Prediction of significant renal function decline after open, laparoscopic, and robotic partial nephrectomy: External validation of the Martini's nomogram on the RECORD2 project cohort

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Abbreviations & Acronyms
AA-CCI = age-adjusted CCI
AKI = acute kidney injury
ASA PS = American Society of Anesthesiologists classification Physical Status
AUC = area under the curve
BMI = body mass index
CART = classification and regression tree
CCI = Charlson Comorbidity Index
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration
eGFR = estimated glomerular filtration rate
LPN = laparoscopic partial nephrectomy
OPN = open partial nephrectomy
PN = partial nephrectomy
POD = postoperative day
RAPN = robot-assisted partial nephrectomy
RF = renal function
RN = radical nephrectomy
ROC = receiver operating characteristic
SIU = Italian Society of Urology

Objectives: Martini *et al.* developed a nomogram to predict significant (>25%) renal function loss after robot-assisted partial nephrectomy and identified four risk categories. We aimed to externally validate Martini's nomogram on a large, national, multi-institutional data set including open, laparoscopic, and robot-assisted partial nephrectomy.

Methods: Data of 2584 patients treated with partial nephrectomy for renal masses at 26 urological Italian centers (RECORD2 project) were collected. Renal function was assessed at baseline, on third postoperative day, and then at 6, 12, 24, and 48 months postoperatively. Multivariable models accounting for variables included in the Martini's nomogram were applied to each approach predicting renal function loss at all the specific timeframes.

Results: Multivariable models showed high area under the curve for robot-assisted partial nephrectomy at 6- and 12-month (87.3% and 83.6%) and for laparoscopic partial nephrectomy (83.2% and 75.4%), whereas area under the curves were lower in open partial nephrectomy (78.4% and 75.2%). The predictive ability of the model decreased in all the surgical approaches at 48 months from surgery. Each Martini risk group showed an increasing percentage of patients developing a significant renal function reduction in the open, laparoscopic and robot-assisted partial nephrectomy group, as well as an increased probability to develop a significant estimated glomerular filtration rate reduction in the considered time cutoffs, although the predictive ability of the classes was <70% at 48 months of follow-up.

Conclusions: Martini's nomogram is a valid tool for predicting the decline in renal function at 6 and 12 months after robot-assisted partial nephrectomy and laparoscopic partial nephrectomy, whereas it showed a lower performance at longer follow-up and in patients treated with open approach at all these time cutoffs.

Key words: laparoscopy, nephron-sparing surgery, renal cell carcinoma, renal function, robotics.

Introduction

Kidney cancer accounts for 2–3% of solid malignancies and its incidence in developed countries is increasing with the widespread diffusion of diagnostic tools.[1] Guidelines prioritize PN

over RN as the current standard of care for cT1 renal masses[2] because saving RF might reduce long-term mortality.[3,4] On the other hand, PN is a complex procedure that exposes patients to an augmented risk of surgical complications[5] and local relapse.[6] In this regard, the prediction of postoperative RF is crucial, but such a step is often not linear as a multiplicity of potentially influent factor need to be considered.

In the last years, several study groups aimed to provide predicting models to forecast functional outcomes after renal surgery. McIntosh *et al*. developed a model to predict RF after RN,[7] while, more recently, Aguilar Palacios and colleagues proposed a simple equation to predict postoperative eGFR after RN and PN;[8] however, these predictive models did not evaluate the impact of relevant surgical factors (including surgical approach) on postoperative RF.

In addition, Xu *et al*. based on a large unicentric series, generated a model to predict postoperative AKI after RN and PN; however, the inclusion of numerous baseline laboratory values makes the model of poor clinical applicability.[9]

Recently, to facilitate this task, Martini and coworkers[10] firstly developed a nomogram that predicts the significant (>25%) reduction in eGFR after RAPN. This tool was generated on a single-center cohort of approximately 1000 RAPNs and includes patient's features – age, sex, comorbidities, eGFR – data on tumor complexity, and the occurrence of postoperative AKI. The nomogram's output allows to discriminate patients into four classes bearing a risk of significant impairment that ranges from 4% – low risk – to 79% – very high risk.[11] Martini's nomogram has been already externally validated on a single-surgeon series of 406 RAPNs, confirming good predictive performances although inferior to those shown in the original studies.[12] On the other side, the Martini's nomogram has never been validated in patients undergone OPN and LPN, while a different surgical approach could influence the functional outcomes.[13]

The aim of the present study was to assess the short-, medium-, and long-term functional outcomes and to externally validate the Martini's nomogram according to the surgical approach and the timing of follow-up in patients treated with PN relying on a large multi-institutional data set (the RECORD2 project).

