Albumin-to-Alkaline Phosphatase Ratio as a Novel Prognostic Marker of Nivolumab Monotherapy for Previously Treated Metastatic Renal Cell Carcinoma

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Abstract. *Background/Aim:* The relationship between albumin-to-alkaline phosphatase ratio (AAPR) and the outcome of patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors remains unresolved. We aimed to clarify the prognostic role of AAPR in nivolumab monotherapy for previously treated mRCC. *Patients and Methods:* We retrospectively evaluated 60 patients with mRCC treated with nivolumab after failure of at least one molecular targeted therapy. The patients were stratified into two groups based on the baseline AAPR. The threshold of AAPR was determined using receiver-operating characteristics and Youden index analyses. Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) of nivolumab therapy were compared between the high and low AAPR groups. *Results:* The threshold of AAPR was set at 0.3, and 20 patients (33%) were assigned to the low AAPR group. The median OS and PFS were significantly lower in the low AAPR group than those in the high group (OS: 8.3 months vs. not reached, $p < 0.0001$; PFS: 2.9 vs. 10.4 months, $p = 0.0006$). Moreover, ORR was significantly lower in the low AAPR group than in the high group (16% vs. 45%, $p = 0.0397$). Multivariate analyses further showed that AAPR was an independent factor for OS [HR=0.27 (95% CI=0.09-0.77), $p = 0.0151$] but not for PFS ($p = 0.174$). *Conclusion:* Baseline AAPR was significantly associated with outcome in

patients with mRCC receiving nivolumab monotherapy and may, therefore, constitute an effective prognostic factor for nivolumab treatment.

Immune checkpoint inhibitors (ICIs) play an important role in the treatment of various types of cancers, including renal cell carcinoma (RCC) (1). Nivolumab is the first approved ICI for the treatment of metastatic RCC (mRCC) (2). In the current strategy of systemic therapy for mRCC, nivolumab monotherapy as a second- or further-line therapy is not strongly recommended (3); however, nivolumab is still used in combination with ipilimumab (4) or cabozantinib (5) in a first-line setting. Therefore, nivolumab is still considered indispensable in the systematic therapy for mRCC.

A previous CheckMate 025 trial showed that nivolumab exhibits a higher anti-tumor effect than that of everolimus (2). However, the objective response rate (ORR) of nivolumab therapy remains 25%, indicating that a certain number of patients do not benefit from this therapy. Therefore, we need to identify effective prognostic factors for patient selection in nivolumab therapy.

The albumin-to-alkaline phosphatase ratio (AAPR) was first reported to be associated with overall survival (OS) and disease-free survival in patients who received curative surgery for hepatocellular carcinoma (6). Subsequently, several studies have indicated that a low AAPR is associated with a worse patient outcome in metastatic nasopharyngeal carcinoma treated with chemotherapy (7), advanced hepatocellular carcinoma not treated with the standard chemotherapy (8), small-cell lung cancer treated with chemoradiotherapy (9), cervical cancer treated with surgery (10), pancreatic ductal carcinoma treated with chemotherapy (11), and non-metastatic RCC treated with curative nephrectomy (12). However, the prognostic role of AAPR in patients with mRCC treated with ICIs remains unknown.

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In this context, we retrospectively investigated the potential role of AAPR as a prognostic factor of outcome in patients that underwent nivolumab monotherapy for previously treated mRCC.

Patients and Methods

Patients. Sixty-eight patients who received nivolumab monotherapy after failure of at least one molecular targeted therapy for mRCC between June 2013 and February 2020 at our two institutions (Tokyo Women's Medical University Hospital, Tokyo, Japan, and Tokyo Women's Medical University Medical Center East, Tokyo, Japan) were evaluated. Among them, eight patients were excluded due to lack of clinical data, including serum albumin or alkaline phosphatase (ALP) levels. The remaining 60 patients were evaluated in this retrospective study.

All clinical and laboratory data were obtained from our electronic database and patient medical records. The study protocol was approved by the Institutional Ethics Review Board of the Tokyo Women's Medical University (ID: 2020-0009). The present study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1964 and its later amendments. Due to the retrospective and observational nature of the study, the requirement of informed consent was waived.

Albumin-to-alkaline phosphatase ratio (AAPR). Patients were stratified into two groups based on a threshold of baseline (pre-treatment) AAPR (for example, high and low). Subsequently, the overall survival (OS) and progression-free survival (PFS) were compared between the two groups. The threshold of AAPR was determined by generating a receiver operating characteristic (ROC) curve and performing maximum Youden index analyses for OS. In addition, we further compared the OS and PFS based on a change in AAPR at baseline and the initial AAPR three months after the initiation of nivolumab treatment. In patients whose treatment duration was less than 3 months, we determined the maximum AAPR during the entire duration of nivolumab treatment.

