The development and validation of a prognostic nomogram and nomogram application software among men treated with abiraterone acetate and/or enzalutamide for metastatic castration-resistant prostate cancer

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Research article

Keywords: CRPC, prognosis, Enzalutamide, Abiraterone acetate, nomogram

Posted Date: October 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-58034/v2

Abstract

BACKGROUND:

With widespread medication choices for metastatic castration-resistant prostate cancer (mCRPC) is now available, on the other hand biomarker to predict the efficacy of each mCRPC treatment has not been established.

Objective:

This study developed prognostic nomogram to predict prognosis in CRPC patients who received abiraterone acetate (ABI) and/or enzalutamide (ENZ).

Design, Setting, and Participants:

A total of 568 mCRPC patients received ABI and/or ENZ from 2012 to 2017 were enrolled in this study. We developed prognostic nomogram based on the risk factors by Cox proportional hazards regression model.

Outcome Measurements and Statistical Analysis:

The nomogram was also assessed for discriminatory ability with the concordance index (C-index). We repeated 5-fold cross-validation 2000 times to estimate the C-index and reported the means of the estimated C-index for the training and validation sets. And we also developed nomogram application software (app) based on this nomogram.

Results and Limitations:

The median overall survival (OS) was 24.7 months. A multivariable analysis showed that the time to CRPC, pre-chemotherapy, baseline PSA, baseline ALP, and baseline LDH were independent risk factors for the OS (HR: 0.521, 1.681, 1.439, 1.827, 12,123, p:0.001, 0.001, <0.001, 0.019, <0.001)). C-index was 0.72 in training cohort and 0.71 in validation cohort.

CONCLUSIONS:

We developed nomograms to predict the OS for Japanese mCRPC patients who received ABI and/or ENZ. The advent of mCRPC prognosis prediction app will facilitate greater accessibility for clinical use.

Patient Summary

This study developed and validated a nomogram for predicting the prognosis of mCRPC patients who receive ABI/ENZ treatment using clinical information. This study also developed mobile app to facilitate clinical usage.

Background

A recent clinical trial revealed the efficacy of abiraterone acetate (ABI), enzalutamide (ENZ), Radium-223 (Ra-223), and cabazitaxel in addition to docetaxel chemotherapy in metastatic castration-resistant prostate cancer (mCPRC) patients [1-3]. In the next few years, poly(ADP-ribose) polymerase (PARP) inhibitors and immune-checkpoint inhibitors are expected to be used in clinical practice to similar ends [4, 5]. With widespread medication choices now available, clinicians should take care to select the most appropriate medicine in order not to lose their chance to administer the best therapy possible to a patient. Predicting the prognosis is thus important, because a lack of biomarker to predict the efficacy of each mCRPC treatment.

Recent studies have demonstrated the efficacy of tumor markers for predicting the prognosis, such as inflammatory markers, including the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ration, and platelet-to-lymphocyte ratio, as well as the alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels [6]. However, to more accurately predict the prognosis, a nomogram using multiple prognostic parameters is needed [7, 8].

In the present study, we developed and validated a nomogram for predicting the prognosis of mCRPC patients who receive ABI and/or ENZ treatment using clinical information and also developed application software (app) to facilitate clinical usage.

Methods

Patients

A total of 568 metastatic CRPC (mCRPC) patients received ABI and/or ENZ in Yokohama City University, Nagoya University, Kitasato University, and affiliated hospitals from 2012 to 2017. All cases were pathologically confirmed to have prostate cancer and received androgen deprivation therapy (ADT) but proved refractory.

The institutional review board of Yokohama City University Medical Center was approved this study (D1603004). The definition of CRPC was set by the Prostate Cancer Working Group 2 [9]. Patients' background characteristics, including the initial prostate-specific antigen (PSA) level, initial metastatic status, Gleason score, observation period, time to CRPC, pre-chemotherapy, age at baseline, PSA at baseline, ALP at baseline, LDH as baseline, and initial ABI/ENZ treatment, are shown in Table 1.

