenous drip, taking 8 g AChE (40 ml) and diluting it with 5% glucose injection 100 mL for 1 time/d for 7-14d.

Endpoints

(1) Clinical data: Patients' age, gender, underlying diseases, etc. were collected. (2) Clinical condition assessment: The FRAIL Scale (Simsek & Ucar, 2022) (including fatigue, endurance, mobility, disease and body mass dimensions, with a higher score suggesting more obvious frailty) and the Acute Physiology and Chronic Health Evaluation (APACHE II; higher scores indicate more serious symptoms) (Ringle *et al.*, 2021) scores were investigated before and after the intervention. (3) Vital signs: Heart rate (HR), mean arterial pressure (MAP) and blood oxygen saturation (SpO_2) were recorded before and after the intervention. (4) Inflammation, oxidative stress damage and nutritional proteins: 6 mL of fasting venous blood was drawn from patients for the quantification of C-reactive protein (CRP), procalcitonin (PCT), tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) levels by enzyme-linked immunosorbent assay, the measurement of superoxide dismutase (SOD) and malondialdehyde (MDA) levels using xanthine oxidase assay and thio barbituric acid

assay, respectively, as well as the determination of serum albumin (ALB), prealbumin (PA) and hemoglobin (Hb) with an automatic biochemical analyzer.

STATISTICAL ANALYSIS

This study used SPSS 23.0 statistical analysis software to conduct statistical analysis on the collected data. The chi-square test was used for count data [n (%)], represented by χ^2 and the independent sample t-test and paired t-test were used for measurement data (Mean ±SD), represented by t, with $P<0.05$ considered statistically significant.

RESULTS

Comparison of general clinical data

No statistical difference was identified between two groups in sex, age and other clinical data ($P>0.05$), table 1.

Comparison of clinical conditions

The two groups showed similar FRAIL and APACHE II scores before the intervention ($P>0.05$). After the intervention, the scores of both groups decreased, with even lower scores in the observation group ($P<0.05$), fig. 1.

Comparison of vital signs

No significant inter-group differences were identified in vital signs before the intervention ($P>0.05$). Both groups showed decreased HR after the intervention, especially in the observation group; while an increase in MAP and SpO_2 was observed in both groups, with even higher levels in the observation group ($P<0.05$), fig. 2.

Comparison of inflammatory responses

CRP, PCT, TNF-α and IL-8 of both groups decreased after the intervention, with their levels being (106.12±41.48) pg/mL, (4.61±2.28) pg/mL, (31.35±1.55) ng/L and (18.53±4.56) ng/L in the observation group, respectively, all of which were lower compared with the control group ($P<0.05$), fig. 3.

Comparison of oxidative stress damage

Similarly, the two groups were not statistically different in SOD and MDA before the intervention ($P>0.05$). After the intervention, SOD in both groups increased, but it was higher in the observation group than in the control group; MDA levels were significantly lower in the observation group compared to the control group ($P<0.05$), fig. 4.

Comparison of nutritional status

Finally, the nutritional protein test results of the two groups showed that the nutritional proteins of the control group did not change significantly before and after the intervention ($P>0.05$), while the ALB, PA and Hb of the observation group after the intervention were (32.65±2.89) g/L, (207.91±29.43) mg/L and (126.81±14.43) g/L, respectively, all of which were elevated compared to the pre-interventional levels and those of the control group ($P<0.05$), fig. 5.

