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Efficacy and safety of ciprofol versus propofol for anesthesia in patients undergoing gastrointestinal endoscope: a systematic review and meta-analysis of randomized controlled trials (RCT)

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Abstract

Background Ciprofol is considered an alternative to propofol and can be used to achieve anesthesia at a lower dose with a lower incidence of adverse events. The primary objective of this study was to compare the efficacy and safety of ciprofol and propofol used in patients undergoing gastrointestinal endoscopes.

Methods The databases of PubMed, Embase, Cochrane Library, Web of Science, and China National Knowledge Infrastructure were retrieved for randomized controlled trials of ciprofol and propofol used in gastrointestinal endoscopes from inception to May 10, 2024. All statistical analyses were conducted using Stata 14.0. Primary outcomes encompassed a successful rate of sedation and other safety outcomes, including injection pain, hypotension, bradycardia, overall respiratory disorders, and hypoxemia. Secondary outcomes concluded time to onset of successful induction, waking time, and discharge time.

Results A total of 20 studies were included, involving 3779 patients. The results of the meta-analysis showed that the successful rate of anesthesia and waking time were not significantly different between ciprofol and propofol, while ciprofol was better than propofol in injection pain (RR: 0.10, 95% CI: 0.07 to 0.16, $p < 0.001$, $I^2 = 46.4\%$, moderate certainty), hypotension (RR: 0.68, 95% CI: 0.59 to 0.77, $p < 0.001$, $I^2 = 49.2\%$, moderate certainty), bradycardia (RR: 0.67, 95% CI: 0.52 to 0.85, $p = 0.001$, $I^2 = 0.0\%$, moderate certainty), hypoxemia (RR: 0.45, 95% CI: 0.33 to 0.61, $p < 0.001$, $I^2 = 9.2\%$, moderate certainty), and overall respiratory disorders (RR: 0.45, 95% CI: 0.27 to 0.75, $p < 0.001$, $I^2 = 77.1\%$, moderate certainty). In addition, compared to propofol, shorter time to onset of successful induction (MD: -0.16, 95% CI: -0.24 to −0.08, $p < 0.001$, $I^2 = 97.2\%$, very low certainty) and longer discharge time (MD: 0.420, 95% CI: 0.29 to 0.54, $p < 0.001$, $I^2 = 29.4\%$, moderate certainty) were related to ciprofol.

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Conclusion Based on the results of pooled analysis, we conclude that ciprofol takes longer for cipofol to recover after surgery, it may greatly improve the pain problem and hemodynamic stability of intravenous propofol. Therefore, we believe that ciprofol can be used as an excellent substitute for propofol.

Keywords Anesthesia, Ciprofol, Efficacy, Propofol, Safety

Introduction

The gastrointestinal endoscope has become one of the common methods for clinical examination and diagnosis of gastrointestinal diseases. The patient's mood, body movement, and other factors also easy to affect the results of gastrointestinal endoscopes, so higher requirements are needed for anesthesia during gastrointestinal endoscopes [1]. Propofol (PRO) is the short-acting intravenous anesthetic most used for gastrointestinal endoscopes [2, 3]. However, the current known side effects of using propofol mainly include local pain, cardiovascular and respiratory depression, potential headache, nausea and vomiting, and a drop in blood pressure [4, 5]. Of these, propofol injection pain is one of these problems and it was ranked seventh among the most important 33 low-morbidity clinical anesthesia problems by a panel of expert anesthesiologists [6]. In addition, propofol infusion syndrome is a rare but potentially fatal adverse event that can lead to metabolic disorders, organ system failure, and death [7].

Ciprofol (CIP) injection (HSK3486) is a new short-acting intravenous anesthetic that is a class 1 innovative drug independently developed by China and with global independent intellectual property [4]. It adds a steric effect to the chemical structure of propofol by adding cyclopropyl groups to form a chiral structure. This enhances the ability of ciprofol to bind to GABA receptors, giving it the advantage of rapid onset of action, rapid recovery, and a significant reduction in the risk of injection pain and hypotension [3, 8]. In addition, the potency of ciprofol is about five times that of propofol [9]. Currently, ciprofol has only been on the market for a short period, so ciprofol is now frequently used for anesthesia during gastrointestinal endoscopes with limited experience. Therefore, we systematically reviewed all the retrieved studies to evaluate the safety and efficacy of ciprofol for gastrointestinal endoscopes, and to further analyze the sources of heterogeneity through subgroup analysis, with a view to providing a more evidence-based basis for the clinical use of ciprofol.

Methods

Ethic statement

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions, and the results were presented according to the PRISMA (preferred reportingitems for systematic reviews and meta-analyses) statement. The protocol for this meta-analysis was registered on PROSPERO (registration number: CRD42024550466). Our data was derived directly from previously published studies, so institutional review approval and informed consent were not required.

Search strategy

Two researchers (Z. W. and S. W.) searched the studies independently, using PubMed, Embase, Cochrane Library, Web of Science (WOS), and China National Knowledge Infrastructure (CNKI) databases as search sources. The search mainly adopted the method of combining subject words and free words. Among them, the subject words included ciprofol, propofol, and random controlled trial. There were no restrictions on the type of research and the type of language. The search time was from inception to May 10, 2024. In addition, the search strategies for all databases were detailed in Supplemental Table 1.

Selection criteria

We developed a patient, intervention, comparison, outcome, and study design (PICOS) approach as the selection criteria. (a) Patient: patients with painless gastrointestinal endoscope requiring anesthesia, regardless of age, gender, or nationality; (b) Intervention: the interventions were intravenous infusion or intravenous injection; (c) Comparison: the treatment group was ciprofol and the control group was propofol, both with or without opioids, but other interventions were the same between the two groups; (d) Outcome: they reported at least one of the following outcomes, including successful rate of anesthesia, time to onset of successful induction, waking time, discharge time, overall respiratory disorders, hypotension, bradycardia, injection pain, and hypoxemia; (e) Study design: the study was a randomized controlled trial (RCT) to compare the efficacy and safety of ciprofol and propofol.

The exclusion criteria were as follows: (a) case reports, literature reviews, trial protocols, animal experiments, basic research trials, and non-randomized controlled trials; (b) unpublished study which the full text is not available; (c) the study does not provide valid data for comprehensive analysis; (d) outcome indicators do not meet the requirements of this study.

Data collection

Two researchers (Z. W. and S. W.) used EndNote X9.1 to search the literature independently, remove duplicates, and extract the data using a unified extraction table, then cross-checked. In case of disagreement, the third researcher made the final decision after a group discussion. The extraction content included authors, publication year, study location, study design, gender, body mass index (BMI), American Society of Anesthesiologists (ASA), dosage, study population size, age, and intervention measures.

Outcomes and definition

Primary outcomes encompassed a successful rate of sedation and other safety outcomes, including injection pain, hypotension, bradycardia, overall respiratory disorders, and hypoxemia. Secondary outcomes concluded time to onset of successful induction, waking time, and discharge time. The definition and criteria used for each outcome were based on the definitions provided in the individual studies, rather than imposing a single standardized definition across all studies [10]. Successful anesthesia is defined as the successful completion of a gastrointestinal endoscope without the use of other anesthetic remedies and the addition of anesthesia no more than 5 times within 15 min of the first dose. Time to onset of successful induction referred to Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≤ 1 after administration of the first dose. Waking time referred to the time finishing the procedure until the patient is awake. Discharge time referred to the time giving the last dosing until the patient was discharged from the hospital.

