Sevoflurane *vs.* Propofol Anaesthesia and the Risk of Perioperative Acute Kidney Injury

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ABSTRACT

Sevoflurane has been suggested to lower the incidence of acute kidney injury (AKI) after heart surgery compared to intravenous anaesthetics. However, recent studies indicated opposite results. Therefore, this meta-analysis was conducted on randomised controlled trials (RCTs) to determine if sevoflurane decreases the risk of AKI compared to propofol. Relevant RCTs were identified from PubMed, EMBASE databases, and reference lists of reviews and related articles till June 6, 2023. Review Manager was used for statistical analysis. In this study, 10 RCTs were included. Compared with propofol, sevoflurane increased the incidence of AKI (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.62-4.65; p = 0.0002; I^2 = 13%) and prolonged the length of intensive care unit (standard mean difference [SMD], 0.29; 95% CI, 0.06–0.53; p = 0.01; I^2 = 0%) and hospital stays (mean difference [MD], 1.62; 95% CI, 0.59–2.64; p = 0.002; I^2 = 0%). Based on current evidence, sevoflurane was linked to an increased risk of perioperative AKI compared to propofol. To verify the results, more high-quality RCTs are necessary.

Key Words: *Acute kidney injury, Sevoflurane anaesthesia, Propofol anaesthesia, Perioperative renal complications, Serum creatinine.*

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INTRODUCTION

As a perioperative complication, acute kidney injury (AKI) affects patient prognosis, hospital stay, and hospital costs.[1-3] The pathogenesis of perioperative AKI was still unclear. Numerous risk factors are linked to perioperative AKI, including blood loss and prolonged hypotension after surgery, as well as patient variables such as age, comorbidities, and medication. It has been demonstrated that certain anaesthetics impact perioperative renal function. For instance, dexmedetomidine's anti-inflammatory, anti-sympathetic, and apoptotic effects help lessen kidney damage.[4]

Both propofol and sevoflurane were widely used anaesthetics. The perioperative renal function effects of propofol or sevoflurane were still unresolved. Volatile anaesthetics such as sevoflurane have been shown to have a protective effect against ischaemia-reperfusion injury and other organ functions during the perioperative period.[5-8]

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However, studies have indicated that sevoflurane had an impact on renal excretion function, leading to decreased urine output and sodium excretion, increased plasma renin and serum creatinine, and the development of AKI.[9-11] Propofol was viewed as having a divine protective function compared to sevoflurane because of its anti-inflammatory and antioxidant effects.[12] Even though Cai *et al*. carried out a meta-analysis on the effects of volatile anaesthetics and total intravenous anaesthesia on renal function in patients undergoing heart surgery in 2014, current studies still yield conflicting results.[13] The effect of propofol or sevoflurane on perioperative renal function remains controversial, based on current research. This meta-analysis was conducted to investigate if sevoflurane anaesthesia increases the risk of perioperative AKI compared to propofol.

METHODOLOGY

This analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered on the International Prospective Register of Systematic Reviews platform (No. CRD42022338813). Medical Subject Headings (MeSH) terms and keywords including propofol, sevoflurane, surgical treatment or perioperative period, and kidney were used as search strategies for literature search. The relevant research on PubMed and the Excerpta Medica Database (EMBASE) up to March 2023 was selected. The relevant studies and their literature lists were searched manually to make sure there were no omissions.

Inclusion criteria were randomised controlled trials (RCTs) exploring the occurrence of perioperative renal complications. During the maintenance stage, the experimental group was given sevoflurane anaesthesia without propofol, while the control group was given propofol anaesthesia without sevoflurane. The study contained detailed information, including the number of cases, controls, and completed trials. Measurement indicators included AKI, serum creatinine, cystatin C, creatinine clearance, neutrophil gelatinase-associated lipocalin (NGAL), urine output, length of hospital stay, and intensive care unit (ICU) stay. The studies published in English language and conducted on adult subjects were included. Exclusion criteria were those studies that did not meet any of the aforementioned and inclusion criteria. In this meta-analysis, all studies included explicitly stated that they were conducted after an approval by ethical review committee.

