# RESEARCH

**BMC** Anesthesiology



# Intravenous esketamine as a detumescence agent for intraoperative penile erection during urological surgeries: a retrospective clinical analysis



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# Abstract

**Background** Intraoperative penile erection (IPE) is an uncommon yet complex issue, and numerous approaches to achieving detumescence fall short of providing consistently satisfactory outcomes. Esketamine, with its sympathomimetic properties, may offer a promising solution for managing this condition. The present study aimed to evaluated the efficiency and safety of intravenous esketamine in addressing IPE.

**Methods** We conducted a review of 3,848 patients who underwent endourological, penile or testicular surgeries under general anesthesia from 2021 to 2023, and cases with IPE and received pharmacological intervention were included in this study. Intravenous esketamine or ephedrine were preferred for managing IPE. The primary outcomes evaluated were the rate of successful penile detumescence, time to detumescence, rapid response rate, remedial measures, intraoperative hypertension, tachycardia and neuropsychiatric adverse events. Additionally, data regarding age, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, type of surgeries, anesthesia methods, medication dosage, and recovery time were documented. We performed meticulously statistical analyses to evaluate the endpoints.

**Results** Overall, 37 cases with IPE were assigned to an esketamine group (K group, n = 27) or an ephedrine group (E group, n = 10) based on intraoperative medication. No statistically significant differences were noted regarding age, BMI, ASA grade, type of surgeries, anesthesia methods, rate of successful penile detumescence (96.3% vs. 80.0%), recovery time or the occurrence of postoperative psychiatric complications such as dizziness, restlessness or delirium(P > 0.05). However, compared to ephedrine, esketamine produced a shorter time to detumescence (3.0 ± 0.4 min vs. 5.5 ± 1.1 min, log-rank P = 0.006)), higher rapid response rate achieved detumescence  $\leq 3$  min (85.2% vs. 50%, P = 0.041), and a lower incidence of cardiovascular adverse events (intraoperative hypertension and tachycardia) (P < 0.05).

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**Conclusion** Our research establishes intravenous esketamine as a practical and reliable therapeutic intervention for prompt resolution of IPE, demonstrating high clinical efficacy with rapid symptom alleviation.

Keywords Intraoperative penile erection, Esketamine, Detumescence, Urological surgeries

# Introduction

Intraoperative penile erection (IPE) is a relatively infrequent but challenging condition during transurethral or penile surgeries [1]. The engorged corpora cavernosa induces anatomical distortion of the urethral lumen and displacement of surgical landmarks, complicating catheterization and instrument navigation, these pathophysiological alterations elevate risks of iatrogenic urethral injury, compromised surgical field visibility, and postoperative complications including urethral rupture and erectile dysfunction [1, 2].

Clinical treatments for IPE remain predominantly empirical, intracavernosal injections of vasoactive agents (e.g., phenylephrine, noradrenaline, ephedrine) have been proved effective to promote detumescence via  $\alpha$ -adrenergic stimulation [3–5]. However, these invasive injections carry risks of localized complications such as pain, hematoma, infection [6–9], and even systemic adverse events (hypertension, arrhythmias) due to vasoconstrictor absorption [8, 10]. Such limitations underscore the urgent need for non-invasive, rapidly acting alternatives with improved safety profile.

The pathophysiology of IPE involves anesthesiainduced disruption of the sympathetic-parasympathetic equilibrium regulating penile vascular tone [11]. This mechanistic understanding suggests that agents restoring sympathetic dominance may offer a targeted therapeutic strategy for IPE. Esketamine, the S-enantiomer of ketamine, was prioritized over traditional intracavernosal  $\alpha$ -agonists for three key reasons: (I) Dual mechanism: Simultaneously maintains possesses sedative, analgesic, and sympathomimetic properties which can restore sympathetic-parasympathetic balance via norepinephrine reuptake inhibition; (II) Non-invasive superiority: intravenous administration circumvents risks of intracavernosal injections; (III) Safety advantage: ketamine's psychomimetic and cardiovascular complications are reduced with esketamine due to its enhanced N-methyl-D-aspartate (NMDA) receptor affinity and lower dosing requirements.