Risk of bias assessment

Two authors (Z. W. and S. W.) used the revised Cochrane risk of bias (RoB2) tool to assess the risk bias of each eligible study independently [11]. This tool covers 5 assessment domains, which are randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain would be assessed as 'low risk,' 'some concerns,' or 'high risk' based on the details provided by each study. The overall risk of an individual study was assessed as low if 5 domains were marked as low risk, and if one or more domains were assessed as high risk, the overall risk was assessed as high. In addition, the overall risk of an individual study was assessed as having some concerns if there was one or more domains of some concerns but no domain of high risk.

Statistical analysis

All statistical analyses were conducted using STATA 14.0 [12]. RR (risk ratio) and 95% CI (confidence interval) were used to express effect sizes for count variables and MD (mean difference) was used for continuous variables. Hypothesis testing was performed using the χ^2 test to determine the heterogeneity among the results of the included studies, and $p < 0.05$ was considered a statistically significant difference. The magnitude of heterogeneity was also quantified using I^2. $I^2 < 25\%$ was considered low heterogeneity, $25\% \leq I^2 < 50\%$ was considered moderate heterogeneity, and $I^2 \geq 50\%$ was considered high heterogeneity. When there was no statistical heterogeneity or there was low moderate statistical heterogeneity, meta-analysis was performed using a fixed-effects model. All of results and heterogeneity data of this study were presented using forest maps. When high statistical heterogeneity existed, Meta-analysis was performed using a random-effects model. We also employed the leave-one-out method to conduct sensitivity analysis. This iterative process involved systematically excluding one study at a time from the dataset and then recalculating the effect size. After excluding an article, observe whether the pooled effect estimate falls outside the 95% confidence interval (CI), thereby determining if there is a significant difference in effects before and after the article's exclusion. In this way, we were able to assess the contribution of each study to the overall results and determine the robustness and stability of the meta-analysis results. To explore the possibility of publication bias, we used funnel plots for this assessment. Funnel plots provide a graphical depiction of study effect sizes versus corresponding precision metrics, allowing for a visual assessment of potential asymmetries in the distribution of data points [13]. In addition, Egger's test has been used to assess publication bias. If $p > 0.05$, there is no publication bias in the result.

The quality of evidence

Two reviewers assessed the quality of the evidence using GRADE of Recommendations Assessment, Development, and Evaluation (GRADE) [14]. The study results were evaluated using the GRADEpro software based on bias, inconsistency, indirection, imprecision, and publication bias. The quality levels were categorized as high, moderate, low, or very low [14].

Result

Search results

A total of 20 articles [3, 15–33] were obtained. We excluded 101 duplicates as well as 117 articles with titles and abstracts that did not meet the inclusion criteria. In the end, 79 potentially eligible studies were reviewed in full. After deleting another 59 articles based on inclusion and exclusion criteria, we included 20 RCTS of ciprofol and propofol for gastrointestinal endoscope as sedation and anesthesia. They were published between 2020 and

2024 in the current meta-analysis. In the end, a total of 3779 patients were involved (Fig. 1).

Study and patient characteristic

The studies and patients' characteristics of the included studies are shown in Table 1. The study included 3779 patients, and all patients in the study underwent a gastrointestinal endoscope. The mean age of the included individuals ranged from 29 to 70 years. The sample size of the included studies ranged from 20 to 185 patients. Although all studies compared ciprofol and propofol for sedation and anesthesia, the dosage and combination of drugs differed in each study. The doses in the ciprofol group ranged from 0.2 to 0.5 mg/kg and were mostly 0.4 mg/kg. The dose in the propofol group was usually 2 mg/kg, but all studies ranged from 1 to 3 mg/kg.

Assessment of risk of bias

All of studies [3, 15–33] were accessed as low risk in randomization process and deviations from the intended

