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Review article

Dexmedetomidine and acute kidney injury after non-cardiac surgery: A meta-analysis with trial sequential analysis

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication after surgery and is associated with detrimental outcomes. This systematic review and meta-analysis evaluated perioperative dexmedetomidine on AKI and renal function after non-cardiac surgery.

Methods: PubMed, Embase, and Cochrane Library databases were searched until August 2023 for randomised trials comparing dexmedetomidine with normal saline on AKI and renal function in adults undergoing non-cardiac surgery. The primary outcome was the incidence of AKI (according to Kidney Disease Improving Global Outcomes or Acute Kidney Injury Network criteria). Meta-analysis was performed using a random-effect model. We conducted sensitivity analysis, trial sequential analysis (TSA), and Grading of Recommendations Assessment, Development and Evaluation level of evidence.

Results: Twenty-three trials involving 2440 patients were included. Dexmedetomidine administration, as compared to normal saline, significantly reduced the incidence of AKI (7.4% *vs.* 13.2%; risk ratio = 0.57, 95% CI = 0.40–0.83, P = 0.003, I^2 = 0%; a high level of evidence); TSA and sensitivity analyses suggested the robustness of this outcome. For the renal function and inflammation parameters, dexmedetomidine decreased serum creatinine, blood urea nitrogen, cystatin C, tumour necrosis factor-α, and interleukin-6, and increased urine output and estimated glomerular filtration rate. Additionally, dexmedetomidine reduced postoperative nausea and vomiting and length of hospital stay. Dexmedetomidine was associated with an increased rate of bradycardia, but not hypotension.

Conclusion: Dexmedetomidine administration reduced the incidence of AKI and improved renal function after non-cardiac surgery. Based on a high level of evidence, dexmedetomidine is recommended as a component of perioperative renoprotection.

Registration: International Prospective Register of Systematic Reviews; Registration number: CRD42022299252.

Introduction

Acute kidney injury (AKI) is a common complication after surgery and a major healthcare burden worldwide. According to a recent multinational study, the incidence of AKI was 18.4% in patients undergoing major surgery [1]. AKI is associated with detrimental surgical outcomes such as chronic kidney disease, sepsis, multiorgan failure, prolonged intensive care unit stay, increased length of hospital stay, and death [2,3]. Risk factors of AKI include advanced age, diabetes, hypertension, nephrotoxin exposure, hypovolemia, kidney ischemia, inflammation, duration of surgery, and type of surgery (especially urologic, abdominal, and cardiac procedures) [1,4].

Dexmedetomidine, a highly selective α2-adrenergic agonist, has been widely used in clinical anaesthesia and intensive care. Dexmedetomidine has sedative, sympatholytic, analgesic, and anti-inflammatory effects [5]. A growing body of research demonstrated the renoprotective benefits of dexmedetomidine in patients undergoing cardiac surgery [6,7]; however, these

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benefits have yet to be validated in non-cardiac surgery. Recently, a meta-analysis involving six studies suggested that dexmedetomidine did not alter the risk of AKI after non-cardiac surgery [8]. Nevertheless, their study mixed both randomised controlled trials (RCTs) and retrospective cohorts and did not include the recently published studies that reported the AKI outcome [9,10].

With this context in mind, we conducted this systematic review and meta-analysis to determine whether the administration of dexmedetomidine reduces postoperative AKI and improves renal function in adult patients undergoing non-cardiac surgery based on evidence from RCTs only. Furthermore, we evaluated the robustness of our outcome using sensitivity analysis and trial sequential analysis (TSA) and rated the level of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Methods

Registration and reporting

This meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (registration number: CRD42022299252; available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=299252). This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [11]. The PRISMA 2020 checklist is presented in Table S1.

Literature search

Two reviewers independently conducted the literature search in the PubMed, Embase, and Cochrane Library databases from inception to August 27, 2023. The full search strategy is available in Table S2. There were no language or other restrictions. All search results were imported into EndNote X9.

Selection criteria

This meta-analysis used the following inclusion criteria: (1) RCT only, (2) adult patients undergoing non-cardiac surgery, (3) perioperative administration (before, during, and/or after surgery) of dexmedetomidine as an adjuvant to anaesthesia compared to normal saline placebo, and (4) outcomes reported on AKI or renal function after surgery. The exclusion criteria were as follows: (1) duplicate publications, (2) observational studies, reviews, editorials, letters, or case reports, (3) animal studies, (4) pediatric patients, (5) irrelevant studies, or (6) no specific results or insufficient data. Any discrepancy at this step was resolved by re-evaluation of the article and group discussion.

Data extraction

Relevant data were independently extracted by two review authors, including author name, publication year, region, type of surgery, sample size, usage of dexmedetomidine (dosage and timing of administration), maintenance of anaesthesia (propofol, remifentanil, desflurane, sevoflurane, etc.), and main outcomes reported. Any discrepancy during this procedure was resolved by re-checking the published data and group discussion.

Primary and secondary outcomes

The primary outcome was the incidence of postoperative AKI at any stage (stage 1, 2, or 3), which was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) or Acute Kidney Injury Network (AKIN) [2]. The secondary outcomes included postoperative levels of serum creatinine, urine output, blood urea nitrogen (BUN), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys C), estimated glomerular filtration rate (eGFR), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) at different times (0–2 h, 3–8 h, 24 h, 48 h, and 72 h). Need for renal replacement therapy (RRT), hypotension, bradycardia, postoperative nausea and vomiting (PONV), and length of hospital stay were also analysed.

Quality assessment

The Cochrane evaluation system was used to assess the quality of the included studies by two reviewers independently [12,13]. The risk of bias was evaluated in the following aspects: generation of random sequence, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. In each aspect, the risk of bias was judged as "low", "high", or "unclear". The risk of bias in the included study was assessed to be low (low risk in all aspects), high (high risk in at least one aspect), or unclear (unclear risk in at least one aspect without any high-risk aspect). Thereafter, the quality of evidence for the main outcomes was assessed using the GRADE approach (available at: https://gradepro.org) [7,14,15]. The outcomes were evaluated in the following aspects: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The certainty of evidence was rated as "high", "moderate", "low", or "very low". Any disagreement during the quality assessment process was resolved through the consensus of all reviewers.

