

# Comparison of Effect Sevoflurane-Based Anesthesia and Propofol-Based Anesthesia on the Early Postoperative Renal Function of Living Kidney Transplant Donors: A Randomized Controlled Trial

Jianyue Cai<sup>1,\*</sup>, Fang Kang<sup>1,\*</sup>, Mingming Han<sup>1</sup>, Xiang Huang<sup>1</sup>, Wenlong Yan<sup>1</sup>, Fuzhen Wan<sup>2,3</sup>, Juan Li<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, People's Republic of China; <sup>2</sup>Department of Gastrointestinal Surgery, The second Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China; <sup>3</sup>Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia

\*These authors contributed equally to this work

Correspondence: Juan Li, Administrative Director, Department of Anesthesia, First Affiliated Hospital of the University of Science and Technology of China, Tel +8613956005465, Email huamuzi1999@163.com

**Purpose:** Living kidney transplantation is a common treatment for end-stage renal disease. The impact of anaesthetics on post-operative biomarkers of renal injury in living kidney transplant donors is not well understood.

**Patients and Methods:** 70 transplant donors who underwent kidney extraction were randomly assigned to following two groups: sevoflurane (S group) and propofol (P group). Urine and blood were collected before induction and 1, 2, 6 days after operation. Kidney injury marker-1 (KIM-1), interleukin-18 (IL-18) and tissue inhibitor of metalloproteinase-2 (TIMP-2) were measured by enzyme-linked immunosorbent assay. Record the cystatin C, glomerular filtration rate, urine output during perioperative period.

**Results:** There were both increases in biomarkers of kidney injury before and 1, 2 and 6 days after the anaesthetic surgery in donors, However, no statistical differences in KIM-1 (P (0.42 pg/mL (95% CI 0.21 to 0.63 pg/mL)) vs S (0.26 pg/mL (95% CI 0.02 to 0.49 pg/mL)), -0.16 pg/mL (95% CI -0.48 to 0.16 pg/mL)), IL-18 (P (178.54 pg/mL (95% CI 110.15 to 24693 pg/mL)) vs S (175.86 pg/mL (95% CI 100.35 to 251.38 pg/mL)), -2.68 pg/mL (95% CI -105.61 to 100.25 pg/mL)), and TIMP-2 (P (12.88 ng/mL (95% CI 8.69 to 17.07 ng/mL)) vs S (14.85 ng/mL (95% CI 10.23 to 19.46 ng/mL)), 1.97 ng/mL (95% CI -4.30 to 8.23 ng/mL)) concentration changes between the two types of anaesthesia.

**Conclusion:** There was no difference between sevoflurane and propofol anaesthesia on postoperative changes in biomarkers of renal injury in living kidney transplant donors.

**Keywords:** general anesthetics, sevoflurane, propofol, renal transplantation

## Introduction

Kidney transplantation is an ideal treatment for end-stage renal disease.<sup>1</sup> Furthermore, the utilization of living kidney donors has been widely recognized. Over 25,000 living kidney transplants are performed globally on an annual basis.<sup>2</sup> A meta-analysis of 52 studies with 24 years of follow-up reported a significant 8.83 (95% CI 1.02–20.93) increase in the relative risk of ESRD in living kidney transplant donors.<sup>3</sup> A study conducted by Hanson et al,<sup>4</sup> which assessed the values and perceptions of living kidney donors from three transplant units in Australia and Canada, identified that the primary prognostic concern for these individuals was fear of kidney impairment. Outcomes for kidney donors may not be as benign as previously reported.<sup>5,6</sup> Short-term reduction of glomerular filtration rate after nephrectomy is a known consequence of kidney donation.<sup>7</sup>

According to Kidney Disease Improvement Global Outcomes (KDIGO), Acute kidney injury (AKI) is defined by an abrupt decrease in kidney function, focusing on the level of change in serum creatinine (Scr) over time.<sup>8</sup> Nonetheless, Scr fails to reflect the severity of the inflicted damage until AKI has attained a state of equilibrium. This necessitates the identification of new, early-stage, accurate, robust, and easily accessible markers of injury for the effective characterization and evaluation of AKI. In pursuit of early detection of renal function abnormalities, several early markers of renal injury have recently been identified.<sup>9</sup> Urinary kidney injury molecule-1 (KIM-1), Tissue inhibitor of metalloproteinases-2 (TIMP-2) and interleukin-18 (IL-18) have all been recognized to be produced in large quantities in injured renal tubular epithelial cells.<sup>10</sup> These biomarkers have shown the potential to improve diagnosis and risk stratification and provide a prognosis for patients with AKI.<sup>11</sup>

Several studies examining risk predictors of postoperative AKI suggest that the choice of general anaesthetic may have an impact on postoperative renal function.<sup>12</sup> Propofol may inhibit the development of renal fibrosis by attenuating ischemia-reperfusion injury (IRI) through its antioxidant properties.<sup>13,14</sup> A clinical examination conducted in 2014 involving cardiac surgery determined that propofol exhibited a renal-protective effect in contrast to sevoflurane.<sup>15</sup> Sevoflurane has anti-inflammatory properties and prevents acute kidney injury due to surgical stress.<sup>16</sup> Sevoflurane has been found to affect many processes in the pathophysiology of IRI in *in vitro* and *in vivo* experiments in animals. Improvement of graft outcomes after kidney transplantation.<sup>17</sup> However, there is a paucity of reports concerning the impacts of propofol or sevoflurane as general anaesthetics on postoperative renal function in kidney transplant donors.

Therefore, the primary objective of this study was to compare the effects of sevoflurane-based versus propofol-based anesthesia on postoperative levels of kidney injury biomarkers (KIM-1, TIMP-2, and IL-18) in living kidney donors. We hypothesized that propofol-based anesthesia would have lower biomarkers of kidney injury compared with sevoflurane-based anesthesia in a population of living kidney donors at a provincial medical center in China.

## Methods

### Design Overview

This study was a single center, randomized controlled clinical trial in participants who were living kidney transplant donors. Participants were recruited from January 2021 to December 2021. Informed consent was given by all participants, and the protocol was approved by the China Ethics Committee of Registering Clinical Trials (Ethical review number: ChiECRCT20200156). The trial was conducted in accordance with the Declaration of Helsinki and reported in accordance with the CONSORT 2010 guidelines. This study has been registered in the China Ethics Committee of Registering Clinical Trials (<http://www.chictr.org.cn/index.aspx>; registered id: ChiCTR2000029879). The patients' personal information was confidential to the researchers, and the study was conducted in compliance with the Declaration of Helsinki. The primary outcome of this study was to compare the effects of sevoflurane and propofol anesthesia on the expression of biomarkers such as: KIM-1 in donors on the baseline, 1<sup>st</sup>, 2<sup>nd</sup> and 6<sup>th</sup> day postoperatively.

### Setting and Participants

Recruitment was conducted by the Anhui Provincial Hospital, located in Hefei, Anhui Province, China. Each kidney transplant donor voluntarily signs informed consent to donate a donor kidney in accordance with the Declaration of Istanbul. Participants were invited to join this study after hospital admission, but before undergoing living kidney transplantation. Patients were subjected to face-to-face screening following an initial evaluation of their hospitalization records. All donors underwent open surgical procedures (Detailed surgical procedures are available in the [supplementary material SDC 1](#)). To be eligible for the study, participants must be of at least 18 years of age but no older than 65; their connection to the donor and recipient was restricted to being a spouse, an immediate family member, or a collateral relative within three generations; American Society of Anesthesiology (ASA) Physical Status Classification I–II and a body mass index (BMI) less than 30 kg/m<sup>2</sup>. Exclusion criteria included severe hypertension (graded 2 as per the 2020 guidelines promulgated by the International Society of Hypertension (ISH)), severe cardiac disease (cardiac function classification exceeding 3 according to the New York Heart Association (NYHA)), psychiatric afflictions, concurrent renal disease, and any variant of tumor.