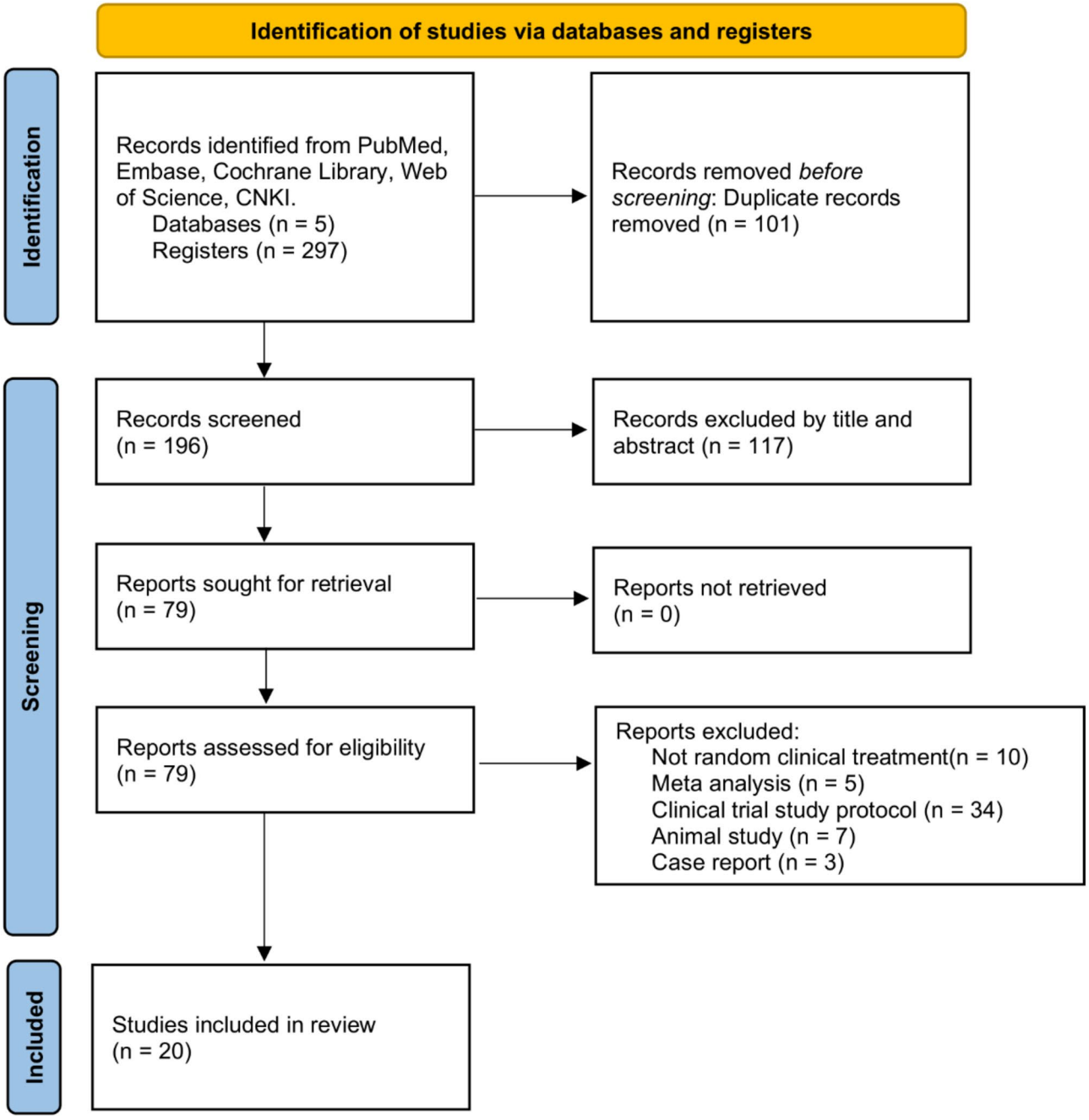

Fig. 1 PRISMA flow diagram

Table 1 Study characteristics of the included studies

Study	Study Location	Study Design	Group	No. of Participants (*n*)	Sex (Male)	Mean Age(year)	Mean BMI(kg/m^2)	ASA	Dosages(mg/kg)
Teng et al., 2021	China	RCT	Ciprofol	20	NR	44.3 ± 6.3	22.7 ± 1.5	I-II	0.4, 0.5
			Propofol	20	NR	47.4 ± 9.6	24.3 ± 3.4		2
Chen et al., 2022	China	RCT	Ciprofol	47	22	41.22 ± 11.63	25.22 ± 10.12	I-II	0.4
			Propofol	49	17	43.20 ± 12.29	23.46 ± 3.43		2
Huang et al., 2022	China	RCT	Ciprofol	82	37	47 ± 13	22.0 ± 2.4	I-II	0.4
			Propofol	82	45	46 ± 10	23.0 ± 2.7		1.5
Zhang et al., 2022	China	RCT	Ciprofol	50	28	58.12 ± 4.26	-	-	0.3–0.4
			Propofol	50	27	58.44 ± 4.25	-		1–2
Yi et al., 2022	China	RCT	Ciprofol	79	40	69.6 ± 2.8	23.2 ± 3.0	I-II	0.2
			Propofol	80	43	70.2 ± 2.9	24.1 ± 3.1		1
Li et al., 2022	China	RCT	Ciprofol	144	55	43.8 ± 11.8	23.2 ± 2.5	I-II	0.4
			Propofol	145	63	44.1 ± 11.3	23.4 ± 2.6		1.5
Chen et al., 2023	China	RCT	Ciprofol	105	22	43.55 ± 16.19	22.16 ± 3.06	I-III	0.2, 0.3, 0.4
			Propofol	44	17	47.45 ± 11.9	22.99 ± 3.01		1.5
Xia et al., 2022	China	RCT	Ciprofol	144	77	40.12 ± 2.11	22.11 ± 2.35	-	0.2
			Propofol	146	79	40.04 ± 2.13	-		1
Gao et al., 2023	China	RCT	Ciprofol	61	24	68.03 ± 4.91	24.40 ± 3.32	I-II	0.3–0.4
			Propofol	60	25	67.32 ± 3.02	24.76 ± 2.98		1.2–1.6
Liang et al., 2023	China	RCT	Ciprofol	120	59	41.3 ± 9.5	21.8 ± 2.6	I-II	0.4, 0.5, 0.6
			Propofol	39	18	42.1 ± 7.8	22.5 ± 2.9		2
Liao et al., 2023	China	RCT	Ciprofol	185	87	44.98 ± 11.74	23.07 ± 2.28	I-II	0.4
			Propofol	183	77	45.35 ± 11.12	23.13 ± 2.23		2
Liu et al., 2023	China	RCT	Ciprofol	49	26	49.02 ± 10.42	23.90 ± 2.87	I-II	0.5
			Propofol	49	27	50.78 ± 10.43	24.73 ± 2.69		2
Xiang et al., 2023	China	RCT	Ciprofol	104	48	42. 79 ± 10. 70	22. 82 ± 2.93	I-II	0.4
			Propofol	96	42	42. 97 ± 11. 54	23.57 ± 3.31		2
Xu et al., 2023	China	RCT	Ciprofol	164	89	69.6 ± 3.6	24.5 ± 2.9	I-II	0.4
			Propofol	166	90	68.9 ± 3.3	24.4 ± 2.8		2
Yang et al., 2023	China	RCT	Ciprofol	50	29	48.5 ± 4.5	-	-	0.3–0.4
			Propofol	50	31	50.5 ± 4.83	-		1–2
Zhu et al., 2023	China	RCT	Ciprofol	100	54	18–65	61.1 ± 9.6	I-II	0.4
			Propofol	100	45	18–65	62.1 ± 8.4		2
Liu et al., 2023	China	RCT	Ciprofol	175	90	39.81 ± 5.25	24.53 ± 1.22	I-II	0.2
			Propofol	175	89	39.76 ± 5.2	24.65 ± 1.33		1
Zhang et al., 2024	China	RCT	Ciprofol	93	25	18–65	-	I-II	0.3
			Propofol	92	44	18–65	-		1.2
Li et al., 2024	China	RCT	Ciprofol	109	49	47.34 ± 11.20	23.42 ± 2.79	I-II	2
			Propofol	108	48	46.36 ± 12.33	23.19 ± 3.01		0.5
Gao et al., 2024	China	RCT	Ciprofol	82	34	54	23.4 ± 3.0	I-II	0.4
			Propofol	82	32	54	23.7 ± 3.0		2

interventions. Sixteen studies [3, 15, 17, 18, 20–22, 25–33] were accessed as having low risk in terms of measurement of the outcome, while one study and three studies [16, 19, 23, 24] were accessed as having high risk and some concerns in this domain, respectively. All of studies [3, 15–33] were accessed as having low risk in missing outcome data. Seventeen studies [3, 15–22, 25, 27–33] selection of the reported result, whereas the other three studies [23, 24, 26] were accessed as having some concern in this domain. Finally, fourteen studies [15, 16, 18, 20, 22, 24–26, 28–33] were rated as having a low risk of overall bias, while three studies [3, 21, 27] and three studies [17, 19, 23] were accessed as having some concerns and high risk for overall bias (Fig. 2).

