scientific reports

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Fibroblast growth factor-23 as an early biomarker of ischemic acute kidney injury after partial nephrectomy: prospective observational study

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Partial nephrectomy (PN) is a clinical model for ischemic acute kidney injury (AKI), which occurs in up to 39% of cases and increases long-term morbidity and mortality. Given that Fibroblast Growth Factor-23 (FGF23) rises rapidly with kidney dysfunction, this study assessed whether intraoperative FGF23 elevation predicts ischemic AKI after PN. Twenty-seven PN patients and sixteen controls with non-ischemic surgical kidney injury were enrolled. Blood samples for FGF23 ELISA were collected at baseline, 1 h post-ischemia (PN) or at the first surgical access (controls), and at 24 and 72 h postoperatively. AKI was defined by KDIGO criteria. AKI occurred in 44.4% of partial nephrectomy (PN) patients. Only patients with PN who developed AKI showed a significant early rise in FGF23, averaging 18.6 ± 9.5 pg/mL ($p < 0.0001$) one hour post-ischemia. This early increase in FGF23 is predictive of AKI (AUC = 0.75; 95% CI: 0.56–0.95; $P = 0.026$). An optimal cut-off increase of 19.35 pg/mL offered 58.3% sensitivity and 93.3% specificity. Intraoperative FGF23 elevation predicts AKI after PN and may be an early marker of ischemic kidney injury. Validation in larger cohorts is required.

Keywords Acute kidney injury, Biomarkers, Nephrectomy, Fibroblast growth factor 23

Postoperative acute kidney injury (AKI) is an independent risk factor for long-term morbidity and mortality.[1,2] Up to 25% of affected patients progress to chronic kidney disease (CKD) within one year, and as many as 8.6% eventually require renal replacement therapy (RRT).[3] In the surgical setting, ischemic injury is the principal pathophysiological mechanism underlying AKI.[4] Currently, the diagnosis of AKI relies on increases in plasma creatinine concentration and reductions in urine output.[5] However, both markers present essential limitations. Plasma creatinine is not an early indicator, as its levels typically rise only 48–72 h after the insult, once glomerular filtration rate (GFR) has already declined. Similarly, urine output criteria show limited diagnostic accuracy, with sensitivity only slightly above 50% and a poor positive predictive value.[6] Current methods for detecting AKI are limited by medication effects and fluid balance, underscoring the critical need for earlier, more precise biomarkers.

In this context, partial nephrectomy (PN) provides a clinically relevant model for studying ischemic AKI. This procedure is performed to achieve oncological control while preserving renal parenchyma. To minimize bleeding during tumor resection, transient ischemia is usually induced by clamping the renal artery. This ischemic insult can trigger postoperative AKI, with reported incidences of up to 39%.[7,8] Given the controlled and reproducible nature of ischemic injury, PN offers an ideal environment for evaluating novel biomarkers of surgical AKI.

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In this regard, we propose Fibroblast Growth Factor-23 (FGF23) as a promising candidate. Initially described in the context of CKD, FGF23 levels increase early and almost linearly with the degree of renal function decline.[9,10] Moreover, studies in intensive care settings have shown that FGF23 can identify kidney injury at an early stage and provide information on its severity.[11,12] Finally, elevated FGF23 levels in cardiac surgery are predictive of several adverse outcomes, including the need for RRT and increased hospital mortality.[13] Additionally, FGF23 levels measured six hours after cardiopulmonary bypass demonstrated a significant correlation with all stages of in-hospital acute kidney injury following cardiac surgery.[14].

Thus, this study evaluates FGF23 as an early biomarker for AKI following ischemic injury in a group of patients undergoing PN. To distinguish the effects of ischemia from general surgical stress or mechanical trauma, a control group of patients undergoing hemicolectomy (HC) or percutaneous nephrolithotomy (NL) were included.

Materials and methods

Study design

This prospective observational study received approval from the local ethics committees at Hospital Clínico de la Universidad de Chile and Instituto Nacional del Cáncer (the ethical approval number for both centers was 868/17). It was also registered on ClinicalTrials.gov (NCT04693962). All methods were carried out in accordance with relevant guidelines and regulations (including the Declaration of Helsinki). Informed consent was obtained from all participants and/or their legal guardians. Forty-three patients were enrolled in the study after providing written informed consent. The inclusion criteria were patients over 18 years old with an American Society of Anesthesiologists Physical Status (ASA-PS) classification of 1 or 2,[15] normal preoperative plasma creatinine levels, and a baseline estimated glomerular filtration rate (eGFR) of greater than 60 mL/min/1.73 m^2. All enrolled patients underwent laparoscopic PN, laparoscopic HC, or NL. Exclusion criteria encompassed patients with a history of chronic kidney disease (defined as an eGFR < 60 mL/min/1.73 m^2 for three or more months, regardless of cause), anemia (hemoglobin < 13 g/dL for men and < 12 g/dL for women, according to World Health Organization criteria), any known clinical history of disorders affecting the parathyroid hormone (PTH) or vitamin D axis, pregnant women, and individuals concurrently using nephrotoxic drugs.