Methods

The Italian Registry of Conservative and Radical Surgery for Cortical Renal Tumor Disease (RECORD2 project) is a prospective observational multicenter project promoted by the SIU. Overall, the data of 2584 PNs for cT1/2 renal masses treated at 26 urological Italian centers between January 2013 and December 2016 were collected. The surgical approach was established at each Institution according to institutional or surgeon's preference.

An online central data server was generated and centrally controlled to limit missing or wrong data inputs, as previously described.[14] All data of patients undergoing surgery were prospectively recorded by medical doctors. The database involved six main folders: (i) patients' characteristics and preoperative data; (ii) imaging, indications (elective, relative, and absolute), and comorbidities; (iii) intraoperative data; (iv) postoperative data; (v) histological analysis; and (vi) follow-up.

The eGFR was assessed at baseline, on first and third POD, and then at 6, 12, and 48 months postoperatively, as calculated by the CKD-EPI equation. A 25% eGFR drop from baseline was considered as a clinically significant RF loss according to the RIFLE criteria.[15] Similarly, postoperative AKI was defined as a 25% eGFR drop from baseline at time of patient discharge from hospital.[15]

Statistical analysis

First, patients' characteristics and outcomes were stratified according to the surgical approach. Continuous variables were reported as median and interquartile range, whereas categorical variables were reported as number and proportions. The Student's *t*-test or Mann–Whitney *U* test were used to compare continuous variables, and the Pearson's chi-squared test was used for categorical variables.

Second, the impact of the variables included in the Martini nomogram on the development of AKI at 3rd POD, and at 6th, 12th, and 48th postoperative month was assessed. Multivariable logistic regression analyses were performed to investigate the predictors of these outcomes.

The external validity of the nomogram to predict significant eGFR reduction after robotic PN was assessed in patients treated with RAPN from our series at 3rd POD and at 6th, 12th, and 48th month postoperatively. Furthermore, the validity of the nomogram in patients treated with OPN and LPN at the same time points. Of note, in the first multivariable model, 3rd POD AKI was considered as a dependent value and was removed from the variables of the nomogram. The calibration of the Martini nomogram was assessed by comparing the predicted probabilities with the actual observed proportions using as functional outcome the eGFR reduction at the time point of 12 months in the OPN, LPN, and RAPN cohorts. The performance of the models was assessed in terms of calibration and discrimination using the ROC curve and AUC. Diagnostic accuracy of each model was considered poor for an AUC value <0.6, fair for an AUC value between 0.6 and 0.7, good for an AUC value between 0.7 and 0.8, and high if AUC >0.8.[16] Third, risk group categories were created through the CART analysis for each surgical approach. CART analyses are a set of techniques for classification and prediction to develop models that can classify subjects into various risk categories. For this study, we used the four risk groups (and their respective cutoffs) from the original study by Martini *et al*.[11] and calculation was performed using through the online platform (available at www.evidencio.com/models/show/1602). From the risk group categories, the discrimination to detect a significant eGFR loss at 6th, 12th, and 48th month postoperatively in patients included in our series (validation cohort) was calculated using a logistic univariable regression and the ROC curve and the AUC. Differences were considered statistically significant with $P < 0.05$, and all P values were two sided. Analyses were carried out using STATA, version 14.1 (StataCorp LP, College Station, TX, USA).

Results

Overall, the cohort included 2584 patients, of whom 981 were submitted to RAPN (38%), 717 to LPN (28%) and

886 to OPN (34%). The baseline patient's features were similar between groups in terms of age, sex, comorbidities and eGFR (RAPN 86.2 mL/min, LPN 87.0 mL/min, OPN 83.7 mL/min). Concerning tumor's features, a higher proportion of cT1b-2 cases in the RAPN and OPN compared with the LPN group (29.2% and 30.4% *vs* 21.8%, respectively; OPN *vs* LPN $P = 0.04$, OPN *vs* RAPN $P = 0.05$); nephrometric scores confirmed that the OPN and RAPN groups included more complex masses (high complexity rate in 21.2% *vs* 14.8% *vs* 10.7%, RAPN *vs* LPN $P = 0.04$, OPN *vs* LPN $P = 0.002$) (Table 1).

