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Effect of subanesthetic dose of esketamine induction on quality of recovery from general anesthesia: a propensity-score-matched retrospective study

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Page 2 of 33

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1	Effect of subanesthetic dose of esketamine induction on quality of recovery from
2	general anesthesia: a propensity-score-matched retrospective study
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20	Keywords: esketamine; general anesthesia with tracheal intubation; abdominal
21	surgery; postoperative adverse event; subanesthetic dose
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23 Abstract

Background: Subanesthetic doses of esketamine may attenuate the opioid-induced cough reflex and prevent intraoperative hemodynamic fluctuations. However, studies on its effect on the quality of postoperative recovery are limited. This study aims to provide clinical evidence on the effect of using subanesthetic doses of esketamine on the quality of recovery in abdominal surgery patients.

Methods: Patients undergoing abdominal surgery with tracheal intubation between 29 December 20, 2022, and April 30, 2023, were retrospectively reviewed. Patients were 30 31 assigned to the esketamine or control group based on whether they received a subanesthetic dose of esketamine. Recovery time, quality of recovery, postoperative 32 pain, and occurrence of other adverse events in the post-anesthesia care unit (PACU) 33 34 were recorded. Propensity score matching (PSM) analysis was used to minimize confounding bias. The primary outcome was PACU recovery time, and secondary 35 outcomes included postoperative pain and other adverse events. 36

37 **Results:** A total of 2,177 patients underwent abdominal surgery. After PSM, 598 patients were included in each group. The use of subanesthetic doses of esketamine 38 for induction of anesthesia significantly reduced the recovery time (20.00 vs. 23.00, 39 p=0.001). There were no significant differences in PACU observation time after 40 41 extubation. Total PACU time was shorter in the esketamine group than in the control group (62 vs. 66 minutes, p = 0.015). Compared to the control group, the esketamine 42 43 group had significantly less severe postoperative pain immediately after extubation (0.33% vs. 2.01%, p = 0.007) and a lower incidence of respiratory depression (2.68%) 44

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 vs. 5.35%, p=0.027). However, the esketamine group had a higher incidence of hypertension (9.53% vs. 6.35%, p=0.042). There were no significant differences of other adverse events between the two groups. other adverse events between the two groups. Conclusions: The use of subanesthetic doses of esketamine for induction of anesthesia in patients undergoing abdominal surgery may shorten the recovery times.
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 9 47 other adverse events between the two groups. 10 11 12 48 Conclusions: The use of subanesthetic doses of esketamine for induction of a subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the recovery times and the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery may shorten the subanesthesia in patients undergoing abdominal surgery m
 48 Conclusions: The use of subanesthetic doses of esketamine for induction of 13 14 anesthesia in patients undergoing abdominal surgery may shorten the recovery time
14 anesthesia in patients undergoing abdominal surgery may shorten the recovery tim
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 and reduce the incidence of postoperative complications.
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52 Strengths and limitations of this study

- 53 This study represents a retrospective investigation of the effect of using subanesthetic
- 54 doses of esketamine on the quality of recovery in abdominal surgery patients.
- 55 Using propensity score matching to ensure the baseline characteristics of patients.
- As a single-center study focusing on the quality of recovery after anesthesia, the
 external validity of the results may be limited.

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60 Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anesthesia with tracheal intubation is the most commonly used anesthetic technique.¹² Advances in medical technology have significantly reduced anesthesia-related mortality rates.³ However, this approach can still lead to adverse events, such as intubation cough, intraoperative hemodynamic fluctuations, postoperative pain and postoperative cognitive dysfunction (POCD).⁴⁻⁷ These reactions can prolong hospital stay and increase healthcare costs. Therefore, improving the efficacy and comfort of general anesthesia with tracheal intubation has become a pressing concern.

Esketamine is a modified version of the anesthetic ketamine that acts primarily by inhibiting the N-methyl-D-aspartate (NMDA) receptor, resulting in sedative and analgesic effects. Compared to ketamine, esketamine has a higher potency, stronger analgesic and sedative effects, and fewer side effects.⁸ ⁹ Previous research indicates that subanesthetic doses of esketamine, administered intravenously at 0.1-0.3 mg/kg or by infusion at 0.1-0.3 mg/kg·h can effectively reduce cough reflexes caused by opioid induction,¹⁰ prevent intraoperative hemodynamic fluctuations,¹¹ and reduce the need for intraoperative propofol and opioid medications.¹² ¹³ However, it remains unclear whether subanesthetic doses of esketamine in general anesthesia affect patient emergence and the incidence of postoperative delirium and agitation.¹⁴¹⁵

80 This study retrospectively analyzes the effect of subanesthetic doses of esketamine
81 used for intubation of general anesthesia on recovery quality, postoperative pain and

 adverse events in patients undergoing abdominal surgery. The objective is to provide
clinical evidence regarding the effect of esketamine on recovery quality for abdominal
surgery patients.

86 Methods

87 Study design and patient population

This retrospective, single-center study was conducted at the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China), after receiving approval by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20230403A). Informed consent from patients was waived by the ethics committee. It was registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154, 05/06/2023). The medical records used in this study were obtained from the medical database of the First Affiliated Hospital, Zhejiang University School of Medicine.

From December 20, 2022 to April 30, 2023, patients who undergoing abdominal surgery under general anesthesia with tracheal intubation were included in the study. Inclusion criteria included an American Society of Anesthesiologists (ASA) physical status of I to II, concurrent routine induction (sufentanil) with or without a subanesthetic dose of esketamine for general anesthesia. Exclusion criteria were age <18 years or > 80 years, hepatic or renal dysfunction, severe pulmonary disease, severe cardiac dysfunction (New York Heart Association [NYHA] Classification 3-4), central nervous system disorders, psychiatric disorders, severe preoperative anemia,

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Patients were transferred to the PACU after surgery, and endotracheal tubes were removed as soon as certain criteria were met (patients were awake, RR > 10 breaths

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All patients were routinely fasted, anesthesia induction and management. On admission to the operating room, patients were monitored with electrocardiogram

(ECG), non-invasive upper arm blood pressure, pulse oxygen saturation (SpO₂), partial pressure of end-tidal carbon dioxide (PetCO₂), body temperature, and bispectral index (BIS). Invasive continuous arterial pressure monitoring and central venous pressure monitoring were performed as needed.

Patients in the control group received with midazolam (0.04 mg/kg), propofol (1.0-2.0 mg/kg), rocuronium (0.6 mg/kg), and sufentanil (0.3-0.5 µg/kg). The esketamine group receives subanesthetic doses of esketamine (0.2 mg/kg) in addition to the above induction agents. During surgery, 0.8-1.5 minimum alveolar concentration (MAC) sevoflurane, 4-6 mg/kg·h propofol, and 0.1-0.3 µg/kg·min remifentanil were maintained. After surgery, 5 mg tropisetron and 50 mg ketorolac were administered intravenously. Postoperative analgesia was achieved with 0.375% ropivacaine for nerve block (transversus abdominis plane block, TAP) or local wound

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per minute and tidal volume > 5 ml/kg). Inadequate muscle strength was treated with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine intravenously. Supplemental oxygen at a rate of 2L/min was administered via nasal catheter after extubation. Pain was assessed using the Numeric Rating Scale (NRS) immediately, 15 minutes and 30 minutes after extubation. Hydromorphone (0.01mg/kg) was administered for pain relief if the NRS score exceeded 4 points. A jaw thrust or positive pressure ventilation with a face mask was used to treat respiratory depression. For dysphoria or delirium, propofol 0.5 mg/kg was used for sedation. If hypertension is diagnosed, intravenous amlodipine 5 mg is recommended. If hypotension occurs, ephedrine 6 mg should be administered. If shivering occurs, intravenous tramadol 50 mg is recommended. Discharge from the PACU was assessed using the modified Aldrete score, with a score of \geq 9 indicating readiness for discharge.^{16 17}

139 Data collection

Demographic and perioperative data were collected from the clinical information system (Seenew, Hangzhou, China) and institutional electronic Anesthesia Data Sysytem (Medical System, Suzhou, China), including: 1) preoperative data: gender, age, body mass index (BMI), medical history, and ASA classification; 2) intraoperative data: type of surgery, surgery duration, anesthesia duration, intraoperative blood loss, and use of the patient-controlled analgesia (PCA); 3) PACU data: heart rate, blood pressure, oxygen saturation, anesthesia recovery time, PACU observation time, the total PACU time, postoperative pain (NRS score), analgesic use,

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incidence of hypertension, hypotension, and medication use. Additionally, the modified Aldrete respiratory depression, delirium and agitation, score, nausea/vomiting, shivering, and other PACU adverse events (e.g., reintubation) were recorded. **Primary outcome** The primary outcome was anesthesia recovery time (T1), defined as the time from cessation of anesthetic drugs to extubation. Secondary outcome Secondary outcomes included postoperative pain immediately after extubation, at 15minutes, and at 30 minutes, and analgesic use. The modified Aldrete score at PACU discharge and the incidence of PACU adverse events including respiratory depression, hypertension, hypotension, delirium, agitation, nausea/vomiting, shivering, reintubation, and use of symptomatic treatment were recorded. Respiratory depression was defined as respiratory rate falling below 8 breaths per minute or SpO₂ < 90% for more than 1 minute.¹⁸ ¹⁹ In addition, the comparison of PACU observation time (T2), defined as the time from extubation to PACU discharge, total PACU time (T3), and PACU discharge delay rate, defined as the percentage of patients with a PACU time greater than 120 minutes, were analyzed.

Patient and Public Involvement

170	Patients or the public were not involved in the design, or conduct, or reporting, or
171	dissemination plans of this research.
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173	Statistical analysis
174	Sample size was calculated using PASS statistical software (NCSS LLC, Kaysville,
175	USA). This is a retrospective case-control study, based on the previous results of the
176	average anesthesia recovery time for both groups, with a two-tailed test, α set at 0.05,
177	power set at 90%, and 1:1 Sample ratio, a minimum sample size of 361 participants
178	per group was required.
179	Propensity score matching (PSM) analysis was performed using R Project for
180	Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the
181	matchIt package to reduce differences between the two groups based on the
182	esketamine administration to minimize confounding factors. Nearest-neighbor
183	matching method was used in a 1:1 ratio, with a caliper value of 0.05. Matching
184	variables included age, gender, BMI, medical history, ASA physical status
185	classification, surgical category, surgery duration, anesthesia duration, intraoperative
186	blood loss, and PCA use. Multiple linear regression analysis was used to complete the
187	matching process.
188	All quantitative data were assessed for normality using the Shapiro-Wilk test.
189	Normally distributed continuous data were presented as mean (standard deviation),
190	and differences between groups were analyzed using t-tests or analysis of variance
191	(ANOVA). Skewed data were presented as median (25th-75th percentile) and were

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analyzed using the nonparametric Mann-Whitney U test. Categorical data were
analyzed using the chi-squared test or Fisher's exact test. Ordinal data were analyzed
using the Wilcoxon rank-sum test. All statistical analyses were performed with the
SPSS software 22.0 (IBM corp., NY, USA). Statistical significance was defined as a P
value < 0.05.

Results

199 Demographic and patient characteristics

A total of 2,177 patients with ASA physical status of I to II under suferianil anesthesia underwent abdominal surgery, including hepatobiliary, gastrointestinal, and colorectal surgery, at the First Affiliated Hospital, Zhejiang University School of Medicine. Based on the inclusion and exclusion criteria, a final of 1,718 patients were enrolled, with 633 patients in the esketamine group and 1,085 patients in the control group. PSM successfully matched 598 patients in each group, achieving the required sample size (Figure 1). The use of PSM ensured that the baseline characteristics were similar between the two groups, as indicated by absolute standardized mean differences (SMD) of less than 0.1 for all variables (Figure 2). The distributions of the propensity scores and the SMD of the covariates were well balanced after PSM adjustment (Figure 3).

Patient characteristics in the esketamine group and control groups before and after PSM are shown in Table 1. After PSM, there were no significant differences in the patient characteristics in gender, age, BMI, medical history, ASA classification, type

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4	214	of surgery, surgery duration, anesthesia duration, intraoperative blood loss, and use of
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6	215	the PCA between the two groups ($P > 0.05$).
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11	217	Primary outcome
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14 15	218	The results showed that the anesthetic recovery time (T1) in the esketamine group
16 17	240	was 20 (11, 22) minutes, while the T1 in the control group was 22 (12, 27) minutes (D
18	219	was 20 (11, 32) minutes, while the T1 in the control group was 23 (13, 37) minutes (P
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	220	= 0.001), indicating that patients induced with subanesthetic doses of esketamine had
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22	221	faster recovery in the PACU (Table 2).
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28	223	Secondary outcome
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30	224	The number of patients with severe postoperative pain immediately after extubation
31	224	The number of patients with severe postoperative pair infinediately after extubation
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33	225	was significantly higher in the control group (12, 2.01%) than that in the esketamine
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35	226	groups $(2, 0.33\%)$ (p = 0.007). In addition, the number of patients requiring additional
36	220	groups $(2, 0.5576)$ (p = 0.007). In addition, the number of patients requiring additional
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38	227	hydromorphone for postoperative pain during PACU treatment was significantly
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40	220	bisher in the control group $(04, 15, 720/)$ then in the caletoning group $(70, 11, 710/)$ (r
41	228	higher in the control group (94, 15.72%) than in the esketamine group (70, 11.71%) (p
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43	229	= 0.044). However, there were no statistically significant differences in the number of
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46	230	patients with postoperative pain between the two groups at 15 and 30 minutes after
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48	231	extubation, as shown in Table 3.
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51	232	During the PACU period, the number of patients with respiratory depression in the
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53	233	control group was 32 (5.35%), significantly higher than the 16 (2.68%) cases in the
54	255	control group was 52 (5.5576), significantly ingher than the 10 (2.0076) cases in the
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56	234	esketamine group (p=0.027). The esketamine group had a significantly higher rate of
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58	235	hypertension than the control group (9.53% vs. 6.35%, p=0.042). There were no
59	200	hypertension mun me control group (7.5570 vs. 0.5570, p 0.042). There were no
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236	significant differences in hypotension, delirium and agitation, nausea and vomiting, or
237	shivering between the two groups. There were no emergencies requiring reintubation
238	in either group. There were also no statistically significant differences in the modified
239	Aldrete scores between the two groups when patients left the PACU (Table 4).
240	In addition, the total PACU time (T3) was also shorter in the esketamine group
241	(62.00 vs. 66.00, p=0.015). However, there was no significant difference in the PACU
242	observation time (T2) between the two groups, with median times of 38 minutes in
243	the control group and 37 minutes in the esketamine group ($p = 0.738$). The number of
244	patients with delayed discharge from the PACU was 30 (5.02%) in the esketamine
245	group and 38 (6.35%) in the control group, respectively ($p = 0.318$) (Table 2).
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247	Discussion
	Discussion The results of the current study indicate that the use of subanesthetic doses of
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247 248	The results of the current study indicate that the use of subanesthetic doses of
247 248 249	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for
247 248 249 250	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce
247 248 249 250 251	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce postoperative pain without increasing post-extubation side effects.
247 248 249 250 251 252	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce postoperative pain without increasing post-extubation side effects. Previously, it was thought that the combining different mechanisms, such as
247 248 249 250 251 252 253	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce postoperative pain without increasing post-extubation side effects. Previously, it was thought that the combining different mechanisms, such as esketamine with midazolam, propofol, or sevoflurane, could deepen the level of
247 248 249 250 251 252 253 254	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce postoperative pain without increasing post-extubation side effects. Previously, it was thought that the combining different mechanisms, such as esketamine with midazolam, propofol, or sevoflurane, could deepen the level of anesthesia and influence patient recovery. ^{20 21} However, recent studies have shown
247 248 249 250 251 252 253 254 255	The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative recovery time in the PACU for patients undergoing abdominal surgery. In addition, esketamine was found to reduce postoperative pain without increasing post-extubation side effects. Previously, it was thought that the combining different mechanisms, such as esketamine with midazolam, propofol, or sevoflurane, could deepen the level of anesthesia and influence patient recovery. ^{20 21} However, recent studies have shown that esketamine not only increases the depth of anesthesia but also accelerates

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neurons, particularly those in the paraventricular thalamus (PVT), thereby reducing anesthetic recovery time. Clinical studies have also shown that patients who received subanesthetic doses of esketamine intraoperatively had faster and better recovery of postoperative respiratory rate and tidal volume.²³ The current study supports these findings and suggests that the use of subanesthetic doses of esketamine may accelerate patient recovery.

