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Perioperative anemia predicts kidney injury after partial nephrectomy

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Purpose: Partial nephrectomy (PN) induced kidney injury is still a challenging clinical matter that has not been completely conquered. This study aimed to explore the influences of perioperative anemia on renal function after PN.

Materials and Methods: A total of 114 patients undergoing PN were retrospectively studied. Serum creatinine was tested preoperatively and 24 hours and 3 days after PN to evaluate the occurrence of acute kidney injury (AKI). Perioperative anemia was evaluated on the basis of the hemoglobin (Hb) value at 24 hours and 3 days postoperation. Patients were then followed up for the development of chronic kidney disease (CKD). Associations between perioperative anemia and postoperative AKI and CKD were determined.

Results: The cumulative incidence of perioperative anemia was 33.33% in the study. A total of 32.46% of patients suffered from postoperative AKI, and 16.67% of patients progressed to CKD. The incidences of AKI and CKD in perioperative anemia patients were dramatically exceeded in those without anemia. Further statistical analyses indicated that perioperative anemia was a relevant factor for postoperative kidney injury, presenting the highest odds ratio of 31.272 for postoperative AKI and 17.179 for postoperative CKD. Receiver operating characteristic curve analysis showed that Δ Hb=(preoperative Hb)-(postoperative Hb nadir) was a meaningful predictor of postoperative kidney injury, with an area under the curve of 0.784 for predicting postoperative AKI and 0.805 for postoperative CKD.

Conclusions: Perioperative anemia can predict kidney injury after PN, and Δ Hb shows a meaningful predictive value for postoperative AKI and CKD.

Keywords: Acute kidney injury; Anemia; Chronic kidney failure; Hemoglobins; Nephrectomy

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INTRODUCTION

Partial nephrectomy (PN) has been considered as a standard surgical strategy for patients with T1-T2 renal tumors [1]. A main advantage of PN is to preserve postoperative renal function to the utmost extent while simultaneously yielding equivalent cancer outcomes as radical nephrectomy (RN). Nevertheless, some nonnegligible issues during PN surgery, such as the loss of functioning nephrons caused by excessive excision of renal parenchyma and reconstruction, as well as ischemia-reperfusion injury induced by temporary occlusion of renal hilar vessels will significantly impair

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the advantages of traditional PN on the protection of residual renal function.

As reported, the event of kidney failure was less frequent with PN than with RN. However, approximately 20% of patients treated with PN suffer from acute kidney injury (AKI) [2]; approximately 50% of these patients evolve to chronic kidney disease (CKD), and 8.1% ultimately develop end-stage renal disease [3]. To date, several studies have assessed the significance of a wide variety of factors as predictors of postoperative kidney injury, including renal ischemia time (IT), age at surgery, diabetes mellitus (DM), hypertension, preoperative estimated glomerular filtration rate (eGFR), and surgical approach. [4]. However, it is difficult to interpret the outcomes of these studies, and there is still a lack of any established biomarkers for predicting the onset of kidney injury after PN in clinical settings.

Baranauskas et al. [5] reported that hemodilution developed during cardiopulmonary bypass (CPB) surgery. Although the potential in reducing thrombosis risk was promising, it would otherwise decrease oxygen supply and

Table 1. Characteristics of the study population (n=114)

provoke tissue or organ hypoxia, thus contributing to organ dysfunction. Perioperative hemodilutional anemia was closely associated with postoperative AKI after CPB surgery [5,6]. Whereas, whether perioperative anemia is also a predictor of kidney injury after PN has not been reported yet. Consequently, this study was conducted to determine the detailed associations between perioperative anemia and postoperative kidney injury in patients who underwent PN for a single nonmetastatic renal tumor.

