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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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Running title: Effect of esketamine on anesthetic recovery quality

Keywords: esketamine; general anesthesia with tracheal intubation; abdominal surgery; postoperative adverse event; subanesthetic dose

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

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 for induction of anesthesia significantly reduced the recovery time (20.00 vs. 23.00, p=0.001). There were no significant differences in PACU observation time after 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 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%

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 in 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 time and reduce the incidence of postoperative complications.

Strengths and limitations of this study

- This study represents a retrospective investigation of the effect of using subanesthetic doses of esketamine on the quality of recovery in abdominal surgery patients.
- 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.

Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anesthesia with tracheal intubation is the most commonly used anesthetic technique.[1] [2] 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.[14] [15]

This study retrospectively analyzes the effect of subanesthetic doses of esketamine 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.

Methods

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 Ⅲ, 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,

intraoperative bleeding ≥ 500 ml or intraoperative hemodynamic fluctuations, duration of surgery > 240 min, postoperative intensive care unit (ICU) admission, and patients not transferred to the PACU after surgery.

Anesthetic procedure

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 (SpO_2), respiratory rate, partial pressure of end-tidal carbon dioxide ($PetCO_2$), 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 anesthesia.

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

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]

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,

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 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 $SpO_2 < 90\%$ 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), 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

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

Statistical analysis

Sample size was calculated using PASS statistical software (NCSS LLC, Kaysville, USA). This is a retrospective case-control study, based on the previous results of the average anesthesia recovery time for both groups, with a two-tailed test, α set at 0.05, power set at 90%, and 1:1 Sample ratio, a minimum sample size of 361 participants per group was required.

Propensity score matching (PSM) analysis was performed using R Project for Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the matchIt package to reduce differences between the two groups based on the esketamine administration to minimize confounding factors. Nearest-neighbor matching method was used in a 1:1 ratio, with a caliper value of 0.05. Matching variables included age, gender, BMI, medical history, ASA physical status classification, surgical category, surgery duration, anesthesia duration, intraoperative blood loss, and PCA use. Multiple linear regression analysis was used to complete the matching process.

All quantitative data were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean (standard deviation), 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

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

Demographic and patient characteristics

A total of 2,177 patients with ASA physical status of I to Ⅲ under sufentanil 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

of surgery, surgery duration, anesthesia duration, intraoperative blood loss, and use of the PCA between the two groups (P > 0.05).

Primary outcome

The results showed that the anesthetic recovery 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).

Secondary outcome

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

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 esketamine group (p=0.027). The esketamine group had a significantly higher rate of 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).

Discussion

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 recovery from anesthesia.[22] Animal studies have shown that ketamine, the parent compound of esketamine, can shorten the peak activation time of the glutamatergic

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

explain the prolonged analgesic effect of esketamine in the PACU.[23]

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 20% of cases of respiratory depression are associated with the use of opioid medications.[27] Elevated carbon dioxide (CO_2) levels can stimulate central 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 CO_2 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 anesthesia 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 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.

Conclusions

Subanesthetic doses of esketamine have been shown to be effective in reducing the recovery time in patients undergoing abdominal surgery under general endotracheal anesthesia, 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 shorter overall PACU time, and ultimately contributing to the overall recovery process for patients.

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Ethics statement

The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20230403A), and registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154).

Author contribution

Dongdong Wang and Yue Jin contributed to the study design and drafting of the paper. Mengcao Weng, Kunwei Chen, Xiaojun Wu, Yuanfang Xiao, Yijie Wu Minyue Qian and Zhongteng Lu contributed to data acquisition. Dongdong Wang contributed to data analysis. All authors approved the version to be submitted.

Data availability statement

Data will be made available on request.

Conflict of interest

All authors declare no conflicts of interest.

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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.

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

	Before PSM						After PSM					
	Total (n=1718)	Control Group（n=1085)	Esketamie Group (n=633)	Statistic	P	SMD	Total (n=1196)	Control Group (n=598)	Esketamine Group (n=598)	Statistic	P	SMD
Age (yr)	58.00 (45.00, 66.00)	57.00 (43.00, 66.00)	58.00 (49.00, 66.00)	Z=-1.783	0.075	0.106	58.00 (47.00, 66.00)	58.00 (47.00, 67.00)	58.00 (48.00, 65.00)	Z=-0.711	0.477	-0.038
Gender										χ^2=0.023	0.954	
Male	777 (45.23)	495 (45.62)	282 (44.55)			-0.022	533 (44.57)	266 (44.48)	267 (44.65)			0.003
Female	941 (54.77)	590 (54.38)	351 (55.45)			0.022	663 (55.43)	332 (55.52)	331 (55.35)			-0.003
BMI	23.41 (21.23, 25.39)	23.39 (21.23, 25.40)	23.44 (21.23, 25.34)	Z=-0.179	0.858	-0.024	23.40 (21.19, 25.39)	23.37 (21.10, 25.40)	23.44 (21.24, 25.35)	Z=-0.173	0.862	-0.018
Chronic disease												
Hypertension				χ^2=0.087	0.768					χ^2=0.023	0.880	
No	1412 (82.19)	894 (82.40)	518 (81.83)			-0.015	982 (82.11)	492 (82.27)	490 (81.94)			-0.009
Yes	306 (17.81)	191 (17.60)	115 (18.17)			0.015	214 (17.89)	106 (17.73)	108 (18.06)			0.009
Diabetes				χ^2=0.788	0.375					χ^2=1.559	0.212	
No	1618 (94.18)	1026 (94.56)	592 (93.52)			-0.042	1128 (94.31)	569 (95.15)	559 (93.48)			-0.068
Yes	100 (5.82)	59 (5.44)	41 (6.48)			0.042	68 (5.69)	29 (4.85)	39 (6.52)			0.068
Coronary heart disease				χ^2=1.716	0.190					χ^2=1.831	0.176	
No	1690 (98.37)	1064	626 (98.89)			0.079	1176	585 (97.83)	591 (98.83)			0.093

		(98.06)					(98.33)				
Yes	28 (1.63)	21 (1.94)	7 (1.11)			-0.079	20 (1.67)	13 (2.17)	7 (1.17)		-0.093
COPD				χ^2=2.058	0.151					χ^2=0.253	0.615
No	1699 (98.89)	1076 (99.17)	623 (98.42)			-0.060	1180 (98.66)	591 (98.83)	589 (98.49)		-0.027
Yes	19 (1.11)	9 (0.83)	10 (1.58)			0.060	16 (1.34)	7 (1.17)	9 (1.51)		0.027
ASA physical status										χ^2=3.668	0.160
I	143 (8.32)	100 (9.22)	43 (6.79)			-0.096	97 (8.11)	57 (9.53)	40 (6.69)		-0.114
Ⅱ	1441 (83.88)	901 (83.04)	540 (85.31)			0.064	1016 (84.95)	503 (84.11)	513 (85.79)		0.048
Ⅲ	134 (7.8)	84 (7.74)	50 (7.90)			0.006	83 (6.94)	38 (6.35)	45 (7.53)		0.044
Surgery type				χ^2=20.815	<0.001					χ^2=1.326	0.515
Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)			-0.209	597 (49.92)	302 (50.50)	295 (49.33)		-0.023
Gastrointestinal surgery	460 (26.78)	279 (25.71)	181 (28.59)			0.064	333 (27.84)	158 (26.42)	175 (29.26)		0.062
Colorectal surgery	339 (19.73)	184 (16.96)	155 (24.49)			0.175	266 (22.24)	138 (23.08)	128 (21.40)		-0.041
Surgery duration (min)	60.00 (38.00, 121.00)	55.00 (37.00, 112.00)	68.00 (41.00, 135.00)	Z=-3.687	<0.001	0.173	62.00 (39.00, 127.00)	62.00 (38.25, 127.75)	63.00 (40.00, 126.75)	Z=-0.310	0.757	0.000
Anesthesia duration (min)	82.00 (58.00, 155.00)	79.00 (56.00, 147.00)	90.00 (60.00, 170.00)	Z=-3.327	<0.001	0.166	86.00 (58.00, 159.25)	85.50 (57.00, 161.00)	86.00 (59.00, 157.75)	Z=-0.179	0.858	-0.005
Intraoperative	10.00 (10.00,	10.00	10.00	Z=-2.868	0.004	0.006	10.00	10.00	10.00	Z=-0.553	0.580	-0.044

blood loss (ml)	50.00)	(10.00, 50.00)	(10.00, 50.00)				(10.00, 50.00)	(10.00, 50.00)	(10.00, 50.00)			
PCA				χ^2=2.677	0.102					χ^2=1.680	0.195	
Yes	1197 (69.67)	771 (71.06)	426 (67.30)			-0.080	807 (67.47)	393 (65.72)	414 (69.23)			0.076
No	521 (30.33)	314 (28.94)	207 (32.70)			0.080	389 (32.53)	205 (34.28)	184 (30.77)			-0.076

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

ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PCA: Patient controlled analgesia; PSM: propensity score matching; SMD: standardized mean differences

Table 2. Recovery time after surgery.

