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ORIGINAL ARTICLE

External validation of nomograms for prediction of progression-free survival and liver toxicity in patients with advanced renal cell carcinoma treated with pazopanib

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Abstract

Background Nomograms have been developed for the prediction of progression-free survival (PFS) and liver toxicity in patients with advanced renal cell carcinoma (RCC) who are treated with pazopanib. The objectives of this study were to review clinical outcomes, to perform an external validation of these nomograms and to develop a new nomogram in Japanese patients.

Methods A retrospective chart review of 150 Japanese patients with advanced RCC who received pazopanib at Kobe University Hospital and affiliated hospitals from March 2014 to June 2017 was performed. We evaluated the clinical efficacy and safety of pazopanib using logistic regression analysis to analyze the prognostic factors for overall survival (OS) and PFS. For nomogram validation, concordance index (C-index) and calibration were used.

Results The median PFS and OS in this study was 13.1 and 37.4 months, respectively. Multivariate analyses identified prognostic factors for OS (number of metastasis, white blood cell (WBC) count and lactate dehydrogenase) and PFS (number of metastasis, WBC count). The C-index of nomograms for 12-month PFS was 0.598. The C-index of nomograms for liver toxicity was 0.558. A new Nomogram for predicting 12-month PFS for patients who received pazopanib was developed and performed internal validation. The C-index of the nomogram was 0.768.

Conclusion The clinical effect and safety of pazopanib reported in this study was similar to previous studies. This study suggests careful application of nomograms to Japanese patients treated with pazopanib. We have developed a new nomogram for predicting 12-month PFS with pazopanib therapy from Japanese patients.

Keywords Renal cell carcinoma · Pazopanib · Nomogram · Validation · Japanese

Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer. Seventy-five percent of RCC patients present with local progression or metastasis [1]. However, RCC is resistant to chemotherapy and radiotherapy [2, 3]. Previously, cytokine therapies were the primary systematic treatments for advanced RCC but more recently molecular targeted drugs and immune checkpoint inhibitors have been indicated for the treatment of advanced RCC. Pazopanib is a molecular targeted drug approved for the treatment of advanced RCC in the EU, United States, Japan and other countries. Several real-world studies of advanced RCC patients treated with pazopanib have reported a median progression-free survival (PFS) range from 7.7 to 13.7 months with a median overall survival (OS) range from 17 to 40 months [4]. However, there have been no such studies that included a comparatively large number of Japanese patients. Efficacy and tolerability of pazopanib may be influenced by ethnic differences.

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The most widely used prognostic model for metastatic RCC is the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria [5]. The MSKCC criteria is used in selecting molecular targeted drugs (from drugs currently in the major American and European treatment guidelines) for patient treatment [6, 7]. However, the MSKCC criteria was developed using clinical data from patients treated with cytokine therapies. Because molecular targeted drugs have replaced cytokine therapy as the primary treatment of advanced RCC, there is a need to develop new prognostic models. Heng et al. described the International Metastatic RCC Database Consortium (IMDC) model that was developed in patients with metastatic RCC treated with molecular targeted drugs such as sunitinib, sorafenib and bevacizumab [8]. The IMDC model is a new prognostic model that reflects the paradigm shift in the treatment of metastatic RCC. However, patients treated with pazopanib were excluded in the IMDC model. Motzer et al. developed a nomogram that predicts treatment outcome for patients with advanced RCC treated with sunitinib [9], and Kattan et al. developed one for pazopanib [10]. Liver toxicity is a serious adverse event (AE) for patients treated with pazopanib. To address this, Kattan et al. developed a nomogram that predicts the possibility of liver toxicity in these patients [11]. However, the prediction probabilities of these nomograms are limited because they were developed using studies in Europe and America. It is unknown whether these nomograms are useful for predicting treatment outcome and liver toxicity in Japanese patients.

The objectives of this study were to review clinical outcomes, to validate the use of nomograms for pazopanib and to develop a novel nomogram in Japanese patients treated with pazopanib for advanced RCC.

Materials and methods

This study was approved by the institutional review board of Kobe University Hospital (Approval No. 170159). After approval, charts from 150 patients with advanced RCC treated with pazopanib from March 2014 to June 2017 at Kobe University Hospital and affiliated hospitals were studied.

