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ORIGINAL ARTICLE

Impact of nutritional status on the prognosis of patients with metastatic hormone-naïve prostate cancer: a multicenter retrospective cohort study in Japan

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Abstract

Purpose To investigate the association between the Geriatric Nutritional Risk Index (GNRI) and prognosis of patients with metastatic hormone-naïve prostate cancer (mHNPC) and to design the optimal risk score predicting for prognosis.

Methods We retrospectively reviewed data from the Michinoku Japan Urological Cancer Study Group database, containing information about 656 patients with mHNPC who initially received androgen-deprivation therapy between 2005 and 2017. The baseline GNRI was calculated using serum albumin level and body mass index. Poor nutrition was defined as GNRI < 92.0. The impact of GNRI, CHAARTED criteria, and laboratory parameters on oncological outcomes was investigated using the multivariable Cox regression models. We developed the risk comprising GNRI and laboratory parameters and compared its prognostic performance with the CHAARTED criteria using the receiver operating characteristic curve with the DeLong method.

Results Of 339 patients with sufficient data, 66 (19%) were diagnosed with poor nutrition. Multivariate analyses showed that GNRI < 92.0 was an independent prognostic factor of cancer-specific survival [hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.04–2.98, $P = 0.035$] and overall survival (HR 1.80; 95% CI 1.13–2.89, $P = 0.013$), in addition to hemoglobin (Hb) and lactic dehydrogenase (LDH) levels. We designed the risk score comprising GNRI < 92.0, Hb < 13.0 g/dL, and LDH > 222 IU/L. The predictive value of the risk score was significantly superior to that of the CHAARTED criteria.

Conclusions Poor nutrition may predict mortality in patients with mHNPC. Risk factors, such as nutritional status and laboratory parameters, may be useful in decision-making regarding aggressive treatments for patients with mHNPC.

Keywords Metastatic hormone-naïve prostate cancer · Malnutrition · Geriatric Nutritional Risk Index · CHAARTED · Survival

Introduction

Prostate cancer (PC) is one of the common malignancies worldwide, and it is the second most frequent cause of cancer-related death among men in western countries [1]. In Japan, approximately 10% of patients who were diagnosed with PC have distant metastases [2]. Most patients with metastatic hormone-naïve prostate cancer (mHNPC) eventually develop castration-resistant prostate cancer (CRPC), which has a high mortality rate, regardless of the high response rate for initial androgen-deprivation therapy (ADT) [3, 4]. Several risk criteria, such as the (CHAARTED (upfront docetaxel plus ADT)) and LATITUDE (abiraterone acetate plus low-dose prednisone) criteria, were designed mainly for aggressive therapies based on metastatic status (extent of bone and visceral metastases) [5, 6]. Baseline laboratory parameters, such as hemoglobin (Hb) and lactate dehydrogenase (LDH) levels, at diagnosis, are also

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important predictive factors among patients with mHNPC [7, 8], and these factors were not taken into consideration in terms of risk stratification and decision-making for optimal treatments.

Nutritional status was significantly associated with the clinical outcomes of patients with malignant tumors [9]. The Geriatric Nutritional Risk Index (GNRI), which consists of serum albumin level and body mass index (BMI), is an objective and simple nutritional assessment tool [10]. Several studies have shown that the GNRI was a prognostic factor of some malignancies [9, 11]. However, the association between nutritional status at diagnosis and prognosis among patients with mHNPC has not yet been fully understood. We hypothesized that baseline GNRI could predict the prognosis of patients with mHNPC. This study, therefore, aimed to develop the optimal risk score comprising Hb level, LDH level, and GNRI and to investigate the impact of the risk model on the oncological outcomes of patients with mHNPC.

Materials and methods

Study population and patient selection

The present retrospective, multicenter study was performed in accordance with the ethical standards of the Declaration of Helsinki, and it was approved by the ethics review board of Hirosaki University School of Medicine (authorization number: 2017-089). Pursuant to the provisions of the ethics committee and the ethics guidelines in Japan, a written informed consent was not required for the public disclosure of study information in the case of retrospective and/or observational study using materials, such as the existing documents.