MATERIALS AND METHODS

1. Study design and patient selection

This was a retrospective cohort study conducted on patients who underwent PN for a single nonmetastatic renal tumor between October 2018 and May 2020 in Xinhua Hospital. Ethics approval was obtained from the Ethics Committee of Xinhua Hospital (approval no. XHEC-D-2021-111) and consent for publication was obtained from the patients. The exclusion criteria were: 1) anatomic or functional solitary

Characteristic	Patients with perioperative anemia (n=38)	Patients without perioperative anemia (n=76)	p-value
Age (y)	61.2±11.2	55.2±13.0	0.0167 ^ª *
Sex	-	-	0.8321 ^b
Male	27 (71.05)	52 (68.42)	-
Female	11 (28.95)	24 (31.58)	-
Tumor maximum diameter (cm)	3.56±1.71	2.94±1.59	0.0548ª
GFR-BL (mL/min)	72.22±13.36	78.08±13.86	0.0333°*
eGFR-BL (mL/min/1.73 m ²)	94.63±27.01	106.5±23.23	0.0161°*
Hb-BL (g/L)	135.5±14.0	143.9±12.9	0.0018 ^ª **
sCr-BL (μmol/L)	72.87±18.40	65.28±14.05	0.0160°*
ΔHb (g/L)	30.3±11.6	15.3±8.2	<0.001 ^a ***
Ischemia time (min)	29.71±7.69	30.66±7.98	0.5467°
Blood loss (mL)	200.5±155.0	87.11±102.0	< 0.001 ^a ***
Transfusion		-	0.1574 ^b
Yes	5 (13.16)	4 (5.26)	-
No	33 (86.84)	72 (94.74)	-
Surgical approach		-	0.1367 ^b
Laparoscopic	27 (71.05)	64 (84.21)	-
Open	11 (28.95)	12 (15.79)	-
Acute kidney injury	26 (68.42)	11 (14.47)	< 0.001 ^b ***
Chronic kidney disease	16 (42.10)	3 (3.95)	<0.001 ^b ***

Values are presented as mean±standard deviation or number (%).

Hb-BL, sCr-BL, eGFR-BL, GFR-BL represented preoperative Hb, sCr, eGFR and GFR; ΔHb was calculated by (preoperative Hb)-(postoperative Hb nadir); GFR was measured by ^{99m}Tc-DTPA.

GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; sCr, serum creatinine; -, not significant.

^a:Student's t-test.

^b:Chi-squared test.

*p<0.05, **p<0.01, ***p<0.001 were assumed as statistically significant.

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kidney; 2) abnormal contralateral renal function (normal contralateral renal function was defined as a differential renal function >40% as determined by radionuclide scintigraphy using Tc-99m diethylenetriaminepentaacetic acid [^{99m}Tc-DTPA]; 3) abnormal preoperative eGFR (<60 mL/min/1.73 m²); 4) preoperative anemia (hemoglobin [Hb] <120 g/L for males or <110 g/L for females); 5) DM, uncontrolled hypertension or heart failure; and 6) concomitant intrinsic kidney disease, including but not limited to glomerulopathy, tubulointerstitial nephritis, urolithiasis, and hydronephrosis, which could deteriorate the residual renal function.

Overall, 114 patients were reviewed. Specific demographic and medical information on age, sex, serum creatinine (sCr), Hb, eGFR, surgical approach (laparoscopic or open), IT, and blood loss was organized and analyzed. Hb <120 g/L for males or <110 g/L for females at any of the above time points. Renal function was assessed based on sCr variation, which was recorded preoperatively and 24 hours and 3 days after PN. Patients were attributed to the AKI group when there was a sCr increase of \geq 0.3 mg/dL (26.5 µmol/L) within 48 hours or of \geq 50% from baseline within 7 days [7] eGFR was achieved by using the Modification of Diet in Renal Disease Study Group (MDRD) equation, and CKD was defined as an eGFR <60 mL/min/1.73 m² by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria during the follow-up [7,8]. A derivative parameter of perioperative anemia, Δ Hb, was calculated by "(preoperative Hb)(postoperative Hb nadir)".