Despite these theoretical advantages, critical knowledge gaps hinder clinical translation: First, current  $\alpha$ -agonists fail to address anesthesia-induced sympathetic suppression, often resulting in delayed detumescence. Second, intracavernosal injection protocols vary widely, risking under-/overtreatment. Third, esketamine's dose-response relationship, comparative efficacy against  $\alpha$ -agonists, and hemodynamic stability in urological contexts remain uncharacterized. This study therefore aims to evaluate the efficacy and safety of esketamine for controlling IPE, address existing knowledge gaps and provide evidence-based insights to optimize its clinical application.

# Methods

# **Study population**

This single-center, retrospective study was conducted at Wuhan No.1 Hospital, China. We reviewed and analyzed data from male patients who underwent endourological, penile or testicular surgeries between January 2021 and December 2023. Among 3,848 eligible cases, those who developed IPE and received pharmacological intervention were included.

Patients received intravenous esketamine (esketamine group, K group) or ephedrine (ephedrine group, E group) for IPE treatment based on individualized clinical judgment, including patient comorbidities, drug availability, and anesthesiologist preference. Randomization was not available for the retrospective study due to the emergent nature of IPE appearance and limited number of cases. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Ethics Committee of Wuhan No.1 Hospital (No. [2024]31).

#### **Treatment of IPE**

All patients received general anesthesia, with no documented contraindications or allergies to the study medications. Upon occurrence of IPE that impeded surgical instrument accurate placement or procedural progress, intravenous esketamine (0.3–0.5 mg/kg)) or ephedrine (5–10 mg) was administered based on the anesthesiologists' experiences and the patients' conditions, and additional dose ( $\leq$  50% initial dose) may be given if the initial injection failed to achieve satisfactory results within 5 min. Penile dorsal nerve block (5–10mL 1% lidocaine) was performed as a remedial preferred option if pharmacological measures failed (no detumescence within 10 min), allowing uninterrupted surgical continuation.

# Data collection and outcome measures

Data on age, BMI, ASA grade, type of surgeries and anesthesia methods were recorded for each patient.

#### Efficacy outcomes

Successful penile detumescence: Defined as resolution of erection enabling surgical continuation within 10 min of intravenous pharmacological intervention. Time to detumescence (minutes): From medication administration to complete flaccidity.

Rapid response rate: Proportion achieving detumescence  $\leq 3$  min.

Remedial measures: Secondary intervention required after intravenous pharmacological failure. (e.g., penile dorsal nerve block (preferred option), cold compresses or intracavernous medication).

# Safety outcomes

Intraoperative hypertension: MAP increase > 20% from baseline (pre-medication MAP).

Tachycardia: Heart rate increase>20% from baseline sustained>2 min.

Neuropsychiatric adverse events: Documented incidents of dizziness, restlessness, or delirium within 24 h postoperatively.

Recovery Time: Interval from drug discontinuation to Aldrete score  $\geq$  9.

### Statistical analysis

Statistical analyses were conducted using SPSS version 22.0. Quantitative data are presented as mean (range) or means  $\pm$  standard deviations (SDs), and comparisons between groups were made using one-way ANOVA and Log-rank test when appropriate. Count data are expressed as the number of cases (percentage), and the  $\chi^2$  test or Fisher's exact test were performed for comparisons between groups. All statistical differences were considered significant at a *P*-value < 0.05.

 Table 1
 Comparison of general informations between the two groups

Indicators		K group ( <i>n</i> = 27)	E group ( <i>n</i> = 10)	<i>P-</i> value
Age (years), mean±SD		43.9±14.5	44.9±12.3	0.841
BMI (kg/m²), mean±SD		24.5±1.9	24.3±2.5	0.757
ASA grade, n	1/11/111	3/23/1	0/9/1	0.326
Type of surgery, n (%)	Lithiasis in uri- nary system	18(66.7)	8(80.0)	0.766
	Bladder or pros- tate cancer	3(11.1)	0	
	Surgery for penile, scrotal or testicular	4(14.8)	2(20.0)	
	Other operation	2(7.4)	0	

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists

Note: The general informations did not significantly differ between the two groups.

# Results

#### Study population characteristics

Among 3,848 urological procedures reviewed, 37 cases (0.96%) developed IPE were stratified into K group (27 cases) and E group (10 cases). The cohort had a mean age of 45.2 years (range: 13–71 years), with no statistically significant differences in age, BMI, ASA grade, type of surgeries between the two groups (P>0.05; Table 1). Respectively, 1.12% (15/1,336) and 0.88% (22/2,512) cases experienced unwanted IPE during total intravenous anesthesia (propofol + remifentanil) and combined intravenous-inhalational anesthesia (propofol + remifentanil) significant difference in the morbidity between the two anesthesia methods (P>0.05).

