



The platelet-to-lymphocyte ratio as a significant prognostic factor to predict survival outcomes in patients with synchronous metastatic renal cell carcinoma

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Purpose: The clinical impact of the platelet-to-lymphocyte ratio (PLR) on the prognosis of patients with metastatic renal cell carcinoma (mRCC) remains controversial. We investigated the associations between elevation of the PLR and disease prognosis in patients with synchronous mRCC.

Materials and Methods: The data of 1,505 patients with synchronous mRCC were retrospectively analyzed. The entire cohort was stratified into two subgroups according to PLR. Kaplan–Meier and Cox proportional analyses were performed to investigate the possible associations between the PLR and disease prognosis.

Results: There were 921 patients with a high PLR and 584 patients with a low PLR by use of the cutoff of 146. The patients with a high PLR had worse clinical characteristics in terms of advanced clinical stage ($p < 0.001$) and rate of lymph node invasion ($p = 0.036$). The Kaplan–Meier analysis showed that patients with a high PLR had significantly shorter overall survival (OS) ($p < 0.001$) and cancer-specific survival (CSS) ($p < 0.001$). The multivariate Cox analysis revealed that the PLR was an independent predictor for shorter OS (hazard ratio [HR], 1.345; 95% confidence interval [CI], 1.183–1.530; $p < 0.001$) and CSS (HR, 1.318; 95% CI, 1.156–1.502; $p < 0.001$). In the subgroup analyses, the PLR showed a significant association with survival outcomes in the subgroup with clear cell type (all $p < 0.05$) but not in the subgroup with the non–clear cell type.

Conclusions: The PLR was an independent prognostic factor for survival outcomes in patients with mRCC. However, the association was statistically significant only in patients with clear cell type mRCC.

Keywords: Biomarkers; Blood platelets; Kidney neoplasms; Lymphocytes; Neoplasm metastasis

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INTRODUCTION

Renal cell carcinoma (RCC) is the sixth most frequently diagnosed cancer in men and the tenth most common cancer in women in the United States [1]. According to the World Health Organization, overall 140,000 people die every year of RCC, which is the 13th most common cause of cancer-related death worldwide [2]. The continuous development of imaging technology and implementation of frequent health checkups have resulted in a higher incidence of RCC and a trend for down-staging [3,4]. However, a significant number of patients are still diagnosed as having metastatic RCC (mRCC) at the time of diagnosis [3]. The most frequent sites of metastasis are the bones, lungs, liver, brain, and lymph nodes [5]. Approximately 40% of patients with mRCC eventually die of the disease [2,6-8].

Once cancer cells are identified inside a thrombus, platelets play a significant role in the spread of cancer [9]. Several previous studies have demonstrated a significant association between the platelet count and the spread of cancer [10,11]. Other previous studies have also shown that thrombocytosis is significantly related to worse prognosis in the presence of several malignancies including that of the prostate and the kidney [12-15]. The platelet-to-lymphocyte ratio (PLR) is a new biomarker that can be easily calculated from a routine blood test and that reflects the host's inflammatory status and platelet activation [16]. An elevated preoperative PLR has been reported to have a significant association with worse prognosis in patients with localized RCC [16,17]. However, there are few studies of the clinical impact of the PLR on the survival of patients with mRCC. As there are still not many prognostic biomarkers that can accurately predict the prognosis of patients with mRCC, it would be clinically meaningful to reveal a possible association between the PLR and the prognosis of mRCC. Therefore, in the present study, we tried to evaluate the prognostic value of the PLR by analyzing our multi-institutional mRCC database.

