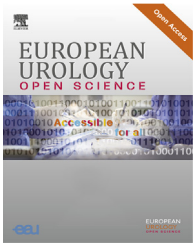
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Kidney Cancer

New-onset Chronic Kidney Disease After Surgery for Localised Renal Masses in Patients with Two Kidneys and Preserved Renal Function: A Contemporary Multicentre Study

Alessio Pecoraro [a], *Eduard Roussel* [b,c], *Daniele Amparore* [c,d], *Andrea Mari* [e,f], *Antonio Andrea Grosso* [e], *Enrico Checcucci* [d], *Francesco Montorsi* [g,h], *Alessandro Larcher* [g,h], *Hendrik Van Poppel* [b], *Francesco Porpiglia* [d], *Umberto Capitanio* [g,h], *Andrea Minervini* [e,f], *Maarten Albersen* [b], *Sergio Serni* [a,f], *Riccardo Campi* [a,c,f,*]

[a] *Unit of Urological Robotic Surgery and Renal Transplantation, Careggi Hospital, University of Florence, Florence, Italy;* [b] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [c] *Young Academic Urologists (YAU) Renal Cancer Working Group, Arnhem, The Netherlands;* [d] *Division of Urology, Department of Oncology, School of Medicine, San Luigi Hospital, University of Turin, Orbassano, Turin, Italy;* [e] *Unit of Urological Oncologic Minimally Invasive Robotic Surgery and Andrology, Careggi Hospital, University of Florence, Florence, Italy;* [f] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;* [g] *Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy;* [h] *University Vita-Salute San Raffaele, Milan, Italy*

Article info

Article history:
Accepted April 18, 2023

Associate Editor:
Silvia Proietti

Statistical Editor:
Andrew Vickers

Keywords:
Acute kidney injury
Chronic kidney disease
Partial nephrectomy
Radical nephrectomy
Renal cell carcinoma
Renal mass

Abstract

Background: There is a lack of evidence on acute kidney injury (AKI) and new-onset chronic kidney disease (CKD) after surgery for localised renal masses (LRMs) in patients with two kidneys and preserved baseline renal function.
Objective: To evaluate the prevalence and risk of AKI and new-onset clinically significant CKD (csCKD) in patients with a single renal mass and preserved renal function after being treated with partial (PN) or radical (RN) nephrectomy.
Design, setting, and participants: We queried our prospectively maintained databases to identify patients with a preoperative estimated glomerular filtration rate (eGFR) of $\geq$60 ml/min/1.73 m^2 and a normal contralateral kidney who underwent PN or RN for a single LRM (cT1-T2N0M0) between January 2015 and December 2021 at four high-volume academic institutions.
Intervention: PN or RN.
Outcome measurements and statistical analysis: The outcomes of this study were AKI at hospital discharge and the risk of new-onset csCKD, defined as eGFR <45 ml/min/1.73 m^2, during the follow-up. Kaplan-Meier curves were used to examine csCKD-free survival according to tumour complexity. A Multivariable logistic regression analysis assessed the predictors of AKI, while a multivariable Cox regression analysis assessed the predictors of csCKD. Sensitivity analyses were performed in patients who underwent PN.

* Corresponding author. Chirurgia Urologica Robotica Mini-Invasiva e dei Trapianti Renali, Azienda Ospedaliero-Universitaria Careggi, Viale San Luca, 50134 Firenze, Italy. Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Largo Brambilla, 3 - 50134 Firenze, Italy. Tel. +39 055 2758020; Fax: +39 0552758014.
E-mail address: riccardo.campi@gmail.com (R. Campi).

https://doi.org/10.1016/j.euros.2023.04.011
2666-1683/© 2023 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Results and limitations: Overall, 2469/3076 (80%) patients met the inclusion criteria. At hospital discharge, 371/2469 (15%) developed AKI (8.7% vs 14% vs 31% in patients with low- vs intermediate- vs high-complexity tumours, $p < 0.001$). At the multivariable analysis, body mass index, history of hypertension, tumour complexity, and RN significantly predicted the occurrence of AKI. Among 1389 (56%) patients with complete follow-up data, 80 events of csCKD were recorded. The estimated csCKD-free survival rates were 97%, 93% and 86% at 12, 36, and 60 mo, respectively, with significant differences between patients with high- versus low-complexity and high- versus intermediate-complexity tumours ($p = 0.014$ and $p = 0.038$, respectively). At the Cox regression analysis, age-adjusted Charlson Comorbidity Index, preoperative eGFR, tumour complexity, and RN significantly predicted the risk of csCKD during the follow-up. The results were similar in the PN cohort. The main limitation of the study was the lack of data on eGFR trajectories within the 1st year after surgery and on long-term functional outcomes.

Conclusions: The risk of AKI and de novo csCKD in elective patients with an LRM and preserved baseline renal function is not clinically negligible, especially in those with higher-complexity tumours. While baseline nonmodifiable patient/tumour-related characteristics modulate this risk, PN should be prioritised over RN to maximise nephron preservation if oncological outcomes are not jeopardised.

Patient summary: In this study, we evaluated how many patients with a localised renal mass and two functioning kidneys, who were candidates for surgery at four referral European centres, experienced acute kidney injury at hospital discharge and significant renal functional impairment during the follow-up. We found that the risk of acute kidney injury and clinically significant chronic kidney disease in this patient population is not negligible, and was associated with specific baseline patient comorbidities, preoperative renal function, tumour anatomical complexity, and surgery-related factors, in particular the performance of radical nephrectomy.

