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Efficacy and safety of esketamine for emergency endotracheal intubation in ICU patients: a double-blind, randomized controlled clinical trial

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Emergency endotracheal intubation in critically ill patients are dangerous procedures with a greater risk of severe hypotension The efficacy and safety of esketamine with sympathoexcitatory effects for rapid sequence induction in critically ill patients remain unclear. In this prospective double-blinded randomized controlled trial, adult patients were randomly assigned to receive either esketamine or midazolam/sufentanil admixture for induction. The primary outcomes were the effects of induction with esketamine or midazolam/sufentanil admixture on hemodynamic responses (heart rate (HR) and mean arterial pressure (MAP) during and after induction). Secondary outcomes were the duration of ventilation support, length of intensive care unit (ICU) stay, 28-day mortality. We enrolled 80 patients, of whom 38 were assigned to the esketamine group and 42 to the midazolam/sufentanil admixture group. The MAP in group esketamine was significantly higher than that in group midazolam/sufentanil admixture during the induction, and at 1 min, 5 min and 10 min after intubation. No significant differences in HR between groups were observed. The duration of ventilation support [105.3 (interquartile range (IQR) 40.9 – 248.3) hours vs. 211.5 (IQR 122.1 – 542.1) hours, P = 0.002] and the length of ICU stay [7.0 (IQR 4.0 – 16.3) days vs. 15.0 (IQR 8.0 – 26.0) days, P = 0.002] were significantly decreased in group esketamine, compared to that in group midazolam/sufentanil admixture. In group esketamine, less norepinephrine [0.00 (IQR 0.00 – 0.10) μg/kg/min vs. 0.09 (IQR 0.00 – 0.29) μg/kg/min, P = 0.016] was needed. There was no significant difference in 28-day mortality between the two groups. No serious adverse events occurred. In conclusion, esketamine is a hemodynamically stable induction agent in critically ill patients, which could reduce the length of ICU stay and the duration of ventilation support.

Trial registration: clinicaltrials.gov (19/07/2022; NCT05464979).

Keywords Esketamine, Anesthesia induction, Emergency endotracheal intubation, Intensive care, Hypotension

Abbreviations

HR	Heart rate
MAP	Mean arterial pressure
IQR	Interquartile range
BMI	Body mass index
CPOT	Critical-Care Pain Observation Tool
RASS	Richmond Agitation and Sedation Scale

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APACHE II	Acute physiology and chronic health evaluation
GCS	Glasgow coma scale
SOFA	Sepsis-related organ failure assessment
SpO_2	Peripheral arterial oxygen saturation

Emergency endotracheal intubation is one of the most essential measures for the management of respiratory function in critically ill patients[1,2]. The incidence of adverse events are higher with emergency endotracheal intubation done in the intensive care unit (ICU) compared to that performed in the operating room under non-emergent condition[3,4], which can impact morbidity and mortality[5]. Emergency endotracheal intubation in critically ill patients are dangerous procedures with a greater risk of severe hypotension (10–43%), severe hypoxemia (9–25%), and cardiac arrest (2–3%)[6,7]. Severe cardiovascular collapse surrounding endotracheal intubation is one of the most common complications, independently associated with poor clinical outcomes and could be influenced by the choice of induction agents[6,7]. Proper sedation, analgesia, and muscular relaxation are not only important for providing appropriate endotracheal intubation circumstances, but also for minimizing the unfavorable physiological consequences (e.g., discomfort, agitation, reflex bradycardia) and severe adverse effects[8,9]. At present, in China, for endotracheal intubation in ICU critically ill patients, benzodiazepines[10], analgesics and non-depolarizing neuromuscular antagonists are frequently used[11,12]. Among them, Benzodiazepines have a slow onset and long recovery period, excessive dosages might impair cardiovascular function[13]. Opioids may cause respiratory depression, cardiovascular depression, gastrointestinal responses, and other negative side effects[14,15]. Non-depolarized neuromuscular blockers mainly play a crucial role in relaxing muscles and have no sedative or analgesic effect[16]. Anesthesia induction in critically ill patients still lacks ideal induction agents, which should be effective and safe with little effects on hemodynamic parameters. For emergency endotracheal intubation in ICU critically ill patients, it is crucial to find induction agents with a rapid onset, minimal influence on breathing and circulation and few adverse effects.

