Original Study

Pretreatment Lymphocyte to Monocyte Ratio is an Independent Prognostic Factor in Metastatic Clear Cell Renal Cell Carcinoma

Liangyou Gu,[1] Xin Ma,[1] Yongpeng Xie,[2] Hongzhao Li,[1] Lei Wang,[1] Luyao Chen,[1] Wenlei Zhao,[2] Yu Zhang,[1] Xu Zhang[1]

Abstract

The prognostic value of pretreatment lymphocyte to monocyte ratio (LMR) in metastatic clear cell renal cell carcinoma is not well-described. In this retrospective series of 145 patients with metastatic clear cell renal cell carcinoma, we found a decreased LMR is independently associated with poor progression-free and overall survival. Adding the LMR to well-established prognostic models might improve their predictive ability.

Background: The prognostic value of pretreatment lymphocyte to monocyte ratio (LMR) in metastatic clear cell renal cell carcinoma (ccRCC) is not well-described. The purpose of this study was to assess the prognostic role of pretreatment LMR in surgically treated metastatic ccRCC. **Patients and Methods:** One hundred forty-five patients with metastatic ccRCC who underwent cytoreductive nephrectomy between 2006 and 2013 at our institute were identified. Pretreatment LMR was calculated within 1 week before surgical intervention. Progression-free survival (PFS) and overall survival (OS) were assessed using the Kaplan-Meier method. Pretreatment LMR, as a continuous variable and as a dichotomized variable at a cutoff of 3.0, were analyzed in univariable and multivariable Cox regression models, respectively. Moreover, the impact of the LMR on the predictive accuracy of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) models was evaluated using the Harrell concordance index (*C*-index). **Results:** Decreased LMR was statistically correlated with some clinicopathologic characteristics that are indicative of disease aggressiveness and poor prognosis. As both the continuous and dichotomized variable, decreased pretreatment LMR was demonstrated to be independently associated with poorer PFS ($P = .041$ and $P < .001$, respectively) and OS ($P = .014$ and $P < .001$, respectively). Further study indicated that the dichotomized LMR could improve the predictive accuracy of the IMDC and MSKCC models. **Conclusion:** Pretreatment LMR appears to be an independent prognostic factor of PFS and OS for patients with metastatic ccRCC after surgery, and it can be utilized to enhance the predictive ability of well-established prognostic models.

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Introduction

Renal cell carcinoma (RCC) originating from the renal cortex makes up 85% of primary renal tumors. Clear cell RCC (ccRCC), which represents approximately 60% to 70% of all renal tumors, is the most common type of kidney cancer. Nearly 30% of patients with RCC present with metastatic disease on initial diagnosis, and ~20% of patients with localized RCC relapse with metastasis following operation.[1] In those with localized RCC, surgical resection could be curative. Nevertheless, in metastatic disease, long-term survival cannot be obtained. The advent of targeted drugs has revolutionized the treatment of metastatic RCC and has led to a dramatic improvement in oncologic outcomes. The identification of

L.G., X.M., and Y.X. contributed equally to this work as first authors.

[1]Department of Urology/State Key Laboratory of Kidney Diseases, Chinese PLA General Hospital/PLA Medical School, Beijing, China
[2]School of Medicine, Nankai University, Tianjin, China

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Address for correspondence: Xu Zhang, MD, PhD, Department of Urology/State Key Laboratory of Kidney Diseases, Chinese PLA General Hospital, Beijing 100853, P.R. China
E-mail contact: xzhang@tjh.tjmu.edu.cn

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novel prognosis predictors would facilitate the evaluation of individual risk and guide clinical decision-making. Presently, several clinicopathologic prognosis-predicting models have been reported for metastatic RCC patients. These models include the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model evaluating the overall survival (OS),[2] and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model that more accurately predicts OS.[3] Owing to the fact that cases with similar clinicopathologic features could experience varied oncologic outcome, the discovery of tumor-related markers might therefore be needed to refine the prognosis prediction for patients with metastatic ccRCC.

The systemic inflammatory response, which is commonly evaluated based on surrogate peripheral blood-based variables, such as platelet, neutrophil count, or C-reactive protein, have been reported to be independently associated with oncologic outcomes in various cancers.[4,5] Key immune cell lymphocytes and monocytes have been shown to be independent prognosis predictors for several kinds of malignancy.[6,7] The decreased lymphocyte to monocyte ratio (LMR), as a fine reflection of both a decreased lymphocyte count and mononucleosis, has been proven to be associated with adverse outcome in various malignancies.[8] Particularly, Hutterer et al[9] and Chang et al[10] found that the pretreatment LMR can independently predict recurrence-free survival, cancer-specific survival, and OS for cases of nonmetastatic ccRCC after operation. In contrast, the prognostic significance of LMR in patients with metastatic ccRCC remains ill-defined. Hence, we evaluate the prognostic role of pretreatment LMR in metastatic ccRCC. Furthermore, we utilize it to optimize prognosis prediction supplied by existent risk models.