Duplicate studies were eliminated. The screening was done by the third and fourth authors separately and the reasons for exclusion for each study were documented. For controversial studies, the inclusion was decided by the second author. The third and fourth authors utilised standard data extraction forms to extract the data. The extracted information included the number and race of subjects, surgery type, anaesthesia protocol, number of perioperative AKI, the concentration of renal injury markers (serum creatinine, cystatin C, NGAL, creatinine clearance, and urine output), ICU, and hospital stay time.

Each study was evaluated for bias by the second and third authors using Review Manager (Revman 5.4, UK) separately, which included the generation of random sequences, allocation concealment, investigator and subject blindness, blindness in outcome assessment, completeness of outcome data, and other biases.[14]

The study's primary outcome was the incidence of perioperative AKI. Secondary outcomes included the levels of markers linked to renal injury, the length of hospital stay, and ICU stay. The estimated mean and standard deviation were calculated and extracted in studies that reported medians and interquartile ranges (IQR).

Revman was used for the statistical analysis. In this study, the effect size of dichotomous variables was reflected by the odds ratio (OR), and the effect size of continuous variables was depicted in either the standardised mean difference (SMD) or mean difference (MD), and the 95% confidence intervals (CI) of both were calculated simultaneously. I^2 was used to represent the heterogeneity of the study. The random-effect model was employed when there was heterogeneity, and the fixed-effect model was utilised when there was no significant heterogeneity between the studies. Subgroup analyses were conducted to prevent bias if necessary. Moreover, when there was significant heterogeneity, sensitivity analysis was used to determine if the results were influenced by individual studies by calculating pooled effect sizes after removing one study at a time to find the source of heterogeneity.[12] Publication bias was evaluated using Begg's and Egger's tests conducted by STATA (version 10.0, USA), and the criteria for significant bias was a p-value of less than 0.05.

RESULTS

After removing 178 duplicate research, 2,072 papers were initially obtained. Following a preliminary review, 1,908 items were excluded. The remaining 164 research were evaluated in further detail. Finally, 10 studies were included in the analysis.[11,12,15-22] The process of choosing literature is present in Figure 1.

A total of 1,216 subjects (610 in the sevoflurane group and 606 in the propofol group) were enrolled in this analysis (Table I). Of those, 851 individuals received cardiothoracic surgery. The remaining 365 individuals had non-cardiothoracic surgery.

As a part of the characteristics of the included research, the authors eventually developed a risk of bias figure and a summary risk of bias figure describing all judgements from all studies included in this analysis (Figure 2).

The incidence of AKI was indicated in four investigations. The international diagnostic criteria for AKI were defined as follows: A rise in serum creatinine concentration of 0.3 mg/dl, or a rise in creatinine concentration of ≤150% from the baseline value within 48 hours after surgery, or a rise in urine volume of 0.5 ml/kg/h for >6 hours after surgery. More stringent diagnostic criteria were defined as a creatinine increase of more than 44 uM (0.5 mg/dL). The results showed that the incidence of perioperative AKI was significantly higher in the sevoflurane group than propofol group (OR, 2.74; 95% CI, 1.62-4.65; p = 0.0002; I^2 = 13%, Figure 3, Table II).

Serum creatinine levels on postoperative day 1 were collected in six studies, according to the overall results, no statistically significant difference was found between the sevoflurane and the propofol groups on serum creatinine levels at postoperative 24-hour (SMD, 0.60; 95% CI, -0.09–1.29; p = 0.09; I^2 = 96%, Table II).

Due to the high heterogeneity in the overall results, the authors performed subgroup analyses to explore whether the type of surgery and race affected the results. As a result, in two studies involving non-cardiac surgery, the sevoflurane group had significantly higher serum creatinine levels in postoperative 24-hour than the propofol group (SMD, 1.64; 95% CI, 0.28–2.99; p = 0.02; I^2 = 93%). However, no significant differences were found in the remaining four studies involving cardiac surgery (SMD, 0.09; 95% CI, -0.11–0.28; p = 0.38; I^2 = 43%, Table II).

In addition, the authors found no statistically significant differences in subgroup analyses of race (Table II).

The levels of serum creatinine on postoperative day-2 were collected in four studies. The authors conducted a meta-analysis based on a random-effect model, and no statistically significant difference was found between the two groups (SMD, 0.12; 95% CI, -0.02–0.26; p = 0.10; I^2 = 0%, Table II).

