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ORIGINAL ARTICLE

Lactate Dehydrogenase-to-Lymphocyte Ratio Represents a Powerful Prognostic Tool of Metastatic Renal Cell Carcinoma Patients Treated with Tyrosine Kinase Inhibitors

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Abstract

Inflammation parameters were verified to predict clinical outcomes of metastatic renal cell carcinoma (mRCC) patients treated with tyrosine kinase inhibitors (TKIs). Here, we developed a novel marker, lactate dehydrogenase (tumor burden marker) to lymphocytes (inflammation marker) ratio (LLR), aimed to reveal the prognostic role of LLR for mRCC patients treated with TKIs. We collected clinical data of mRCC patients treated with TKIs. Receiver operating curve analysis was used to determine the optimal cut-off value. The c-index method was used to determine the best predictive marker for overall survival (OS). Clinicopathological characteristics on OS and progression-free survival (PFS) were evaluated by univariate analysis, and multivariate analyses. LLR provided the greatest improvement in the c-index, and displayed the best marker of the prognostic accuracy for OS. Univariate analysis revealed that LLR, ECOG PS and IMDC risks were significant predictors of OS and PFS. However, multivariate analysis indicated that IMDC risks failed to predict PFS, and only showed predictor of OS. We finally stratifed patients into low LLR (<150) and high LLR (≥150) group with different clinical outcomes. LLR represents a powerful prognostic tool of clinical outcome in mRCC patients treated with TKIs.

Keywords International metastatic renal cell carcinoma database consortium · Metastatic renal cell carcinoma · Lactate dehydrogenase to lymphocytes ratio · Tyrosine kinase inhibitors · Prognostic factors

Introduction

Most of kidney cancer in adults is renal cell carcinoma (RCC) and 30% kidney cancer patient will finally develop to the metastatic stage, i.e. metastatic RCC (mRCC) [1]. RCC has been considered as an immune-responsive tumor, and thus immunotherapy with high dose IL-2 has been successfully used in clinics for a subset of patients [2]. With the development of molecular targeted therapies, targeting agents including the vascular endothelial growth factor (VEGF), mammalian target of rapamycin pathways (mTOR), and tyrosine kinase inhibitors (TKI), have been introduced to mRCC

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treatment scheme [3]. More recently, immune checkpoint inhibition is more refined and novel immunotherapy approach for mRCC. Programmed cell death protein-1 (PD-1) antibody, Nivolumab, was the first checkpoint inhibitor to be approved by the US Food and Drug Administration for the second line mRCC treatment in November 2015 [4]. However, only a subset of patients may gain survival amelioration from these therapies [3]. Thus, identification of predictive or prognostic biomarkers may be needed to stratificate mRCC patients for precision therapy [3].

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model was first specifically established and widely used for mRCC patients in 2009 [5], and subsequently additional prognostic factors were identified including systematic inflammation markers [6]. A series of systematic inflammation-based prognostic parameters, such as C-reactive protein (CRP) [7], Glasgow prognostic score (GPS) [8], platelet-to-lymphocyte ratio (PLR) [9], neutrophil-to-lymphocyte ratio (NLR) [10], the systemic inflammation response index (SIRI) [11], and the systemic immune-inflammation index (SII) [12], were used to examine their predictive or prognostic roles for mRCC patients. And, NLR was identified as the most useful inflammation based prognostic score for predicting survival in patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy [12]. However, inflammation markers alone were not enough to predict clinical outcomes, and tumor burden associated markers were suggested as the prognostic marker in the recent study [13].

In the present study, we aimed to reveal the prognostic roles of tumor burden marker, lactate dehydrogenase (LDH) to lymphocytes ratio (LLR) for mRCC patients. We developed pre-treatment LLR, and examined the prognostic value of LLR in our mRCC patients. To our best of knowledge, this is the first study to investigate the prognostic value of LLR in mRCC patients.

