DOI: *10.4081/aiua.2023.11242*

ORIGINAL PAPER

C reactive protein/Albumin ratio as predictor of prognosis in castration resistant metastatic prostate cancer

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Summary *Objective: To assess the association of C reactive protein/Albumin ratio (CAR) with progression free survival (PFS) and overall survival (OS) in castration resistant metastatic prostate cancer (mCRPC) patients.*
Materials and methods: A transversal study was conducted, including all patients diagnosed with mCRPC within a Central Hospital Urological Oncology consultation between December 2019 and December 2021 (n = 178) and that were submitted to systemic therapy. CRP and albumin results were collected at the beginning of the systemic treatment for mCRPC in 103 patients and, in 75 patients already under treatment at the start of the study, on that occasion (December 2019). All patients were then followed. CAR was correlated with PFS and OS. OS and PFS were measured from the day the CRP and Alb were collected until the event of interest or the final date of follow-up. The sample was divided in two groups according to an optimal cut-off point found in a ROC curve.
Results: The sample showed a median age of 75.76 ± 9.17 years old. Using a cut-off point of 0.22, patients with a CAR ≤ 0.22 (63.2%) showed, compared to CAR > 0.22, longer PFS (15.92 vs. 9.46 months, r = -0.13, p < 0.05) and OS (p = < 0.05, 25,72 vs. 15.79 months, r = -0,24, p < 0.05). Better OS in patients with CAR ≤ 0.22 vs > 0.22 was detected on both the group evaluated at the beginning of systemic treatment (26.96 vs 17.63 months, p < 0.05) and the group of patients already under treatment (23.90 vs 11.54 months, p < 0.05). Dividing the sample according to the first line treatment chosen, we found OS of 26.25 vs 5.9 months (p < 0.05), 27.71 vs 22.57 months (p < 0.05) and 27.36 vs 23.75 months (p = 0.12), for docetaxel, abiraterone and enzalutamide, respectively.
Conclusions: According to this study, higher values of CAR are associated with lower PFS and OS in mCRPC patients. We found a cut-off value of 0.22 providing the best discrimination for prognosis. CAR is a good prognosis biomarker, irrespective of the moment of evaluation and chosen treatment option.

KEY WORDS: *Prostatic cancer; C-reactive protein; Albumin; Biomarker; Prognosis.*

Submitted 6 February 2023; Accepteed 25 February 2023

INTRODUCTION

Prostate cancer (PCa) is the most common non cutaneous malignancy among men (1), and the second leading cause of death from cancer in this population (2). It is estimated that approximately 1 in 8 men (12.9%) will be diagnosed with prostate cancer, and 1 in 40 (2.5%) will die from this disease (3). Despite a substantial shift to a more favourable stage at presentation of newly diagnosed disease, average age of death from prostate cancer is 77 years of age and has remained stable over the past three decades (3, 4).
Since *Huggins* reported that surgical castration is an effective treatment for advanced prostate cancer (5), hormonal manipulation with the suppression of gonadal testosterone is a cornerstone for systemic treatment of metastatic prostate cancer (3). However, the disease eventually evolves into mCRPC and death (3).
In recent years, the addition of several newly approved combination therapies to *androgen deprivation therapy* (ADT) for treatment in *metastatic hormone-sensitive prostate cancer* (mHSPC), such as abiraterone, docetaxel, apalutamide, enzalutamide or darolutamide, have shown improvements in OS and PFS (6-11). Despite being extremely effective initially, almost all patients under ADT for mHSPC eventually develop biochemical and/or clinical evidence of treatment resistance. Median OS after mCRPC diagnosis is estimated to be between 13.2 to 23.2 months depending on the burden of metastasis at presentation (12). mCRPC is a very heterogeneous disease, representing a vast group of patients with a wide range of characteristics and prognosis. Many factors have been pointed out to stratify these patients, such as PSA, metastatic burden, age, Gleason score and time to castration resistance (13). However, new methods or biomarkers to help clinicians sub-classify and manage these patients are still needed.
Some inflammation-based and/or nutritional markers have been studied with this goal, such as neutrophil/lymphocyte ratio (14), *platelet/lymphocyte ratio* (PLR) (15), prognostic nutritional index (PNI) (16), among others (17-22). Serum *C-reactive protein* (CRP), and acute phase reactant, has been used as a surrogate marker of systemic inflammation (17-19). Systemic inflammatory response has been shown to be associated with carcinogenesis, tumour progression and metastasis (20). Serum *albumin* (Alb) is accepted as a marker of the nutritional status of the body (18). The lower the serum albumin, the more frail the patients tend to be. Several recent studies have reported the utility of the CAR as a prognosis factor in cancer patients (20-22). A higher CAR corresponds to a status of elevated systemic inflammation and lower nutritional status, suggesting that the patient's overall condition is poor (18). CAR value as a prognostic marker has been previously reported in some cancers, such as hepa-

