9-1-2022

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Recommended Citation
Modonutti D, Majdalany SE, Corsi N, Li P, Sood A, Dalela D, Jamil ML, Hwang C, Menon M, Rogers CG, Trinh QD, Novara G, and Abdollah F. A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis. Prostate 2022.

Authors

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Received: 24 January 2022 | Accepted: 27 May 2022

DOI: 10.1002/pros.24403

ORIGINAL ARTICLE

The Prostate WILEY

A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis

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Abstract

Purpose: Generalizable, updated, and easy-to-use prognostic models for patients with metastatic castration-resistant prostate cancer (mCRPC) are lacking. We developed a nomogram predicting the overall survival (OS) of mCRPC patients receiving standard chemotherapy using data from five randomized clinical trials (RCTs).

Methods: Patients enrolled in the control arm of five RCTs (ASCENT 2, VENICE, CELGENE/MAINSAIL, ENTHUSE 14, and ENTHUSE 33) were randomly split between training ($n = 1636$, 70%) and validation cohorts ($n = 700$, 30%). In the training cohort, Cox regression tested the prognostic significance of all available variables as a predictor of OS. Independent predictors of OS on multivariable analysis were used to construct a novel multivariable model (nomogram). The accuracy of this model was tested in the validation cohort using time-dependent area under the curve (tAUC) and calibration curves.

Results: Most of the patients were aged 65–74 years (44.5%) and the median (interquartile range) follow-up time was 13.9 (8.9–20.2) months. At multivariable analysis, the following were independent predictors of OS in mCRPC patients: sites of metastasis (visceral vs. bone metastasis, hazard ratio [HR]: 1.24), prostate-specific antigen (HR: 1.00), aspartate transaminase (HR: 1.01), alkaline phosphatase (HR: 1.00), body mass index (HR: 0.97), and hemoglobin (≥13 g/dl vs. <11 g/dl, HR: 0.41; all $p < 0.05$). A nomogram based on these variables was developed and showed favorable discrimination (tAUC at 12 and 24 months: 73% and 72%, respectively) and calibration characteristics on external validation.

Conclusion: A new prognostic model to predict OS of patients with mCRPC undergoing first line chemotherapy was developed. This can help urologists/oncologists in counseling patients and might be useful to better stratify patients for future clinical trials.

KEYWORDS

castration resistant, prognostic model, prostate cancer, survival

1 | INTRODUCTION

Prostate cancer, with 191,930 and 33,330 estimated new cases and deaths, respectively, in the United States during 2020, represents a national and global concern.[1] For patients with locally advanced or metastatic disease, androgenic deprivation therapy (ADT) is an effective treatment.[2] However, in the context of chronic androgen depletion, sooner or later, the disease develops mechanisms capable of making cell proliferation independent from the driving force of the androgens. This late phase of the disease is known as castration-resistant prostate cancer (CRPC). The latter is a hard-to-manage disease that eventually leads to a grim prognosis. The median survival in these patients ranges from 9 to 30 months and further decreases to 9–13 months in the metastatic stage (mCRPC).[3] The aggressiveness of the disease varies in this population of patients and the underlying causes of this variability are not yet fully understood.

Several drugs have been developed for the treatment of these patients. Therapeutic schemes are based on the combined and sequential use of chemotherapeutic agents (docetaxel and cabazitaxel), new molecules disrupting the androgen axis (enzalutamide, abiraterone, and apalutamide), immunotherapy (Sipuleucel-T), and bone-targeting drugs (Radium-223). Despite these advances, many Phase I and II trials investigating these treatments have shown limited benefits in mCRPC patients.[4] As well, being the only Food and Drug Administration-approved cancer vaccine, Sipuleucel-T has limited use clinically. In a Phase III trial, overall survival (OS) was only 2.8 months more in the Sipuleucel-T arm compared with placebo, in high-quartile prostate-specific antigen (PSA) and 13 months in the lower PSA.[4,5] However, its use is quite limited, where in a real-world study of 7272 mCRPC patients, only 10% were treated with Sipuleucel-T.[4–6] More recently developed therapeutics include antibody-drug conjugates, with five types currently in Phase 1 trials in mCRPC patient population.[7] In the setting of a vast array of therapeutics, the application of reliable prognostic model would permit the assignment of patients into risk classes. This in turn can yield a more accurate risk-benefit assessment of the current therapies and might help identifying the most suitable timing or indication of these. Moreover, such a model can have a critical role in the study design of future clinical trials investigating the efficacy of new interventions.

For the aforementioned reasons, several models predicting cancer control outcomes in mCRPC patients were developed over the years.[8–15] However, none of these showed enough reliability to make it universally accepted and broadly applicable in a real-world setting. Moreover, virtually all of these models are outdated or were based on a limited sample size. To circumvent these limitations, our objective was to develop an updated and easy-to-use prognostic model to predict OS among mCRPC patients employing a large data pool derived from the control arm of five randomized clinical trials (RCTs).

2 | MATERIALS AND METHODS

2.1 | Data source

The data set used in this study was obtained merging the Prostate Cancer Dialogue for Reverse Engineering Assessments and Methods (DREAM) Challenge database[16] with the control arm of the ENTHUSE 14 trial[17] database. Both these databases are available on the Project Data Sphere platform (https://www.projectdatasphere.org/projectdatasphere/html/pcdc). The latter is a free digital library-laboratory where researchers can share and analyze data from Phase III cancer clinical trials.

The DREAM challenge data set includes data from four control arms of the following clinical trials: ASCENT 2, CELGENE/MAINSAIL, VENICE, and ENTHUSE 33.[18–21] Demographic, clinical, and pathological variables were extracted from the final data set.