As baseline assessments, patients' background characteristics, laboratory data, treatment history, clinical stage of RCC before pazopanib treatment and prognostic profiles were recorded. Most commonly, 800 mg pazopanib was orally administered daily. Dose reductions for pazopanib (600–200 mg) were determined by the treating physician according to the severity of AEs. Therapy was continued until objective disease progression, unacceptable AE or patient refusal. Patient treatment responses were generally evaluated every 4 weeks by chest and abdominopelvic computed tomography. Responses and AEs were evaluated by the treating physician using the Response Evaluation Criteria in Solid Tumors 1.0 and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, respectively.

Statistical analysis

The PFS and OS rates were calculated using the Kaplan–Meier method. The prognostic significance of certain parameters was assessed using the Cox proportional hazards regression model.

We assessed the predictive accuracy of the nomograms for pazopanib by the concordance index (C-index), which is the area under the receiver operating curve for probability predicted by the nomograms. A C-index of 0.5 represents no predictive discrimination while an index of 1 represents perfect ability to distinguish patients. Calibration was assessed by plotting the nomogram predicted probabilities vs the observed probabilities. The prognostic factors that we used in developing nomogram were based on knowledge of their prognostic significance from previous studies [8–10] and this study. We calculated C-index and plotted calibration for internal validation of the nomogram that we developed. All statistical analyses were performed using R for Windows v3.4.4 software (R Core Team, Vienna, Austria; http://www.Rproject.org). Probability (P) values < 0.05 were considered significant.

Results

The background details for the study patients are shown in Table 1. The average age at the time the patients received pazopanib was 78.3 years. The median patient observation period was 9.6 months [interquartile range (IQR) 4.6–-16.0]. The median period of treatment with pazopanib in these patients was 4.4 months (IQR 1.3–10.2). Pazopanib was introduced as first-line therapy for 77 patients (52.3%), second-line therapy for 20 (13.3%), third-line therapy for 11 (7.3%) and fourth-line or later therapy for 42 (28.0%). Of the 150 patients, 38 (25.3%) continued treatment with pazopanib, while the remaining 112 (74.6%) discontinued treatment because of disease progression [41 patients (27.3%)], intolerable AEs [54 patients (36.0%)] or patient refusal [17 patients (11.3%)].

Tumor responses to pazopanib were as follows: complete response (CR), 0 patients (0%); partial response (PR), 32 patients (21.3%); stable disease (SD), 75 patients (50.0%); or progressive disease (PD), 18 patients (12.0%). The objective response rate (ORR) and clinical benefit rate in this study were 21.3% and 71.3%, respectively.

Table 1 Patient characteristics ($N = 150$)

Characteristics	*N* (%)
Age, years	
Median (IQR)	78.3 (63.0–76.0)
Gender	
Male	104 (69.3)
Female	46 (30.7)
ECOG PS	
0	88 (58.6)
1	43 (28.6)
≥ 2	15 (10.0)
Unknown	4 (2.6)
Histological type	
Clear cell carcinoma	115 (76.6)
Others	12 (8.0)
Unknown	23 (15.3)
MSKCC risk group	
Favorable	37 (24.7)
Intermediate	81 (54.0)
Poor	20 (13.3)
Unknown	12 (8.0)
Resection of the primary lesion	
Present	110 (73.3)
Absent	40 (26.7)
Treatment sequence of pazopanib	
1st	77 (52.3)
2nd	20 (13.3)
3rd	11 (7.3)
After 4th	42 (28.0)

ECOG PS Eastern Cooperative Oncology Group performance status, *IQR* interquartile range, *MSKCC* Memorial Sloan Kettering Cancer Center

The median PFS and OS in this study was 13.1 and 37.4 months, respectively (Fig. 1).

The influence of several factors on PFS and OS in these 150 patients were analyzed (Table 2). Univariate analyses identified the following significant prognostic predictors: lymphovascular invasion, number of metastasis, white blood cell (WBC) count, alkaline phosphatase (ALP) and albumin for PFS; Eastern Cooperative Oncology Group (ECOG) performance status, bone metastasis, lymph node metastasis, number of metastasis, MSKCC classification, WBC count, hemoglobin, lactate dehydrogenase (LDH), and albumin for OS.

Multivariate analyses, including the above mentioned significant prognostic predictors, were conducted. The following factors appeared to have independent prognostic impacts: number of metastasis and WBC count for PFS; number of metastasis, WBC count and LDH for OS.

