

Article

Evaluation of Chronic Kidney Disease Risk Factors after Radical Nephrectomy

Jurijus Makevičius^{1,2,*}, Akvilė Pajaurytė³, Artūras Samuilis^{4,5}, Raminta Lukšaitė-Lukštė^{4,5}, Eugenijus Jasiūnas⁶, Feliksas Jankevičius^{1,2} and Marius Miglinas^{1,7,*}

- ¹ Institute of Clinical Medicine, Clinic of Gastroenterology, Nephrourology and Surgery, Faculty of Medicine, Vilnius University, M. K. Čiurlionio Str. 21/27, 03101 Vilnius, Lithuania
 - ² Center of Urology, Vilnius University Hospital Santaros Klinikos, Santariškių Str. 2, 08660 Vilnius, Lithuania
 - ³ Faculty of Medicine, Vilnius University, M. K. Čiurlionio Str. 21/27, 03101 Vilnius, Lithuania
 - ⁴ Department of Radiology, Nuclear Medicine and Physics of Medicine, Center for Radiology and Nuclear Medicine, Faculty of Medicine, Vilnius University, M. K. Čiurlionio Str. 21/27, 0310, Vilnius, Lithuania
 - ⁵ Center of Radiology and Nuclear Medicine, Vilnius University Hospital Santaros Klinikos, Santariškių Str. 2, 08661 Vilnius, Lithuania
 - ⁶ Centre of Informatics and Development, Vilnius University Hospital Santaros Klinikos, Santariškių Str. 2, 08661 Vilnius, Lithuania
 - ⁷ Center of Nephrology, Vilnius University Hospital Santaros Klinikos, Santariškių Str. 2, 08661 Vilnius, Lithuania
- * Correspondence: mak.jurijus@gmail.com (J.M.); marius.miglinas@santa.lt (M.M.)

Abstract: Intraoperative hypotension (IOH) and loss of blood during radical nephrectomy (RN) cause postoperative clinically significant renal dysfunction, which after 12 months can cause a reduction in serum creatinine clearance of <60 mL/min. We conducted a prospective study of 93 adult patients in which we investigated the risk factors for developing chronic kidney disease (CKD) after RN. Forty-six (49.5%) patients had CKD, and of them, 43 patients had acute kidney injury (AKI) 48 h after surgery. Sixty-six (73.1%) of the postoperative AKI patients had CKD upstage. With each 1 mL estimated blood loss during RN (OR 1.01, $p < 0.001$), IOH was evaluated as the main risk factor of postoperative CKD development (OR 1.09, $p < 0.01$). Dunn's t -test revealed that only clinically significant AKI had a main effect ($g = -1.08$, $p < 0.0001$) on renal function 1 year after RN. A higher preoperative estimated glomerular filtration rate (eGFR), OR 0.89, $p = 0.02$, and contralateral kidney CT volume (OR 0.97, $p = 0.04$) had a clinically significantly decreased risk of postoperative CKD. Risk factors of AKI with CKD upstage were a small contralateral kidney CT volume (OR 46.70), NLR > 3.5 (OR 1.42), higher primary eGFR (OR 1.13) and longer IOH (OR 1.05), and for all of these, $p < 0.03$. A half of all patients after RN are at increased risk of CKD. Longer IOH and increased blood loss during RN are significant risk factors for CKD. Clinically significant postoperative AKI is related with a developed risk for postoperative eGFR decline and the presence of CKD 12 months after RN, and can be predicted by NLR > 3.5. A higher preoperative eGFR and contralateral kidney CT volume reduces the risk of postoperative CKD.

Keywords: radical nephrectomy; intraoperative hypotension; blood loss; chronic kidney disease; clinically significant acute kidney injury



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1. Introduction

The kidney is an essential organ for maintaining proper water, electrolyte balance, blood pressure and adequate ridding of waste products in the human body. Worldwide, kidney cancer is the third most common urological malignancy preceded by prostate cancer and bladder cancer, with the largest prevalence in Europe and North America. Amid population growth, aging and improved routine diagnostics, incidence rates of kidney cancer are increasing globally, with some variation between different regions [1]. The

estimated incidence of kidney cancer increases roughly 0.5% per year of age peaking between the ages 60 and 70 and is more prevalent in males than females (1.5:1) across all age groups [2].

Despite progress being made in understanding the pathology, morphology and natural history of kidney neoplasms, the etiology of renal cancer remains unknown. While there is no recommendation for the screening and primary prevention of renal cell carcinoma (RCC), the extensive use of non-invasive abdominal imaging methods has led to improved early detection of localized kidney tumors. Risk factors for the incidence of RCC are fairly well-studied and include smoking, obesity, hypertension (HTN) and diabetes mellitus (DM) [3–5]. Mortality of RCC is higher in patients who smoke and consume alcohol [3]. The typical age of patients with RCC is about 64 years with near-normal distribution [6]. In young patients, hereditary kidney cancer syndromes should be suspected [7,8]. Approximately 5–8% of RCC cases are known to be hereditary [9]. In the management of RCC with the increasing use of a minimally invasive operative approach and nephron-sparing surgery techniques, radical nephrectomy (RN) is performed less frequently. However, this type of kidney surgery remains the preferred treatment method for patients with large (T2) tumors; tumor thrombus and kidney masses cannot be safely removed during partial nephrectomy (PN) [10]. RN is also a method of choice for treating RCC with vascular invasion and thrombosis of the inferior vena cava (IVC) occurring in 4–10% of the cases [11]. RN is performed by removing the affected kidney within Gerota's fascia, and sometimes lymphadenectomy and the ipsilateral adrenal gland. No significant differences in oncological outcomes of open versus laparoscopic RN were reported; however, laparoscopic RN is associated with a shorter hospitalization time, reduced blood loss and lower postoperative demand for analgesics than open RN [10]. However, even when generally accepted criteria for selection are met, some patients do poorly after surgery due to a decline in renal function (RF). CKD is a progressive disease, which, if untreated, leads to kidney damage and the need for transplantation or dialysis due to the loss of RF [12]. Damage to kidneys eventually leads to a significant risk of all-cause mortality [13]. Thus, the evaluation of individual risk factors can be invaluable for both patient and surgeon when discussing possible treatment options and follow-up plans.

Intraoperative hypotension (IOH) caused by anesthetic induction, a common event during non-cardiac surgery, can decrease RF [14]. During RN, IOH can appear due to kidney removal and intraoperative blood loss. Some studies showed that controlled IOH was related to a higher rate of acute kidney injury (AKI) after surgery [15,16]. However, none of the previous studies analyzed the IOH effect on CKD after RN. Surgery remains the leading cause of AKI in an inpatient setting. Even when the course of surgery is uncomplicated, AKI may occur due to transient renal hypoperfusion, which reduces the glomerular filtration rate (GFR) [17–19]. With the persistence of intraoperative hypotension, as physiological adaptation mechanisms are exhausted, renal ischemia begins to develop. An inadequate oxygen supply to the cells and inadequate production of ATP leads to eventual necrosis of the nephrons. The damaged nephrons are unable to participate in filtration, and as a consequence, renal function deteriorates leading to a decrease in GFR and an increasing risk for detrimental outcomes in the long term, including CKD [20,21]. Moreover, while some patients with AKI after RN have CKD, we suggest that only clinically significant AKI has an impact on CKD status.