(R, S)-ketamine, a racemic mixture containing two optical isomers, esketamine and (R)-ketamine[17], is a sedative-hypnotic agent that is widely used as an anesthetic and sedative agent mainly by noncompetitive antagonism of the *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system[18]. (R, S)-ketamine could inhibit hyperalgesia, and bind to μ and δ receptors in opioid receptors to produce analgesic effects[19,20]. Esketamine has been postulated to be a four times more potent anesthetic and analgesic than (R)-ketamine and approximately two times more effective than the racemic mixture of (R, S)-ketamine (Table S1). The pharmacological action site and mechanism of esketamine are basically the same as (R, S)-ketamine[18,21,22]. Esketamine had no significant effects on the body's metabolism, endocrine system, liver, renal, or intestinal function. In terms of medication metabolism, esketamine has a high bioavailability and short half-life, allowing patients to wake up quickly and more comfortably[21]. Intravenous injection of esketamine 0.5 mg/kg and (R, S)-ketamine 1 – 1.25 mg/kg (after injection within 10s) could achieve the same anesthetic effect, esketamine has a shorter recovery time from anesthesia[23]. Esketamine combined with sedative drugs could achieve satisfactory anesthetic effects during operation[24,25]. Moreover, esketamine, but not (R)-ketamine, had a small hemodynamic effects by increasing cardiac output in a dose-dependent manner[26]. Low-dose esketamine could offer stable hemodynamics during endotracheal intubation without adverse effects in the elderly undergoing knee arthroplasty in the operation room[27]. Esketamine effectively countered remifentanil-induced respiratory depression in the of healthy volunteers on the basis of respiratory depression induced by remifentanil[28]. Esketamine also possesses antidepressant and anti-inflammatory properties[21,29–32].

This study aims to compare the efficacy and safety of esketamine versus midazolam/sufentanil admixture in ICU critically ill patients undergoing emergency endotracheal intubation, with the goal of providing an important theoretical foundation for the safe and effective use of esketamine in the induction of tracheal intubation in critically ill patients.

Methods

Study design

The trial was registered before enrollment at clinicaltrials.gov (19/07/2022; NCT05464979). This single-center, prospective, randomized, controlled pilot study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number: 2022-0351-01; approval date: February 22, 2021), and it conforms to the provisions of the 1964 Helsinki Declaration. Written informed consent was obtained from all patients or surrogates.

Patients selection and randomization

The inclusion criteria were age ≥ 18 years, no use of sedatives within the half-life of their elimination before inclusion. To be included, a signed informed consent was mandatory. In patients who are incompetent such as comatose, a medical witness or legal guardian signed a provisional informed consent form. The exclusion criteria were as follows: (1) age < 18 years; (2) allergic to esketamine or midazolam; (3) patients requiring endotracheal intubation without sedative medication such as those in cardiac arrest, those neurologically obtunded, or those requiring awake intubation; (4) patients with suspected increased intracranial pressure; (5) bradycardia (heart rate (HR) below 50 beats/min) or atrioventricular block; (6) untreated or undertreated patients with hyperthyroidism; (7) chronic nephrosis; (8) severe chronic liver disease (child-Pugh: Grade C); (9) alcohol or opioid dependence, mental illness, or severe cognitive impairment; (10) pregnant or breastfeeding; and (11) lack of informed consent. Upon meeting the criteria for inclusion in the study, the patient was randomized to group esketamine or group midazolam/sufentanil. Randomization was performed by a coin toss (patients received esketamine for induction when the coin fell with the number up).

Study interventions

The study was double-blind, and the drug injectors, data analyzers, and patients (or surrogates) were not aware of the treatment groups they received. The person in charge of randomization dispenses the induction agents. Dispensers were not involved in the subsequent experimental process.

In group esketamine, esketamine (5 mg/ml, 0.5 – 1.0 mg/kg; Hengrui Medicine Co., Ltd., China) was administered for induction[21]. In group midazolam/sufentanil, a combination of midazolam (40 μg/kg; Yichang Renfu Pharmaceutical Co., Ltd., China)[33,34]and sufentanil citrate (1.5 μg/kg; Yichang Renfu Pharmaceutical Co., Ltd., China)[35] were prepared to be mixed in a syringe in the same volume as esketamine to avoid the drug injectors knowing the grouping. If effective sedation was difficult to achieve within 2 min in group esketamine, midazolam (2 mg; Yichang Renfu Pharmaceutical Co., Ltd., China) intravenously would be administered as a remedial treatment. Nonetheless, no patients in the esketamine cohort necessitated a second dosage of midazolam owing to sedation failure.

Both groups were given roccuronium bromide (0.6 mg/kg; Yichang Renfu Pharmaceutical Co., Ltd., China)[36]before intubation. Video laryngoscopy was used to complete all endotracheal intubation in one attempt. Sufentanil citrate (0.08–0.15 μg/kg/h; Yichang Renfu Pharmaceutical Co., Ltd., China) combined with remimazolam besylate (0.15 – 0.25 mg/kg/h; Yichang Renfu Pharmaceutical Co., Ltd., China) was administered intravenously to sustain a Critical-Care Pain Observation Tool (CPOT) score 0 and a Richmond Agitation and Sedation Scale (RASS) score between − 3 and 0 following intubation[37]. Before and during the induction, continuous electrocardiograph (ECG), pulse oximetry (SpO_2), continuous arterial blood pressure monitoring were monitored.

During and subsequent to intubation, appropriate treatment protocols were implemented to ensure hemodynamic stability, particularly for hypotension (systolic blood pressure < 90 mm Hg) and tachycardia (heart rate > 100 beats per minute). Norepinephrine was administered as a continuous intravenous infusion at an initial dosage of 0.20 μg/kg/min to manage hypotension (systolic blood pressure < 90 mm Hg). The norepinephrine dosage was adjusted in real-time according to the patient's blood pressure to maintain optimal perfusion pressure, hence enhancing organ performance and mitigating the risk of secondary complications. Blood pressure and heart rate were continuously monitored, and norepinephrine and esmolol dosages were titrated in real time based on this monitoring to ensure stable hemodynamic management during and after the intubation procedure. This strategy was consistently implemented in both groups to mitigate the potential influence of blood pressure management on research outcomes.