Study groups

Patients were categorized into two groups for this study: PN group, comprised 27 patients who underwent PN involving transient and controlled renal ischemia via renal artery clamping; and Control group consisted of 16 patients: 10 underwent HC surgery and 6 underwent NL surgery. All patients undergoing surgery for cancer had pre-operative imaging to rule out dissemination, and none of the included patients had any form of metastases.

Samples

Blood samples were collected from each patient at four time points to measure plasma creatinine, blood urea nitrogen (BUN), and intact FGF23 levels. The initial sample was taken upon the patient's arrival at the operating room. A second sample was obtained during surgery: one hour after renal artery clamping in the PN group, and one hour after the first surgical access in the Control group. The third and fourth samples were collected at 24 and 72 h post-surgery, respectively. However, only the first three samples were collected for the NL surgery. All surgeries were performed under general anesthesia, as determined by the clinical judgment of the surgical and anesthesiology teams.

Plasmatic creatinine and BUN were measured by the clinical laboratory of our center using a Roche/Hitachi Modular P800 Analyzer (Roche Diagnostics, Indianapolis, IN). The intact FGF23 concentration was determined through an Enzyme-Linked ImmunoSorbent Assay (ELISA) using a commercial kit (Immutopics, Inc., Human Intact FGF-23 cat # 60-6600). The diagnosis of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

End points

The primary outcome was the development of AKI according to KDIGO criteria. Therefore, this study primarily aimed to assess the effectiveness of FGF23 in predicting postoperative AKI. Secondary aims included determining the temporal pattern of FGF23 elevation and exploring whether increased FGF23 levels are attributable to structural kidney injury or to the physiological impact of major laparoscopic abdominal surgery performed under general anesthesia.

Statistical analyses

The sample size for the PN group ($n = 20$) was calculated to detect a 20 ± 10 pg/mL difference in plasma FGF23 concentration between individuals who developed and did not develop AKI after PN surgery. This calculation assumed a 39% incidence of AKI, 80% power, 5% alpha error, and a two-tailed analysis, and was performed using G*Power (version 3.1.9.4). The non-renal ischemia control group was projected to comprise at least 50% of the total study sample to ensure similar dispersion to the primary sample. To evaluate differences between patients who developed AKI and those who did not within the partial nephrectomy group, a specific subgroup analysis was performed. Continuous variables are expressed as mean ± standard deviation (SD) and were compared using the independent Student's t-test. The variables without normal distribution were used as median (interquartile range) and were analyzed using Mann-Whitney *U* test. Categorical variables are presented as frequencies and percentages (n, %) and were analyzed using Fisher's exact test. To quantify the magnitude of the effect, mean differences (for continuous variables) and risk differences (for categorical variables) were calculated, along with their corresponding 95% confidence intervals (95% CI). Moreover, repeated measures of FGF23 across time and groups were analyzed using a linear mixed-effects model. Since biological data often violate the assumption

Variable	Overall ($n=43$)	PN group ($n=27$)	Control group ($n=16$)	SMD	*P*-value
Age, years, median [IQR]	51.0 (42.5–57.5)	48.0 (40.5–55.0)	56.0 (48.8–59.2)	0.532	0.059
Female sex, n (%)	23 (53.5%)	12 (44.4%)	11 (68.8%)	0.506	0.206
Weight, kg, median [IQR]	76.0 (65.5–84.5)	78.0 (67.5–87.0)	71.0 (62.8–82.5)	0.335	0.339
Height, m, median [IQR]	1.62 (1.55–1.65)	1.62 (1.54–1.69)	1.62 (1.56–1.63)	0.277	0.442
BMI, kg/m^2, median [IQR]	28.5 (26.0–32.2)	29.4 (26.2–32.2)	27.0 (24.2–32.2)	0.221	0.393
ASA-PS, n (%)					
1	13 (30.2%)	8 (29.6%)	5 (31.2%)	0.035	1
2	30 (69.8%)	19 (70.4%)	11 (68.8%)	0.035	1
Current Smoking, n (%)	15 (34.9%)	10 (37.0%)	5 (31.2%)	0.122	0.752
Diabetes Mellitus, n (%)	2 (4.7%)	2 (7.4%)	0 (0.0%)	0.4	0.522
Hypertension, n (%)	14 (32.6%)	9 (33.3%)	5 (31.2%)	0.045	1
Dyslipidemia, n (%)	7 (16.3%)	3 (11.1%)	4 (25.0%)	0.367	0.394
Obesity, n (%)	19 (44.2%)	13 (48.1%)	6 (37.5%)	0.216	0.542
Baseline creatinine, mg/dL, median [IQR]	0.70 (0.60–0.80)	0.75 (0.60–0.85)	0.65 (0.60–0.80)	0.48	0.298

