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

3

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1
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4 19 **Abstract**

5
6 20 **Objective:** The association of nonsteroidal anti-inflammatory drugs with postoperative acute kidney
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9 21 injury is controversial. However, there are few studies focusing on the association between parecoxib
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12 22 and postoperative acute kidney injury.

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14 23 **Design:** A retrospective cohort study

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17 24 **Setting:** Third Xiangya Hospital of Central South University in Hunan Province, China

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19 25 **Participants:** The electronic medical records and laboratory results were obtained from 9,246 adult
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21
22 26 patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August
23
24
25 27 31, 2017. Study groups were treated with or without parecoxib.

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27 28 **Interventions:** Univariable analysis identified demographic, preoperative laboratory, and
28
29
30 29 intraoperative factors associated with acute kidney injury. Logistic stepwise regression was used to
31
32
33 30 calculate the adjusted odds ratio of parecoxib and acute kidney injury association.

34
35 31 **Results:** The incidence of postoperative acute kidney injury was 6.06% and parecoxib was used in
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38 32 10.5% of the patients. The mortality was 4.64% in the acute kidney injury group. The incidence of
39
40
41 33 acute kidney injury was lower in the parecoxib-administered group (4%) than that in the group without
42
43
44 34 parecoxib (6.3%, $p = 0.005$). Postoperative acute kidney injury risk reduced by 39% in the parecoxib-
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46
47 35 administered group after adjusting for interference factors.

48 36 **Conclusions:** Thus, parecoxib might have potential protective effects against postoperative acute
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51 37 kidney injury risk in adult patients undergoing non-cardiac surgery.

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56 39 **Keywords:** acute kidney injury; parecoxib; non-cardiac surgery

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4 41 **Strengths and limitations of this study:** Large study population including all adult patients (18–60
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6 42 years) undergoing non-cardiac surgery in Third Xiangya Hospital of Central South University in China
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9 43 between 2012 to 2017.□

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11 44 □ Our study indicated that parecoxib might have potential protective effects against postoperative
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14 45 acute kidney injury risk.

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17 46 This retrospective single-center observational study may have had some selection bias, and the
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19 47 timing of the serum creatinine measurement may vary with different doctors.
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48 **Background**

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

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

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

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

72

73 **Methods**

74 Design and selection criteria

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

86

87 Data collection

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

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4 92 intraoperative data including emergency, surgical grade, operative time, anesthesia
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6 93 method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte
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9 94 transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive
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11 95 drugs. 5) postoperative outcomes such as occurrence of AKI, admission to ICU, and
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14 96 mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were
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17 97 obtained by a retrospective review of the computerized patient record system of our
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19 98 hospital.

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23 24 25 100 Definitions

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27 101 Postoperative AKI was defined according to the Kidney Disease: Improving Global
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30 102 Outcomes (KDIGO) 2012 creatinine criteria [11], as one of the following: an increase in
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32 103 serum creatinine by ≥ 0.3 mg/dL within 48 h or a ≥ 1.5 -times increase in serum creatinine
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35 104 from baseline within 7 postoperative days. The baseline serum creatinine level was
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38 105 calculated using the lowest level at preoperative day 7. The primary outcome was the
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40 106 impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days.
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43 107 Parecoxib administration was defined during the operative time. Surgical grade was
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45
46 108 classified using the surgical classification catalogue constituted by the Chinese Ministry
47
48 109 of Health, published in 2018. Intraoperative hypotension was defined as mean arterial
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51 110 pressure (MAP) < 65 mmHg for a duration of at least 5 min.

52
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54 55 56 112 Patient and public involvement

57
58 113 No patient involvement.
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115 **Statistical analysis**

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

129

130 **Results**

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

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

139

140 AKI

141 The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the
 142 probability of admission to the intensive care unit (ICU) and mortality were 10.18% and
 143 4.64%, respectively (Table 1).

144

145 **Table 1.** Baseline characteristics of patients aged 18–60 years with and without acute
 146 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	916.67 (625.00–		1125.00 (703.12–	
(10 mL/24 h)	1432.29)		1604.17)	<0.001
Amount of fluid out			375.00 (208.33–	
(10 mL/24 h)	333.33 (145.83–541.67)		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

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

152
 153 There was no difference in age, body mass index (BMI), angiotensin receptor blockers
 154 (ARBs) use and intraoperative hypotension among patients with and without AKI (Table
 155 1). Significant differences between patients with AKI and without AKI are shown in
 156 Table 1 (all $p < 0.05$).

158 Parecoxib

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

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

Clinical features	Without parecoxib (n=8273)	With parecoxib (n=973)	p-value
Age (year)	44.23 \pm 10.46	44.89 \pm 10.04	0.06
BMI	22.89 \pm 4.99	23.03 \pm 3.76	0.409
eGFR	101.66 \pm 16.66	101.56 \pm 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	

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

167

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

176

177 Univariable analysis

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

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

180

181 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

182 OR: odds ratio, BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB:

183 angiotensin receptor blockers, CCB: calcium-channel blockers, ASA: American Society of

184 Anesthesiologists.

185

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

191 Parecoxib (OR, 0.62; 95%CI, 0.45–0.87, $p = 0.005$), eGFR (OR, 0.96; 95%CI, 0.96–
 192 0.97, $p < 0.0001$), no general anesthesia (OR, 0.44; 95%CI, 0.30–0.65, $p < 0.0001$) and
 193 vasoactive drug use (OR, 0.06; 95%CI, 0.03–0.09, $p < 0.0001$) were independently
 194 associated with a decreased risk of postoperative AKI (Table 3). Age (OR, 1.01; 95%CI,
 195 1.00–1.02, $p = 0.0737$), BMI (OR, 0.98; 95%CI, 0.95–1.00, $p = 0.0396$), and ARB use
 196 (OR, 1.76; 95%CI, 0.98–3.14, $p = 0.0570$) were not correlated with AKI (Table 3).

197

198 Multivariable regression analysis

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

202

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

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

204 Model 1: Non-adjusted.

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

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

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

210

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

214

215 Sensitivity analysis

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

217

218 Table 5 Sensitivity analysis of association between postoperative acute kidney injury
 219 (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-smoker	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)
		0.0040	0.0046	0.0052	0.0043
AKI RANK	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)
		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)

220 Model 1: Non-adjusted.

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

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

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

226
 227 For patients with an eGFR $<90 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{(2)}^{-1}$ or who were non-smokers, single-
 228 dose parecoxib (40 mg or 80 mg) was associated with a lower incidence of postoperative
 229 AKI. We divided the outcome of postoperative AKI into three groups: stage 0, no AKI;
 230 stage 1, AKI grade 1; and stage 2, AKI grade 2 and 3. The results showed that parecoxib
 231 exerted protective effects in postoperative AKI in differently ranked AKIs.