2.2 | Population

The five trials used in this study had similar inclusion and exclusion criteria. In particular, patients were aged ≥ 18 years, chemonaïve, with progressive mCRPC, with an adequate hematologic, cardiac, renal, and hepatic function, presenting an Eastern Cooperative Oncology Group (ECOG) between 0 and 2.[18–21] Patients enrolled in these control arms received the standard docetaxel-based chemotherapy with glucocorticoids or standard supportive/palliative treatment. Of note, patients enrolled in the ENTHUSE 33 trial were symptomatic, whereas only asymptomatic or mildly symptomatic patients were enrolled in the ENTHUSE 14 trial. Moreover, these two trials included only patients with metastasis to bone and/or visceral but excluded patients with lymph node only involvement. The detailed description of inclusion and exclusion criteria is reported in Supporting Information: Table 1 and 2. We excluded from the study a total of 69 patients (49 in the training and 20 in the testing cohort) because of missing values (Figure 1).

2.3 | Covariates

In this study, we employed patient-level variables, including age (18–64, 65–74, and ≥75 years), race (White, Asian, and Others), body mass index (BMI), and the ECOG scale of performance status (from 0 to 2). Noteworthy, we were unable to discern the Black race as a separate category, because this was not done in the included trials.

We also included information regarding the pathological sites of metastasis. This last variable was defined hierarchically based on the most advanced metastatic stage as follows: visceral versus bone versus lymph nodes metastasis. Finally, we also abstracted laboratory variables, which consisted of PSA, white blood cells, neutrophils, platelets (PLTs), hemoglobin (<11, 11–12.9, and ≥13 g/dl), creatinine, alanine transaminase, aspartate transaminase (AST), total bilirubin, calcium, and alkaline phosphatase (ALP). Hemoglobin was stratified according to the World Health Organization criteria for the diagnosis

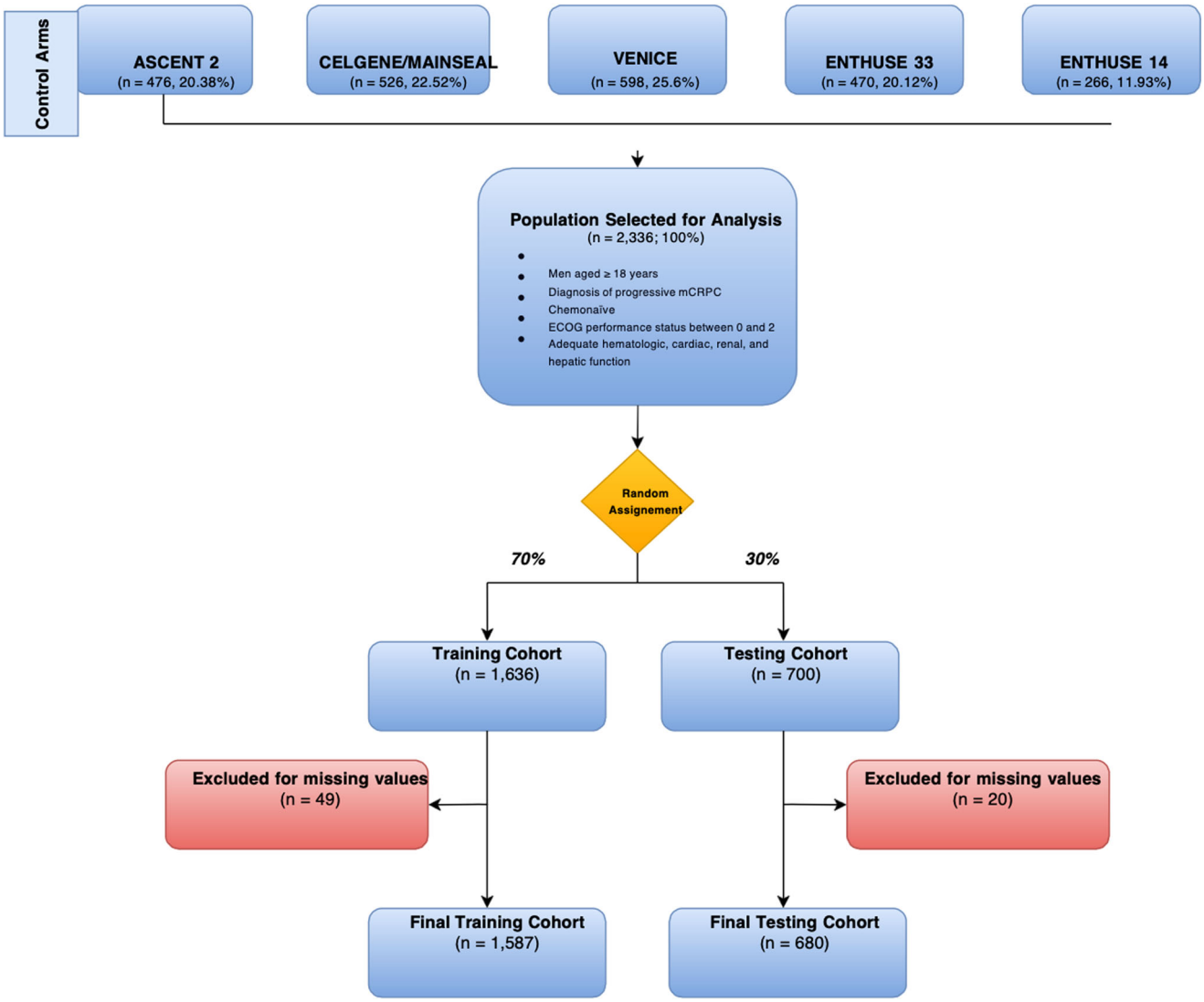

FIGURE 1 Flowchart describing the selection process of the patients included in this study. [Color figure can be viewed at wileyonlinelibrary.com]

of anemia.[22] We merged the categories <8 and 8–10.9 mg/dl in a single group (<11 mg/dl) because of the low number of patients presenting with such values of hemoglobin.