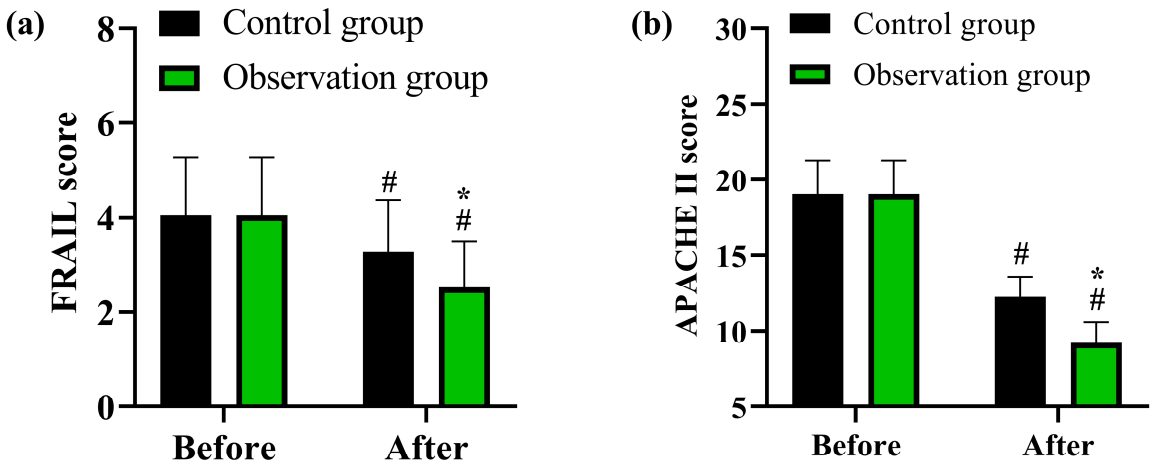
DISCUSSION

SS, as a clinical critical syndrome, is usually accompanied by serious organ failure and blood infection, with a high mortality (Salomao *et al.*, 2019). In this study, we discussed the intervention effect of FRAIL management combined with AChE on SS. First, the FRAIL and APACHE II scores of the observation group showed a more significant decrease compared to the control group. SS patients suffer from impaired organ function due to insufficient circulatory perfusion, leading to symptoms such as fatigue and decreased endurance and mobility (Colantuoni *et al.*, 2020). Through comprehensive patient assessments, FRAIL management clarifies disease manifestations and current status. This enables individualized care (e.g., ensuring balanced nutrition and rest) and the formulation of tailored treatment plans aligned with patient capabilities. These measures can solve patients' problems in a targeted manner, alleviate their clinical symptoms, relieve their subjective and objective physical and mental pain and reduce their frailty (Breccia *et al.*, 2018). This also explains the lower FRAIL and APACHE II scores of the two groups mentioned above. In previous studies, we also found that FRAIL management has a positive effect on the rehabilitation of patients with heart failure (Son *et al.*, 2022). In addition, the MAP and SpO_2 were elevated and HR was decreased in both groups after treatment, which also confirmed a more significant improvement in their vital signs. We believe that the conventional clinical management of SS, mainly using drugs and other therapeutic means to control inflammatory indicators, lacks a holistic and comprehensive approach to the care of SS. However, drug use is associated with certain adverse effects and there is a lack of long-term sustained effects on symptom control. FRAIL management, on the other hand, evaluates from a holistic perspective, covering the prevention and observation of SS. For patients whose infection has not been well controlled for a long time, prevention should be emphasized and measures should be taken from the root cause. The combined application of various measures can effectively control the levels of inflammatory reaction and stress injury, so that the infection symptoms of patients can be controlled to some extent and the condition can be observed and cared for comprehensively, thus contributing to the stability of patients' vital signs. The important role of AChE in the treatment of SS cannot be ignored.

In the comparison of inflammatory and oxidative stress responses, CRP, PCT, TNF-α, IL-8 and MDA in the observation group were lower than those in the control group, while SOD was higher, which also suggests that FRAIL management combined with AChE is more effective in relieving acute injury in SS patients.

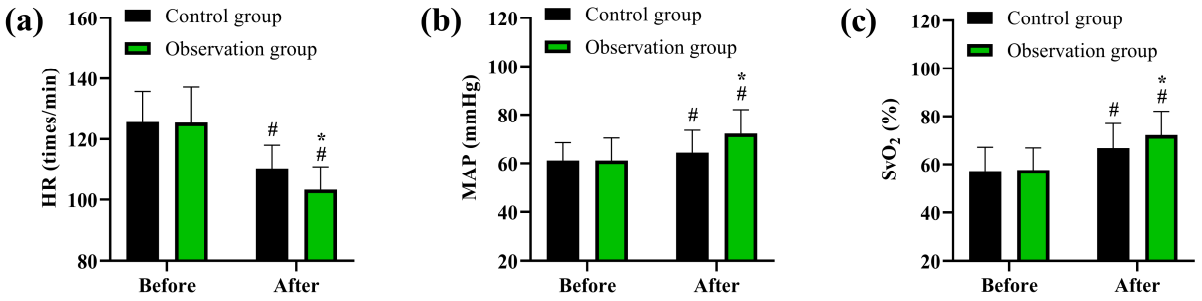
Table 1: Comparison of general clinical data

