Is CRP/Albumin Ratio (CAR) a New Parameter to be Added to Risk Stratification Systems in Metastatic Renal Cell Carcinoma Patients?

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ABSTRACT

Objective: To evaluate the effect of pretreatment C-reactive protein (CRP)/Albumin ratio (CAR) on prognosis and its association with IMDC (International metastatic renal cell carcinoma database consortium) risk score and overall survival (OS) in metastatic renal cell carcinoma (mRCC) patients.

Study Design: Descriptive study.

Place and Duration of Study: Department of Medical Oncology, Dokuz Eylul University, Izmir, Turkey, between 2007 and 2020.

Methodology: Clinico-pathological and treatment-related data of mRCC patients were retrospectively evaluated and included in the study. CAR was used as a prognostic inflammatory score. CAR threshold value for OS has been obtained by ROC analysis. The prognostic value of CAR was tested using Kaplan-Meier and Cox-regression models. IMDC-CAR model was created by adding CAR to IMDC risk stratification.

Results: OS was 91 months in patients with CAR below the threshold value of 0.072 (<0.072), while OS was 51 months in patients with CAR of 0.072 and above (p=0.005). According to IMDC risk stratification, intermediate and poor risk groups showed similar survival times (p>0.05). However, when CAR was added to the IMDC risk score in the intermediate group, it was divided into 3 subgroups with different prognoses (p=0.02).

Conclusion: CAR is an independent predictor of OS in mRCC patients. In this study, it has been demonstrated that more accurate prognosis prediction could be made by adding CAR to IMDC indicators in the intermediate risk group, which constitutes a highly heterogeneous group according to IMDC risk stratification.

Key Words: *Renal cell cancer, Albumin, C-reactive protein, IMDC, Prognosis.*

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INTRODUCTION

Renal cell carcinoma (RCC) constitutes approximately 3% of all adult malignancies, and 20-25% of patients are metastatic at the time of diagnosis.[1] Renal cell carcinoma is a tumour that usually does not cause prominent symptoms in the early period and has no clinical findings, and its most important feature is its resistance to cytotoxic chemotherapy and radiotherapy. The use of targeted agents and immunotherapy in the treatment of mRCC has led to significant improvements in the prognosis of patients.[2,3] However, with the introduction of many effective agents, the determination of the treatment strategy in patients with mRCC has become more complex.[4]

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There are many prognostic factors in patients with RCC and many prognostic models are constructed with these factors. Currently, there are two widely accepted risk stratification models for renal cell carcinoma: 'Memorial Sloan Kettering Cancer Centre' (MSKCC) and 'International Metastatic Renal Cell Carcinoma Database Consortium' (IMDC).[5,6] The most striking problem in both models is the unbalanced distribution between risk groups. More than half of the patients with mRCC are in the intermediate-risk group.[7] In recent years, easy-to-use and inexpensive prognostic biomarkers have been studied in many cancer types. Many systemic inflammatory markers such as CRP and neutrophil/lymphocyte ratio (NLR) have been suggested to play an important role in the prognosis of mRCC.[8] CAR has also been studied as a new inflammatory prognostic score in many cancer types in recent years.[9-11]

The heterogeneous survival data of patients in the intermediate risk group have brought new biomarkers to guide the most effective prognosis prediction. The aim of this study was to determine whether integrating the CAR score into the IMDC risk scoring can be effective in better predicting prognosis in mRCC patients.

METHODOLOGY

The information of patients with mRCC, who were followed up from the Medical Oncology Clinics at the Dokuz Eylul University, Izmir, Turkey, from 2007 to 2020 was reviewed retrospectively. Patients who were histologically diagnosed with RCC and at least one metastatic deposit staged, based on American Joint Committee on Cancer (AJCC) 8th edition criteria, were included. Those patients with sufficient follow-up data were included in the study as a retrospective cohort. Clinico-pathological variables such as age, gender, performance status (PS), treatments received, histopathology type, metastasis localisation, comorbidities, IMDC risk classification and CRP, lymphocyte, haemoglobin, and serum albumin values that were examined at the time of metastasis were recorded with an electronic medical record system. Patients who were aged <18 years, with non-metastatic RCC, a secondary malignancy and/or did not have adequate laboratory results were excluded from the study. Comorbidities were learned from the history of the patients at the time of admission. Karnofsky performance scale was used to evaluate performance status. Survival was defined as the time from diagnosis to death or the patient's last known date of survival. A total of 87 mRCC patients were included in the study.