We aimed to identify the CKD rate after RN due to kidney lesions, to estimate the risk factors of CKD and to find the influence of clinically significant postoperative AKI for participants with primary serum creatinine (sCr) clearance ≥ 60 mL/min without proteinuria and renal insufficiency history.

2. Materials and Methods

We conducted this one-hospital prospective observational study between 2017 and 2019, Figure 1. The study was approved by the local Ethics Committee of Biomedical Research (approval Nr 158200-16-882-389) 2016 12 13 and the State Data Protection In-

spectorate. The study complied with the Declaration of Helsinki, as a statement of ethical principles for medical research involving people, human materials and participants' protection. Patients were provided with detailed information about the RN, possible risks of surgery, follow-up visits and tests that were to be performed for research together with health management purposes. Written informed consent was taken from all patients. This is the third part of the research, previously investigated AKI and CKD after PN.

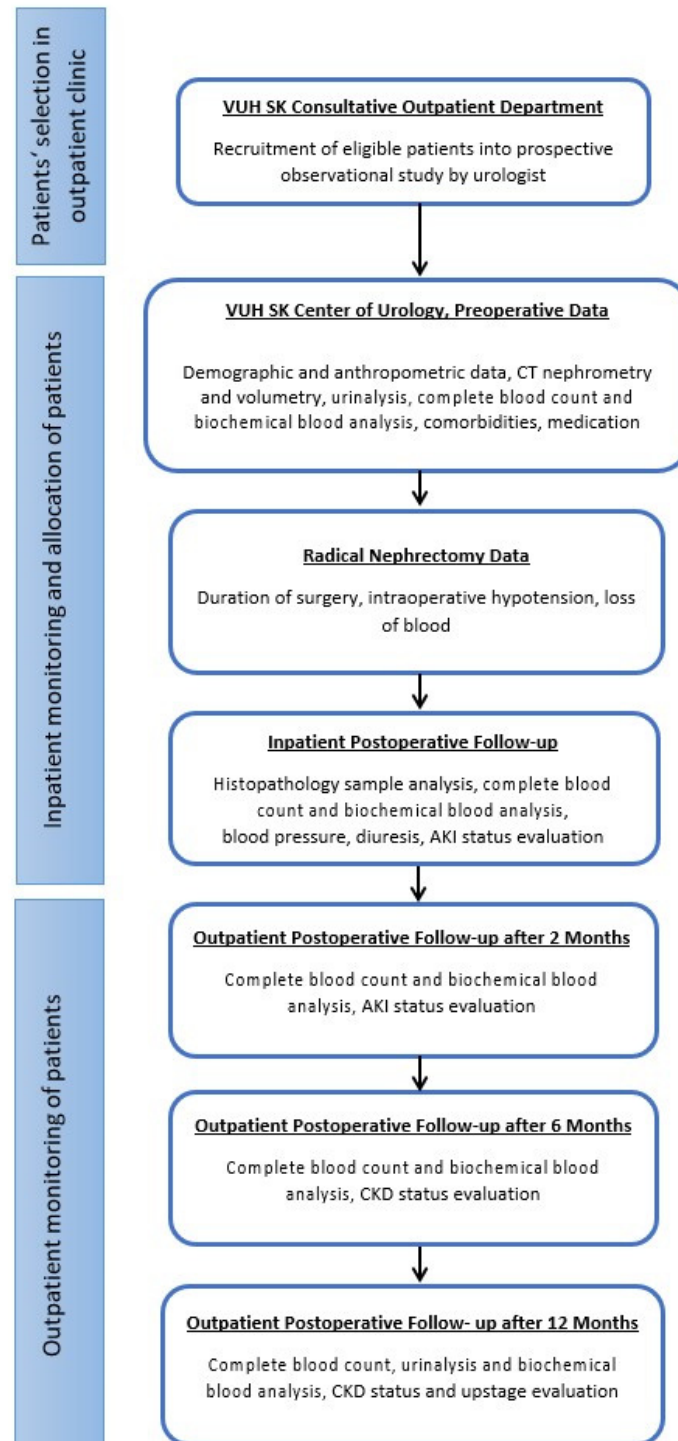


Figure 1. The study design and methodology. Abbreviations: VUH SK—Vilnius University Hospital Santaros Klinikos; CT—computed tomography; AKI—acute kidney injury; CKD—chronic kidney disease.

2.1. Criteria of Inclusion in the Study

All individuals were over 18 years, and were planned to undergo RN with laparoscopic or open approach due to RCC with primary sCr clearance ≥ 60 mL/min/1.73 m². RCC was found after computed tomography (CT) scan.

2.2. Criteria of Exclusion in the Study

Individuals with history of renal insufficiency (CKD or AKI) or surgery, albuminuria ≥ 30 mg/g or ≥ 3 mg/mmoL, hyperkalemia without uremia, hyperuricemia, pregnant or planning pregnancy, unregulated HTN and DM were excluded.

2.3. Surgical Procedure

The same protocol was used for all patients' treatment. For the anesthetic management, endotracheal intubation with sevoflurane was used. RN was offered to patients when PN was not technically feasible or/and tumor > 7 cm.

Open RN:

Patients were on opposite side position, and the typical retroperitoneal flank incision was performed. The renal artery and veins were ligated and divided. The affected kidney was then separated from the surrounding tissue and removed together with surrounding fat. In some cases, when a tumor was close or invaded the adrenal gland, adrenalectomy and visible/palpable lymph node dissection was performed too. Tumor thrombus excision from the vein was performed during nephrectomy.

Laparoscopic RN:

Patients were placed in the modified side decubitus position. Transperitoneal approach was performed, three to four ports were placed. The renal vein and artery were found, clipped and divided. The kidney with tumor was dissected and exposed from surrounding organs. The kidney and surrounding fat, in some cases adrenal gland and surrounding lymph nodes, were removed through a horizontal incision in the lower abdomen part.

2.4. Data and Definitions

Patients' age, sex, sCr, calculated neutrophil-to-lymphocyte ratio (NLR), albumin and creatinine ratio in urine (uACR), serum glucose, cholesterol with lipoprotein fractionation were collected.

