Development and Validation of a Prognostic Nomogram for Progression-Free Survival in Patients with Advanced Renal Cell Carcinoma Treated with Pazopanib

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**Key Words**
Angiogenesis inhibitors · COMPARZ · Nomogram · Pazopanib · Prognosis · Renal cell carcinoma

**Abstract**

**Objective:** To develop and validate a prognostic nomogram for predicting the probability of 12-month progression-free survival (PFS) for patients receiving first-line pazopanib for advanced renal cell carcinoma (RCC). **Methods:** Statistical modeling was performed with data from 557 pazopanib-treated patients in the phase 3 COMPARZ trial. A multivariable Cox model was fit using known prognostic indicators. Variables included neutrophil count, serum levels of albumin and alkaline phosphatase, time from diagnosis to treatment, and bone metastases. Data from the pazopanib arm of a placebo-controlled phase 3 trial were used for validation. **Results:** The model included ten prognostic variables and was plotted as a nomogram for predicting the probability of 12-month PFS. Calibration plots suggested reasonable correspondence between predicted probabilities and actual proportions of PFS. The concordance index for 12-month PFS was 0.625. Significant associations (p < 0.05) were observed between PFS and bone metastases, time from diagnosis to treatment, albumin, and alkaline phosphatase. Albumin and alkaline phosphatase appeared to be influential predictors. **Conclusion:** The nomogram predicts, with reasonable accuracy, PFS in patients with advanced RCC receiving pazopanib, based on their baseline clinical characteristics.

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**Introduction**

Renal cell carcinoma (RCC) is the most common form of kidney cancer [1]. Approximately 90% of all kidney cancers may be classified as RCC, with up to 80% having clear-cell histology [1, 2]. More than 75% of RCC patients present with locally advanced or metastatic disease [3]. Before the development of targeted agents, the primary systemic treatment for advanced RCC was therapy with cytokines, including interferon-α and interleukin-2. Several targeted agents are now approved for the treatment of RCC.
of advanced or metastatic RCC. The angiogenesis inhibitors pazopanib, sunitinib, sorafenib, and bevacizumab, as well as the mTOR inhibitor temsirolimus, are approved in the first-line setting [4]; the angiogenesis inhibitor axitinib and the mTOR inhibitor everolimus are approved in the second-line setting [4]. Clinical practice guidelines have been updated to reflect approval of these agents [5].

Predicting treatment outcome on the basis of baseline factors can aid treatment planning and patient counseling. A widely used prognostic model for patients with RCC, developed at Memorial Sloan-Kettering Cancer Center (MSKCC), groups patients into three risk categories (favorable, intermediate, and poor) based on the number of clinical indicators of poor survival [6]. The MSKCC criteria were developed during the cytokine era of RCC treatment and were later validated and extended by Heng et al. [7] to account for the availability of antiangiogenic targeted therapy. Both the MSKCC criteria and those by Heng et al. [7] are commonly used in clinical practice, but are based solely on the categorical evaluation of potential prognostic variables. A continuous model that incorporates both categorical and continuous variables and does not combine subgroups of patients with potentially heterogeneous outcomes would be of additional value to clinicians.

Nomograms are graphical tools that allow clinicians to use individual patient data to predict the probability of a clinical event. In oncology, nomograms have been used to combine clinical predictors to estimate an individual patient’s prognosis and have been developed for a number of specific agents [8–11]; among these is a prognostic nomogram for patients with metastatic RCC treated with sunitinib [8]. The objective of the current research was to develop and validate a prognostic nomogram for 12-month progression-free survival (PFS) for patients with advanced RCC treated with pazopanib, a multitargeted tyrosine kinase inhibitor.

**Patients and Methods**

**Patients**

The development dataset consisted of pazopanib-treated patients with advanced RCC enrolled in a randomized, open-label, phase 3 trial (COMPARZ; NCT00720941 and NCT01147822) [12] that assessed noninferiority of pazopanib compared to sunitinib in the first-line setting. Eligible patients were ≥18 years of age, had advanced or metastatic RCC with clear-cell histology, and had not received systemic therapy for their disease. Patients with brain metastases, poorly controlled hypertension, or significant cardiac and vascular conditions within 6 months of screening were excluded from the study population. The primary endpoint was PFS by independent central review. Disease assessments were performed at baseline, every 6 weeks until week 24, and then every 12 weeks until disease progression per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0. Patients were randomized 1:1 to receive either pazopanib (n = 557) or sunitinib (n = 553). Pazopanib (COMPARZ) and pazopanib (VEG105192)
Panib 800 mg was administered orally once daily, with continuous dosing. Sunitinib was administered orally once daily in 6-week cycles at a dose of 50 mg for 4 weeks followed by 2 weeks of no treatment. Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, or death.

