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The effect of dexmedetomidine on acute kidney injury after elective major abdominal surgery : a retrospective single-center propensity score matched study

Haibei Liu[1,2,4†], Rong Luo[1,2†], Liu Qian[1,2], Yujun Zhang[1,2], Wensheng Zhang[1,2], Juan Tan[3] and Ling Ye[2,4*]

Abstract

Background Major abdominal surgery is a kind of high-risk surgery type for postoperative acute kidney injury (AKI) among non-cardiac surgeries. Despite dexmedetomidine exerts significant renal protective effects in cardiac surgeries and animal studies, whether it is associated with a lower incidence of AKI in major abdominal surgeries remains unclear.

Methods From January 2019 to July 2021, patients undergoing elective major abdominal surgery in West China Hospital were enrolled. Participants were divided into two groups based on exposure to continuous intravenous dexmedetomidine: the Dex group (exposed) and the Control group (not exposed). The primary outcome was the incidence of AKI in the postoperative 7 days. Secondary outcomes included intraopertive average urine output, renal function on the first day after surgery, incidence of postoperative dialysis, postoperative intensive care unit (ICU) admission, in-hospital mortality, length of hospital stay, incidence of intraoperative hypotension and bradycardia, and intraoperative use of inotropes and vasopressors. Propensity score matching (PSM), based on participants' baseline and intraoperative characteristics, was performed to minimize potential bias. Furthermore, a subgroup analysis was conducted based on the infusion rate and the use of a loading dose to explore the effects of different methods of dexmedetomidine administration on AKI. The subgroups included: loading dose, non-loading dose, low-infusion rate (infusion rate ≤ 0.4 μg/kg/h), and high-infusion rate (infusion rate > 0.4 μg/kg/h).

Results After PSM with a ratio of 1:1, a total of 8836 patients were successfully matched. Dexmedetomidine administration had no association with the incidence of postoperative AKI, serum creatinine (Scr) level on the first postoperative day, incidence of postoperative dialysis, postoperative ICU admission, in-hospital mortality, length of hospital stay, intraoperative hypotension, or the use of inotropes and vasopressors, but had association with increased intraoperative average urine output (122.95 (76.80, 189.27) vs. 104.65 (67.04, 161.07) ml/h, $P < 0.001$), higher value of estimated glomerular filtration rate (eGFR) (97.33 ± 15.95 vs. 96.13 ± 16.35 ml/min/1.73m^2, $P < 0.001$) on the first day

†Haibei Liu and Rong Luo contributed equally to this work.

*Correspondence:
Ling Ye
zerodq_hx@163.com

Full list of author information is available at the end of the article

after surgery and a higher incidence of intraoperative bradycardia (37.0% vs. 30.6%; $P < 0.001$). In the loading dose subgroup, dexmedetomidine use was significantly associated with a reduced incidence of postoperative AKI (odds ratio (OR): 0.44, 95% confidence interval (CI): 0.23–0.76, $P = 0.006$).The association between dexmedetomidine and postoperative AKI was absent in subgroups of high or low infusion rate and no loading dose use.

Conclusion In this single-center retrospective propensity-matched study, we did not detect a significant overall difference in post-operative AKI rates between patients treated with or without dexmedetomidine during major abdominal surgery. However, though additional prospective data are needed, our study found that administering dexmedetomidine with a loading dose may be associated with lower rates of AKI, potentially indicating a renoprotective effect of loading-dose dexmedetomidine in this setting.

Keywords Dexmedetomidine, Adult, Acute kidney injury, Major abdominal surgery

Introduction

Acute kidney injury (AKI) is a severe complication in patients undergoing surgery that contributes to prolonged hospital stay and high incidence of mortality, with an incidence of 3-41% depending on surgery type and patients' preoperative condition [1–4]. Postoperative AKI occurs most frequently following cardiac surgery, with major abdominal surgery also being a notable contributor [5]. The incidence of AKI following major abdominal surgery varies, ranging from 6.8–39.3% [6–8]. The underlying causes of AKI in this context include large fluid shifts, intraperitoneal factors that can impair renal blood flow, inflammation, and increased intra-abdominal pressure [9]. AKI is associated with adverse outcomes, including chronic kidney disease, end-stage renal disease, and multiorgan dysfunction. These complications contribute to prolonged hospital stays, reduced quality of life, and increased mortality, placing a significant burden on society [10, 11]. Furthermore, research by Kork et al. highlights that even a minor increase in creatinine levels, which does not meet the criteria for AKI, is associated with an increased mortality and a longer hospital stays, particularly in patients undergoing non-cardiac surgery [12]. Therefore, it is essential to raise awareness of AKI following major abdominal surgery [11].

Dexmedetomidine is a kind of selective α adrenoreceptor agonist known for its sedative, analgesic and sympathetic nerve activity reduction properties [13]. Preclinical studies have shown that dexmedetomidine can alleviate various forms of renal injury, including ischemia-reperfusion injury, lipopolysaccharide-induced renal injury, and cisplatin-induced renal injury. It achieves this by reducing inflammation, oxidative stress, and apoptosis through multiple pathways [14–16]. Clinical studies have also explored the renal protective effects of dexmedetomidine. A single-center randomized controlled trial (RCT) involving 72 patients revealed that dexmedetomidine reduced the incidence of postoperative AKI and increased the intraoperative urine output in patients undergoing cardiac valve replacement under cardiopulmonary bypass (CPB) [17]. Additionally, a meta-analysis of RCTs in cardiac surgery indicated that dexmedetomidine had a beneficial effect in preventing AKI and reducing intensive care unit (ICU) stays [1]. However, studies in non-cardiac surgery settings have yielded inconsistent results [18, 19]. Major abdominal surgery is one of the high-risk noncardiac surgeries for AKI, yet the renoprotective impact of dexmedetomidine in this context remains unclear. Consequently, this retrospective study was designed to investigate the association between dexmedetomidine administration and the incidence of postoperative AKI, as well as other postoperative outcomes, in a matched cohort of patients undergoing major abdominal surgery.

Methods

The West China Hospital of Sichuan University Institutional Review Board approved this retrospective observational study and waived the requirement for informed consent. The study was registered on the Chinese Clinical Trial Registry (ChiCTR2300073505, registration date: July 12th 2023). This study was designed and reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data collection

Data were extracted from the electronic medical records of patients at West China Hospital, encompassing demographic information, anesthesia records, laboratory findings, diagnoses, etc. Data collection spanned from January 2019 to July 2021.West China Hospital, affiliated with Sichuan University in Chengdu, China, stands as one of the largest single-center hospitals in the country, with 4,300 beds and over 14,000 employees. In 2022, the hospital handled 207,500 surgeries, accommodated 8.79 million outpatient visits, and discharged 302,300 patients.

