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Novel metastatic burden-stratified risk model in de novo metastatic hormone-sensitive prostate cancer

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Abstract

The metastatic burden is a critical factor for decision-making in the treatment of metastatic hormone-sensitive prostate cancer (HSPC). This study aimed to develop and validate a novel risk model for survival in patients with de novo low- and high-burden metastatic HSPC. The retrospective observational study included men with de novo metastatic prostate cancer who were treated with primary androgen-deprivation therapy at 30 institutions across Japan between 2008 and 2017. We created a risk model for overall survival (OS) in the discovery cohort (n = 1449) stratified by the metastatic burden (low vs high) and validated its predictive ability in a separate cohort (n = 951). Based on multivariate analyses, lower hemoglobin levels, higher Gleason grades, and higher clinical T-stage were associated with poor OS in low-burden disease. Meanwhile, lower hemoglobin levels, higher Gleason grade group, liver metastasis, and higher extent of disease scores in bone were associated with poor OS in patients with high-burden disease. In the discovery and validation cohorts, the risk model using the aforementioned parameters exhibited excellent discriminatory ability for progression-free survival and OS. The predictive ability of this risk model was superior to that of previous risk models. Our novel metastatic burden-stratified risk model exhibited excellent predictive ability for OS, and it is expected to have several clinical uses, such as precise prognostic estimation.

KEYWORDS

androgen-deprivation therapy, hormone-sensitive prostate cancer, metastatic burden, metastatic prostate cancer, risk model

1 | INTRODUCTION

In 2015, upfront docetaxel chemotherapy with androgen-deprivation therapy (ADT) (CHAARTED and STAMPEDE [arm C] trials) was revealed to provide survival benefits in patients with metastatic hormone-sensitive prostate cancer (HSPC).[1-3] Subsequently, androgen receptor pathway inhibitors (ARPI), including abiraterone (LATITUDE and STAMPEDE [arm G] trials), and the second-generation antiandrogens enzalutamide (ENZAMET trial) and apalutamide (TITAN trial) also improved survival when combined with ADT.[4-7] In addition to pharmacotherapy, a potential survival benefit of radiotherapy to the prostate for oligo-metastatic HSPC (≤4 bone metastases) was observed in two randomized trials (HORRAD and STAMPEDE [arm H] trials).[8,9] Based on these findings from phase 3 clinical trials, novel therapeutic strategies have emerged as gold standard therapies for metastatic HSPC.[10]

Intriguingly, the survival benefits of these novel therapies have been suggested to differ according to the tumor aggressiveness and metastatic burden. A recent meta-analysis illustrated that a robust survival benefit of ARPI was recognized for low- and high-volume disease, whereas the survival benefit of docetaxel may be limited to high-volume disease.[11] Meanwhile, a survival benefit of local radiotherapy has been observed in patients with oligo-metastatic but not high-volume disease.[12] These differing benefits suggest that the metastatic burden is a critical parameter when selecting therapeutic strategies for patients with metastatic HSPC. Thus, prognostic

estimation based on the metastatic burden is important for clinical decision-making.

To date, several prognostic models of ADT have been developed.[13-16] However, these risk models were not developed for low- and high-burden disease; instead, they were created for only metastatic disease or both non–metastatic and metastatic disease, which may decrease the fitness of the risk models. In fact, we recently revealed that clinicopathological parameters differentially affected the differentiation of prognosis between low- and high-burden diseases.[17] Accordingly, this study aimed to develop and validate a novel risk classification model using pre–treatment clinical parameters for survival in de novo low- and high-burden metastatic HSPC in ADT that can be widely be used in clinical practice.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively enrolled patients who were newly diagnosed with de novo metastatic prostate cancer between 2008 and 2017 at 30 institutions, mainly academic hospitals and cancer centers, participating in the Japanese Urological Oncology Group.[18] The study was approved by the institutional review board of each institute.[18] All patients were pathologically diagnosed with adenocarcinoma of the prostate, and distant metastasis was detected through computed tomography and bone scans performed at the time of diagnosis. Of the 2829 patients with metastatic prostate cancer described in our previous report,[18] we excluded 379 patients for the following reasons: (a) unknown number of bone metastases; (b) unknown M1 sub-stage; (c) unknown/undetermined Gleason grade group or pathological diagnosis other than adenocarcinoma; (d) initial treatment (eg, upfront docetaxel and upfront ARPI) other than castration monotherapy or combined androgen blockade (CAB); or (e) unknown prognosis. In addition, we excluded 44 patients in the validation cohort for whom hemoglobin (Hb) levels or the clinical T-stage were unknown. In total, data were analyzed for 2400 patients.