	Control Group (n=598)	Esketamine Group (n=598)	statistic	*P* value
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 discharge	38 (6.35)	30 (5.02)	0.998	0.318

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.

Table 3. Postoperative pain scores and analgesic requirements.

	Control Group (n=598)	Esketamine Group (n=598)	statistic	*P* value
Postoperative pain immediately after extubation			7.227	0.007
NRS：1-3	586 (97.99)	596 (99.67)		
NRS：≥4	12 (2.01)	2 (0.33)		
Postoperative pain, 15 minutes after extubation			1.411	0.235
NRS: 1-3	524 (87.63)	537 (89.80)		
NRS: ≥4	74 (12.37)	61 (10.20)		
Postoperative pain, 30 minutes after extubation			0.820	0.365
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

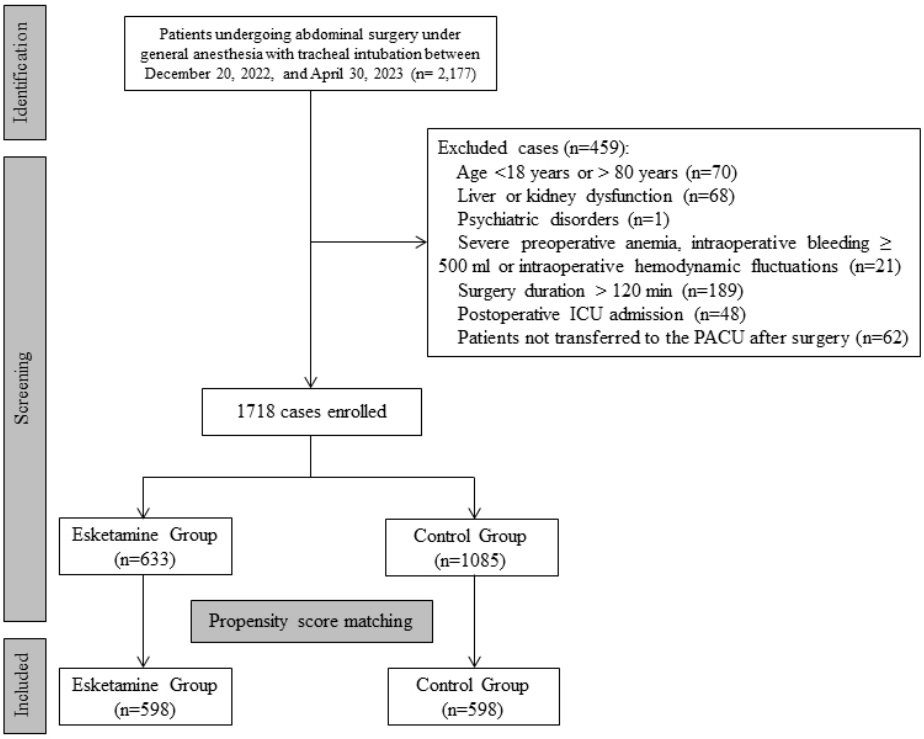
Data are presented as n (%).

NRS: Numeric Rating Scale

Table 4. Postoperative adverse events and the modified Aldrete score

	Control Group (n=598)	Esketamine Group (n=598)	statistic	*P* value
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 score			0.451	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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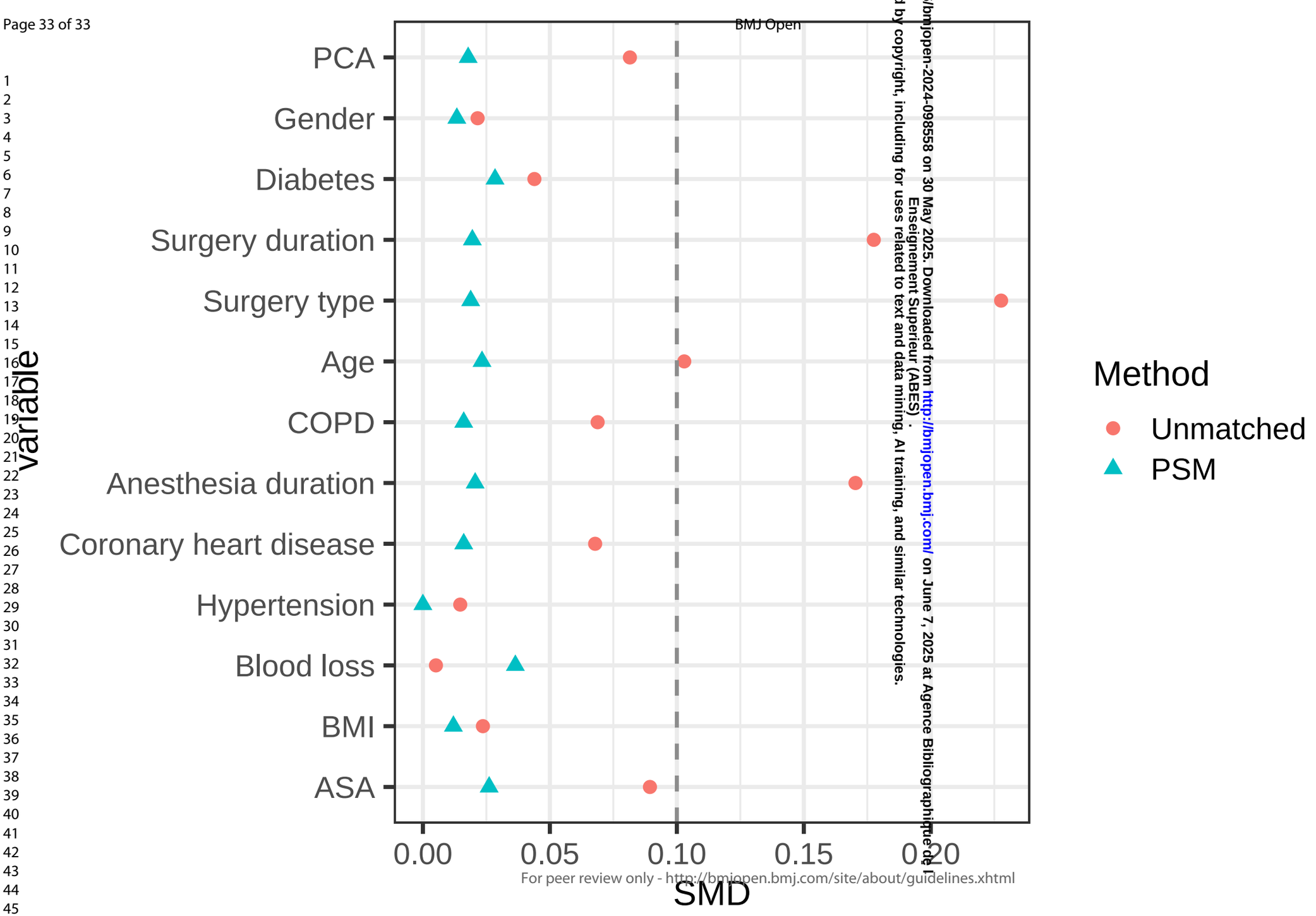

