Systematic Review and Meta-Analysis

Efficacy and safety of ciprofol versus propofol for induction of general anaesthesia or sedation: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Propofol has been used in medical practice as an anaesthetic drug for producing and sustaining general anaesthesia due to its advantages. However, it also has drawbacks, including injection-related discomfort. Recently, ciprofol has emerged as a promising anaesthetic drug that may overcome many drawbacks associated with propofol. In this systematic review and meta-analysis, we assess the efficacy and safety of ciprofol compared to propofol in different anaesthesia procedures. **Methods:** The study protocol was registered in the International Prospective Register of Systematic Reviews (ID: CRD42023458170). Central, PubMed, EMBASE, Scopus and WOS were searched for English literature until 26 February 2024. Meta-analysis was performed using RevMan. The risk of bias was assessed using the RoB 2.0 tool. Results were reported as risk ratios (RRs), mean differences (MDs) and 95% confidence intervals (CIs). **Results:** Nineteen randomised controlled trials were included in our analysis, with 2841 participants. There was no difference between ciprofol and propofol in the success rate of endoscopy (RR: 1.01, 95% CI: 0.99, 1.02; $P = 0.44$), while ciprofol showed a significant increase in the success rate of general anaesthesia/sedation (RR: 1.01, 95% CI: 1.00, 1.02; $P = 0.04$). Ciprofol showed significantly lower pain on injection (RR: 0.14, 95% CI: 0.09, 0.22; $P < 0.001$), lower adverse events (RR: 0.80, 95% CI: 0.69, 0.92; $P = 0.002$) and higher patient satisfaction (standardised mean difference (SMD): 0.36, 95% CI: 0.24, 0.48; $P < 0.001$). **Conclusion:** Ciprofol exhibited a comparable efficacy to propofol in inducing general anaesthesia and sedation with fewer adverse events, less pain on injection and higher patient satisfaction. These collective findings may suggest that ciprofol can be used as an alternative drug to ensure effective general anaesthesia/sedation induction in the future.

Keywords: Ciprofol, general anaesthesia, meta-analysis, pain, propofol, sedation, systematic review

INTRODUCTION

With the increasing complexity of diagnostic and therapeutic interventions involving many procedures, it is essential to carefully manage sedation and anaesthesia to ensure the procedure's smooth execution.[1] For decades, propofol has been used in medical practice as an anaesthetic agent to induce and maintain general anaesthesia (GA).[2] It

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likely functions as a potentiator for the inhibitory effects of the gamma-aminobutyric acid (GABA) neurotransmitter on GABA receptors, thereby maintaining the openness of chloride channels for an extended period, allowing hyperpolarisation to occur.[3] Propofol boasts several advantages, including rapid onset, antiemetic properties, and upper airway and bronchodilatory effects.[4,5] Nevertheless, it also carry drawbacks and limitations, such as injection-related pain, dose-dependent respiratory depression, haemodynamic instability and the absence of a counteractive agent.[6,7]

Ciprofol, a 2,6-disubstituted phenol analogue, shares several chemical and pharmacokinetic similarities with propofol, such as its rapid onset of action and excellent hepatic metabolism.[8] However, numerous studies have highlighted the advantages of ciprofol over propofol in various clinical aspects. These benefits include, but are not limited to, reducing the incidence of hypertriglyceridemia and alleviating injection-related pain.[8,9]

Multiple clinical trials were conducted to investigate the properties, safety and efficacy of ciprofol and compare its profile to that of propofol.[10–15] Many recent systematic reviews (SRs) have investigated ciprofol compared to propofol. However, our SR stands out for its comprehensive inclusion of the most published randomised controlled trials (RCTs), offering a robust comparative analysis against recent studies. In addition, our findings challenge prevailing notions by revealing a significant association between ciprofol and increased systolic blood pressure (SBP) and diastolic blood pressure (DBP), in contrast to the prevailing belief that it does not affect these vital measures.[16]

The objective of this SR of published RCTs was to evaluate the anaesthetic and sedative efficacy and safety of ciprofol compared to propofol in adult patients undergoing elective surgery, endoscopy and bronchoscopy. We investigated the effectiveness of sedation during endoscopy, the success rate of GA induction, and the impact of both drugs on various vital signs and patient and provider satisfaction.

METHODOLOGY

Protocol registration

We established this SR and meta-analysis with the standards of the Cochrane Handbook for Systematic Reviews of Interventions 2019[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020.[18] The protocol was registered on the International Prospective Register of Systematic Reviews (ID: CRD42023458170).

Search strategy

A comprehensive literature search was initiated through online libraries (Central, Web of Science, Scopus, Embase and PubMed) until June 2023, with no timeline restrictions. Then, we updated the search results until 26 February 2024. Ciprofol was additionally marketed as 'Cipepofol' and 'HSK3486', while '2,6-Diisopropylphenol', '2,6-Bis (1-methylethyl) phenol', 'Disoprofol', 'Diprivan', 'Disoprivan', 'Fresofol', 'ICI-35868', 'Ivofol', 'Recofol' and 'Aquafol' were all synonyms for propofol. An extensive search strategy was forged using these terms to include all available English-written articles from online libraries [Table S1].

Eligibility criteria

We adopted the PICOS framework (population, interventions, comparators, outcomes, and study design) to determine eligible studies, as follows: population (P): adult patients undergoing endoscopy or elective surgery under GA or sedation; intervention (I): ciprofol (HSK3486); control (C): propofol; outcome (O): 1) primary end points: success rate of GA induction [the proportion of patients with successful GA induction, which was defined according to the following criteria: (i) Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale ≤1 after administration of a study drug (up to two top-up doses given) and (ii) did not require an alternative sedative] and success rate of endoscopy (the proportion of patients requiring ≤5 top-up doses of ciprofol or propofol within any 15-min time period to completion of the surgical procedure. 2) Secondary end points: patient and anaesthesiologist satisfaction, adverse events, pain on injection (referred to the pain reported verbally by patients after the first injection), time for induction (time from the start of study drug administration to MOAA/S ≤1), eyelash reflex disappearance (time until complete loss of the eyelash reflex), insertion (for endoscope such as the gastroscope or colonoscope), awakening (time from the last drug administration to an MOAA/S score of 5 for three consecutive measurements), and discharge (time from the last drug administration to reach modified Aldrete score ≥9), and vitals [bispectral index (BIS), mean arterial pressure (MAP), SBP, DBP, heart rate (HR), peripheral capillary oxygen saturation (SpO_2)]; study design (S): RCTs.

We excluded non-randomised and uncontrolled trials, protocols, conference abstracts, reviews, animal studies, observational studies, and case reports.

Study selection

Independently, four reviewers screened titles and abstracts of the included studies; after removing duplicates using Covidence online software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), they proceeded with full-text screening, depending on the inclusion and exclusion criteria, to reach the final included studies. After reviewing the full text, any conflicts were resolved by discussing them with supervisors.

Data extraction

The four reviewers independently used a predefined spreadsheet to extract the following data: summary characteristics (study design, country, total participants, type of procedure/endoscopy, population, dose of ciprofol and propofol, other drugs added during the procedure, main inclusion criteria and primary outcome); baseline characteristics [number of participants in each group, duration of procedure, age, gender (male), height, weight, body mass index, American Society of Anesthesiologists (ASA) physical status, and vitals (SBP, DBP, MAP, HR and SpO_2)]; efficacy data [success rate of endoscopy, success rate of GA induction, time for induction (min), eyelash reflex disappearance (sec), insertion (min), awakening (min) and discharge (min)]; patient and anaesthesiologist satisfaction; number of patients who required top-up doses; pain on injection, adverse events and serious adverse events (SAEs); vitals at 2 min after drug administration and T3 (time point 3, when the endoscope passes through the mouth) - BIS score, SBP, DBP, MAP, HR and SpO_2.

Quality assessment

The Cochrane RoB 2.0 tool (Cochrane tool for assessing the risk of bias in randomised trials; Cochrane Collaboration, London, UK)[19] was used to assess the risk of bias in the included RCTs. The four independent reviewers used the full text to assess the quality of the included trials in five domains: randomisation process, deviation of intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. After reviewing the full text, conflicts were solved by discussing them with supervisors.

Data analysis

This meta-analysis was handled using Review Manager software (RevMan v5.4; Cochrane Collaboration, London, UK).[20] A fixed-effects model was applied through pool analysis, as the risk ratio (RR) was delivered for dichotomous outcomes with a 95% confidence interval (CI). Continuous outcomes were represented with a mean difference (MD) of 95% CI. A random-effects model was applied in cases of significant heterogeneity, detected by the Chi-square test with an alpha level below 0.1. An I^2 test surpassing 50% indicated significant heterogeneity; in that case, sensitivity analysis was applied repetitively by excluding one study at a time until heterogeneity's origin was identified.

Certainty assessment

GRADEpro GDT software [GRADEpro Guideline Development Tool (Software); McMaster University and Evidence Prime, Hamilton, Canada] was used to assess the certainty of evidence of specific outcomes under five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Finally, JASP (version 0.16.3)[21] was used to assess the publication bias by performing Egger's test[22] and visual inspection of the funnel plot.

RESULTS

Search results and study selection

A total of 220 studies were imported while searching databases. After removing 100 duplicates, 120 studies underwent title and abstract screening. The resulting 96 full-text articles were screened for eligibility, leaving 14 included RCTs after excluding 82 irrelevant articles. Finally, five RCTs were included manually by updating search results, leaving 19 included RCTs for qualitative and quantitative analyses [Figure 1].

Characteristics of included studies

We included 19 RCTs that met our inclusion criteria with 2841 patients (1517 in the ciprofol group and 1324 in the propofol group). Nine RCTs[2,9,13,23–28] were multi-centre studies, and 10[10–12,14,15,29–33] were single-centre studies. All trials were conducted in China except for the study of Gan *et al*.,[23] which was conducted in the USA. Five RCTs focused on elective surgery, seven on endoscopy, three on bronchoscopy, two on gynaecology and three on other aspects. The summary and baseline characteristics are presented in Tables 1 and 2, respectively.

Risk of bias and quality of evidence

Twelve RCTs[2,9–15,23,24,26,31] showed an overall low risk of bias, while five RCTs[25,28,29,32,33] showed an overall

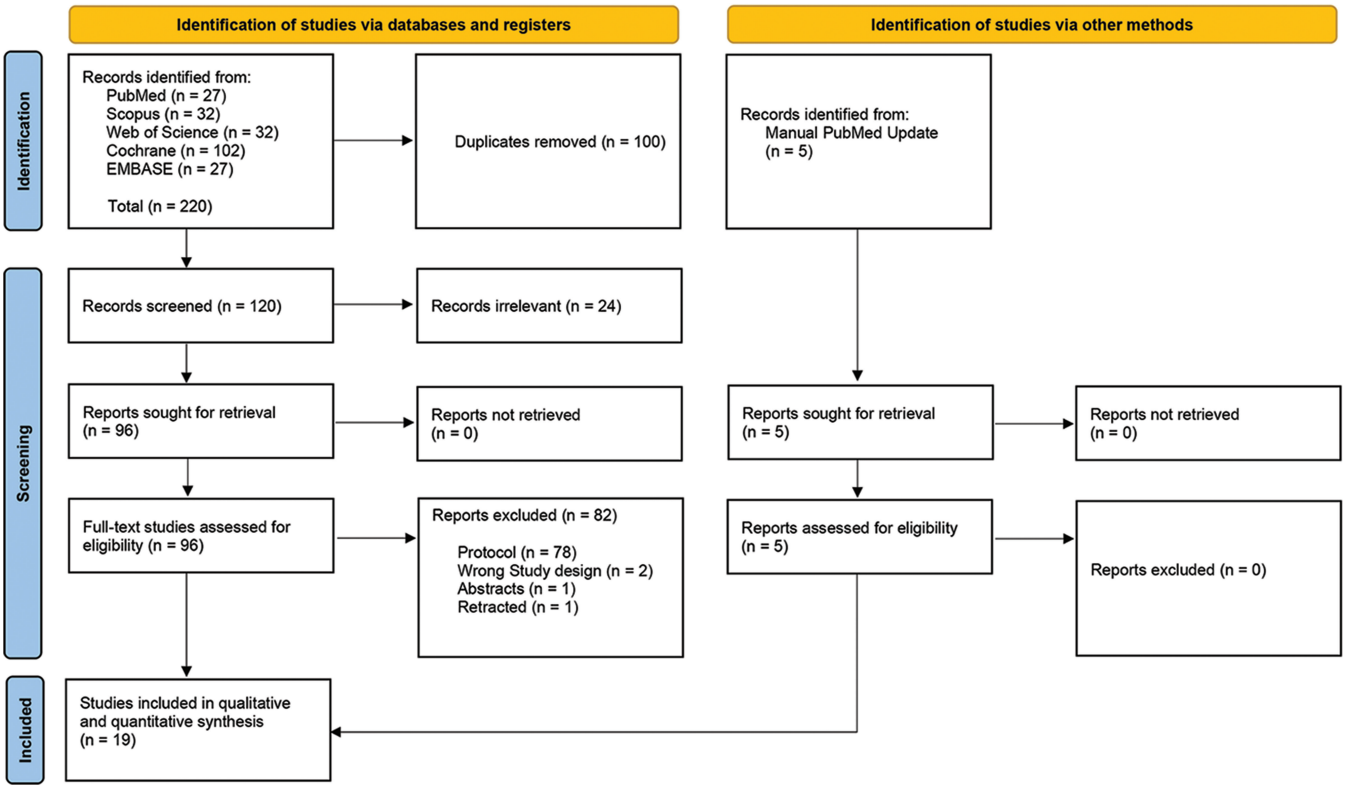

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

high risk of bias. Furthermore, only two RCTs[27,30] showed some concerns overall. Detailed risk of bias is illustrated in Figure S1. The quality of evidence is detailed in a Grading of Recommendations, Assessment, Development and Evaluation evidence profile [Table 3].

Efficacy outcomes

Primary outcomes

Success rate of endoscopy and GA/sedation induction success rate: There was no significant difference between ciprofol and propofol in the success rate of endoscopy (RR: 1.01, 95% CI: 0.99, 1.02; $P = 0.44$) (high-quality evidence) [Figure 2a, Table 3], while ciprofol showed a significant increase in the success rate of GA/sedation induction compared to propofol (RR: 1.01, 95% CI: 1.00, 1.02; $P = 0.04$) (high-quality evidence) [Figure 2b, Table 3]. Pooled studies were homogenous in endoscopy success rate ($P = 0.92$, $I^2 = 0\%$) and the success rate of GA/sedation induction ($P = 0.08$, $I^2 = 37\%$).

Subgroup analysis was conducted for GA/sedation induction success rate based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.57$) [Figure 2c].

Secondary outcomes

Induction, eyelash reflex disappearance, insertion, awakening and discharge times: There was no significant difference between ciprofol and propofol in induction time (min) (MD: 0.10, 95% CI: −0.04, 0.23; $P = 0.16$) (low-quality evidence) [Figure 2d, Table 3], time to eyelash reflex disappearance (sec) (MD: −1.87, 95% CI: −9.26, 5.52; $P = 0.62$) [Figure 3a], insertion time (min) (MD: 0.44, 95% CI: −0.07, 0.96; $P = 0.09$) [Figure 3b] and discharge time (min) (MD: 1.08, 95% CI: −0.08, 2.25; $P = 0.07$) [Figure 3c]. However, ciprofol showed a significant increase in awakening time (min) versus propofol (MD: 1.04, 95% CI: 0.45, 1.62; $P < 0.001$) (very-low-quality evidence) [Figure 3d, Table 3]. Pooled studies were heterogenous in induction time ($P < 0.001$, $I^2 = 97\%$), time to eyelash reflex disappearance ($P < 0.001$, $I^2 = 99\%$), insertion time ($P < 0.001$, $I^2 = 98\%$), awakening time ($P < 0.001$, $I^2 = 84\%$) and discharge time ($P < 0.001$, $I^2 = 93\%$).

Subgroup analysis was conducted for induction time, awakening time and eyelash reflex disappearance time based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.58$, $P = 0.25$ and $P = 0.66$, respectively) [Figures 3e, 4a, b].