Table 3 summarizes AEs associated with pazopanib treatment. One hundred and thirty-six patients (90.6%) experienced AEs. The most common AEs corresponding to ≥ grade 3 were reported as: liver toxicity [defined as aspartate aminotransferase (AST)], alanine aminotransferase (ALT), ALP > 5–20 × upper limit of normal range (ULN), or total bilirubin (T-Bil) > 3–10 × ULN], 17 patients (11.3%); hypertension, 9 patients (6.0%); and thrombocytopenia, 7 patients (4.6%). In this study, there were no cases of treatment-related death. The liver toxicity predicted using the nomogram (ALT > 3 × ULN and T-Bil > 2 × ULN) was seen in 7 patients (4.6%).

For validation of the nomograms, C-index was calculated. The C-index of the nomograms for 12-month PSF was 0.598. The C-index of the nomograms for liver toxicity was 0.565. Calibration plots predicting 12-month PFS and liver toxicity are shown in Fig. 2. The calibration plots did not show good agreement between predicted and actual probability. A Nomogram to predict 12-month PFS for Japanese patients with RCC who were treated with pazopanib was constructed from the 6 parameters that were determined before treatment (Fig. 3). The C-index of the nomogram for internal validation was 0.768. Calibration plot of the nomogram for internal validation was shown in Fig. 4.

Discussion

In this study, we retrospectively reviewed clinical outcomes for 150 Japanese patients with advanced RCC treated with pazopanib for the purpose of validating nomograms to predict probably of 12-month PFS and liver toxicity using data from these patients.

In a randomized, placebo-controlled phase III clinical trial (VEG105192) conducted in patients with advanced RCC, pazopanib significantly improved PFS compared with placebo in both treatment-naïve and cytokine-pretreated patients [12]. In the COMPARZ trial, the efficacy and safety of pazopanib and sunitinib as first-line therapy were compared; pazopanib was non-inferior to sunitinib with respect to PFS, and safety and quality of life profiles were better in patients treated with pazopanib [13]. Pazopanib is recommended as a first-line treatment for advanced RCC with favorable risk in the major American and European guidelines [6, 7]. However, the clinical trial patient populations were selected using specific inclusion and exclusion criteria and likely do not accurately reflect the patient populations seen by treating physicians in daily practice. It remains to be determined whether the data from these clinical trials are inclusively representative of all patients with RCC. Differences in efficacy and tolerability of sunitinib between Western and Asian populations have been reported [14, 15], making it likely

