

The prognostic value of preoperative controlling nutritional status score in non-metastatic renal cell carcinoma treated with surgery: a retrospective single-institution study

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Purpose: This study aimed to investigate the significance of the controlling nutritional status (CONUT) score as a predictor for survival outcomes for non-metastatic renal cell carcinoma (RCC) patients.

Methods: We retrospectively reviewed 325 patients who received surgical treatment for renal cell carcinoma between 2010 and 2012 at Peking University First Hospital. Patients were divided into two groups according to the optimal cut-off value of CONUT score. Kaplan–Meier method and log-rank test were used for survival analysis according to different CONUT groups. Cox proportional hazards regression models were performed to assess the prognostic value of clinicopathological parameters for overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS) respectively.

Results: The optimal cut-off value of CONUT score was 3. High CONUT score significantly correlated to higher tumor grade ($P<0.001$), later pathological T stage ($P<0.001$) and tumor necrosis ($P<0.001$). Patients with higher CONUT score had worse OS (HR 5.34, 95% CI 2.29–12.46, $P<0.001$), CSS (HR 5.51, 95% CI 2.12–14.33, $P<0.001$) and DFS (HR 4.23, 95% CI 2.16–8.29, $P<0.001$). In multivariable analysis, high CONUT score was an independent risk factor for OS, CSS and DFS (OS: HR=3.36, 95% CI 1.73–6.56, $P<0.001$; CSS: HR=3.34, 95% CI 1.59–6.98, $P=0.001$; DFS: HR=1.85, 95% CI 1.07–3.21, $P=0.029$).

Conclusion: Preoperative CONUT score was an independent prognostic factor for OS, CSS and DFS in non-metastatic RCC patients treated with surgery.

Keywords: CONUT score, renal cell carcinoma, surgery, survival, biomarker

Introduction

Renal cell carcinoma is one of the most common malignancies in urological cancers which accounts for about 2–3% of the adult malignant solid tumors.¹ With regular medical checkup increasing, its incidence continues to rise. Over decades, surgical resection is still the foremost treatment strategy for non-metastatic renal cell carcinoma. However, almost 20–40% of the postoperative patients will experience metastasis or local recurrence.^{2,3} Therefore, it is necessary to seek biomarkers which can precisely predict the prognosis, because early identification of patients with bad prognosis may help risk stratification and appropriate therapeutic decision making and consequently improve survival outcomes.

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Increasing evidence has revealed that immune and inflammatory factors played an important role in cancer development, growth and metastasis. Several biomarkers, such as the platelet to lymphocyte ratio (PLR), the neutrophil to lymphocyte ratio (NLR) and the C-reactive protein (CRP), have been reported to be independent prognostic factors in various malignancies, including renal cell carcinoma.^{4–6} Nutritional status was also reported to be associated with cancer progression and prognosis in RCC. For example, body mass index (BMI),⁷ prognostic nutritional index (PNI),^{8,9} sarcopenia¹⁰ and modified Glasgow Prognostic Score (mGPS).¹¹ Controlling Nutritional Status (CONUT) is a newly proposed scoring system which is used to assess patient nutritional and immune status. It is calculated from the serum albumin concentration, total blood cholesterol level and total peripheral lymphocyte count.¹² Some studies showed that CONUT score can predict prognosis in many solid tumors, such as esophageal carcinoma,¹³ gastric cancer,¹⁴ colorectal cancer¹⁵ or upper tract urothelial carcinoma.¹⁶ But there are few studies for renal cell carcinoma. Therefore, we investigate the usefulness of CONUT score for predicting prognosis in non-metastatic renal cell carcinoma patients treated with surgery in this study.

Materials and methods

Patients

We retrospectively reviewed a database of patients who underwent radical/partial nephrectomy for renal cell carcinoma between 2010 and 2012 at Peking University First Hospital. We excluded patients with distant metastasis at surgery, those with other tumors, those with immune system disease, those with insufficient data from medical record and those without follow-up information. At last, 325 patients were included in final evaluation in this study.

Both radical and partial nephrectomy were performed following a standard procedure either in laparoscopic or open approach. The pathological slides were made and reviewed by professional urological pathologists. Pathological T stage was determined according to the 2010 TNM classification and tumor grade according to the Fuhrman grading system. Clinical information was obtained from medical records of each patient. Blood samples were collected and measured within 1 week before surgery as regular preoperative laboratory tests. Body mass index (BMI) was calculated using patient height and weight

which was measured when patients were admitted to the hospital before surgery.

