Original Article

Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a prospective multicenter randomized controlled study

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Background: Current data supporting the use of prone positioning (PP) during venovenous extracorporeal membrane oxygenation (VV-ECMO) in patients with acute respiratory distress syndrome (ARDS) are limited. This prospective randomized controlled study aimed to determine whether PP implemented within 24 hours of ECMO can improve survival in these patients.

Methods: From June 2021 to July 2023, 97 adult patients receiving VV-ECMO for ARDS in three centers were enrolled and 1:1 randomized into PP (n=49) and control groups (n=48). Patients in the PP group receiving prone positioning, while the control group were maintained in the supine position. The primary outcome was 30-day survival, and secondary outcomes included in-hospital survival and other clinical outcomes.

Results: All 97 patients were included for analysis. Patient characteristics did not significantly differ between the two groups. The median duration of PP was 81 hours, and the median number of PP sessions was 5 times. PP improved oxygenation and ventilator parameters. The incidence of complications during PP was low, with pressure sores being the most frequent (10.2%). The 30-day survival was significantly higher in the PP group (67.3% *vs.* 45.8%; P=0.033), as was in-hospital survival (61.2% *vs.* 39.6%; P=0.033). In the PP group, the successful ECMO weaning rate was significantly higher (77.5% *vs.* 50.0%; P=0.005), and the duration of ECMO support was significantly shorter {10 [8–11] *vs.* 10 [8–14] days; P=0.038}. However, in subgroup analysis of COVID patients the 30-day survival, in-hospital survival, successful ECMO weaning rate and the duration of ECMO support did not differ between the groups. The duration of mechanical ventilation, length of intensive care unit stay, and length of hospital stay did not significantly differ between the groups.

Conclusions: When initiated within 24 hours of ECMO, PP can improve 30-day survival in patients with ARDS receiving VV-ECMO. In addition, it may improve the successful ECMO weaning rate and reduce the duration of ECMO support. However, considering the limitations, more strictly designed, large sample prospective randomized controlled trials are proposed.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300075326.

Keywords: Prone positioning (PP); extracorporeal membrane oxygenation (ECMO); acute respiratory distress syndrome (ARDS); adult

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Introduction

Since the publication of the Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA) study (1), prone positioning (PP) has been considered a strategy to improve outcomes in patients with moderate to severe acute respiratory distress syndrome (ARDS). PP leads to increased aeration and recruitment of dorsal regions, decreases the effects of ventilator induced lung injury by redistribution of strain across lung tissue and, is beneficial for the failing right ventricle by reversing Cor pulmonale (2,3). Patients with severe ARDS who fail to respond to PP, venovenous extracorporeal membrane oxygenation (VV-ECMO) is used to facilitate gas exchange and reduce the intensity of mechanical ventilation (4). However, PP is not routinely used in patients on ECMO. Current data supporting the use of PP during VV-ECMO support is limited and inconsistent (5-12). This study aimed to evaluate the effect of PP on survival in patients with severe ARDS receiving VV-ECMO support. We hypothesized that PP would improve survival. We present this article in accordance with the CONSORT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/rc).

Highlight box

Key findings

- Prone positioning (PP) within 24 hours of extracorporeal membrane oxygenation (ECMO) initiation may improve 30-day survival in adult patients receiving venovenous extracorporeal membrane oxygenation (VV-ECMO) for acute respiratory distress syndrome (ARDS).

What is known and what is new?

- PP can improve outcomes in patients with moderate to severe ARDS.
- PP for at least 16 hours per day can improve 30-day survival in patients with ARDS receiving VV-ECMO.

What is the implication, and what should change now?

- In patients with ARDS receiving VV-ECMO early PP could be considered as a standard therapy in eligible centers.

Methods

Setting and participants

This prospective multicenter randomized controlled study of patients with ARDS receiving VV-ECMO was conducted from June 2021 to July 2023 in three tertiary hospitals in China (Jinhua Municipal Central Hospital, The First Hospital of Jiaxing, The Fourth Affiliated Hospital of Zhejiang University School of Medicine). Patients over the age of 18 years receiving VV-ECMO support for ARDS were eligible for inclusion. Those who were pregnant or had contraindications to PP (e.g., thoracic deformity, recent thoracoabdominal surgery, facial, pelvic, or spinal fractures) were excluded. We also excluded patients whose legal representatives did not agree to participation.