Statistical analysis

RevMan software (version 5.3, Cochrane Collaboration, Copenhagen, Denmark) was used in this meta-analysis. For dichotomous variables, risk ratio (RR) with 95% confidence interval (CI) was calculated; for continuous variables, mean difference (MD) with 95% CI was presented. A random-effect model was utilized for data pooling. The I^2 statistic test was applied to evaluate the heterogeneity, and $I^2 > 50\%$ suggested significant heterogeneity among studies [13,16]. Publication bias was analysed with Egger's linear regression test and visualized in Begg's funnel plot using the STATA software (version 17.0, Stata Corp, College Station, TX) [17]. A P value < 0.05 indicates a statistically significant difference.

To assess the reliability of the primary outcome, TSA was performed using the TSA viewer software (version 0.9.5.5 beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen) [7,18]. If a cumulative Z curve in a TSA diagram crosses the trial sequential monitoring boundary or futility boundary, the current evidence is assessed as sufficient to reach a conclusion; in such circumstances, further studies may not be required. If the Z curve does not cross a boundary and the required information size is not reached, the current evidence is inadequate for a conclusion. Furthermore, a sensitivity analysis for the primary outcome was conducted to evaluate the impact of a single study on the overall treatment effect by omitting one study at a time, and the result was visualized using a sensitivity plot [7]. In addition, we performed a subgroup analysis on the level of AKI according to the KDIGO and AKIN criteria.

To explore the heterogeneity for the main secondary outcomes, we utilized random-effect meta-regression to assess the associations between outcomes and moderators as sources of heterogeneity (including type of surgery and type of anaesthesia) using the residual maximum likelihood model [19]. If meta-regression detected a potential source of heterogeneity, subgroup analyses were further performed.

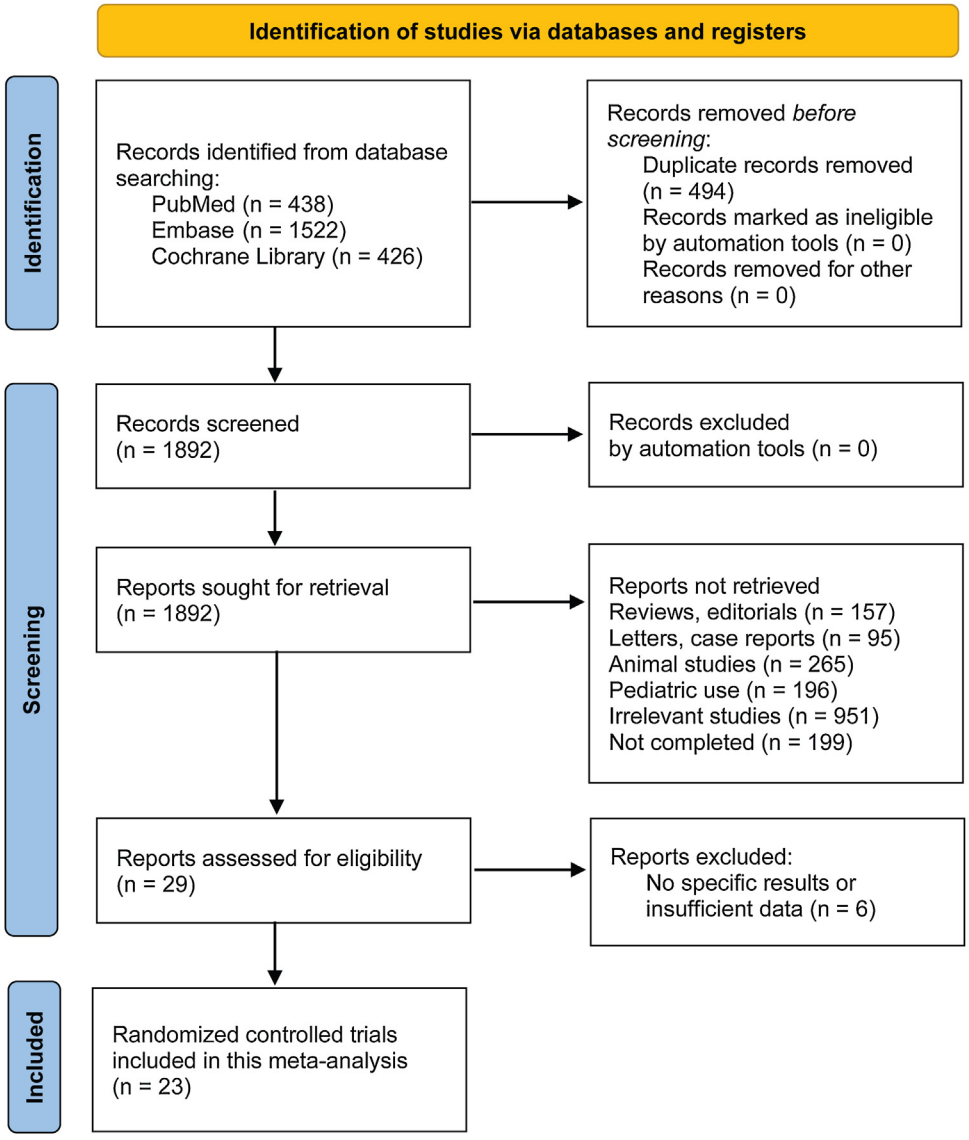

Fig. 1. PRISMA 2020 flow diagram.

Results

Literature search

The initial search identified 2386 publications (438 from PubMed, 1522 from Embase, and 426 from Cochrane Library). After 494 duplicates were excluded, 1892 studies underwent title and abstract screening, and 29 studies were included for full-text review. Thereafter, six articles were excluded due to a lack of specific results or insufficient data. Finally, 23 RCTs involving 2440 patients were included in this meta-analysis [9,10,20–40]. The PRISMA 2020 flow diagram is illustrated in Fig. 1.

Trial characteristics

Table 1 shows the trial characteristics. Eleven studies were carried out in patients undergoing urological surgery [20–24,26,28,29,32,35,39], of which four involved kidney transplantation [26,28,29,32]. Twelve trials reported renal outcomes after other major non-cardiac surgery (gastrointestinal, hepatobiliary, orthopaedic, interventional surgery, and cesarean section) [9,10,25,27,30,31,33,34,36–38,40]. The administration of dexmedetomidine consisted of a loading dose of 0.4–1.5 μg/kg intravenously before or after anaesthesia induction, and/or a continuous infusion at a rate of 0.1–1 μg/kg/h intraoperatively and postoperatively. Three studies extended the duration of administration into the postoperative period [9,29,32]. The patients received a range of anaesthetic techniques which included total intravenous anaesthesia (propofol and remifentanil/fentanyl), inhalational anaesthesia (desflurane, sevoflurane, and N_2O), combined intravenous and inhalational anaesthesia, and neuraxial blocks.

