Tumor Volume and Tumor Crossing of the Axial Renal Midline as Preoperative Predictors of Reduced Estimated Glomerular Filtration Rate After Robotic Partial Nephrectomy

Haruyuki Ohsugi
Kansai Medical University
Kyojiro Akiyama
Kansai Medical University
Hisanori Taniguchi
Kansai Medical University
Masaaki Yanishi
Kansai Medical University
Motohiko Sugi
Kansai Medical University
Tadashi Matsuda
Kansai Medical University
Hidefumi Kinoshita (kinoshih@hirakata.kmu.ac.jp)
Kansai Medical University

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Abstract

The ability of nephrometry scoring systems, including the radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines (R.E.N.A.L.), to predict loss of renal function after robotic partial nephrectomy (RPN) is still controversial. Therefore, we verified which combination of factors from nephrometry scoring systems, including tumor volume, was the most significant predictor of postoperative renal function. Patients who underwent RPN for cT1 renal tumors in our hospital were reviewed retrospectively (n=163). The preoperative clinical data (estimated glomerular filtration rate [eGFR], comorbidities, and nephrometry scoring systems including R.E.N.A.L.) and perioperative outcomes were evaluated. We also calculated the tumor volume using the equation applied to an ellipsoid by three-dimensional computed tomography. The primary outcome was reduced eGFR, which was defined as an eGFR reduction of ≥20% from baseline to 6 months after RPN. Multivariate logistic regression analyses were used to evaluate the relationships between preoperative variables and reduced eGFR. Of 163 patients, 24 (14.7%) had reduced eGFR. Multivariate analyses indicated that tumor volume (cutoff value≥14.11 cm^3, indicating a sphere with a diameter≥approximately 3 cm) and tumor crossing of the axial renal midline were independent factors for reduced eGFR (odds ratio [OR], 4.57; P=0.003 and OR, 3.21; P=0.034, respectively). Our classification system using these two factors showed a higher area under the receiver operating characteristic curve (AUC) than previous nephrometry scoring systems (AUC=0.786 vs. 0.653–0.719), and it may provide preoperative information for counseling patients about renal function after RPN.

Introduction

Partial nephrectomy (PN) is the current standard treatment for the management of small renal tumors to prevent postoperative chronic kidney disease (CKD). In particular, a warm ischemic time (WIT) within 25 minutes is considered to be associated with preventing short- and long-term loss of renal function [1]. Recent meta-analyses have shown that the WIT is significantly shorter in robotic partial nephrectomy (RPN) than in laparoscopic partial nephrectomy [2]; thus, RPN is generally accepted as a favorable procedure for preserving kidney function.

There are some nephrometry scoring systems such as the radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines (R.E.N.A.L.), preoperative aspects and dimensions used for anatomic (PADUA) classification, and diameter-axial-polar (DAP) scores for predicting surgical complexity and potential perioperative morbidity [3,4,5]. Whether these nephrometry scoring systems have the ability to predict loss of renal function after PN is still controversial [6,7]. Furthermore, some reports that used mathematical calculated scores determined from preoperative images, such as the centrality index (c-index) and tumor contact surface area, predicted that the estimated glomerular filtration rate (eGFR) decreases after PN [8,9]. However, to our knowledge, the combination of nephrometry scoring systems and mathematically calculated scores has not been evaluated for predicting renal function after RPN.

Therefore, we verified which combination of factors from the nephrometry scoring systems, including tumor volume accurately calculated by three-dimensional computed tomography (3D-CT), was the most significant predictor of reduced postoperative renal function. Finally, we described the accuracy of this new classification system including significant factors for predicting eGFR reduction compared with that of R.E.N.A.L., PADUA, and DAP scores.

Results

Patient Characteristics. The clinical patient characteristics are shown in Table 1. The median percent decrease in eGFR six months after RPN was 7.55% (IQR: 1.42–15.29%). Of 163 patients, 24 (14.7%) had an eGFR reduction of ≥ 20% from baseline to 6 months after RPN. The accurately calculated median tumor volume was 6.28 cm^3 (IQR: 2.70–14.68 cm^3). The nephrometry scores (R.E.N.A.L. and DAP scores) are shown in Table 2. The median R.E.N.A.L. score was six, and the median DAP score was five. No postoperative complications greater than Grade 3 in Clavien-Dindo Classification were observed.