The method used for measuring ALP levels differs between Japan (Japan Society of Clinical Chemistry, JSCC) and western countries (International Federation of Clinical Chemistry, IFCC). Therefore, we multiplied an ALP value obtained *via* the JSCC method by 0.35 to correspond to the ALP value obtained *via* the IFCC method, and then we calculated the AAPR.

Protocol for nivolumab monotherapy. Nivolumab was intravenously administered every two weeks at a dose of 3 mg/kg or at a flat dose of 240 mg/body. Dose modifications were not performed; however, the dosage interval could be modified based on the condition of the patient or in the case of adverse events. Post-treatment imaging examinations including plain or enhanced computed tomography, or magnetic resonance imaging of the chest, abdomen, and pelvis were conducted at regular intervals of 4-12 weeks depending on the condition of the patient. Nivolumab was administered until radiographic or clinical disease progression was observed, or intolerable adverse events occurred. The radiographic evaluation of tumor response was conducted according to the Response Evaluation Criteria in Solid Tumors version 1.1. (13).

Statistical analysis. We evaluated the OS and PFS after the initiation of nivolumab treatment. The data of patients lost to follow-up were

Table I. Patient characteristics.

Variable	All (n=60)	High (n=40)	Low (n=20)	p-Value
Gender				
Male (ref. female)	48 (80%)	35 (88%)	13 (65%)	0.04
Age, years				
>65 (ref. ≤65)	35 (58%)	23 (58%)	12 (60%)	0.85
Histopathology				
Clear-cell carcinoma	48 (81%)	33 (83%)	15 (79%)	0.74
Non-clear-cell carcinoma	11 (19%)	7 (17%)	4 (21%)	
IMDC risk at nivolumab initiation				0.0049
Favorable	2 (3%)	2 (5%)	0 (0%)	
Intermediate	37 (62%)	30 (75%)	7 (35%)	
Poor	20 (33%)	7 (18%)	13 (65%)	
KPS				
<80 (ref. ≥80)	12 (20%)	4 (10%)	8 (40%)	0.0087
Number of prior systemic therapies				
1	33 (57%)	22 (56%)	11 (58%)	0.91
≥2	25 (43%)	17 (44%)	8 (42%)	
Number of metastatic organs				
1	20 (33%)	14 (35%)	6 (30%)	0.69
≥2	40 (67%)	26 (65%)	14 (70%)	
Liver metastasis				
Yes (ref. No)	9 (15%)	3 (8%)	6 (30%)	0.0256
Alb g/L* (continuous variable)	33 (28-38)	37 (33-39)	26 (22-31)	<0.0001
Alb<LLN	32 (53%)	13 (33%)	19 (95%)	<0.0001
ALP U/L* (continuous variable)	87.3 (73.6-110)	81.5 (65.0-89.3)	126.5 (108.8-186.6)	<0.0001
ALP>ULN	14 (23%)	0 (0%)	14 (0%)	<0.0001
AAPR* (continuous variable)	0.38 (0.24-0.49)	0.45 (0.37-0.58)	0.19 (0.13-0.24)	<0.0001
Follow-up period, months*	20.8 (6.9-29.3)	21.8 (9.2-36.2)	7.8 (1.5-25.4)	0.0125

*Median (interquartile range). IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal; AAPR, albumin-to-alkaline phosphatase ratio; Alb, albumin; ALP, alkaline phosphatase.

censored at the time of last contact. Survival data were collected until the end of September 2020. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard regression models were conducted to identify risk factors for OS and PFS. Risk was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using JMP version 15 (SAS Institute Inc., Cary, NC, USA); a value of $p < 0.05$ was considered significant.

Results

Patient characteristics. An AAPR threshold of 0.30 was determined based on the ROC curve and the maximum

Figure 1. Survival according to baseline AAPR. (A) Overall survival and (B) progression-free survival. AAPR, Albumin-to-alkaline phosphatase ratio; CI, confidence interval; N.R., not reached.

Youden index analyses. The area under the curve of AAPR was 0.69, and this value was higher than those of single albumin (0.65) and ALP levels (0.57). Based on the threshold of AAPR, the patients were classified into high (≥ 0.3) and low (< 0.3) AAPR groups.

The clinicopathological characteristics of the patients are summarized in Table I. Forty (67%) and twenty (33%) patients were assigned to the high and low AAPR groups, respectively. The number of patients classified as poor risk by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) was significantly higher in the low group than in the high group (33% vs. 18%, $p=0.0006$) (Table I). In contrast, there was no significant difference in other factors, including sex, age, histopathology, number of prior systematic therapies, or number of metastatic organs (all $p>0.05$).