As regards surgical features, the way of access in RAPN *vs* LPN was significantly different compared with OPN (retroperitoneal approach in 13.7% *vs* 61.8% *vs* 83.5%, respectively; RAPN *vs* LPN $P < 0.0001$, OPN *vs* RAPN $P < 0.0001$), resection technique (pure enucleation 65.0% *vs* 27.3% *vs* 11.3%; RAPN *vs* LPN $P < 0.0001$, OPN *vs* RAPN $P < 0.0001$), clamping strategy (ischemia in 63.7% *vs* 46.9% *vs* 44.2%; RAPN *vs* LPN $P = 0.001$, OPN *vs* RAPN $P = 0.001$), operative time and blood loss (Table 2). Concerning functional results, AKI occurred most frequently after OPN than RAPN and LPN (32.5% *vs* 21.2% *vs* 20.1%, LPN

Table 1 Preoperative characteristics of patients treated with RAPN, LPN, and OPN (the RECORD2 project)

Preoperative characteristics† (*n* = 2564)	RAPN (*n* = 981)	LPN (*n* = 717)	OPN (*n* = 886)	*P*-value*	*P*-value**	*P*-value***
Sex, *n* (%)						
Male	612 (62.4%)	493 (68.8%)	566 (63.9%)	0.06	0.09	0.37
Female	369 (37.6%)	224 (31.2%)	320 (36.1%)			
Age (years)	64.2 (54.3–71.4)	62.8 (54.8–71.0)	65.9 (55.8–73.4)	0.18	**0.01**	0.62
BMI (kg/m^2)	25.7 (23.6–28.3)	25.8 (23.9–28.5)	26.0 (23.7–29.0)	0.58	0.42	0.49
ASA PS score						
Continuous	2 (2–3)	2 (2–3)	2 (2–3)	0.23	0.16	0.67
≥3	157 (16.0%)	198 (27.6)	345 (38.9%)	0.37	0.31	0.79
CCI PS score	1 (0–2)	0 (0–2)	1 (0–2)	0.12	0.09	0.47
AA-CCI PS score	4 (2–5)	4 (2–5)	4 (3–5)	0.24	**0.02**	0.21
Surgical indication, *n* (%)						
Elective	795 (81.0%)	579 (80.8%)	748 (84.4%)	0.28	0.11	0.37
Relative	151 (15.4%)	124 (17.3%)	97 (10.9%)			
Imperative	35 (3.6%)	14 (2.0%)	41 (4.6%)			
Tumor side, *n* (%)						
Right	485 (49.4%)	350 (48.8%)	460 (51.9%)	0.73	0.58	0.64
Left	496 (50.6%)	367 (51.2%)	426 (48.1%)			
Clinical T, *n* (%)						
T1a	695 (70.8%)	561 (78.2%)	616 (69.5%)	0.05	**0.04**	0.12
T1b	259 (26.4%)	141 (19.7%)	228 (25.7%)			
T2	27 (2.8%)	15 (2.1%)	42 (4.7%)			
Multiple ipsilateral lesion, *n* (%)	58 (5.9%)	28 (3.8%)	65 (7.3%)	0.26	0.09	0.36
Tumor growth pattern, *n* (%)						
≥50% exophytic	578 (58.9%)	392 (54.7%)	474 (53.5%)	0.24	0.32	0.17
<50% exophytic	338 (34.5%)	275 (38.4%)	320 (36.1%)			
Entirely endophytic	65 (6.6%)	50 (7.0%)	92 (10.4%)			
Tumor location relative to the polar line, *n* (%)						
Entirely above polar line	563 (57.4%)	366 (51.0%)	403 (45.5%)	0.19	0.72	0.26
≤50% crosses polar line	307 (31.3%)	233 (32.5%)	344 (38.8%)			
>50% crosses polar line	111 (11.3%)	118 (16.5%)	139 (15.7%)			
Nearingness to the collecting system, *n* (%)						
≥7 cm	630 (64.2%)	431 (60.1%)	444 (50.1%)	0.18	0.001	0.23
>4 but <7 cm	209 (21.3%)	203 (28.3%)	204 (23.0%)			
≤4 cm	142 (14.5%)	83 (11.6%)	238 (26.9%)			
PADUA score, median IQR	7 (7–9)	7 (7–8)	8 (7–9)	0.02	0.001	0.52
RENAL score, median IQR	6 (5–7)	6 (4–7)	6 (5–8)	0.01	0.001	0.08
PADUA score complexity index, *n* (%)						
6–7	517 (52.7%)	373 (52.0%)	384 (43.3%)	0.04	0.002	0.57
8–9	319 (32.5%)	267 (37.2%)	314 (35.4%)			
≥10	145 (14.8%)	77 (10.7%)	188 (21.2%)			
Hemoglobin (mg/dL), (continuous)	14.2 (13.2–15.1)	14.5 (13.4–15.3)	14.0 (13.1–15.7)	0.64	0.37	0.78
Creatinine (mg/dL), (continuous)	0.9 (0.7–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.21	0.47	0.38
eGFR (mL/min), (continuous)	86.2 (70.7–101.4)	86.97 (71.27–100.49)	83.72 (67.78–97.16)	0.46	0.19	0.12