CRP/Albumin ratio has been calculated for each patient. ROC analysis was performed for CAR and the cut-off point was determined as 0.072. Patients with CAR <0.072 were grouped as CAR-low and patients with CAR ≥0.072 were grouped as CAR-high (AUC=0.630, sensitivity: 72%, specificity: 54%, p=0.047).

Descriptive statistical analyses of the demographic, clinico-pathological and treatment characteristics of the patients have been performed. Analyses were performed using IBM SPSS Statistics 24.0 software. Variables were analysed using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. Quantitative variables will be shown in the tables as mean±std. (standard deviation) and median range (Maximum-Minimum), while categorical variables will be shown as n (%). One-Way ANOVA test, which is a parametric method, was used to compare more than two independent groups according to quantitative data, and Fisher's least significant difference (LSD) test was used for post hoc analyses. Survival analyses were performed and survival curves according to variables were plotted by Kaplan-Meier method. Differences between variables were tested using Log-rank. Multivariate analysis was investigated using Cox-Regression model. Mardia; (Dornikand Hansen omnibus) test and homogeneity of variance were evaluated by Levene's test. The results are evaluated at 95% confidence interval and significance is at p<0.05 level.

RESULTS

Nineteen (21.8%) of the patients were females and 68 (78.2%) were males. The mean age of all patients was calculated as 56.0±10.8 years. The laboratory data of the patients and the statistical comparative analysis of the IMDC risk groups among themselves are shown in Table I.