Of six trials reporting the incidence of postoperative AKI, four defined AKI according to the KDIGO [10,30,31,35], one according to the AKIN [9], and one did not describe the details of the definition [22]. The detailed characteristics of AKI are available in Table S3. Three studies determined AKI according to serum creatinine and urine output, two studies determined AKI according to serum creatinine only, and one study did not report the details. Two studies showed that their patients with AKI were all at stage 1, while four studies did not report the stages of AKI in detail.

Table 1
Trial characteristics.

Studies	Region	Surgery	Group: n[a]	DEX usage	Anesthesia	Main outcomes reported
Bai, Y 2021	China	Percutaneous nephrolithotomy	DEX: 91 Control: 86	Loading dose 1 μg/kg i.v. for 10 min before induction Maintenance 0.5 μg/kg/h i.v. during the surgery	TIVA with propofol and remifentanil	SCr/BUN/Cys C/TNF-α/IL-6 at 24/48 h, PONV, hypotension
Bayram, A 2011	Turkey	Percutaneous nephrolithotomy	DEX: 20 Control: 20	Loading dose 1 μg/kg i.v. for 10 min after induction Maintenance 1 μg/kg/h i.v. during the surgery	Inhalation with desflurane and N_2O	SCr/BUN/NGAL/Cys C at 2/8/24 h
Deng, Y 2018	China	Percutaneous nephrolithotomy	DEX: 95 Control: 95	Loading dose 1.5 μg/kg i.v. for 15 min before induction Maintenance 0.5 μg/kg/h i.v. during the surgery	Inhalation with sevoflurane	AKI, TNF-α/IL-6 at 0/24/48 h, hypotension, bradycardia, length of hospital stay
Jiang, L 2022	China	Laparoscopic partial nephrectomy	DEX: 39 Control: 38	Bolus dose 0.6 μg/kg i.v. for 10 min after the renal artery was unclamped	TIVA with propofol and remifentanil	Serum NGAL at 2/6 h, PONV, length of hospital stay
Li, H 2013	China	Radical nephrectomy	DEX: 30 Control: 30	Loading dose 1 μg/kg i.v. for 15 min after induction Maintenance 0.2–0.5 μg/kg/h i.v. during the surgery	TIVA with propofol and remifentanil	SCr/BUN/TNF-α/IL-6 at 0/24/72 h
Li, JQ 2023	China	Hip replacement	DEX: 49 Control: 49	Loading dose 4 μg/mL i.v. for 10 min before induction Maintenance 0.2 μg/kg/h i.v. during the surgery	Combined anesthesia with sevoflurane, propofol and remifentanil	SCr/BUN/TNF-α at 6 h, hypotension, bradycardia, length of hospital stay
Liu, Z 2022	China	Kidney transplantation	DEX: 33 Control: 32	Loading dose 0.6 μg/kg i.v. for 15 min before induction Maintenance 0.4 μg/kg/h i.v. until 30 min after reperfusion of transplanted kidney	Inhalation with sevoflurane	SCr/BUN/urine output on days 1–6, RRT
Ou, Y 2022	China	Laparoscopic hepatectomy	DEX: 20 Control: 20	Loading dose 0.5 μg/kg i.v. for 10 min before induction Maintenance 0.5 μg/kg/h i.v. until 30 min before the end of surgery	Combined anesthesia with sevoflurane, propofol and remifentanil	SCr/BUN at 24/72 h, TNF-α/IL-6 at 0.5/24 h, length of hospital stay
Park, J 2022	Korea	Kidney transplantation	DEX: 51 Control: 52	I.V. infusion of 0.4 μg/kg/h from induction to the end of surgery	Combined anesthesia with sevoflurane and remifentanil	SCr/eGFR on days 1–7, Cys C at 24/48 h, urine output on day 1–3, RRT, length of hospital stay
Shan, XS 2021	China	EVAR of Stanford B aortic dissection	DEX: 48 Control: 50	I.V. infusion of 0.5 μg/kg/h from induction to the end of surgery and 0.1 μg/kg/h in ICU until 24 h	Inhalation with sevoflurane	AKI, Cys C/eGFR on day 1/2/7, RRT, hypotension, bradycardia, length of hospital stay
Shan, XS 2022	China	Kidney transplantation	DEX: 56 Control: 55	I.V. infusion of 0.4 μg/kg/h from induction to the end of surgery and 0.1 μg/kg/h in designated transplant unit until 24 h	Inhalation with sevoflurane	SCr/Cys C/urine output on day 1–3, RRT, hypotension, bradycardia, length of hospital stay
Song, Y 2018	Korea	Cytoreductive surgery and HIPEC	DEX: 19 Control: 19	Loading dose 1 μg/kg i.v. for 20 min after induction Maintenance 0.5 μg/kg/h i.v. until 30 min before closing the peritoneum	Combined anesthesia with sevoflurane and remifentanil	AKI, RRT, length of hospital stay
Sun, W 2021	China	Laparoscopic colorectal cancer surgery	DEX: 28 Control: 28	Loading dose 1 μg/kg i.v. for 10 min after induction Maintenance 0.5 μg/kg/h i.v. during the surgery	Combined anesthesia with sevoflurane and remifentanil	AKI, sCr/BUN on day 1, serum NGAL at 2 h/on day 1, RRT, length of hospital stay
Wang, YC 2022	China	Kidney transplantation	DEX: 30 Control: 30	I.V. infusion of 0.1–0.7 μg/kg/h from induction to 2 h after surgery	Inhalation with desflurane	SCr/BUN on day 1/2/3, serum NGAL at 24/48 h, RRT
Wang, ZX 2014	China	Hepatectomy with inflow occlusion	DEX: 22 Control: 22	Loading dose 1 μg/kg i.v. for 10 min after induction Maintenance 0.3 μg/kg/h i.v. during the surgery	TIVA with propofol and fentanyl	SCr/BUN/TNF-α/IL-6 at 0/6/24/72 h, length of hospital stay
Wu, F 2019	China	Surgery for malignant obstructive jaundice	DEX: 20 Control: 20	Loading dose 0.5 μg/kg i.v. for 10 min before induction Maintenance 0.5 μg/kg/h i.v. until 30 min before the end of surgery	TIVA with propofol and remifentanil	SCr/BUN/Cys C at 0/24/72 h, hypotension, bradycardia, PONV, length of hospital stay
Wu, S 2019	China	Laparoscopic radical prostatectomy	DEX: 44 Control: 45	Loading dose 1 μg/kg i.v. for 10 min Maintenance 0.5 μg/kg/h i.v. until 30 min before the end of surgery	Combined anesthesia with sevoflurane and remifentanil	AKI, sCr/BUN/eGFR/Cys C at 6/24/48 h, urine output on day 1–3, bradycardia, PONV, length of hospital stay
Xing, MW 2023	China	Major non-cardiac surgery	DEX: 309 Control: 310	Loading dose 0.6 μg/kg i.v. for 10 min before induction Maintenance 0.5 μg/kg/h i.v. until 1 h before the end of surgery	TIVA/inhalation without details	AKI, length of hospital stay
Zhang, QL 2019	China	Cesarean section	DEX: 67 Control: 67	Bolus dose 0.4 μg/kg/h i.v. for 10 min before surgery	Combined epidural-spinal anesthesia with ropivacaine	SCr/BUN on days 1–5, TNF-α/IL-6 at 1/3/6/12/24 h, hypotension, bradycardia, PONV
Zhang, Y 2020	China	Hepatectomy	DEX: 29 Control: 29	Loading dose 0.5 μg/kg i.v. for 10 min Maintenance 0.5 μg/kg/h i.v. until resection of the liver lobes	TIVA with propofol and remifentanil	SCr/BUN/TNF-α/IL-6 at 2/24 h, length of hospital stay

