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Original Article

The prognostic immune nutritional index is a predictive biomarker in metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide

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Abstract

Objective: To investigate the predictive efficacy of the geriatric nutritional risk index (GNRI) and novel prognostic immune nutritional index (PINI) in patients with metastatic castration–resistant prostate cancer (mCRPC) receiving abiraterone or enzalutamide.

Methods: We reviewed patients with mCRPC who received abiraterone or enzalutamide at the Suleyman Demirel University Hospital between 2015 and 2019. The GNRI was calculated using serum albumin and body mass index, with a GNRI <92.0 indicating poor nutritional status, and PINI was calculated using albumin and monocyte counts. The risk of survival was assessed using multivariate cox-regression analysis.

Results: No statistically significant difference was found between the mean age of men and women in the study. Eighty-three patients with mCRPC were included. In the low PINI group, it was 77.1% (PINI≤3.42). The median overall survival (OS) was 17 months in the low PINI group and 25 months in the high PINI group (p=0.001). The median OS was 21 and 25 months in the abiraterone and enzalutamide groups respectively; however the difference was not statistically significant (p=0.88). In a multivariate model, only low PINI was an independent risk factor for OS (Hazard Ratio [HR]=5.89, 95% Confidence Interval [CI]=2.07 to 16.7, p< 0.001).

Conclusion: In mCRPC patients treated with abiraterone or enzalutamide, a low PINI≤ 3.42 is associated with a shorter OS. The GNRI assessment for OS in patients with mCRPC treated with abiraterone or enzalutamide was not appropriate for our patients because only one patient had a low nutritional status (GNRI<92). There was no statistically significant difference in OS between the patients treated with abiraterone and those treated with enzalutamide.

Keywords: Abiraterone, castration resistant prostate cancer, enzalutamide, prognostic immune nutritional index.

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INTRODUCTION

Prostate cancer is the second most common cancer diagnosed in men with 1.414.515 (14.1%) cases and 375.308 (6.8%) deaths in 2020 (1). The cornerstones of treatment for metastatic prostate cancer are androgen deprivation and androgen receptor inhibition. Unfortunately, the majority of patients eventually reach the castration-resistant stage, which is lethal within months. Systemic inflammation and nutritional status of patients are strongly associated with the development and prognosis of cancer. There are many types of markers proposed for the prognosis of cancer patients, such as the prognostic nutritional index, geriatric nutritional risk index (GNRI), systemic inflammatory index, CRP-albumin ratio, neutrophil-lymphocyte ratio calculated using the number of inflammatory cells, albumin, weight and height of patients. The GNRI, calculated using the weight, height, and albumin levels of patients, has recently been identified as a prognostic marker for metastatic castration-resistant prostate cancer (mCRPC) patients (2). Jung et al. recently proposed a novel strong prognostic marker named the prognostic immune nutritional index (PINI) for evaluating the prognosis of metastatic colorectal cancer patients (3). The purpose of this study was to determine the prognostic value of the GNRI and PINI in mCRPC patients receiving abiraterone or enzalutamide. In a phase 3 trial, docetaxel plus prednisolone was evaluated in patients with mCRPC versus mitoxantrone and prednisolone in 2004. Median overall survival (OS) was better 18.9 and 16.4 months in the docetaxel group versus mitoxantrone respectively (4). Abiraterone acetate an inhibitor of androgen biosynthesis, has been evaluated for patients with mCRPC after chemotherapy. Median OS was superior 14.8 and 10.9 months in the abiraterone group versus the placebo respectively (5). In a phase 3 study published in 2015, abiraterone acetate was also evaluated in metastatic chemotherapy- naive prostate cancer patients. In comparison to the placebo group, the abiraterone group's median OS was longer (33.4 vs 23.4 months) (6). Enzalutamide, an androgen receptor signaling pathway inhibitor, was evaluated in multiple steps in the AFFIRM study in patients with mCRPC after chemotherapy. Enzalutamide was superior to placebo, with a median overall survival of 18.4 vs 13.6 months respectively (7). In the PREVAIL study, enzalutamide was superior to placebo in mCRPC, chemotherapy-naive patients had a 29% risk reduction of death at the cut-off date of the trial (8). All patients had mCRPC and were administered enzalutamide or abiraterone before chemotherapy. The first purpose of the current study was to determine the effect of the GNRI and PINI on the prognosis of mCRPC patients receiving the novel antiandrogen agents abiraterone and enzalutamide, and the second was the real-world experience with these agents in mCRPC patients.

