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Correlation between perioperative parecoxib use and postoperative acute kidney injury in patients undergoing non-cardiac surgery: A retrospective cohort analysis

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Abstract

Objective: The association of nonsteroidal anti-inflammatory drugs with postoperative acute kidney injury is controversial. However, there are few studies focusing on the association between parecoxib and postoperative acute kidney injury.

Design: A retrospective cohort study

Setting: Third Xiangya Hospital of Central South University in Hunan Province, China

Participants: The electronic medical records and laboratory results were obtained from 9,246 adult patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August 31, 2017. Study groups were treated with or without parecoxib.

Interventions: Univariable analysis identified demographic, preoperative laboratory, and intraoperative factors associated with acute kidney injury. Logistic stepwise regression was used to calculate the adjusted odds ratio of parecoxib and acute kidney injury association.

Results: The incidence of postoperative acute kidney injury was 6.06% and parecoxib was used in 10.5% of the patients. The mortality was 4.64% in the acute kidney injury group. The incidence of acute kidney injury was lower in the parecoxib-administered group (4%) than that in the group without parecoxib (6.3%, $p = 0.005$). Postoperative acute kidney injury risk reduced by 39% in the parecoxib-administered group after adjusting for interference factors.

Conclusions: Thus, parecoxib might have potential protective effects against postoperative acute kidney injury risk in adult patients undergoing non-cardiac surgery.

Keywords: acute kidney injury; parecoxib; non-cardiac surgery

Strengths and limitations of this study: Large study population including all adult patients (18–60 years) undergoing non-cardiac surgery in Third Xiangya Hospital of Central South University in China between 2012 to 2017.

- Our study indicated that parecoxib might have potential protective effects against postoperative acute kidney injury risk.

This retrospective single-center observational study may have had some selection bias, and the timing of the serum creatinine measurement may vary with different doctors.

Background

Acute kidney injury (AKI), a long-recognized complication of surgery with a high incidence of morbidity and mortality, increases health care costs and length of hospital stay [1-3]. Even in patients undergoing non-cardiac surgery with low-grade American Society of Anesthesiologists (ASA) physical status such as ASA I–II, the incidence of postoperative AKI can reach 6% [4]. Mild kidney injury, such as a small increase in postoperative serum creatinine, is associated with renal dysfunction for as long as 1 to 2 years after surgery [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used perioperative anesthetic adjuvants, with anti-inflammatory and analgesic effects. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX) enzymes, which can ultimately result in the reduction of prostanoids and thromboxane [6]. COX exists in two forms: COX-1, which is present in most body tissues body including the stomach and intestines and COX-2, which is primarily found at sites of inflammation [7]. Accumulating evidence suggests that traditional NSAIDs, such as aspirin and ibuprofen, are associated with acute and chronic gastrointestinal bleeding and kidney disease [8, 9]. These NSAIDs are nonselective COX (COX-1 and COX-2) inhibitors and their side effects are mostly COX-1 related.

Parecoxib is a parenteral specific COX-2 inhibitor, which enhances its therapeutic gain with minimal adverse effects [6, 10]. Parecoxib is used as a perioperative analgesic in over 80 countries, however, clinical data about effect of parecoxib on postoperative AKI are scarce. Therefore, it is important to establish its safety during the perioperative period.

The aim of this study was to assess the correlation between the perioperative use of parecoxib and postoperative AKI in patients undergoing non-cardiac surgery.

Methods

Design and selection criteria

This retrospective study was performed at the Third Xiangya Hospital of Central South University from January 1, 2012, to August 31, 2017. The inclusion criterion was patients aged 18–60 years who underwent non-cardiac surgery. The exclusion criteria were ASA grade VI, administration of local anesthesia, liver transplantation, cardiac surgery, urological surgery (including kidney transplantation), lack of serum creatinine or covariate data, and preoperative combined CKD, defined as estimate glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1} \cdot 1.73m^{(2)\ -1}$, ≥3 months). Parecoxib doses larger than 80 mg were not included because the routine dose is not more than 80 mg/day based on the drug instructions. The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (approval number 2020S264) that waived the need for informed consent because of the observational nature of the study.

Data collection

The following information was collected: 1) epidemiological data including age, sex, and BMI; 2) individual history including preoperative complications and medication history; 3) laboratory data including serum creatinine and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; 4)

intraoperative data including emergency, surgical grade, operative time, anesthesia method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive drugs. 5) postoperative outcomes such as occurrence of AKI, admission to ICU, and mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were obtained by a retrospective review of the computerized patient record system of our hospital.

Definitions

Postoperative AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 creatinine criteria [11], as one of the following: an increase in serum creatinine by ≥0.3 mg/dL within 48 h or a ≥1.5-times increase in serum creatinine from baseline within 7 postoperative days. The baseline serum creatinine level was calculated using the lowest level at preoperative day 7. The primary outcome was the impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days. Parecoxib administration was defined during the operative time. Surgical grade was classified using the surgical classification catalogue constituted by the Chinese Ministry of Health, published in 2018. Intraoperative hypotension was defined as mean arterial pressure (MAP) <65mmHg for a duration of at least 5 min.

Patient and public involvement

No patient involvement.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, NC, USA) and CRAN R (v3.4.3). Missing data of covariates were handled by multiple imputation model. The continuous results are expressed as mean(SD), whereas categorical variables are expressed as numbers with percentages. The Kruskal-Wallis rank sum test was used to compare continuous variables between groups, whereas the chi-square ($\chi 2$) test or Fisher's exact probability method was used for categorical variables. Univariable logistic regression analysis was used to identify epidemiological, preoperative laboratory, and intraoperative factors that were significantly associated with AKI development. The data were adjusted for potential confounders in multivariable regression models. In addition, the sensitivity test or subgroup analysis were performed. The results of the classification variable are expressed as odds ratio (OR) or "Beta" and 95% CI; a p-value < 0.05 indicated a statistically significant difference.

Results

Of the 108,198 records identified, those of 9,246 patients were included in the analysis (Fig. 1). Reasons for excluding patients were age <18 or >60 years (n = 4,783), ASA grade VI (n = 13), exposure to local anesthesia (n = 12,054), cardiac surgery (n = 387), urological surgery including kidney transplantation (n = 3,589), liver transplantation (n = 107), no recorded preoperative or postoperative creatinine data (n=73,093), no recorded

covariate data such as routine blood panel or infusion volume (n = 4,114), preoperative chronic kidney disease (CKD) (n = 472), and administration of parecoxib doses >80 mg (n = 340).

AKI

The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the probability of admission to the intensive care unit (ICU) and mortality were 10.18% and 4.64%, respectively (Table 1).

Table 1. Baseline characteristics of patients aged 18–60 years with and without acute kidney injury (AKI)

Clinical features	without AKI (n=8686)	With AKI (n=560)	p-value
Age (years)	44.25±10.43	45.06±10.18	0.074
BMI	22.93±4.93	22.54±3.83	0.07
eGFR	101.98±16.38	94.41±19.78	<0.001
Male	4267 (49.13%)	300 (53.57%)	0.041
Smoking	1213 (13.97%)	105 (18.75%)	0.002
Alcohol consumption	822 (9.46%)	74 (13.21%)	0.004
Anemia	1538 (17.71%)	161 (28.75%)	<0.001
Hypertension	1884 (21.69%)	211 (37.68%)	<0.001

Diabetes mellitus	509 (5.86%)	52 (9.29%)	<0.001
ACEI	189 (2.18%)	21 (3.75%)	0.015
ARB	116 (1.34%)	13 (2.32%)	0.054
CCB	1125 (12.95%)	119 (21.25%)	<0.001
Diuretics	77 (0.89%)	19 (3.39%)	<0.001
ASA grade			<0.001
I–II	6633 (76.36%)	317 (56.61%)	
III–V	2053 (23.64%)	243 (43.39%)	
Anesthesia method			<0.001
General anesthesia	7735 (89.05%)	531 (94.82%)	
No general anesthesia	951 (10.95%)	29 (5.18%)	
Emergency	1395 (16.06%)	130 (23.21%)	<0.001
Surgical Grade			<0.001
1	245 (2.82%)	14 (2.50%)	
2	2746 (31.61%)	118 (21.07%)	
3	5349 (61.58%)	386 (68.93%)	
4	346 (3.98%)	42 (7.50%)	
Operative time (min)			<0.001
≤60	1338 (15.4%)	63 (11.25%)	
61–120	2176 (25.05%)	111 (19.82%)	
121–180	2032 (23.39%)	135 (24.11%)	
>180	3140 (36.15%)	251 (44.82%)	

Intraoperative erythrocyte Transfusion, mL (%)			<0.001
<100	6735 (77.54)	339 (60.54)	
100–600	868 (9.99)	82 (14.64)	
601–1000	508 (5.85)	42 (7.50)	
>1000	575 (6.62)	97 (17.32)	
Amount of Blood loss, mL (%)			<0.001
<100	2623 (30.20)	131 (23.39)	
100–600	4771 (54.93)	292 (52.14)	
601–1000	670 (7.71)	60 (10.71)	
>1000	622 (7.16)	77 (13.75)	
Amount of fluid infusion (10 mL/24 h)	916.67 (625.00–1432.29)	1125.00 (703.12–1604.17)	<0.001
Amount of fluid out (10 mL/24 h)	333.33 (145.83–541.67)	375.00 (208.33–687.50)	<0.001
Intraoperative Hypotension	930 (10.71%)	81 (14.46%)	0.006
Vasoactive drugs	664 (7.64%)	71 (12.68%)	<0.001
Parecoxib	934 (10.75%)	39 (6.96%)	0.005
Admission to ICU	376 (4.33%)	57 (10.18%)	<0.001
Death	32 (0.37%)	26 (4.64%)	<0.001

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AKI: acute kidney injury, BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, ICU, intensive care unit. Data are expressed as number of patients (%) or mean ± standard deviation (SD).

There was no difference in age, body mass index (BMI), angiotensin receptor blockers (ARBs) use and intraoperative hypotension among patients with and without AKI (Table 1). Significant differences between patients with AKI and without AKI are shown in Table 1 (all $p < 0.05$).

Parecoxib

Parecoxib was used in 10.5% (973/9,246) of patients (Table 2).

Table 2. Baseline characteristics of patients aged 18–60 years treated with and without parecoxib

Clinical features	Without parecoxib (n=8273)	With parecoxib (n=973)	p-value
Age (year)	44.23±10.46	44.89±10.04	0.06
BMI	22.89±4.99	23.03±3.76	0.409
eGFR	101.66±16.66	101.56±16.23	0.858
Male	4062 (49.1%)	508 (52.2%)	0.063

Smoking	1175 (14.2%)	146 (15%)	0.479
Alcohol consumption	811 (9.8%)	89 (9.1%)	0.544
Anemia	1547 (18.7%)	152 (15.6%)	0.019
Hypertension	1903 (23%)	189(19.4%)	0.011
Diabetes mellitus	505 (6.1%)	56 (5.8%)	0.666
ACEI	199 (2.4%)	14 (1.4%)	0.065
ARB	116 (1.4%)	14 (1.4%)	0.902
CCB	1142 (13.8%)	103 (10.6%)	0.006
Diuretics	91 (1.1%)	8 (0.8%)	0.482
ASA grade			0.09
I–II	6196 (74.9%)	753 (77.4%)	
III–V	2077 (25.1%)	220 (22.6%)	
Anesthesia method			<0.001
General anesthesia	7363 (89%)	907 (93.2%)	
No general anesthesia	910 (11%)	66 (6.8%)	
Emergency	1406 (17%)	119 (12.2%)	<0.001
Surgical grade			<0.001
1	240 (2.9%)	19 (2%)	
2	2623 (31.7%)	243 (25%)	
3	5080 (61.4%)	656 (67.4%)	
4	330 (4%)	55 (5.7%)	
Operative time (min)			<0.001

≤60	1315 (15.9%)	88 (9%)	
61–120	2085 (25.2%)	204 (21%)	
121–180	1919 (23.2%)	246 (25.3%)	
>180	2954 (35.7%)	435 (44.7%)	
Intraoperative erythrocyte Transfusion, mL (%)			0.94
<100	6329 (76.5%)	744 (76.5%)	
100–600	852 (10.3%)	98 (10.1%)	
601–1000	496 (6%)	56 (5.8%)	
>1000	596 (7.2%)	75 (7.7%)	
Amount of Blood loss, mL (%)			0.003
<100	2507 (30.3%)	251 (25.8%)	
100–600	4500 (4.4%)	559 (57.5%)	
601–1000	662 (8%)	70 (7.2%)	
>1000	604 (7.3%)	93 (9.6%)	
Intraoperative Hypotension	10.8	11.9	0.297
Vasoactive drugs	7.8	8.9	0.227
Amount of fluid infusion (10 mL/24 h)	1037.07±565.54	1159.31±579.85	<0.001
Amount of fluid out	410.17±374.16	373.74±334.53	0.004

(10 mL/24 h)			
AKI	521 (6.3%)	39 (4%)	0.005
AKI.RANK			0.013
0	93.7	96	
1	4.5	2.6	
2	1.8	1.4	

BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, AKI: acute kidney injury. Data are expressed as number of patients (%) or mean ± standard deviation (SD).

