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Serum Prognostic Factors of Androgen-deprivation Therapy Among Japanese Men With *De Novo* Metastatic Prostate Cancer

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Abstract. *Background/Aim: To date, several serum prognostic factors have been reported in metastatic prostate cancer. In this study, we examined the prognostic value of these serum markers in Japanese men. Patients and Methods: This study included 104 patients with metastatic prostate cancer who were treated with primary androgen-deprivation therapy from 2001 to 2013. Clinicopathological factors including several serum markers were investigated for association with progression-free (PFS) and overall (OS) survival. Results: During a median follow-up of 48.1 months, median PFS and OS were 24.0 months and 67.4 months, respectively. When adjusted by age, prostate-specific antigen at diagnosis, Gleason score, and clinical stage, serum lactate dehydrogenase value was significantly associated with PFS [hazard ratio (HR)=1.42, 95% confidence interval (CI)=1.15-1.74; p=0.0004] and OS (HR=1.46, 95% CI=1.13-1.82; p=0.0014), in addition to alkaline phosphatase value for OS (HR=1.04; 95% CI=1.00-1.07; p=0.015). Conclusion: This study demonstrates the prognostic significance of alkaline phosphatase and lactate dehydrogenase values in Japanese men with de novo metastatic hormone-sensitive prostate cancer.*

Androgen-deprivation therapy (ADT) has been the standard treatment for recurrent or advanced prostate cancer since 1941 (1). In 2015, docetaxel chemotherapy with ADT for metastatic hormone-sensitive prostate cancer (HSPC) was shown to prolong both time to progression and overall survival (OS) in the CHAARTED and STAMPEDE trials (2, 3). In addition, survival benefit from the cytochrome *P450* family 17 subfamily inhibitor abiraterone with ADT for metastatic HSPC was also demonstrated in the LATITUDE and STAMPEDE trials in 2017 (4, 5). Accordingly, up-front docetaxel chemotherapy and abiraterone with ADT have become standard therapies for metastatic HSPC (6).

To date, several prognostic factors in ADT have been reported. In addition to utilization of single parameters, the Glass model, which incorporates metastatic site, performance status, Gleason score and prostate-specific antigen (PSA) level, was classically proposed as a prognostic model using these multiple prognostic factors in combination. Later, the J-CAPRA score, which includes clinical TNM stage, Gleason score and PSA level, was developed to more accurately predict prognosis (7). In addition to these clinicopathological prognostic characteristics, several serum parameters were reported to be prognostic in various cancer types. Among them, hemoglobin (Hb), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) are well known (8). In addition, inflammatory parameters of serum, such as the neutrophil–lymphocyte ratio (NLR) and C-reactive protein (CRP) as well as sodium were recently suggested to be prognostic (9-11). In this study, we aimed to examine the significance of these serum parameters in Japanese men with *de novo* metastatic prostate cancer treated with ADT.

Patients and Methods

Patients. This study retrospectively enrolled 104 Japanese men who were treated with primary ADT for *de novo* metastatic prostate cancer at Kyushu University Hospital, Fukuoka, Japan, from 2001 to 2013, for whom any serum parameters were available. We excluded: (i) patients of any ethnicity other than Japanese; (ii) patients who had received local treatment before primary ADT; and (iii) patients who received other treatments (such as chemotherapy) before disease progression. This study was approved by the Institutional Review Board of Kyushu University Hospital (29-438). All patients were histopathologically diagnosed with adenocarcinoma of the prostate, including 93 men (89.4%) who were biopsied at Kyushu University Hospital and 11 men (10.6%) who were biopsied at another institution (three biopsy specimens of which were reviewed at our Institution). Clinical staging was determined using the unified TNM criteria based on results of digital rectal examinations, transrectal ultrasound, magnetic resonance imaging, computed tomography, and bone scans (12).

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Key Words: Androgen-deprivation therapy, ALP, LDH, metastatic prostate cancer.

Table I. *Patient characteristics*.

