Impact of neutrophil-to-lymphocyte ratio on effects of targeted therapy for metastatic renal cell carcinoma patients with extrapulmonary metastasis

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Abstract

Introduction: The aim of our present study was to investigate the impact of the pretreatment neutrophil-to-lymphocyte ratio (NLR) on the antitumour effects of targeted agents in patients with metastatic renal cell carcinoma (mRCC).
Methods: The NLRs in 283 cases of molecular targeted therapy for mRCC were measured before starting the prescription of the molecular targeted agent. The significance of pretreatment NLR on the site of metastatic organs and on progression-free survival (PFS) in each case was analyzed.
Results: Metastases other than lung, which is defined as "extrapulmonary metastasis," were observed in 190 cases (67.1%). The median of pretreated NLR was 2.39 (0.49–68.7). In 97 of the 283 cases, pretreated NLR was 3.0 or higher. These cases were categorized as the high NLR group and the rest as the low NLR group. When the cases with extrapulmonary metastasis were investigated and classified based on their pretreated NLR, 50% PFS in the high NLR and low NLR groups was 6.7 months and 12 months (p=0.0001), respectively. Multivariate analysis revealed that high NLR (>3.0) was an independent predictive factor for PFS in the cases with extrapulmonary metastasis (hazard ratio 2.762; p<0.0001), while there was no significant difference between PFS in the high and low NLR groups in cases with no extrapulmonary metastasis (p=0.3457).
Conclusions: Our data indicate that the predictive significance of the NLR in mRCC cases involving targeted therapy depends on the metastatic organs. NLR is an independent predictive factor of PFS in cases of mRCC with extrapulmonary metastasis treated with targeted therapy.

Introduction

Renal cell carcinoma (RCC) is the third most common malignant disease in genitourinary organs, and 30% of RCC patients have metastases at initial diagnosis.[1] Molecular targeted therapies have recently become standard options in the treatment for metastatic RCC (mRCC) through randomized, control trials reporting the efficacy of targeted agents.[2-7] Due to the rapid spread of such therapy, clinicians have recognized the difference in clinical outcomes of targeted therapy in each case. Therefore, it has been important to identify novel biomarkers for predicting the effects of targeted agents for mRCC.

It is well-known that systemic inflammatory response plays an important role in the development and progression of several malignant diseases.[8,9] Parameters of inflammatory response, such as C-reactive protein (CRP), have been reported as prognostic markers in urological cancers.[10-12] The implication of CRP for predicting the prognosis or the effect of agents has also been demonstrated with targeted therapy in RCC.[13]

Besides CRP, the elevation of the neutrophils-to-lymphocytes ratio (NLR) has been reported as a prognostic factor in cancers, including RCC.[14] Although various studies have shown the association between high NLR and poor prognosis of RCC,[14,15] there has been no report on determining the impact of the NLR on the effects of targeted agents regarding metastatic organ status. We therefore investigated the impact of pretreatment NLR on the effect of molecular targeted therapy for mRCC by focusing on the site of metastatic organs.

Methods

The study was approved by the Ethics Committee of Hiroshima University (Hiroshima, Japan). Two hundred eighty-three cases of molecular targeted therapy for mRCC at our institute and other hospitals in Hiroshima Prefecture from 2007–2015 whose clinical and pathological information have been clarified were included in this study. Neutrophils and lymphocytes were measured within 14 days prior to starting the prescription of molecular targeted agents and when computed tomography (CT) scan was conducted in order to elucidate its effect. We chose three as a threshold value of pretreatment NLR based on the previous

report.[15] Cases for which the pretreatment NLR was three or higher and the others were classified into high and low NLR groups, respectively.

All cases were further classified according to age, gender, histological finding, performance status, anemia, serum calcium, lactate dehydrogenase (LDH), pretreatment serum CRP, metastatic organs, prior nephrectomy, choice of drug, and timing of treatment. Metastases other than lung were defined as extrapulmonary metastasis. The distribution of each subgroup in the high and low NLR groups and their progression-free survival (PFS) were compared.

The differences in the distribution of variables among the groups were analyzed using the chi-square test for categorical variables and Mann-Whitney test for continuous variables. The PFS was determined using the Kaplan-Meier method and analyzed using log-rank testing. The relationship between the variables and PFS was examined using the Cox proportional hazard model. Variables with p values less than 0.05 on univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using the JMP 10.0.0 (SAS Institute Inc., NC, U.S), and p values less than 0.05 were considered to be statistically significant.