Bold type if *P*-value <0.05. †Numbers and column percentages and median and interquartile range (IQR) are reported for nominal and continuous variables. **P*-value stands for the comparison of RAPN *vs* LPN. ***P*-value stands for the comparison of LPN *vs* OPN. ****P*-value stands for the comparison of OPN *vs* RAPN.

Table 2 Perioperative and follow-up features of patients treated with RAPN, LPN, and OPN (the RECORD2 project)

Perioperative and follow-up features	RAPN (n = 981)	LPN (n = 717)	OPN (n = 886)	P-value*	P-value**	P-value***
Surgical access, n (%)						
Transperitoneal	847 (86.3%)	274 (38.2%)	146 (16.5%)	**<0.0001**	0.27	**<0.0001**
Retroperitoneal	134 (13.7%)	443 (61.8%)	740 (83.5%)			
Type of resection, n (%)						
Enucleation	638 (65.0%)	196 (27.3%)	100 (11.3%)	**<0.0001**	0.38	**<0.0001**
Standard PN	343 (35.0%)	521 (72.7%)	786 (88.7%)			
Pedicle clamping, n (%)						
Off-clamp	356 (36.3%)	381 (53.1%)	494 (55.8%)	**0.001**	0.38	**0.001**
On-clamp	625 (63.7%)	336 (46.9%)	392 (44.2%)			
Ischemia time (min)	16 (12–20)	16 (13–20)	16 (13–21)	0.04	0.27	0.02
Ischemia time >20 min	127 (12.9%)	83 (11.6%)	110 (12.4%)	0.38	0.43	0.62
Ischemia time >25 min	63 (6.4%)	30 (4.2%)	47 (5.3%)	0.62	0.49	0.37
Estimated blood loss (mL)	100 (70–200)	150 (80–250)	200 (100–300)	**<0.0001**	**0.001**	**<0.0001**
Operative time (min)	150 (120–200)	120 (90–160)	130 (105–170)	**0.001**	**0.001**	**0.01**
AKI at discharge	208 (21.2%)	144 (20.1%)	312 (35.2%)	0.29	**<0.0001**	**<0.0001**
Preop- 6th month Δ eGFR (mL/min)	10.08 (0–21.86)	9.91 (0–18.58)	10.60 (0–21.54)	0.42	0.21	0.74
Preop- 6th month Δ eGFR (%)	12.7 (0–25.17)	11.4 (0–24.0)	15.0 (0–26.0)	0.13	**0.01**	**0.02**
Preop- 12th month Δ eGFR (mL/min)	21.01 (12.55–28.33)	20.74 (11.89–27.54)	21.46 (12.76–29.28)	0.48	0.32	0.53
Preop- 12th month Δ eGFR (%)	25.8 (16.20–33.74)	24.6 (15.0–28.3)	26.2 (16.2–35.2)	0.73	0.38	0.53
Preop- 48th month Δ eGFR (mL/min)	8.79 (0–18.57)	10.12 (0–23.22)	10.08 (0–22.36)	0.31	0.42	0.33
Preop- 48th month Δ eGFR (%)	8.8 (0–22.70)	11.45 (0–25.2)	12.7 (0–28.3)	0.13	0.21	0.07

Bold type if P-value <0.05. *P-value stands for the comparison of RAPN *vs* LPN. **P-value stands for the comparison of LPN *vs* OPN. ***P-value stands for the comparison of OPN *vs* RAPN.