The stopping criteria were the occurrence of adverse events (e.g., drug allergy, severe neuropsychiatric symptoms, requirement for surgical airway as well as acute interventions for cardiovascular collapse such as cardiopulmonary resuscitation with chest compressions). Patients were followed up for 28 days after randomization.

Data collection

Data was obtained from the hospital's electronic medical records, vital signs monitor, nurse records, and laboratory findings. All data were checked by two researchers.

We collected data on age, sex, body mass index, and comorbidities (smoking and drinking history, cardiovascular and cerebrovascular diseases, chronic respiratory disease, chronic hepatopathy, chronic nephrosis, endocrine, nervous system diseases, autoimmune diseases, and malignant tumor). The acute physiology and chronic health evaluation (APACHE II) score[38], Glasgow coma scale (GCS) score[39], sepsis-related organ failure assessment (SOFA) score[40], suspected or proven sepsis (known or suspected infection with SOFA score ≥ 2), and presence of shock (patients with blood pressure maintained via infusions of vasopressor prior to start of study drug) at randomization, as well as the main cause of ICU admission and the reasons for emergency intubation were recorded. According to the previous study[35], the vital signs (SpO_2, HR, mean arterial pressure (MAP)) before induction, during induction, during intubation, and five time points after intubation (1 min, 5 min, 10 min, 30 min, and 60 min) were collected. The duration of ventilation support, ICU length of stay, and 28-day survival after randomization were recorded.

Outcomes

The primary outcomes were the effects of rapid sequence induction using esketamine or midazolam/sufentanil on HR and MAP at various designated time points as specified. Secondary outcomes were selected to examine the wider therapeutic implications of esketamine and midazolam/sufentanil in critically ill patients, beyond the immediate hemodynamic effects. The parameters included the length of invasive ventilator support, intensive care unit time, and 28-day mortality rate. While not directly linked to the mechanisms of the induction agents, these outcomes were selected to evaluate the overall impact on patient recovery and long-term results in a critically ill cohort. The safety outcomes encompassed hypotension (systolic blood pressure < 90 mm Hg), norepinephrine dosage, tachycardia (heart rate > 100 beats per minute), dosage of the β-blocker esmolol, and cardiotonic treatment.

Statistical analysis

Based on a previous study[27], the MAP immediately before endotracheal intubation in the esketamine group was 89 ± 14 mm Hg. We calculated a conservative sample size that could detect a mean difference of about 10% (i.e. 8.9 mm Hg) between study groups. Using SPASS 15.0 software, a sample size of 40 patients per group was needed to have a study power of 80% and alpha error of 0.05.

Continuous data points were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)). Categorical data are expressed as number (percentage (%)). The Shapiro-Wilk test was used to check the normality of the data. Normally distributed data were compared between the groups using the two sample-

independent t tests. Categorical data were compared using the Chi-square or Fisher's exact test. Ordinal data and non-normally distributed continuous data were calculated using the Mann-Whitney U-test to test differences between groups for their statistical significance. The comparison of single indices at multiple time points between the two groups was detected by the general linear repeated-measures analysis of variance. Proportional hazard ratios with 95% confidence interval (CI) were calculated using Mantel-Haenszel test, and Kaplan–Meier curves were depicted to compare the length of ICU stay and the cumulative incidence of mortality 28 days after randomization. There were no missing values for the variables examined in the statistical analysis. Analyses were conducted using IBM SPSS Statistics (Version 20) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). All tests were two-sided, and a p-value of < 0.05 was considered statistically significant.

Results

Patients' baseline characteristics

From 27st August 2022 to 31th May 2023, a total of 1179 patients were screened, with 167 patients meeting inclusion criteria. 87 patients could not be included because of various reasons (74 patients with COVID-19 refused to participate; 8 patients: induced without the use of midazolam/sufentanil admixture or esketamine; 5 patients: intubated without any induction agent). Thus, 80 patients (38 in group esketamine and 42 in group midazolam/sufentanil admixture) from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology were included and randomized (Fig. 1). There were no significant differences between the two groups regarding age, sex, body mass index (BMI), APACHE II score, GCS score, SOFA score, suspected or proven sepsis, presence of shock, main cause of ICU admission, reasons for emergency intubation, and pre-existing comorbidities before induction (Table 1). The most frequent reason for intubation was acute respiratory failure (65.8% vs. 66.7%).

Primary outcome

The basal mean arterial pressure and HR were similar in both groups. In group esketamine, MAP slightly increased during induction and remained elevated during 30 min after intubation. However, in group midazolam/sufentanil admixture, MAP decreased markedly during induction. The MAP in group esketamine was significantly higher than that in group midazolam/sufentanil admixture during the induction (94 ± 17 mm Hg vs. 81 ± 19 mm Hg, $p < 0.01$), and at 1 min (100 ± 18 mm Hg vs. 90 ± 18 mm Hg, $p < 0.05$), 5 min (97 ± 17 mm Hg vs. 86 ± 15 mm Hg, $p < 0.01$) and 10 min (96 ± 16 mm Hg vs. 86 ± 20 mm Hg, $p < 0.05$) after intubation.