MATERIALS AND METHODS

After obtaining the approval of the Institutional Review Board of Bundang Seoul National University Hospital (approval number: B-1907/553-106), data for 1,505 patients with synchronous mRCC who were diagnosed at nine institutions in the Republic of Korea from 2003 to 2018 were retrospectively analyzed. The clinicopathologic information was retrieved from our multi-institutional database, which is centrally managed. The initial imaging evaluation was performed by use of abdominal computed tomography (CT),

chest CT, and bone scan (BS). Further workups, such as magnetic resonance imaging (MRI) or ultrasonography, were also performed at the clinicians' discretion. When metastasis was found, positron emission tomography-CT of the torso or MRI or CT of the brain was additionally performed to accurately evaluate the site of metastasis. Most patients who underwent cytoreductive surgery as an initial treatment had CT, MRI, and BS performed every 3 months after surgery. Also, most of the patients who underwent systemic treatments such as tyrosine kinase inhibitor therapy had CT, MRI, and BS performed of the metastatic sites every 3 cycles to evaluate therapeutic efficacy. The clinical and pathologic stages were determined according to the 7th edition of the cancer staging manual from the American Joint Committee on Cancer [15]. The PLR was calculated by using the laboratory results at the time of diagnosis. The cutoff value for low and high PLRs was set at 146, which was observed to have the highest Youden's score after analyzing the receiver operating characteristic curve of the PLR on cancer-specific survival (CSS). The entire cohort was divided into two subgroups according to PLR values. The survival data were acquired from the national database of the Statistics Korea and also from the medical records. Overall survival (OS) and CSS were defined as the duration from the date of diagnosis to death.

Independent t-test and chi-square test were performed to compare the clinicopathologic characteristics between the subgroups. The Kaplan–Meier analysis with a log-rank test was performed to compare the survival outcomes between the subgroups. Multivariate Cox proportional hazard analyses were performed to identify the possible predictors of each survival outcome. All statistical analyses were performed by use of the IBM SPSS Statistics ver. 25.0 (IBM Corp, Armonk, NY, USA). All p-values were two-sided and a p-value of <0.05 was considered statistically significant.

RESULTS

The clinicopathologic data of 1,505 subjects are summarized in Table 1. The median age of the patients was 60.0 years (interquartile range [IQR], 50.6–68.0), and the median duration of survival after diagnosis was 14.0 months (IQR, 6.1–30.0). Among the total number of patients, 855 (56.8%) underwent cytoreductive nephrectomy (Supplementary Table 1). With respect to the location of metastases at the time of diagnosis, 994 patients (66.0%) had lung metastasis, 553 (36.7%) had lymph node metastasis, 405 (26.9%) had bone metastasis, 62 (4.1%) had brain metastases, and 1,396 (92.8%) had multiple metastases at diagnosis, including metastases