The incidence of AKI was lower in the parecoxib-administered group (4%) than in the group without parecoxib (6.3%, p = 0.005). There was no difference in age, BMI, estimated glomerular filtration rate (eGFR), sex, smoking, alcohol consumption, presence of diabetes mellitus, use of angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or diuretics, ASA grade, incidence of intraoperative erythrocyte transfusion and intraoperative hypotension, and use of vasoactive drugs between patients treated with and without parecoxib (Table 2). Significant differences between patients treated with and without parecoxib are shown in Table 2 (all $p < 0.05$).

Univariable analysis

The factors shown by the univariable analysis to influence AKI development in patients

aged 18–60 years who underwent non-cardiac surgery are listed in Table 3.

Table 3. Univariable analysis of acute kidney injury (AKI)

Variable	Statistics	Univariable	
		OR (95% CI)	p-value
Parecoxib	0.11± 0.31	0.62 (0.45, 0.87)	0.0050
Age (year)	44.30 ± 10.42	1.01 (1.00, 1.02)	0.0737
Male	4567 (49.39%)	1.19 (1.01, 1.42)	0.0416
BMI	22.90 ± 4.87	0.98 (0.95, 1.00)	0.0396
Smoking	1318 (14.25%)	1.42 (1.14, 1.77)	0.0018
Alcohol consumption	896 (9.69%)	1.46 (1.13, 1.88)	0.0038
Anemia	1699 (18.38%)	1.88 (1.55, 2.27)	<0.0001
Hypertension	2095 (22.66%)	2.18 (1.83, 2.61)	<0.0001
Diabetes mellitus	561 (6.07%)	1.64 (1.22, 2.22)	0.0011
ACEI	210 (2.27%)	1.75 (1.11, 2.77)	0.0167
ARB	129 (1.40%)	1.76 (0.98, 3.14)	0.0570
CCB	1244 (13.45%)	1.81 (1.47, 2.24)	<0.0001
Diuretics	96 (1.04%)	3.93 (2.36, 6.54)	<0.0001
eGFR	97.94±22.36	0.96 (0.96, 0.97)	<0.0001
ASA grade III–V	2296 (24.83%)	2.48 (2.08, 2.95)	<0.0001
No general anesthesia	980 (10.60%)	0.44 (0.30, 0.65)	<0.0001
Emergency	1525 (16.49%)	1.58 (1.29, 1.94)	<0.0001

Surgical grade 4	388 (4.20%)	2.12 (1.14, 3.98)	0.0184
Operative time (min)			
≤60	1401 (15.15%)	1	
61–120	2287 (24.74%)	1.08 (0.79, 1.49)	0.6200
121–180	2167 (23.44%)	1.41 (1.04, 1.92)	0.0279
>180	3391 (36.68%)	1.70 (1.28, 2.25)	0.0003
Intraoperative Hypotension	1011 (10.93%)	1.41 (1.10, 1.80)	0.0060
Vasoactive drugs	735 (7.95%)	0.06 (0.03, 0.09)	<0.0001
Intraoperative erythrocyte transfusion, mL (%)			
<100	7074 (76.51%)	1	
100–600	950 (10.27%)	1.88 (1.46, 2.41)	<0.0001
601–1000	550 (5.95%)	1.64 (1.18, 2.29)	0.0035
>1000	672 (7.27%)	3.35 (2.63, 4.27)	<0.0001
Amount of Blood loss, mL (%)			
<100	2754 (29.79%)	1	
100–600	5063 (54.76%)	1.23 (0.99, 1.51)	0.0596
601–1000	730 (7.9%)	1.79 (1.31, 2.46)	0.0003
>1000	699 (7.56%)	2.48 (1.85, 3.33）	<0.0001

OR: odds ratio, BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of

Anesthesiologists.

In the univariable analysis, male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, calcium channel blocker (CCB) use, diuretic use, ASA grade III–V, emergency, surgical grade 4, duration of the operation, incidence of intraoperative hypotension and erythrocyte transfusion, and amount of blood loss were independently associated with an increased risk of postoperative AKI (Table 3).

Parecoxib (OR, 0.62; 95%CI, 0.45–0.87, p = 0.005), eGFR (OR,0.96; 95%CI, 0.96–0.97, p < 0.0001), no general anesthesia (OR, 0.44; 95%CI, 0.30–0.65, p < 0.0001) and vasoactive drug use(OR, 0.06; 95%CI, 0.03–0.09, p < 0.0001) were independently associated with a decreased risk of postoperative AKI (Table 3). Age (OR, 1.01; 95%CI, 1.00–1.02, p = 0.0737), BMI (OR, 0.98; 95%CI, 0.95–1.00, p = 0.0396), and ARB use (OR, 1.76; 95%CI, 0.98–3.14, p = 0.0570) were not correlated with AKI (Table 3).

Multivariable regression analysis

The occurrence of postoperative AKI was regarded as a dependent variable, and the administration of parecoxib, an independent variable when we performed the stepwise regression analysis (Table 4).

Table 4 Odds ratio of postoperative acute kidney injury (AKI) associated with parecoxib

	Non-adjusted:	Adjusted I:	Adjusted II:	Adjusted III:

	Model 1	Model 2	Model 3	Model 4
OR (95%	0.62 (0.45, 0.87)	0.64 (0.46, 0.90)	0.63 (0.44, 0.89)	0.61(0.43, 0.87)
CI) p-value	0.0050	0.0096	0.0095	0.0069

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time.

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

The risk adjustment models were constructed using logistic stepwise regression. After adjusting for these interference factors, parecoxib was still independently associated with postoperative AKI (OR, 0.61; 95% CI, 0.43–0.87, model 4 in Table 4).

Sensitivity analysis

Table 5 shows the sensitivity analysis of postoperative AKI associated with parecoxib.

Table 5 Sensitivity analysis of association between postoperative acute kidney injury (AKI) and parecoxib

	Model 1	**Model 2**	**Model 3**	**Model 4**
Without	Parecoxib (40 or 80 mg)			

	parecoxib				
eGFR	1	0.49 (0.31, 0.79)	0.54 (0.33, 0.87)	0.50 (0.30, 0.84)	0.49(0.29,0.82)
<90		0.0032	0.0119	0.0084	0.0065
Non-	1	0.57 (0.39, 0.84)	0.56 (0.37, 0.84)	0.56 (0.38, 0.84)	0.55(0.37,0.83)
smoker		0.0040	0.0046	0.0052	0.0043
AKI	0	-0.03 (-0.05, -0.00)	-0.02 (-0.05, -0.00)	-0.02 (-0.04, -0.00)	-0.02(-0.04,-0.00)
RANK		0.0176	0.0283	0.0254	0.0271

AKI RANK (outcome of postoperative AKI was divided into three groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and 3)

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

For patients with an eGFR <90 $mL \cdot min^{-1} \cdot 1.73\ m^{(2)\,-1}$ or who were non-smokers, single-dose parecoxib (40 mg or 80 mg) was associated with a lower incidence of postoperative AKI. We divided the outcome of postoperative AKI into three groups: stage 0, no AKI; stage 1, AKI grade 1; and stage 2, AKI grade 2 and 3. The results showed that parecoxib exerted protective effects in postoperative AKI in differently ranked AKIs.

Discussion

According to the surgery type and AKI diagnostic criteria, the incidence of postoperative AKI ranges from 1.0% to 31% [12-14], and our study revealed an incidence of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac surgery. The incidence was similar to that in the recently published data by Nishimoto (6%, non-cardiac surgery; mean age, 63 years) [15]. In our study, the univariable analysis identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode, emergency, surgical grade 4, duration of the operation (>120 min), incidence of intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which are similar to previously published data [16, 17].

However, age and BMI did not correlate with AKI in our study, which is inconsistent with the findings of previous studies [18]. This discrepancy can be explained by the difference in mean age and BMI between the studies, which were both lower in our study population. The results of the sensitivity analysis suggested that single-dose (40 mg or 80 mg) parecoxib might have potential protective effects against postoperative AKI in differentially ranked AKI.

Numerous studies have investigated the association between NSAIDs and AKI [9, 19]. An updated Cochrane systematic review and meta-analysis published in 2018 indicated that NSAIDs have uncertain effects on the rate of AKI and may slightly increase serum creatinine in patients with normal kidney function following surgery [19]. In another

meta-analysis, a significant risk of AKI was observed with most traditional NSAIDs but not with two COX-2 specific inhibitors (rofecoxib and celecoxib) [9]. A pooled analysis of 28 randomized clinical trials investigating the safety of parecoxib for the management of postoperative pain showed that its associated risk of renal failure and impairment was 1%, similar to that with the placebo (0.9%) [20].

However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80 mg) might provide potential protective effects against postoperative AKI in patients aged 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a renoprotective effect has been postulated for parecoxib. For example, a study also showed that a single-dose of parecoxib (20 mg/kg) reduced tubular renal injury and serum inflammatory cytokines level (interleukin (IL)-1α, IL-β, IL6, and tumor necrosis factor (TNF)-α) in an ischemic rat model [21]. Moreover, several animal studies have suggested that pretreatment with COX-2 inhibitors improved outcomes in function and histology in not only the kidney but also other organs after ischemia [21, 22, 24]. To the best of our knowledge, this is the first clinical report to suggest that single-dose (40 mg or 80 mg) parecoxib may be renoprotective in patients aged 18–60 years who underwent non-cardiac surgery.

The mechanism by which parecoxib decreases the risk of postoperative AKI is unknown. However, one possible underlying mechanism is likely related to inflammation. A previous study showed that inflammation is a predictor of postoperative AKI and a mediator of increased mortality after AKI in non-cardiac surgery [25]. However, perioperative parecoxib reduced local and systemic inflammatory cytokines

postoperatively [26, 27]. Another possible mechanism is associated with hemodynamic change. COX-1 contributes to controlling renal GFR, whereas COX-2 is involved in sodium and water excretion [28]. COX-2 inhibitors are associated with mild hypertension owing to modest sodium retention in the first few days of therapy [29]. The renoprotective mechanism of parecoxib may be related to its anti-inflammatory effects and sodium regulation.

Our study had some limitations that are worth mentioning. First, this was a retrospective single-center observational study; thus, it may have had some selection bias. Second, the timing of the serum creatinine measurement was based on clinical discretion; thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years who underwent non-cardiac surgery as the target to research, therefore, our results should be extrapolated cautiously.