Table 1
Patients' characteristics

Variables	n (%), median (range)
Initial PSA, ng/mL	123.0(2.1-19840.0)
Initial stage	
M0	215 (37.9%)
M1	353 (62.1%)
Gleason score	
6,7	128 (22.5%)
8–10	440 (77.5%)
Observation period, months	13.3 (0.2–52.2)
Time to CRPC, months	14.2 (0.4-189.1)
Previous use of chemotherapy	202 (35.6%)
Age at baseline, yeas	76 (47–92)
PSA at baseline, ng/mL	23.6 (0.1–10,000)
ALP at baseline, IU/L	261 (60 – 6,908)
LDH at baseline, IU/L	215 (93-3201)
Treatment	
ABI	234 (41.2%)
ENZ	334 (58.8%)
PSA: Prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRPC: Castration-resistant prostate cancer, ABI: Abiraterone acetate, ENZ: Enzalutamide	

Statistical analyses

The overall survival (OS) was calculated from the date of the baseline evaluation (initial ABI/ENZ treatment data) to the last follow-up. The OS rates were estimated using the Kaplan–Meier method. A Cox proportional hazards model was used for the univaridate and multivariable analyses. P values of <0.05 were considered to indicate statistical significance in all statistical tests. The statistical analyses were performed using the SPSS (version 25.0; SPSS Inc., Chicago, IL, USA), R version 3.5.1 (R, Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (La Jolla, CA, USA) software programs.

Nomogram development

The nomogram for the OS was developed using a Cox proportional hazards regression model with the age, initial PSA, initial stage (M0/M1), Gleason score, time to CRPC, Chemotherapy, PSA at baseline, ALP at baseline, and LDH at baseline as the predictors. Calibration was performed using the methods described by Iasonos et al. [10]. The data were randomly separated into training and validation data sets to calibrate the nomogram prediction. The prediction was evaluated by comparing the predicted survival probability at two years with the observed survival probability using the training and validation data sets. The nomogram was also assessed for discriminatory ability with the concordance index (C-index). We repeated 5-fold cross-validation 2000 times to estimate the C-index and reported the means of the estimated C-index using the training and validation sets.

Results

The median (range) observational period was 13.3 (0.2-52.2) months. A total of 189 of the 589 patients (33.2%) died, and the median OS was 24.7 months [Fig. 1]. A total of 202 patients (34.9%) were administered docetaxel systemic chemotherapy as a treatment for CRPC and therefore developed to resistance of docetaxel. None of the patients received either upfront ABI or ENZ treatment at the initial treatment for metastatic hormone naïve prostate cancer. Thirteen of 568 (2.4%) patients were administered ABI or ENZ as the participants of clinical trials. The patients' characteristics are summarized in Table 1. A multivariable analysis showed that the time to CRPC, pre-chemotherapy, baseline PSA, baseline ALP, and baseline LDH were independent risk factors for the OS (time to CRPC: hazard ratio [HR]=0.521, 95% confidence interval [CI]=0.349-0.776, p=0.001, pre-chemotherapy: HR=1.683, 95% CI=1.232-2.300, p=0.001, baseline PSA: HR=01.439, 95% CI=1.179-1.755, p<0.001, baseline ALP= HR=1.827, 95% CI=1.102-3.028, p=0.019, baseline LDH: HR=12.123, 95% CI=5.343-27.51, p<0.001) [Table 2].

Table 2
Univariate and multivariable analysis to predict prognosis

	Univariate analysis				Multivariate analysis			
	p value	HR	95.0% CI		p value	HR	95.0% CI	
			Lower	Upper			Lower	Upper
Initial PSA	0.820	1.020	0.863	1.204	0.157	0.862	0.701	1.059
Initial stage M0 vs M1	0.091	0.776	0.578	1.042	0.469	0.876	0.611	1.254
Gleason score 8–10 vs 6–7	0.848	1.034	0.737	1.450	0.550	0.897	0.629	1.280
Time to CRPC	< 0.001	0.434	0.304	0.621	0.001	0.521	0.349	0.776
Chemotherapy Yes vs No	< 0.001	2.300	1.731	3.057	0.001	1.683	1.232	2.300
Age at baseline	0.600	0.995	0.975	1.015	0.250	1.012	0.992	1.032
PSA at baseline	< 0.001	1.958	1.680	2.282	< 0.001	1.439	1.179	1.755
ALP at baseline	< 0.001	5.138	3.509	7.524	0.019	1.827	1.102	3.028
LDH at baseline	< 0.001	45.886	23.15	90.953	< 0.001	12.123	5.343	27.51

PSA: Prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRPC: Castration-resistant prostate cancer

