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Kidney Cancer

# Development and Validation of a Nomogram Predicting Intraoperative Adverse Events During Robot-assisted Partial Nephrectomy

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#### Abstract

Background: Ability to predict the risk of intraoperative adverse events (IOAEs) for patients undergoing partial nephrectomy (PN) can be of great clinical significance.
Objective: To develop and internally validate a preoperative nomogram predicting IOAEs for robot-assisted PN (RAPN).
Design, setting, and participants: In this observational study, data for demographic, preoperative, and postoperative variables for patients who underwent RAPN were extracted from the Vattikuti Collective Quality Initiative (VCQI) database.
Outcome measurements and statistical analysis: IOAEs were defined as the occurrence of intraoperative surgical complications, blood transfusion, or conversion to open surgery/radical nephrectomy. Backward stepwise logistic regression analysis was used to identify predictors of IOAEs. The nomogram was validated using bootstrapping, the area under the receiver operating characteristic curve (AUC), and the goodness of fit. Decision curve analysis (DCA) was used to determine the clinical utility of the model.

**Results and limitations:** Among the 2114 patients in the study cohort, IOAEs were noted in 158 (7.5%). Multivariable analysis identified five variables as independent predictors of IOAEs: RENAL nephrometry score (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.02–1.25); clinical tumor size (OR 1.01, 95% CI 1.001–1.024); PN indication as absolute

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Please cite this article as: G. Sharma, M. Shah, P. Ahluwalia et al., Development and Validation of a Nomogram Predicting Intraoperative Adverse Events During HSEVEL as Sectore 135 (1922) Physics of the provided and the provided and the provided and the provided at the versus elective (OR 3.9, 95% CI 2.6–5.7) and relative versus elective (OR 4.2, 95% CI 2.2–8); Charlson comorbidity index (OR 1.17, 95% CI 1.05–1.30); and multifocal tumors (OR 8.8, 95% CI 5.4–14.1). A nomogram was developed using these five variables. The model was internally valid on bootstrapping and goodness of fit. The AUC estimated was 0.76 (95% CI 0.72–0.80). DCA revealed that the model was clinically useful at threshold probabilities >5%. Limitations include the lack of external validation and selection bias. *Conclusions:* We developed and internally validated a nomogram predicting IOAEs dur-

ing RAPN. *Patient summary:* We developed a preoperative model than can predict complications

that might occur during robotic surgery for partial removal of a kidney. Tests showed that our model is fairly accurate and it could be useful in identifying patients with kidney cancer for whom this type of surgery is suitable.

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### 1. Introduction

Advances in modern imaging modalities and the dissemination of ultrasound technology have led to frequent detection of renal masses [1]. These incidentally detected renal masses are often organ-confined and relatively small in size [2]. Hence, removal of the entire kidney may be viewed as overtreatment considering that partial nephrectomy (PN) has similar oncological and better functional outcomes [3,4]. The latest American and European guidelines recommend PN as the treatment of choice for small renal masses (SRMs) [5,6]. With the availability of robotic platforms and their numerous advantages, many SRMs (irrespective of their complexity) may be eligible for PN [7,8]. Thus, it is imperative for the operating surgeon to identify patients at higher risk of intraoperative adverse events (IOAEs) during robot-assisted PN (RAPN).

An IOAE could include surgical complications, a need for blood transfusion, or conversion to open surgery/radical nephrectomy. Some studies have reported predictors of intraoperative complications [9]. However, to the best of our knowledge, no studies have reported on a comprehensive outcome that includes intraoperative complications, conversion to radical nephrectomy/open surgery, and blood transfusion. Furthermore, no currently available predictive model or nomogram can reliably predict IAOEs. The past two decades have seen rapid adoption of robotic surgery for PN procedures worldwide. Therefore, a nomogram that can predict IOAEs using clinical preoperative variables could be of significant clinical importance. Such a nomogram could potentially be used for patient counseling and prognostication, thereby helping in decision-making. The aim of this Vattikuti Collective Quality Initiative (VCQI) study was to identify preoperative clinical variables that could predict IOAEs for RAPN and create a clinically relevant nomogram.