Table 1. Baseline characteristics. PN: partial nephrectomy; SMD: standard mean difference; IQR: interquartile range; Body Mass Index; ASA-PS: American Society of Anesthesiologists Physical Status.

Variable	Overall ($n=43$)	PN group ($n=27$)	Control group ($n=16$)	SMD	*P*-value
Time Duration, min, median [IQR]	205.0 (180.0–245.0)	205.0 (185.0–240.0)	206.5 (172.0–256.2)	0.014	0.96
Propofol, mg, median [IQR]	150.0 (120.0–180.0)	150.0 (120.0–190.0)	145.0 (120.0–180.0)	0.029	0.809
Fentanyl, mcg, median [IQR]	350.0 (300.0–350.0)	325.0 (287.5–400.0)	350.0 (300.0–350.0)	0.209	0.906
Lidocaine, mg, median [IQR]	60.0 (60.0–80.0)	60.0 (60.0–80.0)	60.0 (55.0–65.0)	0.181	0.608
Rocuronium, mg, median [IQR]	40.0 (35.0–50.0)	40.0 (37.5–50.0)	40.0 (30.0–46.2)	0.427	0.289
Dexametasone, mg, median [IQR]	4.0 (4.0–4.0)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	0.662	0.074
Ondansetron, mg, median [IQR]	4.0 (4.0–4.0)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	0.476	0.11
Cefazoline, g, median [IQR]	2.0 (2.0–2.0)	2.0 (2.0–2.0)	2.0 (1.0–2.0)	0.806	0.012
MAC Sevoflurane, median [IQR]	0.8 (0.8–0.9)	0.8 (0.8–0.9)	0.8 (0.8–0.9)	0.128	0.83
Ephedrine, mg, median [IQR]	15.0 (6.0–36.0)	30.0 (9.8–48.0)	9.0 (6.0–13.5)	0.928	0.016
Ketorolac, mg, n (%)	18 (41.9%)	10 (37.0%)	8 (50.0%)	0.264	0.526
Ketoprofen, mg, n (%)	10 (23.3%)	6 (22.2%)	4 (25.0%)	0.065	1
Metamizole, g, n (%)	36 (83.7%)	24 (88.9%)	12 (75.0%)	0.367	0.394
Acetaminophen, g, n (%)	15 (34.9%)	8 (29.6%)	7 (43.8%)	0.296	0.509
Bleeding (500 mL or more), n (%)	7 (16.3%)	6 (22.2%)	1 (6.2%)	0.47	0.229
Crystalloids, mL, median [IQR]	775.0 (500.0–1000.0)	1000.0 (600.0–1500.0)	500.0 (375.0–775.0)	1.129	0.002
Ischemia time, min, median [IQR]	-	20.0 (18.0–30.5)	-	-	-

Table 2. Intraoperative variables. PN: partial nephrectomy; SMD: standard mean difference; IQR: interquartile range; MAC: Minimum Alveolar Concentration.

of sphericity, the Geisser-Greenhouse correction was applied to all mixed-effects model analyses, followed by multiple comparisons against baseline values. Receiver-operating characteristic (ROC) curves were generated to determine diagnostic accuracy by calculating the area under the curve (AUC) and Youden's index. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 10.6.1.