This study was in compliance with the Helsinki declaration and approved by the Institutional Ethical Review Board of Peking University First Hospital. Written informed consent was waived because of the retrospective nature of this study. During the follow-up, patients or their next of kin were informed in detail about the study and verbal consents were obtained. All data were maintained with confidentiality.

Follow-up and endpoint

Follow-up surveillance after surgery included routine laboratory and image examination every 3 months within the first 3 years, every 6 months for the next 2 years and then annually until the death. Imaging methods included chest X-ray, abdominal ultrasonography, CT or MRI. Death was confirmed according to medical records in our hospital and information provided by relatives of the patients during phone call following-up. The primary outcome of this study is overall survival (OS), and the secondary outcome is cancer-specific survival (CSS) and disease-free survival (DFS). CSS was defined as the time (in months) from date of surgery to a cancer-related death. OS was defined as the time (in months) from the date of surgery to individuals' death of any cause. DFS was defined as the time (in months) from date of surgery to the radiologically or histologically confirmed recurrence or metastasis.

Definition and cut-off value of CONUT score

The preoperative CONUT score was calculated using serum albumin concentration, peripheral lymphocyte count and the total cholesterol concentration, as described in Table 1. The optimal cut-off value for the CONUT score was investigated using the receiver operating characteristic (ROC) curve (Figure 1). According to the maximum Youden index value, the optimal cut-off value for the CONUT score was 3 (AUC: 0.723, 95% CI: 0.670–0.771, $P < 0.001$, sensitivity: 51.28%, specificity: 82.52%). Then, we classified the patients into high CONUT group ($\text{CONUT} \geq 3$) and low CONUT group ($\text{CONUT} < 3$).

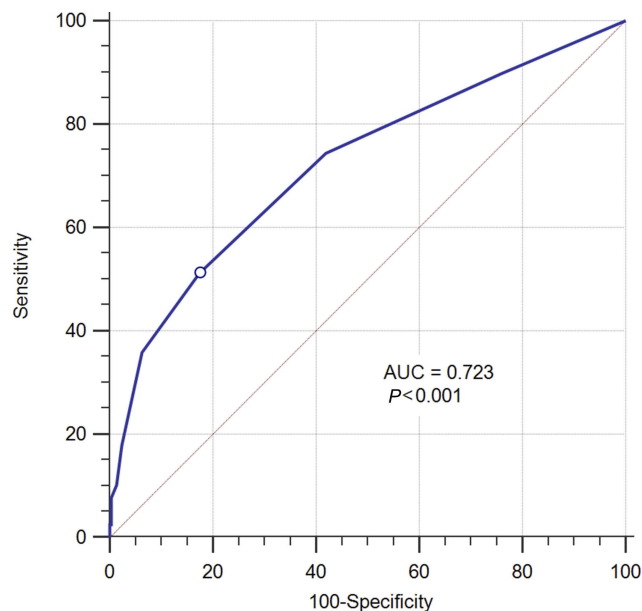
Statistical analysis

The clinicopathological characteristics of different groups, including age, gender, hypertension, diabetes mellitus, tumor

Table I Assessment of nutrition status by controlling nutritional status (CONUT) scoring system

Parameter	Undernutrition degree			
	None	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.50	3.00–3.49	2.50–2.99	<2.50
Score	0	2	4	6
Total lymphocyte (/mm ³)	≥1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3

Note: CONUT score=serum albumin score+total lymphocyte count score+total cholesterol score.

**Figure I** ROC curve for CONUT score.

Abbreviations: ROC, receiver operating characteristic; CONUT score, controlling nutritional status score.

grade, pathological T stage, histological subtype and surgery type were compared using the chi-square test. The Kaplan–Meier method and log-rank test were used for survival analysis according to different CONUT groups. We performed multi-variable analyses using Cox proportional hazards regression models to assess the prognostic value of clinicopathological parameters (age, gender, tumor grade, pathological T stage, histological subtype and CONUT score group) for OS, CSS and DFS, respectively. The hazard ratios (HRs) with 95% confidence intervals (CIs) were presented for each independent factor. The predictive ability of each risk model in the study population was evaluated using the Harrell's c-index, as previously described.¹⁷ Models were refit 200 times using a bootstrap resampling technique to decrease overfit bias. All statistical analyses were performed using Medcalc

(Version 16.8, Ostend, Belgium), the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, MA). GraphPad Prism version 7 (GraphPad Software, La Jolla California USA, www.graphpad.com) was used to generate survival curve. A two-sided $P < 0.05$ was considered statistically significant.