## Randomization and Blind

Participants were apportioned to either the S group (sevoflurane) or the P group (propofol) in a 1:1 ratio, pursuant to computer-generated random numerals prepared by statisticians not associated with the trial. The group designations and patient numerals were contained within opaque, sealed envelopes that were opened by the attending anaesthetist immediately prior to the commencement of surgery. Those involved in postoperative follow-up, specimen collection, laboratory testing, and data analysis were kept oblivious to the group assignments.

## Anaesthetic Protocol

Anaesthetic and haemodynamic management were strictly protocolized. The anesthetic procedure is standardized. General anesthesia was induced with etomidate ( $0.2\text{--}0.4\text{ mg}\cdot\text{kg}^{-1}$ ), sufentanil ( $0.4\text{ ug}\cdot\text{kg}^{-1}$ ), cis-atracurium ( $0.15\text{ mg}\cdot\text{kg}^{-1}$ ) succeeded by the insertion of a laryngeal mask. Anesthesia is maintained by target-controlled infusion of propofol (effect chamber concentration target  $1.5\text{--}2.5\text{ ug}\cdot\text{mL}^{-1}$ , Marsh model) or sevoflurane (End-expiratory tidal concentration target  $0.8\text{--}2.5$  minimum alveolar concentration (MAC); fresh gas flow  $2\text{ L}\cdot\text{min}^{-1}$ ). Both groups were administered remifentanyl (effect chamber concentration target  $3\text{--}5\text{ ug}\cdot\text{mL}^{-1}$ , Minto model), sufentanil, cisatracurium general anesthesia. Intravenous oxycodone was administered half an hour before the end of the surgery for analgesia. The dosage of anesthetic drugs was modulated according to the EEG bispectral index monitoring of the depth of anesthesia (maintaining bispectral index, BIS at  $40\text{--}60$ ). Standard monitoring incorporated a five-lead ECG, pulse oximetry, invasive arterial pressure and Masimo LiDCO™ Hemodynamic Monitoring System (Masimo Corporation, CA, USA). A Foley urinary catheter was inserted post-induction of anesthesia, and all patients received goal-directed fluid therapy (less than 20% change in blood pressure and SVV < 13%) with the option of crystalloid rehydration. Intraoperative rehydration with sodium lactate solution. If required, phenylephrine was administered for hypotension. All clinical parameters and medications were recorded by patient monitoring software (Medicalsystem Co, Ltd. China). Intraoperative doses of various anesthetics used and invasive kinetic indices such as MAP, SVR, SVV, CO were recorded. Immediately after surgery, the patient was transferred to the post-anesthesia care unit (PACU), where standardized recovery protocols were followed. Once the patient met established extubation criteria—such as adequate spontaneous ventilation, stable hemodynamics, and appropriate oxygen saturation—extubation was performed under the close supervision of the PACU team.

## Sample Measurements

A total of 70 patients were initially recruited; however, 8 patients were excluded due to withdrawal of consent, not receiving the assigned intervention, or loss to follow-up. Thus, 62 patients were included in the final analysis. Considering the low response of participants and the limitations of the resources invested in this trial, we did not choose a continuous sampling method for recruiting participants.

Blood specimens were collected from patients before the procedure, on the first day postoperatively, on the second day postoperatively as and on the sixth day postoperatively. Blood samples were collected into two test tubes, one EDTA anticoagulation tube and one isolated gel procoagulant tube and tested in the hospital biochemistry laboratory within 24 hours. Urine samples were collected at the same time points as above and centrifuged (2700 rpm for 20 min) and the supernatant was collected and stored in a  $-80$ -degree refrigerator.

Urine samples collected pre-surgery, and on days 1, 2, and 6 post-surgery, were analyzed using the Enzyme-Linked Immunosorbent Assay (ELISA; DL-TIMP2-Hu, DL-Kim1-Hu, and DL-IL-18-Hu, DL-develop Systems, Wuxi, China) to measure the concentrations of TIMP-2, KIM-1, and IL-18 (Detailed in the [Supplementary material SDC 2](#)). Hemoglobin, blood creatinine, uric acid and cysteine protease inhibitors were tested within 24 hours of samples collection in the biochemistry laboratory of the First Hospital of the University of Science and Technology of China. The definitions and descriptions of the variables in the study are detailed in [Supplementary Material Table S1](#).

## Sample Size Calculation

We calculated the sample size based on primary outcome KIM-1 data from previous randomized controlled trial.<sup>18</sup> In the PASS 15 software, we used the “Tests for Two Means in a Repeated Measures Design” module (Detailed in the

[Supplementary material SDC 3](#)). In a design with four repeated measurements, we suspected a sequence of mean differences of 0,60,500,90 ng/mL, with a common SD within the group of 90 ng/mL. We needed 27 patients per group (significance level of 0.05, power of 90%). Considering the possible staff mobility restrictions resulting from the dynamic zero-case policy implemented in China during COVID-19,<sup>19</sup> we presupposed a 30% lost to follow-up rate and enrolled n=40 each group.

## Statistical Analysis

All data analyses were performed on the basis of the original allocation group. Analyses were performed by using Stata, version 15 (StataCorp). A p value less than 0.05 was deemed statistically significant. Continuous data were tested for normality with the use of the Shapiro–Wilk test. Values are given as the mean (standard deviation, SD) or mean (95% confidence intervals). For normally distributed variables, Student's *t*-tests were used. For normally distributed data not satisfying homogeneity of variance, Welch *t*-test were used. If variables were not normally distributed, the Mann–Whitney *U*-test was applied.

TIMP-2, KIM-1, IL-18, haemodynamic indicators, Cys-C, estimated glomerular filtration rate (eGFR), uric acid (UA) and urine volume were compared by using a repeated-measures mixed-effects linear regression model with terms of anesthesia methods, time, and corresponding baseline values as covariates (in addition to age, sex, and body mass index). Due to the multiple comparisons involved in the statistical analysis of this section; in order to reduce Type I error, we employ the Bonferroni correction method to control the relevant significance thresholds. We additionally constructed a model adjusted for the dosage of sufentanil as a confounder, these results are displayed in [Supplementary Material Table S2](#) of the Supplementary Material. The correlation within the repeated measures was addressed by using individual participant identification as a random effect. The effect of anaesthesia at baseline and days 1, 2 and 6 was evaluated by adding an intervention-by-time interaction to the models.

## Results

From January 2021 to December 2021, 80 kidney transplant donors accepted the invitation to participate in the study. Consequently, a total of 62 donors were eligible for follow-up ([Figure 1](#). Consort diagram).