Table I: Characteristics of studies included in the analysis.

Study	Year	Race	Surgery	Sample size (sev/pro)	Sevoflurane group		Propofol group	
					Induction	Maintenance	Induction	Maintenance
Jellish *et al.*[15]	1996	Caucasian	Musculoskeletal, intra-abdominal, genitourinary, other	93/93	3.5%-4% sev + 67% N_2O	Sev + 67% N_2O	1.5-2 mg kg^{-1} pro	Pro + 67% N_2O
Story *et al.*[16]	2001	Caucasian	Heart	118/119	0.1 mg kg^{-1} diazepam	1– 4% sev	0.1 mg kg^{-1} diazepam	1–8 ug ml^{-1} pro TCI
Lorsomradee *et al.*[17]	2006	Caucasian	Heart	160/160	sev	0.5–2% sev	2ug ml^{-1} pro TCI	2–4 ug ml^{-1} pro TCI
Bignami *et al.*[18]	2012	Caucasian	Heart	50/50	1–2 mg kg^{-1} pro	0.5–2% sev	1–2 mg kg^{-1} pro	2-3 mg kg^{-1} h^{-1} pro
Jovic *et al.*[19]	2012	Caucasian	Heart	11/11	0.3 mg kg^{-1} midazolam	1-2 MAC sev	1–1.5 mg kg^{-1} pro	Pro 10 mg kg-1 h^{-1} for 10 minutes, 8 mg kg^{-1} h^{-1} for the next 10 minutes and 6 mg kg^{-1} h^{-1}
Song *et al.*[20]	2013	Asian	Liver resection	52/50	8% sev	1.5–2.5% sev	4–6 mg ml^{-1} pro TCI	2–4 ug ml^{-1} pro TCI
Yoo *et al.*[12]	2014	Asian	Heart	56/56	0.05 mg kg^{-1} midazolam	0.6–1.5% sev	1mg kg^{-1} pro	60–250 mg kg^{-1} $minutes^{-1}$ pro
Ammar and Mahmoud[21]	2016	Caucasian	Abdominal	25/25	1.5-2 mg kg^{-1} pro	1 MAC sev	1.5-2 mg kg^{-1} pro	4-6 mg kg^{-1} h^{-1} pro
Kim *et al.*[22]	2017	Asian	Cardiopulmonary	31/29	NR	NR	NR	NR
Franzen *et al.*[11]	2022	Caucasian	Spine	14/13	2.0 mg kg^{-1} pro	0.8-1.2 MAC sev	2.0 mg kg^{-1} pro	4-6 ug ml^{-1} pro TCI

MAC, Minimum alveolar concentration; NR, Not reported; TCI, Target control infusion; Sev, Sevoflurane; Pro, Propofol.

Table II: Effect sizes summary for all outcomes.

Outcome	Studies	OR	SMD	MD	95% CI	p-value	I^2
AKI	4[16,21,24,27]	2.74			1.62-4.65	0.0002*	13%
Serum creatinine at postoperative day 1							
The overall result	6[16,20,21-23,26]		0.60		-0.09-1.29	0.09	96%
Subgroup (surgery)							
Cardiac	4[16,21-23]		0.09		-0.11-0.28	0.38	43%
Non-cardiac	2[20,26]		1.64		0.28-2.99	0.02*	93%
Subgroup (race)							
Caucasian	5[20,21-23,26]		0.63		-0.20-1.46	0.14	97%
Asian	1[16]		0.46		0.08-0.84	0.02	—
Serum creatinine at postoperative day 2	4[16,21-23]		0.12		-0.02-0.26	0.10	0%
Serum creatinine at postoperative day 3	3[16,21,26]		0.27		0.07-0.48	0.008*	0%
Cystatin C at postoperative 24-hour	2[16,26]		1.80		-0.68-4.27	0.16	97%
Creatinine clearance at postoperative 24-hour	2[17,22]		0.10		-0.11-0.31	0.33	0%
NGAL at postoperative 24-hour	2[17,27]		0.43		-0.47-1.32	0.35	74%
Urine output at postoperative 24-hour	2[16,25]			76.51	-190.04-343.06	0.57	41%
ICU stay time	4[16,23,24,26]		0.29		0.06-0.53	0.01*	0%
Hospital stay time	5[16,23-26]			1.62	0.59-2.64	0.002*	0%

*AKI, Acute kidney injury; CI, Confidence interval; ICU, Intensive care unit; MD, Mean difference; NGAL, Neutrophil gelatinase-associated lipocaline; OR, Odds ratio; SMD, Standard mean difference; *p <0.05.*

Three studies collected serum creatinine levels on the third day postoperatively. The results revealed that the concentration in the propofol group was significantly lower than that in the sevoflurane group (SMD, 0.27; 95% CI, 0.07–0.48; p = 0.008; I^2 = 0%, Table II).