Patient inclusion and exclusion criteria

The study included adult patients (aged 18 years and older) who underwent elective major abdominal surgery at West China Hospital. Major abdominal surgery

was defined as any intraperitoneal procedure (including biliary tract, gastric, intestinal, liver surgeries, liver transplantation, pancreatic, and splenic surgeries) performed under general anesthesia with a minimum duration of 120 min [20]. The exclusion criteria were as follows: (1) patients classified as American Society of Anesthesiologists (ASA) Grade V or VI; (2) those who did not receive intravenous dexmedetomidine; (3) patients with missing serum creatinine (Scr) measurements before or after surgery; (4) patients with incomplete hospital discharge data; (5) patients with missing information on dexmedetomidine dosage; (6) patients with pre-existing chronic renal disease or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m^2 prior to surgery [21].

Exposure variable

The exposure variable in our study was the continuous intravenous administration of dexmedetomidine during surgery (Dex group), without restrictions on infusion rate or duration, and regardless of whether a bolus dose was used, while the control variable was the absence of dexmedetomidine administration during surgery (Control group). At our institution, anesthesia is managed by an attending anesthesiologist, with dexmedetomidine typically used as an adjunct to balanced general anesthesia.The decision regarding the loading dose, infusion rate and duration of dexmedetomidine is left to the anesthesiologist's discretion. In general, a loading dose of 0.2–1.0 μg/kg is administered within 15 min immediately following anesthesia induction for major abdominal surgeries, followed by a continuous infusion at a rate of 0.1–0.8 μg/kg/h.

Confounding variables

We considered a range of variables that could potentially influence the development of postoperative AKI (as shown in Supplementary Fig. 1). Baseline characteristics of the cohort included age, sex, body mass index (BMI), ASA classification, and comorbidities (such as hypertension, diabetes, cardiac dysfunction, cirrhosis, respiratory diseases, and peripheral vascular disease). Preoperative laboratory variables included hemoglobin (Hb), albumin (Alb), and Scr concentrations. The most recent preoperative laboratory measurements were used as the baseline data. Anesthesia-related variables comprised anesthesia type (general anesthesia alone, or in combination with thoracic epidural anesthesia, peripheral nerve block or paravertebral block), and anesthesia duration. Surgical variables included the type of surgery (biliary tract surgery, gastric surgery, intestinal surgery, liver surgery, liver transplantation, pancreatic surgery, or splenic surgery), laparoscope use, operation duration and intraoperative blood loss. Other intraoperative variables included average fluid infusion (measured in ml/kg/h), ratio of colloid (colloid solutions/the total amount of intravenous fluids), transfusion of blood products, use of Non-steroid anti-inflammatory drugs (NSAIDs), maximum lactic acid concentration, and minimum hemoglobin level during surgery [22].

Outcomes

The primary outcome was the incidence of AKI within the first 7 days postoperatively, diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [23]. Due to challenges in obtaining the postoperative urine output data, AKI was identified based solely on the creatinine-based KDIGO criteria: defined as either an increase in Scr by ≥0.3 mg/dL (26.5 μmol/L) within 48 h, or an increase in SCr to ≥1.5 times the baseline value recorded in the previous seven days. The most recent preoperative SCr measurement was used as the baseline. Secondary outcomes included Scr and eGFR levels on the first postoperative day, intraoperative urine output, length of hospital stay, in-hospital mortality, incidence of dialysis, incidence of ICU admission, and intraoperative events such as hypotension (defined as a minimum mean arterial pressure (MAP) of less than 60 mmHg), bradycardia (defined as a minimum heart rate (HR) of less than 50 bpm) and the use of inotropes and vasopressors.

Propensity score matching

Given the inherent selection bias in non-randomized studies, we used propensity-score matching (PSM) to minimize potential bias in our cohort study [24]. In this process, each patient who received dexmedetomidine was matched to a control patient within a 0.2 caliper. Propensity scores were generated using a multivariable logistic regression model, incorporating covariates with standardized mean differences (SMD)≥0.1, as well as key factors such as age, sex, BMI, and ASA classification. The balance between the two groups was evaluated using SMD, with a SMD<0.1 indicating a well-balanced comparison [24].

Sensitivity analysis and subgroup analysis

Sensitivity analyses were conducted to evaluate the robustness of the primary outcome. First, we assessed the association between dexmedetomidine administration and AKI using two additional statistical methods beyond PSM to control the confounding factors: In the analysis adjusted for propensity score, we included the score as an additional covariate in a multivariable logistic regression model; In the inverse-probability- weighted (IPW) analysis, we conducted a logistic regression model that employed stabilized inverse probability weights. These weights were derived from predicted probabilities from the propensity-score model, following Rubin's rules [25].

Second, a complete case analysis was performed, repeating the primary analysis using only cases with complete data. Third, given that patients with chronic kidney disease (CKD) at stage 3 may retain some renal function reserve [26], we repeated the primary analysis on a dataset that included patients with a baseline eGFR of 30–60 mL/min/1.7 m^2. The most recent preoperative eGFR measurement was used as the baseline.

A prespecified subgroup analysis was conducted to examine the association between different dexmedetomidine administration methods and the incidence of AKI. The subgroups were defined based on whether a loading dose was used and the infusion rate: loading dose subgroup, non-loading dose subgroup, low-infusion rate subgroup (infusion rate≤0.4 μg/kg/h), and high-infusion rate subgroup (infusion rate>0.4 μg/kg/h). This analysis aimed to provide a more detailed understanding of how these variables influence AKI.

Sample size calculation

The sample size calculation was conducted using PASS 22.0 software. Based on previous studies, the incidence of postoperative AKI in abdominal surgery ranges from 6.8 to 39.2% [6–8]. For this study, we estimated the incidence of AKI at 6.8%. A 30% reduction in the incidence of AKI was deemed clinically significant. With an anticipated 1:1 ratio between the Dex group and the control group and accounting for a 20% data missing rate, each group was determined to require 2564 patients to ensure adequate statistical power.

Statistical analysis

To assess continuous variables, the Kolmogorov-Smirnov test was employed to evaluate normality. Continuous data following a normal distribution were presented as mean±standard deviation, while those with a non-normal distribution were presented as medians with interquartile range (IQR). Categorical variables were summarized by case counts (frequencies). Certain continuous variables were converted into clinically relevant categories to align with the practicalities of clinical documentation. The unpaired t-test was used for continuous variables with a normal distribution, and the Mann-Whitney U-test was applied for non-normal distributed data. Categorical variables were analyzed using the Chi-square (X^2) test or Fisher's exact test, as appropriate. If covariables remained imbalanced (SMD≥0.1) after PSM, a multivariable conditional regression model was applied to further assess the association between dexmedetomidine use and the outcomes. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported.