MATERIALS AND METHODS

The patients with metastatic CRPC who were treated with novel antiandrogen therapies abiraterone or enzalutamide at Suleyman Demirel University Hospital, Turkey, from 2015 to 2019 were enrolled in the present study. All patients had metastatic prostate adenocarcinoma that progressed under castration levels of testosterone of <50 ng/dL. This study was approved with number 127-19.04.2022 by the ethics committee of the Suleyman Demirel University. Because the investigation was retrospective, there was no need for a scientific research funding. Informed consent was obtained from all patients.

Ninety-eight patients were identified, but 15 were excluded from the study because they dropped out of follow-up or applied to an external center. Eighty-three patients with metastatic prostate cancer who were treated at the medical oncology outpatient clinic were assessed. All patients were over the age of 18, had follow-up and treatment in our unit, and had records that we could access. Patients' ages, body mass index (BMI), co-morbid diseases, pathology reports, grade groups, Gleason scores, PSA levels at diagnosis and the CRPC period, previous treatments, metastasis locations and numbers, laboratory results of hemogram and biochemical values, last polyclinic control, and death dates were recorded retrospectively.

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Similar to previous studies, GNRI values were calculated as 1.489 serum albumin level (g/L) + 41.7 [actual body weight (kg)/ideal body weight (kg)], and poor nutritional status was defined as GNRI<92 (2, 9, 10). Compared to low-volume disease, visceral metastases or four or more bony lesions that extend beyond the vertebral bodies and pelvis were considered indicators of high-volume as in previous studies (11). A patient with a high-risk condition had two or more of the following: a Gleason sum of eight, three or more bone metastases found by a bone scan, and any visceral metastases (12). The cut-off point for PINI for predicting mortality in study patients was determined using receiver operating characteristic (ROC) analysis. The validity of the novel PINI cut-off value was expressed in terms of sensitivity and specificity. ROC analysis revealed an area under the curve (AUC) value of 0.65 (95% CI: 0.54 to 0.57; p=0.01) for PINI in predicting mortality. A cut-off value of ≤3.42 with a sensitivity of 91.1% and a specificity of 39.4% was determined using the Youden index.

Statistical analysis:

Statistical Package for the Social Sciences (IBM SPSS) 23.0 program and MedCalc 20.110 were used to analyze the study's data. Interquartile range (IQR) and median are used to communicate numerical data, whereas rates are used to represent frequently occurring data. The Mann-Whitney U test was used to compare the two groups using numeric data. Pearson's chi-square and Fischer's exact tests were used to compare the two groups with categorical variables. Overall survival comparisons of abirateron and enzalutamide treatments, GNRI, and PINI were performed using Kaplan-Meier curves and median survival times. A comparison of the two groups in Kaplan-Meier analysis was carried out using the log-rank test. Univariate and multivariate Cox regression analyses were used to establish hazard ratios with 95% confidence intervals for each variable. A P-value lower than 0.05 was considered statistically significant.