Two studies addressed the concentration of cystatin C at postoperative 24-hour. No statistically significant difference was found between the two groups (SMD, 1.80; 95% CI, -0.68–4.27; p = 0.16; I^2 = 97%, Table II).

Two studies collected creatinine clearance levels at postoperative 24-hour. Under the condition of the fixed-effect model, no statistically significant difference was found (SMD, 0.10; 95% CI, -0.11–0.31; p = 0.33; I^2 = 0%, Table II).

Concentration levels of NGAL, a biomarker of AKI, were collected at 24-hour after surgery in two studies. According to the SMD result, there was no significant difference (SMD, 0.43; 95% CI, -0.47–1.32; p = 0.35; I^2 = 74%, Table II).

In two studies, urine volume was collected during the first 24 hours after surgery. The sevoflurane group and the propofol group did not show statistical difference (MD, 76.51; 95% CI, -190.04–343.06; p = 0.57; I^2 = 41%, Table II).

The length of ICU stay was collected in four studies. Results revealed that patients' ICU stay in the sevoflurane group were significantly longer than in the propofol group (SMD, 0.29; 95% CI, 0.06–0.53; p = 0.01; I^2 = 0%, Table II).

Additionally, the duration of hospital stay was extracted from five studies and a meta-analysis was conducted. The results showed that sevoflurane anaesthesia significantly extended the length of hospital stay compared with propofol anaesthesia (MD, 1.62; 95% CI, 0.59–2.64; p = 0.002; I^2 = 0%, Table II).

The symmetrical funnel plot of Begg's test indicated that no significant publication bias was detected (Figure 4). Egger's test further verified this result (t = 0.98, p = 0.431).

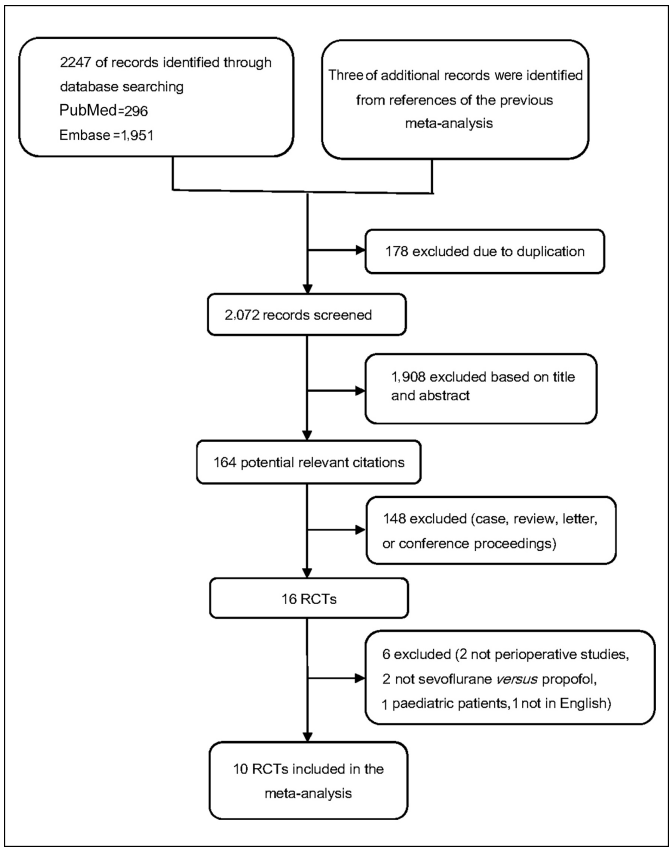

Figure 1: Flowchart.
RCT, Randomised controlled trial.

