Systematic Review and Meta-Analysis

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Etomidate versus propofol for sedation in gastrointestinal endoscopy

A systematic review and meta-analysis of outcomes

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Abstract

Background: Propofol is increasingly being used for sedation in gastrointestinal endoscopy; however, owing to its side effects, an alternative drug is needed. We aimed to compare the safety, satisfaction, and efficacy outcomes of etomidate versus propofol in patients undergoing gastrointestinal endoscopy, including advanced endoscopic procedures.

Methods: We systematically searched Embase, PubMed, Cochrane Central Register of Controlled Trials, CINAHL (via EBSCO), China National Knowledge Infrastructure, and Web of Science (1946–April 2020) databases for randomized controlled trials of gastrointestinal endoscopy (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy) using etomidate or propofol as sedatives. We pooled odds ratios (ORs) for the safety profile and patient and anesthesiologist satisfaction using mixed-effects conditional logistic models and standardized mean differences for efficiency outcomes using random-effects models.

Results: Twenty-four studies involving 3875 patients were included. Compared with propofol, etomidate resulted in significantly reduced apnea (OR: 0.22; 95% confidence interval [CI]: 0.13–0.37; $P < .001$), hypoxemia (OR: 0.43; 95% CI: 0.35–0.54; $P < .001$), hypotension (OR: 0.20; 95% CI: 0.11–0.36; $P < .001$), and bradycardia (OR: 0.52; 95% CI: 0.30–0.91; $P = .02$) but led to increased myoclonus (OR: 8.54; 95% CI: 5.20–14.01; $P < .001$) and lowered anesthesiologist satisfaction (OR: 0.60; 95% CI: 0.39–0.91; $P = .02$).

Conclusion: Etomidate may be a good alternative to propofol for gastrointestinal endoscopy, especially advanced endoscopy. Etomidate appears to be safe as an inducer for hemodynamically unstable patients or older adult patients undergoing gastrointestinal endoscopy.

Abbreviations: CI = confidence interval, OR = odds ratio, RCT = randomized controlled trial, WMD = weighted mean difference.

Keywords: anesthesia, endoscopy, hemodynamic, intravenous anesthetic agent, respiratory stability

1. Introduction

Sedation is preferred over anesthesia during gastrointestinal endoscopy to minimize patient discomfort and allow examination in a stable state.[1–3] To successfully implement therapeutic endoscopy, the selection of an appropriate sedative is crucial for patient safety, patient and physician satisfaction, and maximum efficacy.

Currently, the most commonly used sedatives are midazolam and propofol. In a 2006 survey in the US, midazolam and propofol were used for endoscopy in approximately 75% and 25% of the patients, respectively.[4] In a 2016 South Korean survey, propofol was used for gastroscopy in approximately 54% of cases.[5] Propofol has amnesic characteristics, the advantage of a short recovery time due to rapid induction of sedation, and high metabolic clearance but also has side effects such as hypotension, respiratory depression, and injection pain.[6–9] Additionally, because of the narrow therapeutic window, propofol can induce an unintentional deep sedation state, and there is no antagonist. Especially in high-risk procedures and therapeutic endoscopy requiring a long procedure time, the demand for propofol is inevitably high, causing concerns about dose-dependent side effects.[10] Contrarily, etomidate has been used as a relatively stable drug to induce anesthesia in hemodynamically unstable patients and is being considered as an alternative to propofol.

Meta-analyses on the 2 drugs are scarce; most of the studies are from China, and none have included advanced endoscopic procedures. Recently, studies comparing the 2 drugs for diagnostic endoscopy and advanced endoscopic procedures have demonstrated different results. Thus, we conducted a meta-analysis to compare the safety, patient and anesthesiologist satisfaction, and efficacy of propofol and etomidate for optimal sedation in gastrointestinal endoscopy, including advanced endoscopy.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[11] The protocol for this systematic review was prospectively registered with PROSPERO (CRD42020184276).

2.1. Literature search and selection

The following databases were systematically searched: Embase, PubMed, the Cochrane Central Register of Controlled Trials, CINAHL (via EBSCO), China National Knowledge Infrastructure, and Web of Science (from 1946 to April 2020). Supplementary data and clinicaltrials.gov for unpublished trials were assessed for potentially eligible studies, including a manual search among conference proceedings between 2001 and 2020.

The keywords used were "colonoscopy" OR "colonoscopies" OR "colonoscopes" OR "endoscopy" OR "diagnostic" OR "procedure" OR "technique" OR "advanced" OR "EUS" OR "ERCP" OR "EMR" OR "ESD" OR "endoscopic submucosal dissection" OR "FNA" OR "endoscopic ultrasound" OR "endoscopic retrograde cholangiopancreatography" OR "endoscopic mucosal resection" OR "fine needle aspiration" OR "intervention" OR "gastrointestinal" OR "gastroscopy." The results were combined with search terms for the sedatives used ("etomidate" AND "propofol"). Additionally, the reference lists from the retrieved articles were manually searched to identify any missed studies. No language restrictions were applied. For non-English papers, we consulted a professional translator.

Both authors independently reviewed the titles and abstracts of all identified and relevant citations that were aggregated and categorized using EndNote X8 (Thomson Reuters, New York, NY). The inclusion criteria were as follows: prospective randomized controlled trials (RCTs); studies including adults aged ≥18 years who underwent a scheduled elective outpatient gastrointestinal endoscopy; studies comparing a propofol-based sedative regimen with an etomidate-based regimen; and studies assessing the incidence of sedation-related side effects, satisfaction, or efficacy measures as outcomes of interest. We excluded the following studies: non-RCTs, reviews, nonclinical studies, conference abstracts, and case observations; studies with groups that received etomidate plus propofol or propofol plus etomidate; studies reporting the results of a combination of various endoscopic procedures (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy); and studies not reporting at least 1 outcome of interest.