### 2. Patients and methods

VCQI is an electronic prospective multinational collaborative database maintained by the Vattikuti Foundation [10–13] for a variety of robotic procedures. For RAPN, data are added by 18 centers from nine countries (USA, UK, India, Italy, Portugal, Belgium, Turkey, and South Korea) for patients with localized renal masses. Ethics clearance was obtained from each participating institution before data sharing Data for demographic

variables, such as age, sex (male/female), and body mass index (BMI), as well as preoperative and postoperative parameters were extracted for every patient (Table 1 and Supplementary material). Data were also collected on the indication for PN as elective (tumor in young and healthy patients), relative (genetic syndrome with multiple tumors, contralateral abnormal kidney such as renal stones or nephropathy), or absolute (single kidney, bilateral renal tumors, severe renal dysfunction).

#### 2.1. IOAEs

Data on IOAEs were obtained by combining three domains reported separately in the Vattikuti database: intraoperative complications; conversion to radical nephrectomy/open surgery; and intraoperative blood transfusion. Data for intraoperative complications are entered in a closed question with six options to select from: "Gross violation of tumor bed"; "Major bleeding from the tumor bed"; "Injury to major vessels"; "Injury to abdominal organs"; "Conversion to open"; and "Others".

#### 2.2. Statistical analysis

Results for continuous variables are presented as the mean with standard deviation or median with range. Results for categorical variables are reported as the frequency and proportion. Univariate and multivariable backward regression analysis were used to identify predictors of IOAEs. Backward regression analysis was initiated using all the variables that had a p value of <0.1 on univariate analysis. At every step, variables with a *p* value >0.05 were excluded. Finally, the best reduced model was selected for developing the nomogram [14]. The nomogram was internally validated using bootstrapping (5000 repetitions), a maximum area under the receiver operating characteristic (ROC) curve (AUC), and the goodness of fit, calculated using the Hosmer-Lemeshow test. ROC curves were used to assess the ability of the nomogram to predict IOAEs. The model calibration was checked using calibration plots. All statistical tests were two-sided for a significance level of p < 0.05. Statistical analyses were performed using SPSS v23.0 for Windows (SPSS, Chicago, IL, USA) and Stata v16 (StataCorp LLC, College Station, TX, USA) [15].

#### 3. Results

From October 2014 to March 2020, the participating centers contributed data for 3801 patients who underwent RAPN. Of these, 2114 patients with complete data on IOAEs were included in the final analysis. The median age of the patients included in the study was 59 yr and most were male (65.8%). The median tumor size was 31 mm (range 8–105). A descriptive analysis of patients included in the study is presented in Table 1. IOAEs were noted in 158

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Table 1 –	Descriptive	analysis	of the	2114	patients	included	in	the
study								

Parameter	Result					
Median age, yr (range)	59 (16-87)					
Sex, n (%)	, ,					
Male	1390 (65.8)					
Female	724 (34.2)					
Mean body mass index (kg/m <sup>2</sup> )	28.4 ± 5.9					
Median tumor size, mm (range)	31 (8-105)					
Median Charlson comorbidity index (range)	1 (0-14)					
Clinical symptoms, $n$ (%)						
Asymptomatic	1749 (82.7)					
Local	334 (15.8)					
Systemic	31 (1.5)					
Single kidney, n (%)	64 (3)					
Multifocal tumor, n (%)	107 (5.1)					
Tumor side, n (%)						
Right	840 (39.7)					
Left	1274					
	(60.3)					
Tumor face, n (%)						
Anterior	1086					
	(51.4)					
Posterior	1028 (48.6)					
Polar location of the tumor, n (%)						
Upper pole	672 (31.8)					
Mid pole	810 (38.3)					
Lower pole	632 (29.9)					
Median RENAL nephrometry score (range)	7 (4-12)					
Partial nephrectomy indication, n (%)						
Absolute	71 (3.4)					
Relative	287 (13.6)					
Elective	1759					
	(83.1)					
Mean preoperative hemoglobin (g/dl)	13.1 ± 1.8					
Mean preoperative creatinine (mg/dl)	0.94 ± 0.31					
Mean preoperative estimated glomerular filtration rate	87.8 ± 30.7					
(ml/min)						
Clinical stage, n (%)						
T1a	633 (29.9)					
T1b	1413					
	(66.8)					
T2	68 (3.2)					
Surgical access, n (%)						
Transperitoneal	1814 (85.8)					
Retroperitoneal	300 (14.2)					
Off-clamp surgery, n (%)	210 (9.9)					
Fluorescence use, n (%)	504 (23.8)					
Mean warm ischemia time (min)	23.0 ± 9.1					
Intraoperative adverse event, n (%)	158 (7.5)					
Intraoperative blood transfusion	21					
Conversion to open surgery	3					
Gross violation of the tumor bed	69					
Injury to major vessels	7					
Major bleed from the tumor bed	15					
Injury to abdominal organs	5					
Other	6					
Conversion to radical nephrectomy	39					
<sup>a</sup> For parameters reported as the mean, the result is presented as mean ± stan-						
dard deviation.						