Results

Baseline and intraoperative characteristics

A total of 69 patients were assessed for eligibility, and 43 patients were recruited and analyzed (Supplemental Figure 1). These patients were classified into two groups: the PN group ($n=27$) and the Control group ($n=16$). Baseline characteristics are shown in Table 1 and intraoperative variables in Table 2. The two groups were comparable, except for the use of ephedrine and crystalloids. The mean age of all patients was 50.7 ± 10.3 years, and 53.5% of the participants were female. All participants had normal baseline renal function and an ASA-PS score of 1 or 2. The most prevalent comorbidities were obesity (44.2%) and hypertension (32.6%). Regarding intraoperative variables, the mean surgical duration was 215.7 ± 50.6 min. No significant differences were observed between the groups concerning anesthetic agents. The PN group experienced a mean ischemia time of

23.6 ± 8.9 min. This group also exhibited a higher incidence of bleeding exceeding 500 mL, necessitating a greater amount of crystalloid administration.

End points

Among the PN group, 12 patients (44.4%) were diagnosed with postoperative AKI based on creatinine levels 24 and 72 h after surgery (Supplemental Table 1). Of these, 11 (40.7%) were classified as Stage 1 and one (3.7%) as Stage 2; no patients reached Stage 3. In the Control group, only one patient (6.3%) developed AKI at the 24-hour mark. Notably, there was no significant difference in urine output during the first 24 h between patients who developed AKI and those who did not (2.0 ± 1.3 mL/kg/h vs. 1.5 ± 0.8 mL/kg/h; $p = 0.2$). Furthermore, no patient presented a urine output below 0.5 mL/kg/h. Finally, a subgroup analysis within the PN cohort compared patients who developed AKI versus those who did not. Baseline characteristics, including age, sex, and BMI, were similar between groups. However, regarding intraoperative variables, the duration of surgery was significantly longer in patients who developed AKI compared to those who did not (237.25 ± 52.18 vs. 198.93 ± 35.85 min; $P = 0.033$). No significant differences were found in ischemia time or bleeding volume No significant differences were found in ischemia time, bleeding ≥ 500 mL, total crystalloid administration, and hypotension time (MAP < 65 mmHg) (Table 3).

Repeated measures of FGF23 across time and groups were analyzed using a linear mixed-effects model with the Geisser-Greenhouse correction. Analysis of the fixed effects revealed that only the time factor was statistically significant. Specifically, in PN patients who developed AKI, FGF23 levels increased significantly at 1 h, showing a mean rise of 18.6 ± 9.5 pg/mL from baseline ($p < 0.0001$). Conversely, FGF23 levels did not increase in PN patients who did not develop AKI, nor in the Control group (Table 4). Lastly, FGF23 levels in patients who developed AKI returned to baseline values at 24 and 72 h, and no significant differences in FGF23 levels were observed between male and female patients. On the other hand, the single patient in the Control group who developed postoperative AKI did not show an early elevation of FGF23.

Receiver Operating Characteristic (ROC) curve analysis

Finally, we performed a ROC curve analysis to determine the ability of FGF23 to predict AKI in PN subjects (for all patients, see Supplemental Fig. 2). To optimize the predictive assessment, we evaluated both the absolute change and the percentage change in FGF23 levels from baseline to one hour post-surgery. The analysis demonstrated that the absolute change yielded a superior discriminative capacity (AUC = 0.75; 95% CI: 0.56–0.95; $P = 0.026$) compared to the percentage change, which was not statistically significant (AUC = 0.61; $P = 0.33$). Consequently, the absolute increase was used for the final analysis (Fig. 1). An absolute increase of 19.35 pg/mL was identified as the optimal Youden index for predicting AKI development, with a sensitivity of 58.3% and a specificity of 93.3%.

Discussion

In this prospective study of 43 patients with no significant comorbidities (ASA-PS 1–2), we evaluated two groups: PN (with ischemia), and Control (without ischemia, with surgical and physical kidney damage). Our key finding is that plasma FGF23 levels increased significantly one hour after renal ischemia exclusively in PN patients who subsequently developed AKI, returning to baseline within 24 h. In contrast, no significant elevation in FGF23 was detected in the Control group. These findings suggest that an intraoperative increase in FGF23 is an early and specific predictor of ischemic AKI following PN. Furthermore, FGF23 levels do not rise as a result of major surgery under general anesthesia or mechanical kidney damage.