Association between Reduced eGFR and Each Factor of the Nephrometry Scoring Systems including the Tumor Volume Accurately Calculated by 3D-CT. The appropriate cutoff value of tumor volume calculated by 3D-CT for predicting reduced eGFR was 14.11 cm^3 (sensitivity = 0.625 and specificity = 0.806) (Fig. 1a). The tumor volume factor (cutoff value ≥ 14.11 cm^3, indicating a sphere with a diameter ≥ approximately 3 cm) showed a higher AUC than the size factor of the DAP and R.E.N.A.L. classification systems (0.715 vs 0.547–0.636; Fig. 1b). Univariate analyses of each factor of the nephrometry scoring systems are shown in Table 3. The N and L factors of the R.E.N.A.L. system, the P factor of the DAP system, and size factors were found to be significantly associated with the outcome of interest (all $P < 0.05$). The number of patients with 3 points for the L factor of the R.E.N.A.L. system was the same as the number of patients with 3 points for the P factor of the DAP system (n = 41); these factors indicate the presence of a tumor crossing of the axial renal midline. These results implied that the N factor of the R.E.N.A.L. system (2 or 3 points) and the P factor of the DAP system (3 points) are significant factors for predicting reduced eGFR.

Uni- and Multivariate Analyses Predicting Reduced eGFR. Those significant nephrometry factors including tumor volume factor (cutoff value ≥ 14.11 cm^3) and preoperative clinical patient characteristics were investigated on uni- and multivariate analyses. The univariate analyses showed that a comorbidity of DM, the tumor volume, the N factor of the R.E.N.A.L., and the P factor of the DAP system were significantly associated with reduced eGFR (all $P < 0.05$, Table 4). The multivariate analysis showed that 3 points for the P factor of the DAP system (OR: 3.50, $P = 0.014$) and tumor volume (OR: 4.57, $P = 0.003$) were significant independent factors for predicting reduced eGFR (Table 4).

Accuracy of Our Classification System for Predicting Decreased Renal Function. According to the number of independent factors (3 points for the P factor of the DAP system and tumor volume), all patients were stratified into the following three groups: low-risk group (0 factors, n = 102), intermediate-risk group (1 factor, n = 39), and high-risk group (2 factors, n = 22). The classification system showed a statistically significant trend for predicting postoperative decreases in eGFR (continuous variable) 6 months after RPN ($P < 0.001$; Fig. 2a) and for predicting the WIT ($P < 0.001$; Fig. 2b). To ascertain whether our classification system was useful for predicting postoperative reduced eGFR, we compared the predictive accuracy between our classification system and nephrometry scoring systems such as the R.E.N.A.L. score (low, intermediate, and high), PADUA score (low, intermediate, and high), and DAP sum score. Our classification system showed a higher AUC than these nephrometry scoring systems (0.786 vs. 0.653–0.719) in our cohort (Fig. 2c).

Discussion

The current study demonstrated that tumor volume (cutoff value ≥ 14.11 cm^3, indicating a sphere with a diameter ≥ approximately 3 cm) and 3 points for the P factor of the DAP system, indicating a tumor crossing the axial renal midline, were significant factors for predicting eGFR reduction after RPN. The simple classification system using these two factors had the best accuracy for predicting eGFR reduction after RPN compared with existing nephrometry scoring systems such as the R.E.N.A.L., DAP, and PADUA scores. Our classification system can provide prognostic information for counseling patients about renal function after RPN and assist in preoperative decision making.

To assess overall survival benefits in patients with renal cell carcinoma (RCC) after partial or radical nephrectomy, predicting both oncologic outcomes and decreased renal function to avoid chronic kidney disease is essential [12,13]. Some studies have determined that an SCr level > 2.0 mg/dl or the occurrence of stage-5 CKD is the endpoint of postoperative renal function [14,15]. However, a limitation of these endpoints is that the outcome can depend on the preoperative state. To circumvent this limitation, analysis of eGFR reduction from baseline to a point after surgery is crucial for predicting accurate postoperative renal function. General functional reduction after PN averages approximately 10% in the two-kidney and 20% in the one-kidney model [16]. Thus, we set the cutoff point for reduced eGFR to 20% with reference to a previous report [9].