Characteristic		n=104
Age, years	Median (IQR)	72 (68-77)
PSA at diagnosis, ng/ml	Median (IQR)	209.5 (73.8-524.3)
Gleason score, n (%)	≤7	16 (15.4%)
	8-10	88 (84.6%)
cT stage, n (%)	T2/3a	40 (38.5%)
	T3b	29 (27.9%)
	T4	35 (33.7%)
cN stage, n (%)	N0	39 (37.5%)
	N1	65 (62.5%)
cM stage, n (%)	M1a	8 (7.7%)
	M1b	92 (88.5%)
	M1c	4 (3.8%)
Hb at diagnosis, ng/ml	Median (IQR)	13.6 (12.7-14.4)
NLR at diagnosis	Median (IQR)	2.5 (1.8-3.5)
	NA, n	5
ALP at diagnosis, U/l	Median (IQR)	304 (217-546)
LDH at diagnosis, U/l	Median (IQR)	202 (181-247)
	NA, n	10
Na at diagnosis, mmol/l	Median (IQR)	140 (139-142)
	NA, n	14
CRP at diagnosis, mg/dl	Median (IQR)	0.16 (0.06-0.66)
	NA, n	4

PSA: Prostate-specific antigen; Hb: hemoglobin; NLR: neutrophil–lymphocyte ratio; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; Na: sodium; CRP: C-reactive protein.

Treatment and outcome. All patients were primarily treated with ADT with surgical castration, or medical castration using a luteinizing hormone-releasing hormone agonist/antagonist (goserelin acetate, leuprorelin acetate, or degarelix acetate) with/without an anti-androgen agent (bicalutamide or flutamide); 98 men were primarily treated with combined androgen blockade, and six men were treated with castration alone. Progression was judged by a PSA increase of >2 ng/ml and a 25% increase over the nadir, or radiographic progression defined as the appearance of two new lesions or progression of one or more known lesions, as classified by the Response Evaluation Criteria in Solid Tumours (RECIST) (13).

Statistical analysis. All statistical analyses were performed using JMP13 software (SAS Institute, Cary, NC, USA). Continuous and categorical data were analyzed by Wilcoxon rank-sum and Pearson's chi-square tests, respectively. Survival analyses were conducted using the Kaplan–Meier method and log-rank test. The Cox proportional hazards model was used to estimate hazard ratios (HRs). All *p*-values were two-sided; values of $p<0.05$ were considered significant.

Results

During a median follow-up of 48.1 months (interquartile range=25.0-68.4 months), 72 men (69.2%) experienced progression to castration-resistant prostate cancer (CRPC) and 48 men (46.2%) died from any cause. Median PFS and OS were 24.0 months (interquartile range=11.3-74.1 months) and 67.4 months (interquartile range=43.3 months–not reached), respectively. Most patients presented with high PSA levels, high Gleason score, and advanced TNM stage at initial diagnosis (Table I). Hb, NLR, ALP, LDH, sodium, and CRP values were within a normal range for most patients (Table I).

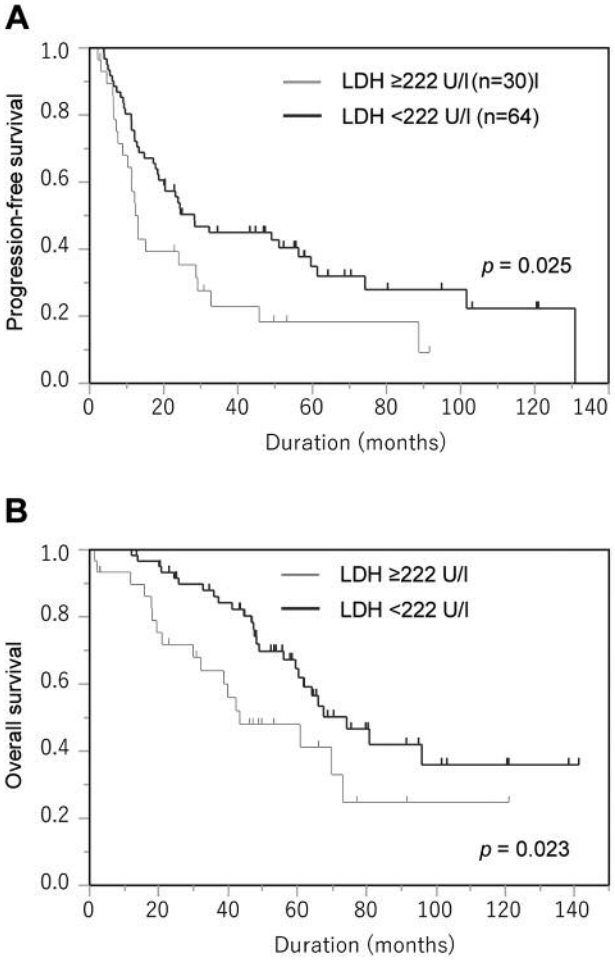

Figure 1. *Prognosis according to serum lactate dehydrogenase (LDH) value among men with metastatic prostate cancer. Progression-free survival (A) and overall survival (B) according to serum LDH value using the upper limit of normal as a cut-off.*