The legal representatives of patients provided written informed consent at the time of enrollment. The study was approved by the Ethics Review Board of Jinhua Municipal Central Hospital (approval No. 2022-279), The First Hospital of Jiaxing (No. 2023-LP-025), and The Fourth Affiliated Hospital of Zhejiang University School of Medicine (No. K2023101) and was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013).

Sample size

The primary outcome was 30-day survival. Guervilly *et al.* (13) reported a 30-day survival of 43.0% in patients with ARDS receiving ECMO in the supine position. Assuming that the 30-day survival could be as high as 71.0% (13), a total of 92 participants would be required to find a significant difference between the experimental and control groups based on calculations performed with PASS sample size software version 11.0 (NCSS, Kaysville, UT, USA) using a power of 0.8 and a 2-sided α of 0.05. Assuming a dropout rate of 5%, we aimed to enroll 97 patients.

Randomization and blinding

One of the researchers (Qianqian Wang) used Stata

software version 14 (StataCorp., College Station, TX, USA) to generate random numbers. A series of consecutively numbered, opaque, sealed envelopes were used to store the random numbers. After enrollment, the envelope was opened by the participant (patients' relatives and researchers); moreover, the patients were randomly allocated in a 1:1 ratio into PP and control groups based on the number in the envelope. The physicians implemented PP, and the patients were unaware of the trial-group assignments.

Interventions

In our institutions, the criteria for ECMO initiation were as follows: (I) hypoxemic respiratory failure (PaO_2/FiO_2 <80 mmHg), after optimal medical management. (II) Hypercapnic respiratory failure (pH <7.25), despite optimal conventional mechanical ventilation [respiratory rate 35 bpm and plateau pressure (Pplat) ≤30 cmH_2O]. ECMO cannulation were under the guidance of ultrasound using jugular and femoral veins as access, either a SORIN SCPC (London, UK) or MAQUET (Rastatt, Germany) system was used. Patients in the PP group received prone ventilation within 24 hours of ECMO initiation. The duration of prone ventilation was at least 16 hours per day until the patient's PaO_2/FiO_2 ratio exceeded 150 mmHg. The upper limit for the duration of prone positioning was 20 hours per day. PP was ceased when any of the following occurred: nonscheduled removal of endotracheal or ECMO tubes, endotracheal tube obstruction, hemoptysis, cardiac arrest, heart rate (HR) <30 beats per minute for >1 min, systolic blood pressure (SBP) <60 mmHg for more than 5 min, and any life-threatening condition. Patients in the control group were maintained in the supine position. All the patients were sedated and adopted low tidal volume ventilation as a "lung rest" mechanical ventilation strategy in control mode. Respiratory parameters were measured at the time just before ECMO initiation, start and end PP.

Primary and secondary outcomes

The primary outcome was 30-day survival. The secondary outcomes were in-hospital survival, duration of ECMO support, duration of mechanical ventilation, length of intensive care unit stay, length of hospital stay, and rate of successful ECMO weaning.

Statistical analysis

Statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY, USA) and R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous data are presented as the mean with standard deviation or median with first and third quartiles. Categorical variables are presented as numbers with percentages. The normality of data was tested using the Kolmogorov-Smirnov test. Comparison of continuous variables between two independent groups was performed using the independent samples *t*-test or Mann-Whitney test; categorical data were compared using the Fisher exact test or Pearson χ^2 test. Continuous data in paired groups were compared using the paired samples *t*-test or Wilcoxon test. Survival was analyzed using the Kaplan-Meier method and compared using the log-rank test. P<0.05 was considered significant.

Results

Baseline characteristics

Ninety-seven patients were included in the study, 49 in the PP group and 48 in the control group. The study flowchart is presented in *Figure 1*. The PP group comprised 55.1% men and 44.9% women, while the control group comprised 50.0% men and 50.0% women. The median age in the PP and control groups was 53 and 49 years, respectively. ARDS cause, respiratory rate (RR), HR, temperature (T), SBP, diastolic blood pressure (DBP), Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, and comorbidities did not significantly differ between the PP and control groups. Patient characteristics are shown in *Table 1*.