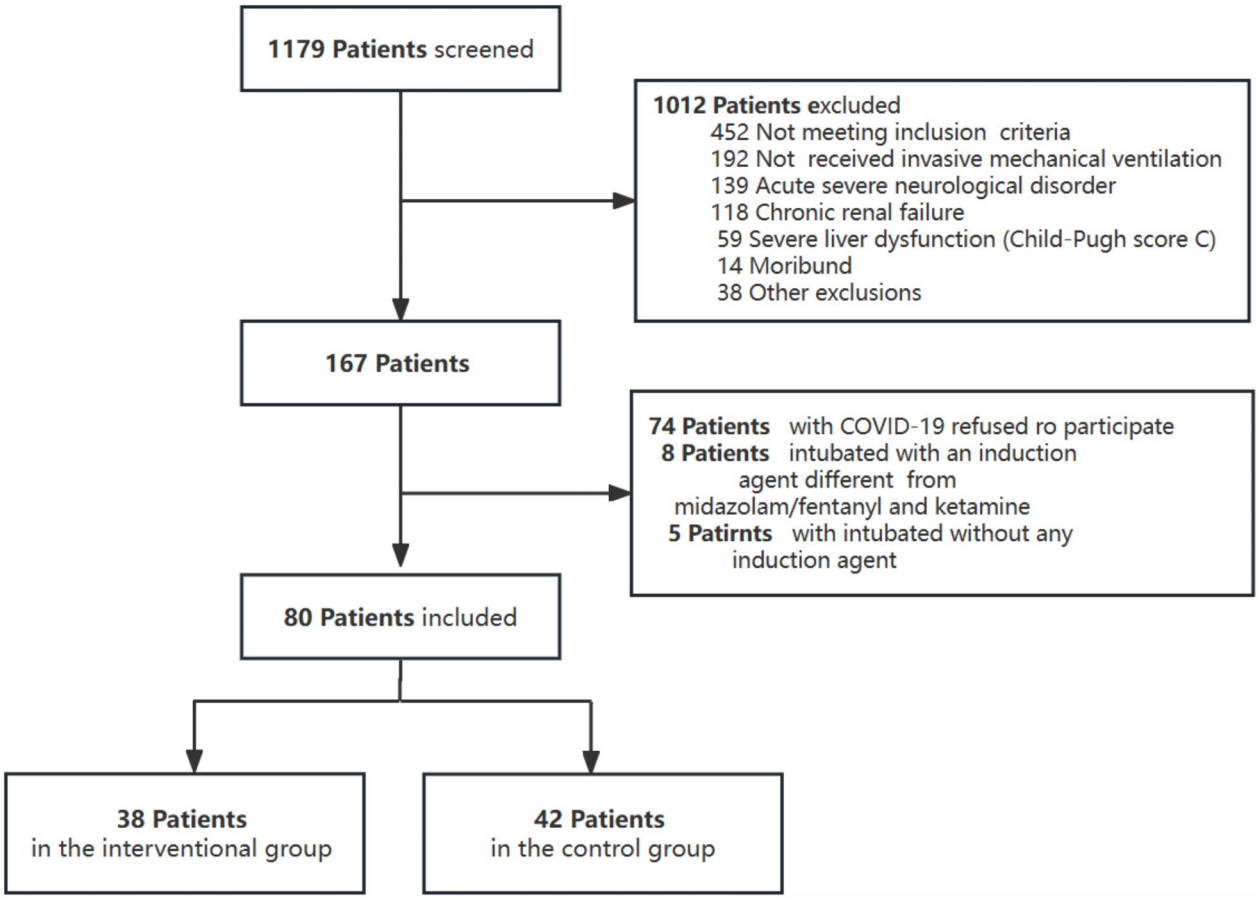

Fig. 1. Concort flow diagram.

	Esketamine ($n=38$)	Midazolam + fentanyl ($n=42$)	*P* value
Age	59.0 (44.5 – 69.0)	66.5 (53.0 – 75.0)	0.066
Male	30 (78.9%)	32 (76.2%)	0.768[a]
BMI, kg/m^2	22.5 (3.3)	23.6 (3.8)	0.206
APACHE II score	21.8 (5.6)	22.3 (4.9)	0.658
GCS score	5.0 (4.0 – 6.0)	5.0 (5.0 – 6.0)	0.149
SOFA score	8.5 (3.0)	8.0 (2.7)	0.460
Suspected or proven sepsis	25 (65.8%)	26 (61.9%)	0.718[a]
Shock	19 (50.0%)	14 (43.8%)	0.130[a]
Main cause of ICU admission			0.859[a]
Medical	30 (78.9%)	34 (81.0%)	0.824
Surgical	3 (7.9%)	4 (9.5%)	0.798
Trauma	5 (13.2%)	4 (9.5%)	0.610
Reasons for emergency intubation			0.990[a]
Comatose	8 (21.1%)	8 (19.0%)	0.824
Acute respiratory failure	25 (65.8%)	28 (66.7%)	0.934
Unplanned tube withdrawal	3 (7.9%)	4 (9.5%)	0.798
Others	2 (5.3%)	2 (4.8%)	0.919
Comorbidities			0.149[a]
Smoking history	15 (39.5%)	21 (50%)	0.348
Drinking history	13 (34.2%)	20 (47.6%)	0.227
Hypertension	7 (18.4%)	12 (28.6%)	0.290
Diabetes	5 (13.2%)	11 (26.2%)	0.148
Cardiovascular disease	7 (18.4%)	3 (7.1%)	0.130
Arrhythmia	6 (15.8%)	5 (11.9%)	0.617
COPD	0	2 (4.8%)	0.176
Chronic hepatopathy	5 (13.2%)	2 (4.8%)	0.187
Chronic nephrosis	7 (18.4%)	5 (11.9%)	0.418
Autoimmune diseases	5 (13.2%)	1 (2.4%)	0.069
Malignant tumor	5 (13.2%)	8 (19.0%)	0.479

