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Clinical-Kidney cancer

Development and validation of a multicenter Cox regression model to predict all-cause mortality in patients with renal masses suspicious for renal cancer

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Abstract

Objective: Life expectancy models are useful tools to support clinical decision-making. Prior models have not been used widely in clinical practice for patients with renal masses. We sought to develop and validate a model to predict life expectancy following the detection of a localized renal mass suspicious for renal cell carcinoma.

Materials and methods: Using retrospective data from 2 large centers, we identified patients diagnosed with clinically localized renal parenchymal masses from 1998 to 2018. After 2:1 random sampling into a derivation and validation cohort stratified by site, we used age, sex, log-transformed tumor size, simplified cardiovascular index and planned treatment to fit a Cox regression model to predict all-cause mortality from the time of diagnosis. The model's discrimination was evaluated using a C-statistic, and calibration was evaluated visually at 1, 5, and 10 years.

Results: We identified 2,667 patients (1,386 at Corewell Health and 1,281 at Johns Hopkins) with renal masses. Of these, 420 (16%) died with a median follow-up of 5.2 years (interquartile range 2.2−8.3).

Statistically significant predictors in the multivariable Cox regression model were age (hazard ratio [HR] 1.04; 95% confidence interval [CI] 1.03−1.05); male sex (HR 1.40; 95% CI 1.08−1.81); log-transformed tumor size (HR 1.71; 95% CI 1.30−2.24); cardiovascular index (HR 1.48; 95% CI 1.32−1.67), and planned treatment (HR: 0.10, 95% CI: 0.06−0.18 for kidney-sparing intervention and HR: 0.20, 95% CI: 0.11−0.35 for radical nephrectomy vs. no intervention). The model achieved a C-statistic of 0.74 in the derivation cohort and 0.73 in the validation cohort. The model was well-calibrated at 1, 5, and 10 years of follow-up.

Conclusions: For patients with localized renal masses, accurate determination of life expectancy is essential for decision-making regarding intervention vs. active surveillance as a primary treatment modality. We have made available a simple tool for this purpose.

Keywords: Comorbidity index; Kidney neoplasms; Life expectancy; Mortality tool; Renal cell carcinoma; Renal mass

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1. Introduction

The incidence of renal cell carcinoma (RCC) continues to rise, in large part based on the incidental detection of renal masses rather than symptomatic presentation with advanced RCC [1]. There have been significant advances in local and systemic therapies for RCC, but despite these, the mortality for advanced disease remains high. For those with apparently localized disease, however, cancer-specific survival is quite good, and much attention has been paid to the impact of various treatments on renal function and overall health [2,3]. Comparisons between radical nephrectomy (RN) and kidney-sparing interventions (KSI) have revealed functional benefits to KSI. Partial nephrectomy (PN) is the reference standard for localized RCC that is amenable to such an approach in guidelines from the AUA, NCCN, and EAU [4−6]. Nonsurgical KSI, including thermal ablation and stereotactic ablative radiotherapy, are considered alternatives in select patients [4,7,8]. Several studies, though, have questioned the magnitude of the benefit of treatment vs. surveillance [4,9−11].

Like active surveillance for prostate cancer, active surveillance of RCC has been gaining acceptance worldwide [4,5,8]. First, not all enhancing renal masses are malignant tumors [12]. Second, most small renal masses (SRM) pursue an indolent course, with metastases rarely observed (<1%−2%) in patients with SRM managed with surveillance [4,6]. Third, many patients with suspected RCC also suffer from comorbid conditions that pose a significant impact on their survival, making competing causes more important than cancer-related causes of mortality.

Several prior groups have investigated the role of comorbidities in all-cause mortality and have developed survival models accounting for competing causes of death (noncancer vs. cancer-specific mortality) [13−15]. Prior studies have relied upon comorbidity indices, such as the Charlson comorbidity index (CCI) and its subsequent iterations [16−18]. These prognostic tools are hindered though by the extensive amount of information required to estimate mortality risk; thereby, limiting their utility in clinical practice. In our prior work, we found that the simplified cardiovascular index (CVI) provides similar estimates of mortality to the CCI and its derivatives while requiring only seven elements of patient information [19]. In this study, we gathered pretreatment data and survival information from patients managed at 2 institutions to develop and validate a model to predict all-cause mortality in patients with localized renal masses suspicious for RCC.

