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Urinary NephroCheck® test, as a marker of subclinical postoperative AKI, correlates with long-term GFR decline in patients undergoing partial nephrectomy: a prospective bicentric observational study

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Abstract

Background Nephron-sparing surgery (NSS) represents the preferred technique to treat localized renal lesions, not being exempted from the risk of postoperative acute kidney injury (AKI) to happen, though. Patients experiencing postoperative AKI, either clinical or subclinical, are more susceptible to develop chronic kidney disease.

Methods Patients scheduled for NSS in localized renal cell carcinoma were recruited. Patients were grouped according to postoperative AKI development and postoperative NephroCheck value: group 1 (normal), no AKI and no increased biomarker; group 2 (subclinical AKI), no AKI but increased NephroCheck (> 0.3 at 4 h postoperatively); group 3, AKI and no increased NephroCheck; group 4 (clinical AKI), AKI and increased NephroCheck. Samples were collected pre- and post-operatively; renal function was re-assessed up to 24 months.

Results Among 131 patients included, 42% developed clinical AKI. Based on NephroCheck® and clinical AKI criteria, patients could be divided in four groups with significantly different eGFR at 24 months ($p = 0.0003$). Multivariate analysis confirmed clinical AKI as an independent predictor of eGFR decline at 24 months ($p < 0.0003$). In subclinical AKI's subgroup [20/131 (15%)], characterized by urinary NephroCheck® >0.3 and serum creatinine increase < 0.3 mg/dL, NephroCheck® appeared as an independent predictor of severe eGFR decline at 24 months (OR 3.76, $p = 0.02$); in this subgroup, eGFR decline resulted significantly more severe compared to eGFR decline in patients with neither serum creatinine nor tubular damage markers' elevation.

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Conclusions In patients undergoing NSS, the most reliable predictor of long-term eGFR decline is represented by the occurrence of postoperative clinical AKI. In this setting, NephroCheck® appeared able to identify 'subclinical AKI' and consequently patients at increased risk of 24-month-eGFR decline.

Keywords Acute kidney injury, Partial nephrectomy, Renal cell carcinoma, TIMP-2, IGFBP7, NephroCheck

Introduction

Postoperative AKI is a severe complication of renal surgery [1]. By minimizing parenchymal mass loss and ischemia-related damages, nephron-sparing surgery (NSS) represents the preferred technique to treat localized renal lesions [2, 3] and better preserve kidney function [4]. However, patients undergoing NSS are not exempted from the risk of postoperative AKI, with an incidence ranging from 5.5–34% [5]. In this setting, the contribute of the parenchymal mass reduction is generally minimal, since T1 TNM lesions are characterized by an average small tumour size and surgical approach is focused on maximal preservation of functional renal parenchyma. Postoperative AKI commonly has a multifactorial aetiology [such as ischaemia–reperfusion injury (e.g. clamp), microembolization, intraoperative hypotension and decreased renal perfusion pressure (e.g. bleeding, anesthetics, pneumoperitoneum during laparoscopic surgery), inflammation, and use of nephrotoxic drugs] [1] and can be related to chronic kidney disease (CKD) development or worsening [1, 5–7]. Among patients undergoing renal surgery, a subset will develop CKD during follow-up, even though they haven't developed postoperative AKI at the time of surgery [6]. The presence of an unrecognized acute kidney insult (not reaching KDIGO criteria for clinical AKI) potentially able to determine CKD in the long run is connsistent with the definition of subclinical AKI [2–4, 8, 9]. Subclinical AKI occurs when a biomarker of tubular stress/damage is positive while serum creatinine (sCr) is not rising [10]. In the majority of individuals who suffered from AKI, once recovered, a variable degree of CKD usually lasts; this happens in those suffering from subclinical AKI as well, as Ronco et al. formerly underlined [10]. The extent of the long-term GFR decline is also an expression of several other variables which can add to the renal damage mediated by AKI or act independently, such as advanced age, pre-existing CKD, baseline comorbidities (diabetes, obesity, heart failure), and parenchymal mass reduction.

Consequently, the global incidence and prevalence of CKD in people who underwent renal surgery is likely to be largely underreported [11] so identifying those patients suffering from subclinical AKI becomes essential, together with early identification of clinical AKI and long-term CKD development [10].

Several novel biomarkers have been identified in recent years [12–15] some of whom allow early prediction of kidney damage, rising before sCr elevation [16, 17] and allowing clinicians to adopt nephroprotective strategies and optimize perioperative care.

In 2014 the FDA approved NephroCheck®, the first test for AKI's risk assessment made by combining two urinary biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7). To date, NephroCheck® is the only commercially available test for the product of the urinary concentration of [TIMP-2] × [IGFBP7]. TIMP-2 (distal tubule origin) and IGFBP7 (proximal tubule origin) are markers of cell-cycle arrest that may signal, in autocrine and paracrine fashions, that the renal epithelium has been stressed.