232

233 Discussion

234 According to the surgery type and AKI diagnostic criteria, the incidence of
235 postoperative AKI ranges from 1.0% to 31% [12-14], and our study revealed an incidence
236 of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac
237 surgery. The incidence was similar to that in the recently published data by Nishimoto
238 (6%, non-cardiac surgery; mean age, 63 years) [15]. In our study, the univariable analysis
239 identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes
240 mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode,
241 emergency, surgical grade 4, duration of the operation (>120 min), incidence of
242 intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of
243 blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which
244 are similar to previously published data [16, 17].

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

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

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4 255 meta-analysis, a significant risk of AKI was observed with most traditional NSAIDs but
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6 256 not with two COX-2 specific inhibitors (rofecoxib and celecoxib) [9]. A pooled analysis
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9 257 of 28 randomized clinical trials investigating the safety of parecoxib for the management
10
11 258 of postoperative pain showed that its associated risk of renal failure and impairment was
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13
14 259 1%, similar to that with the placebo (0.9%) [20].

16 260 However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80
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18 261 mg) might provide potential protective effects against postoperative AKI in patients aged
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20 262 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a
21
22 263 renoprotective effect has been postulated for parecoxib. For example, a study also showed
23
24 264 that a single-dose of parecoxib (20 mg/kg) reduced tubular renal injury and serum
25
26 265 inflammatory cytokines level (interleukin (IL)-1 α , IL- β , IL6, and tumor necrosis factor
27
28 266 (TNF)- α) in an ischemic rat model [21]. Moreover, several animal studies have suggested
29
30 267 that pretreatment with COX-2 inhibitors improved outcomes in function and histology in
31
32 268 not only the kidney but also other organs after ischemia [21, 22, 24]. To the best of our
33
34 269 knowledge, this is the first clinical report to suggest that single-dose (40 mg or 80 mg)
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36 270 parecoxib may be renoprotective in patients aged 18–60 years who underwent non-
37
38 271 cardiac surgery.

39
40 272 The mechanism by which parecoxib decreases the risk of postoperative AKI is
41
42 273 unknown. However, one possible underlying mechanism is likely related to inflammation.
43
44 274 A previous study showed that inflammation is a predictor of postoperative AKI and a
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46 275 mediator of increased mortality after AKI in non-cardiac surgery [25]. However,
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48 276 perioperative parecoxib reduced local and systemic inflammatory cytokines
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4 277 postoperatively [26, 27]. Another possible mechanism is associated with hemodynamic
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6 278 change. COX-1 contributes to controlling renal GFR, whereas COX-2 is involved in
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9 279 sodium and water excretion [28]. COX-2 inhibitors are associated with mild hypertension
10
11 280 owing to modest sodium retention in the first few days of therapy [29]. The renoprotective
12
13
14 281 mechanism of parecoxib may be related to its anti-inflammatory effects and sodium
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16
17 282 regulation.

18
19 283 Our study had some limitations that are worth mentioning. First, this was a
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21
22 284 retrospective single-center observational study; thus, it may have had some selection bias.
23
24
25 285 Second, the timing of the serum creatinine measurement was based on clinical discretion;
26
27 286 thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years
28
29
30 287 who underwent non-cardiac surgery as the target to research, therefore, our results should
31
32
33 288 be extrapolated cautiously.

34
35 289

36 37 38 290 **Conclusions**

39
40 291 In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80
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42
43 292 mg) may have potential protective effects against postoperative AKI in those aged 18–60
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45
46 293 years. However, these short-term effects may not represent the benefit of this drug in the
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48
49 294 long term. Furthermore, more comprehensive studies are needed to confirm the effects of
50
51 295 parecoxib on the risk of postoperative AKI.

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5
6 **300 Author's Contributions**

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10
11 302 drafting and revising the manuscript. Pingping Zeng and Yan Liao helped in collecting,
12
13
14 303 analyzing and interpreting the data, and drafting and revising the manuscript. Zheng Qin,
15
16
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20
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22
23
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25

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41

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43 314

44
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56 **319 Ethics approval:** This study was approved by the ethics committee of the third Xiangya
57
58 320 hospital of Central South University (2020S264). Because of the observational nature of
59
60

1
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4 321 the study, informed consent was waived.

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9 323 **Data sharing statement:** The data used and analyzed in this study are available from

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11 324 the corresponding author on reasonable request.
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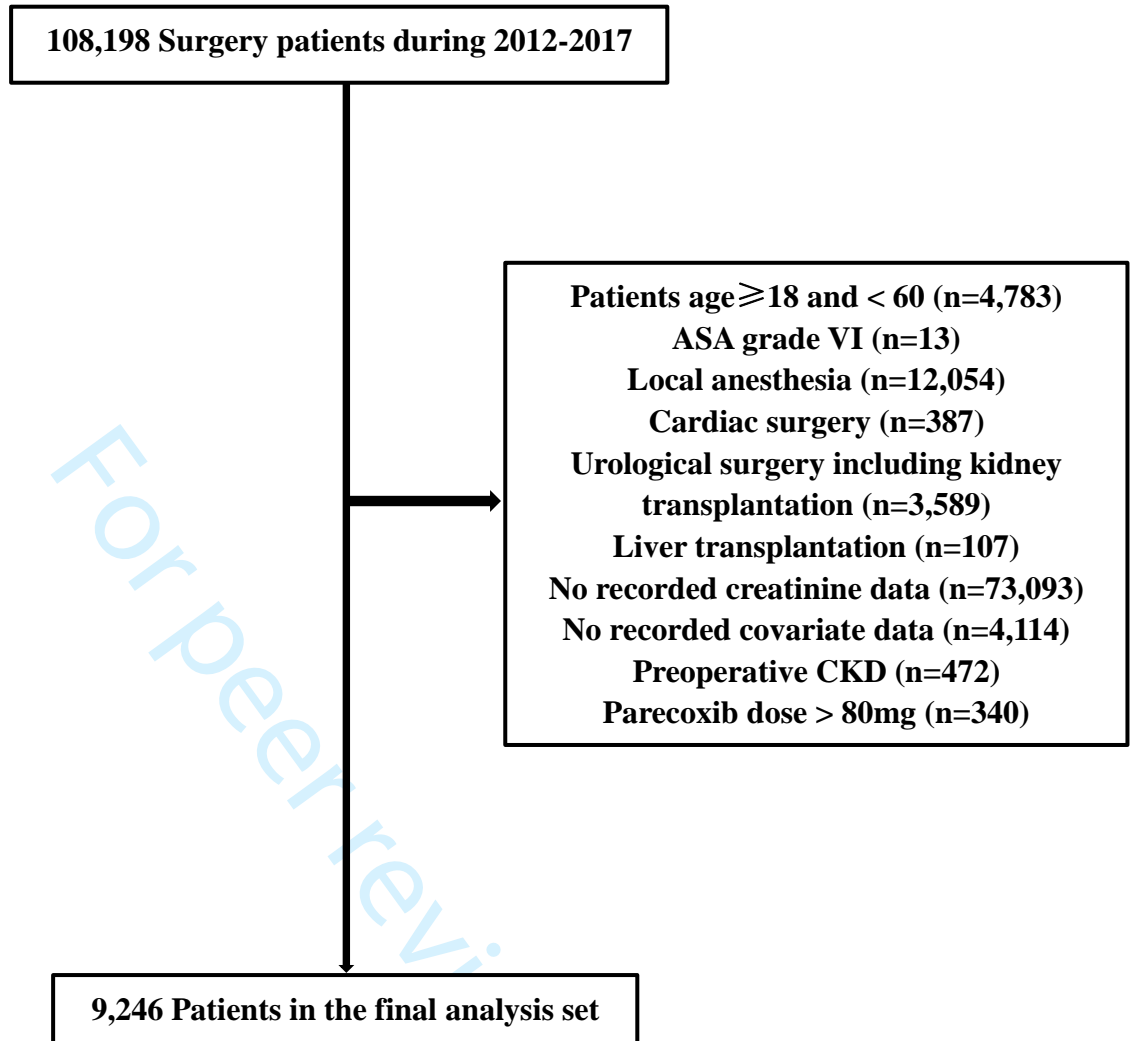