Table 1 (*Continued*)

Studies	Region	Surgery	Group: n[a]	DEX usage	Anesthesia	Main outcomes reported
Zheng, SS 2016	China	Interventional therapy for acute cerebral hemorrhage	DEX: 50 Control: 48	I.V. infusion of 0.5 μg/kg/h from induction to 20 min before the end of surgery	Inhalation with sevoflurane	SCr/BUN at 24 h
Zhou, H 2020	China	Lithotripsy	DEX: 55 Control: 50	I.V. infusion of 4 μg/mL (dose unclear) during the surgery	Spinal anesthesia with bupivacaine	Cys C at 0 h, length of hospital stay
Zhou, W 2020	China	Shoulder arthroscopy	DEX: 20 Control: 20	I.V. infusion of 0.4 μg/kg/h during the surgery	Combined anesthesia with sevoflurane, propofol and remifentanil	SCr/BUN/Cys C at 2/24 h, urine output at 24 h

DEX: dexmedetomidine; TIVA: total intravenous anesthesia; PONV: postoperative nausea and vomiting; BUN: blood urea nitrogen; sCr: serum creatinine; Cys C: cystatin C; TNF-α: tumor necrosis factor α; IL-6: interleukin-6; NGAL: neutrophil gelatinase-associated lipocalin; AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; EVAR: endovascular aortic repair; ICU: intensive care unit; HIPEC: hyperthermic intraperitoneal chemotherapy; RRT: renal replacement therapy.

[a] Normal saline placebo was given in all control groups.

Table 2
Summary of outcomes.

Outcomes	No. of studies	DEX (n)	Control (n)	Effect size (95% CI)	*P* value	I^2 (%)
Primary outcome						
AKI	6	40/543	72/547	RR = 0.57 (0.40, 0.83)	0.003	0
Secondary outcomes						
Serum creatinine, μmol/L						
0–2 h postoperatively	6	172	173	MD = −8.99 (−25.38, 7.41)	0.28	95
3–8 h postoperatively	3	115	116	MD = −6.34 (−8.42, −4.26)	<0.00001	9
24 h postoperatively	15	584	581	MD = −8.37 (−14.13, −2.61)	0.004	87
48 h postoperatively	6	274	279	MD = −11.18 (−18.68, −3.68)	0.003	64
72 h postoperatively	9	346	344	MD = −4.66 (−8.73, −0.59)	0.02	45
Urine output, mL						
Postoperative day 1	4	160	156	MD = 354.2 (79.9, 628.4)	0.01	0
Postoperative day 2	3	140	139	MD = 37.04 (−279.77, 353.85)	0.82	0
Postoperative day 3	3	140	139	MD = −54.07 (−371.91, 263.77)	0.74	0
BUN, mmol/L						
0–2 h postoperatively	5	121	121	MD = −3.33 (−5.90, −0.77)	0.01	98
3–8 h postoperatively	3	115	116	MD = −0.57 (−0.84, −0.31)	<0.0001	51
24 h postoperatively	13	477	474	MD = −1.28 (−2.14, −0.42)	0.004	94
48 h postoperatively	4	167	171	MD = −1.02 (−2.26, 0.21)	0.10	84
72 h postoperatively	8	306	304	MD = −0.29 (−0.54, −0.03)	0.03	20
NGAL, μg/L						
0–2 h postoperatively	3	87	86	MD = −28.53 (−82.87, 25.80)	0.30	90
Cys C, mg/L						
0–2 h postoperatively	5	166	162	MD = −0.47 (−0.99, 0.05)	0.08	98
24 h postoperatively	8	350	348	MD = −0.46 (−0.71, −0.20)	0.0004	98
48 h postoperatively	4	199	202	MD = −0.09 (−0.16, −0.03)	0.007	34
eGFR, ml/min/1.73 m^2						
24 h postoperatively	3	143	147	MD = 6.11 (0.55, 11.68)	0.03	0
48 h postoperatively	3	143	147	MD = 5.68 (−1.49, 12.86)	0.12	0
Need for RRT postoperatively	7	39/271	51/273	RR = 0.78 (0.48, 1.26)	0.31	36
TNF-α, ng/L						
0–2 h postoperatively	6	263	263	MD = −3.89 (−5.79, −1.98)	<0.0001	95
24 h postoperatively	7	354	349	MD = −1.37 (−2.64, −0.09)	0.04	91
72 h postoperatively	3	143	138	MD = −4.30 (−11.14, 2.53)	0.22	98
IL-6, ng/L						
0–2 h postoperatively	6	263	263	MD = −14.00 (−26.52, −1.49)	0.03	94
24 h postoperatively	7	354	349	MD = −15.15 (−20.51, −9.79)	<0.00001	87
72 h postoperatively	3	143	138	MD = −5.14 (−10.00, −0.29)	0.04	80
Other outcomes						
Hypotension	7	48/426	35/422	RR = 1.32 (0.87, 2.00)	0.19	0
Bradycardia	7	79/379	37/381	RR = 2.02 (1.45, 2.83)	<0.0001	0
PONV	5	7/261	20/256	RR = 0.39 (0.16, 0.91)	0.03	0
Length of hospital stay, d	16	928	925	MD = −0.53 (−0.96, −0.10)	0.02	75