Results

This study cohort consisted of 283 cases of molecular targeted therapy for mRCC. The characteristics of the cases are listed in Table 1. One hundred eighty-six (65.7%) cases and 97 (34.3%) cases were categorized as low and high NLR groups, respectively. Of all cases pathologically diagnosed as RCC, 255 cases were performed prior nephrectomy, which included 116 cytoreductive nephrectomies and 139 radical ones. Median of time from surgery to the start of targeted therapy was 24.7 (3–239) months in cases of radical nephrectomy. The rates of cases of 1 or higher Eastern Cooperative Oncology Group (ECOG)-performance status (PS) score, anemia, hypercalcemia, higher CRP, high LDH, or without prior nephrectomy in the high NLR group were significantly higher than those in the low NLR group.

The PFS curve for the entire cohort is shown in Fig. 1. Disease progression was shown in 125 of 253 cases. The 50% PFS for the entire cohort was 11 months. When they were classified into low and high NLR groups, the 50%PFS for the low NLR group (12 months) was significantly better than that for the high NLR group (eight months, p=0.0015) (Fig. 2). Univariate analyses revealed that several variables were significantly associated with PFS, including histological findings, PS, anemia, hypercalcemia, prior nephrectomy, number of metastatic organs, timing of treatments, and pretreated NLR. Multivariate analyses revealed that pretreated NLR, as well as the histological findings, PS, and timing of treatment were independent prognostic factors for PFS (Table 2).

While there was no significant difference in the distribution of lung metastasis between the low and high NLR

Table 1. Characteristics of 283 cases with mRCC involving molecular targeted therapy

	Pretreated NLR			Total
	Low (≤3.0)	High (>3.0)	p	
No. of patients	186	97		283
Age range (median)	4–85 (65)	44–85 (66)	0.6284	40–85 (65)
Gender, n (%)				
Male	148 (79.6)	82 (84.5)	0.3094	230 (81.3)
Female	38 (20.4)	15 (15.5)		53 (18.7)
Histological type, n (%)				
Clear	165 (88.7)	83 (85.6)	0.4459	253 (89.4)
Non-clear	21 (11.3)	14 (14.4)		35 (12.4)
ECOG performance status, n (%)				
0	160 (86.0)	71 (73.2)	0.0082	231 (81.6)
≥1	26 (14.0)	26 (26.8)		52 (18.4)
Anemia, n (%)				
(-)	95 (51.1)	28 (28.9)	0.0003	123 (43.5)
(+)	91 (48.9)	69 (71.1)		160 (56.5)
Hypercalcemia, n (%)				
(-)	184 (98.9)	89 (91.8)	0.0438	273 (96.5)
(+)	2 (1.1)	8 (8.2)		10 (3.5)
LDH, n (%)				
≤1.5 x ULN	179 (96.2)	87 (89.7)	0.0278	266 (4.0)
>1.5 x ULN	7 (3.8)	10 (10.3)		17 (6.0)
Pretreated CRP, n (%)				
<0.3mg/dL	113 (60.8)	25 (25.8)	<0.0001	138 (48.8)
≥0.3mg/dL	73 (39.2)	72 (74.2)		145 (51.2)
Metastatic organs, n (%)				
Lung				
(-)	46 (24.7)	27 (27.8)	0.5711	73 (25.8)
(+)	140 (75.3)	70 (72.2)		210 (74.2)
Liver				
(-)	155 (83.3)	83 (85.6)	0.6258	238 (84.1)
(+)	31 (16.7)	14 (14.4)		45 (15.9)
Bone				
(-)	148 (79.6)	62 (63.9)	0.0043	210 (74.2)
(+)	38 (20.4)	35 (36.1)		73 (25.8)
Brain				
(-)	182 (97.8)	88 (90.7)	0.0066	270 (95.4)
(+)	4 (2.2)	9 (9.3)		13 (4.6)

groups, the rate of the cases with bone, brain, or extrapulmonary metastases in the high NLR group were significantly higher than that in the low NLR group (Table 1), suggesting that there might be some associations between metastatic status and the impact of NLR. Therefore, we focused on the cases with extrapulmonary metastasis. As shown in Table 3, the rates of the anemia and hypercalcemia cases were significantly higher and that with prior nephrectomy was significantly lower than those in the low NLR group. In the

Table 1 (cont'd). Characteristics of 283 cases with mRCC involving molecular targeted therapy