patients (7.5%). The most common IOAE was gross violation of the tumor bed (3.2%), followed by conversion to radical nephrectomy (1.8%) and blood transfusion (0.9%). A further description of each IOAE is provided in Table 1. Some patients had multiple intraoperative complications: conversion to radical nephrectomy and a blood transfusion were required in four patients; a blood transfusion because of major bleeding from the tumor bed was needed in three patients; a blood transfusion because of injury to a major vessel was needed in one patient; and conversion to open radical nephrectomy was needed in one patient.

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#### 3.1. Predictors of IOAE

#### 3.1.1. Univariate analysis

We performed univariate analysis considering 18 variables for prediction of IOAEs. Of these, age (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.005-1.032), BMI (OR 1.03, 95% CI 1.007-1.058), clinical tumor size (OR 1.01, 95% CI 1.002-1.02), solitary kidney (OR 2.08, 95% CI 1.01-4.30), preoperative creatinine (OR 1.45, 95% CI 1.08-1.95), Charlson comorbidity index (CCI; OR 1.10, 95% CI 0.99-1.22), RENAL nephrometry score (RNS: OR 1.10, 95% CI 1.01-1.20), PN indication, tumor multifocality (OR 10.03, 95% CI 6.51-15.4), surgical access (OR 2.38, 95% CI 1.63-3.47), and off-clamp surgery (OR 3.15, 95% CI 3.11-4.7) were identified as predictors of IOAEs.

#### 3.1.2. Multivariable analysis

Preoperative variables with a p value <0.1 on univariate analysis (age, tumor size, CCI, creatinine, solitary kidney, RNS, tumor multifocality, and PN indication) were entered into stepwise backward regression analysis. Finally, the five variables RNS (OR 1.13, 95% CI 1.02-1.25), clinical tumor size (OR 1.01, 95% CI 1.001-1.024), PN indication (absolute vs elective: OR 3.9, 95% CI 2.6-5.7; relative vs elective: OR 4.2, 95% CI 2.2-8), CCI (OR 1.17, 95% CI 1.05-1.30), and tumor multifocality (OR 8.8, 95% CI 5.4-14.1) were identified as independent predictors of IOAEs (Table 2).

#### 3.2. Development and validation of the nomogram

A multivariable model derived via stepwise backward regression analysis was used to develop the nomogram (Fig. 1). The nomogram is easy to use; for example, a patient with a single tumor (0 points) of 40 mm in size (2.5 points) with RNS of 7 (5 points), and CCI of 0 (0 points) for elective PN indication will have an IOAE risk of approximately 5%.

The model was found to be internally valid on bootstrapping with 5000 repetitions, and the Hosmer-Lemeshow goodness-of-fit test returned a p value of 0.610. As estimated from ROC analysis, the AUC was 0.76 (95% CI 0.72-0.80; Fig. 2). The AUC for RNS alone was 0.56 (95% CI 0.51–0.60), which was significantly lower than the AUC for our prediction model (p < 0.0001). The calibration plot showed acceptable concordance between observed and predicted frequencies (Fig. 2). However, it showed slight underestimation for predicted probabilities >30%. Decision curve analysis revealed a net clinical benefit of using the model at threshold probabilities >5% (Fig. 3).

## 4. Discussion

Utilization of PN for the management of localized SRMs has seen an upward trend [16,17]. PN involves finely orchestrated critical substeps such as hilar control, tumor delineation, resection, and renal reconstruction. Every step requires the utmost diligence, experience, and skills on the part of the operating surgeon to avoid intraoperative and postoperative complications. Hence, PN can be considered one of the most challenging urological procedures and is undoubtedly more intricate than radical nephrectomy. Studies comparing PN to radical nephrectomy have

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#### Table 2 - Univariate and multivariable regression analysis of factors predicting intraoperative adverse events