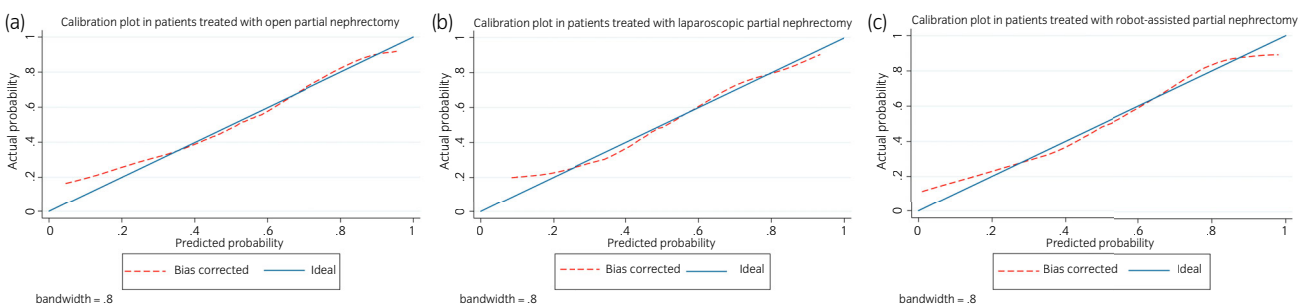

Fig. 1 Calibration plots of the Martini nomogram in the (a) OPN, (b) LPN, and (c) RAPN cohorts.

vs OPN $P < 0.0001$, OPN *vs* RAPN $P < 0.0001$). The relative decrease in eGFR was higher for OPN at 6 months (OPN *vs* LPN *vs* RAPN 15.0% *vs* 12.7% *vs* 11.4%; LPN *vs* OPN $P = 0.01$; OPN *vs* RAPN $P = 0.02$), for OPN and LPN at 48 months (12.7% *vs* 11.5% *vs* 8.8%, OPN *vs* RAPN $P = 0.07$); no differences were noted in relative changes at 12 months as well as for the absolute variations at any time point (Table 2).

Figure 1 depicts the calibration plots of the Martini nomogram in the OPN (a), LPN (b), and RAPN (c) cohorts. In the OPN group, a higher overestimation of the predicted risk was reported until 40% compared with the LPN and RAPN, where a similar overestimation was limited until 20% of the predicted risk.

Table 3 shows the multivariable analyses testing the nomogram's variables for clinically significant RF loss at 3rd POD, 6th, 12th, and 48th postoperative month in each surgical approach. The AUC showed poor prediction of the model referred to the 3-day outcome in either RAPN (66.2%) or LPN (63.1%) or OPN (62.7%) group, while it was indicative of high prediction for the 6-month outcome in the RAPN (87.3%) and LPN (83.2%) groups, as well as for the 12-month prediction in the RAPN (83.6%) group. The AUC decreased in all the approaches (74.1%, 71.1% and 72.4% in RAPN, LPN and OPN, respectively) when the model was tested for the RF loss at 48th postoperative month.

Lastly, the entire cohort was stratified according to risk classes and 808 patients (31.3%) were at low risk, 906 (35%) at intermediate risk, 754 (29.2%) at high risk, and 116 (4.3%) at very high risk (Table 4). For each surgical approach, the odds ratio of developing a significant eGFR reduction at 6/12/48 months progressively increased, consistently to the risk class. The AUC estimating the predictive ability of the modeling in risk classes was descriptive of good performances when referred to the RAPN group, at 6 and 12 months, and for the LPN at 12 months only; in all other cases, the AUC indicated just fair prediction.

Table 3 Multivariable models predicting the impact of the variables included in the Martini nomogram on the development of AKI at 3rd POD and clinically significant RF loss at 6th, 12th, and 48th postoperative month

