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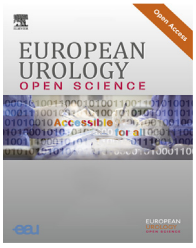

Brief Correspondence

Split Renal Function Is Fundamentally Important for Predicting Functional Recovery After Radical Nephrectomy

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Abstract

While partial nephrectomy (PN) is generally preferred for localized renal cell carcinoma (RCC), radical nephrectomy (RN) is occasionally required. A new-baseline glomerular filtration rate (NBGFR) >45 ml/min/1.73 m^2 after kidney cancer surgery is associated with strong survival outcomes. If NBGFR after RN will be above this threshold and the tumor has increased oncologic potential, RN may be a relevant consideration. Predicting NBGFR, defined as the GFR at 3–12 mo after RN, has been challenging owing to omission of two important parameters: split renal function (SRF) and renal function compensation (RFC). Our objective was to evaluate a simple SRF-based model in comparison to five published non–SRF-based models using data from a retrospective cohort of 445 RN patients. SRF was obtained via readily available semiautomated software (FUJIFILM Medical Systems) that provides differential parenchymal volume analysis on the basis of preoperative imaging. Our conceptually simple and clinically implementable SRF-based model more accurately predicts NBGFR after RN than five published non–SRF-based models (all $p < 0.01$). The SRF-based model also improved prediction of the clinically relevant threshold of NBGFR >45 ml/min/1.73 m^2 (all $p < 0.05$).

Patient summary: We validated a novel approach for more accurate prediction of kidney function after removal of one kidney. Our approach can be used in clinical and practice and will help in making decisions on full or partial removal of a kidney for kidney cancer.

Partial nephrectomy (PN) is the preferred surgical option for most patients with localized renal cell carcinoma (RCC) owing to better preservation of renal function. However, radical nephrectomy (RN) remains an important consideration for tumors with high oncologic potential, particularly for cases with greater tumor complexity, no preexisting chronic kidney disease (CKD), and a normal contralateral kidney that can provide a new-baseline glomerular filtration rate (NBGFR) >45 ml/min/1.73 m^2 [1]. This threshold is associated with strong survival outcomes after RN, similar to those for patients without CKD after surgery [1]. Thus, accurate prediction of NBGFR after RN can facilitate decision-making regarding PN versus RN in challenging cases. Previous models for predicting NBGFR after RN are methodologically