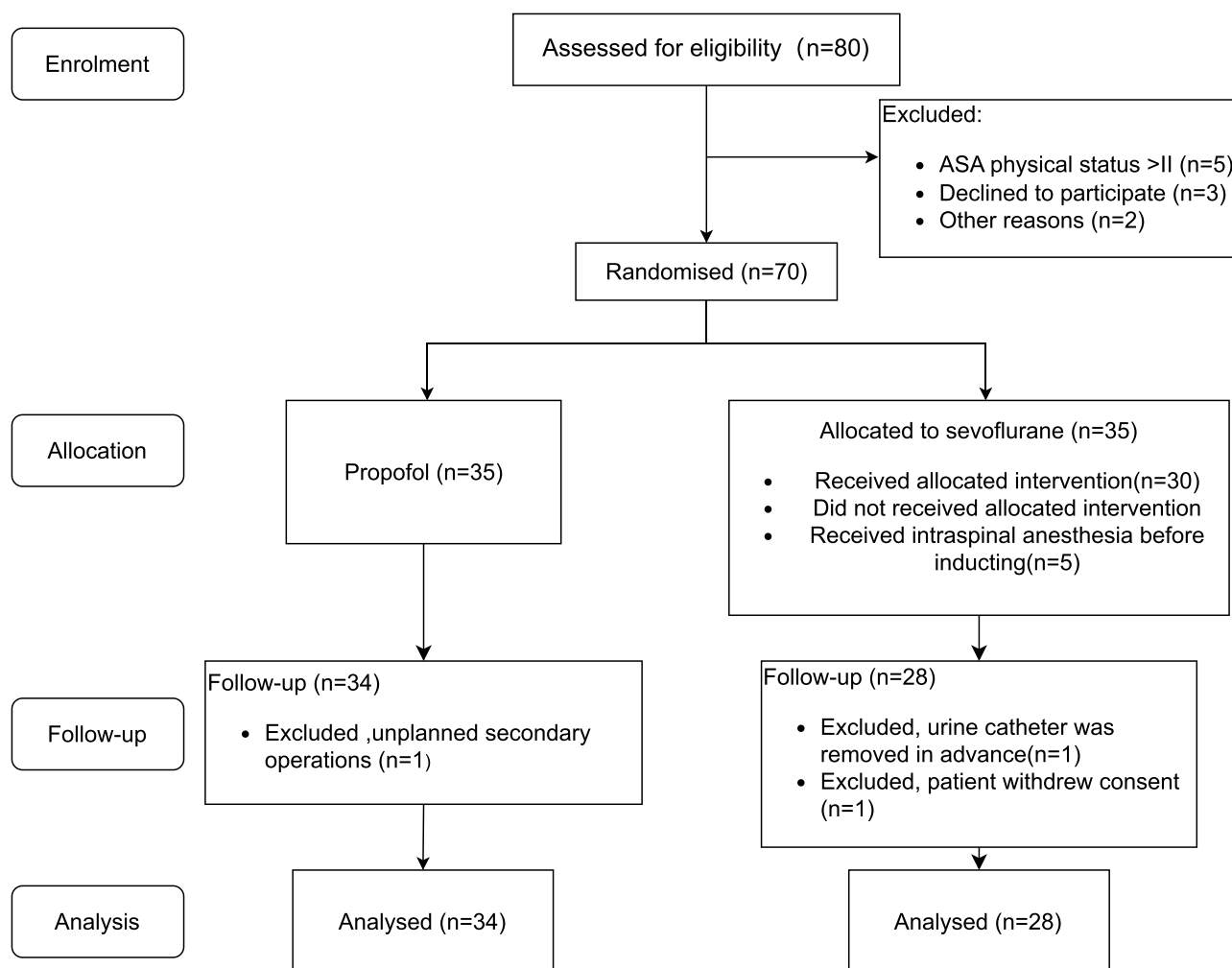
## Patients

[Table 1](#) summarises the characteristics of the two groups of living kidney transplant donors. The donors are mainly a relatively healthy middle-aged population (P (55.3(8.5)) vs S (55.7(8.9)), [Table 1](#)). The most common comorbidities are hypertension (P (10(34)) vs S (8(28)), [Table 1](#)). In some donors with combined diabetes mellitus and asymptomatic lacunar cerebral infarction. Specifically, one donor in the propofol group and three donors in the sevoflurane group with co-morbid diabetes, and three donors in both groups had asymptomatic lacunar cerebral infarction.

## Intraoperative Parameters and Anaesthesia

The parameters of intraoperative and postoperative clinical relevance for the two groups of donors are summarized in [Table 2](#). There was no statistical difference between the two donor groups in terms of and anesthetic time (P (145.5 (24.6)) vs S (150.5(18.6)),  $P=0.385$ ; [Table 2](#)) and operative time (P (120.3(21.0)) vs S (124.3(20.3)),  $P=0.460$ ; [Table 2](#)). In addition to this, during the maintenance phase of general anesthesia, the doses of remifentanyl (P (957.8(308.4)) vs S (899.5(178.1)),  $P=0.837$ ; [Table 2](#)) and cis-atracurium (P (24.5(5.8)) vs S (23.4(4.4)),  $P=0.395$ ; [Table 2](#)) used did not differ statistically between the two groups. A higher dose of phenylephrine was applied to maintain blood pressure in donors anaesthetized with sevoflurane compared to those anaesthetized with propofol (P (296.8(415.2)) vs S (903.2 (650.1)),  $P=0.001$ ; [Table 2](#)). At the same time, the dose of sufentanil was higher in the sevoflurane group than in the propofol group (P (27.4(6.6)) vs S (33.9(9.0)),  $P=0.002$ ; [Table 2](#)).

Crystalloid solutions were selected for rehydration in all study groups, adjusted for pre-set haemodynamic parameters, and the results showed no statistical difference in intraoperative fluid input between the two groups (P (1857.9 (451.1)) vs S (2005.4(415.7)),  $P=0.190$ ; [Table 2](#)). There was no statistically significant difference in the degree of intraoperative haematocrit decline between the two groups and we approximated that the degree of intraoperative blood



**Figure 1** Consort diagram of recruitment and inclusion of subjects throughout the study protocol (that is, enrolment, allocation of interventions, follow-up, and data analysis): 80 kidney transplant donors were assessed for eligibility. Of those 80, three donors did not give informed consent, five donors with ASA grading higher than grade 2, and two donors participated in other clinical studies. Therefore, 70 donors were randomly divided into two groups. In the propofol group, one donor was excluded because he underwent an unplanned secondary operation. In the sevoflurane group, five donors who received combined epidural anesthesia at the same time did not receive the assigned intervention, and two donors were excluded because no follow-up data were collected or withdrew from the study. Consequently, a total of 62 donors were eligible for follow-up.

loss was similar ( $P$  (7.2(5.9)) vs S (9.4(4.9)),  $P=0.119$ ; Table 2). Intraoperative urine output did not differ ( $P$  (823.5 (255.9)) vs S (948.2(324.7)),  $P=0.096$ ; Table 2). In summary, there were no statistical differences in intraoperative fluid intake and output between the two groups.

## Urine Markers of Acute Kidney Injury

Urine was collected from donors 1 hour before surgery, and days 1, 2 and 6 after surgery and measured for TIMP-2, KIM-1 and IL-18 concentrations. The mean changes and trends in concentration for each group at different time points are displayed in Figure 2. There was a significant increase in these acute kidney injury biomarkers after nephrectomy. The increase in TIMP-2 was greater in the sevoflurane (14.85 ng/mL (CI 10.23 to 19.46 ng/mL)) anesthesia groups compared to the propofol (12.88 ng/mL (CI 8.69 to 17.07 ng/mL)) anesthesia group, although this difference was not statistically significant (1.97 ng/mL (CI -4.30 to 8.23 ng/mL)) (Table 3 and Figure 2A). No differences were seen in Kim-1, or IL-18 concentrations changes between the two groups (Table 3 and Figure 2).

**Table 1** Baseline Characteristics of Donors

	P(n=34)	S(n=28)
Age (year)	55.3 ± 8.5	55.7 ± 8.9
Male (n (Ratio))	8 (8:26)	4 (4:24)
High (cm)	157.9 ± 6.8	159.5 ± 5.3
Weight (kg)	61.5 ± 7.5	61.9 ± 8.7
BMI (kg/m <sup>2</sup> )	24.5 ± 2.3	24.3 ± 2.9
ASA (n)		
I	20	14
II	14	14
III	0	0
IV	0	0
Complications (n)		
Hypertension	10	8
Diabetes	1	3
Heart disease	0	0
Cerebrovascular disease	3	3
Smoking (n)	3	0
Relation (n)		
Parent-child	32	27
Couples	2	1