The hazard ratio for pazopanib versus sunitinib was 1.05 [95% confidence interval (CI) 0.90–1.22], which met the predefined criterion for noninferiority. Median PFS as assessed by independent central review was 8.4 months (95% CI 8.3–10.9) with pazopanib (fig. 1). Values of median PFS as assessed by the local investigator were similar, and PFS by the investigator was used as the primary endpoint during the development of the nomogram.

Parameters tested as nomogram variables included levels of neutrophils, platelets, hemoglobin, alkaline phosphatase, and lactate dehydrogenase relative to normal limits; number of metastases; presence or absence of liver, lung, and bone metastases; levels of serum albumin and calcium; Karnofsky performance score (KPS), and time from diagnosis to treatment. These parameters were chosen based on previous investigations from groups including MSKCC [6], the Cleveland Clinic Foundation (CCF criteria) [13], and Heng et al. [7] (Heng criteria) into risk factors associated with poor prognosis for survival after a diagnosis of RCC.

Next, we assessed the performance of the model in a patient population external to the development dataset. The validation dataset included 281 patients with a median follow-up of 16.3 months.

Table 1. Descriptive statistics

| Variable                      | Nomogram development (COMPARZ; n = 557) | Nomogram validation (pivotal phase 3; n = 281) |
|-------------------------------|----------------------------------------|-----------------------------------------------|
| Neutrophil count              |                                        |                                               |
| <ULN                          | 494 (89)                               | 218 (78)                                      |
| ≥ULN                          | 61 (11)                                | 62 (22)                                       |
| Platelet count                |                                        |                                               |
| <ULN                          | 474 (85)                               | 228 (81)                                      |
| ≥ULN                          | 85 (15)                                | 53 (19)                                       |
| Liver metastases              |                                        |                                               |
| Yes                           | 86 (15)                                | 69 (25)                                       |
| No                            | 470 (84)                               | 212 (75)                                      |
| Lung metastases               |                                        |                                               |
| Yes                           | 424 (76)                               | 205 (73)                                      |
| No                            | 132 (24)                               | 76 (27)                                       |
| Bone metastases               |                                        |                                               |
| Yes                           | 110 (20)                               | 81 (29)                                       |
| No                            | 446 (80)                               | 200 (71)                                      |
| Hemoglobin                    |                                        |                                               |
| <LLN                          | 238 (43)                               | 129 (46)                                      |
| ≥LLN                          | 319 (57)                               | 152 (54)                                      |
| ECOG PS1                      |                                        |                                               |
| 0                             | 413 (74)                               | 118 (42)                                      |
| 1                             | 138 (25)                               | 163 (58)                                      |
| Calcium, mg/dl                |                                        |                                               |
| Minimum                       | 7.44                                   | 7.09                                          |
| First quartile                | 9.08                                   | 8.98                                          |
| Median                        | 9.44                                   | 9.38                                          |
| Mean                          | 9.46                                   | 9.41                                          |
| Third quartile                | 9.80                                   | 9.78                                          |
| Maximum                       | 12.77                                  | 11.94                                         |
| Number of metastases          |                                        |                                               |
| Minimum                       | 0                                      | 0                                             |
| First quartile                | 1                                      | 2                                             |
| Median                        | 2                                      | 2                                             |
| Mean                          | 2.25                                   | 2.64                                          |
| Third quartile                | 3                                      | 3                                             |
| Maximum                       | 8                                      | 7                                             |
| Time from Dx to Tx, months    |                                        |                                               |
| Minimum                       | 0.03                                   | 0.4                                           |
| First quartile                | 1.69                                   | 5.57                                          |
| Median                        | 6.81                                   | 16.35                                         |
| Mean                          | 28.03                                  | 27.66                                         |
| Third quartile                | 35.17                                  | 40.62                                         |
| Maximum                       | 301.39                                 | 184.1                                         |
| ALP/ULN                       |                                        |                                               |
| Minimum                       | 0.15                                   | 0.24                                          |
| First quartile                | 0.53                                   | 0.55                                          |
| Median                        | 0.68                                   | 0.77                                          |
| Mean                          | 0.81                                   | 0.98                                          |
| Third quartile                | 0.86                                   | 1.04                                          |
| Maximum                       | 7.38                                   | 5.76                                          |
| LDH/ULN                       |                                        |                                               |
| Minimum                       | 0.28                                   | 0.27                                          |
| First quartile                | 0.60                                   | 0.58                                          |
| Median                        | 0.73                                   | 0.76                                          |
| Mean                          | 0.84                                   | 0.88                                          |
| Third quartile                | 0.89                                   | 0.98                                          |
| Maximum                       | 7.61                                   | 3.81                                          |
| KPS                           |                                        |                                               |
| Minimum                       | 70                                     | NC                                            |
| First quartile                | 85                                     | NC                                            |
| Median                        | 90                                     | NC                                            |
| Mean                          | 90.45                                  | NC                                            |
| Third quartile                | 100                                    | NC                                            |
| Maximum                       | 100                                    | NC                                            |
| Albumin, g/dl                 |                                        |                                               |
| Minimum                       | 2.20                                   | 2.70                                          |
| First quartile                | 3.80                                   | 3.70                                          |
| Median                        | 4.20                                   | 4.01                                          |
| Mean                          | 4.09                                   | 4.00                                          |
| Third quartile                | 4.50                                   | 4.40                                          |
| Maximum                       | 5.17                                   | 5.01                                          |

