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Ciprofol versus propofol for long-term sedation in mechanically ventilated patients with sepsis: a randomized controlled trial

Feng-Zhi Zhao[1†], Long-Zhu Li[1†], Pei-Yan Luo[2†], Xiang-Jie Duan[1], Shi-Fang Huang[1*], Hai-Yan Yin[1*] and Wan-Jie Gu[1*]

Abstract

Background Sedatives are often used to facilitate mechanical ventilation in patients with sepsis. Ciprofol is a new promising sedated candidate with a higher binding activity to the gamma-aminobutyric acid-A receptor than propofol. This study aimed to compare the efficacy and safety of ciprofol and propofol for long-term sedation in mechanically ventilated patients with sepsis.

Methods In this single-center randomized clinical trial, mechanically ventilated adults with sepsis in the intensive care unit (ICU) who anticipated to require long-term sedation ≥ 24 h were randomly assigned to receive intravenous ciprofol or propofol. The target sedation goal was − 3 to 0 according to the Richmond Agitation-Sedation Scale. The primary outcome was weaning time. Secondary outcomes included the percentage of time within the target sedation range, successful sedation (the percentage of time within the target sedation range ≥ 70% without rescue sedation), ICU and in-hospital mortality, length of ICU and hospital stay, hypotension, and bradycardia.

Results A total of 60 patients were randomized, 4 were excluded because of withdrawing treatment, 28 were assigned to ciprofol group and 28 to propofol group. Weaning time in ciprofol group was shorter than propofol group (median [interquartile range (IQR)], 104.0 [40.8–147.3] hours vs 132.5 [69.8–207.8] hours), but not reached significant difference between groups ($P = 0.123$). Ciprofol had significantly higher percentage of time within the target sedation range (median [IQR], 72.2% [14.3–92.7%] vs 22.6% [0.0–45.4%]) and successful sedation (53.6% [15/28] vs 14.3% [4/28]) than propofol. No significant differences were observed in ICU mortality, in-hospital mortality, length of ICU stay, length of hospital stay, hypotension, and bradycardia between groups.

Conclusions Ciprofol is an effective and safe agent among mechanically ventilated patients with sepsis who anticipated to require long-term sedation.

Trial registration number The trial was registered at the Chinese Clinical Trial Registry (ChiCTR2200066835) on December 19, 2022.

†Feng-Zhi Zhao, Long-Zhu Li and Pei-Yan Luo contributed equally as co-first authors.

*Correspondence:
Shi-Fang Huang
huangsf@jnu.edu.cn
Hai-Yan Yin
haiyanyin1867@126.com
Wan-Jie Gu
guwanjie@jnu.edu.cn
Full list of author information is available at the end of the article

Keywords Ciprofol, Propofol, Sedation, Mechanical ventilation, Sepsis

Background

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, often progressing to multiple organ failure [1–3]. It is a lethal syndrome affecting millions of people worldwide and killing as many as one in four, according to the latest global estimates [4]. Sepsis is a leading cause of mortality and morbidity in critically ill patients. Among patients with sepsis, over 20% of them required mechanical ventilation [5]. Sedation is often required to reduce anxiety and stress and to facilitate mechanical ventilation. In clinical practices, benzodiazepines, propofol, and dexmedetomidine are the most used sedatives [6]. Benzodiazepines, typically midazolam, exhibit slow metabolism in critically ill patients, which may lead to drug accumulation and prolonged awakening time [7]. Propofol is preferable to midazolam as a priority for sedation due to its rapid onset, fast recovery, high clearance rate, good tolerance, and improved outcomes [8]. However, propofol has some adverse effects, including hypotension, respiratory depression, or injection pain [9]. Compared with midazolam and propofol, dexmedetomidine has an analgesic effect and does not cause severe respiratory depression but increases the incidence of bradycardia and hypotension [10]. Thus, the ideal sedative with adequate sedation and more safety remains explored.