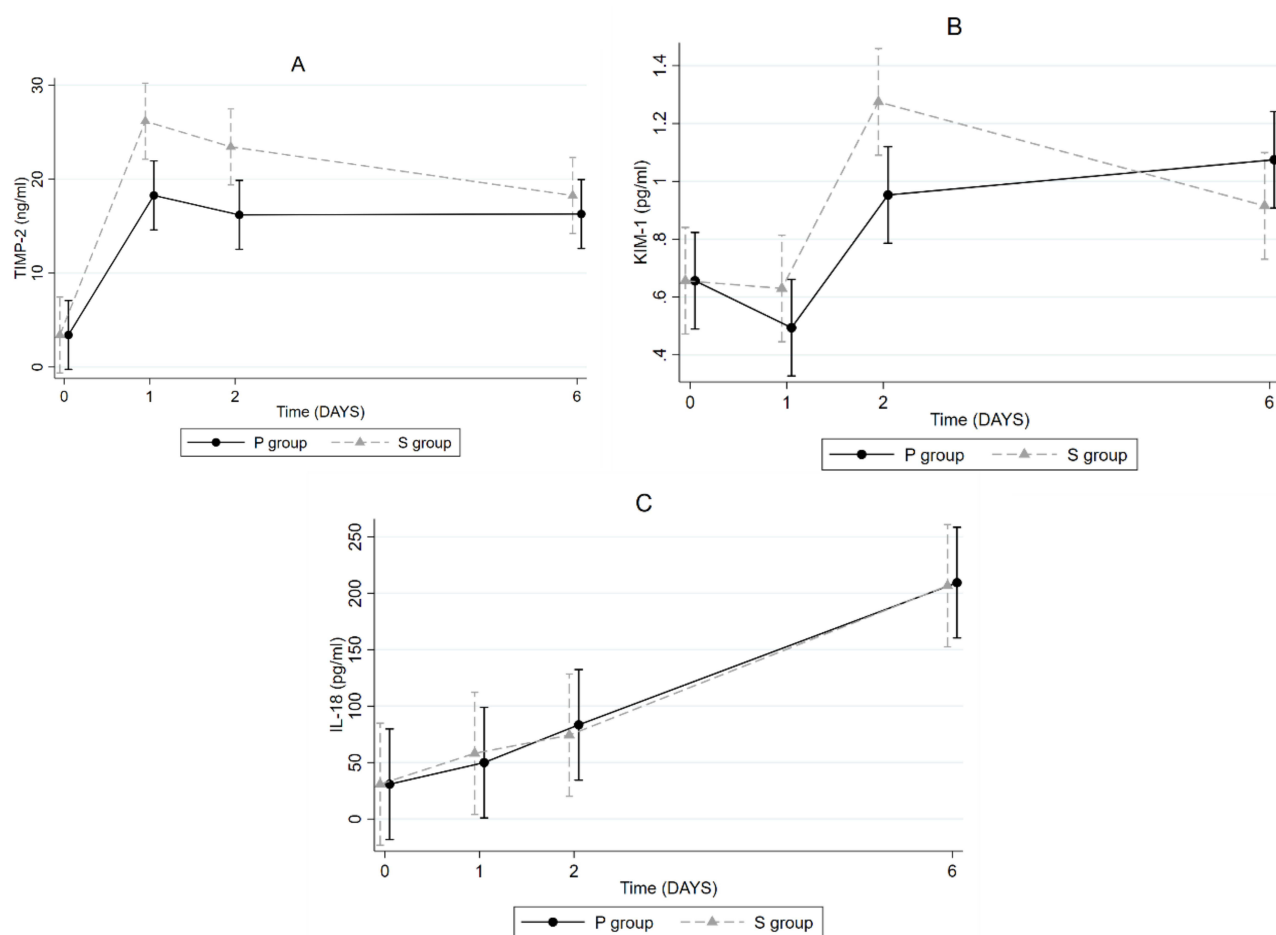
**Notes:** Groups are follows: P (the propofol group) and S (the sevoflurane group). Data are presented as the mean ± SD or n.

**Table 2** Intraoperative and Postoperative Parameters

	P(n=34)	S(n=28)	P
Propofol (ug mL <sup>-1</sup> )	2.1 ± 0.2	–	–
Sevoflurane (%) concentration	–	2.1 ± 0.2	–
Phenylephrine (ug)	80 [0 to 600]	750 [460 to 1200]	<0.001 <sup>#</sup>
Sufentanil (ug)	27.4 ± 6.6	33.9 ± 9.0	0.002
Remifentanil (ug)	875 [750 to 1200]	900 [750 to 1050]	0.357*
Cisatracurium (mg)	24.5 ± 5.8	23.4 ± 4.4	0.395
Oxycodone (mg)	5 [5 to 5]	5 [5 to 5]	0.196 <sup>#</sup>
Operation time (min)	120.3 ± 21.0	124.3 ± 20.3	0.460
Anesthesia time (min)	145.5 ± 24.6	150.5 ± 18.6	0.385
PACU (min)	51.9 ± 10.9	52.0 ± 12.1	0.958
Discharge time (d)	12.1 ± 1.6	12.2 ± 1.7	0.726
Infusion (mL)	1857.9 ± 451.1	2005.4 ± 415.7	0.190
Urine output (mL)	823.5 ± 255.9	948.2 ± 324.7	0.096
PONV (n(%))	10/34	7/28	0.770 <sup>#</sup>
PreHb (g/l)	124.1 ± 10.9	124.4 ± 10.2	0.930
PostHb (g/l)	116.9 ± 11.5	115.0 ± 10.4	0.490
DeHb (g/l)	7.2 ± 5.9	9.4 ± 4.9	0.119
eGFR (baseline)	105.8 ± 28.1	105.6 ± 28.4	0.983

**Notes:** Groups are follows: P (the propofol group) and S (the sevoflurane group). Data are presented as the mean ± SD or median [25% to 75% interquartile range], with the P representing the significance level for differences between propofol and sevoflurane anaesthesia (Normally distributed data meet homogeneity of variance using the independent samples t-test, <sup>#</sup>means non normally distributed data using Mann Whitney test, \* means not satisfying homogeneity of variance using Welch t-test).

**Abbreviations:** DeHb, Decreased haemoglobin; PACU, postanesthesia care unit; PONV, Postoperative Nausea and Vomiting, Discharge time, postoperative discharge time from hospital; PreHb, Pre-operative hemoglobin; PostHb, Post-operative hemoglobin. eGFR (baseline), Pre-operative estimated glomerular filtration rate measured with Cockcroft-Gault equation. The concentration of sevoflurane is the concentration at which the volatile tank is opened during the operation.



**Figure 2** Urine biomarkers of acute kidney injury: The influence of propofol and sevoflurane groups on changes in biomarker concentrations of postoperative acute kidney injury. **(A):** The levels of TIMP-2 in both the propofol group and the sevoflurane group showed a significant increase on the first day after surgery, followed by a gradual decrease. The graph shows that the increase in the sevoflurane group exceeded that of the propofol group, but there was no statistically significant difference in the trend of changes between the two groups. **(B):** On the first day after surgery, the level of Kim-1 decreased or stabilized, then significantly increased on the second day, and subsequently stabilized. However, there was no statistical difference between the two groups. **(C):** After the surgery, the level of IL-18 in both the propofol group and the sevoflurane group showed a continuous upward trend, with no statistically significant difference between the changes in the two groups.

## Changes in Blood Biochemical Parameters and Urine Output

Postoperative eGFR and uric acid decreased significantly irrespective of the anesthesia used. However, the degree of decrease in eGFR ( $-1.00 \text{ mL/min} / (1.73\text{m})^2$  (CI  $-5.98$  to  $3.97 \text{ mL/min} / (1.73\text{m})^2$ ) and uric acid ( $-8.38 \text{ umol/l}$  (CI  $-29.27$  to  $12.51 \text{ umol/l}$ ) did not differ statistically between the two groups (Table 3, Figure 3). There was no statistical differences between the two anesthesia groups in the changes in perioperative Cys-C ( $-0.01\text{mg/l}$  (CI  $-0.08$  to  $0.06 \text{ mg/l}$ )). Urine output decreased on the second day of the first postoperative day compared to the intraoperative day, regardless of the anesthetic used, and the degree of change did not differ statistically between groups ( $-0.26 \text{ mL/kg/h}$  (CI  $-0.56$  to  $0.05 \text{ mL/kg/h}$ ) (Table 3, Figure 3).