© 2023 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Contemporary shared decision-making for patients with localised renal masses is influenced by a variety of patient-, tumour-, and provider-related factors [1,2]. Among these, renal function preservation still represents one of the most critical aspects impacting both patients and clinicians [2]. While a proportion of patients may have chronic kidney disease (CKD) prior to any treatment, the risk of *surgically* induced new-onset renal function impairment after surgery in those with two kidneys and normal baseline renal function should be assessed carefully and balanced properly with oncological and perioperative considerations [2,3].

Notably, these patients may not experience worse survival outcomes or changes in life expectancy after surgical resection [4], but overall survival has been correlated with an estimated glomerular filtration rate (eGFR) decline below 45 ml/min/1.73 m^2 [2]. The American Urological Association guidelines indeed propose radical nephrectomy (RN) as the preferred option in patients with tumours of higher complexity who have no pre-existing CKD, a normal contralateral kidney, and an estimated new baseline eGFR greater than the abovementioned cut-off (if RN is performed) [4].

While potentially less clinically relevant than medically induced CKD [2,3], surgically induced CKD might lead to a cascade of further potential detrimental consequences, such as a higher risk of cardiovascular events, reduced overall survival [5], worse patients' quality of life, and increased overall costs of care [6]. Lastly, even though still an object of debate, postoperative renal function impairment may also be associated with worse oncological outcomes [5,7–9].

Despite the recent development of promising models to estimate postoperative renal function [10–13], predicting the trajectory of postoperative renal function after partial nephrectomy (PN) or RN for localised renal masses in patients with preserved renal function in daily clinical practice is still highly complex and nuanced [1,2,14]. In addition, it is difficult to disentangle the effect of patient-, surgery-, or tumour-related factors (such as tumour complexity) for the risk of postoperative CKD.

To fill these gaps, we sought to evaluate the prevalence and predictors of acute kidney injury (AKI) and new-onset clinically significant CKD (csCKD) in contemporary patients with a single renal mass and preserved renal function, treated with PN or RN at four high-volume European centres.

2. Patients and methods

2.1. Study population

After institutional review board approval, prospectively maintained databases from five urological units at four high-volume academic institutions were queried to identify patients with a preoperative eGFR of $\geq$60 ml/min/1.73 m^2 and a normal contralateral kidney who underwent PN or RN for a single localised (cT1-T2N0M0) renal mass between January 2015 and December 2021.

Patients with a single kidney, multiple tumours, or bilateral tumours were excluded from the analysis.

Oncological and functional follow-up was performed according to institutional protocols, following established guidelines [1].

Tumour complexity was reported according to the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score and classified as low-complexity (PADUA scores 6–7) versus intermediate-complexity (PADUA scores 8–9) and high-complexity (PADUA scores ≥10) tumours [1].

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [15].

Tumour stage was classified according to the 2009 TNM classification system [1].

The decision to perform PN or RN was based on a careful preoperative assessment of patient- and tumour-related factors, as well as on surgeon's experience, preference, and skills [2]. Surgery was performed using an open or minimally invasive approach.

AKI was defined according to the RIFLE criteria as a >25% reduction in preoperative baseline eGFR or a >1.5-fold increase in preoperative creatinine at hospital discharge [13].

CKD stage was defined according to the Kidney Disease: Improving Global Outcomes criteria. Patients with stage ≥3b (eGFR <45 ml/min/1.73 m^2) were considered to have csCKD [16].

Postoperative complications were reported according to the Clavien-Dindo grading system [17].

2.2. Outcomes

The study outcomes were as follows: (1) proportion of patients experiencing AKI at hospital discharge, (2) probability of developing de novo csCKD during the follow-up, and (3) predictors of AKI and csCKD during the follow-up among patient-, tumour-, and surgery-related factors.

Follow-up time was defined as the time elapsed between surgery (PN or RN) and the onset of csCKD or the last follow-up.

2.3. Statistical analysis

Statistical analyses were performed and reported following established guidelines [18].

Descriptive statistics are reported as the median and interquartile range (IQR) for continuous variables, and the frequency and proportion for categorical variables, as appropriate.

Differences in baseline characteristics among patients with tumours of low versus intermediate versus high complexity were evaluated by the Pearson chi-square and Mann-Whitney U tests as appropriate. The same tests were used for a sensitivity analysis aiming to explore differences in preoperative characteristics among patients with and without complete follow-up data.

A multivariable *logistic* regression analysis was used to evaluate the potential predictors of AKI among patient-, tumour-, and surgery-related variables.

Kaplan-Meier curves were used to examine csCKD-free survival according to tumour complexity. The log-rank test was used to compare csCKD rates by tumour complexity groups (low vs intermediate vs high).

Multivariable Cox regression models were fitted to assess the predictors of the risk of csCKD among the following covariates: body mass index (BMI), age-adjusted Charlson Comorbidity Index, preoperative eGFR, history of hypertension, history of diabetes, tumour complexity (according to the PADUA score: low vs intermediate vs high), surgical approach (open vs minimally invasive), and intervention (RN vs PN).

Multivariable models were developed, selecting the covariates based on the knowledge of predictors of csCKD, and all variables were kept in the model, irrespective of statistical significance.

Sensitivity analyses were performed in patients who underwent PN.

The analyses were performed using IBM SPSS statistics (version 28.0.1.0) and the R statistical package v.3.0.2 (R Project for Statistical Computing, http://www.r-project.org/). All tests were two sided, with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Overall, 3076 patients were identified. Of these, 2469 (80%) met the inclusion criteria and were included in the analytic cohort (Fig. 1). Baseline patients' characteristics, as well as intra- and postoperative outcomes, stratified by tumour complexity, are shown in Table 1.