2.4 | Endpoints

The outcome of interest in this study was the OS of mCRPC patients, calculated from the time of randomization to time of death, and/or last available follow-up.

2.5 | Statistical analysis

We reported categorical variables using frequencies and percentages, while continuous variables were reported using median and interquartile ranges (IQRs). We tested the statistical significance of differences in categorical and continuous variables using the χ^2 test and analysis of variance test, respectively.

Our statistical analysis consisted of several steps. First, we randomly split our cohort into a training cohort, which included 70% of our original cohort, and a validation cohort, which included the remaining 30%. Second, we performed a univariable Cox regression to test the prognostic significance of each of our covariates as a predictor of OS. Depending on the distribution, highly skewed variables underwent a restricted cubic spline transformation to achieve a better fit. Third, we utilized only the variables that reached a statistical significance status at univariable analysis to develop a multivariable model predicting OS, based on Cox regression. Linear assumption was examined not only with the distribution of the variables but also with the proportional hazard assumptions in COX PH models and the assumptions were appropriate for other continuous variables. Finally, we ran multiple sensitivity analyses to test the robustness of our results. The discrimination of the novel

model was tested using the time-dependent area under the curve (tAUC). Time-dependent receiver operating characteristic curves for censored survival data was estimated using Kaplan–Meier (KM) method.[23] Furthermore, the calibration of our prognostic model was tested by comparing the predicted survival probability with the actual survival of the training and validation cohorts. Finally, KM curves were used to depict the OS in our validation cohort, after stratifying patients into low- versus high-risk groups based on the median predicted value of our novel nomogram. The data analysis was performed using SAS® software 9.4 (SAS Institute). The statistical significance of the two-sided p was set at ≤0.05.

3 | RESULTS

3.1 | Patient characteristics

The descriptive data of our population are reported in Table 1. Overall, 80.5% of patients were White, the majority aged between 65 and 74 years (44.5%), with a median BMI of 27.2 (IQR: 24.7–30.3), and an ECOG performance status of 0 (51.1%) or 1 (45.9%). The median (IQR) PSA was 81.7 ng/ml (29.0–239.1 ng/ml) and 59.4% of the patients presented bone metastasis with or without lymph node involvement. The median (IQR) hemoglobin at the baseline was 12.7 g/dl (11.6–13.6 g/dl), the median (IQR) creatinine was 82.0 µmol/L (71.0–97.0 µmol/L), and the median (IQR) ALP was 132.0U/L (85.0–263.0 U/L).

The median (IQR) length of follow-up was 14 (9.1–19.9) months for the overall cohort. This was 14 (9.1–19.9) months for the training cohort and 13.8 (8.6–20.8) months for the validation cohort.

3.2 | Nomogram development

In the training cohort (n = 1587 patients), the following variables were significant as predictors of OS on univariable analysis: age (only ≥ 75 years), BMI, ECOG performance status, PSA, sites of metastasis, PLT, hemoglobin, neutrophils, AST, ALP, and calcium (Table 2, all $p < 0.05$). Due to the skewed distribution, PSA, PLT, and calcium underwent restricted cubic spline transformation. Cubic spline was used on PSA and ALP. The reported HR was the estimation at a specified PSA value instead of the entire range, that is, PSA at 85 ng/ml and specified ALP value of 131 U/L.

On multivariable Cox proportional hazard analysis (Table 2), only the following variables resulted as independent predictors of OS: ALP (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 1.00–1.01), PSA (HR: 1.00; 95% CI: 1.00–1.00), AST (HR: 1.01; 95% CI: 1.00–1.01), BMI (HR: 0.97; 95% CI: 0.95–0.99), hemoglobin (≥13g/dl vs. <11 g/dl, HR: 0.41; 95% CI: 0.32–0.51), and sites of metastasis (visceral vs. bone, HR: 1.24; 95% CI: 1.06–1.44; all $p < 0.05$). Interestingly, bone metastasis was not associated with a statistically significant higher OS risk, when compared with lymph nodes metastasis only in these patient settings ($p = 0.55$). Independent predictors on multivariable analysis were used to develop our novel nomogram (Figure 2) predicting OS in mCRPC patients.

3.3 | Nomogram validation

The tAUC for the training cohort at 12, 24, 36, and 48 months were 0.74, 0.73, 0.72, and 0.67, respectively. In the validation cohort (n = 680), the tAUC was 0.71, 0.68, 0.77, and 0.78, respectively, for the same time period (Figure 3). The calibration of our model was favorable, as shown in Figure 4A,B. We used KM survival curves to depict survival of patients categorized in low- versus high-risk groups, based on median predicted OS (81%) of our novel nomogram in the training cohort. The 2-year OS rate in the low-risk versus high-risk groups was 59.9% versus 27.7% (log-rank $p < 0.0001$) in the training cohort and 56.8% versus 29.3% (log-rank $p < 0.0001$) in the validation cohort (Figure 5A,B). From Figure 5A,B, the KM plots show that few patients are at risk after 2 years and the SEs are large for 3- and 4-year tAUC. The tAUC at 3 and 4 years are not significantly different in training and testing data set.

3.4 | Sensitivity analysis

The 12-months tAUC was tested separately within each sub-cohort of the five included trials and resulted in the range between 0.71 and 0.77. Similarly, when patients were divided into two subcohorts based on metastasis sites (visceral, bone, and lymph nodes) the 12-month tAUC value ranged between 0.68 and 0.73.