We calculated R.E.N.A.L. standardized scoring system of nephrometry to evaluate the renal lesions on CT imaging and calculated contralateral kidney volume in three dimensions before RN (low: <100 cm³ for men and <80 cm³ for women; medium: 100 – 200 cm³ for men and 80 – 170 cm³ for women; high: >200 cm³ for men and >170 cm³ for women). We also analyzed intraoperative data such as the blood loss, the duration of surgery and the IOH time. Metabolic syndrome (MetS) was calculated according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria.

sCr clearance was classified using by next means: (G1 ≥ 90 mL/min, G2 89–60 mL/min, G3a 59–45 mL/min, G3b 44–30 mL/min, G4 29–15 mL/min, G5 < 15 mL/min) before RN, 2 days, 2, 6, 9 and 12 months after surgery. Postoperative AKI is defined as increase in sCr within 2 days after RN: 1st stage sCr 1.5- to 1.9-fold from baseline; 2nd stage sCr from 2.0- to 2.9-fold from baseline; 3rd stage sCr > 3.0 -fold from baseline. New lowest developed sCr group 1 year after RN was defined as CKD upstage. Clinically significant postoperative AKI is AKI with developed CKD upstage 1 year after RN. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for >3 months with/without uACR of ≥ 3 mg/mmoL was defined as CKD. IOH was registered with a non-invasive method, and defined as $<90/60$ mm Hg for an intraoperative blood pressure.

Mostly, participants were divided by postoperative AKI status into 2 groups. Then we formed a clinically significant postoperative group. After that, we formed CKD and non-CKD groups, see Figure 2.

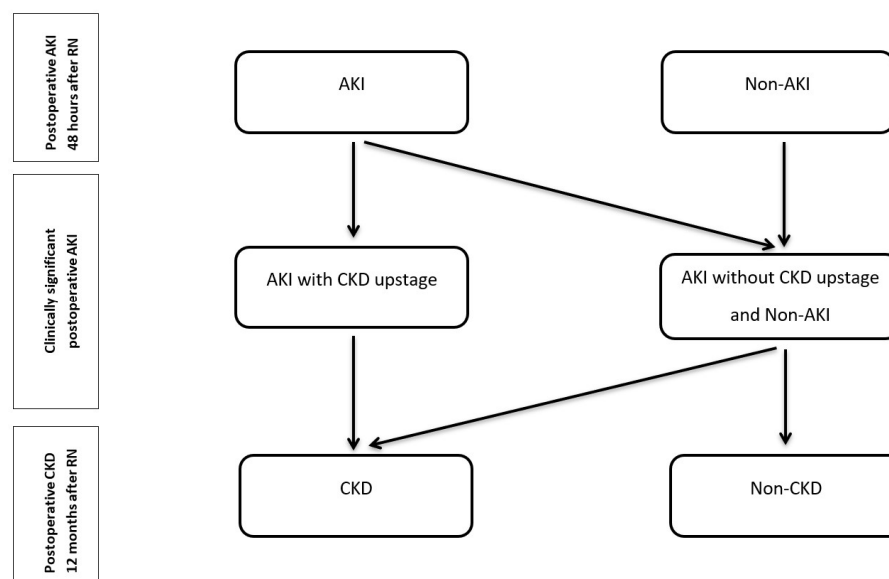


Figure 2. The formation of study cohorts. Abbreviations: RN—radical nephrectomy; CKD—chronic kidney disease; AKI—acute kidney injury.

2.5. Statistical Analysis

Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check the data normality distribution. The continuous variables were described by medians with first quartiles (Q1) and third quartiles (Q3), and the categorical variables—as frequencies with percentages. In order to highlight the characteristics of the data more fully, next to the median, we also presented means with standard deviations (SD). Nominal and ordinal variables we characterized by frequencies and percentages across the corresponding subset of the sample. To assess the statistically significant differences among the CKD and AKI status groups, for categorical variables, we used Pearson’s chi-squared test and Fisher’s exact test (for small sample sizes), and for the continuous, but not normally distributed variables, we used Mann–Whitney U test.

Univariate linear models were performed with the dependent variables, such as CKD and clinically significant AKI after RN, and independent variables factors, such as preoperative uACR and eGFR, age, BMI, gender, comorbidities, CCI, contralateral kidney CT volume, R.E.N.A.L. score, MetS, intraoperative blood loss, IOH time, postoperative NLR, but in the final result, only the statistically significant were shown, $p < 0.05$.

The optimization of multivariate analysis with the variable controlling effect was performed to calculate a statistically significant influence of relevant independent variables on postoperative CKD and clinically significant AKI. We created models, based on generalized linear regression equations, and the ROC curve’s graph showed an optimal cut-off value.

The rank epsilon squared ordinal ($\epsilon^2_{\text{ordinal}}$) effect size was used to evaluate the effect size between interval variables, not satisfying the condition for normal distribution. We assumed that the effect size was small if $0.01 \leq \epsilon^2_{\text{ordinal}} < 0.06$, moderate if $0.06 \leq \epsilon^2_{\text{ordinal}} < 0.14$ and large if $\epsilon^2_{\text{ordinal}} \geq 0.14$. Dunns’ test was used to evaluate which pairs between AKI statuses are significant from the others by sCr clearance after 12 months.

R statistical software package V 4.0.2 (2020-06-22) was used for statistical analysis. p -value < 0.05 was considered statistically significant.

3. Results

Following the inclusion and exclusion criteria, our study included 93 patients. The main clinical and sociodemographic data of the operated-on participants are summarized in Table 1.

Table 1. Clinical and sociodemographic data of CKD and non-CKD study patients.

Parameters	Estimate	Patients without Chronic Kidney Disease	Patients with Chronic Kidney Disease	<i>p</i> -Value ¹
Age, y	Median (Q1, Q3)	56.0 (48.0 to 62.5)	70.5 (62.5 to 74.0)	<0.001
Hospital stay, day	Median (Q1, Q3)	7.0 (5.0 to 7.0)	7.0 (6.0 to 8.8)	0.071
Gender:	N (%)			0.678
Female		19 (40.4)	21 (45.7)	
Male		28 (59.6)	25 (54.3)	
BMI, kg/m ²	Median (Q1, Q3)	27.8 (24.7 to 30.3)	28.9 (26.2 to 33.5)	0.021
CCI, score	Median (Q1, Q3)	3.0 (2.0 to 3.5)	4.5 (3.0 to 6.0)	<0.001
CT nephrometry result, points	Median (Q1, Q3)	9.0 (8.0 to 10.0)	10.0 (9.0 to 10.8))	0.002
Contralateral kidney CT volume, cm ³	Median (Q1, Q3)	255.4 (228.3 to 319.5)	191.8 (157.8 to 223.3)	<0.001
Contralateral kidney CT volume classification:	N (%)			<0.001
Low		1 (2.1)	30 (65.2)	
Medium		20 (42.6)	14 (30.4)	
High		26 (55.3)	2 (4.3)	
Metabolic syndrome:	N (%)			0.003
Yes		19 (40.4)	33 (71.7)	
No		28 (59.6)	13 (28.3)	
Radical nephrectomy:	N (%)			0.063
Laparoscopic		29 (61.7)	19 (41.3)	
Open		18 (38.3)	27 (58.7)	
Duration of surgery, min	Median (Q1, Q3)	120.0 (90.0 to 145.0)	120.0 (80.0 to 195.0)	0.869
Loss of blood, mL	Median (Q1, Q3)	210.0 (175.0 to 250.0)	525.0 (275.0 to 600.0)	<0.001
Loss of blood classification, mL:	N (%)			<0.001
≤500		46 (97.9)	19 (41.3)	
>500		1 (2.1)	27 (58.7)	
ASA, classification:	N (%)			<0.001
1		8 (17.0)	1 (2.2)	
2		29 (61.7)	16 (34.8)	
3		10 (21.3)	29 (63.0)	
Intraoperative hypotension, min	Median (Q1, Q3)	0.0 (0.0 to 10.0)	40.0 (20.0 to 60.0)	<0.001
Removed kidney volume, cm ³	Median (Q1, Q3)	398.0 (358.5 to 497.0)	409.0 (288.8 to 486.5)	0.377
Tumor volume, cm ³	Median (Q1, Q3)	118.3 (87.0 to 166.9)	179.0 (100.3 to 320.0)	0.032
AKI status:	N (%)			<0.001
Non-AKI		10 (21.3)	3 (6.5)	
AKI non-CKD upstage		14 (29.8)	-	
AKI CKD upstage		23 (48.9)	43 (93.5)	
Focal global glomerulosclerosis	N (%)			<0.001
Yes		14 (29.8)	40 (87.0)	
None		33 (70.2)	6 (13.0)	