2. Patients and methods

2.1. Data source

Our data were obtained from tumor registries at Corewell Health (Grand Rapids, MI) and Johns Hopkins University (Baltimore, MD). Our study was approved by the institutional review boards (SH#2010-082 and JH#00204473) for the use of data maintained within our institutional tumor registries.

2.2. Study population

Patients were included if they had clinical evidence of a localized renal parenchymal mass suspicious for renal cancer on cross-sectional abdominal imaging and pretreatment information about comorbidities and renal functional status between 1998 and 2015 at Corewell Health, and between 1999 and 2018 at Johns Hopkins University. Among these patients, we excluded patients with radiographic evidence of locally-advanced or metastatic disease ($n = 274$); missing clinical stage ($n = 37$); ≤18 years old ($n = 70$); with a diagnosis other than suspected renal cancer ($n = 280$), such as urothelial carcinoma, Wilm's tumor, or other reason for nephrectomy; having neither urinalysis or eGFR prior to surgery ($n = 292$); having no available comorbidity information ($n = 214$); or having no follow-up after diagnosis ($n = 64$). The diagnostic pathway at both institutions was largely similar, with metastatic evaluation including chest imaging generally performed for patients with tumors ≥3.0 cm. Although increasingly performed in recent years, renal mass biopsy was infrequent during the study timeframe. Planned treatment was determined by the treating urologist and treatment received was recorded within the institutional registries.

2.3. Outcome

The outcome was all-cause mortality from the time of diagnosis. Date of death was determined based on review of the electronic medical record at each institution with review of the Social Security Death Index.

2.4. Predictors

Predictors (i.e. covariates) in the model were age, sex, log-transformed radiographic tumor size, simplified CVI, and planned treatment type (categorized as no intervention, kidney-sparing intervention, or radical nephrectomy). Using pretreatment GFR, calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration formulas, and proteinuria, obtained from urinalysis or albumin-to-creatinine ratio, CKD risk was classified according to the Kidney Disease Improving Global Outcomes guidelines as low, moderately-increased, high, and very-high [20]. In brief, patients with GFR <60 ml/min/1.73m^2 and/or >30 mg/dl proteinuria were categorized as having CKD. Simplified CVI was used as previously described, with 1 point assigned for CKD, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), cerebrovascular disease (CVD), and 2 points for congestive heart failure (CHF) [19].

2.5. Model development and validation

The patient cohort was divided into a derivation and validation cohort using 2:1 random sampling. The sampling was stratified by site to ensure that both cohorts had representation from patients from each institution. A Cox regression model was trained to predict all-cause mortality from time of diagnosis using the above predictors. The model's discrimination was evaluated using a C-statistic, and calibration was evaluated visually at 1, 5, and 10 years.

In Table 1, Supplementary Table 1, and Supplementary Table 2, continuous variables are reported as the median with the interquartile range ([IQR]; 25th, 75th percentile), or as the mean ± standard deviation. Categorical variables are reported as the frequency (%). Differences between quantitative variables were analyzed using the Wilcoxon test, while differences for categorical variables were determined using the chi-square test. Statistical significance was assessed at $P < 0.05$. Survival time was calculated from the date of diagnosis to the date of last available follow-up. Overall survival was estimated using Kaplan−Meier analysis, with 5-year survival estimates and 95% confidence interval (CI) provided for each subgroup.

2.6. Software

All statistical analyses were performed with R version 4.2.2 [21], and using the following R packages: tidyverse [21,22], survival [21−23], survminer [24], and pec [25].

3. Results

During the study period, 1,386 patients met inclusion criteria at Corewell Health, and 1,281 met inclusion criteria