Table 1. Baseline characteristics. Data are number (percentage), mean (standard deviation) or median (interquartile range). Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease. [a]is the Crosstab chi-square test.

Regarding HR or SpO_2, there were no significant differences between two groups during and after induction (all $p > 0.05$) (Table S2 and Fig. 2).

Secondary and safety outcomes

The invasive ventilator support [105.3 (IQR 40.9 – 248.3) hours vs. 211.5 (IQR 122.1 – 542.1) hours, $P = 0.002$] and the length of ICU stay [7.0 (IQR 4.0 – 16.3) days vs. 15.0 (IQR 8.0 – 26.0) days, $P = 0.002$] were significantly decreased in group esketamine, compared to that in group midazolam/sufentanil admixture. However, no significant difference in 28-day mortality between the two groups was observed ($P = 0.796$) (Table 2; Fig. 3).

The incidence of hypotension during induction and within 1 h after intubation was significantly lower in group esketamine than in group midazolam/sufentanil admixture [11 (28.90%) vs. 24 (57.10%), $P = 0.011$]. The dosage of intravenous norepinephrine used in group esketamine was significantly lower than that in group midazolam/sufentanil admixture [0.00 μg/kg/min (IQR 0.00–0.10 μg/kg/min) vs. 0.09 μg/kg/min (IQR 0.00–0.29 μg/kg/min), $P = 0.016$]. However, the proportion of tachycardia requiring β-blocker esmolol [13 (34.20%) vs. 6 (14.30%), $P = 0.037$] and the dosage of esmolol used [0.00 μg/kg/min (IQR 0.00–25.35 μg/kg/min) vs. 0.00 (IQR 0.00 –0.00 μg/kg/min), $P = 0.045$] were significantly higher in group esketamine than in group midazolam/sufentanil admixture. Cardiotonic drug dobutamine was administered to one patient in group esketamine and two patients in group midazolam/sufentanil admixture for improving hemodynamics (2.60% vs. 4.80%, $P = 1.000$) (Table 2).

Discussion

Emergency endotracheal intubation is an essential procedure in the management of critically ill patients, despite the absence of an ideal induction agent. This is the inaugural prospective randomized controlled trial evaluating the efficacy and safety of esketamine for rapid sequence induction and tracheal intubation in critically ill ICU patients. Esketamine's mild elevation in blood pressure during induction may safeguard against the adverse