#### **Treatment outcomes**

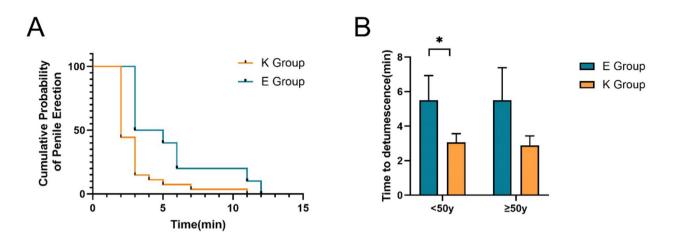
Intravenous pharmacological intervention with esketamine or ephedrine resolved IPE in 34 patients, with failure rates of 3.7% (1/27) in the K group and 20% (2/10) in the E group. Rescued penile dorsal nerve block was performed to facilitate the surgical continuation. While overall successful penile detumescence rate (96.3% vs. 80.0%, P = 0.172) and remedial measures rate (3.7% vs. 20%, P=0.172) showed no intergroup difference (P > 0.05). Esketamine demonstrated superior performance than ephedrine: Faster detumescence:  $3.0 \pm 0.4$  min vs.  $5.5 \pm 1.1$  min (log-rank test P = 0.006) (Fig. 1A); Higher rapid response rate: 85.2% (23/27) achieved detumescence  $\leq 3 \text{ min vs. } 50\% (5/10) (P = 0.041).$ Subgroup analysis by age showed comparable detumescence times between patients aged < 50 and  $\ge 50$  years in either group, however, esketamine demonstrated numerically faster resolution in younger patients compared to ephedrine (*P* = 0.045) (Fig. 1B).

#### Safety profile of esketamine

The average dosage of esketamine administered was 40.1 mg (range, 25.0–80.0 mg, 0.3-0.8 mg/kg). The findings revealed a significant lower incidence of cardiovascular adverse events, including intraoperative hypertension and tachycardia, in the K group compared to the E group (P < 0.05). While, there were no significant intergroup differences in recovery time and the occurrence of postoperative neuropsychiatric complications such as dizziness, restlessness or delirium(P > 0.05) (Table 2).

# Discussion

The prevalence of IPE under anesthesia has been reported to range from 0.1 to 2.4% overall, with specific incidences of 0.3-3.5% for general anesthesia, 0.1-0.3% for spinal anesthesia and 1.7-3.8% for epidural anesthesia [7, 12]. In the present study, all patients were administered



**Fig. 1** The evaluation of time to detumescence. (A) Esketamine demonstrated superior performance faster detumescence than ephedrine  $(3.0 \pm 0.4 \text{ min} \text{ vs. } 5.5 \pm 1.1 \text{ min}, \log$ -rank test P=0.006). (B) Subgroup analysis by age showed comparable detumescence times between patients aged <50 and ≥50 years in either group, however, esketamine demonstrated numerically faster resolution in younger patients compared to ephedrine. \* P<0.05.

 Table 2
 Safety evaluation via indicators of cardiovascular events, recovery time and postoperative complications in the two groups

Indicators		K group ( <i>n</i> = 27)	E group ( <i>n</i> = 10)	<i>P-</i> value
Recovery time (min), mean±SD		16.9±5.4	16.8±6.1	0.966
Cardiovascular events, n (%)	Intraoperative hypertension (MAP increase exceeding 20%)	4(14.8)	6(60.0)	0.012*
	Increased heart rate (increase exceeding 20%)	6(22.2)	8(80.0)	0.002**
Postoperative complications, n (%)	Dizziness	4(14.8)	1(10.0)	0.722
	Restlessness	10(37.0)	4(40.0)	
	Delirium	2(7.4)	1(10.0)	

Abbreviations: MAP, mean artery pressure

Note: The incidence of cardiovascular adverse events (intraoperative hypertension and elevated heart rate) in group K were obviously lower compared to group E. The recovery time and the occurrence of postoperative psychiatric complications such as dizziness, restlessness or delirium exhibited no significant differences between the two groups. \*\* P<0.01; \* P<0.05.

general anesthesia, yielding an overall incidence of IPE at 0.96%, which aligns with previous research findings. Prior studies have observed that IPE is more predominant in younger individuals aged 5–10 and 20–50 years [13]. Consistent with these findings, our study found that a significant proportion of patients (70.3%) with IPE were < 50 years old. This age group is known to have higher levels of male hormones and increased sensitivity in the genital region, factors which may contribute to erection even with relatively minor stimulation.