Figures in parentheses are percentages. ALP = Alkaline phosphatase; Dx = diagnosis; LDH = lactate dehydrogenase; LLN = lower limit of normal range; NC = not collected; Tx = treatment; ULN = upper limit of normal range.

1 ECOG PS values for the COMPARZ population were converted from KPS (ECOG PS 0 = KPS 90–100; ECOG PS 1 = KPS 70–80).
A taset consisted of pazopanib-treated patients with advanced RCC enrolled in the pivotal, randomized, double-blind, phase 3 trial (VEG105192; NCT00334282) [14] comparing pazopanib to placebo (table 1). Key eligibility and exclusion criteria were similar to those of COMPARZ, with the exception that prior cytokine treatment was allowed; of 435 patients enrolled, 223 (54%) were treatment naive and 202 (46%) had received cytokine therapy. Patients were randomized 2:1 to receive either pazopanib 800 mg once daily, with continuous dosing, or placebo. The primary endpoint was PFS as assessed by the local investigator. Disease assessments were performed at baseline, every 6 weeks until week 24, and then every 8 weeks until disease progression. Median PFS was 9.2 months with pazopanib (fig. 1) and 4.2 months with placebo.

Because a nomogram has been developed for sunitinib in metastatic RCC, we compared the two models by applying both the present pazopanib nomogram and the previous sunitinib nomogram to the patients who received pazopanib in VEG105192 (n = 281). In addition, we applied the previous sunitinib nomogram to both sunitinib and pazopanib patients in COMPARZ.

Statistical Methods
A multivariable Cox proportional hazards regression model was constructed to evaluate potential prognostic factors. Restricted cubic splines were utilized to allow for nonlinear effects when statistically significant. With only a few discrete levels, KPS was modeled as a categorical variable. Missing values were imputed using chained equations. The Cox model was reduced through a stepdown process which removed predictors that did not contribute to the bias-corrected concordance index, estimated with a bootstrapping process [15]. This stepdown was based on the concordance index rather than on a statistical significance level; this approach can retain certain variables that are not statistically significant, but necessary to maximize prognostic accuracy [16]. A nomogram was constructed for the reduced model to facilitate predictions of PFS in future patients. The nomogram was validated externally using the dataset from the pivotal phase 3 trial; discrimination was measured using the concordance index, and calibration was assessed visually by plotting predicted proportions versus observed outcomes. The predictions from the nomogram were compared to those of the previously published sunitinib nomogram [8]. All analyses were conducted with R software version 2.14 (Free Software Foundation, Boston, Mass., USA) with the Multivariable Imputation by Chained Equations (MICE) and Regression Modeling Strategies (RMS) libraries.

Results
Descriptive statistics of the baseline values are listed in table 1. Baseline characteristics were generally similar between the development and validation groups. However, the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and the median time from diagnosis to treatment were higher in the validation group than in the development group.
these differences are likely due to the exclusion of pretreated patients from the COMPARZ trial.

In the Cox model, significant associations (p < 0.05) were detected between PFS and the presence of bone metastases, time from diagnosis to treatment, and serum levels of albumin and alkaline phosphatase (table 2). There was no significant association with PFS (p > 0.05) for the remaining variables. The nonlinear effects for continuous predictors were removed because none were significant.

A nomogram for predicting the probability of 12-month PFS in patients treated with pazopanib was developed from the Cox model (fig. 2); variables that did not contribute substantially to the overall concordance index of the model were removed. Reduced serum albumin level contributed up to 100 points toward the variation in 12-month PFS and thus was the prognostic factor with the greatest potential impact. The other strong potential indicator of poor prognosis was elevated alkaline phosphatase level (approximately 95 points).