Table 1: Summary of characteristics of the included RCTs

Study ID	Study design	Country	Total participants	Type of procedure/ endoscopy	Type of anaesthesia	Population
Zhen *et al*. 2022[11]	Prospective, double-blind, single-centre, randomised clinical trial	China	120	Elective gynaecological surgery	Induction of GA	Females undergoing gynaecological surgery
Chen *et al*. 2022[29]	Randomised clinical trial	China	96	Gastroenteroscopy	Sedation	Males and females undergoing gastroenteroscopy
Chen *et al*. 2023[30]	Prospective, single-blind RCT	China	75	Gastrointestinal endoscopy	Sedation	Males and females who underwent elective painless gastrointestinal endoscopy
Gan *et al*. 2023[23]	Multi-centre, double-blind, Phase 3 RCT	USA	255	Elective surgery with endotracheal intubation	Induction of GA	Males and females undergoing elective surgery with endotracheal intubation
Lan *et al*. 2023[10]	Prospective randomised clinical trial	China	149	Hysteroscopy	Sedation	Females undergoing hysteroscopic examination
Li *et al*. 2022[9]	A multi-centre, non-inferiority, randomised controlled, Phase 3 clinical trial	China	289	Gastroscopy and colonoscopy	Sedation	Males and females undergoing gastroscopy and colonoscopy
Liang *et al*. 2023[24]	A multi-centre, single-blind, randomised, parallel-group, Phase 3 clinical trial	China	128	Elective surgery	Induction of GA	Males and females undergoing elective surgery
Liao *et al*. 2023[31]	Double-blind, single-centre, parallel RCT	China	368	Gastrointestinal endoscopy	Sedation	Patients who were scheduled for painless gastrointestinal endoscopy
Liu *et al*. 2022[25]	Multi-centre, open-label, randomised, Phase 2 trial conducted	China	39	ICU patients undergoing intubation and MV	Sedation	ICU patients
Liu *et al*. 2023[26]	A multi-centre, single-blind, Phase 3 RCT	China	135	MV	Sedation	ICU patients undergoing MV
Luo *et al*. 2022[27]	Multi-centre, double-blind, randomised, propofol-controlled, non-inferiority, prospective Phase 3 trial	China	267	FB	Sedation	Male and female patients receive diagnostic and/or therapeutic FB LMA-assisted
Man *et al*. 2023[12]	Randomised, double-blind, controlled study	China	128	Gynaecological ambulatory surgery (uteroscope, conisation of cervix)	Induction of GA	Patients who were about to undergo gynaecological ambulatory surgery
Qin *et al*. 2022[32]	Prospective, randomised, single-blind study	China	105	Kidney transplant	Induction of GA	Patients who had a kidney transplant under GA with tracheal intubation
Teng *et al*. 2021 (II b)[2]	A multi-centre, randomised, double-blind and propofol-controlled study	China	62	Colonoscopy	Sedation	Patients scheduled to undergo routine colonoscopy procedures
Wang *et al*. 2022[13]	A multi-centre, randomised, propofol-controlled, double-blind trial	China	176	Elective surgery	Induction of GA	Patients scheduled for elective surgery require tracheal intubation
Wu *et al*. 2022[14]	Prospective, randomised, double-blind, non-inferiority trial	China	92	FB	Sedation	Patients who underwent FB with sedation and without endotracheal intubation or MV
Zeng *et al*. 2022[28]	Multi-centre, randomised, open-label, propofol-controlled Phase 2 trial	China	40	Elective surgery	Induction of GA	Patients undergoing elective surgery, excluding emergency, cardiothoracic, cerebral or endoscopic sinus cases
Zhang *et al*. 2023[33]	Single-centre, prospective, double-blind RCT	China	202	Bidirectional endoscopy (oesophago gastroduodenoscopy followed by colonoscopy), including polypectomy	Sedation	Patients scheduled to undergo diagnostic endoscopy (oesophago gastroduodenoscopy followed by colonoscopy), including polypectomy
Zhong *et al*. 2023[15]	A prospective, randomised, double-blind, parallel-group clinical trial	China	138	ESD, ERCP or FB	Sedation	Patients scheduled for ESD, ERCP or FB

Contd...

Table 1: Contd...

Study ID	Dose		Other drugs added during the procedure	Main inclusion criteria	Primary outcome
	Ciprofol	Propofol			
Zhen *et al*. 2022[11]	0.4 mg/kg	2 mg/kg	Midazolam (0.03 mg/kg), sufentanil (0.3 μg/kg), rocuronium (0.6 mg/kg), sevoflurane in oxygen 50%	Adult females between the ages of 18 and 60 (ASA physical status: I or II) who were scheduled to undergo elective gynaecological surgery under general anaesthesia	Success rate of induction of general anaesthesia
Chen *et al*. 2022[29]	0.4 mg/kg	1.5-2.0 mg/kg	2% lidocaine 2– 3 ml was added to propofol, dopamine 1–2 mg was injected IV when the blood pressure dropped by more than 30% and atropine 0.5 mg was injected IV when the HR was <60 beats/min	The vital signs were stable, and the patients were between 18 and 80. For various reasons, gastroenteroscopy or treatment was performed for ASA physical status: I–III. The patients included in the study were not allergic to anaesthetics, and there were no contraindications to anaesthesia	Comparison of vitals and satisfaction between two arms
Chen *et al*. 2023[30]	0.4 mg/kg	1.5 mg/kg	All groups received an IV injection of fentanyl at a dose of 2 μg/kg. If the HR was <50 beats/min, IV atropine 0.5 mg was administered. If the SBP decreased more than 30% compared to the baseline value, IV ephedrine 5 mg was administered.	Patients who underwent elective painless gastrointestinal endoscopy and were aged 18–80 years, with a BMI of 18–28 kg/m^2 and an ASA physical status: I–III	Time for disappearance of the eyelash reflex
Gan *et al*. 2023[23]	0.4 mg/kg	2 mg/kg	All participants received IV fentanyl 1 μg/kg; IV rocuronium bromide 0.6 mg/kg was administered as a neuromuscular blockade.	Participants were included if they were ≥18 years of age, had an ASA physical status of I–IV and had a BMI ≥18 kg/m^2 with no upper limit. Female participants were eligible if they had a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1)	Successful anaesthesia induction
Lan *et al*. 2023[10]	0.4 mg/kg	2 mg/kg	Sufentanil citrate 0.1 μg/kg, ephedrine or atropine if hypotension or bradycardia	Patients aged 18–70 years, ASA physical status I or II and body mass index of 18–30 kg/m^2	Success rate of hysteroscopy
Li *et al*. 2022[9]	0.4 mg/kg	1.5 mg/kg	300–500 ml of sterile 0.9% sodium chloride solution, 50 μg fentanyl, atropine for bradycardia, ephedrine to treat hypotension	Adult patients (18–65 years) with an ASA physical status: I–II who were due to undergo elective gastroscopy or colonoscopy were eligible.	Success rate of colonoscopy
Liang *et al*. 2023[24]	0.4 mg/kg	2 mg/kg	Midazolam 0.04 mg/kg, sufentanil 0.3 mg/kg, rocuronium bromide 0.6 mg/kg, remifentanil 0.1–0.3 mg/kg/min, and sugammadex sodium injection (2 mg/kg) were administered over 10 sec	Patients who underwent general anaesthesia, ASA physical status: I–II; aged >18 and <65 years; scheduled for more than 1-h nonemergency, no cardiothoracic, and nonbrain elective surgery; and who required tracheal intubation	Success rate of anaesthetic maintenance, the incidence of intraoperative awareness
Liao *et al*. 2023[31]	0.4 mg/kg	2 mg/kg	Sufentanil	ASA physical status: I or II patients aged between 18 and 65 were scheduled for painless gastroscopy.	Swallowing function and occurrence of vocal cord adduction reflex
Liu *et al*. 2022[25]	0.1–0.2 mg/kg	0.5–1.0 mg/kg	Remifentanil loading dose of 0.5–1.0 g/kg (if required)	ICU patients aged 18–80 years, who were expected to require sedation (RASS scores range from -2 to+1) for 6–24 h due to endotracheal intubation and MV, were enroled	Average time to reach sedation compliance
Liu *et al*. 2023[26]	0.1 mg/kg	0.5 mg/kg	Remifentanil	ICU patients 18–80 years old with endotracheal intubation and undergoing MV, who were expected to require sedation for 6–24 h	Sedation success rate

Contd...

Table 1: Contd...

Study ID	Dose		Other drugs added during the procedure	Main inclusion criteria	Primary outcome
	Ciprofol	Propofol			
Luo *et al*. 2022[27]	0.4 mg/kg	2.0 mg/kg	Inhaled 2% lidocaine (10 ml) delivered by atomisation within 1 h before the bolus dose. If sedation was still insufficient, sufentanil (0.05–0.1 μg/kg) was given up to a maximum dose of 0.4 μg/kg. Patients aged <65 years were given 0.2 μg/kg sufentanil IV before procedures	Patients aged between 18 and 80, male or female, with ASA physical status: I–III, were to receive diagnostic and/or therapeutic FB LMA-assisted	Success rate of FB
Man *et al*. 2023[12]	0.5 mg/kg	2 mg/kg	Flurbiprofen axetil (50 mg), dexamethasone (5 mg) (pre), 0.2 mg/kg mivacurium chloride, 20 μg/kg alfentanil, ephedrine (6 mg)	Patients (18–64 years) with an ASA physical status: I or II, BMI between 18 and 28 kg/m^2, who were about to undergo gynaecological ambulatory surgery	Overall incidence of adverse events
Qin *et al*. 2022[32]	0.4 mg/kg	2.0 mg/kg	Sufentanil 0.4–0.5 μg/kg, cisatracurium 0.2 mg/kg, diuretics (furosemide and mannitol), hormones and immunosuppressants were given routinely; dopamine (1–10 μg/kg/min)	Patients who had a kidney transplant under general anaesthesia with tracheal intubation, aged 18–65 years, with a BMI of 18–30 kg/m^2 and an ASA physical status: of III–IV	Success rate of sedation
Teng *et al*. 2021 (II b)[2]	0.4 mg/kg	2.0 mg/kg	Fentanyl before	Aged 18–70 years, ASA classification I, II or III, with a BMI of 18–30 kg/m^2, respiratory rate of 10–24 breaths/min, HR 50–100 bpm, SBP ≥90 mmHg, DBP ≥60 mmHg and a SpO_2 value >95% when inhaling with room air. Patients were scheduled for colonoscopy	Success rate of colonoscopy
Wang *et al*. 2022[13]	0.4 mg/kg	2 mg/kg	0.04 mg/kg midazolam, 0.3 μg/kg sufentanil, 0.6 mg/kg rocuronium	Patients aged 18–64 years with a BMI between 18 and 30 kg/m^2, ASA physical status of I or II and scheduled to undergo elective surgery under general anaesthesia	Percentage of patients with successful general anaesthesia induction
Wu *et al*. 2022[14]	0.3 mg/kg	1.2 mg/kg	50 μg of fentanyl 2 min before, during maintenance: 0.05–0.2 μg/kg/min of remifentanil, midazolam was the only permitted alternative sedative in this trial, 25 μg of fentanyl was permitted once (maximum, 150 μg) until adequate analgesia could be achieved	FB with sedation and without endotracheal intubation or MV, patient age 45–65 years, ASA physical status: I–II, and SpO_2 >93% under air conditions	Success rate of FB
Zeng *et al*. 2022[28]	0.4 mg/kg	2.0 mg/kg	Pre-anaesthesia drugs midazolam (0.04 mg/kg, 15 s), sufentanil (0.3 μg/kg, 30 s), remifentanil	Patients aged 18–65 years with an ASA rating of Class I–III, who required endotracheal intubation under general anaesthesia, with an expected operation duration of 1–6 h and a blood loss of ≤1000 ml were included	Successful anaesthesia maintenance
Zhang *et al*. 2023[33]	0.3 mg/kg	1.2 mg/kg	Alfentanil	Inpatients aged 18–65 were enroled and were scheduled to undergo diagnostic endoscopy (oesophagogastroduodenoscopy followed by colonoscopy), including polypectomy	Rate of cardiopulmonary adverse events
Zhong *et al*. 2023[15]	0.4 mg/kg	2.0 mg/kg	For ERCP 0.2 mg/kg esketamine before induction, for the FB remifentanil 0.5–1.0 ng/ml., for the FB 1% lidocaine (5–7 mg/kg)	Patients 18 years old or older and scheduled for ESD, ERCP or FB were eligible for the study	Success rate of sedation or anaesthesia for the procedures in non-operating room settings

ASA=American Society of Anesthesiologists, BMI=body mass index, DBP=diastolic blood pressure, ERCP=endoscopic retrograde cholangiopancreatography, ESD=endoscopic submucosal dissection, FB=fibreoptic bronchoscopy, HR=heart rate, ICU=intensive care unit, LMA=laryngeal mask airway, MV=mechanical ventilation, RASS=Richmond Agitation and Sedation Scale, RCT=randomised controlled trial, SBP=systolic blood pressure, SpO_2=saturation of peripheral oxygen, IV= intravenous

Table 2: Baseline characteristics of the participants

Study ID	Number of participants in each group		Duration of procedure (min), Mean (SD)		Age (years), Mean (SD)		Gender (male), *n* (%)		Height (cm), Mean (SD)		Weight (kg), Mean (SD)	
	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol
Zhen *et al*. 2022[11]	60	60	55.2 (20.5)	51.4 (23.1)	33.9 (9.1)	33.8 (9.6)	0	0	159.3 (3.8)	158.5 (5.2)	56.9 (7.9)	54.0 (9.1)
Chen *et al*. 2022[29]	47	49	6.11 (2.52)	4.71 (2.09)	41.22 (11.63)	43.20 (12.29)	22 (46.8)	17 (34.69)	165.33 (7.75)	160.26 (8.47)	60.25 (11.22)	60.74 (12.46)
Chen *et al*. 2023[30]	31	44	19.77 (9.28)	15.98 (6.63)	47.45 (11.90)	43.55 (16.19)	11 (35.4)	18 (40.9)	NA	NA	NA	NA
Gan *et al*. 2023[23]	168	83	NA	NA	48.9 (13.89)	50.9 (14.30)	49 (29.2)	26 (31.3)	NA	NA	83.85 (19.72)	81.87 (20.16)
Lan *et al*. 2023[10]	75	74	20.8 (8.1)	21.4 (10.9)	41.7 (11.5)	43.7 (11.1)	0	0	158.3 (4.0)	159.3 (4.3)	57.6 (6.9)	59.8 (7.6)
Li *et al*. 2022[9]	144	145	N/A	N/A	43.8 (11.8)	44.1 (11.3)	55 (38.2)	63 (43.4)	161.5 (8.2)	163.1 (8.4)	60.0 (9.6)	61.5 (9.7)
Liang *et al*. 2023[24]	86	42	94.6 (39.2)	93.6 (35.8)	38.5 (10.1)	40.5 (10.1)	23 (26.7)	10 (23.8)	161.6 (8.0)	161.4 (8.5)	60.0 (11.1)	59.3 (8.8)
Liao *et al*. 2023[31]	185	183	10.62 (5.95)	10.21 (5.77)	44.98 (11.74)	45.35 (11.12)	87 (47)	77 (42.1)	N/A	N/A	N/A	N/A
Liu *et al*. 2022[25]	26	13	N/A	N/A	50.5 (13.38)	52.5 (13.15)	11 (42.3)	8 (61.5)	161.5 (8.84)	164.75 (7.47)	61 (9.84)	64.5 (10.76)
Liu *et al*. 2023[26]	88	45	NA	NA	56.7 (12.7)	52.2 (12.9)	58 (65.9)	26 (57.8)	N/A	N/A	N/A	N/A
Luo *et al*. 2022[27]	134	133	19 (11.6)	19.2 (11.9)	46.60 (15.31)	46.90 (13.98)	62 (46.3)	73 (54.9)	161 (8)	163 (8)	60.60 (9.47)	61.13 (9.18)
Man *et al*. 2023[12]	64	64	N/A	N/A	42.2 (9.46)	44.1 (9.4)	0	0	160.6 (4.4)	160.2 (4.9)	58.7 (6.1)	59.8 (6.9)
Qin *et al*. 2022[32]	52	53	175.88 (42.22)	165.49 (34.27)	39.00 (10.10)	41.25 (10.63)	18 (34.6)	18 (34.0)	N/A	N/A	N/A	N/A
Teng *et al*. 2021 (II b)[2]	31	31	9.6 (6.3)	7.1 (2.4)	46.2 (13.0)	48.4 (13.7)	12 (38.7)	16 (51.6)	160 (10)	160 (10)	59.7 (10.2)	62.5 (13.6)
Wang *et al*. 2022[13]	88	88	N/A	N/A	38.5 (12.1)	41.1 (11.1)	32 (36.36)	31 (35.23)	163.0 (8.5)	162.1 (8.1)	62.2 (11.1)	61.4 (10.6)
Wu *et al*. 2022[14]	46	46	17.98 (5.57)	18.09 (6.20)	58.02 (5.47)	57.48 (5.28)	26 (56.52)	24 (52.17)	167.15 (5.75)	165.89 (5.53)	67.87 (6.91)	67.39 (6.71)
Zeng *et al*. 2022[28]	30	10	105.3 (62.6)	76.7 (36.1)	42.5 (10.3)	46.4 (11.2)	11 (36.7)	3 (30.0)	163.3 (9.1)	161.7 (7.7)	63.3 (11.5)	62.2 (13.4)
Zhang *et al*. 2023[33]	93	92	13.96 (3.0)	14.06 (2.5)	54.0 (11.1)	51.6 (11.1)	52 (56)	52 (57)	167 (7.5)	167 (8.4)	66 (12)	65 (11)
Zhong *et al*. 2023[15]	69	69	32.8 (17.2)	31.1 (20.1)	57.6 (13.3)	56.9 (13.1)	33 (47.8)	41 (59.4)	160 (10)	170 (10)	61.5 (9.8)	61.5 (10.5)