tocellular, colorectal, esophageal, pancreatic, small cell lung and cervical neoplasia (14-16, 20-22). However, there is only limited data in prostate cancer patients.
The objective of this study was to assess the association of CAR with PFS and OS in a group of mCRPC patients.

Materials and methods

A transversal study was conducted, including all patients diagnosed with mCRPC with a follow-up in a urological oncology consultation at a Central Hospital in Portugal, between December 2019 and December 2021 (n = 178) and that were submitted to systemic therapy (74 abiraterone, 56 enzalutamide and 48 docetaxel). Twenty-two patients had received docetaxel before for *metastatic hormone-sensitive prostate cancer* (mHSPC).
Seventy-five patients were already under treatment and follow-up in December 2019 and this group had the CRP and albumin data collected at that date. The remaining 103 patients had the biochemical data collected in the beginning of the systemic treatment (between December 2019 and December 2021).
The participants' characteristics were gathered from the medical records including age, histological grade, disease risk and volume, treatment modality, CRP, Alb, progression free survival and overall survival. The follow up data were collected until August of 2022.
A taxane-based chemotherapy was chosen in the presence of clinical criteria of poor prognosis (short period of response under ADT, high metastatic burden, visceral metastasis or poor prognostic genetic mutations) or in patients progressing after novel hormonal agents (NHA; abiraterone or enzalutamide). NHA were preferred in patients with less aggressive features (asymptomatic, durable response under previous ADT, low metastatic burden and no visceral metastases), and as second line therapy in patients that progressed under taxane-based chemotherapy. In the absence of contraindication for either pharmaceutical drugs, patients were sequentially assigned to either enzalutamide or abiraterone group.
Castration resistance was defined using the *European Association of Urology* criteria: 1) three consecutives rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL, or 2) appearance of new lesions (either two or more new bone lesions or a soft lesion using *Response Evaluation Criteria in Solid Tumours* [RECIST]), or 3) clinical deterioration.
OS was measured from the day the CRP and Alb were collected to death from any cause or the final date of follow-up. PFS was also measured from the day the CRP and Alb were collected until one of the above-mentioned criteria were met or the final date of follow-up. Comparisons between groups were performed using the chi-square test. CAR was correlated with PFS and OS. For that, samples were divided in two groups according to the optimal cut-off point found in a ROC curve. OS and PFS curves were generated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. All data were analysed using a linear regression model and Kaplan-Meier survival curves. The statistical hypothesis tests with p-value < 0.05 were considered significant. Statistical analyses were performed using SPSS software ver. 25.0 (*IBM, Armonk, NY, USA*).

Table 1.
Patients' characteristics and comparison between studied groups.

Variables		Total n %	CAR ≤ 0.22 n %	CAR > 0.22 n %	p value
ISUP Score	ISUP1	6.0%	5.6%	6.7%	n.s.
	ISUP2	20.2%	24.1%	13.3%	n.s.
	ISUP3	34.5%	33.3%	36.7%	n.s.
	ISUP4	17.9%	18.5%	16.7%	n.s.
	ISUP5	21.4%	18.5%	26.7%	n.s.
Disease burden	Low volume	49.4%	52.5%	43.3%	n.s.
	High volume	50.6%	47.5%	56.7%	n.s.
Disease risk	Low risk	64.1%	74.6%	45.5%	**0.005**
	High risk	35.9%	25.4%	54.5%	**0.005**
Local treatment (LT)	With LT	67.0%	61.7%	75.7%	n.s.
	Without LT	33.0%	38.3%	24.3%	n.s.
First-line treatment for mCRPC	Docetaxel	23.5%	15.6%	36.8%	**0.015**
	Abiraterone	46.1%	51.6%	36.8%	n.s.
	Enzalutamide	30.4%	32.8%	26.3%	n.s.