Conclusions

In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80 mg) may have potential protective effects against postoperative AKI in those aged 18–60 years. However, these short-term effects may not represent the benefit of this drug in the long term. Furthermore, more comprehensive studies are needed to confirm the effects of parecoxib on the risk of postoperative AKI.

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Author's Contributions

Yongzhong Tang helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript. Pingping Zeng and Yan Liao helped in collecting, analyzing and interpreting the data, and drafting and revising the manuscript. Zheng Qin, Hao Zhang and Bo Li helped in analyzing and interpreting the data. Wen Ouyang helped in Supervising, Funding acquisition and drafting and revising the manuscript. Dan Li helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript.

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Patient Consent for publication： Not applicable.

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the study, informed consent was waived.

Data sharing statement： The data used and analyzed in this study are available from the corresponding author on reasonable request.

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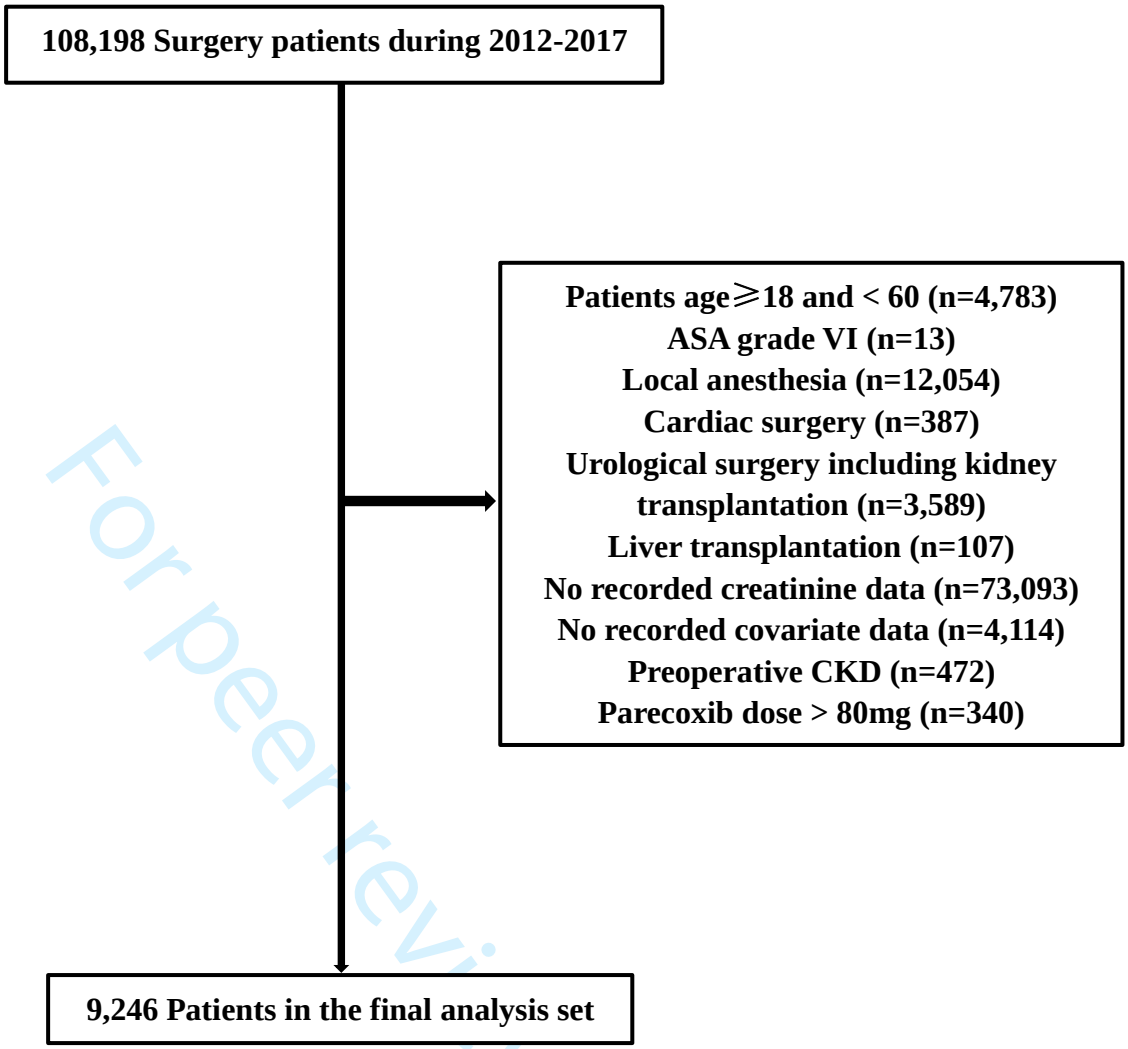

Fig 1. Enrollment of patients undergoing non-cardiac surgery.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-17
		(*b*) Report category boundaries when continuous variables were categorized	8-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-22
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Correlation between perioperative parecoxib use and postoperative acute kidney injury in patients undergoing non-cardiac surgery: A retrospective cohort analysis

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Abstract

Objective: The association of nonsteroidal anti-inflammatory drugs with postoperative acute kidney injury is controversial. However, there are few studies focusing on the association between parecoxib and postoperative acute kidney injury. Our study aimed at the possible correlation between the intraoperative administration of COX-2 inhibitors parecoxib and perioperative AKI.

Design: A retrospective cohort study

Setting: Third Xiangya Hospital of Central South University in Hunan Province, China

Participants: The electronic medical records and laboratory results were obtained from 9,246 adult patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August 31, 2017. Study groups were treated with or without parecoxib.

Interventions: Univariable analysis identified demographic, preoperative laboratory, and intraoperative factors associated with acute kidney injury. Logistic stepwise regression was used to calculate the adjusted odds ratio of parecoxib and acute kidney injury association.

Results: The incidence of acute kidney injury was lower in the parecoxib-administered group (4%) than that in the group without parecoxib (6.3%, p = 0.005). In the Multivariable regression analysis, postoperative acute kidney injury risk reduced by 39% (OR, 0.61; 95% CI, 0.43–0.87) in the parecoxib-administered group after adjusting for interference factors. Sensitivity analysis showed that postoperative AKI risk reduced in four subgroups: eGRF<90 $mL \cdot min^{-1} \cdot 1.73m^{(2)-1}$ (OR, 0.49; 95%CI, 0.29-0.82)，non-smoker (OR, 0.55; 95%CI, 0.37-0.83), blood loss <1000ml (OR, 0.55; 95%CI, 0.37-0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

Conclusions: Thus, parecoxib may slightly hint at a protective effect against postoperative acute kidney injury risk in adult patients undergoing non-cardiac surgery.

Keywords: acute kidney injury; parecoxib; non-cardiac surgery

Strengths and limitations of this study: Large study population including all adult patients (18–60 years) undergoing non-cardiac surgery in Third Xiangya Hospital of Central South University in China between 2012 to 2017.

- Our study indicated that parecoxib may slightly hint at a protective effect against postoperative acute kidney injury risk.
- The selection bias and some unknown confounders in this retrospective single-center observational study may limit the generalisablity of the results.

Background

Acute kidney injury (AKI), a long-recognized complication of surgery with a high incidence of morbidity and mortality, increases health care costs and length of hospital stay[1-3]. Even in patients undergoing non-cardiac surgery with low-grade American Society of Anesthesiologists (ASA) physical status such as ASA I–II, the incidence of postoperative AKI can reach 6%[4]. Mild kidney injury, such as a small increase in postoperative serum creatinine, is associated with renal dysfunction for as long as 1 to 2 years after surgery [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used perioperative anesthetic adjuvants, with anti-inflammatory and analgesic effects. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX) enzymes, which can ultimately result in the reduction of prostanoids and thromboxan[6]. Within the kidneys, prostaglandins act as vasodilators to ensure adequate flow to the organ. NSAIDs inhibit this mechanism and can lead to acute kidney injury (AKI). The second form of NSAID-induced AKI is acute interstitial nephritis, which may related to the prolonged exposure to NSAIDs, and interstitial infiltrate with predominance of T-lymphocytes[7].

COX exists in two forms: COX-1, which is present in most body tissues body including the stomach and intestines and COX-2, which is primarily found at sites of inflammation[8]. Accumulating evidence suggests that traditional NSAIDs, such as aspirin and ibuprofen, are associated with acute and chronic gastrointestinal bleeding and kidney disease[9 10]. These NSAIDs are nonselective COX (COX-1 and COX-2) inhibitors and their side effects are mostly COX-1 related.

Parecoxib is a parenteral specific COX-2 inhibitor, which enhances its therapeutic gain with minimal adverse effects[6 11]. Parecoxib is used as a perioperative analgesic in over 80 countries, however, clinical data about effect of parecoxib on postoperative AKI are scarce. Therefore, it is important to establish its safety during the perioperative period. The aim of this study was to assess the correlation between the perioperative use of parecoxib and postoperative AKI in patients undergoing non-cardiac surgery.

Methods

Design and selection criteria

This retrospective study was performed at the Third Xiangya Hospital of Central South University from January 1, 2012, to August 31, 2017. The inclusion criterion was patients aged 18–60 years who underwent non-cardiac surgery. The exclusion criteria were ASA grade VI, administration of local anesthesia, liver transplantation, cardiac surgery, urological surgery (including kidney transplantation), lack of serum creatinine or covariate data, and preoperative combined CKD, defined as estimate glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1} \cdot 1.73m^{(2)\ -1}$, ≥3 months). Parecoxib doses larger than 80 mg were not included because the routine dose is not more than 80 mg/day based on the drug instructions. The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (approval number 2020S264) that waived the need for informed consent because of the observational nature of the study.

Data collection

The following information was collected: 1) epidemiological data including age, sex, and BMI; 2) individual history including preoperative complications and medication history; 3) laboratory data including serum creatinine and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; 4) intraoperative data including emergency, surgical grade, operative time, anesthesia method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive drugs. 5) postoperative outcomes such as occurrence of AKI, admission to ICU, and mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were obtained by a retrospective review of the computerized patient record system of our hospital.

Definitions

Postoperative AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 creatinine criteria[12], as one of the following: an increase in serum creatinine by ≥0.3 mg/dL within 48 h or a ≥1.5-times increase in serum creatinine from baseline within 7 postoperative days. The baseline serum creatinine level was calculated using the lowest level within preoperative day 7. The primary outcome was the impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days. Parecoxib administration was defined during the operative time. Surgical grade was classified using the surgical classification catalogue constituted by the Chinese Ministry of Health, published in 2018. Intraoperative hypotension was defined as mean arterial

pressure (MAP) <65mmHg for a duration of at least 5 min.

Patient and public involvement

No patient involvement.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, NC, USA) and CRAN R (v3.4.3). Missing data of covariates (including BMI and eGFR) were handled by multiple imputation model. The continuous results are expressed as mean (SD), whereas categorical variables are expressed as numbers with percentages. The Kruskal-Wallis rank sum test was used to compare continuous variables between groups, whereas the chi-square ($\chi 2$) test or Fisher's exact probability method was used for categorical variables. Univariable logistic regression analysis was used to identify epidemiological, preoperative laboratory, and intraoperative factors that were significantly associated with AKI development. The data were adjusted for potential confounders in multivariable regression models. To further validate these results in a number of specific populations that may influence the incidence of AKI. The sensitivity test was performed in the following four different subgroups: eGFR<90 $mL \cdot min^{-1} \cdot 1.73m^{(2)\,-1}$, non-smoker, blood loss <1000ml, and non-hypotension. The results of the classification variable are expressed as odds ratio (OR) or "Beta" and 95% CI; a p-value < 0.05 indicated a statistically significant difference.