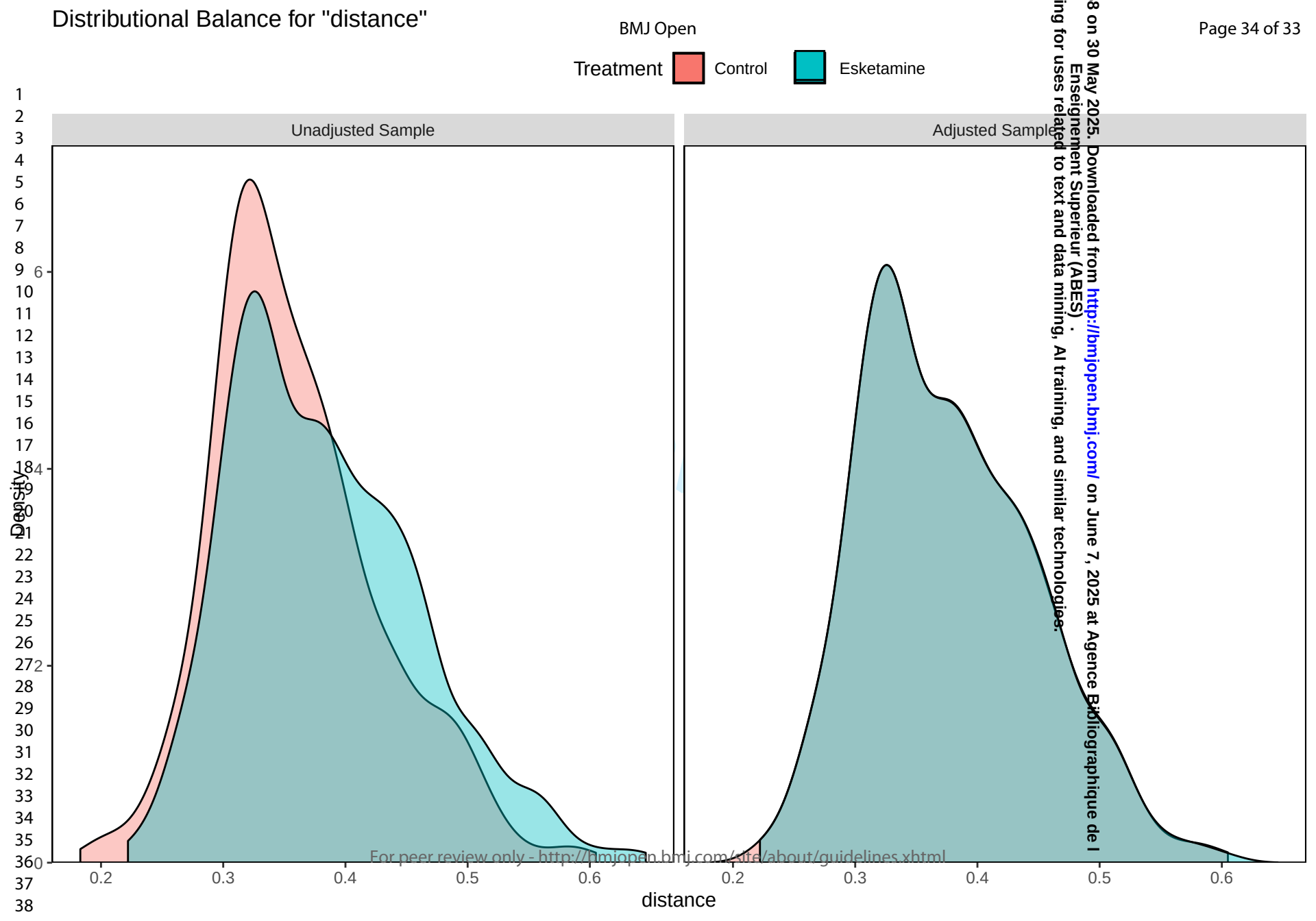

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Effect of subanesthetic dose of esketamine induction on quality of recovery from general anaesthesia in abdominal surgery: a propensity-score-matched retrospective study

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Running title: Effect of esketamine on anesthetic recovery quality

Keywords: esketamine; general anaesthesia with tracheal intubation; abdominal surgery; postoperative adverse event; subanesthetic dose

Abstract

Objectives: Subanesthetic doses of esketamine may attenuate the opioid-induced 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 abdominal surgery patients.

Design: Retrospective cohort study using propensity-score matching (PSM) methodology.

Setting: A tertiary academic hospital.

Participants: Patients who underwent abdominal surgery under general anaesthesia with tracheal intubation between 20 December, 2022, and 30 April, 2023, were retrospectively reviewed. Patients were assigned to the esketamine or control group based on whether they received a subanesthetic dose of esketamine.

Primary and secondary outcome measures: The primary outcome was extubation time (T1). Secondary outcomes included PACU observation time (T2), total PACU time (T3), postoperative pain at multiple time points, and adverse events including respiratory depression, hypertension, and others.

Results: A total of 2,177 patients underwent abdominal surgery. After PSM, 1196 patients were analysed, 598 in each group. Esketamine significantly reduced the extubation time compared to the control group (20.00 min vs. 23.00 min, p=0.001). Total PACU time was shorter in the esketamine group than in the control group (62 vs. 66 minutes, p = 0.015), although PACU observation time did not how a significant 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.

Strengths and limitations of this study

- Propensity score matching (PSM) was used to minimise selection bias and to balance baseline characteristics between the groups of patients with and without esketamine.
- A relatively large sample size from a real clinical setting was included, which increasing the generalisability of the results.
- As a single-centre retrospective study, the generalisability of the findings may be limited.
- Residual confounding from unmeasured variables may still be present, potentially affecting the results of the propensity score analysis.
- Sensitivity analysis was not performed, which may affect the robustness of the findings regarding residual confounding.

Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anaesthesia with tracheal intubation is the most commonly used anesthetic technique.[1] [2] 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.[14] [15]

This study retrospectively analyzes the effect of subanesthetic doses of esketamine used for intubation of general anaesthesia 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. Propensity score matching (PSM) was used to adjust pairs of patients with and without esketamine for potential confounders.

Methods

Study design and patient population

This retrospective, single-centre study was conducted at the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). 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 had abdominal surgery under general anaesthesia with tracheal intubation were included in the study. Inclusion criteria included an American Society of Anesthesiologists (ASA) physical status of I to Ⅲ, concurrent routine induction (sufentanil) with or without a subanesthetic dose of esketamine for general anaesthesia. 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, intraoperative bleeding ≥ 500 ml or severe intraoperative haemodynamic fluctuations

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 pressure, pulse oxygen saturation (SpO_2), respiratory rate, partial pressure of end-tidal carbon dioxide ($PetCO_2$), 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

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]

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,

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.

Patient and Public Involvement

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

Propensity score matching

Propensity score matching (PSM) analysis was performed using R Project for Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the matchIt package to reduce differences between the two groups based on the 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 good fit. For binary variables, the SMD is the difference in event rates between the 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 variables, the variable is split into several binary dummy variables and the SMD is 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 0.05. Matching variables included age, gender, BMI, chronic disease, ASA physical status classification, surgical category, surgery duration, anaesthesia duration, intraoperative blood loss, and PCA use, as indicated by absolute standardized mean differences (SMD) of less than 0.1 for all variables. Multiple linear regression analysis was used to complete the matching process.

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.

All quantitative data were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean (standard deviation), 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 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

Demographic and patient characteristics

A total of 2,177 patients with ASA physical status of I to Ⅲ under sufentanil 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).

Secondary outcome

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

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 esketamine group (p=0.027). The esketamine group had a significantly higher rate of 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).