DEX, dexmedetomidine; AKI, acute kidney injury; BUN, blood urea nitrogen; NGAL, neutrophil gelatinase-associated lipocalin; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; TNF-α: tumor necrosis factor α; IL-6, interleukin-6; PONV, postoperative nausea and vomiting; RR, risk ratio; MD, mean difference; CI, confidence interval.

Primary outcome

Six studies reported the incidence of postoperative AKI (Table 2 and Fig. 2) [9,10,22,30,31,35], and the majority of studies originated from China. Dexmedetomidine infusion significantly reduced the risk of AKI (40/543 [7.4%] *vs.* 72/547 [13.2%], RR = 0.57, 95% CI = 0.40 to 0.83, $P = 0.003$, $I^2 = 0\%$; Fig. 2A), with no evidence of publication bias in the Egger's test ($P = 0.218$, Fig. 2B) or Begg's funnel plot ($P = 0.573$, Fig. 2C).

In the TSA diagram, although the required information size was not reached, the Z-curve (blue) crossed the conventional benefit boundary (brown) and the trial sequential monitoring boundary (red), suggesting reliable evidence for this outcome (Fig. 2D). In the sensitivity analysis, the estimated benefits of dexmedetomidine in

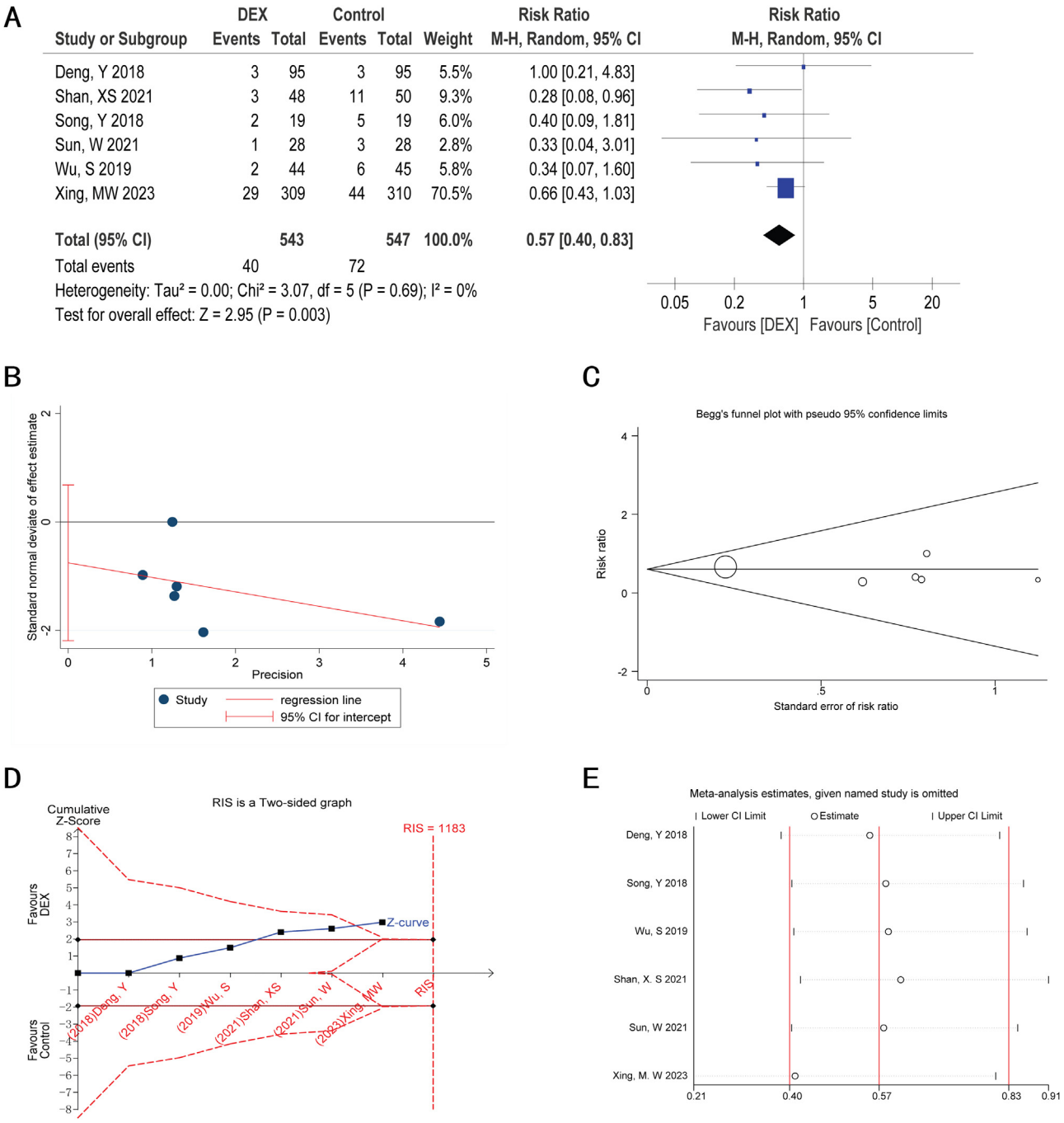

Fig. 2. Effect of dexmedetomidine on acute kidney injury. (A) Forest plot. (B) Egger's publication bias plot. (C) Begg's funnel plot. (D) Trial sequential analysis. (E) Sensitivity analysis. DEX, dexmedetomidine; RIS, required information size.

reducing AKI ranged from RR = 0.41 (95% CI = 0.21 to 0.80) to RR = 0.62 (95% CI = 0.42 to 0.91), suggesting the robustness of this outcome (Fig. 2E). The subgroup analysis showed no significant heterogeneity between the subgroups of AKI stage 1 and unclear stage (Figure S1).