Results

Of the 108,198 records identified, those of 9,246 patients were included in the analysis (Fig. 1). Reasons for excluding patients were age <18 or >60 years (n = 4,783), ASA grade VI (n = 13), regional anesthesia administrated by a surgeon (n = 12,054), cardiac surgery (n = 387), urological surgery including kidney transplantation (n = 3,589), liver transplantation (n = 107), no recorded preoperative or postoperative creatinine data (n=73,093), no recorded covariate data such as routine blood panel or infusion volume (n = 4,114), preoperative chronic kidney disease (CKD) (n = 472), and administration of parecoxib doses >80 mg (n = 340).

AKI

The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the probability of admission to the intensive care unit (ICU) and mortality were 10.18% and 4.64%, respectively (Supplemental Table 1).

Supplemental Table 1. Baseline characteristics of patients aged 18–60 years with and without acute kidney injury (AKI)

Clinical features	without AKI (n=8686)	With AKI (n=560)	p-value
Age (years)	44.25±10.43	45.06±10.18	0.074
BMI	22.93±4.93	22.54±3.83	0.07

eGFR	101.98±16.38	94.41±19.78	<0.001
Male	4267 (49.13%)	300 (53.57%)	0.041
Smoking	1213 (13.97%)	105 (18.75%)	0.002
Alcohol consumption	822 (9.46%)	74 (13.21%)	0.004
Anemia	1538 (17.71%)	161 (28.75%)	<0.001
Hypertension	1884 (21.69%)	211 (37.68%)	<0.001
Diabetes mellitus	509 (5.86%)	52 (9.29%)	<0.001
ACEI	189 (2.18%)	21 (3.75%)	0.015
ARB	116 (1.34%)	13 (2.32%)	0.054
CCB	1125 (12.95%)	119 (21.25%)	<0.001
Diuretics	77 (0.89%)	19 (3.39%)	<0.001
ASA grade			<0.001
I–II	6633 (76.36%)	317 (56.61%)	
III–V	2053 (23.64%)	243 (43.39%)	
Anesthesia method			<0.001
General anesthesia	7735 (89.05%)	531 (94.82%)	
Non-general anesthesia	951 (10.95%)	29 (5.18%)	
Emergency	1395 (16.06%)	130 (23.21%)	<0.001
Surgical Grade			<0.001
1	245 (2.82%)	14 (2.50%)	
2	2746 (31.61%)	118 (21.07%)	
3	5349 (61.58%)	386 (68.93%)	

4	346 (3.98%)	42 (7.50%)	
Operative time (min)			<0.001
≤60	1338 (15.4%)	63 (11.25%)	
61–120	2176 (25.05%)	111 (19.82%)	
121–180	2032 (23.39%)	135 (24.11%)	
>180	3140 (36.15%)	251 (44.82%)	
Intraoperative erythrocyte Transfusion, mL (%)			<0.001
<100	6735 (77.54)	339 (60.54)	
100–600	868 (9.99)	82 (14.64)	
601–1000	508 (5.85)	42 (7.50)	
>1000	575 (6.62)	97 (17.32)	
Amount of Blood loss, mL (%)			<0.001
<100	2623 (30.20)	131 (23.39)	
100–600	4771 (54.93)	292 (52.14)	
601–1000	670 (7.71)	60 (10.71)	
>1000	622 (7.16)	77 (13.75)	
Amount of fluid infusion (10 mL/24 h)	916.67 (625.00–1432.29)	1125.00 (703.12–1604.17)	<0.001
Amount of fluid out (10 mL/24 h)	333.33 (145.83–541.67)	375.00 (208.33–687.50)	<0.001

Intraoperative Hypotension	930 (10.71%)	81 (14.46%)	0.006
Vasoactive drugs	664 (7.64%)	71 (12.68%)	<0.001
Parecoxib	934 (10.75%)	39 (6.96%)	0.005
Admission to ICU	376 (4.33%)	57 (10.18%)	<0.001
Death	32 (0.37%)	26 (4.64%)	<0.001

AKI: acute kidney injury, BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia, ICU: intensive care unit. Data are expressed as number of patients (%) or mean ± standard deviation (SD).

There was no difference in age, body mass index (BMI), angiotensin receptor blockers (ARBs) use and intraoperative hypotension among patients with and without AKI (Supplemental Table 1). Significant differences between patients with AKI and without AKI are shown in Supplemental Table 1 (all $p < 0.05$).

Parecoxib

Parecoxib was used in 10.5% (973/9,246) of patients (Table 1).

Table 1. Baseline characteristics of patients aged 18–60 years treated with and without parecoxib

Clinical features	Without parecoxib (n=8273)	With parecoxib (n=973)	p-value
Age (year)	44.23±10.46	44.89±10.04	0.06
BMI	22.89±4.99	23.03±3.76	0.409
eGFR	101.66±16.66	101.56±16.23	0.858
Male	4062 (49.1%)	508 (52.2%)	0.063
Smoking	1175 (14.2%)	146 (15%)	0.479
Alcohol consumption	811 (9.8%)	89 (9.1%)	0.544
Anemia	1547 (18.7%)	152 (15.6%)	0.019
Hypertension	1903 (23%)	189(19.4%)	0.011
Diabetes mellitus	505 (6.1%)	56 (5.8%)	0.666
ACEI	199 (2.4%)	14 (1.4%)	0.065
ARB	116 (1.4%)	14 (1.4%)	0.902
CCB	1142 (13.8%)	103 (10.6%)	0.006
Diuretics	91 (1.1%)	8 (0.8%)	0.482
ASA grade			0.09
I–II	6196 (74.9%)	753 (77.4%)	
III–V	2077 (25.1%)	220 (22.6%)	
Anesthesia method			<0.001
General anesthesia	7363 (89%)	907 (93.2%)	
Non-general anesthesia	910 (11%)	66 (6.8%)	
Emergency	1406 (17%)	119 (12.2%)	<0.001

Surgical grade			<0.001
1	240 (2.9%)	19 (2%)	
2	2623 (31.7%)	243 (25%)	
3	5080 (61.4%)	656 (67.4%)	
4	330 (4%)	55 (5.7%)	
Operative time (min)			<0.001
≤60	1315 (15.9%)	88 (9%)	
61–120	2085 (25.2%)	204 (21%)	
121–180	1919 (23.2%)	246 (25.3%)	
>180	2954 (35.7%)	435 (44.7%)	
Intraoperative erythrocyte Transfusion, mL (%)			0.94
<100	6329 (76.5%)	744 (76.5%)	
100–600	852 (10.3%)	98 (10.1%)	
601–1000	496 (6%)	56 (5.8%)	
>1000	596 (7.2%)	75 (7.7%)	
Amount of Blood loss, mL (%)			0.003
<100	2507 (30.3%)	251 (25.8%)	
100–600	4500 (4.4%)	559 (57.5%)	
601–1000	662 (8%)	70 (7.2%)	
>1000	604 (7.3%)	93 (9.6%)	

Intraoperative Hypotension	10.8	11.9	0.297
Vasoactive drugs	7.8	8.9	0.227
Amount of fluid infusion (10 mL/24 h)	1037.07±565.54	1159.31±579.85	<0.001
Amount of fluid out (10 mL/24 h)	410.17±374.16	373.74±334.53	0.004
AKI	521 (6.3%)	39 (4%)	0.005
AKI Stages			0.029
0	93.7	96	
1	4.5	2.6	
2	1	0.7	
3	0.7	0.7	

BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia, AKI: acute kidney injury. Data are expressed as number of patients (%) or mean ± standard deviation (SD). AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

The incidence of AKI was lower in the parecoxib-administered group (4%) than in the group without parecoxib (6.3%, p = 0.005). There was no difference in age, BMI,

estimated glomerular filtration rate (eGFR), sex, smoking, alcohol consumption, presence of diabetes mellitus, use of angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or diuretics, ASA grade, incidence of intraoperative erythrocyte transfusion and intraoperative hypotension, and use of vasoactive drugs between patients treated with and without parecoxib (Table 1). Significant differences between patients treated with and without parecoxib are shown in Table 1 (all $p < 0.05$).

Univariable analysis

The factors shown by the univariable analysis to influence AKI development in patients aged 18–60 years who underwent non-cardiac surgery are listed in Table 2.

Table 2. Univariable analysis of acute kidney injury (AKI)

Variable	Statistics	Univariable	
		OR (95% CI)	p-value
Parecoxib	0.11± 0.31	0.62 (0.45, 0.87)	0.0050
Age (year)	44.30 ± 10.42	1.01 (1.00, 1.02)	0.0737
Male	4567 (49.39%)	1.19 (1.01, 1.42)	0.0416
BMI	22.90 ± 4.87	0.98 (0.95, 1.00)	0.0396
Smoking	1318 (14.25%)	1.42 (1.14, 1.77)	0.0018
Alcohol consumption	896 (9.69%)	1.46 (1.13, 1.88)	0.0038
Anemia	1699 (18.38%)	1.88 (1.55, 2.27)	<0.0001
Hypertension	2095 (22.66%)	2.18 (1.83, 2.61)	<0.0001

Diabetes mellitus	561 (6.07%)	1.64 (1.22, 2.22)	0.0011
ACEI	210 (2.27%)	1.75 (1.11, 2.77)	0.0167
ARB	129 (1.40%)	1.76 (0.98, 3.14)	0.0570
CCB	1244 (13.45%)	1.81 (1.47, 2.24)	<0.0001
Diuretics	96 (1.04%)	3.93 (2.36, 6.54)	<0.0001
eGFR	97.94±22.36	0.96 (0.96, 0.97)	<0.0001
ASA grade III–V	2296 (24.83%)	2.48 (2.08, 2.95)	<0.0001
Non-general anesthesia	980 (10.60%)	0.44 (0.30, 0.65)	<0.0001
Emergency	1525 (16.49%)	1.58 (1.29, 1.94)	<0.0001
Surgical grade 4	388 (4.20%)	2.12 (1.14, 3.98)	0.0184
Operative time (min)			
≤60	1401 (15.15%)	1	
61–120	2287 (24.74%)	1.08 (0.79, 1.49)	0.6200
121–180	2167 (23.44%)	1.41 (1.04, 1.92)	0.0279
>180	3391 (36.68%)	1.70 (1.28, 2.25)	0.0003
Intraoperative Hypotension	1011 (10.93%)	1.41 (1.10, 1.80)	0.0060
Vasoactive drugs	735 (7.95%)	0.06 (0.03, 0.09)	<0.0001
Intraoperative erythrocyte transfusion, mL (%)			
<100	7074 (76.51%)	1	
100–600	950 (10.27%)	1.88 (1.46, 2.41)	<0.0001
601–1000	550 (5.95%)	1.64 (1.18, 2.29)	0.0035

>1000	672 (7.27%)	3.35 (2.63, 4.27)	<0.0001
Amount of Blood loss, mL (%)			
<100	2754 (29.79%)	1	
100–600	5063 (54.76%)	1.23 (0.99, 1.51)	0.0596
601–1000	730 (7.9%)	1.79 (1.31, 2.46)	0.0003
>1000	699 (7.56%)	2.48 (1.85, 3.33）	<0.0001

OR: odds ratio, BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists. Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia.

In the univariable analysis, male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, calcium channel blocker (CCB) use, diuretic use, ASA grade III–V, emergency, surgical grade 4, duration of the operation, incidence of intraoperative hypotension and erythrocyte transfusion, and amount of blood loss were independently associated with an increased risk of postoperative AKI (Table 2).