DISCUSSION

AKI is a frequent perioperative complication that has an impact on the patient's hospitalisation expenses and prognosis. The particular effects of different anaesthetic medications on perioperative renal function and the prevalence of AKI are still debated. To further examine the consequences, the authors conducted the study based on the notion of evidence-based medicine. In the end, 10 RCTs were included in this meta-analysis. Ultimately, it was shown that sevoflurane anaesthesia considerably raised the incidence of postoperative AKI compared to propofol anaesthesia.

The result of the present study is opposite to the results of a meta-analysis reported by Cai *et al*. in 2014.[13] They observed that sevoflurane was connected to a considerably decreased incidence of AKI after cardiac operation compared with propofol and other intravenous anaesthetics. The two researches were thoroughly analysed in order to investigate the conflict. In Cai *et al*.'s study, sevoflurane was compared against all the intravenous anaesthetics, and they focused on heart surgery.[13] The present study focused primarily on sevoflurane *versus* propofol, but included all surgery types, which made the study fundamentally different, hence the results differ appropriately. Although the particular mechanism is not entirely understood, propofol was efficient in anti-oxidative stress and controlling inflammation in animal and clinical experiments.[23-27] In addition, according to a retrospective cohort research comprising 4,320 patients, the AKI incidence with propofol was considerably lower than that with sevoflurane.[28]

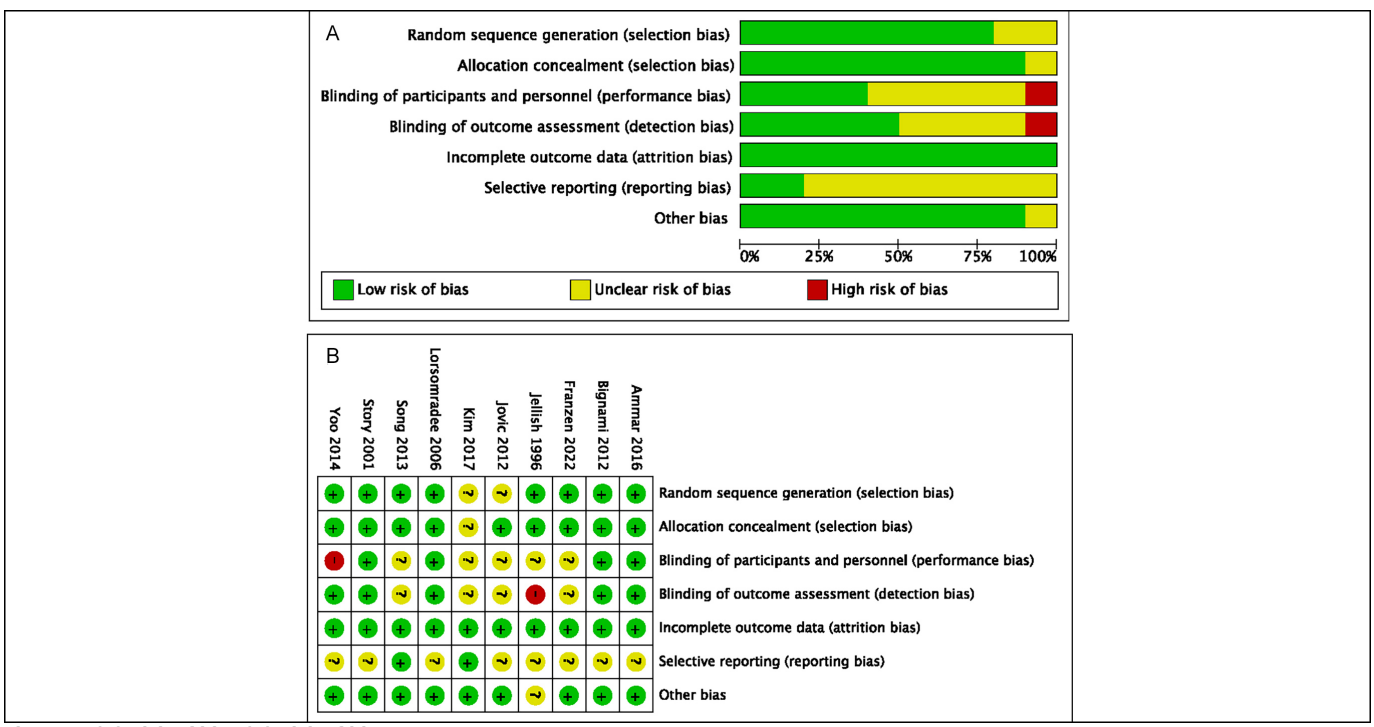

Figure 2: (A) Risk of bias (B) Risk of bias summary.