Recent reports have shown that a nomogram with the sum of the R.E.N.A.L. score incorporated accurately predicts significant eGFR reduction after PN [17,18]. Therefore, the nephrometry scoring systems might be able to predict a decline in renal function after PN. Simmons et al. reported that the DAP score, which is a modified version of the R.E.N.A.L. classification and c-index, had simplified methodology and was associated with volume loss and renal function after PN. Although the cutoff value for each factor was different, similar to the DAP score including tumor diameter, axial distance from the center point, and polar distance from the midline, tumor volume, nearness to the collecting system (distance from the tumor to the collecting system), and location relative to polar lines were significantly associated with eGFR decline after RPN in this study. Among these three factors, nearness to the collecting system was not an independent factor associated with the outcome of interest. However, the distance from the tumor to the collecting system tended to be shorter as the P factor score of the DAP system increased, and it was negatively correlated with tumor volume (Supplementary Fig. 2, $R = 0.481$, $p < 0.001$). Thus, the two independent factors used in our classification system may also reflect proximity to the collecting system.

In complex cases, long ischemia times are required for complete tumor resection [19]. For renal function preservation, various techniques during PN have been described (e.g., off-clamp, selective/super-selective clamp, and early unclamp, or cooling techniques for hypothermia) [20,21]. We showed that our classification system was significantly correlated with the WIT (Fig. 2B); thus, our classification system might be related to the complexity of the surgery. Therefore, our classification system might help to select patients who need various surgical techniques to avoid renal insufficiency.

Our results should be interpreted with caution because of several limitations. First, this study was based on data from patients who were treated at a single center, and external validation is needed before applying the classification system to select patients. Second, the study was retrospective in design with, and the follow-up period was relatively short. Third, while perioperative variables such as the WIT and estimated blood loss were not considered, these variables are likely important influencers of postoperative renal function. However, the purpose of this study was to determine which combination of preoperative factors such as nephrometry scoring systems were best for predicting eGFR reduction. We also calculated the tumor volume assuming that each tumor was an ellipsoid. This was not a true volume, but the calculation of tumor volume is easily obtained from preoperative 3D-CT scans.

Conclusion

Accurate calculation of tumor volume and tumor crossing of the axial renal midline were independent predictors of eGFR reduction after RPN. Our classification system using these two factors had the best accuracy for predicting postoperative eGFR reduction when compared with previous nephrometry scoring systems such as the R.E.N.A.L., DAP, and PADUA scores.

Methods

Patient Selection. The medical records of 165 patients who underwent RPN for localized cT1 renal tumors with warm ischemia at Kansai Medical University Hospital between August 2014 and December 2019 were retrospectively reviewed. Patients with multiple renal tumors or a solitary kidney were excluded from this study. No patient underwent presurgical treatment with tyrosine kinase inhibitors or immune checkpoint inhibitors. All procedures were performed by experienced robotic surgeons at a single institution. Among these patients, two patients who underwent conversion to nephrectomy or open partial nephrectomy were excluded from the analysis. Ultimately, 163 patients were considered for further analyses.

Data Collection. The preoperative clinical data (sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, comorbidities of diabetes mellitus (DM) and hypertension (HTN), previous abdominal surgery, and antiplatelet or anticoagulant therapy), perioperative outcomes, and pathological features were evaluated. Renal function was assessed by serum creatinine (SCr) and eGFR, which was calculated using the following equation established for the Japanese population [10]: eGFR (mL/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ (× 0.739 for females) (Eq. 1). The percent reduction in renal function was calculated with the preoperative and postoperative (6 months after RPN) eGFRs. All patients underwent preoperative 3D-CT with or without contrast. Based on the imaging findings, nephrometry scoring systems including R.E.N.A.L., PADUA, and DAP scores were evaluated with several urologists at a preoperative conference. The lengths of the horizontal axis and vertical axis were measured at the transverse plane where the tumor area was the largest (x and y, respectively), and the length of maximal z axis was measured in the coronal or sagittal plane (z). Then, the tumor volume was calculated using the following equation applied to an ellipsoid (Supplementary Fig. 1): Tumor volume (cm^3) = $4/3 \times \pi(3.14) \times x/2 \times y/2 \times z/2$ (Eq. 2). The lengths of these three directions and the distance from the tumor to the collecting system were measured independently by two observers (HO and KA), each of whom was blinded to the clinical outcome.