4 | DISCUSSION

Metastatic CRPC represents the most advanced stage of prostate cancer. During the last decades, many new treatments have been developed to improve the survival of these individuals. That said, the probability of OS in these patients is heterogeneous and depends on several clinical and pathological features at the time of diagnosis. Unfortunately, the literature is scarce in models predicting the OS of such individuals. To fill this void, we developed, and externally validated, a “multi-trial” based, user-friendly nomogram.

Several of our findings are worth highlighting. First, the overall discrimination (tAUC) our model was high, in the range of 69%–78% (in the validation setting), with variations based on the predicted time point. Similar variations were observed in the calibration of the model. However, the overall calibration was favorable, as most predicting values were very close to the actual survival values. Second, age was not an independent predictor of OS in individuals with mCRPC, which implies that the survival of these patients is highly dictated by cancer survival. This is a key finding, as it implies that attempts should be made to maximize cancer control in these individuals, regardless of their age. Third, in our report, higher BMI was an independent predictor of more favorable OS. To the best of

TABLE 1 Descriptive statistics of the 2267 mCRPC patients enrolled in the control arm of five RCTs (ASCENT 2, CELGENE/MAINSAIL, VENICE, ENTHUSE 33, ENTHUSE 14).

Grouping	Overall	ASCENT 2	CELGENE/MAINSAIL	VENICE	ENTHUSE 33	ENTHUSE 14	*p*
Patients, *n* (%)	2267 (100%)	468 (20.6%)	505 (22.3%)	581 (25.6%)	455 (20.1%)	258 (11.4%)	
Race, *n* (%)							
White	1825 (80.5%)	411 (87.8%)	418 (82.8%)	522 (89.8%)	321 (70.5%)	153 (59.3%)	<0.001
Asian	212 (9.4%)	5 (1.1%)	0 (0.0%)	36 (6.2%)	72 (15.8%)	99 (38.4%)	
Others	230 (10.1%)	52 (11.1%)	87 (17.2%)	23 (4.0%)	62 (13.6%)	6 (2.3%)	
Age, *n* (%)							
18–64 years	695 (30.7%)	109 (23.3%)	163 (32.3%)	215 (37.0%)	153 (33.6%)	55 (21.3%)	<0.001
65–74 years	1,009 (44.5%)	208 (44.4%)	236 (46.7%)	244 (42.0%)	213 (46.8%)	108 (41.9%)	
≥75 years	563 (24.8%)	151 (32.3%)	106 (21.0%)	122 (21.0%)	89 (19.6%)	95 (36.8%)	
BMI, kg/m^2 (median [IQR])	27.2 (24.7–30.3)	27.70 (25.4–30.9)	27.8 (25.1–31.1)	27.3 (25.0–30.1)	26.9 (24.3–29.7)	26.1 (23.8–28.6)	<0.001
ECOG performance status, *n* (%)							
0	1158 (51.1%)	216 (46.2%)	248 (49.1%)	267 (46.0%)	239 (52.5%)	188 (72.9%)	<0.001
1	1040 (45.9%)	230 (49.1%)	237 (46.9%)	287 (49.4%)	216 (47.5%)	70 (27.1%)	
2	69 (3.0%)	22 (4.7%)	20 (4.0%)	27 (4.6%)	0 (0.0%)	0 (0.0%)	
PSA, ng/ml (median [IQR])	81.7 (29.0–239.1)	69.1 (23.8–189.9)	87.1 (33.7–275.0)	92.8 (30.9–261.4)	101.0 (34.0–237.5)	52.3 (16.8–155.0)	
Metastasis sites, *n* (%)							
Lymph nodes only	181 (8.0%)	107 (22.9%)	42 (8.3%)	32 (5.5%)	0 (0.0%)	0 (0.0%)	<0.001
Bone w/o lymph nodes	1,346 (59.4%)	326 (69.7%)	276 (54.7%)	308 (53.0%)	264 (58.0%)	172 (66.7%)	
Any visceral	740 (32.6%)	35 (7.5%)	187 (37.0%)	241 (41.5%)	191 (42.0%)	86 (33.3%)	
WBC, 10^9/L (median [IQR])	6.8 (5.5–8.6)	6.6 (5.4–8.1)	7.0 (5.4–9.2)	6.9 (5.5–8.2)	7.2 (5.9–9.5)	6.6 (5.5–7.8)	<0.001
Neutrophils, 10^9/L (median [IQR]	4.65 (3.6–6.3%)	4.4 (3.4–5.7)	4.9 (3.7–7.2)	4.43 (3.5–5.8)	5.44 (4.2–7.5)	4.22 (3.4–5.3)	<0.001
Hemoglobin, g/dl (median [IQR])	12.7 (11.6–13.6)	12.6 (11.6–13.6)	12.7 (11.5–13.7)	12.7 (11.7–13.5)	12.5 (11.3–13.5)	12.9 (12.1–13.7)	0.001
<11 g/dl	315 (13.9%)	57 (12.2%)	81 (16.0%)	70 (12.0%)	90 (19.8%)	17 (6.6%)	
11–12.9 g/dL	1009 (44.5%)	227 (48.5%)	214 (42.4%)	262 (45.1%)	189 (41.5%)	117 (45.3%)	
≥13 g/dl	943 (41.6%)	184 (39.3%)	210 (41.6%)	249 (42.9%)	176 (38.7%)	124 (48.1%)	
PLT10^9/L (median [IQR])	253.0 (207.0–316.0)	253.0 (207.0–308.5)	279.0 (229.0–350.0)	247.0 (205.0–308.0)	248.0 (205.0–318.0)	229.0 (191.5–273.0)	<0.001
Creatinine, µmol/L (median [IQR])	82.0 (71.0–97.0)	88.0 (75.8–106.0)	80.0 (70.0–93.0)	83.10 (71.0–97.2)	82.0 (71.0–96.0)	81.0 (70.3–95.0)	<0.001
ALT, U/L (mean [SD])	23.7 (16.9)	22.2 (13.6)	23.6 (17.1)	24.3 (15.4)	25.4 (22.4)	22.5 (13.0)	0.035