	Pretreated NLR			Total
	Low (≤3.0)	High (>3.0)	p	
Ipsilateral kidney				
(-)	167 (89.8)	93 (95.9)	0.0751	260 (91.9)
(+)	19 (10.2)	4 (4.1)		23 (8.1)
Adrenal gland				
(-)	175 (94.1)	91 (93.8)	0.9273	266 (94.0)
(+)	11 (5.9)	6 (6.2)		17 (6.0)
Pancreas				
(-)	176 (94.6)	93 (95.9)	0.6446	269 (95.0)
(+)	10 (5.4)	4 (4.1)		14 (5.0)
Soft tissue				
(-)	170 (91.4)	89 (91.8)	0.9190	259 (91.5)
(+)	16 (8.6)	8 (8.2)		24 (8.5)
Lymph node				
(-)	135 (72.6)	67 (69.1)	0.5354	202 (71.4)
(+)	51 (27.4)	30 (30.9)		81 (28.6)
Extrapulmonary metastasis, n (%)				
(-)	75 (40.3)	18 (18.6)	0.0002	93 (32.9)
(+)	111 (59.7)	79 (81.4)		190 (67.1)
No. of metastatic organs, n (%)				
1	116 (62.4)	43 (44.3)	0.0037	159 (56.2)
≥2	70 (37.6)	54 (55.7)		124 (43.8)
Prior nephrectomy, n (%)				
Yes	174 (93.5)	81 (83.5)	0.0072	255 (90.1)
No	12 (6.5)	16 (16.5)		28 (9.9)
Targeted agents (%)				
Tyrosine kinase inhibitor	149 (80.1)	70 (72.2)	0.1295	219 (77.4)
mTOR inhibitor	37 (19.9)	27 (27.8)		64 (22.6)
Timing of treatment (%)				
First-line	77 (41.4)	43 (44.3)	0.6357	120 (42.4)
Second-line or later	109 (58.6)	54 (55.7)		163 (57.6)

CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; mRCC: metastatic renal cell carcinoma; NLR: neutrophil-to-lymphocyte ratio; ULN: upper limits of normal.

Fig. 1. Progression-free survival (PFS) for all cases.

Discussion

In this study, we demonstrated the impact of pretreatment NLR on predicting the response to targeted therapy in mRCC cases with extrapulmonary metastasis. To the best of our knowledge, the present study is the first report in which the significance of the pretreatment NLR differed depending on the metastatic organs in each case.

A previous study was focused on the significant implication of inflammatory response in the progression of mRCC.[15] Patients with advanced RCC sometimes show paraneoplastic syndrome with fever and leukocytosis. The involvement of several molecules related to inflammation, such as interleukin-6 ,[16] nuclear factor-kappa B,[17] and CRP,[10,11,13] on the progression of RCC have been previously demonstrated. A high NLR is associated with a poor prognosis in many solid tumours.[14] We focused on the NLR as a biomarker candidate for the response for targeted therapy in cases of mRCC. In the present study, high NLR was a predictive factor for poor PFS (Fig. 2, Table 2). These results were consistent with previous studies.[14,18] However, as shown in Table 1, the characteristics of cases in the low NLR group were quite different compared with those in the high NLR group. The rate of cases involving risk factors such as anemia, higher LDH, higher CRP, worse PS, and hypercalcemia in the high NLR group were higher than those in the low NLR group. In addition, the rate of extrapulmonary metastasis cases and that with two or more metastatic organs in the high NLR group were higher than those in the low NLR group, suggesting the possibility that the NLR is associated with metastatic status. Investigators have previously reported that systemic therapy, including targeted therapy and cytokine therapy, was expected to be effective in mRCC patients with lung metastasis. Cases with extrapulmonary metastasis were often resistant to these agents and showed poor prognosis. In retrospective studies,