HSK3486 (Trade name: Ciprofol, Haisco Pharmaceutical Group Co., Ltd, Chengdu, China) is a new intravenous anesthetic with a similar chemical structure to propofol [11]. Ciprofol has a higher binding activity to the gamma-aminobutyric acid-A (GABA) receptor than propofol, which suggests that ciprofol is a promising and potent sedated candidate [12]. The major circulating metabolite of ciprofol in plasma is the glucuronide conjugate of HSK3486 (M4) (79.3%), which has little residual effects and is finally excreted by the kidney in urine [13]. Phase 1 trials suggest ciprofol has the potential for clinical application for continuous intravenous infusion to maintain sedation with the same safety as propofol [14, 15]. Phase 2 or 3 trials also suggest ciprofol is comparable to propofol with good tolerance and efficacy for the induction and maintenance of general anesthesia in surgery [16, 17], bronchoscopy [18], and gastrointestinal endoscopy [19, 20]. The indications of ciprofol also include sedation for ICU patients. A phase 2 trial suggests that ciprofol is comparable to propofol, with good tolerance and efficacy for sedation in ICU patients undergoing mechanical ventilation [21]. A phase 3 trial also suggested ciprofol was well tolerated, with a noninferior sedation profile to propofol in Chinese ICU patients undergoing mechanical ventilation for a period of 6–24 h [22]. However, up to now, the role of ciprofol for long-term sedation in mechanically ventilated patients with sepsis has not been well assessed. Thus, we aimed to evaluate the efficacy and safety of ciprofol versus propofol for long-term sedation in mechanically ventilated adults with sepsis.

Methods

Design

We conducted an investigator-initiated, single-center, randomized controlled trial at the ICU of The First Affiliated Hospital of Jinan University, Guangzhou, China. This trial has been approved by the Scientific Research Ethics Committee of the First Affiliated Hospital of Jinan University (KY- 2022–090). Patients' legally authorized representatives provided written informed consent before enrollment. The trial was prospectively registered at Chinese Clinical Trial Registry (ChiCTR2200066835) on December 19, 2022. The first patient was enrolled in February 2023 and the trial was completed in July 2023. The study adheres to the CONsolidated Standards Of Reporting Trials (CONSORT) statement.

Population

We included adults who were admitted to ICU, had sepsis, and were expected to treat with continuous sedation for invasive mechanical ventilation with at least 24 h. Sepsis was defined as recommended by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis- 3) and had suspected or documented infection and a total Sequential Organ Failure Assessment (SOFA) score increase of at least 2 (1). Patients were excluded if they had (1) psychological illness or severe cognitive dysfunction; (2) severe chronic liver disease (Child–Pugh grade B or C) or chronic kidney disease requiring dialysis; (3) left ventricular ejection fraction less than 30%; (4) heart rate less than 50 beats/min or second- or third-degree heart block in the absence of a pacemaker; or (5) refractory shock (systolic blood pressure less than 90 mm Hg after appropriate intravenous volume replacement and continuous infusions of 2 vasopressors). Additional details on exclusion and inclusion criteria are provided in Additional file 1.

Randomization

We randomly assigned patients to receive ciprofol or propofol in a 1:1 ratio. The randomization sequence was generated using Microsoft Excel software in a block size of

4. Researchers, patients, and families, outcome assessors, and statisticians were unaware of the group assignments.

Intervention

Once eligibility is confirmed, subjects will receive standard treatment according to the 2021 surviving sepsis campaign guidelines [23], including antimicrobial therapy, fluid management, vasoactive agents, and other treatments as needed. Patients in the ciprofol group will receive ciprofol (Haisco Pharmaceutical Group Co., Ltd., Chengdu, China) intravenously at an initial infusion rate of 0.1 mg/kg/h and adjusted to maintain a Richmond Agitation-Sedation Scale (RASS) score between- 3 and 0. Patients in the propofol group received propofol intravenously at an initial infusion rate of 1.0 mg/kg/h and adjusted to maintain a RASS score between- 3 and 0. The sedation effects were assessed using the RASS score every hour by the bedside nurse [24]. The nurse adjusted the medications to maintain the target sedation level, in consultation with the attending intensivist. Analgesics were primarily opioids, chosen based on the attending intensivist's preference and the patient's condition. The dose of analgesics was adjusted according to the Critical Care Pain Observation Tool (CPOT) [25]. In some cases, patients required more than one sedative medication, and neuromuscular blockade was used when necessary.