## Intraoperative Haemodynamic Indices

Intraoperative hemodynamic parameters remained relatively stable in both groups. Changes in SVV were minimal and not significantly different between the propofol anaesthesia group (0.14% (95% CI,  $-0.97$  to  $1.26\%$ )) and the sevoflurane anaesthesia group (0.94% (95% CI 0.06 to  $1.86\%$ )), with an estimated between-group difference of 0.80% (95% CI,  $-0.64$  to  $2.24\%$ ) (Table 3 and Figure 4C). Similarly, the decrease in MAP was slightly more pronounced in the sevoflurane group ( $-0.88 \text{ mmHg}$  (95% CI  $-5.49$  to  $3.73 \text{ mmHg}$ )) compared to the propofol group ( $1.87 \text{ mmHg}$  (95% CI  $-2.30$  to  $6.05 \text{ mmHg}$ )), but this difference was not statistically significant ( $-2.75 \text{ mmHg}$  (95% CI  $-9.00$  to

**Table 3** Donors' Clinical Follow-up Outcomes

	<b>P Group (n=34)</b> Mean Change (95% CI)	<b>S Group (n=28)</b> Mean Change (95% CI)	<b>Mean Between-group Difference</b> <b>in Change (95% CI)</b>
PPrimary outcome			
KIM-1 (pg mL <sup>-1</sup> )	0.42 (95% CI 0.21 to 0.63)	0.26 (95% CI 0.02 to 0.49)	-0.16 (95% CI -0.48 to 0.16)
Secondary outcome			
TIMP-2 (ng mL <sup>-1</sup> )	12.88 (95% CI 8.69 to 17.07)	14.85 (95% CI 10.23 to 19.46)	1.97 (95% CI -4.30 to 8.23)
IL-18 (pg mL <sup>-1</sup> )	178.54 (95% CI 110.15 to 246.93)	175.86 (95% CI 100.35 to 251.38)	-2.68 (95% CI -105.61 to 100.25)
MAP (mmHg)	1.87 (95% CI -2.30 to 6.05)	-0.88 (95% CI -5.49 to 3.73)	-2.75 (95% CI -9.00 to 3.49)
SVR (dyn s cm <sup>-5</sup> )	249.93 (95% CI 135.04 to 364.82)	218.19 (95% CI 103.30 to 333.08)	-31.74 (95% CI -195.09 to 131.61)
SVV (%)	0.14 (95% CI -0.97 to 1.26)	0.94 (95% CI 0.06 to 1.86)	0.80 (95% CI -0.64 to 2.24)
CO (L min <sup>-1</sup> )	-0.42 (95% CI -0.76 to -0.08)	-0.38 (95% CI -0.65 to -0.11)	0.04 (95% CI -0.40 to 0.48)
Cys-C (mg L <sup>-1</sup> )	0.29 (95% CI 0.24 to 0.34)	0.28 (95% CI 0.23 to 0.33)	-0.01 (95% CI -0.08 to 0.06)
eGFR (mL min <sup>-1</sup> (1.73m) <sup>-2</sup> )	-35.44 (95% CI -38.76 to -32.12)	-36.44 (95% CI -40.11 to -32.78)	-1.00 (95% CI -5.98 to 3.97)
UA (umol L <sup>-1</sup> )	-23.63 (95% CI -37.60 to -9.66)	-32.01 (95% CI -47.41 to -16.60)	-8.38 (95% CI -29.27 to 12.51)
Urine output (mL kg <sup>-1</sup> h <sup>-1</sup> )	-3.80 (95% CI -4.01 to -3.60)	-4.06 (95% CI -4.29 to -3.83)	-0.26 (95% CI -0.56 to 0.05)

**Note:** Haemodynamic indices during anaesthesia, presented as mean (95% confidence intervals).

**Abbreviations:** CO, cardiac output; eGFR, estimated glomerular filtration rate measured with Cockcroft-Gault equation; IL-18, interleukin-18; KIM-1, kidney injury marker-1; MAP, mean arterial pressure; TIMP-2, tissue inhibitor of metalloproteinase-2; UA, uric acid; SVR, systemic vascular resistance; SVV, stroke volume variation. Regression analysis was conducted using a repeated-measures mixed-effects linear regression model.

3.49mmHg)) (Table 3 and Figure 4A). Although the sevoflurane anaesthesia group required more phenylephrine to maintain blood pressure (Table 2,  $P < 0.01$ ), no statistically significant differences were observed in SVR or CO between the two groups (Table 3 and Figure 4). These results suggest that intraoperative hemodynamic stability was effectively maintained regardless of the anaesthetic regimen used.

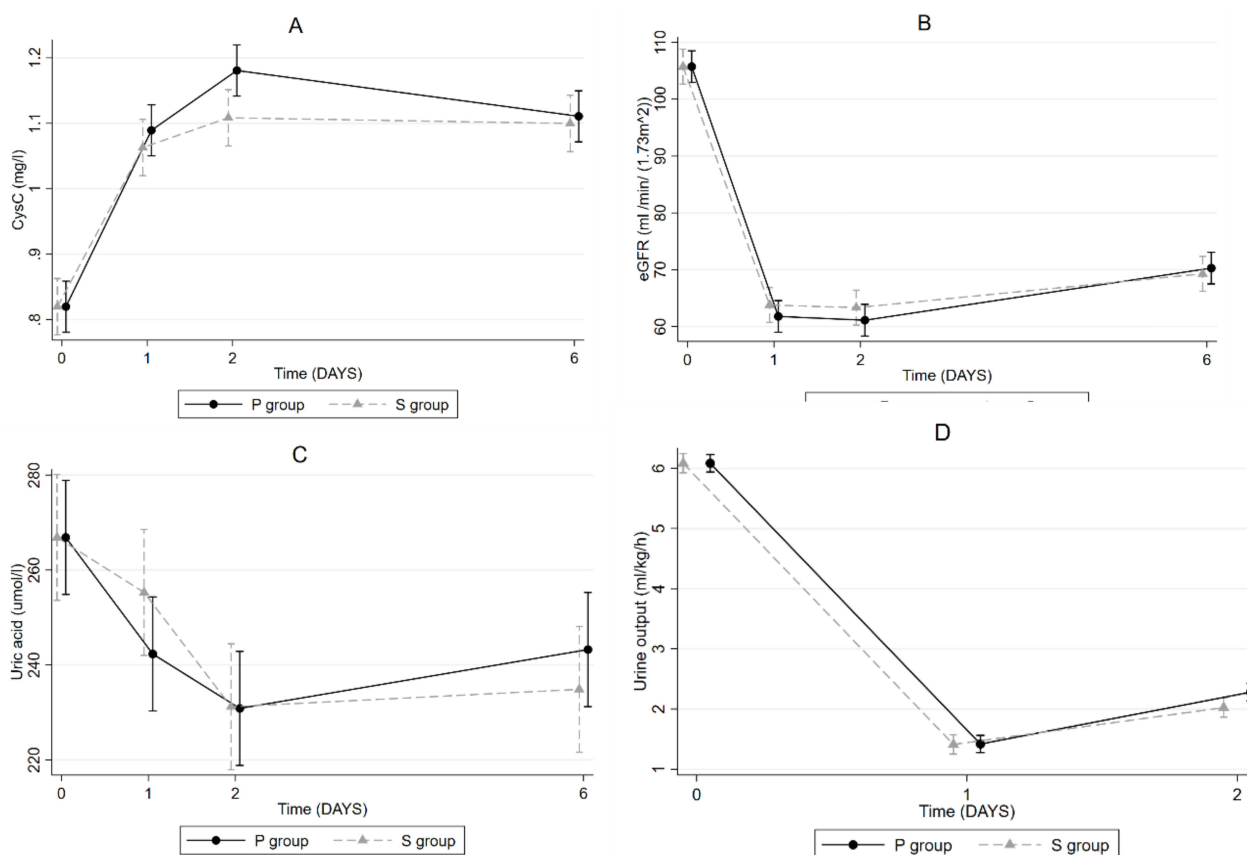
## Discussion

In this randomized controlled study, we explored the effects of propofol or sevoflurane anesthesia on renal function and biomarkers of AKI in living kidney transplant donors. Previous studies have shown that volatile anesthetics can lead to decreased eGFR and urine output. For example, sevoflurane decreased urine output in patients undergoing colorectal surgery.<sup>20</sup> In heart valve surgery, sevoflurane anesthesia prolonged the postoperative use of the diuretics compared to propofol anesthesia. However, there was no statistical difference in postoperative changes in biomarkers of acute kidney injury between the two groups.<sup>15</sup> In VAPOR-1 study, both donors and recipients were anesthetized with sevoflurane, and KIM-1 concentrations on postoperative day 2 were significantly higher than those in the control group, but were not associated with inferior graft outcomes. In spinal surgery, there was no statistical difference between the groups in the effect of choosing sevoflurane or propofol anesthesia on postoperative changes in urinary KIM-1.<sup>18,21</sup> Similarly, we found no statistical difference between the two groups in the postoperative changes in renal injury biomarkers, blood creatinine, and urine output, regardless of the anesthesia chosen.