	RAPN			LPN			OPN		
Variables	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Multivariable analysis for the prediction of 3rd day significant eGFR reduction									
Age at surgery	1.03	1.01–1.04	<0.001	1.02	1.01–1.04	<0.001	1.03	1.01–1.05	0.001
Preoperative eGFR	1.01	1.01–1.02	<0.001	1.00	0.99–1.01	0.167	1.01	1.00–1.02	0.016
Female sex	1.06	0.76–1.48	0.720	1.06	0.76–1.48	0.720	1.13	0.75–1.69	0.580
RENAL score	1.32	1.21–1.45	<0.001	1.23	1.14–1.33	<0.001	1.19	1.07–1.34	0.002
CCI									
0	*Ref*			*Ref*			*Ref*		
1	1.34	0.88–2.05	0.172	0.89	0.60–1.33	0.594	1.18	0.71–1.94	0.261
2	1.40	0.91–2.13	0.122	0.93	0.63–1.39	0.737	1.02	0.48–2.15	0.953
3	1.52	0.77–2.99	0.226	1.10	0.63–1.87	0.739	0.74	0.43–1.25	0.526
≥4	1.55	0.69–3.50	0.291	1.42	0.50–4.05	0.510	0.71	0.29–1.71	0.448
AUC of multivariable models	0.662			0.631			0.627		
Multivariable analysis for the prediction of 6th month significant eGFR reduction									
Age at surgery	1.09	1.07–1.11	<0.001	1.05	1.03–1.08	<0.001	1.03	1.02–1.05	<0.001
Preoperative eGFR	0.99	0.98–0.99	0.014	0.99	0.98–1.00	0.368	0.99	0.98–1.00	0.180
3rd day postoperative AKI	3.48	2.30–5.27	<0.001	6.28	3.86–10.20	<0.001	3.68	2.59–5.21	<0.001
Female sex	0.38	0.25–0.41	<0.001	0.41	0.32–0.64	<0.001	0.59	0.45–0.73	<0.001
RENAL score	1.90	1.69–2.13	<0.001	1.07	1.04–1.20	0.04	1.06	1.03–1.17	0.03
CCI									
0	*Ref*			*Ref*			*Ref*		
1	0.86	0.53–1.40	0.539	0.82	0.44–1.53	0.541	1.03	0.64–1.65	0.608
2	1.67	1.05–2.66	0.029	0.79	0.43–1.43	0.443	3.07	1.70–5.53	<0.001
3	2.08	1.89–4.84	<0.001	2.35	1.08–5.11	0.032	4.18	1.36–12.82	0.012
≥4	4.20	2.08–8.49	<0.001	3.49	1.53–7.98	0.003	6.65	3.17–13.98	<0.001
AUC of the multivariable models	0.873			0.832			0.784		
Multivariable analysis for the prediction of 12th month significant eGFR reduction									
Age at surgery	1.06	1.04–1.08	<0.001	1.02	1.01–1.04	0.004	1.03	1.02–1.05	<0.001
Preoperative eGFR	0.99	0.98–0.99	0.04	0.99	0.98–1.00	0.169	0.98	0.98–0.99	<0.001
3rd day postoperative AKI	1.54	1.05–2.26	0.026	1.64	1.11–2.41	0.013	1.45	1.05–2.00	0.02
Female sex	0.54	0.39–0.75	<0.001	0.35	0.25–0.49	<0.001	0.33	0.24–0.45	<0.001
RENAL score	1.59	1.44–1.76	<0.001	1.08	1.02–1.19	0.03	1.07	1.02–1.15	0.04
CCI									
0	*Ref*			*Ref*			*Ref*		
1	0.82	0.52–1.30	0.408	0.83	0.50–1.36	0.464	0.98	0.66–1.45	0.935
2	3.72	2.47–5.62	<0.001	2.42	1.59–3.68	<0.001	1.72	1.13–2.60	0.011
3	6.18	3.27–11.7	<0.001	7.57	4.10–14.1	<0.001	2.00	1.08–3.71	0.03
≥4	18.10	7.41–27.3	<0.001	8.56	4.16–17.6	<0.001	2.73	1.45–6.63	<0.001
AUC of the multivariable models	0.836			0.754			0.752		
Multivariable analysis for the prediction of 48th month significant eGFR reduction									
Age at surgery	1.01	1.01–1.03	0.02	1.02	1.01–1.04	0.04	1.02	1.01–1.02	0.03
Preoperative eGFR	0.99	0.98–0.99	<0.001	0.98	0.97–0.99	0.01	0.98	0.98–0.99	0.02
3rd day postoperative AKI	1.13	0.87–1.36	0.23	1.93	1.33–2.98	0.007	1.42	1.02–1.99	0.04
Female sex	0.77	0.65–0.92	0.01	0.51	0.37–0.79	<0.001	0.77	0.41–0.85	0.001
RENAL score	1.02	0.96–1.07	0.130	1.04	0.97–1.13	0.06	0.96	0.88–1.05	0.428
CCI									
0	*Ref*			*Ref*			*Ref*		
1	1.27	1.15–1.49	0.001	1.53	0.88–2.66	0.13	2.35	1.22–4.10	<0.001
2	3.45	2.07–4.74	<0.001	3.12	1.85–5.28	<0.001	4.62	2.66–8.04	<0.001
3	5.89	3.65–8.71	<0.001	5.50	2.52–12.0	<0.001	9.21	4.55–18.62	<0.001
≥4	9.63	6.35–19.3	<0.001	6.83	3.29–14.2	<0.001	10.53	3.52–31.52	<0.001
AUC of the multivariable models	0.741			0.711			0.724		