Outcomes

The primary outcome was weaning time, defined as the duration from randomization to successful extubation. Secondary outcomes included the percentage of time within the target sedation range, successful sedation (the percentage of time within the target sedation range $\geq 70\%$ without rescue sedation), ICU mortality, in-hospital mortality, length of ICU stay, length of hospital stay. During the study period, occurrence of hypotension (decrease in systolic blood pressure $\geq 20\%$ from the baseline) and bradycardia (heart rate less than 50 bpm) were recorded.

Statistical analysis

The study is an exploratory randomized controlled trial. Since there is no data on ciprofol for long-term sedation in mechanically ventilated patients with sepsis, our study will firstly provide data to calculate sample size for further larger sample-sized trials. Continuous variables are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on the normality of the distribution, and analyzed using either Student's t-test or Mann–Whitney U-test. Categorical variables are presented as number and percentage and analyzed using Chi-square or Fisher's exact test. For all analyses, a two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R software (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Enrollment and patient characteristics

From February 2023 to July 2023, we screened 63 patients for eligibility. 60 of them were randomized, 4 were excluded because of withdrawing treatment. 28 were assigned to the ciprofol group and 28 to the propofol group (Fig. 1). The median age of enrolled patients

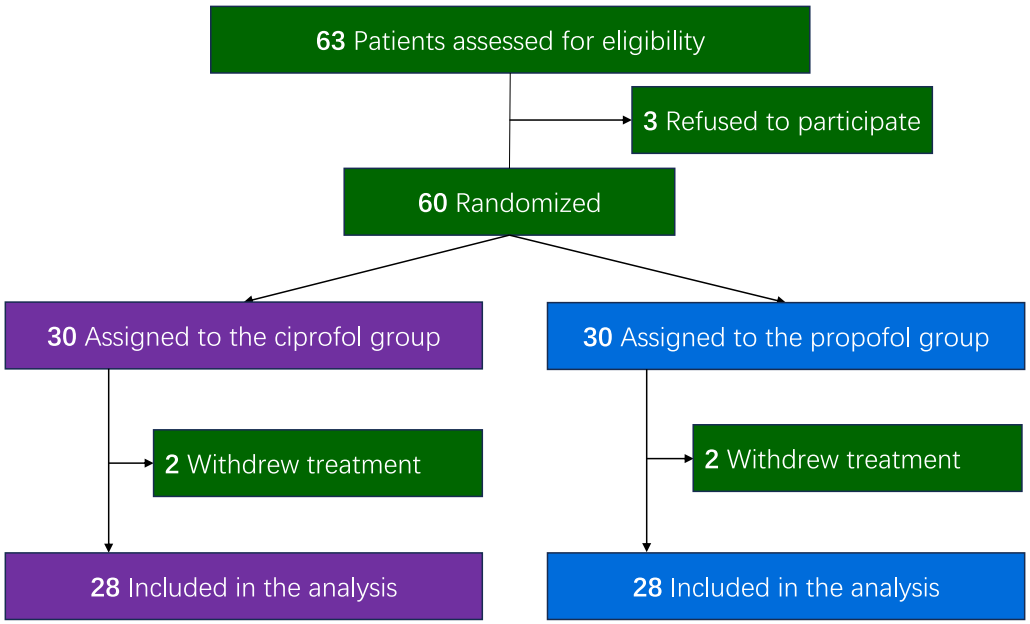

Fig. 1 Patient screening, enrollment, and randomization

was 69.0 years and 64.3% were male. The main infection source was pulmonary (73.2%), followed by abdominal (16.1%) and urinary (10.7%). Most of the patients (78.6%) had septic shock and received at least one type of vasopressor (91.1%). The mean baseline APACHE II and SOFA scores were 29.5 (7.8) and 10.9 (3.7), respectively. Patient characteristics were similar between the two groups (Table 1).

Primary outcome

The median weaning time in ciprofol group was shorter than propofol group (104.0 h [IQR, 40.8–147.2 h] vs 132.5 h [IQR, 69.8–207.8 h]; Table 2), but not reached significant difference between groups ($P = 0.123$) (Fig. 2).