¹ Mann–Whitney U test; Pearson’s Chi-squared test; Fisher’s exact test. Abbreviations: CCI—Charlson comorbidity index; BMI—body mass index; IQR—interquartile range; ASA—American Society of Anesthesiologists score; CT—computed tomography; AKI—acute kidney injury.

Eighty (86%) study participants appeared to have postoperative AKI after RN, and of them, 68 (85%) patients showed the first and 12 (15%), second stage. Two months after surgery, 63 (67.7%) patients still had AKI. In total, 77 (82.8%) patients had postoperative CKD upstage; 66 (73.1%) of postoperative AKI patients had CKD upstage; and 43 out of 46 (49.5% from all) patients with CKD had postoperative kidney injury.

The preoperative eGFR and age between AKI and non-AKI participants included in the cohort were not significantly different, 86.0 (70.2; 94.8) vs. 86.0 (74.0; 89.0) mL/min, $p = 0.687$ and 62.5 (50.2; 72.8) vs. 62.0 (54.5; 65.5) years, $p = 0.71$. A longer IOH time and higher loss of blood during RN was found in AKI patients, 20.0 (0.0; 43.8) vs. 0.0 (0.0 to 17.5) min $p = 0.024$ and 282.5 (201.2; 530.0) vs. 220.0 (162.5; 275.0) mL $p = 0.044$, respectively. Moreover, we found that AKI patients had a higher NLR mean, 4.1 (3.1; 6.7) vs. 2.7 (2.3; 2.9), $p < 0.001$.

The primary and postoperative eGFR means were lower in the CKD than in the non-CKD patients group, see Figure 3. All perioperative and postoperative laboratory data of CKD and non-CKD patients are summarized in Supplementary Table S1: CKD and non-CKD patients' perioperative and postoperative laboratory data.

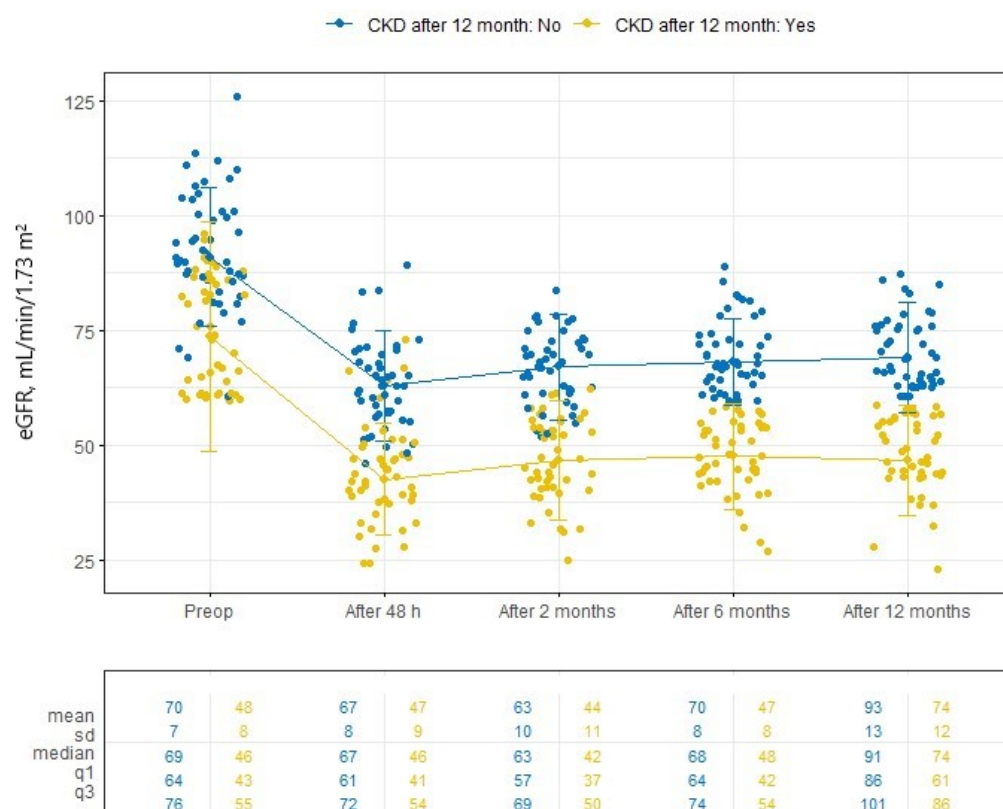


Figure 3. Preoperative and postoperative eGFR changes after RN. Abbreviations: eGFR—estimated glomerular filtration rate; CKD—chronic kidney disease.

Table 2 demonstrates the CKD possible risk factors after RN.

With each 1 mL estimated loss of blood (OR 1.01, 95% CI 1.00–1.02, $p < 0.001$) during RN, it was evaluated that a longer IOH was the main predictor of postoperative CKD with an OR of 1.09 (95% CI 1.02–1.17, $p < 0.01$). Having a higher eGFR and contralateral kidney CT volume before RN were related with a decreased risk of postoperative CKD; the ORs were 0.89 (95% CI 0.80–0.98) and 0.97 (95% CI 0.94–1.00) and p -values were 0.02 and 0.04, respectively. This multivariable analysis is presented in Figure 4.

The ROC analysis with sensitivity 95.6% and specificity 95.7% of this logistic regression model is shown in Figure 5.

Dunn's test (Figure 6) revealed that non-AKI and AKI without CKD upstage have no impact on eGFR 1 year after RN except clinically significant AKI (effect size ($g = -1.08$), $p < 0.001$).

Table 2. Clinical characteristics of CKD potential predictors in the univariate analysis.