Variable	PN-No AKI ($n = 15$)	PN-AKI ($n = 12$)	SMD	*P*-value
Demographics				
Age, years, mean (SD)	48.47 (9.59)	49.00 (12.81)	0.53 (-8.34 to 9.40)	0.902
Female sex, n (%)	8 (53.3%)	4 (33.3%)	-0.20 (-0.57 to 0.17)	0.441
BMI, kg/m², mean (SD)	29.59 (3.65)	29.75 (5.19)	0.17 (-3.34 to 3.67)	0.923
ASA-PS, n (%)				0.236
1	6 (40.0%)	2 (16.7%)	-0.23 (-0.56 to 0.09)	
2	9 (60.0%)	10 (83.3%)	0.23 (-0.09 to 0.56)	
Clinical - Intraoperative				
Baseline creatinine, mg/dL, mean (SD)	0.72 (0.21)	0.79 (0.20)	0.07 (-0.09 to 0.24)	0.378
Time duration, min, mean (SD)	198.93 (35.85)	237.25 (52.18)	38.32 (3.39 to 73.25)	0.033
Ischemia time, min, mean (SD)	21.75 (7.29)	25.83 (10.44)	4.08 (-2.95 to 11.12)	0.243
Bleeding ≥ 500 mL, n (%)	3 (20.0%)	3 (25.0%)	0.05 (-0.27 to 0.37)	1.000
Crystalloids, mL, mean (SD)	1066.67 (641.06)	1166.67 (533.14)	100.00 (-375.39 to 575.39)	0.669
Hypotension time, min, mean (SD)	10.80 (11.04)	13.75 (10.27)	2.95 (-5.59 to 11.49)	0.483

Table 3. Univariate analysis of factors associated with AKI in the PN cohort. SMD: standard mean difference; BMI: Body Mass Index; ASA-PS: American Society of Anesthesiologists Physical Status; Hypotension time: defined as the cumulative duration with a Mean Arterial Pressure < 65 mmHg.

Group	Baseline	1 h	24 h	72 h
Control (n = 16)				
Absolute values (pg/mL)	37.55 (19.29)	41.86 (21.93)	29.58 (20.46)	21.18 (5.81)
Change from baseline (pg/mL)	0.00 (0.00)	4.30 (18.97)	-7.98 (22.93)	-13.73 (23.15)
Partial nephrectomy no-AKI (n = 15)				
Absolute values (pg/mL)	27.90 (24.44)	33.41 (14.60)	21.03 (7.70)	19.75 (12.83)
Change from baseline (pg/mL)	0.00 (0.00)	5.50 (19.66)	-6.87 (27.12)	-8.77 (25.55)
Partial nephrectomy AKI (n = 12)				
- Absolute values (pg/mL)	27.62 (12.76)	46.21*** (16.25)	38.54 (22.70)	20.04 (10.04)
- Change from baseline (pg/mL)	0.00 (0.00)	18.60*** (9.46)	10.92 (16.13)	-4.17 (13.40)

Table 4. FGF23 biomarker levels: baseline and post-surgical time points. AKI: Acute Kidney Injury. ***: $p < 0.0001$ vs. baseline. p-values were calculated using a linear mixed-effects model with the Geisser-Greenhouse correction. Separate analyses were performed for absolute values and changes from baseline.

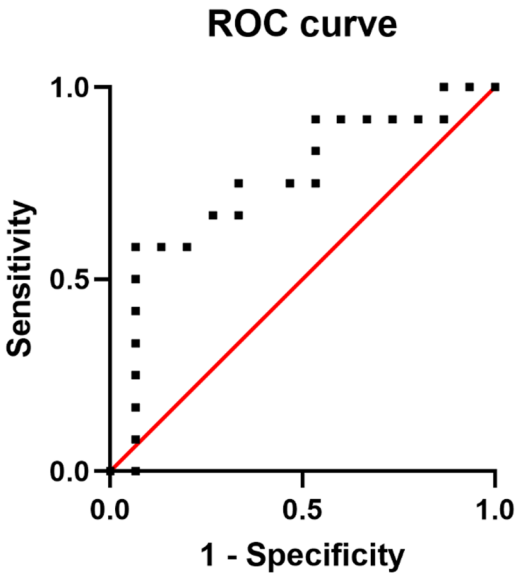

Fig. 1. Receiver Operating Characteristic (ROC) curve analysis to determine the ability of the absolute elevation of FGF23 to predict AKI in all groups. Absolute elevation of FGF23 predicted AKI within one day after surgery with an AUC of 0.75 (95% CI: 0.56–0.95, $p = 0.026$).

Because baseline FGF23 values showed considerable variability, we assessed the biomarker's predictive capacity using the change from baseline. ROC curve analysis identified an optimal cut-off of 12.5 pg/mL based on Youden's index, which provided a sensitivity of 69.2% and a specificity of 71.0%. These results support FGF23's potential as an early predictive and diagnostic biomarker for AKI, underscoring the need for further validation in larger studies.