Secondary outcomes

Ciprofol had significantly higher percentage of time within the target sedation range (median [IQR], 72.2%

Table 1 Patient characteristics

Characteristics	Ciprofol group ($n = 28$)	Propofol group ($n = 28$)	*P* value
Age, years	73.0 (60.8, 78.0)	65.5 (62.2, 77.8)	0.749
Sex			0.780
Female	11 (39.3%)	9 (32.1%)	
Male	17 (60.7%)	19 (67.9%)	
Type of admission			0.205
Medical	19 (67.9%)	24 (85.7%)	
Surgical	9 (32.1%)	4 (14.3%)	
Infection source			0.158
Pulmonary	21 (75.0%)	20 (71.4%)	
Urinary	1 (3.6%)	5 (17.9%)	
Abdominal	6 (21.4%)	3 (10.7%)	
Septic shock	21 (75.0%)	23 (82.1%)	0.745
Vasopressor			0.893
No	2 (7.1%)	3 (10.7%)	
One type	19 (67.9%)	18 (64.3%)	
Two or more types	7 (25.0%)	7 (25.0%)	
Severity of illness			
SOFA	10.2 (3.5)	11.6 (3.8)	0.159
APACHE II	28.6 (8.2)	30.4 (7.4)	0.406
Comorbidities			
Hypertension	12 (42.9%)	11 (39.3%)	1.000
Diabetes	11 (39.3%)	13 (46.4%)	0.787
Heart disease	12 (42.9%)	8 (28.6%)	0.403
Cerebrovascular disease	7 (25.0%)	10 (35.7%)	0.561
Cancer	12 (42.9%)	6 (21.4%)	0.153
Vital signs			
Heart rate,/min	110.2 (26.8)	101.8 (19.5)	0.184
Systolic blood pressure, mmHg	125.2 (29.9)	121.8 (28.2)	0.657
Diastolic blood pressure, mmHg	69.9 (20.0)	64.4 (21.8)	0.326
Laboratory tests			
White blood cell, 10^9/L	9.8 (4.3, 13.8)	12.7 (10.0, 18.1)	0.120
Platelets, 10^9/L	131.4 (58.8, 213.8)	122.0 (69.1, 250.6)	1.000
Lymphocyte, 10^9/L	0.49 (0.28, 0.69)	0.54 (0.41, 1.06)	0.310
Lactate, mmol/L	2.8 (1.6, 4.3)	2.3 (1.6, 3.2)	0.544
C-reactive protein, mg/L	121.4 (65.1, 147.6)	141.4 (76.2, 155.2)	0.372
Procalcitonin, ng/mL	3.8 (1.2, 64.3)	2.1 (0.70, 19.9)	0.294

Data are number (%) mean (standard deviation), or median (interquartile range)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment

Table 2 Study outcomes

Outcomes	Ciprofol group ($n = 28$)	Propofol group ($n = 28$)	*P* value
Primary outcome			
Weaning time, hours	104.0 (40.8, 147.2)	132.5 (69.8, 207.8)	0.123
Secondary outcomes			
The percentage of time within the target sedation range, %	72.2 (14.3, 92.7)	22.6 (0.0, 45.4)	0.004
Successful sedation	15 (53.6%)	4 (14.3%)	0.005
ICU mortality	11 (39.3%)	10 (35.7%)	1.000
Hospital mortality	12 (42.9%)	10 (35.7%)	0.784
Length of ICU stay, days	8.5 (5.0, 14.8)	9.5 (5.8, 17.8)	0.401
Length of hospital stay, days	18.5 (11.5, 28.2)	15.0 (9.0, 28.0)	0.787
Hypotension	4 (14.3%)	6 (21.4%)	0.727
Bradycardia	0	0	NA

Data are number (%) or median (interquartile range)