2.2. Outcome measures

The primary outcome was the safety profile of etomidate and propofol (hypotension, bradycardia, myoclonus, hypoxemia, and apnea). Secondary outcomes were satisfaction or efficacy (patient satisfaction, anesthesiologist-reported satisfaction, and procedure time) (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/I434).

2.3. Data extraction and quality assessment in individual studies

Both authors extracted the following data independently from each study: author names, journal, year of publication, country of origin, study population, sample size, study design, patient characteristics (age, sex), sedative characteristics (sedative regimen, protocol, administrator), and primary and secondary study outcomes (number of adverse events per group, time of measurement, satisfaction). Any disagreements in trial eligibility or data extraction between the 2 authors were resolved via consensus. Data were collected from all studies for the full analysis set.

2.4. Methodological quality appraisal

Both authors independently evaluated the methodological quality of all included trials according to the Cochrane Collaboration's Risk of Bias assessment tool Version 2[12] using the following methodological parameters: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of appropriate reported findings, and overall risk of bias (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I437).

2.5. Quality assessment and risk of bias

Both authors performed this analysis independently using the Cochrane risk-of-bias tool. Disagreements were resolved through discussions. We recorded the method used to generate the randomization schedule and conceal treatment allocation; whether blinding was implemented for participants, personnel, and outcome assessment; and whether there was evidence of incomplete outcome data and selective reporting of outcomes.

2.6. Data synthesis and statistical analyses

Data analyses were performed using Review Manager Version 5.3 (RevMan v 5.3, The Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis 3.3.070 (Biostat, Englewood, NJ).[13] We also performed 2 additional sets of sensitivity analyses: meta-analyses of only older patients and meta-analyses excluding studies with older adults and patients with obesity. A weighted random-effects meta-analysis was performed to compare etomidate with propofol.[14] The relative risk of each outcome was used as the primary outcome measure. The results were presented as forest plots. I^2 values were used to evaluate the heterogeneity. An I^2 value > 50% was considered significantly heterogeneous. Publication bias was tested using funnel plots, and $P < .05$ was considered significant (see Figure S2, Supplemental Digital Content, http://links.lww.com/MD/I438). In this study, ethical approval was not necessary because the included data were based on previously published articles, and no original clinical data were collected or utilized.

3. Results

3.1. Study and patient characteristics

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for the selection process. The initial search strategy identified 16,163 citations. We excluded 11,423 studies by eliminating duplicates and irrelevant studies. After a full-text review of the remaining 64 reports, we identified 24 studies that met the inclusion criteria.[15–38] The characteristics of the included RCTs are presented in **Table 1**. These studies were published between 2006 and 2020 and investigated a total of 3875 patients: 1913 received etomidate and 1962 received propofol. Twelve studies involved esophagogastroduodenoscopy (2640 patients), 5 involved colonoscopy (534 patients), and 7 involved advanced endoscopy (701 patients). Of the 7 studies involving advanced endoscopy, 4 included endoscopic retrograde cholangiopancreatography (347 patients), 2 included endoscopic ultrasonography (168 patients), and 1 involved a mixture of advanced endoscopy procedures (186 patients).

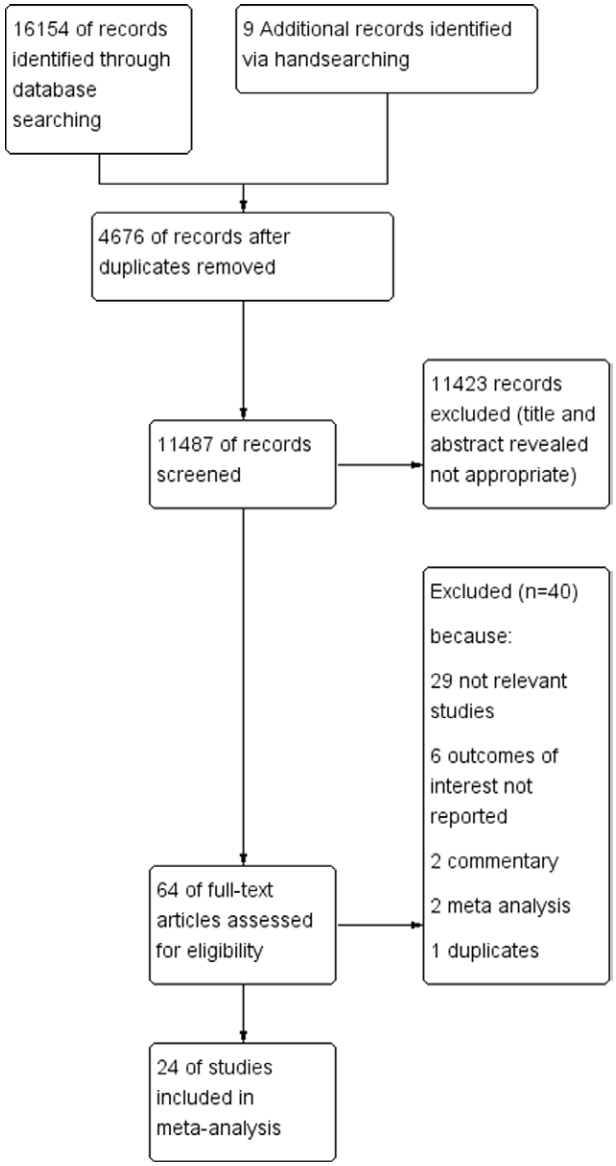

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of assessment procedures.