IPE is a painless experience during urological surgical procedures. A complex process is involved encompassing a wide array of factors, including neurological, psychological, vascular and endocrine components, but the specific mechanism(s) has not yet been unequivocally clarified [14]. They can be roughly summarized to be as follows: (I) Penile erection is essentially a neuro-endocrine mediated congestive response of the penile vasculature, which is dominated by sympathetic and parasympathetic nerves. Sympathetic activation induces vasoconstriction and penile softening, via norepinephrine and  $\alpha$ -adrenoceptors. While parasympathetic nerve excitation prompts an augmented release of acetylcholine, subsequently triggering the relaxation of cavernous smooth muscle, vasodilatation and congestion within the cavernous sinus [15]. Under general anesthesia, the coordinated physiological alterations of sympathetic inhibition and relative parasympathetic dominance facilitate IPE [12]. (II) IPE is believed to be triggered by both reflexogenic and psychological factors under general anesthesia, with the former probably being the more common cause [6, 16]. Inadequate anesthesia depth or incomplete blocking range may fail to fully suppress the reflex arc extending from the penis dorsal nerve to the sacral cord and parasympathetic system. Consequently, external stimuli such as washing or touching the genital area, along with internal stimulation of pelvic organs, can evoke reflexogenic responses. Additionally, psychogenic stimulation stemming from heightened sensory input or dreams during anesthesia is thought to contribute to the elicitation of IPE [3, 12]. (III) Anesthetic drugs can potentially aid in achieving or maintaining penile erection. Clinical practice has found that application of propofol during general anesthesia may increase the occurrence of IPE. Patients may experience a sub-anesthesia state with insufficient propofol dosage or in the recovery period of drug metabolism, this state easily triggering sexual hallucinations, pleasure and euphoria, eliciting erection [17, 18]. Further studies have indicated that propofol may weaken the tension of the cavernous smooth muscle and erect the penis

by altering voltage-dependent calcium channels and decreasing transmembrane calcium flux [19]. The study conducted by Bakan et al. concluded that remifentanil may potentially increase the occurrence of IPE during pediatric cystoscopy under general anesthesia, as in some cases, erections disappeared after a reduction or discontinuation of remifentanil use [20]. Abbasi et al. found a visibly higher rate of penile erection in halothane group during pediatric hypospadiasis repair. They speculated that halothane increased penile blood flow by inhibiting the autonomic nervous system and altering penile vascular resistance, hence, penile erection occurred [21]. However, it has also been suggested that sevoflurane or isoflurane can inhibit penile erection by inhibiting synthesis or activation of nitric oxide [22]. These findings imply a potential correlation between IPE and commonly used anesthetics, offering an insight into why IPE occurs during both total intravenous anesthesia and combined inhalational-intravenous anesthesia in our study.

Understanding these mechanisms aids in tailoring anesthesia protocols, selecting agents with inhibitory profiles or pharmacological interventions to mitigate IPE risks during urological procedures.

Ketamine has been widely used for the management of IPE at an early stage, but its efficacy remains controversial, due to its slow regression of the erection, cardiovascular side effects and psychiatric symptoms during the recovery period [23, 24]. Esketamine, a pure dextroisomer of ketamine, shares pharmacological mechanism akin to ketamine, exhibits approximately twofold greater affinity for NMDA receptors and enhanced anesthetic potency. This pharmacological profile enables equivalent therapeutic efficacy at half doses, while reducing cardiovascular burden and psychiatric risks [25]. Notably, esketamine's sympathomimetic activity provides a strong theoretical foundation for IPE management by modulating sympathetic-parasympathetic equilibrium balance. Whereas, clinical evidences supporting its effectiveness in treating IPE are still deficient. Guided by these mechanistic insights, we pioneered the use of intravenous esketamine for IPE intervention. Clinical data revealed remarkable efficacy within safe dosing parameters at 0.3-0.8 mg/kg: complete penile detumescence was achieved in 96.3% of cases, with 85.2% of issues responding rapidly within 3 min after medication. This outcome was clearly superior to ephedrine application. Timely and effective treatment not only mitigated surgical interruptions but also significantly shortened operative duration.