This research shows that subanesthetic doses of esketamine are effective in relieving immediate post-extubation pain after extubation. Animal studies have suggested that the combining of NMDA receptor antagonists with opioids may result in synergistic or additive analgesic effects.²⁴ Numerous clinical studies have supported this concept by demonstrating that administration of 0.15-0.5 mg/kg of esketamine reduces intraoperative opioid consumption and improves postoperative pain management.^{12 13 25 26} Consistent with these findings, the present study shows similar results. The subgroup that receiving subanesthetic doses of esketamine reported significantly lower pain levels immediately after extubation. While there was no significant difference in pain scores between the two groups at 15 and 30 minutes post-extubation, the PACU observation period showed a significant reduction in the number of patients in the esketamine group requiring additional analgesics for postoperative pain relief compared to the control group, indicating the beneficial effect of subanesthetic doses of esketamine on overall postoperative pain relief. The major metabolite of esketamine is S-norketamine, which has approximately one-third the analgesic potency of esketamine and a longer elimination half-life. This may

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280	explain the prolonged analgesic effect of esketamine in the PACU. ²³
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The results of this study indicate that the incidence of respiratory depression was 281 significantly lower in the esketamine group than that in the control group. Respiratory 282 depression is a common adverse event in the PACU, with an incidence rate of 283 approximately 5%,¹⁸ which is similar to the incidence observed in the control group of 284 this study. Causes of respiratory depression during the anesthetic recovery period 285 include the use of opioids, residual effects of muscle relaxants, and the incomplete 286 recovery of the respiratory system after surgery. It's worth noting that approximately 287 288 20% of cases of respiratory depression are associated with the use of opioid medications.²⁷ Elevated carbon dioxide (CO₂) levels can stimulate central 289 chemoreceptors, leading to an increase in respiratory drive. However, the use of 290 opioid medications attenuates this response.²⁸ Both animal and clinical studies have 291 shown that ketamine can enhance CO₂ sensitivity and provide moderate protection 292 against respiratory depression and bronchoconstriction.^{29 30} Research by Jonkman et 293 294 al. also suggests that low-dose esketamine may counteract the respiratory depressant effects of opioid drugs.³¹ This suggests that the use of subanesthetic doses of 295 esketamine to induce anesthesia may not only reduce opioid consumption but also 296 stabilize respiration, thereby reducing the likelihood of fatal events. 297

The most common adverse events associated with esketamine primarily are psychological symptoms such as delirium, agitation, nightmares, and dissociative phenomena, which often follow a dose-dependent pattern.^{32 33} Bornemann-Cimenti H and *et al.* have confirmed that subanesthetic doses can reduce the incidence of

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psychological symptoms associated with esketamine.³⁴ Our study supports this view
and shows that subanesthetic doses of esketamine do not increase the incidence of
delirium or agitation. In addition, there is no effect on the incidence of nausea and
vomiting. The sympathomimetic effects of esketamine, which manifest as increased
blood pressure and heart rate.^{11 35} The incidence of hypertension was higher in the
esketamine group than in the control group. This may be due to the increased blood
pressure induced by esketamine.

The primary goal of the PACU is to improve turnover efficiency between surgical procedures and to increase patient satisfaction. Factors such as delirium, agitation, and postoperative pain can prolong the PACU stay.³⁶ However, the current study shows that the use of a subanesthetic dose of esketamine doesn't increase the incidence of these complications. Furthermore, the total PACU time for the esketamine group is shorter than that of the control group, suggesting that the use of esketamine may improve the efficiency of the PACU.

This study has several limitations to this study. First, it is a single-center, retrospective study. Second, the study dose of esketamine is subanesthetic, and the study did not investigate potential problems associated with other doses. Finally, this study focuses exclusively on patients undergoing abdominal surgery and does not include other types of surgery. Therefore, further research should include large, multicenter, prospective studies to fully address these limitations.

323 Conclusions

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324	Subanesthetic doses of esketamine have been shown to be effective in reducing the
325	recovery time in patients undergoing abdominal surgery under general endotracheal
326	anesthesia, without compromising the overall quality of recovery. In addition, the use
327	of subanesthetic doses of esketamine has the potential to reduce the incidence of
328	severe postoperative pain, thereby reducing the need for analgesia in the PACU. This
329	approach also helps to reduce the incidence of respiratory depression, resulting in a
330	shorter overall PACU time, and ultimately contributing to the overall recovery
331	process for patients.
332	
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336	Ethics statement
337	The study was approved by the Clinical Research Ethics Committee of the First
338	Affiliated Hospital, Zhejiang University School of Medicine (IIT20230403A), and
339	registered in the Chinese Clinical Trial Registry (www.chictr.org.cn,
340	ChiCTR2300072154).
341	Author contribution
342	Dongdong Wang and Yue Jin contributed to the study design and drafting of the
343	paper. Mengcao Weng, Kunwei Chen, Xiaojun Wu, Yuanfang Xiao, Yijie Wu
344	Minyue Qian and Zhongteng Lu contributed to data acquisition. Dongdong Wang
345	contributed to data analysis. All authors approved the version to be submitted.
346	Data availability statement

- 3 4 5	347	Data will be made available on request.
6 7	348	Conflict of interest
8 9 10	349	All authors declare no conflicts of interest.
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477	Figure	legends
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- Figure 1. Flowchart of patient selection. 478
- 479 Figure 2. Standardized mean differences of covariates after PSM.
- .ot. Figure 3. Distributions of propensity scores after PSM. 480

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BMJ Open BMJ Open BMJ Open Table 1. Comparison between the esketamine and control groups before and after propensity-score matching of 30 BMJ Open

			Before PSM				Total Control r e G G G G G G G G G G						
	Total	Control	Esketamie				Total	Control a	Setamine				
	(n=1718)	Group	Group	Statistic	Р	SMD	(n=1196)	1 (1)	····	Statistic	Р	SM	
		(n=1085)	(n=633)					(n=598) 6	Do (n=598)				
Age (yr)	58.00 (45.00,	57.00	58.00				58.00	58.00 g	t Su 58.00				
	66.00)	(43.00,	(49.00,	Z=-1.783	0.075	0.106	(47.00,	(47.00, a	per (48.00,	Z=-0.711	0.477	-0.0	
	88.00)	66.00)	66.00)				66.00)	67.00) a	eur 65.00)				
Gender								ata r		χ ² =0.023	0.954		
Male	777 (45.23)	495 (45.62)	282 (44.55)			-0.022	533 (44.57)	266 (44.48	67 (44.65)			0.00	
Female	941 (54.77)	590 (54.38)	351 (55.45)			0.022	663 (55.43)	332 (55.5 g	• 331 (55.35)			-0.0	
BMI	23.41 (21.23,	23.39	23.44				23.40	23.37	2 . 23.44				
	25.39)	(21.23,	(21.23,	Z=-0.179	0.858	-0.024	(21.19,	(21.10, ra i	e (21.24,	Z=-0.173	0.862	-0.0	
	23.37)	25.40)	25.34)				25.39)	25.40) jing	25.35)				
Chronic disease								and	j. Co				
Hypertension				χ ² =0.087	0.768			d sii	Ž	χ ² =0.023	0.880		
No	1412 (82.19)	894 (82.40)	518 (81.83)			-0.015	982 (82.11)	492 (82.27)	9 90 (81.94)			-0.0	
Yes	306 (17.81)	191 (17.60)	115 (18.17)			0.015	214 (17.89)	106 (17.73	J 08 (18.06)			0.00	
Diabetes				χ²=0.788	0.375			chn	, 8	χ ² =1.559	0.212		
No	1618 (94.18)	1026 (94.56)	592 (93.52)			-0.042	1128 (94.31)	569 (95.1 gies	2025 59 (93.48) at			-0.0	
Yes	100 (5.82)	59 (5.44)	41 (6.48)			0.042	68 (5.69)	29 (4.85)	A 39 (6.52)			0.06	
Coronary heart disease				χ²=1.716	0.190				ence Bi	χ²=1.831	0.176		
	1690 (98.37)	1064	626 (98.89)			0.079	1176	585 (97.83)	5 91 (98.83)			0.09	

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			(98.06)					(98.33)		л хо С			
	Yes	28 (1.63)	21 (1.94)	7 (1.11)			-0.079	20 (1.67)	13 (2.17) ද්	a ⁷ (1.17)			-0.09
	COPD				χ ² =2.058	0.151			ΣĒ	5	χ ² =0.253	0.615	
	No	1699 (98.89)	1076 (99.17)	623 (98.42)			-0.060	1180 (98.66)	591 (98.8 pretated to t 7 (1.17) o t	< 289 (98.49) ת			-0.02
	Yes	19 (1.11)	9 (0.83)	10 (1.58)			0.060	16 (1.34)	7 (1.17) 5 m	9 (1.51)			0.02
	ASA physical status								o text and dat 57 (9.53)dat		χ ² =3.668	0.160	
	Ι	143 (8.32)	100 (9.22)	43 (6.79)			-0.096	97 (8.11)	57 (9.53) d	40 (6.69)			-0.11
	Ш	1441 (83.88)	901 (83.04)	540 (85.31)			0.064	1016 (84.95)	503 (84.1 min	313 (85.79)			0.04
	Ш	134 (7.8)	84 (7.74)	50 (7.90)			0.006	83 (6.94)		45 (7.53)			0.04
S	Surgery type				χ ² =20.815	<0.001			≥		χ²=1.326	0.515	
s	Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)			-0.209	597 (49.92)	302 (50.50	295 (49.33)			-0.0
s	Gastrointestinal	460 (26.78)	279 (25.71)	181 (28.59)			0.064	333 (27.84)	158 (26.42)	75 (29.26)			0.06
s	Colorectal	339 (19.73)	184 (16.96)	155 (24.49)			0.175	266 (22.24)	138 (23.08)	1 28 (21.40)			-0.04
S	Surgery duration	60.00 (38.00,	55.00	68.00				62.00	62.00 m g	∞ 63.00			
((min)	121.00)	(37.00,	(41.00,	Z=-3.687	< 0.001	0.173	(39.00,	(38.25, o	2 (40.00,	Z=-0.310	0.757	0.00
		121.00)	112.00)	135.00)				127.00)	127.75) e	ת 126.75)			
	Anesthesia duration	82.00 (58.00,	79.00	90.00				86.00	85.50	86.00 (59.00,			-
((min)	155.00)	(56.00,	(60.00,	Z=-3.327	< 0.001	0.166	(58.00,		0	Z=-0.179	0.858	-0.00
т	Intraoperative	10.00 (10.00,	147.00) 10.00	170.00) 10.00	Z=-2.868	0.004	0.006	159.25) 10.00	161.00) 10.00	157.75) 10.00	Z=-0.553	0.580	-0.04
1	initiaoperative	10.00 (10.00,	10.00	10.00	<i>L</i> 2.808	0.004	0.000	10.00	10.00		Z0.333	0.380	-0.0

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								including (10.00,g	-09855			
blood loss (ml)	50.00)	(10.00,	(10.00,				(10.00,	(10.00, j	or (10.00,			
		50.00)	50.00)				50.00)	50.00) o	n 30 50.00)			
PCA				χ²=2.677	0.102			393 (65.72) 205 (34.28)	May	χ²=1.680	0.195	
Yes	1197 (69.67)	771 (71.06)	426 (67.30)			-0.080	807 (67.47)	393 (65.72)	e . 1 4 (69.2	3)		0.076
No	521 (30.33)	314 (28.94)	207 (32.70)			0.080	389 (32.53)	205 (34.28	De 10 84 (30.7	7)		-0.076
Data are prese ASA: America	an Society of A	Anesthesiolo	ogists; BMI	: body ma	ss index	x; COPD: c	hronic obstruc	ctive pulna	Superative dise	ase; PCA: P	atient contr	colled
analgesia; PSN	A: propensity s	score matchi	ng; SMD: s	tandardize	d mean	differences		ata m	from http://bmjopen.bmj.com/ on June 8, 2025 at . Jr (ABES) .			
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		Control Group	Esketamine Group	statistic	P value
		(n=598)	(n=598)		
T1 (min)		23.00 (13.00, 37.00)	20.00 (11.00, 32.00)	-3.256	0.001
T2 (min)		38.00 (31.00, 50.00)	37.00 (31.00, 50.00)	-0.334	0.738
T3 (min)		66.00 (51.00, 85.00)	62.00 (48.00, 82.00)	-2.425	0.015
Delayed	PACU	22 ((25)	30 (5.02)	0.998	0.318
discharge		38 (6.35)			

Data are presented as median (quartile) or n (%).

PACU: post-anesthesia care unit; T1: anesthesia recovery time; T2: PACU observation time; T3: The total PACU time.