Our results are consistent with previous evidence linking FGF23 to kidney disease. While initially described as rising early in patients with CKD,[9,10] increasing data support its role in AKI. Earlier studies in hospitalized and critically ill patients have shown that FGF23 levels rise in those who develop AKI.[11,12] Perioperative studies in cardiac surgery have also demonstrated that elevated FGF23 predicts the need for RRT and in-hospital mortality.[13,16] However, most existing studies measured FGF23 after AKI was already established, evaluating its prognostic rather than its predictive capacity. To our knowledge, this is the first study to assess the predictive value of FGF23 for early ischemic AKI in the perioperative setting of elective, non-cardiac surgery.

FGF23 is synthesized by osteocytes and osteoblasts, highlighting a bone–kidney communication axis in AKI.[17,18] Several regulatory pathways have been proposed to explain its rapid elevation. For example, erythropoietin may induce the expression of FGF23.[19–21] Recent studies suggest associations between hypoxia, iron deficiency, and FGF23 upregulation.[22] Furthermore, experimental metabolomics data indicate that renal

glycerol-3-phosphate production under ischemic stress stimulates bone marrow FGF23 synthesis.[23] These mechanisms may explain the rapid FGF23 increase observed in our study after renal ischemia.

An additional observation was a non-significant intraoperative rise of FGF23 in some patients undergoing hemicolectomy, despite the absence of overt AKI. This finding may reflect early kidney stress or an increased susceptibility to injury, underscoring FGF23's potential role in identifying patients at risk before functional impairment becomes apparent.

The main limitation of our study is its small sample size. Nevertheless, the homogeneity of the study population (ASA I–II patients) and the inclusion of a control group with two types of damage—one for systemic stress and another for mechanical renal injury—strengthen the conclusion that the early rise in FGF23 is associated with the ischemic context of PN. Second limitation is the lack of direct comparison with biomarkers like NGAL or KIM-1. However, while these markers typically rise 2–4 h and 12–24 h post-injury[24,25], FGF23 significantly increased at 1 h. This ultra-early response is critical, potentially allowing for therapeutic intervention while the patient is still in the operating room. Third limitation of our study is that most AKI cases were mild, which restricts the evaluation of FGF23 for predicting severe renal failure. Nevertheless, the detection of mild injury remains clinically relevant given its established association with adverse long-term outcomes. Fourth limitation, we did not systematically measure baseline serum calcium, phosphate, PTH, or vitamin D levels, relying instead on known medical history for exclusion. As these parameters are physiological regulators of FGF23, their absence limits a deeper mechanistic interpretation. Fifth limitation, intraoperative blood draws beyond the study protocol, such as C-reactive protein, white blood cell count or lactate, were not routinely performed at the 1-hour mark, limiting our ability to correlate FGF23 with other early stress markers. Finally, per our established protocol, serum creatinine was not assessed at 48 h, which could theoretically lead to delayed identification or underestimation of peak creatinine levels in borderline cases.

In conclusion, although evidence supports FGF23 as a biomarker in AKI, no studies have evaluated its role in the perioperative period of non-cardiac surgery. This proof-of-concept study provides preliminary evidence regarding the diagnostic utility of FGF23 after major elective surgery, particularly in partial nephrectomy, where transient ischemic injury is induced. Notably, the absolute increase in FGF23 demonstrated promising diagnostic potential when measured intraoperatively. While these preliminary findings are encouraging, larger multicenter studies are required to confirm its clinical utility. With further validation, FGF23 could become a valuable decision-making tool in the surgical setting. For instance, in the event of intraoperative hemorrhage leading to ischemic kidney injury, an early rise in FGF23 within one hour may help identify patients at risk of developing AKI, allowing for timely intervention.

Data availability

The data that support the findings of this study are available from the corresponding author, AP, upon reasonable request.

Received: 15 December 2025; Accepted: 26 May 2026
Published online: 02 June 2026

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Acknowledgements

We thank the Department of Postgraduate and Postdoctoral Studies, Office of the Vice-Rector for Academic Affairs, for providing financial support to NV.

Author contributions

N.V., R.A., and A.P. conceptualized and designed the study. N.V. and A.P. performed the formal analysis. N.V., C.A., and F.M. were responsible for patient recruitment and data acquisition. N.V., L.T., and A.P. drafted the original manuscript. All authors contributed to manuscript review, editing, and approved the final version.

Funding

This work was supported by the FONDECYT Initiation Grant 2015, No. 11150416.

Declarations

Competing interests

No competing interests or funding declared.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-026-55636-0.

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