Survival according to baseline AAPR. The median follow-up duration was 20.8 months (interquartile range=7.40-32.8). During the follow-up, 44 (73%) patients showed disease progression and 21 (37%) patients died due to any cause. OS was significantly lower in the low AAPR group than in the high group [median: 8.3 (95% CI=1.4 - not reached (N.R.)) vs. N.R. (N.R.-N.R.) months, $p<0.0001$] (Figure 1A). PFS was significantly lower in the low AAPR group than in the high group [median: 2.9 (95% CI=1.8-5.5) vs. 10.5 (5.1-15.1) months, $p=0.0009$] (Figure 1B).

Univariate analysis for OS showed that the AAPR was a significant factor, together with histopathology and IMDC risk (all, $p<0.05$). Multivariate analysis using these factors

further showed that the AAPR was an independent factor for OS (HR=0.27, 95% CI=0.09-0.77, $p=0.0151$) (Table II). Univariate analysis for PFS showed that the AAPR was a significant factor, together with sex, histopathology, and IMDC risk (14) (all, $p<0.05$); however, multivariate analysis using these factors showed that none of them were independent factors (all, $p>0.05$) (Table III).

ORR according to baseline AAPR. The ORR according to the AAPR is shown in Figure 2. Complete response, partial response, stable disease, and progressive disease were observed in five (13%), 12 (32%), 13 (32%), and 10 (23%) patients in the high AAPR group, and in 0 (0%), three (16%), six (32%), and 11 (52%) patients in the low group, respectively. ORR was significantly lower in the low AAPR group than in the high group (16% vs. 45%, $p=0.0397$).

Survival according to the change in AAPR. To further analyze the prognostic role of AAPR, we stratified the patients into three groups based on the change in AAPR within the initial three months after the initiation of nivolumab treatment. Twenty patients whose baseline AAPR was low and AAPR during three months post-treatment remained low (< 0.3) were assigned to a remained-low group. Twenty-three patients whose baseline AAPR was high and AAPR during three months post-treatment declined to low were assigned to a declined group. Seventeen patients whose baseline AAPR was high and AAPR during at the three months post-treatment remained high (≥ 0.3) were assigned to the

Table II. Univariate and multivariate analyses of overall survival.

	Univariate HR (95% CI)	p-Value	Multivariate HR (95% CI)	p-Value
Age, years				
>65 (ref. ≤65)	1.40 (0.55-3.51)	0.470		
Gender				
Male (ref. female)	0.41 (0.15-1.08)	0.0723		
Histopathology				
Clear-cell carcinoma (ref. non-clear cell carcinoma)	0.32 (0.12-0.89)	0.0266	0.41 (0.15-1.14)	0.0896
IMDC risk at nivolumab initiation				
Poor (ref. favorable/intermediate)	2.70 (1.11-6.55)	0.0279	1.32 (0.48-3.61)	0.577
Number of metastatic organs				
≥2 (ref. <2)	0.56 (0.23-1.37)	0.212		
Liver metastasis				
Yes (ref. no)	1.99 (0.66-5.98)	0.221		
AAPR				
High (ref. low)	0.20 (0.08-0.52)	0.0009	0.27 (0.09-0.77)	0.0151

CI, Confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; AAPR, albumin-to-alkaline phosphatase ratio.

Table III. Univariate and multivariate analyses of progression-free survival.

	Univariate HR (95% CI)	p-Value	Multivariate HR (95% CI)	p-Value
Age, years				
>65 (ref. ≤65)	0.77 (0.42-1.40)	0.399		
Gender				
Male (ref. female)	0.39 (0.19-0.81)	0.0116	0.49 (0.22-1.07)	0.0770
Histopathology				
Clear-cell carcinoma (ref. non-clear cell carcinoma)	0.36 (0.16-0.79)	0.0113	0.60 (0.25-1.43)	0.253
IMDC risk at nivolumab initiation				
Poor (ref. favorable/intermediate)	1.83 (0.99-3.38)	0.0526	1.30 (0.65-2.66)	0.445
Number of metastatic organs				
≥2 (ref. <2)	0.72 (0.39-1.33)	0.296		
Liver metastasis				
Yes (ref. no)	1.14 (0.47-2.71)	0.764		
AAPR				
High (ref. low)	0.42 (0.22-0.79)	0.0069	0.60 (0.29-1.24)	0.174

CI, Confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; AAPR, albumin to alkaline phosphatase ratio.

remained-high group. When the OS was compared among the three groups, OS values were significantly different [median: 8.3 (95% CI=1.4-NR) *vs.* N.R. (23.1- N.R.) *vs.* N.R. (95% CI=7.4-N.R.) months, *p*=0.0003] (Figure 3A). Additionally, PFS was significantly different among the three groups [median: 2.9 (95% CI=1.8-5.5) *vs.* 7.6 (5.0-12.7) *vs.* 17.9 (95% CI=1.8-NR) months, *p*=0.0036] (Figure 3B).