3.2. Primary outcome (adverse events)

1.3.2. Myoclonus. Twenty studies (3445 patients) were analyzed. Overall, the etomidate group had a significantly higher proportion of patients with myoclonus than did the propofol group (255/1719 [14.8%] vs 28/1726 [1.6%]; odds ratio [OR]: 8.54; 95% confidence interval [CI]: 5.20–14.01; $P <$ .001; Fig. 2). Subgroup analysis indicated significantly increased myoclonus in the etomidate group compared with the propofol group for each subgroup (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy) (Fig. 2).

2.3.2. Apnea. Eleven studies (1900 patients) were analyzed. Overall, the etomidate group had a significantly lower side effect of apnea than did the propofol group (25/946 [2.64%] vs 82/954 [8.60%]; OR: 0.22; 95% CI: 0.13–0.37; $P <$ .001; Fig. 2). A low level of heterogeneity across the studies was noted (I^2 = 0%; P = .85). Subgroup analysis indicated significantly decreased apnea with the etomidate group compared with the propofol group for all subgroups.

3.3.2. Hypoxemia. Sixteen studies (3205 patients) were analyzed. Overall, the etomidate group had a significantly lower hypoxemia side effect than did the propofol group (182/1599 [11.38%] vs 335/1606 [20.86%]; OR: 0.45; 95% CI: 0.36–0.55; $P <$ .001; Fig. 2). A low level of heterogeneity across the studies was noted (I^2 = 0%; P = .83). Subgroup analysis indicated that etomidate provided significantly decreased hypoxemia compared with propofol for advanced endoscopy (OR 0.34; 95% CI 0.16–0.69; P = .003) and upper gastrointestinal endoscopy (OR 0.46; 95% CI 0.36–0.58; $P <$ .001), but no difference was found for colonoscopy (OR 0.44; 95% CI 0.15–1.29; P = .14). The I^2 was 0% both for upper gastrointestinal endoscopy and colonoscopy and 9% for advanced endoscopy.

4.3.2. Hypotension. Twenty studies (3428 patients) were analyzed. Overall, the etomidate group had a significantly lower hypotension side effect than did the propofol group (92/1711 [5.38%] vs 298/1717 (17.36%); OR: 0.20; 95% CI: 0.11–0.36; $P <$ .001; Fig. 2). A high level of heterogeneity across the studies was noted (I^2 = 70%; $P <$ .001). Subgroup analysis indicated significantly decreased hypotension with the etomidate group compared with the propofol group for all subgroups (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy) (Fig. 2). The I^2 was 82%, 55%, and 0% for upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy, respectively.

5.3.2. Bradycardia. Thirteen studies (1521 patients) were analyzed. Overall, the etomidate group had a significantly lower bradycardia side effect than did the propofol group (34/760 [4.47%] vs 70/761 [9.20%]; OR: 0.52; 95% CI: 0.30–0.91; P = .02; Fig. 2). Heterogeneity across the studies was noted (I^2 = 23%; P = .21). However, subgroup analysis indicated no significant difference in bradycardia between the propofol and etomidate groups for each subgroup (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy).

3.3. Secondary outcomes (anesthetic performance)

1.3.3. Patient satisfaction. Twelve studies (2620 patients) were analyzed. No significant difference was observed in patient satisfaction between the propofol and etomidate groups (OR: 1.071; 95% CI: 0.710–1.614; P = .745; Fig. 3); heterogeneity was observed across the studies (I^2 = 43.2%; P = .062).

2.3.3. Anesthesiologist satisfaction. Four studies (1615 patients) were analyzed, all on upper gastrointestinal endoscopy. The etomidate group had a significantly lower physician satisfaction than did the propofol group (688/805 [85.47%] vs 729/810 [90%]; OR: 0.60; 95% CI: 0.39–0.91; P = .02; Fig. 3); heterogeneity was observed across the studies (I^2 = 36%).

3.3.3. Procedure time. Seventeen studies (3110 patients) were analyzed. No overall difference in procedure time was observed between propofol and etomidate (weighted mean difference [WMD]: –0.03 min; 95% CI: –0.17–0.12; P = .71; Fig. 3). Heterogeneity across the studies was noted (I^2 = 18%; P = .24). However, subgroup analysis indicated that etomidate had a significantly shorter procedure time than did propofol for advanced endoscopy (WMD: –2.15 min; 95% CI: –4.11–-0.19; P = .03; Fig. 3) but a longer procedure time for colonoscopy (WMD: 1.40 min; 95% CI: 0.13–2.68; P = .03; Fig. 3); no difference was found for upper gastrointestinal endoscopy (WMD: 0.00 min; 95% CI: –0.07–0.08; P = .91; Fig. 3). I^2 was 0% for both upper gastrointestinal endoscopy and colonoscopy and 17% for advanced endoscopy.

Table 1

Characteristics of the randomized controlled trials for etomidate versus propofol during gastrointestinal endoscopy.