Fig 1. Enrollment of patients undergoing non-cardiac surgery.

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.

BMJ Open

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

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

3

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18

19 Abstract

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

24 **Design:** A retrospective cohort study

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

26 **Participants:** The electronic medical records and laboratory results were obtained from 9,246 adult
27 patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August
28 31, 2017. Study groups were treated with or without parecoxib.

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

32 **Results:** The incidence of acute kidney injury was lower in the parecoxib-administered group (4%)
33 than that in the group without parecoxib (6.3%, $p = 0.005$). In the Multivariable regression analysis,
34 postoperative acute kidney injury risk reduced by 39% (OR, 0.61; 95% CI, 0.43–0.87) in the
35 parecoxib-administered group after adjusting for interference factors. Sensitivity analysis showed that
36 postoperative AKI risk reduced in four subgroups: eGFR < 90 mL · min⁻¹ · 1.73m⁽²⁾⁻¹ (OR, 0.49; 95%CI,
37 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-
38 0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

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

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4 **Keywords:** acute kidney injury; parecoxib; non-cardiac surgery
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9 **Strengths and limitations of this study:** Large study population including all adult patients (18–60
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11 years) undergoing non-cardiac surgery in Third Xiangya Hospital of Central South University in China
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14 between 2012 to 2017.□

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17 □ Our study indicated that parecoxib may slightly hint at a protective effect against postoperative
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19 acute kidney injury risk.
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22 The selection bias and some unknown confounders in this retrospective single-center
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25 observational study may limit the generalisability of the results.
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51 **Background**

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

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

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

73 Parecoxib is a parenteral specific COX-2 inhibitor, which enhances its therapeutic gain
74 with minimal adverse effects[6 11]. Parecoxib is used as a perioperative analgesic in over
75 80 countries, however, clinical data about effect of parecoxib on postoperative AKI are
76 scarce. Therefore, it is important to establish its safety during the perioperative period.
77 The aim of this study was to assess the correlation between the perioperative use of
78 parecoxib and postoperative AKI in patients undergoing non-cardiac surgery.

80 **Methods**

81 Design and selection criteria

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

94 Data collection

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4 95 The following information was collected: 1) epidemiological data including age, sex,
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6 96 and BMI; 2) individual history including preoperative complications and medication
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9 97 history; 3) laboratory data including serum creatinine and eGFR calculated using the
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11 98 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; 4)
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14 99 intraoperative data including emergency, surgical grade, operative time, anesthesia
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17 100 method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte
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20 101 transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive
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22 102 drugs. 5) postoperative outcomes such as occurrence of AKI, admission to ICU, and
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24 103 mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were
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27 104 obtained by a retrospective review of the computerized patient record system of our
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30 105 hospital.

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35 107 Definitions

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37 108 Postoperative AKI was defined according to the Kidney Disease: Improving Global
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40 109 Outcomes (KDIGO) 2012 creatinine criteria[12], as one of the following: an increase in
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43 110 serum creatinine by ≥ 0.3 mg/dL within 48 h or a ≥ 1.5 -times increase in serum creatinine
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46 111 from baseline within 7 postoperative days. The baseline serum creatinine level was
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49 112 calculated using the lowest level within preoperative day 7. The primary outcome was the
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52 113 impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days.
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55 114 Parecoxib administration was defined during the operative time. Surgical grade was
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58 115 classified using the surgical classification catalogue constituted by the Chinese Ministry
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60 116 of Health, published in 2018. Intraoperative hypotension was defined as mean arterial

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4 117 pressure (MAP) <65mmHg for a duration of at least 5 min.
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9 119 Patient and public involvement

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11 120 No patient involvement.
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17 122 Statistical analysis

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19 123 All statistical analyses were performed using SAS version 9.4 software (SAS
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21
22 124 Institute, Inc., Cary, NC, USA) and CRAN R (v3.4.3). Missing data of covariates
23
24 125 (including BMI and eGFR) were handled by multiple imputation model. The continuous
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27 126 results are expressed as mean (SD), whereas categorical variables are expressed as
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29
30 127 numbers with percentages. The Kruskal-Wallis rank sum test was used to compare
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33 128 continuous variables between groups, whereas the chi-square (χ^2) test or Fisher's exact
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36 129 probability method was used for categorical variables. Univariable logistic regression
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39 130 analysis was used to identify epidemiological, preoperative laboratory, and
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42 131 intraoperative factors that were significantly associated with AKI development. The
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45 132 data were adjusted for potential confounders in multivariable regression models. To
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48 133 further validate these results in a number of specific populations that may influence the
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51 134 incidence of AKI. The sensitivity test was performed in the following four different
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53
54 135 subgroups: eGFR<90 mL·min⁻¹·1.73m⁽²⁾⁻¹, non-smoker, blood loss <1000ml, and non-
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57 136 hypotension. The results of the classification variable are expressed as odds ratio (OR)
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59
60 137 or "Beta" and 95% CI; a p-value < 0.05 indicated a statistically significant difference.
138

139 Results

140 Of the 108,198 records identified, those of 9,246 patients were included in the analysis
 141 (Fig. 1). Reasons for excluding patients were age <18 or >60 years (n = 4,783), ASA
 142 grade VI (n = 13), regional anesthesia administered by a surgeon (n = 12,054), cardiac
 143 surgery (n = 387), urological surgery including kidney transplantation (n = 3,589), liver
 144 transplantation (n = 107), no recorded preoperative or postoperative creatinine data
 145 (n=73,093), no recorded covariate data such as routine blood panel or infusion volume (n
 146 = 4,114), preoperative chronic kidney disease (CKD) (n = 472), and administration of
 147 parecoxib doses >80 mg (n = 340).