2.2 | Methods

Demographic, clinicopathological, and survival data were obtained from patients' medical records. Clinical staging was determined using the unified TNM criteria.[19] Gleason grade group at initial diagnosis was defined as follows: <3 + 4 = 7 (I); 3 + 4 (II); 4 + 3 (III); 4 + 4 (IV); or 9-10 (V). Gleason scores of 3 + 5 and 5 + 3 were included in group IV according to a previous report.[20] Patients were dichotomized into low-burden (lymph node metastasis and/or <4 bone metastases without visceral metastasis) and high-burden (≥4 bone metastases and/or visceral metastasis) disease groups. Extent of disease (EOD) score was divided into five EOD grades according to the extent of bone metastasis on bone scans as follows: 0, normal; 1, fewer than 6 bone metastases, each of which is <50% of the size of a vertebral

body (one lesion approximately the size of a vertebral body would be counted as two lesions); 2, between 6 and 20 bone metastases; 3, more than 20 bone metastases but less than a "super scan"; and 4, "superscan" or bone metastases involving more than 75% of the ribs, vertebrae, and pelvic bones.[21] Hormone therapy was administered as castration monotherapy (surgical or medical castration) or CAB (surgical or medical castration plus a first-generation non–steroidal antiandrogen [bicalutamide and flutamide]). Progression-free survival (PFS) was calculated from the date of diagnosis to that of progression, defined as a 25% increase in prostate-specific antigen (PSA) levels from nadir and levels exceeding 2.0 ng/mL. Overall survival (OS) was calculated as the date of diagnosis to that of death from any cause. Surviving patients without disease progression or death were censored at the last follow-up visit.

2.3 | Model development

The discovery cohort was used to develop the prognostic model, which was subsequently validated in the independent validation cohort. Patients from academic and non–academic hospitals were assigned to the discovery and validation cohorts, respectively. The optimal cutoff for variables was determined as a clinically approximate value using receiver operating characteristic curve analysis. Multivariate analysis was performed to identify prognostic factors using the discovery cohort, and risk categories were determined based on the number of risk factors. External validation was performed by applying data from the independent validation cohort. Discrimination was evaluated using Harrell's C-index.[22]

2.4 | Statistical analysis

All analyses were performed using JMP14 software (SAS Institute). Continuous and categorical data were analyzed using Wilcoxon's rank-sum and Pearson's χ^2-tests, respectively. Survival analyses were conducted using the Kaplan-Meier method and the log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HR) with multivariate analysis. Harrell's C-index was calculated using Stata version 17 as described previously.[23,24] All P-values were two-sided, and P < .05 was considered significant.

3 | RESULTS

3.1 | Development of the risk model

The baseline characteristics in the discovery cohort (academic hospitals, n = 1449) are presented in Table 1. As anticipated, clinicopathological characteristics differed between the low and high metastatic burden groups, excluding age (Table 1). The median follow-up time for men alive at the date of censor was 38.9 months (interquartile range, 21.2-67.8 months). During follow up, 87 (19.1%) and 25 (5.5%)

TABLE 1 Backgrounds of patients with low and high metastatic burden in the discovery cohort

Variable	Low burden (n = 456)	High burden (n = 993)	P-value
Age at diagnosis, y (IQR)	72 (66-78)	72 (66-78)	.29
NA	0	3	
Hb value at diagnosis, g/dL (IQR)	14.0 (12.9-14.8)	13.2 (11.7-14.5)	<.0001*
NA	46	72	
PSA value at diagnosis, ng/mL (IQR)	69.7 (23.1-213)	341 (104-999)	<.0001*
NA	1	2	
Percentage of biopsy positive core, n (%)			
≤66%	172 (39.5%)	236 (24.9%)	
>66%	263 (60.5%)	710 (75.1%)	<.0001*
NA	21	47	
Biopsy Gleason grade group, n (%)			
Group ≤III	67 (14.7%)	75 (7.6%)	
Group IV	129 (28.3%)	260 (26.2%)	
Group V	260 (57.0%)	658 (66.3%)	<.0001*
Clinical T-stage, n (%)			
T1/2	105 (23.8%)	156 (16.3%)	
T3a	112 (25.4%)	233 (24.4%)	
T3b	123 (27.9%)	244 (25.5%)	
T4	101 (22.9%)	323 (33.8%)	<.0001*
Tx	15	37	
Clinical N-stage, n (%)			
N0	206 (45.8%)	378 (38.4%)	
N1	244 (54.2%)	607 (61.6%)	.0081*
Nx	6	8	
Clinical M-stage, n (%)			
M1a	88 (19.3%)	—	
M1b	368 (80.7%)	828 (83.4%)	
M1c (lung)	—	147 (14.8%)	
M1c (liver)	—	18 (1.8%)	<.0001*
EOD score, n (%)			
EOD0	88 (19.3%)	40 (4.0%)	
EOD1	368 (80.7%)	208 (20.9%)	
EOD2	—	389 (39.2%)	
EOD3	—	254 (25.6%)	
EOD4	—	102 (10.3%)	<.0001*

EOD, extent of disease; Hb, hemoglobin; IQR, interquartile range; NA, not available; PSA, prostate-specific antigen.