Discussion

The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative extubation 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 anaesthesia and influence patient recovery.[20 21] However, recent studies have shown that esketamine not only increases the depth of anaesthesia but also accelerates recovery from anaesthesia.[22] Animal studies have shown that ketamine, the parent compound of esketamine, can shorten the peak activation time of the glutamatergic neurons, particularly those in the paraventricular thalamus (PVT), thereby reducing extubation 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 explain the prolonged analgesic effect of esketamine in the PACU.[23]

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 20% of cases of respiratory depression are associated with the use of opioid medications.[27] Elevated carbon dioxide (CO_2) levels can stimulate central

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 CO_2 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

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.

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

shorter overall PACU time, and ultimately contributing to the overall recovery process for patients.

Contributions DW, XF and YJ contributed to the study design. MW, KC, XW, YX, YW, MQ and ZL contributed to data acquisition. DW contributed to data analysis and drafting of the paper. XF and YJ contributed to manuscript revision. YJ contributed to final approval of the version. All authors read and approved the final version. YJ is the guarantor.

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Conflicting interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20230403A), and registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154).

Data availability statement Data will be made available on request. Further inquiries 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.

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

	Before PSM				After PSM			
	Total (n=1718)	Control Group（n=1085）	Esketamie Group (n=633)	P	Total (n=1196)	Control Group (n=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)	58.00 (48.00, 67.00)	58.00 (48.00, 65.00)	0.477
Gender, n (%)								0.954
Male	777 (45.23)	495 (45.62)	282 (44.55)		533 (44.57)	266 (44.48)	267 (44.65)	
Female	941 (54.77)	590 (54.38)	351 (55.45)		663 (55.43)	332 (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)	23.37 (21.10, 25.40)	23.44 (21.24, 25.35)	0.862
Chronic disease								
Hypertension, n (%)				0.768				0.880
No	1412 (82.19)	894 (82.40)	518 (81.83)		982 (82.11)	492 (82.27)	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				0.212
No	1618 (94.18)	1026 (94.56)	592 (93.52)		1128 (94.31)	569 (95.15)	559 (93.48)	
Yes	100 (5.82)	59 (5.44)	41 (6.48)		68 (5.69)	29 (4.85)	39 (6.52)	
Coronary heart disease, n (%)				0.190				0.176
No	1690 (98.37)	1064 (98.06)	626 (98.89)		1176 (98.33)	585 (97.83)	591 (98.83)	
Yes	28 (1.63)	21 (1.94)	7 (1.11)		20 (1.67)	13 (2.17)	7 (1.17)	
COPD, n (%)				0.151				0.615
No	1699 (98.89)	1076 (99.17)	623 (98.42)		1180 (98.66)	591 (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 (%)								0.160
I	143 (8.32)	100 (9.22)	43 (6.79)		97 (8.11)	57 (9.53)	40 (6.69)	

Ⅱ	1441 (83.88)	901 (83.04)	540 (85.31)		1016 (84.95)	503 (84.11)	513 (85.79)	
Ⅲ	134 (7.8)	84 (7.74)	50 (7.90)		83 (6.94)	38 (6.35)	45 (7.53)	
Surgery type, n (%)				<0.001				0.515
Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)		597 (49.92)	302 (50.50)	295 (49.33)	
Gastrointestinal surgery	460 (26.78)	279 (25.71)	181 (28.59)		333 (27.84)	158 (26.42)	175 (29.26)	
Colorectal surgery	339 (19.73)	184 (16.96)	155 (24.49)		266 (22.24)	138 (23.08)	128 (21.40)	
Surgery duration (min) , median (IQR)	60.00 (38.00, 121.00)	55.00 (37.00, 112.00)	68.00 (41.00, 135.00)	<0.001	62.00 (39.00, 127.00)	57.00 (38.25, 117.75)	63.00 (40.00, 126.75)	0.757
Anaesthesia duration (min), median (IQR)	82.00 (58.00, 155.00)	79.00 (56.00, 147.00)	90.00 (60.00, 170.00)	<0.001	86.00 (58.00, 159.25)	80.00 (57.00, 151.00)	86.00 (59.00, 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)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	0.580
PCA, n (%)				0.102				0.195
Yes	1197 (69.67)	771 (71.06)	426 (67.30)		807 (67.47)	393 (65.72)	414 (69.23)	
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 pulmonary 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 (n=598)	Esketamine Group (n=598)	*P* value
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.

Table 3. Postoperative pain scores and analgesic requirements.

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

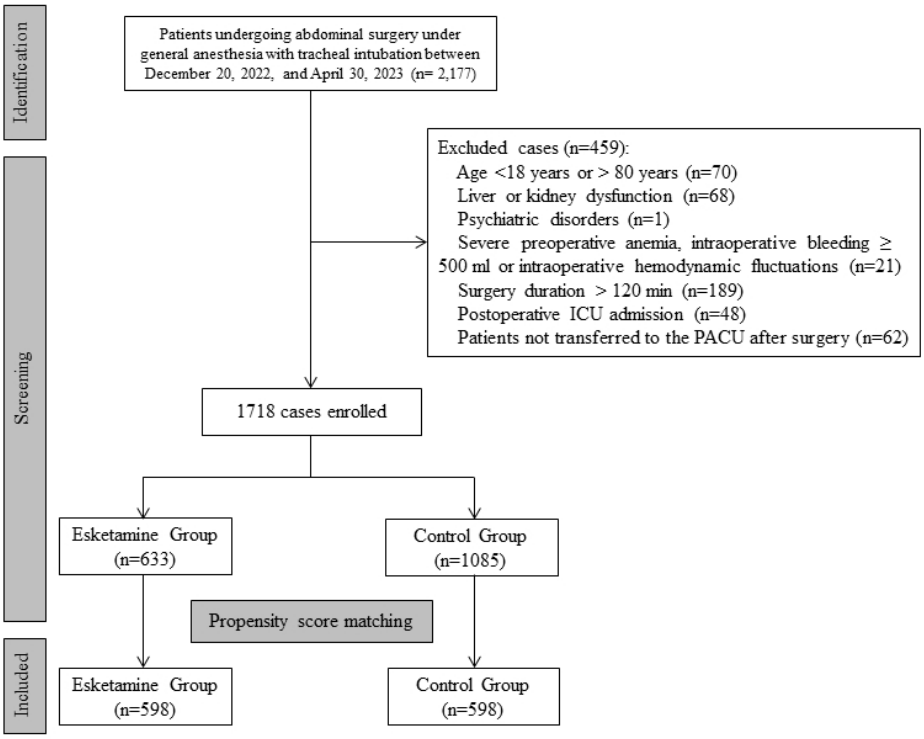
Data are presented as n (%).