		Control group (n=36)	Observation group (n=42)	t/χ^2	P
Sex					
	male	21 (58.33)	23 (54.76)	0.101	0.751
	female	15 (41.67)	19 (45.24)		
Age		64.4±5.4	63.8±6.7	0.431	0.668
Smoking					
	yes	19 (52.78)	25 (59.52)	0.359	0.549
	no	17 (47.22)	17 (40.48)		
Drinking					
	yes	21 (58.33)	26 (61.90)	0.103	0.748
	no	15 (41.67)	16 (38.10)		
Cause of disease					
	infection	20 (55.56)	24 (57.14)	0.082	0.960
	trauma	13 (36.11)	14 (33.33)		
	malignant tumor	3 (8.33)	4 (9.52)		



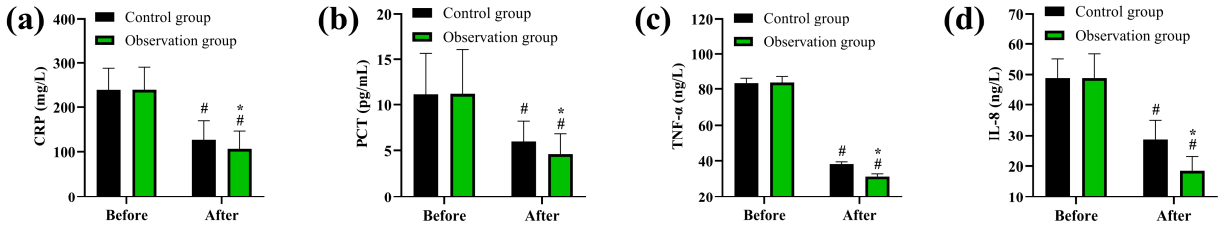
(a) Changes in FRAIL scores. (b) Change in APACHE II score. *, # indicate statistically significant differences from the control group and before intervention, respectively (i.e., P<0.05). Fatigue, Resistance, Ambulation, Illness, and Loss of weight, FRAIL; Acute Physiology and Chronic Health Evaluation, APACHE II.

Fig. 1: Comparison of clinical conditions.



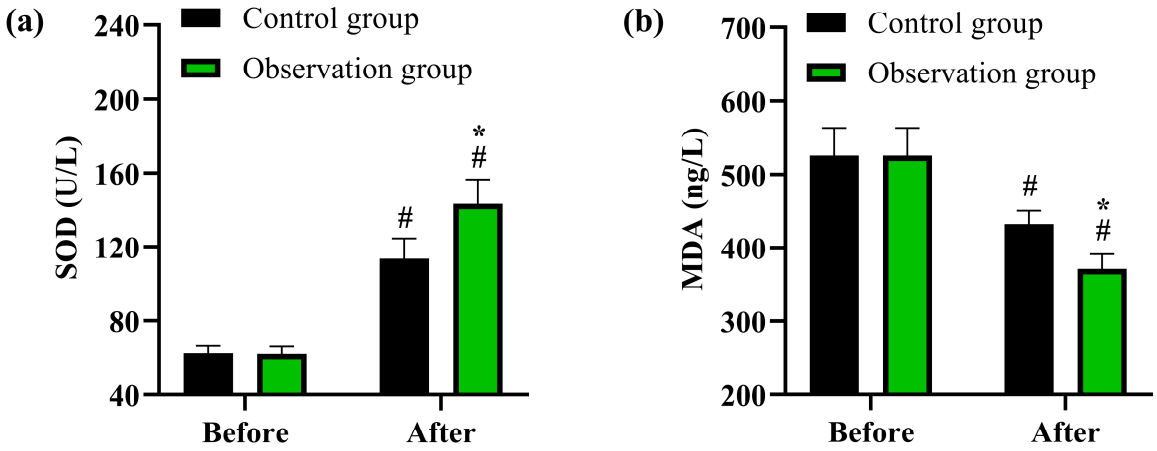
(a) Changes in HR. (b) Change in MAP. (c) Change in SpO_2. *, # indicate statistically significant differences from the control group and before intervention, respectively (i.e., P<0.05). Heart rate, HR; Mean arterial pressure, MAP; blood oxygen saturation, SpO_2.