Study ID	BMI (in kg/m²), Mean (SD)		ASA status, *n* (%)							
			ASA 1		ASA 2		ASA 3		ASA 4	
	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol
Zhen *et al*. 2022[11]	22.2 (3.2)	21.4 (2.8)	32 (53.3)	34 (56.7)	28 (46.7)	26 (43.3)	N/A	N/A	N/A	N/A
Chen *et al*. 2022[29]	25.22 (10.12)	23.46 (3.43)	45 (95.7)	43 (87.8)	4 (8.5)	6 (12.2)	N/A	N/A	N/A	N/A
Chen *et al*. 2023[30]	22.99 (3.01)	22.16 (3.06)	14 (45.16)	19 (43.18)	12 (38.7)	19 (43.18)	5 (16.13)	6 (13.63)	0	0
Gan *et al*. 2023[23]	29.89 (5.81)	29.25 (6.23)	70 (41.7)	34 (41.0)	86 (51.2)	44 (53.0)	12 (7.1)	5 (6.0)	0	0
Lan *et al*. 2023[10]	23.0 (2.6)	23.6 (2.8)	43 (57.3)	36 (48.6)	32 (42.7)	38 (51.4)	N/A	N/A	N/A	N/A
Li *et al*. 2022[9]	23.2 (2.5)	23.4 (2.6)	115 (79.9)	118 (81.4)	29 (20.1)	27 (18.6)	N/A	N/A	N/A	N/A
Liang *et al*. 2023[24]	23.3 (2.8)	23.3 (3.0)	48 (55.8)	22 (52.4)	38 (44.2)	20 (47.6)	N/A	N/A	N/A	N/A
Liao *et al*. 2023[31]	23.07 (2.28)	23.13 (2.23)	79 (42.7)	62 (33.9)	106 (57.3)	121 (66.1)	0	0	0	0
Liu *et al*. 2022[25]	23.4 (2.35)	23 (3.23)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liu *et al*. 2023[26]	23.6 (3.2)	23.8 (3.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Luo *et al*. 2022[27]	23.20 (2.64)	22.92 (2.60)	63 (47.0)	50 (37.6)	68 (50.7)	82 (61.7)	3 (2.2)	1 (0.8)	N/A	N/A
Man *et al*. 2023[12]	22.8 (2.2)	23.3 (2.6)	18 (28.1)	14 (21.9)	46 (71.9)	50 (78.1)	N/A	N/A	N/A	N/A
Qin *et al*. 2022[32]	23.38 (3.33)	22.63 (2.38)	N/A	N/A	N/A	N/A	42 (80.8)	44 (83.0)	10 (19.2)	9 (17.0)
Teng *et al*. 2021 (II b)[2]	N/A	N/A	25 (80.6)	25 (80.6)	6 (19.4)	6 (19.4)	N/A	N/A	N/A	N/A
Wang *et al*. 2022[13]	23.3 (2.9)	23.3 (3.1)	51 (57.95)	48 (54.55)	37 (42.05)	40 (45.45)	N/A	N/A	N/A	N/A
Wu *et al*. 2022[14]	24.26 (1.75)	24.49 (2.09)	10 (21.74)	8 (17.39)	36 (78.26)	38 (82.61)	N/A	N/A	N/A	N/A
Zeng *et al*. 2022[28]	23.7 (3.0)	23.6 (3.6)	16 (53.3)	4 (40.0)	14 (46.7)	6 (60.0)	N/A	N/A	N/A	N/A
Zhang *et al*. 2023[33]	23.4 (3.3)	23.3 (3.2)	75 (81)	69 (75)	18 (19)	23 (25)	0	0	0	0
Zhong *et al*. 2023[15]	22.6 (2.5)	22.2 (3.2)	10 (14.5)	14 (20.3)	53 (76.8)	49 (71.0)	6 (8.7)	6 (8.7)	N/A	N/A

Contd...

Table 2: Contd...

Study ID	Vitals, Mean (SD)									
	SBP		DBP		MAP		HR		SPO_2	
	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol	Ciprofol	Propofol
Zhen *et al*. 2022[11]	121 (13.2)	119.7 (13.9)	76.7 (9.2)	75.8 (8.7)	90.2 (11)	89.2 (11.1)	77.2 (12.9)	79.4 (14.6)	N/A	N/A
Chen *et al*. 2022[29]	127.3 (29.33)	135.17 (17.3)	87.32 (10.22)	87.16 (11.18)	99.22 (10.25)	100.53 (11.92)	81.33 (11.25)	82.69 (15.56)	97.63 (3.34)	99.53 (0.84)
Chen *et al*. 2023[30]	128.9 (18.48)	132 (17.88)	73.87 (10.81)	74.84 (10.44)	NA	NA	77.84 (11.06)	75.86 (9.81)	0.99 (0.01)	0.99 (0.01)
Gan *et al*. 2023[23]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lan *et al*. 2023[10]	127.0 (17.7)	128.5 (21.5)	78.3 (9.1)	77.7 (12.7)	94.5 (11.1)	94.6 (14.8)	77.2 (10.5)	76.8 (13.4)	N/A	N/A
Li *et al*. 2022[9]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liang *et al*. 2023[24]	119.9 (14.8)	116.66 (12.77)	75.2 (8.68)	73.5 (8.18)	87.5 (10.5)	84.7 (9.8)	75.90 (11.9)	74.4 (12.1)	99.8 (0.45)	99.8 (0.5)
Liao *et al*. 2023[31]	125.8 (15.3)	127.62 (16.32)	80.23 (8.52)	77.95 (12.78)	N/A	N/A	79.9 (8.06)	80.93 (9.92)	98.98 (0.99)	98.98 (0.99)
Liu *et al*. 2022[25]	129.8 (16.35)	135.25 (22)	69.66 (10.9)	70.6 (12.3)	88.6 (11.3)	93.13 (16.9)	81.95 (16.6)	77.89 (19.9)	99.5 (1.1)	99.62 (0.65)
Liu *et al*. 2023[26]	128.55 (20.93)	126.68 (19.9)	70.11 (13.19)	70.27 (12.87)	89.13 (13.7)	89.35 (12.61)	83.35 (16.6)	82.39 (18.83)	98.98 (1.71)	99.27 (1.31)
Luo *et al*. 2022[27]	116 (14)	115.6 (12.7)	74.7 (9.9)	75.3 (7.9)	86.4 (11.6)	86 (10.8)	69.7 (1.3)	68.9 (8.8)	97.7 (1.42)	97.9 (1.53)
Man *et al*. 2023[12]	129.0 (14.6)	132.2 (17.8)	N/A	N/A	N/A	N/A	81.4 (15.1)	77.2 (11.8)	N/A	N/A
Qin *et al*. 2022[32]	N/A	N/A	N/A	N/A	122 (18.19)	123 (15.29)	97 (16.57)	96 (16.57)	N/A	N/A
Teng *et al*. 2021 (II b)[2]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wang *et al*. 2022[13]	121.8 (17.5)	122.2 (16.2)	75.3 (10.7)	75.6 (10.2)	88.4 (12.5)	89.3 (12.3)	72.1 (10.2)	70.8 (10.1)	N/A	N/A
Wu *et al*. 2022[14]	141 (8.81)	142 (10.06)	81 (4.84)	80 (3.06)	100.62 (3.84)	100.62 (5.14)	78 (4.66)	79 (4.91)	95.66 (1.09)	95.56 (1.27)
Zeng *et al*. 2022[28]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zhang *et al*. 2023[33]	127.7 (16.4)	131.0 (19.9)	79.26 (11.65)	80.54 (11.65)	95.5 (12.0)	97.4 (12.9)	66.6 (10.9)	66.3 (12.9)	97.4 (2.4)	97.6 (2.0)
Zhong *et al*. 2023[15]	137.73 (7.72)	136.98 (7.78)	N/A	N/A	N/A	N/A	81.47 (4.6)	78.71 (4.47)	99.46 (5.59)	99.74 (5.59)

ASA=American Society of Anesthesiologists, BMI=body mass index, DBP=diastolic blood pressure, HR=heart rate, MAP=mean arterial pressure, N/A=not available, SBP=systolic blood pressure, SD=standard deviation, SpO_2=saturation of peripheral oxygen. SBP, DBP and MAP in mmHg; HR in beats per minute and SpO_2 in %

Table 3: Grading of Recommendations, Assessment, Development and Evaluation evidence profile

Certainty assessment							Summary of findings			
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With placebo	With efficacy		Risk with placebo	Risk difference with efficacy
Success rate of endoscopy											
997 (six RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	491/498 (98.6%)	495/499 (99.2%)	RR 1.01 (0.99–1.02)	986 per 1000	10 more per 1000 (from 10 fewer to 20 more)
Success rate of sedation/GA induction											
2109 (13 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	938/958 (97.9%)	1140/1151 (99.0%)	RR 1.01 (1.00–1.02)	979 per 1000	10 more per 1000 (from 0 fewer to 20 more)
Induction time											
1664 (11 RCTs)	Not serious	Very serious[a]	Not serious	Not serious	None	⊕⊕◯◯ Low	779	885	-	The mean induction time was 0	MD 0.1 higher (0.04 lower to 0.23 higher)
Awakening time											
1899 (14 RCTs)	Not serious	Very seriousa	Not serious	Not serious	Publication bias strongly suspected[b]	⊕◯◯◯ Very low	896	1003	-	The mean awakening time was 0	MD 1.04 higher (0.45 higher to 1.62 higher)
Patient satisfaction											
1037 (six RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	519	518	-	-	SMD 0.36 higher (0.24 higher to 0.48 higher)
Pain on injection											
2629 (16 RCTs)	Not serious	Serious[c]	Not serious	Not serious	Publication bias strongly suspected[d]	⊕⊕◯◯ Low	549/1255 (43.7%)	71/1374 (5.2%)	RR 0.14 (0.09–0.22)	437 per 1000	376 fewer per 1000 (from 398 fewer to 341 fewer)
Adverse events											
2073 (14 RCTs)	Not serious	Very serious[a]	Not serious	Serious[e]	None	⊕◯◯◯ Very low	652/933 (69.9%)	621/1140 (54.5%)	RR 0.80 (0.69–0.92)	699 per 1000	140 fewer per 1000 (from 217 fewer to 56 fewer)

CI=confidence interval, MD=mean difference, RCT=randomised controlled trial, RR=risk ratio, SMD=standardised mean difference. [a]I^2 >75%. [b]Egger's test revealed significant publication bias (z=2.859, P=0.004). [c]I^2 >50%. [d]Egger's test revealed significant publication bias (z=3.007, P=0.003). [e]Wide confidence interval that does not exclude appreciable harm/benefit

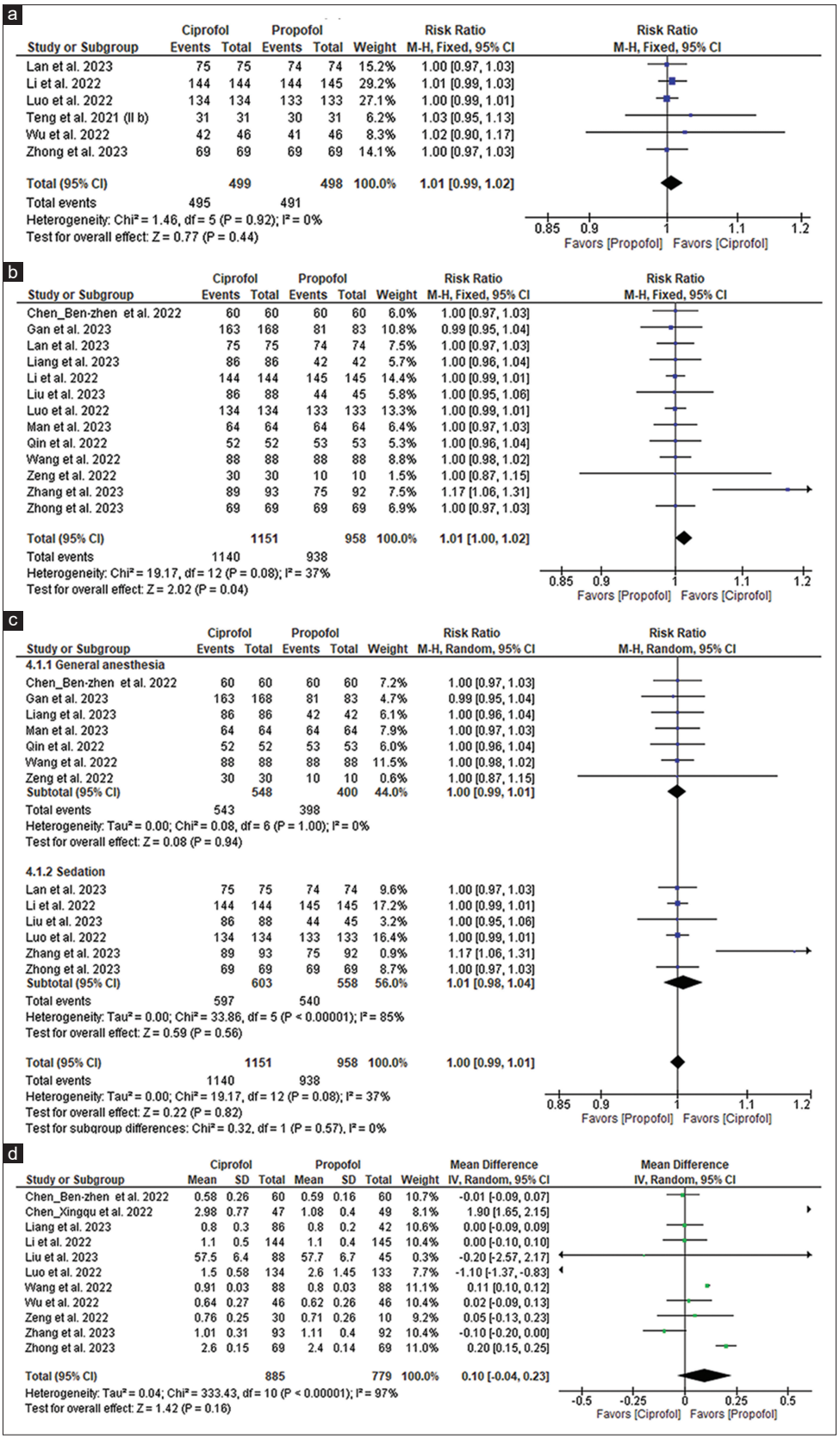

Figure 2: Forest plot of the efficacy outcomes: (a) success rate of endoscopy; (b) success rate of sedation/GA induction; (c) success rate of sedation/GA induction, subgrouped based on the type of anaesthesia; (d) induction time (min). CI=confidence interval, GA=general anaesthesia, SD=standard deviation