Results

A total of 200 patients diagnosed with mCRPC were included, median age at inclusion being 75.76 ± 9.17 years old. After a median follow-up of 23 months, 72 patients (36.1%) had died. The most prescribed treatment was abiraterone. Table 1 resumes the baseline characteristics of the population.
Mean CRP was 2.30 mg/dL (range from 0.02 to 24.08 mg/dL), mean Alb was 3.99 g/dL (range from 1.7 to 5.5 g/dL) and mean CAR was 0.64.
In the present study, the value of 0.22 for CAR was used as the cut-off value. It provided the maximal Youden index values, with an *area under the curve* (AUC) of 0.71 (Figure 1).
CAR showed an inverse and significant correlation with

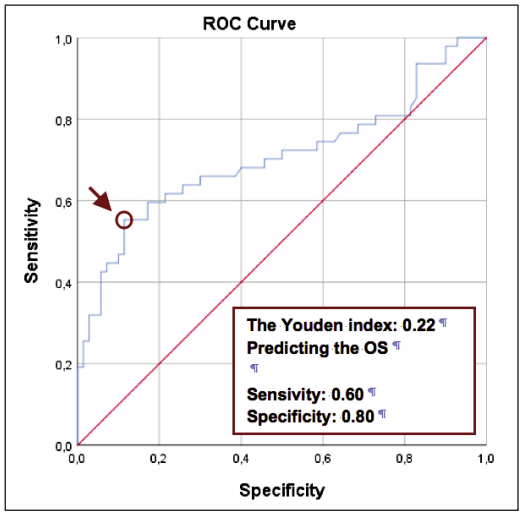


Figure 1.
ROC curve.

both PFS and OS (r = -0.13 and r = -0.24, p = < 0.05, respectively). Correlations shown in Figure 2.
Using a cut-off value of 0.22, patients with a CAR ≤ 0.22 (63.2%) showed longer PFS (15.92 *vs.* 9.46 months, p = < 0.05) and OS (25.72 *vs.* 15.79 months, p = < 0.05). Survival curves shown in Figure 3.
When dividing the sample according to when the biochemical parameters were collected, the OS of the group evaluated at the beginning of systemic treatment was 26.96 *vs* 17.63 months, for a CAR ≤ 0.22 *vs* > 0.22, respectively (p < 0.05). In the group evaluated during follow-up, the OS using the same cut-off point was 23.90 *vs* 11.54 months, respectively (p < 0.05). Survival curves below.
Dividing the sample according to the first line treatment chosen for mCRPC, it was observed an OS of 26.25 *vs* 5.9 months (p < 0.05), 27.71 *vs* 22.57 months (p < 0.05) and 27.36 *vs* 23.75 months (p = n.s.), for docetaxel, abiraterone and enzalutamide, respectively.

Figure 2,.
Correlations between CAR and clinical outcomes.