Respiratory parameters before ECMO

Inspiratory pressure, positive end expiratory pressure (PEEP), FiO_2, PaO_2/FiO_2 ratio, tidal volume, dynamic lung compliance (CLdyn), plateau pressure, and driving pressure before ECMO did not significantly differ between the groups. The median day of duration of mechanical ventilation before ECMO was significantly shorter in the PP group (3 *vs.* 4 days). The cannula size including the artery and vein was not statistically different (P>0.05). The detailed data are shown in *Table 2*.

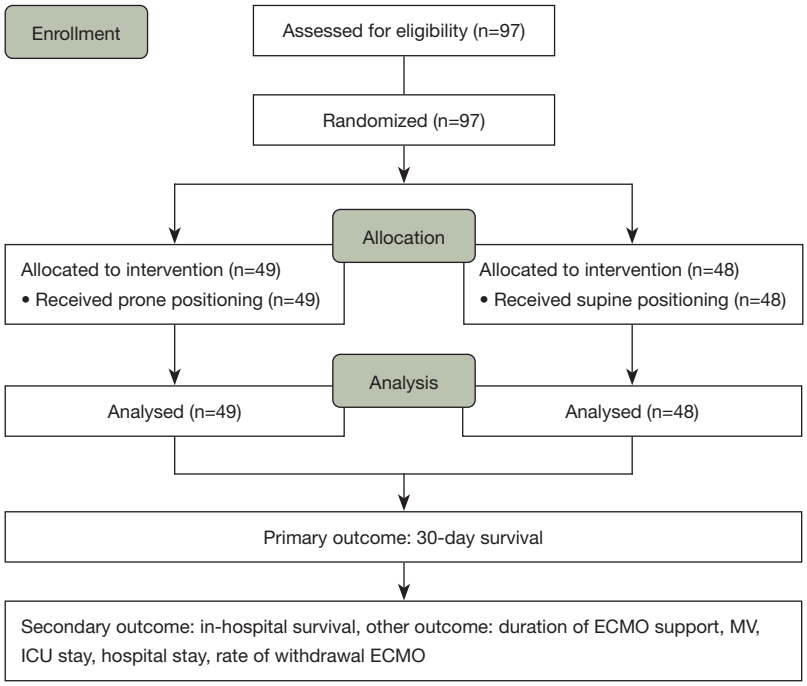

Figure 1 Flowchart demonstrating the process used to select the patients included in the analysis. ECMO, extracorporeal membrane oxygenation, MV, mechanical ventilation; ICU, intensive care unit.

Table 1 Baseline characteristics of the two groups

Variables	PP group (n=49)	Control group (n=48)	P value
Gender			0.615
Male	27 (55.1)	24 (50.0)	
Female	22 (44.9)	24 (50.0)	
Age (years)	53 [44–62]	49 [40–58]	0.213
Cause of ARDS			0.906
Bacterial pneumonia	12 (24.5)	15 (31.3)	
Viral pneumonia	5 (10.2)	3 (6.3)	
COVID-19 pneumonia	25 (51.0)	23 (47.9)	
Others	7 (14.3)	7 (14.6)	
RR (/min)	19 [18–22]	20 [18–23]	0.833
HR (bpm)	86 [75–107]	95 [76–112]	0.346
T (℃)	37.8 [36.6–38.9]	37.9 [37.0–39.3]	0.171
SBP (mmHg)	115 [104–137]	122 [106–129]	0.702
DBP (mmHg)	74±7	75±8	0.257
APACHE II score	21 [18–24]	20 [17–22]	0.164

Table 1 (*continued*)

Table 1 (*continued*)

Variables	PP group (n=49)	Control group (n=48)	P value
Comorbidities			
Hypertension	8 (16.3)	10 (20.8)	0.568
Diabetes	9 (18.4)	5 (10.4)	0.265
COPD	3 (6.1)	3 (6.3)	>0.99
Chronic heart failure	11 (22.4)	6 (12.5)	0.198
Chronic renal disease	4 (8.2)	4 (8.3)	>0.99
Cannula size (G)			
Artery	15 [15–16]	15 [14–16]	0.568
Vein	23 [23–24]	23 [23–23]	0.374

Data are presented as n (%) or median [quartile 1, quartiles 3] or mean ± standard deviation. PP, prone positioning; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; RR, respiratory rate; HR, heart rate; T, temperature; SBP, systolic blood pressure; DBP, diastolic blood pressure; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease.