In our study, we found a significant increase in TIMP-2 secretion in the urine after nephrectomy. TIMP-2 is a recently identified positive biomarker for the early diagnosis of AKI and involved in G1 cell-cycle arrest. The biomarker was initially found to predict AKI in the Discovery study, a multicenter cohort study of critically ill patients at risk for AKI and were validated in the Sapphire study.<sup>22</sup> Insulin growth factor-binding protein 7 (IGFBP7), is also a marker of renal stress associated with cell cycle arrest. It has been bundled with TIMP-2 in a number of clinical trials. Risk stratification according to different [TIMP-2] \* [IGFBP-7] thresholds has been assessed for the prevention of AKI in high-risk patients, but results obtained from different studies have been inconsistent.<sup>23–25</sup> [TIMP-2] \* [IGFBP-7] is mostly used in patients with severe renal impairment in the intensive care unit and may be needed to evaluate general low-risk patients from other perspectives.<sup>26</sup> We observed a higher TIMP-2 rising curve in the sevoflurane group than in the propofol group. However, the longitudinal comparison did not show any statistical difference in the trends between the two groups.

Normally, levels of KIM-1 are low, and KIM-1 can be found in proximal tubular epithelial cells 48 hours after the onset of ischemia-reperfusion injury.<sup>27</sup> It has been approved for use in animal and clinical studies to identify and monitor

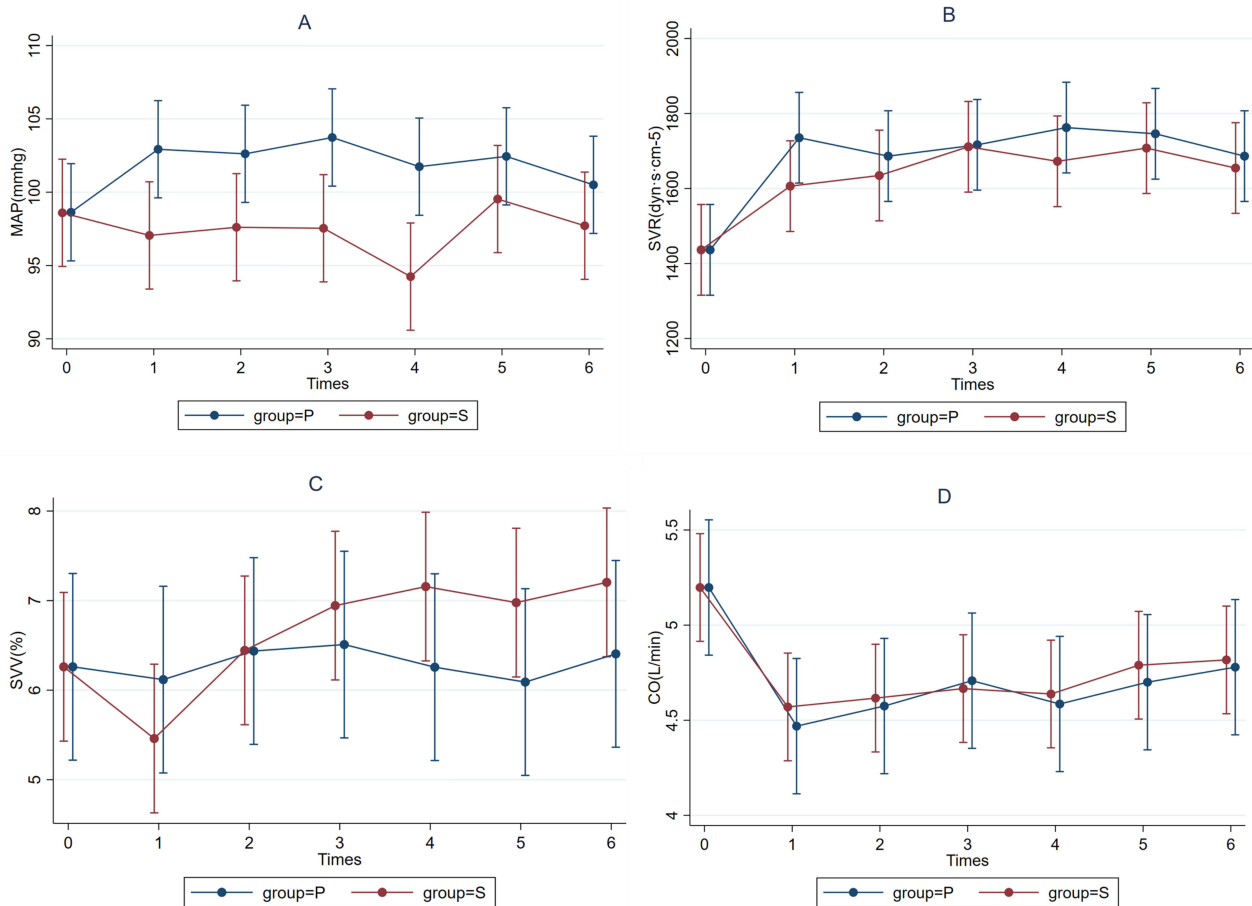




**Figure 3** The influence of propofol and sevoflurane groups on postoperative renal function blood biochemical parameters and urine output. **(A):** After the surgery, the levels of cystatin C in donor plasma significantly increased and then slowly decreased, while there was no statistically significant difference in this change between the two groups. **(B):** Donors in the propofol group or the sevoflurane group showed a significant decrease in postoperative eGFR levels, which then gradually increased, with no statistically significant difference in the trend between the two groups. **(C):** The levels of uric acid in both donor groups decreased after surgery and then slowly rebounded, with no significant statistical difference between the changes in the two groups. **(D)** The propofol group and the sevoflurane group experienced a significant decrease in urine output on the first day after surgery, followed by an increase on the second day compared to the first day, with no statistical difference between the two groups.

renal tubular injury.<sup>28</sup> In a study including 4750 patients followed for over 10 years, raised KIM-1 levels might help connected with a decrease in eGFR, proposing that this biomarker might be utilized to foresee renal capacity decay in solid moderately aged patients.<sup>29</sup> Similarly, the subjects of our study were middle-aged people with a mean age of 55 years, all of whom had a significant increase in urinary KIM-1 within 2 days of nephrectomy. KIM-1 mediates phagocytosis of apoptotic cells and oxidized lipids by renal proximal tubular cells (PTCs), and its long-term expression leads to progressive renal fibrosis and chronic renal failure.<sup>30,31</sup> In addition to its role in phagocytosis, a recent study in a KIM-1 transgenic mouse model demonstrated that KIM-1 exerts anti-inflammatory effects through interaction with p85 and subsequent phosphatidylinositol 3-kinases (PI3K)-dependent downregulation of nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B). KIM-1 may protect the kidney after acute injury by down-regulating innate immunity and inflammation.<sup>32</sup> This suggests that KIM-1 can be used not only as a standard for kidney injury but that his changes also indicate the repair process of kidney injury. We observed that KIM-1 secretion peaked at 48 hours postoperatively. In particular, KIM-1 expression in the sevoflurane anesthesia group declined rapidly after 48 hours, which may imply that the repair of the injury has been completed, but longer follow-up is needed to demonstrate this.