The effectiveness of NephroCheck® in early detection of AKI has been assessed in several studies [18, 19] and many Centers have confirmed its effectiveness in different surgical settings [20].

In a previous monocentric study [21] our group identified NephroCheck® as a promising biomarker likely able to efficiently identify clinical AKI and predict long-term eGFR decline after NSS; however, the monocentric design and the small number of patients made it necessary to confirm these results in a bicentric study with a larger cohort.

Still we need to focus on pursuing systematic identification of those patients suffering from subclinical AKI, likewise identifying the potential role of new biomarkers such as NephroCheck® in predicting long-term CKD. This would allow a customized postoperative surveillance [22] in order to promote strategies of nephroprotection [23] and reduce the development, progression of CKD and end-stage kidney disease (ESKD) [24].

The primary aim of the study is to describe the incidence of clinical and subclinical AKI in a group of patients undergoing NSS. The secondary aim of the study is to test a potential association between clinical and subclinical AKI with long-term CKD.

Materials and methods

In this prospective observational study, we evalueted all consecutive patients scheduled for NSS in suspected localized RCC at Careggi University Hospital, Florence, Italy, and at the University Medical Centre Mannheim, Baden-Württemberg, Germany, between 1st May 2018 and 30th November 2018.

The study was conducted in accordance with the Declaration of Helsinki. Written.

Informed consent was obtained from each subject involved in the study.

Inclusion criteria were: (1) age ≥ 18 years; (2) clinical evidence of a localized renal cell carcinoma (T1, N0, M0); (3) partial nephrectomy as surgical treatment.

Exclusion criteria were: (1) radical nephrectomy; (2) the need for re-operation within 2 years; (3) length of follow-up < 2 years.

Collected data included demographic, surgical variables, preoperative and postoperative clinical and laboratory parameters.

A sCr increase ≥ 0.3 mg/dL within 48 h or a sCr increase of 1.5 times the baseline value known to have occurred within the prior 7 days were identified as postoperative "clinical AKI", according to the Kidney Disease: Improving Global Outcomes [KDIGO] criteria [25]. Although the urine output criterion of 0.5 ml/kg/hour for 6 h represents a criterion of AKI, it has not been included in our definition of clinical AKI.

Blood and urine samples were collected preoperatively and at predefined time points postoperatively (4 h, 24 h, 48 h). Plasma levels of sCr, urine levels of [TIMP-2] × [IGFBP7] (*NephroCheck® Test*, *San Diego*, *CA*, *USA*) were analyzed. NephroCheck® test was tested preoperatively and at 4 h postoperatively.

Subclinical AKI was defined by an increase of the biomarker of tubular stress/damage (NephroCheck® value > 0.3 at 4 h postoperatively) with a concomitant stable sCr (or sCr increase < 0.3 mg/dL).

Kidney function (sCr and eGFR) was re-assessed at 6, 12, 18, and 24 months postoperatively, to quantify the long-term eGFR decline and identify a potential correlation with NephroCheck® test. Those patients who didn't reach a 24-month follow-up post-surgery were excluded.

The expected rate of decline in eGFR in adults without CKD was about 0.9 ml/min/1.73 m2 per year, while adults with CKD had an expected decline in eGFR that ranged from − 1.92 to − 4.12 ml/min/1.73 m2 per year [26] depending on the different underlying causes of CKD. Consequently, a decrease in GFR of ≥ 4.12 per year and ≥ 8.3 mL/min/1.73 m2 during the 2-year follow-up was considered a "severe GFR decline".

The partial nephrectomy procedure was carried out in a standardised way via open, pure laparoscopic, or robot-assisted laparoscopic approach.

Surgery was performed by experienced surgeons (> 500 PNs) in both centers.

Among surgical variables we collected: tumour characteristics (radiological maximum tumour diameter), PADUA [preoperative aspects and dimensions used for an anatomical] nephrometry score, intra-operative data (operating time, ischaemic time, estimated blood loss), and postoperative outcomes (overall and severe complications according to the Clavien-Dindo scale).

Statistical analysis

Data were reported as absolute count (percentage) for categorical variables, and median and interquartile range (IQR) for continuous variables. The receiver operating characteristics (ROC) curve and univariate logistic regression analysis assessed the ability of biomarkers to predict eGFR decline and AKI. Odds ratios and ROC-AUC are expressed with their own 95% confidence intervals [95%CI]. Correlation between biomarkers levels postoperatively and the amount of GFR decline at 24 months was tested using Pearson correlation coefficient; ROC curve and univariate regression analysis assessed the ability of biomarkers to predict GFR decline at the same time point. Finally, to evaluate the association between different parameters with GFR decline at 24 months, a multiple linear regression model was performed including known predictive biomarkers and known risk factors for long-term eGFR decline as covariates (such as postoperative NephroCheck® value, age, preoperative/baseline eGFR, clinical AKI and tumor size). A p-value < 0.05, 2 sided, was considered statistically significant.