Table 2 Respiratory parameters before ECMO

Variables	PP group (n=49)	Control group (n=48)	P value
pH	7.18 [7.14–7.26]	7.19 [7.15–7.25]	0.568
Inspiratory pressure (cmH_2O)	20 [18–21]	21 [18–22]	0.239
PEEP (cmH_2O)	12 [10–12]	12 [10–13]	0.329
FiO_2 ventilator (%)	80 [75–83]	75 [65–85]	0.281
PaO_2/FiO_2 (mmHg)	109 [93–121]	103 [93–116]	0.455
Tidal volume (mL)	265 [242–294]	269 [231–283]	0.634
CLdyn (mL/cmH_2O)	16.1±2.6	15.5±2.9	0.333
Plateau pressure (cmH_2O)	28 [27–29]	29 [27–30]	0.064
Driving pressure (cmH_2O)	17 [16–18]	17 [16–19]	0.203
Duration of MV before ECMO (days)	3 [2–4]	4 [3–5]	0.007
PP before ECMO	5 (10.2)	7 (14.6)	0.513

Data are presented as the median [quartile 1, quartile 3] or mean ± standard deviation or n (%). ECMO, extracorporeal membrane oxygenation; PP, prone positioning; PEEP, positive end expiratory pressure; CLdyn, dynamic lung compliance; MV, mechanical ventilation.

Respiratory and ECMO parameters before and after PP

Inspiratory pressure, ventilator FiO_2, plateau pressure, driving pressure, $PaCO_2$, ECMO gas flow, and ECMO FiO_2 were significantly lower after PP, while the PaO_2/FiO_2 ratio, tidal volume, CLdyn, PaO_2, and SpO_2 were higher. The detailed data are shown in *Table 3*.

Complications and duration of PP

The median number of PP session was 5 times, and the median duration of PP sessions was 81 hours. Forty-five patients (91.8%) reached the PP target. Complications of PP included ECMO flow drop, pressure sores, decreased blood pressure, bleeding, kinking of the endotracheal tube,

Table 3 Respiratory and ECMO parameters before and after prone positioning

Variables	Start PP	End PP	P value
Inspiratory pressure (cmH_2O)	18 [16–19]	16 [14–17]	<0.001
PEEP (cmH_2O)	12 [10–12]	12 [10–12]	0.122
FiO_2 ventilator (%)	65 [60–75]	65 [60–70]	<0.001
PaO_2/FiO_2 (mmHg)	101±21	126±27	<0.001
Tidal volume (mL)	280 [251–311]	311 [287–343]	<0.001
CLdyn (mL/cmH_2O)	19.4 [16.6–21.9]	24.1 [20.4–28.2]	<0.001
Plateau pressure (cmH_2O)	26 [24–28]	24 [22–26]	<0.001
Driving pressure (cmH_2O)	14 [13–16]	13 [12–14]	<0.001
RR (/min)	20 [17–23]	20 [17–23]	0.696
PaO_2 (mmHg)	67.9 [60.3–74.9]	79.0 [71.6–87.7]	<0.001
$PaCO_2$ (mmHg)	49.2 [44.9–53.7]	46.0 [42.7–50.6]	<0.001
pH	7.34 [7.29–7.38]	7.34 [7.29–7.39]	0.324
Lac (mmol/L)	2.05 [1.11–2.85]	1.79 [1.26–2.58]	0.082
SpO_2 (%)	95 [94–97]	97 [96–98]	<0.001
Gas flow (L/min)	7.5 [7.0–8.0]	7.0 [7.0–8.0]	<0.001
FiO_2 ECMO (%)	90 [80–95]	80 [75–90]	<0.001
Blood flow (L/min)	3.8 [3.5–4.1]	3.8 [3.6–4.0]	0.051

Data are presented as the median [quartile 1, quartile 3] or mean ± standard deviation. ECMO, extracorporeal membrane oxygenation; PP, prone positioning; PEEP, positive end expiratory pressure; CLdyn, dynamic lung compliance; RR, respiratory rate.