Meta-analysis of primary outcomes

Successful rate of anesthesia

Ten studies [15–21, 28, 32, 33] evaluated to successful rate of anesthesia between ciprofol ($n = 982$) and propofol ($n = 903$). The merged result showed that there was no difference in this outcome between ciprofol and propofol groups (RR: 1.00, 95% CI: 0.99 to 1.02, $p = 0.727$,

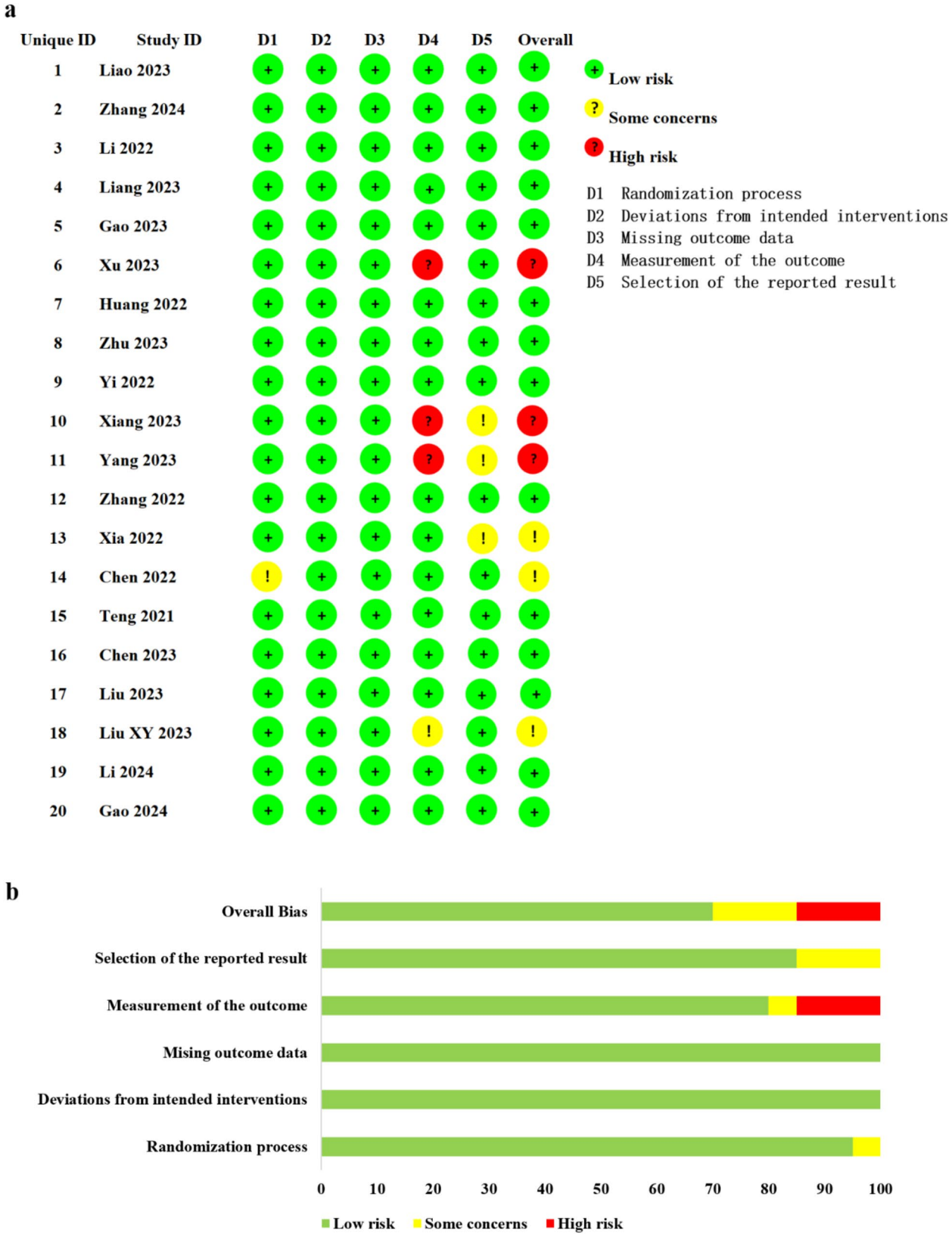

Fig. 2 Risk of bias summary (**a**) and graph (**b**)

$I^2 = 0.0\%$, moderate certainty, critical) (Figs. 3 and 4a). Sensitivity analysis was provided in Fig. S1a which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S3a and publication bias was not detected using Egger's test ($p = 0.596$). In addition, subgroup analysis showed that dose, age, and risk of bias were not factors influencing heterogeneity (Table 2, Fig. S5).

Bradycardia

Nine studies [16, 17, 19, 22, 25, 28–30, 33] evaluated the incidence of bradycardia between ciprofol ($n = 1019$) and propofol ($n = 1024$). The merged result showed that there was no statistical difference in the incidence of bradycardia between ciprofol and propofol (RR: 0.67, 95% CI: 0.52 to 0.85, $p = 0.001$, $I^2 = 0.0\%$, moderate certainty, critical) (Figs. 3 and 4b). Sensitivity analysis was provided in Fig. S2c which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S4c and publication bias was not detected using Egger's test ($p = 0.326$).

Injection pain

Fifteen studies [3, 15–20, 22, 24, 26–28, 30, 32, 33] evaluated the incidence of injection pain between ciprofol ($n = 1507$) and propofol ($n = 1369$). The merged result showed that, compared with propofol, ciprofol was associated with lower incidence of injection pain (RR: 0.10, 95% CI: 0.07 to 0.16, $p < 0.001$, $I^2 = 46.4\%$, moderate certainty, critical) (Figs. 3 and 4c). Sensitivity analysis was provided in Fig. S2a which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S4a and publication bias was not detected using Egger's test ($p = 0.076$). However, 12 studies [3, 15–20, 24–26, 28] did not provide any scoring. One study [27] included a score description but did not conduct any related statistical analysis. One study [23] expressed the pain scores using means and standard deviations. Three studies [29, 30, 32] categorized injection pain into three levels: mild, moderate, and severe pain.

Overall respiratory disorders

Thirteen studies [3, 16–18, 22–26, 28–30, 33] evaluated the incidence of overall respiratory disorders between ciprofol ($n = 1308$) and propofol ($n = 1253$). The merged result showed that, compared with propofol, ciprofol was associated with lower incidence of overall respiratory disorders (RR: 0.45, 95% CI: 0.27 to 0.75, $p < 0.001$, $I^2 = 77.1\%$, moderate certainty, critical) (Figs. 3 and 4d). Sensitivity analysis was provided in Fig. S2e which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S4e and Egger's test ($p = 0.076$) showed it was not at risk of publication bias. Subgroup analysis indicated that age ($p = 0.023$) was the cause of high heterogeneity. Besides, there was a lower incidence of overall respiratory disorders in patients older than 65 years of age (RR: 0.19, 95% CI: 0.09 to 0.39, $p < 0.001$, $I^2 = 0.0\%$) (Table 2, Fig. S15).