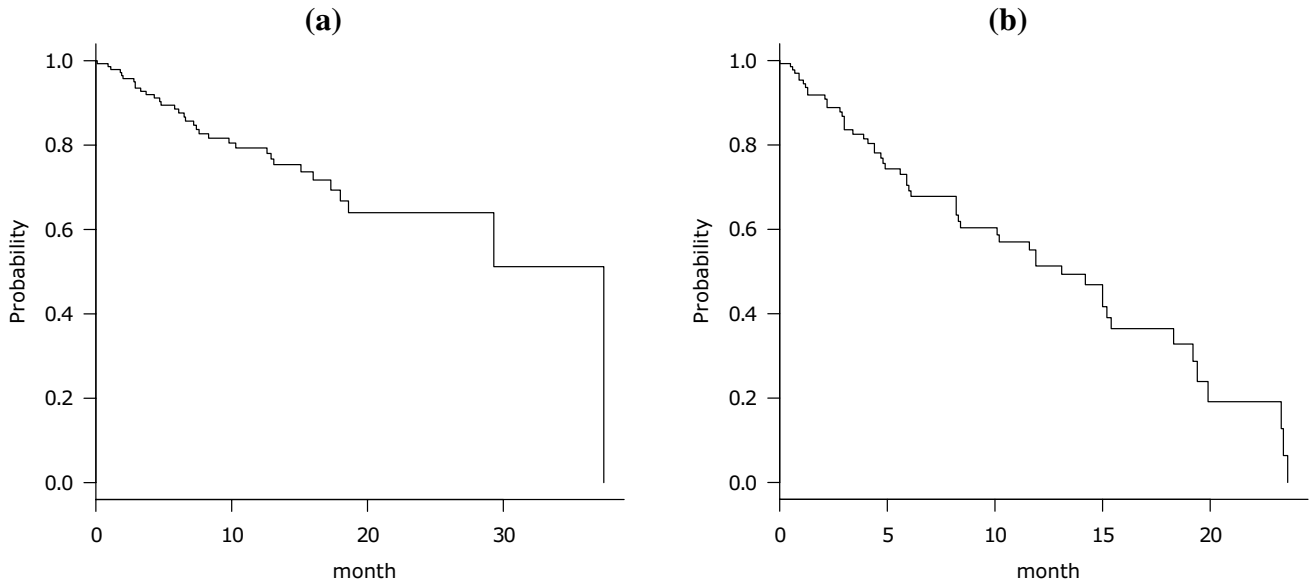

Fig. 1 Survival curves for patients treated with pazopanib. **a** Overall survival and **b** progression-free survival of the 150 patients with advanced renal cell carcinoma treated with pazopanib

that the efficacy and tolerability of pazopanib may differ between Western and Asian populations. We retrospectively investigated clinical outcomes in a total of 150 Japanese patients who received pazopanib for advanced RCC to clarify the significance of pazopanib in real-world clinical practice in Japan. To our knowledge, this was the largest study of Japanese patients with advanced RCC treated with pazopanib.

In this study, the median OS and PFS were 37.4 and 13.1 months, respectively. OS and PFS in a meta-analysis of real-world studies were 22.7 and 10.0 months, respectively. In the phase III trial, VEG105192, the median OS and PFS were 22.9 and 9.2 months, respectively [12]. The COMPARZ trial reported a median OS of 28.4 and a median PFS of 8.4 months [13]. Although patients after second-line treatment were included, our data were favorable when compared with these results.

Prognostic factors identified through multivariate analyses that were common between OS and PFS were number of metastasis and WBC count. In an effort to predict the prognosis of metastatic RCC, several models have been developed including the MSKCC criteria [5], the ICDM model [8], the Cleveland Clinic Foundation model [16], the updated French model adapted to the AVOREN trial [17] and the International Kidney Cancer Working Group model [18]. The number of metastasis, WBC count and LDH were included as factors in these models. Although these models used patients receiving different treatment regimens, many of the prognostic factors were similar among the models. These common findings for prognostic factors may elucidate a specific biology of advanced RCC.

AEs occurred in a total of 136 (90.6%) patients, the reported AEs included: hypertension (26.7%), liver toxicity (26%) and diarrhea (20%). No grade 4 AEs were reported and grade 3 AEs occurred in 34 (22.6%) patients. Fifty-four (36.0%) patients discontinued pazopanib because of AEs. Dose reduction resulting from AEs and the discretion of the clinical doctors occurred in 84 (56%) patients. The rate of grade 3 AEs, pazopanib discontinuation and dose reduction were more frequent in previous studies compared with our retrospective real-world study [19]. Liver toxicity is a characteristic AE for patients treated with pazopanib. Powles et al. reported that G3–4 liver toxicity occurred in 7–9% of patients treated with pazopanib [20]. In the present study, grade 3 liver toxicity occurred in 17 (11.3%) patients. The liver toxicity predicted in the nomogram (ALT > 3 × ULN and T-Bil > 2 × ULN) is a criterion for immediate discontinuation of pazopanib administration. In the present study, liver toxicity predicted in the nomogram was seen in 4.6% of patients, while Kattan et al. reported that this was seen in 3% of patients [11]. Previous studies reported that Asian patients treated with sunitinib had more AEs than Caucasian patients [15, 21]. Our results suggest that pazopanib may also be more toxic in Asian patients compared with Caucasian patients.

The MSKCC criteria is the most widely used prognostic model for metastatic RCC, but this model was developed in patients treated with cytokine therapy. Thus, it is necessary to develop prognostic models that are suitable for molecular targeted treatment. The development of tools that predict the prognosis of each patient may be helpful in directing individualized therapy. Nomograms are a graphical tool

Table 2 Univariate and multivariate analyses of factors affecting progression-free and overall survival