(Continues)

TABLE 1 (Continued)

Grouping	Overall	ASCENT 2	CELGENE/MAINSAIL	VENICE	ENTHUSE 33	ENTHUSE 14	p
AST, U/L (median [IQR])	24.0 (20.0–31.0)	24.0 (20.0–31.0)	24.0 (19.0–31.0)	25.0 (20.0–33.0)	25.0 (20.0–33.0)	24.0 (19.0–29.0)	0.096
Total bilirubin, Umol/L (median [IQR])	7.0 (5.0–9.0)	7.0 (5.0–9.0)	6.0 (4.0–8.0)	8.6 (6.0–10.9)	5.0 (5.0–7.0)	7.0 (5.0–9.0)	<0.001
ALP, U/L (median [IQR])	132.0 (85.0–263.0)	113.0 (80.0–213.0)	125.0 (82.0–269.0)	136.00 (85.0–273.0)	158.00 (99.5–334.0)	132.00 (83.0–224.3)	<0.001
Calcium, mmol/L (median [IQR])	2.4 (2.3–2.4)	2.37 (2.3–2.5)	2.30 (2.2–2.4)	2.33 (2.2–2.4)	2.35 (2.3–2.5)	2.35 (2.3–2.4)	<0.001

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; ECOG performance status, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; PLT, platelets; PSA, prostate-specific antigen; RCTs, randomized clinical trials; WBC, white blood cells.

our knowledge, previous models failed to observe a statistically significant association between BMI and OS in mCRPC patients. This might be due to the limited sample size in previous reports. In the literature, there is evidence about the protective role of BMI on the survival of metastatic prostate cancer patients, but the underlying mechanism involved is still unclear.[24,25] One reasonable hypothesis is that the patients with high BMI show a better survival because of a higher lean-to-fat ratio that puts them at a lower risk of sarcopenia.[26] That said, a full understanding of the mechanisms of this relationship is beyond the scope of this study. Finally, our results highlight the striking heterogeneity of outcomes in patients with mCRPC, as those in the high-risk group, based on our new model classification, and have almost half the survival rate of their counterparts in the low-risk group for the same time point. Thus, models and trials not accounting for the heterogeneity in the baseline features represented in our nomogram risk producing significantly biased outcomes.

Our multi-trial design (total of five trials), using random splitting to develop our training and validation subcohorts, significantly improves the generalizability of our novel model. In comparison, the only other contemporary trial-based nomogram, which was published by Halabi et al.[12] was based on a single trial for training and a separate trial for validation. Although the Halabi et al. model is one of the best developed nomograms in current literature, its generalizability might be limited by the aforementioned factors. These trials do have eligibility criteria and may not be representative of all patients in the clinical setting, however, randomized trials are meant to capture a random selection, which may allow for a broader capture of samples. In addition, compared to previous prognostic models, our nomogram has great potential as an updated and generalizable prognostic tool. The sample sized used in our nomogram is greater in both training and validation arms, more than twice the amount in the widely utilized Halabi nomogram. Together, the random splitting of cohorts and the large sample size allows for a more generalizability of use for our nomogram.

Our results are even more interesting, because patients in our study are chemonaïve at the time of randomization and underwent only the standard chemotherapy with docetaxel or standard supportive/palliative treatment, representing, in this way, a proxy of the natural history of the disease in contemporary patients. This means that our nomogram could be useful to define subgroups of patients, based on the clinical risk, to use in future clinical trials. This applicability to outline subgroups of patients based on clinical risk factors amplifies the generalizability of our nomogram for use in future and real-world patients.

In this study, we used the same data set that Guinney et al.[16] employed in their open-data, crowdsourced, DREAM challenge. Their model showed an excellent prognostic accuracy that outperformed all previously developed models. Having said that, such a complex model can hardly find a place in the daily busy clinical practice. The model herein presented, instead, using a relatively small number of readily available variables, represents a more straightforward prognostic tool, whether it is used for clinical or research purposes.

The development of nomograms is usually designed using similar covariates and there seems to be a knowledge gap in the analysis

TABLE 2 Univariable and multivariable Cox regression analysis predicting OS in 1587 patients (training cohort) with mCRPC.