For missing data on dexmedetomidine use and Scr levels before and after surgery, we initially filled the missing values through manual review. Cases lacking this critical data were excluded, as specified in our inclusion and exclusion criteria. Variables with more than 20% missing data were discarded, while imputation was performed for variables with less than 20% missing data [27]. Continuous variables were assumed to follow a normal distribution and were imputed using predictive mean matching, while binary variables were imputed using logistic regression [28].

Data processing and analysis were performed using R version 4.3.0, along with Storm Statistical Platform (www.medsta.cn/software). All statistical tests were two-sided, and a p-value of ≤0.05 was considered statistically significant.

Results

A total of 16,431 patients undergoing major abdominal surgery met the inclusion criteria. Of them, 4 patients were excluded due to an ASA grade of V or VI, 171 because dexmedetomidine was not administered intravenously, 1,118 due to missing data on Scr concentration, 153 for incomplete hospital discharge information, and 1924 for missing dosage of dexmedetomidine. Additionally, 605 cases were excluded due to chronic kidney disease or a preoperative GFR of less than 60 ml/min/1.73m^2. This left 12,456 patients were eligible for matching (Fig. 1). The missing rate was under 8.57% for all the included variables except intraoperative blood loss (69.54%), which was excluded due to the high missing rate (above 20%).

Before matching, 5,354 patients received dexmedetomidine, while 7,102 did not. Nine covariates exhibited a SMD greater than 0.10: ASA classification, preoperative Hb, preoperative Alb, preoperative Scr, surgery type, laparoscope use, average fluid infusion, ratio of colloid, and use of NSAIDs during surgery. After performing 1:1 PSM for these covariates, 8,836 patients were successfully matched, with 4,418 in each group. This resulted in a balance of preoperative and intraoperative covariates between the two groups (as shown in Tables 1 and 2). Figure 2 illustrates the distribution of the estimated propensity scores for receiving dexmedetomidine in both the unmatched and matched populations. After matching, the differences between the two groups were less pronounced, indicating improved comparability in the matched cohort.

Postoperative acute kidney injury

In the matched cohort (n=8,836), postoperative AKI developed in 299 patients (3.38%). The majority of these cases (79.6%) were classified as grade 1, representing 238 patients. In the matched cohort, there was no significant difference in the incidence of postoperative AKI between the Dex group and the control group (3.4% vs. 3.3%, P=0.769), as shown in Fig. 3A.

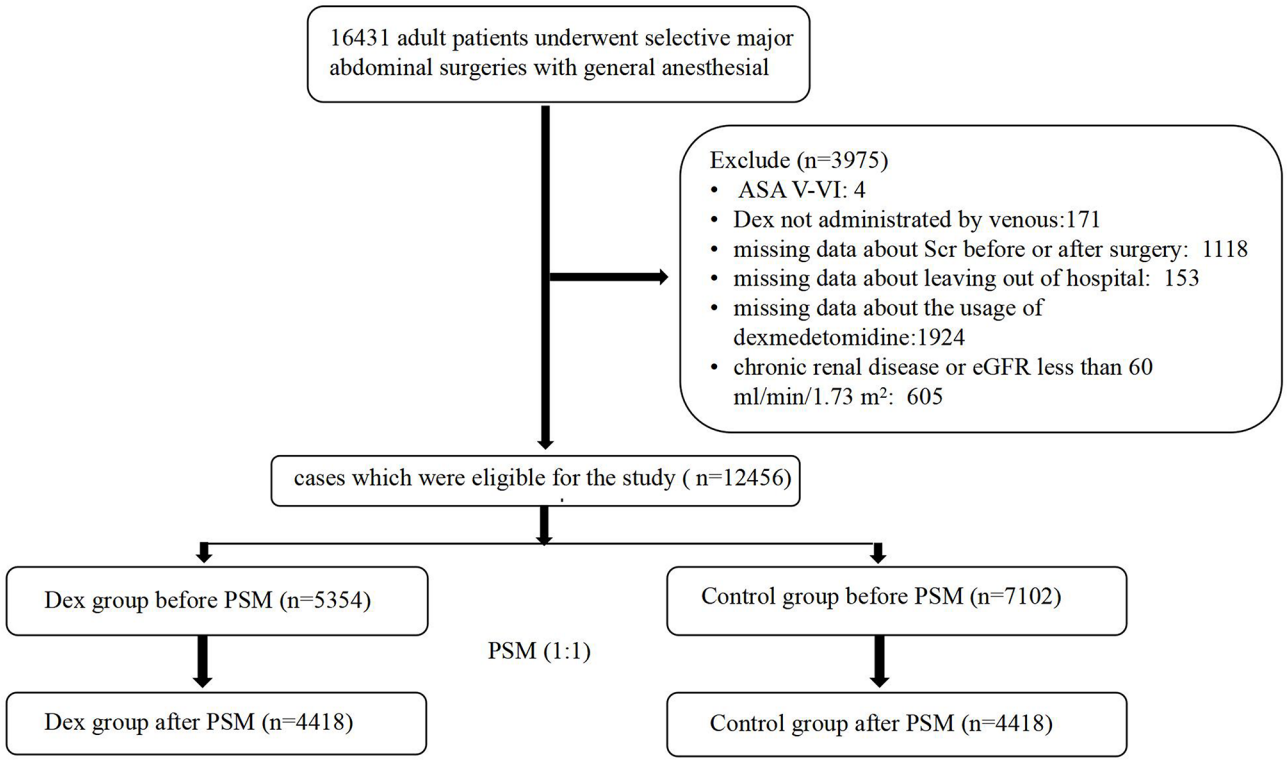

Fig. 1 Consolidated Standards of Reporting Trials diagram detailing selection of patients within each cohort, including numbers of patients in each cohort before and after matching

Abbreviations: ASA, American Society of Anesthesiologists; Dex, dexmedetomidine; Scr, serum creatine; eGFR, estimated glomerular filtration rate; PSM, propensity score matching

Table 1 Demographics, medical comorbidities and preoperative experimental data before and after propensity score matching