Discussion

In the present study, we assessed the functional outcomes of a wide cohort of patients treated with PN to investigate in detail the performances of the Martini's nomogram at different time of follow-up and in the different surgical approaches. Our main finding is that in our cohort, the Martini's nomogram showed a good accuracy in the mid-term – 6/12 months – prediction and mostly for the robotic approach. On the contrary, the performances were inferior in earlier and later predictions and, in general, for the LPN and OPN groups. Such results suggest that this predictive tool –

Table 4 Relation between significant eGFR loss rate and risk group categories predicting this event after OPN, LPN, and RAPN according to the CART analysis developed from the nomogram by Martini *et al.*

Months after RAPN	Low risk (n = 337)	Intermediate risk (n = 364)	High risk (n = 237)	Very high risk (n = 43)	ROC curve
6	8.31% (ref.)	21.53% (3.21 [2.02–5.07])	33.33% (5.52 [3.44–8.84])	67.44% (9.92 [13.41–14.35])	0.702
12	8.01% (ref.)	27.75% (5.54 [4.04–7.60])	36.71% (5.03 [3.78–8.41])	60.47% (19.88 [12.51–31.60])	0.716
48	9.79% (ref.)	21.43% (2.86 [2.12–3.76])	34.60% (4.71 [3.63–6.28])	44.19% (7.71 [5.01–11.86])	0.631
Months after LPN	Low risk (n = 252)	Intermediate risk (n = 266)	High risk (n = 177)	Very high risk (n = 22)	
6	8.73% (ref.)	16.54% (2.07 [1.20–3.57])	32.2% (4.96 [2.89–8.51])	72.73% (9.34 [4.43–13.37])	0.696
12	5.56% (ref.)	25.56% (5.83 [3.19–10.70])	40.68% (9.42 [6.29–17.60])	63.64% (18.79 [7.91–29.30])	0.731
48	8.33% (ref.)	22.18% (2.13 [1.04–5.33])	40.1% (4.12 [3.21–7.31])	59.1% (5.88 [3.42–8.23])	0.674
Months after OPN	Low risk (n = 219)	Intermediate risk (n = 276)	High risk (n = 340)	Very high risk (n = 51)	
6	9.13% (ref.)	23.55% (3.06 [1.79–5.24])	38.53% (6.24 [3.75–10.38])	54.9% (10.67 [5.91–16.84])	0.682
12	5.02% (ref.)	29.35% (6.85 [3.06–14.17])	38.24% (7.03 [4.53–11.83])	52.94% (17.12 [7.38–24.23])	0.686
48	12.79% (ref.)	30.43% (2.98 [1.86–4.78])	32.65% (3.30 [2.09–5.22])	43.14% (5.17 [2.62–10.22])	0.609

Data are reported for each risk category as percentage of patients with eGFR loss >25% during follow-up (odds ratio [95% confidence interval] to develop a significant (>25%) eGFR loss at 6, 12, and 48 months of follow-up according to the risk categories). The area under the receiver operating characteristic (ROC) curve graphically depicts the trade-off between sensitivity and specificity of the risk category stratification to discriminate the event of significant eGFR loss at 6, 12, and 48 months of follow-up.

with valuable clinical and scientific applications – is unsuitable for a relevant rate of contemporary PNs.