Sr. no.	Study	Country and number of centers	Sample size (E:P)	Operation	Study population	Etomidate group				Propofol group				Outcomes	Protocol
						Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI		
1	Shen et al, 2015[14]	China, 1 site	715 (355:360)	Gastrointestinal endoscopy	Elderly patients	Remifentanil + etomidate	66.3 ± 4.87	200/155	BMI 21.58 ± 3.45	Remifentanil + propofol	66.31 ± 6.9	203/157	BMI 21.86 ± 3.4	a, b, c, d, e, f, g	E: 0.4–0.6 μg/kg remifentanil, etomidate at 0.1–0.15 mg/kg followed by 4–6 mg P: 0.4–0.6 μg/kg remifentanil, propofol at 1–2 mg/kg followed by 20–40 mg
2	Meng et al, 2016[15]	China, 1 site	100 (50:50)	Gastrointestinal endoscopy	Elderly patients	Fentanyl + etomidate	69.7 (65–80)	25/25	BW 62.4 (52–82)	Fentanyl + propofol	68.4 (65–78)	24/26	BW 60.7 (50–84)	a, d, e, f, g, h	E: 1.0 μg/kg fentanyl, etomidate at 0.15– 0.2 mg/kg followed by 0.4 μg/kg/h P: 1.0 μg/kg fentanyl, propofol at 1.5–2.0 mg/kg, 4.0 mg/kg/h maintenance dose of propofol
3	Liu et al, 2017a [17]	China, 1 site	14 5 (72:73)	Gastrointestinal endoscopy	Adult patients (aged 18–80 yr)	Fentanyl + etomidate	51.1 ± 14.2	38/34	BW 67.2 ± 13.9	Fentanyl + propofol	48.4 ± 10.8	34/39	BW 66.6 ± 14.3	d, f	E: 0.8 mg/kg fentanyl, etomidate induction at 0.3 mg/kg, maintenance infusion of 0.06 mg/kg P: 0.8 mg/kg fentanyl, propofol at 1–2 mg/kg, 0.50 mg/kg maintenance dose of propofol
4	Xiao 2018[16]	China, 1 site	300 (150:150)	Gastrointestinal endoscopy	Overweight or obese patients	Remifentanil + etomidate	44.54 ± 10.02	101/49	BMI 28.53 ± 2.21	Remifentanil + propofol	43.67 ± 9.13	103/47	BMI 28.75 ± 2.48	a, b, c, d, e, f, g	E: 0.4–0.6 μg/kg remifentanil, etomidate at 0.1– 0.15 mg/kg followed by 4–6 mg P: 0.4–0.6 μg/kg remifentanil, propofol at 1–2 mg/kg followed by 20–40 mg
5	Toklu et al, 2009[18]	Turkey, 1 site	60 (30:30)	Colonoscopy	Adult patients (aged 18–65 yr)	Remifentanil + etomidate	48 ± 11 (28–65)	12/18	BW 72 ± 12 (51–95)	Remifentanil + propofol	51 ± 11 (21–64)	13/17	BW 68 ± 11 (48–87)	c, d, e, g, h	E: 0.1 μg/kg/min remifentanil, etomidate at 0.1 mg/kg followed by 0.05 mg/kg P: 0.1 μg/kg/min remifentanil, propofol at 0.5 mg/kg followed by 0.25 mg/kg
6	Banihashem et al, 2015[19]	Iran, 1 site	90 (43:47)	Colonoscopy	Adult patients (aged 18–55 yr)	Fentanyl + etomidate	36.6 ± 9.7	23/20	NA	Fentanyl + propofol	36.6 ± 11.4	23/24	NA	c, e	E: 1 μg/kg fentanyl, etomidate at 0.1 mg/kg (15 μg/kg/min) P: 1 μg/kg fentanyl, propofol at 0.5 mg/kg (25 μg/kg/min)
7	Lee et al, 2019[20]	South Korea, 1 site	200 (100:100)	Colonoscopy	Adult patients	Etomidate + midazolam	58.17 ± 16.28	54/46	BMI 23.14 ±3.23	Propofol + midazolam	57.14 ± 14.5	50/50	BMI 23.83 ± 3.52	a, c, d, f, g, h	E: 0.05 mg/kg midazolam, etomidate at 0.1 mg/kg followed by 0.05 mg/kg P: 0.05 mg/kg midazolam, propofol at 0.5 mg/kg followed by 0.25 mg/kg
8	Lee et al, 2018[21]	South Korea, 1 site	124 (62:62)	Colonoscopy	Elderly patients	Etomidate + midazolam	71.37 ± 5.20	41/21	BMI 23.32 ± 3.02	Propofol + midazolam	71.26 ± 4.53	37/25	BMI 24.84 ± 2.97	a, c, d, f, g	E: 0.035 mg/kg midazolam, etomidate at 0.07 mg/kg followed by 0.035 mg/kg P: 0.035 mg/kg midazolam, propofol at 0.35 mg/kg followed by 0.175 mg/kg
9	Wu et al, 2017[22]	China, 1 site	40 (20:20)	Endoscopic ultrasonography	Adult patients	Fentanyl + etomidate	51.3 ± 10.7	11/9	BMI 22.4 ± 3.5	Fentanyl + propofol	50.7 ± 11.4	8/12	BMI 22.7 ± 3.6	c, d, f, g	E: 0.5 μg/kg fentanyl, etomidate at 0.3 mg/kg followed by 0.8–1.0 mg/kg/h P: 0.5 μg/kg fentanyl, propofol at 2.0 mg/kg, 4.0–6.0 mg/kg/h

(*Continued*)

Table 1

(*Continued*)