149 AKI

150 The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the
 151 probability of admission to the intensive care unit (ICU) and mortality were 10.18% and
 152 4.64%, respectively (Supplemental Table 1).

154 **Supplemental Table 1.** Baseline characteristics of patients aged 18–60 years with and
 155 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			<0.001
Transfusion, mL (%)			
<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	916.67 (625.00–	1125.00 (703.12–	<0.001
(10 mL/24 h)	1432.29)	1604.17)	
Amount of fluid out		375.00 (208.33–	<0.001
(10 mL/24 h)	333.33 (145.83–541.67)	687.50)	

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

156

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

162

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

167

168 Parecoxib

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

170

171 Table 1. Baseline characteristics of patients aged 18–60 years treated with and without
 172 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	

173 BMI: body mass index, eGFR: estimated glomerular filtration rate, ACEI: angiotensin-converting
 174 enzyme inhibitors, ARB: angiotensin receptor blockers, CCB: calcium-channel blockers, ASA:
 175 American Society of Anesthesiologists, Non-general anesthesia include neuraxial anesthesia (spinal
 176 or epidural) and nerve block anesthesia, AKI: acute kidney injury. Data are expressed as number of
 177 patients (%) or mean ± standard deviation (SD). AKI Stages (outcome of postoperative AKI was
 178 divided into four groups: stage 0, no AKI; stage 1, AKI grade 1; stage 2, AKI grade 2 and stage 3,
 179 AKI grade 3)
 180
 181 The incidence of AKI was lower in the parecoxib-administered group (4%) than in the
 182 group without parecoxib (6.3%, p = 0.005). There was no difference in age, BMI,

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

189

190 Univariable analysis

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

193

194 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 anaesthesia	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

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

199

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

205 Parecoxib (OR, 0.62; 95%CI, 0.45–0.87, $p = 0.005$), eGFR (OR, 0.96; 95%CI, 0.96–
 206 0.97, $p < 0.0001$), non-general anesthesia (OR, 0.44; 95%CI, 0.30–0.65, $p < 0.0001$) and
 207 vasoactive drug use (OR, 0.06; 95%CI, 0.03–0.09, $p < 0.0001$) were independently
 208 associated with a decreased risk of postoperative AKI (Table 2). Age (OR, 1.01; 95%CI,
 209 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).

211

212 Multivariable regression analysis

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

216

217 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)
	<i>p</i>-value	<i>p</i>-value	<i>p</i>-value	<i>p</i>-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

218 AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1,

219 AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

220 Model 1: Non-adjusted.

221 Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes

222 mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid

223 infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

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

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

226

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

231

232 Sensitivity analysis

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

236

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

		Model 1	Model 2	Model 3	Model 4
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
		<i>p</i>-value	<i>p</i>-value	<i>p</i>-value	<i>p</i>-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-smoker	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)
		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	

239 Model 1: Non-adjusted.

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

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

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

245

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

251

252 Discussion

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

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4 255 of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac
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6 256 surgery. The incidence was similar to that in the recently published data by Nishimoto
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9 257 (6%, non-cardiac surgery; mean age, 63 years)[16]. In our study, the univariable analysis
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11 258 identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes
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14 259 mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode,
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17 260 emergency, surgical grade 4, duration of the operation (>120 min), incidence of
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19 261 intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of
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22 262 blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which
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25 263 are similar to previously published data by Mathis MR (2020) and Cho E (2014) [17 18].

26
27 264 However, age and BMI did not correlate with AKI in our study, which is inconsistent
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30 265 with the findings from Wang J's studies[19]. This discrepancy can be explained by the
31
32 266 difference in mean age and BMI between the studies, which were both lower in our study
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35 267 population. The results of the sensitivity analysis suggested that single-dose (40 mg or 80
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37 268 mg) parecoxib might have potential protective effects against postoperative AKI in
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40 269 differentially ranked AKI. eGFR <90 mL·min⁻¹·1.73 m⁽²⁾⁻¹ represented the population
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43 270 with preoperative glomerular filtration impairment, while non-hypertension and blood-
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46 271 loss<1000ml, represented people with relatively stable intraoperative circulation and
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48 272 relatively good renal perfusion pressure. The subgroup analysis showed parecoxib might
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51 273 reduce the AKI risk in these patients.

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53 274 Numerous studies have investigated the association between NSAIDs and AKI[10 20].
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56 275 An updated Cochrane systematic review and meta-analysis published by Bell S in 2018
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58 276 indicated that NSAIDs have uncertain effects on the rate of AKI and may slightly increase
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4 277 serum creatinine in patients with normal kidney function following surgery[20]. In
5
6 278 another meta-analysis (Ungprasert P, 2015), a significant risk of AKI was observed with
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9 279 most traditional NSAIDs but not with two COX-2 specific inhibitors (rofecoxib and
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11 280 celecoxib) [10]. A pooled analysis of 28 randomized clinical trials investigating the safety
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14 281 of parecoxib for the management of postoperative pain showed that its associated risk of
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16 282 renal failure and impairment was 1%, similar to that with the placebo (0.9%)[21].

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18
19 283 However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80
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21 284 mg) might provide potential protective effects against postoperative AKI in patients aged
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24 285 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a
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26
27 286 renoprotective effect has been postulated for parecoxib. For example, the study of Takaku
28
29 287 M et al. also showed that a single-dose of parecoxib (20 mg/kg) reduced tubular renal
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31 288 injury and serum inflammatory cytokines level (interleukin (IL)-1 α , IL- β , IL6, and tumor
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33 289 necrosis factor (TNF)- α) in an ischemic rat model[22]. Moreover, several animal
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36 290 studies(Takaku M 2018, Feitoza CQ 2005, Feitoza CQ 2004, Candelario-Jalil E 2007)
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38 291 have suggested that pretreatment with COX-2 inhibitors improved outcomes in function
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40
41 292 and histology in not only the kidney but also other organs after ischemia[22-25]. To the
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43
44 293 best of our knowledge, this is the first clinical report to suggest that single-dose (40 mg
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46 294 or 80 mg) parecoxib may be renoprotective in patients aged 18–60 years who underwent
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48
49 295 non-cardiac surgery.