We found a sustained and significant increase in IL-18 in the urine of the donor after nephrectomy. However, there was no significant difference between the two anesthetic groups. The hallmarks of AKI are inflammation and renal tubular cell death. Interleukin 18 (IL-18) is synthesized as an inactive precursor at multiple sites, including bone marrow-derived macrophages, proximal tubular epithelial cells, and intercalated cells in the collecting duct.<sup>33</sup> IL-18 is cleaved by caspase-1 and released into the renal tubular lumen and serum, leading to neutrophil infiltration and tubular damage.<sup>34</sup> In an observational study of AKI



**Figure 4** Intraoperative haemodynamic indices. **(A):** Changes in mean arterial pressure (MAP) at half-hour intervals from the start of surgery in both groups. The decrease in MAP was greater in the sevoflurane ( $-0.88$  mmHg (95% CI  $-5.49$  to  $3.73$  mmHg)) anaesthesia groups compared to the propofol ( $1.87$  mmHg (95% CI  $-2.30$  to  $6.05$  mmHg)) anaesthesia group, although this difference was not statistically significant ( $-2.75$  mmHg (95% CI  $-9.00$  to  $3.49$  mmHg)). **(B):** Changes in systemic vascular resistance (SVR) at half-hour intervals after the start of surgery in both groups. The SVR fluctuated relatively smoothly between the two groups during the procedure, and there was no statistical difference between the two groups. **(C):** Changes in stroke volume variation (SVV) at half-hour intervals between the two groups after the start of surgery. Intraoperative changes in SVV were small in both the propofol anaesthesia groups ( $0.14\%$  (95% CI,  $-0.97$  to  $1.26\%$ )) and the sevoflurane anaesthesia groups ( $0.94\%$  (95% CI  $0.06$  to  $1.86\%$ )), and there were no statistical differences ( $0.80\%$  (95% CI  $-0.64$  to  $2.24\%$ )) between the groups. **(D):** Changes in cardiac output (CO) at half-hour intervals between the two groups after the start of surgery. After the start of surgery, CO began to decrease significantly in the propofol anaesthesia group and then leveled off afterwards ( $-0.42$  mg L<sup>-1</sup> (95% CI  $-0.76$  to  $-0.08$  mg L<sup>-1</sup>)), and the trend of change was the same in the sevoflurane anaesthesia group ( $-0.38$  mg L<sup>-1</sup> (95% CI  $-0.65$  to  $-0.11$  mg L<sup>-1</sup>)), and there was no statistical difference between the two groups ( $0.04$  mg L<sup>-1</sup> (95% CI  $-0.40$  to  $0.48$  mg L<sup>-1</sup>)).

associated with cardiac surgery, IL-18 was found to be an independent predictor of the development of AKI after weaning from cardiopulmonary bypass.<sup>35</sup> Urinary IL-18 as an early diagnostic indicator of AKI has been associated with mortality after cardiac surgery and in the ICU setting.<sup>36,37</sup> In difference to the changes in other markers of kidney injury, we observed that the secretion of IL-18 has been elevated after surgery, with no tendency to decrease. This is probably because he is not only a marker of kidney injury, but also a pro-inflammatory factor. Implying a persistent presence of perioperative anti-inflammatory, immune function recovery in the body. Several studies have shown that by inhibiting IL-18 can improve the prognosis of kidney inflammation, fibrotic injury and is a new therapeutic target.<sup>38–40</sup>

The biomarkers TIMP-2, KIM-1, and IL-18 are sensitive markers that mainly indicate tubular damage and therefore help in the diagnosis of intrinsic AKI. Perioperative eGFR reflects renal hypoperfusion and our study found a decrease in eGFR in both donors postoperatively, but there was no difference between the two types of anesthesia. This is also consistent with the fact that there were also no differences in intraoperative mean arterial pressure changes between the two groups. A recent study has shown that sevoflurane increases renal sympathetic nerve activity and plasma renin, resulting in decreased urine output, sodium excretion and renal blood flow.<sup>41</sup> However, the effect of propofol on renal

excretion and plasma renin was less pronounced.<sup>42</sup> In a randomized controlled trial of spinal surgery, sevoflurane anesthesia was found to reduce urinary output and sodium excretion more significantly than propofol anesthesia, with higher postoperative plasma creatinine.<sup>21</sup> Although levels of sodium excretion were not tested, there was no difference in the intraoperative and postoperative changes in urine output between patients receiving both sevoflurane and propofol anesthesia in our study. We used goal-directed fluid therapy, which may account for the different results from other studies. Therefore, we suggest that intraoperative fluid management and hemodynamic stabilization may perhaps be more important for the prognosis or surgical patients than the choice of anesthetic.

The strengths of this study include measurements in a controlled clinical setting, in the perioperative period, in a homogeneous group of patients. Group undergoing the same type of surgery. This reduced inter- and intra-group variability. And the present study used longitudinal data collection for the primary outcome observation in an attempt to observe a pattern of dynamic change in perioperative outcome variables, which differs from the cross-sectional associations observed in previous studies.<sup>18,21</sup> However, our study also had some limitations. This study only observed patients on postoperative day 6 and may still not be representative of long-term postoperative changes in renal function, which will be further investigated in future follow-ups. Most relative donors in this study were parents donating to their children. Caution should be advised in applying/extrapolating the findings of this study to other populations. Due to the low donor attention and lack of data in this field, experimental designs such as sample size calculations were derived based on limited experimental data. Future studies with larger sample sizes and longer time spans may be needed to verify the sustainability of this variable relationship over a longer time frame. Last but not least, considering the context of the COVID-19 pandemic, none of the participants in this study had a history of developing or having developed COVID-19 during their participation in the study. The conclusions of this study should be limited to a situation in which there is no effect of COVID-19.

## Conclusion

There were no differences in the short-term postoperative changes in biomarkers of acute kidney injury in kidney transplant donors receiving intravenous anesthesia with propofol or inhalation anesthesia with sevoflurane, nor did they show a differential decrease in postoperative urine output and eGFR. Our study shows that renal dysfunction in patients undergoing nephrectomy surgery under sevoflurane anesthesia is similar to that in patients under sevoflurane anesthesia in short-term longitudinal changes.

## Abbreviations

AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; KIM-1, kidney injury marker-1; IL-18, interleukin-18; TIMP-2, tissue inhibitor of metalloproteinase-2; Cys-C, cystatin C; eGFR, estimated glomerular filtration rate; Scr, serum creatinine.

## Data Sharing Statement

Individual deidentified participant-level data underlying the results reported in this article, as well as the study protocol and statistical analysis plan, will be made available upon reasonable request. Data are available beginning 3 months after online publication and for up to 24 months thereafter. To request data, please contact the corresponding author (Dr. Juan Li). Requests must include a methodologically sound proposal, and approval will be at the discretion of the study investigators.

## Ethics Approval and Informed Consent

This trial was registered retrospectively on China Ethics Committee of Registering Clinical Trials (<https://www.chictr.org.cn/index.html>; registered id: ChiCTR2000029879). Registered on 16 February 2020, the recruitment started in January 2021 and closed in December 2021. Informed consent was given by all participants and the protocol was approved by the Chinese Ethics Committee of Registering Clinical Trials (Ethical review number: ChiECRCT20200156; Chairperson Prof. Taixiang Wu) on June 26, 2020. The trial was performed in accordance with the Declaration of Helsinki and updated CONSORT 2010 guidelines for reporting randomized clinical trials.

## Acknowledgments

Authors would like to thank all the participants and their families; We also thank the team for cohort coordination and data collection.

## Funding

This work was supported by the Fundamental Research Funds for Central Universities of the University of Science and Technology of China (grant number: WK9110000059).

## Disclosure

The authors declare no conflicts of interest in this work.