We retrospectively evaluated patients with mHNPC who were registered in the Michinoku Japan Urological Cancer Study Group database, which contains information about 656 consecutive patients with newly diagnosed mHNPC who were initially treated with ADT between 2005 and 2017 at Hirosaki University Hospital, Akita University Hospital, Tohoku University Hospital, Yamagata University Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Iwate Prefectural Isawa Hospital, Aomori Prefectural Central Hospital, and Sendai City Hospital. Patients with mHNPC were defined as those having distant lymph node metastases (other than regional lymph node metastases), bone metastases, and/or visceral metastases at diagnosis. Tumor stage and grade were assigned on the basis of the 2009 TNM classification of the Union of International Cancer Control [12]. We excluded 317 of the 656 participants who had insufficient baseline information, such as BMI ($n=190$), Gleason score (GS) ($n=21$), serum albumin level ($n=67$), LDH level ($n=4$), alkaline phosphatase (ALP) level ($n=3$), the use of bone-modifying agents ($n=1$), and the CHAARTED risk criteria ($n=1$), and those who were lost to follow-up ($n=30$). Finally, we included 339 patients who had sufficient data.

Evaluation of variables

The following variables were analysed at diagnosis: age; year of diagnosis; Eastern Cooperative Oncology Group performance status (ECOG-PS); BMI; and serum albumin, Hb, LDH, ALP, and prostate-specific antigen (PSA) levels. Anemia was defined as an Hb level < 13.0 g/dL according to the definition of the World Health Organization [13]. The cutoff values for LDH and ALP levels were set at 222 and 322 IU/L, respectively, according to the standard common reference of clinical laboratory tests in Japan [14].

Assessment of metastatic status

We evaluated metastatic status via chest and body computed tomography scan and bone scintigraphy before initiating ADT. Grades were divided into five based on the extent of disease (EOD) on bone scintigraphy [15]. We defined high-volume disease (HVD) as the presence of visceral metastases and/or four more bone metastases with at least one outside of the vertebral column and pelvis according to the risk criteria of CHAARTED in PC [5].

Nutritional assessment using the GNRI

The following equation was used to calculate the GNRI: GNRI= 14.89 × serum albumin (g/dL) + 41.7 × (body weight/ideal body weight). Ideal body weight was identified using height and BMI (22.0 kg/m^2) [10]. Body weight/ideal body weight was set at 1 when the patient's body weight exceeded the ideal body weight, according to a previous study [10]. We defined poor nutrition as a GNRI < 92.0 based on previous studies [9–11]. The patients were divided into two groups: poor nutrition group (a GNRI < 92.0) and normal nutrition group (a GNRI ≥ 92.0).

Treatment protocol

All the patients were initially treated with ADT (medical or surgical castration with or without anti-androgen receptor antagonists). Some of the patients received bone-modifying agents, such as bisphosphonate or denosumab, for bone pain or prophylactic use against skeletal-related events. Attending physicians decided the use of bone-modifying agents according to the volume of bone metastasis. The definition of CRPC was according to the recommendations of the Cancer Clinical Trials Working Group 2 [16]. After the

diagnosis of CRPC, almost all the patients received subsequent treatments, such as alternative anti-androgen therapy, anti-androgen withdrawal therapy, estramustine, and/or low-dose oral steroid therapy. Some patients underwent chemotherapy (docetaxel and/or cabazitaxel) and/or a new type of anti-androgen receptor antagonist therapy (abiraterone acetate and/or enzalutamide) based on the preference of the attending physicians.

Outcome evaluation

We retrospectively compared the laboratory data and oncological status, including GS, PSA level, and metastatic status, of the poor and normal nutrition groups. The CRPC-free survival and overall survival (OS) were investigated using the Kaplan–Meier method and were compared with log-rank test. Multivariate Cox regression analyses were performed to identify the independent predictors of CRPC-free survival, cancer-specific survival (CSS), and OS.