Fig. 2: Comparison of vital signs.



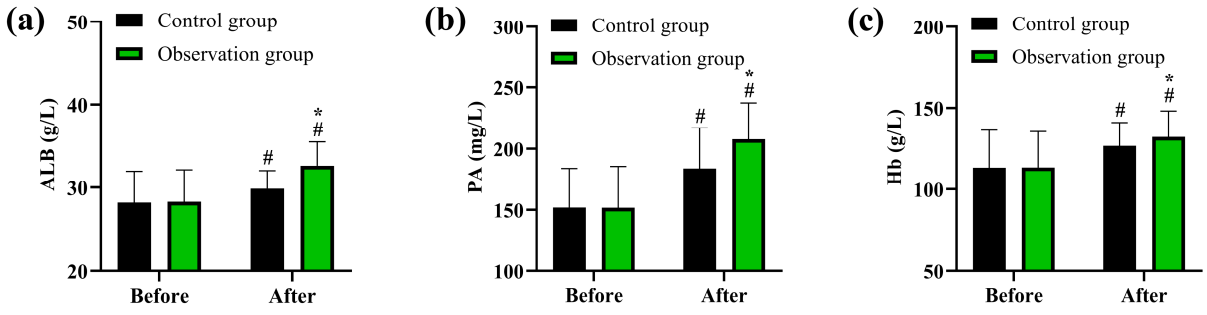
(a) Changes in CRP. (b) Change in PCT. (c) Change in TNF-α. (d) Changes in IL-8. *, # indicate statistically significant differences from the control group and before intervention, respectively (i.e., P<0.05). C-reactive protein, CRP; Procalcitonin, PCT; Tumor necrosis factor-α, TNF-α; Interleukin-8, IL-8.

Fig. 3: Comparison of inflammatory responses.



(a) Changes in SOD. (b) Change in MDA. *, # indicate statistically significant differences from the control group and before intervention, respectively (i.e., P<0.05). Superoxide dismutase, SOD; Malondialdehyde, MDA.

Fig. 4: Comparison of oxidative stress damage.



(a) Changes in ALB. (b) Change in PA. (c) Change in Hb. *, # indicate statistically significant differences from the control group and before intervention, respectively (i.e., P<0.05). Albumin, ALB; Prealbumin, PA; Hemoglobin, Hb.

Fig. 5: Comparison of nutritional status.

Research has shown that AChE can enhance the body's anti-inflammatory activity and the killing effect of neutrophils on pathogens, repair vascular endothelial damage, improve endothelial barrier function (Calverley *et al.*, 2021). Its anti-inflammatory mechanism mainly proceeds through the inhibition of inflammatory transcription factor-activating protein-1 and nuclear transcription factor-κB (Amore *et al.*, 2013) and the nuclear transcription factor-κB pathway plays a central role in the activation of interleukins (Lin *et al.*, 2020). For