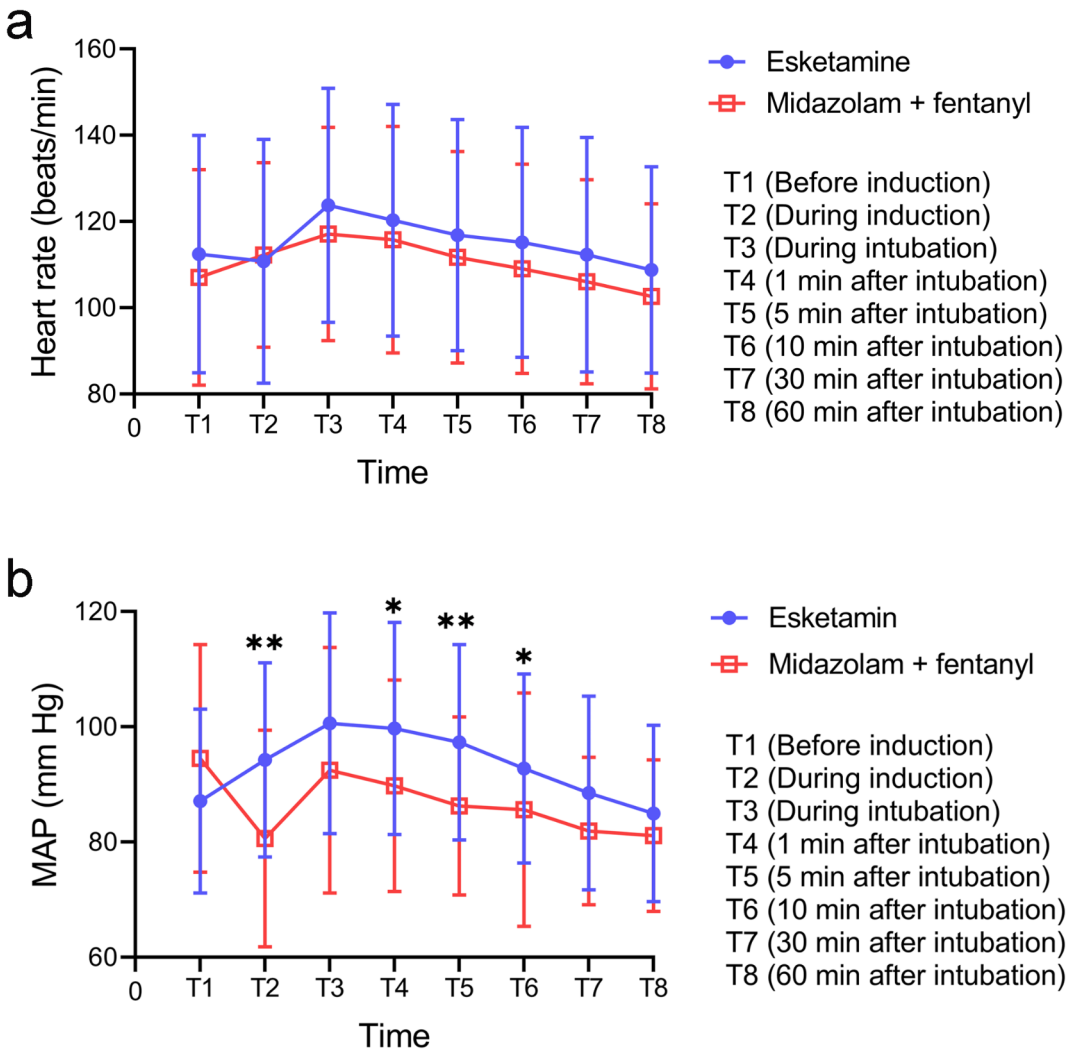

Fig. 2. Changes in heart rate (**a**) and mean arterial pressure (MAP) (**b**) during the rapid sequence induction with either esketamine (blue) or midazolam/sufentanil admixture (red) in critically ill patients. The hemodynamic variables were recorded before induction (T1), during induction (T2), during intubation (T3), and five time points (T4→T8) after intubation (1 min, 5 min, 10 min, 30 min, and 60 min). $^{*}p < 0.05$ and $^{**}p < 0.01$ compared between groups.

effects of severe hypotension, commonly observed in critically ill patients. Moreover, our results demonstrate that esketamine induction correlates with a reduced duration of ICU admission and diminished reliance on invasive ventilatory assistance, underscoring its potential advantages in the management of critically ill patients. Although secondary outcomes like ICU stay duration and 28-day mortality were not directly associated with the choice of induction agent, they were incorporated to offer a thorough evaluation of the overall impact of esketamine compared to midazolam/sufentanil on patient recovery and survival in the ICU. These secondary outcomes may indirectly reflect the broader therapeutic advantages or challenges of each medicine, including its ability to expedite recovery, diminish ICU dependence, or enhance patient stability post-intubation.

Rapid sequence induction and emergency tracheal intubation significantly impact cardiovascular parameters and elevate the risk of complications, including hypoxemia, hypotension, arrhythmias, cardiac arrest, and mortality, especially in critically ill patients with impaired cardiopulmonary function[41]. (R, S)-ketamine is widely used as an anesthetic, sedative and analgesic agent. In patients with an intact autonomic nervous system, (R, S)-ketamine is sympathomimetic, working to release centrally mediated catecholamines and impede their absorption[42,43], which may explain why (R, S)-ketamine is hemodynamically stable. Rapid sequence induction with 1.5 mg/kg (R, S)-ketamine in emergency anaesthesia was observed to elevate MAP by 10%[43]. Esketamine, the dextral enantiomer of (R, S)-ketamine, is documented to possess double the potency in its anesthetic and analgesic effects[21,22]. Notably, low doses of esketamine can achieve equivalent anesthetic and analgesic effects and are widely used in clinical practice[23,27]. Since the side effects of (R, S)-ketamine are dose-dependent, esketamine at the equivalent dose could reduce the incidence of psychotropic side effects and anesthetic side reactions. For instance, in senior patients having knee arthroplasty, esketamine has demonstrated the ability to maintain hemodynamic stability without negative consequences[27]. Esketamine sustains effective anesthetic

	Esketamine ($n=38$)	Midazolam + fentanyl ($n=42$)	*P* value
Secondary Outcomes			
Duration of ventilation support, h	105.3 (40.9 – 248.3)	211.5 (122.1 – 542.1)	0.002**
ICU length of stay, d	7.0 (4.0 – 16.3)	15.0 (8.0 – 26.0)	0.002**
28-day mortality	9 (23.70%)	11 (26.20%)	0.796
Safety Outcomes			
Hypotension before induction	19 (50.0%)	14 (43.8%)	0.796
Hypotension during induction and within 1 h after intubation	6 (15.8%)	17 (40.5%)	0.015*
Hypotension treated with norepinephrine	11 (28.9%)	24 (57.1%)	0.011*
Dose of norepinephrine, μg/kg/min	0.00 (0.00 – 0.10)	0.09 (0.00 – 0.29)	0.016*
Tachycardia during induction and within 1 h after intubation	32 (84.2%)	35 (83.3%)	0.915
Tachycardia treated with β-blocker esmolol	13 (34.2%)	6 (14.3%)	0.037*
Dose of esmolol, μg/kg/min	0.00 (0.00 – 25.35)	0.00 (0.00 – 0.00)	0.045*
Treated with dobutamine	1 (2.6%)	2 (4.8%)	1.000