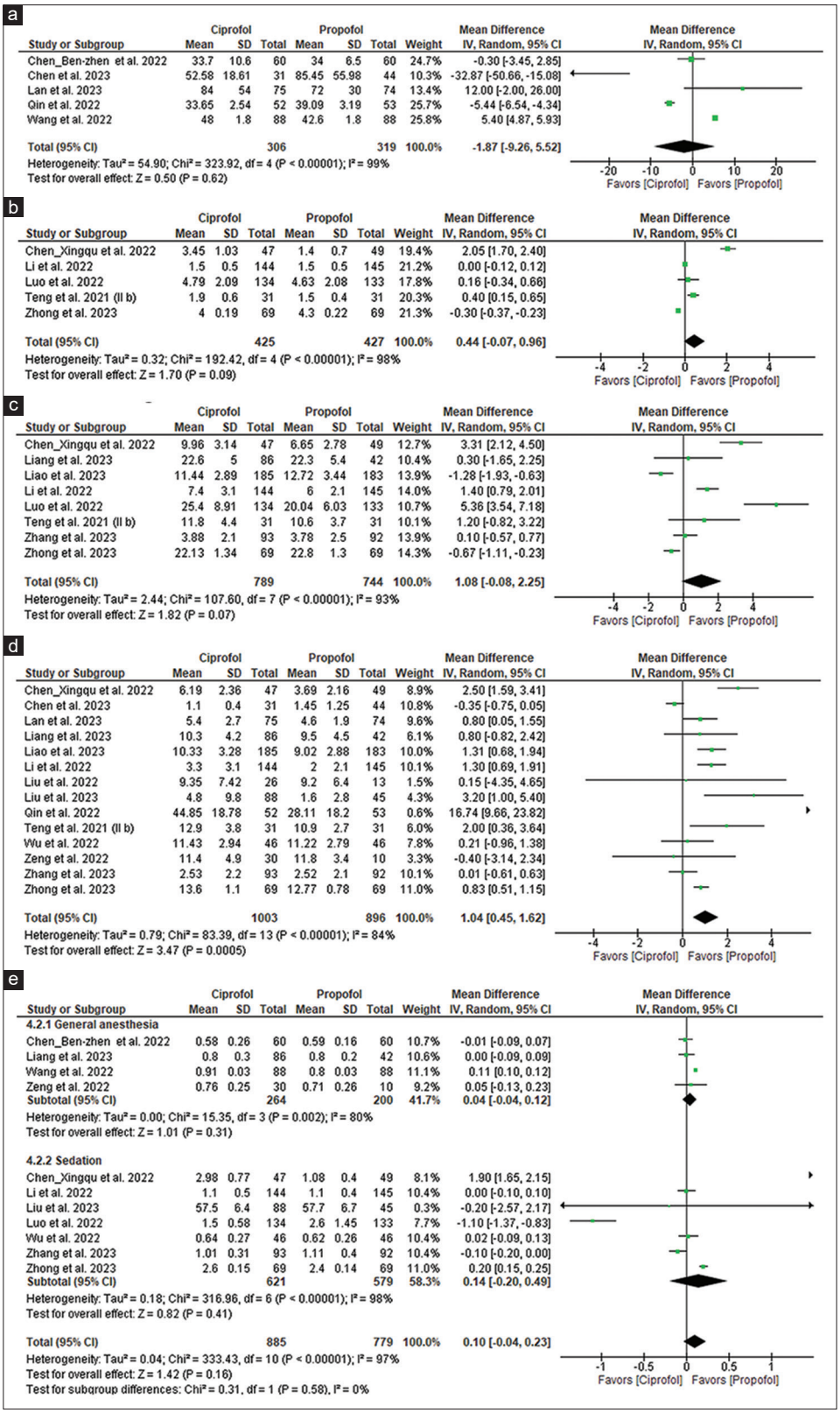

Figure 3: Forest plot of the efficacy outcomes: (a) time to eyelash reflex disappearance (s); (b) insertion time (min); (c) discharge time; (d) awakening time (min); (e) induction time (min), subgrouped based on the type of anaesthesia. CI=confidence interval, SD=standard deviation

Patients' and anaesthesiologist's satisfaction

Ciprofol showed significantly higher patient satisfaction versus propofol [standardised mean difference (SMD): 0.36, 95% CI: 0.24, 0.48; $P < 0.001$] (high-quality evidence) [Figure 4c, Table 3]. However, there was no difference between the two groups

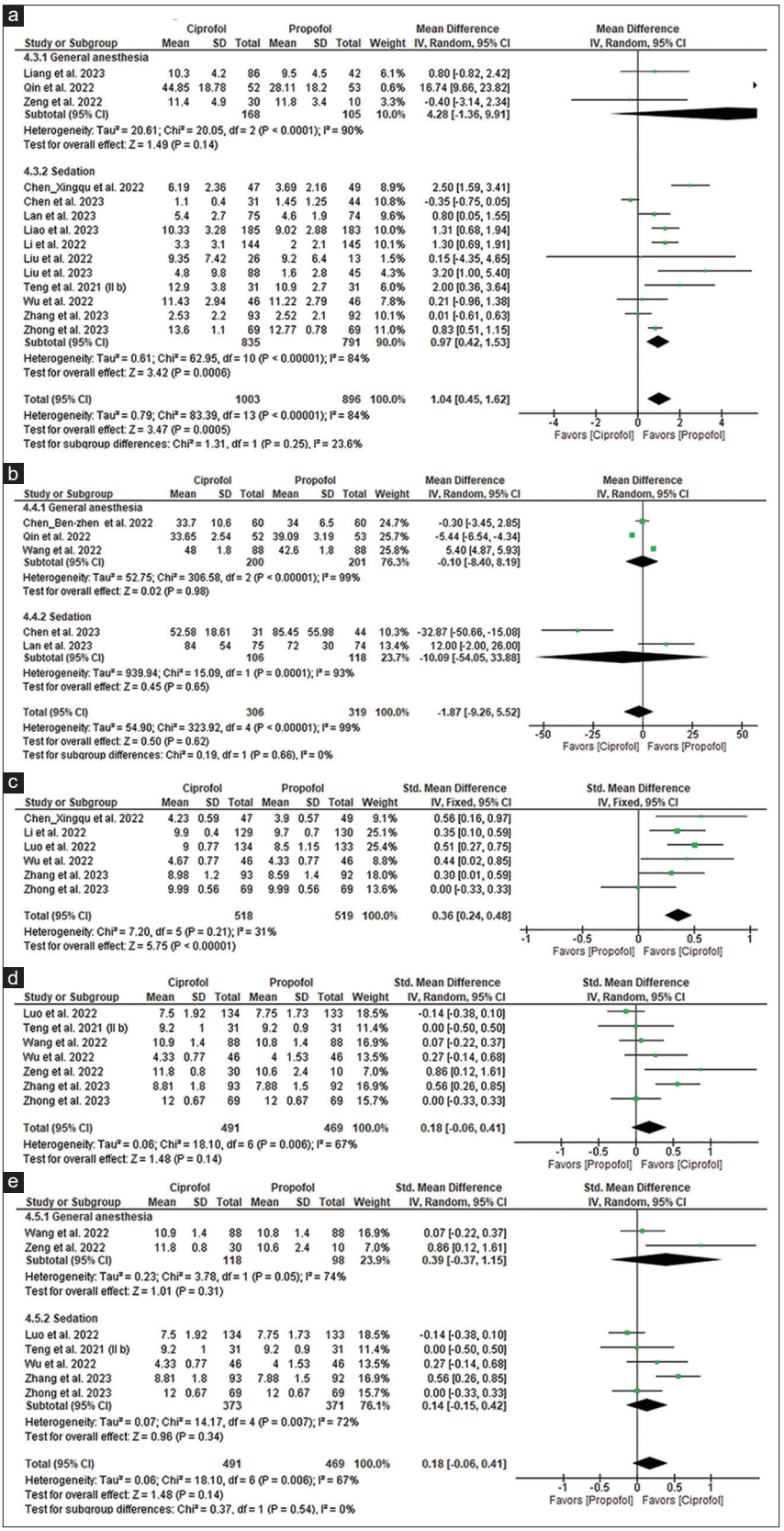

Figure 4: Forest plot of the efficacy outcomes: (a) awakening time (min), subgrouped based on the type of anaesthesia; (b) time to eyelash reflex disappearance (s), subgrouped based on the type of anaesthesia; (c) patient satisfaction; (d) anaesthesiologist satisfaction; (e) anaesthesiologist satisfaction, subgrouped based on the type of anaesthesia. CI=confidence interval, SD=standard deviation

regarding anaesthesiologist satisfaction (SMD: 0.18, 95% CI: −0.06, 0.41; $P = 0.14$) [Figure 4d]. Pooled studies were homogenous in patient satisfaction ($P = 0.21$, $I^2 = 31\%$), but were heterogenous in anaesthesiologist satisfaction ($P = 0.006$, $I^2 = 67\%$).

Subgroup analysis was conducted for anaesthesiologist satisfaction based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.54$) [Figure 4e]. We conducted a sensitivity analysis, and heterogeneity was best resolved in anaesthesiologist satisfaction by excluding Zhang *et al*.[33] ($P = 0.15$, $I^2 = 38\%$) [Table S2].

Number of patients who required top-up doses

There was no difference between ciprofol and propofol in the number of patients who required top-up doses (RR: 0.98, 95% CI: 0.83, 1.16; $P = 0.85$) [Figure 5a]. Pooled studies were homogenous ($P = 0.37$, $I^2 = 8\%$). Subgroup analysis was conducted based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.29$) [Figure S2].

Vitals (BIS score, MAP, SBP, DBP, HR and SpO_2)

There was no significant difference between ciprofol and propofol in BIS score (MD: 1.53, 95% CI: −2.47, 5.54; $P = 0.45$) [Figure S3a], MAP (MD: 2.20, 95% CI: −0.15, 4.5; $P = 0.07$) [Figure S3b], HR (MD: −0.87; 95% CI: −2.58, 0.83; $P = 0.31$) [Figure S3e] and SpO_2 (MD: 0.22, 95% CI: −0.14, 0.57; $P = 0.24$) [Figure S3f]. However, ciprofol showed a significant increase versus propofol in SBP (MD: 2.74, 95% CI: 0.17, 5.31; $P = 0.04$) [Figure S3c] and DBP (MD: 2.32, 95% CI: 0.69, 3.96; $P = 0.005$) [Figure S3d]. Pooled studies were heterogenous in BIS score ($P < 0.001$, $I^2 = 86\%$), SBP ($P < 0.001$, $I^2 = 79\%$), DBP ($P = 0.001$, $I^2 = 66\%$), MAP ($P < 0.001$, $I^2 = 77\%$), HR ($P < 0.001$, $I^2 = 82\%$) and SpO_2 ($P < 0.001$, $I^2 = 89\%$).

Subgroup analysis was conducted for MAP, SBP, DBP and HR based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.18$, $P = 0.57$, $P = 0.05$ and $P = 0.66$, respectively) [Figures S4–S7]. We conducted a sensitivity analysis, and heterogeneity was best resolved in SpO_2 by excluding Liao *et al*.[31] ($P = 0.38$, $I^2 = 6\%$) [Table S2].

Safety outcomes

Ciprofol showed significantly lower pain on injection (RR: 0.14, 95% CI: 0.09, 0.22; $P < 0.001$) (low-quality evidence) [Figure 5b, Table 3] and significantly lower adverse events (RR: 0.80, 95% CI: 0.69, 0.92; $P = 0.002$) (very-low-quality evidence) compared to propofol [Figure 5c, Table 3]. However, there was no difference between both groups in SAEs (RR: 0.39, 95% CI: 0.13, 1.17; $P = 0.09$) [Figure 5d]. Pooled studies were heterogenous in pain on injection ($P = 0.0003$, $I^2 = 64\%$) and adverse events ($P < 0.001$, $I^2 = 83\%$), but were homogenous in SAEs ($P = 0.51$, $I^2 = 0\%$).

Subgroup analysis was conducted for pain on injection, adverse events and SAEs based on the type of anaesthesia, and a test for subgroup differences was not significant ($P = 0.38$, $P = 0.58$ and $P = 0.15$, respectively) [Figure 6a–c].

Publication bias

The publication bias was evaluated by visual inspection of the funnel plot. The result of Egger's test revealed significant publication bias in awakening time ($z = 2.859$, $P = 0.004$) [Figure S8], pain on injection ($z = 3.007$, $P = 0.003$) [Figure S9] and DBP ($z = -1.662$, $P = 0.097$) [Figure S10]. However, there was no publication bias in the success rate of GA/sedation induction ($z = 0.95$, $P = 0.342$) [Figure S11], induction time ($z = -0.14$, $P = 0.889$) [Figure S12], adverse events ($z = 0.189$, $P = 0.85$) [Figure S13], SBP ($z = 0.1$, $P = 0.92$) [Figure S14] and HR ($z = 0.947$, $P = 0.344$) [Figure S15].

DISCUSSION

The meta-analysis revealed that ciprofol is comparable to propofol in terms of GA induction or sedation during different procedures. In addition, pain with injection was significantly less with ciprofol compared to propofol. Moreover, ciprofol exhibited a lower incidence of adverse events. Furthermore, patient satisfaction was significantly higher in the ciprofol group.