Statistical Analysis. The primary outcome of this study was a reduced eGFR, which was defined as an eGFR reduction of ≥ 20% from baseline to 6 months after RPN. All continuous data are shown as median values and interquartile ranges (IQRs). The area under the receiver operating characteristic curve (AUC) was used to decide the cutoff value for continuous variables including tumor volume. Univariate and multivariate logistic regression analyses were used to evaluate the relationship between clinical variables and reduced eGFR. The trend of our classification system for predicting changes in renal function was examined by performing a Jonckheere–Terpstra test. The abilities of our classification systems and previous nephrometry scoring systems to predict reduced eGFR were evaluated and compared using AUC analysis. A post hoc comparison was used to compare the group means. Odds ratios (ORs) estimated from the logistic regression analyses are reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using EZR version 1.65 (Saitama Medical Center, Jichi, Japan) [11]. A two-sided p value < 0.05 was considered as statistically significant.

Ethics approval. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of the Kansai Medical University Hospital, Japan (Approval No. 2020215), and informed consent was obtained from all individual patients prior to robotic partial nephrectomy.

Abbreviations

AML angiomyolipoma

ASA American Society of Anesthesiologists

AUC area under the receiver operating characteristic curve

BMI body mass index

CI confidence interval

CKD chronic kidney disease

DAP diameter-axial-polar

DM diabetes mellitus

eGFR estimated glomerular filtration rate

HTN hypertension

IQR interquartile range

OR odds ratio

PADUA preoperative aspects and dimensions used for anatomic

PN partial nephrectomy

RCC renal cell carcinoma

R.E.N.A.L. radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines

RPN robotic partial nephrectomy

SCr serum creatinine

WIT warm ischemia time

3D-CT three-dimensional computed tomography

Declarations

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

H Ohsugi: project development, data collection, and manuscript writing. K Akiyama: data collection. H Taniguchi: data management and manuscript editing. M Yanishi and M Sugi: data management. T Matsuda: project development and study supervision. H Kinoshita: manuscript editing and study supervision.

Competing interests

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Tables

Table 1.

Clinical patient characteristics.

Variables	
N	163
Age, years, median (IQR)	66 (56 - 73)
Sex, n (%)	
Female	50 (30.7)
Male	113 (69.3)
BMI, kg/m^2, median (IQR)	23.6 (21.9 - 25.6)
ASA, n (%)	
1	34 (20.9)
2	117 (71.8)
3	12 (7.4)
Preoperative SCr, mg/dl, median (IQR)	0.80 (0.67 - 0.98)
Preoperative eGFR, ml/min/1.73 m^2, median (IQR)	70.0 (57.0 - 82.5)
Preoperative eGFR<60, n (%)	47 (28.8)
Comorbidity of DM	30 (18.4)
Comorbidity of HTN	75 (46.0)
Previous abdominal surgery	52 (31.9)
Antiplatelet of anticoagulant therapy	24 (14.7)
Tumor diameter, cm, median (IQR)	2.5 (1.95 - 3.35)
Tumor volume, cm^3, median (IQR)	6.28 (2.70 - 14.68)
Distance from the tumor to the collecting system, mm, median (IQR)	14 (8 - 22)
Approach, n (%)	
Intraperitoneal	99 (60.7)
Retroperitoneal	64 (39.3)
Surgical side, n (%)	
Right	87 (53.4)
Left	76 (46.6)

Pathological subtype, n (%)	
Clear cell RCC	119 (73.0)
Chromophobe RCC	14 (8.6)
Papillary RCC	9 (5.5)
Clear cell papillary RCC	4 (2.5)
Benign neoplasm (AML or Oncocytoma)	9 (5.5)
Others	8 (5.0)
Pathological T stage, n (%)	
pT1a	121 (74.2)
pT1b	12 (7.4)
pT2	0 (0.0)
pT3a	20 (12.3)
Indeterminable	10 (6.1)
WIT, second, median (IQR)	1149 (883 - 1456)
Estimated blood loss, ml, median (IQR)	100 (31 - 200)
Postoperative eGFR decrease, %, median (IQR)	7.55 (1.42 - 15.29)
Postoperative eGFR decrease greater than 20%, n (%)	24 (14.7)

IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension; RCC, renal cell carcinoma; AML, angiomyolipoma; WIT, warm ischemia time.