Tumour complexity was classified as low, intermediate, and high in 1063 (43%), 947 (38%), and 459 (19%) patients, respectively. The three cohorts significantly differ regarding patient-, tumour-, and surgery-related factors (Table 1).

3.2. Prevalence and predictors of AKI at hospital discharge

Overall, 371/2469 (15%) developed AKI at hospital discharge (8.7% vs 14% vs 31% in patients with tumours of low vs intermediate vs high complexity, $p < 0.001$; Fig. 1).

At the multivariable analysis, BMI (odds ratio [OR] for each unit increase: 1.04; 95% confidence interval [CI] 1.01–1.07, $p = 0.023$), history of hypertension (OR: 1.30; 95% CI 1.01–1.68, $p = 0.047$), tumour complexity (OR for high- vs low-complexity tumours: 3.02; 95% CI 2.14–4.26, $p < 0.001$; OR for intermediate- vs low-complexity tumours: 1.54; 95% CI 1.12–2.12, $p = 0.007$), and RN (OR: 10.17; 95% CI 7.26–14.24, $p < 0.001$) significantly predicted the risk of AKI at hospital discharge (Table 2).

In the PN cohort ($n = 2251$, 91%), 239 (11%) patients experienced AKI (7.7% vs 10% vs 20% in patients with low- vs intermediate- vs high-complexity tumours, $p < 0.001$).

At the multivariable analysis, significant predictors of AKI were warm ischaemia time (WIT; OR: 1.05; 95% CI 1.03–1.07, $p < 0.001$), tumour complexity (OR for high- vs low-complexity tumours: 2.18; 95% CI 1.41–3.38, $p < 0.001$), and open (vs minimally invasive) surgical approach (OR: 1.77; 95% CI 1.02–3.10, $p = 0.043$; Table 2).

3.3. Risk of csCKD during follow-up

Overall, 1389 (56%) patients had complete follow-up data and were included in the analysis.

In this cohort, 80 events of csCKD were recorded during the follow-up. The median follow-up for patients who did not develop csCKD was 19 mo (IQR 7–37).

The Kaplan-Meier plots of csCKD-free survival with the estimated probabilities to develop csCKD at 12, 24, 36, 48, and 60 mo, for the overall and PN cohorts, stratified according to tumour complexity, are shown in Figures 2 and 3.

In the overall cohort, the estimated csCKD-free survival rates were 97%, 95%, 93%, 90%, and 86% at 12, 24, 36, 48, and 60 mo, respectively (Fig. 2). We found a significant difference in csCKD-free survival rates between patients with high- and low-complexity tumours, as well as between patients with high- and intermediate-complexity tumours

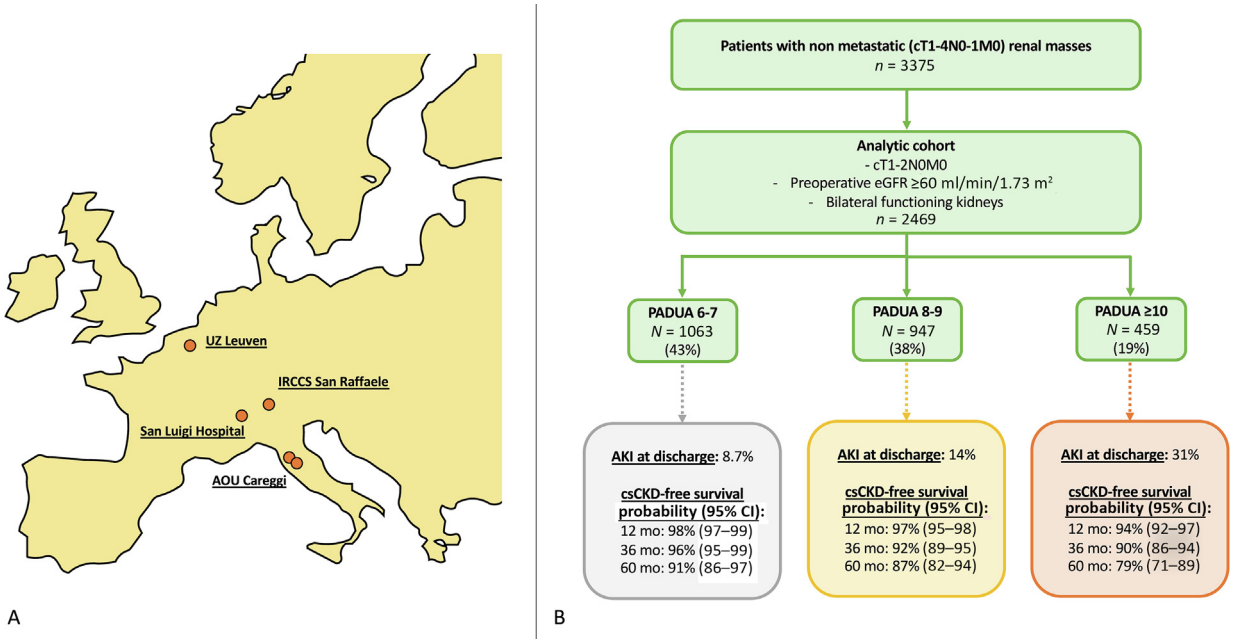


Fig. 1 – Overview of the design and main outcomes of the study. (A) Geographical location of the five urology units participating in the study (Unit of Urological Robotic Surgery and Renal Transplantation, and Unit of Urological Oncologic Minimally Invasive Robotic Surgery and Andrology, Careggi Hospital, University of Florence, Florence, Italy; Division of Urology, San Luigi Hospital, University of Turin, Orbassano, Turin, Italy; Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; and Department of Urology, University Hospitals Leuven, Leuven, Belgium). (B) Flowchart showing the inclusion criteria and the main outcomes of the study (proportion of patients experiencing acute kidney injury and estimated probability of clinically significant chronic kidney disease–free survival during the follow-up, stratified by tumour complexity according to Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score. AKI = acute kidney injury; CI = confidence interval; csCKD = clinically significant chronic kidney disease; eGFR = estimated glomerular filtration rate.