Materials and Methods

Patients

A total of 355 mRCC patients treated with first-line tyrosine kinase inhibitors (TKIs) between January 2010 and December 2017 were included in the study. Patients with immunodeficiency including human immunodeficiency virus seropositivity, other malignancies diagnosed during the observation period, insufficient data, were excluded in the present study. Patients with history of other treatments, such as neoadjuvant, adjuvant or any investigational therapy, before TKIs were also excluded from the present study. The study was approved by the local ethical committee.

Pre-Treatment Systematic Inflammation-Based Prognostic Parameters

Pre-treatment laboratory parameters, including lymphocytes, monocyte/granulocyte, neutrophil, derived neutrophil, platelet and serum levels of LDH, were obtained within 1 week before the initiation of the TKI treatment. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count, dNLR was determined as the absolute derived neutrophil count divided by the absolute lymphocyte count, PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count, M/GLR was calculated as the absolute monocyte/granulocyte count divided by the absolute lymphocyte count, LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count, LLR was determined as the serum level of LDH divided by the absolute lymphocyte count.

Clinical Outcomes

Overall survival (OS) was defined as the time from the date of the start of first-line TKI therapy until death from any cause, or the last follow-up. Progression-free survival (PFS) was calculated from the day of first-line TKI treatment until relapse, disease progression, death from any cause, or the last follow-up.

Statistical Analysis

The optimal cut-off value for NLR, dNLR, PLR, M/GLR, LLR and LMR were defined using receiver operating curve (ROC) analysis. Survival were calculated using the Kaplan-Meier method and compared with the log-rank test. LLR and other clinicopathological characteristics on OS and PFS were evaluated by univariate analysis, and variables with $P < 0.05$ were entered into multivariate analyses using the forward conditional Cox proportional hazards model. All tests were two sided, and $P < 0.05$ was considered statistically significant using SPSS software.

Results

Baseline Patient Characteristics

A total of 355 mRCC patients treated with first-line TKIs were included for analysis in the study. The median age was 62 years (range: 23–87), 71% (252/355) of patients were male gender. The majority of patients (315/355) were clear cell carcinoma type (89%). Based on the Eastern Cooperative Oncology Group performance status (ECOG PS), most of patients (309/355) had classified as 0–1. According to International Metastatic Renal Cell Carcinoma Database

Consortium (IMDC) model, 40% patients (142/355) were classified as favorable-risk group, 51% patients (181/355) were classified as intermediate-risk group, and 9% patients (32/355) were classified as poor-risk group. 59% (209/355) of patients had low LLR level (<150) and 41% (146/355) of patients had high LLR level (≥150).

Determination the Optimal Cut-off Values

We used OS as the endpoint of the study, and adopted ROC analysis to calculate the optimal cut-off value for NLR, dNLR, PLR, M/GLR, LLR and LMR. The area under receiver operating curve (AUC) for NLR, dNLR, PLR, M/GLR, LLR and LMR were 0.735, 0.705, 0.761, 0.706, 0.730, 0.760, and the optimal cut-off value corresponding to the maximum joint sensitivity and specificity were 3.5, 2.0, 180, 2.8, 150, and 2.9, respectively (Table 1).

LLR Is the Best Marker of the Prognostic Accuracy for OS

To determine the best predictive marker for OS, we used the c-index method. The c-index in the base model was 0.741. The c-index was improved by the addition of NLR (c-index: 0.689), dNLR (c-index: 0.727), PLR (c-index: 0.720), M/GLR (c-index: 0.714), LLR (c-index: 0.812), and LMR (c-index:0.782). LLR showed the best performance on the c-index, so LLR is the best marker of the prognostic accuracy for OS.