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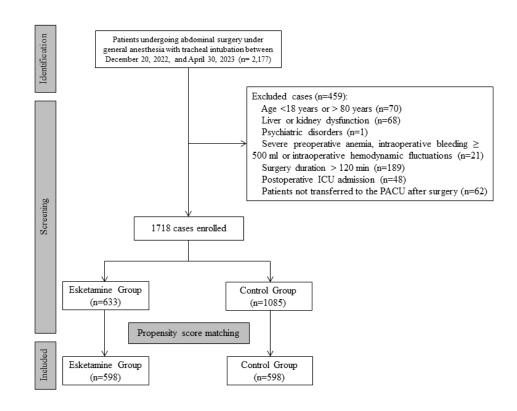
	Control	Esketamine	statistic	P value
	Group	Group (n=598)		
	(n=598)			
Postoperative pain			7.227	0.007
immediately after				
extubation				
NRS: 1-3	586 (97.99)	596 (99.67)		
NRS: ≥4	12 (2.01)	2 (0.33)		
Postoperative pain, 15			1.411	0.235
minutes after extubation				
NRS: 1-3	524 (87.63)	537 (89.80)		
NRS: ≥4	74 (12.37)	61 (10.20)		
Postoperative pain, 30			0.820	0.365
minutes after extubation				
NRS: 1-3	585 (97.99)	590 (98.66)		
NRS: ≥4	12 (2.01)	8 (1.34)		
Use of analgesic drugs	94 (15.72)	70 (11.71)	4.070	0.044

NRS: Numeric Rating Scale

	Control Group	Esketamine Group	statistic	P value
	(n=598)	(n=598)		
Respiratory depression	32 (5.35)	16 (2.68)	4.884	0.027
Hypotension	15 (2.51)	14 (2.34)	0.035	0.851
Hypertension	38 (6.35)	57 (9.53)	4.28	0.042
Delirium and agitation	88 (14.72)	91 (15.22)	0.059	0.808
Nausea and vomiting	24 (4.01)	27 (4.52)	0.184	0.668
Shivering	14 (2.3)	17 (2.8)	0.298	0.584
Reintubation	0	0	-	-
The modified Aldrete			0.451	0.502
score				
9 points	40 (6.69)	46 (7.69)		
10 points	558 (93.31)	552 (92.31)		

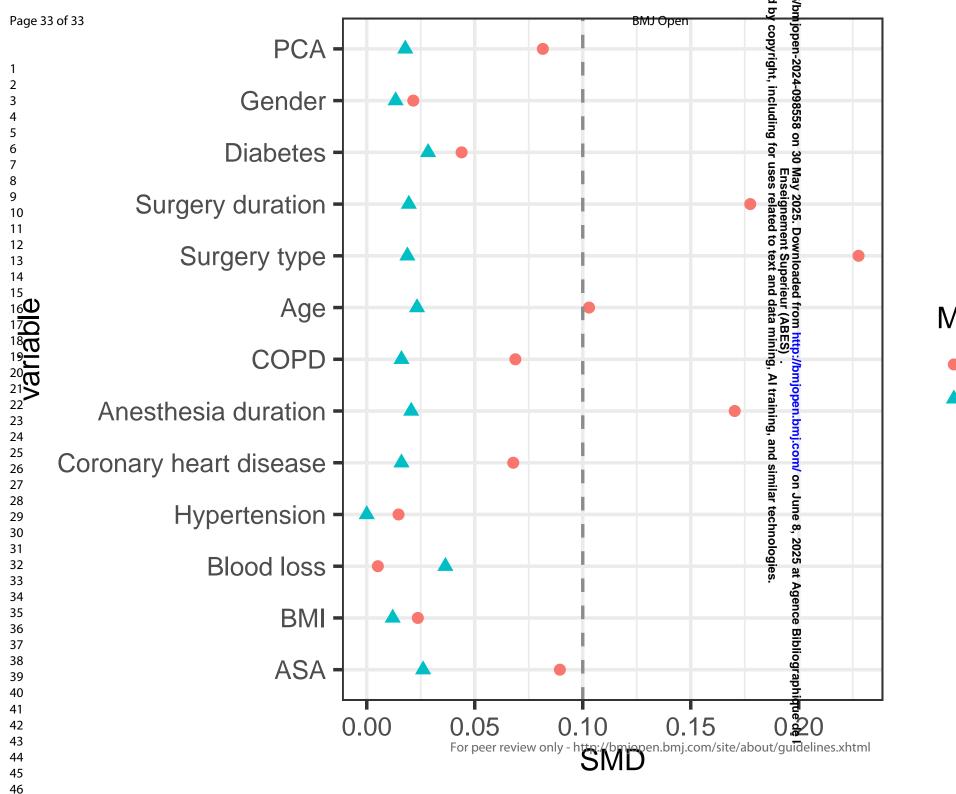
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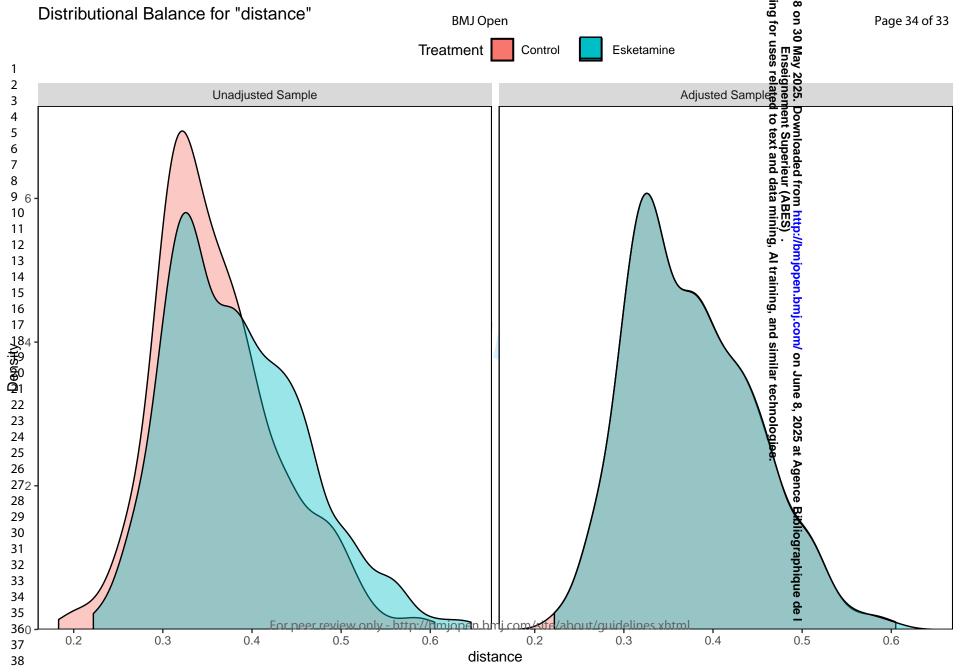


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MethodUnmatchedPSM



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Effect of subanesthetic dose of esketamine induction on quality of recovery from general anaesthesia in abdominal surgery: a propensity-score-matched retrospective study

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Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adverse events < THERAPEUTICS





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1	Effect of subanesthetic dose of esketamine induction on quality of recovery from
2	general anaesthesia in abdominal surgery: a propensity-score-matched
3	retrospective study
4	Dongdong Wang ¹ , Mengcao Weng ² , Kunwei Chen ² , Xiaojun Wu ¹ , Yuanfang Xiao ¹ ,
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20	Running title: Effect of esketamine on anesthetic recovery quality
21	Keywords: esketamine; general anaesthesia with tracheal intubation; abdominal
22	surgery; postoperative adverse event; subanesthetic dose

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23	Abstract
24	Objectives: Subanesthetic doses of esketamine may attenuate the opioid-induced
25	cough reflex and prevent intraoperative hemodynamic fluctuations. This study aims to
26	evaluate the effect of subanesthetic doses of esketamine on the quality of recovery in
27	abdominal surgery patients.
28	Design: Retrospective cohort study using propensity-score matching (PSM)
29	methodology.
30	Setting: A tertiary academic hospital.
31	Participants: Patients who underwent abdominal surgery under general anaesthesia
32	with tracheal intubation between 20 December, 2022, and 30 April, 2023, were
33	retrospectively reviewed. Patients were assigned to the esketamine or control group
34	based on whether they received a subanesthetic dose of esketamine.
35	Primary and secondary outcome measures: The primary outcome was extubation
36	time (T1). Secondary outcomes included PACU observation time (T2), total PACU
37	time (T3), postoperative pain at multiple time points, and adverse events including
38	respiratory depression, hypertension, and others.
39	Results: A total of 2,177 patients underwent abdominal surgery. After PSM, 1196
40	patients were analysed, 598 in each group. Esketamine significantly reduced the
41	extubation time compared to the control group (20.00 min vs. 23.00 min, p=0.001).
42	Total PACU time was shorter in the esketamine group than in the control group (62
43	vs. 66 minutes, $p = 0.015$), although PACU observation time did not how a significant
44	difference. Compared to the control group, the esketamine group had a lower

incidence of severe postoperative pain immediately after extubation (0.33% vs.
2.01%, p = 0.007) and a respiratory depression (2.68% vs. 5.35%, p=0.027), but a
higher incidence of hypertension (9.53% vs. 6.35%, p=0.042). There were no other
significant differences in adverse events between the two groups.
Conclusions: The use of subanesthetic doses of esketamine for induction of
anaesthesia in patients undergoing abdominal surgery may shorten the extubation time
and reduce the incidence of postoperative complications.

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2		
3 4	53	Strengths and limitations of this study
5 6 7	54	• Propensity score matching (PSM) was used to minimise selection bias and to
8 9 10	55	balance baseline characteristics between the groups of patients with and without
11 12	56	esketamine.
13 14 15	57	• A relatively large sample size from a real clinical setting was included, which
16 17 18	58	increasing the generalisability of the results.
19 20	59	• As a single-centre retrospective study, the generalisability of the findings may be
21 22 23	60	limited.
24 25 26	61	• Residual confounding from unmeasured variables may still be present, potentially
27 28	62	affecting the results of the propensity score analysis.
29 30 31	63	• Sensitivity analysis was not performed, which may affect the robustness of the
32 33 24	64	findings regarding residual confounding.
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66 Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anaesthesia with tracheal intubation is the most commonly used anesthetic technique.¹² Advances in medical technology have significantly reduced anaesthesia-related mortality rates.³ However, this approach can still lead to adverse events, such as intubation cough, intraoperative hemodynamic fluctuations, postoperative pain and postoperative cognitive dysfunction (POCD).⁴⁻⁷ These reactions can prolong hospital stay and increase healthcare costs. Therefore, improving the efficacy and comfort of general anaesthesia with tracheal intubation has become a pressing concern.

Esketamine is a modified version of the anesthetic ketamine that acts primarily by inhibiting the N-methyl-D-aspartate (NMDA) receptor, resulting in sedative and analgesic effects. Compared to ketamine, esketamine has a higher potency, stronger analgesic and sedative effects, and fewer side effects.⁸ ⁹ Previous research indicates that subanesthetic doses of esketamine, administered intravenously at 0.1-0.3 mg/kg or by infusion at 0.1-0.3 mg/kg·h can effectively reduce cough reflexes caused by opioid induction,¹⁰ prevent intraoperative hemodynamic fluctuations,¹¹ and reduce the need for intraoperative propofol and opioid medications.¹² ¹³ However, it remains unclear whether subanesthetic doses of esketamine in general anaesthesia affect patient emergence and the incidence of postoperative delirium and agitation.¹⁴¹⁵

86 This study retrospectively analyzes the effect of subanesthetic doses of esketamine87 used for intubation of general anaesthesia on recovery quality, postoperative pain and

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adverse events in patients undergoing abdominal surgery. The objective is to provide
clinical evidence regarding the effect of esketamine on recovery quality for abdominal
surgery patients. Propensity score matching (PSM) was used to adjust pairs of patients
with and without esketamine for potential confounders.

- 92
- 93 Methods
- 94 Study design and patient population

This retrospective, single-centre study was conducted at the First Affiliated 95 Hospital, Zhejiang University School of Medicine (Hangzhou, China). It was 96 97 registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154, 05/06/2023). The medical records used in this study were 98 obtained from the medical database of the First Affiliated Hospital, Zhejiang 99 University School of Medicine. 100

From December 20, 2022 to April 30, 2023, patients who had abdominal surgery 101 102 under general anaesthesia with tracheal intubation were included in the study. Inclusion criteria included an American Society of Anesthesiologists (ASA) physical 103 status of I to II, concurrent routine induction (sufentanil) with or without a 104 subanesthetic dose of esketamine for general anaesthesia. Exclusion criteria were age 105 106 <18 years or > 80 years, hepatic or renal dysfunction, severe pulmonary disease, severe cardiac dysfunction (New York Heart Association [NYHA] Classification 3-4), 107 central nervous system disorders, psychiatric disorders, severe preoperative anemia, 108 intraoperative bleeding \geq 500 ml or severe intraoperative haemodynamic fluctuations 109

with markedly unstable vital signs caused by massive bleeding, duration of surgery > 240 min, postoperative intensive care unit (ICU) admission, and patients not transferred to the PACU after surgery. Anesthetic procedure All patients underwent preoperative fasting. On admission to the operating room, patients were monitored with electrocardiogram (ECG), non-invasive upper arm blood pulse saturation pressure, oxygen $(SpO_2),$ respiratory rate, partial pressure of end-tidal carbon dioxide (PetCO₂), body temperature. and bispectral index (BIS). Invasive continuous arterial pressure monitoring and central venous pressure monitoring were performed as needed. Patients in the control group received with midazolam (0.04 mg/kg), propofol (1.0-2.0 mg/kg), rocuronium (0.6 mg/kg), and sufentanil (0.3-0.5 µg/kg). The esketamine group receives subanesthetic doses of esketamine (0.2 mg/kg) in addition to the above induction agents. During surgery, 0.8-1.5 minimum alveolar concentration (MAC) sevoflurane, 4-6 mg/kg·h propofol, and 0.1-0.3 µg/kg·min remifentanil were maintained. After surgery, 5 mg tropisetron and 50 mg ketorolac were administered intravenously. Postoperative analgesia was achieved with 0.375% ropivacaine for nerve block (transversus abdominis plane block, TAP) or local wound infiltration anaesthesia.