Results

Overall, 131 patients were included. Fifty-five patients underwent open and 73 robotic PN, while 3 were converted to laparoscopic PN, with a mean operative time of 151 ± 49 min and a median ischemia time of 14 ± 9.7 min.

Overall, 55/131 (42%) patients developed clinical AKI within 48 h after renal surgery.

Clinical, demographic, and surgical variables, in relation to clinical or subclinical AKI development, are reported in Table 1.

NephroCheck® value > 0.3 (the previously validated cut-off value for AKI prediction) was observed in 33/55 (60%) and 20/76 (26%) patients respectively for clinical AKI and non-AKI groups at 4 h postoperatively ($p = 0.0001$).

A significant association between NephroCheck® at 4 h and clinical AKI was found (OR 3.07 95% CI 1.39–6.79; $p = 0.0055$).

Considering the whole cohort, the presence of a urinary NephroCheck® value > 0.3 showed a sensitivity of 60% and a specificity of 74%, with a positive predictive value of 62% and a negative predictive value of 74% in predicting the diagnosis of clinical AKI.

Preoperative NephroCheck® values were not significantly different between patients with and without CKD (0.30 vs. 0.39, $p = 0.86$), confirming that its increase is an expression of acute stress/damage.

Group 2 showed a significantly lower tumor size ($p = 0.03$), RENAL score ($p = 0.05$) and warm ischemia time ($p < 0.001$) compared to Group 3.

Table 1 Clinical, demographic, and surgical variables of the patients enrolled in the study, according to postoperative AKI development and postoperative nephrocheck value

	Overall	Group 1 (biomarker -, creatinine -) (normal)	Group 2 (biomarker +, creatinine -) (subclinical AKI)	Group 3 (creatinine +, biomarker -) (clinical AKI)	Group 4 (creatinine +, biomarker +) (clinical AKI)	*p*-values
Patients, n (%)	131	56	20	22	33	
Age (years)	65.1 ± 11.0	63.6 ± 12.7	65.2 ± 9.8	64.3 ± 9.4	68.3 ± 9.4	0.62 (1vs2) 0.76 (2vs3)
Male gender, n (%)	88 (67)	31 (55)	13 (65)	15 (68)	29 (88)	0.45 (1vs2) 0.83 (2vs3)
Preoperative comorbidities						
BMI	27.0 ± 4.2	25.7 ± 4.0	28.8 ± 5.1	27.0 ± 3.5	28.0 ± 4.0	0.007 (1vs2) 0.19 (2vs3)
CKD (eGFR < 60), n (%)	11 (8)	4 (7)	1 (5)	1 (5)	5 (15)	1.00 (1vs2) 1.00 (1vs2)
Diabetes, n (%)	16 (12)	8 (14)	3 (15)	0 (0)	5 (15)	1.00 (1vs2) 0.10 (2vs3)
Cardiovascular disease, n (%)	26 (20)	15 (27)	4 (20)	1 (5)	6 (18)	0.76 (1vs2) 0.17 (2vs3)
Hypertension, n (%)	82 (63)	28 (50)	14 (70)	16 (73)	24 (73)	0.12 (1vs2) 0.85 (2vs3)
Preoperative laboratory values						
Hemoglobin (g/dL)	14.2 ± 1.6	14.1 ± 1.4	14.8 ± 1.9	14.2 ± 1.9	14.0 ± 1.5	0.09 (1vs2) 0.35 (2vs3)
Serum creatinine (mg/dL)	0.97 ± 0.42	0.93 ± 0.29	0.90 ± 0.17	0.92 ± 0.22	1.11 ± 0.69	0.61 (1vs2) 0.79 (2vs3)
Preoperative eGFR (CKD-EPI) (ml/min)	81.3 ± 18.2	82.4 ± 18.0	82.5 ± 13.7	85.4 ± 17.1	76.1 ± 21.0	0.98 (1vs2) 0.56 (2vs3)
NephroCheck® Test	0.39 ± 0.36	0.39 ± 0.35	0.38 ± 0.28	0.20 ± 0.21	0.51 ± 0.47	0.97 (1vs2) 0.13 (2vs3)
Surgical parameters						
Tumor size (cm)	3.7 ± 1.7	3.6 ± 1.4	3.1 ± 1.5	4.2 ± 1.6	4.0 ± 2.2	0.20 (1vs2) 0.03 (2vs3)
RENAL score	7.6 ± 1.8	7.5 ± 1.9	6.9 ± 1.9	8.1 ± 1.7	7.7 ± 1.7	0.20 (1vs2) 0.05 (2vs3)
PADUA score	8.4 ± 2.6	8.1 ± 2.9	8.0 ± 1.8	9.1 ± 2.7	8.9 ± 2.3	0.90 (1vs2) 0.12 (2vs3)
Warm ischemia time (min)	14.3 ± 9.7	15.5 ± 9.9	7.2 ± 8.1	18.8 ± 7.5	13.7 ± 9.5	0.002 (1vs2) < 0.001 (2vs3)
Operative time (min)	151 ± 49	153 ± 50	136 ± 46	158 ± 36	153 ± 56	0.17 (1vs2) 0.09 (2vs3)
Postoperative renal parameters						
NephroCheck® Test	0.55 ± 1.06	0.12 ± 0.08	0.82 ± 0.47	0.12 ± 0.07	1.42 ± 1.78	< 0.001 (1vs2) < 0.001 (2vs3)
AKI stage 2–3, n (%)	10 (8)	0	0	2 (9)	8 (24)	1.00 (1vs2) 0.96 (1vs2)
Outcome						
24-month eGFR decline (ml/min)	-8.3 ± 13.2	-2.6 ± 9.2	-8.2 ± 9.3	-16.6 ± 18.4	-12.3 ± 12.9	0.02 (1vs2) 0.07 (2vs3)
Severe 24-month eGFR decline (≥ 8.3 mL/min), n (%)	57 (43.5%)	13 (23%)	10 (50%)	14 (64%)	20 (61%)	0.01 (1vs2) 0.79 (2vs3)