Sr. no.	Study	Country and number of centers	Sample size (E:P)	Operation	Study population	Etomidate group				Propofol group				Outcomes	Protocol
						Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI		
10	Kim et al, 2017[23]	South Korea, 1 site	128 (64:64)	Endoscopic ultrasonography	Adult patients	Etomidate	54.17 ± 14.47	29/35	BMI 23.42 ± 4.13	Propofol	49.83 ± 16.91	33/31	BMI 23.51 ± 4.31	a, c, d, e, f, g, h	E: etomidate at 0.1 mg/kg followed by 0.05 mg/kg P: propofol at 0.5 mg/kg followed by 0.25 mg/kg
11	Song et al, 2015[24]	China, 1 site	80 (40:40)	ERCP	Adult patients	Etomidate + midazolam	55.8 ± 10.6	28/12	BW 62.4 ± 11.4	Propofol + midazolam	52.4 ± 11.4	28/12	BW 63.5 ± 11.8	a, c, d, e, f, g, h	E: 0.5 μg/kg fentanyl, etomidate at 0.3 mg/kg followed by 0.8–1.0 mg/kg/h P: 0.5 μg/kg fentanyl, propofol at 2.0 mg/kg, 4.0–6.0 mg/kg/h
12	Park et al, 2018[25]	South Korea, 1 site	127 (64:63)	ERCP	Adult patients	Midazolam + meperidine + etomidate	59.2 ± 17.4	35/29	BMI 24.6 ± 4.2	Midazolam + meperidine + propofol	62.7 ± 17.8	25/38	BMI 24.1 ± 4.0	a, c, d, e, f, g, h	E: 1 μg/kg fentanyl, etomidate at 0.3 μg/mL P: 1 μg/kg fentanyl, propofol at 3 μg/mL
13	Han et al, 2019[26]	South Korea, 1 site	186 (92:94)	ERCP, ESD, multiple EMR	Adult patients	Midazolam + fentanyl + etomidate	60.6 ± 12.84	61/31	BMI 23.9 ± 2.98	Midazolam + fentanyl + propofol	63.9 ± 13.06	62/32	BMI 23.0 ± 3.34	a, c, d, f, g, h	E: 0.5 μg/kg remifentanil, etomidate at 0.15–0.3 mg/kg followed by 7.5 mg P: 0.5 μg/kg remifentanil, propofol at 1.0–2.0 mg/kg followed by 15 mg
14	Jain et al, 2020[27]	India, 1 site	60 (30:30)	ERCP	Adult patients (ASA grade IIII, aged 18–70 yr, weight 45–90 kg)	Dexmedetomidine + midazolam + butorphanol etomidate	NA	NA	NA	Dexmedetomidine + midazolam + butorphanol propofol	NA	NA	NA	a, d	E: 50 μg fentanyl, etomidate 6–10 mL (0.2%) followed by 1/3–1/4 of the initial dose P: 50 μg fentanyl, propofol 6–10 mL (1%) followed by 1/3–1/4 of the initial dose
15	Wang et al, 2011[28]	China, 1 site	60 (30:30)	Colonoscopy	Adult patients (ASA grade 1–2, aged 18–70 yr, weight 40–80 kg)	Fentanyl + etomidate	43 ± 10	14/16	BW 59 ± 12	Fentanyl + propofol	45 ± 9	15/15	BW 62 ± 12	f, g, h	E: 5 mg sufentanil, etomidate at 0.2 mg/kg P: 5 mg sufentanil, propofol at 0.2 mg/kg
16	Li et al, 2019[29]	China, 1 site	200 (100:100)	Gastrointestinal endoscopy	Elderly patients (62–73)	Remifentanil + etomidate	63.8 ± 5.2	NA	BW 77.64 ± 9.04	Remifentanil + propofol	62.5 ± 6.8	NA	BW 78.26 ± 7.91	f, g	E: 0.5 μg/kg fentanyl, etomidate at 0.2 μg/kg P: 0.5 μg/kg fentanyl, propofol at 1.5 μg/kg
17	Xu et al, 2015[30]	China, 1 site	200 (100:100)	Gastrointestinal endoscopy	Adult patients (ASA grade 1–2, aged 40–60 yr, weight 55–75 kg)	Sufentanil + etomidate	38.2 ± 5.8	47/53	BW 66.5 ± 2.6	Sufentanil + propofol	37.9 ± 6.5	63/37	BW 65.3 ± 3.8	c, d, f	E: 2% lidocaine 2 mL, etomidate at 0.2 mg/kg followed by 5–7 mg P: 2% lidocaine 2 mL, propofol at 1.6 mg/kg
18	Guo 2017a[31]	China, 1 site	120 (60:60)	Gastrointestinal endoscopy	Adult patients (ASA grade 1–2, aged 22–85 yr, weight 42–82 kg)	Fentanyl + etomidate	57.20 ± 12.56	28/32	BW 63.65 ± 6.72	Fentanyl + propofol	55.15 ± 12.73	26/34	BW 61.87 ± 6.43	d, e, g, h	E: 0.1 μg/kg sufentanil, etomidate 50 mL/h (0.2%) P: 0.1 μg/kg sufentanil, propofol 50 mL/h (1%)