RESULTS

A total of 119 prescriptions were included in the study. 46.22% (n=55) of the prescriptions belonged to women and 53.78% (n=64) of them belonged to men. The average number of drugs in prescriptions was 5.23 (min 4 max 12). The average age of prescription holders was 69.44 years. The mean age of female patients was 69.56 (min 65 max 85); the mean age of male patients was 69.32 (min 66, max 82). There was no significant difference between the mean age of women and men (p=0.061). The data of 83 patients were recorded after 15 patients who did not match the inclusion criteria were excluded. The median age of the patients was 69 years (IQR: 62-73). Table 1 provides a summary of the patient characteristics in this investigation. Fourty-five patients died of mCRPC during the course of a median follow-up of 22 months. In the metastatic castration-sensitive period, 43.4% of patients received docetaxel. Abiraterone and enzalutamide were administered to 75.9% and 24.1% of patients, respectively. Because only one patient in our patient group had a poor nutritional status (GNRI<92), we did not assess the impact of this marker on prognosis. The PSA level at the time of metastatic castration resistance before therapy was significantly higher in patients who died during follow-up (median PSA [IQR: 56 (17-149) vs 26,5 (5-96); p=0.03), but the hazard ratio was not clinically significant in univariate cox regression analysis for OS (HR:1.002). A total of 77.1% of the patients were classified as having low PINI. Table 2 shows two-group comparisons of demographic features on mortality. The results of the univariate cox regression analysis for OS are shown in Table 3, and the results of multivariate cox regression analysis for OS are shown in Table 4. Only PINI≤3.42 (HR=5.89, 95% CI=2.07 to 16.7, p< 0.001) was an independent risk factor affecting overall survival in patients with mCRPC. The median OS was 17 months in the PINI low group and 25 months in the PINI high group; this difference was statistically significant (p<0.001) (Figure 1). The median OS was 21 and 25 months in the abiraterone and enzalutamide groups, respectively; however the difference was not statistically significant (p=0.88) (Figure 2).

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Table 1. Demographic features of study patients

Variable	**Median (IQR)**
Age	69 (62-73)
Gleason score	8 (8-9)
Grade group	4 (4-5)
PSA at baseline	37 (12-136)
PSA at CRPC	38 (11-143)
BMI	27.6 (25-30)
	N (%)
Metastases site	
Lymph node metastases	23 (38.6)
Bone metastases	62 (74.7)
Visceral metastases	5 (6)
Liver metastases	5 (6)
Lung metastases	2 (2.4)
Comorbidity	
Hypertension	33 (40.2)
Diabetes Mellitus	20 (24.1)
Coronary Artery Disease	7 (8.4)
Performance score	
0	37 (44.6)
1	42 (50.6)
2	4 (4.8)
Metastases at diagnosis	68 (81.9)
Abireteron in metastatic CRPC	63 (75.9)
Enzalutamid in metastatic CRPC	20 (24.1)
Docetaxel in metastatic CSPC	36 (43.4)
PINI	
≤3.42	64 (77.1)
>3.42	19 (22.9)
GNRI	
≥92	82 (98.8)
<92	1 (1.2)
High volume metastases	49 (59)
High risk metastases	73 (88)
Exitus	45 (54.2)

Abbreviations: IQR: interquartile range; PSA: Prostate specific antigen; GNRI: Geriatric Nutritional Risk Index; PINI: Prognostic Immune and Nutritional Index; CSPC: Castration sensitive prostate cancer; CRPC: Castration resistant prostate cancer.

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Table 2. Two group comparisons of demographic features for mortality