Patients were transferred to the PACU after surgery, and endotracheal tubes were
removed as soon as certain criteria were met (patients were awake, RR > 10 breaths

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per minute and tidal volume > 5 ml/kg). Inadequate muscle strength was treated with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine intravenously. Supplemental oxygen at a rate of 2L/min was administered via nasal catheter after extubation. Pain was assessed using the Numeric Rating Scale (NRS) immediately, 15 minutes and 30 minutes after extubation. Hydromorphone (0.01mg/kg) was administered for pain relief if the NRS score exceeded 4 points. A jaw thrust or positive pressure ventilation with a face mask was used to treat respiratory depression. For dysphoria or delirium, propofol 0.5 mg/kg was used for sedation. If hypertension is diagnosed, intravenous amlodipine 5 mg is recommended. If hypotension occurs, ephedrine 6 mg should be administered. If shivering occurs, intravenous tramadol 50 mg is recommended. Discharge from the PACU was assessed using the modified Aldrete score, with a score of ≥ 9 indicating readiness for discharge.^{16 17}

145 Data collection

Demographic and perioperative data were collected from the clinical information system (Seenew, Hangzhou, China) and institutional electronic Anaesthesia Data Sysytem (Medical System, Suzhou, China), including: 1) preoperative data: gender, age, body mass index (BMI), medical history, and ASA classification; 2) intraoperative data: type of surgery, surgery duration, anaesthesia duration, intraoperative blood loss, and use of the patient-controlled analgesia (PCA); 3) PACU data: heart rate, blood pressure, oxygen saturation, extubation time, PACU observation time, the total PACU time, postoperative pain (NRS score), analgesic use,

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incidence of hypertension, hypotension, and medication use. Additionally, the modified Aldrete score, respiratory depression, delirium and agitation, nausea/vomiting, shivering, and other PACU adverse events (e.g., reintubation) were recorded. **Primary outcome** The primary outcome was extubation time (T1), defined as the time from discontinuation of anaesthesia to extubation (minitues). Secondary outcome Secondary outcomes included postoperative pain immediately after extubation, at 15minutes, and at 30 minutes, and analgesic use. The modified Aldrete score at PACU discharge and the incidence of PACU adverse events including respiratory depression, hypertension, hypotension, delirium, agitation, nausea/vomiting, shivering, reintubation, and use of symptomatic treatment were recorded. Respiratory depression was defined as respiratory rate falling below 8 breaths per minute or SpO₂ < 90% for more than 1 minute.¹⁸ ¹⁹ In addition, the comparison of PACU observation time (T2), defined as the time from extubation to PACU discharge, total PACU time (T3), defined as the interval from PACU admission to discharge, and PACU discharge delay rate, defined as the percentage of patients with a PACU time greater than 120 minutes, were analyzed.

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176 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, ordissemination plans of this research.

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180 **Propensity score matching**

Propensity score matching (PSM) analysis was performed using R Project for 181 Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the 182 matchIt package to reduce differences between the two groups based on the 183 184 esketamine administration to minimize confounding factors. It is generally accepted that a standardised mean difference (SMD) of less than 0.1 for all variables indicates a 185 good fit. For binary variables, the SMD is the difference in event rates between the 186 187 treatment and control groups divided by the pooled standard deviation, where the pooled p is the weighted average of the event rates in both groups. For multi-category 188 variables, the variable is split into several binary dummy variables and the SMD is 189 190 calculated separately for each dummy variable, taking the maximum absolute value. Nearest-neighbor matching method was used in a 1:1 ratio, with a caliper value of 191 0.05. Matching variables included age, gender, BMI, chronic disease, ASA physical 192 status classification, surgical category, surgery duration, anaesthesia duration, 193 intraoperative blood loss, and PCA use, as indicated by absolute standardized mean 194 differences (SMD) of less than 0.1 for all variables. Multiple linear regression 195 analysis was used to complete the matching process. 196

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198 Statistical analysis

Sample size was calculated using PASS statistical software (NCSS LLC, Kaysville, USA). This was a retrospective case-control study. Based on our previous results, the mean extubation time for both groups were 19.00 ± 11.52 min and 22.15 ± 14.42 min, respectively. A two-tailed test with α set at 0.05, 90% power and a sample size of 1:1 indicated that a minimum sample size of 361 participants per group was required. As PSM will be used for case selection, we included a larger sample size to ensure that the final number after PSM met the required threshold.

206 All quantitative data were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean (standard deviation), 207 and differences between groups were analyzed using t-tests or analysis of variance 208 209 (ANOVA). Skewed data were presented as median (25th-75th percentile) and were analyzed using the nonparametric Mann-Whitney U test. Categorical data were 210 analyzed using the chi-squared test or Fisher's exact test. Ordinal data were analyzed 211 212 using the Wilcoxon rank-sum test. All statistical analyses were performed with the SPSS software 22.0 (IBM corp., NY, USA). Statistical significance was defined as a P 213 value < 0.05. 214

215

216 **Results**

217 Demographic and patient characteristics

A total of 2,177 patients with ASA physical status of I to III under suferitanil
anaesthesia underwent abdominal surgery, including hepatobiliary, gastrointestinal,

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and colorectal surgery, at the First Affiliated Hospital, Zhejiang University School of Medicine. Based on the inclusion and exclusion criteria, a final of 1,718 patients were enrolled, with 633 patients in the esketamine group and 1,085 patients in the control group. PSM successfully matched 598 patients in each group, achieving the required sample size (Figure 1). The use of PSM ensured that the baseline characteristics were similar between the two groups (Figure 2). The distributions of the propensity scores and the SMD of the covariates were well balanced after PSM adjustment (Figure 3). Patient characteristics in the esketamine group and control groups before and after PSM are shown in Table 1. After PSM, there were no significant differences (P >0.05) in the patient characteristics in gender, age, BMI, medical history, ASA classification, type of surgery, surgery duration, anaesthesia duration, intraoperative blood loss, and use of the PCA between the two groups.

Primary outcome

The results showed that the extubation time (T1) in the esketamine group was 20 (11, 32) minutes, while the T1 in the control group was 23 (13, 37) minutes (P = 0.001), indicating that patients induced with subanesthetic doses of esketamine had faster recovery in the PACU (Table 2). Multiple linear regression suggests that ketamine is an independent protective factor for extubation time (Supplementary Table 1).

241 Secondary outcome

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The number of patients with severe postoperative pain immediately after extubation 242 was significantly higher in the control group (12, 2.01%) than that in the esketamine 243 groups (2, 0.33%) (p = 0.007). In addition, the number of patients requiring additional 244 hydromorphone for postoperative pain during PACU treatment was significantly 245 higher in the control group (94, 15.72%) than in the esketamine group (70, 11.71%) (p 246 = 0.044). However, there were no statistically significant differences in the number of 247 patients with postoperative pain between the two groups at 15 and 30 minutes after 248 extubation, as shown in Table 3. 249 250 During the PACU period, the number of patients with respiratory depression in the control group was 32 (5.35%), significantly higher than the 16 (2.68%) cases in the 251 esketamine group (p=0.027). The esketamine group had a significantly higher rate of 252

hypertension than the control group (9.53% vs. 6.35%, p=0.042). There were no
significant differences in hypotension, delirium and agitation, nausea and vomiting, or
shivering between the two groups. There were no emergencies requiring reintubation
in either group. There were also no statistically significant differences in the modified
Aldrete scores between the two groups when patients left the PACU (Table 4).

In addition, the total PACU time (T3) was also shorter in the esketamine group (62.00 vs. 66.00, p=0.015). However, there was no significant difference in the PACU observation time (T2) between the two groups, with median times of 38 minutes in the control group and 37 minutes in the esketamine group (p = 0.738). The number of patients with delayed discharge from the PACU was 30 (5.02%) in the esketamine group and 38 (6.35%) in the control group, respectively (p = 0.318) (Table 2).

2		
3 4	264	
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6 7	265	Discussion
8 9 10 11 12 13	266	The results of the current study indicate that the use of subanesthetic doses of
	267	esketamine can effectively reduce the postoperative extubation time in the PACU for
14 15	268	patients undergoing abdominal surgery. In addition, esketamine was found to reduce
16 17 18	269	postoperative pain without increasing post-extubation side effects.
19 20 21	270	Previously, it was thought that the combining different mechanisms, such as
22 23	271	esketamine with midazolam, propofol, or sevoflurane, could deepen the level of
24 25 26	272	anaesthesia and influence patient recovery. ^{20 21} However, recent studies have shown
27 28 29	273	that esketamine not only increases the depth of anaesthesia but also accelerates
30 31	274	recovery from anaesthesia. ²² Animal studies have shown that ketamine, the parent
32 33 34	275	compound of esketamine, can shorten the peak activation time of the glutamatergic
35 36	276	neurons, particularly those in the paraventricular thalamus (PVT), thereby reducing
37 38 39	277	extubation time. Clinical studies have also shown that patients who received
40 41 42	278	subanesthetic doses of esketamine intraoperatively had faster and better recovery of
43 44	279	postoperative respiratory rate and tidal volume. ²³ The current study supports these
45 46 47	280	findings and suggests that the use of subanesthetic doses of esketamine may
48 49 50	281	accelerate patient recovery.
51 52	282	This research shows that subanesthetic doses of esketamine are effective in
53 54 55	283	relieving immediate post-extubation pain after extubation. Animal studies have
56 57 58	284	suggested that the combining of NMDA receptor antagonists with opioids may result
59 60	285	in synergistic or additive analgesic effects. ²⁴ Numerous clinical studies have

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supported this concept by demonstrating that administration of 0.15-0.5 mg/kg of 286 esketamine reduces intraoperative opioid consumption and improves postoperative 287 pain management.¹² ¹³ ²⁵ ²⁶ Consistent with these findings, the present study shows 288 similar results. The subgroup that receiving subanesthetic doses of esketamine 289 reported significantly lower pain levels immediately after extubation. While there was 290 no significant difference in pain scores between the two groups at 15 and 30 minutes 291 post-extubation, the PACU observation period showed a significant reduction in the 292 number of patients in the esketamine group requiring additional analgesics for 293 294 postoperative pain relief compared to the control group, indicating the beneficial effect of subanesthetic doses of esketamine on overall postoperative pain relief. The 295 major metabolite of esketamine is S-norketamine, which has approximately one-third 296 297 the analgesic potency of esketamine and a longer elimination half-life. This may explain the prolonged analgesic effect of esketamine in the PACU.²³ 298 The results of this study indicate that the incidence of respiratory depression was 299 significantly lower in the esketamine group than that in the control group. Respiratory 300 depression is a common adverse event in the PACU, with an incidence rate of 301

approximately 5%,¹⁸ which is similar to the incidence observed in the control group of this study. Causes of respiratory depression during the anesthetic recovery period include the use of opioids, residual effects of muscle relaxants, and the incomplete recovery of the respiratory system after surgery. It's worth noting that approximately 20% of cases of respiratory depression are associated with the use of opioid medications.²⁷ Elevated carbon dioxide (CO₂) levels can stimulate central

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chemoreceptors, leading to an increase in respiratory drive. However, the use of opioid medications attenuates this response.²⁸ Both animal and clinical studies have shown that ketamine can enhance CO₂ sensitivity and provide moderate protection against respiratory depression and bronchoconstriction.^{29 30} Research by Jonkman et al. also suggests that low-dose esketamine may counteract the respiratory depressant effects of opioid drugs.³¹ This suggests that the use of subanesthetic doses of esketamine to induce anaesthesia may not only reduce opioid consumption but also stabilize respiration, thereby reducing the likelihood of fatal events.

The most common adverse events associated with esketamine primarily are psychological symptoms such as delirium, agitation, nightmares, and dissociative phenomena, which often follow a dose-dependent pattern.^{32 33} Bornemann-Cimenti H et al. have confirmed that subanesthetic doses can reduce the incidence of psychological symptoms associated with esketamine.³⁴ Our study supports this view and shows that subanesthetic doses of esketamine do not increase the incidence of delirium or agitation. In addition, there is no effect on the incidence of nausea and vomiting. The sympathomimetic effects of esketamine, which manifest as increased blood pressure and heart rate.^{11 35} The incidence of hypertension was higher in the esketamine group than in the control group. This may be due to the increased blood pressure induced by esketamine.

The primary goal of the PACU is to improve turnover efficiency between surgical procedures and to increase patient satisfaction. Factors such as delirium, agitation, and postoperative pain can prolong the PACU stay.³⁶ However, the current study shows

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that the use of a subanesthetic dose of esketamine doesn't increase the incidence of
these complications. Furthermore, the total PACU time for the esketamine group is
shorter than that of the control group, suggesting that the use of esketamine may
improve the efficiency of the PACU.

There are several limitations to this study. First, it is a single-centre, retrospective study, which may limit the generalisability of the findings. Although the two groups were matched on several demographic factors, there remains the potential for residual confounding due to unmeasured variables affecting the propensity score analysis. In addition, the lack of sensitivity analysis may affect the robustness of the results. Second, the dose of esketamine is subanesthetic, and the study did not investigate potential problems associated with other doses. Finally, this study focuses exclusively on patients undergoing abdominal surgery and does not include other types of surgery. Therefore, further research should include large, multicentre, prospective studies to fully address these limitations.

345 Conclusions

Subanesthetic doses of esketamine have been shown to be effective in reducing the extubation time in patients undergoing abdominal surgery under general endotracheal anaesthesia, without compromising the overall quality of recovery. In addition, the use of subanesthetic doses of esketamine has the potential to reduce the incidence of severe postoperative pain, thereby reducing the need for analgesia in the PACU. This approach also helps to reduce the incidence of respiratory depression, resulting in a BMJ Open

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352	shorter overall PACU time, and ultimately contributing to the overall recovery
353	process for patients.
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355	Contributions DW, XF and YJ contributed to the study design. MW, KC, XW, YX,
356	YW, MQ and ZL contributed to data acquisition. DW contributed to data analysis and
357	drafting of the paper. XF and YJ contributed to manuscript revision. YJ contributed to
358	final approval of the version. All authors read and approved the final version. YJ is
359	the guarantor.
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362	Conflicting interests None declared.
363	Patient consent for publication Not required.
364	Ethics approval The study was approved by the Clinical Research Ethics Committee
365	of the First Affiliated Hospital, Zhejiang University School of Medicine
366	(IIT20230403A), and registered in the Chinese Clinical Trial Registry
367	(www.chictr.org.cn, ChiCTR2300072154).
368	Data availability statement Data will be made available on request. Further inquiries
369	can be directed to the corresponding authors.
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 Figure legends

- Figure 1. Flowchart of patient selection.
- Figure 2. Standardized mean differences of covariates after PSM.

Figure 3. Distributions of propensity scores after PSM.