Figure 2 shows the nomogram for predicting the one- and two-year survival using five statically significant risk factors (time to CRPC, pre-chemotherapy, baseline PSA, baseline ALP, and baseline LDH) and four clinically important risk factors (age, initial PSA, initial metastatic status, and Gleason score). Figures 3a and 3b show the calibrations of the nomogram for the two-year survival. The blue diagonal line indicated the ideal reference line at which predicted the probabilities match the observed proportions. The vertical lines across the blue line represent the nomogram-predicted probabilities grouped for each of the four quartile groups, along with the respective 95% confidence intervals. From Figure 3a, we can see the predicted survival rate from the nomogram was well correlated with the actual observation of the two-year survival in the training data set. Figure 3b shows the calibration of the nomogram for the two-year survival using randomly selected validation data set. We can also see that the predicted survival rate from the nomogram was well-correlated with the actual observation of the two-year survival in the validation set. The means of estimated c-index were 0.72 for training data sets and 0.71 for validation data sets in the 5-fold cross-validations.

We also developed app to easily use these findings in daily clinical practice [Fig. 4] The app were developed for the Android and iOS systems [Fig. 5].

Discussion

This study developed and validated a nomogram for predicting the prognosis of mCRPC patients who receive ABI and/or ENZ. This nomogram used the initial PSA, initial metastasis status, Gleason score, time to CRPC, previous use of docetaxel or not, age at ABI/ENZ installation, and laboratory data, including the PSA/ALP/LDH at the time of ABI/ENZ installation. The prognosis of mCRPC varies among metastatic lesions. Regarding non-metastatic CRPC (m0CRPC), the PROSPER, SPARTAN, and ARAMIS studies showed the median radiographic progression-free survival (rPFS) to be around 36.6 to 40.4 months [11-13]. Although the final OS was not reached, the OS was expected to be around 67.0 to 73.9 in both groups [14]. Regarding metastatic pre-docetaxel chemotherapy CRPC, the PREVAIL or COU-AA-302 studies showed that the OS was around 32.4 to 34.7 months [1, 15]. Furthermore, regarding metastatic post-docetaxel chemotherapy CRPC, the AFFIRM and COUA-AA-301 showed that the OS was around 14.8 to 18.4 months [2, 16]. Finally, in real-world metastatic CRPC, the OS was found to be 31.6 months in cases of lymph-node metastasis, 21.3 months in cases of bone metastasis, 19.4 months in cases of lung metastasis, and 13.5 months in cases of liver metastasis [17]. While the OS was speculated in metastatic site, the detailed prognostic estimation using multiple risk factors has not been established. To make right treatment decisions for the right patient at right timing, a detailed prognosis estimation is needed.

Previous studies revealed the prognostic factors for metastatic prostate cancer. In terms of tumor markers, systemic inflammatory markers include the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, lymphocyte-to-platelet ratio, De Retis and prognostic nutritional index, which have all been identified to be prognostic factors for prostate cancer [6, 18, 19]. In addition, either a geriatric assessment or determining the status of sarcopenia have been reported as a new prognostic factor for CRPC [20]. Recent studies have shown that elevated tumor markers, such as LDH and ALP, and some inflammatory markers are poor prognostic factors for CRPC [6]. Zhao et al. developed a prognostic nomogram for CRPC among Chinese patients using a 449-patient cohort [21]. This nomogram used the Gleason score, presence of intraductal carcinoma of the prostate, baseline ALP/PSA/Hb, and the Eastern Cooperative Oncology Group performance status. Yang et al. also developed a nomogram using the presence of liver metastasis, hemoglobin level, and time from initial ADT to ABI in 110 Chinese CRPC patients [22]. Lin et al. developed a nomogram using the PSA-doubling time, time to PSA progression, and presence of pain in 167 Chinese CRPC patients [23]. Similar to other studies, we made nomograms to predict OS in 589 mCRPC patients who received ABI/ENZ. This program facilitated the gathering of important information for both patients and physicians. Though various nomograms have been reported, this program contributed easily approach or daily clinical practices.

In mCRPC treatment, newly established medications are more expensive than ADT or docetaxel treatment, which eventually affects a country's insurance system [6, 24]. Previous studies also created nomograms to predict the prognosis in Chinese CRPC patients. The economic range in Asia is vast, so nomograms specific to each country are needed. Under the Japanese medical insurance system, all patients received government-approved CRPC medication, including ABI/ENZ, Ra-223, docetaxel, and cabazitaxel. Speleucel T is not approved in Japan. The present findings are expected to benefit Japanese mCRPC patients who are introduced to ABI/ENZ.