*Statistically significant.

patients experienced cause-specific death and death due to other causes in the low-burden group, while 311 (31.3%) and 67 (6.7%) patients experienced cause-specific death and death due to other causes in the high-burden group, respectively. Next, to develop the risk model for OS, multivariate analyses were performed to identify the parameters associated with OS. As presented in Table 2, lower Hb levels (>12 vs ≤12; HR = 2.24; 95% confidence interval [CI] = 1.30-3.88; P = .0039), higher Gleason grade group (≤IV vs V; HR = 1.61; 95% CI = 1.005-2.57; P = .048), and higher clinical T-stage (T1-3 vs T4; HR = 1.99; 95% CI = 1.23-3.20; P = .0050) were identified to be associated with poor OS in patients with low-burden disease (Table 2). Meanwhile, lower Hb levels (>12 vs ≤12; HR = 1.67; 95% CI = 1.31-2.13; P < .0001), higher Gleason grade group (≤IV vs V; HR = 1.35; 95% CI = 1.05-1.75; P = .021), liver metastasis (absent vs present; HR = 2.46; 95% CI = 1.34-4.52; P = .0038), and higher EOD score (EOD0-3 vs EOD4; HR = 2.28; 95% CI = 1.69-3.08; P < .0001)

TABLE 2 Associations between clinicopathological parameters and overall survival on multivariate analysis in the discovery cohort

Variable	Low burden				High burden			
	n	HR	95% CI	*P*-value	n	HR	95% CI	*P*-value
Age at diagnosis								
≤70 y	185	Ref	—	—	450	Ref	–	–
>70 y	271	.85	.56-1.30	.46	540	1.10	0.87-1.39	.41
Hb value at diagnosis								
≤12 g/dL	61	2.24	1.30-3.88	.0039*	277	1.67	1.31-2.13	<.0001*
>12 g/dL	349	Ref	—	—	644	Ref	–	–
PSA value at diagnosis								
≤100 ng/mL	273	Ref	—	—	239	Ref	–	–
>100 ng/mL	182	1.11	.71-1.74	.64	752	.80	0.61-1.05	.11
Percentage of biopsy positive core								
≤66%	172	Ref	—	—	236	Ref	–	–
>66%	263	1.05	.66-1.69	.82	710	1.18	0.90-1.54	.24
Biopsy Gleason grade group								
Group ≤IV	196	Ref	—	—	335	Ref	–	–
Group V	260	1.61	1.005-2.57	.048*	658	1.35	1.05-1.75	.021*
Clinical T-stage								
T1-3	340	Ref	—	—	633	Ref	–	–
T4	101	1.99	1.23-3.20	.0050*	323	1.12	0.88-1.42	.37
Clinical N-stage								
N0	206	Ref	—	—	378	Ref	–	–
N1	244	.97	.59-1.59	.91	607	1.05	0.82-1.33	.70
Clinical M-stage								
M1a	88	1.09	.59-1.98	.79	—	—	–	–
M1b	368	Ref	—	—	828	Ref	–	–
M1c (lung)	—	—	—	—	147	.60	0.41-0.87	.0071*
M1c (liver)	—	—	—	—	18	2.46	1.34-4.52	.0038*
EOD score								
EOD0-3	456	—	—	—	891	Ref	–	–
EOD4	—	—	—	—	102	2.28	1.69-3.08	<.0001*

CI, confidence interval; EOD, extent of disease; Hb, hemoglobin; HR, hazard ratio; PSA, prostate-specific antigen.
*Statistically significant.

were identified to be associated with poor OS in patients with high-burden disease (Table 2).