Variable	Univariate		Multivariable (final model)					
	OR (95% CI)	p value	OR (95% CI)	p value				
Age (continuous)	1.01 (1.005-1.032)	0.008						
Sex (female vs male)	1.22 (0.87-1.71)	0.231						
Tumor size (continuous)	1.01 (1.002-1.02)	0.016	1.01 (1.001-1.024)	0.022				
Body mass index (continuous)	1.03 (1.007-1.058)	0.013						
Solitary kidney	2.08 (1.01-4.30)	0.046						
Charlson comorbidity index	1.10 (0.99-1.22)	0.053	1.17 (1.05–1.30)	0.003				
Tumor side (left vs right)	0.86 (0.62-1.19)	0.378						
Tumor face (posterior vs anterior)	1.09 (0.78-1.5)	0.600						
Polar location of tumor								
Upper pole	Reference							
Mid pole	0.86 (0.58-1.27)	0.460						
Lower pole	0.86 (0.57-1.29)	0.471						
Preoperative hemoglobin	0.92 (0.83-1.02)	0.142						
Preoperative creatinine	1.45 (1.08-1.95)	0.013						
Preoperative eGFR	0.99 (0.98-1.00)	0.063						
RENAL score (continuous)	1.10 (1.01-1.20)	0.025	1.13 (1.02–1.25)	0.012				
Partial nephrectomy indication								
Elective	Reference		Reference					
Relative	7.09 (4.01–12.5)	<0.0001	4.2 (2.24-8.05)	<0.0001				
Absolute	4.39 (3.04-6.35)	<0.0001	3.9 (2.64–5.75)	<0.0001				
Multifocality	10.03 (6.51-15.4)	<0.0001	8.8 (5.47-14.1)	<0.0001				
Access (retroperitoneal vs transperitoneal)	2.38 (1.63-3.47)	<0.0001						
Off-clamp surgery	3.15 (2.11-4.7)	<0.0001						
Fluorescence use	1.17 (0.81–1.69)	0.401						
eGFR = estimated glomerular filtration rate: OR = odds ratio: CI = confidence interval.								



Fig. 1 – Preoperative nomogram predicting the occurrence of intraoperative adverse events. Rel = relative; Abs = absolute; Prob = probability.

reported higher complication rates following PN [3,18]. The availability of robotic platforms has facilitated minimally invasive accomplishment of this complex procedure. Many renal masses of higher complexity are also now being treated using PN via a robotic approach. This increases the risk of IOAEs during the procedure. Hence, a preoperative model

that can predict IOAEs could be of clinical significance as it could help in counseling and prognostication for patients regarding any such untoward event during surgery.

We developed and internally validated a clinically valuable nomogram for predicting IOAEs that includes five variables: tumor size, RNS, CCI, tumor multifocality, and the

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Fig. 2 – Area under the receiver operating characteristic curve (AUC) and calibration plot for the nomogram predicting intraoperative adverse events. For the AUC values, the 95% confidence interval is shown in parentheses. RNS = RENAL nephrometry score.



Fig. 3 – Decision curve analysis for the nomogram and for treat-all and treat-none strategies. Pr(IOAE) = probability of an intraoperative adverse event.

indication for PN. The variables included in our nomogram can be easily obtained from the initial workup preceding any PN. ROC analysis revealed an AUC of 0.75, which indicates that our model is reasonably accurate in predicting the outcome of interest. Furthermore, the model shows a net clinical benefit at a threshold frequency of 5%. To the best of our knowledge, this is the first nomogram developed and validated for predicting IOAEs during PN. Many studies have reported predictors of postoperative complications following PN. However, the literature on factors predicting IOAEs is limited. Some observational studies have identified predictors of intraoperative complications. However, none of these studies used a comprehensive parameter such as IOAE incidence. Tan et al. [19] combined RNS and Mayo adhesion probability (MAP) scores to develop a nomogram consisting of three variables (tumor size, closeness to the pelvicalyceal system, and perirenal fat stranding) to predict intraoperative complications. The nomogram (AUC 0.837) was superior to the MAP score (AUC 0.729) and RNS (AUC 0.686) in predicting intraoperative complications. In another study, Minervini et al. [20] found that age, indication for surgery (imperative vs elective), and surgical approach (open vs laparoscopic vs robotic) were predictors of intraoperative complications. Our study differs from these previous studies in terms of our outcome of IOAEs, which included conversion to radical nephrectomy, blood transfusion, and intraoperative surgical complications.