Characteristic *n*(%) or median(IQR)	Before Matching		SMD	After Matching		SMD
	Dex (*n* = 5354)	Control (*n* = 7102)		Dex (*n* = 4418)	Control (*n* = 4418)	
Age, years	55.8 (47.5, 65.2)	56.6 (48.5, 65.9)	0.067	56.0 (47.8, 65.6)	56.3 (48.4,65.5)	0.015
Sex, female	1979 (37.0)	2687 (37.8)	0.018	1641(37.1)	1656 (37.5)	0.007
BMI, kg/m^2	22.0 (20.1,26.0)	22.9 (20.1,26.2)	0.026	23.00 (20.2, 26.1)	22.9 (20.1,26.0)	0.016
ASA classification			0.180			0.007
I	29 (0.5)	15 (0.2)		13 (0.3)	12 (0.3)	
II	3936 (73.5)	4706 (66.3)		3154 (71.4)	3162 (71.6)	
III	1362 (25.4)	2302 (32.4)		1224 (27.7)	1216 (27.5)	
IV	27 (0.5)	80 (1.1)		27 (0.6)	28 (0.6)	
Hypertension	787 (14.7)	1032 (14.5)	0.005	689 (15.6)	603 (13.6)	0.055
Diabetes	518 (9.7)	689 (9.7)	0.001	434 (9.8)	415 (9.4)	0.015
Cardiac dysfunction	8 (0.1)	10 (0.1)	0.002	8 (0.2)	4 (0.1)	0.025
Cirrhosis	555 (10.4)	739 (10.4)	0.001	464 (10.5)	464 (10.5)	< 0.001
Respiratory disease	48 (0.9)	77 (1.1)	0.019	42 (1.0)	52 (1.2)	0.022
Peripheral vascular disease	95 (1.8)	174 (2.5)	0.047	78 (1.8)	88 (2.0)	0.017
Preoperative Hb, g/L	132.0 (118.0,146.0)	130.0 (115.0,143.0)	0.139	132.0 (117.0, 144.0)	132.0 (117.0, 145.0)	0.003
Preoperative Alb, g/L	42.1 (39.3, 44.6)	41.6 (38.7, 44.1)	0.129	41.9 (39.1, 44.4)	41.8 (39.1, 44.4)	0.001
Preoperative Scr, μmol/L	69.0 (58.0, 80.0)	71.0 (60.0, 81.0)	0.128	69.0 (59.0, 81.0)	69.0 (59.0, 80.0)	0.008

Abbreviations: Dex: dexmedetomidine; BMI, body mass index; ASA, American Society of Anesthesiologists; Hb, hemoglobin; Alb, albumin; Scr, serum creatine; IQR, interquartile range; SMD, standardized mean difference

Table 2 Intraoperative characteristics of patients before and after propensity score matching

Characteristic *n*(%) or median(IQR)	Before Matching		SMD	After Matching		SMD
	Dex (*n* = 5354)	Control (*n* = 7102)		Dex (*n* = 4418)	Control (*n* = 4418)	
Anesthesia duration, h	4.8 (3.9, 5.9)	4.8 (3.9, 5.9)	0.001	4.7 (3.9,5.9)	4.8 (4.0,5.9)	0.021
Surgery duration, h	3.5 (2.8,4.6)	3.4 (2.7,4.4)	0.046	3.5 (2.8,4.5)	3.5 (2.8,4.5)	0.024
Anesthesia type			0.081			0.072
GA	5318 (99.3)	7081 (99.7)		4392 (99.4)	4408 (99.8)	
GA + TEA	6 (0.1)	13 (0.2)		4 (0.1)	5 (0.1)	
GA + PNB	26 (0.5)	8 (0.1)		19 (0.4)	5 (0.1)	
GA + PVB	4 (0.1)	0 (0.0)		3 (0.1)	0 (0.0)	
Surgery type			0.233			0.031
Biliary tract surgery	283 (5.3)	474 (6.7)		264 (6.0)	286 (6.5)	
Gastric surgery	952 (17.8)	880 (12.4)		682 (15.4)	683 (15.5)	
Intestinal Surgery	1140 (21.3)	1914 (27.0)		1031 (23.3)	1052 (23.8)	
Liver surgery	2040 (38.1)	2420(34.1)		1649 (37.3)	1644 (37.2)	
Liver transplantation	64 (1.2)	200 (2.8)		64 (1.4)	63 (1.4)	
Pancreatic surgery	779 (14.5)	1084 (15.3)		645 (14.6)	613 (13.9)	
Splenic surgery	96 (1.8)	130(1.8)		83 (1.9)	77 (1.7)	
Laparoscope use	1297 (24.2)	2401 (33.8)	0.212	1181 (26.7)	1188 (26.9)	0.004
Average fluid infusion, ml/kg/h	8.2 (6.6,10.2)	9.3 (7.2,12.1)	0.373	8.4 (6.7,10.4)	8.4 (6.7,10.4)	0.001
Ratio of colloid	0.3 (0.2,0.4)	0.3 (0.2,0.3)	0.393	0.3 (0.2,0.4)	0.3 (0.2,0.4)	0.004
Transfusion	911 (17.0)	1445 (20.3)	0.086	785 (17.8)	752 (17.0)	0.020
NSAIDs	1281 (32.1)	2733 (51.0)	0.391	2039 (46.2)	1996 (45.2)	0.020
Lacmax	1.6 (1.3,2.3)	1.6 (1.3,2.3)	0.060	1.6 (1.3,2.3)	1.6 (1.3,2.3)	0.014
Hbmin	109.4 (91.8,123.0)	109.4 (91.8,123.0)	0.074	109.5 (93.5,122.6)	110.8 (95.3,123.9)	0.060

Abbreviations: Dex: dexmedetomidine; GA, general anesthesia; TEA, thoracic epidural anesthesia; PNB, peripheral nerve block; PVB, paravertebral block; NSAIDs, non-steroid anti-inflammatory drugs; Lacmax, the maximum concentration of lactic acid in the blood gas analysis during operation; Hbmin, the minimum concentration of hemoglobin in the blood gas analysis during operation; IQR, interquartile range; SMD, standardized mean difference

Ratio of colloid: colloid solutions/the total amount of intravenous fluids

Secondary outcomes

In the matched cohort, patients in the Dex group had significantly higher intraoperative average urine output compared to the control group (122.95 (76.80, 189.27) vs. 104.65 (67.04, 161.07) ml/h, $P<0.001$)((Fig. 3B). Furthermore, the eGFR value on the first postoperative day was higher in the Dex group than in the control group (97.33±15.95 vs. 96.13±16.35 ml/min/1.73m^2, $P<0.001$)(Fig. 3D). However, no significant difference was observed in Scr level on the first postoperative day between the two groups (68.89±17.96 vs. 68.54±19.06 μmol/L, $P=0.368$)(Fig. 3C).