Several limitations associated with the present study warrant mention. First, this study used a retrospective cohort divided into a training group and control group from Japanese multicenter hospitals. Most of the hospitals were third referral cancer centers. Thus, a further study is needed to confirm the accuracy of these findings using all hospitals, including private clinics. Second, other mCRPC treatment drugs, such as PARP inhibitors and immune-checkpoint inhibitors, will be available in the near future. Once these new treatments are approved, additional validation will likely be needed. In addition, this study did not include any upfront treatment for metastatic hormone naïve prostate cancer (mHNPC). Based on the findings of both TITAN and ARCHES studies, upfront apalutamide and ENZ were approved for mHNPC by the Japanese national insurance system in addition to ABI for LATITUDE high risk mHNPC [25, 26]. Further study is needed to confirm the efficacy of this program for the patients who received upfront treatment for mHNPC. The last limitation is shorter observational period. Most patients were followed up for less than 30 months. In this follow-up, 198 (34.9%) patients died and no correlation was observed between the covariates and the observational period [Supplementary fig.1].

In conclusion, we developed and validated a nomogram for predicting the prognosis of mCRPC patients who receive ABI/ENZ treatment using clinical information and also developed app to facilitate clinical usage.

Conclusion

We developed nomograms to predict the OS for Japanese mCRPC patients who received ABI and/or ENZ. This nomogram might help clinicians make treatment decisions.

Abbreviations

metastatic castration-resistant prostate cancer (mCRPC)

abiraterone acetate (ABI) and/or enzalutamide (ENZ)

concordance index (C-index)

application software (app)

overall survival (OS)

Radium-223 (Ra-223)

poly(ADP-ribose) polymerase (PARP)

alkaline phosphatase (ALP) and lactate dehydrogenase (LDH)

androgen deprivation therapy (ADT)

rostate-specific antigen (PSA)

hazard ratio (HR)

confidence interval (CI)

Declarations

Ethics approval and consent to participate

The institutional review board of Yokohama City University Medical Center approved this study (D1603004).

Consent for publication

Not Applicable

Availability of data and material

Due to ethical restrictions, the raw data underlying this paper are available upon request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

We obtained no funding for this study

Authors' contributions

Conception and design: TK, YM. Developed and validated the nomogram: YS, Acquisition of data: TK, YS, SY, MK, IK, HY, OK, KT, HT, MI, MY, HU, YM. Drafting of the manuscript: TK, YM. All authors have read and approved the manuscript

Acknowledgements

Nomogram app was programmed by Shun Omatsu (Kameciti Create, Tokyo, Japan)