	Overall survival									Progression-free survival		
	Univariate analysis			Multivariate analysis			Multivariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
ECOG PS (≥2 vs < 2)	2.93	1.20–7.15	0.02	1.49	0.46–4.84	0.50	1.85	0.72–4.75	0.20			
Lymphovascular invasion (yes vs no)	0.79	0.31–3.48	0.53				2.48	1.13–5.45	0.02	2.15	0.75–6.17	0.15
Bone metastasis (yes vs no)	2.33	1.15–4.73	0.02	1.98	0.90–4.35	0.09	0.86	0.44–1.69	0.67			
Lymph node metastasis (yes vs no)	2.14	1.07–4.28	0.03	1.45	0.62–3.37	0.39	1.67	0.96–2.89	0.07			
Number of metastasis (≥ 2 vs < 2)	2.75	1.14–3.62	0.01	2.67	1.14–6.23	0.02	1.86	1.04–3.34	0.04	2.71	1.15–6.39	0.02
MSKCC risk group (poor vs other)	2.39	1.03–5.57	0.04	1.36	0.50–3.70	0.55	1.57	0.69–3.55	0.28			
WBC (≥ ULN vs < ULN)	2.56	1.14–5.75	0.02	3.31	1.26–8.70	0.02	3.01	1.32–6.87	0.01	3.80	1.04–13.89	0.04
Hemoglobin (< LLN vs ≥ LLN)	2.98	1.29–6.87	0.01	1.47	0.56–3.85	0.43	1.54	0.88–2.72	0.13			
LDH (≥ ULN × 1.5 vs < ULN × 1.5)	3.51	1.06–11.61	0.04	5.86	1.24–27.62	0.03	1.07	0.26–4.45	0.92			
Albumin (< 3.5 vs ≥ 3.5)	2.48	1.20–5.12	0.01	1.63	0.63–4.23	0.31	4.84	1.26–18.6	0.02	0.59	0.16–2.2	0.43
ALP (≥ ULN vs < ULN)	1.71	0.84–3.48	0.14				1.86	1.05–3.29	0.03	1.83	0.82–4.1	0.14

WBC white blood cell, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *LLN* lower limit of normal, *ULN* upper limit of normal, *ECOG PS* Eastern Cooperative Oncology Group performance status, *MSKCC* Memorial Sloan Kettering Cancer Center

Table 3 Major adverse events and laboratory abnormalities related to treatment with pazopanib

	All grade (%)	Grade 3 (%)
Adverse event		
Diarrhea	30 (20)	1 (< 1)
Hypertension	40 (27)	9 (6)
Nausea	11 (7)	3 (2)
Decreased appetite	18 (12)	2 (1)
Vomiting	3 (2)	1 (< 1)
Fatigue	23 (15)	1 (< 1)
Hemorrhage	4 (3)	1 (< 1)
Proteinuria	4 (3)	2 (1)
Mucositis/stomatitis	7 (5)	0
Hypothyroidism	13 (9)	0
Hand–foot syndrome	17 (11)	1 (< 1)
Myocardial dysfunction	2 (1)	0
Dysgeusia	7 (5)	0
Laboratory abnormality		
Increased AST	28 (19)	12 (8)
Increased ALT	26 (17)	10 (7)
Increased T-Bil	12 (8)	4 (3)
Increased creatinine	7 (5)	3 (2)
Hypokalemia	1 (< 1)	0
Leukopenia	4 (3)	0
Neutropenia	1 (< 1)	1 (< 1)
Thrombocytopenia	26 (17)	7 (5)
Anemia	2 (1)	2 (1)

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *T-Bil* total bilirubin

developed by statistical methods to predict the probability of a clinical event. Motzer et al. developed a nomogram that predicts 12-month PFS for patients with advanced RCC treated with sunitinib [9]. Kattan et al. developed a similar nomogram for pazopanib [10]. The nomogram of 12-month PFS for pazopanib was developed using patients from the COMPARZ trial [13]. The percentage of Asian patients in the phase III trial, VEG105192 [12], and the COMPARZ trial was 12% and 34%, respectively. To confirm the usefulness of the nomogram in the Asian population, external validation using Asian patients was essential. In this study, the C-index of the external validation of the nomogram for 12-month PFS was 0.598. Kattan et al. performed external validation of the nomogram for 12-month PFS in patients from the VEG105192 phase III trial, reporting a C-index of 0.625 [10]. Considering the inclusion of second-line and later patients in our study, we calculated a C-index using only first-line treated patients which we report as 0.569. Neither of C-indexes calculated in this study were high enough to validate the use of this nomogram for our patient population. It might be difficult to apply this nomogram to Japanese patients with advanced RCC.