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BMJ Open BMJ Open BMJ Open Table 1. Comparison between the esketamine and control groups before and after propensity-score matching of 30 BMJ Open

		Before PSM				S AT S PSM		
	Total (n=1718)	Control Group (n=1085)	Esketamie Group (n=633)	Р	Total (n=1196)	ତ୍ୟୁ କୁମ୍ଫ୍ରିକ୍ୟୁଥି Group la en 12598) କୁମୁକ୍ୟୁ 598)	Esketamine Group (n=598)	P
Age (yearr), median (IQR)	58.00 (45.00, 66.00)	57.00 (43.00, 66.00)	58.00 (49.00, 66.00)	0.075	58.00 (47.00, 66.00)	58. 8 0 2 4 9 .00, 67.00)	58.00 (48.00, 65.00)	0.477
Gender, n (%)						nlo: Sup		0.95
Male	777 (45.23)	495 (45.62)	282 (44.55)		533 (44.57)	t Superied t Superied	267 (44.65)	
Female	941 (54.77)	590 (54.38)	351 (55.45)		663 (55.43)	a3527(55.52)	331 (55.35)	
BMI, median (IQR)	23.41 (21.23, 25.39)	23.39 (21.23, 25.40)	23.44 (21.23, 25.34)	0.858	23.40 (21.19, 25.39)	23 24.10, 25.40)	23.44 (21.24, 25.35)	0.86
Chronic disease						ES)		
Hypertension, n (%)				0.768		http://bmj ES) . ining, Al		0.88
No	1412 (82.19)	894 (82.40)	518 (81.83)		982 (82.11)	≥ 1 1 1 1 1 1 1 1 1 1	490 (81.94)	
Yes	306 (17.81)	191 (17.60)	115 (18.17)		214 (17.89)	106 (17.73)	108 (18.06)	
Diabetes, n (%)				0.375		106 ^(17.73)		0.21
No	1618 (94.18)	1026 (94.56)	592 (93.52)		1128 (94.31)	and 569 (95.15)	559 (93.48)	
Yes	100 (5.82)	59 (5.44)	41 (6.48)		68 (5.69)	sin 29 0 (4.85)	39 (6.52)	
Coronary heart disease, n				0.100		n Ju		0.17
(%)				0.190		June ar tec		0.17
No	1690 (98.37)	1064 (98.06)	626 (98.89)		1176 (98.33)	similar technologi 1352.17) 1352.17) at	591 (98.83)	
Yes	28 (1.63)	21 (1.94)	7 (1.11)		20 (1.67)	log 13 3 2.17)	7 (1.17)	
COPD, n (%)				0.151		at A es.		0.61
No	1699 (98.89)	1076 (99.17)	623 (98.42)		1180 (98.66)	59 (98.83)	589 (98.49)	
Yes	19 (1.11)	9 (0.83)	10 (1.58)		16 (1.34)	7 & 1.17)	9 (1.51)	
ASA physical status, n (%)						Bibli 57 2 9.53)		0.16
Ι	143 (8.32)	100 (9.22)	43 (6.79)		97 (8.11)	578(9.53)	40 (6.69)	

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Π	1441 (83.88)	901 (83.04)	540 (85.31)		1016 (84.95)	5 03 0 (84.11)	513 (85.79)	
Ш	134 (7.8)	84 (7.74)	50 (7.90)		83 (6.94)	of 3846.35)	45 (7.53)	
Surgery type, n (%)				< 0.001		May 50.50) Enset 5		0.515
Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)		597 (49.92)	s s 7992,(50.50)	295 (49.33)	
Gastrointestinal surgery	460 (26.78)	279 (25.71)	181 (28.59)		333 (27.84)		175 (29.26)	
Colorectal surgery	339 (19.73)	184 (16.96)	155 (24.49)		266 (22.24)		128 (21.40)	
Surgery duration (min)	, 60.00 (38.00,	55.00 (37.00,	68.00 (41.00,	<0.001	62.00 (39.00,		63.00 (40.00,	0 757
median (IQR)	121.00)	112.00)	135.00)	< 0.001	127.00)		126.75)	0.757
Anaesthesia duration (min	, 82.00 (58.00,	79.00 (56.00,	90.00 (60.00,	<0.001	86.00 (58.00,	nd 250 (57.00,	86.00 (59.00,	0.050
median (IQR)	155.00)	147.00)	170.00)	< 0.001	159.25)		157.75)	0.858
Intraoperative blood los	S	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	0.004	10.00 (10.00, 50.00)		10.00 (10.00 50.00)	0.590
(ml), median (IQR)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	0.004	10.00 (10.00, 50.00)	iu Hate (m.00, 50.00)	10.00 (10.00, 50.00)	0.580
PCA, n (%)				0.102		A		0.195
Yes	1197 (69.67)	771 (71.06)	426 (67.30)		807 (67.47)	1393 (65.72)	414 (69.23)	
No	521 (30.33)	314 (28.94)	207 (32.70)		389 (32.53)	1 205 1 34.28)	184 (30.77)	

 No
 521 (30.33)
 314 (28.94)
 207 (32.70)
 389 (32.53)
 205 (34.28)
 184 (30.77)

 ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulnomary disease; PCA: Patient controlled analgesia; PSM: propensity score matching; SMD: standardized mean differences
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Table 2. Recovery time after surgery.

	Control Group	Esketamine Group	P value
	(n=598)	(n=598)	
T1 (min), median (IQR)	23.00 (13.00, 37.00)	20.00 (11.00, 32.00)	0.001
T2 (min), median (IQR)	38.00 (31.00, 50.00)	37.00 (31.00, 50.00)	0.738
T3 (min), median (IQR)	66.00 (51.00, 85.00)	62.00 (48.00, 82.00)	0.015
Delayed PACU discharge, n (%)	38 (6.35)	30 (5.02)	0.318

PACU: post-anesthesia care unit; T1: extubation time; T2: PACU observation time; T3: The total PACU time.

Page 29 of 34

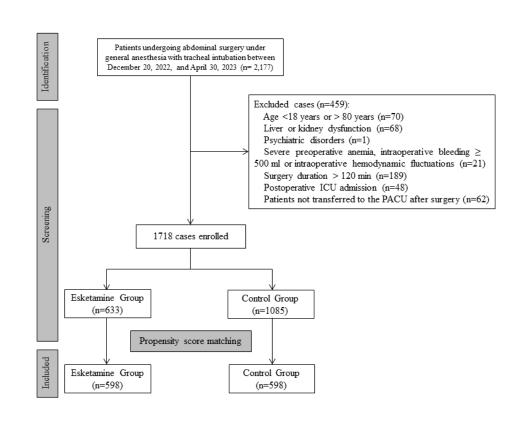
	(n=598)	(n=598)	
Postoperative pain immediately			0.0
after extubation			
NRS: 1-3	586 (97.99)	596 (99.67)	
NRS: ≥4	12 (2.01)	2 (0.33)	
Postoperative pain, 15 minutes			0.2
after extubation			
NRS: 1-3	524 (87.63)	537 (89.80)	
NRS: ≥4	74 (12.37)	61 (10.20)	
Postoperative pain, 30 minutes			0.3
after extubation			
NRS: ≥4	12 (2.01)	8 (1.34)	
Use of analgesic drugs	94 (15.72)	70 (11.71)	0.04
Data are presented as n (%).	2.		
NRS: Numeric Rating Scale			

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	Control Group (n=598)	Esketamine Group (n=598)	P value
Respiratory depression	32 (5.35)	16 (2.68)	0.027
Hypotension	15 (2.51)	14 (2.34)	0.851
Hypertension	38 (6.35)	57 (9.53)	0.042
Delirium and agitation	88 (14.72)	91 (15.22)	0.808
Nausea and vomiting	24 (4.01)	27 (4.52)	0.668
Shivering	14 (2.3)	17 (2.8)	0.584
Reintubation	0	0	-
The modified Aldrete score			0.502
9 points	40 (6.69)	46 (7.69)	
10 points	558 (93.31)	552 (92.31)	
Data are presented as n (%).			

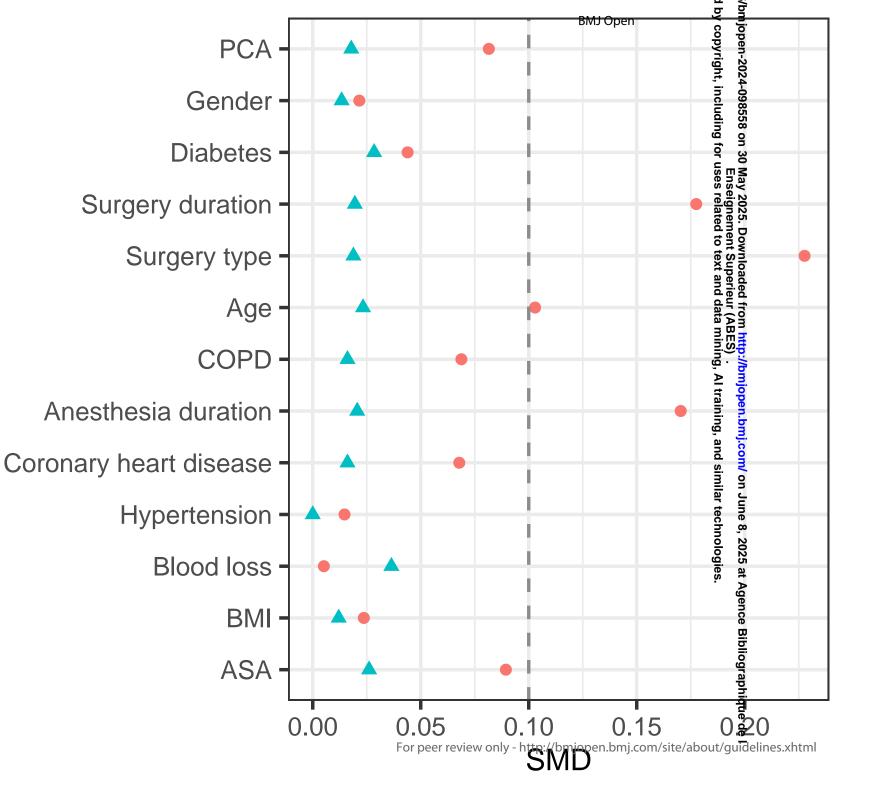
Table 1 Destanarative adverse events and the modified Aldrete score

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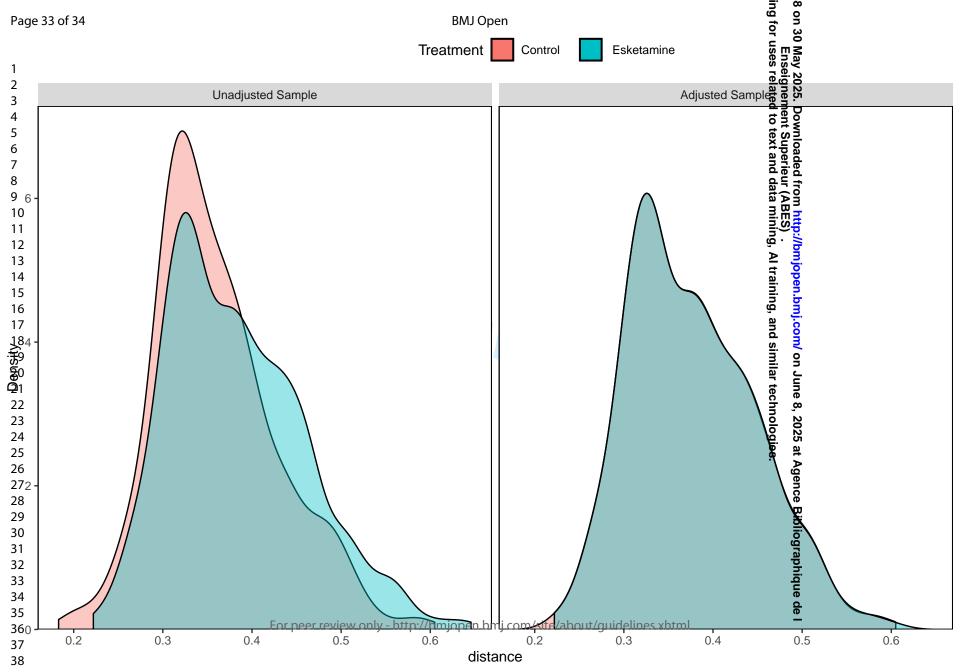
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PSM



				Sumplemen	town dat	ta		iding	
BMJ Open BMJ Open Supplementary data Supplement Table 1. Results of multiple linear regression analysis Variables b S.E t β (95%CI) P m_b m_S.E m_€ aβ (95%CI) al									
Variables	b	S.E	t	<u>β (95%CI)</u>	Р	m_b	m_S.E	m_G s s 20 0.20 (0.12 ~ 0.27) 5.23 s 30 0.20 (0.12 ~ 0.27) -3.8 and data mining, and similar technologies. Al training, and similar technologies. 1.21 nologies. Al training and similar technologies. Al training and similar technologies. Al training and similar technologies. 1.21 nologies. Al training and similar technologies. Al training a	
Age	0.27	0.04	7.09	0.27 (0.20 ~ 0.35)	<.001	0.20	0.04	5.23 0.20 (0.12 ~ 0.27)	
Gender								125. I	
Male				0.00 (Reference)				L to	
Female	1.38	1.12	1.23	1.38 (-0.82 ~ 3.58)	0.218			t Su	
BMI	-0.89	0.17	-5.34	-0.89 (-1.21 ~ -0.56)	<.001	-0.60	0.16	-3.8 a a 0.60 (-0.91 ~ -0.30)	
Chronic disease								nd d	
Hypertension								iron ata	
No				0.00 (Reference)					
Yes	0.20	1.46	0.14	0.20 (-2.65 ~ 3.06)	0.888			ning S)	
Diabetes								у, Э, А	
No				0.00 (Reference)					
Yes	-1.78	2.41	-0.74	-1.78 (-6.51 ~ 2.94)	0.459			aini en.	
Coronary heart disease								ng,	
No				0.00 (Reference)				and	
Yes	3.28	4.35	0.75	3.28 (-5.25 ~ 11.81)	0.451			i sii	
COPD								mila	
No				0.00 (Reference)				to 0.00 (Reference)	
Yes	11.59	4.85	2.39	11.59 (2.10 ~ 21.09)	0.017	5.42	4.48	$1.21\frac{6}{2}$ $c_{\infty}^{0}5.42$ (-3.36 ~ 14.20) (
ASA physical status								100	
Ι				0.00 (Reference)				2025 at A ologies.	
Π	3.82	2.05	1.86	3.82 (-0.20 ~ 7.83)	0.062			is. A	
Ш	3.34	2.88	1.16	3.34 (-2.31 ~ 8.99)	0.246			-3.00 G -3.70 (-6.12 ~ -1.28)	
Surgery type								Ce	
Hepatobiliary surgery				0.00 (Reference)				B 0.00 (Reference)	
Gastrointestinal surgery	-3.97	1.29	-3.08	-3.97 (-6.50 ~ -1.44)	0.002	-3.70	1.23	-3.00 5 -3.70 (-6.12 ~ -1.28) (

Page 34 of 34

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									by copyright, including	ивт јореп - 2024-098558 8 о 1.20 (-1.92 ~ 4.33)	
	Colorectal surgery	7.89	1.39	5.68	7.89 (5.17 ~ 10.61)	<.001	1.20	1.60	0.75	6 1.20 (-1.92 ~ 4.33)	0.451
	Surgery duration (min)	0.09	0.01	9.58	0.09 (0.07 ~ 0.11)	<.001	0.05	0.07	0.81 ਰ੍ਰੰ	3 0.05 (-0.08 ~ 0.18) 3 -0.05 (-0.17 ~ 0.07)	0.417
	Anesthesia duration (min)	0.09	0.01	9.80	0.09 (0.07 ~ 0.10)	<.001	-0.05	0.06	-0.7 % п	≤ -0.05 (-0.17 ~ 0.07)	0.442
	Intraoperative blood loss (ml)	0.10	0.01	10.50	0.10 (0.08 ~ 0.12)	<.001	0.06	0.01	5.37 8 r	4. 0.05 (-0.17 ~ 0.07) 4. 0.06 (0.04 ~ 0.08) 5. 0.00 (Reference) 6. 0.00 (Reference) 6. 0.00 (Reference) 6. 0.4 (2.77 ~ 9.31)	<.001
	Esketamine								ela	202	
	No				0.00 (Reference)				ted	0.00 (Reference)	
	Yes	-3.35	1.11	-3.01	-3.35 (-5.53 ~ -1.17)	0.003	-2.83	1.02	-2.7 2	§ -2.83 (-4.84 ~ -0.83)	0.006
	PCA								lext text		
	No				0.00 (Reference)				an	0.00 (Reference)	
	Yes ASA: American Society of	12.55	1.13	11.06	12.55 (10.32 ~ 14.77)	<.001	6.04	1.67	3.62 0	d 6.04 (2.77 ~ 9.31)	<.001
									nining, Al training, and similar technologies.	njopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l	
			For	peer revie	w only - http://bmjopen.k	omj.com/s	ite/about/	/guideline	es.xhtml	ue de l	

