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Original article

# Lymphopenia is an independent predictor of inferior outcome in papillary renal cell carcinoma

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## Abstract

**Purpose:** Lymphopenia as a likely index of poor systemic immunity is an independent predictor of inferior outcome in patients with clear cell renal cell carcinoma (RCC). We sought to evaluate the prognostic relevance of preoperative absolute lymphocyte count (ALC) in a cohort of patients with papillary RCC (PRCC).

**Materials and methods:** A prospectively maintained, renal cancer database was analyzed. Patients with preoperative ALC, within 3 months before surgery, were eligible for the study. Those with multifocal or bilateral renal tumors were excluded. Correlations between ALC and age, gender, smoking, Charlson comorbidity index, pathologic T category, PRCC subtype, and TNM stage were evaluated. Differences in overall survival (OS) and cancer-specific survival by ALC status were assessed using the log-rank test and cumulative incident estimators, respectively. Cox proportional hazards model was used for multivariable analyses.

**Results:** A total of 192 patients met the inclusion criteria. As a continuous variable, preoperative ALC was associated with higher TNM stage ($P = 0.001$) and older age ($P = 0.01$). As a dichotomous variable, lymphopenia (<1,300 cells/μl) was associated with higher TNM stage ($P = 0.003$). On multivariable analyses, controlling for covariates, after a median follow-up of 37.3 months, lymphopenia was associated with inferior OS (hazard ratio = 2.3 [95% CI: 1.2–4.3], $P = 0.011$) and trended to significance for cancer-specific survival ($P = 0.071$). Among patients with nonmetastatic disease and lymphopenia, OS at 37.5 months was shorter compared with those with normal ALC (83% vs. 93%, $P = 0.0006$).

**Conclusions:** In patients with PRCC, lymphopenia is associated with lower survival independent of TNM stage, age, and histology. ALC may provide an additional preoperative prognostic factor. 

*Keywords:* Renal cell carcinoma; Papillary renal cell carcinoma; Lymphopenia; Inflammatory disease; Biomarker; Survival; Lymphocyte count

## 1. Introduction

Kidney cancer, predominantly renal cell carcinoma (RCC), is among the most lethal of urologic malignancies, and in 2014, in the United States, 63,920 new cases are estimated, with approximately 22% rate of cancer-specific mortality [1]. Although 20% to 30% of patients can experience relapse within the first 3 years, surveillance is the standard of care after the curative-intent surgery for

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localized or locally advanced RCC [2]. Existing preoperative RCC models that risk stratify patients are useful guides after surgery but are of limited value in a preoperative setting. To estimate the risk of disease recurrence for localized RCC, only a limited number of models and nomograms based on TNM stage, nuclear grade, tumor necrosis, microvascular invasion, and performance status have been proposed [2–6]. Moreover, the most commonly used prognostic factor models for RCC are derived from the era of immunotherapy and are limited to a population of patients with advanced RCC [7,8].

Over the past several years, prognostic systemic inflammatory markers such as erythrocyte sedimentation rate [9], platelet count [10], C-reactive protein [11], vascular endothelial growth factors [12], and serum IL-6 levels [13] related to RCC outcomes have been described. More recently, there has been an increased interest in evaluating the host's inflammatory and immune response to tumors. One routinely obtained and readily available maker of the systemic inflammatory response is the absolute lymphocyte count (ALC), and its preoperative prognostic value as an independent predictor of disease-free survival and all-cause overall survival (OS) in clear cell RCC (ccRCC) has been previously described by our group [14].

Papillary RCC (PRCC) is the second most common histologic subtype of RCC that originates from a different biological pathway, and along with clear cell histology, they make up most cases of RCC seen in clinical settings [15]. To our knowledge, the role of ALC as a biomarker has not yet been fully evaluated as a predictor of survival in patients with PRCC. The aim of our study was to evaluate the prognostic significance of preoperative ALC in our large uniform PRCC series, as our group has done for ccRCC before [14]. We hypothesized that preoperative ALC may be a significant predictor of PRCC outcome as well. If preoperative ALC is indeed a significant predictor of outcome in PRCC, and because ccRCC and PRCC constitute the vast majority of RCCs, then ALC can be used as a useful preoperative predictor of RCC outcome even if the histology is not known yet.

## 2. Material and methods

The institutional, prospectively maintained, renal tumor database at the Fox Chase Cancer Center was used to identify patients with PRCC who underwent surgery from 2000 to 2013. Patients who did not have ALC values within 3 months preoperatively were excluded from the analysis. Because the outcome could have been affected by another primary tumor rather than the PRCC index tumor, the patients who had more than 1 surgery for management of multifocal or bilateral renal tumors were also excluded. Age at the time of surgery, gender, clinical and pathologic parameters, Charlson comorbidity index (CCI), and history of smoking were considered as potential confounders [14].

Renal tumors were managed and surgically treated as previously described [16]. Most nephrectomy specimens were examined and graded by 2 uro-oncological pathologist (T.A.S. and E.D.A.). Immunohistochemical stains and cytogenetics were used as adjuncts, as necessary. Type I and type II PRCCs were identified mainly by their nucleolar features, either absent (or very small) or prominent/pleomorphic nucleoli, respectively. Generally, type I is considered as "low grade" and type II as "high grade," and the sarcomatoid PRCC is classified as such [17]. TNM staging was determined using a collaborative stage approach, combining pathologic and clinical findings from patient records, the tumor registry, and the kidney cancer database. Pathologic T (pT) category was designated pathologically and M category was assigned mostly clinically (based on cross-sectional imaging). If lymphadenectomy was not performed at the time of surgery, N category was assigned clinically. Collaborative staging was revised according to the cancer staging manual of the American Joint Committee on Cancer, 7th edition [18]. The postoperative surveillance was physician dependent, often using the recommended follow-up (www.cancernomograms.com).

At our tertiary care cancer center, lymphopenia is defined as ALC of 1,300 cells/μl or less. We examined ALC as both a continuous and a dichotomous variable. One-way analysis of variance or *t* tests were used to assess differences in mean ALC levels, and trends were evaluated using linear regression with the assumption of equal spacing between stage levels. Fisher exact test was used to assess for differences in stage and PRCC type by low ALC, and the Cochran-Armitage test was used for trends.

The association between lymphopenia and mortality in patients with PRCC was examined. OS was estimated using Kaplan-Meier methods, and differences by lymphopenia status were assessed by the log-rank test. Cancer-specific survival (CSS) was estimated using cumulative incident estimators to account for the competing risk of other causes of death. Differences in CSS by lymphopenia status were assessed using Fine and Gray's competing risk regression. As part of the prospective maintenance of the database, date and cause of death were obtained from the death certificate, patient's family, or local physician. Length of follow-up was calculated from the date of surgery to the date of last follow-up or death. OS and CSS were calculated from the date of surgery to the date of death from any cause and date of patients' cancer-related death, respectively. Cox proportional hazards regression was used for inferences about the relationship of overall mortality with low ALC and potential confounders. Potential confounders were consistent with our analysis of ccRCC cohort: age at surgery ($<60$ vs. $60\geq$ y [closest round figure to the median]), CCI ($<2$ vs. $\geq 2$), pT category (pT1p/T2 vs. pT3/pT4), N category (N0 vs. N1), M category (nonmetastatic [M0] vs. M1), PRCC type (I vs. II), and smoking history (ever vs. never) [14]. To determine the effect of low ALC on mortality, covariates that were associated with overall and PRCC-related mortality on univariate analysis were included in the multivariable models. All statistical testing was 2 sided,