The nomogram for liver toxicity was developed using data from patients from various phase III trials, containing 66.3% Caucasians overall [11]. The proportion of Asians in these studies is unknown. In the present study, the C-index for the nomogram for liver toxicity was 0.565. However, subset analysis of the COMPARZ trial reported that incidences of liver toxicity were more frequent in the Asian population than in the North American and European populations [22].

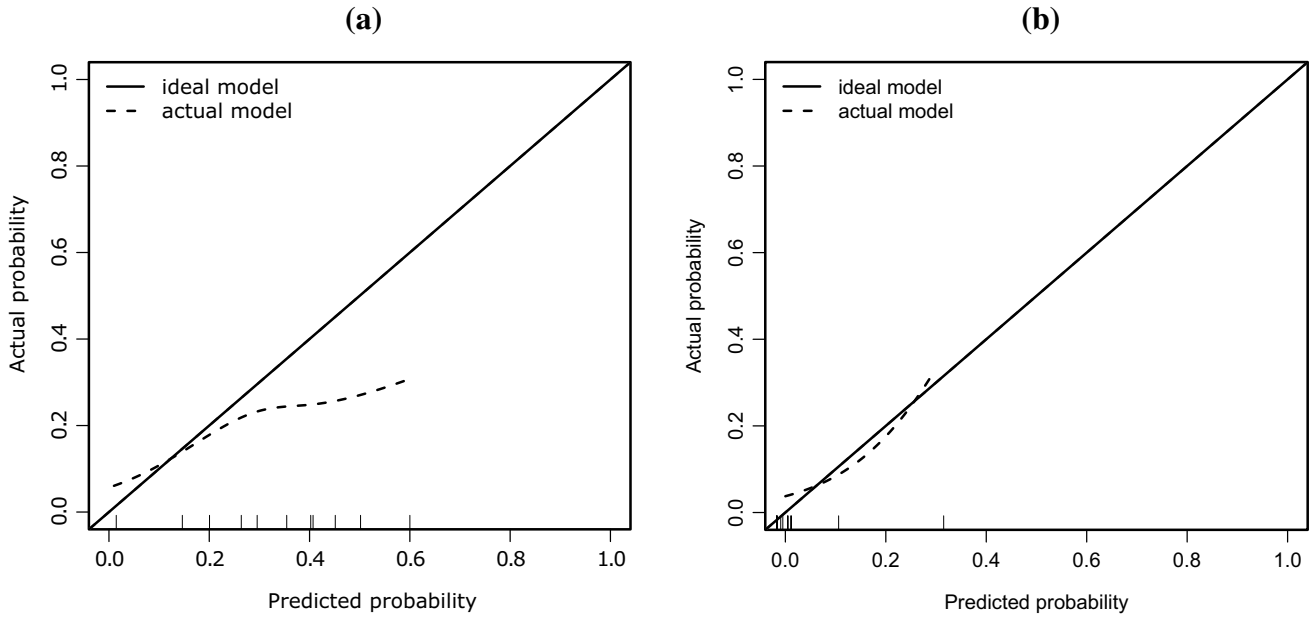

Fig. 2 Calibration plots for nomogram predictions. **a** Calibration plot for nomogram prediction of 12-month progression-free survival. **b** Calibration plot for nomogram prediction of liver toxicity. Perfect predictions correspond to the 45° line