No significant differences were observed between the Dex group and the control group regarding several key postoperative outcomes. The incidence of postoperative dialysis was equal in both groups (0.1% vs. 0.1%, $P=1.000$), as was the rate of postoperative ICU admission (7.4% vs. 7.2%, $P=0.744$) and in-hospital mortality (0.2% vs. 0.2%, $P=0.466$). Additionally, there was no statistically significant difference in the length of hospital stay between the two groups (9.3 (8.0, 12.0) vs. 9.0 (8.0, 12.0), $P=0.057$) (Table 3).

No between-group differences were found in the rates of intraoperative hypotension (19.4% vs. 18.9%, $P=0.607$), use of inotropes (1.6% vs. 1.6%, $P=0.866$) and vasopressors (11.9% vs. 10.7%, $P=0.075$). However, the incidence of intraoperative bradycardia was significantly higher in the Dex group compared to the control group (37.0% vs. 30.6%, $P<0.001$) (Table 3).

Sensitivity analysis

Prespecified additional statistical analyses were performed and the results aligned with the findings from the PSM analysis. In the multivariable logistic model, which incorporated the propensity score as an additional covariate, there was also no significant association between dexmedetomidine use and postoperative AKI (odds ratio (OR): 0.99, 95% confidence interval (CI): 0.81–1.22, $P=0.953$). Similarly, the univariable analysis in the inverse probability weighting cohort showed no significant association between dexmedetomidine use and postoperative AKI (OR:0.98, 95% confidence interval: 0.86–1.12, $P=0.771$) (Table 4).

In subsequent complete case analyses, a total of 9330 patients had complete data. After PSM in the complete cases, all confounding factors were balanced except for anesthesia type (SMD=0.111). A multivariable logistic regression, adjusted for the residual imbalance, yielded results consistent with the primary analysis, showing no significant association between dexmedetomidine

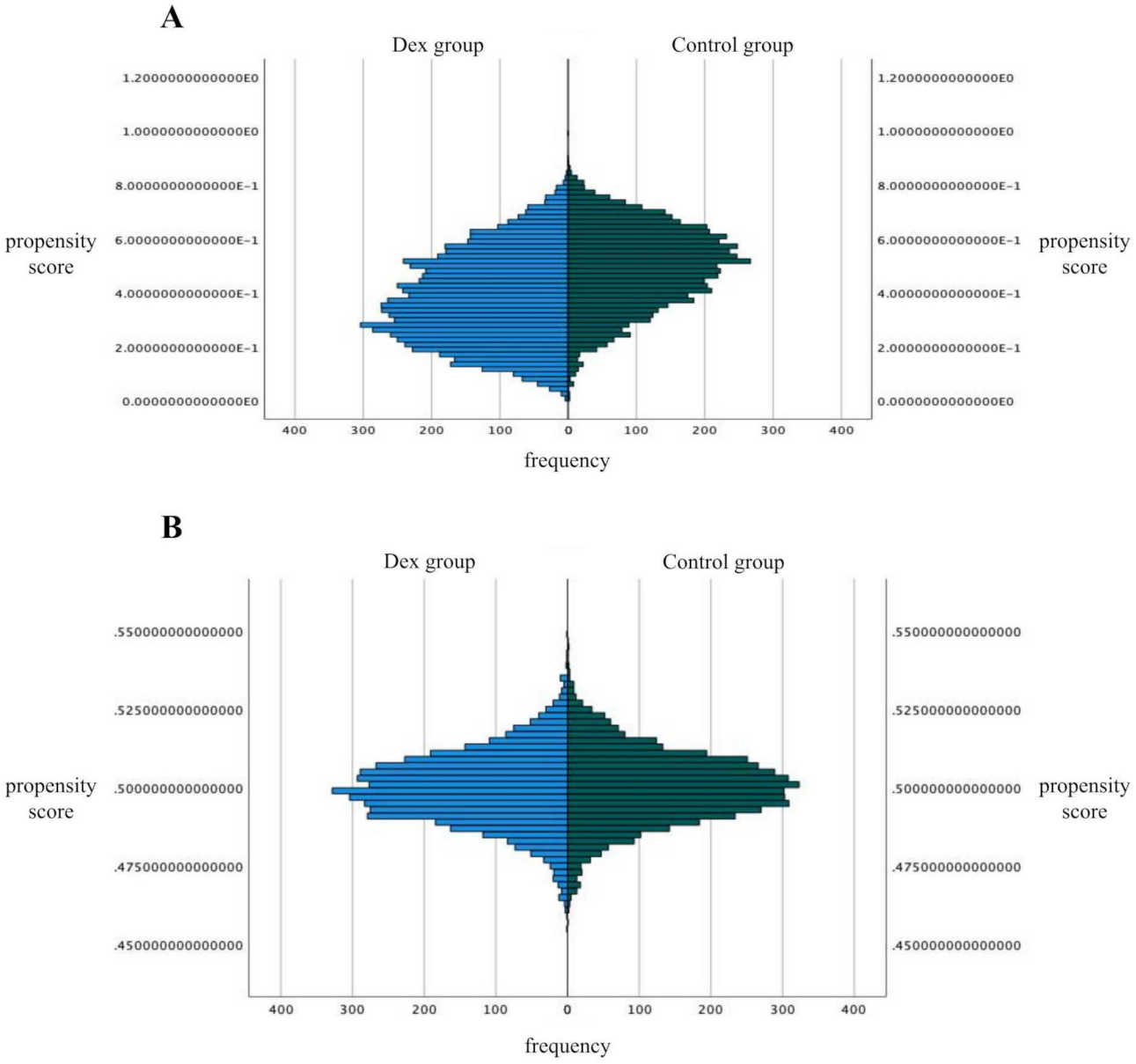

Fig. 2 Histograms of propensity score distribution before and after PSM in the Dex group and the Control group
Picture **A** presents histograms of the propensity scores distribution in the Dex group and the Control group before matching. Picture **B** presents histograms of the propensity scores distribution in the Dex group and the Control group after matching
Abbreviations: PSM, propensity score matching; Dex, dexmedetomidine

exposure and postoperative AKI (OR:0.99, 95% CI: 0.75–1.29, P=0.930). The demographics, medical comorbidities, preoperative experimental data and intraoperative characteristics before and after PSM in complete cases are provided in supplementary Tables 1 and 2).