3. Statistical analysis

2. Assessments

Perioperative anemia was evaluated on the basis of Hb values 24 hours and 3 days after PN and was defined as

Statistical comparisons were performed using the statistical software GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA) and PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the

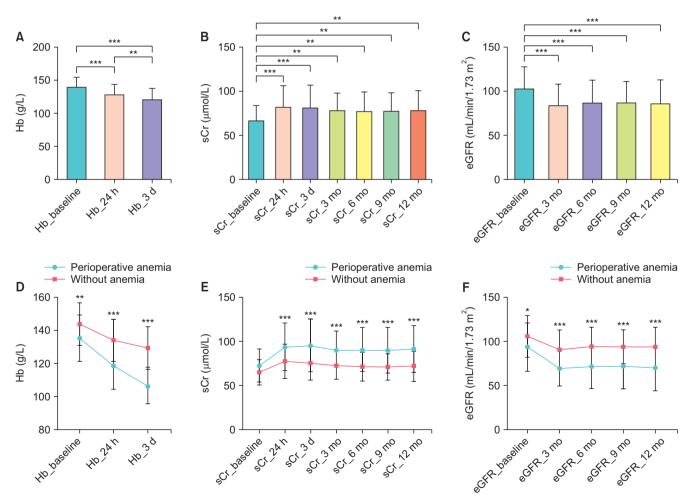


Fig. 1. Perioperative renal function and Hb variations. Postoperative variations of Hb (A), sCr (B), and eGFR (C), respectively. Variations of Hb (D), sCr (E), and eGFR (F) after partial nephrectomy when adjusted for perioperative anemia. Hb, hemoglobin; sCr, serum creatinine; eGFR, estimated glomerular filtration rate. *p<0.05, **p<0.01, ***p<0.001 were assumed as statistically significant.

Variable.			Postoperative AKI				Postoperative CKD	
Variable	Estimate	SE	p-value	OR (95% CI) ^a	Estimate	SE	p-value	OR (95% CI) ^a
Age (y)	0.017	0.017	0.297	1.017 (0.985–1.051)	0.069	0.028	0.012*	1.072 (1.015–1.131)
Sex	0.672	0.465	0.149	1.957 (0.786–4.873)	0.997	0.666	0.134	2.709 (0.735–9.984)
Tumor maximum diameter (cm)	0.239	0.124	0.054	1.270 (0.995–1.621)	0.135	0.138	0.329	1.144 (0.873–1.500)
Baseline Hb (g/L)	0.010	0.015	0.515	1.010 (0.981–1.039)	0.009	0.018	0.611	1.009 (0.974–1.046)
Baseline eGFR (mL/min/1.73 m ²)	-0.012	0.009	0.180	0.989 (0.972–1.005)	-0.056	0.017	0.001**	0.945 (0.915–0.977)
Baseline sCr (µmol/L)	0.030	0.013	0.024*	1.030 (1.004–1.057)	0.069	0.019	<0.001***	1.071 (1.032–1.112)
ΔHb (g/L)	0.112	0.024	<0.001***	1.118 (1.066–1.173)	0.114	0.028	<0.001***	1.121 (1.061–1.184)
Perioperative anemia	2.550	0.478	<0.001***	12.803 (5.021–32.646)	2.873	0.675	<0.001***	17.697 (4.718–66.383)
lschemia time (min)	0.108	0.032	0.001**	1.114 (1.048–1.186)	0.076	0.032	0.016*	1.079 (1.014–1.148)
Blood loss (mL)	0.005	0.002	0.003**	1.005 (1.002–1.008)	0.009	0.002	<0.001***	1.010 (1.005–1.014)
Transfusion	1.048	0.704	0.136	2.852 (0.718–11.322)	2.095	0.730	0.004**	8.125 (1.944–33.956)
Surgical approach	0.117	0.505	0.817	1.124 (0.418–3.025)	-0.424	0.583	0.467	0.655 (0.209–2.052)
Postoperative AKI	ı				2.521	0.613	<0.001***	12.443 (3.742–41.376)

significant. ^a.Binary univariate logistic regression analysis.