Table 1. Patient characteristics according to the platelet-to-lymphocyte ratio

Parameter	Total (n=1,505)	High PLR (n=921)	Low PLR (n=584)	p-value
Age (y)	59.4±12.4	59.0±12.5	60.0±12.2	0.107
BMI (kg/m ²)	23.0±3.4	22.6±3.2	23.6±3.6	<0.001
DM (yes)	290 (19.3)	166 (18.0)	124 (21.2)	0.141
HTN (yes)	632 (42.0)	357 (38.8)	275 (47.1)	0.002
Sex (male)	1,164 (77.3)	696 (75.6)	468 (80.1)	0.046
Smoking				0.091
Nonsmoker	834 (55.4)	521 (56.6)	313 (53.6)	
Ex-smoker	380 (25.2)	241 (26.2)	139 (23.8)	
Current smoker	247 (16.4)	135 (14.7)	112 (19.2)	
Unknown	40 (2.7)	22 (2.4)	18 (3.1)	
MSKCC score				<0.001
Favorable	11 (0.7)	4 (0.4)	7 (1.2)	
Intermediate	855 (56.8)	431 (46.8)	424 (72.6)	
Poor	639 (42.5)	486 (52.8)	153 (26.2)	
ECOG-PS				<0.001
0	805 (53.5)	322 (35.0)	260 (44.5)	
1	116 (7.7)	517 (56.1)	288 (49.3)	
≥2	2 (0.1)	82 (8.9)	36 (6.2)	
Mean KPS (%)	93.3±6.3	92.8±6.3	94.2±6.1	<0.001
Hemoglobin (g/dL)	12.1±2.4	11.4±2.2	13.2±2.3	<0.001
Platelet (10 ⁹ /L)	296.2±111.8	338.0±111.7	230.3±73.5	<0.001
PLR	0.199±0.121	0.257±0.121	0.107±0.027	<0.001
NLR	3.8±3.5	4.7±4.0	2.4±1.6	<0.001
LDH (U/L)	337.9±258.6	346.6±277.6	324.3±225.6	0.322
Ca (mEq/L)	9.5±1.1	9.5± 3.5	9.3± 0.8	0.128
T stage				<0.001
T1		153 (16.6)	174 (29.8)	
T2		203 (22.0)	93 (15.9)	
T3		331 (35.9)	165 (28.3)	
T4		93 (10.1)	75 (12.8)	
Tx		141 (15.3)	77 (13.2)	
N1	537 (35.7)	344 (37.4)	193 (33.0)	0.140
M1		826 (89.7)	517 (88.5)	0.535
Site of metastasis				
Lung	994 (66.0)	624 (67.8)	370 (63.4)	0.089
Brain	62 (4.1)	43 (4.7)	19 (3.3)	0.226
Bone	405 (26.9)	257 (27.9)	148 (25.3)	0.302
Lymph node	553 (36.7)	358 (38.9)	195 (33.4)	0.036
Others	288 (19.1)	181 (19.7)	107 (18.3)	0.571
Histology				0.243
Clear cell	1,235 (82.1)	747 (81.1)	488 (83.6)	
Non clear cell	228 (15.1)	149 (16.2)	79 (13.5)	
Unknown	42 (2.8)	25 (2.7)	17 (2.9)	
Cytoreductive nephrectomy	855 (56.8)	501 (54.4)	354 (60.6)	0.018
Systemic therapy				0.511
Cytokines	187 (12.4)	105 (11.4)	82 (14.0)	
Tyrosine kinase	1,193 (79.3)	740 (80.3)	453 (77.6)	
mTOR inhibitor	104 (6.9)	63 (6.8)	41 (7.0)	
Others	21 (1.4)	13 (1.4)	8 (1.4)	
Time to progression	6.9±8.9	8.2±9.6	6.3±8.6	<0.001

Values are presented as mean±standard deviation or number (%).

PLR, platelet-to-lymphocyte ratio; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; MSKCC, Memorial Sloan Kettering Cancer Center; ECOG-PS, Eastern Cooperative Oncology Group–performance status; KPS, Karnofsky performance status; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase.

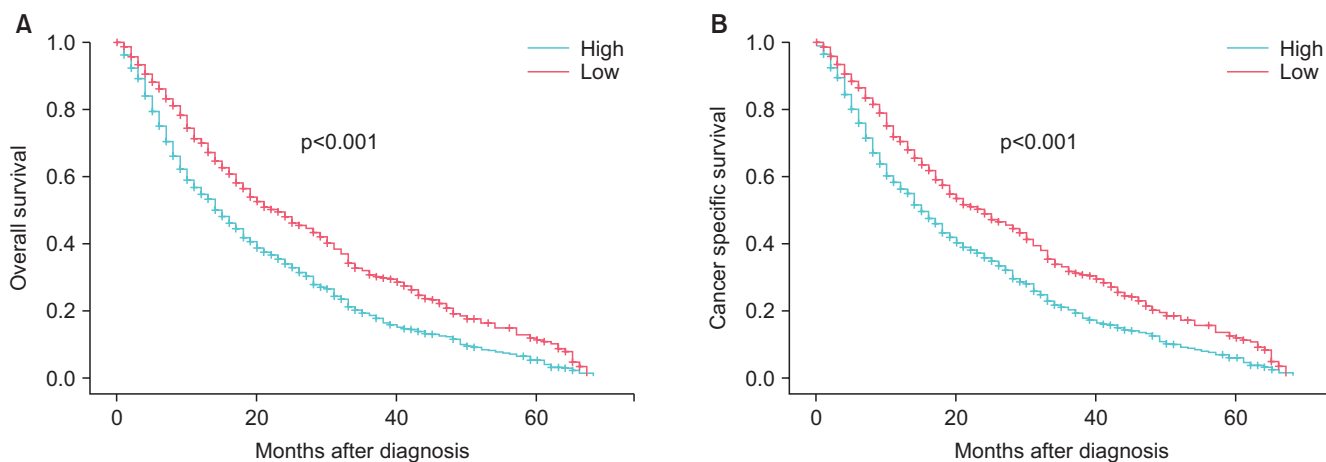


Fig. 1. Kaplan–Meier analyses of overall (A) and cancer-specific (B) survival according to the platelet-to-lymphocyte ratio.