The induction of GA involves maintaining adequate ventilation and a stable haemodynamic condition while guiding the patient into hypnosis, amnesia and other parts of GA.[34] Our study indicated that ciprofol has a higher success rate versus propofol in terms of GA/sedation; it is worth mentioning that we found the statistical significance resolved by excluding Zhang *et al*.,[33] which has a high risk of bias. However, the difference was clinically insignificant, consistent with other studies. It is worth mentioning that several SRs conducted on this matter could not reach the same conclusion.[16,35–37] This discrepancy might be

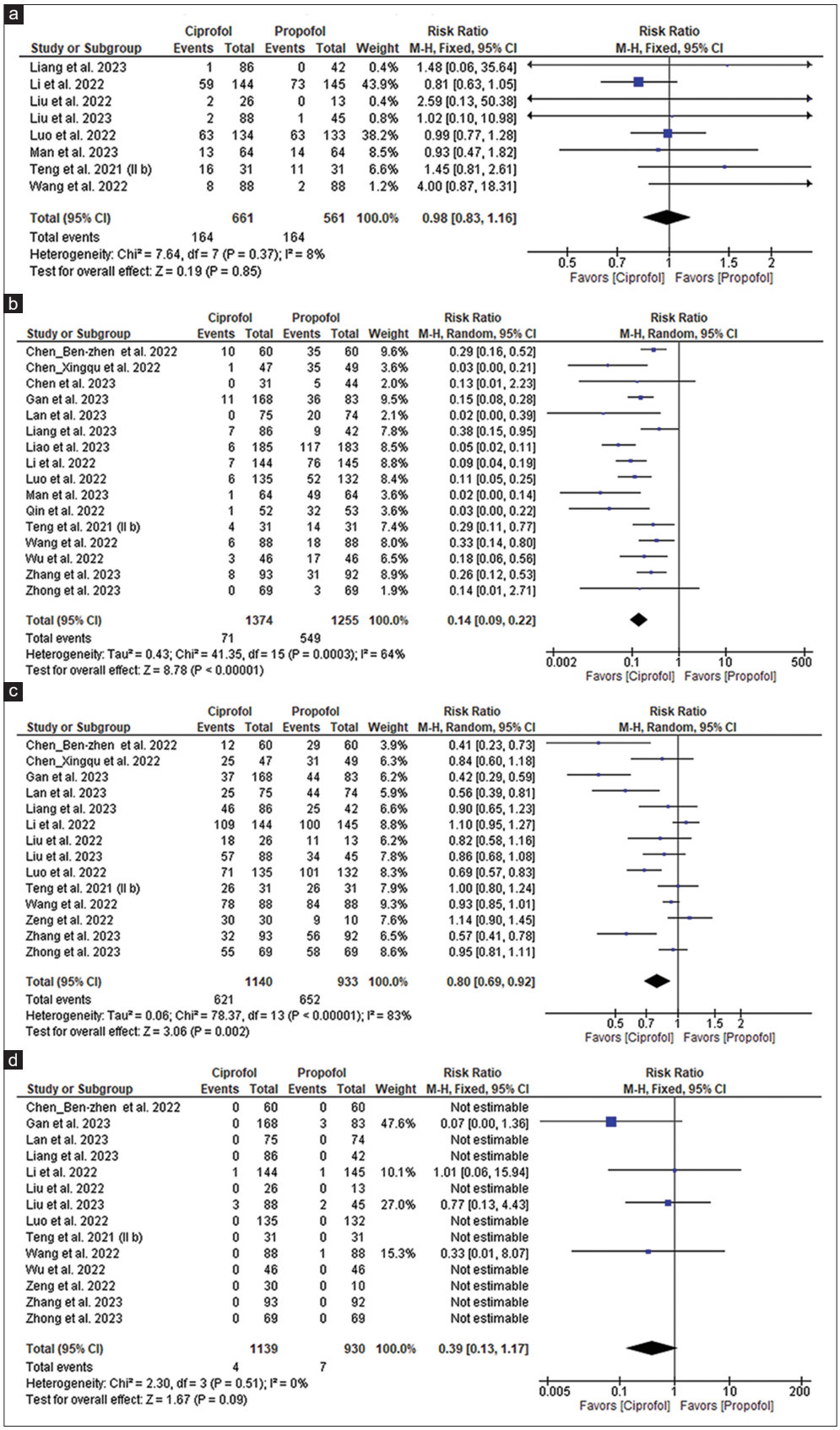

Figure 5: Forest plot of the efficacy and safety outcomes: (a) number of patients who required top-up doses; (b) pain on injection; (c) adverse events; (d) serious adverse events. CI=confidence interval, SD=standard deviation

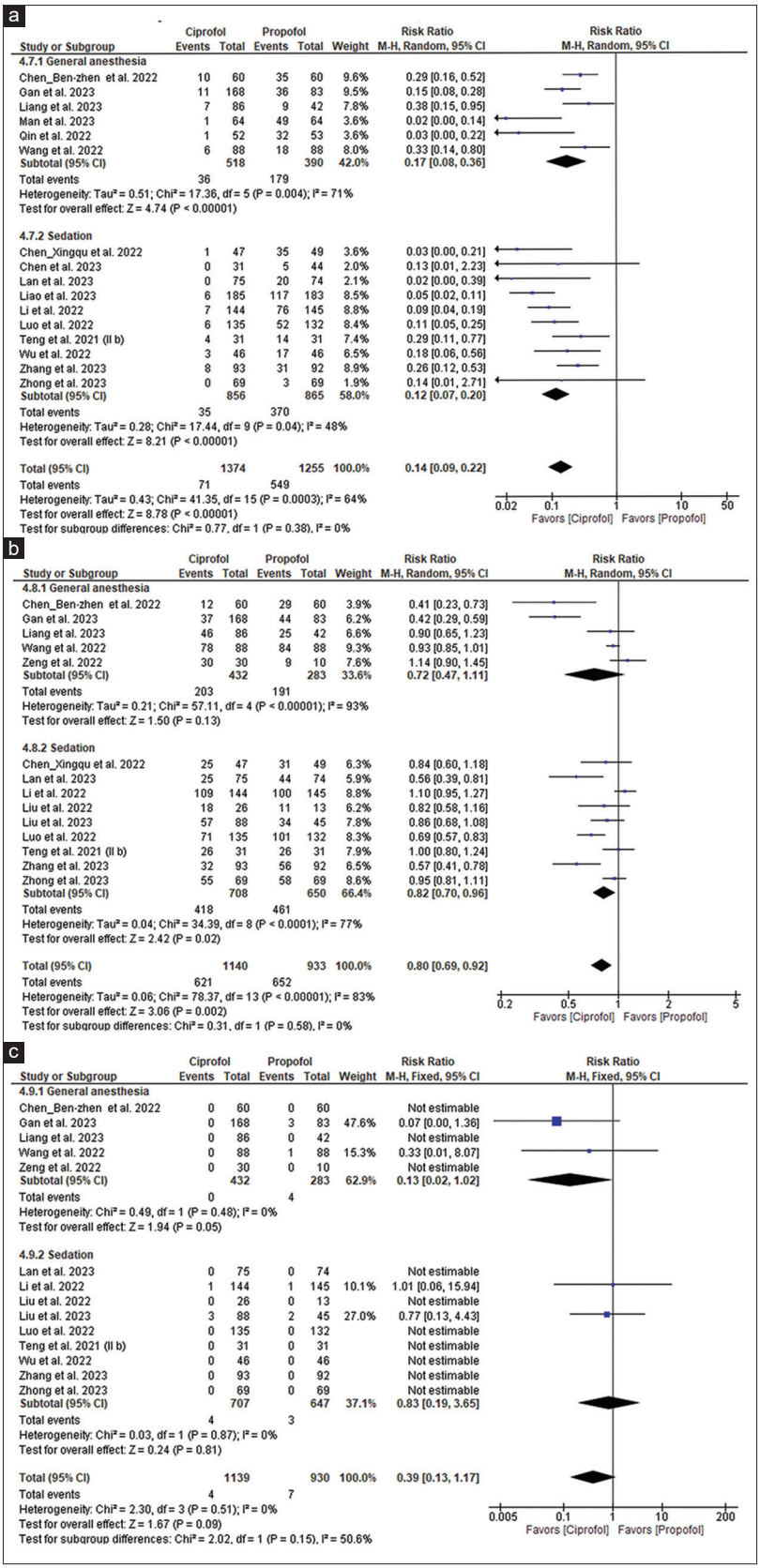

Figure 6: Forest plot of the safety outcomes: (a) pain on injection, subgrouped based on the type of anaesthesia; (b) adverse events, subgrouped based on the type of anaesthesia; (c) serious adverse events, subgrouped based on the type of anaesthesia. CI=confidence interval

attributed to a larger sample size, which could increase the likelihood of a Type I error or indicate a significant difference that requires further investigation. Our research revealed that ciprofol was comparable to propofol in terms of the success rate of endoscopy, induction time and insertion time. These findings mirror the conclusions drawn in other papers and two recent SRs.[2,9,10,14,15,27,36,37] Moreover, BIS, another marker for the success of anaesthesia, was found to be comparable in ciprofol and propofol. These collective findings may suggest that ciprofol can be used as an alternative drug to ensure effective GA and sedation induction during many interventional procedures. As a secondary outcome, Wang *et al*.[13] stated that the eyelash reflex in the ciprofol group took a longer time to disappear, whereas Qin *et al*.[32] showed that propofol took longer. Nevertheless, the differences were within a 1-min range, making them clinically insignificant. Our data showed no significant difference in the eyelash reflex disappearance between propofol and the latter drug, which may also suggest that ciprofol is as effective as propofol in reaching an effective sedative state.

Our study indicated that the discharge time is comparable in both groups. However, ciprofol showed a higher awakening time that can be clinically insignificant. Nevertheless, an RCT by Qin *et al*. suggested that the awakening time in the propofol group was significantly shorter, as ciprofol showed a recovery time with MD: 16.74 (95% CI: 9.66, 23.82). This discrepancy in the awakening time may be attributed to the fact that the Qin *et al*.[32] study focused on patients undergoing renal transplant procedures, and ciprofol is mainly exerted by the kidney, which may explain this result.

Ciprofol enhances the GABA receptor-mediated chloride reflux, making the neurons hyperpolarised. It demonstrated many pharmacokinetic properties similar to those of propofol. However, one of the main drawbacks of propofol is that it can cause significant pain with injection.[29] Thus, such side effects may result in tension and uncomfortable feelings, and sometimes may result in body movements, leading to a lower patient satisfaction rate. Many RCTs studied this effect deeply; they found that ciprofol was unique in lowering the pain with injection.[2,9–15,24,27,32] Our SR revealed a significant reduction in pain with injection when ciprofol was used over propofol, which is consistent with previous research.[2,9–15,24,27,32] Patient satisfaction rate was reported to be higher in the ciprofol group,[9,14,27,29] which also mirrors the findings of our paper. Chen *et al*.,[29] Li *et al*.[9] and Wu *et al*.[14] attributed this outcome to the less unpleasant experience associated with ciprofol, which may be linked to the lesser pain that the patient may experience with propofol injection. Importantly, none of the studies we reviewed indicated differences between propofol and ciprofol regarding the number of patients who required top-up doses. Nonetheless, our study did not reveal a significant difference in the provider's satisfaction rate between propofol and the tested drug.

Many adverse effects (AEs) of propofol include, but are not limited to, hypotension, hypertension, bradycardia, tachycardia and other intubation reactions during drug administration. Many studies have investigated the safety profile of ciprofol, which unveiled that AEs were less pronounced in the ciprofol group.[10,11,27] Notably, many other studies did not reach the same conclusion.[2,9,13,15,24,25,28,29] However, our meta-analysis highlighted that ciprofol has significantly fewer AEs. Thus, further research is necessary to explore this concept in more depth. Nonetheless, our data did not reveal a significant difference in the incidence of SAEs using ciprofol over propofol. This finding aligns with the results reported by Li *et al*.[9] and Wang *et al*.[13] In addition, we also included in our data analysis many RCTs that monitor the vitals of patients, such as SBP, DBP, MAP and HR, during the administration of propofol and ciprofol. Among these trials,[10,27] almost all studies reported that ciprofol resulted in a lesser reduction in MAP, DBP and SBP, with only Luo *et al*.'s[27] study showing a significant reduction in HR. In contrast to a recent preprint meta-analysis by Abdelfattah,[16] DBP and SBP showed no significant differences. However, they have limited patients, which may heighten the false negativity. In a meta-analysis, ciprofol was accompanied by higher values of DBP and SBP. This may suggest that ciprofol has more advantages than propofol in stabilising blood pressure, with no negative impact on other vitals.

Strengths

To our knowledge, this is the most recent SR comparing the two drugs. February 2024 was the endpoint of our literature review, with 2841 being the total number of included cohorts. The study Wen *et al*.[37] used October 2023 as the endpoint, with 2441 being the sample size. This SR investigated many characteristics and aspects of using ciprofol over

propofol. Our analysis included 19 research papers, all clinical trials focusing on this comparison. Among those RCTs, 10 were double-blinded, adding rigour to this research, whereas the other studies were either open labelled or single-blinded. Many of these studies were multi-centre based, enhancing recruitment and sample size, reducing bias and improving the credibility of the studies. In addition, subgroup analysis was conducted on several outcomes to improve the generalisability and to explore potential biases. Importantly, this paper has the highest number of reviewed RCTs, filling a notable knowledge gap in the existing literature.

Limitations

This study has several limitations. First, there was high heterogeneity among the included studies. This heterogeneity originated from variations in sample size, study populations and the use of different drugs before and during the procedures. Second, the limitation of mentoring vitals at 2 min after drug administration and T3 (time point 3, when the endoscope passes through the mouth) introduced time bias, potentially affecting the assessment of the two drugs' effects on patients' vitals. This bias may lead to either underestimation or overestimation of the drug effects. Lastly, the external validity of our results is questionable, given that all the included RCTs were conducted in China. This raises concerns about the generalisability and applicability of this study. Further research is needed to address these limitations and provide a more comprehensive understanding of the topic.

Implications for future research

All the included studies were conducted in China, except Gan *et al*.[23] which was conducted in the USA. As a result, further research is needed in other countries to establish comprehensive guidelines regarding ciprofol over propofol, as many clinical and logistical and geographical factors may vary. In addition, most of the studies were selective in their population. Only patients with ASA I and II classifications were included, while patients with cardiovascular or other comorbidities were excluded from the study. Furthermore, a small number of elderly people were included in the studies. These factors underscore the pressing need for further research trials investigating the effects of the two drugs in the excluded population. In addition, RCTs with further follow-up observations are needed to investigate the long-term safety of the new medication.

CONCLUSION

Ciprofol exhibited a comparable efficacy to propofol in inducing GA/sedation while significantly reducing injection site pain. This reduction in pain may contribute to the heightened patient satisfaction observed. Moreover, the safety profile of ciprofol compared to propofol underscores its promising potential as a medication in the foreseeable future.

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Conflicts of interest

There are no conflicts of interest.

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Table S1: Search Strategy			
Database	**Search Terms**	**Search Field**	**Search Results**
PubMed	(Ciprofol OR Cipepofol OR HSK3486 OR HSK-3486) AND (Propofol OR "2,6-Diisopropylphenol" OR "2,6 Diisopropylphenol" OR "2,6-Bis (1-methylethyl) phenol" OR Disoprofol OR Diprivan OR Disoprivan OR Fresofol OR "ICI-35,868" OR "ICI 35,868" OR "ICI35,868" OR "ICI-35868" OR "ICI 35868" OR "ICI35868" OR Ivofol OR Propofol Fresenius OR "Propofol MCT" OR "Propofol Rovi" OR "Propofol-Lipuro" OR Recofol OR Aquafol OR Propofol Abbott)	All Field	27
Cochrane	(Ciprofol OR Cipepofol OR HSK3486 OR HSK-3486) AND (Propofol OR "2,6-Diisopropylphenol" OR "2,6 Diisopropylphenol" OR "2,6-Bis (1-methylethyl) phenol" OR Disoprofol OR Diprivan OR Disoprivan OR Fresofol OR "ICI-35,868" OR "ICI 35,868" OR "ICI35,868" OR "ICI-35868" OR "ICI 35868" OR "ICI35868" OR Ivofol OR "Propofol Fresenius" OR "Propofol MCT" OR "Propofol Rovi" OR "Propofol-Lipuro" OR Recofol OR Aquafol OR "Propofol Abbott")	Title, Abstract, Keywords	102
WOS	(Ciprofol OR Cipepofol OR HSK3486 OR HSK-3486) AND (Propofol OR "2,6-Diisopropylphenol" OR "2,6 Diisopropylphenol" OR "2,6-Bis (1-methylethyl) phenol" OR Disoprofol OR Diprivan OR Disoprivan OR Fresofol OR "ICI-35,868" OR "ICI 35,868" OR "ICI35,868" OR "ICI-35868" OR "ICI 35868" OR "ICI35868" OR Ivofol OR "Propofol Fresenius" OR "Propofol MCT" OR "Propofol Rovi" OR "Propofol-Lipuro" OR Recofol OR Aquafol OR "Propofol Abbott")	All Field	32
SCOPUS	TITLE-ABS-KEY ((ciprofol OR cipepofol OR hsk3486 OR hsk-3486) AND (propofol OR "2,6-Diisopropylphenol" OR "2,6 Diisopropylphenol" OR "2,6-Bis (1-methylethyl) phenol" OR disoprofol OR diprivan OR disoprivan OR fresofol OR "ICI-35,868" OR "ICI 35,868" OR "ICI35,868" OR "ICI-35868" OR "ICI 35868" OR "ICI35868" OR ivofol OR "Propofol Fresenius" OR "Propofol MCT" OR "Propofol Rovi" OR "Propofol-Lipuro" OR recofol OR aquafol OR "Propofol Abbott"))	Title, Abstract, Keywords	32
EMBASE	#5. #3 AND #4 #4. propofol: ti, ab, kw OR '2,6-diisopropylphenol':ti, ab, kw OR (('2,6 diisopropylphenol':ti, ab, kw OR '2,6 bis':ti, ab, kw) AND '1 methylethyl':ti, ab, kw AND phenol: ti, ab, kw) OR disoprofol: ti, ab, kw OR diprivan: ti, ab, kw OR disoprivan: ti, ab, kw OR fresofol: ti, ab, kw OR 'ici-35,868':ti, ab, kw OR 'ici 35,868':ti, ab, kw OR 'ici 35868':ti, ab, kw OR 'ici35868':ti, ab, kw OR ivofol: ti, ab, kw OR 'propofol fresenius':ti, ab, kw OR 'propofol mct':ti, ab, kw OR 'propofol rovi':ti, ab, kw OR 'propofol lipuro':ti, ab, kw OR recofol: ti, ab, kw OR aquafol: ti, ab, kw OR 'propofol abbott':ti, ab, kw #3. #1 OR #2 #2. 'cipepofol'/exp #1. cipepofol: ti, ab, kw OR hsk3486:ti, ab, kw OR 'hsk 3486':ti, ab, kw	All Field	27