*p<0.05, **p<0.01, ***p<0.001 were assumed as statistically significant.

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mean±standard deviation. The intergroup differences were tested using Student's t-test or analysis of variance (ANOVA). Categorical variables are expressed as the frequencies (percentages), and the chi square test was used to analyze the intergroup differences. Stepwise univariate and multivariate logistic regression analyses were utilized to explore the relevant factors for postoperative kidney injury, and receiver operating characteristic (ROC) curves were used to assess the predictive value. Statistical significance was defined as p<0.05.

RESULTS

1. Demographics and clinical characteristics

In total, 114 patients were ultimately enrolled and systematically reviewed. Perioperative anemia was present in 38 (33.33%) patients. The recorded clinical and demographic characteristics of all patients were divided into two subgroups on the basis of perioperative anemia and are shown in Table 1. Perioperative anemia was positively associated with age at surgery, preoperative sCr, postoperative Hb decrease (Δ Hb), and blood loss during surgery and negatively associated with preoperative glomerular filtration rate and Hb. The pattern of Hb variation after PN is shown in Fig. 1A, presenting a trend of gradual decline from baseline to 3-day postoperation. In addition, patients with perioperative anemia showed a more severe Hb decrease than those without anemia (Fig. 1D).

2. The overall incidence of postoperative AKI and CKD

Generally, sCr significantly increased after PN and then gradually decreased to a level that slightly exceeded the preoperative value (Fig. 1B). Patients with perioperative anemia showed a more obvious sCr increase than those without anemia (Fig. 1E). According to the diagnostic criteria for AKI mentioned above, postoperative AKI was diagnosed in 32.46% (37/114) of patients. Postoperative AKI was more com-

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monly seen in patients with perioperative anemia (26/38 vs. 11/76) (p<0.001).

eGFR was followed up every 3 months after PN until patients progressed to CKD or 12 months postoperation. The variation pattern of eGFR was recorded and is shown in Fig. 1C. The eGFR remained relatively stable 6 months after PN surgery. Patients with perioperative anemia showed a more dramatic eGFR decline than those without anemia (Fig. 1F). Based on the diagnostic criteria for CKD mentioned above, the cumulative incidence of postoperative CKD was 1667% (19/114) during follow-up. Postoperative CKD was more frequently diagnosed in patients with perioperative anemia (16/38 vs. 3/76) (p<0.001).

3. Association of perioperative anemia and postoperative AKI

Univariate logistic regression analysis was carried out on all clinical variables to assess the relevant factors for postoperative AKI (Table 2). Baseline sCr (odds ratio [OR]: 1.030, 95% confidence interval [CI]: 1.004 to 1.057), ΔHb (OR: 1.118, 95% CI: 1.066 to 1.173), perioperative anemia (OR: 12.803, 95% CI: 5.021 to 32.646), IT (OR: 1.114, 95% CI: 1.048 to 1.186) and blood loss during surgery (OR: 1.005, 95% CI: 1.002 to 1.008) were confirmed to be positively correlated with postoperative AKI. Then, multivariate analysis was used to further determine the correlation of perioperative anemia, including its derivative parameters, with postoperative AKI. The results showed that perioperative anemia (adjusted OR: 31.272, 95% CI: 8.623 to 113.413), ΔHb (adjusted OR: 1.131, 95% CI: 1.067 to 1.199) and blood loss during surgery (adjusted OR: 1.005, 95% CI: 1.001 to 1.008) were relevant factors for postoperative AKI, of which perioperative anemia showed the highest OR (Table 3).