Statistical analysis

Statistical analyses were conducted using EzR (R commander version 1.6-3), which is a free software available at websites [17], and GraphPad Prism 5.03 (GraphPadSoftware, San Diego, CA, USA). Categorical, normally distributed continuous variables and non-normally distributed variables were expressed as percentages, means with standard deviations, and medians (interquartile ranges [IQRs]), respectively. The high- and low-risk malnutrition groups were compared using the Chi-square test, Student's *t* test (when data were normally distributed), or Mann–Whitney *U* test (when data were not normally distributed). We calculated the hazard ratio (HR) with 95% confidence intervals (CIs) for each factor after adjusting for potential confounders, such as age, year of diagnosis, ECOG-PS, and PSA level. *P* values < 0.05 were considered statistically significant. The prognostic performance of the risk criteria was compared using the area under the curve (AUC) and receiver operating characteristic curve using the DeLong test [18].

Results

Baseline characteristics of the participants

Table 1 shows the characteristics of the study participants. The median age of the participants was 72 years (IQR 65–78), and the GNRI was 101.3 (93.2–105.7). Over a median follow-up period of 26 (12–53) months, 109 patients died and 190 developed CRPC. The number of patients treated with combined androgen blockage, those with gonadotropin-releasing hormone agonist or antagonist monotherapy, and those with surgical castration was 267 (79%), 37 (11%), and 35 (10%), respectively. Of the 339 patients, 66 (19%) were diagnosed with poor nutrition (a GNRI < 92.0) at diagnosis. Significant between-group differences were observed in terms of age ($P < 0.001$); ECOG-PS ($P = 0.043$); Hb ($P < 0.001$), LDH ($P = 0.003$), ALP ($P = 0.001$), and PSA ($P = 0.041$) levels; and the use of the new type of anti-androgen receptor antagonists ($P = 0.025$). The number of patients with an EOD>1 and CHAARTED-HVD was significantly higher in the poor nutrition group than in the normal nutrition group ($P = 0.026$ and $P = 0.043$, respectively). In contrast, no significant difference was observed in terms of M stage ($P = 0.467$).

Oncological outcomes

The median follow-up periods of the poor and normal nutrition groups were 14 and 31 months, respectively ($P < 0.001$). The patients in the poor nutrition group had a significantly poorer prognosis in terms of CRPC-free survival and OS than those in the normal nutrition group (Fig. 1a, b). The median months of CRPC-free survival and OS of the poor and normal nutrition groups were 15 vs. 21 months ($P = 0.021$) and 36 vs. 82 months ($P < 0.001$), respectively. The patients with CHAARTED-HVD had a significantly poorer prognosis in terms of CRPC-free survival ($P < 0.001$) and OS ($P = 0.048$) than those with CHAARTED-low volume disease (Fig. 1c, d). Similar trends in CRPC-free survival ($P < 0.001$) and OS ($P < 0.001$) were observed when patients were classified according to Hb level (Fig. 1e, f) and LDH level (Fig. 1g, h).

Independent factors associated with oncological outcomes

Table 2 depicts the results of the multivariate Cox proportional hazards regression analyses of oncological outcomes after adjusting for age, year of diagnosis, ECOG-PS, and PSA level. A GNRI < 92.0 was not considered as an independent predictor of CRPC-free survival. In contrast, a GNRI < 92.0 was a significant predictor of CSS (HR 1.76; 95% CI 1.04–2.98; $P = 0.035$) and OS (HR 1.80; 95% CI 1.13–2.87; $P = 0.013$). An Hb level < 13.0 g/dL and LDH level > 222 IU/L were independent predictors of CRPC-free survival, CSS, and OS. However, CHAARTED-HVD was not an independent predictor of clinical outcomes. Based on these results, we developed the risk score, including a GNRI < 92.0, Hb level < 13.0 g/dL, and LDH level > 222 IU/L. Patients were classified according to the number of risk factors into score 0 (0 factor), score 1 (1 factor), and score ≥ 2 (2 or 3 factors) groups.