Table 4 Condition of prone positioning and complications

Variables	Values
Number of PP session	5 [4–6]
Total duration of PP sessions (h)	81 [65–95]
Reached target	45 (91.8)
Complication	
ECMO flow drop	3 (6.1)
Pressure sores	5 (10.2)
Drop of blood pressure	4 (8.2)
Bleeding	3 (6.1)
Kinking of the endotracheal tube	1 (2.0)
Central vein catheter slippage	1 (2.0)

Data are presented as the median [quartile 1, quartile 3] or n (%). PP, prone positioning; ECMO, extracorporeal membrane oxygenation.

and central vein catheter slippage; pressure sores were the most frequent (5 patients, 10.2%). The detailed data are shown in *Table 4*.

Patient outcomes

The 30-day and in-hospital survival rates were higher in the PP group than in the control group (P=0.033). In the Kaplan-Meier analysis, in-hospital survival did not significantly differ between the groups (P=0.11). In the control group, the duration of ECMO support was significantly longer (P=0.038), while the rate of successful ECMO weaning was significantly lower (P=0.005). Duration of mechanical ventilation, length of intensive care unit stay, and length of hospital stay did not significantly differ between the groups. In subgroup analysis of COVID patients, the 30-day, in-hospital survival, duration of

Table 5 Outcomes

Variables	PP group (n=49)	Control group (n=48)	P value
Duration of ECMO support (days)	10 [8–11]	10 [8–14]	0.038
Duration of MV (days)	14 [12–16]	14 [12–16]	0.502
Duration of ICU stay (days)	19 [15–23]	18 [13–24]	0.588
Duration of hospital stay (days)	26 [17–32]	22 [13–32]	0.302
Successful ECMO weaning	38 (77.5)	24 (50.0)	0.005
Survival			
30-day	33 (67.3)	22 (45.8)	0.033
In-hospital	30 (61.2)	19 (39.6)	0.033
Subgroup of COVID patients	n=25	n=23	
30-day survival	16 (64.0)	13 (56.5)	0.597
In-hospital survival	14 (56.0)	11 (47.8)	0.571
Duration of ECMO support (days)	10 [7–12]	11 [8–14]	0.228
Successful ECMO weaning	20 (80.0)	14 (60.9)	0.145

Data are presented as the median [quartile 1, quartile 3] or n (%). PP, prone positioning; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; ICU, intensive care unit; COVID, coronavirus disease.

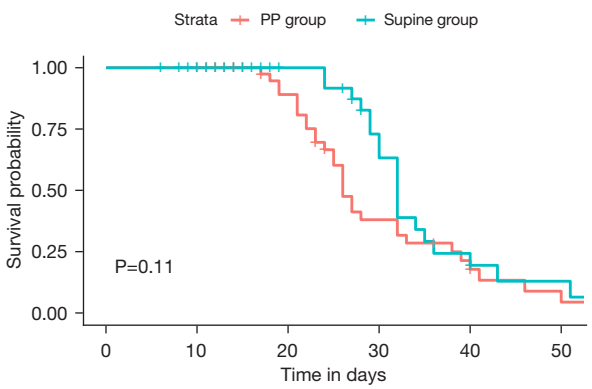

Figure 2 Kaplan-Meier curves representing cumulative in-hospital survival over time. PP, prone positioning.

ECMO support and successful ECMO weaning rate did not significantly differ between the groups. The patient outcomes are shown in *Table 5*, and the in-hospital survival curves are shown in *Figure 2*.

Discussion

Our study demonstrated that PP within 24 hours of ECMO initiation can improve survival in adult patients receiving VV-ECMO for ARDS. This is consistent with 3 previous studies that reported PP is safe during VV-ECMO and associated with a higher probability of survival (5-7). However, subgroup analysis found opposite results.