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53 296 The mechanism by which parecoxib decreases the risk of postoperative AKI is
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55
56 297 unknown. However, one possible underlying mechanism is likely related to inflammation.
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59 298 A previous study of Murashima M et al. showed that inflammation is a predictor of
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4 299 postoperative AKI and a mediator of increased mortality after AKI in non-cardiac surgery
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6 300 [26]. However, perioperative parecoxib reduced local and systemic inflammatory
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9 301 cytokines postoperatively[27 28]. Another possible mechanism is associated with
10
11 302 hemodynamic change. COX-1 contributes to controlling renal GFR, whereas COX-2 is
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13
14 303 involved in sodium and water excretion[7]. COX-2 inhibitors are associated with mild
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17 304 hypertension owing to modest sodium retention in the first few days of therapy[29]. The
18
19 305 renoprotective mechanism of parecoxib may be related to its anti-inflammatory effects
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21
22 306 and sodium regulation.

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24
25 307 Our study had some limitations that are worth mentioning. First, this was a
26
27 308 retrospective single-center observational study; thus, it may have had some selection bias.
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30 309 Second, the timing of the serum creatinine measurement was based on clinical discretion;
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32 310 thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years
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34
35 311 who underwent non-cardiac surgery as the target to research. Fourthly, due to the nature
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37 312 of the retrospective study, some unknown or unmeasured confounders, and those
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40 313 excluded patients who had missing data may interfere the outcomes. Therefore, our
41
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43 314 results should be extrapolated cautiously.

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45 315

46 47 48 316 **Conclusions**

49
50 317 In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80
51
52 318 mg) may slightly hint at a protective effect against postoperative AKI in those aged 18–
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54
55 319 60 years. However, these short-term effects may not represent the benefit of this drug in
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58 320 the long term. Furthermore, more comprehensive studies are needed to confirm the effects
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4 321 of parecoxib on the risk of postoperative AKI.

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9 323 **Figure legends**

10
11 324 Fig 1. Enrollment of patients undergoing non-cardiac surgery. The numbers in brackets
12
13
14 325 represent patients excluded for the reasons described earlier.

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18
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20
21
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26
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28
29
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31
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33
34
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36
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38
39
40 335 in Supervising, Funding acquisition and drafting and revising the manuscript. Dan Li
41
42 336 helped in designing the study, analyzing and interpreting the data, and drafting and
43
44
45 337 revising the manuscript.

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49
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59
60

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344

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346

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348

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350 hospital of Central South University (2020S264). Because of the observational nature of
351 the study, informed consent was waived.

352

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

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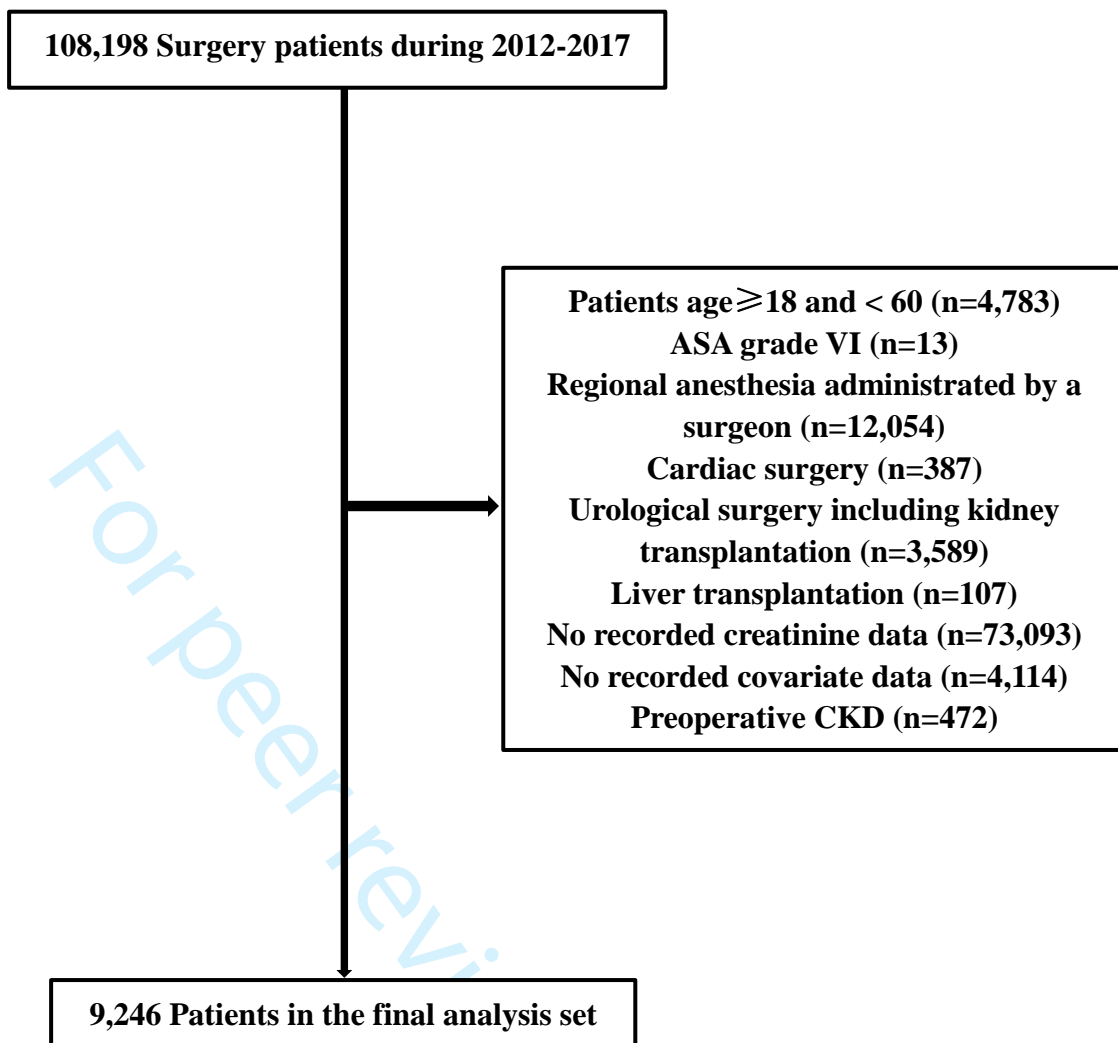


Fig 1

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			<0.001
Transfusion, mL (%)			
<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 \pm 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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1 **Correlation between perioperative parecoxib use and postoperative acute kidney**
2 **injury in patients undergoing non-cardiac surgery: A retrospective cohort analysis**

3

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18

19 Abstract

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

24 **Design:** A retrospective cohort study

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

26 **Participants:** The electronic medical records and laboratory results were obtained from 9,246 adult
27 patients (18–60 years) undergoing non-cardiac surgery performed between January 1, 2012 to August
28 31, 2017. Study groups were treated with or without parecoxib.