4. Association of perioperative anemia and postoperative CKD

Similar to the analysis procedure above, the results of univariate logistic regression analysis showed that age at

	Table 3. The correlation of derivative	parameters of perioperative	anemia and postoperative AKI	(multivariate analysis)
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Variable	Unadjusted OR (95% CI) ^a	p-value	Adjusted OR ^b (95% CI) ^c	p-value
Perioperative anemia	12.803 (5.021–32.646)	<0.001***	31.272 (8.623–113.413)	<0.001***
ΔHb (g/L)	1.118 (1.066–1.173)	<0.001***	1.131 (1.067–1.199)	<0.001***
Blood loss (mL)	1.005 (1.002–1.008)	0.003**	1.005 (1.001–1.008)	0.013*

 Δ Hb was calculated by (preoperative Hb)-(postoperative Hb nadir).

AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; Hb, hemoglobin.

^a:Binary univariate logistic regression analysis.

^b:Influences of confounders included ischemia time and baseline serum creatinine were adjusted.

^c:Binary multivariate logistic regression analysis.

*p<0.05, **p<0.01, ***p<0.001 were assumed as statistically significant.

Table 4. The correlation of derivative parameters of perioperative anemia and postoperative CKD (multivariate analysis)

Variable	Unadjusted OR (95% CI) ^a	p-value	Adjusted OR ^b (95% CI) ^c	p-value
Perioperative anemia	17.697 (4.718–66.383)	<0.001***	17.179 (2.502–117.937)	0.004**
ΔHb (g/L)	1.121 (1.061–1.184)	<0.001***	1.065 (1.001–1.133)	0.048*
Blood loss (mL)	1.010 (1.005–1.014)	<0.001***	1.009 (1.004–1.014)	0.001**
Transfusion	8.125 (1.944–33.956)	0.004**	8.260 (1.165–58.594)	0.035*

 Δ Hb was calculated by (preoperative Hb)-(postoperative Hb nadir).

CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; Hb, hemoglobin.

^b:Influences of confounders included age, ischemia time, baseline serum creatinine, baseline estimated glomerular filtration rate, and the event of acute kidney injury were adjusted.

^c:Binary multivariate logistic regression analysis.

*p<0.05, **p<0.01, ***p<0.001 were assumed as statistically significant.

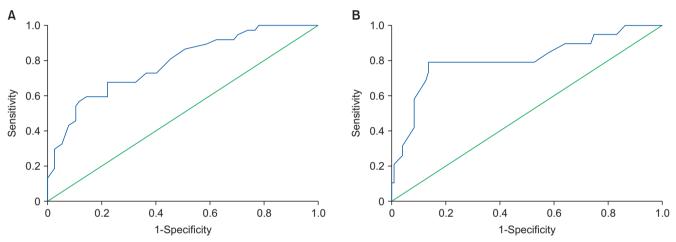


Fig. 2. Prediction value of Δ Hb for postoperative kidney injury. Receiver operating characteristic (ROC) curve showed a Δ Hb of 22.5 g/L had a sensitivity of 67.6% and specificity of 77.9% to predict postoperative acute kidney injury (95% CI: 0.694–0.873, AUC: 0.784, p<0.001; A), a Δ Hb of 28.5 g/L had a sensitivity of 78.9% and specificity of 86.3% to predict postoperative chronic kidney disease (95% CI: 0.681–0.930, AUC: 0.805, p<0.001; B). Δ Hb, (Hb before PN)-(Hb nadir after PN); PN, partial nephrectomy; CI, confidence interval; AUC, area under the ROC curve.