Considering that patients with CKD at stage 3 may retain some renal function reserve [26], we repeated the primary analysis using a dataset that included patients with a baseline eGFR of 30–60 mL/min/1.7 m^2. The result was similar to the primary analysis and showed no association between dexmedetomidine exposure and postoperative AKI in the matched cohort after adjusting residual confounding factor (OR:0.99, 95% CI: 0.79–1.24, P=0.947)(Table 4). The demographics, medical comorbidities, preoperative experimental data and intraoperative characteristics before and after PSM for this dataset are present in supplementary Tables 3 and 4).

Subgroup analysis

In the matched cohort, 5.3% of patients in the Dex group received dexmedetomidine at an infusion rate exceeding 0.4 μg/kg/h, and a loading dose was administered to

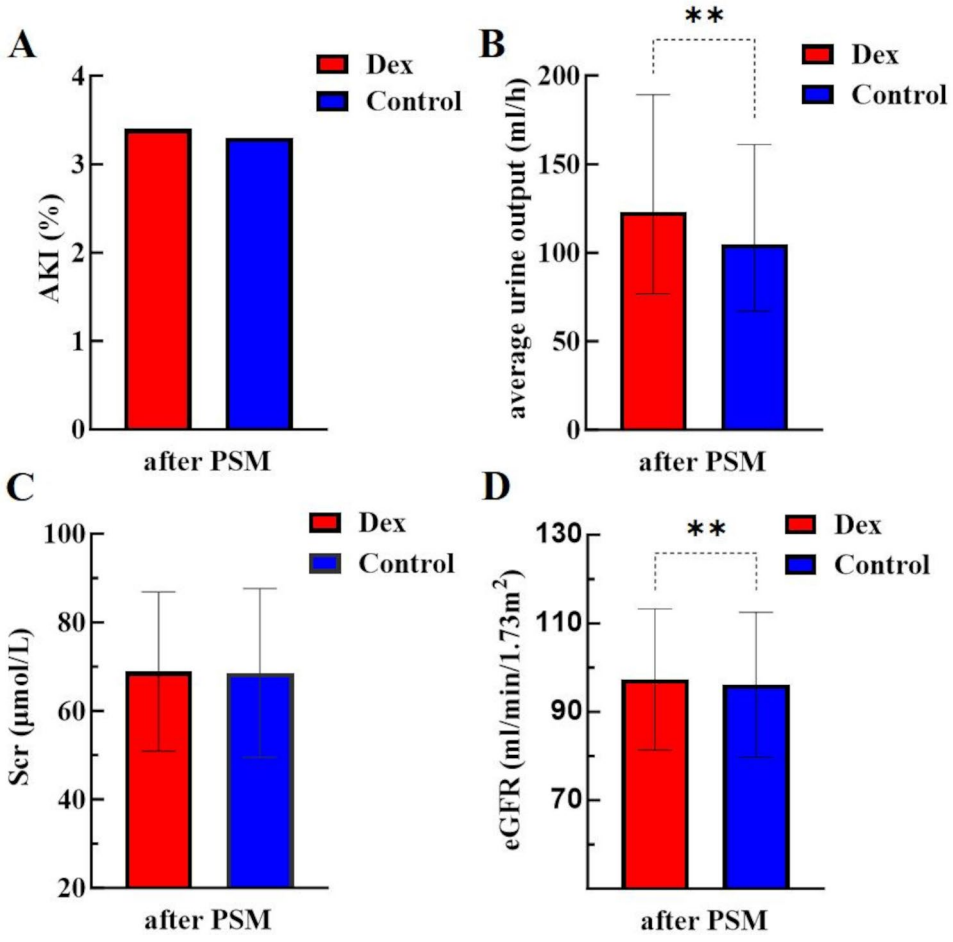

Fig. 3 The comparison of postoperative AKI incidence, intraoperative average urine volume, and renal function indicators on the first postoperative day between the Dex group and the control group
Abbreviations: AKI, acute kidney injury; Scr, serum creatine; eGFR, estimated glomerular filtration; Dex, Dexmedetomidine

Table 3 Secondary outcomes after propensity score matching

Outcomes, *n* (%) or median(IQR)	Dex (*n* = 4418)	Control (*n* = 4418)	*P*
Postoperative dialysis	3 (0.1)	3 (0.1)	1.000
ICU admission	328 (7.4)	320 (7.2)	0.744
In-hospital mortality	10 (0.2)	7 (0.2)	0.466
Hospital stays, days	9.3 (8.0,12.0)	9.0 (8.0,12.0)	0.057
Intraoperative hypotension	855 (19.4)	836 (18.9)	0.607
Intraoperative bradycardia	1634 (37.0)	1354 (30.6)	<0.001*
Inotropes	70 (1.6)	72 (1.6)	0.866
Vasopressors use	527 (11.9)	474 (10.7)	0.075

Abbreviations: Dex: dexmedetomidine; ICU, intention care unit; IQR, interquartile range.*indicates $P<0.05$

18.4% of patients in the Dex group. A subgroup analysis was conducted to explore the association between dexmedetomidine use and AKI in subgroups based on the infusion rate and the application of a loading dose in the matched cohort. In the loading dose subgroup, dexmedetomidine administration was associated with a significantly reduced incidence of postoperative AKI (OR:0.44, 95% CI: 0.23–0.76, $P=0.006$). However, no significant associations were found in the non-loading dose subgroup (OR:1.17, 95% CI: 0.93–1.49, $P=0.183$), the high-infusion rate subgroup (OR:0.75, 95% CI: 0.29–1.58, $P=0.505$) and the low-infusion rate subgroup (OR:1.05, 95% CI: 0.83–1.33, $P=0.674$)(Table 5).

Discussion

In this large population-based cohort study, AKI was observed in 3.80% of patients undergoing selective major abdominal surgery. After PSM, dexmedetomidine did not demonstrate a significant association with AKI. However, it was linked to an increased average urine output during the operation and a higher level of eGFR on the first postoperative day, though these findings lacked clinical significance. Notably, in the matched cohort, dexmedetomidine administration was significantly associated with a reduced incidence of postoperative AKI in the loading dose subgroup (OR = 0.44, 95% CI: 0.23 to 0.76).