Materials and Methods

Patients

The present study analyzed data from 145 consecutive patients with metastatic ccRCC who underwent cytoreductive nephrectomy at our center between January 2006 and December 2013. Only subjects with pathologically confirmed ccRCC were included. We abstracted the clinicopathologic data from our renal tumor database. The variables included age at surgery, gender, symptoms at presentation, surgical approach (open vs. minimally invasive), primary cancer characteristics (tumor site, tumor size, pT stage, N stage, Fuhrman grade, tumor necrosis), metastatic sites and number, IMDC model,[2] MSKCC model,[3] and targeted therapy. Primary lesions were staged based on the TNM system of the 2010 American Joint Committee on Cancer Staging Manual[11] and graded according to the Fuhrman grading system.[12] Tumor size was collected as the largest diameter reported in pathologic examinations. Tumor necrosis was characterized as the existence of microscopic coagulative necrosis. Synchronous lesions were considered as metastases diagnosed at the moment of primary nephrectomy. Pretreatment LMR was calculated within 1 week before surgery.

Patients' postsurgical aftercare embraced routine physical and laboratory examination; computed tomographic or magnetic resonance imaging was conducted based on our hospital's protocol. Chest and abdomen-pelvis scans were both performed at the start of treatment, as well as every 6 to 8 weeks during treatment. Progression-free survival (PFS) was defined as the period (in months) between date of surgery and radiologic evidence of disease progression or censored at the last follow-up. OS was defined as the period (in months) between the date of surgery and death from all causes or censored at the last follow-up. The present study was approved by the Medical Ethics Committee of our hospital, and informed consent was acquired from each patient.

Statistical Analysis

All continuous data were tested for normality using the Kolmogorov-Smirnov test. LMR was assessed as a continuous parameter and was presented as the median and interquartile range (IQR). Differences of LMR among subgroups were determined using the nonparametric Kruskal-Wallis or Wilcoxon rank-sum test. LMR was further assessed as a categorical variable. Two methods were applied for cut-off assessment: (1) standard receiver operating characteristic (ROC) curve analysis according to dualistic outcome, using Manhattan distance to figure optimal cutoffs, and (2) fitting the Cox proportional hazards models to the dichotomized LMR variable and the time-dependent survival parameter, when the optimal cut-off point provided the lowest log-rank *P*-value. Associations of categorized LMR with patient clinicopathologic features were determined using the χ^2 test. We compared the survival of the groups using the Kaplan-Meier method with the log-rank test. The variables with statistical significance in the univariate analysis were then assessed in the multivariable Cox proportional hazards model. The Harrell concordance index (*C*-index) was applied for evaluation of the predictive accuracy of the multivariate model,[13] which ranges from 0.5 (no predictive power) to 1 (perfect prediction). All statistical analyses were performed using SPSS Statistics 20.0 (IBM Corporation, Armonk, NY) and R 3.2.1 software (Institute for Statistics and Mathematics, Vienna, Austria). Two-tailed tests were used for all comparisons, and a P-value $< .05$ was deemed statistically significant.

Results

Associations Between LMR Levels and Patient Features

The detailed clinicopathologic features of included patients are shown in Table 1. For all patients, the median age at surgery was 56 years (IQR, 47-63 years). Median counts of lymphocytes and monocytes were 2.8 $\times$ 10^9/L (IQR, 2.2-3.2 $\times$ 10^9/L) and 0.69 $\times$ 10^9/L (IQR, 0.57-0.78 $\times$ 10^9/L), respectively. The median value of LMR was 3.72 (IQR, 2.95-5.24). After a median follow-up of 24.5 months (IQR, 14.1-36.0 months), 110 (75.9%) patients experienced tumor progression, and 99 (68.3%) patients died from all causes.

As a continuous variable, elevated LMR was related to female gender ($P = .008$), the absence of symptoms at presentation ($P = .003$), smaller tumor size ($P = .001$), lower pathologic T stage ($P < .001$), lower Fuhrman nuclear grade ($P < .001$), fewer number of metastatic sites ($P = .040$), and more favorable IMDC and MSKCC risk groups ($P < .001$ for both).

To make it convenient for clinicians, standard ROC curve analysis and the Cox proportional hazards models were applied to decide the cutoff for LMR. The cutoff value of 3.0 was identified to optimally distinguish patients' outcome. Consequently, low (< 3.0) and high (≥ 3.0) LMR groups were defined. As a categorical variable, a high LMR was statistically related to smaller tumor size (≤ 7), lower pT stage (pT1 + pT2), lower Fuhrman nuclear grade (G1 + G2), a fewer number of metastatic sites, and more favorable IMDC and MSKCC risk groups (all $P < .05$).