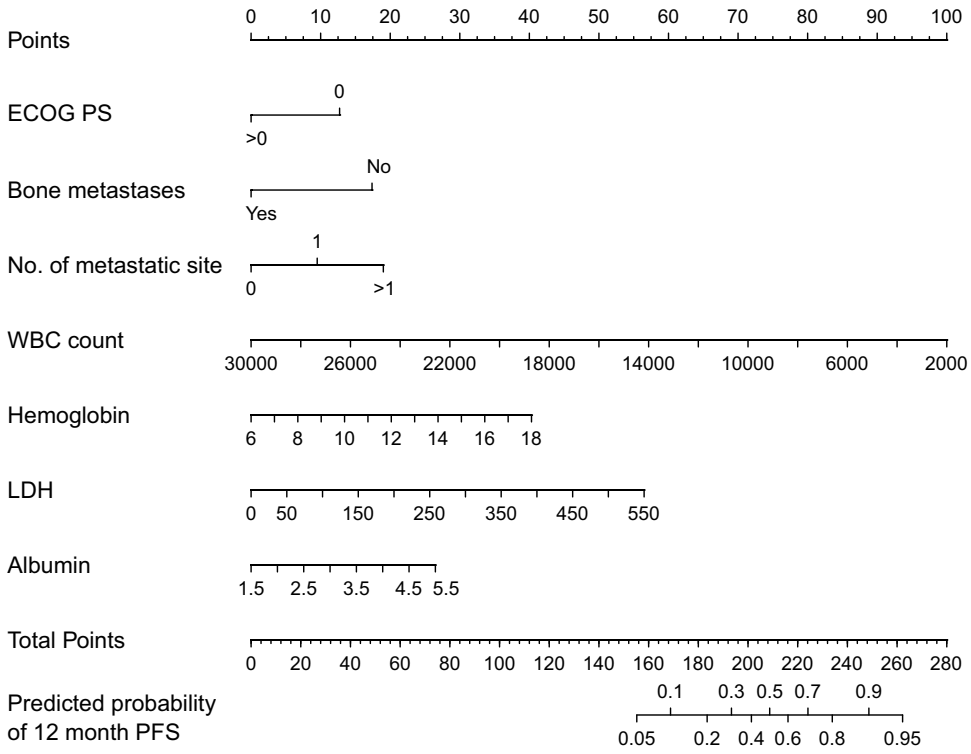

Fig. 3 Nomogram to predict 12-month PFS for patients with RCC who were treated with pazopanib. Draw vertical line from the value of the corresponding factor to the Points axis, and calculated the points. Sum up the points to obtain the total points. Draw vertical line from that value on the total points to the Predicted probability of 12 month PFS axis. The predicted PFS can be estimated

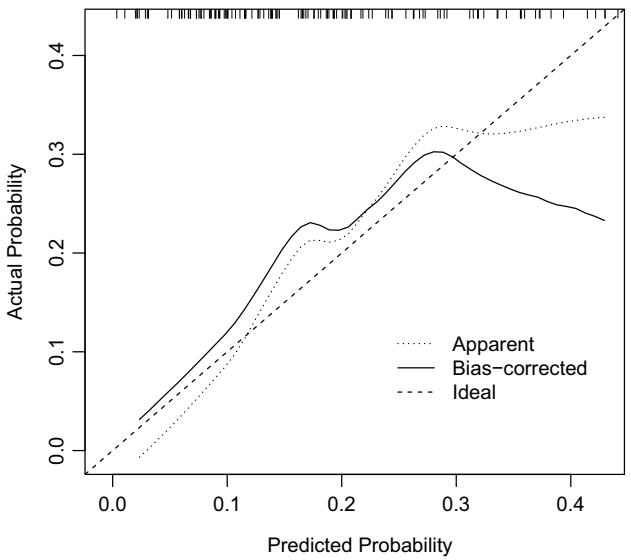

Fig. 4 Calibration plot for nomogram of 12 month PFS developed in the present study

This result supports that liver toxicity from pazopanib treatment is different among population groups.

The nomograms validated in this study may not be suitable for all patients, but the development of tools to predict patient prognosis, therapeutic effectiveness and safety may be useful for treatment planning and developing a follow-up schedule. A prediction tool with higher accuracy and wider applicability should be developed.

We have developed a new nomogram from Japanese patients treated with pazopanib. To our knowledge, it is the first prognostic tool for Japanese patients with RCC, although the number of patients in this study was probably not sufficient to develop valuable nomogram. The nomogram reflects feature of Japanese patient with RCC and may be useful for limited population such as Japanese and other Asian patients. To evaluate the accuracy of the nomogram, external validation is required.

This study had several limitations. First, despite this study being the largest study of Japanese patients with advanced RCC and treated with pazopanib, it was retrospective and had a relatively short observation period. Second, selection bias and issues regarding missing data were present in this study. Additionally, there was a lack of central radiology review and patient charts reported different intervals between computed tomography scans.

In conclusion, the clinical efficacy and safety of pazopanib in this study were similar to previously reported studies. This study suggests that clinicians should be cautious in the application of the described nomograms for pazopanib to Japanese patients receiving pazopanib for the treatment of RCC. We have developed a new nomogram in Japanese patients with RCC, while we still need external validation of this nomogram in different population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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