LLR Is an Independent Prognostic Marker in mRCC Patients

At the time of analysis, 260 of the 355 patients had progressed and 193 of 355 patients died. The median progression-free survival (PFS) was 14.2 months (95% confdence interval (CI) 12.1–17.2) and the median overall survival (OS) was 32.7 months (95% CI 27.1–36.4) (Table 2). We further assessed the impact of LLR and clinicopathological characteristics on OS and PFS by univariate analysis and Cox regression model. LLR showed significant association with OS and PFS (Table 2). In addition, ECOG PS and IMDC risks were significant predictors of OS and PFS (Table 2). Multivariate analysis demonstrated that ECOG PS and LLR were also significant predictors of OS and PFS. However, IMDC risks (poor and intermediate vs good risk) failed to predict PFS, and only showed predictor of OS.

LLR Distinguish Patients with OS and PFS

Finally, we established the novel prognostic model based on LLR. Patients with LLR < 150 had the median OS of 46 months and LLR ≥ 150 had the median OS of 21 months (log Rank:$\chi^2 = 7.820$, df = 1, $p<0.05$), LLR < 150 had median PFS of 18 months and LLR ≥ 150 had the median PFS of 9 months (log Rank:$\chi^2 = 7.034$, df = 1, $p<0.05$) (Fig. 1).

Discussion

In the present study, univariate analysis revealed that LLR, ECOG PS and IMDC risks were significant predictors of OS and PFS. Multivariate analysis demonstrated that ECOG PS and LLR were also significant predictors of OS and PFS. However, IMDC risks (poor and intermediate vs good risk) failed to predict PFS, and only showed predictor of OS. Survival distributions differed between the two groups with median OS of 46 months and 21 months, and median PFS of 18 months and 9 months in low (LLR < 150) and high (LLR ≥ 150) LRR patients, respectively. The major limitation of the present study is that it represents a large single institution series, which may have an inherent selection bias resulting in better than usual outcome or prognostic factors. And, a noteworthy limitation of the present study is its nature of retrospective design. Validation in a larger prospective study design in multi-center is warranted to confirm the conclusion of the present study.

Table 1 Determination the optimal cut-off values for NLR, dNLR, PLR, M/GLR, LLR and LMR in mRCC patients before TKI treatment

Group	AUC	95%CI		*P*	Critical point		Threshold
		Lower	Upper		Sensitivity	Specificity	
NLR	0.735	0.630	0.839	<0.001	78.5%	62.8%	3.5
dNLR	0.705	0.602	0.809	0.001	53.6%	78.6%	2.0
PLR	0.761	0.666	0.856	<0.001	74.8%	66.8%	180
M/GLR	0.706	0.603	0.808	0.001	79.1%	63.8%	2.8
LLR	0.730	0.613	0.847	<0.001	74.9%	65.1%	150
LMR	0.760	0.639	0.884	<0.001	75.6%	83.6%	2.9

Abbreviations: *NLR* neutrophil-to-lymphocyte ratio, *dNLR* derived neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *M/GLR* monocyte/granulocyte-to-lymphocyte ratio, *LLR* lactate dehydrogenase-to -lymphocytes ratio, *LMR* lymphocyte-to-monocyte ratio