Table 1
Patient characteristics, overall and by site

Characteristic *N* (%) or Median (IQR)	Overall (*N* = 2,667)	Johns Hopkins (*N* = 1,281)	Corewell Health (*N* = 1,386)	*P*-value
Mortality	420 (16%)	133 (10%)	287 (21%)	<0.001
Length of follow-up, y	5.2 (2.2, 8.3)	6.2 (2.3, 9.1)	4.6 (2.2, 7.3)	<0.001
Age, y	62 (52, 70)	62 (53, 69)	62 (51, 71)	0.65
Sex				0.005
Female	1,054 (40%)	471 (37%)	583 (42%)	
Male	1,613 (60%)	810 (63%)	803 (58%)	
Race				<0.001
Black	263 (9.9%)	200 (16%)	63 (4.5%)	
White	2,338 (88%)	1,037 (81%)	1,301 (94%)	
Other	66 (2.5%)	44 (3.4%)	22 (1.6%)	
Tumor size, cm	3.3 (2.2, 5.1)	3.3 (2.2, 4.9)	3.4 (2.1, 5.7)	0.29
Missing	89	64	25	
Comorbidity score (CVI)				<0.001
0	1,638 (61%)	888 (69%)	750 (54%)	
1	787 (30%)	326 (25%)	461 (33%)	
2	146 (5.5%)	49 (3.8%)	97 (7%)	
3	72 (2.7%)	16 (1.2%)	56 (4%)	
4	21 (0.8%)	2 (0.2%)	19 (1.4%)	
5	3 (0.1%)	0 (0%)	3 (0.2%)	
Clinical tumor stage				<0.001
T1a	1,672 (63%)	855 (67%)	817 (59%)	
T1b	652 (24%)	314 (24%)	338 (24%)	
T2a	232 (8.7%)	83 (6.5%)	149 (11%)	
T2b	111 (4.2%)	29 (2.3%)	82 (5.9%)	
Chronic kidney disease (CKD)	835 (31%)	301 (23%)	534 (39%)	<0.001
Congestive heart failure (CHF)	98 (4.2%)	16 (1.7%)	82 (5.9%)	<0.001
Missing	330	330	0	
Peripheral vascular disease (PVD)	151 (6.5%)	42 (4.4%)	109 (7.9%)	<0.001
Missing	331	331	0	
Cerebrovascular disease (CVD)	52 (2.2%)	24 (2.5%)	28 (2.0%)	0.42
Missing	329	329	0	
Chronic obstructive pulmonary disease (COPD)	160 (6.8%)	81 (8.5%)	79 (5.7%)	0.0008
Missing	330	330	0	
Management type				<0.001
No intervention	47 (1.8%)	0 (0%)	47 (3.4%)	
Kidney-sparing intervention	1,521 (57%)	910 (71%)	611 (44%)	
Radical nephrectomy	1,099 (41%)	371 (29%)	728 (53%)	

Note: While displayed as categories, the *P*-value for CVI score was calculated using the Wilcoxon test.
CVI = cardiovascular index; IQR = interquartile range.

at Johns Hopkins University, for a total of 2,667 patients in the study cohort. Demographic and clinical features are included in Table 1, Supplementary Table 1, and Supplementary Table 2. Among the overall cohort, 420 (16%) patients died with a median follow-up of 5.2 years (IQR 2.2−8.3). Causes of death included kidney cancer ($n = 63$), other cancers ($n = 45$), noncancer-related ($n = 171$), and unknown ($n = 141$). Median age at diagnosis was 62 years and 60% were male. Median tumor size was 3.3 cm (IQR 2.2−5.1cm), with no significant difference between the 2 cohorts. All patients had clinically localized renal masses, the majority of which were cT1a ($n = 1672$, 61%). Most patients had none of the comorbidities that contribute points to the simplified CVI; the most common condition was CKD ($n = 835$, 31%), followed by COPD (6.8%, $n = 160$), PVD (6.5%, $n = 151$), CHF (4.2%, $n = 98$), and CVD (2.2%, $n = 52$). While hypertension (53%) and diabetes mellitus (35%) were prevalent, neither of these were predictors of mortality in our prior work (manuscript submitted) [19] and did not contribute to CVI score. CVI score was calculated for all patients, 1,638 (61%) scored 0, 787 (30%) scored 1, 146 (5.5%) scored 2, 72 (2.7%) scored 3, 21 (0.8%) scored 4, and 3 (0.1%) scored 5. Initial treatment type was RN ($n = 1,099$, 41%), PN ($n = 1,435$, 54%), thermal ablation ($n = 86$, 3.2%), or no intervention ($n = 47$, 1.8%).

Pathology included RCC ($n = 2229$), benign ($n = 389$), other cancer ($n = 7$), unknown ($n = 42$). RCC subtypes included clear cell (73%), papillary (15%), chromophobe (7.6%), other indolent subtypes (0.9%), and sarcomatoid/unclassified/unknown RCC (3.4%). For resected RCC, pathologic stage was pT1a (59%), pT1b (18%), pT2 (7.2%), pT3/T4 (16%). Various demographic and clinical features were assessed for their significance in predicting mortality using multivariable Cox regression analysis (Table 2). Statistically significant predictors from this model included age (hazard ratio [HR] 1.04; 95% CI 1.03−1.05); male sex (HR 1.40; 95% CI 1.08−1.81); log-transformed tumor size (HR 1.71; 95% CI 1.30−2.24); CVI (HR 1.48; 95% CI 1.32−1.67); and planned treatment type (HR: 0.10, 95% CI: 0.06−0.18 for KSI and HR: 0.20, 95% CI: 0.11−0.35 for RN vs. no intervention, respectively).