Next, we developed a risk model using the aforementioned parameters (anemia [Hb ≤12], Gleason grade group V, and T4 in patients with low-burden disease; anemia [Hb ≤12], Gleason grade group V, and EOD4 or liver metastasis in patients with high-burden disease; Figure 1). We combined EOD4 and the presence of liver metastasis into one group (EOD4/liver metastasis) because the frequencies of EOD4 and liver metastasis were low and liver metastasis had an equivalent prognostic impact on OS to EOD4. When the prognostic model was examined in the discovery cohort, OS significantly differed between the groups (Figure 2). The median OS for the poor-risk group was 78 months in patients with low-burden disease; it was not reached for the favorable- and intermediate-risk groups (*P* < .0001;

Figure 2A). Among patients with low-burden disease, the 5-year OS rates were 84.7%, 77.4%, and 56.7% for the favorable-, intermediate-, and poor-risk groups (Figure 2A). Meanwhile, among patients with high-burden disease, the median OS times for the favorable-, intermediate-, and poor-risk groups were 102, 71, and 44 months, respectively (*P* < .0001; Figure 2B). The 5-year OS rates in these groups were 73.1%, 56.7%, and 34.4%, respectively (Figure 2B).

3.2 | Validation of the risk model for overall survival

Subsequently, we validated the predictive performance of our risk model using an independent validation cohort (non–academic hospitals) of 951 patients for whom complete data on risk factors were

FIGURE 1 The metastatic burden-stratified risk model. The categorization into favorable-, intermediate-, and poor-risk groups was performed using the following risk factors: hemoglobin (Hb) level, Gleason grade group, and clinical T-stage for low-burden disease and Hb level, Gleason grade group, and extent of disease (EOD)/liver metastasis for high-burden disease

Risk factor for low burden								
Anemia								
0 (Hb>12), 1 (Hb≤12)	0	1	0	0	1	1	0	1
Gleason grade group								
0 (Group ≤IV), 1 (Group V)	0	0	1	0	1	0	1	1
Clinical T-stage								
0 (T1-3), 1 (T4)	0	0	0	1	0	1	1	1
Risk category for low burden	Favorable	Intermediate			Poor			
Risk factor for high burden								
Anemia								
0 (Hb>12), 1 (Hb≤12)	0	1	0	0	1	1	0	1
Gleason grade group								
0 (Group ≤IV), 1 (Group V)	0	0	1	0	1	0	1	1
EOD/liver metastasis								
0 (EOD0-3), 1 (EOD4/liver metastasis)	0	0	0	1	0	1	1	1
Risk category for high burden	Favorable	Intermediate			Poor			

available. The median follow-up time for men alive at the date of censor was 40.0 months (interquartile range, 23.1-66.3 months). During follow up, 77 (21.3%) and 42 (11.6%) patients experienced cause-specific death and death due to other causes in the low-burden group, while 231 (39.2%) and 52 (8.8%) patients experienced cause-specific death and death due to other causes in the high-burden group, respectively. Multivariable analysis using four parameters (Hb, Gleason grade group, clinical T-stage, and EOD/liver metastasis) confirmed the significant independent association of each factor with OS (Table 3). When the risk model was applied to the validation cohort, OS significantly differed among the risk groups (Figure 2). The median OS times for patients with low-burden disease were 101 and 51 months in the intermediate- and poor-risk groups, respectively, but it was not reached in the favorable-risk group ($P < .0001$, Figure 2C). The 5-year OS rates in the favorable-, intermediate-, and poor-risk groups were 86.0%, 72.0%, and 47.6%, respectively (Figure 2C). Meanwhile, the median OS times for these groups were 94, 52, and 32 months, respectively ($P < .0001$, Figure 2D). The 5-year OS rates among patients with high-burden disease were 66.2%, 44.5%, and 25.1% in the favorable-, intermediate-, and poor-risk groups, respectively (Figure 2D). Among patients with low-burden disease, Harrell's C-index was .66 (95% CI = .60-.71). Among patients with high-burden disease, Harrell's C-index was .63 (95% CI = .59-.66). Similar results were obtained among patients who survived after 2015, when novel ARPI and novel taxane cabazitaxel became available for castration-resistant prostate cancer (CRPC) in Japan (Figure S1).

3.3 | Validation of the risk model for progression-free survival

Subsequently, we validated the predictive performance of our model for PFS. As anticipated, PFS significantly differed among the risk groups (Figure 3). The median PFS times for the favorable-, intermediate-, and poor-risk groups were 97, 45, and 20 months, respectively, among patients with low-burden disease ($P < .0001$, Figure 3A). Meanwhile, the median PFS times for the aforementioned risk groups among patients with high-burden disease were 35, 16, and 11 months, respectively ($P < .0001$, Figure 3B). Among patients with low-burden disease, Harrell's C-index was .65 (95% CI = .62-.67). Among patients with high-burden disease, Harrell's C-index was .60 (95% CI = .58-.62).