Results

Correlations between CONUT score and clinicopathological characteristics

Of the 325 patients included in the study, 231 were male and 94 were female. The median age at surgery of the entire cohort was 57 (IQR 47–66) years. All patients were divided into two groups according to the optimal cut-off value of CONUT score determined by the ROC curve. Seventy patients were included in high CONUT score group while the remaining 255 patients were classified into the low CONUT score group. High CONUT score was significantly correlated with higher tumor grade ($P < 0.001$), later pathological T stage ($P < 0.001$) and presence of tumor necrosis ($P < 0.001$) (Table 2). There were no significant association between CONUT score and age, gender, diabetes, hypertension, tumor histology and surgery type, respectively.

Survival analysis for CONUT score in patients with RCC

The median follow-up period for survivors was 64 months (IQR 56.5–69 months). In high CONUT group and low CONUT group, 5-year OS rates were 93.7% and 67.8% ($P < 0.001$) (Figure 2A), 5-year CSS rates were 94.9% and 72.9% ($P < 0.001$) (Figure 2B), 5-year DFS rates were 87.0% and 58.8% ($P < 0.001$) (Figure 2C), respectively. In Kaplan–Meier analysis, as is shown in Table 3, high

Table 2 Clinicopathological characteristics of the 325 patients according to different controlling nutritional status (CONUT) groups

Factors	Total (n=328)	CONUT<3 (n=255)	CONUT≥3 (n=70)	P-value*
Age (years)				
≤65	240	193	47	P=0.198
>65	85	62	23	
Gender				
Male	231	177	54	P=0.265
Female	94	78	16	
Diabetes				
Yes	46	35	11	P=0.819
No	279	220	59	
Hypertension				
Yes	128	105	23	P=0.261
No	197	150	47	
Tumor grade				
G1-2	275	226	49	P<0.001
G3-4	50	29	21	
Pathological T stage				
pT1-2	247	212	35	P<0.001
pT3-4	78	43	35	
Necrosis				
Yes	95	62	33	P<0.001
No	230	193	37	
Histology				
Clear cell	292	232	60	P=0.285
Non-clear cell	33	23	10	

Notes: *Chi-square test. Bold values indicates statistical significance in univariate and multivariate analysis which had been detailed in the "Results" section.

CONUT score was significantly associated with poor OS (HR 5.34, 95% CI 2.29–12.46, $P<0.001$), CSS (HR 5.51, 95% CI 2.12–14.33, $P<0.001$) and DFS (HR 4.23, 95% CI 2.16–8.29, $P<0.001$). Besides, advanced pathological T stage, high tumor grade and tumor necrosis also had significant correlation to OS, CSS and DFS (all $P<0.001$).

Multivariate analysis showed that high CONUT score was an independent risk factor for OS, CSS and DFS (OS: HR=3.36, 95% CI 1.73–6.56, $P<0.001$; CSS: HR=3.34, 95% CI 1.59–6.98, $P=0.001$; DFS: HR=1.85, 95% CI 1.07–3.21, $P=0.029$), independent of advanced

pathological T stage and high tumor grade. In addition, tumor necrosis was independently associated with DFS (HR=2.07, 95% CI 1.08–4.02, $P=0.030$), and diabetes was independently associated with OS (HR=2.24, 95% CI 1.06–4.72 $P=0.035$) (Table 3). Other factors, such as age, gender, histology and hypertension, were not related to survival outcomes.