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Figures

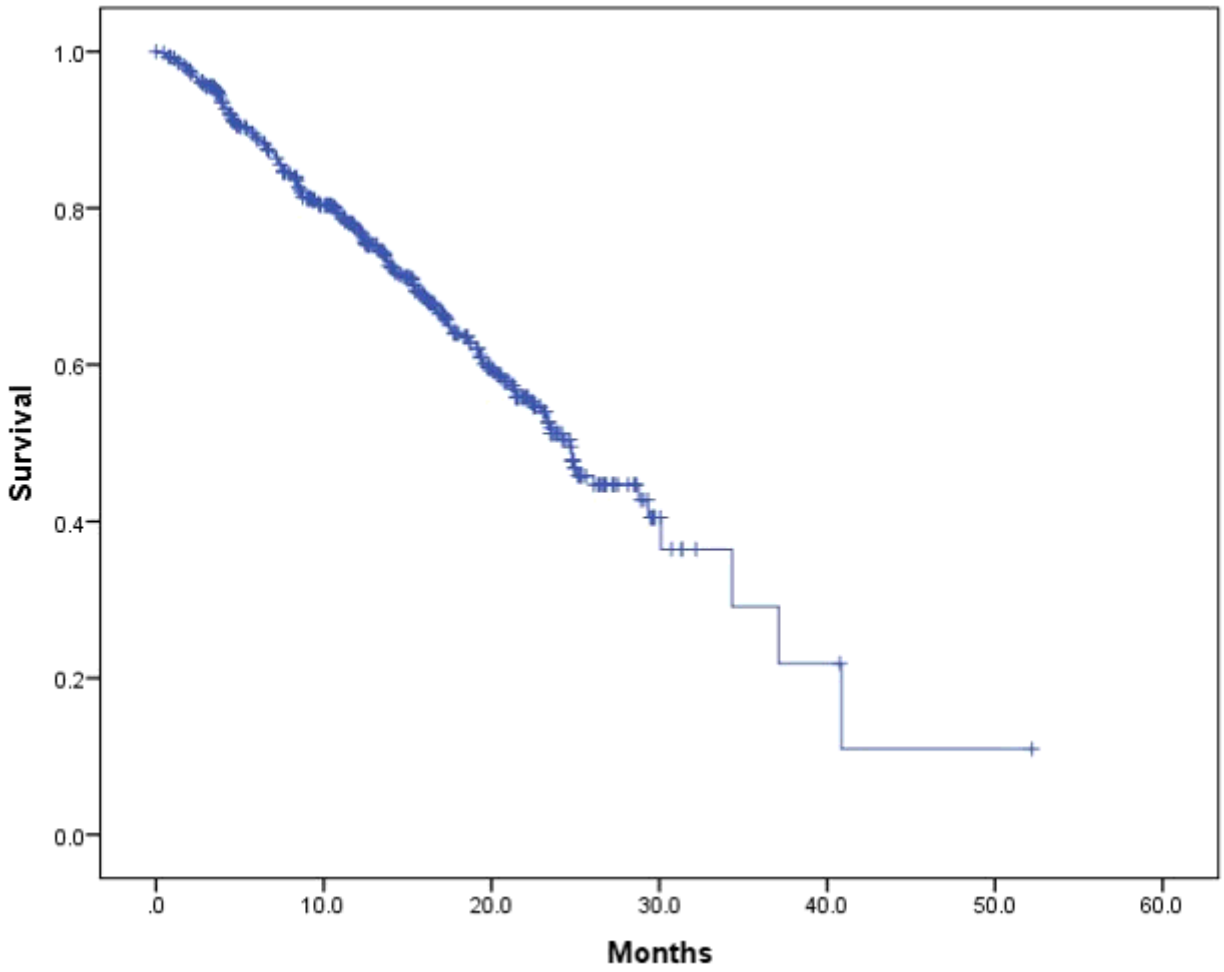

Figure 1

Kaplan-Meier curve for the overall survival in metastatic castration-resistant prostate cancer patients treated with abiraterone and/or enzalutamide