Discussion

In this retrospective study, we found that AAPR may play a potential role in determining the outcomes of nivolumab

monotherapy for previously treated mRCC. A low AAPR was significantly associated with a relatively poorer OS and PFS. Further, multivariate analysis showed that the AAPR was an independent factor for OS. In addition, a low AAPR was significantly associated with a relatively lower ORR.

An association between AAPR and outcome in patients has been observed in various types of cancer, including genitourinary cancer. Particularly, in non-metastatic upper tract urothelial carcinoma and non-metastatic RCC, a significant association between AAPR and outcome was observed (12, 15-17). To the best of our knowledge, this is the first study that demonstrated that AAPR was

Figure 2. Objective response rate according to baseline AAPR. CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

A

Pt. at risk	17	11	9	7
Remained high	23	19	12	7
Declined	20	9	8	3
Remained low				

	Months, median (95% CI)
Remained-high (n = 17)	N.R. (7.4 – N.R.)
Declined (n = 23)	N.R. (23.1 – N.R.)
Remained-low (n = 20)	8.3 (1.4 – N.R.)

B

Pt. at risk	17	9	6	4
Remained high	23	9	4	2
Declined	20	3	2	2
Remained low				

	Months, median (95% CI)
Remained-high (n = 17)	17.9 (1.8 – N.R.)
Declined (n = 23)	7.6 (5.0 – 12.7)
Remained-low (n = 20)	2.9 (1.8 – 5.5)

Figure 3. Survival according to changes in AAPR during the initial three months after treatment. (A) Overall survival and (B) progression-free survival. AAPR, Albumin-to-alkaline phosphatase ratio; CI, confidence interval; N.R., not reached.

significantly associated with the outcome of nivolumab monotherapy for mRCC.

The mechanism underlying the association between AAPR and disease outcome is still not understood. Albumin is a serum protein synthesized in the liver, and its level reflects the nutritional and inflammatory statuses (6, 18). The development of hypoalbuminemia is associated with a

reduced immunological anti-tumor response *via* suppression of T cell activity (19, 20). Multiple studies have indicated a significant association of serum albumin level with survival in patients with cancer (21-24). ALP is a hydrolase enzyme primarily synthesized in the bile duct, liver, kidney, and bone, and the levels of ALP increase in liver disease, kidney disease, and bone metastasis of cancer. In addition, ALP is

synthesized by cancer cells, and regulates tumor development *via* suppression of inflammatory signals, and induces the immune response by regulating purinergic signals (25, 26).

Several prognostic factors that reflect systemic inflammatory or nutritional statuses, which can be assessed using routine blood tests, have been identified in ICIs including nivolumab for treating mRCC (27-33). As the AAPR is calculated based on the ALP and albumin levels, patients do not need to undergo expensive or invasive tests for assessing this factor.

By performing the subgroup analysis based on the AAPR change, we found a comparable survival between the remained-high and declined-groups, and a lower survival in the remained-low group. This finding suggested that the baseline AAPR, rather than the change in value, was closely associated with survival of patients treated with nivolumab.

There are several limitations in this study. First, a selection bias may exist since this study was retrospectively designed and conducted only at two Institutions with a small sample size. Second, we evaluated patients that received nivolumab monotherapy as second- or further-line therapy based on a previous guideline (34), although this protocol is not strongly recommended in the current guidelines (3). Third, we determined the threshold of AAPR as 0.30 in this study; however, the value varies across different studies (12, 16). Therefore, further studies are needed to determine the optimal threshold value of AAPR in mRCC. Despite these limitations, to the best of our knowledge, this is the first study indicating the significant association of AAPR with ICI therapy. Currently, ICIs play a central role in systemic therapy for mRCC, and several regimens can be used as the first-line therapy (4). However, effective predictive or prognostic factors for ICIs remain unidentified. Thus, further studies assessing the value of AAPR as a prognostic marker in other ICI-based regimens are needed to develop more effective systemic treatment protocols for mRCC.

In conclusion, this retrospective study indicated that AAPR may be significantly associated with the outcome of nivolumab monotherapy used as a second- or further-line therapy for previously treated mRCC. This novel factor can be used for outcome prediction; however, further prospective studies are needed to validate our findings.

Conflicts of Interest

Tsunenori Kondo received honoraria from Novartis, Pfizer, and Bristol-Myers Squibb and Ono Pharmaceutical. Toshio Takagi received honoraria from Pfizer and Bristol-Myers Squibb and Ono Pharmaceutical.

Authors' Contributions

Tsunenori Kondo conceived the study. Maki Yoshino designed and analyzed the data. Maki Yoshino and Hiroki Ishihara drafted the

manuscript. All Authors revised the article for important intellectual content, reviewed the data and their analysis, and approved this article.

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