Original Article

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The Prognostic Role of Serum Albumin Level and Prognostic Nutritional Index in Patients With Localized Clear Cell Renal Cell Carcinoma

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Abstract

Aim: We investigated the relationship between serum albumin level and the prognostic nutritional index (PNI) with tumor histopathology, especially in localized clear cell renal cell carcinoma (ccRCC) patients. Moreover, the prognostic value of these markers in predicting metastatic progression was assessed.

Methods: A total of 120 RCC patients who underwent nephrectomy between January 2016 and January 2021 were evaluated. The inclusion criteria were having a ccRCC subtype. Patients who had metastatic disease and N+ status at the time of diagnosis were not included. Serum albumin level and PNI were compared between several tumor histopathology parameters and between patients who exhibited and did not exhibit metastatic progression.

Results: The serum albumin level and PNI exhibited significant differences in patients with pathologically higher tumor grade and metastatic progression during follow-up compared to patients with lower tumor grade and non-metastatic follow-up. Serum albumin levels and PNI were correlated with tumor grade and metastasis. In the univariate model, serum albumin and PNI were associated with metastasis [hazard ratio (HR): 0.29; 95% confidence interval (CI): 0.09-0.97; p=0.04; and HR: 0.88; 95% CI: 0.78-0.99; p=0.04].

Conclusion: Lower serum albumin and PNI are associated with higher tumor grades in patients with localized ccRCC. Moreover, they were prognostic role in metastatic progression during the follow-up of the patients after nephrectomy.

Keywords: Albumin, nutrition index, renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) is a heterogeneous group of cancers (1,2). It is a lethal urological cancer with up to a 40% mortality rate (2). Deaths from RCC are commonly associated with the clear cell RCC (ccRCC) subtype of RCC (1,3). Radical or partial nephrectomy procedures are common treatment options for curative intent in patients with ccRCC. However, the eventually developed metastase rate is about 30% in patients with localized ccRCC (1).

The most commonly used disease predictors for ccRCC have been tumor grade, stage, and tumor size until today. Multiple studies have proved their usefulness and clearly shown their correlation with survival rates (4). However, parameters such as tumor stage and grade along with tumor size may be insufficient because of the co-existence of patient-specific factors that largely affect their oncologic outcome. As a result, identifying patient-specific prognostic factors is still required to aid clinical decision-making.

Serum albumin level and the prognostic nutritional index (PNI) calculated by combining it with total lymphocyte count are individually specific parameters for patients and have prognostic value for some cancers, and several studies have clearly confirmed their prognostic role in patients with RCC (5-7). Although several studies have reported a potential prognostic impact of serum albumin and PNI in RCC patients, their role in predicting the tumor histopathology is still controversial and remains to be verified. In this study, we investigated the relationship between serum albumin levels and PNI and tumor histopathology, specifically in patients with localized

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ccRCC. Moreover, the prognostic value of these markers in predicting metastatic progression was assessed.

Materials and Methods

Compliance with Ethical Standards

The research was conducted as a retrospective observational study, which is ethically in accordance with the World Medical Association Declaration of Helsinki. An ethics approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (2022/22.22). An informed consent form was obtained from all participants. No investigation was performed on human subjects, and no personal or special information was provided in the text for the included cases.

Study Design

We retrospectively evaluated 120 RCC patients treated with nephrectomy procedures in our clinic during the period of January 2016 and January 2021. Patients having a clear cell subtype of RCC with no history of previous or concomitant malignancy other than kidney cancer are included in the study. Patients with metastatic disease and N+ status, as well as cases with benign pathology and papillary and chromophobe subtypes, were excluded.

The size, side, polarity, localization, and egzofitic or endophytic nature of the kidney cancers were assessed by abdominal computerized tomography and/or magnetic resonance imaging. Serum albumin levels and lymphocyte count before the surgery were extracted from our institutional data. PNI was estimated as 10×serum albumin (g/dL)+(0.005×lymphocytes/μL). Pathological findings were also extracted from our institutional data, which were performed by an uro-pathologist based on the 2010 TNM classification, Fuhrman, and WHO/ISUP grading systems. The last survival follow-up date was June 1, 2021. In patients with localized ccRCC, MFS was calculated as the time from surgery to metastasis or the last follow-up.