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Table 1

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Sr. no.	Study	Country and number of centers	Sample size (E:P)	Operation	Study population	Etomidate group				Propofol group				Outcomes	Protocol
						Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI		
19	Guo et al, 2014[32]	China, 1 site	80 (40:40)	Gastrointestinal endoscopy	Elderly patients (ASA grade 1–2, aged 65–77 yr, weight 46–82 kg)	Fentanyl + etomidate	NA	NA	NA	Fentanyl + propofol	NA	NA	NA	d	E: 0.4–0.6 μg/kg remifentanil, etomidate at 0.1–0.15 μg/kg followed by followed by 1/3–1/4 of the initial dose P: 0.4–0.6 μg/kg remifentanil, propofol at 1–2 μg/kg followed by followed by 1/3–1/4 of the initial dose
20	Chen 2017[33]	China, 1 site	120 (60:60)	Gastrointestinal endoscopy	Elderly patients p (ASA grade 1–2, aged 60–72 yr, weight 50–80 kg)	Sufentanil + etomidate	56.25 ± 1.89	31/29	BW 61.07 ± 1.61	Sufentanil + propofol	55.15 ± 2.38	30/30	BW 59.69 ± 1.38	c, d, e, g, h	E: 0.05 mg/kg midazolam, 25 mg im meperidine etomidate at 0.05 mg/kg P: 0.05 mg/kg midazolam, propofol at 0.25 mg/kg
21	Chun and Zhen 2018[34]	China, 1 site	200 (100:100)	Gastrointestinal endoscopy	Adult patients (ASA grade I–III, aged 18–65 yr, weight 40–90 kg)	Remifentanil + etomidate	45.87 ± 12.43	66/34	BMI 20.89 ± 2.69	Remifentanil + propofol	46.05 ± 11.02	68/32	BMI 21.37 ± 3.16	a, b, c, d, f, g, h	E: Dexmedetomidine 1 μg/kg 2 mg midazolam, 1 mg butorphanol etomidate at 0.3 mg/kg followed by 8–10 μg/kg/min P: dexmedetomidine 1 μg/kg, 2 mg midazolam, 1 mg butorphanol propofol at 1.5 mg/kg followed by 100–150 μg/kg/min
22	Guo et al, 2017b[35]	China, 1 site	400 (200:200)	Gastrointestinal endoscopy	Elderly patients (ASA grade 1–3, aged 60–80 yr)	Remifentanil + etomidate	67.01 ± 6.92	111/89	BMI 21.83 ± 3.36	Remifentanil + propofol	66.83 ± 6.73	113/87	BMI 21.62 ± 3.25	a, b, c, d, f, g	E: 2–2.5 mg midazolam, 30 μg/kg/min followed by 8–12 μg/kg/min P: 2–2.5 mg midazolam, 0.3 mg/kg/min, followed by 0.12–0.18 mg/kg/min
23	Liu et al, 2020[36]	China, 1 site	80 (40:40)	ERCP	Adult patients (ASA grade I–III, aged 18–65 yr)	Remifentanil + dexmedetomidine + etomidate	53 ± 10	22/18	BW 65 ± 13 (BMI 23.3 ± 3.2)	Remifentanil + dexmedetomidine + propofol	49 ± 11	23/17	BW 68 ± 10 (BMI: 24.5 ± 2.5)	c, g, h	E: 2.0 ng/mL remifentanil, dexmedetomidine 0.5 μg/kg/h 2 min, etomidate at 0.5 μg/mL/ P: 2.0 ng/mL remifentanil, dexmedetomidine 0.5 μg/kg/h 2 min, propofol at 2.0 μg/mL
24	Liu et al, 2017b[37]	China, 1 site	60 (30:30)	Gastrointestinal endoscopy	Elderly patients (ASA grade 1–2, aged 60 yr)	Fentanyl + etomidate	70.1 ± 8.2	20/10	BW 69.8 ± 14.3	Fentanyl + propofol	68.7 ± 5.7	18/12	BW 71.5 ± 18.1	c, d, e, g, h	E: 1 μg/kg fentanyl, etomidate at 0.3 mg/kg P: 1 μg/kg fentanyl, propofol at 1.5 mg/kg

Outcomes: (a) patient satisfaction; (b) anesthesiologist satisfaction; (c) procedure time; (d) myoclonus; (e) apnea; (f) hypoxemia; (g) hypotension; and (h) bradycardia.

ASA = American Society of Anaesthesiology, BMI = body mass index, BW = body weight, E = etomidate, EMR = endoscopic mucosal resection, ERCP = endoscopic retrograde cholangiopancreatography, ESD = endoscopic submucosal dissection, F = female, M = male, NA = not available, P = propofol.