	Univariable analysis			Multivariable analysis					
				Overall model			Final model		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Race									
White	REF	–	–	–	–	–	–	–	–
Asian	1.20	0.96–1.50	0.11						
Others	0.99	0.75–1.31	0.94						
Age (years)						0.15			
18–64*	REF	–	–	–	–	–	–	–	–
65-74	0.99	0.83–1.17	0.88	1.04	0.87–1.25	0.64			
≥75	1.24	1.02–1.50	0.03	1.21	0.99–1.48	0.065			
BMI (kg/m^2)	0.78	0.70–0.87	<0.0001	0.97	0.96–0.99	0.0062	0.97	0.95–0.99	0.0022
ECOG performance status						0.15			
0*	REF	–	–	–	–	–	–	–	–
1	1.41	1.21–1.63	<0.0001	1.16	0.99–1.35	0.07			
2	2.54	1.75–3.70	<0.0001	1.26	0.84–1.90	0.26			
PSA (ng/ml)	1.05	1.03–1.06	<0.0001	1.00	1.00–1.00	0.0007	1.00	1.00–1.00	0.0002
Site of metastasis						0.016			0.027
Bone w/o lymph nodes	REF	–	–	–	–	–	–	–	–
Lymph nodes only	0.70	0.50–1.00	0.05	1.12	0.77–1.61	0.55	1.11	0.77–1.60	0.55
Visceral	1.29	1.11–1.50	0.001	1.26	1.08–1.47	0.0042	1.24	1.06–1.44	0.0073
WBC (10^9/L)	1.06	0.98–1.16	0.15						
Neutrophils (10^9/L)	1.08	1.00–1.17	0.04	1.03	0.94–1.12	0.50			
Hemoglobin (g/dl)	0.52	0.47–0.58	<0.0001			<0.0001			<0.0001
<11 g/dl*	REF	–	–	–	–	–	–	–	–
11-12.9 g/dl	0.39	0.32–0.48	<0.0001	0.58	0.46–0.72	<0.0001	0.54	0.44–0.66	<0.0001
≥13 g/dl	0.27	0.22–0.34	<0.0001	0.45	0.35–0.58	<0.0001	0.41	0.32–0.51	<0.0001
PLT (10^9/L)	1.20	1.10–1.31	<0.0001	1.06	0.97–1.16	0.20			
Creatinine (μmol/L)	1.07	0.99–1.17	0.09						
ALT (U/L)	1.02	0.97–1.07	0.48						
AST (U/L)	1.10	1.08–1.13	<0.0001	1.01	1.00–1.01	0.0001	1.01	1.00–1.01	<0.0001
Total bilirubin (Umol/L)	0.92	0.85–1.00	0.06						
ALP (U/L)	1.14	1.11–1.17	<0.0001	1.00	1.00–1.01	<0.0001	1.00	1.00–1.01	<0.0001
Calcium (mmol/L)	0.87	0.82–0.93	<0.0001	0.60	0.15–2.35	0.31			

Note: Univariable and multivariable Cox regression analysis predicting OS in 1587 patients (training cohort) with mCRPC, who underwent systemic chemotherapy with docetaxel plus glucocorticoid or standard supportive/palliative treatment.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; ECOG performance status, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PLT, platelets; PSA, prostate-specific antigen; WBC, white blood cells.

among them. Researchers are continually seeking to analyze which covariates contribute to OS when they are constructing nomograms. In a recent study investing predictors from time of diagnosis of mCRPC to all-cause mortality, Moreira et al.[13] found that age, greater distant year of diagnosis, greater number of bone metastasis, higher PSA levels and shorter PSA doubling time were associated with worse OS. Halabi et al.[12] saw worse outcomes with poor performance status, visceral metastasis, higher lactate dehydrogenase, more opioid

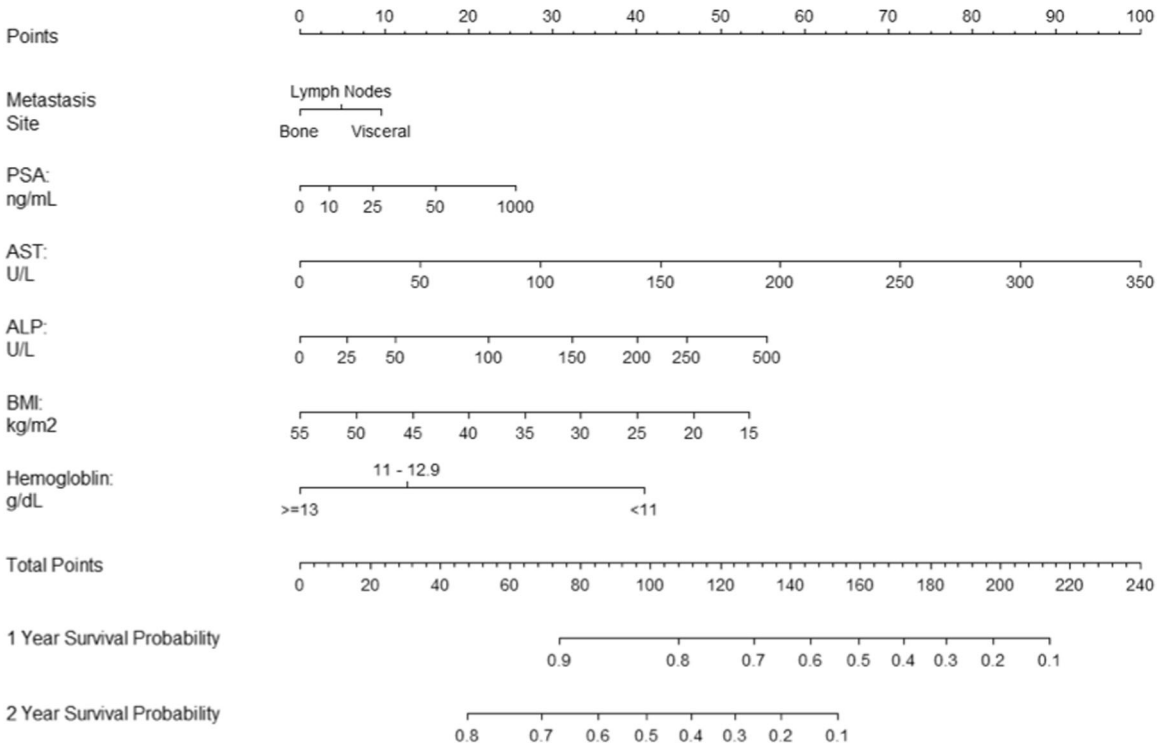

FIGURE 2 Novel nomogram predicting the overall survival (OS) at 12 and 24 months of metastatic castration-resistant prostate cancer (mCRPC) patients undergoing systemic chemotherapy with docetaxel plus glucocorticoids or standard supportive/palliative treatment.