Table 4 Sensitivity analysis of the association between Dex and AKI

Analysis	OR (95% CI)	*P*
Analysis by different propensity-score methods in the imputed dataset		
Propensity-score adjusting[a]	0.99 (0.81, 1.22)	0.963
IPW[b]	0.98 (0.86, 1.12)	0.771
Analysis by different management strategy for missing data		
PSM and adjusted in complete cases[c]	0.99 (0.75, 1.29)	0.930
Analysis by different exclusion criteria		
PSM and adjusted in the imputed dataset including patients with CKD stage 3[d]	0.99 (0.79, 1.24)	0.947

Abbreviations: OR, odds ratio; CI: confidence interference; PSM, propensity score matching; IPW, inverse probability weighting; CKD, chronic kidney disease

a: a multivariable logistic analysis adjusting for propensity score; b: the predicted probabilities from the propensity-score model were used to calculate stabilized inverse-probability weights following Rubin's rules; c: a multivariable logistic analysis adjusting for residual imbalanced confounding factor (anesthesia type) of the matched cohort from the complete cases dataset; d: a multivariable logistic analysis adjusting for residual imbalanced confounding factor (anesthesia type) of the matched cohort from the imputed dataset including patients with CKD stage 3

Table 5 Subgroup analysis of the association between Dex exposure and AKI

The association between Dex and AKI	Dex(Event/Total)	Control(Event/Total)	OR (95% CI)	*P*
Subgroups according to the infusion rate				
Low-dose (≤ 0.4 μg/kg/h)	146/4181	147/4418	1.05 (0.83–1.33)	0.674
High-dose (> 0.4 μg/kg/h)	6/237	147/4418	0.75 (0.29–1.58)	0.505
Subgroups according to the use of a loading dose				
Non-loading dose	140/3606	147/4418	1.17 (0.93–1.49)	0.183
Loading dose	12/812	147/4418	0.44 (0.23–0.76)	0.006*

Abbreviations: Dex: dexmedetomidine; OR, odds ratio; CI, confidence interval. *indicates $P < 0.05$

The association between dexmedetomidine exposure and postoperative AKI

In the matched cohort, the study did not observe the association between dexmedetomidine exposure and postoperative AKI. Previous meta-analyses, including RCTs focused on patients undergoing cardiac surgery, have reported that dexmedetomidine can decrease the incidence of AKI [1, 29]. However, retrospective cohort studies in non-cardiac surgery settings have yielded inconsistent results [18, 19]. For instance, Paredes-Flores et al. defined dexmedetomidine exposure as an infusion of 0.3 μg/kg/h and found no association between dexmedetomidine use and AKI in patients undergoing non-cardiothoracic cancer surgery [18]. Conversely, Zhu et al. defined exposure as an infusion rate of 0.2–0.7 μg/kg/h with or without a loading dose of 0.5–1.0 μg/kg, and reported that dexmedetomidine was associated with a lower incidence of postoperative AKI in major joint replacement surgeries [19]. Some RCTs in non-cardiac surgery indicated renal protection from dexmedetomidine based on renal injury biomarkers, though they did not report the AKI incidence [30, 31].

Several factors may explain our study's failure to find an association between dexmedetomidine use and postoperative AKI. First, we did not restrict the usage of exposure variable (dexmedetomidine administration), resulting in the inclusion of patients receiving lower doses of dexmedetomidine in the Dex group. This may have masked the overall renal protective effect in the Dex group. Second, many patients undergoing major abdominal surgery were expected to have their tracheal tubes removed as soon as possible postoperatively, resulting in the early discontinuation of dexmedetomidine before the procedure was complete. In contrast, studies that demonstrated a renoprotective effect of dexmedetomidine, particularly in cardiac surgery or ICU patients, often administered the drug for more than 24 h [32, 33]. Therefore, the shortened duration of dexmedetomidine use in major abdominal surgery may have diminished its renal protective effect. Third, the development of postoperative AKI after major abdominal surgery is complex and differs from that in cardiac surgery. AKI following cardiac surgery is relatively homogeneous, primarily driven by renal ischemia, inflammatory responses, and sympathetic hyperactivation associated with CPB [34], which decreased variability [35]. Conversely, AKI after major abdominal surgery involves multiple contributing factors, including fluid loss, bleeding, neuroendocrine responses to anesthesia and surgery, damage-associated molecular pattern (DAMP)-induced inflammation, as well as issues related to urinary obstruction and increased intra-abdominal pressure [7, 9]. These diverse mechanisms may influence the efficacy of dexmedetomidine's renal protective effects in patients undergoing major abdominal surgeries compared to those undergoing cardiac procedures.

The association between loading dose dexmedetomidine and postoperative AKI

Considering the potential dose-dependency of dexmedetomidine's renal protective effects [36] and the

variability in its administration in our study, we conducted a subgroup analysis. Similar to other retrospective studies [19, 37], the observational design of our study did not allow for standardized dexmedetomidine administration. Different studies had produced varying results regarding the optimal use of dexmedetomidine for renal protection [1, 32, 36]. For instance, a meta-analysis in cardiac surgery showed that the preventive effect of dexmedetomidine was weakened when the infusion rate was ≤0.4 μg/kg/min [1]. Additionally, a retrospective study in ICU patients with sepsis-associated AKI found that an infusion rate ranging from 0.3 to 1.0 μg/kg/h was associated with a reduced incidence of AKI [32]. Both the loading dose and the maintenance infusion rate affect the plasma concentration of dexmedetomidine, which influences its efficacy [38]. A RCT demonstrated that higher plasma concentrations of dexmedetomidine were associated with more pronounced renal protective effects [36]. However, there are no clear guidelines on how to administer dexmedetomidine to balance its renoprotective effects with the risk of hemodynamic instability. Furthermore, no RCTs have directly compared different dexmedetomidine dosing strategies to determine the optimal regimen for preventing AKI in non-cardiac surgeries.

In our subgroup analysis, administration of a loading dose of dexmedetomidine was associated with a more than 50% reduction in the incidence of postoperative AKI. However, no significant association was found in the non-loading dose, low-infusion rate, or high-infusion rate subgroups. Several factors may explain the more pronounced reduction in AKI incidence within the loading dose subgroup. First, in our study, the loading dose was administered in addition to continuous infusion, potentially leading to higher plasma concentrations of dexmedetomidine in the loading dose subgroup, regardless of the infusion rate. Unfortunately, due to the retrospective nature of the study, we lacked data on blood drug concentrations. Moreover, using a single infusion rate without considering the duration of infusion may not accurately reflect the total administered dose of dexmedetomidine. In previous studies reporting the renoprotective effects of dexmedetomidine, it was administered either with a loading dose or through continuous infusion after surgery [17, 33, 39]. Variations in infusion duration could explain the similar outcomes seen in the low- and high-infusion rate subgroups. Second, in our center, the loading dose of dexmedetomidine was administered after anesthesia induction and completed within 15 min, allowing the drug to reach peak concentrations before renal injury occurred. Animal studies have shown that preemptive administration of dexmedetomidine before surgical injury provides significant renal protection [40]. Other researchers also found preconditioning with dexmedetomidine, was more effective than postconditioning in attenuating renal injury in animal model [41]. Third, due to the retrospective design, there might be unknown confounding factors influencing the selection of loading dose, although we adjusted for confounding factors related to the selection consideration. Prospective researches are needed to explore the causal relationship between a loading dose of dexmedetomidine and renal protection.