Table 2. Multivariate Cox proportional hazards analyses of the platelet-to-lymphocyte ratio on overall survival and cancer-specific survival

Parameter	Overall survival	p-value	Cancer-specific survival	p-value
Age	0.997 (0.992–1.002)	0.266	0.996 (0.991–1.002)	0.172
Smoking status		0.106		0.096
Nonsmoker	Reference		Reference	
Ex-smoker	1.068 (0.701–1.626)	0.760	1.059 (0.889–1.628)	0.793
Current smoker	1.101 (0.956–1.269)	0.183	1.103 (0.955–1.274)	0.181
PLR	1.345 (1.183–1.530)	<0.001	1.318 (1.156–1.502)	<0.001
MSKCC score		<0.001		<0.001
Favorable	Reference		Reference	
Intermediate	1.724 (0.817–3.637)	0.153	1.664 (0.788–3.511)	<0.182
Poor	2.355 (1.113–4.985)	0.026	2.309 (1.091–4.889)	<0.029
LN positive	1.188 (1.048–1.346)	0.007	1.194 (1.051–1.355)	0.006
Cytoreductive nephrectomy	0.511 (0.451–0.580)	<0.001	0.506 (0.445–0.576)	<0.001

Values are presented as hazard ratio (95% confidence interval).

PLR, platelet-to-lymphocyte ratio; MSKCC, Memorial Sloan Kettering Cancer Center; LN, lymph node.

to the lungs, liver, lymph nodes, bone, brain, soft tissue, skin, adrenal gland, gallbladder, thyroid, colon, stomach, pancreas, and parotid gland. After a median follow-up of 120 months (IQR, 6.0–25.0), 1,164 patients died of RCC. Overall, 1,205 subjects died of all causes (all-cause mortality) after a median follow-up of 120 months (IQR, 6.0–25.0).

When we stratified the patients into two subgroups according to high and low PLR, there were 921 and 584 patients with high and low PLR, respectively. Median survival in the group with a high PLR was 10 months (IQR, 0–68 months), and median survival in the group with a low PLR was 16 months (IQR, 0–67 months). The Kaplan–Meier analysis revealed that there were significant statistical differences in OS and CSS between the two subgroups ($p < 0.05$) (Fig. 1). Subsequent multivariate Cox proportional analysis revealed that an elevated PLR at diagnosis was an independent predictor for shorter OS (hazard ratio [HR], 1.345; 95%

confidence interval [CI], 1.183–1.530; $p < 0.001$) and CSS (HR, 1.318; 95% CI, 1.156–1.502; $p < 0.001$) (Table 2). Furthermore, the Memorial Sloan Kettering Cancer Center (MSKCC) risk factor and cytoreductive nephrectomy also showed significant associations in the multivariate Cox proportional analysis with OS (HR, 0.511; 95% CI, 0.451–0.580; $p < 0.001$) and CSS (HR, 0.506; 95% CI, 0.445–0.576; $p < 0.001$).