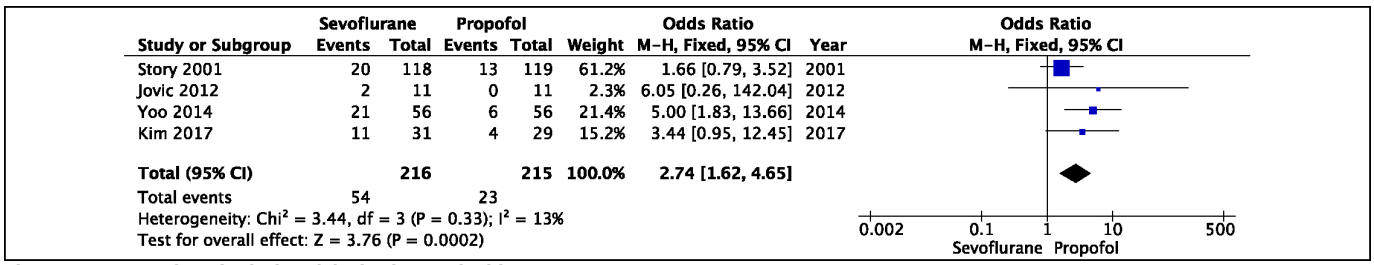

Figure 3: Forest plot of relative risks in the AKI incidence.
AKI, Acute kidney injury.

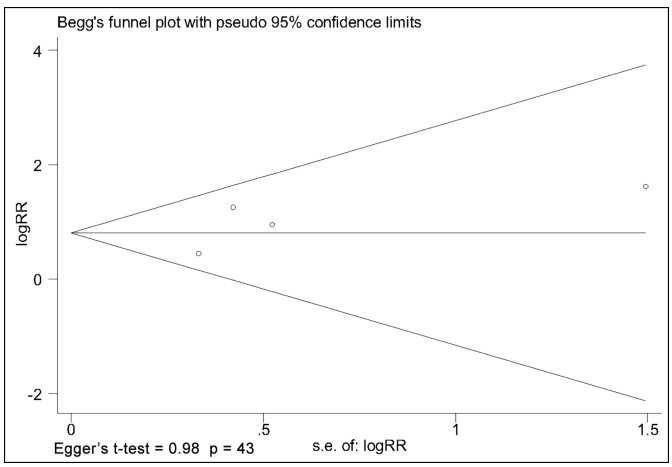

Figure 4: Funnel plot for publication bias.

Furthermore, no discernible variations existed in other indicators of kidney damage between the two cohorts. On the third day following sevoflurane anaesthesia, serum creatinine levels were noticeably higher than those of propofol. This aligns with the findings of Cai *et al*.'s research. Because AKI is more concerned with the degree of elevation of serum creatinine concentration than with the absolute value of serum creatinine concentration, there is a discrepancy between the concentration levels of these indicators and the incidence of AKI.

Sevoflurane anaesthesia considerably increased hospital and ICU stays. It is hypothesised that the rising prevalence of AKI could be the cause of sevoflurane anaesthesia. This served as a guide for the upcoming clinical work because it will surely result in higher hospitalisation expenses and other outcomes.

Notably, this study is the first to compare sevoflurane and propofol precisely in order to assess how they affect renal function following surgery. There are still a few restrictions to be aware of, though. First, only English studies were evaluated, thus relevant studies in other languages may be missed out. Second, additional subgroup analysis is not possible since several of the clinical indicators impacting renal function are not covered in detail in the original articles.

CONCLUSION

This meta-analysis indicated that sevoflurane may raise the incidence of perioperative AKI in comparison to propofol. More well-designed RCTs were still warranted.

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AUTHORS' CONTRIBUTION:
ML: Project development, data analysis, and manuscript writing/editing.
WY, XC, MN: Data collection, management, and data analysis.
AX: Project development and manuscript writing/editing.
All authors approved the final version of the manuscript to be published.

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