Univariate						
Parameters	Estimate	Non-CKD	CKD	OR	95% CI	p-Value ¹
Age	Mean (SD)	56.1 (9.7)	67.3 (9.6)	1.12	1.07–1.18	<0.001
BMI	Mean (SD)	31.1 (25.4)	30.3 (5.3)	1.00	0.97–1.02	0.825
Comorbidities:	N (%)					
No data		32 (80.0)	8 (20.0)	–	–	–
HTN		14 (30.4)	32 (69.6)	9.14	3.51–26.17	<0.001
HTN and DM		1 (14.3)	6 (85.7)	24.00	3.46–489.01	0.006
CT nephrometry score	Mean (SD)	9.0 (1.1)	9.8 (1.2)	1.85	1.28–2.82	0.002
No metabolic syndrome	Mean (SD)	28 (68.3)	13 (31.7)	0.27	0.11–0.62	0.003
Preoperative eGFR	Mean (SD)	92.6 (12.8)	74.2 (12.2)	0.89	0.84–0.93	<0.001
Estimated blood loss	Mean (SD)	222.8 (84.0)	480.7 (249.5)	1.01	1.01–1.02	<0.001
Intraoperative hypotension time	Mean (SD)	6.9 (11.3)	41.1 (24.0)	1.11	1.07–1.16	<0.001
Contralateral kidney CT volume	Mean (SD)	289.4 (85.7)	190.1 (42.1)	0.96	0.94–0.98	<0.001
NLR	Mean (SD)	3.8 (2.2)	5.7 (3.3)	1.34	1.12–1.66	0.004

p-value describes the mathematical relationship between each independent variable and the dependent variable CKD. ¹ Mann–Whitney U test; Pearson’s Chi-squared test; Fisher’s exact test. Abbreviations: BMI—body mass index; DM—diabetes mellitus; HTN—hypertension; CKD—chronic kidney disease; OR—odds ratio; CT—computed tomography; CI—confidence interval; eGFR—estimated glomerular filtration rate; NLR—neutrophil-to-lymphocyte ratio.

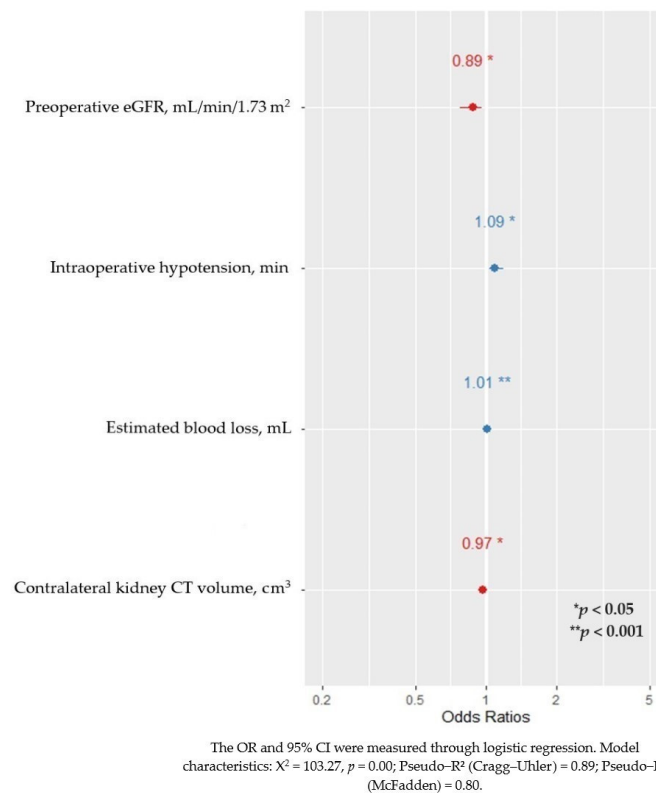


Figure 4. Risk factors of CKD 12 months after radical nephrectomy. Abbreviations: CT—computed tomography; eGFR—estimated glomerular filtration rate.

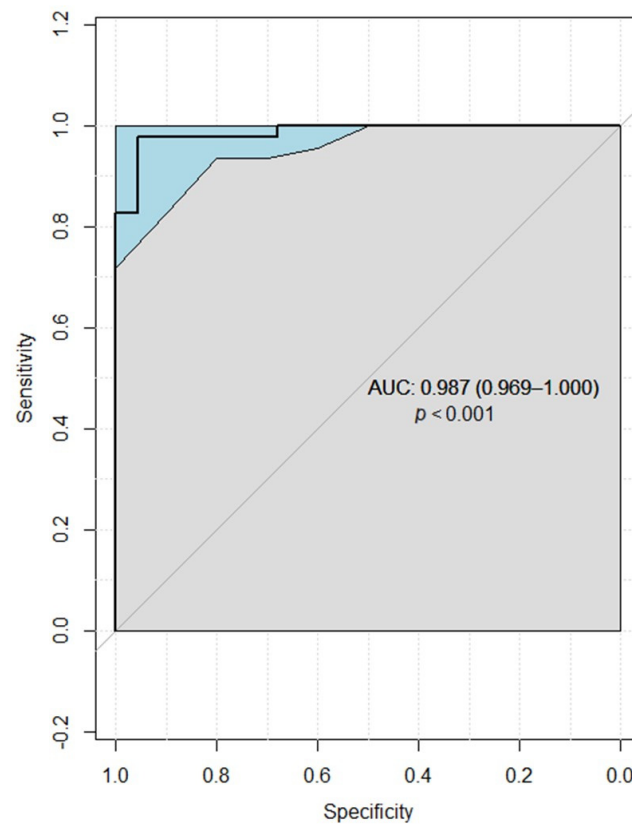


Figure 5. ROC analysis of predicting CKD after radical nephrectomy. Abbreviations: AUC—area under the curve.