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

32 **Results:** The incidence of acute kidney injury was lower in the parecoxib-administered group (4%)
33 than that in the group without parecoxib (6.3%, $p = 0.005$). In the Multivariable regression analysis,
34 postoperative acute kidney injury risk reduced by 39% (OR, 0.61; 95% CI, 0.43–0.87) in the
35 parecoxib-administered group after adjusting for interference factors. Sensitivity analysis showed that
36 postoperative AKI risk reduced in four subgroups: eGFR<90 mL·min⁻¹·1.73m⁽²⁾⁻¹ (OR, 0.49; 95%CI,
37 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-
38 0.83) and non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).

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

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

43

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

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

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

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

53 **Background**

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

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

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

75 effects are mostly COX-1 related.

76 Parecoxib is a parenteral specific COX-2 inhibitor, which enhances its therapeutic gain
77 with minimal adverse effects[6 11]. Parecoxib is used as a perioperative analgesic in over
78 80 countries, however, clinical data about the effect of parecoxib on postoperative AKI
79 are scarce. Therefore, it is important to establish its safety during the perioperative period.
80 The aim of this study was to assess the correlation between the perioperative use of
81 parecoxib and postoperative AKI in patients undergoing non-cardiac surgery.

82

83 **Methods**

84 Design and selection criteria

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

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6 98 Data collection

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9 99 The following information was collected: 1) epidemiological data including age, sex,
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11 and BMI; 2) individual history including preoperative complications and medication
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13 history; 3) laboratory data including serum creatinine and eGFR calculated using the
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15 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; 4)
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17 intraoperative data including emergency, surgical grade, operative time, anesthesia
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19 method, ASA grade, amount of fluid infusion and out, intraoperative erythrocyte
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21 transfusion volume, amount of blood loss, intraoperative hypotension and vasoactive
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23 drugs. 5) postoperative outcomes such as the occurrence of AKI, admission to ICU, and
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25 mortality. All clinical data of the 9,246 patients who underwent non-cardiac surgery were
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27 obtained by a retrospective review of the computerized patient record system of our
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29 hospital.
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40 111 Definitions

43 112 Postoperative AKI was defined according to the Kidney Disease: Improving Global
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45 Outcomes (KDIGO) 2012 creatinine criteria[12], as one of the following: an increase in
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47 serum creatinine by ≥ 0.3 mg/dL within 48 h or a ≥ 1.5 -times increase in serum creatinine
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49 from baseline within 7 postoperative days. The baseline serum creatinine level was
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51 calculated using the lowest level within preoperative day 7. The primary outcome was the
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53 impact of parecoxib on AKI, defined as AKI occurring within 7 postoperative days.
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56 117 Parecoxib administration was defined during the operative time. The surgical grade was
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4 119 classified using the surgical classification catalog constituted by the Chinese Ministry of
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6 120 Health, published in 2018. Intraoperative hypotension was defined as mean arterial
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9 121 pressure (MAP) <65mmHg for a duration of at least 5 min.
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14 123 Patient and public involvement

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17 124 No patient involvement.
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22 126 Statistical analysis

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24 127 All statistical analyses were performed using SAS version 9.4 software (SAS
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27 128 Institute, Inc., Cary, NC, USA) and CRAN R (v3.4.3). Missing data of covariates
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30 129 (including BMI and eGFR) were handled by a multiple imputation model. The
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33 130 continuous results are expressed as mean (SD), whereas categorical variables are
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36 131 expressed as numbers with percentages. The Kruskal-Wallis rank sum test was used to
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39 132 compare continuous variables between groups, whereas the chi-square (χ^2) test or
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42 133 Fisher's exact probability method was used for categorical variables. Univariable
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45 134 logistic regression analysis was used to identify epidemiological, preoperative
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48 135 laboratory, and intraoperative factors that were significantly associated with AKI
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51 136 development. The data were adjusted for potential confounders in multivariable
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54 137 regression models. To further validate these results in a number of specific populations
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57 138 that may influence the incidence of AKI. The sensitivity test was performed in the
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60 139 following four different subgroups: eGFR<90 mL·min⁻¹·1.73m⁽²⁾⁻¹, non-smoker, blood
60 140 loss <1000ml, and non-hypotension. The results of the classification variable are

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4 141 expressed as odds ratio (OR) or “Beta” and 95% CI; a p-value < 0.05 indicated a
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6 142 statistically significant difference.
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11 144 **Results**

14 145 Of the 108,198 records identified, those of 9,246 patients were included in the analysis
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17 146 (Fig. 1). Reasons for excluding patients were age <18 or >60 years (n = 4,783), ASA
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19 147 grade VI (n = 13), regional anesthesia administered by a surgeon (n = 12,054), cardiac
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22 148 surgery (n = 387), urological surgery including kidney transplantation (n = 3,589), liver
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25 149 transplantation (n = 107), no recorded preoperative or postoperative creatinine data
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27 150 (n=73,093), no recorded covariate data such as routine blood panel or infusion volume (n
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30 151 = 4,114), preoperative chronic kidney disease (CKD) (n = 472), and administration of
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32 152 parecoxib doses >80 mg (n = 340).
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37 154 **AKI**

40 155 The incidence of postoperative AKI was 6.06% (560/9,246). In the AKI group, the
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43 156 probability of admission to the intensive care unit (ICU) and mortality was 10.18% and
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45 157 4.64%, respectively (Supplemental Table 1).
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48 158 There were no differences in age, body mass index (BMI), angiotensin receptor blockers
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50 159 (ARBs) use and intraoperative hypotension among patients with and without AKI
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53 160 (Supplemental Table 1). Significant differences between patients with AKI and without
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55 161 AKI are shown in Supplemental Table 1 (all p < 0.05).
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4 163 Parecoxib

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6 164 Parecoxib was used in 10.5% (973/9,246) of patients (Table 1).