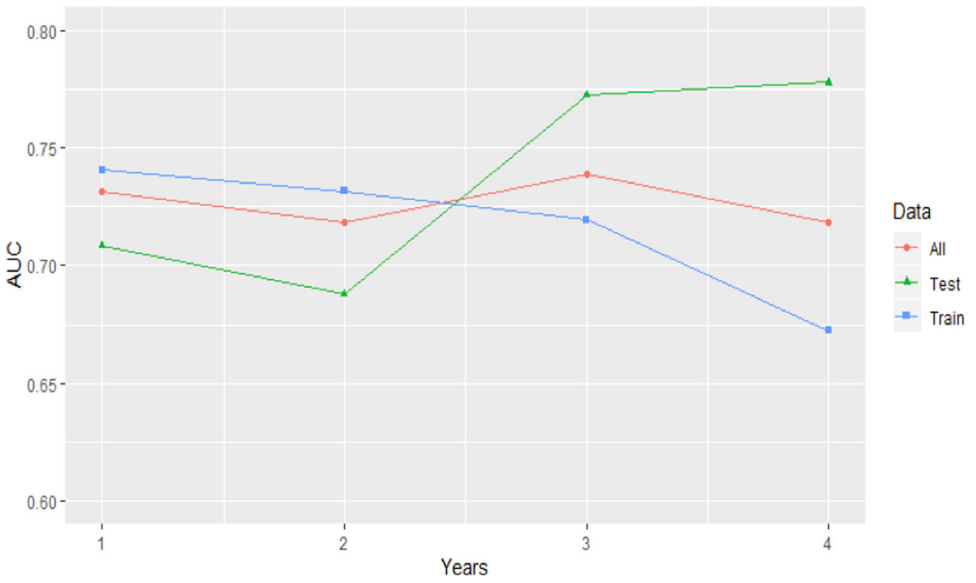

FIGURE 3 Time-dependent area under the curve (tAUC) of the training cohort, validation cohort, and the entire cohort. [Color figure can be viewed at wileyonlinelibrary.com]

analgesic use, lower serum albumin, lower hemoglobin, higher PSA levels, and higher ALP. Our validation compared similar covariates yet found that bone metastasis was not associated significantly associated with worse OS. These differences among factors influencing OS from various studies is a knowledge gap in the creation of nomograms that require more detailed analysis.

Our study is not devoid of limitations. For example, as we did not have access to data of patients enrolled in the interventional arms, we are unable to estimate the effect of the experimental therapy on the OS of these patients. Secondly, we understand that the clinical trials used do have eligibility criteria and may not be representative of all patients in the clinical setting. Thirdly, the accuracy of our model is