Patients were grouped according to postoperative AKI development and postoperative nephrocheck value: group 1 (normal), no AKI and no increased biomarker; group 2 (subclinical AKI), no AKI but increased nephrocheck; group 3, AKI and no increased nephrocheck; group 4 (clinical AKI), AKI and increased nephrocheck. Definitions: AKI (creatinine +) was defined by KDIGO guidelines as a serum creatinine increase ≥ 0.3 mg/dl within 48 h or a serum creatinine increase of 1.5 times the baseline value known to have occurred within the prior 7 days; increased biomarker (biomarker +) was defined as a nephrocheck ≥ 0.30 at 4 h postoperatively

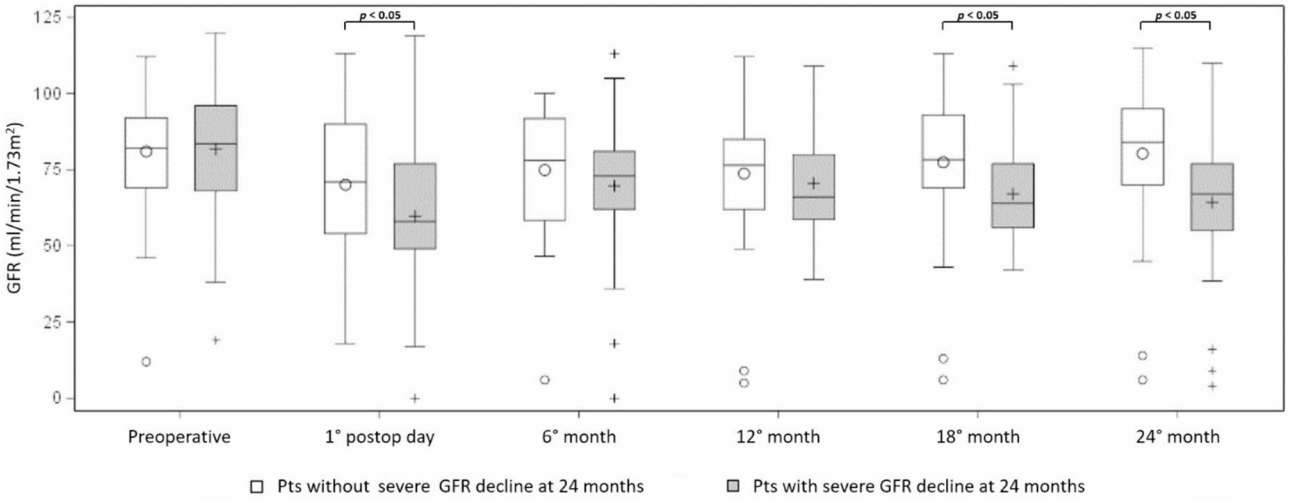

Fig. 1 Trends in estimated glomerular filtration rate (eGFR) decline in patients with and without a severe eGFR decline at 24 months postoperatively. Boxplot show eGFR trends in patients with (≥ 8.3 mL/min) and without a severe eGFR decline at 24 months postoperatively. In the group with a severe eGFR decline, eGFR resulted statistically different at 24 h postoperatively, and 18 and 24 months ($p < 0.05$). Asterisks indicate a significant difference among groups ($p < 0.05$)