Variable	**Exitus Median (IQR)**	**Alive Median (IQR)**	**P value**
Age	70 (63-76)	65.5 (61-71)	0.10
Gleason score	8 (8-9)	8.5 (7-9)	0.92
Grade group	4 (4-5)	4.5 (3-5)	0.87
PSA at diagnosis	50 (16-146)	21.5 (15-41)	0.14
PSA at CRPC	56 (17-149)	26,5 (5-96)	0.03
GNRI	109.6 (104-117)	114 (105-118)	0.34
PINI	3.1 (2.8-3.3)	3.3 (3-3.5)	0.01
BMI	27.4 (25-30)	27.6 (25-30)	0.94
	N (%)	**N (%)**	
Metastases at diagnosis	37 (82.2)	31 (81.6)	0.94
Docetaxel in metastatic CSPC	23 (51.1)	13 (34.2)	0.12
Abireteron in metastatic CRPC	35 (77.8)	28 (73.7)	0.66
Enzatulamid in metastatic CRPC	10 (22.2)	10 (26.3)	0.66
GNRI			
≥92	44 (97.8)	38 (100)	1
<92	1 (2.2)	0	
PINI			
≤3.42	41 (91.1)	23 (60.5)	<0.001
>3.42	4 (8.9)	15 (39.5)	
Volume			
High volume	29 (64.4)	20 (52.6)	0.27
Low volume	16 (35.6)	18 (47.4)	
High risk metastases			
High risk	41 (91.1)	32 (84.2)	0.50
Low risk	4 (8.9)	6 (15.8)	
Gleason score			
≤7	7 (15.6)	10 (26.3)	0.22
>7	38 (84.4)	28 (73.7)	

Abbreviations: IQR: interquartile Range; PSA: Prostate specific antigen; BMI: Body Mass Index; GNRI: Geriatric Nutritional Risk Index; PINI: Prognostic Immune and Nutritional Index; CSPC: Castration sensitive prostate cancer; CRPC: Castration resistant prostate cancer.

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Table 3. Univariate cox regression analysis for overall survival

Variable	Hazard Ratio	95% Confidence Interval	P value
Age	1.03	0.99 to 1.03	0.07
Gleason score	1.04	0.76 to 1.43	0.77
Gleason (>7)	1.4	0.63 to 3.2	0.38
Grade group	1.06	0.77 to 1.46	0.69
PSA at diagnosis	1	0.99 to 1	0.89
PSA at CRPC	1.002	1.0003 to 1.003	0.01
GNRI	0.96	0.93 to 0.99	0.02
PINI	0.2	0.08 to 0.47	P<0.001
PINI (≤3.42)	5.85	2.07 to 16.5	P<0.001
BMI	0.97	0.91 to 1.03	0.45
Metastases at diagnosis	1.24	0.55 to 2.8	0.59
Docetaxel in metastatic CSPC	0.97	0.53 to 1.77	0.93
Abireteron in metastatic CRPC	1.05	0.51 to 2.13	0.88
Enzatulamid in metastatic CRPC	0.94	0.47 to 1.9	0.88
High volume metastases	1.41	0.76 to 2.64	0.27
High risk metastases	1.27	0.45 to 3.5	0.64

Abbreviations: PSA: Prostate specific antigen; GNRI: Geriatric Nutritional Risk Index; PINI: Prognostic Immune and Nutritional Index; BMI: Body Mass Index; CSPC: Castration sensitive prostate cancer; CRPC: Castration resistant prostate cancer.

Table 4. Multivariate cox regression analysis for overall survival

Covariate	Hazard Ratio	95% Confidence Interval	P value
Gleason (>7)	1.38	0.61 to 3.12	0.43
Treatment (Enzalutamide vs Abireteron)	1.04	0.49 to 2.22	0.90
PINI (≤ 3.42)	5.89	2.07 to 16.7	P<0.001
High volume metastases	1.38	0.70 to 2.69	0.34