Parecoxib (OR, 0.62; 95%CI, 0.45–0.87, p = 0.005), eGFR (OR, 0.96; 95%CI, 0.96–0.97, p < 0.0001), non-general anesthesia (OR, 0.44; 95%CI, 0.30–0.65, p < 0.0001) and vasoactive drug use (OR, 0.06; 95%CI, 0.03–0.09, p < 0.0001) were independently associated with a decreased risk of postoperative AKI (Table 2). Age (OR, 1.01; 95%CI, 1.00–1.02, p = 0.0737), BMI (OR, 0.98; 95%CI, 0.95–1.00, p = 0.0396), and ARB use

(OR, 1.76; 95%CI, 0.98–3.14, p = 0.0570) were not correlated with AKI (Table 2).

Multivariable regression analysis

The occurrence of postoperative AKI or AKI Stages was regarded as a dependent variable, and the administration of parecoxib, an independent variable when we performed the stepwise regression analysis (Table 3).

Table 3 Odds ratio of postoperative acute kidney injury (AKI) associated with parecoxib

	Model 1	**Model 2**	**Model 3**	**Model 4**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
	***p*-value**	***p*-value**	***p*-value**	***p*-value**
AKI	0.62 (0.45, 0.87)	0.64 (0.46, 0.90)	0.63 (0.44, 0.89)	0.61(0.43, 0.87)
	0.0050	0.0096	0.0095	0.0069
AKI Stages	-0.02 (-0.05,	-0.02 (-0.05, -	-0.02 (-0.05, -	-0.03(-0.05,-
	0.00) 0.0627	0.00) 0.0792	0.00) 0.0517	0.00) 0.0236

AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time.

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

The risk adjustment models were constructed using logistic stepwise regression. After adjusting for these interference factors, parecoxib was still independently associated with postoperative AKI (OR, 0.61; 95% CI, 0.43–0.87, model 4 in Table 3) or different postoperative AKI stages (OR, -0.03; 95% CI, -0.05– -0.00, model 4 in Table 3).

Sensitivity analysis

Table 4 presented the association between postoperative AKI and parecoxib in the subgroups of eGFR <90 mL·min^{-1}·1.73 m$^{(2)\ -1}$, non-smokers, blood loss <1000ml, and intraoperative non-hypotension.

Table 4 Sensitivity analysis of association between postoperative acute kidney injury (AKI) and parecoxib

		Model 1	**Model 2**	**Model 3**	**Model 4**
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
		***p*-value**	***p*-value**	***p*-value**	***p*-value**
	Without parecoxib	Parecoxib			
eGFR	1	0.49 (0.31, 0.79)	0.54 (0.33, 0.87)	0.50 (0.30, 0.84)	0.49(0.29,0.82)
<90		0.0032	0.0119	0.0084	0.0065

Non-	1	0.57 (0.39, 0.84)	0.56 (0.37, 0.84)	0.56 (0.38, 0.84)	0.55(0.37,0.83)
smoker		0.0040	0.0046	0.0052	0.0043
blood loss <1000ml	1	0.56 (0.39, 0.82)	0.57 (0.39, 0.84)	0.56 (0.37, 0.83)	0.55 (0.37, 0.83)
		0.0027	0.0042	0.0040	0.0037
non-hypotension	1	0.60 (0.42, 0.87)	0.60 (0.42, 0.87)	0.57 (0.38, 0.84)	
		0.0064	0.0077	0.0050	

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

For patients with an eGFR <90 mL·min^{-1}·1.73 m$^{(2)\,-1}$ or who were non-smokers, single-dose parecoxib (40 mg or 80 mg) was associated with a lower incidence of postoperative AKI (Table 4). Similar results were obtained with the adjusted models. Postoperative AKI risk also reduced in patients with blood loss <1000ml (OR, 0.55; 95%CI, 0.37-0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

Discussion

According to the surgery type and AKI diagnostic criteria, the incidence of postoperative AKI ranges from 1.0% to 31%[13-15], and our study revealed an incidence

of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac surgery. The incidence was similar to that in the recently published data by Nishimoto (6%, non-cardiac surgery; mean age, 63 years)[16]. In our study, the univariable analysis identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode, emergency, surgical grade 4, duration of the operation (>120 min), incidence of intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which are similar to previously published data by Mathis MR (2020) and Cho E (2014) [17 18].

However, age and BMI did not correlate with AKI in our study, which is inconsistent with the findings from Wang J's studies[19]. This discrepancy can be explained by the difference in mean age and BMI between the studies, which were both lower in our study population. The results of the sensitivity analysis suggested that single-dose (40 mg or 80 mg) parecoxib might have potential protective effects against postoperative AKI in differentially ranked AKI. eGFR <90 $mL \cdot min^{-1} \cdot 1.73\ m^{(2)\ -1}$ represented the population with preoperative glomerular filtration impairment, while non-hypertension and blood-loss<1000ml, represented people with relatively stable intraoperative circulation and relatively good renal perfusion pressure. The subgroup analysis showed parecoxib might reduce the AKI risk in these patients.

Numerous studies have investigated the association between NSAIDs and AKI[10 20]. An updated Cochrane systematic review and meta-analysis published by Bell S in 2018 indicated that NSAIDs have uncertain effects on the rate of AKI and may slightly increase

serum creatinine in patients with normal kidney function following surgery[20]. In another meta-analysis (Ungprasert P, 2015), a significant risk of AKI was observed with most traditional NSAIDs but not with two COX-2 specific inhibitors (rofecoxib and celecoxib) [10]. A pooled analysis of 28 randomized clinical trials investigating the safety of parecoxib for the management of postoperative pain showed that its associated risk of renal failure and impairment was 1%, similar to that with the placebo (0.9%)[21].

However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80 mg) might provide potential protective effects against postoperative AKI in patients aged 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a renoprotective effect has been postulated for parecoxib. For example, the study of Takaku M et al. also showed that a single-dose of parecoxib (20 mg/kg) reduced tubular renal injury and serum inflammatory cytokines level (interleukin (IL)-1α, IL-β, IL6, and tumor necrosis factor (TNF)-α) in an ischemic rat model[22]. Moreover, several animal studies(Takaku M 2018, Feitoza CQ 2005, Feitoza CQ 2004, Candelario-Jalil E 2007) have suggested that pretreatment with COX-2 inhibitors improved outcomes in function and histology in not only the kidney but also other organs after ischemia[22-25]. To the best of our knowledge, this is the first clinical report to suggest that single-dose (40 mg or 80 mg) parecoxib may be renoprotective in patients aged 18–60 years who underwent non-cardiac surgery.

The mechanism by which parecoxib decreases the risk of postoperative AKI is unknown. However, one possible underlying mechanism is likely related to inflammation. A previous study of Murashima M et al. showed that inflammation is a predictor of

postoperative AKI and a mediator of increased mortality after AKI in non-cardiac surgery [26]. However, perioperative parecoxib reduced local and systemic inflammatory cytokines postoperatively[27 28]. Another possible mechanism is associated with hemodynamic change. COX-1 contributes to controlling renal GFR, whereas COX-2 is involved in sodium and water excretion[7]. COX-2 inhibitors are associated with mild hypertension owing to modest sodium retention in the first few days of therapy[29]. The renoprotective mechanism of parecoxib may be related to its anti-inflammatory effects and sodium regulation.

Our study had some limitations that are worth mentioning. First, this was a retrospective single-center observational study; thus, it may have had some selection bias. Second, the timing of the serum creatinine measurement was based on clinical discretion; thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years who underwent non-cardiac surgery as the target to research. Fourthly, due to the nature of the retrospective study, some unknown or unmeasured confounders, and those excluded patients who had missing data may interfere the outcomes. Therefore, our results should be extrapolated cautiously.

Conclusions

In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80 mg) may slightly hint at a protective effect against postoperative AKI in those aged 18–60 years. However, these short-term effects may not represent the benefit of this drug in the long term. Furthermore, more comprehensive studies are needed to confirm the effects

of parecoxib on the risk of postoperative AKI.

Figure legends

Fig 1. Enrollment of patients undergoing non-cardiac surgery. The numbers in brackets represent patients excluded for the reasons described earlier.

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Author's Contributions

Yongzhong Tang helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript. Pingping Zeng and Yan Liao helped in collecting, analyzing and interpreting the data, and drafting and revising the manuscript. Zheng Qin, Hao Zhang and Bo Li helped in analyzing and interpreting the data. Wen Ouyang helped in Supervising, Funding acquisition and drafting and revising the manuscript. Dan Li helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript.

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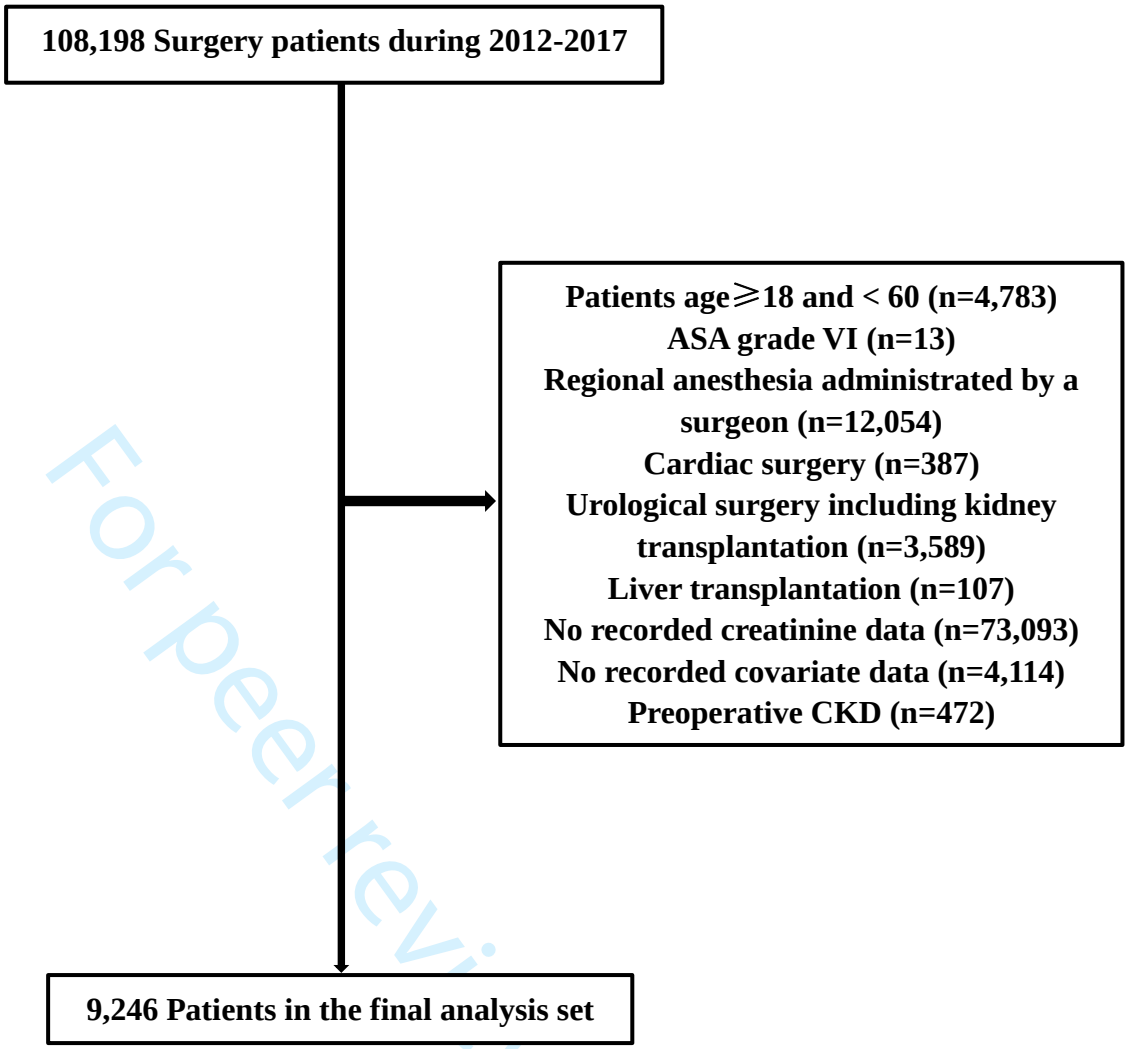