Table 1 Clinical characteristics of the study participants

	Normal nutrition (GNRI ≥ 92.0)	Poor nutrition (GNRI < 92.0)	*P* value
Total number of patients	273 (81%)	66 (19%)	–
Year of diagnosis			0.568
2005–2010	98 (36%)	21(32%)	
2011–2017	175 (64%)	45 (68%)	
Age at diagnosis (years) (median, IQR)	70 (64–77)	77 (72–82)	< 0.001
BMI (median, IQR)	23.3 (21.2–25.4)	19.6 (18.0–21.2)	< 0.001
Initial PSA (ng/mL) (median, IQR)	308.8 (77.9–865.3)	381.0 (154.9–1644.5)	0.041
ECOG performance status	0 (0–1)	1 (0–1)	0.043
Laboratory data at diagnosis (median, IQR)			
Hb (g/dL)	13.8 (12.5–14.8)	11.1 (10.2–12.3)	< 0.001
LDH (IU/L)	207 (179–254)	239 (194–313)	< 0.001
ALP (IU/L)	333 (250–592)	613 (288–1246)	< 0.001
Serum albumin (g/dL)	4.2 (4.0–4.4)	3.3 (2.9–3.5)	< 0.001
Hb < 13.0 g/dL (%)	93 (34%)	56 (85%)	< 0.001
LDH > 222 IU/L (%)	103 (38%)	39 (59%)	0.002
ALP > 322 IU/L (%)	142 (52%)	47 (71%)	0.006
Gleason score ≥ 8 (%)	247 (91%)	60 (91%)	1.000
Metastasis site (%)			
Bone	245 (90%)	107 (96%)	0.646
Lung	21 (7.7%)	7 (11%)	0.456
Liver	5 (1.8%)	2 (3.0%)	0.626
Others	7 (2.6%)	3 (4.5%)	0.416
EOD score > 1 (%)	152 (56%)	47 (71%)	0.026
M stage			0.467
M1a (distant lymphnode metastases only)	19 (7.0%)	3 (4.5%)	
M1b (bone metastases)	222 (81%)	52 (79%)	
M1c (visceral metastases)	32 (12%)	11 (17%)	
CHAARETED-HVD (%)	175 (64%)	51 (77%)	0.043
The use of docetaxel (%)	83 (30%)	17 (26%)	0.548
The use of bone modifying agents (%)	154 (56%)	31 (47%)	0.172
The use of new type of anti-androgen receptor antagonists	73 (27%)	9 (14%)	0.025
Clinical outcomes			
CRPC development (%)	154 (56%)	36 (55%)	0.784
Deseased (%)	87 (32%)	27 (41%)	0.191
Follow-up period (months)	31 (14–56)	14 (6–26)	< 0.001

GNRI Geriatric Nutritional Risk Index, *BMI* body mass index, *PSA* prostate-specific antigen, *ECOG-PS* Eastern Cooperative Oncology Group-performance status, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *EOD* extent of disease, *HVD* high-volume disease, *CRPC* castration-resistant prostate cancer

Oncological outcomes of the risk score and comparison with the CHAARTED criteria

Table S1 shows the characteristics of the study participants according to three risk score groups. The 3-year CRPC-free survival rates of score 0, score 1, and score ≥ 2 groups were 53%, 34%, and 14%, respectively ($P < 0.001$; Fig. 2a). The 3-year OS rates of score 0, score 1, and score ≥2 groups were 88%, 73%, and 53%, respectively ($P < 0.001$; Fig. 2b). The AUC value of the risk score for OS was significantly superior to that of the CHAARTED criteria (AUC: 0.559 vs. 0.658, $P = 0.004$; Fig. 2c). Multivariate Cox proportional hazards regression analyses that included the risk score revealed that scores of 1 and ≥ 2 were independent predictors for CRPC-free survival, CSS, and OS (Table 3).