Table 2 Univariate analysis for progression-free survival and overall survival

Group		Progression-free survival					Overall survival			
		n.pts	n.events	Median PFS 95%CI	HR 95%CI	*p*	n.events	Median OS 95%CI	HR 95%CI	*p*
Overall		355	260	14.2(12.1–17.2)	–	–	193	32.7(27.1–36.4)	–	–
Age	<62	167	123	14.4(10.8–18.7)	1.00	0.353	83	34.5(29.1–50.1)	1.00	0.061
	≥62	188	137	14.2(10.4–17.2)	1.12(0.88–1.43)		110	27.1(20.3–35.7)	1.31(0.99–1.75)	
ECOG PS	0–1	309	236	14.9(13.3–18.4)	1.00	<0.001	171	33.9(29.1–40.6)	1.00	<0.001
	2	46	24	3.0(2.5–5.6)	3.63(2.37–5.57)		22	6.5(2.7–9.6)	4.50(2.86–7.09)	
Histotype	Clear cell	315	233	14.3(12.4–17.4)	1.00	–	179	33.6(27.8–37.3)	1.00	–
	others	40	27	10.4(1.1–22.6)	2.00(0.89–4.51)	0.125	14	12.4(1.7-nr)	1.90(0.78–4.63)	0.209
IMDC score	Good	142	91	21.4(17.2–26.5)	1.00	–	48	56.6(38.6–75.2)	1.00	–
	Intermediate	181	139	13.3(9.2–17.4)	1.43(1.09–1.87)	0.010	115	29.4 (24.0–36.0)	1.99(1.41–2.80)	<0.001
	Poor	32	30	4.0(2.7–5.2)	5.09(3.39–7.66)	<0.001	30	5.3(3.7–8.0)	11.12(6.95–17.80)	<0.001
	Good	142	91	21.4(17.2–26.5)	1.00	–	48	56.6(38.6–75.2)	1.00	–
	Intermediate + poor	213	169	9.4(7.5–12.4)	1.65(1.27–2.15)	<0.001	145	23.7(14.6–28.1)	2.42(1.74–3.36)	<0.001
LLR	<150	209	153	18 (14.7–22.8)	1.00	<0.001	99	46(35.3–52.1)	1.00	<0.001
	≥150	146	107	9 (5.5–8.9)	1.84(1.43–2.36)		94	21(9.8–18.5)	2.36(1.78–3.15)	

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *LLR* lactate dehydrogenase-to -lymphocytes ratio, *CI* Confdence Interval, *HR* Hazard Ratio, *n.* number, *pts.* patients, *PS* Performance Status

TKIs, such as sorafenib, sunitinib, and pazopanib, have been recommended as the first-line treatment options for mRCC patients. However, treatment response for TKIs treatment is largely different among different individuals [10]. Currently available prognostic scores achieve a concordance of 0.68 to 0.89 for cancer-specific survival and 0.74 to 0.82 for recurrence-free survival, so new prognostic factors and models are needed to improve the prediction of the response to therapy [14]. A series of systematic inflammation-based prognostic parameters were established and tested their prediction of the response to TKIs therapy in mRCC patients. Some parameters, such as CRP and GPS, are not routinely examined in daily clinical work, and extra costs and technical issue often limit their clinical use [15]. Other study further suggested that combination of multiple well-established inflammation-based scoring systems incrementally improved the prognostic accuracy [16]. Recent study indicated that inflammation markers alone were not enough to predict clinical outcomes, and tumor burden associated markers were suggested as the prognostic marker [13]. The serum level of