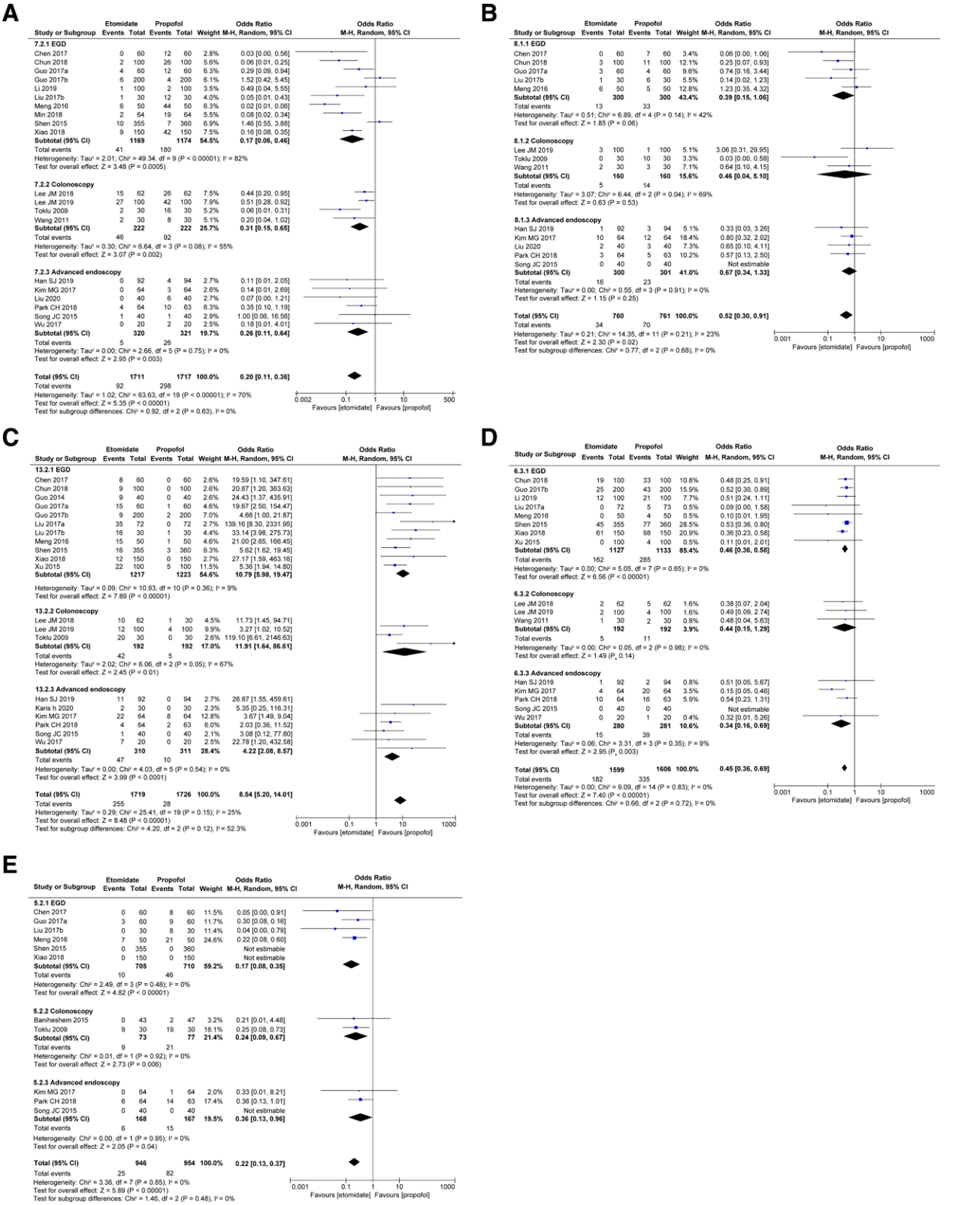

Figure 2. Forest plot of randomized controlled trials on the safety profile of etomidate and propofol. (A) Hypotension. (B) Bradycardia. (C) Myoclonus. (D) Hypoxemia. (E) Apnea. CI = confidence interval.

4. Discussion

Our meta-analysis found no significant overall difference in procedure time or patient satisfaction between etomidate and propofol. However, compared with propofol, etomidate resulted in significantly reduced apnea or hypoxemia, hypotension, and bradycardia but increased myoclonus.

Based on the analysis of endoscopy type, no/low heterogeneity was found for procedure time, apnea, and hypoxemia in

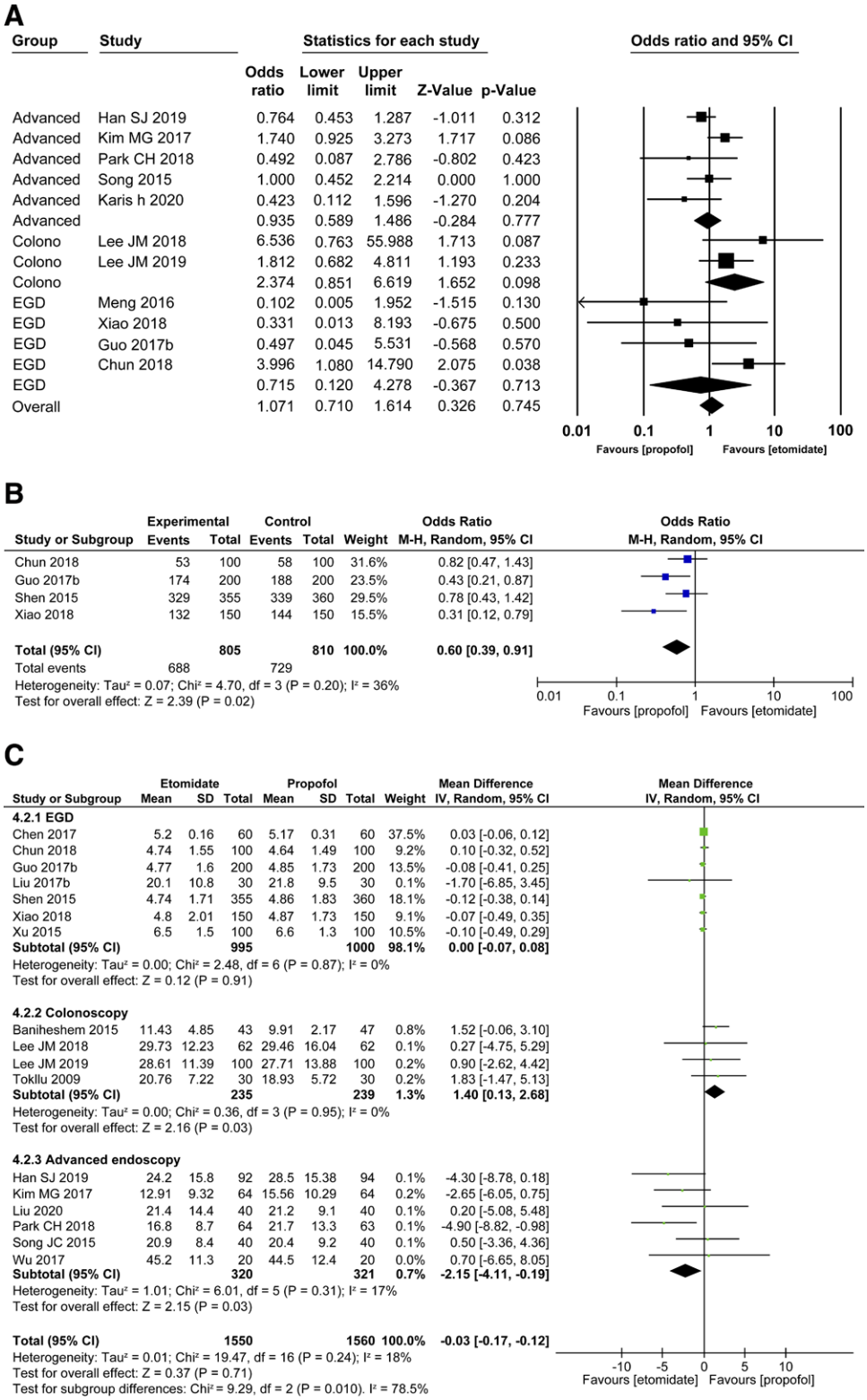

Figure 3. Forest plot of satisfaction or efficacy of etomidate and propofol. (A) Patient-reported satisfaction. (B) Anesthesiologist-reported satisfaction. (C) Procedure time. CI = confidence interval.