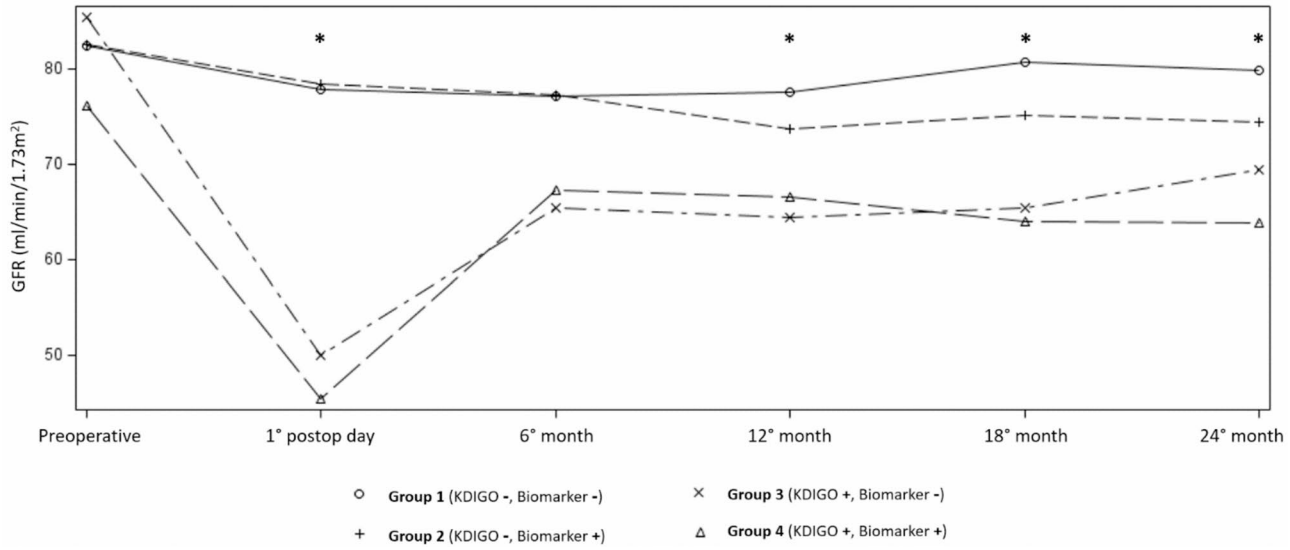

Fig. 2 Trends in estimated glomerular filtration rate (eGFR) decline in four groups defined by eGFR and NephroCheck® test. Line graph show eGFR trends in four groups of patients, defined by eGFR and NephroCheck® test. In the different groups eGFR resulted statistically different at 24 h postoperatively, and 12, 18 and 24 months ($p < 0.05$). Group one (no clinical AKI, NephroCheck® ≤0.3) and group two (no clinical AKI, NephroCheck® >0.3) present almost identical pre-operative characteristics, but postoperative NephroCheck® test. Asterisks indicate a significant difference among groups ($p < 0.05$)

Group 2 showed a significantly higher BMI ($p = 0.007$) but lower warm ischemia time ($p = 0.002$) compared to Group 1.

After 24 months, patients undergone NSS showed a median eGFR decline of -8.3 ± 13.2 ml/min. A severe eGFR decrease (≥ 8.3 mL/min) during the 2-year follow-up was reported in 43.5% of patients, identified by a lower eGFR 24 h postoperatively (Fig. 1).

Overall, 56/131 (43%) patients presented with neither clinical AKI (defined by KDIGO criteria) nor subclinical AKI (no NephroCheck® >0.3); this group of patients (group 1) showed a lower median eGFR decline (-2.6 ± 9.2 mL/min) at 24 months after surgery (Fig. 2).

Group 3 and group 4 showed the more severe eGFR decline, -16.6 ± 18.4 and – 12.3 ± 12.9 ml/min respectively, regardless of the NephroCheck® value (Table 1). Group 2, identified by a NephroCheck® value > 0.3 and no clinical AKI (subclinical AKI), showed an intermediate eGFR decline (-8.2 ± 9.3 ml/min) at 24 months.

We found a significantly different prevalence of severe eGFR decrease between the four groups ($p = 0.0006$) (Fig. 3).