Based on esketamine's pharmacological profile and further literatures review, we hypothesize that esketamine can suppress IPE through the following possible mechanisms. (I) Esketamine exerts potent inhibition on thalamocortical projection networks, selectively blocking the transmission of pain impulses, alleviating or eliminating pain perception. Concurrently, it activates the brainstem and limbic system, causing fuzzy consciousness and no response to environmental stimuli, known as "separation anesthesia" [23, 24]. Given that IPE is mainly caused by external stimuli, so esketamine can abolish the conscious response to external stimuli, disrupt the reflexogenic pathways driving erection initiation, thus inhibiting penile erection. (II) Catecholamines play a pivotal regulatory role in penile hemodynamics, with  $\alpha$ -adrenergic activation promoting detumescence via vasoconstriction [26]. Esketamine's sympathomimetic excitatory induces catecholamine release directly and inhibits norepinephrine reuptake, causing increased norepinephrine concentrations [27], which acts on the  $\alpha$ -adrenoceptors of the penile arterioles and corpus cavernosum smooth muscle, thus leaving the penis in a flaccid state. (III) Research has confirmed that NMDA receptors and nitric oxide are vital physiological regulatory factors of sexual behaviors and penile erection in the central nervous system. During sexual stimulation, excitatory amino acids bind to NMDA receptors in the hypothalamus and spinal cord leading to the activation of neuronal nitric oxide synthase (NOS), producing nitric oxide, a neurotransmitter that is synthesized locally in the penis nerve terminals, that causes cavernous relaxation and erection [16, 28]. Esketamine is a non-competitive NMDA receptor antagonist that may affect the NOS signaling pathway and regulate nitric oxide levels by restraining the functions of NMDA receptors, thereby suppressing IPE [29, 30]. Interestingly, experiments in vitro performed by Nestor et al. verified that all essential NMDA receptor subunits may exist in the isolated penile, prostate and other lower urogenital tract tissues in both rats and humans, and several NMDA receptor blockers such as ketamine could relax isolated penile corpus cavernosum, prostate and bladder tissues. So they speculated that a nitric oxide-independent systolic/diastolic cascade existed in these tissues and the relaxation effect may be caused by local NMDA receptormediated closure of calcium channels in smooth muscle and a reduction in the intracellular calcium concentration [31]. Thus, esketamine possesses dual anti-erectile effects through central suppression of psychogenic/ reflexogenic arousal and peripheral inhibition of NMDA receptor-mediated cavernosal contractility. Its unique polypharmacological profile, encompassing dissociative anesthesia, catecholaminergic potentiation, and NMDA receptor antagonism, works synergistically to combat IPE via both neural and vascular mechanisms. This multidimensional mechanism offers distinct advantages over ephedrine's predominant vasoconstrictive effects, potentially explaining its rapid efficacy and high clinical success rates observed in practice.

Esketamine exhibits intrinsic sympathomimetic properties—primarily through catecholamine release and norepinephrine reuptake inhibition-that theoretically elevate blood pressure and heart rate [27]. However, Clinical trial revealed that the hemodynamics were stable as the doses of esketamine were 0.25 and 0.5 mg/kg [32]. Our data showed that transient, self-limited cardiovascular fluctuations (hypertension/tachycardia) occurred in only 15-20% of cases following esketamine administration, a rate 4-fold lower than the 60–80% incidence with ephedrine-induced variations. Notably, these circulation fluctuations rapidly normalized to the pre-medication state without pharmacological intervention. This may be because of the low-dose application and the cardiovascular excitatory effects of esketamine have been offset by cardiovascular depression of propofol, sevoflurane and other general anesthetics. While, ephedrine - an  $\alpha/\beta$ adrenergic receptor agonist - causes marked increases in blood pressure and heart rate, limiting repeated or high-dose administration and compromising therapeutic efficacy. Additionally, esketamine manifested numerically faster resolution in younger patients, and this trend may stem from dose-limiting comorbidities (e.g., hypertension) in older adults that reduce medication responsiveness.