Pathologic information on cellular type was available for 1,463 patients. Among them, 855 underwent cytoreductive nephrectomy and 608 underwent biopsies on the metastatic sites. There were 1,235 patients with clear cell type and 228 patients with non-clear cell type. We performed further subgroup analyses separately in both the clear cell and non-clear cell type subgroups to confirm whether the previous association had any cell type specificity. The multivariate analyses demonstrated that only the PLR showed significant results in the clear cell type subgroup (OS: HR, 1.351;

Table 3. Multivariate Cox proportional hazards analyses of the platelet-to-lymphocyte ratio on overall survival and cancer-specific survival in the clear cell type subgroup

Parameter	Overall survival	p-value	Cancer-specific survival	p-value
Age	0.996 (0.990–1.003)	0.247	0.995 (0.989–1.001)	0.130
Smoking status		0.091		0.068
Nonsmoker	Reference		Reference	
Ex-smoker	0.830 (0.688–1.001)	0.052	0.820 (0.677–0.993)	0.062
Current smoker	1.033 (0.883–1.209)	0.686	1.041 (0.887–1.221)	0.622
PLR	1.351 (1.171–1.559)	<0.001	1.338 (1.156–1.548)	<0.001
MSKCC score		<0.001		<0.001
Favorable	Reference		Reference	
Intermediate	1.885 (0.841–4.222)	0.124	1.831 (0.817–4.104)	0.142
Poor	2.620 (1.165–5.890)	0.020	2.546 (1.132–5.727)	0.024
LN positive	1.188 (1.031–1.369)	0.017	1.193 (1.032–1.378)	0.017
Cytoreductive nephrectomy	0.528 (0.458–0.609)	<0.001	0.525 (0.454–0.607)	<0.001

Values are presented as hazard ratio (95% confidence interval).

PLR, platelet-to-lymphocyte ratio; MSKCC, Memorial Sloan Kettering Cancer Center; LN, lymph node.

95% CI, 1.171–1.559; $p < 0.001$; CSS: HR, 1.338; 95% CI, 1.156–1.548; $p < 0.001$), but not in the non-clear cell subgroup (all $p > 0.05$) (Table 3). Moreover, cytoreductive nephrectomy also showed significant associations upon multivariate Cox proportional analysis with OS (HR, 0.528; 95% CI, 0.458–0.609; $p < 0.001$) and CSS (HR, 0.525; 95% CI, 0.454–0.607; $p < 0.001$) in the clear cell type subgroup.

DISCUSSION

The present study demonstrated that an elevated PLR at diagnosis was significantly associated with shorter CSS and OS in patients with mRCC. In addition, MSKCC risk group, lymph node positivity, and cytoreductive nephrectomy were associated with survival outcomes in mRCC patients. An elevated PLR independently predicted shorter survival outcomes when analyzed together with previously known risk factors, including MSKCC risk group. Interestingly, these associations were observed only in the clear cell type subgroup and not in the non-clear cell type subgroup.

The PLR is defined as the ratio of platelets to lymphocytes. Platelets are traditionally known to be a component of the coagulation process. A debated view is that they may also have a role related to tissue repair, immune activation, primary tumor formation, and cancer metastasis [9]. In addition to hemostasis, platelets release multiple growth factors, such as vascular endothelial growth factor, an angiogenic factor, and platelet-derived growth factor through the release of metalloproteases [9,16]. Lymphocytes play an important role in tumor defense by inducing cytotoxic death and inhibiting tumor cell proliferation and migration [9].

Platelets and leukocytes interact with each other to contribute to cell activation [17]. Cytokines or chemokines caused by inflammation activate platelets, and activated platelets induce the accumulation of leukocytes at the inflammatory site, causing leukocytosis. Once induced, leukocytosis reactivates the platelets, causing thrombocytosis [17]. The released growth factors enable tumor growth and metastasis [16]. Platelets also protect circulating tumor cells from killer T cell-mediated cytotoxicity, and cancer cells promote an increase in platelet count and activation through the release of thrombopoietic cytokines and platelet agonists [9]. Some lymphocytes destroy host cells that have been transformed to a cancerous state [9].