($p = 0.014$ and $p = 0.038$, respectively). For instance, at 12 mo after surgery, the estimated probability of csCKD-free survival rates were 98%, 97%, and 94% in patients with low-, intermediate-, and high-complexity tumours, respectively (Fig. 3A). At 36 mo, these estimates were 96%, 92%, and 90%, respectively.

On the contrary, there was no significant difference in csCKD-free survival rates in the PN cohort stratified by tumour complexity (Fig. 3B).

At the multivariable Cox regression analysis, age-adjusted Charlson Comorbidity Index (OR: 1.31; 95% CI 1.16–1.48, $p < 0.001$), preoperative eGFR (OR for each 10 ml/min increase: 0.58; 95% CI 0.47–0.71, $p < 0.001$), tumour complexity (OR for high- vs low-complexity tumours: 2.72; 95% CI 1.32–5.59, $p = 0.006$; OR for intermediate- vs low-complexity tumours: 1.82; 95% CI 1.11–3.71, $p = 0.043$), and RN (OR: 3.90; 95% CI 2.21–6.86, $p < 0.001$) significantly predicted the risk of developing csCKD during the follow-up (Table 3). The results were similar in the sensitivity analysis restricted to patients who underwent PN.

4. Discussion

Renal function preservation represents one of the most critical aspects impacting decision-making and management of patients with localised renal masses [1,2].

Of note, in surgical candidates who have a single renal mass, two kidneys, and preserved baseline renal function, especially those with a highly complex renal mass, clinicians could recommend RN over PN relying on its presumed potentially less burdensome functional consequences [4,19,20].

However, even in this elective setting, the risk of surgically induced CKD should not be overlooked, given the adverse sequelae and the increased risk of mortality caused by CKD [2,6]. Interestingly, the prognostic impact of medical versus surgical CKD has been debated [6], as CKD after nephrectomy was associated with a tangible risk of kidney failure and death, comparable with other major causes of CKD [21]. In this regard, a landmark study by Wu et al [22] using a competing-risk analysis showed significantly reduced non–renal cancer–related survival for surgically induced CKD with eGFR <45 ml/min/1.73 m^2 compared with no-CKD or surgically induced CKD with eGFR 45–60 ml/min/1.73 m^2.

In this scenario, an individualised risk-based approach to identify patients at a higher risk of developing new-onset csCKD after PN or RN, as well as the triggers for nephrological assessment, is still controversial across European and American guidelines [1,4].

To the best of our knowledge, this is one of the largest series exploring the pattern and predictors of renal function deterioration in contemporary patients with two functioning kidneys undergoing PN or RN for a single renal mass at four referral academic centres. Interestingly, this elective cohort represented 80% of our patients with localised renal masses treated during the study period (Fig. 1).

Table 1 – Pre-, intra-, and postoperative characteristics of the study cohort, stratified according to tumour complexity according to the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score