Table S2: Sensitivity Analysis									
Outcome	No. of participants (Ciprofol/Propofol)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			RR/MD	95% CI	*Z*	*P*	df	*P*	I^2 (%)
Induction Time (min)									
All Studies	885/779	11	0.10	[-0.04, 0.23]	1.42	0.16	10	<0.00001	97
Omitting Chen_Ben-zhen *et al*. 2022	825/719	10	0.11	[-0.04, 0.26]	1.44	0.15	9	<0.00001	97
Omitting Chen_Xingqu *et al*. 2022	838/730	10	-0.03	[-0.13, 0.06]	0.75	0.45	9	<0.00001	93
Omitting Liang *et al*. 2023	799/737	10	0.11	[-0.04, 0.26]	1.44	0.15	9	<0.00001	97
Omitting Li *et al*. 2022	741/634	10	0.11	[-0.04, 0.26]	1.45	0.15	9	<0.00001	97
Omitting Liu *et al*. 2023	797/734	10	0.10	[-0.04, 0.23]	1.43	0.15	9	<0.00001	97
Omitting Luo *et al*. 2022	751/646	10	0.19	[0.07, 0.31]	3.0	0.003	9	<0.00001	96
Omitting Wang *et al*. 2022	797/691	10	0.10	[-0.11, 0.31]	0.91	0.36	9	<0.00001	97
Omitting Wu *et al*. 2022	839/733	10	0.11	[-0.04, 0.25]	1.42	0.15	9	<0.00001	97
Omitting Zeng *et al*. 2022	855/769	10	0.10	[-0.04, 0.24]	1.40	0.16	9	<0.00001	97
Omitting Zhang *et al*. 2023	792/687	10	0.12	[-0.02, 0.26]	1.63	0.10	9	<0.00001	97
Omitting Zhong *et al*. 2023	816/710	10	0.09	[-0.09, 0.26]	0.98	0.33	9	<0.00001	97
Insertion Time (min)									
All Studies	425/427	5	0.44	[-0.07, 0.96]	1.70	0.09	4	<0.00001	98
Omitting Chen_Xingqu *et al*. 2022	378/378	4	0.04	[-0.26, 0.33]	0.24	0.81	3	<0.00001	93
Omitting Li *et al*. 2022	281/282	4	0.57	[-0.39, 1.54]	1.16	0.25	3	<0.00001	98
Omitting Luo *et al*. 2022	291/294	4	0.51	[-0.07, 1.08]	1.72	0.09	3	<0.00001	98
Omitting Teng *et al*. 2021 (II b)	394/396	4	0.46	[-0.14, 1.05]	1.51	0.13	3	<0.00001	98
Omitting Zhong *et al*. 2023	356/358	4	0.65	[-0.17, 1.47]	1.55	0.12	3	<0.00001	97
Awakening Time (min)									
All Studies	1003/896	14	1.04	[0.45, 1.62]	3.47	0.0005	13	<0.00001	84
Omitting Chen_Xingqu *et al*. 2022	956/847	13	0.87	[0.30, 1.44]	2.98	0.003	12	<0.00001	82
Omitting Chen *et al*. 2023	972/852	13	1.18	[0.62, 1.73]	4.15	<0.0001	12	<0.00001	76
Omitting Lan *et al*. 2023	928/822	13	1.08	[0.44, 1.72]	3.29	0.0010	12	<0.00001	86
Omitting Liang *et al*. 2023	917/854	13	1.06	[0.45, 1.67]	3.39	0.0007	12	<0.00001	86
Omitting Liao *et al*. 2023	818/713	13	1.02	[0.38, 1.65]	3.14	0.002	12	<0.00001	85
Omitting Li *et al*. 2022	859/751	13	1.02	[0.38, 1.66]	3.13	0.002	12	<0.00001	85
Omitting Liu *et al*. 2022	977/883	13	1.05	[0.46, 1.65]	3.48	0.0005	12	<0.00001	86
Omitting Liu *et al*. 2023	915/851	13	0.94	[0.35, 1.52]	3.12	0.002	12	<0.00001	85

Contd...

Table S2: Contd...									
Outcome	**No. of participants (Ciprofol/Propofol)**	**No. of trials**	**Quantitative data synthesis**				**Heterogeneity analysis**		
			RR/MD	**95% CI**	***Z***	***P***	**df**	***P***	I^2 **(%)**
Awakening Time (min)									
Omitting Qin *et al*. 2022	951/843	13	0.92	[0.40, 1.44]	3.45	0.0006	12	<0.00001	81
Omitting Teng *et al*. 2021 (II b)	972/865	13	0.98	[0.37, 1.58]	3.17	0.002	12	<0.00001	85
Omitting Wu *et al*. 2022	957/850	13	1.11	[0.49, 1.73]	3.52	0.0004	12	<0.00001	86
Omitting Zeng *et al*. 2022	973/886	13	1.09	[0.49, 1.69]	3.56	0.0004	12	<0.00001	86
Omitting Zhang *et al*. 2023	910/804	13	1.16	[0.53, 1.80]	3.58	0.0003	12	<0.00001	85
Omitting Zhong *et al*. 2023	934/827	13	1.12	[0.39, 1.84]	3.03	0.002	12	<0.00001	85
Discharge Time (min)									
All Studies	789/744	8	1.08	[-0.08, 2.25]	1.82	0.07	7	<0.00001	93
Omitting Chen_Xingqu *et al*. 2022	742/695	7	0.73	[-0.40, 1.85]	1.27	0.20	6	<0.00001	92
Omitting Liang *et al*. 2023	703/702	7	1.18	[-0.08, 2.44]	1.84	0.07	6	<0.00001	94
Omitting Liao *et al*. 2023	604/561	7	1.47	[0.19, 2.75]	2.25	0.02	6	<0.00001	93
Omitting Li *et al*. 2022	645/599	7	1.04	[-0.26, 2.35]	1.56	0.12	6	<0.00001	93
Omitting Luo *et al*. 2022	655/611	7	0.55	[-0.52, 1.62]	1.01	0.31	6	<0.00001	92
Omitting Teng *et al*. 2021 (II b)	758/713	7	1.07	[-0.17, 2.32]	1.69	0.09	6	<0.00001	94
Omitting Zhang *et al*. 2023	696/652	7	1.27	[-0.14, 2.68]	1.76	0.08	6	<0.00001	94
Omitting Zhong *et al*. 2023	720/675	7	1.40	[-0.01, 2.81]	1.94	0.05	6	<0.00001	93
Time to Eyelash Reflex Disappearance (s)									
All Studies	306/319	5	-1.87	[-9.26, 5.52]	0.50	0.62	4	<0.00001	99
Omitting Chen_Benzhen *et al*. 2022	246/259	4	-2.52	[-11.41, 6.37]	0.56	0.58	3	<0.00001	99
Omitting Chen *et al*. 2023	275/275	4	1.68	[-5.97, 9.32]	0.43	0.67	3	<0.00001	99
Omitting Lan *et al*. 2023	231/245	4	-4.02	[-11.98, 3.93]	0.99	0.32	3	<0.00001	99
Omitting Qin *et al*. 2022	254/266	4	0.12	[-6.95, 7.18]	0.03	0.97	3	<0.00001	90
Omitting Wang *et al*. 2022	218/231	4	-3.89	[-10.46, 2.69]	1.16	0.25	3	<0.0001	88
Anaesthesiologist Satisfaction									
All Studies	491/469	7	0.18	[-0.06, 0.41]	1.48	0.14	6	0.006	67
Omitting Luo *et al*. 2022	357/336	6	0.25	[0.01, 0.49]	2.01	0.04	5	0.04	56
Omitting Teng *et al*. 2021 (II b)	460/438	6	0.21	[-0.06, 0.47]	1.52	0.13	5	0.003	72
Omitting Wang *et al*. 2022	403/381	6	0.21	[-0.08, 0.50]	1.41	0.16	5	0.003	72
Omitting Wu *et al*. 2022	445/423	6	0.17	[-0.10, 0.44]	1.22	0.22	5	0.003	72
Omitting Zeng *et al*. 2022	461/459	6	0.13	[-0.10, 0.35]	1.09	0.28	5	0.01	65

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Table S2: Contd...

Outcome	No. of participants (Ciprofol/Propofol)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			RR/MD	95% CI	*Z*	*P*	df	*P*	I^2 (%)
Anesthesiologist Satisfaction									
Omitting Zhang *et al*. 2023	398/377	6	0.07	[-0.12, 0.26]	0.71	0.48	5	0.15	38
Omitting Zhong *et al*. 2023	422/400	6	0.22	[-0.06, 0.50]	1.53	0.13	5	0.004	71
BIS Score									
All Studies	474/347	5	1.53	[-2.47, 5.54]	0.75	0.45	4	<0.0001	86
Omitting Chen_Benzhen *et al*. 2022	414/287	4	2.71	[-2.20, 7.62]	1.08	0.28	3	<0.00001	89
Omitting Gan *et al*. 2023	309/264	4	0.68	[-3.64, 5.00]	0.31	0.76	3	0.0002	85
Omitting Lan *et al*. 2023	399/273	4	2.78	[-1.33, 6.88]	1.33	0.18	3	0.006	76
Omitting Liang *et al*. 2023	388/305	4	1.08	[-3.51, 5.67]	0.46	0.65	3	<0.0001	88
Omitting Wang *et al*. 2022	386/259	4	0.48	[-3.59, 4.56]	0.23	0.82	3	0.0005	83
Mean Arterial Pressure (mmHg)									
All Studies	717/629	9	2.20	[-0.15, 4.54]	1.83	0.07	8	<0.0001	77
Omitting Chen_Benzhen *et al*. 2022	657/569	9	2.33	[-0.25, 4.91]	1.77	0.08	7	<0.0001	79
Omitting Chen_Xingqu *et al*. 2022	670/580	9	2.27	[-0.24, 4.79]	1.77	0.08	7	<0.0001	80
Omitting Lan *et al*. 2023	642/555	9	1.43	[-0.90, 3.75]	1.20	0.23	7	0.0004	74
Omitting Liang *et al*. 2023	631/587	9	2.08	[-0.55, 4.70]	1.55	0.12	7	<0.00001	80
Omitting Liu *et al*. 2023	629/584	9	2.63	[0.22, 5.03]	2.14	0.03	7	<0.0001	77
Omitting Luo *et al*. 2022	583/496	9	1.90	[-0.78, 4.58]	1.39	0.17	7	<0.0001	80
Omitting Wang *et al*. 2022	629/541	9	2.99	[0.90, 5.08]	2.8	0.005	7	0.002	68
Omitting Wu *et al*. 2022	671/583	9	1.71	[-0.98, 4.41]	1.25	0.21	7	0.0003	74
Omitting Zhang *et al*. 2023	624/537	9	2.43	[-0.11, 4.97]	1.87	0.06	7	<0.0001	78
Systolic Blood Pressure (mmHg)									
All Studies	1002/925	12	2.74	[0.17, 5.31]	2.09	0.04	11	<0.00001	79
Omitting Chen_Benzhen *et al*. 2022	942/865	11	2.76	[-0.06, 5.57]	1.92	0.05	10	<0.00001	80
Omitting Chen_Xingqu *et al*. 2022	955/876	11	2.75	[0.03, 5.47]	1.98	0.05	10	<0.00001	81
Omitting Chen *et al*. 2023	971/881	11	2.87	[0.16, 5.57]	2.08	0.04	10	<0.00001	80
Omitting Lan *et al*. 2023	927/851	11	2.05	[-0.39, 4.49]	1.65	0.10	10	<0.0001	74
Omitting Liang *et al*. 2023	916/883	11	2.45	[-0.27, 5.17]	1.77	0.08	10	<0.00001	79
Omitting Liao *et al*. 2023	817/742	11	2.73	[-0.21, 5.67]	1.82	0.07	10	<0.00001	80
Omitting Liu *et al*. 2023	914/880	11	2.85	[0.13, 5.56]	2.05	0.04	10	<0.00001	80
Omitting Luo *et al*. 2022	868/792	11	2.34	[-0.33, 5.02]	1.72	0.09	10	<0.00001	78

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Table S2: Contd...									
Outcome	**No. of participants (Ciprofol/Propofol)**	**No. of trials**	**Quantitative data synthesis**				**Heterogeneity analysis**		
			RR/MD	**95% CI**	***Z***	***P***	**df**	***P***	I^2 **(%)**
Omitting Wang *et al*. 2022	914/837	11	3.43	[0.92, 5.94]	2.68	0.007	10	<0.0001	75
Omitting Wu *et al*. 2022	956/879	11	2.34	[-0.34, 5.03]	1.71	0.09	10	<0.00001	77
Omitting Zhang *et al*. 2023	909/833	11	3.02	[0.25, 5.79]	2.14	0.03	10	<0.00001	80
Omitting Zhong *et al*. 2023	933/856	11	3.34	[0.89, 5.80]	2.67	0.008	10	0.0002	70
Diastolic Blood Pressure (mmHg)									
All Studies	933/856	11	2.32	[0.69, 3.96]	2.79	0.005	10	0.001	66
Omitting Chen_Benzhen *et al*. 2022	873/796	10	2.43	[0.69, 4.17]	2.74	0.006	9	0.001	68
Omitting Chen_Xingqu *et al*. 2022	886/807	10	2.29	[0.56, 4.02]	2.59	0.010	9	0.0006	69
Omitting Chen *et al*. 2023	902/812	10	2.33	[0.58, 4.07]	2.61	0.009	9	0.0007	69
Omitting Lan *et al*. 2023	858/782	10	1.85	[0.24, 3.45]	2.25	0.02	9	0.007	60
Omitting Liang *et al*. 2023	847/814	10	2.34	[0.58, 4.10]	2.61	0.009	9	0.0007	69
Omitting Liao *et al*. 2023	748/673	10	2.17	[0.30, 4.04]	2.27	0.02	9	0.0006	69
Omitting Liu *et al*. 2023	845/811	10	2.85	[1.37, 4.33]	3.77	0.0002	9	0.02	55
Omitting Luo *et al*. 2022	799/723	10	2.14	[0.32, 3.96]	2.31	0.02	9	0.0006	69
Omitting Wang *et al*. 2022	845/768	10	2.80	[1.28, 4.33]	3.6	0.0003	9	0.01	57
Omitting Wu *et al*. 2022	887/810	10	1.96	[0.15, 3.77]	2.12	0.03	9	0.007	60
Omitting Zhang *et al*. 2023	840/764	10	2.39	[0.63, 4.14]	2.67	0.008	9	0.0009	68
Heart Rate (bets per min)									
All Studies	1002/925	12	-0.87	[-2.58, 0.83]	1.01	0.31	11	<0.00001	82
Omitting Chen_Benzhen *et al*. 2022	942/865	11	-0.73	[-2.51, 1.05]	0.80	0.42	10	<0.00001	83
Omitting Chen_Xingqu *et al*. 2022	955/876	11	-1.06	[-2.82, 0.71]	1.17	0.24	10	<0.00001	83
Omitting Chen *et al*. 2023	971/881	11	-1.11	[-2.90, 0.68]	1.22	0.22	10	<0.00001	83
Omitting Lan *et al*. 2023	927/851	11	-0.81	[-2.64, 1.03]	0.86	0.39	10	<0.00001	83
Omitting Liang *et al*. 2023	916/883	11	-0.81	[-2.60, 0.98]	0.89	0.38	10	<0.00001	83
Omitting Liao *et al*. 2023	817/742	11	-0.33	[-1.85, 1.19]	0.43	0.67	10	<0.0001	73
Omitting Liu *et al*. 2023	914/880	11	-0.95	[-2.71, 0.81]	1.06	0.29	10	<0.00001	83
Omitting Luo *et al*. 2022	868/792	11	-0.58	[-2.35, 1.19]	0.65	0.52	10	<0.00001	78
Omitting Wang *et al*. 2022	914/837	11	-0.93	[-2.75, 0.90]	0.99	0.32	10	<0.00001	83
Omitting Wu *et al*. 2022	956/879	11	-0.96	[-3.01, 1.10]	0.91	0.36	10	<0.00001	83