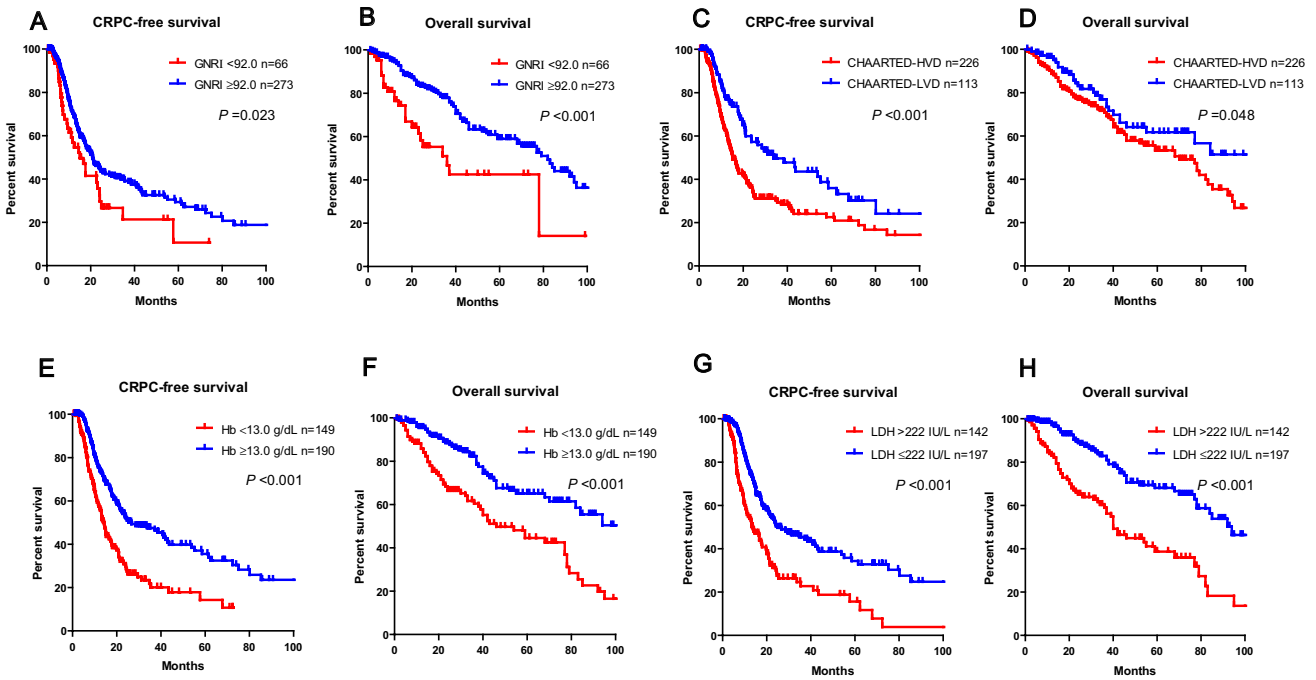

Fig. 1 Castration-resistant prostate cancer (CRPC)-free survival and overall survival (OS) stratified by risk factors for prognosis. Patients with a Geriatric Nutritional Risk Index (GNRI) < 92.0 had a significantly poorer CRPC-free survival ($P=0.023$; **a**) and OS ($P<0.001$; **b**) than those with a GNRI ≥ 92.0. Patients with CHAARTED-high-volume disease (HVD) had a significantly poorer CRPC-free survival ($P<0.001$; **c**) and OS ($P=0.048$; **d**) than those with CHAARTED-low volume disease (LVD). Hemoglobin level < 13.0 g/dL was significantly associated with CRPC-free survival ($P<0.001$; **e**) and OS ($P<0.001$; **f**). Patients presenting with lactate dehydrogenase (LDH) level > 222 IU/L had a significantly poorer prognosis in terms of CRPC-free survival ($P<0.001$; **g**) and OS ($P<0.001$; **h**) than those with an LDH level ≤ 222 IU/L

Discussion

We assessed the prognostic significance of poor nutrition in patients with mHNPC and identified that the GNRI was a significant predictor of both CSS and OS. To the best of our knowledge, this study first showed the significant value of the GNRI on the prognosis of patients with mHNPC. Furthermore, the risk score comprising a GNRI < 92.0, Hb level < 13.0 g/dL, and LDH level > 222 IU/L can better predict clinical outcomes than the CHAARTED criteria in patients with mHNPC.