Hypotension

Eleven studies [16, 17, 19, 20, 22, 23, 25, 28–30, 33] evaluated the incidence of hypotension between ciprofol ($n = 1205$) and propofol ($n = 1202$). The merged result showed that, compared with propofol, ciprofol was associated with lower incidence of hypotension (RR: 0.68, 95% CI: 0.59 to 0.77, $p < 0.001$, $I^2 = 49.2\%$, moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofol	Propofol	Relative (95% CI)	Absolute		
Successful rate of anaesthesia												
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	957/982 (97.5%)	882/903 (97.7%)	RR 1.00 (0.99 to 1.02)	0 fewer per 1000 (from 10 more to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Time to onset of successful induction (Better indicated by lower values)												
14	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	reporting bias[4]	1482	1432	-	MD 0.16 lower (0.24 to 0.08 lower)	⊕OOO VERY LOW	CRITICAL
Waking time (Better indicated by lower values)												
16	randomised trials	serious[5]	serious[6]	no serious indirectness	no serious imprecision	reporting bias[7]	1355	1283	-	MD 0.07 higher (0.01 lower to 0.15 higher)	⊕OOO VERY LOW	IMPORTANT
Discharge time (Better indicated by lower values)												
6	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	481	-	MD 0.42 higher (0.29 to 0.54 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Injection pain												
15	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/1507 (3.3%)	506/1369 (37%)	RR 0.10 (0.07 to 0.16)	333 fewer per 1000 (from 310 fewer to 344 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Hypotension												
11	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	230/1205 (19.1%)	341/1202 (28.4%)	RR 0.68 (0.59 to 0.77)	91 fewer per 1000 (from 65 fewer to 116 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Bradycardia												
9	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89/1019 (8.7%)	134/1024 (13.1%)	RR 0.67 (0.52 to 0.85)	43 fewer per 1000 (from 20 fewer to 63 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Hypoxemia												
6	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/797 (8.2%)	116/713 (16.3%)	RR 0.45 (0.33 to 0.61)	89 fewer per 1000 (from 63 fewer to 109 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Overall respiratory disorders												
13	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148/1308 (11.3%)	241/1253 (19.2%)	RR 0.45 (0.27 to 0.75)	106 fewer per 1000 (from 48 fewer to 140 fewer)	⊕⊕⊕O MODERATE	CRITICAL

1
2

Fig. 3 GRADE evidence profile of all outcomes. GRADE evidence profile of all outcomes. CI, confidence interval; MD, mean difference; RR, risk ratio. Not all studies were double-blin: 1, 2, 5, 8, 9, 10, 11, 12, 13. An inconsistency factor of 97.2% was estimated: 3. An inconsistency factor of 95.2% was estimated: 6. Egger's test shows the risk of publication bias: 4, 7

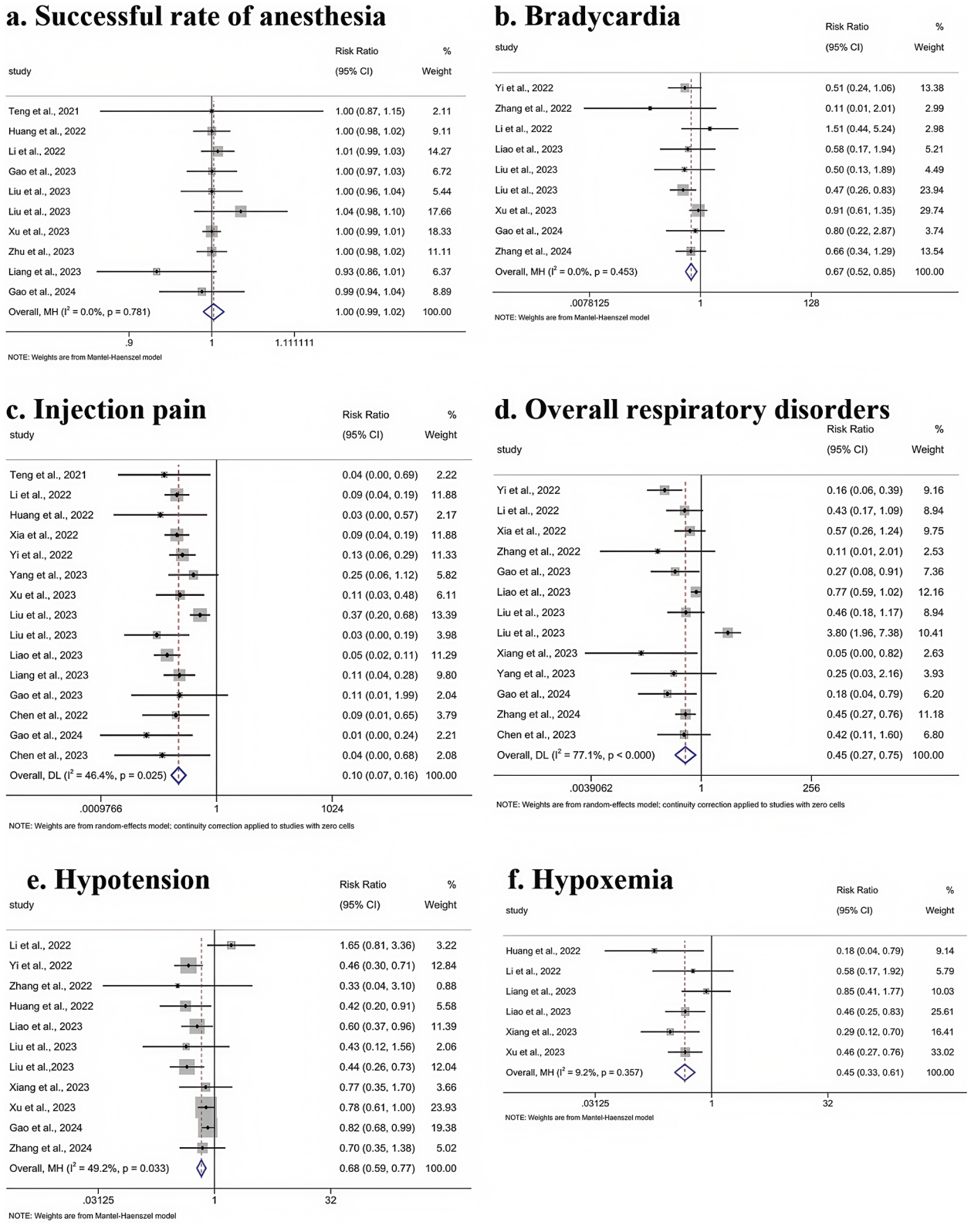

Fig. 4 Forest plot comparing successful rate of anesthesia (**a**), bradycardia (**b**), injection pain (**c**), overall respiratory disorders (**d**), hypotension (**e**), and hypoxemia (**f**) between ciprofol and propofol groups