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Table S2: Contd...									
Outcome	No. of participants (Ciprofol/Propofol)	No. of trials	Quantitative data synthesis				Heterogeneity analysis		
			RR/MD	95% CI	*Z*	*P*	df	*P*	I^2 (%)
Heart Rate									
Omitting Zhang *et al*. 2023	909/833	11	-0.85	[-2.69, 0.99]	0.91	0.37	10	<0.00001	83
Omitting Zhong *et al*. 2023	933/856	11	-1.39	[-2.93, 0.15]	1.77	0.08	10	0.0002	71
Spo_2 (%)									
All Studies	686/611	8	0.00	[-0.01, 0.01]	0.16	0.87	7	<0.00001	89
Omitting Chen_Xingqu *et al*. 2022	639/562	7	0.00	[-0.01, 0.01]	0.16	0.87	6	<0.00001	90
Omitting Chen *et al*. 2023	655/567	7	0.14	[-0.01, 0.30]	1.78	0.07	6	<0.00001	90
Omitting Liang *et al*. 2023	600/569	7	0.00	[-0.01, 0.02]	0.19	0.85	6	<0.00001	90
Omitting Liao *et al*. 2023	501/428	7	-0.00	[-0.01, 0.01]	0.04	0.97	6	0.38	6
Omitting Liu *et al*. 2023	598/566	7	0.00	[-0.01, 0.02]	0.21	0.83	6	<0.00001	90
Omitting Luo *et al*. 2022	552/478	7	0.00	[-0.01, 0.01]	0.14	0.89	6	<0.00001	90
Omitting Wu *et al*. 2022	640/565	7	0.00	[-0.01, 0.01]	0.13	0.90	6	<0.00001	90
Omitting Zhong *et al*. 2023	617/542	7	0.00	[-0.01, 0.01]	0.16	0.87	6	<0.00001	90
Pain on Injection									
All Studies	1374/1255	16	0.14	[0.09, 0.22]	8.78	<0.00001	15	0.0003	64
Omitting Chen_Benzhen *et al*. 2022	1314/1195	15	0.13	[0.08, 0.20]	8.69	<0.00001	14	0.001	61
Omitting Chen_Xingqu *et al*. 2022	1327/1206	15	0.15	[0.10, 0.23]	8.60	<0.00001	14	0.0006	63
Omitting Chen *et al*. 2023	1343/1211	15	0.14	[0.09, 0.22]	8.57	<0.00001	14	0.0002	66
Omitting Gan *et al*. 2023	1206/1172	15	0.13	[0.08, 0.22]	7.90	<0.00001	14	0.0001	66
Omitting Lan *et al*. 2023	1299/1181	15	0.14	[0.09, 0.22]	8.64	<0.00001	14	0.0004	64
Omitting Liang *et al*. 2023	1288/1213	15	0.13	[0.08, 0.20]	8.95	<0.00001	14	0.0008	62
Omitting Liao *et al*. 2023	1189/1072	15	0.16	[0.10, 0.24]	8.69	<0.00001	14	0.005	55
Omitting Li *et al*. 2022	1230/1110	15	0.14	[0.09, 0.23]	8.01	<0.00001	14	0.0003	65
Omitting Luo *et al*. 2022	1239/1123	15	0.14	[0.09, 0.23]	8.02	<0.00001	14	0.0002	66
Omitting Man *et al*. 2023	1310/1191	15	0.15	[0.10, 0.23]	8.79	<0.00001	14	0.001	60
Omitting Qin *et al*. 2022	1322/1202	15	0.15	[0.09, 0.23]	8.58	<0.00001	14	0.0005	63
Omitting Teng *et al*. 2021 (II b)	1343/1224	15	0.13	[0.08, 0.21]	8.59	<0.00001	14	0.0003	65
Omitting Wang *et al*. 2022	1286/1167	15	0.13	[0.08, 0.20]	8.75	<0.00001	14	0.0005	63
Omitting Wu *et al*. 2022	1328/1209	15	0.13	[0.08, 0.22]	8.34	<0.00001	14	0.0001	66

Contd...

Table S2: Contd...									
Outcome	**No. of participants (Ciprofol/Propofol)**	**No. of trials**	**Quantitative data synthesis**				**Heterogeneity analysis**		
			RR/MD	**95% CI**	***Z***	***P***	**df**	***P***	I^2 **(%)**
Pain on Injection									
Omitting Zhang *et al*. 2023	1281/1163	15	0.13	[0.08, 0.21]	8.42	<0.00001	14	0.0003	64
Omitting Zhong *et al*. 2023	1305/1186	15	0.14	[0.09, 0.22]	8.58	<0.00001	14	0.0002	66
Adverse Events									
All Studies	1140/933	14	0.80	[0.69, 0.92]	3.06	0.002	13	<0.00001	83
Omitting Chen_Benzhen *et al*. 2022	1080/873	13	0.82	[0.71, 0.94]	2.77	0.006	12	<0.00001	82
Omitting Chen_Xingqu *et al*. 2022	1093/884	13	0.79	[0.68, 0.92]	2.96	0.003	12	<0.00001	85
Omitting Gan *et al*. 2023	972/850	13	0.84	[0.74, 0.96]	2.66	0.008	12	<0.00001	77
Omitting Lan *et al*. 2023	1065/859	13	0.82	[0.71, 0.94]	2.75	0.006	12	<0.00001	83
Omitting Liang *et al*. 2023	1054/891	13	0.79	[0.68, 0.92]	3.00	0.003	12	<0.00001	85
Omitting Li *et al*. 2022	996/788	13	0.77	[0.65, 0.91]	3.15	0.002	12	<0.00001	84
Omitting Liu *et al*. 2022	1114/920	13	0.79	[0.68, 0.93]	2.94	0.003	12	<0.00001	85
Omitting Liu *et al*. 2023	1052/888	13	0.79	[0.67, 0.92]	2.93	0.003	12	<0.00001	85
Omitting Luo *et al*. 2022	1005/801	13	0.81	[0.70, 0.94]	2.77	0.006	12	<0.00001	83
Omitting Teng *et al*. 2021 (II b)	1109/902	13	0.78	[0.67, 0.91]	3.12	0.002	12	<0.00001	84
Omitting Wang *et al*. 2022	1052/845	13	0.78	[0.66, 0.92]	2.89	0.004	12	<0.00001	83
Omitting Zeng *et al*. 2022	1110/923	13	0.77	[0.67, 0.90]	3.33	0.0009	12	<0.00001	83
Omitting Zhang *et al*. 2023	1047/841	13	0.82	[0.71, 0.95]	2.74	0.006	12	<0.00001	82
Omitting Zhong *et al*. 2023	1071/864	13	0.78	[0.66, 0.92]	2.99	0.003	12	<0.00001	85

Table S3: Comparison between our study and the other published literature					
	Abdelfattah *et al*. 2023	**Hung *et al*. 2023**	**Wen *et al*. 2023**	**Akhtar *et al*. 2024**	**Our study**
	Pre-print	Peer-reviewed	Peer-reviewed	Peer-reviewed	Peer-reviewed
Total studies included in meta-analysis	5	12	15	13	19
Study design of included studies	RCTs only	RCTs & 1 non-randomised trial	RCTs & 1 non-randomised trial	RCTs only	RCTs only
Total sample size	463	1793	2441	1998	2841
Language of included studies	English	English	English & Chinese	English	English
Search results until	March 2023	April 2023	October 2023	July 2023	February 2024
Number of outcomes analyzed	10	13	14	8	19
Success rate of anaesthesia induction	No significant difference	No significant difference	No significant difference	No significant difference	Increase with Ciprofol
Induction time	----	No significant difference	No significant difference	Increase with Ciprofol	No significant difference
Systolic blood pressure	No significant difference	----	----	----	Increase with Ciprofol
DBP	No significant difference	----	----	----	Increase with Ciprofol

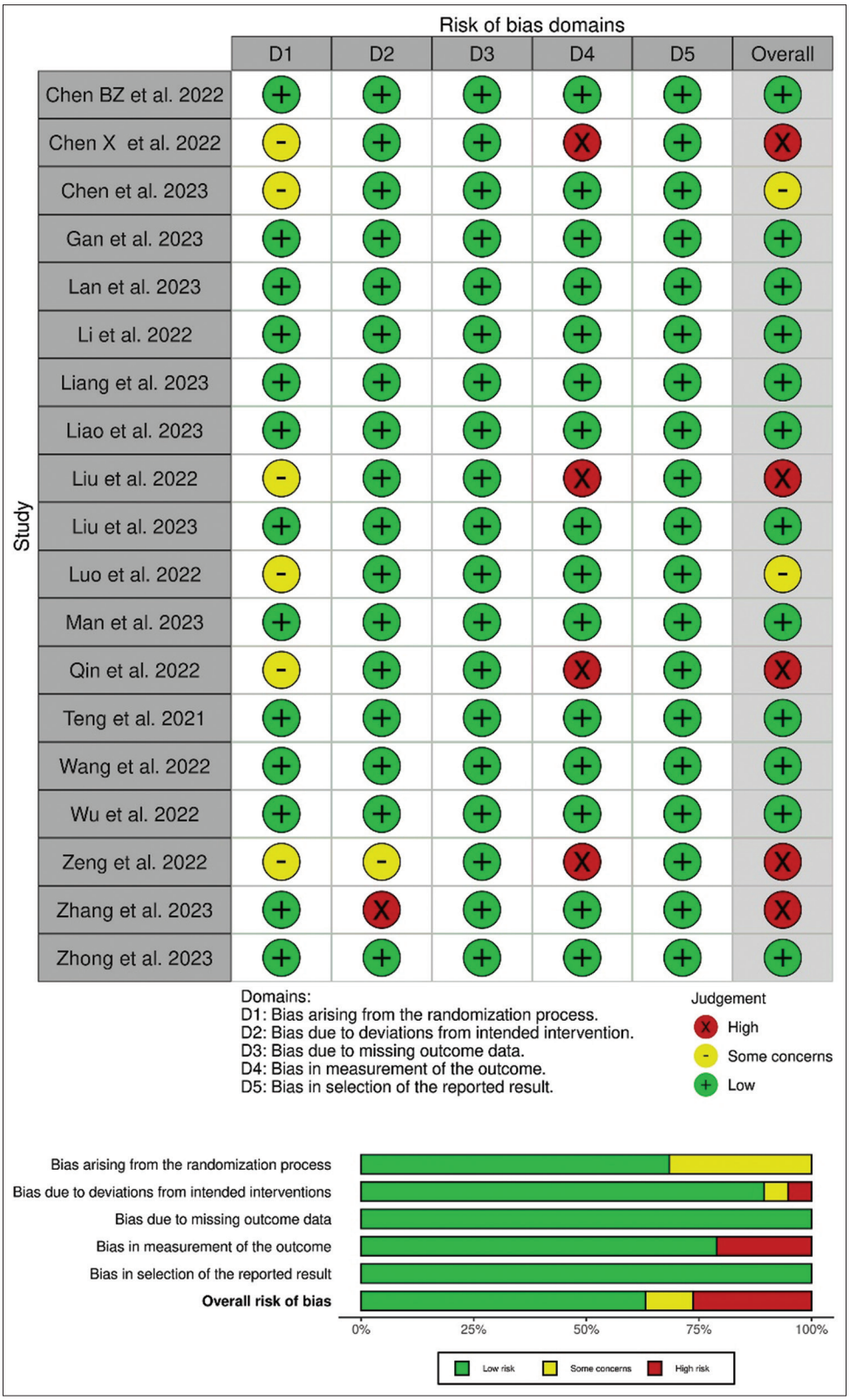

Figure S1: Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = red, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = red, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review

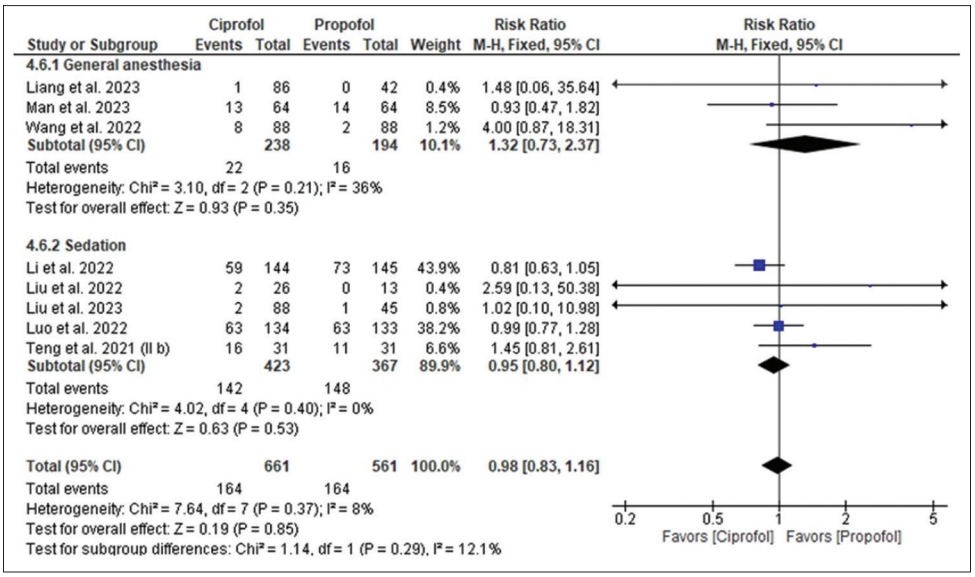

Figure S2: Forest plot of the number of patients required top-up doses, subgrouped based on type of anaesthesia. CI = confidence interval, MH = Mantel-Haenszel Method