BMJ Open

Effect of subanesthetic dose of esketamine induction on quality of recovery from general anaesthesia in abdominal surgery: a propensity-score-matched retrospective study

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Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adverse events < THERAPEUTICS





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1	Effect of subanesthetic dose of esketamine induction on quality of recovery from
2	general anaesthesia in abdominal surgery: a propensity-score-matched
3	retrospective study
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20	Running title: Effect of esketamine on anesthetic recovery quality
21	Keywords: esketamine; general anaesthesia with tracheal intubation; abdominal
22	surgery; postoperative adverse event; subanesthetic dose

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23 Abstract Objectives: Subanesthetic doses of esketamine may attenuate the opioid-induced 24 25 cough reflex and prevent intraoperative hemodynamic fluctuations. This study aims to evaluate the effect of subanesthetic doses of esketamine on the quality of recovery in 26 abdominal surgery patients. 27 Design: Retrospective cohort study using propensity-score matching (PSM) 28 methodology. 29 Setting: A tertiary academic hospital. 30 Participants: Patients who underwent abdominal surgery under general anaesthesia 31 with tracheal intubation between 20 December, 2022, and 30 April, 2023, were 32 33 retrospectively reviewed. Patients were assigned to the esketamine or control group based on whether they received a subanesthetic dose of esketamine. 34 35 Primary and secondary outcome measures: The primary outcome was extubation time (T1). Secondary outcomes included PACU observation time (T2), total PACU 36 time (T3), postoperative pain at multiple time points, and adverse events including 37 respiratory depression, hypertension, and others. 38 Results: A total of 2,177 patients underwent abdominal surgery. After PSM, 1196 39 patients were analysed, 598 in each group. Esketamine significantly reduced the 40 extubation time compared to the control group (20.00 min vs. 23.00 min, p=0.001). 41

43 vs. 66 minutes, p = 0.015), although PACU observation time did not how a significant

Total PACU time was shorter in the esketamine group than in the control group (62

44 difference. Compared to the control group, the esketamine group had a lower

 incidence of severe postoperative pain immediately after extubation (0.33% vs. 2.01%, p = 0.007) and a respiratory depression (2.68% vs. 5.35%, p=0.027), but a higher incidence of hypertension (9.53% vs. 6.35%, p=0.042). There were no other significant differences in adverse events between the two groups. Conclusions: The use of subanesthetic doses of esketamine for induction of anaesthesia in patients undergoing abdominal surgery may shorten the extubation time and reduce the incidence of postoperative complications. 		
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 48 significant differences in adverse events between the two groups. 49 Conclusions: The use of subanesthetic doses of esketamine for induction of 50 anaesthesia in patients undergoing abdominal surgery may shorten the extubation time 51 and reduce the incidence of nector proting complications. 	46	2.01%, $p = 0.007$) and a respiratory depression (2.68% vs. 5.35%, p=0.027), but a
49 Conclusions: The use of subanesthetic doses of esketamine for induction of 50 anaesthesia in patients undergoing abdominal surgery may shorten the extubation time	47	higher incidence of hypertension (9.53% vs. 6.35%, p=0.042). There were no other
50 anaesthesia in patients undergoing abdominal surgery may shorten the extubation time	48	significant differences in adverse events between the two groups.
Et and reduce the insidence of next mention complications	49	Conclusions: The use of subanesthetic doses of esketamine for induction of
31 and reduce the incidence of postoperative complications.	50	anaesthesia in patients undergoing abdominal surgery may shorten the extubation time
	51	and reduce the incidence of postoperative complications.
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2		
3 4	53	Strengths and limitations of this study
5 6 7	54	• Propensity score matching (PSM) was used to minimise selection bias and to
8 9 10	55	balance baseline characteristics between the groups of patients with and without
11 12 13	56	esketamine.
14 15	57	• A relatively large sample size from a real clinical setting was included, which
16 17 18	58	increasing the generalisability of the results.
19 20	59	• As a single-centre retrospective study, the generalisability of the findings may be
21 22 23	60	limited.
24 25 26	61	• Residual confounding from unmeasured variables may still be present, potentially
27 28	62	affecting the results of the propensity score analysis.
29 30 31	63	• Sensitivity analysis was not performed, which may affect the robustness of the
32 33 34	64	findings regarding residual confounding.
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66 Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anaesthesia with tracheal intubation is the most commonly used anesthetic technique.¹² Advances in medical technology have significantly reduced anaesthesia-related mortality rates.³ However, this approach can still lead to adverse events, such as intubation cough, intraoperative hemodynamic fluctuations, postoperative pain and postoperative cognitive dysfunction (POCD).⁴⁻⁷ These reactions can prolong hospital stay and increase healthcare costs. Therefore, improving the efficacy and comfort of general anaesthesia with tracheal intubation has become a pressing concern.

Esketamine is a modified version of the anesthetic ketamine that acts primarily by inhibiting the N-methyl-D-aspartate (NMDA) receptor, resulting in sedative and analgesic effects. Compared to ketamine, esketamine has a higher potency, stronger analgesic and sedative effects, and fewer side effects.⁸ ⁹ Previous research indicates that subanesthetic doses of esketamine, administered intravenously at 0.1-0.3 mg/kg or by infusion at 0.1-0.3 mg/kg·h can effectively reduce cough reflexes caused by opioid induction,¹⁰ prevent intraoperative hemodynamic fluctuations,¹¹ and reduce the need for intraoperative propofol and opioid medications.¹² ¹³ However, it remains unclear whether subanesthetic doses of esketamine in general anaesthesia affect patient emergence and the incidence of postoperative delirium and agitation.¹⁴¹⁵

86 This study retrospectively analyzes the effect of subanesthetic doses of esketamine87 used for intubation of general anaesthesia on recovery quality, postoperative pain and

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adverse events in patients undergoing abdominal surgery. The objective is to provide
clinical evidence regarding the effect of esketamine on recovery quality for abdominal
surgery patients. Propensity score matching (PSM) was used to adjust pairs of patients
with and without esketamine for potential confounders.

- 92
- 93 Methods
- 94 Study design and patient population

This retrospective, single-centre study was conducted at the First Affiliated 95 Hospital, Zhejiang University School of Medicine (Hangzhou, China). It was 96 97 registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154, 05/06/2023). The medical records used in this study were 98 obtained from the medical database of the First Affiliated Hospital, Zhejiang 99 University School of Medicine. 100

From December 20, 2022 to April 30, 2023, patients who had abdominal surgery 101 102 under general anaesthesia with tracheal intubation were included in the study. Inclusion criteria included an American Society of Anesthesiologists (ASA) physical 103 status of I to II, concurrent routine induction (sufentanil) with or without a 104 subanesthetic dose of esketamine for general anaesthesia. Exclusion criteria were age 105 106 <18 years or > 80 years, hepatic or renal dysfunction, severe pulmonary disease, severe cardiac dysfunction (New York Heart Association [NYHA] Classification 3-4), 107 central nervous system disorders, psychiatric disorders, severe preoperative anemia, 108 intraoperative bleeding \geq 500 ml or severe intraoperative haemodynamic fluctuations 109

with markedly unstable vital signs caused by massive bleeding, duration of surgery > 240 min, postoperative intensive care unit (ICU) admission, and patients not transferred to the PACU after surgery. Anesthetic procedure All patients underwent preoperative fasting. On admission to the operating room, patients were monitored with electrocardiogram (ECG), non-invasive upper arm blood pulse saturation pressure, oxygen $(SpO_2),$ respiratory rate, partial pressure of end-tidal carbon dioxide (PetCO₂), body temperature. and bispectral index (BIS). Invasive continuous arterial pressure monitoring and central venous pressure monitoring were performed as needed. Patients in the control group received with midazolam (0.04 mg/kg), propofol (1.0-2.0 mg/kg), rocuronium (0.6 mg/kg), and sufentanil (0.3-0.5 µg/kg). The esketamine group receives subanesthetic doses of esketamine (0.2 mg/kg) in addition to the above induction agents. During surgery, 0.8-1.5 minimum alveolar concentration (MAC) sevoflurane, 4-6 mg/kg·h propofol, and 0.1-0.3 µg/kg·min remifentanil were maintained. After surgery, 5 mg tropisetron and 50 mg ketorolac were administered intravenously. Postoperative analgesia was achieved with 0.375% ropivacaine for nerve block (transversus abdominis plane block, TAP) or local wound infiltration anaesthesia.

Patients were transferred to the PACU after surgery, and endotracheal tubes were
removed as soon as certain criteria were met (patients were awake, RR > 10 breaths

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per minute and tidal volume > 5 ml/kg). Inadequate muscle strength was treated with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine intravenously. Supplemental oxygen at a rate of 2L/min was administered via nasal catheter after extubation. Pain was assessed using the Numeric Rating Scale (NRS) immediately, 15 minutes and 30 minutes after extubation. Hydromorphone (0.01mg/kg) was administered for pain relief if the NRS score exceeded 4 points. A jaw thrust or positive pressure ventilation with a face mask was used to treat respiratory depression. For dysphoria or delirium, propofol 0.5 mg/kg was used for sedation. If hypertension is diagnosed, intravenous amlodipine 5 mg is recommended. If hypotension occurs, ephedrine 6 mg should be administered. If shivering occurs, intravenous tramadol 50 mg is recommended. Discharge from the PACU was assessed using the modified Aldrete score, with a score of \geq 9 indicating readiness for discharge.^{16 17}

145 Data collection

Demographic and perioperative data were collected from the clinical information system (Seenew, Hangzhou, China) and institutional electronic Anaesthesia Data Sysytem (Medical System, Suzhou, China), including: 1) preoperative data: gender, age, body mass index (BMI), medical history, and ASA classification; 2) intraoperative data: type of surgery, surgery duration, anaesthesia duration, intraoperative blood loss, and use of the patient-controlled analgesia (PCA); 3) PACU data: heart rate, blood pressure, oxygen saturation, extubation time, PACU observation time, the total PACU time, postoperative pain (NRS score), analgesic use,

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incidence of hypertension, hypotension, and medication use. Additionally, the modified Aldrete score, respiratory depression, delirium and agitation, nausea/vomiting, shivering, and other PACU adverse events (e.g., reintubation) were recorded. **Primary outcome** The primary outcome was extubation time (T1), defined as the time from discontinuation of anaesthesia to extubation (minitues). Secondary outcome Secondary outcomes included postoperative pain immediately after extubation, at 15minutes, and at 30 minutes, and analgesic use. The modified Aldrete score at PACU discharge and the incidence of PACU adverse events including respiratory depression, hypertension, hypotension, delirium, agitation, nausea/vomiting, shivering, reintubation, and use of symptomatic treatment were recorded. Respiratory depression was defined as respiratory rate falling below 8 breaths per minute or $SpO_2 < 90\%$ for more than 1 minute.¹⁸ ¹⁹ In addition, the comparison of PACU observation time (T2), defined as the time from extubation to PACU discharge, total PACU time (T3), defined as the interval from PACU admission to discharge, and PACU discharge delay rate, defined as the percentage of patients with a PACU time greater than 120 minutes, were analyzed.

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176 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, ordissemination plans of this research.

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180 **Propensity score matching**

Propensity score matching (PSM) analysis was performed using R Project for 181 Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the 182 matchIt package to reduce differences between the two groups based on the 183 184 esketamine administration to minimize confounding factors. It is generally accepted that a standardised mean difference (SMD) of less than 0.1 for all variables indicates a 185 good fit²⁰. For binary variables, the SMD is the difference in event rates between the 186 187 treatment and control groups divided by the pooled standard deviation, where the pooled p is the weighted average of the event rates in both groups. For multi-category 188 variables, the variable is split into several binary dummy variables and the SMD is 189 190 calculated separately for each dummy variable, taking the maximum absolute value. Nearest-neighbor matching method was used in a 1:1 ratio, with a caliper value of 191 0.05. Matching variables were selected based on prior literature where there was 192 evidence of being potential confounders²¹ and included age, gender, BMI, chronic 193 disease, ASA physical status classification, surgical category, surgery duration, 194 anaesthesia duration, intraoperative blood loss, and PCA use. The absolute 195 standardised mean differences (SMD) are less than 0.1 for all variables. Multiple 196 linear regression analysis was used to complete the matching process. 197

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Results

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199	Statistical analysis
200	Sample size was calculated using PASS statistical software (NCSS LLC, Kaysville,
201	USA). This was a retrospective case-control study. In the preliminary study, we
202	included 20 patients in each group, and the mean extubation times for the two groups
203	were 19.00±11.52 min and 22.15±14.42 min, respectively. A two-tailed test with α set
204	at 0.05, 90% power and a sample size of 1:1 indicated that a minimum sample size of
205	361 participants per group was required. As PSM will be used for case selection, we
206	included a larger sample size to ensure that the final number after PSM met the
207	required threshold.
208	All quantitative data were assessed for normality using the Shapiro-Wilk test.
209	Normally distributed continuous data were presented as mean (standard deviation),
210	and differences between groups were analyzed using t-tests or analysis of variance
210 211	and differences between groups were analyzed using t-tests or analysis of variance (ANOVA). Skewed data were presented as median (25 th -75 th percentile) and were
211	(ANOVA). Skewed data were presented as median (25th-75th percentile) and were
211 212	(ANOVA). Skewed data were presented as median (25 th -75 th percentile) and were analyzed using the nonparametric Mann-Whitney U test. Categorical data were
211 212 213	(ANOVA). Skewed data were presented as median (25 th -75 th percentile) and were analyzed using the nonparametric Mann-Whitney U test. Categorical data were analyzed using the chi-squared test or Fisher's exact test. Ordinal data were analyzed
211 212 213 214	(ANOVA). Skewed data were presented as median (25 th -75 th percentile) and were analyzed using the nonparametric Mann-Whitney U test. Categorical data were analyzed using the chi-squared test or Fisher's exact test. Ordinal data were analyzed using the Wilcoxon rank-sum test. All statistical analyses were performed with the

219 Demographic and patient characteristics

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A total of 2,177 patients with ASA physical status of I to III under suferianil anaesthesia underwent abdominal surgery, including hepatobiliary, gastrointestinal, and colorectal surgery, at the First Affiliated Hospital, Zhejiang University School of Medicine. Based on the inclusion and exclusion criteria, a final of 1,718 patients were enrolled, with 633 patients in the esketamine group and 1,085 patients in the control group. PSM successfully matched 598 patients in each group, achieving the required sample size (Figure 1). The use of PSM ensured that the baseline characteristics were similar between the two groups (Figure 2). The distributions of the propensity scores and the SMD of the covariates were well balanced after PSM adjustment (Figure 3). Patient characteristics in the esketamine group and control groups before and after PSM are shown in Table 1. After PSM, there were no significant differences (P >0.05) in the patient characteristics in gender, age, BMI, medical history, ASA classification, type of surgery, surgery duration, anaesthesia duration, intraoperative blood loss, and use of the PCA between the two groups.