Table 2 Subgroup analysis for all of outcomes

Subgroup	No. patients		MD/RR	95% CI	*p*	I^2	*P*-SD
	Ciprofol	Propofol					
Successful rate of anesthesia							
Age							
< 65	757	677	1.00	(0.99, 1.02)	0.727	0.0%	-
≥ 65	225	226	1.00	(1.00, 1.00)	Insufficient data	0.0%	
Dose							
≤ 0.4	793	795	1.01	(0.99, 1.02)	0.274	0.0%	0.073
> 0.4	189	108	0.97	(093, 1.01)	0.129	44.9%	
Risk of bias							
Low	494	413	0.99	(0.97, 1.01)	0.269	13.4%	0.100
Some concern or high	488	490	1.01	(0.99, 1.03)	0.222	57.4%	
Time to onset of successful induction							
Age							
< 65	1275	1206	-0.18	(-0.27, -0.1)	<0.001	97.6%	0.215
≥ 65	225	226	-0.05	(-0.24, 0.13)	0.563	0.0%	
Risk of bias							
Low	924	925	-0.05	(-0.14, 0.05)	0.332	97.7%	<0.001
Some concern or high	414	507	-0.36	(-0.48, -0.23)	<0.001	96.3%	
Waking time							
Age							
< 65	1051	977	0.04	(-0.05, 0.13)	0.407	96.1%	0.187
≥ 65	304	306	0.16	(0.00, 0.32)	0.046	0.0%	
Dose							
≤ 0.4	1250	1178	-0.01	(-0.09, 0.07)	0.812	95.4%	<0.001
> 0.4	59	59	0.82	(0.44, 1.20)	<0.001	30.8%	
Risk of bias							
Low	644	565	0.00	(-0.11, 0.12)	0.936	96.5%	0.144
Some concern or high	691	698	0.12	(0.02, 0.23)	0.024	93.7%	
Discharge time							
Age							
< 65	488	401	0.43	(0.30, 0.57)	<0.001	39.8%	0.505
≥ 65	79	80	0.32	(0.01, 0.63)	0.046	0.0%	
Dose							
≤ 0.4	327	322	0.47	(0.34, 0.61)	<0.001	0.0%	<0.001
> 0.4	190	149	-0.19	(-0.17, 0.54)	0.307	85.9%	
Risk of bias							
Low	219	139	0.22	(-0.01, 0.44)	0.056	0.0%	<0.001
Some concern or high	348	342	0.51	(0.36, 0.66)	<0.001	0.0%	
Overall respiratory disorders							
Age							
< 65	1168	1113	0.54	(0.32, 0.92)	0.023	74.9%	0.023
≥ 65	140	140	0.19	(0.09, 0.39)	<0.001	0.0%	
Dose							
≤ 0.4	1270	1204	0.44	(0.25, 0.77)	0.004	78.8%	0.943
> 0.4	38	49	0.46	(0.18, 1.77)	0.102	0.0%	
Risk of bias							
Low	692	694	0.36	(0.21, 0.63)	0.486	68.4%	0.486
Some concern or high	578	510	0.56	(0.19, 1.68)	0.300	82.0%	
Hypotension							
Age							
< 65	633	547	0.45	(0.31, 0.65)	<0.001	27.6%	0.961
≥ 65	164	166	0.46	(0.27, 0.76)	0.003	0.0%	
Dose							

Table 2 (continued)

Subgroup	No. patients		MD/RR	95% CI	*p*	I^2	*P*-SD
	Ciprofol	Propofol					
≤ 0.4	677	674	0.41	(0.29, 0.56)	<0.001	0.0%	0.069
> 0.4	120	39	0.85	(0.41, 1.77)	0.670	0.0%	
Risk of bias							
Low	529	451	0.50	(0.33, 0.75)	0.001	25.2%	0.476
Some concern or high	268	262	0.40	(0.26, 0.62)	<0.001	0.0%	
Bradycardia							
Age							
< 65	776	778	0.58	(0.41, 0.82)	0.002	0.0%	0.168
≥ 65	243	246	0.79	(0.56, 1.11)	0.172	47.5%	
Dose							
≤ 0.4	970	975	0.68	(0.53, 0.87)	0.002	7.5%	0.663
> 0.4	49	49	0.50	(0.13, 1.89)	0.306	0.0%	
Risk of bias							
Low	631	634	0.63	(0.42, 0.93)	0.021	0.0%	0.679
Some concern or high	388	390	0.70	(0.51, 0.95)	0.024	47.7%	
Injection pain							
Age							
< 65	1203	1063	0.09	(0.07, 0.12)	<0.001	62.8%	0.471
≥ 65	304	306	0.12	(0.06, 0.24)	<0.001	0.0%	
Dose							
≤ 0.4	1318	1261	0.10	(0.07, 0.13)	<0.001	57.4%	0.182
> 0.4	189	108	0.05	(0.02, 0.13)	<0.001	32.8%	
Risk of bias							
Low	926	787	0.07	(0.05, 0.10)	<0.001	0.0%	0.020
Some concern or high	581	582	0.14	(0.09, 0.21)	<0.001	72.5%	
Hypoxemia							
Age							
< 65	962	956	0.68	(0.52, 0.89)	0.004	42.8%	0.753
≥ 65	243	246	0.62	(0.37, 1.03)	0.063	76.9%	
Dose							
≤ 0.4	1156	1153	0.67	(0.54, 0.83)	<0.001	50.2%	0.502
> 0.4	49	49	0.43	(0.12, 1.56)	0.199	0.0%	
Risk of bias							
Low	713	716	0.68	(0.50, 0.92)	0.014	57.3%	0.822
Some concern or high	492	486	0.64	(0.46, 0.90)	0.009	32.9%	

CI, confidence interval; RR, relative risk; P-SD, p for subgroup difference; MD, mean difference

certainty, critical) (Figs. 3 and 4e). Sensitivity analysis was provided in Fig. S2b which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S4b and publication bias was not detected using Egger's test ($p = 0.217$).

Hypoxemia

Six studies [15, 19, 20, 23, 28, 30] evaluated the incidence of hypoxemia between ciprofol ($n = 797$) and propofol ($n = 713$). The merged result showed that, compared with propofol, ciprofol was associated with lower incidence of injection pain (RR: 0.45, 95% CI: 0.33 to 0.61, $p < 0.001$, $I^2 = 9.2\%$, moderate certainty, critical) (Figs. 3 and 4f). Sensitivity analysis was provided in Fig. S2d which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S4d and publication bias was not detected using Egger's test ($p = 0.530$).

Meta-analysis of secondary outcomes

Time to onset of successful induction

Fourteen studies [3, 16, 18–23, 26–29, 31, 33] evaluated to time to onset of successful induction between ciprofol ($n = 1482$) and propofol ($n = 1432$). When using ciprofol instead of propofol for anesthesia induction, patients had a shorter time to be anesthetized (MD: -0.16, 95% CI: -0.24 to −0.08, $p < 0.001$, $I^2 = 97.2\%$, very low certainty, critical) (Figs. 3 and 5a). One study[20] was evidenced as a source of substantial heterogeneity (Fig. S1b). After removing it, both of overall heterogeneity (92.5%) and two subgroup analyses (93.8%, 78.5%) of time to onset