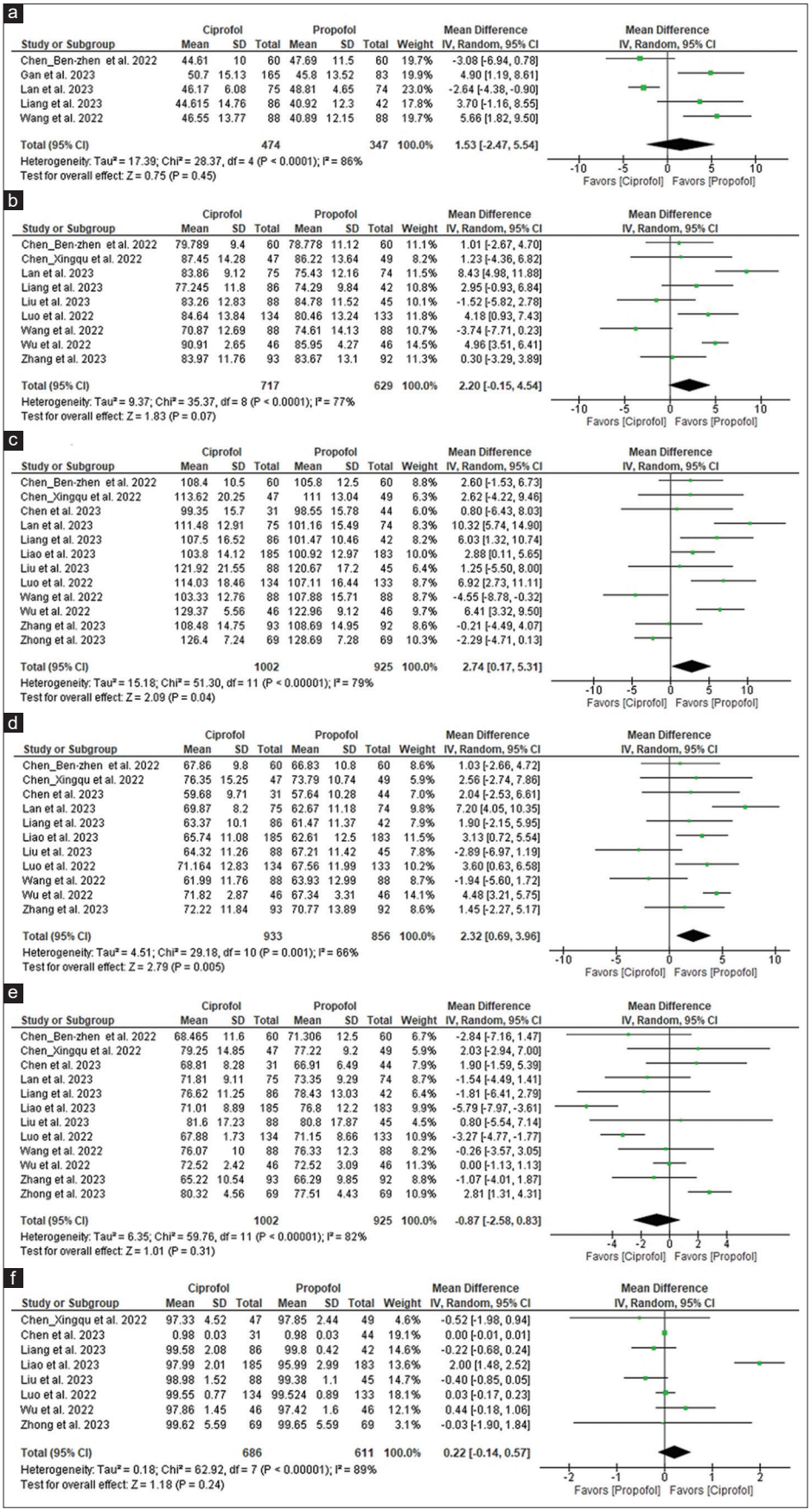

Figure S3: Forest plot of the vitals (a- BIS score, b- Mean arterial pressure, c- Systolic blood pressure, d- Diastolic blood pressure, e- Heart rate, f- SpO_2). BIS = bispectral index, CI = confidence interval, MD = mean difference, SD = standard deviation, SpO_2 = Oxygen saturation

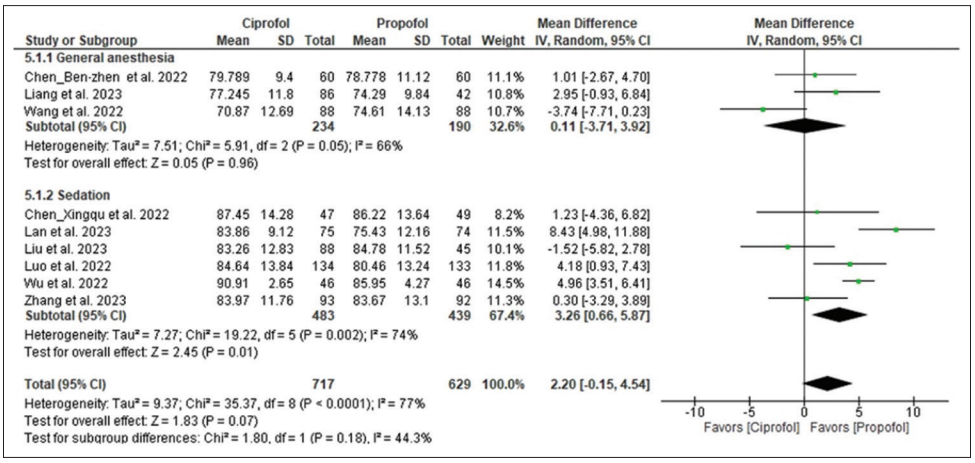

Figure S4: Forest plot of mean arterial pressure, subgrouped based on type of anaesthesia. CI = confidence interval, MD = mean difference, SD = standard deviation

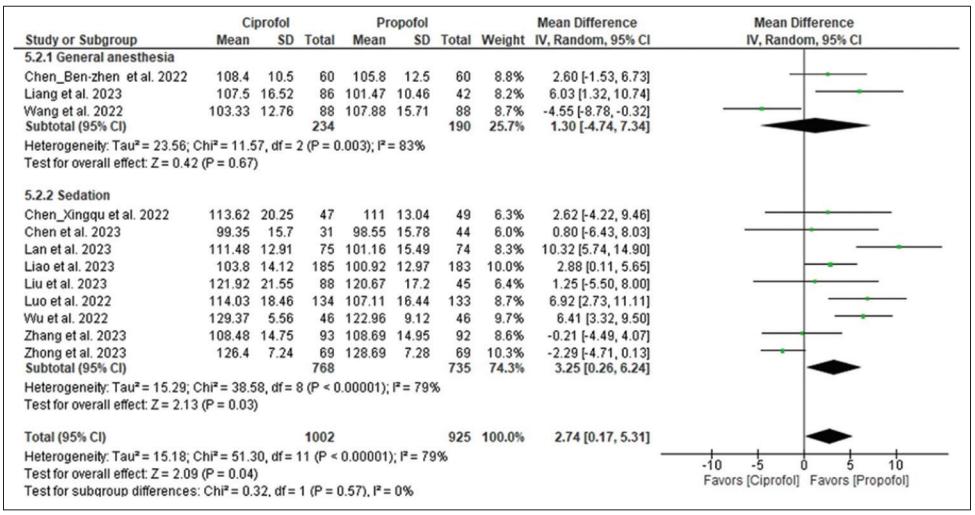

Figure S5: Forest plot of systolic blood pressure, subgrouped based on type of anaesthesia. CI = confidence interval, MD = mean difference, SD = standard deviation

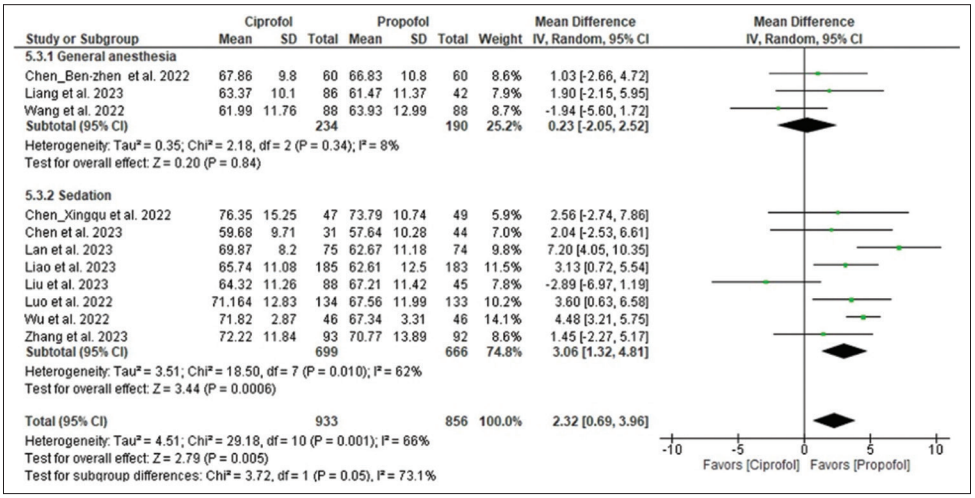

Figure S6: Forest plot of diastolic blood pressure, subgrouped based on type of anaesthesia. CI = confidence interval, MD = mean difference, SD = standard deviation

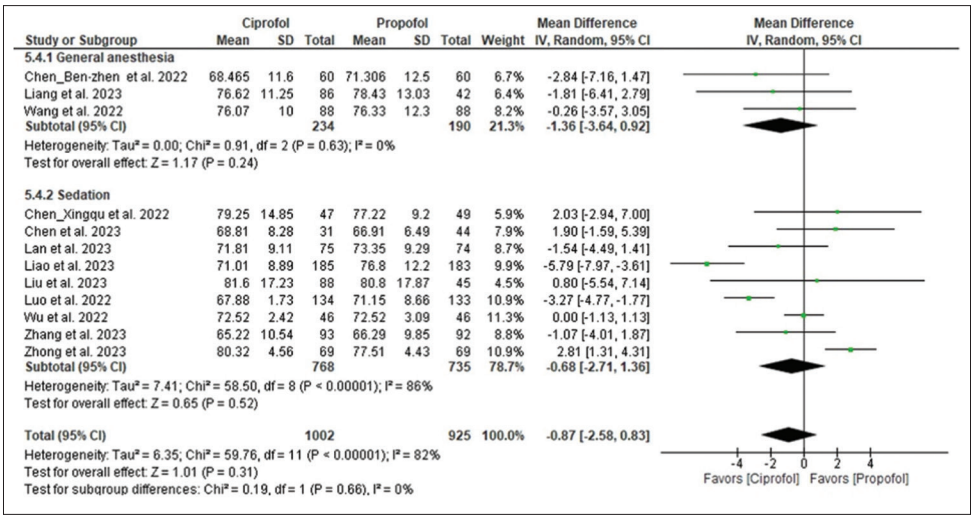

Figure S7: Forest plot of heart rate, subgrouped based on type of anaesthesia. CI = confidence interval, MD = mean difference, SD = standard deviation

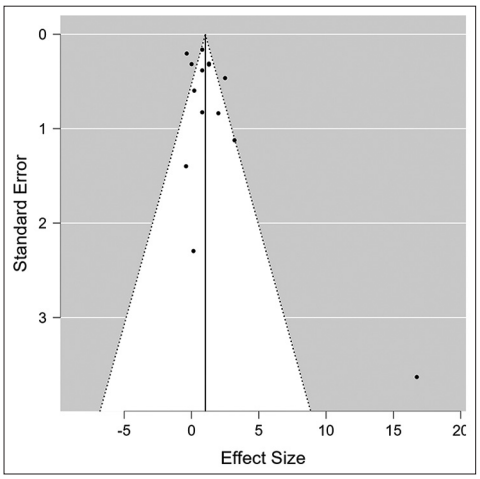

Figure S8: Funnel plot of publication bias of awakening time

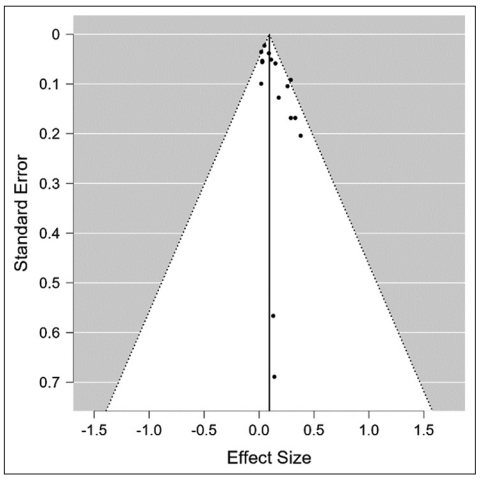

Figure S9: Funnel plot of publication bias of pain on injection

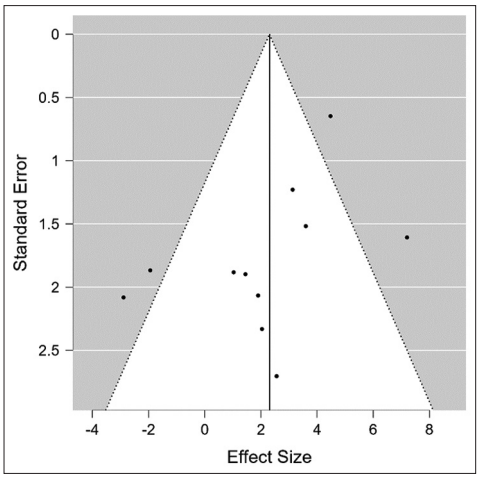

Figure S10: Funnel plot of publication bias of diastolic blood pressure

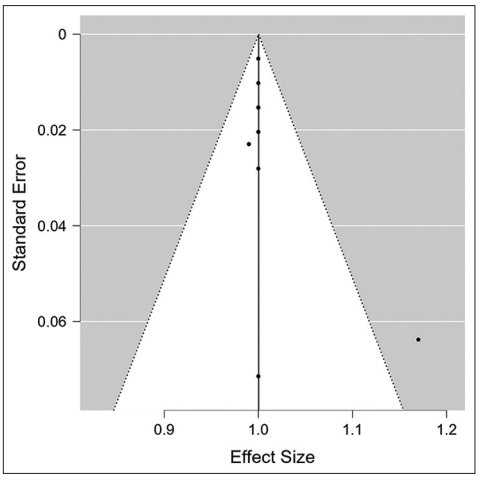

Figure S11: Funnel plot of publication bias of success rate of GA/ sedation induction

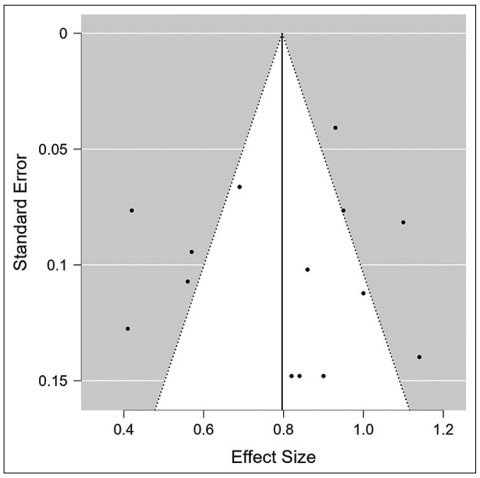

Figure S12: Funnel plot of publication bias of induction time

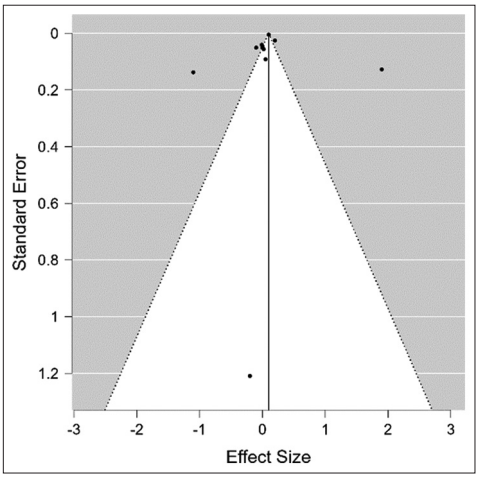

Figure S13: Funnel plot of publication bias of adverse events

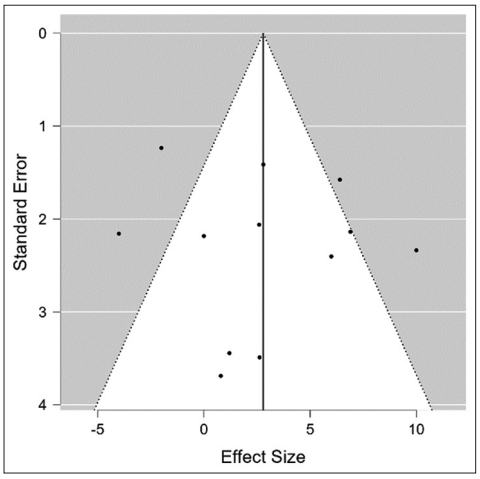

Figure S14: Funnel plot of publication bias of systolic blood pressure

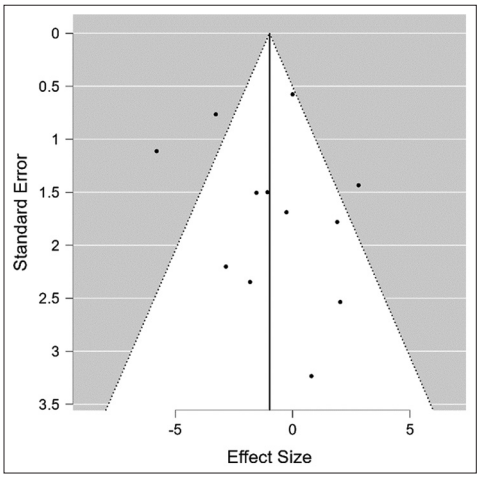

Figure S15: Funnel plot of publication bias of heart rate