Previous studies have shown a significant association between nutritional status (serum albumin level and BMI) and poor oncological outcomes in metastatic PC [19, 20]. However, our additional analysis could not show the significance of serum albumin level (HR 0.82; $P=0.330$) and BMI (HR 0.94; $P=0.050$) in OS (Table S2). When underweight was defined as BMI of < 18.5 [21], patients with BMI < 18.5 had a significantly shorter median OS than those with BMI ≥ 18.5 in this study (36 vs. 79 months, $P<0.001$). However, the number of patients with BMI < 18.5 was only 38 (11%) in this study. Because the limited number of events may weaken the statistical power, we used the GNRI to show the clinical significance of malnutrition. In our cohort, approximately 20% of patients with mHNPC were diagnosed with poor nutrition, which might be a similar finding in a previous cross-sectional study showing that 13.9% of patients with localized or metastatic PC were diagnosed with malnutrition using BMI and age [21]. Furthermore, we found that a GNRI < 92.0 was an independent predictor of mortality in patients with mHNPC. Similar results have been obtained, which show that a GNRI < 92.0 was significantly associated with poor survival in individuals with esophageal cancer and metastatic renal cell carcinoma [9, 11].

Poor nutritional status among patients with cancer is largely attributed to cancer cachexia, which is a complex syndrome characterized by severe, unintentional, and progressive weight loss caused by a negative protein and energy balance. This negative energy balance is driven by the combination of inadequate feeding due to anorexia and metabolic factors (e.g., insulin resistance and excessive muscle protein catabolism) [22]. Malnutrition and inflammation suppress albumin synthesis particularly in the later stages of the disease [23]. Furthermore, cancer-related anemia is caused by inflammation, iron metabolism, malnutrition, and oxidative stress in patients with cancer [24]. Then, we designed the risk score comprising the GNRI, Hb level, and LDH level, which was a simple and objective predictor of clinical

Table 2 Background (age, year of diagnosis, ECOG-PS, and PSA)-adjusted multivariate Cox proportional analyses for clinical outcomes

Variables	Factor	Hazard ratio	95% CI	*P* value
CRPC				
CHAARTED	HVD	1.24	0.86–1.80	0.250
ALP	> 322 IU/L	1.26	0.91–1.76	0.160
GNRI	< 92.0	1.10	0.74–1.64	0.640
LDH	> 222 IU/L	1.63	1.20–2.23	0.002
H b	< 13.0 g/dL	1.69	1.20–2.37	0.002
CSS				
CHAARTED	HVD	1.18	0.66–2.10	0.580
ALP	> 322 IU/L	1.18	0.72–1.95	0.510
GNRI	< 92.0	1.76	1.04–2.98	0.035
LDH	> 222 IU/L	2.64	1.68–4.16	< 0.001
Hb	< 13.0 g/dL	1.65	1.03–2.63	0.036
OS				
CHAARTED	HVD	1.02	0.62–1.70	0.930
ALP	> 322 IU/L	1.07	0.69–1.67	0.760
GNRI	< 92.0	1.80	1.13–2.87	0.013
LDH	> 222 IU/L	2.65	1.77–3.98	< 0.001
Hb	< 13.0 g/dL	1.73	1.14–2.62	0.011

ECOG-PS Eastern Cooperative Oncology Group-performance status, *PSA* prostate-specific antigen, *CRPC* castration-resistant prostate cancer, *CI* confidence interval, *HVD* high-volume disease, *ALP* alkaline phosphatase, *GNRI* Geriatric Nutritional Risk Index, *LDH* lactate dehydrogenase, *Hb* hemoglobin, *CSS* cancer-specific survival, *OS* overall survival

outcomes, since several studies have reported the association between anemia and LDH level, as well as poor oncological outcomes in patients with metastatic disease [7, 8]. In the present study, patients with a risk score > 0 (higher LDH level, lower Hb level, or GNRI < 92.0) had a significantly higher proportion of EOD > 1 and CHAARTED-HVD than those with a risk score of 0 (Table S1). Based on these findings, our risk stratification could reflect cancer cachexia and metastatic tumor burden, and may be an appropriate predictor of oncological outcomes in patients with mHNPC. Further investigation should be conducted to validate our risk stratification.