Primary outcome

The results showed that the extubation time (T1) in the esketamine group was 20 (11, 32) minutes, while the T1 in the control group was 23 (13, 37) minutes (P = 0.001), indicating that patients induced with subanesthetic doses of esketamine had faster recovery in the PACU (Table 2). Multiple linear regression suggests that ketamine is an independent protective factor for extubation time (Supplementary Table 1).

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243	Secondary	outcome
275	Secondary	outcome

244	The number of patients with severe postoperative pain immediately after extubation
245	was significantly higher in the control group (12, 2.01%) than that in the esketamine
246	groups (2, 0.33%) ($p = 0.007$). In addition, the number of patients requiring additional
247	hydromorphone for postoperative pain during PACU treatment was significantly
248	higher in the control group (94, 15.72%) than in the esketamine group (70, 11.71%) (p
249	= 0.044). However, there were no statistically significant differences in the number of
250	patients with postoperative pain between the two groups at 15 and 30 minutes after
251	extubation, as shown in Table 3.

During the PACU period, the number of patients with respiratory depression in the 252 253 control group was 32 (5.35%), significantly higher than the 16 (2.68%) cases in the esketamine group (p=0.027). The esketamine group had a significantly higher rate of 254 hypertension than the control group (9.53% vs. 6.35%, p=0.042). There were no 255 significant differences in hypotension, delirium and agitation, nausea and vomiting, or 256 shivering between the two groups. There were no emergencies requiring reintubation 257 in either group. There were also no statistically significant differences in the modified 258 Aldrete scores between the two groups when patients left the PACU (Table 4). 259

In addition, the total PACU time (T3) was also shorter in the esketamine group (62.00 vs. 66.00, p=0.015). However, there was no significant difference in the PACU observation time (T2) between the two groups, with median times of 38 minutes in the control group and 37 minutes in the esketamine group (p = 0.738). The number of

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264	patients with delayed discharge from the PACU was 30 (5.02%) in the esketamine
265	group and 38 (6.35%) in the control group, respectively ($p = 0.318$) (Table 2).
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267	Discussion
268	The results of the current study indicate that the use of subanesthetic doses of
269	esketamine can effectively reduce the postoperative extubation time in the PACU for
270	patients undergoing abdominal surgery. In addition, esketamine was found to reduce
271	postoperative pain without increasing post-extubation side effects.
272	Previously, it was thought that the combining different mechanisms, such as
273	esketamine with midazolam, propofol, or sevoflurane, could deepen the level of
274	anaesthesia and influence patient recovery. ^{22 23} However, recent studies have shown
275	that esketamine not only increases the depth of anaesthesia but also accelerates
276	recovery from anaesthesia. ²⁴ Animal studies have shown that ketamine, the parent
277	compound of esketamine, can shorten the peak activation time of the glutamatergic
278	neurons, particularly those in the paraventricular thalamus (PVT), thereby reducing
279	extubation time. Clinical studies have also shown that patients who received
280	subanesthetic doses of esketamine intraoperatively had faster and better recovery of
281	postoperative respiratory rate and tidal volume. ²⁵ The current study supports these
282	findings and suggests that the use of subanesthetic doses of esketamine may
283	accelerate patient recovery.

This research shows that subanesthetic doses of esketamine are effective in relieving immediate post-extubation pain after extubation. Animal studies have

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286	suggested that the combining of NMDA receptor antagonists with opioids may result
287	in synergistic or additive analgesic effects. ²⁶ Numerous clinical studies have
288	supported this concept by demonstrating that administration of 0.15-0.5 mg/kg of
289	esketamine reduces intraoperative opioid consumption and improves postoperative
290	pain management. ^{12 13 27 28} Consistent with these findings, the present study shows
291	similar results. The subgroup that receiving subanesthetic doses of esketamine
292	reported significantly lower pain levels immediately after extubation. While there was
293	no significant difference in pain scores between the two groups at 15 and 30 minutes
294	post-extubation, the PACU observation period showed a significant reduction in the
295	number of patients in the esketamine group requiring additional analgesics for
296	postoperative pain relief compared to the control group, indicating the beneficial
297	effect of subanesthetic doses of esketamine on overall postoperative pain relief. The
298	major metabolite of esketamine is S-norketamine, which has approximately one-third
299	the analgesic potency of esketamine and a longer elimination half-life. This may
300	explain the prolonged analgesic effect of esketamine in the PACU. ²⁵

The results of this study indicate that the incidence of respiratory depression was significantly lower in the esketamine group than that in the control group. Respiratory depression is a common adverse event in the PACU, with an incidence rate of approximately 5%,¹⁸ which is similar to the incidence observed in the control group of this study. Causes of respiratory depression during the anesthetic recovery period include the use of opioids, residual effects of muscle relaxants, and the incomplete recovery of the respiratory system after surgery. It's worth noting that approximately

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20% of cases of respiratory depression are associated with the use of opioid 308 medications.²⁹ Elevated carbon dioxide (CO₂) levels can stimulate central 309 chemoreceptors, leading to an increase in respiratory drive. However, the use of 310 opioid medications attenuates this response.³⁰ Both animal and clinical studies have 311 shown that ketamine can enhance CO₂ sensitivity and provide moderate protection 312 against respiratory depression and bronchoconstriction.^{31 32} Research by Jonkman et 313 al. also suggests that low-dose esketamine may counteract the respiratory depressant 314 effects of opioid drugs.³³ This suggests that the use of subanesthetic doses of 315 316 esketamine to induce anaesthesia may not only reduce opioid consumption but also stabilize respiration, thereby reducing the likelihood of fatal events. 317

The most common adverse events associated with esketamine primarily are 318 319 psychological symptoms such as delirium, agitation, nightmares, and dissociative phenomena, which often follow a dose-dependent pattern.^{34 35} Bornemann-Cimenti H 320 et al. have confirmed that subanesthetic doses can reduce the incidence of 321 psychological symptoms associated with esketamine.³⁶ Our study supports this view 322 and shows that subanesthetic doses of esketamine do not increase the incidence of 323 delirium or agitation. In addition, there is no effect on the incidence of nausea and 324 vomiting. The sympathomimetic effects of esketamine, which manifest as increased 325 blood pressure and heart rate.^{11 37} The incidence of hypertension was higher in the 326 esketamine group than in the control group. This may be due to the increased blood 327 pressure induced by esketamine. 328

The primary goal of the PACU is to improve turnover efficiency between surgical

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procedures and to increase patient satisfaction. Factors such as delirium, agitation, and postoperative pain can prolong the PACU stay.³⁸ However, the current study shows that the use of a subanesthetic dose of esketamine doesn't increase the incidence of these complications. Furthermore, the total PACU time for the esketamine group is shorter than that of the control group, suggesting that the use of esketamine may improve the efficiency of the PACU.

There are several limitations to this study. First, it is a single-centre, retrospective study, which may limit the generalisability of the findings. Although the two groups were matched on several demographic factors, there remains the potential for residual confounding due to unmeasured variables affecting the propensity score analysis. In addition, the lack of sensitivity analysis may affect the robustness of the results. Second, the dose of esketamine is subanesthetic, and the study did not investigate potential problems associated with other doses. Finally, this study focuses exclusively on patients undergoing abdominal surgery and does not include other types of surgery. Therefore, further research should include large, multicentre, prospective studies to fully address these limitations.

347 Conclusions

Subanesthetic doses of esketamine have been shown to be effective in reducing the extubation time in patients undergoing abdominal surgery under general endotracheal anaesthesia, without compromising the overall quality of recovery. In addition, the use of subanesthetic doses of esketamine has the potential to reduce the incidence of

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4	352	severe postoperative pain, thereby reducing the need for analgesia in the PACU. This
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6	353	approach also helps to reduce the incidence of respiratory depression, resulting in a
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10	354	shorter overall PACU time, and ultimately contributing to the overall recovery
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12	355	process for patients.
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16	357	Contributions DW, XF and YJ contributed to the study design. MW, KC, XW, YX,
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18	358	YW, MQ and ZL contributed to data acquisition. DW contributed to data analysis and
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21	359	drafting of the paper. XF and YJ contributed to manuscript revision. YJ contributed to
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23	360	final approval of the version. All authors read and approved the final version. YJ is
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34	364	Conflicting interests None declared.
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37	365	Patient consent for publication Not required.
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40 41	366	Ethics approval The study was approved by the Clinical Research Ethics Committee
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43	367	of the First Affiliated Hospital, Zhejiang University School of Medicine
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Figure legends

- Figure 1. Flowchart of patient selection.
- Figure 2. Standardized mean differences of covariates after PSM.

Figure 3. Distributions of propensity scores after PSM.

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941 (54.77)	590 (54.38)	351 (55.45)		663 (55.43)	03552 <u>4</u> 55.52)	331 (55.35)
.41 (21.23, 25.39)	23.39 (21.23, 25.40)	23.44 (21.23, 25.34)	0.858	23.40 (21.19, 25.39)	23 - 25.40)	23.44 (21.24, 25.
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19 (1.11)	9 (0.83)	10 (1.58)		16 (1.34)	ω	9 (1.51)
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-	41 (21.23, 25.39) 1412 (82.19) 306 (17.81) 1618 (94.18)	41 (21.23, 25.39) 23.39 (21.23, 25.40) 1412 (82.19) 894 (82.40) 306 (17.81) 191 (17.60) 1618 (94.18) 1026 (94.56) 100 (5.82) 59 (5.44) 1690 (98.37) 1064 (98.06) 28 (1.63) 21 (1.94) 1699 (98.89) 1076 (99.17)	41 (21.23, 25.39) $23.39 (21.23, 25.40)$ $23.44 (21.23, 25.34)$ $1412 (82.19)$ $894 (82.40)$ $518 (81.83)$ $306 (17.81)$ $191 (17.60)$ $115 (18.17)$ $1618 (94.18)$ $1026 (94.56)$ $592 (93.52)$ $100 (5.82)$ $59 (5.44)$ $41 (6.48)$ $1690 (98.37)$ $1064 (98.06)$ $626 (98.89)$ $28 (1.63)$ $21 (1.94)$ $7 (1.11)$ $1699 (98.89)$ $1076 (99.17)$ $623 (98.42)$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	941 (54.77) 590 (54.38) 351 (55.45) 663 (55.43) 663 (55.43) 643 (55.52) $(41 (21.23, 25.39) 23.39 (21.23, 25.40) 23.44 (21.23, 25.34) 0.858 23.40 (21.19, 25.39) 23 (492 (21.10) 25.40) (412 (21.23, 25.34) 0.858 23.40 (21.19, 25.39) 23 (492 (21.10) 25.40) (492 (21.10) 25.40) 115 (18.17) 214 (17.89) 110 (21.77) 214 (17.89) 0.375 1618 (94.18) 1026 (94.56) 592 (93.52) 1128 (94.31) 6569 (95.15) 100 (5.82) 59 (5.44) 41 (6.48) 68 (5.69) 1176 (98.33) 29 (4.85) 0.190 0.191 0.15$

			ВМЈ Ор	en		/bmjopen-2024-09 4 by copyright, inc		27
П	1441 (83.88)	901 (83.04)	540 (85.31)		1016 (84.95)	200 200 200 200 200 200 200 200 200 200	513 (85.79)	
Ш	134 (7.8)	84 (7.74)	50 (7.90)		83 (6.94)	o 3846.35)	45 (7.53)	
Surgery type, n (%)				< 0.001		0 Ma En		0.515
Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)		597 (49.92)	s s 2 63922(50.50)	295 (49.33)	
Gastrointestinal surgery	460 (26.78)	279 (25.71)	181 (28.59)		333 (27.84)		175 (29.26)	
Colorectal surgery	339 (19.73)	184 (16.96)	155 (24.49)		266 (22.24)		128 (21.40)	
Surgery duration (min) ,	60.00 (38.00,	55.00 (37.00,	68.00 (41.00,	<0.001	62.00 (39.00,	ja 2000 (38.25,	63.00 (40.00,	0.757
median (IQR)	121.00)	112.00)	135.00)	< 0.001	127.00)	an el <u>a</u> 7.75)	126.75)	0.757
Anaesthesia duration (min), 82.00 (58.00, 79.00 (56.00, 90.00 (60.00,		-0.001	86.00 (58.00,	d e (57.00,	86.00 (59.00,	0.050		
median (IQR)	155.00)	147.00)	170.00)	< 0.001	159.25)	ata (A Bal.00)	157.75)	0.858
Intraoperative blood loss (ml), median (IQR)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	0.004	10.00 (10.00, 50.00)	10 10 10 10 10 10 10 10 10 10	10.00 (10.00, 50.00)	0.580
PCA, n (%)				0.102		, bmj		0.195
Yes	1197 (69.67)	771 (71.06)	426 (67.30)		807 (67.47)	1393 (65.72)	414 (69.23)	
No	521 (30.33)	314 (28.94)	207 (32.70)		389 (32.53)	n n 205 q 34.28)	184 (30.77)	

 No
 521 (30.33)
 314 (28.94)
 207 (32.70)
 389 (32.53)
 205 (34.28)
 184 (30.77)

 ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulnionary disease; PCA: Patient controlled analgesia; PSM: propensity score matching; SMD: standardized mean differences
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Table 2. Recovery time after surgery.

	Control Group	Esketamine Group	P value
	(n=598)	(n=598)	
T1 (min), median (IQR)	23.00 (13.00, 37.00)	20.00 (11.00, 32.00)	0.001
T2 (min), median (IQR)	38.00 (31.00, 50.00)	37.00 (31.00, 50.00)	0.738
T3 (min), median (IQR)	66.00 (51.00, 85.00)	62.00 (48.00, 82.00)	0.015
Delayed PACU discharge, n (%)	38 (6.35)	30 (5.02)	0.318

PACU: post-anesthesia care unit; T1: extubation time; T2: PACU observation time; T3: The total PACU time.