## References

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med.* 1999;341(23):1725–1730. doi:10.1056/NEJM199912023412303
2. global observatory on donation and transplantation: kidney transplants. 2020. Available from: <http://www.transplant-observatory.org/countkidney/>. Accessed July 2, 2022.
3. O’Keeffe LM, Ramond A, Oliver-Williams C, et al. Mid- and long-term health risks in living kidney donors: a systematic review and meta-analysis. *Ann Intern Med.* 2018;168(4):276–284. doi:10.7326/M17-1235
4. Hanson CS, Chapman JR, Gill JS, et al. Identifying outcomes that are important to living kidney donors: a nominal group technique study. *Clin J Am Soc Nephrol.* 2018;13(6):916–926. doi:10.2215/CJN.13441217
5. Mjoen G, Holdaas H. Mid- and long-term health risks in living kidney donors. *Ann Intern Med.* 2018;169(4):265. doi:10.7326/L18-0340
6. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. *JAMA.* 2014;311(6):579–586. doi:10.1001/jama.2013.285141
7. Garg AX, Muirhead N, Knoll G, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. *Kidney Int.* 2006;70(10):1801–1810. doi:10.1038/sj.ki.5001819
8. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care.* 2013;17(1):204. doi:10.1186/cc11454
9. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. *Clin J Am Soc Nephrol.* 2015;10(1):147–155. doi:10.2215/CJN.12191213
10. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in acute kidney injury - pathophysiological basis and clinical performance. *Acta Physiol.* 2017;219(3):554–572. doi:10.1111/apha.12764
11. Wen Y, Parikh CR. Current concepts and advances in biomarkers of acute kidney injury. *Crit Rev Clin Lab Sci.* 2021;58(5):354–368. doi:10.1080/10408363.2021.1879000
12. Motayagheni N, Phan S, Eshraghi C, Nozari A, Atala A. A review of anesthetic effects on renal function: potential organ protection. *Am J Nephrol.* 2017;46(5):380–389. doi:10.1159/000482014
13. Li Y, Zhong D, Lei L, Jia Y, Zhou H, Yang B. Propofol prevents renal ischemia-reperfusion injury via inhibiting the oxidative stress pathways. *Cell Physiol Biochem.* 2015;37(1):14–26. doi:10.1159/000430329
14. Gentz BA, Malan TP Jr. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs.* 2001;61(15):2155–2162. doi:10.2165/00003495-200161150-00001
15. Yoo YC, Shim JK, Song Y, Yang SY, Kwak YL. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. *Kidney Int.* 2014;86(2):414–422. doi:10.1038/ki.2013.532
16. Kong HY, Zhu SM, Wang LQ, He Y, Xie HY, Zheng SS. Sevoflurane protects against acute kidney injury in a small-size liver transplantation model. *Am J Nephrol.* 2010;32(4):347–355. doi:10.1159/000319623
17. Nieuwenhuijs-Moeke GJ, Bosch DJ, Leuvenink HGD. Molecular aspects of volatile anesthetic-induced organ protection and its potential in kidney transplantation. *Int J Mol Sci.* 2021;22(5):2727. doi:10.3390/ijms22052727
18. Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ, et al. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-I randomized controlled trial. *Br J Anaesth.* 2017;118(5):720–732. doi:10.1093/bja/aex057
19. Department of Publicity CHCC. A transcript of the 2021 of the state council’s joint defense and control mechanism at a press conference on December 29. Available from: <http://www.nhc.gov.cn/xcs/yqfkdt/202112/72c7929f82d541c89d846d8a67f35995.shtml>. Accessed January 16, 2025.
20. Bang JY, Lee J, Oh J, Song JG, Hwang GS. The influence of propofol and sevoflurane on acute kidney injury after colorectal surgery: a retrospective cohort study. *Anesth Analg.* 2016;123(2):363–370. doi:10.1213/ANE.0000000000001274
21. Franzen S, Semenas E, Taavo M, Martensson J, Larsson A, Frithiof R. Renal function during sevoflurane or total intravenous propofol anaesthesia: a single-centre parallel randomised controlled study. *Br J Anaesth.* 2022;128(5):838–848. doi:10.1016/j.bja.2022.02.030
22. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care.* 2013;17(1):R25. doi:10.1186/cc12503
23. Schanz M, Wasser C, Allgaeuer S, et al. Urinary [TIMP-2].[IGFBP7]-guided randomized controlled intervention trial to prevent acute kidney injury in the emergency department. *Nephrol Dial Transplant.* 2019;34(11):1902–1909. doi:10.1093/ndt/gfy186
24. Gocze I, Jauch D, Gotz M, et al. Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. *Ann Surg.* 2018;267(6):1013–1020. doi:10.1097/SLA.0000000000002485

25. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med.* 2017;43(11):1551–1561. doi:10.1007/s00134-016-4670-3
26. Kane-Gill SL, Peerapornratana S, Wong A, et al. Use of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 [TIMP2]\*[IGFBP7] as an AKI risk screening tool to manage patients in the real-world setting. *J Crit Care.* 2020;57:97–101. doi:10.1016/j.jcrc.2020.02.002
27. Bonventre JV. Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. *Nephrol Dial Transplant.* 2009;24(11):3265–3268. doi:10.1093/ndt/gfp010
28. Faught LN, Greff MJ, Rieder MJ, Koren G. Drug-induced acute kidney injury in children. *Br J Clin Pharmacol.* 2015;80(4):901–909. doi:10.1111/bcp.12554
29. Schulz CA, Engstrom G, Nilsson J, et al. Plasma kidney injury molecule-1 (p-KIM-1) levels and deterioration of kidney function over 16 years. *Nephrol Dial Transplant.* 2020;35(2):265–273. doi:10.1093/ndt/gfy382
30. Humphreys BD, Xu F, Sabbisetti V, et al. Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. *J Clin Invest.* 2013;123(9):4023–4035. doi:10.1172/JCI45361
31. Ichimura T, Asseldonk EJ, Humphreys BD, Gunaratnam L, Duffield JS, Bonventre JV. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. *J Clin Invest.* 2008;118(5):1657–1668. doi:10.1172/JCI34487
32. Yang L, Brooks CR, Xiao S, et al. KIM-1-mediated phagocytosis reduces acute injury to the kidney. *J Clin Invest.* 2015;125(4):1620–1636. doi:10.1172/JCI75417
33. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. *Clin Chem Lab Med.* 2017;55(8):1074–1089. doi:10.1515/cclm-2016-0973
34. Melnikov VY, Eceder T, Fantuzzi G, et al. Impaired IL-18 processing protects caspase-1-deficient mice from ischemic acute renal failure. *J Clin Invest.* 2001;107(9):1145–1152. doi:10.1172/JCI12089
35. Udzik J, Waszczyk A, Safranow K, et al. Assessment and prognosis in CSA-AKI using novel kidney injury biomarkers: a prospective observational study. *Biology.* 2021;10(9):823. doi:10.3390/biology10090823
36. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol.* 2005;16(10):3046–3052. doi:10.1681/ASN.2005030236
37. Zheng J, Xiao Y, Yao Y, et al. Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. *Pediatr Cardiol.* 2013;34(4):880–886. doi:10.1007/s00246-012-0563-6
38. Thomas JM, Ling YH, Huuskes B, et al. IL-18 (Interleukin-18) produced by renal tubular epithelial cells promotes renal inflammation and injury during deoxycorticosterone/salt-induced hypertension in mice. *Hypertension.* 2021;78(5):1296–1309. doi:10.1161/HYPERTENSIONAHA.120.16437
39. Liang H, Xu F, Zhang T, et al. Inhibition of IL-18 reduces renal fibrosis after ischemia-reperfusion. *Biomed Pharmacother.* 2018;106:879–889. doi:10.1016/j.biopha.2018.07.031
40. Yasuda K, Nakanishi K, Tsutsui H. Interleukin-18 in health and disease. *Int J Mol Sci.* 2019;20(3). doi:10.3390/ijms20030649
41. Taavo M, Rundgren M, Frykholm P, et al. Role of renal sympathetic nerve activity in volatile anesthesia's effect on renal excretory function. *Function.* 2021;2(6):zqab042. doi:10.1093/function/zqab042
42. Iguchi N, Kosaka J, Booth LC, et al. Renal perfusion, oxygenation, and sympathetic nerve activity during volatile or intravenous general anaesthesia in sheep. *Br J Anaesth.* 2019;122(3):342–349. doi:10.1016/j.bja.2018.11.018

## Drug Design, Development and Therapy

**Dovepress**  
Taylor & Francis Group

### Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>