Secondary outcomes on renal function

The use of dexmedetomidine was associated with reduced level of serum creatinine within 3–8 h and at 24 h (MD = −8.37 μmol/L, 95% CI = −14.13 to −2.61 μmol/L, P = 0.004, I^2 = 87%; Figure S2), 48 h, and 72 h postoperatively (Table 2). In terms of urine output, the dexmedetomidine group had a higher urine output on postoperative day 1 (MD = 354.2 mL, 95% CI = 79.9 to 628.4 mL, P = 0.01, I^2 = 0%; Figure S3), but not on day 2 or 3. The level of BUN was reduced in the dexmedetomidine group during 0–2 h and 3–8 h, and at 24 h (MD = −1.28 mmol/L, 95% CI = −2.14 to −0.42 mmol/L, P = 0.004, I^2 = 94%; Figure S4) and 72 h after surgery (Table 2). The reduction in NGAL levels in the dexmedetomidine group was not statistically significant. The dexmedetomidine administration reduced the level of Cys C at 24 h (MD = −0.46 mg/L, 95% CI = −0.71 to −0.20 mg/L, P = 0.0004, I^2 = 98%; Figure S5) and 48 h postoperatively. Regarding the eGFR, the dexmedetomidine group showed an increased value of eGFR at

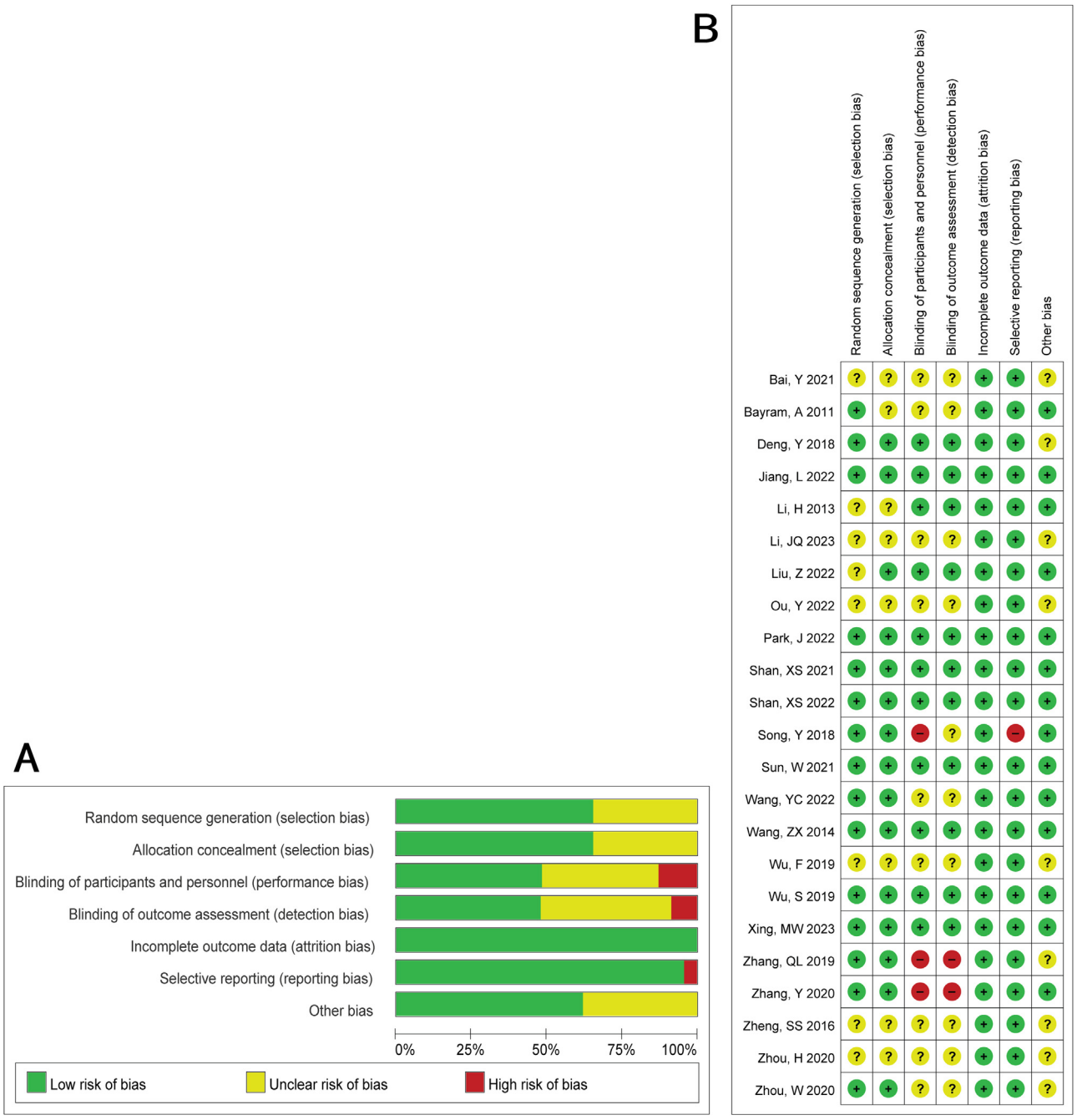

Fig. 3. Risk of bias assessment. (A) Risk of bias graph. (B) Risk of bias summary.

24 h after surgery (MD = 6.11 ml/min/1.73 m^2, 95% CI = 0.55 to 11.68 ml/min/1.73 m^2, $P = 0.03$, $I^2 = 0\%$; Figure S6). The two groups showed a similar rate of need for postoperative RRT (RR = 0.78, 95% CI = 0.48 to 1.26, $P = 0.31$, $I^2 = 36\%$; Figure S7), which did not differ between the subgroups of kidney transplantation and other types of surgery.

We performed meta-regression for the outcomes of serum creatinine, BUN, and Cys C at 24 h after surgery. Meta-regression suggested that type of surgery might be a potential source of heterogeneity (coefficient = 71.1, 95% CI = 4.2 to 138.0, $P = 0.039$) for serum creatinine, and the subgroup analysis showed that the reduced serum creatinine in the dexmedetomidine group was only significant in patients undergoing surgical procedures other than kidney transplantation (Figure S8). In terms of BUN and Cys C, meta-regression did not show any significant source of heterogeneity.