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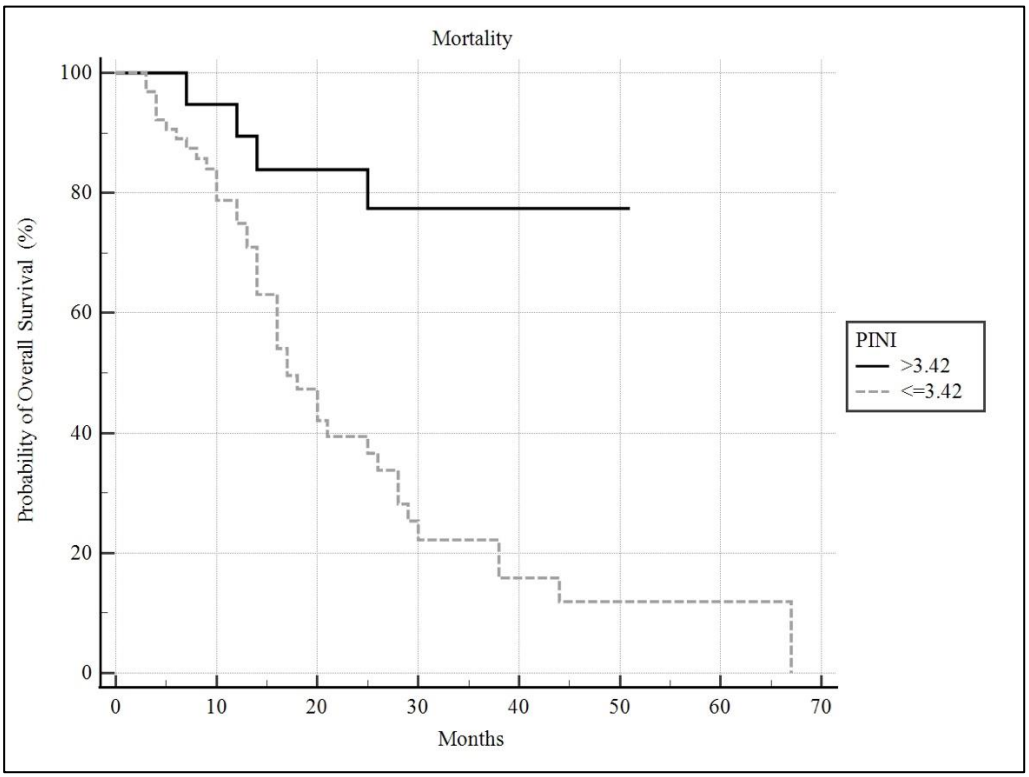

Figure 1. Kaplan-Meier curve for Overall Survival (OS) among low PINI group (PINI≤3.42) and high PINI group (PINI>3.42), median 17 months vs. 25 months, respectively (p=0.001)