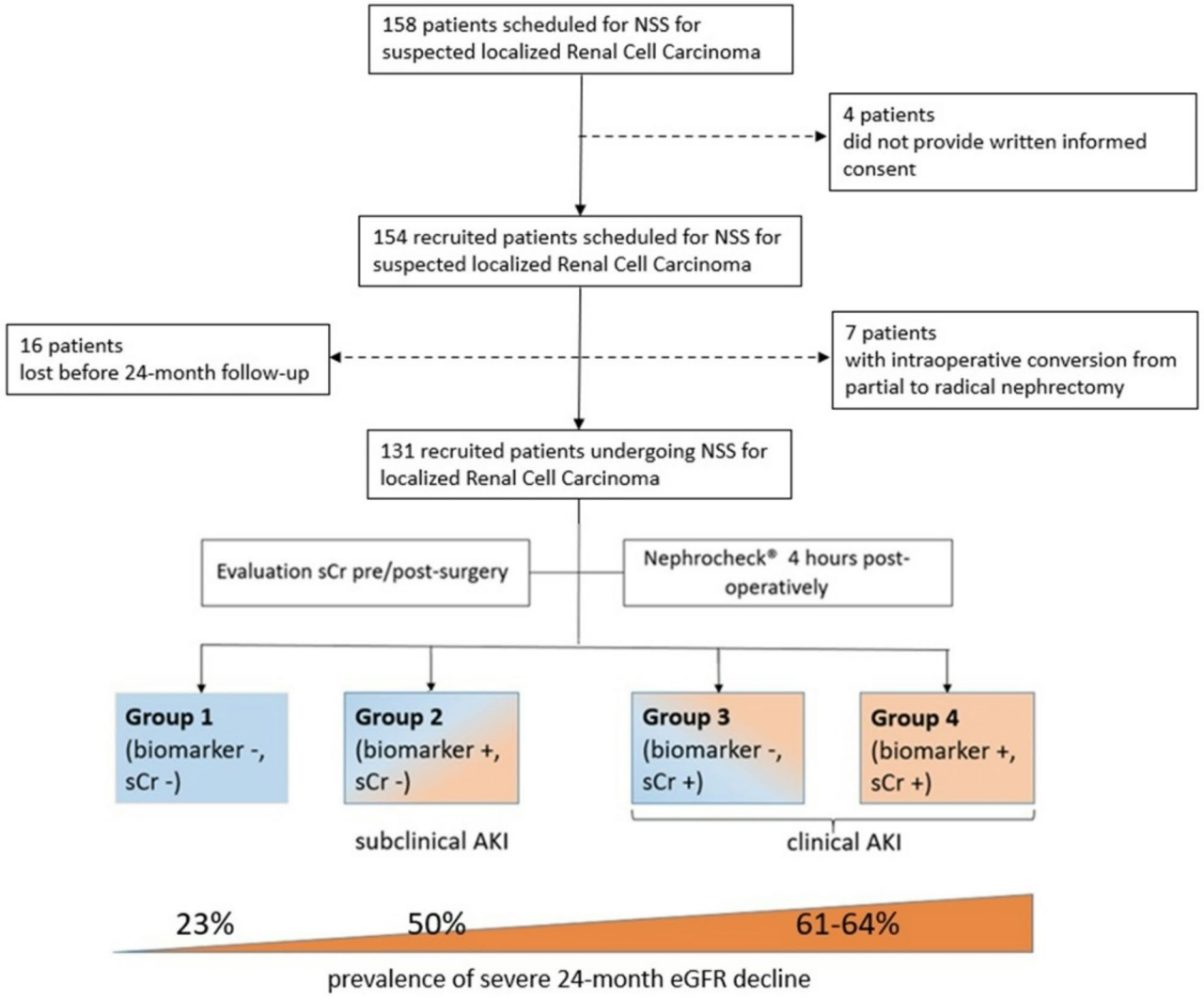

Fig. 3 Flow chart illustrating the selection criteria for the study population. This flow diagram illustrates inclusion and exclusion criteria for patient selection from the two Centers. Measurement of the NephroCheck® values complements the information obtained by measurement of sCr levels in establishing the diagnosis of clinical/subclinical AKI and predicting patients' renal prognosis

A multivariate logistic analysis was performed to evaluate the independent role of different variables in predicting severe eGFR decline at 24 months. Among different covariates, only clinical AKI (OR 13.2, $p < 0.0003$) appeared as an independent predictor of eGFR decline at 24 months, while postoperative NephroCheck® ($p = 0.92$), age ($p = 0.57$), preoperative/baseline eGFR ($p = 0.41$), and tumor size ($p = 0.86$) did not.

Not considering patients who experienced clinical AKI, the independent role of different parameters in predicting severe eGFR decline at 24 months was evaluated by multivariate logistic analysis; in this subgroup of patients, NephroCheck® evaluated at 4 h postoperatively appears as an independent factor able to predict a severe eGFR decline at 24 months (OR 3.76, $p = 0.02$) (Table 2).

Values of the variance inflation factor (VIF) for the multivariate logistic model are approxiamtely 1-1.5 (Table 3). It does not imply a major concern of potential multicollinearity, supporting the validity of the regression model.