Table 2.

Nephrometry scores.

Variables		
N, (%)		163
R.E.N.A.L. score, median (IQR)		6 (5 - 7)
R.	1	142 (87.1)
	2	21 (12.9)
E.	1	58 (35.6)
	2	88 (54.0)
	3	17 (10.4)
N.	1	118 (72.4)
	2	19 (11.7)
	3	26 (16.0)
A.	x	28 (17.2)
	a	60 (36.8)
	p	75 (46.0)
L.	1	72 (44.2)
	2	50 (30.7)
	3	41 (25.2)
R.E.N.A.L. score risk categorization, n (%)		
Low (4-6)		100 (61.3)
Intermediate (7-9)		52 (31.9)
High (≥10)		11 (6.7)
DAP score, median (IQR)		5 (4 - 6)
Diameter	1	72 (44.2)
	2	81 (49.7)
	3	10 (6.1)
Axial	1	61 (37.4)
	2	69 (42.3)
	3	33 (20.2)

Polar	1	67 (41.1)
	2	55 (33.7)
	3	41 (25.2)

R.E.N.A.L., Radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines; DAP, Diameter-Axial-Polar; IQR, interquartile range.

Table 3.

Univariate analysis of each factor of nephrometry scores for predicting postoperative eGFR decrease.

Variable	Univariate analysis	
	OR (95% CI)	P value
R.E.N.A.L.-R. (1 vs. 2)	2.02 (0.66–6.17)	0.215
R.E.N.A.L.-E. (1 vs. 2)	2.54 (0.88–7.32)	0.085
R.E.N.A.L.-E. (1 vs. 3)	1.41 (0.25–8.03)	0.696
R.E.N.A.L.-N. (1 vs. 2)	3.47 (1.05–11.50)	0.041
R.E.N.A.L.-N. (1 vs. 3)	4.32 (1.53–12.20)	0.006
R.E.N.A.L.-A. (x vs. a)	0.56 (0.18–1.82)	0.338
R.E.N.A.L.-A. (x vs. p)	0.56 (0.18–1.73)	0.317
R.E.N.A.L.-L. (1 vs. 2)	0.59 (0.15–2.41)	0.465
R.E.N.A.L.-L. (1 vs. 3)	4.81 (1.75–13.20)	0.002
DAP-Diameter (1 vs. 2)	3.56 (1.24–10.20)	0.018
DAP-Diameter (1 vs. 3)	3.35 (0.56–20.20)	0.187
DAP-Axial (1 vs. 2)	1.74 (0.60–5.02)	0.307
DAP-Axial (1 vs. 3)	2.47 (0.75–8.08)	0.135
DAP-Polar (1 vs. 2)	1.24 (0.34–4.52)	0.745
DAP-Polar (1 vs. 3)	6.43 (2.10–19.6)	0.001

R.E.N.A.L., Radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines; DAP, Diameter-Axial-Polar; OR, Odds ratio; CI, confident interval.

Table 4.

Univariate and multivariate analysis of preoperative clinical factors for predicting postoperative eGFR decrease.

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years (<75 vs. ≥75)	0.48 (0.13–1.71)	0.255	-	-
Sex (female vs. male)	1.39 (0.52–3.74)	0.515	-	-
BMI, kg/m^2 (<25 vs. ≥25)	1.25 (0.51–3.08)	0.623	-	-
Preoperative eGFR, ml/min/1.73m^2 (≥60 vs. <60)	1.02 (0.39–2.65)	0.969	-	-
DM (absent vs. present)	2.66 (1.01–6.97)	0.047	-	-
HTN (absent vs. present)	1.21 (0.51–2.87)	0.672	-	-
Antiplatelet of anticoagulant therapy (absent vs. present)	0.48 (0.11–2.21)	0.348	-	-
Previous abdominal surgery (absent vs. present)	0.67 (0.25–1.81)	0.434	-	-
N factor in R.E.N.A.L. (1 vs. 2/3)	3.95 (1.61–9.67)	0.003	-	-
P factor in DAP (1/2 vs. 3)	5.81 (2.33–14.50)	<0.001	3.50 (1.30–9.46)	0.014
Tumor volume, cm^3 (<14.11 vs. ≥14.11)	6.91 (2.74–17.50)	<0.001	4.57 (1.69–12.30)	0.003

BMI, body mass index; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension; R.E.N.A.L., Radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines; DAP, Diameter-Axial-Polar; OR, odds ratio; CI, confidence interval.