Table 2
Multivariable Cox regression model hazard ratios

Term	Hazard ratio (95% CI)	*P*-value
Age, y	1.04 (1.03−1.05)	<0.001
Sex		
Female	Reference	
Male	1.40 (1.08−1.81)	0.011
Tumor size + 1, log-transformed	1.71 (1.30−2.24)	<0.001
CVI score, unit	1.48 (1.32−1.67)	<0.001
Management type		
No intervention	Reference	
Kidney-sparing intervention	0.10 (0.06−0.18)	<0.001
Radical nephrectomy	0.20 (0.11−0.35)	<0.001

CI = confidence interval; CVI = cardiovascular index.

3.1. Model performance

The Cox regression model achieved a C-statistic of 0.74 in the derivation cohort and 0.73 in the validation cohort (Supplementary Table 3). Kaplan−Meier survival curves were constructed for each cohort and showed that there were statistically significant differences in survival between the 2 centers ($P < 0.0001$) (Fig. 1). The cohort was subsequently broken into quartiles based on their score from our constructed model and survival probability of each quartile was plotted on a Kaplan−Meier curve (Fig. 2). Differences in survival probability for each quartile were statistically significant ($P < 0.0001$). In quartiles 1, 2, 3, and 4, the 10-year survival probabilities were 94%, 87%, 69%, and 50%, respectively. The model was generally well-calibrated at 1 and 5 years of follow-up (Fig. 3). At 10 years of follow-up, the model underestimated risk in the Corewell Health cohort, potentially due to the lower baseline survival rate observed.

4. Discussion

Prediction of mortality in patients newly diagnosed with localized renal masses suspicious for RCC is an essential component of shared decision-making. This information is central to the decision to treat or actively surveil each individual patient. Until recently, there have been no easy-to-use tools to obtain this information in the urology clinic. In this study, we found that a Cox regression model can accurately predict all-cause mortality in a diverse cohort consisting of patients treated at one community-based health system and one large, tertiary referral center. Based on this model, we have developed just such a tool and have made it freely available at https://askmusic.med.umich.edu/tools/kidney-cancer-mortality-tool/(Supplementary Fig. 3).

The intended use for the tool is during discussion between the clinician and the patient and loved ones, during which the concepts of life expectancy and relative value of intervention for the suspected malignancy are discussed. For example, a 59-year-old female with CKD, COPD, a 5.6 cm enhancing renal mass, and a plan for no intervention, has a life expectancy of 77% at 1 year, 36% at 5 years, and 9.5% at 10 years. Despite the relatively young age of this patient, the competing risks of death from comorbidity are high; communication can; therefore, be centered on these and the limited likelihood that the SRM will impact the patient's life expectancy. Active surveillance can be offered supported by the recommendation of a panel of urologists regarding the appropriateness of surveillance in this scenario (Supplementary Fig. 2). The model is well calibrated overall and at Johns Hopkins. However, at Corewell Health there is modest overestimation of 1-year-mortatlity and underestimation of 10-year-mortality. Quartiles of risk identified by the Cox model showed good separation of risk, again suggesting that this model is suitable to guide medical decision making when deciding between

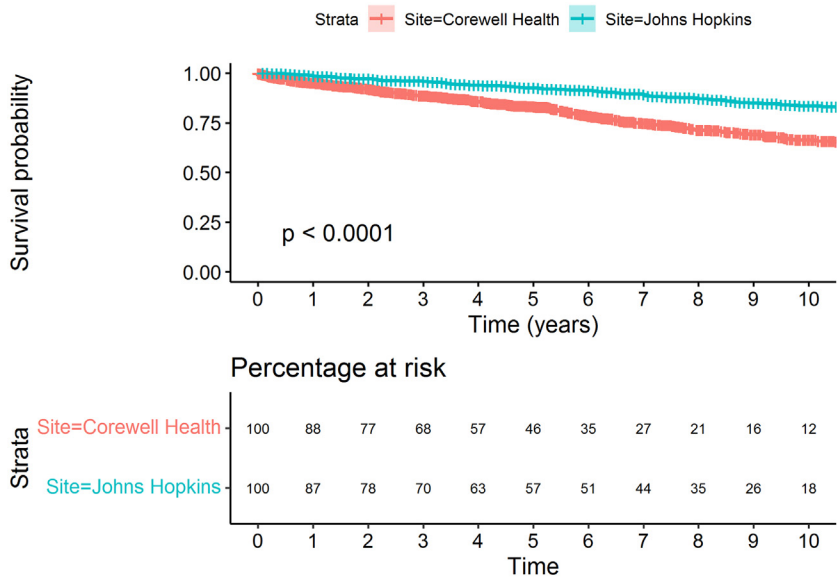

Fig. 1. Survival curve of patients in the overall cohort, stratified by site.

intervention and noninterventional approaches for suspected renal cancer (Supplementary Figs. 1–3).