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12 166 Table 1. Baseline characteristics of patients aged 18–60 years treated with and without
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15 167 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			0.94
Transfusion, mL (%)			
<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	

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

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

175

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

184

185 Univariable analysis

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

188

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

Variable	Statistics	Univariable	
		OR (95% CI)	p-value
Parecoxib	0.11 \pm 0.31	0.62 (0.45, 0.87)	0.0050
Age (year)	44.30 \pm 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

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

194

195 In the univariable analysis, male sex, smoking, alcohol consumption, anemia,
 196 hypertension, diabetes mellitus, ACEI use, calcium channel blocker (CCB) use, diuretic
 197 use, ASA grade III–V, emergency, surgical grade 4, duration of the operation, the
 198 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)
	<i>p</i>-value	<i>p</i>-value	<i>p</i>-value	<i>p</i>-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

214 AKI Stages (outcome of postoperative AKI was divided into four groups: stage 0, no AKI; stage 1,

215 AKI grade 1; stage 2, AKI grade 2 and stage 3, AKI grade 3)

216 Model 1: Non-adjusted.

217 Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes

218 mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid

219 infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

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

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

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223 The risk adjustment models were constructed using logistic stepwise regression. After

224 adjusting for these interference factors, parecoxib was still independently associated with

225 postoperative AKI (OR, 0.61; 95% CI, 0.43–0.87, model 4 in Table 3) or different

226 postoperative AKI stages (OR, -0.03; 95% CI, -0.05–-0.00, model 4 in Table 3).

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228 Sensitivity analysis

229 Table 4 presented the association between postoperative AKI and parecoxib in the

230 subgroups of eGFR $<90 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{(2)}^{-1}$, non-smokers, blood loss $<1000\text{ml}$, and

231 intraoperative non-hypotension.

232

233 Table 4 Sensitivity analysis of the association between postoperative acute kidney injury

234 (AKI) and parecoxib

		Model 1	Model 2	Model 3	Model 4
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
		<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -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-smoker	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)
		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	

235 Model 1: Non-adjusted.

236 Model 2: Adjusted for age, sex, BMI, smoking, alcohol consumption, anemia, hypertension, diabetes

237 mellitus, ACEI, CCB, diuretics, ASA, anesthesia method, emergency, surgical grade, amount of fluid

238 infusion and out, intraoperative erythrocyte transfusion, and amount of blood loss.

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

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

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242 For patients with an eGFR <90 mL·min⁻¹·1.73 m⁽²⁾⁻¹ or who were non-smokers, single-

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4 243 dose parecoxib (40 mg or 80 mg) was associated with a lower incidence of postoperative
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6 244 AKI (Table 4). Similar results were obtained with the adjusted models. Postoperative AKI
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9 245 risk also reduced in patients with blood loss <1000ml (OR, 0.55; 95%CI, 0.37-0.83) and
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11 246 non-hypotension (OR, 0.57; 95%CI, 0.38-0.84).
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17 248 **Discussion**

19 249 According to the surgery type and AKI diagnostic criteria, the incidence of
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22 250 postoperative AKI ranges from 1.0% to 31%[13-15], and our study revealed an incidence
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25 251 of 6.06% in the study population of patients aged 18–60 years who underwent non-cardiac
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27 252 surgery. The incidence was similar to that in the recently published data by Nishimoto
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30 253 (6%, non-cardiac surgery; mean age, 63 years)[16]. In our study, the univariable analysis
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32 254 identified male sex, smoking, alcohol consumption, anemia, hypertension, diabetes
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35 255 mellitus, ACEI use, CCB use, diuretic use, eGFR, ASA grade III–V, anesthesia mode,
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37 256 emergency, surgical grade 4, duration of the operation (>120 min), the incidence of
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40 257 intraoperative hypotension, intraoperative erythrocyte transfusion (>100 mL), amount of
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43 258 blood loss (>600 mL), and vasoactive drug use to be associated with AKI, some of which
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45 259 are similar to previously published data by Mathis MR (2020) and Cho E (2014) [17 18].
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48 260 However, age and BMI did not correlate with AKI in our study, which is inconsistent
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51 261 with the findings from Wang J's studies[19]. This discrepancy can be explained by the
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53 262 difference in mean age and BMI between the studies, which were both lower in our study
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56 263 population. The results of the sensitivity analysis suggested that single-dose (40 mg or 80
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58 264 mg) parecoxib might have potential protective effects against postoperative AKI in
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4 265 differentially ranked AKI. eGFR $<90 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{(2)}^{-1}$ represented the population
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6 266 with preoperative glomerular filtration impairment, while non-hypertension and blood-
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9 267 loss $<1000 \text{ ml}$, represented people with relatively stable intraoperative circulation and
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11 268 relatively good renal perfusion pressure. The subgroup analysis showed parecoxib might
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14 269 reduce the AKI risk in these patients.

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17 270 Numerous studies have investigated the association between NSAIDs and AKI[10 20].
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19 271 An updated Cochrane systematic review and meta-analysis published by Bell S in 2018
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21 272 indicated that NSAIDs have uncertain effects on the rate of AKI and may slightly increase
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23 273 serum creatinine in patients with normal kidney function following surgery[20]. In
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25 274 another meta-analysis (Ungprasert P, 2015), a significant risk of AKI was observed with
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27 275 most traditional NSAIDs but not with two COX-2 specific inhibitors (rofecoxib and
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29 276 celecoxib) [10]. A pooled analysis of 28 randomized clinical trials investigating the safety
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31 277 of parecoxib for the management of postoperative pain showed that its associated risk of
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33 278 renal failure and impairment was 1%, similar to that with the placebo (0.9%)[21].
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40 279 However, our study indicated that intraoperative single-dose parecoxib (40 mg or 80
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42 280 mg) might provide potential protective effects against postoperative AKI in patients aged
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44 281 18–60 years who underwent non-cardiac surgery. Moreover, this is not the first time a
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46 282 renoprotective effect has been postulated for parecoxib. For example, the study of Takaku
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48 283 M et al. also showed that a single-dose of parecoxib (20 mg/kg) reduced tubular renal
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50 284 injury and serum inflammatory cytokines level (interleukin (IL)- 1α , IL- β , IL6, and tumor
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52 285 necrosis factor (TNF)- α) in an ischemic rat model[22]. Moreover, several animal
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54 286 studies(Takaku M 2018, Feitoza CQ 2005, Feitoza CQ 2004, Candelario-Jalil E 2007)
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4 287 have suggested that pretreatment with COX-2 inhibitors improved outcomes in function
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6 288 and histology in not only the kidney but also other organs after ischemia[22-25]. To the
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9 289 best of our knowledge, this is the first clinical report to suggest that single-dose (40 mg
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11 290 or 80 mg) parecoxib may be renoprotective in patients aged 18–60 years who underwent
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14 291 non-cardiac surgery.