*Backward step-down selection was used.

Figures

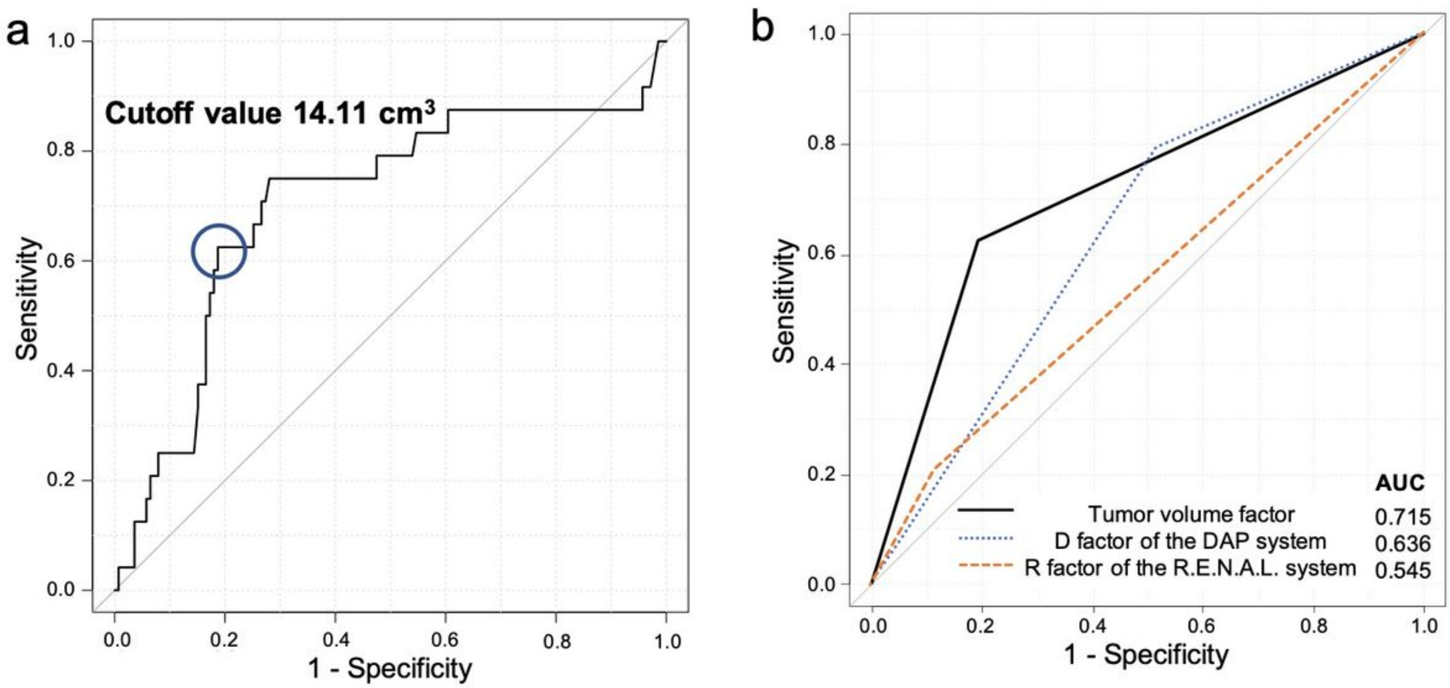

Figure 1

a Receiver operating characteristic curve of tumor volume and cutoff value for predicting eGFR reduction of ≥20%. b Comparison of the AUC values of the tumor volume (cut off value≥14.11 cm3), D factor of the DAP system, and R factor of the R.E.N.A.L. system for predicting eGFR reduction of ≥20%. AUC area under the receiver operating characteristic curve, DAP diameter-axial-polar, R.E.N.A.L. radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines

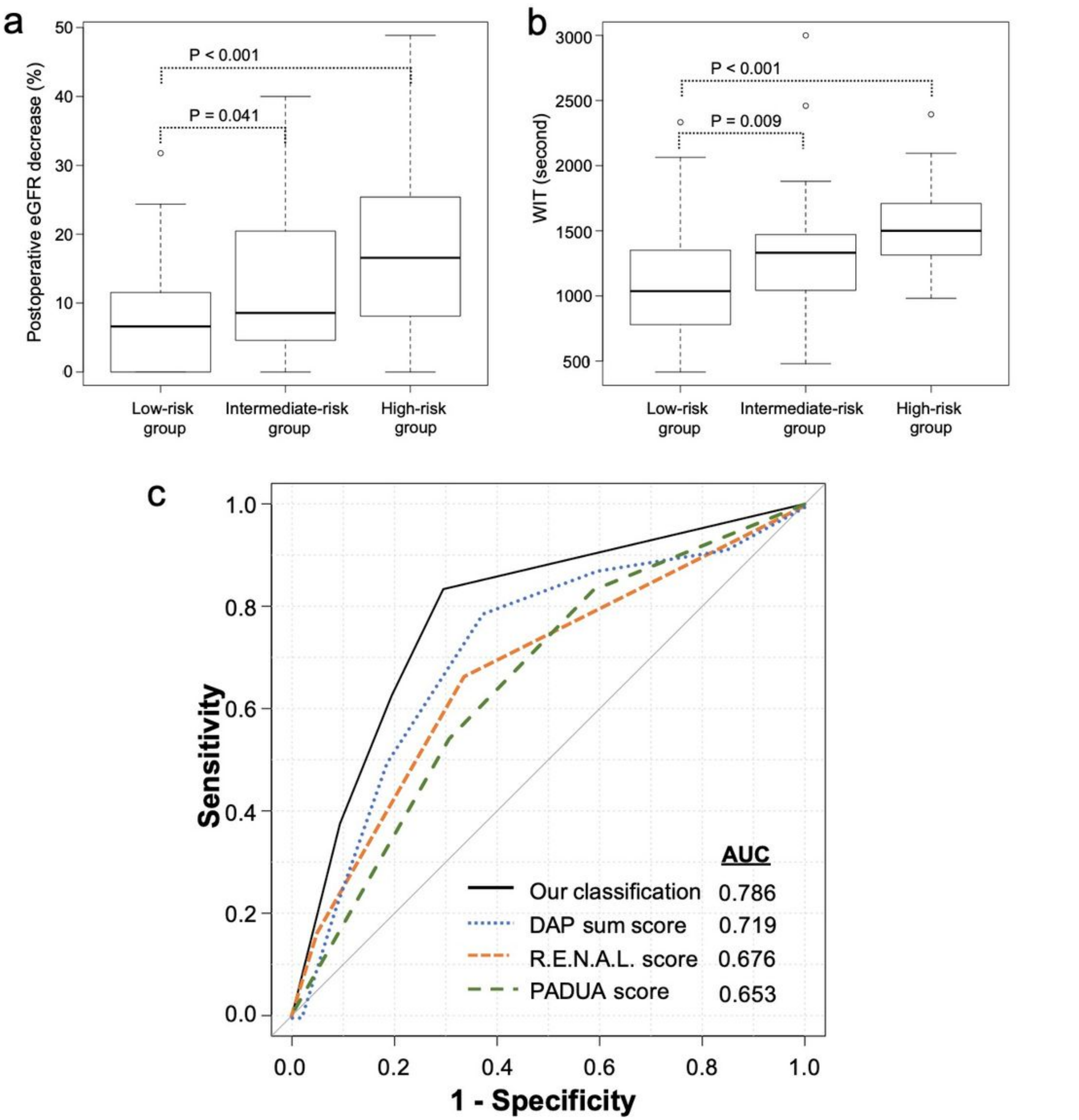

Figure 2

a Postoperative eGFR decrease (continuous variable) with our classification system. b Intraoperative WIT with our classification system. c Comparison of the AUCs of our classification system, the DAP sum score, the R.E.N.A.L. score, and the PADUA score for predicting eGFR reduction of ≥20%. AUC area under the receiver operating characteristic curve, DAP diameter-axial-polar, eGFR estimated glomerular filtration rate, PADUA preoperative aspects and dimensions used for anatomic, R.E.N.A.L. radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines, WIT warm ischemic time

Supplementary Files

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