Statistical Analysis

The SPSS Version 22.0 statistic software package (IBM SPSS Inc., Chicago, IL) was used to evaluate the statistical analysis. The tests of normality were evaluated with the Shapiro-Wilk test. Descriptive statistics methods (mean±standard deviation, median± interquartile range, and percentages) were used to evaluate the data. Serum albumin level and PNI were compared in patients with and without lower and higher tumor grade, lower and higher pT stage, tumor necrosis, lymphovascular infiltration, variant differentiation, and metastasis. The independent t-test was used to compare groups. Differences were considered significant at a two-sided $p<0.05$ and 95% CI. Receiver operating characteristic (ROC) curves were generated for the cut-off levels of serum albumin and PNI to predict tumor histopathology and metastatic progression. A univariate Cox regression model for the role of serum albumin and PNI on metastatic progression was also performed.

Results

We included a total of 80 localized ccRCC patients among our 120 RCC patients who met the inclusion and exclusion criteria. The mean age and the mean tumor volume were 56.76±11.33 years and 54.35±28.89 mm, respectively. The mean operative time was 180.187±66.43 min. The median ASA score was 2±2. The median hospital stay was 4±3 days. The median pT stage and Fuhrman/WHO-ISUP grade were 1±2 and 2±2, respectively. The median postoperative follow-up period was 48.00±22.00 months with 4 to 50-month interval.

Out of 80 patients, 35 (43.75%) were female and 55 (56.25%) were male. A total of 47 (58.3%) patients had comorbidities, and 17 (21.3%) of them had multiple comorbid disorders. Table 1 provides associated details. Seven patients exhibited metastatic progression during the follow-up. Two of them were in regional lymph nodes and five were in the lungs. Mean MFS time was determined as 13.57±3.74 months [95% confidence interval (CI): 6.22-20.96].

On pathological examination, the serum albumin level and PNI did not differ significantly between patients with and without tumor necrosis, lymphovascular infiltration, or variant differentiation. They were similar in patients with lower and higher pT stage tumors, as well. However, both parameters exhibited significant differences in patients with a higher pathological tumor grade and metastatic progression during follow-up compared to patients with a lower tumor grade and non-metastatic follow-up (Tables 2 and 3). The ROC analysis revealed that the optimal predictive cut-off values for serum albumin were 4.10 g/dL with 70% sensitivity and 52% specificity, and 73% sensitivity and 63.5% specificity in predicting the higher tumor grade and metastasis, respectively. The cut-off values of PNI were 42.65 with 81% sensitivity and 58% specificity, and 85% sensitivity and 64% specificity in predicting higher tumor grade and metastasis, respectively. Figures 1 and 2 show the ROC curves and AUC levels.

Lower serum albumin levels and PNI were also linked to higher tumor grade and metastasis. Spearman's correlation analysis revealed a significant negative correlation between serum albumin levels and tumor grade and between serum PNI and tumor grade (Table 4). In the univariate Cox regression model, serum albumin and PNI were associated with metastasis [hazard ratio (HR): 0.29; 95% CI: 0.09-0.97; p=0.04; and HR: 0.88; 95% CI:

0.78-0.99; p=0.04]. However, multivariate analysis could not be performed due to the small number of metastatic patients.

Discussion

Today, it is well known that nutritional and inflammatory statuses play a role during carcinogenesis, and they are accepted as some of the most important predictive parameters in oncologic patients (8,9). Previous associated studies have revealed the prognostic role of several nutritional and inflammatory parameters in several cancer subtypes, and multiple immuno-nutritional scores have been developed, such as the PNI, Glasgow Prognostic Score, Modified Glasgow Prognostic Score, Granulocyte/Lymphocyte Ratio, Neutrophile/Lymphocyte Ratio, and Platelet/Lymphocyte ratio (7-13). These have been mainly related to the prognosis of various neoplasms, but their relationship with the tumor histopathology and metastatic progression during follow-up has not been studied that much (7,13). Serum albumin, which is a marker of nutritional status, may be affected by the inflammatory response in the body. Several studies have indicated that serum albumin can be used as a reliable indicator of inflammation. Because cancer is often accompanied by malnutrition and chronic inflammation, many studies have investigated the role of serum albumin levels in cancer patients and indicated that pretreatment serum albumin levels are associated with tumor prognosis (6,14-16). The initiation and progression of cancer are often accompanied by malnutrition and chronic inflammation. Malnutrition in cancer patients is usually caused by loss of appetite and malignant tumor depletion, which is reflected in hypoalbuminemia. The systematic inflammatory response in cancer patients also alters the concentration of serum

Table 1. Frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cyctic discrimination, and pathological tumor characteristics

	n	%
Comorbidity		
DM	26	32.5
HT	35	43.8
CAD	26	32.5
CRF	8	10
HF	1	1.3
Tumor laterality		
Left	37	46.2
Right	43	53.8
Polar tumor localization		
Superior	25	31.2
Middle	34	42.5
Lower	17	21.2
The whole kidney	3	3.8
Anterior-posterior tumor localization		
Anterior	30	37.5
Posterior	30	37.5
Medial	20	25
Egzofitic mass	64	80
Tumor nature		
Solid	53	66.3
Cystic	9	11.3
Mist	18	22.4
Tumor necrosis	21	26.3
Lymphovascular invasion	21	26.3
Variant differentiation	10	12.5
pT stage		
T1	48	60
T2	13	16.2
T3	17	21.3
T4	2	2.5
Tumor grade		
1	5	6.3
2	38	38
3	27	27
4	10	10