	Patients with low-complexity tumour (PADUA 6–7; *N* = 1063)	Patients with intermediate-complexity tumour (PADUA 8–9; *N* = 947)	Patients with high-complexity tumour (PADUA ≥10; *N* = 459)	*p* value
Preoperative characteristics				
Age (yr), median (IQR)	64 (55–72)	64 (55–72)	61 (51–70)	**<0.001**
Male gender, *n* (%)	702 (66)	654 (69)	311 (68)	0.3
Charlson Comorbidity Index without age, median (IQR)	2 (0–4)	2 (0–3)	1 (0–2)	**<0.001**
Body mass index (kg/m^2), median (IQR)	25.3 (23.2–28.2)	25.5 (23.4–28.4)	25.5 (23.5–28.3)	0.4
ASA score, *n* (%)				0.11
1	174 (16)	163 (17)	100 (22)	
2	701 (66)	649 (69)	288 (63)	
3	186 (18)	134 (14)	69 (15)	
4	2 (0.2)	1 (0.1)	2 (0.4)	
Previous abdominal surgery, *n* (%)	330 (31)	296 (31)	141 (31)	0.9
History of hypertension, *n* (%)	431 (41)	422 (45)	206 (45)	0.11
History of diabetes, *n* (%)	223 (21)	171 (18)	64 (14)	**<0.001**
Preoperative eGFR (ml/min/1.73 m^2), median (IQR)	82.7 (79.3–93.2)	82.2 (78.2–92.2)	84.0 (77.0–95.5)	0.2
Maximal diameter at preoperative imaging (cm), median (IQR)	3 (2–4)	4 (3–5)	5 (4–6)	**<0.001**
cT stage, *n* (%)				**<0.001**
cT1a	919 (87)	528 (56)	143 (31)	
cT1b	144 (14)	333 (35)	222 (48)	
cT2a	0 (0)	64 (6.8)	75 (16)	
cT2b	0 (0)	22 (2.3)	19 (4.1)	
Left side, *n* (%)	556 (52)	474 (50)	225 (49)	0.4
Intraoperative features				
Partial nephrectomy, *n* (%)	1035 (97)	871 (92)	345 (75)	**<0.001**
Warm ischaemia time (min), median (IQR)	13 (8–16)	16 (11–20)	20 (15–25)	**<0.001**
Minimally invasive surgical approach, *n* (%)	1037 (98)	866 (91)	390 (85)	**<0.001**
Operative time (min), median (IQR)	120 (90–154)	135 (107–175)	149 (115–180)	**<0.001**
Estimated blood loss (ml), median (IQR)	206 (100–357)	200 (100–369)	200 (100–345)	0.9
Intraoperative complications, *n* (%)	30 (2.8)	44 (4.6)	28 (6.1)	**<0.001**
Early postoperative outcomes				
Hospital stay (d), median (IQR)	4 (4–6)	5 (4–6)	5 (4–7)	**<0.001**
Acute kidney injury, *n* (%)	93 (8.7)	134 (14)	144 (31)	**<0.001**
Any-grade postoperative complications, *n* (%)	194 (18)	208 (22)	111 (24)	**0.023**
High grade (Clavien-Dindo grade ≥3) postoperative complications, *n* (%)	12 (1.1)	15 (1.6)	6 (1.3)	0.7
Histopathological outcomes				
Histotype, *n* (%)				**<0.001**
Clear cell RCC	475 (45)	495 (52)	269 (59)	
Papillary RCC	200 (19)	130 (14)	54 (12)	
Chromophobe RCC	79 (7.4)	91 (9.6)	34 (7.4)	
Oncocytoma	147 (14)	106 (11)	54 (12)	
Angiomyolipoma	71 (6.7)	44 (4.6)	18 (3.9)	
Other	69 (6.5)	64 (6.7)	30 (6.5)	
NA	22 (2.1)	17 (1.8)	0 (0.0)	
Benign tumour, *n* (%)	233 (22)	158 (17)	76 (10)	**<0.001**
NA	22 (2.1)	17 (1.8)	0 (0)	
pT stage (*N* = 1990), *n* (%)				**<0.001**
pT1	755 (92)	628 (80)	245 (64)	
pT2	9 (1.1)	46 (5.9)	43 (11)	
pT3	57 (6.9)	109 (14)	94 (25)	
pT4	2 (0.2)	1 (0.1)	1 (0.3)	
pN1 stage, *n* (%)	4 (0.4)	21 (2.2)	11 (2.4)	0.066
NA	22 (2.1)	17 (1.8)	0 (0)	

ASA = American Society of Anesthesiologists; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NA = not available; RCC = renal cell carcinoma.

Our study provides several key findings.

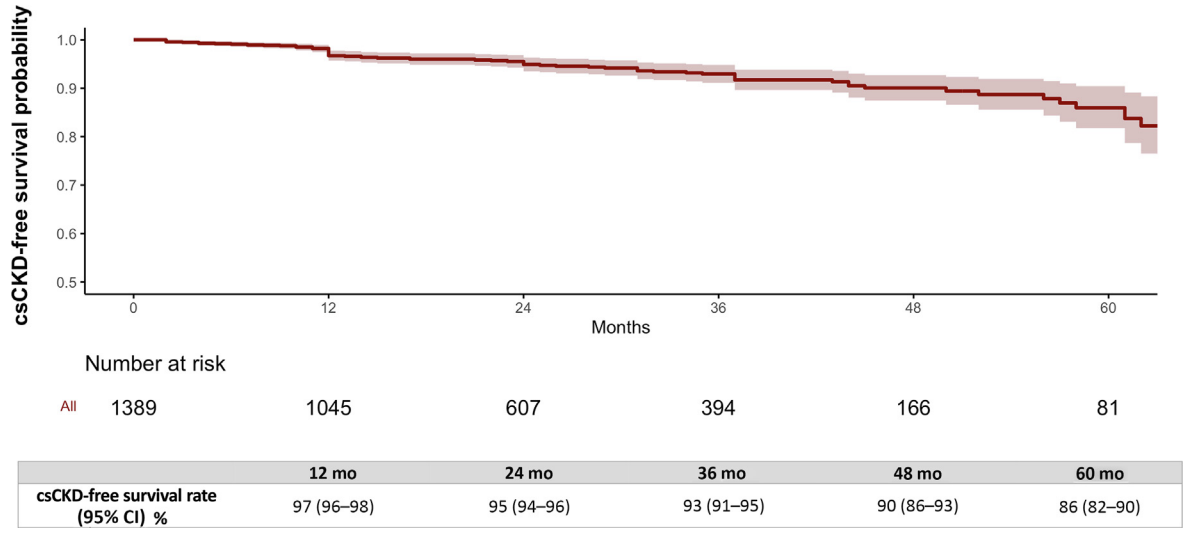
First, a tangible proportion of patients (15%) experienced AKI at hospital discharge, especially those with higher-complexity tumours. This result was confirmed in patients who underwent PN, stressing the clinical relevance of this event regardless of the surgical procedure. Moreover, recent evidence points to AKI being a potential driver of subsequent renal function decline in the longer follow-up [13,23].