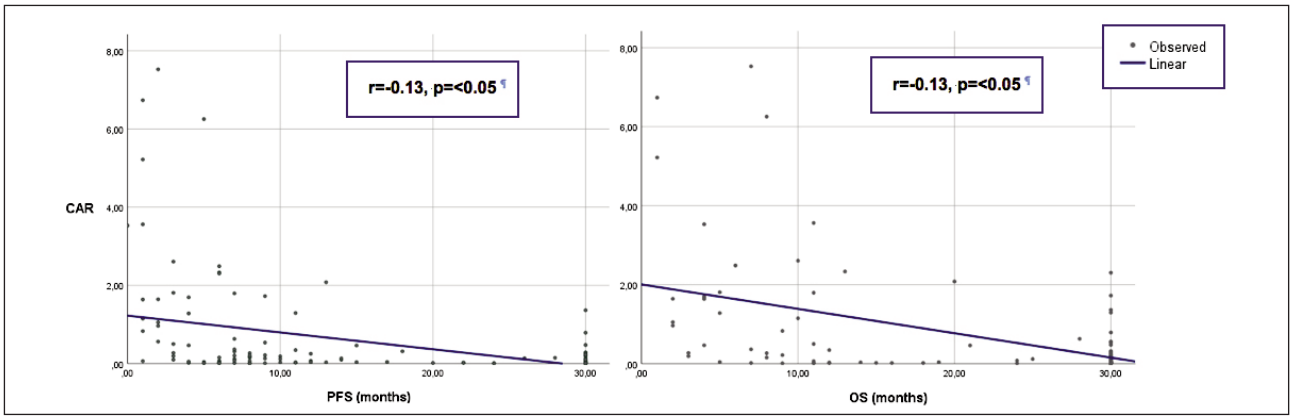


Figure 3.
Comparing progression free survival (PFS) and overall survival (OS) between groups according to CAR.

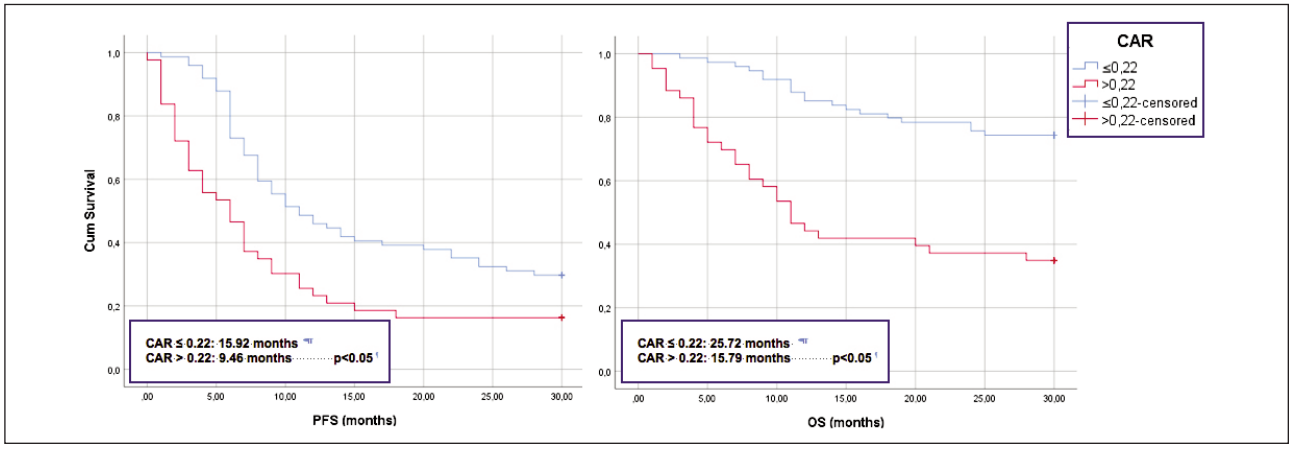
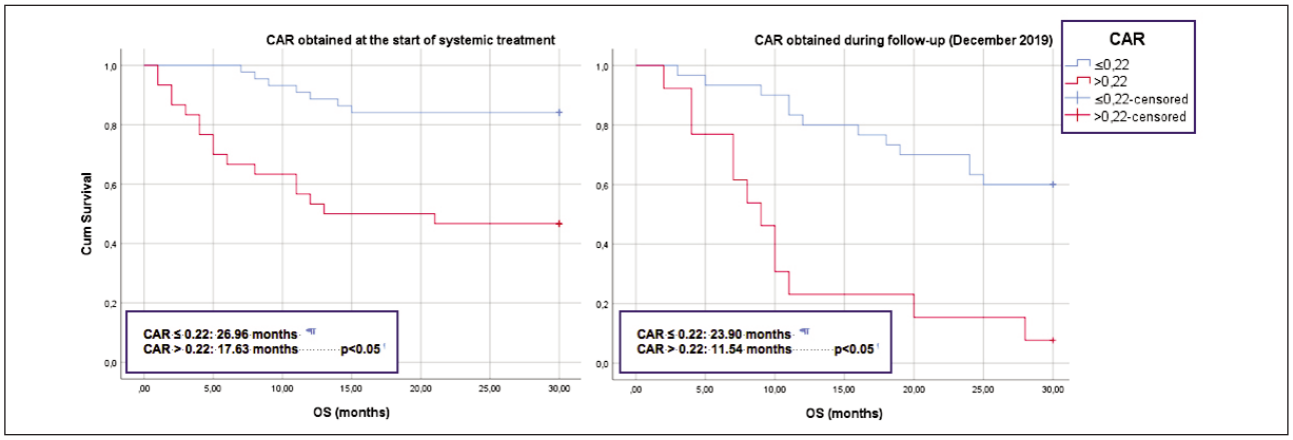