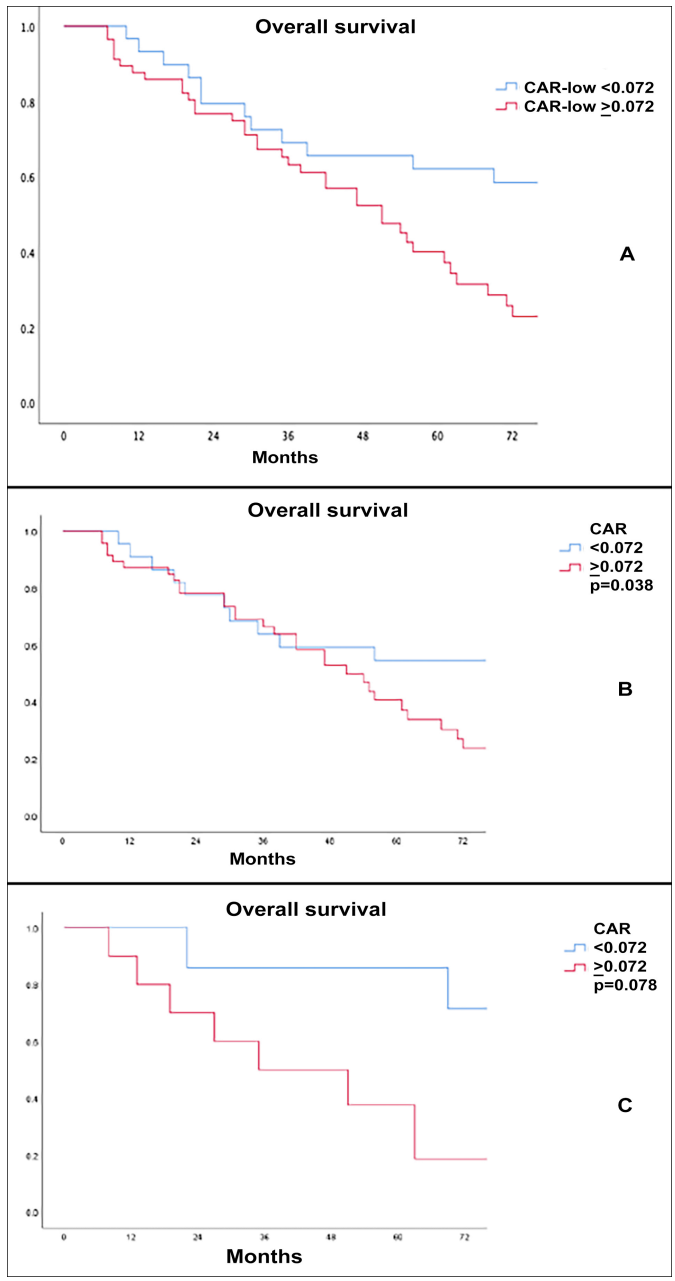


Figure 1: Overall Survival According to CAR. (A) Entire study population. (B) Clear cell group. (C) Non-clear cell group.

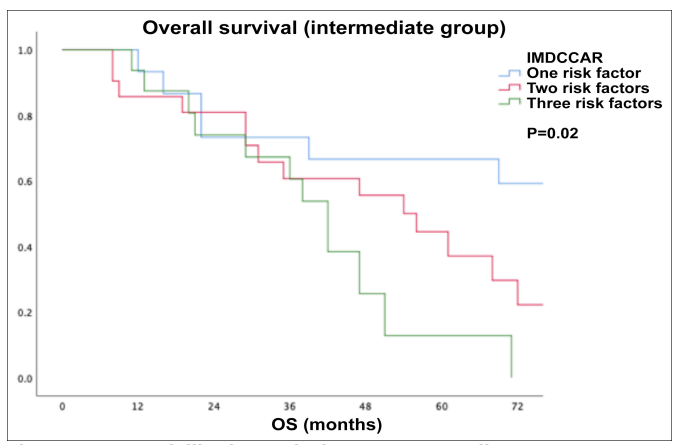


Figure 2: New modelling by CAR in the IMDC intermediate group.

Table I: Analysis of laboratory data according to risk groups of patients.

	Favourable (I) Median (Min.-Max.)	Intermediate(II) Median (Min.-Max.)	Poor (III) Median (Min.-Max.)	Total Median (Min.-Max.)	p	I-II	I-III	II-III
Age (years)	63 (45-79)	62 (21-79)	64 (52-81)	63 (21-81)	0.513	0.953	0.334	0.278
GFR (mL/min)	72.5 (5-174)	75.5 (10-131)	70 (39-115)	71 (5-174)	0.780	0.547	0.518	0.863
Creatinine (mg/dL)	1.1 (0.7-4.7)	1,1 (0,4-9.4)	1.1 (0.6-3.2)	1.1 (0.4-9.4)	0.658	0.464	0.990	0.463
Calcium (mg/dL)	9.2 (7.1-10.1)	9.3 (8-10)	9.4 (7.3-10.8)	9.3(7.1-10.8)	0.058	0.492	0.142	0.017
Albumin (g/dL)	4 (3.3-4.4)	3.9 (1.5-4.6)	3.7 (2.9-4.6)	4 (1.5-4.6)	0.258	0.150	0.138	0.731
CRP (mg/L)	3.4 (0.1-115)	5.1 (0-174)	9.9 (0.2-136)	5.4 (0-174)	0.464	0.591	0.224	0.361
LDH (U/L)	213 (110-474)	189 (110-686)	223 (171-313)	200 (110-686)	0.800	0.540	0.883	0.668
ALP (U/L)	79.5 (31-173)	98 (51-332)	100 (41-289)	93 (31-332)	0.224	0.118	0.130	0.797
Neutrophil (/uL)	4100 (1600-6700)	4615 (1200-15410)	6700 (2300-15240)	4400 (1200-15410)	0.012	0.162	0.003	0.032
Lymphocyte (/uL)	1550 (800-2690)	1600 (100-8000)	1180 (200-2800)	1500 (100-8000)	0.175	0.641	0.231	0.063
OS (months)	75 (19-198)	42 (8-112)	31 (7-109)	47 (7-198)	<0.001	<0.001	<0.001	0.369
NLR	2.4 (0,8-6)	2.7 (0.4-43)	4.4 (1.1-22)	2.9 (0.4-43)	0.141	0.151	0.052	0.370