extrapulmonary metastasis cases, disease progression was shown in 90 of 190 cases. The 50%PFS for the low NLR group (12 months) was significantly (p=0.0001) better than that for the high NLR group (6.7 months), while there was no significant difference in PFS between them in other cases (p=0.3457) (Fig. 3). Univariate analyses showed that several variables are significantly associated with PFS including histological findings, PS, prior nephrectomy, number of metastatic organs, timing of treatments, and pretreated NLR. Multivariate analyses revealed that pretreated NLR was an independent and the strongest prognostic factor for PFS in mRCC cases with extrapulmonary metastasis (Table 4).
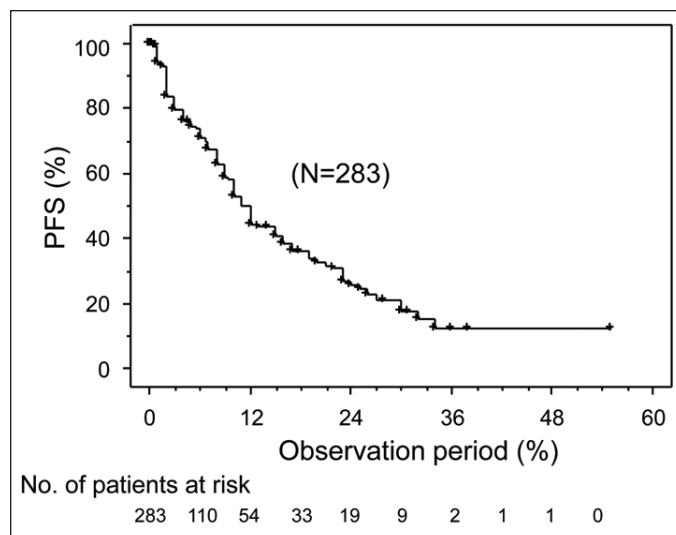
Table 2. Univariate and multivariate analyses to predict progression-free survival in all cases

	Univariate		Multivariate		
	HR	p	HR	95% CI	p
Age					
<65	reference	0.3560			
≥65	1.175				
Gender					
Male	reference	0.7668			
Female	1.042				
Histological findings					
Non-clear	reference	0.0002	reference		0.0001
Clear	0.391		0.360	0.214–0.604	
ECOG performance status					
0	reference	< 0.0001	reference		0.0053
≥1	2.380		1.905	1.210–2.997	
Anemia					
No	reference	0.0130	reference		0.3439
Yes	1.574		1.203	0.820–1.765	
Hypercalcemia					
No	reference	0.0241	reference		0.1817
Yes	2.863		1.905	0.740–4.905	
High LDH					
No	reference	0.7207			
Yes	1.162				
Prior nephrectomy					
No	reference	0.0051	reference		0.3259
Yes	0.403		0.703	0.348–1.420	
No. of metastatic organs					
≥2	reference	0.0032	reference		0.0781
1	0.588		0.712	0.488–1.039	
Targeted agent					
TKI	reference	0.0839			
mTORi	1.459				
Timing of treatment					
First-line	reference	0.0016	reference		0.0014
Second-line or later	1.814		1.929	1.288–2.889	
Pretreated NLR					
<3	reference	0.0022	reference		0.0014
≥3	1.769		1.805	1.281–2.806	

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; TKI: tyrosine-kinase inhibitor.

bone metastasis was significantly associated with a poor PFS and overall survival (OS) in clear-cell mRCC patients treated with sunitinib[19] and with everolimus after progression on vascular endothelial growth factor (VEGF)-targeted therapy.[20] Liver metastasis was also associated with shorter PFS and OS treated with first-line sunitinib[19] and was an independent risk factor for poor PFS and OS in cases treated with everolimus.[20] In a review from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), bone and liver metastases have been reported as predictive factors for poor prognosis.[21] Brain metastasis in mRCC was associated with poor prognosis, but improved compared with that

in the era of cytokine therapy.[22] This evidence indicates the importance of considering the metastatic status in predicting the therapeutic effect in mRCC cases. Therefore, we focused on the relationship between the NLR and metastatic status. As a result, PFS in the low NLR group was significantly better than that in the high NLR group, and a high NLR was an independent predictive factor for worse PFS in the cases with extrapulmonary metastasis, while there was no significant difference in those of other cases (Fig. 3, Table 4). These data suggest that the impact of high NLR as an adverse predictive factor on the effects of targeted therapy is more predominant in mRCC cases with extrapulmonary metastasis
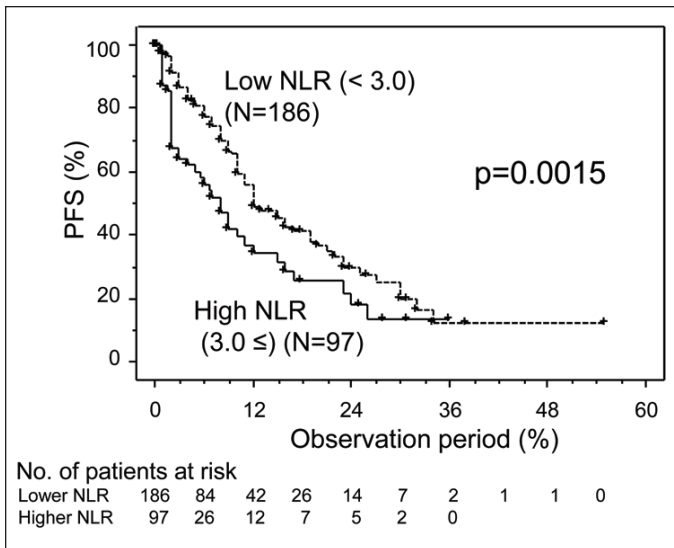
Fig. 2. Progression-free survival (PFS) for all cases of metastatic renal cell carcinoma (mRCC) involving targeted therapy further classified in accordance with neutrophil-to-lymphocyte ratio (NLR).