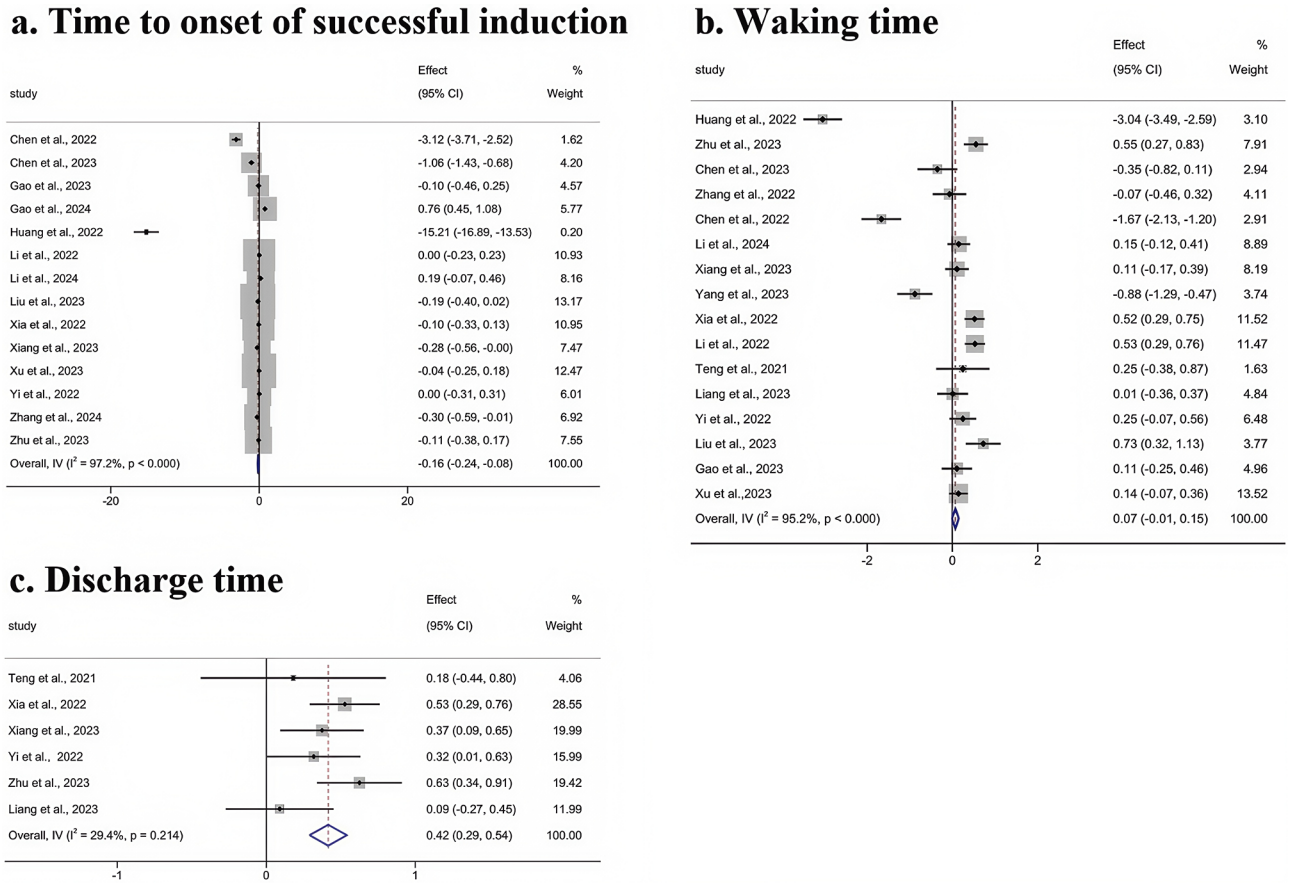

Fig. 5 Forest plot comparing time to onset of successful induction (**a**), waking time (**b**), and discharge time (**c**) between ciprofol and propofol groups

of successful induction had a minor reduction (Fig. S7). Funnel plot of this outcomes was shown in Fig. S3b and Egger's test ($p = 0.000$) showed it was at risk of publication bias. Due to the high heterogeneity, subgroup analysis was performed to identify potential sources of heterogeneity. The subgroup analysis revealed that the source of heterogeneity was different from that of the risk of bias ($p < 0.001$) (Table 2, Fig. S6). Besides, there was a statistically significant difference with the risk of some concern or high (MD: -0.36, 95% CI: -0.48 to − 0.23, $p < 0.001$, $I^2 = 96.3\%$) (Table 2, Fig. S6).

Waking time

Sixteen studies [3, 15, 17–28, 31, 32] examined the difference between ciprofol ($n = 1355$) and propofol ($n = 1283$) in terms of waking time. There was no difference in this outcome between two groups (MD: 0.07, 95% CI: -0.01 to 0.15, $p < 0.001$, $I^2 = 95.2\%$, very low certainty, important) (Figs. 3 and 5b). The same study [20] was evidenced as a source of substantial heterogeneity (Fig. S1c). After removing it, both of overall heterogeneity (88.7%%) and three subgroup analyses of waking time (91.1%, 88.6%, 44.3%) decreased slightly (Fig. S9). Funnel plot of this outcomes was shown in Fig. S3c and Egger's test ($p = 0.028$) showed it was at risk of publication bias. Subgroup analysis showed that the source of heterogeneity was from dose of ciprofol ($p < 0.001$). Besides, a statistically significant difference with ciprofol > 0.4 mg/kg (MD: 0.82, 95% CI: 0.44 to 1.20, $p < 0.001$, $I^2 = 30.8\%$) and age ≥ 65 mg/kg (MD: 0.16, 95% CI: 0.00 to 0.32, $p < 0.046$, $I^2 = 0.0\%$) result in a longer time to wake comparing propofol (Table 2, Fig. S8).

Discharge time

Six studies [15, 21–23, 26, 32] reported the difference between ciprofol ($n = 67$) and propofol ($n = 481$) in terms of discharge time. Compare to propofol, patients using ciprofol had a longer time to discharge (MD: 0.420, 95% CI: 0.29 to 0.54, $p < 0.001$, $I^2 = 29.4\%$, moderate certainty, important) (Figs. 3 and 5c). Sensitivity analysis was provided in Fig. S1d which confirmed the robustness of this results. Funnel plot of this outcomes was shown in Fig. S3d and publication bias was not detected using Egger's test ($p = 0.185$). Subgroup analysis showed that dose ($p < 0.001$) and risk of bias ($p < 0.001$) were sources of heterogeneity. Furthermore, ciprofol ≤ 0.4 mg/kg (MD: 0.47, 95% CI: 0.34 to 0. 16, $p < 0.001$, $I^2 = 0.0\%$) and risk of bias of some concern or high (MD: 0.51, 95% CI: 0.36 to 0.66,

$p < 0.001$, $I^2 = 0.0\%$) related to the longer discharge time with ciprofol comparing to propofol (Table 2, Fig. S10).

Discussion

This meta-analysis, which included 20 RCTs published from 2021 to 2024, compared ciprofol and propofol for gastrointestinal endoscopes in terms of efficacy and safety outcomes. The results showed that there was no significant difference in the success rate of anesthesia between the ciprofol and propofol groups. while ciprofol was better than propofol in overall respiratory disorders, hypotension, bradycardia, injection pain and hypoxemia. All the safety outcomes were supported by moderate evidence. In addition, comparing to propofol, shorter time to onset of successful induction and longer discharge time were related to ciprofol. This indicated that ciprofol and propofol have similar curative effects. However, ciprofol is superior to propofol in terms of injection pain and potential safety of the cardiovascular and respiratory systems. Therefore, ciprofol can be used as a good alternative to general anesthesia.

This study showed no significant difference between ciprofol and propofol in the success rate of anesthesia, presumably due to their similar molecular structure and pharmacokinetics [30]. This is in line with a previous study titled meta-analysis of the efficacy and safety of ciprofol and propofol used in painless gastrointestinal disease endoscopy matched the results [34]. A subgroup analysis of the results was performed, and we found that age, dose, and risk of bias did not affect the results. These results are of great interest to anesthesiologists, suggesting that both ciprofol and propofol are valid options that clinicians can make the proper choice based on their patients' specific circumstances and preferences.