Prior predictive models for RCC have relied on either the original or modified versions of the CCI. Until recently, a validated, prognostic tool that predicts all-cause mortality and suitable for integration into clinical practice, has not been available [26]. The tool recently proposed shows great promise; however, it relies on CCI score, which complicates its ability to provide a prediction of mortality during a typical office visit. Although such tools may work well when used retrospectively on data held within institutional databases, they are time-consuming and impractical to ascertain in routine clinical practice [19,26]. In contrast, our Cox model was fit using only 9 variables: age, sex, tumor size, planned treatment type, and 5 comorbid conditions: CKD, COPD, CHF, PVD, and CVD that can be obtained during the patient encounter. These variables are also "easily abstractable" potentially by artificial intelligence algorithms or natural language processing [27]. In addition, except for tumor size and planned treatment, which are generally recorded in text format in clinical documentation, all the remaining variables can be readily ascertained or even directly abstracted from the electronic health record as structured data elements making use of this tool facile in research settings as well.

There are an increasing number of tools used by urologists to help guide conversations with patients surrounding management of newly diagnosed RCC [26,28]. Renal mass biopsy and interpretation of radiographic studies with artificial intelligence have provided more certainty in the characteristics of a patient's mass preoperatively [29,30]. Though these tools have helped decrease the incidence of unnecessary interventions, they lack prognostic data, which can add further granularity to this decision. Determining the appropriateness of immediate intervention vs. active surveillance for a patient's suspected RCC is often best discussed in the

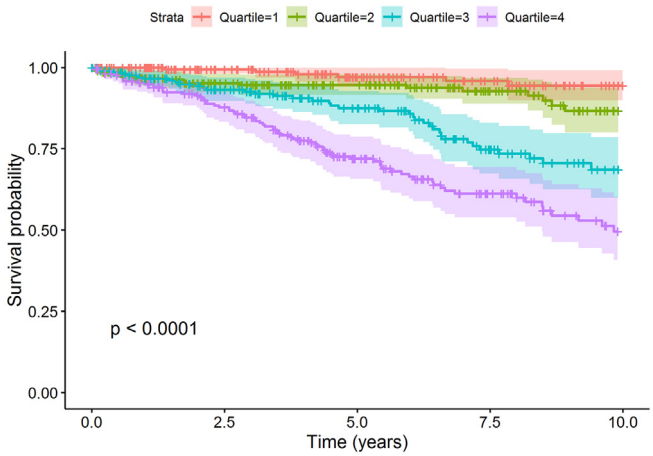

Fig. 2. Survival curves stratified by quartiles of predicted model scores in the validation cohort.

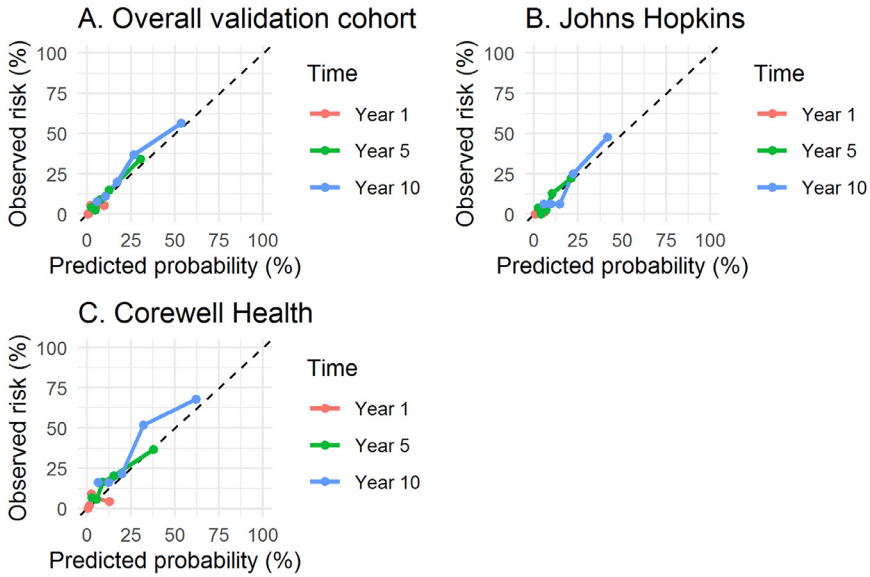

Fig. 3. Calibration of the Cox regression model by quintiles of predicted risk at 1, 5, and 10 years in the A) overall validation cohort, B) Johns Hopkins validation cohort, and C) Corewell Health validation cohort.