In the overall cohort, specific patient-, tumour-, and surgery-related factors significantly influenced the risk of AKI (Table 2). Namely, while tumour complexity and RN were the strongest predictors, patient BMI and a history of hypertension also played a role; as such, even in patients with preserved baseline renal function, comorbidities might modulate the risk of AKI and could be the triggers for a nephrological preoperative assessment [4]. In the PN cohort,

Table 2 – Multivariable logistic regression analysis assessing the predictors of acute kidney injury at hospital discharge in patients with a localised renal mass, two functioning kidneys, and preserved baseline renal function included in the overall cohort and in the partial nephrectomy cohorts

	Overall cohort			PN cohort		
	OR	95% CI	*p* value	OR	95% CI	*p* value
BMI	1.04	1.01–1.07	**0.023**	1.02	0.98–1.06	0.3
Age-adjusted Charlson Comorbidity Index	0.97	0.91–1.04	0.4	0.98	0.90–1.06	0.9
History of hypertension	1.30	1.01–1.68	**0.047**	1.34	0.97–1.85	0.11
History of diabetes	0.95	0.61–1.46	0.8	1.09	0.64–1.86	0.8
Preoperative eGFR (ml/min/1.72 m^2)	1.03	0.98–1.03	0.081	1.03	0.99–1.04	0.072
Tumour complexity: High (PADUA ≥10) vs low (PADUA 6–7)	3.02	2.14–4.26	**<0.001**	2.18	1.41-3.38	**<0.001**
Intermediate (PADUA 8–9) vs low (PADUA 6–7)	1.54	1.12–2.12	**0.007**	1.32	0.90-1.93	0.2
Open vs minimally invasive surgery	1.32	0.86–2.00	0.12	1.77	1.02–3.10	**0.043**
Warm ischaemia time (min)	–			1.05	1.03–1.07	**<0.001**
RN vs PN	10.17	7.26–14.24	**<0.001**	–		

BMI = body mass index; CI = confidence interval; eGFR = estimated Glomerular Filtration Rate; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical Classification; OR = odds ratio; PN = partial nephrectomy; RN = radical nephrectomy.



	12 mo	24 mo	36 mo	48 mo	60 mo
csCKD-free survival rate (95% CI) %	97 (96–98)	95 (94–96)	93 (91–95)	90 (86–93)	86 (82–90)

Fig. 2 – Kaplan-Meier plot of clinically significant chronic kidney disease (csCKD)-free survival in the overall cohort. CI = confidence interval.

the risk of AKI was mainly related to tumour complexity and surgery-related factors, including WIT and surgical approach (Table 2), as reported previously [24,25]. In this context, tumour complexity might represent a surrogate metrics for the quantity of vascularised parenchyma preserved during PN [26].

A second key finding of our study is that, during the follow-up, the risk of csCKD after surgery in patients with two kidneys, preserved preoperative renal function, and a single localised renal mass was relatively low, but not clinically negligible (Fig. 2). In fact, while the estimated risk of csCKD was 3% at 12 mo, it increased with time, up to 14% at 60 mo. The risk was higher among patients with high-complexity tumours, for whom the estimated probability of experiencing csCKD ranged from 6% at 12 mo up to 21% at 60 mo (Fig. 3A). A similar pattern for the risk of csCKD was reported for patients who underwent PN, yet with a less pronounced influence of tumour complexity (Fig. 3B).

In the overall cohort, predictors of new-onset csCKD during the follow-up included nonmodifiable patient-related characteristics, namely, the preoperative "functional reserve" (ie, higher baseline eGFR), age-adjusted Charlson Comorbidity Index, and tumour complexity, as well as RN. Interestingly, the same factors were associated with the risk of csCKD also in the PN cohort (Table 3). Overall, these findings suggest that, beyond the early perioperative period, the risk of csCKD after surgery is influenced by both the baseline quality of the kidney and the "quantity" of nephrons spared during surgery [27].

From a clinical standpoint, our data raise awareness on the risk of csCKD in the "best scenario" of patients with two kidneys and preserved preoperative renal function, reinforcing the concept that the choice between PN and RN has a significant functional impact beyond perioperative and oncological outcomes [1,2,28]. In this elective setting, if oncological outcomes are not jeopardised, PN should be