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after extubation NRS: 1-3 $586 (97.99)$ $596 (99.67)$ NRS: ≥ 4 12 (2.01) 2 (0.33) Postoperative pain, 15 minutes (0) after extubation (1) NRS: 1-3 $524 (87.63)$ $537 (89.80)$ NRS: ≥ 4 74 (12.37) 61 (10.20) Postoperative pain, 30 minutes (1) after extubation (1) NRS: ≥ 4 12 (2.01) 8 (1.34)		Control Group (n=598)	Esketamine Group (n=598)	P valu
NRS: 1-3 586 (97.99) 596 (99.67) NRS: ≥ 4 12 (2.01) 2 (0.33) Postoperative pain, 15 minutes 0 after extubation 524 (87.63) 537 (89.80) NRS: 1-3 524 (87.63) 537 (89.80) NRS: ≥ 4 74 (12.37) 61 (10.20) Postoperative pain, 30 minutes 0 after extubation 12 (2.01) 8 (1.34) Use of analgesic drugs 94 (15.72) 70 (11.71) 0 Data are presented as n (%). $(\%)$ $(\%)$ $(\%)$	Postoperative pain immediately			0.007
NRS: ≥ 4 12 (2.01)2 (0.33)Postoperative pain, 15 minutes(0)after extubation(1)NRS: 1-3524 (87.63)NRS: ≥ 4 74 (12.37)Postoperative pain, 30 minutes(1)after extubation(1)NRS: ≥ 4 12 (2.01)NRS: ≥ 4 12 (2.01)08 (1.34)Use of analgesic drugs94 (15.72)070 (11.71)00	after extubation			
Postoperative pain, 15 minutesOafter extubationNRS: 1-3 $524 (87.63)$ $537 (89.80)$ NRS: ≥ 4 74 (12.37)61 (10.20)Postoperative pain, 30 minutesOafter extubationafter extubationNRS: ≥ 4 12 (2.01)8 (1.34)Use of analgesic drugs94 (15.72)70 (11.71)Data are presented as n (%).O	NRS: 1-3	586 (97.99)	596 (99.67)	
after extubation NRS: 1-3 $524 (87.63)$ $537 (89.80)$ NRS: ≥ 4 74 (12.37) 61 (10.20) Postoperative pain, 30 minutes 0 after extubation 12 (2.01) 8 (1.34) Use of analgesic drugs 94 (15.72) 70 (11.71) 0 Data are presented as n (%). $(%)$ $(%)$ $(%)$ $(%)$	NRS: ≥4	12 (2.01)	2 (0.33)	
NRS: 1-3 $524 (87.63)$ $537 (89.80)$ NRS: ≥ 4 74 (12.37) 61 (10.20) Postoperative pain, 30 minutes 0 after extubation 12 (2.01) 8 (1.34) Use of analgesic drugs 94 (15.72) 70 (11.71) 0 Data are presented as n (%). $(%)$ $(%)$ $(%)$ $(%)$	Postoperative pain, 15 minutes			0.235
NRS: ≥ 4 74 (12.37)61 (10.20)Postoperative pain, 30 minutes0after extubation0NRS: ≥ 4 12 (2.01)8 (1.34)Use of analgesic drugs94 (15.72)70 (11.71)0Data are presented as n (%).	after extubation			
Postoperative pain, 30 minutes0after extubation $12 (2.01)$ $8 (1.34)$ NRS: ≥ 4 $12 (2.01)$ $8 (1.34)$ Use of analgesic drugs $94 (15.72)$ $70 (11.71)$ 0 Data are presented as n (%).	NRS: 1-3	524 (87.63)	537 (89.80)	
after extubationNRS: ≥ 4 12 (2.01)8 (1.34)Use of analgesic drugs94 (15.72)70 (11.71)0Data are presented as n (%).	NRS: ≥4	74 (12.37)	61 (10.20)	
NRS: ≥ 4 12 (2.01) 8 (1.34) Use of analgesic drugs 94 (15.72) 70 (11.71) 0 Data are presented as n (%). \sim \sim \sim \sim	Postoperative pain, 30 minutes			0.365
Use of analgesic drugs 94 (15.72) 70 (11.71) 0 Data are presented as n (%).	after extubation			
Data are presented as n (%).	NRS: ≥4	12 (2.01)	8 (1.34)	
	Use of analgesic drugs	94 (15.72)	70 (11.71)	0.044
NRS: Numeric Rating Scale	Data are presented as n (%).			
	NRS: Numeric Rating Scale			

Page 31 of 35

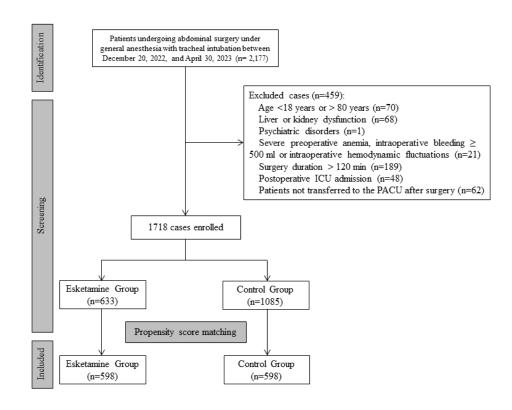
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	Control Group (n=598)	Esketamine Group (n=598)	P value
Respiratory depression	32 (5.35)	16 (2.68)	0.027
Hypotension	15 (2.51)	14 (2.34)	0.851
Hypertension	38 (6.35)	57 (9.53)	0.042
Delirium and agitation	88 (14.72)	91 (15.22)	0.808
Nausea and vomiting	24 (4.01)	27 (4.52)	0.668
Shivering	14 (2.3)	17 (2.8)	0.584
Reintubation	0	0	-
The modified Aldrete score			0.502
9 points	40 (6.69)	46 (7.69)	
10 points	558 (93.31)	552 (92.31)	

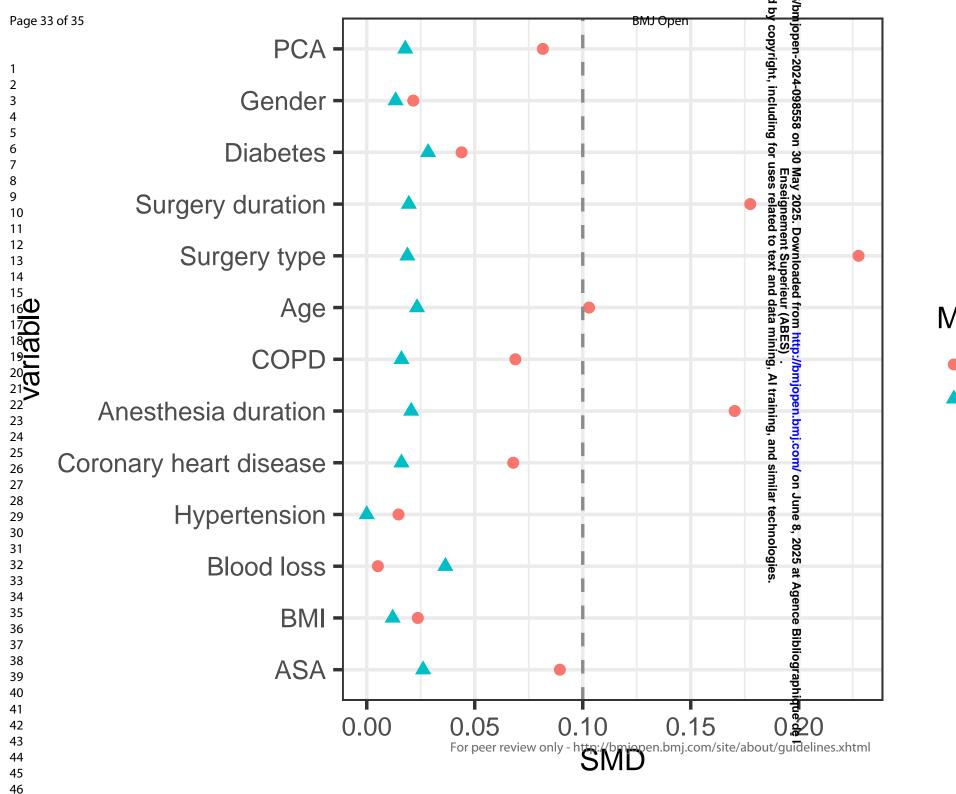
Data are presented as n (%).

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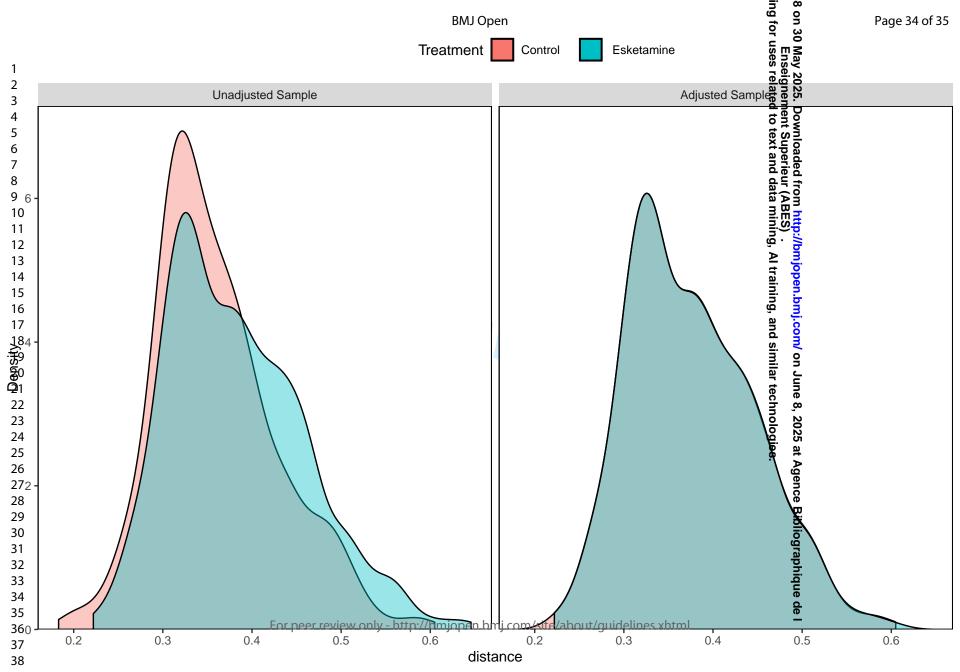
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MethodUnmatchedPSM



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Supplement Table 1. Res	ults of m	-	linear re	egression analysis				_	n 30 <u>N</u>	
Variables	b	S.E	t	β (95%CI)	Р	m_b	m_S.E	m_tses	aβ (95%CI)	aP
Age	0.27	0.04	7.09	0.27 (0.20 ~ 0.35)	<.001	0.20	0.04	5.23 e ign	8 0.20 (0.12 ~ 0.27)	<.00
Gender								ted	5. D	
Male				0.00 (Reference)				to t	low loss	
Female	1.38	1.12	1.23	1.38 (-0.82 ~ 3.58)	0.218			text Su	nlo	
BMI	-0.89	0.17	-5.34	-0.89 (-1.21 ~ -0.56)	<.001	-0.60	0.16	-3.8 an per	0.60 (-0.91 ~ -0.30)	<.00
Chronic disease								ieur d d	rð f	
Hypertension								ata (A	rom	
No				0.00 (Reference)				mir	ht	
Yes	0.20	1.46	0.14	0.20 (-2.65 ~ 3.06)	0.888			s) .		
Diabetes								Ι , Α	Ъ Т	
No				0.00 (Reference)				ltra	jop	
Yes	-1.78	2.41	-0.74	-1.78 (-6.51 ~ 2.94)	0.459			aini	en.	
Coronary heart disease								ng,	b m	
No				0.00 (Reference)				and	Ļ. S	
Yes	3.28	4.35	0.75	3.28 (-5.25 ~ 11.81)	0.451			ABES) . ta mining, Al training, and similar te <u>ch</u> nologies. 1.2	2	
COPD								mila	on	
No				0.00 (Reference)				ar te	u 0.00 (Reference)	
Yes	11.59	4.85	2.39	11.59 (2.10 ~ 21.09)	0.017	5.42	4.48	1.21 5	6 5 .42 (-3.36 ~ 14.20)	0.22
ASA physical status								nol	20	
I				0.00 (Reference)				ogi	25	
Π	3.82	2.05	1.86	3.82 (-0.20 ~ 7.83)	0.062			es.	2025 at A	
Ш	3.34	2.88	1.16	3.34 (-2.31 ~ 8.99)	0.246					
Surgery type				. , ,					gence	
Hepatobiliary surgery				0.00 (Reference)					B 0.00 (Reference) 6 3.70 (-6.12 ~ -1.28)	
Gastrointestinal surgery	-3.97	1.29	-3.08	-3.97 (-6.50 ~ -1.44)	0.002	-3.70	1.23	-3.00	6 -3 70 (-6 12 ~ -1 28)	0.00

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								ght, ir	-2024-0	
								ncludi	4-09855	
Colorectal surgery	7.89	1.39	5.68	7.89 (5.17 ~ 10.61)	<.001	1.20	1.60	0.75	$\begin{array}{c} & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$	0.45
Surgery duration (min)	0.09	0.01	9.58	0.09 (0.07 ~ 0.11)	<.001	0.05	0.07	0.81 ਰ੍ਰੰ	$\frac{1}{20}0.05(-0.08 \sim 0.18)$	0.41
Anesthesia duration (min)	0.09	0.01	9.80	0.09 (0.07 ~ 0.10)	<.001	-0.05	0.06	-0.7 % п	$= 0.05 (-0.17 \sim 0.07)$	0.442
Intraoperative blood loss (ml)	0.10	0.01	10.50	0.10 (0.08 ~ 0.12)	<.001	0.06	0.01	5.37% ise	≤ 0.06 (0.04 ~ 0.08)	<.00
Esketamine								elat	2022	
No				0.00 (Reference)				ted	\mathbf{D} 0.00 (Reference)	
Yes	-3.35	1.11	-3.01	-3.35 (-5.53 ~ -1.17)	0.003	-2.83	1.02	-2.7 2	$\mathbf{S}^{0.00}$ (Reference) $\mathbf{S}^{2.83}$ (-4.84 ~ -0.83)	0.00
PCA								ext		
No				0.00 (Reference)				an	0.00 (Reference)	
Yes	12.55	1.13	11.06	12.55 (10.32 ~ 14.77)	<.001	6.04	1.67	3.62 0 E	$\frac{1}{2}$ 6.04 (2.77 ~ 9.31)	<.00
analgesia; PSM: propensity	Anesthe score m	atching						-S) . ining, Al training, ar	· 8	
analgesia; PSM: propensity	score m	atching) ing	· 8	
analgesia; PSM: propensity	score m	atching) ing	· 8	
analgesia; PSM: propensity	score m	atching) ing	· 8	
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analgesia; PSM: propensity	score m	atching		w only - http://bmjopen.k) . ing, Al training, and similar technologies.	p://bmjopen.bmj.com/ on June 8, 2025	