all types of endoscopies (esophagogastroduodenoscopy, colonoscopy, and advanced endoscopy); no/low heterogeneity was found for myoclonus and bradycardia only in advanced endoscopy. Importantly, the etomidate group showed safer results than the propofol group for hypotension and apnea in all subgroup analyses of esophagogastroduodenoscopy, colonoscopy, and advanced endoscopy. In esophagogastroduodenoscopy and advanced endoscopy, similar results were found for hypoxemia. In colonoscopy, procedure time increased in the etomidate group. However, the etomidate group showed a decrease in procedure time in advanced endoscopy, with etomidate being safer than propofol for sedation and comparable in efficacy.

To date, only 1 meta-analysis has analyzed 6 studies between 2009 and 2016 comparing etomidate and propofol.[39] However, all but 1 study had a relatively small sample size (<100), and both gastroscopy and colonoscopy were analyzed together. The majority of the studies were conducted in China; moreover, inaccessible/unpublished articles and missing data can bias the pooled effect. Therefore, we additionally manually searched extensive databases, including CINAHL and China National Knowledge Infrastructure, through exhaustive and contemporary searches for all possible RCTs. We believe ours is the first meta-analysis to analyze the efficacy and safety of etomidate and propofol by endoscopy type, including advanced endoscopy. Our results were mostly consistent with those of previous meta-analyses (patient satisfaction, apnea, hypoxemia, and myoclonus) but did show a few differing results (hypotension). The different types of endoscopies showed high heterogeneity, except advanced endoscopy, which showed no heterogeneity. In contrast to a previous meta-analysis,[39] we found that etomidate caused hypotension less frequently than propofol. This is consistent with other reports.[6,40–42]

Because etomidate also had safer results than propofol for apnea, hypoxemia, hypotension, and bradycardia, it is considered safe as an inducer in hemodynamically unstable patients and may be considered an alternative to propofol.[43,44] Propofol is preferred for shorter procedures because it is a better inducer than etomidate with fewer side effects, faster action, and faster recovery.[45–47] Therefore, we suggest that etomidate be the sedative of choice for advanced endoscopy with long procedure times; its side effects may be reduced with pretreatment agents or by combining it with other sedatives. The combined use of propofol and etomidate in gastroscopy can be effective[48]; the use of combination drugs in advanced endoscopy can be considered, yet further research is needed.

Lee et al reported that although patients receiving etomidate did not show a significant difference in procedure time from those receiving propofol, the patients who received etomidate presented with more frequent body movements during the procedure and had more frequent side effects that interfered with the procedure than did those who received propofol, making the procedure more difficult for the assistant/nurse than for the endoscopist.[22] In our meta-analyses, similar results were seen in the colonoscopy subgroup analysis of 4 studies.[19–22] Contrastingly, in our meta-analyses, the procedure time for etomidate was decreased in advanced endoscopy. Of the 6 studies analyzed, 5 did not show a significant difference,[23–25,27,37] and only 1 study (Park et al) showed a significant decrease in the etomidate group.[26] When that was excluded as leave-1-out, there was no significant difference between the 2 groups, and heterogeneity was reduced from 17 to 0%. Thus, further research is required, and an appropriate drug should be selected according to the patient's age and general condition and the American Society of Anesthesiology score.

Our study had limitations. First, we excluded the analysis of etomidate and propofol combinations; combined use can reduce individual quantities of propofol and etomidate, thus reducing the side effects of each drug. Therefore, further research is needed for optimal sedation. Second, no analysis of sedation administrators was conducted; anesthesiologists administered sedation in 6 studies,[15–17,20,35,37] nurses – trained and certified in advanced cardiac life support – administered anesthesia in 5 studies,[21,22,24,26,27] and the remainder were insufficiently reported. Administrators of sedation vary – nurses, endoscopists and physicians, and gastroenterologists – and may have different levels of training. Furthermore, different sedation levels may be exhibited depending on the administration method. Therefore, our results need to be interpreted with caution. Third, although etomidate and propofol were being evaluated, other pretreatment agents may cause various side effects. Fourth, although the meta-analysis largely included healthy adults, elderly (>60 years old) and obese individuals were included. The majority of the results of our sensitivity analyses, excluding the older adult and obese patients and including only older adult patients, did not show any significant difference compared with our overall results (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/I435 and Table S3, Supplemental Digital Content, http://links.lww.com/MD/I436). Our meta-analysis demonstrated that etomidate was safer than propofol for sedation and comparable in efficacy, even for the older adult population.

In conclusion, etomidate can be a good alternative to the conventional sedative, propofol, for sedation in gastrointestinal endoscopy, especially advanced endoscopy. Further studies on the efficacy and safety of pretreatment agents and combinations of sedatives are needed.

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Formal analysis: Ji Taek Hong, Sung-Wook Park.
Investigation: Ji Taek Hong.
Methodology: Ji Taek Hong, Sung-Wook Park.
Software: Ji Taek Hong.
Writing – original draft: Ji Taek Hong.
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