Since propofol was first approved for clinical use in 1986, it has become one of the most commonly used intravenous general anesthetic agents, mainly because of its rapid onset and fast recovery characteristics [35]. The results of several meta-analyses indicated that ciprofol exhibited a longer induction time post-infusion compared to propofol [10, 13, 36, 37]. These findings could have implications for clinical practice, as a longer induction time may necessitate additional time for patient preparation and monitoring [13]. In contrast, this study found that ciprofol at a dose of 0.4 mg/kg demonstrated an even greater rapid induction potential than propofol. This result appears to be due to the inclusion of Huang's study. The results of sensitivity analysis for induction time, GRADE, and publication bias assessment all confirm this fact (Fig. S1b, Fig. 3).

It is a vital option to sedate for short-duration procedures, especially for a short gastrointestinal endoscopy. In this study, the analysis indicated that patients administered ciprofol took a longer time to discharge compared to those given propofol. In addition, there was no statistically significant difference in waking time between ciprofol and propofol, but one conclusion can be drawn that patients who had been given ciprofol took longer to wake. Furthermore, subgroup analysis indicated that higher dose of ciprofol and age were associated with longer waking time. Importantly, the rapid elimination of propofol can reduce the risk of residual sedation, furthermore, quicker wake and discharge can enhance patient throughput and optimize resource utilization [38, 39]. Thus, the above reasons make it a valuable drug. However, propofol may result in hypotension, bradycardia, respiratory depression, and loss of protective reflexes, especially in elderly and weak patients [40]. Therefore, monitoring of patients after surgery is very important, especially for the elderly and frail patients.

One of the most important results we had in this meta-analysis was a significant reduction in the incidence of injection pain in patients treated with ciprofol. Injection pain is a frequent complaint, occurring in up to 30% of patients receiving an intravenous bolus of propofol [41, 42]. It influences the quality of anesthesia in patients and causes an unpleasant experience [43]. There are three possible reasons for injection pain, which are the chemical structure of the drug, the concentration of the drug, and the speed of injection. First of all, the lipid solvent irritates the vein intima and activates a local kallikrein-kinin cascade by releasing bradykinin and inflammatory factors, and injection pain has been shown to occur when peripheral nerve endings are directly exposed to propofol [13]. Since ciprofol is the addition of a cyclopropyl group to propofol, it increases the lipophilic and free nature of ciprofol, which leads to a reduction in injection pain [30]. Besides, compared with propofol, ciprofol has a faster onset of action, higher target selectivity, and higher in vitro and in vivo activity, with a potency four to five times that of propofol [44]. Thus, the less injection pain of ciprofol may be related to the reduced concentration of it in the aqueous phase of the emulsion. What's more, patients who experienced injection pain were divided into two subgroups of pump intravenous and manual intravenous by a meta-analysis, which found that the incidence of injection pain was significantly reduced in the pump intravenous group [36]. This suggests that faster injection speeds might lead to higher local concentrations, leading to a higher incidence of injection pain.

Intraoperative and postoperative hypotension has recently been identified as a major risk factor for adverse outcomes in high-risk patients [45]. Reports indicate that a baseline systolic blood pressure drop of 41–50 mmHg for a short duration (>5 min) is associated with more than a threefold increase in the likelihood of myocardial infarction [45]. Additionally, intraoperative hypotension is linked to an increased risk of myocardial injury, acute

kidney failure, delirium, and stroke following non-cardiac surgery [46–50], and it may also be related to the occurrence of respiratory depression, bradycardia, and hypoxemia [51]. The results of this study show that patients using remifentanil had a lower incidence of hypotension. Therefore, hypotension may be an important modifiable risk factor for significant adverse events. For patients requiring sedation, especially high-risk individuals, it is essential to consider remifentanil as an alternative anesthetic agent.

The pooled analysis revealed that the incidence of overall respiratory depression, bradycardia, and hypoxemia in ciprofol was significantly lower than that in propofol. Hypotension may be associated with the development of respiratory depression, bradycardia, and hypoxemia. Makoto et al. think that propofol may cause hemostatic instability due to diminished systemic vascular resistance, hypoventilation due to decreased respiratory drive, and upper airway obstruction due to decreased tone of pharyngeal muscles in dose-dependent fashion [51]. However, compared with intravenous ciprofol 0.4, 0.5 mg/kg, ciprofol 0.6 mg/kg resulted in a significant decrease in SpO_2 and a significantly higher incidence of hypoxemia. This is similar with propofol. Although hypoxemia can be corrected by jaw support or mask-assisted ventilation, it should be taken seriously. If a high dose of ciprofol is applied, the trend of SpO_2 should be monitored, and timely intervention should be carried out if hypoxemia occurs [15].

It should be noted that, there is a protocol [52] that is quite similar to our content, but we are not the same study. Our article has the following main differences: (a) Our data analysis software was STATA 14.0, while this protocol uses Review Manager; (b) Our search time was from inception to May 10, 2024, whereas this protocol's end date is August 2023; (c) Only our study used GRADEpro software to classify the evidence levels of the results, which showed the reliability of the findings; (d) In terms of subgroup analysis, we categorized based on dosage, age, and risk of bias, while this protocol will divide all eligible trials into the endoscopic therapy group and endoscopic examination group or into the gastroscopy group and colonoscopy group.

There were several limitations in the current meta-analysis. First, as ciprofol is a new anaesthetic drug to be developed in China by 2020, the majority of current studies have recruited Chinese people. It may limit the applicability of our findings to patients of different ethnic or geographical backgrounds. Second, there were differences in the definition of some outcomes in those studies, which may have contributed to the large heterogeneity. Third, the dosages and combinations of drugs used in the included literature were slightly different for ciprofloxacin and propofol, which may have posed some risk of bias. Forth, the inconsistency in the pain scoring standards for injection pain prevents us from uniformly processing and comparing the results of all studies. Future research should consider adopting a standardized pain measurement method to enhance data comparability and the accuracy of analyses.

Conclusions

Based on the results of pooled analysis, we conclude that the performance of cipofol and propofol is comparable during anesthesia, and it may takes longer for cipofol to recover after surgery. However, ciprofol may greatly improve the pain problem and hemodynamic stability of intravenous propofol. Therefore, we believe that cipofol can be used as an excellent substitute for propofol.

Abbreviations

CNKI	Chinese national knowledge infrastructure
RCT	Randomized controlled trials
MD	Mean difference
CI	Confidence interval
RR	Risk ratio
GRADE	Grading of recommendations, assessment, development and evaluation
ASA	American society of anesthesiologists
PRO	Propofol
CIP	Ciprofol
WOS	Web of Science
CNKI	China National Knowledge Infrastructure
RoB	Cochrane risk of bias
BMI	Body mass index
HPI	Hypotension Prediction Index

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

Z.W and S.W wrote the main manuscript text and L.L was responsible for the software analysis of the article. M.R managed the data. Q.Z gave methodological guidance. C.L participated in the writing of some of the text and did the final review. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests
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