example, a study by Abdelhafez *et al*. found that AChE inhibited TNF-α-mediated nuclear transcription factor-κB activation and decreased interleukin-6 levels (Abdelhafez *et al.*, 2021). In addition, AChE, as a highly effective antioxidant, can alleviate excessive oxidative stress levels in the body by clearing excess reactive oxygen species and inhibiting the activation of nitrogen oxides (Holford *et al.*, 2020). It is precisely because of the above positive effects that the inflammatory and oxidative stress responses of patients in the observation group were more significantly improved compared to the control group. The observed reductions in CRP, TNF-α and IL-8 in the observation group not only achieved statistical significance but also aligned with clinically meaningful thresholds. For instance, CRP levels below 100 mg/L have been associated with a 20% reduction in 28-day mortality in SS patients (Kubo *et al.*, 2024). Similarly, TNF-α suppression correlates with attenuated systemic inflammation and improved organ perfusion, as evidenced by reduced vasopressor dependency in prior trials (Kassasseya *et al.*, 2024). These biomarker improvements may reflect a decreased risk of multi-organ dysfunction, a critical determinant of sepsis outcomes.

Due to the occurrence of post-SS microcirculation disorders, the stability of the patient's nutritional status is seriously damaged and lose a lot of nutritional proteins is lost (Boomer *et al.*, 2011). The ALB, PA and Hb of the study group were significantly higher than those of the control group, which showed that it played an important role in improving the nutritional status of SS patients. This is of great significance both in preventing the further progression of SS and safeguarding the life safety of patients. Analyzing the reasons, we believe that: (1) antioxidant effect: AChE can increase the synthesis of GSH, which in turn improves the resistance of cells to free radicals (Oliva *et al.*, 2023). Free radicals are the main cause of oxidative damage and many diseases and the antioxidant effect of AChE helps to reduce the damage of free radicals to cells. (2) Improvement of immune function: the antioxidant effect of AChE helps to protect immune cells from damage, thus improving the function of the immune system. The immune system is an important part of the defense against infections and diseases and the action of AChE enhances the body's ability to fight pathogens and diseases (Shahveghar Asl *et al.*, 2023). (3) Reduces the risk of cardiovascular disease: AChE reduces the occurrence of atherosclerosis by lowering homocysteine levels in the blood. Homocysteine is a dangerous indicator of cardiovascular disease and the effects of AChE can reduce the risk of cardiovascular disease by lowering homocysteine levels (Maestro *et al.*, 2023). While AChE demonstrated therapeutic benefits in reducing inflammation and oxidative stress, its safety profile warrants careful consideration. Known side effects of high-dose AChE include nausea, vomiting and allergic reactions (e.g., rash, bronchospasm) due to histamine release (Wang *et al.*, 2020). In rare cases, excessive doses may induce hepatic toxicity or methemoglobinemia (Chiew & Buckley, 2021). In our study, transient hypotension (n=3) and mild gastrointestinal discomfort (n=5) were observed in the AChE group, which resolved spontaneously without intervention. No severe adverse events (e.g., anaphylaxis, hepatotoxicity) were reported, consistent with prior studies indicating the safety of short-term AChE use in critically ill patients (Shi *et al.*, 2020). Nevertheless, clinicians should monitor liver function and hemodynamic stability during treatment, particularly in patients with pre-existing hepatic impairment.

This study has several limitations. First, its single-center design and relatively small sample size may limit generalizability. Second, the short follow-up period (6 months) precludes assessment of long-term outcomes. Third, unmeasured confounders, such as genetic predispositions or microbiome variations, could influence results. Future studies should address these gaps through multicenter cohorts and extended observation. While FRAIL management combined with AChE shows promise in improving sepsis outcomes, further large-scale randomized controlled trials are warranted to validate these findings before widespread clinical adoption. Future research should also explore cost-effectiveness and long-term safety profiles. Also, while our findings highlight the potential clinical relevance of inflammatory marker reduction, this study did not directly assess hard endpoints such as 28-day mortality or ICU length of stay. Future trials should incorporate these outcomes to validate the translational impact of FRAIL management combined with AChE in SS.

CONCLUSION

Collectively, FRAIL management combined with AChE effectively stabilizes vital signs, reduces inflammation and oxidative stress and improves nutritional status, thereby enhancing patient survival. While FRAIL management combined with AChE shows promise in sepsis care, its clinical application should be guided by rigorous monitoring for adverse effects. Further studies are needed to establish optimal dosing regimens and validate long-term safety.

Conflicts of interest

All authors declare no conflicts of interest.

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