Next, the prognostic significance of clinicopathological factors including serum parameters for PFS were evaluated. As shown previously, Gleason score, clinical T-stage, and clinical N-stage were identified to be prognostic, although the PSA level at diagnosis and clinical M-stage were not prognostic in this cohort (Table II). Among serum parameters, only a high LDH level was identified as being associated with an increased risk of progression to CRPC on univariate analysis (HR=1.45, 95% confidence interval

Table II. *Univariate and multivariate analyses for progression-free survival.*

Variable		Univariate		Multivariate	
		HR (95%CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	Per unit	1.03 (0.99-1.07)	0.11		
PSA at diagnosis	Per 100 units	1.01 (0.99-1.02)	0.50		
Gleason score	≤7	Ref			
	8-10	2.04 (1.03-4.65)	**0.039**		
cT stage	T2/3a	Ref			
	T3b	1.39 (0.75-2.58)	0.30		
	T4	2.85 (1.62-5.12)	**0.0003**		
cN stage	N0	Ref			
	N1	1.64 (1.00-2.76)	**0.048**		
cM stage	M1a	Ref			
	M1b	1.53 (0.68-4.38)	0.33		
	M1c	0.60 (0.031-3.74)	0.63		
Hb at diagnosis	Per unit	0.94 (0.80-1.11)	0.45	0.93 (0.75-1.16)	0.54
NLR at diagnosis	Per unit	0.96 (0.81-1.12)	0.64	0.96 (0.80-1.14)	0.68
ALP at diagnosis	Per 100 units	1.01 (0.98-1.03)	0.49	1.02 (0.99-1.04)	0.16
LDH at diagnosis	Per 100 units	1.45 (1.18-1.75)	**0.0009**	1.42 (1.15-1.74)	**0.0004**
Na at diagnosis	Per unit	0.94 (0.84-1.05)	0.30	0.97 (0.86-1.09)	0.63
CRP at diagnosis	Per unit	1.05 (0.91-1.16)	0.45	1.10 (0.94-1.24)	0.18

PSA: Prostate-specific antigen; Hb: hemoglobin; NLR: neutrophil-lymphocyte ratio; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; Na: sodium; CRP: c-reactive protein. Significant *p*-values are shown in bold.

(CI)=1.18-1.75; p=0.0009), which was confirmed on multivariate analysis adjusted by age, PSA at diagnosis, Gleason score, and clinical stage (HR=1.42, 95%CI=1.15-1.74; p=0.0004) (Figure 1A, Table II).

Similar results were obtained for OS. As previously reported, age, Gleason score, and clinical T-stage were identified to be prognostic, although the PSA level at diagnosis, clinical N-stage and clinical M-stage were not prognostic in this cohort (Table III). Among serum parameters, low Hb (HR=0.78, 95%CI=0.64-0.96; p=0.020), high LDH (HR=1.32, 95%CI=1.03-1.62; p=0.028) and low Na (HR=0.86, 95%CI=0.75-0.99; p=0.029) values were identified as associated with increased death risk by any cause on univariate analysis. However, when adjusted by age, PSA at diagnosis, Gleason score, clinical stage, ALP value [HR=1.04, 95%CI=1.00-1.07; p=0.015] and LDH value [HR=1.46, 95%CI=1.13-1.82; p=0.0014] were identified to be prognostic for OS (Figure 1B, Table III).

Discussion

This study showed that the ALP level was a prognostic factor for OS, but not for PFS. Moreover, the LDH level was identified as a robust and prominent prognostic factor for both PFS and OS. However, Hb, NLR, sodium, and CRP values failed to be associated with prognosis.