NRS: Numeric Rating Scale

Table 4. Postoperative adverse events and the modified Aldrete score

	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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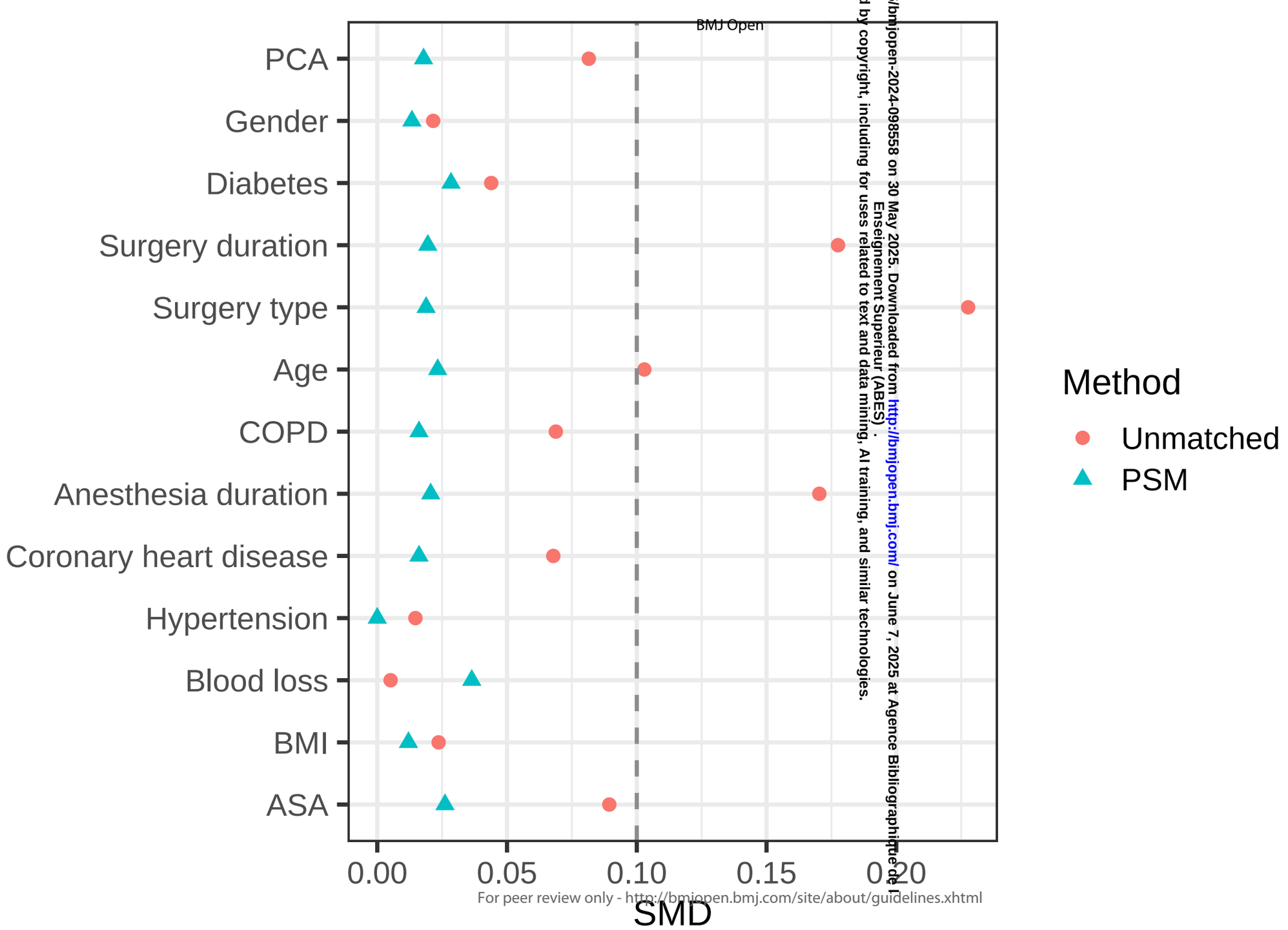

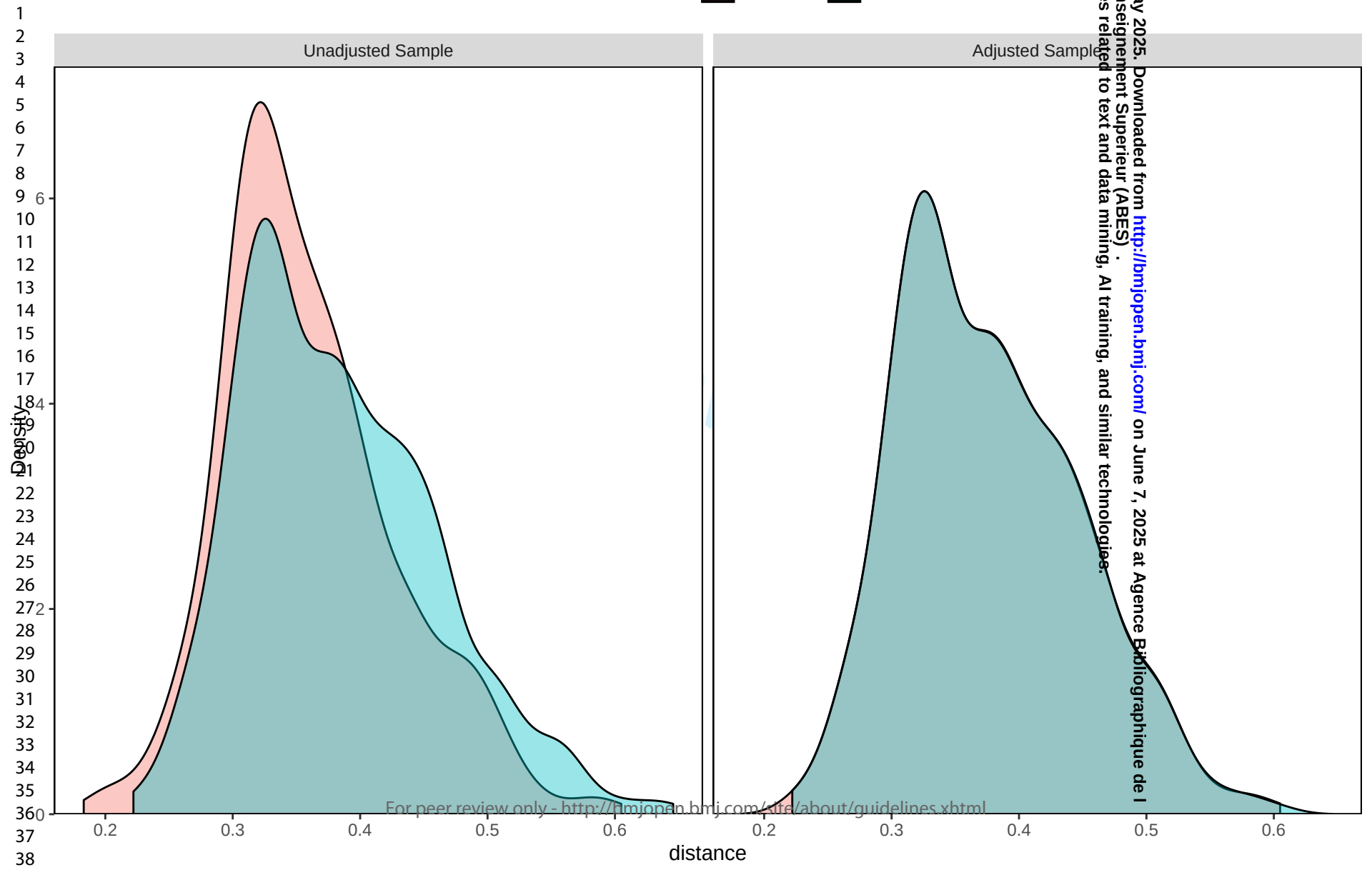

Supplementary data

Supplement Table 1. Results of multiple linear regression analysis

Variables	b	S.E	t	β (95%CI)	P	m_b	m_S.E	m_t	aβ (95%CI)	aP
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)	<.001
Gender										
Male				0.00 (Reference)						
Female	1.38	1.12	1.23	1.38 (-0.82 ~ 3.58)	0.218					
BMI	-0.89	0.17	-5.34	-0.89 (-1.21 ~ -0.56)	<.001	-0.60	0.16	-3.87	-0.60 (-0.91 ~ -0.30)	<.001
Chronic disease										
Hypertension										
No				0.00 (Reference)						
Yes	0.20	1.46	0.14	0.20 (-2.65 ~ 3.06)	0.888					
Diabetes										
No				0.00 (Reference)						
Yes	-1.78	2.41	-0.74	-1.78 (-6.51 ~ 2.94)	0.459					
Coronary heart disease										
No				0.00 (Reference)						
Yes	3.28	4.35	0.75	3.28 (-5.25 ~ 11.81)	0.451					
COPD										
No				0.00 (Reference)					0.00 (Reference)	
Yes	11.59	4.85	2.39	11.59 (2.10 ~ 21.09)	0.017	5.42	4.48	1.21	5.42 (-3.36 ~ 14.20)	0.226
ASA physical status										
I				0.00 (Reference)						
Ⅱ	3.82	2.05	1.86	3.82 (-0.20 ~ 7.83)	0.062					
Ⅲ	3.34	2.88	1.16	3.34 (-2.31 ~ 8.99)	0.246					
Surgery type										
Hepatobiliary surgery				0.00 (Reference)					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	-3.70 (-6.12 ~ -1.28)	0.003