Previous studies have consistently reported that tumor size and complexity (RNS) are predictors of perioperative outcomes (including intraoperative complications) for PN [9,21–30]. A few studies have also reported predictors of conversion to radical nephrectomy during PN. In a previous VCQI study, Arora et al. [31] identified CCI as an independent predictor of conversion to radical nephrectomy, as well as BMI. The authors pointed out that greater medical comorbidity could result in a lower threshold for conversion to radical nephrectomy. We also found that CCI, a comprehensive measure of comorbid illnesses, was an independent predictor of IOAEs. In another study, Petros et al. [32] identified large tumor size, complexity, hilar tumor location, locally advanced tumor stage, and laparoscopic PN as independent predictors of conversion to radical nephrectomy.

Another important finding is that the indication for PN (absolute vs relative vs elective) was an independent predictor of IOAEs. The literature has been divided on the impact of the indication for surgery on perioperative outcomes. Imperative indications for surgery have been identified as predictors of perioperative outcomes such as positive surgical margins [33], intraoperative complications [20], functional loss [34], and minor [35] and major complications [36]. At the same time, other studies have reported no impact of the indication for surgery on perioperative outcomes for PN [37,38]. Absolute and relative indications for PN were associated with higher odds of IOAEs in comparison to elective indications. Absolute indications include a solitary kidney, bilateral tumors, and severe renal dysfunction, whereas relative indications include a genetic syndrome with bilateral tumors, and an abnormal contralateral

kidney. Interestingly, solitary kidney and renal dysfunction (as measured by preoperative estimated glomerular filtration rate) alone were not identified as independent predictors of IOAEs. However, the present study identified tumor multifocality as a strong predictor of IOAEs for RAPN.

#### 4.1. Strength and limitations

Strengths of this study include the large sample used to develop and internally validate the nomogram. Second, the prospective nature of data entry into the VCQI database avoids under-reporting of intraoperative complications, such as conversion to radical nephrectomy. We used a more comprehensive outcome measure—IOAEs—instead of just evaluating intraoperative complications. Lastly, data for this study were collected from different centers across the globe. Thus, the nomogram we developed has wider applicability as it is not limited to a particular region or race. This nomogram can reliably inform the operating surgeon before surgery and help in identifying patients at heightened risk of IAOEs.

Some limitations of the VCOI database have already been highlighted in previous studies [10-13,31]. Surgeon experience and center volume were not considered because of a lack of data in the database. Second, data are lacking on the operative technique for tumor resection (enucleation or resection), use of intraoperative ultrasound, use of Tile-Pro, and the indication for use of fluorescence. Third, there is heterogeneity in surgical techniques, learning curves, and perioperative management of patients because of the wider reach of the VCOI database. However, this probably represents the real-world scenario for RAPN. Fourth, we had to exclude nearly one-third of the patients owing to a lack of data on IOAEs. This could be an important limitation and source of bias in this study. However, large multicenter databases are frequently prone to data loss and such patients have to be excluded. Lastly, the nomogram developed in this study needs further independent external validation before it can be recommended for clinical use.

## 5. Conclusions

We developed an accurate and clinically useful nomogram for predicting IOAEs. However, the model lacks external validation and validation studies are needed.

**Author contributions**: Gagan Gautam 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: Gautam, Shah, Ahluwalia.

*Acquisition of data*: Sharma, Gautam, Shah, Ahluwalia, Dasgupta, Challacombe, Bhandari, Parekh, Sivaraman, Ahlawat, Rawal, Buffi, Porter, Rogers, Mottrie, Abaza, Rha, Moon, Yuvaraja, Capitanio, Maes, Porpiglia, Turkeri.

Analysis and interpretation of data: Sharma, Gautam, Shah, Ahluwalia. Drafting of the manuscript: Sharma, Gautam, Shah, Ahluwalia.

Critical revision of the manuscript for important intellectual content: Sharma, Gautam, Shah, Ahluwalia, Dasgupta, Challacombe, Bhandari, Rawal, Buffi, Porter, Rogers, Parekh, Sivaraman, Ahlawat, Mottrie, Abaza, Rha, Moon, Yuvaraja, Capitanio, Maes, Porpiglia, Turkeri. Statistical analysis: Sharma, Shah. Obtaining funding: None. Administrative, technical, or material support: Gautam, Bhandari. Supervision: Gautam. Other: None.

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**Ethical considerations:** This study is a retrospective analysis of the VCQI database and ethics approval was obtained from all the participating centers before data collection. The need for informed consent was waived by the relevant ethics committees.

**Data sharing statement:** Data are available from the corresponding author on request from genuine researchers.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.09.004.

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