Patient selection for upfront therapy must be assessed. Recently, patients with mHNPC who had high metastatic burden can receive upfront docetaxel plus ADT or abiraterone acetate plus low-dose prednisone as aggressive treatments [5, 6]. However, poor nutrition has been significantly associated with intolerance to chemotherapies [25, 26]. Our results showed that 160 (70%) patients with CHAARTED-HVD were classified ≥ 1 group and had a significantly worse 3-year CRPC-free survival (19% vs. 47%, $P < 0.001$; Figure S1A) and 3-year OS (62% vs. 88%, $P < 0.001$; Figure S1B) than those with a risk score 0. These results suggested that not all patients with high metastatic burden may be candidates for upfront chemotherapy. Furthermore, our results showed that the number of patients who had both a GNRI < 92.0 and CHAARTED-HVD was significantly higher in the risk score ≥ 2 group (score 0: 0%, score 1: 1%, and score ≥ 2: 45%; $P < 0.001$; Figure S1C). We speculated that patients

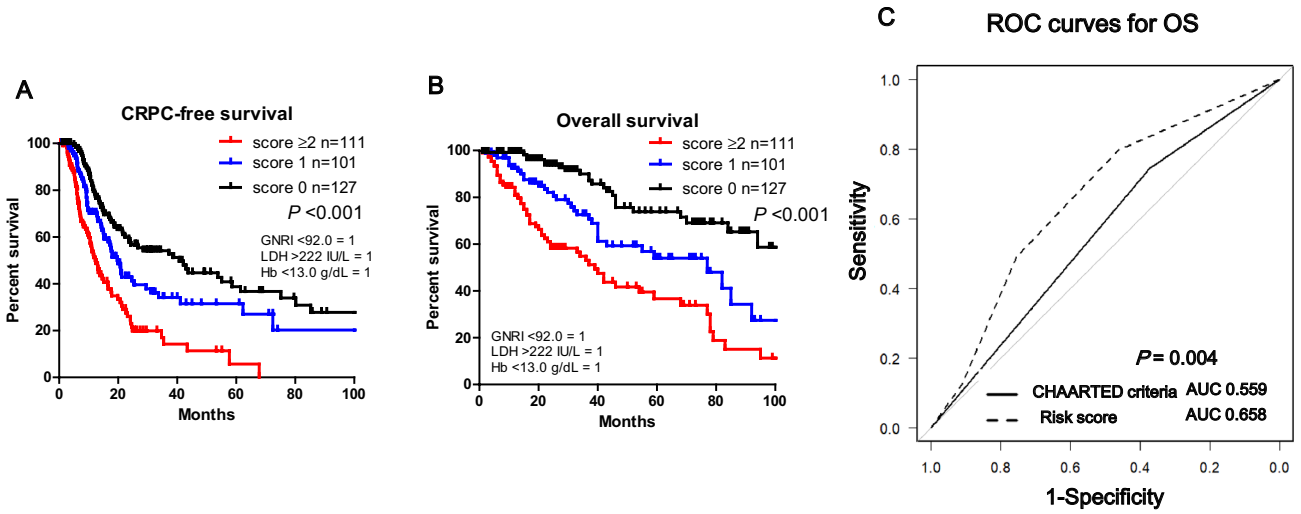

Fig. 2 Castration-resistant prostate cancer (CRPC)-free survival and overall survival (OS) stratified by risk score and compared with CHAARTED criteria. The risk score comprised the following risk factors: Geriatric Risk Nutritional Index score < 92.0, hemoglobin level < 13.0 g/dL, and lactate dehydrogenase (LDH) level > 222 IU/L. The 3-year CRPC-free survival rates of the score 0, score 1, and score ≥ 2 groups were 53%, 34%, and 14%, respectively ($P < 0.001$; **a**). The 3-year OS rates of the score 0, score 1, and score ≥ 2 groups were 88%, 73%, and 53%, respectively ($P < 0.001$; **b**). The area under the curve (AUC) value of the receiver operating characteristic curve of the risk score for OS was significantly superior to that of the CHAARTED criteria (AUC: 0.559 vs. 0.658, $P = 0.004$; **c**)