Colorectal surgery	7.89	1.39	5.68	7.89 (5.17 ~ 10.61)	<.001	1.20	1.60	0.77	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	0.05 (-0.08 ~ 0.18)	0.417
Anesthesia duration (min)	0.09	0.01	9.80	0.09 (0.07 ~ 0.10)	<.001	-0.05	0.06	-0.77	-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	0.06 (0.04 ~ 0.08)	<.001
Esketamine										
No				0.00 (Reference)					0.00 (Reference)	
Yes	-3.35	1.11	-3.01	-3.35 (-5.53 ~ -1.17)	0.003	-2.83	1.02	-2.77	-2.83 (-4.84 ~ -0.83)	0.006
PCA										
No				0.00 (Reference)					0.00 (Reference)	
Yes	12.55	1.13	11.06	12.55 (10.32 ~ 14.77)	<.001	6.04	1.67	3.62	6.04 (2.77 ~ 9.31)	<.001

ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PCA: Patient controlled analgesia; PSM: propensity score matching

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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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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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Running title: Effect of esketamine on anesthetic recovery quality

Keywords: esketamine; general anaesthesia with tracheal intubation; abdominal surgery; postoperative adverse event; subanesthetic dose

Abstract

Objectives: Subanesthetic doses of esketamine may attenuate the opioid-induced 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 abdominal surgery patients.

Design: Retrospective cohort study using propensity-score matching (PSM) methodology.

Setting: A tertiary academic hospital.

Participants: Patients who underwent abdominal surgery under general anaesthesia with tracheal intubation between 20 December, 2022, and 30 April, 2023, were retrospectively reviewed. Patients were assigned to the esketamine or control group based on whether they received a subanesthetic dose of esketamine.

Primary and secondary outcome measures: The primary outcome was extubation time (T1). Secondary outcomes included PACU observation time (T2), total PACU time (T3), postoperative pain at multiple time points, and adverse events including respiratory depression, hypertension, and others.

Results: A total of 2,177 patients underwent abdominal surgery. After PSM, 1196 patients were analysed, 598 in each group. Esketamine significantly reduced the extubation time compared to the control group (20.00 min vs. 23.00 min, p=0.001). Total PACU time was shorter in the esketamine group than in the control group (62 vs. 66 minutes, p = 0.015), although PACU observation time did not how a significant 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.

Strengths and limitations of this study

- Propensity score matching (PSM) was used to minimise selection bias and to balance baseline characteristics between the groups of patients with and without esketamine.
- A relatively large sample size from a real clinical setting was included, which increasing the generalisability of the results.
- As a single-centre retrospective study, the generalisability of the findings may be limited.
- Residual confounding from unmeasured variables may still be present, potentially affecting the results of the propensity score analysis.
- Sensitivity analysis was not performed, which may affect the robustness of the findings regarding residual confounding.

Introduction

Approximately 313 million people worldwide undergo surgery each year, and general anaesthesia with tracheal intubation is the most commonly used anesthetic technique.[1] [2] 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.[14] [15]

This study retrospectively analyzes the effect of subanesthetic doses of esketamine used for intubation of general anaesthesia 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. Propensity score matching (PSM) was used to adjust pairs of patients with and without esketamine for potential confounders.

Methods

Study design and patient population

This retrospective, single-centre study was conducted at the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). 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 had abdominal surgery under general anaesthesia with tracheal intubation were included in the study. Inclusion criteria included an American Society of Anesthesiologists (ASA) physical status of I to Ⅲ, concurrent routine induction (sufentanil) with or without a subanesthetic dose of esketamine for general anaesthesia. 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, intraoperative bleeding ≥ 500 ml or severe intraoperative haemodynamic fluctuations

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 pressure, pulse oxygen saturation (SpO_2), respiratory rate, partial pressure of end-tidal carbon dioxide ($PetCO_2$), 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

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]

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,

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.

Patient and Public Involvement

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

Propensity score matching

Propensity score matching (PSM) analysis was performed using R Project for Statistical Computing (Version 4.2.3, Lucent Technologies, Reston, USA) and the matchIt package to reduce differences between the two groups based on the 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 good fit[20]. For binary variables, the SMD is the difference in event rates between the 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 variables, the variable is split into several binary dummy variables and the SMD is 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 0.05. Matching variables were selected based on prior literature where there was evidence of being potential confounders[21] and included age, gender, BMI, chronic disease, ASA physical status classification, surgical category, surgery duration, anaesthesia duration, intraoperative blood loss, and PCA use. The absolute standardised mean differences (SMD) are less than 0.1 for all variables. Multiple linear regression analysis was used to complete the matching process.

Statistical analysis

Sample size was calculated using PASS statistical software (NCSS LLC, Kaysville, USA). This was a retrospective case-control study. In the preliminary study, we included 20 patients in each group, and the mean extubation times for the two 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.

All quantitative data were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean (standard deviation), 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 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

Demographic and patient characteristics

A total of 2,177 patients with ASA physical status of I to Ⅲ under sufentanil 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).

Secondary outcome

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

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 esketamine group (p=0.027). The esketamine group had a significantly higher rate of 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).

Discussion

The results of the current study indicate that the use of subanesthetic doses of esketamine can effectively reduce the postoperative extubation 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 anaesthesia and influence patient recovery.[22 23] However, recent studies have shown that esketamine not only increases the depth of anaesthesia but also accelerates recovery from anaesthesia.[24] Animal studies have shown that ketamine, the parent compound of esketamine, can shorten the peak activation time of the glutamatergic neurons, particularly those in the paraventricular thalamus (PVT), thereby reducing extubation 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.[25] 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.[26] 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 27 28] 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 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

20% of cases of respiratory depression are associated with the use of opioid medications.[29] Elevated carbon dioxide (CO_2) levels can stimulate central chemoreceptors, leading to an increase in respiratory drive. However, the use of opioid medications attenuates this response.[30] Both animal and clinical studies have shown that ketamine can enhance CO_2 sensitivity and provide moderate protection against respiratory depression and bronchoconstriction.[31 32] Research by Jonkman *et al.* also suggests that low-dose esketamine may counteract the respiratory depressant effects of opioid drugs.[33] 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.[34 35] Bornemann-Cimenti H *et al*. have confirmed that subanesthetic doses can reduce the incidence of psychological symptoms associated with esketamine.[36] 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 37] 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.[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.

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 shorter overall PACU time, and ultimately contributing to the overall recovery process for patients.

Contributions DW, XF and YJ contributed to the study design. MW, KC, XW, YX, YW, MQ and ZL contributed to data acquisition. DW contributed to data analysis and drafting of the paper. XF and YJ contributed to manuscript revision. YJ contributed to final approval of the version. All authors read and approved the final version. YJ is the guarantor.

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Conflicting interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20230403A), and registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2300072154).

Data availability statement Data will be made available on request. Further inquiries 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.