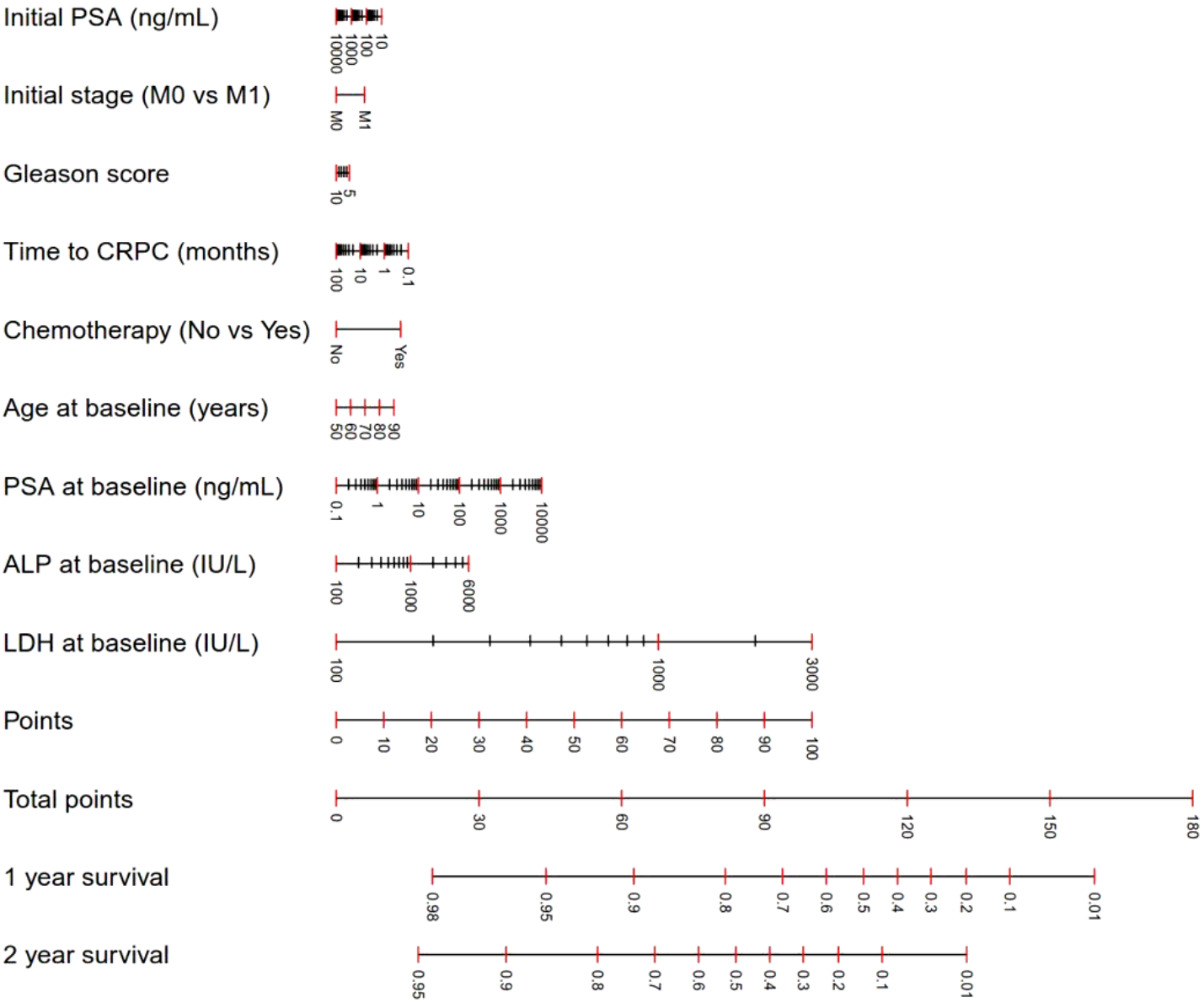

Figure 2

Nomogram for predicting the one- and two-year survival among men treated with abiraterone acetate and/or enzalutamide for metastatic castration-resistant prostate cancer.