Calibration plots suggest reasonable correspondence between predicted and observed proportions of 12-month PFS for patients treated with pazopanib (fig. 3). The concordance index for 12-month PFS was 0.625 when evaluated in the dataset from the pivotal phase 3 trial (fig. 3). The calibration slope is 0.93.

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These nomograms were validated using the data from COMPARZ, where the nomograms were applied to patients treated with pazopanib and sunitinib, respectively. The nomograms were also applied to patients treated with both pazopanib and sunitinib in the VEG105192 trial. The nomograms were compared using concordance indices. The nomograms were found to be accurate and reliable tools for predicting PFS in patients treated with pazopanib and sunitinib.
Discussion

The results of the pivotal phase 3 trial demonstrated that pazopanib significantly prolonged PFS compared to placebo and is a valuable first-line treatment for patients with advanced RCC; COMPARZ established that pazopanib is noninferior to sunitinib in that setting. Baseline clinical characteristics, screening and enrollment parameters, and outcome data from these trials were used to construct and validate a nomogram to predict, with reasonable accuracy, the probability of 12-month PFS for patients treated with pazopanib for advanced RCC. An advantage of using a nomogram compared to other risk calculators is the ability to provide a more personalized prognostic estimate of risk rather than assigning a patient to one of a limited number of risk categories.

Limitations to the nomogram include the lack of variation explained by the model, indicated by the concordance index of 0.625 in the validation dataset. Variations between the ideal nomogram and the observed results may be due in part to differences in the patient population between COMPARZ and the pivotal phase 3 trial. All patients in COMPARZ were treatment naive, whereas 47% of pazopanib-treated patients in the pivotal trial had received prior cytokine therapy [14]. The cytokine-pretreated population of the pivotal trial had shorter median PFS than the treatment-naive population (7.4 vs. 11.1 months, respectively) [14]. However, because all patients in COMPARZ were treatment naive, it was not possible to adjust the nomogram to account for this issue. Although we wanted to demonstrate performance on the external dataset in a simple way, dividing the data in that manner is inefficient. Alternative designs potentially yield better models. Another limitation is that the nomogram is only valid for pazopanib treatment and cannot be extended to other drugs. Also, patients with KPS <70 were excluded from COMPARZ; therefore, the predictive power of the nomogram among patients with lower performance remains unknown. Interestingly, we observed that a longer time from diagnosis to treatment was associated with a more favorable prediction of PFS; this result may suggest that those patients have slower-growing disease.

An important question for any nomogram is what advantage it provides over existing tools. A nomogram for predicting the probability of 12-month PFS was previously developed for sunitinib [8]. The model was based on data from a randomized, phase 3 trial of sunitinib versus interferon-α in patients with metastatic RCC; baseline characteristics and clinical outcomes from patients in the sunitinib arm (n = 375) were used to construct the nomogram. In that analysis, elevated lactate dehydrogenase and corrected calcium levels, number of metastatic sites, and time from diagnosis to treatment were influential predictors and were significantly associated with PFS (p ≤ 0.01).

Because pazopanib and sunitinib share the same mechanism of action and demonstrate similar efficacy in advanced RCC [12], it is important to consider the potential value of a pazopanib-specific nomogram. Both the pazopanib and sunitinib nomograms include time (in months) from diagnosis to treatment and alkaline phosphatase. Predictors unique to the pazopanib nomogram are neutrophils, bone metastases, and albumin; predictors unique to the sunitinib nomogram are calcium, liver metastases, lung metastases, number of metastatic sites, hemoglobin, prior nephrectomy, thrombocytosis, ECOG performance status, and lactate dehydrogenase. Albumin has the largest potential effect in the pazopanib nomogram, whereas lactate dehydrogenase has this position in the sunitinib nomogram. The two nomograms were developed independently and were not designated for use in comparing PFS prognosis of individual patients receiving different treatments. Further, choosing the treatment based solely on which has the superior PFS would not fully consider all the benefits and harms at stake. Therefore, when counseling patients potentially eligible for pazopanib, there is value in using a nomogram specifically developed for those patients to estimate their PFS with pazopanib rather than using a model developed for sunitinib.

The risk group model developed by Heng et al. [7] is commonly used in clinical practice, but a direct comparison between the present nomogram and the Heng criteria is not possible because the Heng criteria are used to predict overall survival rather than PFS. The nomogram described in this report offers a model that may complement that developed by Heng et al. [7].

In conclusion, the nomogram predicts, with reasonable accuracy, the probability of 12-month PFS in patients with advanced RCC treated with pazopanib. It may be a beneficial tool for both clinicians and patients when revisiting the choice of pazopanib to evaluate the overall benefit:risk ratio of pazopanib therapy. The model will appear on our risk calculator website (http://rcalc.ccf.org).

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