Table 2. Secondary and safety outcomes. Data are number (percentage) or median (interquartile range). * and ** is the Crosstab chi-square test.

and analgesic properties while maintaining spontaneous respiration and airway reflexes, necessitating the administration of muscle relaxants throughout induction[25,26]. Furthermore, (R, S)-ketamine, when used as a sole induction agent with rocuronium (0.6 mg/kg), has demonstrated superior intubation conditions compared to other agents[44,45]. Our research similarly shown that the combination of esketamine and rocuronium resulted in stable hemodynamics and optimal intubation circumstances in critically ill ICU patients. Norepinephrine was utilized to regulate hypotension and sustain uniform blood pressure among groups, guaranteeing that any detected variations in blood pressure were exclusively due to the induction drugs, rather than discrepancies in hypotension control. Modifying norepinephrine dosages according to real-time blood pressure monitoring mitigated the confusing effects of antihypertensive therapy. Despite the observed changes in blood pressure among groups, our methodology substantially reduced potential bias, facilitating a more precise comparison between esketamine and midazolam/sufentanil. Esketamine, when administered with rocuronium, mitigated the hypotensive response associated with midazolam/sufentanil induction, both during the procedure and within one hour following intubation. In contrast to midazolam/sufentanil, esketamine induction resulted in a greater occurrence of tachycardia, necessitating the administration of the β-blocker esmolol, indicating elevated sympathetic tone[21]. Considering the similarities between esketamine and (R, S)-ketamine, esketamine may offer a comparatively safe alternative for quick sequence induction, but with potential dangers of cardiac ischemia or increased intracranial pressure[18]. Nevertheless, attention must be observed when administering esketamine to patients with disorders such hypertrophic obstructive cardiomyopathy, aortic valve abnormalities, or aortic dissection, as tachycardia or hypertension could result in significant adverse effects.

Critically ill patients in the ICU are often accompanied by excessive systemic inflammatory response and varying degrees of immune suppression[46,47]. In addition to its anesthetic, sedative and analgesic effects, esketamine has anti-inflammatory and immune-enhancing potential[21,32]. In patients undergoing elective on-pump coronary artery bypass surgery, combined use of esketamine for induction and maintenance of anesthesia could decrease plasma levels of IL-6 and IL-8 at 6 h after aortic unclamping, and increase plasma level of IL-10 at 1 h after unclamping[32]. The observed reductions in ICU duration of stay and ventilator support in the esketamine group are important; nonetheless, they seem improbable to result solely from the early hemodynamic stabilization achieved during induction. The anti-inflammatory and immunomodulatory properties of esketamine may have influenced these results by reducing systemic inflammatory responses, a prevalent concern in critically ill patients, thereby promoting expedited recovery. Furthermore, the sympathomimetic actions of esketamine may have enhanced tissue perfusion during and after induction, thereby mitigating problems related to hypotension, such as ischemia[22]. Research indicates that subanesthetic doses of esketamine improves cognitive dysfunction by inhibiting hippocamphal astrocytosis in mouse models of chronic stress after stroke[48]or by easing microglial activation and reducing inflammatory cytokines in mice with post-stroke anxiety[49]. Furthermore, a prospective, randomized, controlled, single-center clinical study in 2022 showed that (R, S)-ketamine (1 – 2 mg/kg) as an emergency intubation induction drug had a higher survival rate at day 7 than etomidate[2].

This research has several limitations. First, we did not conduct a comprehensive evaluation of the possible influences of other facets of the medical intervention (e.g., anti-infective therapy, fluid management, nutritional support therapy, renal-replacement therapy) on the clinical outcomes after intubation during ICU and hospital stay. Second, some patients still require sedatives and analgesics when the study drug infusion is discontinued, and the treating physician may administer sedatives and analgesics at his or her discretion during the 28-day follow-up. As a result, the influence of other medications on the reported outcomes cannot be ruled out. Although significant differences in ICU stay duration and ventilator support were observed between the esketamine and midazolam/sufentanil groups, the underlying mechanisms for these differences were not fully explored. The mechanisms of action of esketamine, particularly its influence on inflammation, immune response, and neuroprotection, warrant further investigation. Future studies should investigate the specific biological mechanisms by which esketamine exerts its effects, particularly its impact on inflammation,