GFR: Glomerular filtration rate, CRP: C-Reactive protein, ALP: Alkaline phosphatase, NLR: Neutrophil lymphocyte ratio one way ANOVA (robust statistic: Brown-Forsythe), Post Hoc Test: Dunn's Test, Post Hoc Test: Benjamini-hochberg correction.

Table II: Cox-Regression Analysis for OS.

Patient characteristics	Factor	p-value	HR	95% CI
Karnofsky PS	≥70	0.327	1.89	0.53-6.74
Metastasis	De novo	0.518	1.40	0.49-3.97
Age	≥70 years	0.531	1.42	0.47-4.29
IMDC				
Intermediate		0.239	2.17	0.59-7.87
Poor		0.319	2.35	0.43-12.7
CAR	≥0.072	0.038	2.89	1.05-7.89

PS: Performance status, IMDC: International Metastatic Renal Cell Carcinoma Database Consortium CAR: C-reactive protein and albumin ratio.

In terms of OS no statistically significant difference was found between patients over 65 years of age and patients under 65 years of age. There was no difference in median OS between men and women. Median OS in *de novo* metastatic patients at follow-up was statistically significantly lower than in patients with subsequent recurrence (p=0.001). While the median OS was 36.2 months in *de novo* metastatic patients, the median OS was 90.4 months in patients with recurrence at follow-up. Patients received sunitinib in 56.3% of first-line treatments, nivolumab in 33.3% of second-line treatments and axitinib in 26.4% of third-line treatments. Only 11.5% of patients progressed to the third or next treatment step. Patients who progressed with first--line treatment and received immunotherapy in second-line treatment had a statistically significantly longer OS than patients who received tyrosine kinase inhibitor in second--line treatment (p<0.05). It was also found that nivolumab, which provided a significant OS contribution when given in the second line, could not show this success when given in the third line. According to the IMDC risk scoring, the favourable-risk group had a statistically significantly longer OS than the intermediate and poor-risk groups (p=0.027). However, no statistically significant difference was found between the OS durations of the intermediate and poor risk groups. Patients with a CAR score lower than the cut-off value of 0.072 (<0.072) had an OS of 91 months, while patients with a high CAR score (≥0.072) had an OS of 51 months (p=0.005). While 79.3% of the patients had clear cell histology, 20.6% had non-clear cell pathology. While 7 out of 17 patients with non-clear cells were in the CAR score <0.072 group, 10 were in the CAR≥0.072 group. In the non--clear cell group, the median survival was 88 months in patients with a CAR score of <0.072, while it was 35 months in patients with ≥0.072. However, this difference was not statistically significant (p=0.078). Whereas 23 of 70 clear cell patients were in the CAR score <0.072 group, 47 were in the CAR ≥0.072 group. In the clear cell group, median survival was 92 months in patients with CAR score <0.072 and 51 months in patients with CAR score ≥0.072, and this difference was statistically significant (p=0.038, Figure 1).

When multivariate logistic regression analysis was performed, CAR score was found to be an independent prognostic indicator of OS (HR=2.89, CI=1.05-7.89, p=0.038, Table II).

Based on IMDC, 55.8% of the patients were in the intermediate- risk group. In order to better determine the prognosis in these patients, a new prognostic model was created with the addition of the CAR score to the IMDC risk factors.