ICU Intensive Care Unit

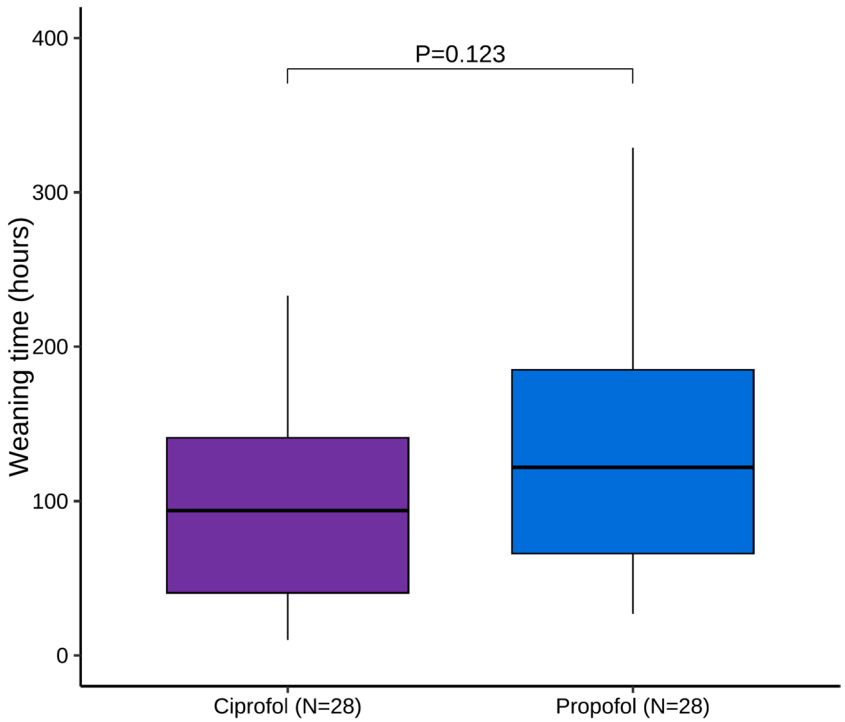

Fig. 2 Weaning time between the ciprofol and propofol groups

[14.3–92.7%] vs 22.6% [0.0–45.4%], Fig. 3A) and successful sedation rate (53.6% [15/28] vs 14.3% [4/28], Fig. 3B) than propofol. No significant differences were observed in ICU mortality, in-hospital mortality, length of ICU stay, and length of hospital stay between groups (Table 2). Hypotension occurred in 4 (14.3%) patients of ciprofol and 6 (21.4%) patients of propofol group. No patient experienced bradycardia.

Discussion

Main finding

In this randomized controlled trial involving mechanically ventilated adults with sepsis in the ICU who anticipated to require long-term sedation ≥ 24 h, we did not find evidence that sedation with ciprofol led to shorter weaning time than propofol. However, we found that ciprofol had significantly higher percentage of time within

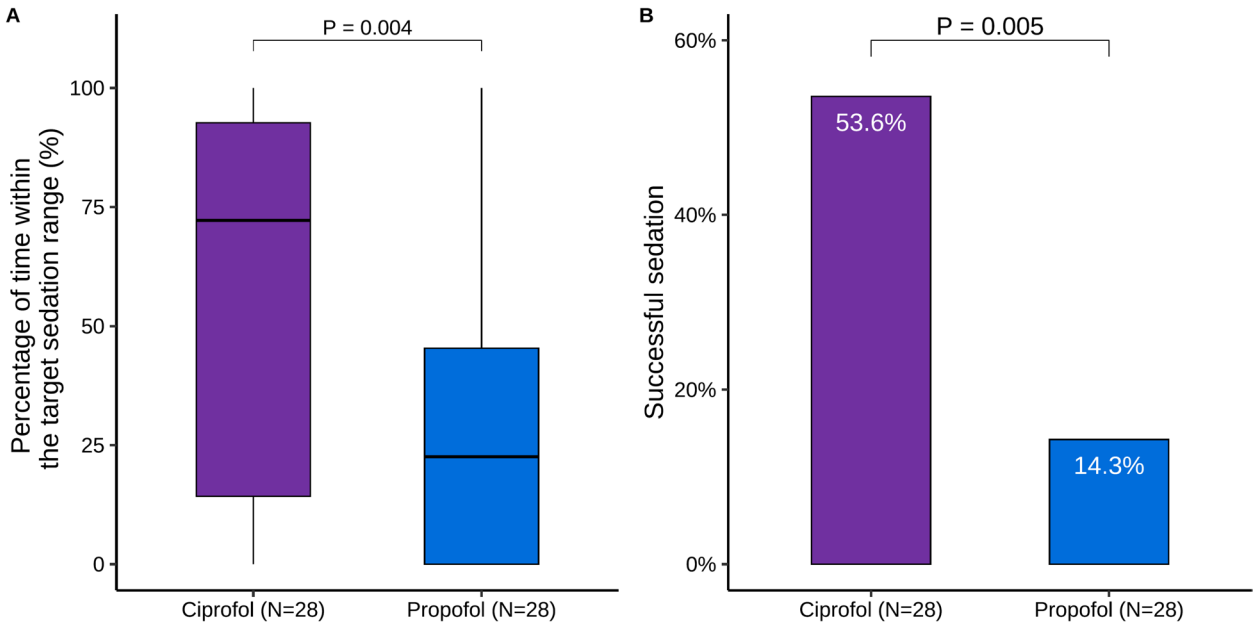

Fig. 3 **A**, percentage of time within the target sedation range (with a RASS score of 3 to 0); **B**, successful sedation