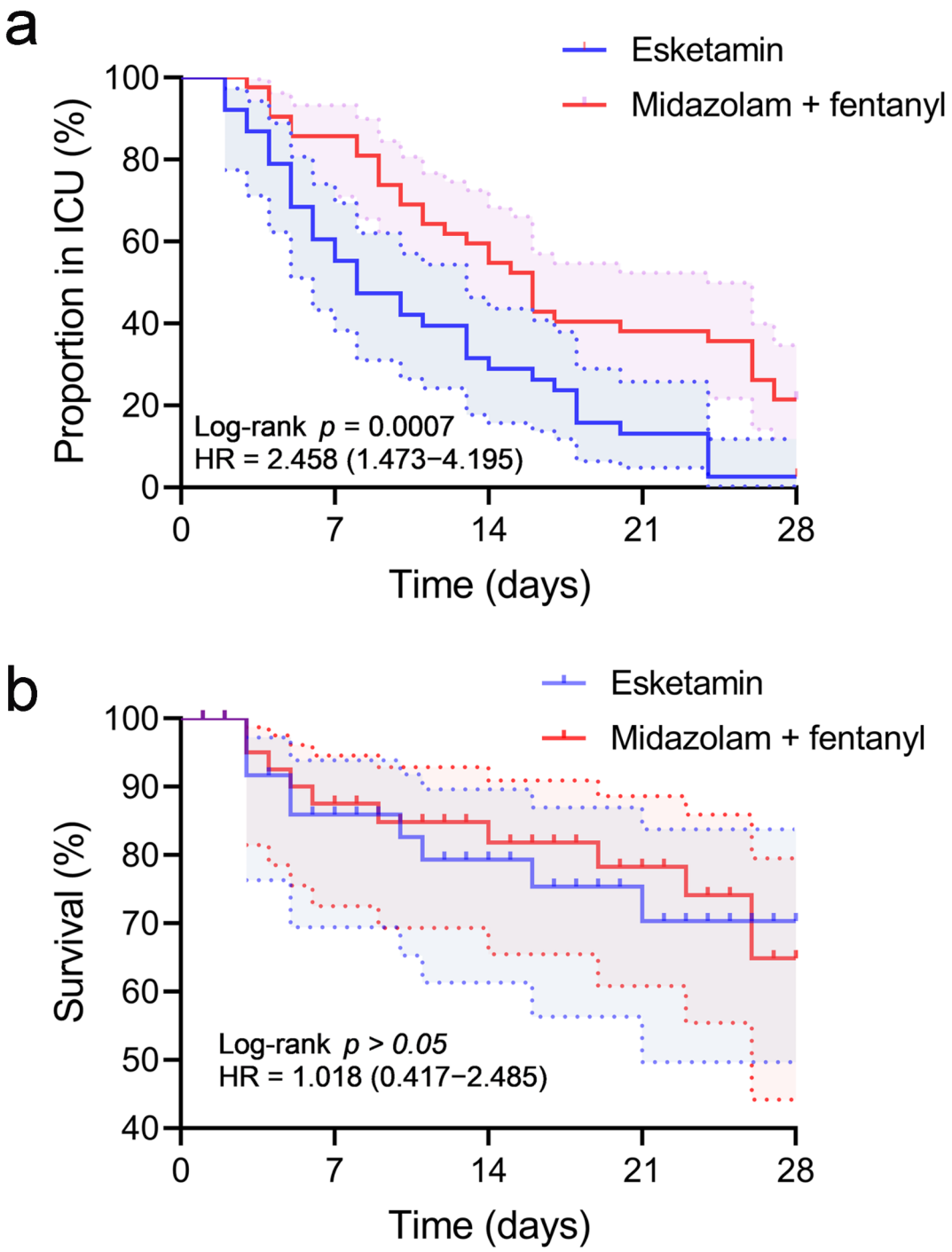

Fig. 3. Kaplan-Meier curves comparing the proportion of patients who remained in the ICU at various time points within 28 days (**a**) and the cumulative mortality within 28 days (**b**) in critically ill patients received anesthetic induction with esketamine (blue) or midazolam/sufentanil admixture (red). $^{*}p < 0.05$ and $^{**}p < 0.01$ compared between groups.

immune response, and neuroprotection. A more thorough comprehension of these pathways might elucidate the therapeutic advantages of esketamine in critically ill patients.

Conclusion

Esketamine for rapid sequence induction is a secure and efficacious therapy alternative for critically ill patients, reducing both ICU duration and ventilator dependency. Esketamine is more prone to induce tachycardia; however, short-acting β-blockers such as esmolol can effectively manage it. This study examines the potential advantages of esketamine, including improved hemodynamic stability. Nonetheless, the fundamental pathways

remain unidentified, requiring further investigation to fully comprehend how esketamine produces its effects, hence enhancing its clinical relevance in this demographic.

Data availability

All data generated and analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Jiancheng Zhang and Shiying Yuan contributed to the study concept and design. Xue Zhang analyzed the data and wrote the first draft of the manuscript. Xue Zhang, Xin Zhao, Jiaxin Xu, and Hong Liu contributed data and contributed to statistical analysis and improved the paper. Jiancheng Zhang and Shiying Yuan contributed to statistical analysis, improved the paper, gave guidance and improved the paper. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

This study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number: 2022-0351-01; approval date: February 22, 2021). Informed consent was obtained.

Additional information

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