After the first report on the existence of cancer cells in tumor thrombi was published [17], several retrospective pieces of evidence have shown that an elevated platelet count is associated with worse survival outcomes in several cancers, including those of the colon, lung, kidney, and prostate [10-15]. Even though the exact mechanism of association between platelet count and cancer prognosis is not known, some studies have suggested several hypotheses. Bastida and Ordinas [16] suggested that platelet activation in cancer cells may involve several mechanisms, including thrombin generation, ADP release, cathepsin B activation, and arachidonate metabolism. These reactions are known to be translated into tumor cell-induced platelet aggregation [18]. Fibrinogen is also known to play some role in bridging the tumor cells with the platelets [19]. Furthermore, platelets seem to have some capacity to activate lymphatic endothelial cells and stimulate lymphangiogenesis [20]. After analyzing pathologic data from patients with esophageal cancer, Seles et al. [21] also

demonstrated that the thrombocytic clusters have a higher lymphatic microvessel density. Even though the exact mechanism underlying the role of platelet function in the tumor microenvironment and tumor progression is not known, it seems evident that platelets do have certain crucial roles.

We were not the first to evaluate the association between platelet count and the prognosis of RCC. Seles et al. [21] retrospectively analyzed the data of 652 patients with non-mRCC and concluded that platelet volume is associated with worse clinical outcomes, such as large tumor volume, higher tumor grade, and certain unfavorable pathologic results (sarcomatoid features and tumor necrosis). They also showed that platelet volume is significantly associated with worse survival outcomes. A different study by Kim et al. [22] that analyzed the data of 309 patients with non-mRCC demonstrated that a higher neutrophil-to-lymphocyte ratio and PLR is associated with shorter recurrence-free survival. More recently, Huszno et al. [23] tried to evaluate the prognostic role of the PLR in patients with mRCC. They retrospectively analyzed the data of 141 patients with mRCC and concluded that an elevated PLR is significantly associated with both shorter OS and progression-free survival. However, they could analyze only a relatively small-sized data set from 141 subjects, which is a noted limitation of a single-institution study. In the present study, we collected and analyzed the data of 1,505 subjects from multiple institutions and found that the PLR was an independent prognostic biomarker for survival outcomes when analyzed with current prognostic predictors such as MSKCC risk groups. Thrombocytosis is a known marker of inflammation and is associated with the negative outcome of RCC [24,25]. In addition to the PLR in our study, previous studies have reported that platelet levels may also play a role in predicting prognosis. The cutoff value of the PLR we used was 146, which was slightly lower than the cutoff values (150 to 210) of the previous studies [26-28]. These subtle differences in cutoff values may be due to differences in timing of tests, differences in disease states, differences in the host's immune response, and differences in tumor characteristics. However, most previous studies also reported the role of the PLR as a poor prognostic factor for survival outcomes in mRCC [21-23,26-28].

Our study had certain limitations. First, our data were collected from multiple institutions in the Republic of Korea and are therefore heterogeneous in nature, which may limit the generalization of our findings to clinical applications. Second, having a retrospective design, our study had the possibility of selection biases as well as recall bias. Third, different treatment protocols and drug sequencing might have influenced the patients' prognosis, which was not investigat-

ed in the present study owing to the lack of data. Notwithstanding these limitations, we believe that our study could provide some valuable information on the clinical impact of the PLR as a novel prognostic factor for predicting oncologic outcomes in patients with mRCC.

CONCLUSIONS

An elevated PLR at diagnosis was significantly associated with worse survival outcomes in patients with mRCC. Interestingly, this association was significant only in the subgroup with the clear cell subtype and not in the subgroup with the non-clear cell subtype.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Hyeong Dong Yuk and Hakmin Lee. Data acquisition: Eu Chang Hwang, Jae Young Park, Chang Wook Jeong, Cheryn Song, Seong Il Seo, Seok-Soo Byun, Cheol Kwak, Sung-Hoo Hong, and Jinsoo Chung. Statistical analysis: Hyeong Dong Yuk and Hakmin Lee. Data analysis and interpretation: Hyeong Dong Yuk and Hakmin Lee. Drafting of the manuscript: Hyeong Dong Yuk. Critical revision of the manuscript: Hakmin Lee and Minyong Kang. Supervision: Jinsoo Chung, Minyong Kang, Sung-Hoo Hong, Cheol Kwak, and Seong Il Seo. Approval of the final manuscript: Hyeong Dong Yuk and Hakmin Lee.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via <https://doi.org/10.4111/icu.20200002>.

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