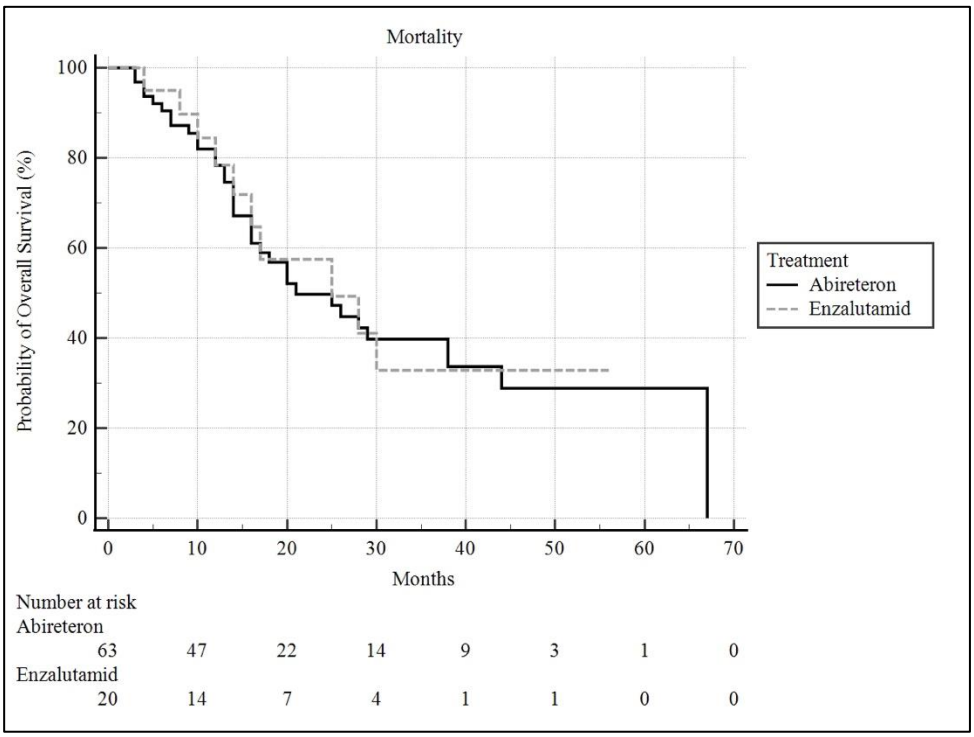

Figure 2. Kaplan-Meier curve for Overall Survival (OS) among the patients receiving abiraterone and enzalutamide, median 21 months vs. 25 months, respectively (p=0.88)

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DISCUSSION

The purpose of therapy is to improve the management of diseases and thus to increase the patients' quality of life. Drug-related side effects or drug interactions are more common in older ages due to the increased frequency of chronic diseases, the increase in the number and types of drugs used, the use of prescription or non-prescription drugs, herbal treatments, dose repetition due to forgetfulness, and differences in the pharmacokinetic and pharmacodynamic properties of drugs. Our findings suggest that the new marker PINI could be used to predict survival in patients with mCRPC who are receiving novel antiandrogen therapy, such as abiraterone or enzalutamide. It was statistically significant that the median OS in the low PINI group was 17 months while the median OS in the high PINI group was 25 months. To the best of our knowledge, this is the first study to look into the prognostic significance of PINI in patients with metastatic prostate cancer. This study demonstrated that the novel prognostic marker PINI can be used in patients other than those with metastatic colon cancer, as proposed by Jung et al. (13). Further research is needed to show that PINI has a prognostic effect in patients with other cancers. Chang et al. investigated the prognostic effect of GNRI in patients with mCRPC receiving docetaxel, and poor GNRI was associated with poor PFS and OS (2). However, because only one patient was in the low GNRI group in our study, we did not conduct a GNRI analysis in patients with mCRPC receiving abiraterone or enzalutamide. The study's second goal was to assess the therapeutic effects of abiraterone and enzalutamide and determine which was superior in real-life experiences. The numerical advantage of enzalutamide over abiraterone (25 vs 21 months) was not statistically significant. The median OS in metastatic chemotherapy-naive CRPC patients receiving abiraterone in the COU-AA-302 study (14) was 35.3 months, the median OS in the AFFIRM study (7) with mCRPC patients receiving enzalutamide after chemotherapy was 18.4 months, and the median OS in the PREVAIL study (15) with metastatic chemotherapy-naive CRPC patients receiving enzalutamide was 35.3 months. Because some patients with mCRPC are receiving chemotherapy during a hormone-sensitive period, the COU-AA-302 and PREVAIL studies do not correspond to real-world experience; as a result, the median OS in our study was shorter, which is consistent with real-world experience. Furthermore, the median OS in the AFFIRM study was shorter than that in this study. The AFFIRM study is also inconsistent with real-world experience, since some of our patients were receiving enzalutamide instead of chemotherapy in the mCRPC period.

Limitations

Due to the retrospective character of our investigation, some restrictions apply as single-center design, and small patient population. To achieve the best results, broader studies with larger numbers of patients are needed.

CONCLUSION

PINI is a novel prognostic marker for patients with mCRPC receiving abiraterone or enzalutamide. High PINI level is associated with longer OS. The median OS is not significantly different in patients with abiraterone or enzalutamide for the patients with mCRPC.

Conflicts of interest: The authors declare no conflict of interest.

Financial support and sponsorship: None.

Ethical approval: The study was approved by the Ethical Committee of Suleyman Demirel University (Date-Number: 19/04/2022 #127). The study was carried out in accordance with the statement of Helsinki Declaration.

Authorship contributions: Design of the study; EK, EF - Supervision; EK, EF - Data collection &/or processing; EK, EF - Performed data analysis; EK, EF - Literature search; EK, EF - Written by; EK - Critical review; EK, EF.

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