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

	Before PSM				After PSM			
	Total (n=1718)	Control Group （n=1085）	Esketamie Group (n=633)	P	Total (n=1196)	Control Group (n=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)	58.00 (48.00, 67.00)	58.00 (48.00, 65.00)	0.477
Gender, n (%)								0.954
Male	777 (45.23)	495 (45.62)	282 (44.55)		533 (44.57)	266 (44.48)	267 (44.65)	
Female	941 (54.77)	590 (54.38)	351 (55.45)		663 (55.43)	332 (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)	23.37 (21.10, 25.40)	23.44 (21.24, 25.35)	0.862
Chronic disease								
Hypertension, n (%)				0.768				0.880
No	1412 (82.19)	894 (82.40)	518 (81.83)		982 (82.11)	492 (82.27)	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				0.212
No	1618 (94.18)	1026 (94.56)	592 (93.52)		1128 (94.31)	569 (95.15)	559 (93.48)	
Yes	100 (5.82)	59 (5.44)	41 (6.48)		68 (5.69)	29 (4.85)	39 (6.52)	
Coronary heart disease, n (%)				0.190				0.176
No	1690 (98.37)	1064 (98.06)	626 (98.89)		1176 (98.33)	585 (97.83)	591 (98.83)	
Yes	28 (1.63)	21 (1.94)	7 (1.11)		20 (1.67)	13 (2.17)	7 (1.17)	
COPD, n (%)				0.151				0.615
No	1699 (98.89)	1076 (99.17)	623 (98.42)		1180 (98.66)	591 (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 (%)								0.160
I	143 (8.32)	100 (9.22)	43 (6.79)		97 (8.11)	57 (9.53)	40 (6.69)	

Ⅱ	1441 (83.88)	901 (83.04)	540 (85.31)		1016 (84.95)	503 (84.11)	513 (85.79)	
Ⅲ	134 (7.8)	84 (7.74)	50 (7.90)		83 (6.94)	38 (6.35)	45 (7.53)	
Surgery type, n (%)				<0.001				0.515
Hepatobiliary surgery	919 (53.49)	622 (57.33)	297 (46.92)		597 (49.92)	302 (50.50)	295 (49.33)	
Gastrointestinal surgery	460 (26.78)	279 (25.71)	181 (28.59)		333 (27.84)	158 (26.42)	175 (29.26)	
Colorectal surgery	339 (19.73)	184 (16.96)	155 (24.49)		266 (22.24)	138 (23.08)	128 (21.40)	
Surgery duration (min) , median (IQR)	60.00 (38.00, 121.00)	55.00 (37.00, 112.00)	68.00 (41.00, 135.00)	<0.001	62.00 (39.00, 127.00)	57.00 (38.25, 117.75)	63.00 (40.00, 126.75)	0.757
Anaesthesia duration (min), median (IQR)	82.00 (58.00, 155.00)	79.00 (56.00, 147.00)	90.00 (60.00, 170.00)	<0.001	86.00 (58.00, 159.25)	80.00 (57.00, 151.00)	86.00 (59.00, 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)	10.00 (10.00, 50.00)	10.00 (10.00, 50.00)	0.580
PCA, n (%)				0.102				0.195
Yes	1197 (69.67)	771 (71.06)	426 (67.30)		807 (67.47)	393 (65.72)	414 (69.23)	
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 pulmonary disease; PCA: Patient controlled analgesia; PSM: propensity score matching; SMD: standardized mean differences

Table 2. Recovery time after surgery.

	Control Group (n=598)	Esketamine Group (n=598)	*P* value
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.

Table 3. Postoperative pain scores and analgesic requirements.

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

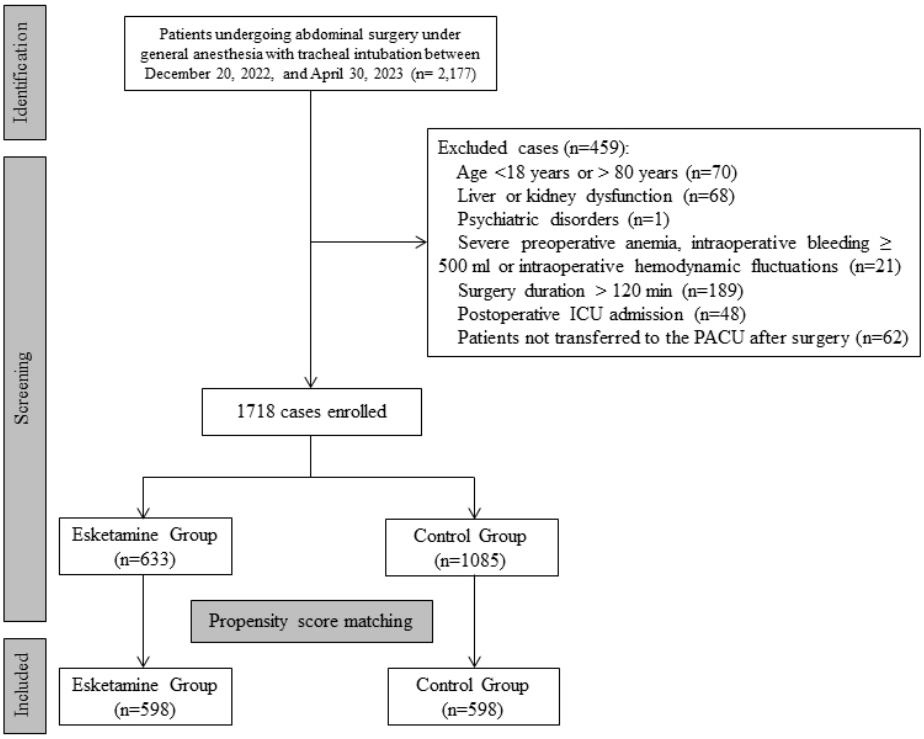
Data are presented as n (%).

NRS: Numeric Rating Scale

Table 4. Postoperative adverse events and the modified Aldrete score

	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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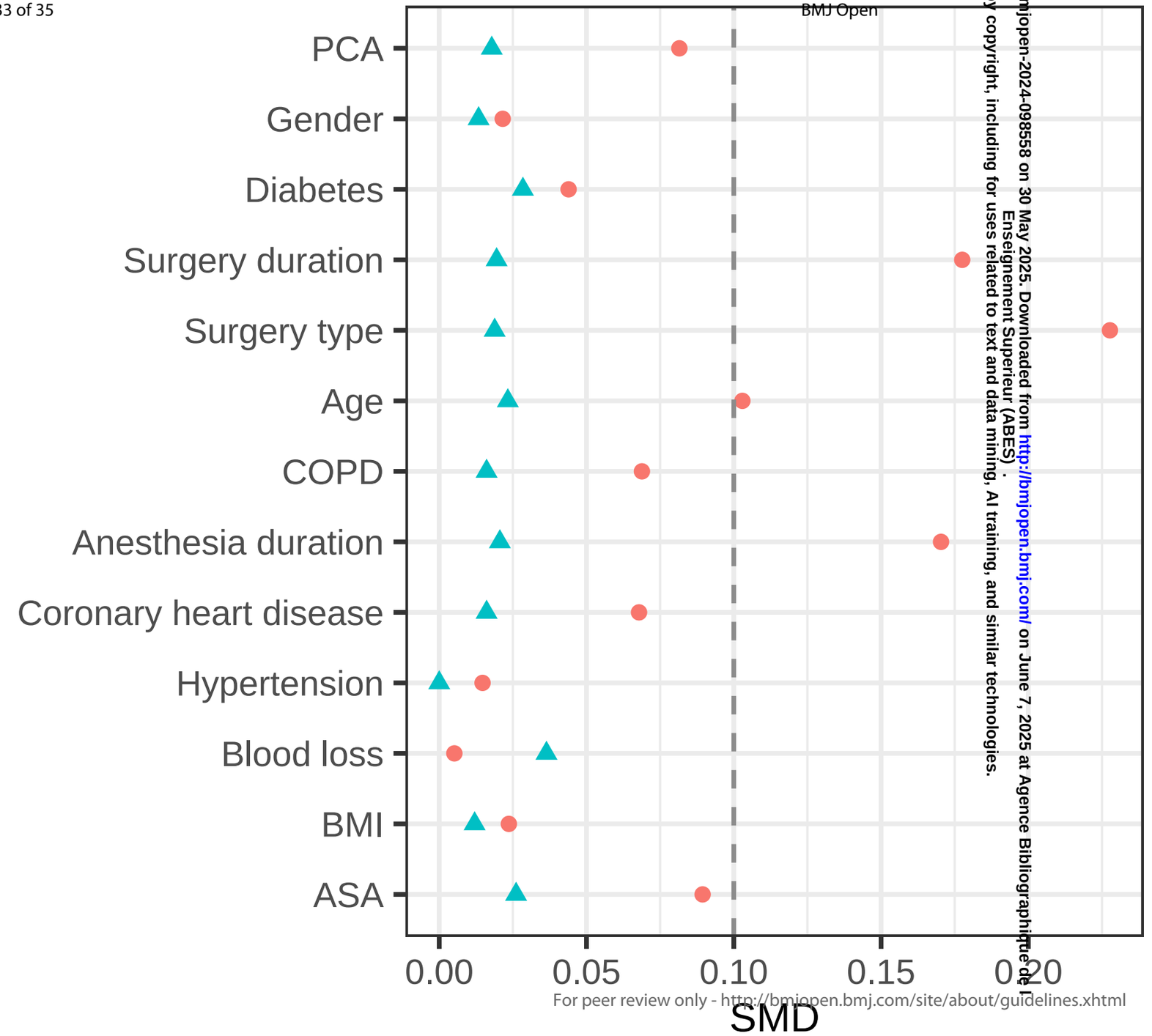