the target sedation range (with a RASS score of − 3 to 0) and successful sedation. No differences in ICU mortality, in-hospital mortality, length of ICU stay, length of hospital stay, hypotension, and bradycardia between groups were observed.

Relation with previous evidence

Currently, the efficacy and safety of ciprofol were mainly investigated in perioperative medicine, including the induction and maintenance of general anesthesia for surgery [16, 17, 26–28], bronchoscopy [18], and gastrointestinal endoscopy [19, 20, 29, 30]. In critically ill patients, the efficacy and safety of ciprofol have not been well established. In a multicenter, open label, randomized controlled, phase 2 trial with 39 ICU patients receiving mechanical ventilation, the results suggest that ciprofol is comparable to propofol, with good tolerance and efficacy for sedation in ICU patients undergoing mechanical ventilation [21]. Recently, another trial suggested ciprofol was well tolerated, with a noninferior sedation profile to propofol in Chinese ICU patients undergoing mechanical ventilation for a period of 6–24 h [22]. Liu et al. performed a pooled post-hoc analysis of data from phase 2 and phase 3 trials and further found that ciprofol had significantly lower rate of hypotension during the early phase of achieving light sedation during a 6–24 h period in ICU patients undergoing mechanical ventilation [31]. However, the efficacy and safety of ciprofol for long-term sedation in mechanically ventilated patients with sepsis has not been well assessed. This trial suggested that sedation with ciprofol did not lead to shorter weaning time than propofol, while with higher percentage of time within the target sedation range (with a RASS score of − 3 to 0) and successful sedation. Ciprofol is a new GABA receptor agonist, structurally similar to propofol. The addition of an R-chiral center and a cyclopropyl group enhances its pharmacological and physical properties with increasing potency [32]. Compared to propofol, ciprofol exhibits higher receptor selectivity, allowing for better effectiveness and safety. To the best of our knowledge, this is the first trial to compare ciprofol with propofol in mechanically ventilated adults with sepsis who anticipated to require long-term sedation ≥ 24 h.

Strength and limitations

The major strength of the present study is that this is the first trial comparing ciprofol with propofol in mechanically ventilated adults with sepsis who anticipated to require long-term sedation ≥ 24 h. Our trial has some notable limitations. First, the sample size is relatively small. Second, medical staffs (clinical physicians and bedside nurses) were not blinded. Third, the results have limited generalizability to other ICUs since the data for analysis was obtained from our center.

Conclusions

In summary, ciprofol was effective and safe among mechanically ventilated sepsis who anticipated to require long-term sedation compared with propofol. The preliminary findings should be warranted in larger multicenter trials.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CPOT	Critical Care Pain Observation Tool
ICU	Intensive care unit
IQR	Interquartile range
RASS	Richmond Agitation-Sedation Scale
SOFA	Sequential Organ Failure Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03042-w.

Supplementary Material 1.

Acknowledgements
Not applicable.

Authors' contributions
FZZ, HYY, and WJG contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, and interpretation of data for the work. WJG contributed to drafting the work. All authors contributed to revising it critically for important intellectual content. All authors contributed to the final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

Declarations

Ethics approval and consent to participate
This trial has been conducted in accordance with the Declaration of Helsinki. This trial has been approved by the Scientific Research Ethics Committee of the First Affiliated Hospital of Jinan University (KY- 2022–090). The trial was registered at the Chinese Clinical Trial Registry (ChiCTR2200066835) on December 19, 2022.
All participants' legally authorized representatives signed written informed consent before enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Intensive Care Unit, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong Province, China. [2]Department of Intensive Care Unit, Liancheng County Hospital, Liancheng, Fujian Province, China.

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