Based on NephroCheck® measured 4 h after surgery and clinical AKI, patients can be divided in four groups with significantly different eGFR at 24 months ($p = 0.0003$). The 4 groups present eGFR values which are significantly different at day 1 ($p < 0.001$), 12 months ($p = 0.039$), 18 months ($p = 0.003$) and 24 months ($p = 0.005$) (Fig. 2).

Discussion

Several complications are linked to postoperative AKI occuring in patients undergoing NSS, such as long-term CKD [7] prolonged hospital stay and overall mortality [5, 27]. CKD itself is a well-known leading cause of mortality worldwide, whose burden trend is likely to sharply

Table 2 Evaluation of different variables in predicting severe eGFR decline at 24 months by multivariate logistic analysis in patients not experiencing clinical AKI. The analysis shows that, among patients who did not experience clinical AKI, NephroCheck® misured at 4h after surgery predicts a severe 24-months eGFR decline (OR 3.76, p=0.02)

Variables	p-value	OR 95% CI
Age	0.95	1.00 (0.95 – 1.05)
Male Gender	0.51	0.70 (0.24 – 2.03)
Baseline eGFR	0.24	1.02 (0.99 – 1.06)
Tumor size	0.58	1.11 (0.76 – 1.62)
NephroCheck 4h >0.3	0.02	3.76 (1.24 – 11.45)

Table 3 Variance inflation factor (VIF), as espression of the potential multicollinearity, supports the validity of the regression model

Covariates	VIF
Age	1.43
Clinical AKI	1.12
Baseline eGFR	1.40
Tumor size	1.03
NephroCheck 4 h postoperatively	1.12

implement in the next few years [28]. This is the reason why a standardized tool for early identification of patients suffering from clinical or subclinical postoperative AKI is required [10, 29].

NephroCheck® test, which measures urinary levels of TIMP-2 and IGFBP7, was successfully tested in patients undergoing NSS only recently [11]. This marker, combined with classic markers of renal function (in accordance with the latest ADQI and KDIGO proposed criteria for diagnosis of AKI) [11, 29] is likely able to enhance diagnostic accuracy.

Furthermore, recent studies identified NephroCheck® as able to detect long-term eGFR decline [30] both in patients who experienced clinical and subclinical AKI [21].

Since this novel biomarker's applicability, accuracy, and cost effectiveness needed to be furtherly assessed prior to entering in clinical practice, we performed a bicentric prospective study, collecting laboratory and clinical data from 131 patients, aiming to identify NeprhoCheck®'s ability in evaluating postoperative AKI and long-term eGFR decline.

Findings of our previous monocentric study [21] were confirmed by the present study, corroborating NephroCheck®'s potential utility as an early (at 4 h) biomarker, although the low sensitivity limits its use as a single marker of AKI in clinical practice, and as a tool able to identify a subset of patients characterized by intermediate risk of developing 24-month eGFR decline (Fig. 2).

The presence of a postoperative urinary NephroCheck® value > 0.3 showed only a moderate (but not high) sensitivity and specificity in predicting the diagnosis of clinical AKI, although we should consider that the gold standard of reference is not an histopathologically documented renal damage, but rather a creatinine-based definition of AKI. And it's widely known that sCr presents several limitations as a biomarker of AKI (serum increases are delayed 48–72 h after injury, and it may not rise until > 50% decrease in kidney functioning units), in particular in a surgical setting (due to the dilutional effect of fluid overload and the use of diuretics).

Group 2, defined by biomarker positive (NephroCheck® >0.3 at 4 h after surgery) and KDIGO negative status (absence of a sCr increase ≥ 0.3 mg/dL after surgery), was indicative of persistent renal dysfunction (subclinical AKI) [10]. Subclinical AKI is a word introduced in 2007 and actually well-known in the field of internal medicine. Only later it spread in the surgical setting, and in the coming years it is likely to acquire more and more importance, especially in the urological field [21]. As a matter of fact, 15–20% of patients who do not fulfil the criteria for AKI are still at risk of having developed an acute tubular damage, which is associated with adverse outcomes [16]. This is consistent with clinical and subclinical AKI to be correlated, belonging to the same spectrum, which is that of AKI [10]. In this sense, they must be deemed equally.

Consistent with this, about 15% of patients in our cohort were found to have elevated markers of acute tubular stress/damage in the absence of increased sCr values. This previously undetectable condition (subclinical AKI) was associated with an increased risk of 24-month eGFR decline as compared to that of patients in whom levels of both sCr and tubular damage markers were not elevated (group 1). These data can be useful in order to define an appropriate nephrological follow-up in patients whose sCr at discharge is apparently in range. Group 2 showed a significantly lower tumor size ($p = 0.03$), RENAL score ($p = 0.05$) and warm ischemia time ($p < 0.001$) compared to Group 3, suggesting which

elements have the strongest impact on the transition between subclinical AKI and clinical AKI.