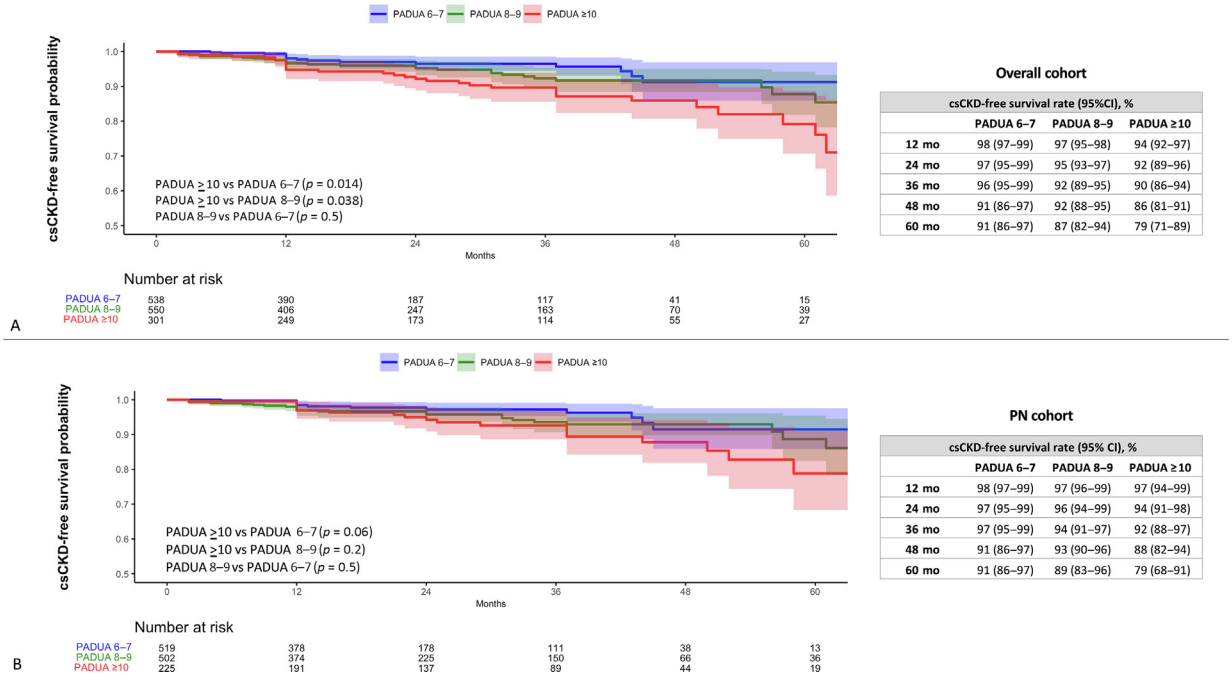


Fig. 3 – Kaplan-Meier plots of clinically significant chronic kidney disease (csCKD)-free survival in the (A) overall cohort and (B) partial nephrectomy cohort, stratified by tumour complexity according to the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score (low complexity: PADUA score 6–7; intermediate complexity: PADUA score 8–9; and high complexity: PADUA score ≥10).

Table 3 – Multivariable Cox regression analysis assessing the predictors of new-onset clinically significant chronic kidney disease (csCKD) during the follow-up

		Overall cohort			PN cohort		
		HR	95% CI	*p* value	HR	95% CI	*p* value
BMI		0.99	0.92–1.06	0.7	1.03	0.97–1.12	0.4
Age-adjusted Charlson Comorbidity Index		1.31	1.16–1.48	**<0.001**	1.32	1.14–1.53	**<0.001**
Preoperative eGFR (10 ml/min increase)		0.58	0.47–0.71	**<0.001**	0.63	0.49–0.80	**<0.001**
No history of hypertension		0.88	0.53–1.45	0.6	0.86	0.47–1.55	0.6
No history of diabetes		1.12	0.57–2.2	0.7	1.04	0.46–2.37	0.9
Tumour complexity	High (PADUA ≥10) vs low (PADUA 6–7)	2.72	1.32–5.59	**0.006**	3.39	1.43–8.02	**0.006**
	Intermediate (PADUA 8–9) vs low (PADUA 6–7)	1.82	1.11–3.71	**0.043**	2.10	1.08–4.84	**0.041**
Open vs minimally invasive surgery		1.27	0.63–2.54	0.5	1.53	0.59–4.00	0.4
RN vs PN		3.90	2.21–6.86	**<0.001**	–		

BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical Classification; PN = partial nephrectomy; RN = radical nephrectomy.

prioritised to minimise the risk of new-onset csCKD, even through centralisation of care [1,4,29–31]).

Lastly, while not routinely considered "at risk" [2,7], selected patients, such as those with higher-complexity tumours, a lower preoperative eGFR, or a higher comorbidity burden, could benefit from nephrological assessment before and after surgery [32].

Our findings should be interpreted in light of the study limitations. First, despite the large sample size and prospective data collection, our dataset lacked granular data on eGFR trajectories within the 1st year after surgery and on potential confounders such as new-onset medical comorbidities (hypertension, diabetes, etc.) that might have influenced the risk of csCKD during the follow-up. As such, the results of our multivariable analyses are hypothesis generating. Moreover, our analysis is based on a midterm follow-up.

Second, the generalisability of our findings might be limited to high-volume referral centres. Third, despite our efforts, a non-negligible proportion of patients included in our dataset lacked complete functional follow-up data (partly due to the tertiary referral nature of our centres). Of note, a sensitivity analysis excluded a significant attrition bias in our cohort, as patients without data on follow-up had similar baseline characteristics to those included in our analysis (Supplementary Table 1).

Acknowledging these limitations, our study provides a foundation for significant research in this field. Further research efforts are needed to improve shared decision-making by predicting the risk of csCKD using preoperative models [14], to explore the differential impact of surgical resection (and its technical nuances) and patients' comorbidities on the risk of csCKD in the long-term follow-up,

and to standardise preoperative risk stratification and postoperative follow-up schedules, selecting patients who are more likely to benefit from a nephrological assessment.

5. Conclusions

The risk of AKI and new-onset csCKD in contemporary patients with two functioning kidneys and preserved baseline renal function undergoing surgery for a localised renal mass is not clinically negligible, especially in those with higher-complexity tumours.

While unmodifiable patient/tumour-related characteristics (medical comorbidities, preoperative eGFR, and tumour complexity) played a role, modifiable surgery-related factors had a significant impact on the risk of AKI and csCKD during the follow-up. As such, even in this elective setting, PN should be prioritised if technically feasible and oncologically safe.

Further research is needed to assess the differential impact of surgical resection and patients' comorbidities on the risk of csCKD in the long-term follow-up, as well as to identify the patients who are more likely to benefit from pre- and postoperative nephrological assessment.