Table 3 Background (age, year of diagnosis, ECOG-PS, and PSA)-adjusted multivariate Cox proportional analyses for clinical outcomes

Variables	Factor	Hazard ratio	95% CI	*P* value
CRPC				
CHAARTED	HVD	1.39	0.99–1.96	0.059
Risk score	Score 0	Reference	–	–
	Score 1	1.60	1.10–2.32	0.014
	Score ≥ 2	2.72	1.84–4.03	< 0.001
CSS				
CHAARTED	HVD	1.33	0.77–2.27	0.300
Risk score	Score 0	Reference	–	–
	Score 1	2.32	1.29–4.20	0.005
	Score ≥ 2	4.81	2.68–8.63	< 0.001
OS				
CHAARTED	HVD	1.11	0.69–1.78	0.670
Risk score	Score 0	Reference	–	–
	Score 1	2.63	1.38–4.02	0.002
	Score ≥ 2	4.93	2.91–8.37	< 0.001

Score; GNRI < 92.0 = 1, LDH > 222 IU/L = 1, and Hb < 13.0 g/dL = 1

ECOG-PS Eastern Cooperative Oncology Group-performance status, *PSA* prostate-specific antigen, *CRPC* castration-resistant prostate cancer, *CI* confidence interval, *HVD* high-volume disease, *CSS* cancer-specific survival, *OS* overall survival, *GNRI* Geriatric Nutritional Risk Index, *LDH* lactate dehydrogenase, *Hb* hemoglobin

with CHAARTED-HVD who had ≥ 2 risk factors require abiraterone acetate plus low-dose prednisone, which have safety profiles in terms of potential vulnerability to chemotherapy. As the choice of aggressive treatments is controversial, our risk score may be useful in decision-making regarding aggressive treatments. Further studies must be conducted to explore the optimal treatments for patients with mHNPC who presented with malnutrition.

The present study had several limitations. First, we excluded 48% of the patients who did not have sufficient data for this analysis. Second, because the GNRI requires only serum albumin level and BMI, we could not address total body composition, which consists of muscle mass, fat, and total body water. Third, we could not stress the changes in nutritional status after the initiation of ADT,which might be a more important prognostic factor in patients with cancer. Fourth, the optimal cutoff value of GNRI for malnutrition among patients with mHNPC may vary in different populations. The median BMI in this cohort was lower than that of the cohorts in previous studies that included non-Asian patients with PC [27], and this may prevent the generalization of our results to non-Asian populations. Fifth, with the advent of a new type of antiandrogen receptor antagonists for CRPC after 2014, we could not exclude historical background bias in this study. Finally, we could not obtain information regarding comorbidities, such as cardiovascular disease and diabetic mellitus, which are significantly associated with mortality.

Conclusion

The GNRI at diagnosis was a prognostic factor of mortality among patients with mHNPC. The risk score comprising a GNRI < 92.0, Hb level < 13.0 g/dL, and LDH level > 222 IU/L is a better predictor of clinical outcomes than the CHAARTED criteria in patients with mHNPC. Our finding may help clinicians to focus more on identifying the type of treatment modalities for patients with mHNPC who presented with poor nutrition.

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Author contributions TO: data analysis, manuscript writing/editing. SH: data collection or management, data analysis, manuscript writing/editing. SN: protocol/project development, data collection or management. MT, TS, SK, SH, MI, TK, SI, JS, HS, KM, and TT: data collection or management. NT, YA, TH, and CO: protocol/project development, supervision.

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