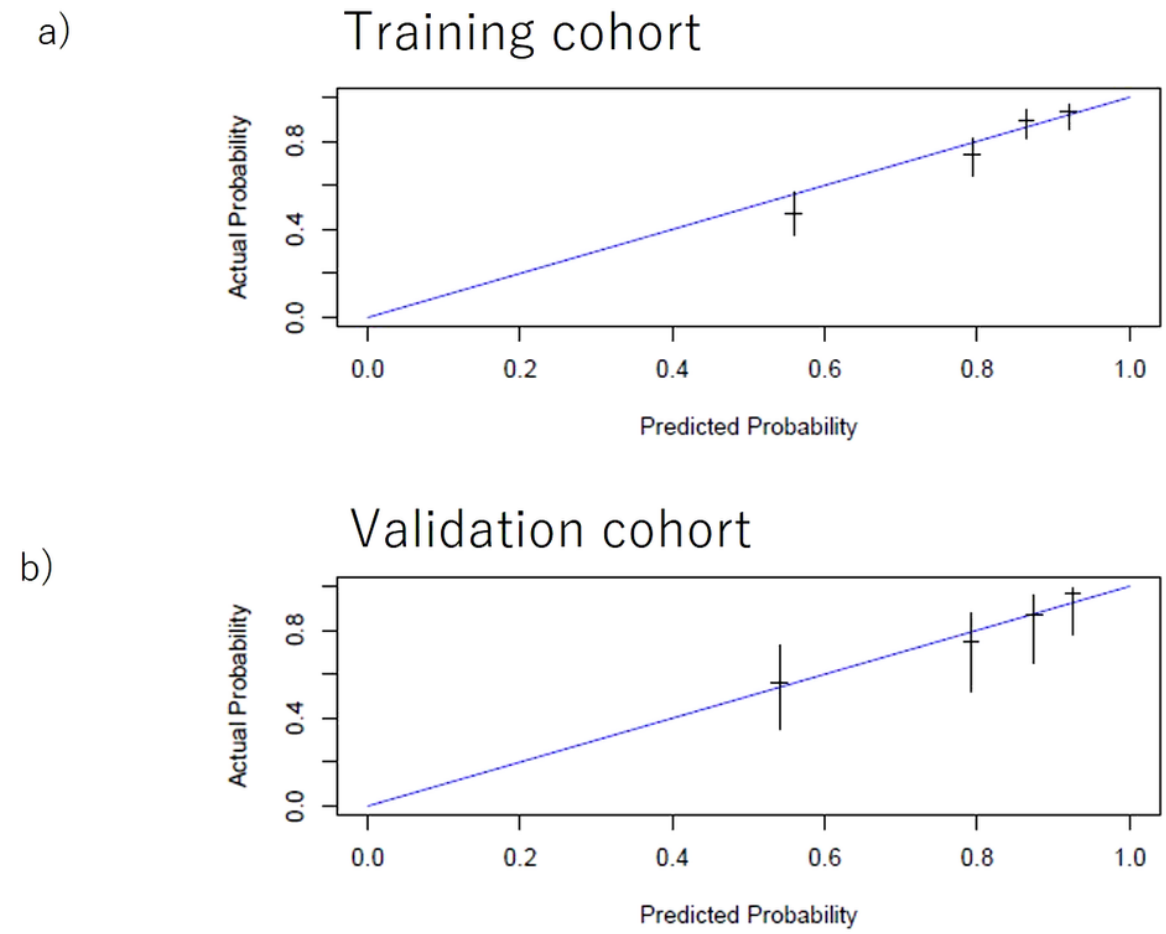

Figure 3

Calibration plots of the nomogram for the two-year survival. a) for training cohort and b) for validation cohort.

Figure 4

Android and iphone/iOS app to predict prognosis for 1-year and 2-year survival among men treated with abiraterone acetate and/or enzalutamide for metastatic castration-resistant prostate cancer.

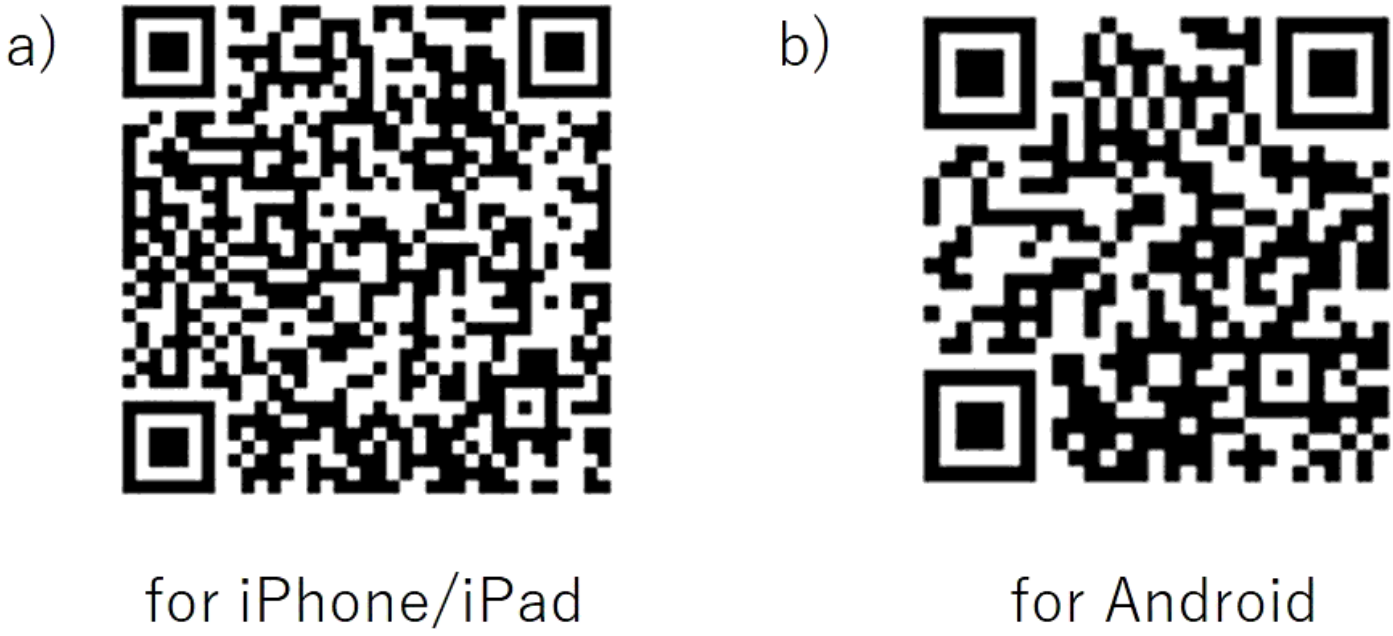

Figure 5

QR code to download the a) Android and b) iPhone/iPad app.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- r1.jpg