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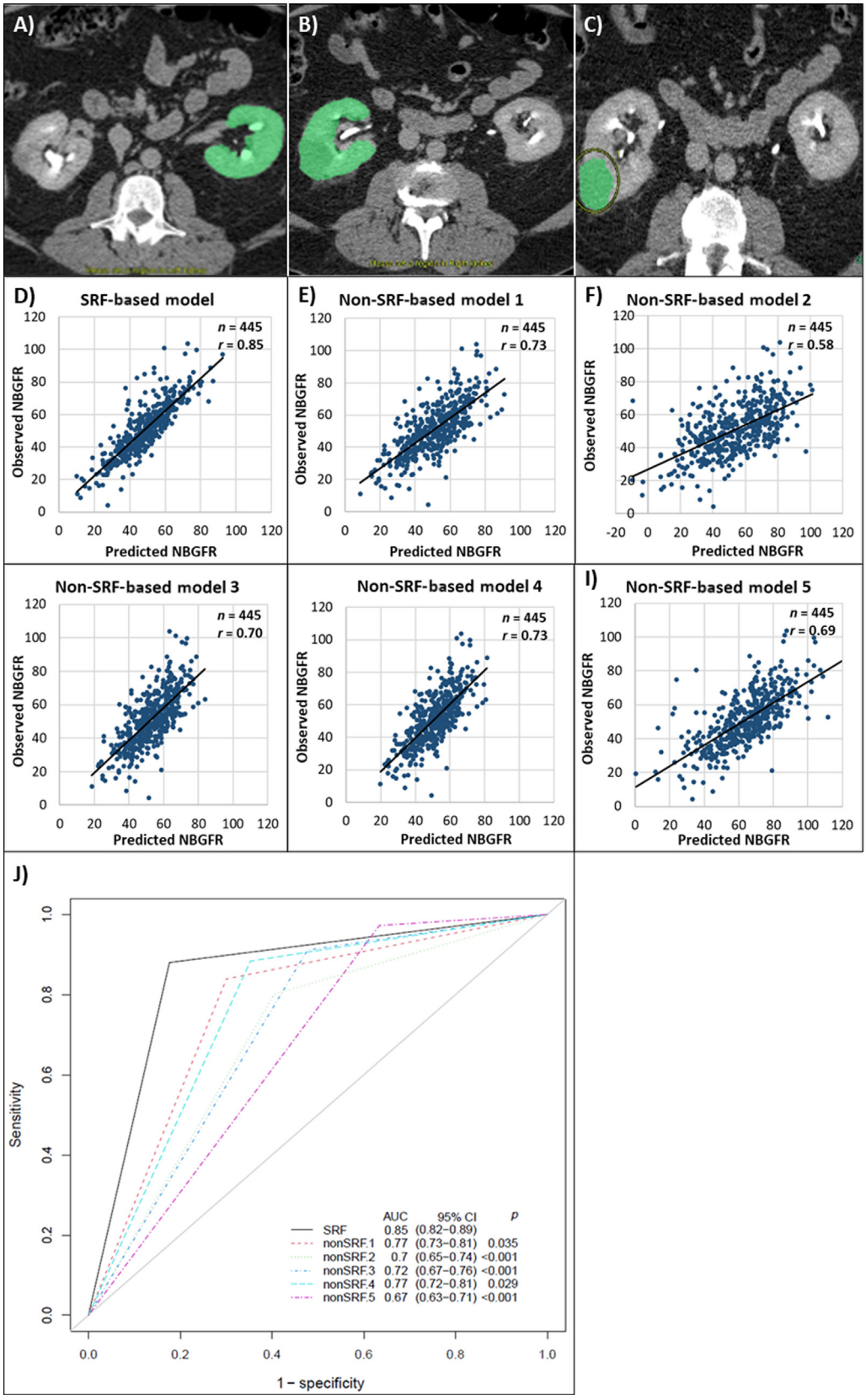
complex and have only moderate predictive accuracy [2–6]. Notably, prior approaches have omitted two fundamentally important functional parameters: split renal function (SRF) and estimates of renal function compensation (RFC) for the contralateral kidney. SRF can be readily obtained via differential parenchymal volume analysis (PVA) using semiautomated software (FUJIFILM Medical Systems) that requires minimal operator intervention (Fig. 1A–C).



We recently developed a simple SRF-based model: NBGFR = global $GFR_{pre\text{-}RN} \times SRF_{contralateral} \times 1.24$, where 1.24 represents the average RFC from a previous independent analysis [7]. Preliminary data supported our hypothesis that SRF and RFC are important for predicting NBGFR after RN [7]. In this analysis, we compare our SRF-based model with five published non–SRF-based models using data from an independent, expanded cohort of RCC patients who underwent RN.

After institutional review board approval, a retrospective review of 816 patients with localized RCC who underwent RN (2010–2014) was performed. A total of 445 patients were included in the final cohort according to availability of preoperative computed tomography (CT) or magnetic resonance imaging (MRI; <6 mo before RN) and both preoperative (<1 mo before RN) and postoperative (3–12 mo after RN) GFR estimates (Supplementary Fig. 1). NBGFR was defined as GFR obtained 3–12 mo after RN to allow sufficient time for recovery of the remaining kidney [8]. Tumor volumes and the ipsilateral (tumor-bearing) and contralateral parenchymal volumes were determined with three-dimensional PVA software (FUJIFILM Medical-Systems) using preoperative CT imaging data (n = 412; Fig. 1A–C). Manual freehand scripting approaches were used to measure analogous volumes if preoperative MRI was available (n = 33) [9]. Previous studies have shown strong correlation between freehand and software-based PVA, and that PVA is more accurate than nuclear renal scans for estimating SRF [10].

We hypothesized that our proposed SRF-based model would outperform non–SRF-based models (Supplementary Table 1) in predicting NBGFR in this independent cohort (n = 445) [2–7]. Predictive accuracy was assessed as the correlation coefficient (r) for comparison of predicted versus observed NBGFR. Additional parameters analyzed for each model included bias, precision, accuracy, and the mean squared error (MSE). Receiver operating characteristic (ROC) curve analyses were used to assess the ability of each model to discriminate NBGFR >45 ml/min/1.73 m^2 (binary variable) and the area under the ROC curve (AUC) was calculated for each model. Comparisons of the SRF-based and non–SRF-based approaches were based on r values, AUC, and performance parameters for 1000 bootstrap resamples, with $p < 0.05$ (two-sided) considered significant. Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria; r-project.org).