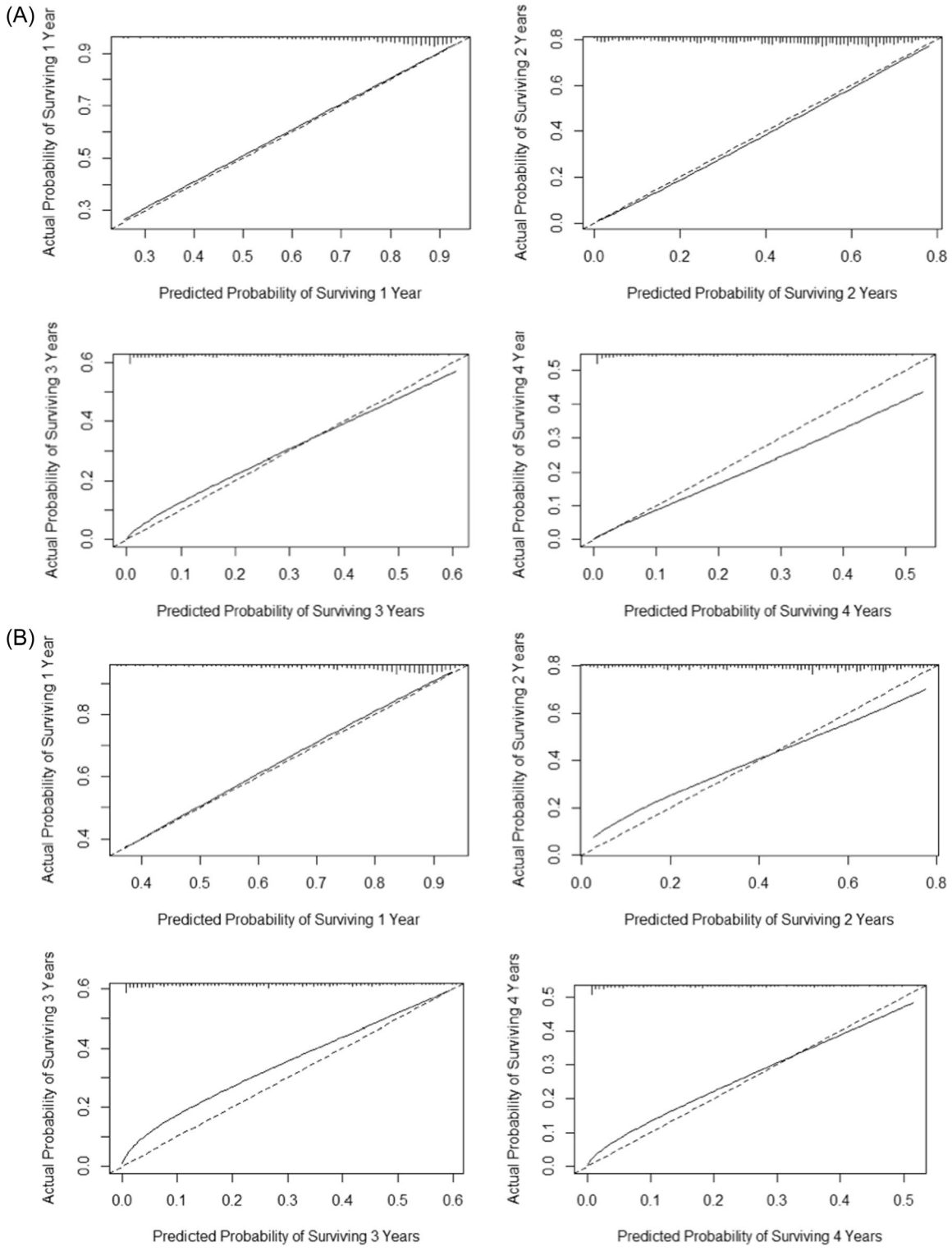

FIGURE 4 (A) Calibration curves of the actual probability of survival versus the predicted probability of overall survival (OS) at 12, 24, 36, and 48 months obtained using the validation cohort (n = 1587 patients). The dashed black line describes an ideal test, the continuous black line represents the prediction of our model, and the black bars on the top of each plot denote the distribution of predicted probabilities. (B) Calibration curves of the actual probability of survival versus the predicted probability of OS at 12, 24, 36, and 48 months obtained using the test cohort (n = 680 patients). The dashed black line describes an ideal test, the continuous black line represents the prediction of our model, and the black bars on the top of each plot denote the distribution of predicted probabilities.

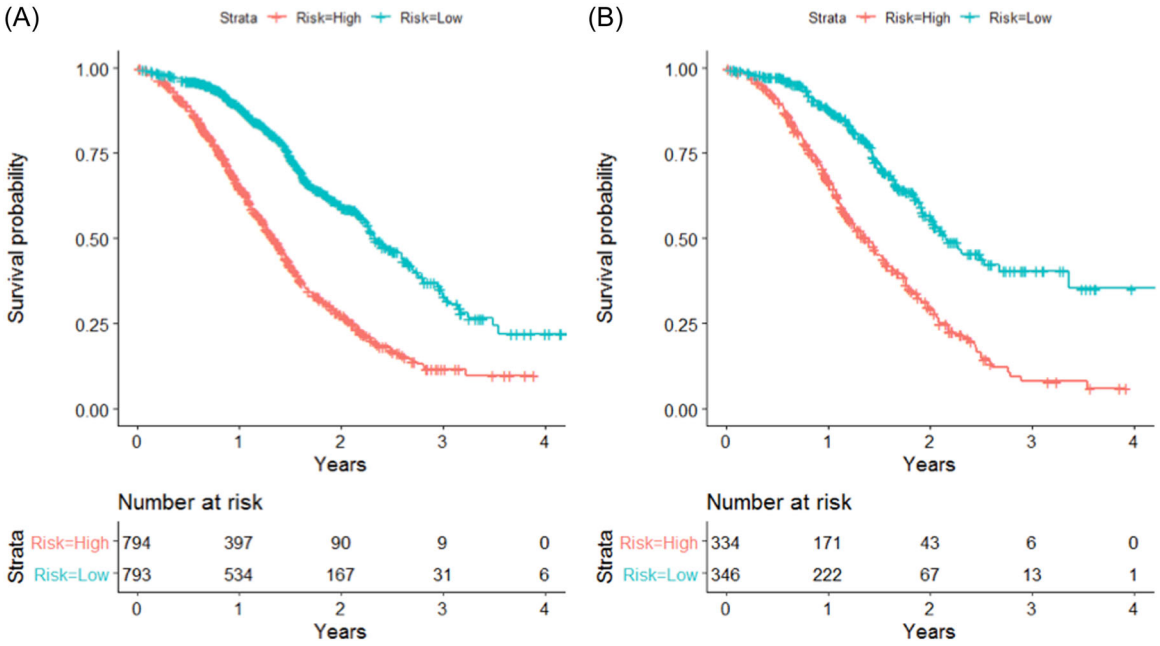

FIGURE 5 Kaplan–Meier survival curves depicting overall survival (OS) of low-risk versus high-risk patients (stratified based on the nomogram predicted median OS in the training cohort) enrolled in the training (A) and validation (B) cohorts. [Color figure can be viewed at wileyonlinelibrary.com]

not perfect. This observation could be due to presence of other confounders, which are not captured by the study database. Further studies are needed to understand the nature of these variables and their weight on the survival of mCRPC patients. A further limitation of our study lies in a certain degree of heterogeneity between the populations enrolled in the five RCTs. Finally, of course our prognostic model will undoubtedly exclude data from more recent trials. However, our sensitivity analysis shows that the accuracy of our novel model is robust across the five different trials and different metastasis sites. This accuracy paves the way for future research to derive individual predictions on survival as well and future prognostic models may be focusing more on cancer-specific survival compared with OS.

5 | CONCLUSIONS

Patients with mCRPC have heterogeneous outcomes, which can be predicted using our novel prognostic tool. This novel model can be of great help in patient counseling and might improve our future ability to choose patients for clinical trials.

ACKNOWLEDGMENTS

This publication is based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere. Neither Project Data Sphere nor the owner(s) of any information from the web site have contributed to, approved or are in any way responsible for the contents of this publication. ID: NCT00002874.

CONFLICT OF INTEREST

Firas Abdollah is an advisor/consultant of Decipher Biosciences.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon request.

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How to cite this article: Modonutti D, Majdalany SE, Corsi N, et al. A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis. *The Prostate*. 2022;82:1293-1303. doi:10.1002/pros.24403