context of overall survival and risk of treatment-related morbidity and mortality. When taken in concert with the information gleaned from biopsy and imaging, a risk model relying on comorbidities can provide clinicians and patients with additional value related to prognosis when deciding upon a treatment plan.

For patients with localized RCC, increasing age and comorbidity are associated with an increase in the risk of mortality [14]. The mortality estimates of the recently proposed tool relying on the CCI may be confounded by the existence of multiple scoring methods, including the age adjusted CCI and updated CCI, and whether or not to incorporate the incident, newly diagnosed RCC as a *comorbid* malignancy when computing the score; there is no guidance on this issue, but most researchers have elected to exclude the incident malignancy. The model we have proposed relies instead on the CVI, which avoids these issues ensuring that the tool can be used consistently. Alternatively, a tool that groups patients according to degree of comorbidity (none, low, high) would also be easy to implement.

Limitations of our work include those of any retrospective analysis of registry data; the merging of data from two large registries resulted in the exclusion of some granular data relating to tumor and patient characteristics and details regarding recurrence and metastasis. Despite these limitations, and the differences in the patient population and diagnostic pathway at a large community-based health system and a major academic institution, the results of the study may be more generalizable as a result. Another major limitation is the relatively small proportion of patients managed without intervention, relative to PN and RN. The small number of patients identified in the two institutional registries as not undergoing treatment are only a subset of patients evaluated at these institutions during the study timeframe. As inclusion required surgery or other hospital-based clinical documentation available to tumor registrars, patients seen in the office only and managed with active surveillance without renal mass biopsy were systematically excluded. As such, the impact of the treatment variable in this prediction tool may be weighted more highly in favor of intervention than would be observed for patients evaluated in the urology office with consideration given to active surveillance according to current indications. This selection bias is readily apparent when compared to DISSRM, MUSIC-KIDNEY, and other prospective registries, but cannot be overcome in any retrospective cohort. Further, the CVI has not been used as widely as CCI and relies on only five comorbid conditions; it therefore may not be as reliable a proxy for comorbidity status although our prior work suggests comparable performance [19]. Validation of this tool and comparison with the tool by Psutka et al. [26] using other contemporary cohorts of patients with expanded use of active surveillance will be important. Our future work will include validation of our model in practices participating in the MUSIC-KIDNEY quality initiative [31].

5. Conclusions

Determining life expectancy is essential in determining the benefit of various therapeutic interventions for a localized renal mass. We have constructed and validated a model based on 9 factors (age, sex, tumor size, CKD, CHF, COPD, PVD, CVD, and planned treatment) that can be assessed routinely during the initial urology office visit for a newly diagnosed renal mass. We believe that this model provides an accurate and understandable prediction of mortality for use during an office visit and is concise enough to be utilized within typical time constraints. It has been made readily available at https://askmusic.med.umich.edu/tools/kidney-cancer-mortality-tool. (Supplementary Fig. 3).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KS's institution receives grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases, Blue Cross Blue Shield of Michigan, and Teva Pharmaceuticals for unrelated work. KS previously served on a scientific advisory board for Flatiron Health. All other authors have no conflicts of interest.

CRediT authorship contribution statement

Brian R. Lane: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Joseph G. Cheaib:** Data curation. **Dennis Boynton:** Data curation, Writing – original draft, Writing – review & editing. **Phillip Pierorazio:** Supervision, Writing – review & editing. **Sabrina L. Noyes:** Data curation, Project administration, Writing – review & editing. **Henry Peabody:** Data curation. **Nirmish Singla:** Supervision, Writing – review & editing. **Anna Johnson:** Data curation. **Khurshid R. Ghani:** Methodology, Supervision, Writing – review & editing. **Andrew Krumm:** Formal analysis, Validation, Writing – review & editing. **Karandeep Singh:** Formal analysis, Validation, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.04.007.

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