diseases,[24,25] and diabetes[26]), were not able to be considered. Furthermore, the association of high NLR and poor outcome of cancer patients has not been sufficiently understood. One of the potential mechanisms of the impact of high NLR on the progression of malignant diseases including mRCC is the association with the inhibition of immune cells, such as lymphocytes, by neutrophils, and another is the association of the activity of neutrophils to secrete cytokines and growth factors that promotes tumour growth.[14] Further study is required to clarify the mechanism of high NLR on the progression of cancers and to confirm the impact of the NLR for predicting the antitumour effect of targeted therapy in mRCC cases with extrapulmonary metastasis.

Conclusion

We demonstrated the significance of the NLR as one of the predictive factors in the response to molecular targeted therapy in mRCC cases with extrapulmonary metastasis. Since hematological tests are routinely conducted for patients with mRCC treated with targeted therapy, the NLR is easy to use in daily clinical practice. The establishment of a novel strategy is expected through the consideration of NLR as a biomarker.

than in cases with only lung metastasis. Recent advances in targeted therapy for mRCC has led to the necessity to predict the therapeutic effect by taking the site of metastasis into consideration. The present data might provide us with meaningful information for targeted therapy in mRCC cases with extrapulmonary metastasis.

The limitations of this study are that it is retrospective and relatively small. In addition, medical conditions other than malignant diseases, which have been reported to be associated with NLR (such as hypertension,[23] cardiovascular
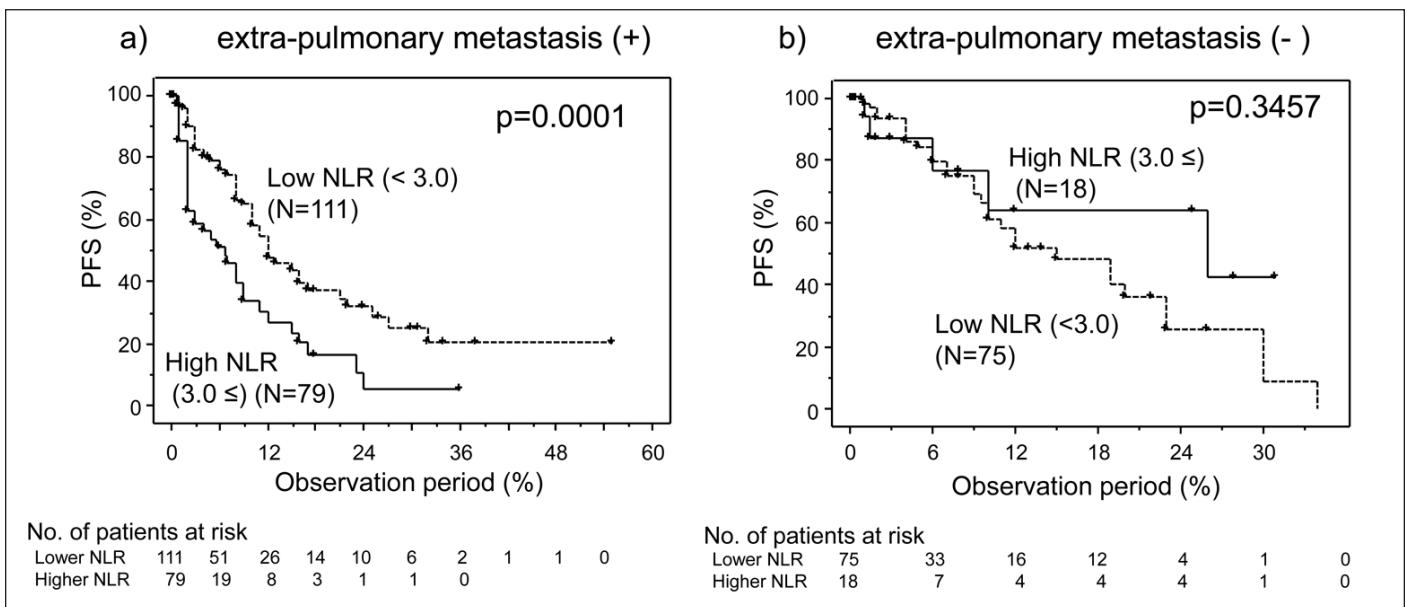