surgery (OR: 1072, 95% CI: 1015 to 1.131), baseline sCr (OR: 1.071, 95% CI: 1.032 to 1.112), AHb (OR: 1.121, 95% CI: 1.061 to 1.184), perioperative anemia (OR: 17.697, 95% CI: 4.718 to 66.383), IT (OR: 1.079, 95% CI: 1.014 to 1.148), blood loss during surgery (OR: 1.010, 95% CI: 1.005 to 1.014), transfusion (OR: 8.125, 95% CI: 1.944 to 33.956) and postoperative AKI (OR: 12.443, 95% CI: 3.742 to 41.376) were positively associated with postoperative CKD, while baseline eGFR (OR: 0.945, 95% CI: 0.915 to 0.977) was a negative indicator (Table 2). The results of the multivariate analysis indicated that perioperative anemia (adjusted OR: 17.179, 95% CI: 2.502 to 117.937), AHb (adjusted OR: 1.065, 95% CI: 1.001 to 1.133), blood loss (adjusted OR: 1.009, 95% CI: 1.004 to 1.014) and transfusion (adjusted OR: 8.260, 95% CI: 1.165 to 58.594) were relevant factors for postoperative CKD when the influences of confounders were adjusted, of which perioperative anemia still showed the highest OR (Table 4).

5. Predictor of postoperative kidney injury

As mentioned above, perioperative anemia could predict kidney injury after PN. Unfortunately, it was a categorical variable. Thus, the derivative parameter, Δ Hb, was hypothesized to be a potential predictor of postoperative AKI and CKD. ROC curve analysis was applied (Fig. 2), and the results indicated that a Δ Hb value of 225 g/L had a sensitivity of 67.6% and specificity of 77.9% to predict postoperative AKI, with an area under the curve (AUC) of 0.784 (95% CI: 0.694 to 0.873, p<0.001; Fig. 2A). Similarly, a Δ Hb value of 285 g/L had a sensitivity of 78.9% and specificity of 86.3% to predict postoperative CKD, with an AUC of 0.805 (95% CI: 0.681 to 0.930, p<0.001; Fig. 2B).

DISCUSSION

PN induced kidney injury remains a challenging clinical matter that has not been completely conquered. It has been reported that renal function recovers to the preoperative

^a:Binary univariate logistic regression analysis.

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level within a few weeks to 6 months after PN, and it does not change appreciably because of prompt compensation of a normal contralateral kidney [9,10]. However, there are still some patients whose renal function does not recover sufficiently [2,3,11,12]. Thus, exploring predictive factors of impaired renal function after PN is of great importance. Many studies have reported the risk factors for kidney injury after PN, but the main attention has been focused on IT, which is experienced during the widely implemented laparoscopic or open PN. In this study, although IT was verified again as a crucial risk factor for postoperative kidney injury, we found that perioperative anemia was another vital predictor, presenting clearly higher ORs than IT.

Anemia is a frequently diagnosed perioperative complication. Multifactorial in origin, preoperative anemia, perioperative blood loss, and progressive blunted erythropoiesis are the main pathogenesis factors of postoperative anemia [6]. Furthermore, hemodilution caused by excessive infusion during or after surgery may cause "dilutional" anemia or exacerbate previous anemia. Several studies have demonstrated a significant correlation of perioperative anemia with postoperative adverse outcomes, such as stroke, myocardial infarction, and kidney injury, mainly among cardiac, orthopedic, and vascular surgical patients [6,13-15]. However, studies investigating the association between postoperative kidney injury and perioperative anemia in PN surgical patients are limited. In this study, we confirmed that perioperative anemia was an important relevant factor for kidney injury after PN. However, it is still ambiguous whether anemia is a pathogenic factor of kidney injury or simply a comorbidity. Hales et al. [16] reported that AKI could evoke the onset of anemia by reducing the production of erythropoietin, increasing the risk of bleeding, and shortening the lifespan of red cells. Nangaku [17] proved that anemia might influence renal function through either a higher incidence of hypotension or a decrease in oxygen-transferring capacity to enhance renal oxidative stress. The detailed causality between perioperative anemia and postoperative kidney injury still needs to be investigated further.