Fig 1

Supplemental Table 1. Baseline characteristics of patients aged 18–60 years with and without acute kidney injury (AKI)

Clinical features	without AKI (n=8686)	With AKI (n=560)	p-value
Age (years)	44.25±10.43	45.06±10.18	0.074
BMI	22.93±4.93	22.54±3.83	0.07
eGFR	101.98±16.38	94.41±19.78	<0.001
Male	4267 (49.13%)	300 (53.57%)	0.041
Smoking	1213 (13.97%)	105 (18.75%)	0.002
Alcohol consumption	822 (9.46%)	74 (13.21%)	0.004
Anemia	1538 (17.71%)	161 (28.75%)	<0.001
Hypertension	1884 (21.69%)	211 (37.68%)	<0.001
Diabetes mellitus	509 (5.86%)	52 (9.29%)	<0.001
ACEI	189 (2.18%)	21 (3.75%)	0.015
ARB	116 (1.34%)	13 (2.32%)	0.054
CCB	1125 (12.95%)	119 (21.25%)	<0.001
Diuretics	77 (0.89%)	19 (3.39%)	<0.001
ASA grade			<0.001
I–II	6633 (76.36%)	317 (56.61%)	
III–V	2053 (23.64%)	243 (43.39%)	
Anesthesia method			<0.001

General anesthesia	7735 (89.05%)	531 (94.82%)	
Non-general anesthesia	951 (10.95%)	29 (5.18%)	
Emergency	1395 (16.06%)	130 (23.21%)	<0.001
Surgical Grade			<0.001
1	245 (2.82%)	14 (2.50%)	
2	2746 (31.61%)	118 (21.07%)	
3	5349 (61.58%)	386 (68.93%)	
4	346 (3.98%)	42 (7.50%)	
Operative time (min)			<0.001
≤60	1338 (15.4%)	63 (11.25%)	
61–120	2176 (25.05%)	111 (19.82%)	
121–180	2032 (23.39%)	135 (24.11%)	
>180	3140 (36.15%)	251 (44.82%)	
Intraoperative erythrocyte Transfusion, mL (%)			<0.001
<100	6735 (77.54)	339 (60.54)	
100–600	868 (9.99)	82 (14.64)	
601–1000	508 (5.85)	42 (7.50)	
>1000	575 (6.62)	97 (17.32)	
Amount of Blood loss, mL (%)			<0.001
<100	2623 (30.20)	131 (23.39)	

100–600	4771 (54.93)	292 (52.14)	
601–1000	670 (7.71)	60 (10.71)	
>1000	622 (7.16)	77 (13.75)	
Amount of fluid infusion (10 mL/24 h)	916.67 (625.00–1432.29)	1125.00 (703.12–1604.17)	<0.001
Amount of fluid out (10 mL/24 h)	333.33 (145.83–541.67)	375.00 (208.33–687.50)	<0.001
Intraoperative Hypotension	930 (10.71%)	81 (14.46%)	0.006
Vasoactive drugs	664 (7.64%)	71 (12.68%)	<0.001
Parecoxib	934 (10.75%)	39 (6.96%)	0.005
Admission to ICU	376 (4.33%)	57 (10.18%)	<0.001
Death	32 (0.37%)	26 (4.64%)	<0.001

AKI: acute kidney injury, BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia, ICU: intensive care unit. Data are expressed as number of patients (%) or mean ± standard deviation (SD).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-17
		(*b*) Report category boundaries when continuous variables were categorized	8-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-22
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Correlation between perioperative parecoxib use and postoperative acute kidney injury in patients undergoing non-cardiac surgery: A retrospective cohort analysis

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Abstract

Objective: The association of nonsteroidal anti-inflammatory drugs with postoperative acute kidney injury is controversial. However, there are few studies focusing on the association between parecoxib and postoperative acute kidney injury. Our study aimed at the possible correlation between the intraoperative administration of COX-2 inhibitors parecoxib and perioperative AKI.

Design: A retrospective cohort study

Setting: Third Xiangya Hospital of Central South University in Hunan Province, China

Participants: The electronic medical records and laboratory results were obtained from 9,246 adult patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August 31, 2017. Study groups were treated with or without parecoxib.

Interventions: Univariable analysis identified demographic, preoperative laboratory, and intraoperative factors associated with acute kidney injury. Logistic stepwise regression was used to calculate the adjusted odds ratio of parecoxib and acute kidney injury association.

Results: The incidence of acute kidney injury was lower in the parecoxib-administered group (4%) than that in the group without parecoxib (6.3%, p = 0.005). In the Multivariable regression analysis, postoperative acute kidney injury risk reduced by 39% (OR, 0.61; 95% CI, 0.43–0.87) in the parecoxib-administered group after adjusting for interference factors. Sensitivity analysis showed that postoperative AKI risk reduced in four subgroups: eGRF<90 $mL \cdot min^{-1} \cdot 1.73m^{(2)-1}$ (OR, 0.49; 95%CI, 0.29-0.82)，non-smoker (OR, 0.55; 95%CI, 0.37-0.83), blood loss <1000ml (OR, 0.55; 95%CI, 0.37-0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

Conclusions: Thus, parecoxib is associated with a modest reduction of postoperative acute kidney injury risk among adult patients undergoing non-cardiac surgery.

Keywords: acute kidney injury; parecoxib; non-cardiac surgery

Strengths and limitations of this study: Large study population including all adult patients (18–60 years) undergoing non-cardiac surgery in Third Xiangya Hospital of Central South University in China between 2012 to 2017.□

Univariable analysis identified demographic, preoperative laboratory, and intraoperative factors associated with acute kidney injury.

Logistic stepwise regression was used to calculate the adjusted odds ratio of parecoxib and acute kidney injury association.

The selection bias and some unknown confounders in this retrospective single-center observational study may limit the generalizability of the results.

Background

Acute kidney injury (AKI), a long-recognized complication of surgery with a high incidence of morbidity and mortality, increases health care costs and length of hospital stay[1-3]. Even in patients undergoing non-cardiac surgery with low-grade American Society of Anesthesiologists (ASA) physical status such as ASA I–II, the incidence of postoperative AKI can reach 6%[4]. Mild kidney injury, such as a small increase in postoperative serum creatinine, is associated with renal dysfunction for as long as 1 to 2 years after surgery [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used perioperative anesthetic adjuvants, with anti-inflammatory and analgesic effects. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX) enzymes, which can ultimately result in the reduction of prostanoids and thromboxan[6]. Within the kidneys, prostaglandins act as vasodilators to ensure adequate flow to the organ. NSAIDs inhibit this mechanism and can lead to acute kidney injury (AKI). The second form of NSAID-induced AKI is acute interstitial nephritis, which may be related to the prolonged exposure to NSAIDs, and interstitial infiltrates with the predominance of T-lymphocytes[7].

COX exists in two forms: COX-1, which is present in most body tissues body including the stomach, intestines and COX-2, which is primarily found at sites of inflammation[8]. Accumulating evidence suggests that traditional NSAIDs, such as aspirin and ibuprofen, are associated with acute and chronic gastrointestinal bleeding and kidney disease[9 10]. These NSAIDs are nonselective COX (COX-1 and COX-2) inhibitors and their side

effects are mostly COX-1 related.

Parecoxib is a parenteral specific COX-2 inhibitor, which enhances its therapeutic gain with minimal adverse effects[6 11]. Parecoxib is used as a perioperative analgesic in over 80 countries, however, clinical data about the effect of parecoxib on postoperative AKI are scarce. Therefore, it is important to establish its safety during the perioperative period. The aim of this study was to assess the correlation between the perioperative use of parecoxib and postoperative AKI in patients undergoing non-cardiac surgery.

Methods

Design and selection criteria

This retrospective study was performed at the Third Xiangya Hospital of Central South University from January 1, 2012, to August 31, 2017. The inclusion criterion was patients aged 18–60 years who underwent non-cardiac surgery. The exclusion criteria were ASA grade VI, administration of local anesthesia, liver transplantation, cardiac surgery, urological surgery (including kidney transplantation), lack of serum creatinine or covariate data, and preoperative combined CKD, defined as estimate glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1} \cdot 1.73m^{(2)\,-1}$, ≥3 months). Whether to use the Parecoxib or not was based on the doctor's preference. Parecoxib doses larger than 80 mg were not included because the routine dose is not more than 80 mg/day based on the drug instructions. The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (approval number 2020S264) that waived the need for informed consent because of the observational nature of the study.

Data collection

The following information was collected: 1) epidemiological data including age, sex, and BMI; 2) individual history including preoperative complications and medication history; 3) laboratory data including serum creatinine and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; 4) intraoperative data including emergency, surgical grade, operative time, anesthesia method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive drugs. 5) postoperative outcomes such as the occurrence of AKI, admission to ICU, and mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were obtained by a retrospective review of the computerized patient record system of our hospital.

Definitions

Postoperative AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 creatinine criteria[12], as one of the following: an increase in serum creatinine by ≥0.3 mg/dL within 48 h or a ≥1.5-times increase in serum creatinine from baseline within 7 postoperative days. The baseline serum creatinine level was calculated using the lowest level within preoperative day 7. The primary outcome was the impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days. Parecoxib administration was defined during the operative time. The surgical grade was

classified using the surgical classification catalog constituted by the Chinese Ministry of Health, published in 2018. Intraoperative hypotension was defined as mean arterial pressure (MAP) <65mmHg for a duration of at least 5 min.

Patient and public involvement

No patient involvement.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, NC, USA) and CRAN R (v3.4.3). Missing data of covariates (including BMI and eGFR) were handled by a multiple imputation model. The continuous results are expressed as mean (SD), whereas categorical variables are expressed as numbers with percentages. The Kruskal-Wallis rank sum test was used to compare continuous variables between groups, whereas the chi-square ($\chi 2$) test or Fisher's exact probability method was used for categorical variables. Univariable logistic regression analysis was used to identify epidemiological, preoperative laboratory, and intraoperative factors that were significantly associated with AKI development. The data were adjusted for potential confounders in multivariable regression models. To further validate these results in a number of specific populations that may influence the incidence of AKI. The sensitivity test was performed in the following four different subgroups: eGFR<90 $mL \cdot min^{-1} \cdot 1.73m^{(2)\,-1}$, non-smoker, blood loss <1000ml, and non-hypotension. The results of the classification variable are

expressed as odds ratio (OR) or "Beta" and 95% CI; a p-value < 0.05 indicated a statistically significant difference.

Results

Of the 108,198 records identified, those of 9,246 patients were included in the analysis (Fig. 1). Reasons for excluding patients were age <18 or >60 years (n = 4,783), ASA grade VI (n = 13), regional anesthesia administrated by a surgeon (n = 12,054), cardiac surgery (n = 387), urological surgery including kidney transplantation (n = 3,589), liver transplantation (n = 107), no recorded preoperative or postoperative creatinine data (n=73,093), no recorded covariate data such as routine blood panel or infusion volume (n = 4,114), preoperative chronic kidney disease (CKD) (n = 472), and administration of parecoxib doses >80 mg (n = 340).

AKI

The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the probability of admission to the intensive care unit (ICU) and mortality was 10.18% and 4.64%, respectively (Supplemental Table 1).

There were no differences in age, body mass index (BMI), angiotensin receptor blockers (ARBs) use and intraoperative hypotension among patients with and without AKI (Supplemental Table 1). Significant differences between patients with AKI and without AKI are shown in Supplemental Table 1 (all $p < 0.05$).

Parecoxib

Parecoxib was used in 10.5% (973/9,246) of patients (Table 1).