Compare CONUT score with other biomarkers in patients with RCC for survival prediction

We used AUCs of ROC curves to estimate the predicting accuracy of CONUT score for the prediction of 5-year OS. The AUC score of PNI and NLR in relation to 5-year OS was 0.701 (95% CI 0.648–0.750) and 0.715 (95% CI 0.662–0.763), respectively. The AUC of CONUT was 0.723 (95% CI 0.670–0.771), which was higher than that of PNI and NLR. However, the difference of AUCs had no statistical significance, which indicates CONUT score may have equivalent accuracy in predicting 5-year OS when compared to NLR and PNI. Similarly, the CONUT score also showed equivalent accuracy in relation to 5-year CSS and DFS prediction. Harrell's c-index was used to assess the predictive accuracy of the model on multivariate analysis. In the base model which include age, gender, diabetes, hypertension, tumor grade, pathological T stage and histology, the predictive accuracies for OS, CSS and DFS are 80.2%, 81.1% and 84.2%, respectively. When CONUT score was added to the base model, the predictive accuracy was enhanced by 2.5% for OS, 2.5% for CSS and 1.5% for DFS. However, NLR just elevated the predictive accuracy by 1.6% for OS, 0.2% for CSS and 1.2% for DFS, and PNI can elevate the predictive accuracy by 1.9% for OS, 1.4% for CSS and 2.1% for DFS.

Discussion

Our study assessed the association between CONUT score and clinicopathological factors and the prognostic value of CONUT score in non-metastatic renal cancer patients treated with surgery. We found that high CONUT score was significantly correlated with high tumor grade, late pathological T stage and high presence of tumor necrosis. High CONUT score was also significantly associated with worse OS, CSS and DFS in patients with renal cell carcinoma after surgery in univariate analysis; it was an independent prognostic factor for OS, CSS and DFS according to multivariate analysis.

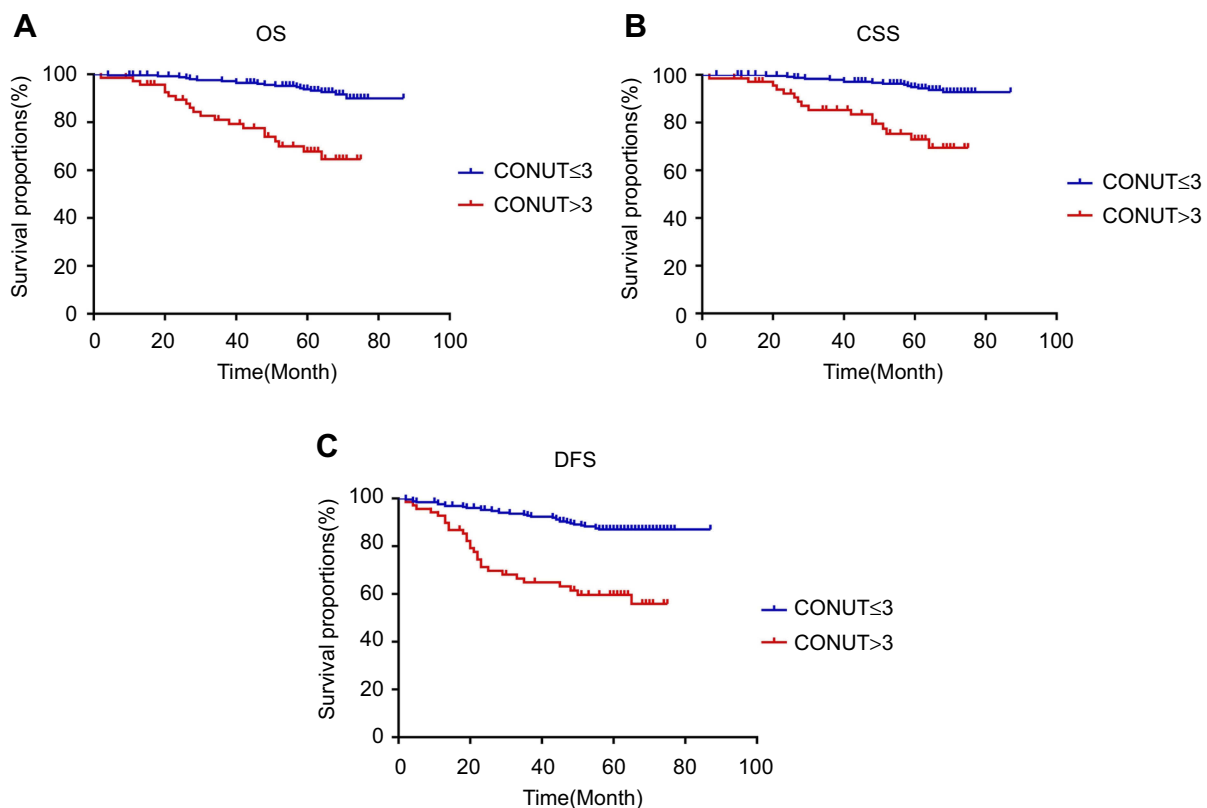


Figure 2 Kaplan-Meier survival curves for non-metastatic RCC patients treated with surgery. Survival curves set at cut-off value 2 for OS (A), CSS (B) and DFS (C). **Abbreviations:** RCC, renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; CONUT, controlling nutritional status.