Patients belonging to group 3 (sCr increase ≥ 0.3 but negative biomarker) were characterized by a more severe surgical impact (higher tumor diameter, higher RENAL and PADUA scores, longer warm ischemia time and operative time). As expected, they developed a clinical AKI. Interestingly, this group had a lower NephroCheck® value postoperatively; if this phenomenon may have an association with lower NephroCheck® values at baseline in this group is an intriguing hypothesis that should addressed in future studies. The four identified groups disclosed an increasing risk of long-term renal complications.

As demonstrated in our cohort and in a previous study [19], preoperative NephroCheck® values were not significantly different between patients with and without CKD, and were not significantly predictive of clinical AKI.

Multivariate analysis showed "postoperative clinical AKI" as the strongest and most reliable predictor of long-term eGFR decline (no correlations with baseline eGFR or tumor size). Therefore, in this scenario, NephroCheck® would be integrated with sCr in the first 48 postoperative hours, to identify patients at risk of developing long-term eGFR decline (Fig. 3), in the context of clinical or subclinical AKI.

In this setting, reassessment of AKI criteria, taking in consideration biomarkers of tubular damage is desirable [16].

Lastly, group 1 and group 2 presented with identical characteristics in terms of preoperative comorbidities and preoperative laboratory values, more or less. Therefore, in patients who did not develop clinical post-operative AKI, NephroCheck®'s increase alone appeared able to predict a severe 24-months eGFR decline (≥ 8.3 mL/min).

NephroCheck® in combination with sCr allows to explore both nephrons' stress/dysfunction and presence of effective damage. Thus, it might allow physicians to be better aware of all the conditions potentially occurring postoperatively and after patient's discharge.

It may have become urgent to make subclinical AKI an index of renal impairment as much significant as clinical postoperative AKI, since patients diagnosed with it actually suffer from worse renal and overall outcomes [10]. Given these clinical practice-related consequences, the concept of subclinical AKI needs to be necessarily caught on, not only by nephrologists, but other specialists as well.

In order to confirm the findings described in this paper, further studies are needed. The goal is to better define efficacy and efficiency of biomarkers such as NephroCheck®, and implement their usage, with the ultimate purpose of improving kidney impairment in postoperative setting (Fig. 3).

A noteworthy study limitation is represented by the fact that urinary output represents a criterion of AKI, but it has not been evaluated in all patients; thus, the rate of clinical AKI might be underestimated. Moreover, considering the comparison between groups 1 and 2 appeared among the main focuses of the study, the small size of group 2 represents a limitation of the study. Larger prospective cohorts are needed to further characterize the subclinical AKI's subgroup and to study the independent contribution of subclinical AKI to long-term GFR decline independently from numerous confounding variables (such as pre-existing CKD, comorbidities, nephrotoxic drugs, and surgical parameters/scores).

Conclusion

In our cohort of patients undergone NSS, the most reliable predictor of long-term eGFR decline was represented by the occurrence of postoperative clinical AKI, defined by sCr increase. In this specific setting, NephroCheck® appeared as an early (at 4 h) biomarker significantly associated with clinical AKI, showing a low sensitivity but a good specificity in predicting the diagnosis of clinical AKI.

NephroCheck® represented an accurate and easy-to-use test, able to early identify 'subclinical AKI' (urinary NephroCheck® >0.3 and sCr increase < 0.3 mg/dL), which is related to an increased risk of 24-months eGFR decline.

Consequently, NephroCheck® (at 4 h postoperatively) and sCr (at 24 and 48 h postoperatively) might be proposed as complementary markers to stratify the risk of long-term GFR decline in patients undergoing NSS.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04242-9.

Supplementary Material 1

Author contributions

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below. Conceptualization, M.A., M.W., G.V., P.N.; methodology, M.A., M.W., S.I., G.V., L.T., L.P., P.N.; writing—original draft preparation, M.A., G.V.; writing—review and editing, M.T.W., M.A.C., P.N.; supervision, M.W., L.T., L.P., A.F. All authors have read and agreed to the published version of the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval

Informed written consent to participate was obtained from all of the participants in the study. The study was conducted in accordance with the Declaration of Helsinki; the study protocol was approved by local ethics committees (Comitato Etico Regionale per la Sperimentazione Clinica della

Regione Toscana, study approval number BIO.16.015, and University of Heidelberg's Ethics Committee II, Medical Faculty Mannheim, study approval number 2015-549N). Clinical trial number: not applicable.

Consent for publication
Informed written consent was obtained from all subjects involved in the study. There are no identifying images or other personal or clinical details of participants that could compromise anonymity.

Competing interests
The authors declare no competing interests.

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