Table 1. Baseline characteristics of patients aged 18–60 years treated with and without parecoxib

Clinical features	Without parecoxib (n=8273)	With parecoxib (n=973)	p-value
Age (year)	44.23±10.46	44.89±10.04	0.06
BMI	22.89±4.99	23.03±3.76	0.409
eGFR	101.66±16.66	101.56±16.23	0.858
Male	4062 (49.1%)	508 (52.2%)	0.063
Smoking	1175 (14.2%)	146 (15%)	0.479
Alcohol consumption	811 (9.8%)	89 (9.1%)	0.544
Anemia	1547 (18.7%)	152 (15.6%)	0.019
Hypertension	1903 (23%)	189(19.4%)	0.011
Diabetes mellitus	505 (6.1%)	56 (5.8%)	0.666
ACEI	199 (2.4%)	14 (1.4%)	0.065
ARB	116 (1.4%)	14 (1.4%)	0.902
CCB	1142 (13.8%)	103 (10.6%)	0.006
Diuretics	91 (1.1%)	8 (0.8%)	0.482
ASA grade			0.09

I–II	6196 (74.9%)	753 (77.4%)	
III–V	2077 (25.1%)	220 (22.6%)	
Anesthesia method			<0.001
General anesthesia	7363 (89%)	907 (93.2%)	
Non-general anesthesia	910 (11%)	66 (6.8%)	
Emergency	1406 (17%)	119 (12.2%)	<0.001
Surgical grade			<0.001
1	240 (2.9%)	19 (2%)	
2	2623 (31.7%)	243 (25%)	
3	5080 (61.4%)	656 (67.4%)	
4	330 (4%)	55 (5.7%)	
Operative time (min)			<0.001
≤60	1315 (15.9%)	88 (9%)	
61–120	2085 (25.2%)	204 (21%)	
121–180	1919 (23.2%)	246 (25.3%)	
>180	2954 (35.7%)	435 (44.7%)	
Intraoperative erythrocyte Transfusion, mL (%)			0.94
<100	6329 (76.5%)	744 (76.5%)	
100–600	852 (10.3%)	98 (10.1%)	
601–1000	496 (6%)	56 (5.8%)	
>1000	596 (7.2%)	75 (7.7%)	

Amount of Blood loss, mL			0.003
(%)			
<100	2507 (30.3%)	251 (25.8%)	
100–600	4500 (4.4%)	559 (57.5%)	
601–1000	662 (8%)	70 (7.2%)	
>1000	604 (7.3%)	93 (9.6%)	
Intraoperative Hypotension	10.8	11.9	0.297
Vasoactive drugs	7.8	8.9	0.227
Amount of fluid infusion (10 mL/24 h)	1037.07±565.54	1159.31±579.85	<0.001
Amount of fluid out (10 mL/24 h)	410.17±374.16	373.74±334.53	0.004
AKI	521 (6.3%)	39 (4%)	0.005
AKI Stages			0.029
0	93.7	96	
1	4.5	2.6	
2	1	0.7	
3	0.7	0.7	

BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia, AKI: acute kidney injury. Data are expressed as the number

of patients (%) or mean ± standard deviation (SD). AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

The incidence of AKI was lower in the parecoxib-administered group (4%) than in the group without parecoxib (6.3%, p = 0.005). There was no difference in age, BMI, estimated glomerular filtration rate (eGFR), sex, smoking, alcohol consumption, presence of diabetes mellitus, use of angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or diuretics, ASA grade, the incidence of intraoperative erythrocyte transfusion and intraoperative hypotension, and use of vasoactive drugs between patients treated with and without parecoxib (Table 1). Significant differences between patients treated with and without parecoxib are shown in Table 1 (all $p < 0.05$).

Univariable analysis

The factors are shown by the univariable analysis to influence AKI development in patients aged 18–60 years who underwent non-cardiac surgery are listed in Table 2.

Table 2. Univariable analysis of acute kidney injury (AKI)

Variable	Statistics	Univariable	
		OR (95% CI)	p-value
Parecoxib	0.11± 0.31	0.62 (0.45, 0.87)	0.0050
Age (year)	44.30 ± 10.42	1.01 (1.00, 1.02)	0.0737

Male	4567 (49.39%)	1.19 (1.01, 1.42)	0.0416
BMI	22.90 ± 4.87	0.98 (0.95, 1.00)	0.0396
Smoking	1318 (14.25%)	1.42 (1.14, 1.77)	0.0018
Alcohol consumption	896 (9.69%)	1.46 (1.13, 1.88)	0.0038
Anemia	1699 (18.38%)	1.88 (1.55, 2.27)	<0.0001
Hypertension	2095 (22.66%)	2.18 (1.83, 2.61)	<0.0001
Diabetes mellitus	561 (6.07%)	1.64 (1.22, 2.22)	0.0011
ACEI	210 (2.27%)	1.75 (1.11, 2.77)	0.0167
ARB	129 (1.40%)	1.76 (0.98, 3.14)	0.0570
CCB	1244 (13.45%)	1.81 (1.47, 2.24)	<0.0001
Diuretics	96 (1.04%)	3.93 (2.36, 6.54)	<0.0001
eGFR	97.94±22.36	0.96 (0.96, 0.97)	<0.0001
ASA grade III–V	2296 (24.83%)	2.48 (2.08, 2.95)	<0.0001
Non-general anesthesia	980 (10.60%)	0.44 (0.30, 0.65)	<0.0001
Emergency	1525 (16.49%)	1.58 (1.29, 1.94)	<0.0001
Surgical grade 4	388 (4.20%)	2.12 (1.14, 3.98)	0.0184
Operative time (min)			
≤60	1401 (15.15%)	1	
61–120	2287 (24.74%)	1.08 (0.79, 1.49)	0.6200
121–180	2167 (23.44%)	1.41 (1.04, 1.92)	0.0279
>180	3391 (36.68%)	1.70 (1.28, 2.25)	0.0003
Intraoperative Hypotension	1011 (10.93%)	1.41 (1.10, 1.80)	0.0060

Vasoactive drugs	735 (7.95%)	0.06 (0.03, 0.09)	<0.0001
Intraoperative erythrocyte transfusion, mL (%)			
<100	7074 (76.51%)	1	
100–600	950 (10.27%)	1.88 (1.46, 2.41)	<0.0001
601–1000	550 (5.95%)	1.64 (1.18, 2.29)	0.0035
>1000	672 (7.27%)	3.35 (2.63, 4.27)	<0.0001
Amount of Blood loss, mL (%)			
<100	2754 (29.79%)	1	
100–600	5063 (54.76%)	1.23 (0.99, 1.51)	0.0596
601–1000	730 (7.9%)	1.79 (1.31, 2.46)	0.0003
>1000	699 (7.56%)	2.48 (1.85, 3.33）	<0.0001

OR: odds ratio, BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists. Non-general anesthesia includes neuraxial anesthesia (spinal or epidural) and nerve block anesthesia.

In the univariable analysis, male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, calcium channel blocker (CCB) use, diuretic use, ASA grade III–V, emergency, surgical grade 4, duration of the operation, the incidence of intraoperative hypotension and erythrocyte transfusion, and amount of blood

loss were independently associated with an increased risk of postoperative AKI (Table 2).

Parecoxib (OR, 0.62; 95%CI, 0.45–0.87, p = 0.005), eGFR (OR, 0.96; 95%CI, 0.96–0.97, p < 0.0001), non-general anesthesia (OR, 0.44; 95%CI, 0.30–0.65, p < 0.0001) and vasoactive drug use (OR, 0.06; 95%CI, 0.03–0.09, p < 0.0001) were independently associated with a decreased risk of postoperative AKI (Table 2). Age (OR, 1.01; 95%CI, 1.00–1.02, p = 0.0737), BMI (OR, 0.98; 95%CI, 0.95–1.00, p = 0.0396), and ARB use (OR, 1.76; 95%CI, 0.98–3.14, p = 0.0570) were not correlated with AKI (Table 2).

Multivariable regression analysis

The occurrence of postoperative AKI or AKI Stages was regarded as a dependent variable, and the administration of parecoxib, an independent variable when we performed the stepwise regression analysis (Table 3).

Table 3 Odds ratio of postoperative acute kidney injury (AKI) associated with parecoxib

	Model 1	**Model 2**	**Model 3**	**Model 4**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
	***p*-value**	***p*-value**	***p*-value**	***p*-value**
AKI	0.62 (0.45, 0.87)	0.64 (0.46, 0.90)	0.63 (0.44, 0.89)	0.61(0.43, 0.87)
	0.0050	0.0096	0.0095	0.0069
AKI Stages	-0.02 (-0.05,	-0.02 (-0.05, -	-0.02 (-0.05, -	-0.03(-0.05,-

	0.00) 0.0627	0.00) 0.0792	0.00) 0.0517	0.00) 0.0236

AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time.

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

The risk adjustment models were constructed using logistic stepwise regression. After adjusting for these interference factors, parecoxib was still independently associated with postoperative AKI (OR, 0.61; 95% CI, 0.43–0.87, model 4 in Table 3) or different postoperative AKI stages (OR, -0.03; 95% CI, -0.05– -0.00, model 4 in Table 3).

Sensitivity analysis

Table 4 presented the association between postoperative AKI and parecoxib in the subgroups of eGFR <90 $mL \cdot min^{-1} \cdot 1.73\ m^{(2)\ -1}$, non-smokers, blood loss <1000ml, and intraoperative non-hypotension.

Table 4 Sensitivity analysis of the association between postoperative acute kidney injury (AKI) and parecoxib

		Model 1	Model 2	Model 3	Model 4
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
		***p*-value**	***p*-value**	***p*-value**	***p*-value**
	Without parecoxib	Parecoxib			
eGFR	1	0.49 (0.31, 0.79)	0.54 (0.33, 0.87)	0.50 (0.30, 0.84)	0.49(0.29,0.82)
<90		0.0032	0.0119	0.0084	0.0065
Non-	1	0.57 (0.39, 0.84)	0.56 (0.37, 0.84)	0.56 (0.38, 0.84)	0.55(0.37,0.83)
smoker		0.0040	0.0046	0.0052	0.0043
blood loss <1000ml	1	0.56 (0.39, 0.82)	0.57 (0.39, 0.84)	0.56 (0.37, 0.83)	0.55 (0.37, 0.83)
		0.0027	0.0042	0.0040	0.0037
non-hypotension	1	0.60 (0.42, 0.87)	0.60 (0.42, 0.87)	0.57 (0.38, 0.84)	
		0.0064	0.0077	0.0050	

Model 1: Non-adjusted.

Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

Model 3: Model 2 plus ARB, eGFR, and operative time

Model 4: Model 3 plus intraoperative hypotension, and vasoactive drugs.

For patients with an eGFR <90 $mL \cdot min^{-1} \cdot 1.73\ m^{(2)\ -1}$ or who were non-smokers, single-

dose parecoxib (40 mg or 80 mg) was associated with a lower incidence of postoperative AKI (Table 4). Similar results were obtained with the adjusted models. Postoperative AKI risk also reduced in patients with blood loss <1000ml (OR, 0.55; 95%CI, 0.37-0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

Discussion

According to the surgery type and AKI diagnostic criteria, the incidence of postoperative AKI ranges from 1.0% to 31%[13-15], and our study revealed an incidence of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac surgery. The incidence was similar to that in the recently published data by Nishimoto (6%, non-cardiac surgery; mean age, 63 years)[16]. In our study, the univariable analysis identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode, emergency, surgical grade 4, duration of the operation (>120 min), the incidence of intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which are similar to previously published data by Mathis MR (2020) and Cho E (2014) [17 18].