Lung inflation is significantly more homogeneous in the prone position than in the supine position; thus, it provides better ventilation-to-perfusion matching (14,15). However, in the prone position, less overdistension in nondependent lung regions and less cyclical opening and closing in dependent lung regions can decrease the occurrence of ventilation-induced lung injury (VILI). Therefore, PP has been recommended in patients with moderate-to-severe ARDS (PaO_2/FiO_2 <150 mmHg). Several studies (1,16,17) have demonstrated that PP significantly reduces mortality in patients with ARDS. ECMO is the treatment of last resort in patients with ARDS who cannot achieve adequate gas exchange on conventional mechanical ventilation. ECMO support may improve oxygenation and ventilation and decrease the intensity of mechanical ventilation. Several studies (18,19) have confirmed the benefit of this "lung rest" strategy in patients with severe ARDS. However, the use of ECMO requires increased use of sedatives and myorelaxants, which may increase the number of collapsed lung units (10). Furthermore, severe ARDS mortality remains high, even with ECMO support. Therefore, it seems reasonable to use PP to attempt to decrease mortality

in these patients.

Data regarding the use of PP during ECMO is limited, and the pertinent studies are small and retrospective in design (5,6,8,9,20), which is why this prospective study was conducted. According to the collected data we found indicated that PP during ECMO could increase 30-day survival by 21.5%, the difference is statistically significant. In addition, the incidence of complications with PP was low and acceptable. Moreover, PP increased the successful ECMO weaning rate and decreased the duration of ECMO support. This finding differs from those of two studies that reported a longer duration of ECMO in patients undergoing prone ventilation (5,10). However, these studies were retrospective and may have suffered from a bias: only the most severe patients were proved. Therefore, the relationship between PP and ECMO duration requires further investigation. Recent study on this aspect found that prone positioning did not significantly reduce time to successful weaning of ECMO (21). Our subgroup analysis was consistent with it. Additionally, one ongoing trial (NCT04139733) should provide more evidence and further elucidate this relationship. Although the in-hospital mortality in our study was 21.6% lower in the PP group than in the control group, according to the log-rank test, the difference was not significant. The reason for this may be that many patients in the control group (supine position) died early, which lowered the length of in-hospital stay. This may also explain why the length of intensive care unit stay and length of hospital stay were longer in the PP group, as reported in previous studies (3,8,9).

In non-ECMO patients, the early initiation of PP is associated with better outcomes (14,22), moreover early PP during ECMO was associated with a higher probability of being discharged alive from the ICU (7). Regarding the duration of PP, two studies (16,23) have recommended at least 12 hours daily. However, other studies in non-ECMO patients have reported that longer durations can provide a greater benefit (24,25). In a single small study of patients on ECMO, prolonged sessions of PP (≥24 hours) improved both oxygenation and respiratory system compliance (26). A meta-analysis (27) found that PP ≥12 hours might improve outcome in patients with ARDS receiving VV-ECMO. However, prolonged PP may be associated with a higher incidence of complications and wasted time, and thus further studies are warranted. In our study, we selected a duration of ≥16 hours per day based on our typical practice.

This study had several limitations. First, the sample size was relatively small; second, we only evaluated short-term outcomes; and third, because we included patients with a wide range of ARDS etiologies, the sample was relatively heterogeneous; fourth, only 10.2% patients received PP before ECMO, maybe many patients could avoid ECMO support after PP; fifth, the median PaO_2/FiO_2 ratio was a little higher than some current literature; sixth the duration of MV before ECMO was different between the two groups, it may influence the outcomes.

Conclusions

When initiated within 24 hours of ECMO, PP for at least 16 hours per day can improve 30-day in patients with ARDS receiving VV-ECMO. In addition, it may improve the successful ECMO weaning rate and reduce the duration of ECMO support. However considering the limitations of this study it should be confirmed in more strictly designed, large sample prospective randomized controlled trials.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/rc

Trial Protocol: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/tp

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1808/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The legal representatives of patients provided written informed consent at the time of enrollment. This study was approved by the Ethics Review Board of Jinhua Municipal Central Hospital (No. 2022-279), The First Hospital of Jiaxing (No. 2023-LP-025), and The Fourth Affiliated Hospital of Zhejiang University School of Medicine (No. K2023101). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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