Fig. 3. Progression-free survival (PFS) for cases of metastatic renal cell carcinoma (mRCC) involving targeted therapy further classified in accordance with neutrophil-to-lymphocyte ratio (NLR) in cases of *(a)* extrapulmonary metastasis; and *(b)* those of no extrapulmonary metastasis.

Table 3. Characteristics of mRCC cases of extrapulmonary metastasis involving molecular targeted therapy

	Pretreated NLR			Total
	Low (≤3.0)	High (>3.0)	p	
No. of patients	111	79		190
Age, range (median)	40–85 (64)	47–85 (67)	0.0762	40–85 (65)
Gender, n (%)				
Male	96 (86.5)	65 (82.3)	0.4267	161 (84.7)
Female	15 (13.5)	14 (17.7)		29 (15.3)
Histological type, n (%)				
Clear	92 (82.9)	65 (82.3)	0.9137	157 (82.6)
Non-clear	19 (17.1)	14 (17.7)		33 (17.4)
ECOG performance status, n (%)				
0	87 (78.4)	57 (72.2)	0.3234	144 (75.8)
≥1	24 (21.6)	22 (27.8)		46 (24.2)
Anemia, n (%)				
(-)	58 (52.3)	59 (74.7)	0.0017	117 (61.6)
(+)	53 (47.7)	20 (25.3)		73 (38.4)
Hypercalcemia, n (%)				
(-)	109 (98.2)	71 (89.9)	0.0113	180 (94.7)
(+)	2 (1.8)	8 (10.1)		10 (5.3)
LDH (%)				
≤1.5 x ULN	105 (94.6)	69 (87.3)	0.0760	174 (91.6)
> 1.5 x ULN	6 (5.4)	10 (12.7)		16 (8.4)
Metastatic organs, n (%)				
1	41 (36.9)	26 (32.9)	0.5671	67 (35.3)
≥2	70 (63.1)	53 (67.1)		123 (64.7)
Prior nephrectomy, n (%)				
Yes	102 (91.9)	64 (81.0)	0.0261	166 (87.4)
No	9 (8.1)	15 (19.0)		24 (12.6)
Targeted agents, n (%)				
TKI	85 (76.6)	57 (72.2)	0.4891	142 (74.7)
mTOR inhibitor	26 (23.4)	22 (27.8)		48 (25.3)
Timing of treatment, n (%)				
First-line	42 (37.8)	34 (43.0)	0.4708	76 (40.0)
Second-line or later	69 (62.2)	45 (57.0)		114 (60.0)

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; mRCC: metastatic renal cell carcinoma; NLR: neutrophil-to-lymphocyte ratio; TKI: tyrosine kinase inhibitor; ULN: upper limits of normal.

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Table 4. Univariate and multivariate analyses to predict progression-free survival in cases of extrapulmonary metastasis

	Univariate		Multivariate		
	HR	p	HR	95% CI	p
Age					
<65	reference	0.6781			
≥65	1.092				
Gender					
Male	reference	0.7756			
Female	1.107				
Histological findings					
Non-clear	reference	0.0003	reference		0.0001
Clear	0.378		0.340	0.195–0.593	
ECOG performance status					
0	reference	0.0003	reference		0.0042
≥1	2.307		2.065	1.257–3.393	
Anemia					
No	reference	0.1287			
Yes	1.391				
Hypercalcemia					
No	reference	0.0714			
Yes	2.338				
High LDH					
No	reference	0.6896			
Yes	1.203				
Prior nephrectomy					
No	reference	0.0079	reference		0.3156
Yes	0.414		0.692	0.338–1.420	
No. of metastatic organs					
≥2	reference	0.0220	reference		0.0784
1	0.582		0.645	0.396–1.051	
Targeted agent					
TKI	reference	0.1318			
mTORi	1.451				
Timing of treatment					
First-line	reference	0.0019	reference		0.0004
Second-line or later	2.016		2.386	1.477–3.583	
Pretreated NLR					
<3	reference	0.0003	reference		<0.0001
≥3	2.192		2.739	1.734–4.328	

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; TKI: tyrosine-kinase inhibitor.

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