The predictive accuracy of CONUT score for survival in postoperative patients with renal cell carcinoma tended to be at least equivalent to other prognostic biomarkers, such as PNI and NLR. The optimal cut-off values of CONUT score were not on all fours in different cancers as reported. In our study, it was 3 according to the ROC curve, which was identical to previous studies.^{14,18}

CONUT was first introduced as an efficient tool for early detection and continuous control of hospital under-nutrition. It was calculated from the serum albumin value, the total cholesterol level and the total lymphocyte count, which can be obtained easily from regular blood examination.¹² Association between high CONUT score and poor prognosis in cancer patients might relate to the function of these three variables. However, the detailed mechanism underlying remains unclear. Serum albumin is a reliable indicator for host nutritional and systematic inflammatory status, low level of serum albumin was not only considered as malnutritional status but also as systematic inflammatory change. It might be caused by the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor- α (TNF- α),

which can modulate the synthesis of albumin by hepatocytes.^{19,20} It can also be influenced by hepatic function and body fluid volume.²¹ Researches conducted over the last decade have demonstrated that serum albumin levels, either considered alone or combined with other parameters, can provide prognostic information regarding various cancers which include gastrointestinal cancers, hepatic cancers, lung cancers, breast cancers, ovarian cancers, colorectal cancers, soft tissue sarcoma and some other cancers.^{22,23}

Cholesterol is an essential lipid for maintaining cellular homeostasis. Many epidemiologic observations since the 1980s have shown an inverse association between total serum cholesterol level and cancer incidence and mortality. Lower cholesterol level in plasma was correlated with higher risk in a variety of cancers.^{24–27} Abnormal lipid metabolism has been proved in close association to the carcinogenesis and tumor development of cancers, but the detailed mechanism is still needed to be clarified. Niendorf et al demonstrated that low-density lipoprotein (LDL) receptor mRNA expression was significantly higher in colorectal tumor tissues than in normal tissues, which

Table 3 Univariate and multivariate analyses of clinicopathological parameters to predict CSS, DFS and OS in patients with non-metastatic RCC

Factors	OS			CSS			DFS		
	Univariate		Multivariate	Univariate		Multivariate	Univariate		Multivariate
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)
Age									
≤65	1.00 (ref)				1.00 (ref)		1.00 (ref)		
>65	1.47 (0.72–3.03)	0.249			0.85 (0.38–1.91)	0.710	0.87 (0.49–1.56)	0.654	
Gender									
Male	1.00 (ref)				1.00 (ref)		1.00 (ref)		
Female	0.73 (0.37–1.46)	0.404			0.84 (0.39–1.83)	0.679	0.74 (0.42–1.29)	0.319	
Pathological T stage									
T1-T2	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
T3-T4	7.69 (3.34–17.66)	<0.001	3.89 (1.76–8.57)	0.001	7.91 (3.08–20.32)	<0.001	3.05 (1.26–7.37)	0.014	1.00 (ref)
							9.05 (4.61–17.74)	<0.001	3.97 (2.05–7.72)
Tumor grade									
G1-G2	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
G3-G4	6.18 (2.37–16.14)	<0.001	2.48 (1.19–5.21)	0.016	8.98 (3.03–26.62)	<0.001	4.07 (1.76–9.43)	0.001	1.00 (ref)
							8.04 (3.59–18.03)	<0.001	2.34 (1.23–4.44)
Histology									
Clear cell	1.00 (ref)				1.00 (ref)		1.00 (ref)		
Non-clear cell	0.99 (0.35–2.78)	0.986			1.28 (0.40–4.04)	0.648	0.93 (0.41–2.09)	0.857	
CONUT score									
<3	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
≥3	5.34 (2.29–12.46)	<0.001	3.36 (1.73–6.56)	<0.001	5.51 (2.12–14.33)	<0.001	3.34 (1.59–6.98)	0.001	1.00 (ref)
							4.23 (2.16–8.29)	<0.001	1.85 (1.07–3.21)
Diabetes									
No	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		
Yes	1.93 (0.77–4.83)	0.079	2.24 (1.06–4.720)	0.035	1.88 (0.67–5.28)	0.135	1.45 (0.69–3.05)	0.259	

(Continued)

Table 3 (Continued).