Patient characteristics and renal function parameters for our cohort (n = 445) were representative of RCC patients under consideration for RN in this era (Table 1). Of note, median preoperative eGFR in the contralateral kidney was 40 ml/min/1.73 m^2 and median postoperative NBGFR was 51 ml/min/1.73 m^2, which corresponded to median actual RFC of 28%. Scatterplots comparing predicted versus observed NBGFR were generated to evaluate the predictive accuracy of the SRF-based and non–SRF-based models (Fig. 1D–I). Correlation coefficients (r) were considered strong for the SRF-based model (r = 0.85) and moderate for the non–SRF-based models (r = 0.58–0.73), with statistically significant differences observed in each instance (all $p < 0.01$). The AUC obtained from ROC analysis of the ability of each model to discriminate NBGFR >45 ml/min/1.73 m^2 (Fig. 1J) was significantly greater for the SRF-based model (AUC 0.85) than for the non–SRF-based models (AUC 0.67–0.77; all $p < 0.05$). Additional performance data for the SRF-based and non–SRF-based models are provided in Supplementary Table 2. In brief, the SRF-based model demonstrated significantly better precision ($p < 0.01$), MSE ($p < 0.01$), and accuracy ($p < 0.05$).

Our data therefore suggest that a conceptually simple SRF-based model can provide greater accuracy for prediction of NBGFR after RN than five previously published non–SRF-based approaches. The non–SRF-based models also provided modest accuracy, but it is concerning that each incorporates a unique combination of variables, such as age, gender, weight, distinct comorbidities, and tumor size [2–6]. This diversity of predictive parameters may reflect differences in patient populations between the respective studies, which could affect the generalizability of the models. Furthermore, the inconsistency in predictive parameters is problematic in that it is difficult to determine which model is most appropriate for a given patient. On the contrary, our SRF-based equation is based on fundamentally important functional parameters, which probably underlies its better predictive accuracy. Moreover, the SRF-based model relies only on preoperative imaging and laboratory studies that RCC patients routinely undergo, and SRF can be obtained in a facile manner at the point of care using readily available and affordable semiautomated PVA software (FUJIFILM Medical Systems), which enhances the practicality of our approach.

As an example of how our SRF-based approach can inform clinical management, consider a patient with a 6.3-cm mid-pole renal mass that is mostly endophytic and in close proximity to the hilum (RENAL score 10). PVA analysis of preoperative imaging reveals a healthy-appearing contralateral kidney with SRF of 59%, and a metabolic panel

Fig. 1 – (A–C) Prediction of new-baseline glomerular filtration rate (NBGFR) after radical nephrectomy (RN). Renal parenchyma and tumor volumes are readily captured with parenchymal volume analysis software and shown in the top row, with the contralateral kidney (tumor-free) highlighted in (A), the ipsilateral kidney and tumor in (B), and the tumor in (C). In this hypothetical case the volume of the left kidney is 200 cm^3, the volume of the right kidney plus tumor is 210 cm^3, and the tumor volume is 40 cm^3. The parenchymal volumes are then 200 cm^3 in the left kidney and 170 cm^3 in the right kidney, corresponding to a split renal function of L 54% and R 46%. If right RN is performed, the NBGFR is estimated to be (preoperative global GFR × 0.54) × 1.24. (D–I) Observed versus predicted NBGFR after RN using (D) the split renal function (SRF)-based model versus (E–I) five different published non–SRF-based models. The correlation coefficient (r) for observed versus predicted NBGFR for each model is shown. The predictive accuracy was significantly greater with the SRF-based model than with all of the non–SRF-based models (all $p < 0.01$). (J) Receiver operating characteristic (ROC) curves comparing the ability of the SRF-based and non–SRF-based models to discriminate postoperative NBGFR >45 ml/min/1.73 m^2. The area under the ROC curve (AUC) was significantly greater for the SRF-based model than for the non–SRF-based models (all $p < 0.05$). When the ROC curve analysis was restricted to patients with preoperative GFR >60 ml/min/1.73 m^2 or preoperative GFR >45 ml/min/1.73 m^2, entirely analogous results were obtained. CI = confidence interval.