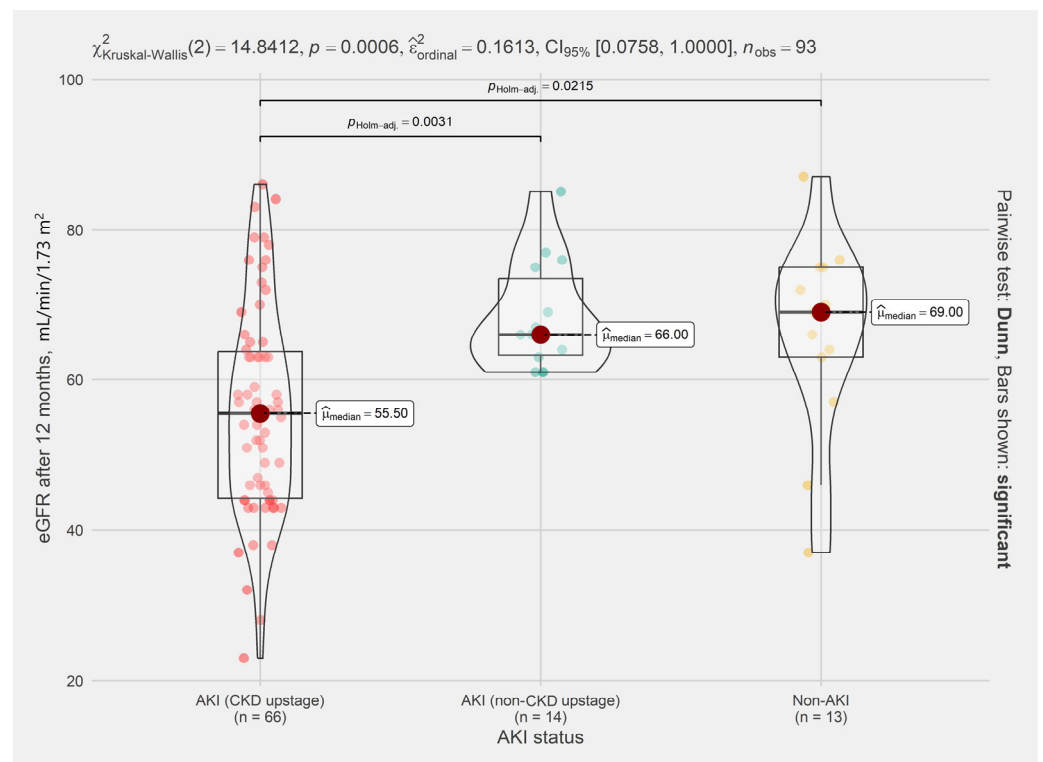
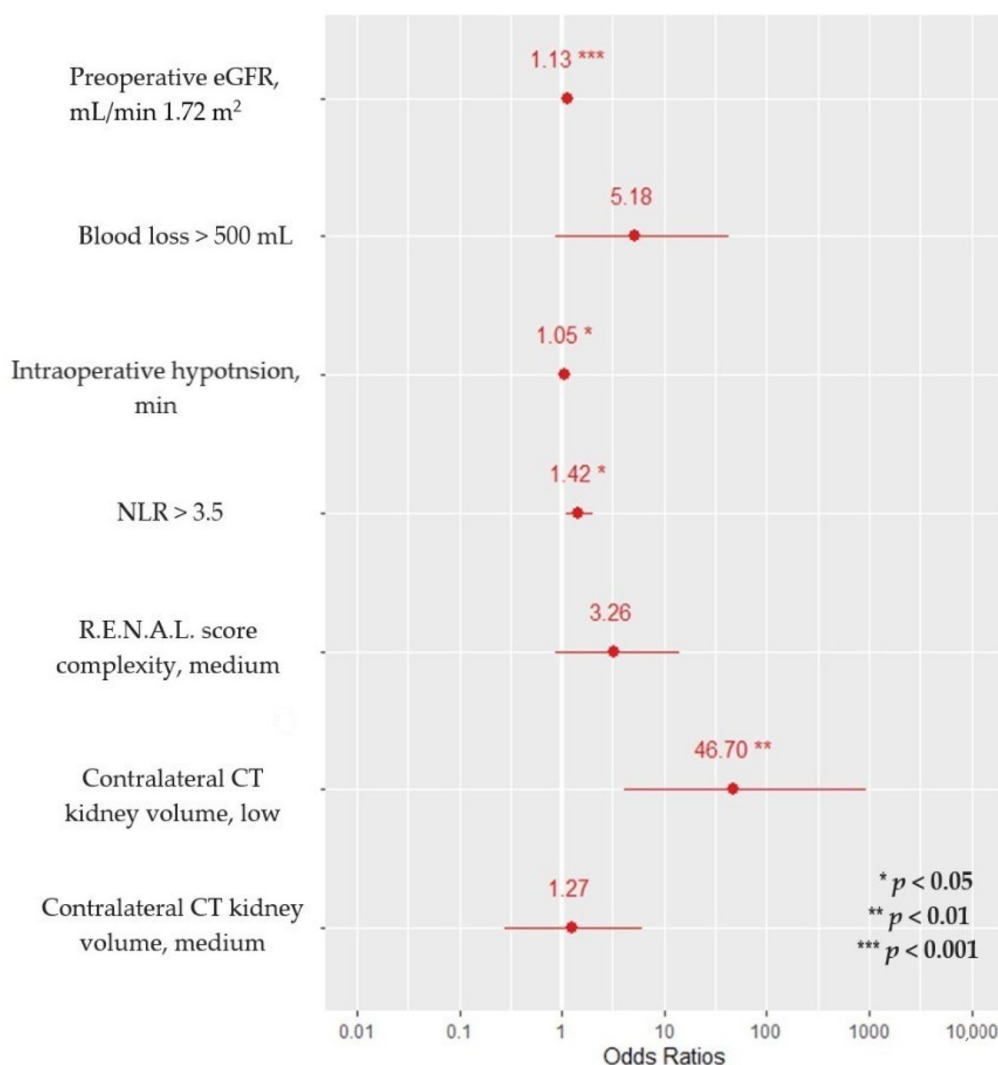


Figure 6. The effect of postoperative clinically significant AKI on eGFR 12 months after RN. Abbreviations: CKD—chronic kidney disease; eGFR—estimated glomerular filtration rate; AKI—acute kidney injury.

Clinically significant AKI has an impact on postoperative eGFR < 60 mL/min, so we analyzed its risk factors. The clinical and demographic parameters of patients grouped by AKI status are presented in Supplementary Table S2: Clinical and sociodemographic data of AKI status patients after radical nephrectomy.

All perioperative and postoperative laboratory data of clinically significant AKI are summarized in Supplementary Table S3: AKI status patients' laboratory data before and after radical nephrectomy.

The adjusted multivariable analysis excluded age, BMI, CCI, comorbidities, MetS, intraoperative loss of blood > 500 mL and CT nephrometry result complexity, and identified four significant variables as clinically significant AKI risk factors, including NLR > 3.5 (OR 1.42, CI 1.06–1.88, $p = 0.02$), low contralateral kidney CT volume (OR 46.70, CI 3.27–667.94, $p < 0.01$), higher preoperative eGFR (OR 1.13, CI 1.05–1.22, $p < 0.001$) and longer IOH (OR 1.05, CI 1.01–1.10, $p = 0.01$), Figure 7.



The OR and 95% CI were measured through logistic regression. Model characteristics: $X^2 = 46.64$, $p = 0.00$; Pseudo-R² (Cragg–Uhler) = 0.56; Pseudo-R² (McFadden) = 0.42.

Figure 7. Risk factors of clinically significant AKI after radical nephrectomy. Abbreviations: eGFR—estimated glomerular filtration rate; NLR—neutrophil-to-lymphocyte ratio; CT—computed tomography; R.E.N.A.L.—CT nephrometry scoring system.

This logistic regression model's ROC analysis showed significant sensitivity of 90.1% with specificity of 66.7% as presented in Figure 8.