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery diseases, CRF: Chronic renal failure, and HF: Heart failure

albumin (17). In this regard, some of these papers have revealed the relationship between pretreatment serum albumin and the prognosis of patients with RCC. Combining the lymphocyte count with the serum albumin level, PNI is considered to reflect both cancer-related malnutrition status and cancer-related immune status of the patient. Additionally, PNI was further associated with the long-term prognosis of malignancies, including RCC (17). However, most of the research protocols exhibit some differences, and the direct relationship between serum albumin levels and tumor histopathology was not studied sufficiently (6). In this study, our primary aim was to determine the direct association of serum albumin with tumor histopathology and tumor metastasis.

Our findings revealed that serum albumin levels and PNI were different in patients with higher-grade tumors than those with lower-grade RCC. Similarly, they exhibited significantly lower levels in patients with metastasis during follow-up after nephrectomy. Based on the cut-off value, patients with lower serum albumin and PNI indeed showed a worse prognosis in our cohort in terms of metastasis. Serum albumin and PNI correlated with the higher tumor grade, as well. In a recent meta-analysis that included 11 studies and 7,629 patients, lower PNI was associated with worse survival parameters in RCC patients.It was correlated with a higher Fuhrman grade and T stage, as well (18). In this regard, our findings are consistent with the literature. We only investigated the localized ccRCC patients, whereas the above-mentioned studies investigated all subtypes of RCC, and most of them (8/11) included metastatic patients. Therefore, they could not evaluate the role of PNI on metastatic progression. In addition, we performed a ROC analysis to assess their predictive role for higher tumor grade and metastatic progression.Both

Table 2. Serum albumin levels according to tumor histopathology and metastasis

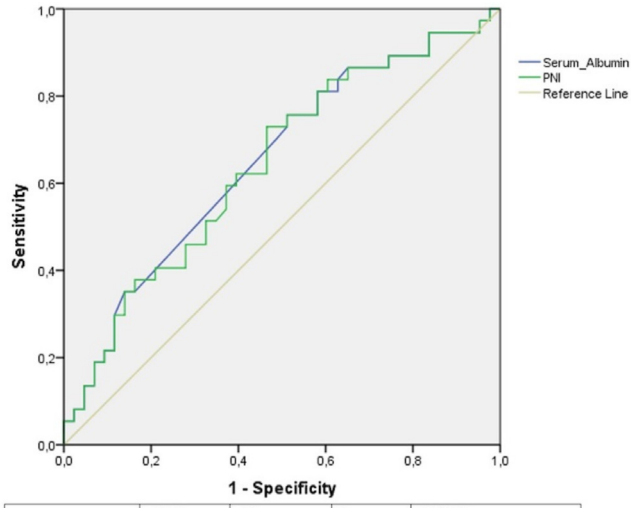
Serum albumin (Mean±SD)	**pT1 (n=48)**	**pT2-T4 (n=32)**	**p**
	4.18±0.53	4.02±0.34	0.13*
	Grade 1-2 (n=43)	**Grade 3-4 (n=37)**	**p**
	4.27±0.50	3.94±0.62	0.03*
	Tumor necrosis - (n=59)	**Tumor necrosis + (n=21)**	**p**
	4.12±0.50	4.09±0.36	0.76*
	LVI- (n=59)	**LVI+ (n=21)**	**p**
	4.13±0.50	4.07±0.37	0.64*
	VD- (n=70)	**VD+ (n=10)**	**p**
	4.13±0.47	3.97±0.46	0.30*
	Metastasis- (n=73)	**Metastasis+ (n=7)**	**p**
	4.15±0.43	3.73±0.63	0.02*

SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation,
*Independent t-test

Table 3. Serum prognostic nutritional index according to tumor histopathology and metastasis