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17 292 The mechanism by which parecoxib decreases the risk of postoperative AKI is
18
19 293 unknown. However, one possible underlying mechanism is likely related to inflammation.
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22 294 A previous study by Murashima M et al. showed that inflammation is a predictor of
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24 295 postoperative AKI and a mediator of increased mortality after AKI in non-cardiac surgery
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27 296 [26]. However, perioperative parecoxib reduced local and systemic inflammatory
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30 297 cytokines postoperatively[27 28]. Another possible mechanism is associated with
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33 298 hemodynamic change. COX-1 contributes to controlling renal GFR, whereas COX-2 is
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35 299 involved in sodium and water excretion[7]. COX-2 inhibitors are associated with mild
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38 300 hypertension owing to modest sodium retention in the first few days of therapy[29]. The
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41 301 renoprotective mechanism of parecoxib may be related to its anti-inflammatory effects
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43 302 and sodium regulation.

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45 303 Our study had some limitations that are worth mentioning. First, this was a
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48 304 retrospective single-center observational study; thus, it may have had some selection bias.
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51 305 Second, the timing of the serum creatinine measurement was based on clinical discretion;
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54 306 thus, it may vary with different doctors. Third, we simply chose patients aged 18-60 years
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57 307 who underwent non-cardiac surgery as the target to research. Fourthly, due to the nature
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59 308 of the retrospective study, some unknown or unmeasured confounders, and those
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4 309 excluded patients who had missing data may interfere with the outcomes. Therefore, our
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6 310 results should be extrapolated cautiously.
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11 312 **Conclusions**

13
14 313 In conclusion, in non-cardiac surgery patients, a single dose of parecoxib (40 mg or 80
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16 314 mg) may be associated with a modest reduction of postoperative AKI in those aged 18–
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18 315 60 years. However, these short-term effects may not represent the benefit of this drug in
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20 316 the long term. Furthermore, more comprehensive studies are needed to confirm the effects
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22 317 of parecoxib on the risk of postoperative AKI.
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27 319 **Figure legends**

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30 320 Fig 1. Enrollment of patients undergoing non-cardiac surgery. The numbers in brackets
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32 321 represent patients excluded for the reasons described earlier.
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41 326 **Author's Contributions**

42
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44
45 328 drafting and revising the manuscript. Pingping Zeng and Yan Liao helped in collecting,
46
47 329 analyzing and interpreting the data, and drafting and revising the manuscript. Zheng Qin,
48
49 330 Hao Zhang and Bo Li helped in analyzing and interpreting the data. Wen Ouyang helped
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8
9 333 revising the manuscript.
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13
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18
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21
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30 341 **Competing interests:** The authors declare they have no competing interests.
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35 343 **Patient Consent for publication:** Not applicable.
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40 345 **Ethics approval:** This study was approved by the ethics committee of the third Xiangya
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42 346 hospital of Central South University (2020S264). Because of the observational nature of
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45 347 the study, informed consent was waived.
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50 349 **Data sharing statement:** The data used and analyzed in this study are available from
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53 350 the corresponding author on reasonable request.
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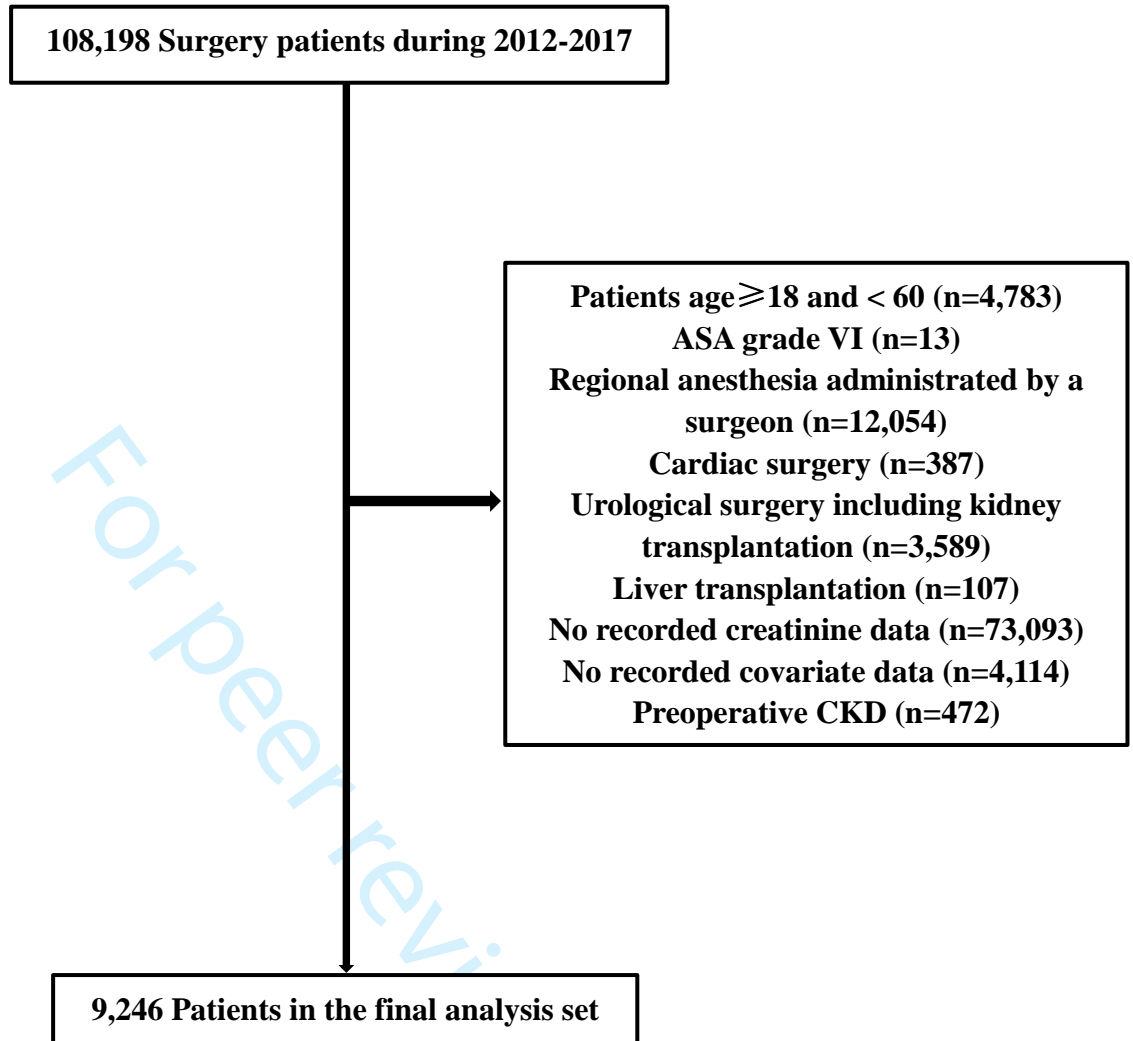


Fig 1

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			<0.001
Transfusion, mL (%)			
<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 \pm 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.