Factors	OS				CSS				DFS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Hypertension												
No	1.00 (ref)				1.00 (ref)				1.00 (ref)			
Yes	1.04 (0.55–1.98)	0.897			0.94 (0.46–1.93)	0.866			0.91 (0.54–1.53)	0.736		
Necrosis												
No	1.00 (ref)				1.00 (ref)				1.00 (ref)			
Yes	4.45 (2.14–9.23)	<0.001			5.73 (2.51–13.04)	<0.001			5.82 (3.22–10.52)	<0.001	1.00 (ref) 2.07 (1.08–4.02)	0.030

Notes: Bold values indicate statistical significance in univariate and multivariate analysis which had been detailed in the "Results" section.

Abbreviations: RCC, renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; CONUT, controlling nutritional status.

induced higher intake of LDL and the plasma cholesterol level decreased consequently. It is indicated that tumor tissues might act as high consumers of cholesterol-rich particles, thus inducing hypocholesterolemia.²⁸ A study from Cengiz et al indicated that hypocholesterolemia was associated with poor tumor prognosis and they hypothesized that tumor activity is a major cause of lowered serum cholesterol values.²⁹

The functional status of immune system significantly affects the prognosis of many human malignancies.³⁰ Lymphocytes play a pivotal role in inhibiting cancer cell proliferation, invasion and migration by initiating a cytotoxic immune response. Studies have proved that tumor-infiltrating lymphocytes (TILs) in tumor microenvironment are associated to prognosis and clinical outcome of immunotherapy in a variety of cancers. It is reported that cancer cells exploit immune checkpoints to inactivate in order to escape from immune surveillance. The presence of TILs in tumor tissues suggests a favorable prognostic role in melanoma, breast cancer, lung cancer and RCC.^{31,32} As blood lymphocytes represent the level of TILs in a way. Total serum lymphocyte count indicates host immunological status and decreased lymphocyte count predicts worse prognosis in diverse cancers as a result of the insufficient immune response to cancer cells.^{33,34} Biomarkers based on blood lymphocytes such as PLR and NLR were proved to be useful and easy-available index for immune status and showed prognostic value for diverse solid tumors.^{35,36}

Results of this study remind us the importance of nutritional support in RCC patients. Nutritional intervention should be emphasized during the treatment and follow-up of renal malignancies. Detailed nutritional support strategy needs to be individualized based on nutritional baseline of RCC patients and CONUT score may serve as an index for evaluation of nutritional status. Immunotherapy is emerging as a promising strategy for the treatment of many cancers. Ströhlein et al reported that relative lymphocyte count can predict responding cancer patients to catumaxomab therapy and it is also independently associated with a prolonged survival time.³⁷ So CONUT score may also have potential predictive value for efficacy of immunotherapy in renal cancer patients, while further investigations are needed for this speculation.

Our study has certain limitations. First, it is a small cohort, retrospective study from a single center. Further internal and external validations are needed to clarify the accurate prognostic role of postoperative CONUT score. Second, postoperative CONUT score was not followed-up and taken into account in our study. So, we are not clear

whether the change of CONUT score after surgery can influence the survival of RCC patients. Third, due to the lack of relative information, several other nutritional and immune markers, such as mGPS, sarcopenia and PLR were not assessed in this study.

Conclusion

In conclusion, our study suggests that preoperative CONUT score can not only reflect host nutritional and immune status but also is an effective and convenient biomarker for predicting prognosis in patients with non-metastatic RCC treated by surgery. Perioperative nutritional support should be emphasized of RCC patients.

Abbreviations

RCC, renal cell carcinoma; CONUT, controlling nutritional status; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PLR, platelet to lymphocyte ratio; NLR, the neutrophil to lymphocyte ratio; CRP, C-reactive protein; BMI, body mass index; PNI, prognostic nutritional index; mGPS, modified Glasgow Prognostic Score; HR, hazard ratio; 95% CI, 95% confidence intervals; ROC, receiver operating characteristic; IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha; LDL, low-density lipoprotein; TILs, tumor-infiltrating lymphocytes.

Disclosure

The authors report no conflicts of interest in this work.

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