Secondary outcomes of inflammatory factors

The effects of dexmedetomidine on inflammatory factors including TNF-α and IL-6 are shown in Table 2. The TNF-α level in the dexmedetomidine group was significantly decreased during 0–2 h and at 24 h (MD = −1.37 ng/L, 95% CI = −2.64 to −0.09 ng/L, $P = 0.04$, $I^2 = 91\%$; Figure S9) after surgery. The use of dexmedetomidine also reduced the IL-6 level during 0–2 h and at 24 h (MD = −15.15 ng/L, 95% CI = −20.51 to −9.79 ng/L, $P < 0.00001$, $I^2 = 87\%$; Figure S10) and 72 h postoperatively.

Other secondary outcomes

The between-group difference in the incidence of hypotension was not significant (48/426 *vs.* 35/422, RR = 1.32, 95% CI = 0.87 to

Table 3
GRADE evidenceprofile.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEX	placebo	Relative (95% CI)	Absolute (95% CI)		
The incidence of AKI												
6	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	40/543 (7.4%)	72/547 (13.2%)	**RR 0.57** (0.40 to 0.83)	**57 fewer per** 1,000 (from 79 fewer to 22 fewer)	⊕⊕⊕⊕ High	CRITICAL
Serum creatinine at 24 h postoperatively (μmol/L)												
15	Randomised trials	Very serious[a]	Very serious[b]	Not serious	Not serious	None	584	581	–	MD **8.37 lower** (14.13 lower to 2.61 lower)	⊕◯◯◯ Very low	IMPORTANT
Urine output on postoperative day 1 (mL)												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	160	159	–	MD **354.15 higher** (79.88 higher to 628.43 higher)	⊕⊕⊕⊕ High	IMPORTANT
BUN at 24 h postoperatively (mmol/L)												
13	Randomised trials	Very serious[a]	Very serious[c]	Not serious	Not serious	None	477	474	–	MD **1.28 lower** (2.14 lower to 0.42 lower)	⊕◯◯◯ Very low	IMPORTANT
Cys C at 24 h postoperatively (mg/L)												
8	Randomised trials	Not serious	Very serious[d]	Not serious	Not serious	None	350	348	–	MD **0.46 lower** (0.71 lower to 0.2 lower)	⊕⊕◯◯ Low	IMPORTANT
eGFR at 24 h postoperatively (ml/min/1.73 m^2)												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	143	147	–	MD **6.11 higher** (0.55 higher to 11.68 higher)	⊕⊕⊕⊕ High	IMPORTANT
TNF-α at 24 h postoperatively (ng/L)												
7	Randomised trials	Very serious[e]	Very serious[f]	Not serious	Not serious	None	354	349	–	MD **1.37 lower** (2.64 lower to 0.09 lower)	⊕◯◯◯ Very low	IMPORTANT
IL-6 at 24 h postoperatively (ng/L)												
7	Randomised trials	Very serious[e]	Very serious[b]	Not serious	Not serious	None	354	349	–	MD **15.15 lower** (20.51 lower to 9.79 lower)	⊕◯◯◯ Very low	IMPORTANT
Incidence of hypotension												
7	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	48/426 (11.3%)	35/422 (8.3%)	**RR 1.32** (0.87 to 2.00)	**27 more per** 1,000 (from 11 fewer to 83 more)	⊕⊕⊕⊕ High	IMPORTANT
Incidence of bradycardia												
7	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	79/379 (20.8%)	37/381 (9.7%)	**RR 2.02** (1.45 to 2.83)	**99 more per** 1,000 (from 44 more to 178 more)	⊕⊕⊕⊕ High	IMPORTANT
Length of hospital stay (d)												
16	Randomised trials	Very serious[g]	Very serious[h]	Not serious	Not serious	None	928	925	–	MD **0.53 lower** (0.96 lower to 0.1 lower)	⊕◯◯◯ Very low	IMPORTANT

DEX, dexmedetomidine; AKI, acute kidney injury; BUN, blood urea nitrogen; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CI, confidence interval; MD, mean difference; RR, risk ratio.
Explanations: a. Two trials were at high risk of bias and eight trials were at unclear risk of bias. b. Heterogeneity: I^2 = 87%. c. Heterogeneity: I^2 = 94%. d. Heterogeneity: I^2 = 98%. e. Two trials were at high risk of bias and three were at unclear risk of bias. f. Heterogeneity: I^2 = 91%. g. Two trials were at high risk of bias and six trials were at unclear risk of bias. h. Heterogeneity: I^2 = 75%.

2.00, $P = 0.19$, $I^2 = 0\%$; Figure S11), whereas the use of dexmedetomidine was associated with an increased incidence of bradycardia (79/379 *vs.* 37/381, RR = 2.02, 95% CI = 1.45 to 2.83, $P < 0.0001$, $I^2 = 0\%$; Figure S12). In addition, the dexmedetomidine group had a lower risk of PONV (RR = 0.39, 95% CI = 0.16 to 0.91, $P = 0.03$, $I^2 = 0\%$) and a shorter length of hospital stay (MD = −0.53 d, 95% CI = −0.96 to −0.10 d, $P = 0.02$, $I^2 = 75\%$; Figure S13).

Risk of bias and quality of evidence

The risk of bias for each included study is shown in Fig. 3. Two studies had a high risk of performance and detection bias [36,37], eight trials had a low risk of bias in all aspects [9,10,23,28,29,31,33,35], and 13 had an unclear risk for selection, performance, and attrition bias [20–22,24–27,30,32,34,38–40].

The GRADE evidence profile of the main outcomes is presented in Table 3. The level of evidence for the primary outcome of AKI was high. In terms of the secondary outcomes, a high level of evidence was judged for urine output on postoperative day 1, eGFR at 24 h postoperatively, hypotension, and bradycardia; a low level of evidence for Cys C at 24 h postoperatively; and a very low level of evidence for serum creatinine, BUN, TNF-α, and IL-6 at 24 h postoperatively and length of hospital stay.