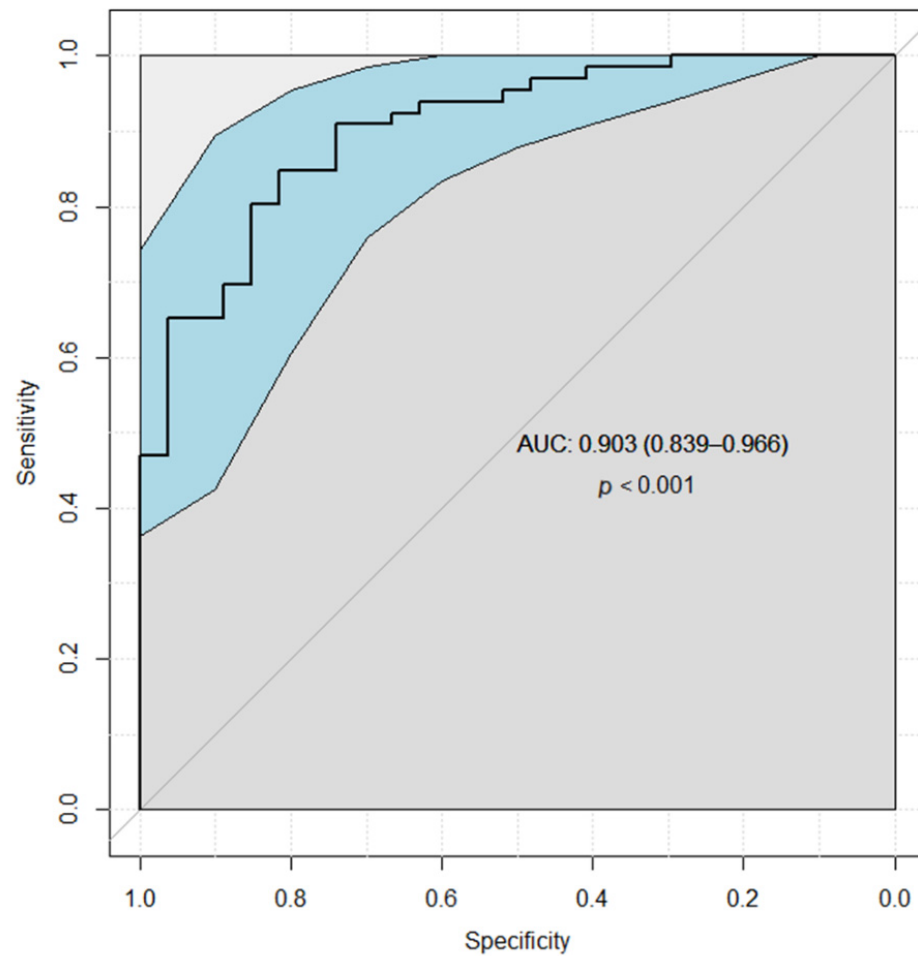


Figure 8. ROC analysis of predicting clinically significant AKI after radical nephrectomy. Abbreviations: AUC—area under the curve.

4. Discussion

In our study we determined that CKD is a frequent complication following RN. A longer IOH time, higher perioperative blood loss and postoperative AKI with CKD upstage were factors of increased risk for postoperative eGFR decline and a higher chance of CKD 12 months after RN. Other findings suggest that patients with higher preoperative eGFR and contralateral kidney CT volume are associated with a decreased probability of postoperative RF reduction. Risk factors found in the study, due to their potentially avoidable nature, are important for the prevention of postoperative adverse effects.

Preoperative RF depends on preexisting risk factors, such as age, hypertension and DM [4,5]. Previous authors' analysis found that 20–25% of patients with kidney lesions have already developed CKD before surgical treatment [22,23]. The association between RCC and CKD is bidirectional and includes multiple factors. An increase in tumor mass, intratumoral neovascularization and blood flow can further worsen RF, as it decreases nephron mass and the blood flow of healthy kidney parenchyma [24]. The likelihood of further decline in RF is a major problem to consider when deciding on the surgical approach and the follow-up plan for oncological patients. In Ohno et al.'s study, it was found that the mean decrease in eGFR after RN was 24.2 ± 12.40 mL/min/1.73 m² [22]. RF is generally better preserved using nephron-sparing techniques such as PN [25]. However, these techniques are not always feasible when dealing with larger tumors. The preservation of RF after RN depends on both patient and tumor characteristics. Previous studies have shown that RF deteriorates significantly 3 years following RN with 37% developing postoperative CKD [26].

Older age was found to be a major risk factor for new-onset CKD and CKD upstage after RN. During the natural aging process, eGFR decreases by approximately 1% with each additional year of age [27]. Age as an independent predictor of postoperative CKD is consistent with previous studies. There is an association between older age and lower eGFR 3 years after RN (OR = 1.041, 95% CI 1.007–1.078, $p = 0.017$) [26,28]. As shown in Olcucuoglu et al.'s study, the mean ages of participants who developed postoperative CKD and those who did not were 63.7 ± 3.5 and 52.7 ± 13.3 years, respectively ($p < 0.001$). In a veteran study by Leppert et al., the association between age and increased rate of CKD after RN was particularly pronounced as 15% of patients over 70 years developed stage 4 CKD with decreased sCr clearance up to 15–29 mL/min compared with 1.4% in patients <50 years. The risk of developing stage 4 or higher CKD increased by 18% with every 10 year increase in age in patients with normal or near-normal RF (HR = 1.64, 95% CI 1.43–1.89) [17]. Data from the RESURGE project suggests that PN is the recommended surgical treatment for patients of advanced age, whenever possible [29].

Preoperative eGFR is described as a significant factor of RF change after surgery [30,31]. Finding an abnormal eGFR preoperatively is related with an increased risk of mortality in RN patients with every 10 mL/min decrease in eGFR; however, in patients with normal preoperative sCr clearance, this risk is uncommon (HR = 1.11, CI 1.07–1.14) [32]. Further data showed that even slightly decreased eGFR (60–89 mL/min) before RN suggested the presence of CKD of stage 3a or lower 1 year after RN (OR = 4.4, CI 2.1–9.5, $p < 0.001$) [31]. The reason behind this association may be that preoperative eGFR reflects not only the function of the affected kidney but also the function of the remaining kidney, which becomes the main contributor to RF after RN. Lower preoperative eGFR may indicate the existence of other comorbidities that affect the remaining kidney.

RN of high-volume tumors is one of the most difficult surgical procedures performed in urology because of high intraoperative blood loss [33]. Even when RN is performed by a highly skilled urologist, there is still the opportunity for excess blood loss. The open operative approach, Neves classification IV level of renal thrombus extension and resection of IVC are independently associated with increased blood loss during RN [34]. While there are not a lot of prospective studies on the impact of intraoperative blood loss on postoperative CKD after RN, studies have shown that perioperative blood loss of over 250 mL during open PN might be associated with the risk of postoperative GFR decrease by over 25%. The risk increases by 0.1% for every mL of blood loss (OR = 1.001; $p = 0.05$) [35]. In a study by Nientiedt et al., blood loss requiring blood transfusions during PN is related with a three-fold chance of CKD (HR = 2.96; $p < 0.0001$) [18]. In large tumors (>7 cm), the estimated blood loss and risk for complications is higher for kidney resection than RN ($p < 0.001$) [36]. In our study, loss of blood was assessed by measuring the amount of blood in the pump tank and the weight of the surgical dressing. It was evident that each 1 mL of estimated blood loss during RN was allied with a higher incidence of CKD (OR = 1.01, $p < 0.001$).