Figure 4.
Comparing overall survival (OS) between groups at the start of systemic treatment and during follow-up.



Discussion

In this study, we analysed the prognostic value of CAR in 178 mCRPC patients. We found CAR to be an independent prognostic factor for patients with mCRPC, either at diagnosis and start of systemic treatment and at any point during follow-up.

CRP production in the liver is up-regulated by proinflammatory cytokines (e.g. interleukin-6 [IL-6]) (25). Increased CRP levels have been reported in many types of malignancies (23). Cancer cell proliferation, necrosis, invasion, and hypoxia trigger immune responses in the tumour microenvironment that leads to the generation of various proinflammatory factors (25, 26). Two meta-analyses evaluated the role of CRP in kidney, bladder and prostate cancers and found a potential prognostic value in all three malignancies (24, 26).

Despite not being a perfect marker of nutritional status, because of its long half-life and susceptibility to other systemic factors, albumin is well correlated with nutrition status (25). Low serum albumin levels are caused by low nutrient intakes and tumour overconsumption (26). Protein malnutrition can lead to oedema, impaired organ function and immunosuppression. Moreover, hypoalbuminemia is associated with higher mortality in cancer patients (23, 25, 26).

Recently, several studies have reported the relation between high CAR and poor prognosis in cancer patients (20-22). Accordingly, we found a mean CRP and Alb, respectively, above (2.30 mg/dL) and below (3.99 g/dL) normal range values. In this study, we used the ROC analysis to yield a CAR 0.22 cut-off value for predicting PFS and OS in mCRPC and we were able to find a significant difference between patients with a CAR ≤ 0.22 or > 0.22. Taking advantage of the study design, we tried to find if the ratio was useful at the start of systemic treatment and during follow-up. We found a significant correlation irrespectively of the analysis timing. These findings are in line with previous studies (23, 25, 26). However, all those studies have only evaluated patients in the beginning of systemic treatment. Although not surprising, this study proves the usefulness of CAR predicting outcomes during the oncological follow-up.

The number of drugs approved for treatment of mCRPC is vast (27-30). In our study, 27% of the patients received docetaxel, 41.6% abiraterone and 31.5% enzalutamide. We observed a significantly higher proportion of patients with CAR > 0.22 receiving docetaxel vs NHA. This can be due to the higher disease stress associated with the poor risk factors present in these sub-group. Because docetaxel was prescribed in patients with more aggressive disease, their OS were also lower. However, CAR was still able to differentiate patients receiving docetaxel according to their prognosis. The groups receiving abiraterone and enzalutamide were more homogenous. When grouping the sample by treatment type, we found longer OS for patients with CAR ≤ 0.22 taking abiraterone, however, patients on enzalutamide didn´t showed a significant difference in OS, CAR (p = 0.12), with patients showing an OS of 27.36 and 23.75 months, for a CAR ≤ 0.22 *vs* > 0.22, respectively. We attribute this lack of significance to the small sample size.

It should be noted that the current study has limitations, including its retrospective nature and a relatively small sample size, which might have caused selection bias. Large-scale and prospective studies are further warranted to confirm our preliminary findings.

Conclusions

In conclusion, according to this study, higher values of CAR are associated with lower PFS and OS in mCRPC patients. These results suggest that CAR is a good prognosis biomarker, irrespective of the moment of evaluation and chosen treatment option.

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Conflict of interest: The authors declare no potential conflict of interest.