Table 1 – Patient characteristics and renal function parameters for the 445 patients in the study cohort

Parameter	Result
Patient demographics and tumor characteristics	
Median age, yr (IQR)	64 (55–72)
Gender, *n* (%)	
Male	294 (66)
Female	151 (34)
Race, *n* (%)	
Caucasian	376 (85)
African-American	51 (11)
Other	18 (4)
Median American Society of Anesthesiologists score (IQR)	3 (3–3)
Median body mass index, kg/m^2 (IQR)	29.0 (25.7–34.0)
Diabetes, *n* (%)	103 (23)
Hypertension, *n* (%)	298 (67)
Cardiovascular disease, *n* (%)[a]	61 (14)
Smoking status, *n* (%)	
Never smoker	184 (41)
Active or former smoker	258 (58)
Median tumor size, cm (IQR)	7.0 (5.0–9.3)
Preoperative chronic kidney disease stage, *n* (%)	
Stage 2 (eGFR 60–90 ml/min/1.73 m^2)	113 (25)
Stage 3 (eGFR 30–60 ml/min/1.73 m^2)	109 (24)
Stage 4 (eGFR 15–30 ml/min/1.73 m^2)	4 (1)
Median RENAL score (IQR)[b]	10 (9–11)
Surgical approach, *n* (%)	
Laparoscopic	185 (42)
Robotic	69 (15)
Open	191 (43)
pT stage, *n* (%)	
pT1	118 (27)
pT2	46 (10)
pT3	276 (62)
pT4	5 (1)
pN stage, *n* (%)	
pN0	123 (28)
pN1	23 (5)
pNx	295 (66)
Renal cell carcinoma histology, *n* (%)	
Clear cell	345 (78)
Papillary	45 (10)
Chromophobe	28 (6)
Other or unclassified	27 (6)
Renal function and parenchymal volume	
Median preoperative eGFR, ml/min/1.73 m^2 (IQR)	
Global	77 (60–90)
Contralateral kidney	40 (32–47)
Ipsilateral kidney (with malignancy)	37 (27–45)
Median preoperative parenchyma volume, cm^3 (IQR)	
Contralateral kidney	181 (149–221)
Ipsilateral kidney (excluding tumor)	164 (129–206)
Tumor alone	153 (59–333)
Median eGFR at 3–12 mo after surgery, ml/min/1.73 m^2 (IQR)	51 (41–61)
Median RFC at 3–12 mo after surgery, % (interquartile range)[c]	28 (18–38)

eGFR = estimated glomerular filtration rate; RFC = renal function compensation; IQR, interquartile range.
[a] Includes preoperative cardiovascular disease, congestive heart failure, and myocardial infarction.
[b] Data available for 315 patients.
[c] RFC = $\frac{\text{Postoperative eGFR} - \text{preoperative contralateral eGFR}}{\text{Preoperative contralateral eGFR}} \times 100$.

shows preoperative global eGFR of 63 ml/min/1.73 m^2. For this patient, PN would typically be considered to preserve renal function, but it could be challenging because of the endophytic nature of the tumor and its proximity to the hilum. Alternatively, RN would minimize perioperative risk and, in such patients, could potentially provide an oncologic advantage. Application of our SRF-based model would predict NBGFR of 46 ml/min/1.73 m^2 if RN is performed, which further supports RN as a viable option in this setting. In reality, the American Urological Association guidelines, which now provide more granular descriptions of who should be considered for RN versus PN, would favor RN in this setting [1]. Conversely, if the predicted NBGFR was substantially less than 45 ml/min/1.73 m^2, significant postoperative functional concerns would push the needle towards PN.

Limitations of our analysis include the retrospective patient cohort from a single institution and limited representation from the African-American population, which represented only 11% of our patients. However, our cohort is representative of RCC patients under consideration for RN, and all patients with relevant data and imaging feasible for PVA were included. Notably, our study directly compares SRF-based and non–SRF-based models across several informative performance parameters in a large, independent cohort of RCC patients managed with RN.

Author contributions: Steven C. Campbell 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: Rathi, Campbell.
Acquisition of data: Rathi, Yasuda, Aguilar Palacios, Campbell.
Analysis and interpretation of data: Rathi, Yasuda, Aguilar Palacios, Li, Campbell.
Drafting of the manuscript: Rathi, Campbell.
Critical revision of the manuscript for important intellectual content: Rathi, Yasuda, Aguilar Palacios, Attawettayanon, Li, Bhindi, Thompson, Liss, Derweesh, Weight, Eltemamy, Abouassaly, Campbell.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.04.008.

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