3.4 | Comparison with other risk models

Subsequently, we compared predictive values between our model and other risk models, including the J-CAPRA model and models developed by Gravis et al (Gravis model) and Akamatsu et al (Akamatsu model) using the validation cohort.[14-16] As anticipated, OS significantly differed between the groups in all models (Figure 4). Among patients with low-burden disease, Harrell's C-indices were .53 (95% CI = .49-.58), .61 (95% CI = .55-.66), and .57 (95% CI = .52-.62) in the J-CAPRA, Gravis, and Akamatsu models, respectively. Among patients with high-burden disease, Harrell's C-indices were .51 (95%
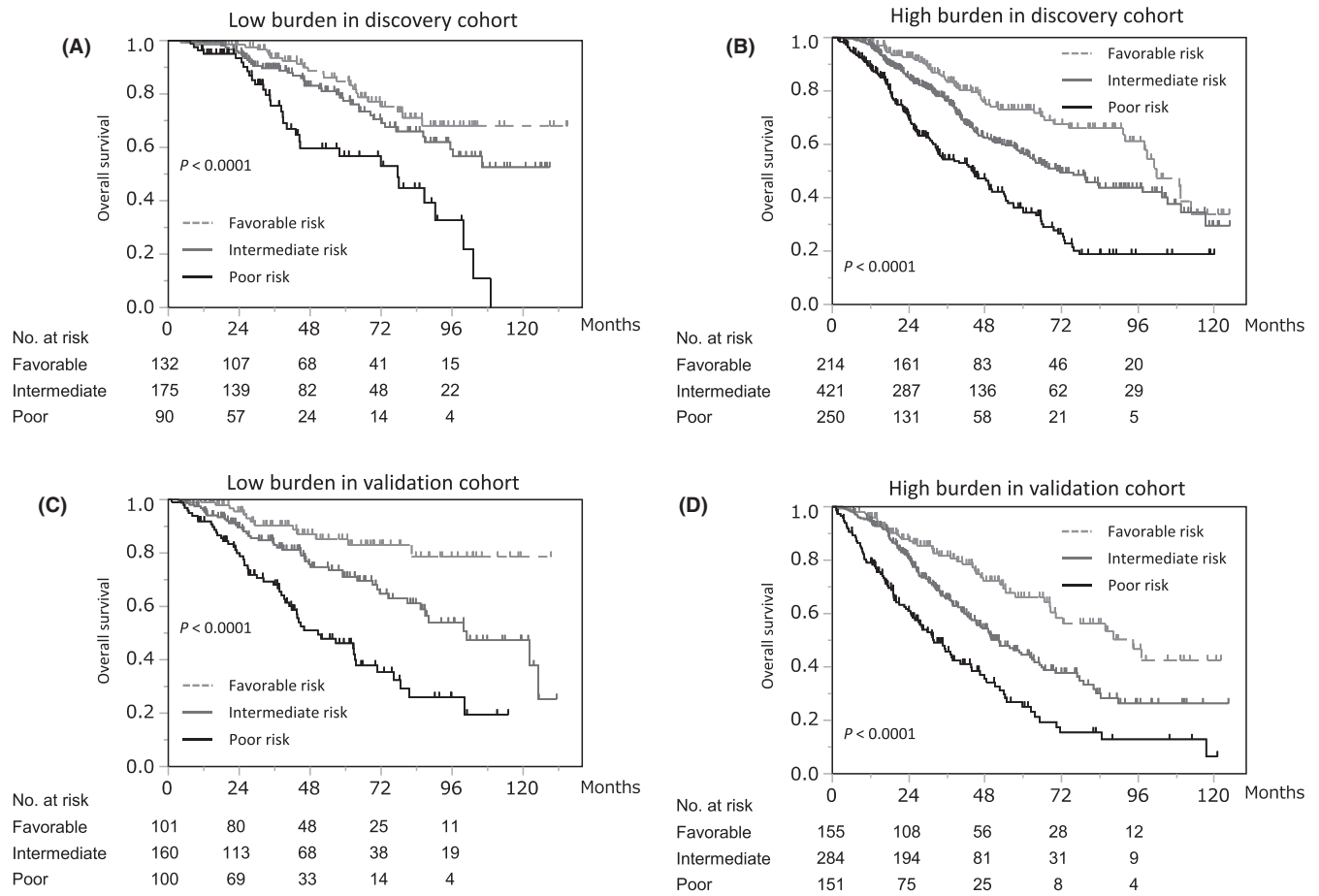
FIGURE 2 Kaplan-Meier analysis of overall survival for patients with low- and high-burden disease in the discovery cohort when stratified using the risk model. A and B, Patients in the discovery cohort with a low (A) or high (B) metastatic burden stratified using the risk model. C and D, Patients in the validation cohort with a low (C) or high (D) metastatic burden stratified using the risk model