However, age and BMI did not correlate with AKI in our study, which is inconsistent with the findings from Wang J's studies[19]. This discrepancy can be explained by the difference in mean age and BMI between the studies, which were both lower in our study population. The results of the sensitivity analysis suggested that single-dose (40 mg or 80 mg) parecoxib might have potential protective effects against postoperative AKI in

differentially ranked AKI. eGFR <90 mL·min^{-1}·1.73 m$^{(2)\ -1}$ represented the population with preoperative glomerular filtration impairment, while non-hypertension and blood-loss<1000ml, represented people with relatively stable intraoperative circulation and relatively good renal perfusion pressure. The subgroup analysis showed parecoxib might reduce the AKI risk in these patients.

Numerous studies have investigated the association between NSAIDs and AKI[10 20]. An updated Cochrane systematic review and meta-analysis published by Bell S in 2018 indicated that NSAIDs have uncertain effects on the rate of AKI and may slightly increase serum creatinine in patients with normal kidney function following surgery[20]. In another meta-analysis (Ungprasert P, 2015), a significant risk of AKI was observed with most traditional NSAIDs but not with two COX-2 specific inhibitors (rofecoxib and celecoxib) [10]. A pooled analysis of 28 randomized clinical trials investigating the safety of parecoxib for the management of postoperative pain showed that its associated risk of renal failure and impairment was 1%, similar to that with the placebo (0.9%)[21].

However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80 mg) might provide potential protective effects against postoperative AKI in patients aged 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a renoprotective effect has been postulated for parecoxib. For example, the study of Takaku M et al. also showed that a single-dose of parecoxib (20 mg/kg) reduced tubular renal injury and serum inflammatory cytokines level (interleukin (IL)-1α, IL-β, IL6, and tumor necrosis factor (TNF)-α) in an ischemic rat model[22]. Moreover, several animal studies(Takaku M 2018, Feitoza CQ 2005, Feitoza CQ 2004, Candelario-Jalil E 2007)

have suggested that pretreatment with COX-2 inhibitors improved outcomes in function and histology in not only the kidney but also other organs after ischemia[22-25]. To the best of our knowledge, this is the first clinical report to suggest that single-dose (40 mg or 80 mg) parecoxib may be renoprotective in patients aged 18–60 years who underwent non-cardiac surgery.

The mechanism by which parecoxib decreases the risk of postoperative AKI is unknown. However, one possible underlying mechanism is likely related to inflammation. A previous study by Murashima M et al. showed that inflammation is a predictor of postoperative AKI and a mediator of increased mortality after AKI in non-cardiac surgery [26]. However, perioperative parecoxib reduced local and systemic inflammatory cytokines postoperatively[27 28]. Another possible mechanism is associated with hemodynamic change. COX-1 contributes to controlling renal GFR, whereas COX-2 is involved in sodium and water excretion[7]. COX-2 inhibitors are associated with mild hypertension owing to modest sodium retention in the first few days of therapy[29]. The renoprotective mechanism of parecoxib may be related to its anti-inflammatory effects and sodium regulation.

Our study had some limitations that are worth mentioning. First, this was a retrospective single-center observational study; thus, it may have had some selection bias. Second, the timing of the serum creatinine measurement was based on clinical discretion; thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years who underwent non-cardiac surgery as the target to research. Fourthly, due to the nature of the retrospective study, some unknown or unmeasured confounders, and those

excluded patients who had missing data may interfere with the outcomes. Therefore, our results should be extrapolated cautiously.

Conclusions

In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80 mg) may be associated with a modest reduction of postoperative AKI in those aged 18–60 years. However, these short-term effects may not represent the benefit of this drug in the long term. Furthermore, more comprehensive studies are needed to confirm the effects of parecoxib on the risk of postoperative AKI.

Figure legends

Fig 1. Enrollment of patients undergoing non-cardiac surgery. The numbers in brackets represent patients excluded for the reasons described earlier.

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Author's Contributions

Yongzhong Tang helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript. Pingping Zeng and Yan Liao helped in collecting, analyzing and interpreting the data, and drafting and revising the manuscript. Zheng Qin, Hao Zhang and Bo Li helped in analyzing and interpreting the data. Wen Ouyang helped

in Supervising, Funding acquisition and drafting and revising the manuscript. Dan Li helped in designing the study, analyzing and interpreting the data, and drafting and revising the manuscript.

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Patient Consent for publication：Not applicable.

Ethics approval: This study was approved by the ethics committee of the third Xiangya hospital of Central South University (2020S264). Because of the observational nature of the study, informed consent was waived.

Data sharing statement：The data used and analyzed in this study are available from the corresponding author on reasonable request.

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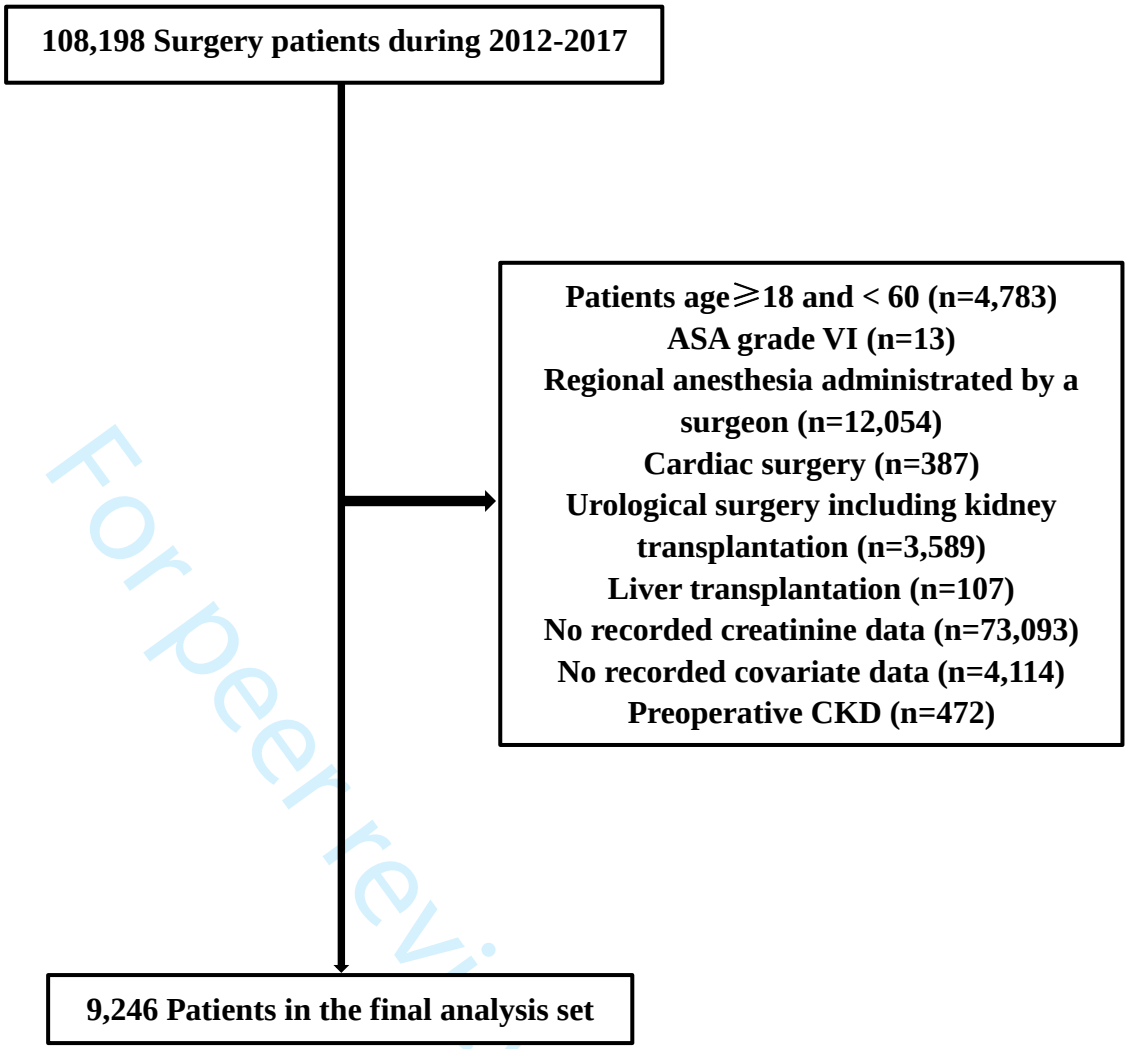

Fig 1

Supplemental Table 1. Baseline characteristics of patients aged 18–60 years with and without acute kidney injury (AKI)

Clinical features	without AKI (n=8686)	With AKI (n=560)	p-value
Age (years)	44.25±10.43	45.06±10.18	0.074
BMI	22.93±4.93	22.54±3.83	0.07
eGFR	101.98±16.38	94.41±19.78	<0.001
Male	4267 (49.13%)	300 (53.57%)	0.041
Smoking	1213 (13.97%)	105 (18.75%)	0.002
Alcohol consumption	822 (9.46%)	74 (13.21%)	0.004
Anemia	1538 (17.71%)	161 (28.75%)	<0.001
Hypertension	1884 (21.69%)	211 (37.68%)	<0.001
Diabetes mellitus	509 (5.86%)	52 (9.29%)	<0.001
ACEI	189 (2.18%)	21 (3.75%)	0.015
ARB	116 (1.34%)	13 (2.32%)	0.054
CCB	1125 (12.95%)	119 (21.25%)	<0.001
Diuretics	77 (0.89%)	19 (3.39%)	<0.001
ASA grade			<0.001
I–II	6633 (76.36%)	317 (56.61%)	
III–V	2053 (23.64%)	243 (43.39%)	
Anesthesia method			<0.001

General anesthesia	7735 (89.05%)	531 (94.82%)	
Non-general anesthesia	951 (10.95%)	29 (5.18%)	
Emergency	1395 (16.06%)	130 (23.21%)	<0.001
Surgical Grade			<0.001
1	245 (2.82%)	14 (2.50%)	
2	2746 (31.61%)	118 (21.07%)	
3	5349 (61.58%)	386 (68.93%)	
4	346 (3.98%)	42 (7.50%)	
Operative time (min)			<0.001
≤60	1338 (15.4%)	63 (11.25%)	
61–120	2176 (25.05%)	111 (19.82%)	
121–180	2032 (23.39%)	135 (24.11%)	
>180	3140 (36.15%)	251 (44.82%)	
Intraoperative erythrocyte Transfusion, mL (%)			<0.001
<100	6735 (77.54)	339 (60.54)	
100–600	868 (9.99)	82 (14.64)	
601–1000	508 (5.85)	42 (7.50)	
>1000	575 (6.62)	97 (17.32)	
Amount of Blood loss, mL (%)			<0.001
<100	2623 (30.20)	131 (23.39)	

100–600	4771 (54.93)	292 (52.14)	
601–1000	670 (7.71)	60 (10.71)	
>1000	622 (7.16)	77 (13.75)	
Amount of fluid infusion (10 mL/24 h)	916.67 (625.00–1432.29)	1125.00 (703.12–1604.17)	<0.001
Amount of fluid out (10 mL/24 h)	333.33 (145.83–541.67)	375.00 (208.33–687.50)	<0.001
Intraoperative Hypotension	930 (10.71%)	81 (14.46%)	0.006
Vasoactive drugs	664 (7.64%)	71 (12.68%)	<0.001
Parecoxib	934 (10.75%)	39 (6.96%)	0.005
Admission to ICU	376 (4.33%)	57 (10.18%)	<0.001
Death	32 (0.37%)	26 (4.64%)	<0.001

AKI: acute kidney injury, BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal or epidural) and nerve block anesthesia, ICU: intensive care unit. Data are expressed as the number of patients (%) or mean ± standard deviation (SD).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-17
		(*b*) Report category boundaries when continuous variables were categorized	8-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-22
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.