Multiple studies have shown that growing RCC reduces the mass of renal parenchyma and induces an increase in the parenchymal volume of the contralateral kidney. This process is known as compensatory hypertrophy and is more apparent in larger tumors (>7 cm) [37]. Studies using multivariate analysis have shown that higher preoperative contralateral kidney volume is associated with better postoperative RF outcomes (OR = 0.98, CI 0.96–0.99, $p < 0.001$) [38]. Before surgery, kidney volume is associated with postoperative eGFR in PN as well as in RN patients ($p < 0.001$) [28,37]. Joong with colleagues found that sCr clearance < 60 mL/min after kidney surgery can be predicted by a remnant parenchymal volume of 170 mL, data sensitivity of 0.59 and specificity of 0.74 [30].

MetS can negatively influence the perioperative outcome after RN. MetS is a type of anabolism and catabolism disorder, including visceral overweight, HTN, dyslipidemia and hyperglycemia associated with increased morbidity. A study of Zhang et al. presented that oncological patients with MetS demonstrated a much lower recovery rate after RN as well as an increased risk for progressing renal insufficiency. Patients with MetS were

more likely to have a lower CKD class 2 years after RN than patients without MetS (OR 4.28; $p = 0.017$) [39]. It is important to note that MetS is prevalent in RCC patients and is correlated with worse survival rates without disease progression than in patients without MetS (HR = 1.98; $p = 0.04$) [40]. Our univariate analysis showed that patients without MetS were at increased risk for postoperative CKD (OR = 0.27, CI 0.11–0.62, $p = 0.003$); however, the adjusted multivariable test did not find any difference between MetS and non-MetS participants in postoperative CKD group. The impact of the independent effect of MetS components on RF after RN has been poorly investigated. Isolated increased BMI is common in patients with RCC and requires a more careful surgical approach as it is associated with an increased operating time (OR = 1.174; $p = 0.030$) and greater loss of blood ($p = 0.017$) during laparoscopic and open RN [41]. However, another study found that increased BMI alone is not associated with intraoperative and postoperative complications ($p = 0.790$) so it need not be regarded as a contraindication for RN [42].

The ratio of neutrophil-to-lymphocyte is a novel marker for inflammation detection and is estimated from complete blood count and used as a prognostic indicator for progression of CKD. High NLR correlates with high CRP and is associated with chronic inflammation and inflammatory processes in glomerula. A rise in neutrophils count along with increased NLR has been found to be strongly associated with higher all-cause death with a hazard ratio of 1.14, including renal dysfunction (HR = 1.62, CI 1.21–2.17) [43]. NLR also has a prognostic impact on adverse effects after cardiac and non-cardiac surgery [44,45]. Other publications have described that higher NLR is related with CKD upstage and poorer renal outcomes (from dialysis till death) among patients with 1 and 4 CKD stages (HR = 1.67, 95% CI 1.02–2.77) [46]. Cross-sectional data from Chia-Ho et al. presented that every additional unit of NLR was related with a higher risk for CKD in obesity but not in patients with normal BMI ($p = 0.03$) [47].

Hypotension is an adverse reaction following general anesthesia during surgery and is defined by a systolic pressure of blood (SBP) of <90 mm Hg, mean arterial pressure (MAP) of <60 mm Hg or 20% lower in baseline SBP or MAP [48]. IOH is highly prevalent in non-cardiac, non-cesarean section surgery, with a minimum 1 MAP report ≤ 65 mm Hg in 19.3% cases [49]. The pathophysiological mechanism of IOH includes decreased reperfusion of vital organs, including the heart and kidney. The longer duration of IOH during RN and PN is related with a higher risk of postoperative AKI, (OR = 1.14, CI 0.98–1.32); however, these results do not meet the criteria for clinically significant findings [14], although the results are more definitive for RN, as a study by Hua et al. found that 20 min of IOH during RN is associated with AKI (OR = 1.30, $p < 0.03$) [16]. Time under 65 mm Hg MAP threshold increases the odds for postoperative AKI compared to patients not going under 65 mm Hg MAP during non-cardiac surgery ($p < 0.001$) [50]. However, there are few data about IOH as a causative factor for postoperative CKD. In our multivariate analysis, we found that longer IOH is a major risk factor associated with postoperative CKD 1 year after RN with odds of 1.09 ($p < 0.01$).

Another important predictor of the development of CKD after RN is AKI [51]. Our definition of postoperative AKI ≥ 1.5 times the baseline value 48 h after surgery was in line with practical guidelines [52]. The pathophysiological mechanisms behind the AKI effect on the progression of CKD are fairly well-studied and include inflammatory cell infiltration, matrix remodeling and angiogenesis impairment [53]. A recent study showed that hospitalized participants with AKI are at significant chance of new-onset CKD and further disease development. (HR = 2.67, CI 1.99–3.58) [54]. AKI is more prevalent in patients undergoing RN over PN ($p < 0.001$) and in those who were dehydrated or mildly dehydrated ($p = 0.05$) [51]. A retrospective study of non-cardiac surgery by Alparslan et al. found that patients who developed AKI were at 2.8 times increased risk of developing CKD compared to patients without postoperative AKI [55]. This study confirmed findings by Cho et al., who reported that half of RCC patients who suffered AKI after RN, ended up with CKD compared to 32% of patients who did not have AKI diagnosed after RN ($p = 0.003$) [56].

We conducted a prospective study in which we investigated the risk factors of developing CKD after RN. Our study may be invaluable for better prediction of postoperative CKD that allows better patient selection for surgical treatment, more individualized surgery and follow-up plans and risk management. This is the first study to evaluate IOH together with blood loss during RN as a risk factor of developing CKD 12 months postoperatively. However, our study has some limitations. First of all, a small study sample from a single hospital may produce inconclusive results and weaken some statistical analyses; therefore, a larger sample study is needed to achieve true representation for the population of patients. Furthermore, we used the IOH definition of <70 mmHg MAP measured by using a non-invasive monitoring technique. Different thresholds may achieve different results as there is no uniform IOH definition. Intermittent data of all episodes of IOH for one patient surgery were summarized. A more precise method of measuring IOH could be used to achieve more conclusive results. Finally, there were some time constraints as we evaluated patients 12 months postoperatively. A longer-term following of participants would be useful to further describe the course of CKD after RN.

5. Conclusions

Half of all patients after RN are at increased risk of CKD. A longer IOH and increased loss of blood during RN are significant risk factors for CKD. Clinically significant postoperative AKI is related with the developed risk for postoperative eGFR decline and the presence of CKD 12 months after RN, and can be predicted by NLR > 3.5. A higher preoperative eGFR and contralateral kidney CT volume reduces the risk of postoperative CKD.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app13063921/s1>, Table S1: CKD and non-CKD patients' perioperative and postoperative laboratory data; Table S2: Clinical and sociodemographic data of AKI status patients after radical nephrectomy; Table S3: AKI status patients' laboratory data before and after radical nephrectomy.

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