***Author contributions*:** Riccardo Campi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept *and design*: Pecoraro, Campi.
Acquisition of data: Pecoraro, Roussel, Amparore, Mari, Grosso, Checcucci, Larcher.
Analysis and interpretation of data: Pecoraro, Campi, Capitanio, Amparore.
Drafting of the manuscript: Pecoraro, Campi.
Critical revision of the manuscript for important intellectual content: Montorsi, Van Poppel, Porpiglia, Capitanio, Minervini, Albersen, Serni.
Statistical analysis: Pecoraro, Campi.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Albersen.
Other: None.

Financial disclosures: Riccardo Campi certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.04.011.

References

[1] Ljungberg B, Albiges L, Bedke J, et al. European Association of Urology (EAU) guidelines on renal cell carcinoma. Version 2022. Arnhem, The Netherlands: EAU Guidelines Office. https://uroweb.org/guideline/renal-cell-carcinoma/#1.
[2] Chandrasekar T, Boorjian SA, Capitanio U, Gershman B, Mir MC, Kutikov A. Collaborative review: factors influencing treatment decisions for patients with a localized solid renal mass. Eur Urol 2021;80:575–88.
[3] Lane BR, Demirjian S, Derweesh IH, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. Eur Urol 2015;68:996–1003.
[4] Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. J Urol 2021;206:199–208.
[5] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[6] Ellis RJ. Chronic kidney disease after nephrectomy: a clinically-significant entity? Transl Androl Urol 2019;8:S166–74.
[7] Capitanio U, Larcher A, Kriegmair MC, et al. Do we truly care about the functional outcomes for renal cancer patients? Multidisciplinarity is still far away. Eur Urol 2019;75:349–50.
[8] Antonelli A, Minervini A, Sandri M, et al. Below safety limits, every unit of glomerular filtration rate counts: assessing the relationship between renal function and cancer-specific mortality in renal cell carcinoma. Eur Urol 2018;74:661–7.
[9] Palacios DA, Zabor EC, Munoz-Lopez C, et al. Does reduced renal function predispose to cancer-specific mortality from renal cell carcinoma? Eur Urol 2021;79:774–80.
[10] Rathi N, Palacios DA, Abramczyk E, et al. Predicting GFR after radical nephrectomy: the importance of split renal function. World J Urol 2022;40:1011–8.
[11] Tanaka H, Wang Y, Suk-Ouichai C, et al. Can we predict functional outcomes after partial nephrectomy? J Urol 2019;201:693–701.
[12] Bhindi B, Lohse CM, Schulte PJ, et al. Predicting renal function outcomes after partial and radical nephrectomy. Eur Urol 2019;75:766–72.
[13] Martini A, Cumarasamy S, Beksac AT, et al. A nomogram to predict significant estimated glomerular filtration rate reduction after robotic partial nephrectomy. Eur Urol 2018;74:833–9.
[14] Pecoraro A, Campi R, Bertolo R, et al. Estimating postoperative renal function after surgery for nonmetastatic renal masses: a systematic review of available prediction models. Eur Urol Oncol 2023. https://doi.org/10.1016/j.euo.2022.11.007, In press.
[15] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[16] Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825–30.
[17] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[18] Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. Eur Urol 2019;75:358–67.
[19] Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2007;51:1606–15.
[20] Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014;65:372–7.
[21] Ellis RJ, Cameron A, Gobe GC, et al. Kidney failure, CKD progression and mortality after nephrectomy. Int Urol Nephrol 2022;54:2239–45.
[22] Wu J, Suk-Ouichai C, Dong W, et al. Analysis of survival for patients with chronic kidney disease primarily related to renal cancer surgery. BJU Int 2018;121:93–100.
[23] Bravi CA, Vertosick E, Benfante N, et al. Impact of acute kidney injury and its duration on long-term renal function after partial nephrectomy. Eur Urol 2019;76:398–403.
[24] Campi R, Di Maida F, Lane BR, et al. Impact of surgical approach and resection technique on the risk of Trifecta Failure after partial nephrectomy for highly complex renal masses. Eur J Surg Oncol 2022;48:687–93.

[25] Minervini A, Campi R, Lane BR, et al. Impact of resection technique on perioperative outcomes and surgical margins after partial nephrectomy for localized renal masses: a prospective multicenter study. J Urol 2020;203:496–504.
[26] Campbell SC, Campbell JA, Munoz-Lopez C, Rathi N, Yasuda Y, Attawettayanon W. Every decade counts: a narrative review of functional recovery after partial nephrectomy. BJU Int 2023;131:165–72.
[27] Mir MC, Ercole C, Takagi T, et al. Decline in renal function after partial nephrectomy: etiology and prevention. J Urol 2015;193:1889–98.
[28] Capitanio U, Larcher A, Cianflone F, et al. Hypertension and cardiovascular morbidity following surgery for kidney cancer. Eur Urol Oncol 2020;3:209–15.
[29] Kim SP, Campbell SC, Gill I, et al. Collaborative review of risk benefit trade-offs between partial and radical nephrectomy in the management of anatomically complex renal masses. Eur Urol 2017;72:64–75.
[30] Grande P, Campi R, Rouprêt M. Relationship of surgeon/hospital volume with outcomes in uro-oncology surgery. Curr Opin Urol 2018;28:251–9.
[31] Williams SB, Ray-Zack MD, Hudgins HK, et al. Impact of centralizing care for genitourinary malignancies to high-volume providers: a systematic review. Eur Urol Oncol 2019;2:265–73.
[32] Stewart GD, Klatte T, Cosmai L, et al. The multispeciality approach to the management of localised kidney cancer. Lancet 2022;400:523–34.