Recently, Gravis *et al*. showed that the serum ALP value is the most prominent prognostic factor for OS among men treated with ADT with or without docetaxel in the GETUG-AFU15 trial, which mainly enrolled Caucasian patients (8). Similarly, in Asian populations including Japanese, Chinese and Korean individuals, it was reported that a high ALP level was associated with worse prognosis in metastatic HSPC (14-16). The ALP value is associated with the extent of disease in bone metastasis, which is also a well-known prognostic factor for OS (16-18). The ALP value, however, was not prognostic for PFS. Intriguingly, ALP was shown to be a prognostic factor in patients with CRPC when treated with docetaxel and androgen receptor axis-targeting agents such as abiraterone and enzalutamide (19, 20). Therefore, differential prognostic significance for PFS and OS may be explained by the prognostic value of ALP in CRPC.

The LDH value has also been reported to be prognostic for OS in HSPC. Gravis *et al*. demonstrated that the LDH value in addition to the ALP value is a prognostic factor for OS among men treated with ADT in the GETUG-AFU15 trial (8). Similarly, in an Asian population of Japanese, Chinese and Korean individuals, it was reported that a high LDH level was associated with worse prognosis in metastatic HSPC (15, 16, 21). A high LDH value seems to originate from cancer cells in most patients, reflecting the total cancer volume, although the ALP level mirrors only bony lesions of prostate cancer. Therefore, LDH may reflect the whole-body cancer status more accurately than ALP, resulting in more precise prognostic ability.

Table III. *Univariate and multivariate analyses for overall survival.*

Variable		Univariate		Multivariate	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age	Per unit	1.07 (1.02-1.12)	**0.0045**		
PSA at diagnosis	Per 100 units	1.01 (0.99-1.03)	0.33		
Gleason score	≤7	ref			
	8-10	3.62 (1.32-14.99)	**0.0095**		
cT stage	T2/3a	ref			
	T3b	1.33 (0.62-2.86)	0.46		
	T4	2.42 (1.22-4.98)	**0.011**		
cN stage	N0	ref			
	N1	1.13 (0.63-2.11)	0.69		
cM stage	M1a	ref			
	M1b	1.04 (0.42-3.46)	0.94		
	M1c	1.25 (0.064-8.61)	0.84		
Hb at diagnosis	Per unit	0.78 (0.64-0.96)	**0.020**	0.80 (0.60-1.06)	0.11
NLR at diagnosis	Per unit	0.85 (0.67-1.03)	0.098	0.85 (0.67-1.09)	0.20
ALP at diagnosis	Per 100 units	1.02 (0.99-1.05)	0.17	1.04 (1.00-1.07)	**0.015**
LDH at diagnosis	Per 100 units	1.32 (1.03-1.62)	**0.028**	1.46 (1.13-1.82)	**0.0014**
Na at diagnosis	Per unit	0.86 (0.75-0.99)	**0.029**	0.89 (0.77-1.03)	0.12
CRP at diagnosis	Per unit	1.05 (0.89-1.19)	0.49	1.17 (0.96-1.35)	0.070

PSA: Prostate-specific antigen; Hb: hemoglobin; NLR: neutrophil–lymphocyte ratio; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; Na: sodium; CRP: c-reactive protein. Significant *p*-values are shown in bold.

The present study had several limitations. The sample size was relatively small, and the study design was retrospective. In addition, a small number of cases lacked information regarding several serum markers. The accrual period was long, and included the era before novel agents for CRPC (abiraterone acetate, enzalutamide, radium-223, docetaxel and cabazitaxel) were introduced. However, an advantage was that this study included only Japanese men with *de novo* metastasis, which highlighted the similarity among cases.

Conclusion

This study demonstrated the prognostic significance of ALP, as well as LDH Levels among Japanese men with *de novo* metastatic HSPC, confirming the universal significance of these serum parameters. However, this study failed to show the significance of other serum parameters among Japanese men, suggesting ALP and LDH values are more robust than other serum parameters.

Conflicts of Interest

The Authors declare that there are no financial disclosures or conflict of interest regarding this article.

Authors' Contributions

MS designed the study, and wrote the draft of the article. TK analyzed the data. All other Authors contributed to data collection and interpretation, and critically reviewed the article. EM supervised the study.

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