TABLE 3 Associations between clinicopathological parameters and overall survival based on multivariate analysis in the validation cohort

	Low burden (n = 361)				High burden (n = 590)			
Variable	n	HR	95% CI	*P*-value	n	HR	95% CI	*P*-value
Hb value at diagnosis								
≤12 g/dL	68	2.10	1.39-3.16	.0004*	176	1.89	1.46-2.44	<.0001*
>12 g/dL	293	Ref	—	—	414	Ref	—	–
Biopsy Gleason grade group								
Group ≤IV	143	Ref	—	—	217	Ref	—	–
Group V	218	2.44	1.55-3.84	.0001*	373	1.87	1.43-2.44	<.0001*
Clinical T-stage								
T1-3	275	Ref	—	—	—	—	—	–
T4	86	2.01	1.36-2.96	.0005*	—	—	—	–
EOD4 or liver metastasis								
Absence	—	—	—	—	524	Ref	—	–
Presence	—	—	—	—	66	1.46	1.03-2.08	.033*

CI, confidence interval; EOD, extent of disease; Hb, hemoglobin; HR, hazard ratio.
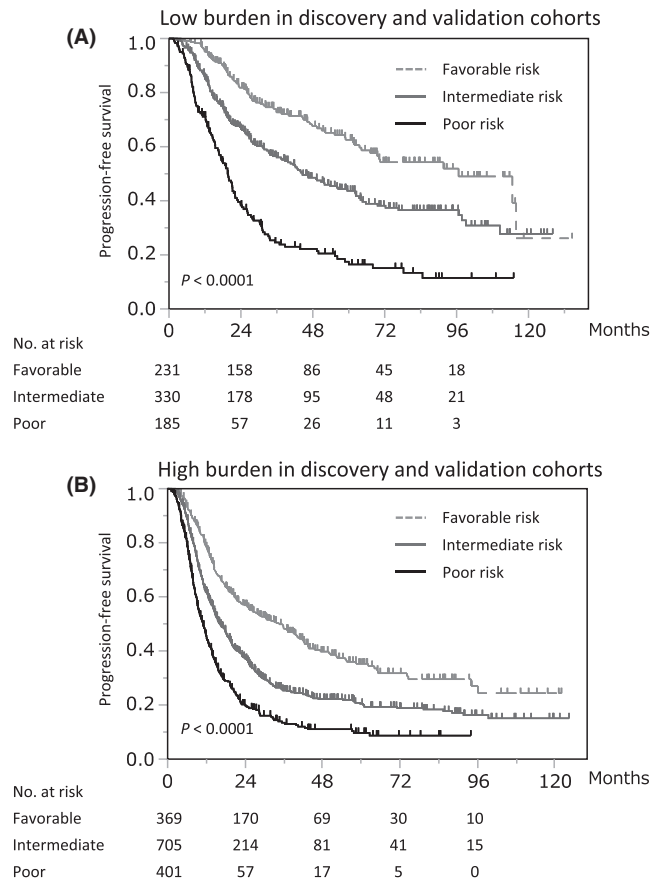
*Statistically significant.

FIGURE 3 Kaplan–Meier analysis of progression-free survival for patients with low- and high-burden disease in the discovery and validation cohorts when stratified the using risk model. A and B, Patients with a low (A) or high (B) metastatic burden stratified using the risk model

CI = .49-.53), .54 (95% CI = .51-.57), and .63 (95% CI = .59-.66) in the J-CAPRA, Gravis, and Akamatsu models, respectively. When the prognostic ability of the models was compared for OS, J-CAPRA was determined to be inferior to our model for both low-burden (P = .000) and high-burden disease (P = .000), the Gravis model was inferior for high-burden disease (P = .000), and the Akamatsu model was inferior for low-burden disease (P = .014).