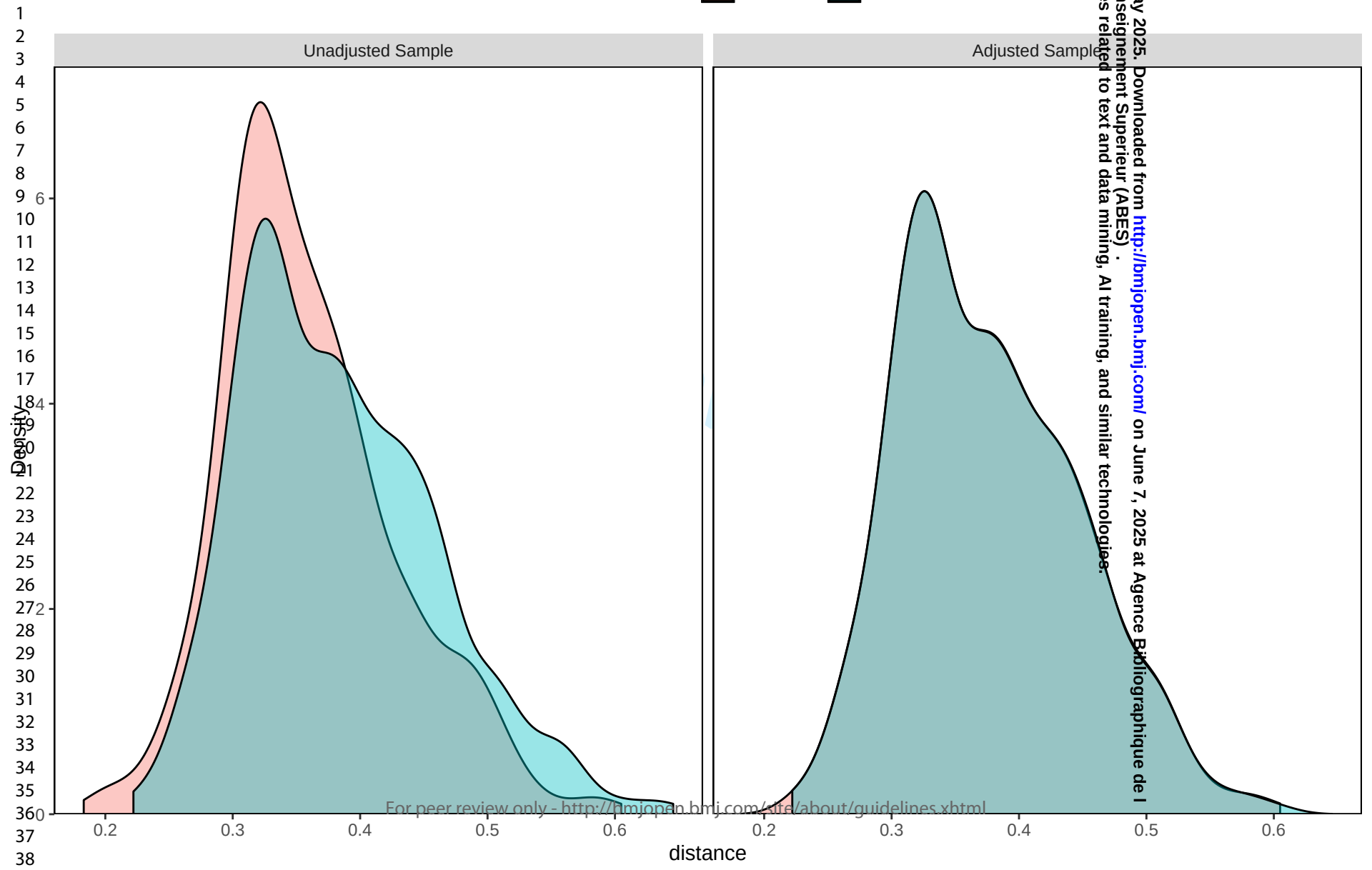

Supplementary data

Supplement Table 1. Results of multiple linear regression analysis

Variables	b	S.E	t	β (95%CI)	P	m_b	m_S.E	m_t	aβ (95%CI)	aP
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)	<.001
Gender										
Male				0.00 (Reference)						
Female	1.38	1.12	1.23	1.38 (-0.82 ~ 3.58)	0.218					
BMI	-0.89	0.17	-5.34	-0.89 (-1.21 ~ -0.56)	<.001	-0.60	0.16	-3.87	-0.60 (-0.91 ~ -0.30)	<.001
Chronic disease										
Hypertension										
No				0.00 (Reference)						
Yes	0.20	1.46	0.14	0.20 (-2.65 ~ 3.06)	0.888					
Diabetes										
No				0.00 (Reference)						
Yes	-1.78	2.41	-0.74	-1.78 (-6.51 ~ 2.94)	0.459					
Coronary heart disease										
No				0.00 (Reference)						
Yes	3.28	4.35	0.75	3.28 (-5.25 ~ 11.81)	0.451					
COPD										
No				0.00 (Reference)					0.00 (Reference)	
Yes	11.59	4.85	2.39	11.59 (2.10 ~ 21.09)	0.017	5.42	4.48	1.21	5.42 (-3.36 ~ 14.20)	0.226
ASA physical status										
I				0.00 (Reference)						
Ⅱ	3.82	2.05	1.86	3.82 (-0.20 ~ 7.83)	0.062					
Ⅲ	3.34	2.88	1.16	3.34 (-2.31 ~ 8.99)	0.246					
Surgery type										
Hepatobiliary surgery				0.00 (Reference)					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	-3.70 (-6.12 ~ -1.28)	0.003

Colorectal surgery	7.89	1.39	5.68	7.89 (5.17 ~ 10.61)	<.001	1.20	1.60	0.77	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	0.05 (-0.08 ~ 0.18)	0.417
Anesthesia duration (min)	0.09	0.01	9.80	0.09 (0.07 ~ 0.10)	<.001	-0.05	0.06	-0.77	-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	0.06 (0.04 ~ 0.08)	<.001
Esketamine										
No				0.00 (Reference)					0.00 (Reference)	
Yes	-3.35	1.11	-3.01	-3.35 (-5.53 ~ -1.17)	0.003	-2.83	1.02	-2.77	-2.83 (-4.84 ~ -0.83)	0.006
PCA										
No				0.00 (Reference)					0.00 (Reference)	
Yes	12.55	1.13	11.06	12.55 (10.32 ~ 14.77)	<.001	6.04	1.67	3.62	6.04 (2.77 ~ 9.31)	<.001

ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PCA: Patient controlled analgesia; PSM: propensity score matching