Discussion

This meta-analysis included 23 RCTs with 2440 patients who underwent non-cardiac surgery to show the renoprotective benefits of dexmedetomidine. Postoperative AKI was significantly reduced by dexmedetomidine administration (high level of GRADE evidence), and this result was not affected by heterogeneity or publication bias. TSA and sensitivity analysis showed that this outcome was reliable and robust. Renoprotection offered by dexmedetomidine was further supported by decreased levels of serum creatinine, BUN, and Cys C, increased urine output and eGFR, and reduced TNF-α and IL-6. The use of dexmedetomidine was associated with an increased rate of bradycardia, but not hypotension. We also noted a shorter length of hospital stay in patients who received dexmedetomidine.

A meta-analysis published in 2021 suggested that dexmedetomidine may have renoprotective effects, but this study mixed cardiac and non-cardiac procedures in both adult and pediatric patients [41]. Another study by Hu, *et al.* included four RCTs and two retrospective studies to show that dexmedetomidine did not reduce the rate of AKI after non-cardiac surgery [8]; however, the results were limited by a small number of trials, low quality of evidence, and lack of renal function parameters. Abuelazm and colleagues performed a meta-analysis evaluating the impact of dexmedetomidine on renal outcomes in kidney transplantation only, without other types of surgery [42]. A recent retrospective cohort study of 2391 patients undergoing non-cardiac surgery suggested that intraoperative dexmedetomidine was associated with a reduced incidence and severity of AKI [43]. Thus, dexmedetomidine administration may provide renoprotection in non-cardiac surgery, but the previous studies did not yield a firm conclusion with a robust level of evidence.

In contrast, our meta-analysis comprehensively searched the literature and included the most recent RCTs. Our primary outcome of AKI has a high level of evidence, and the benefits of dexmedetomidine are further reflected by the secondary outcomes of renal function indicators. Our pooled data showed an AKI incidence of 13.2% in the normal saline group, which is similar to the results of recent studies in non-cardiac surgery [44,45]. We found that the administration of dexmedetomidine led to a significant decrease in the incidence of AKI by 43% (an absolute reduction of 5.8%), and its 95% CI ranging from 0.40 to 0.83 suggests an adequate level of precision. We also revealed that secondary renal outcomes including serum creatinine, urine output, BUN, Cys C, and eGFR were improved in the dexmedetomidine group. In addition, our results did not find a correlation between the use of dexmedetomidine and hypotension. Notably, perioperative hypotension is closely related to postoperative AKI [46]. Among the included studies, dexmedetomidine was infused at a common dose, which did not increase the risk of hypotension.

There is evidence that normal saline induced hyperchloremia and metabolic acidosis, which was associated with an increased risk of AKI in critically ill patients [47]. However, recent studies suggested that the use of balanced crystalloid solutions *vs.* normal saline remained controversial [48–50]. Specifically, a balanced crystalloid compared with normal saline for fluid resuscitation did not reduce AKI or RRT in critically ill patients. In this meta-analysis, normal saline was used for dexmedetomidine delivery in the dexmedetomidine group and was given as a placebo in the control group. In both groups, normal saline was administered at a much smaller volume (50–150 ml) compared with the amount used for fluid resuscitation (typically 1500–3000 ml) in critically ill patients. Thus, the infusion of normal saline in the included studies of this meta-analysis was unlikely to exert clinically adverse consequences.

There are some possible mechanisms underlying postoperative AKI, especially renal ischemia/reperfusion (I/R) injury and inflammation [4]. Our meta-analysis showed that the administration of dexmedetomidine significantly reduced the levels of inflammatory factors such as TNF-α and IL-6. The renoprotection offered by dexmedetomidine can be explained as follows. First, the sedative, analgesic, and sympatholytic effects of dexmedetomidine help to reduce the consumption of anaesthetics and narcotics and maintain a stable hemodynamics [51]. Second, dexmedetomidine attenuates stress responses, inhibits inflammation, and protects immune function in surgical patients, contributing to reduced postoperative complications and better clinical outcomes [52]. Third, dexmedetomidine induces renal vasodilatation by regulating endothelial nitric oxide, which increases renal blood flow, glomerular filtration, and urine output [53,54]. Fourth, recent experimental studies showed that the attenuation of renal I/R injury by dexmedetomidine involves inhibition of ferroptosis, activation of the cholinergic anti-inflammatory pathway, and regulation of renal microvascular endothelial cells [55–57].

This meta-analysis has several strengths. We systematically and comprehensively reviewed the current literature and included the most recent RCTs. It is noteworthy that there was no heterogeneity or publication bias in our primary outcome, and the reliability was validated by the results of TSA and sensitivity analyses. Moreover, the GRADE level of evidence was high for the primary outcome. This meta-analysis was of high significance for the clinical practice of anaesthesia management in surgical patients. Our results suggest a renoprotective effect of dexmedetomidine on reducing AKI after several types of surgery. Although we showed a good safety profile of dexmedetomidine, practitioners should still be aware of individual patient risk of adverse effects (dose-related bradycardia and hypotension) in clinical scenarios. Based on these findings, the use of dexmedetomidine can be incorporated into the therapy of renoprotection for patients undergoing non-cardiac surgery.

Our study has several limitations. First, a limited number of trials were available for the primary outcome of AKI, which precludes subgroup analysis on different patient populations (*e.g.*, age, type of surgery, and type of anaesthesia) and dexmedetomidine dosage. Second, the definitions of AKI were not uniform among studies, and the levels of AKI were not clearly reported in four studies. Third, several secondary outcomes were rated as low

or very low levels of evidence, due to the inclusion of high-risk studies and significant heterogeneity among studies. Last, the regions of the included studies were Asian countries (China, Korea, and Turkey); therefore, the generalisability of our findings to Western countries needs to be tested in future studies.

Conclusion

This meta-analysis of RCTs demonstrates that dexmedetomidine administration leads to a significant reduction in the incidence of AKI and an improvement of renal function after non-cardiac surgery. Based on a high level of GRADE evidence, our findings support the clinical use of dexmedetomidine for renoprotection in patients undergoing non-cardiac surgery.

Disclosure of interest

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Author contributions

All authors made substantial contributions to the design of this study, data acquisition and interpretation, statistical plan, drafting the manuscript, or revising the manuscript critically. All authors agreed to be accountable for all aspects of the work and gave their final approval of this version to be published.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2024.101359.

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