4 | DISCUSSION

To our knowledge, this is the first study to create a risk model for metastatic prostate cancer prognosis according to the metastatic burden. We identified that Hb levels and the Gleason grade group were independent prognostic factors for OS for both low- and high-burden disease. In addition, the clinical T-stage was prognostic for OS in patients with low-burden disease but not for those with high-burden disease, whereas the EOD score and liver metastasis were prognostic for OS in patients with high-burden disease. Consistently, these parameters have been repeatedly reported to be prognostic for OS in metastatic HSPC.[13-16]

Accordingly, distinct risk models incorporate T4 and EOD4/liver metastasis in addition to anemia (Hb ≤12) and Gleason grade group V as common parameters for both low- and high-burden metastatic prostate cancer. Thus far, several categorical risk models for OS in metastatic HSPC have been created for patients treated with ADT alone or combined with docetaxel.[15,16] In addition, the J-CAPRA score was created for both non–metastatic and metastatic HSPC.[14] In these risk models, various prognostic parameters, including serum markers (PSA, Hb, lactate dehydrogenase [LDH], and alkaline phosphatase [ALP]), pathological characteristics (Gleason score), and disease extensions (TNM stage, EOD score, and metastatic sites) were used as factors predicting OS. The risk model created in this study used one parameter from each characteristic (serum marker, pathological characteristic, and disease extensions) to predict patient prognosis. Although previous models were validated using distinct cohorts, Harrell's C-index was less than .65 in metastatic HSPC.[15,16] In addition, the J-CAPRA score was repeatedly validated in several cohorts, as indicated by a high C-index.[14,23,24] However, because the J-CAPRA model was developed for HSPC, including non–metastatic disease, the fitness of the model when applied to metastatic HSPC may be limited. Similarly, because Gravis and Akamatsu models were developed regardless of metastatic burden, these models showed modest ability for high- and low-burden disease, respectively. Instead, the risk model for low- and high-burden disease developed in this study was validated, exhibiting a superior C-index, indicating better ability to predict OS. In the Gravis and Akamatsu models, serum markers including ALP and LDH were used as parameters for risk estimation.[15,16] However, we did not use these markers to achieve universality because their levels differ according to the laboratory test method. This inter-test variation leads to difficulty in applying these markers to other cohorts, which may account for excellent discrimination of the survival curve using the Akamatsu model but limited discrimination of the survival curve using the Gravis model.[25,26] Meanwhile, we did not use pain as a parameter because the objective evaluation of pain in clinical settings is a difficult and uncommon procedure. Therefore, this categorical risk model is relatively simple and robust to use in clinical settings, in which all parameters are usually available, the number of parameters is relatively small, and physicians can calculate the score without instrumentation.

In recent years, the therapeutic strategy has been determined based on risk classification using the CHAARTED criteria (low and high volume), which is similar to the categorization of patients into low- and high-burden metastatic disease groups in this study; most categorizations overlapped between the criteria. Risk stratification according to the metastatic burden has been used to determine the optimal therapeutic strategy for patients with metastatic prostate cancer. ARPI, including CYP17 inhibitors and novel antiandrogens, have been revealed to improve the survival of patients with HSPC regardless of the metastatic burden, and they are currently in clinical use. By contrast, upfront docetaxel chemotherapy and local radiotherapy are considered more suitable for patients with high- and low-volume metastatic disease, respectively.[11,12] Notably, prognosis
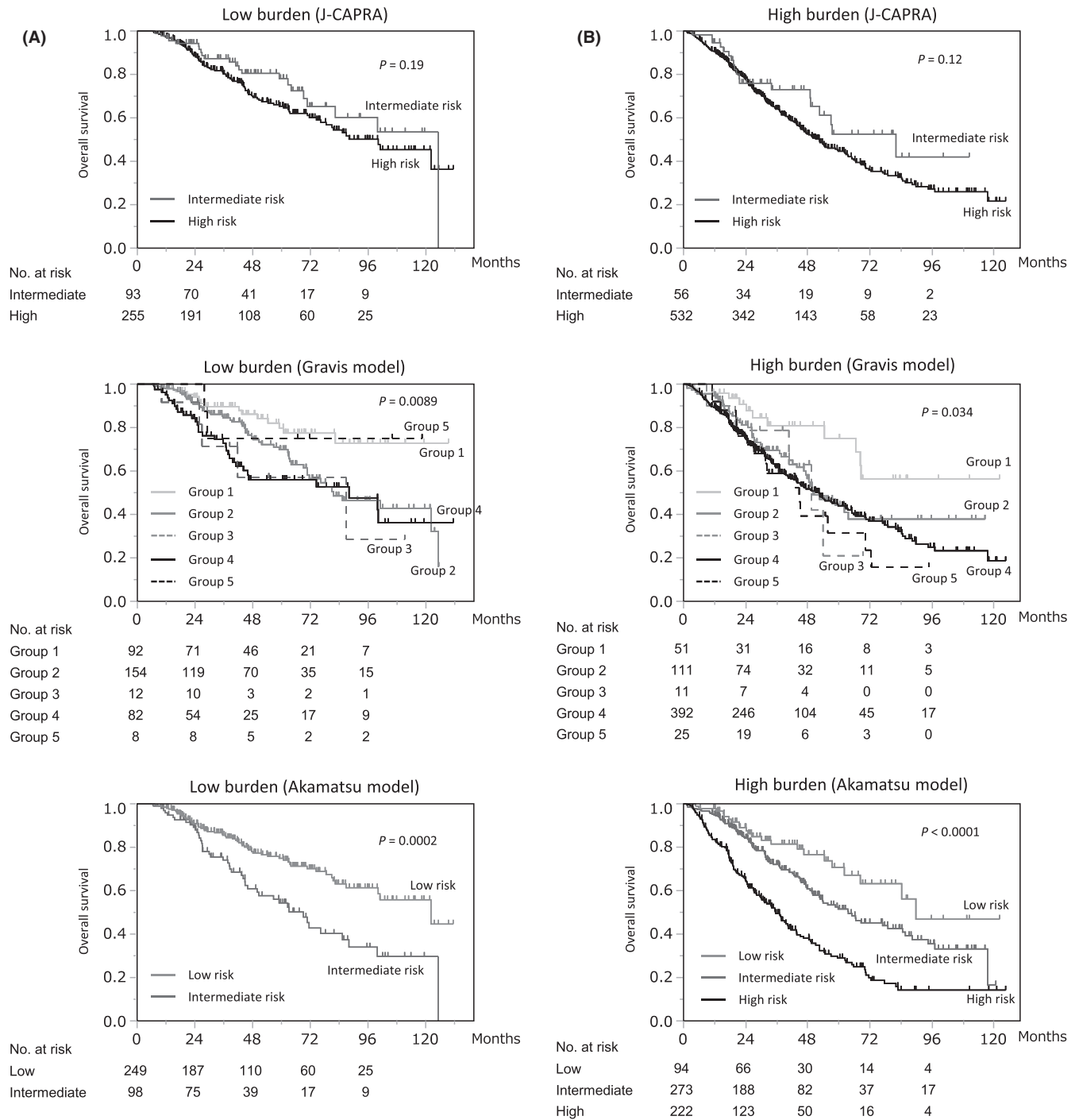
FIGURE 4 Kaplan–Meier analysis of overall survival for patients with low- and high-burden disease in the validation cohort when stratified using the J-CAPRA, Gravis, and Akamatsu models. A, Patients with a low metastatic burden stratified using the J-CAPRA (upper panel), Gravis (middle panel), and Akamatsu models (lower panel). B, Patients with a high metastatic burden stratified using the J-CAPRA (upper panel), Gravis (middle panel), and Akamatsu models (lower panel)