The association between dexmedetomidine exposure and urine output and eGFR

Our research indicated that the Dex group experienced a statistically higher average intraoperative urine output and an elevated eGFR on the first postoperative day. However, these differences were minimal and lacked clinical significance. As a selective alpha-2 adrenergic agonist, dexmedetomidine inhibits vasopressin secretion from the pituitary gland, reducing its effects on renal collecting tubules [42]. An animal study showed that dexmedetomidine promotes aqueous diuresis and water clearance by suppressing vasopressin [43]. Similarly, a RCT involving patients undergoing hepatectomy also found increased intraoperative urine output with dexmedetomidine treatment, yet no significant difference in the incidence of AKI [44]. Urine output can be influenced by several factors, including intravascular volume status and hypotension, and should be interpreted alongside other markers of renal function and clinical severity [45]. In our study, the increased intraoperative urine output in the Dex group was minimal and was not accompanied by a decrease in the Scr level on the first postoperative day. A pilot RCT also reported higher eGFR in patients treated with dexmedetomidine without a difference in the incidence of AKI [46]. Moreover, a meta-analysis showed a nearly linear relationship between eGFR and AKI risk within the eGFR range of 15 to 90 ml/h/1.73m^2 [47]. In our trial, the average of eGFR in both groups exceeded 90 ml/h/1.73m^2, with only minimal intergroup differences. Therefore, the statistically significant differences in intraoperative average urine output and postoperative eGFR observed in our trial were not clinically meaningful.

Safety of dexmedetomidine administration in major abdominal surgery

The comparison of safety endpoints showed a higher incidence of bradycardia in the Dex group during surgery, with no significant difference in the incidence rate of hypotension between the two groups. This finding aligns with a previous retrospective study in joint surgeries that reported similar results [19]. Long-term persistent hypotension can lead to tissue hypoperfusion, affect organ function, and increase the risk of postoperative AKI [48]. However, prior observational data suggested

that transient bradycardia occuring with dexmedetomidine use had minimal effect on tissue perfusion [19]. Additionally, the proportion of patients treated with vasopressors and inotropes did not differ significantly between the Dex group and the control group, which was consistent with previous studies and meta-analyses [19, 31]. These findings indicated that the use of dexmedetomidine during major abdominal surgery was generally safe.

Strengths and limitations

The primary strength of this study is its large sample size, involving over 10,000 cases undergoing major abdominal surgery. This robust dataset enabled us to account for a wide range of confounding factors, including demographic characteristics, preoperative comorbidities and intraoperative management. Additionally, although cohort studies are inherently subject to selection bias, we minimized this through the use of PSM. We also enhanced the rigor of our findings by performing multiple sensitivity analyses, which included modifying the propensity-score methods, altering the strategy for managing missing data, and adjusting exclusion criteria. A further strength is our focus on dexmedetomidine administration methods related to renal protection—a relatively underexplored topic in non-cardiac surgeries. Since administration methods can significantly influence efficacy, our findings underscore the need for future prospective studies to investigate the impact of loading-dose dexmedetomidine in major abdominal surgery.

However, our study had several limitations. Firstly, we defined postoperative AKI solely based on changes in Scr, due to a lack of postoperative data on urine output. Although this definition is widely accepted in retrospective research, it may underestimate the actual incidence [49]. Second, despite extensive adjustments for confounding factors, some variables, such as intraoperative blood loss, could not be accounted for due to the high missing rate [50]. Third, as a single-center retrospective cohort study, the study design could only indicate the association between dexmedetomidine use and outcomes, which limited the generalizability in clinical practice. Further prospective researches are needed to explore the causal relationship between intraoperative dexmedetomidine use and AKI after major abdominal surgery. Finally, while we examined dexmedetomidine administration methods related to renal protection through subgroup analysis, we did not conduct direct comparisons between these methods. Future RCTs designed with specific groups based on different administration strategies are needed to clarify the most effective approach.

Conclusion

In conclusion, our study did not detect an significant overall association between dexmedetomidine treating and AKI after major abdominal surgery. Although patients in the Dex group showed slightly higher intraoperative urine output and eGFR level on the first postoperative day, these differences were not clinically significant. However, though additional prospective data are needed, our study found that the use of dexmedetomidine with a loading dose was associated with lower rates of postoperative AKI, possibly suggesting a renoprotective effect of loading-dose dexmedetomidine in this setting. The retrospective design of this study renders these results hypothesis-generating and therefore has limited direct impact on clinical practice. Well-designed RCTs are needed to further explore the renal protective effects of dexmedetomidine in major abdominal surgery.

Supplementary Information

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Supplementary Figure 1: Directed acyclic graph for the association between dexmedetomidine use (exposure) and postoperative acute kidney injury (outcome).Blue color variables indicate ancestors of the outcome and red color variables indicate ancestors of both the exposure and outcome.Abbreviations: Dex: dexmedetomidine; BMI, body mass index; ASA, American Society of Anesthesiologists; Hb, hemoglobin; Alb, albumin; Scr, serum creatine; NSAIDs, non-steroid anti-inflammatory drugs; Lacmax, the maximum concentration of lactic acid in the blood gas analysis during operation; Hbmin, the minimum concentration of hemoglobin in the blood gas analysis during operation; AKI, acute kidney injury

Supplementary Tables 1, 2, 3 and 4

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Author contributions

Study design: all authors. Data acquisition: QL, TJ. Data analysis: LHB, LR. Drafting of the manuscript: all authors. Revision of manuscript: all authors.

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Data availability

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

Declarations

Ethics approval and consent to participate

The ethics committee of the West China Hospital of Sichuan University approved this study, the approval number: 2022(1329). The requirement for informed consent was waived by the ethics committee of West China Hospital of Sichuan University because this research only involved existing retrospective data. The study was registered on the Chinese Clinical Trial Registry (ChiCTR2300073505, registration date: July 12th 2023).

Consent for publication

Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
[2]Laboratory of Anesthesia and Critical Care Medicine, National-Local Joint Engineering Research Center of Translational Medicine of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
[3]Department of Anesthesiology, Chengdu Third People's Hospital, Sichuan University, Chengdu, China
[4]Department of Pain Management, West China Hospital, Sichuan University, Chengdu, China

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