DISCUSSION

In this study; CAR was shown to be an independent prognostic factor effective on OS. CAR has been evaluated as a prognostic biomarker in many cancers, but cut-off values vary significantly depending on tumour type, tumour stage and population.[9-13] In most of the studies investigating the prognostic value of CAR in mRCC, both early and advanced-stage RCC patients were evaluated together.[14] In the literature, there are only two studies evaluating the CAR score in mRCC patients. The study by Barua *et al*. included 31 patients with non-clear cell mRCC, and the CAR cut-off value was determined as 0.11 in this study.[15] However, this study was performed on rare histological subtypes and did not include the most common clear cell histological subtype. In the study of Konishi *et al*., there were 176 mRCC patients, and the CAR cut-off value effective on OS was found to be 0.05 in this study.[12] In this study, all mRCC patients were included, as in this study, with the clear cell subtype being pre-dominant. In a meta-analysis of 8 studies investigating the prognostic value of CAR score in RCC, high CAR score was found to be associated with poor prognosis in patients with RCC (HR=2.95 for OS, HR=1.75 for progression-free-survival (PFS)/*disease-free survival* (DFS).[14] This study is the first to be conducted in a non-far eastern population demonstrating that a high CAR score (>0.072) is an indicator of poor prognosis in patients with mRCC. Although the relationship between cancer and inflammation has been demonstrated today, the underlying mechanisms are still not fully known.[16] CRP is an acute phase protein that increases with inflammation.[17]Albumin, on the other hand, is both a nutritional status

marker and a protein that decreases in chronic inflammation.[18] CAR was initially started to be studied as a prognostic indicator in sepsis patients and then it was started to be used in cancer patients.[19] However, the mechanism underlying the prognostic ability of CAR has still not been fully elucidated. In the treatment of mRCC, a significant improvement was observed in the survival of these patients with combinations of immunotherapy-TKI or immunotherapy-immunotherapy.[20,21] However, after these important developments, both the toxicities of drugs and financial toxicities raised questions about patient selection. In this study, it was observed that the IMDC risk stratification could not distinguish between intermediate and poor risk groups in terms of OS. The IMDC-CAR model was applied in order to create a better prognosis in the intermediate-risk group, which consists of a highly heterogeneous group.[22] According to the IMDC-CAR model, the intermediate risk group was divided into 3 groups. It was shown that those with IMDC-CAR score 1 had an OS of 88 months, while those with score 2 and score 3 had OS of 56 and 42 months, respectively (p=0.02, Figure 2).

Based on IMDC, the prognosis of these patients in the same risk group is very different and this requires different treatment approaches. This study has many limitations. Retrospective study design and its susceptibility to bias are one of the most important limitations. Another limitation is that the treatment of the patients was not homogenous. Heterogeneous patient group was formed due to the limited number of patients and the inclusion of patients with non-clear cell histology. The authors thought that the OS difference in the non-clear group was clinically significant but not statistically significant due to the small number of patients. In this study, it was attempted to draw attention to the fact that there is no ideal risk stratification system in the selection of current treatment models and that a more effective model may be developed with additional prognostic markers. This research should be supported by prospective studies and more patients, as more effective prognosis determinations will provide a better chance of treatment.

CONCLUSION

With the addition of CAR score to the IMDC risk scoring system, a clearer OS differentiation was made in the intermediate risk group from the IMDC risk scoring system. CAR seems to be a weakly effective marker. Furthermore, the IMDC scoring system does not strongly predict prognosis.

ETHICAL APPROVAL:
Ethical approvals were obtained prior to the initiation of the research work. Approval for the study was granted by the Clinical Research Ethics Committee of Dokuz Eylul University of Health Sciences (Decision No. 2022/02-17, dated: 2022).

PATIENTS' CONSENT:
Written consent were obtained from the participants.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MU: Contributed to the design, data analysis, writing, and translation of the manuscript.
ECY: Contributed to data analysis and writing of the manuscript.
ECY, FE, HSS: Contributed to writing and supervision of the manuscript.
All the authors have approved the final version of the manuscript to be published.

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