Ipsilateral RF decline after PN relies on a multiplicity of factors,[17] and huge efforts have been done to identify which could be modified or subject of preventive measures. With this regard, the role of clamping strategy has been extensively investigated,[18] but except for the single-kidney patients,[19] there are no conclusive data supporting any significant differences between limited *vs* no ischemia, as also confirmed by a couple of randomized trials.[20,21] On the contrary, there is a growing evidence showing that postoperative function depends mostly from the baseline "nephrons quality," that is the patient's functional reserve, and the "nephrons quantity" loss with the resection and reconstruction.[22] Accordingly, the Martini's nomogram included only a few and significant patient's features (age, sex, and CCI), the baseline eGFR, and the tumor complexity, but not data on the clamping approach. The absence of surgical characteristics might explain the very low predictive accuracy of the Martini's nomogram of early RF loss. On this regard, in a previous paper[22] on a large series of patients treated with OPN, LPN or RAPN (RECORd1 project), open and laparoscopic (*vs* robotic) approaches and pedicle clamping were independent predictors of early RF impairment; on the other hand, we recently developed a model for the prediction of 48-month RF deterioration after RAPN relying on the RECORD2 cohort; in this study, no surgical factors were significantly related with the development of RF loss.[23] Taken together, these results suggest that late/ultimate RF impairment is mostly determined by tumor- and patient-related features rather than surgical factors that, instead, affect early postoperative RF. Although robotics is steadily becoming the standard approach at referral Institutions, the open and laparoscopic routes do not completely disappear, as they represent up to the 40% of cases according to recent US and British registry data.[24,25] Notably, the open and laparoscopic cases covered two-thirds of the RECORD1 sample, dating back to 2012,[26] and a quite similar proportion of the RECORD2, well representative of the contemporary practice in Italy, one of the countries with the higher penetrance of robotic systems.[13] The nomogram to date has been tested on cases exclusively submitted to RAPN, and this represents a significant limitation. A different surgical approach to PN, indeed, involves baseline imbalances due to selection and implies differences in the intra- and perioperative courses.[27] More in detail, significant disparities in patient's features, tumor complexity, use of ischemia, resection technique, operative time, blood loss, and complication rate have been highlighted by retrospective studies and prospective registries.[14,28] Noteworthy, it has been reported that the surgical approach has an independent impact on functional outcomes, and that patients undergone a robotic approach are less exposed to the risk of AKI and have an advantage on early and long-term function.[22] Such differences reasonably rely on the augmented precision given by robotic instrumentations, which translates in more accurate resection and reconstruction, with a larger preservation of healthy parenchyma.[29–31] Finally, minimally invasive PN could benefit of the preconditioning effect of pneumoperitoneum to ischemia.[32]

Some limitations need to be acknowledged. First, the retrospective analysis of data, although based on a prospective and centrally managed registry that included more than 70 variables for each patient. Second, the multicentric nature of our project and the non-randomized comparisons, that could have implied unaccounted differences in patient's and tumor's features, as well as in pre-, intra-, and postoperative management could have led to unexpected selection or treatment biases; in detail, the inherent multisurgeon nature of this study could have introduced unpredictable alterations in functional results (due to different surgical experience and techniques). Third, the limited length (4 years) of follow-up time could not provide robust evidence on the predictive ability of these nomograms at a long-term follow-up.

To conclude, the prediction of postoperative RF loss in patients undergone RAPN has important consequences on the clinical practice and the development of a specific tool to predict this outcome is crucial. Basing on the external validation performed on our data, the Martini's nomogram and its risk group categories had a good accuracy in the mid-term prediction of functional outcome after minimally invasive – LPN and RAPN, decreasing at long-term follow-up. On the other hand, they indicated just a fair prediction of mid-term functional outcome in the cohort of patients treated with OPN. As such, despite the relevant clinical utility of Martini's model, there is a need of different specific models to accurately forecast RF impairment after LPN and OPN as well as at a longer-term evaluation; furthermore, resection and renorrhaphy techniques should be specifically evaluated in future studies as well as the potential clinical utility of urinary and serum biomarkers in predicting renal impairment.

Author contributions

Alessandro Antonelli: Conceptualization; Methodology; Writing – original draft; Writing – review & editing. Andrea Mari: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing. Alessandro Tafuri: Investigation; Methodology. Riccardo Tellini: Investigation; Methodology. Umberto Capitanio: Investigation; Methodology. Paolo Gontero: Investigation; Methodology. Antonio Andrea Grosso: Investigation; Methodology. Vincenzo Li Marzi: Investigation; Methodology. Nicola Longo: Investigation; Methodology. Francesco Porpiglia: Investigation; Methodology. Angelo Porreca: Investigation; Methodology. Bernardo Rocco: Investigation; Methodology. Claudio Simeone: Investigation; Methodology. Riccardo Schiavina: Investigation; Methodology. Luigi Schips: Investigation; Methodology. Salvatore Siracusano: Investigation; Methodology. Carlo Terrone: Investigation; Methodology. Vincenzo Ficarra: Investigation; Methodology. Marco Carini: Investigation; Methodology; Project administration; Writing – review & editing. Andrea Minervini: Conceptualization; Investigation; Methodology; Project administration; Writing – review & editing.

Conflict of interest

None declared.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of AOU Careggi, Approval No. FI10176.

Informed consent

All informed consent was obtained from the subject(s) and/or guardian(s).

Registry and the Registration No. of the study/trial

Not applicable.

Animal studies

Not applicable.

Collaborators

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