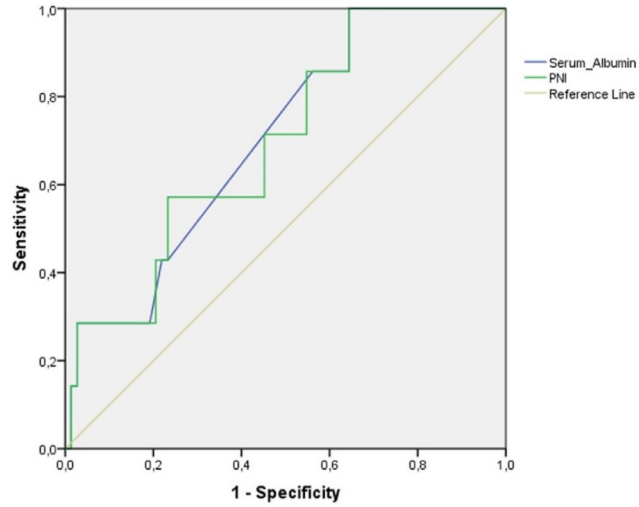
Serum PNI (Mean±SD)	**pT1(n=48)**	**pT2-T4 (n=32)**	**p**
	41.93±5.32	40.31±3.42	0.13*
	Grade 1-2 (n=43)	**Grade 3-4 (n=37)**	**p**
	42.31±4.17	40.09±5.03	0.03*
	Tumor necrosis - (n=59)	**Tumor necrosis + (n=21)**	**p**
	41.38±5.04	41.01±3.63	0.75*
	LVI- (n=59)	**LVI+ (n=21)**	**p**
	41.43±5.01	40.86±3.76	0.63*
	VD- (n=70)	**VD+ (n=10)**	**p**
	41.49±4.70	39.86±4.68	0.30*
	Metastasis- (n=73)	**Metastasis+ (n=7)**	**p**
	41.61±4.38	37.39±6.39	0.02*

PNI: Prognostic nutritional index, SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation
*Independent t-test



	AUC	SE	P	95% CI
Serum Albumin	0.649	0.062	0.02	0.528 - 0.770
PNI	0.643	0.062	0.02	0.522 - 0.765

Figure 1. The ROC curves and AUC levels of serum albumin and PNI in determining the higher tumor grade
ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, AUC: Area under the curve, SE: Standard error, CI: Confidence interval



	AUC	SE	P	95% CI
Serum Albumin	0.703	0.091	0.03	0.525 - 0.880
PNI	0.697	0.094	0.04	0.512 - 0.881

Figure 2. The ROC curves and AUC levels of serum albumin and PNI in determining tumor metastasis
ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, AUC: Area under the curve, SE: Standard error, CI: Confidence interval

Table 4. Correlations of serum albumin levels and PNI with tumor grade

	Spearman's correlation coefficient	p-value
Serum albumin with tumor grade	-0.263	0.01
Serum PNI with tumor grade	-0.248	0.02

PNI: Prognostic nutritional index

parameters successfully predicted a higher tumor grade and metastatic progression. According to the established cut-off levels, the univariate Cox regression model showed that the prognostic effects of serum albumin and PNI on metastatic progression were significant. Our findings provided new evidence on the potential independent correlation between serum albumin and PNI with tumor grade and metastatic progression.

Recent evidence suggests that the nutritional and immunological statuses of patients with RCC can predict long-term outcomes, cancer progression, and patient survival after treatment (7,19-21). However, a few studies have primarily investigated the correlation between them and tumor histopathology. Moreover, the prognostic value of serum albumin and PNI remains controversial in localized ccRCC, primarily due to variations in study design and cohort size, as well as other factors, among studies. For instance, most previous studies included localized and metastatic RCC patients and did not investigate specifically ccRCC in their study (7). In this regard, this study provided more clear results about the role of serum albumin and PNI in predicting the tumor histopathology and metastatic progression of localized ccRCC. To our knowledge, this is the first study that specifically investigated those parameters in localized ccRCC.

Study Limitations

Our study had some limitations. The major one is the small sample size. However, this study specifically investigated localized ccRCC. The main handicap of the small sample size was that we could not perform multivariate analysis. This is the second major limitation of this study. The retrospective nature of the study protocol is another limiting factor. However, long-term follow-up results were obtained prospectively. Beyond limitations, the major strength of the paper is that we only investigated localized ccRCC patients and avoided the potential effects of tumoral heterogeneity on our results.

Conclusion

This study showed that lower serum albumin and PNI are associated with a higher tumor grade in localized ccRCC patients. Moreover, they played a prognostic role in metastatic progression during the follow-up of the patients after nephrectomy.

Ethics

Ethics Committee Approval: An ethics approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (2022/22.22).

Informed Consent: An informed consent form was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.C., M.Z.T., E.K., A.S., A.Y.M., Design: A.C., M.Z.T., Data Collection or Processing: A.C., Y.C.F., S.S., R.O.Y., Analysis or Interpretation: M.Z.T., Literature Search: A.C., Y.C.F., S.S., R.O.Y., M.Z.T., Writing: A.C., M.Z.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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