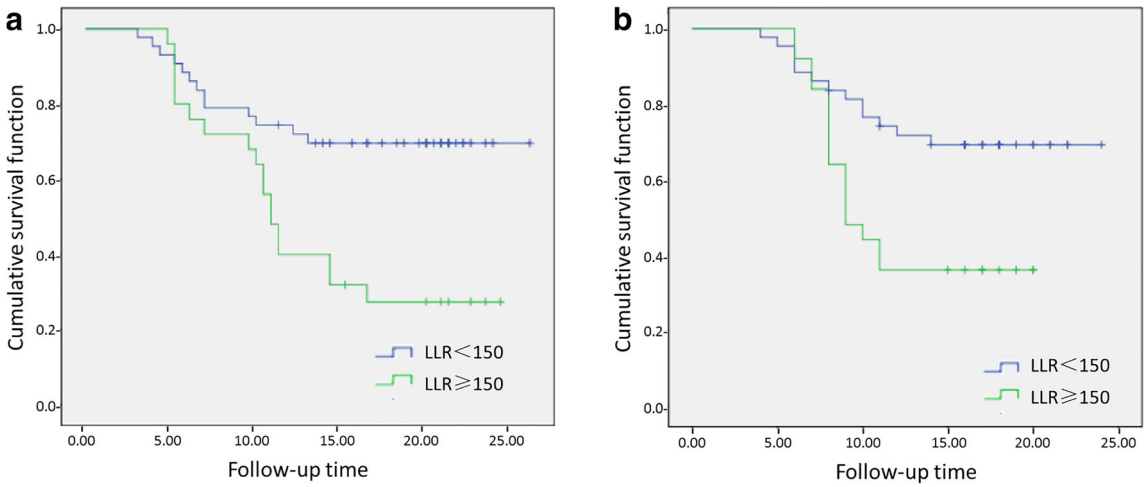

Fig. 1 Overall survival (OS) and progression-free survival (PFS) stratifed by LLR. a Kaplan-Meier plots illustrating OS according to LLR. **b** Kaplan-Meier plots illustrating PFS according to LLR

LDH before treatment has been suggested as the negative marker for survival in cancer patients [17–19]. LDH was one of most important indirect markers of hypoxia and neoangiogenesis, which supported the proliferation, metabolism, and metastasis of cancer cells [20].

Serum LDH has been considered as the potential circulating surrogate for the tumor burden. In addition, serum LDH is cost-affordable and can be easily examined in daily clinical work [13, 21]. Serum LDH was found to be an excellent surrogate marker of tumor burden in diffuse large B cell lymphoma (DLBCL) patients, and the ratio of lymphocyte to monocyte ratio (LMR)/lactate dehydrogenase (LDH) levels was an independent prognostic biomarker of predicting survival in DLBCL patients [21]. The ratio of LDH to lymphocytes was an independent prognostic biomarker of predicting survival in extranodal natural killer/T cell lymphoma (ENKTL) patients, and developed a novel prognostic model based on three adverse parameters, including Ann Arbor Stage, β2-microglobin to lymphocytes ratio index, and LDH to lymphocytes ratio index [22]. Based on these analysis from previous studies, we hypothesized that development of tumor burden marker (LDH) to inflammation marker (lymphocytes) ratio (LLR) may demonstrate the better prediction accuracy of the response to TKIs therapy in mRCC patients.

The previously published cut-off value for each parameter were inconsistent among different cohorts in the same type of cancer [23], thus we first screened the optimal cut-off value for NLR, dNLR, PLR, M/GLR, LLR and LMR using ROC analysis. After we determined the optimal cut-off value, these parameters were simultaneously examined in the same patient cohort to determine the best marker of the prognostic accuracy for OS, and LLR showed the best performance on the c-index, so LLR is the best marker of the prognostic accuracy for OS.

To further validate the valuable clinical practice of LLR, we compared the new LLR with existing IMDC risk stratification system. Unfortunately, multivariate analysis demonstrated that IMDC risks (poor and intermediate vs good risk) failed to predict PFS, and only showed predictor of OS. LLR displayed better predictive ability than IMDC risk stratification system. We finally evaluated the prognostic value of LLR, and Patients with LLR ≥ 150 displayed worse survival including OS and PFS.

To the best of our knowledge, this is the first study to directly explore the prognostic value of LLR in the large cohort of mRCC patients. We have evaluated the prognostic value of a series of systematic inflammation-based prognostic parameters (NLR, dNLR, PLR, M/GLR, LLR and LMR) with clinical factors in mRCC, and identified LLR was the best marker of the prognostic accuracy for OS based on c-index analysis. We finally established the novel prognostic model using LLR. LLR may be useful prognostic biomarker to stratificate mRCC patients for TKIs treatment in clinics.

Author Contributions Tao LI, Heng LI, Sheng XIE, Yan TAN, and Zi-Ping XIE collected and analyzed the data, Tao LI wrote the manuscript, Wen-Yi LI and Fen AI designed and supervised the research, interpreted and discussed the data, and finally approved the manuscript.

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Compliance with Ethical Standards

Conflict of Interest There are no potential conflicts of interest.

Research Involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional approval from Remin Hospital, Hubei University of Medicine was granted to perform this retrospective study on human subjects. No animals were involved in this study.

Informed Consent The study was approved to perform this retrospective study on human subjects and consequently no requirement for individual consent by the local ethical committee.

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