Renal ischemia-reperfusion injury (RIRI) is one of the leading causes of kidney injury and temporarily interrupts the supply of oxygen and nutrients to the kidney, initiating a cascade of deleterious cellular and molecular responses [18,19]. After RIRI, the acutely damaged kidney experiences a self-healing process to restore structural integrity and physiological function, but if the injury is too severe, maladaptive repair may result in incomplete recovery and progression to CKD [20-22]. Many studies have reported the risk factors for AKI to CKD progression, including the severity and frequency of AKI, albuminuria, age, sex, preexisting CKD, and other chronic diseases, such as uncontrolled hypertension, heart failure, obesity and DM [23-25]. The molecular mechanisms of AKI to CKD progression are still unclear. Cell cycle arrest, epithelial-mesenchymal transition, endothelial-to-mesenchymal transition, capillary rarefaction, tubular epithelial cell senescence, matrix expansion and remodeling, and inflammatory cell infiltration have all been implicated in this process. Thus, further investigation of the pathological mechanisms could reveal new targets for potential interventions.

A recent meta-analysis including 154 studies with more than 3.5 million AKI patients demonstrated a pooled incidence as high as 21.6% and a mortality rate of 23.9% [26]. These rates are even higher for patients in intensive care units, which reaches up to 50%. The high hospitalization rate of AKI will cause enormous health care costs [27,28]. In addition, the progression from AKI to CKD contributes to comorbidity development and to a further rise in medical expenditure. Given the grim health burden of AKI and CKD, there is an urgent need for biomarkers that can predict the risk of postoperative AKI and CKD after PN, which is also of great clinical significance. Using ROC curve analysis, we found a Δ Hb value of 22.5 g/L showing a sensitivity of 67.6% and specificity of 77.9% to predict postoperative AKI, and a Δ Hb value of 28.5 g/L showing a sensitivity of 78.9% and specificity of 86.3% for predicting postoperative CKD. These findings indicate that, when patients present an appreciable Hb decline in the first 3 days after PN, timely and essential clinical strategies should be provided, such as hemostasis sustaining and transfusion.

A potential limitation of this study is that it was retrospective and conducted in a single center that might have undergone selection bias, such as distribution differences in age, baseline Hb, sCr, and eGFR between groups. Second, the pathogenesis of anemia, due to blood loss or hemodilution, the loss of nephrons caused by excision of renal tissues adjacent to the tumor and reconstruction, and the RENAL nephrometry score, which was recommended in the preoperative evaluation of PN, were not discussed in this study, which limited the clinical application of our findings to some extent. Third, the influences of blood transfusion and blood loss were not further examined in this study, although we verified that they were also relevant factors for postoperative kidney injury. Fakhari et al. [29] reported that transfusion was an independent predictor of AKI. However, other sources maintained that anemia was the main cause, and the transfusions performed were only consequences [30]. In order to interpret these issues, further better-designed

prospective larger-scale studies conducted in multiple institutions are expected.

CONCLUSIONS

In conclusion, perioperative anemia can predict kidney injury after PN. Δ Hb shows a meaningful predictive value for postoperative AKI and CKD. Thus, to prevent kidney failure after PN, efforts should be made in presurgical evaluation and preparation, precise intraoperative isolation and suture, and postoperative surveillance and maintenance of hemostasis to control anemia-related risk factors. Meanwhile, when patients present an apparent Hb decline in the first 3 days after PN, timely and essential clinical strategies should be provided.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Quan Li, Yunteng Huang, and Subo Qian. Data acquisition: Quan Li, Subo Qian, Lin Zhang, and Liujian Duan. Statistical analysis: Quan Li, Yunteng Huang, and Subo Qian. Data analysis and interpretation: Quan Li, Yunteng Huang, and Subo Qian. Drafting the manuscript: Quan Li, Lin Zhang, Liujian Duan, and Subo Qian. Critical revision of the manuscript: Yunteng Huang and Subo Qian. Obtaining funding: Subo Qian. Administrative, technical, or material support: none. Supervision: Yunteng Huang and Subo Qian. Approval of the final manuscript: all authors.

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