as stratified by metastatic burden can be estimated using the developed risk model. Intriguingly, the prognosis among patients with poor-risk, low-burden disease was comparable with that among patients with intermediate-risk, high-burden disease but worse than that among patients with favorable-risk, high-burden disease. Accordingly, patients with poor-risk, low-burden disease may require intensive therapies such as radiotherapy to the prostate and ARPI to

improve outcomes, and this combination is under investigation in the PEACE-I trial. Similarly, patients with poor-risk, high-burden disease may require more intensive therapies such as docetaxel in combination with ARPI to improve outcomes, and this regimen is under investigation in the PEACE-I and ARASENS trials. Meanwhile, de-escalated therapies may be appropriate for elderly or frail patients with favorable-risk, low-burden disease.

The present study had several limitations. First, the study design was retrospective, resulting in insufficient data, such as lack of comorbidity information, and loss to follow up. Second, the study cohort consisted mostly of Japanese patients, which may limit the applicability of the findings to other ethnicities. Third, several of our patients died before abiraterone acetate, enzalutamide, radium-233, and cabazitaxel became available, although all patients had access to docetaxel-based regimens. Currently, novel ARPI and taxanes are sequentially used for CRPC after ADT, as proposed by Chi et al[27] Most patients included in this study survived up to the time when novel treatments for CRPC became available, and consistent results were obtained, suggesting an invariable utility of this model. In addition, information on treatment response and subsequent treatments after first-line treatment were lacking. However, the model without a post–treatment parameter can be applied for treatment with other upfront intensive therapies. Furthermore, tissue specimens were not evaluated by central pathology. Finally, most metastases were diagnosed only using imaging modalities without biopsy, and the accuracy of diagnosis is dependent on the diagnostic ability of imaging. Therefore, validation studies in other cohorts, including other ethnic backgrounds, are required to confirm the utility of this metastatic burden-stratified risk model.

This study developed a novel metastatic burden-stratified risk model. This model has several potential clinical implications, such as providing more accurate prognoses for patients with metastatic HSPC and permitting refinement of therapeutic strategies according to the precise prognostic estimation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.