Esketamine, a non-barbiturate intravenous anesthetic, has raised concerns regarding its association with delayed recovery, postoperative agitation and other psychiatric manifestations. Nevertheless, these adverse reactions increase exhibit dose-dependent severity, remaining predominantly mild in clinical settings [33]. Evidence indicates that low-dose esketamine infrequently triggers these psychiatric symptoms, with only 10% of cases exhibiting such effects at higher dosages [25]. Low-dose esketamine has been confirmed to be safe in older and obese populations, and may even improve early cognitive dysfunction through neuroprotective and anti-inflammatory effects [34, 35]. This safety profile is further supported by the drug's favorable pharmacokinetics, characterized by rapid metabolism and clearance, which likely contribute to its transient clinical effects. Our findings demonstrated no significant association between esketamine administration and prolonged anesthetic recovery or persistent psychiatric sequelae. Additionally, postoperative dysphoria showed a disproportionate prevalence in endourological procedures compared to other surgeries. This phenomenon may be mechanistically linked to localized tissue trauma from urethral instrumentation and sustained mechanical irritation caused by indwelling catheters.

# Limitations

This study has several limitations that warrant consideration. First, the single-center retrospective observational design inherently restricts the generalizability of findings. Selection bias may arise from the exclusion of IPE cases with incomplete documentation or those occurring in non-urologic surgeries. The small sample size further weakens the external validity. So prospective randomized controlled trial studies larger sample capacity, multicenter validation should be performed to confirm these findings across diverse surgical populations and clinical settings. Second, while intravenous esketamine and ephedrine were the primary IPE treatments, concurrent adjustments to propofol infusion rates or sevoflurane concentrations-common in clinical practice-were inconsistently documented. These unmeasured confounders may have influenced penile hardness grading, complicating the precise evaluation of esketamine's standalone efficacy. Future trials should standardize anesthetic protocols and record the additional interventions in detail to isolate esketamine's therapeutic effects. Third, esketamine was used primarily guided by anesthesiologists' experiences and the patients' conditions, with variations in the initial dose, additional doses, redosing frequency, and maximum limits, leading to uncertainty regarding optimal dosing thresholds. To address this, we propose a standardized esketamine regimen (e.g., 0.4 mg/ kg initial bolus, each additional 0.2 mg/kg, maximum 1 mg/kg, appropriate reduction in elderly patients) for future prospective studies, with stratification by patient factors such as age and BMI. This approach would help clarify potential pharmacokinetic differences-for instance, reduced clearance in older adults or altered volume of distribution in obese patients-that may modulate therapeutic responses. Finally, the study's retrospective nature means incomplete data collection or reporting biases. The absence of a standardized IPE management protocol across cases likely introduced heterogeneity in outcome assessments. Further studies should incorporate validated methods and predefined criteria for IPE resolution to enhance data reliability.

#### Conclusions

In summary, IPE is a rare but problematic event in urological procedures, frequently leading to surgical delays or even cancellations, and aggressive management of this anomaly is crucial. The study provides preliminary evidence that intravenous esketamine may serve as an effective and timely intervention for IPE, exhibiting a favorable safety profile with minimal perioperative complications. These findings Despite the methodological limitations of this retrospective study, our findings provide valuable insights and references for handling IPE, positioning esketamine as an appealing therapeutic option for acute IPE management. Future prospective research with multicenter trials, stricter criteria, standardized protocols and detailed intervention analysis should be considered to enhance evidence-based strategies for optimizing IPE management in surgical practice.

#### Abbreviations

IPE	Intraoperative penile erection
BMI	Body mass index
ASA	American Society of Anesthesiologists
MAP	Mean artery pressure
NMDA	N-methyl-D-aspartate
NOS	Nitric oxide synthase

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Not applicable.

#### Author contributions

WJ-Y, L-Z designed the study and collected the data. RS-S performed data collation and analysis. WJ-Y and RS-S drafted the manuscript. JF-W, ZJ-C revised, and reviewed the manuscript. All authors read and approved the final manuscript.

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#### Data availability

No datasets were generated or analysed during the current study.

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Wuhan No. 1 Hospital (No. [2024]31). The informed consent was waived due to the retrospective nature of the study. Additionally, we did not intervene in the diagnosis or treatment of patients in this retrospective analysis.

#### **Consent for publication**

Not applicable.

#### **Competing interests**

The authors declare no competing interests.

# **Registry and the registration NO. of the study/trial** Not applicable.

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