Original Article

Prognostic value of peripheral blood T lymphocyte subsets in clear cell renal cell carcinoma

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Background: To date, few studies have evaluated the role of peripheral blood T lymphocyte subsets in patients with clear cell renal cell carcinoma (ccRCC). Here we measured the levels of peripheral blood T lymphocyte subsets and evaluated its prognostic value in ccRCC.

Methods: Data from 122 patients with RCC from January 2018 to January 2020 were collected. Preoperative peripheral blood T lymphocyte subsets and medical records were analyzed. Kaplan-Meier cures and log rank test were used for analyzing overall survival (OS). Univariate and multivariate survival analyses were underwent by performing the Cox proportional hazards models. Correlations were tested by Pearson's correlation analysis.

Results: Of 122 patients, a total of 80 ccRCC patients was enrolled. Patients with low $CD3^+$ T cells and low $CD4^+/CD8^+$ ratio displayed a worse OS than patients with high $CD3^+$ T cells and high $CD4^+/CD8^+$ ratio (P=0.029 and 0.002, respectively). Multivariate analyses showed $CD3^+$ T cells and $CD4^+/CD8^+$ ratio were independent predictive factors for the OS (HR: 0.295, 95% CI, 0.091–0.956; P=0.042 and HR: 0.244, 95% CI, 0.065–0.920; P=0.037, respectively). Moreover, NLR negatively correlated with both levels of $CD3^+$ T cells and $CD4^+/CD8^+$ ratio (P<0.001, r=–0.398 and P=0.012, r=–0.280, respectively).

Conclusions: The findings of our study suggest that preoperative $CD3^+$ T cells and $CD4^+/CD8^+$ ratio in peripheral blood are independent predictors for patients with ccRCC.

Keywords: Clear cell renal cell carcinoma (ccRCC); $CD3^+$ T cells; $CD4^+/CD8^+$ ratio; prognosis

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 90% of all renal tumors. Histologically, clear cell RCC (ccRCC) is the majority of RCC, accounting for 75–80% of total cases (1). Nowadays surgical treatment is still an effective measure option for early ccRCC, however the treatment of advanced and metastatic ccRCC remains challenging. What's worse, more than 30% of ccRCC patients exhibit metastatic lesions at the time of initial diagnosis and the probability of metastases in the remaining patients is approximately 30% (2).

Poor host immune function is a main factor leading to ccRCC progression. Peripheral blood T lymphocyte subsets is an effective way to reflect systemic immune status (3,4). Several studies have shown the immunological effects of peripheral blood T lymphocyte subsets by different treatments in tumor patients. For example, anti-PD-1 treatment (nivolumab) declined $CD4^+$ cell levels but increased the proportion of $CD8^+$ T cell in oral cavity squamous cell carcinoma (5). For patients with esophageal

cancer, $CD3^+$ T cell as well as $CD4^+$ T cells and $CD4^+/CD8^+$ ratio were significantly increased in peripheral blood after radiotherapy (6). Moreover, peripheral blood T lymphocyte subsets can be acted as prognostic indicators. For patients with small cell lung cancer, analysis of progression free survival showed that $CD8^+$ T cells in circulating lymphocytes was an independent predictive factor (7).

Recent studies have demonstrated most RCC patients suffer from local or systemic immune deficiencies, leading to low immune functions (8,9). However, few studies have evaluated the role of peripheral blood T lymphocyte subsets in patients with ccRCC. In this study, we detected the level of peripheral blood T lymphocyte subsets in pathologically diagnosed ccRCC patients preoperatively and performed prognosis assessment. In addition, we also analyzed relevant factors that affect the level of peripheral blood T lymphocytes subsets. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1066).

Methods

Patients

A cohort of 122 patients with RCC was admitted to the fifth affiliated hospital of Sun Yat-sen University from January 2018 to January 2020. Eligible patients were pathologically diagnosed as ccRCC, peripheral blood T lymphocyte subsets and computed tomography were underwent preoperatively. Finally, a total of 80 patients was enrolled into this study. All of the 80 ccRCC patients received neither neoadjuvant chemotherapy nor immunity therapy preoperatively, and no patients had any coexisting immune system disorders or known active infections before treatment. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Ethics Committee of the fifth affiliated hospital of Sun Yat-sen University (No.: 2020#L101-1). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Data collection

Patient information and laboratory data were collected from the patient records. Preoperative peripheral blood T lymphocyte subsets and complete blood counts within a week were analyzed. The levels of peripheral blood T lymphocyte subsets were determined using the Beckman DxFLEX flow cytometer (California, USA). The subsets of T lymphocyte cells include $CD3^+$, $CD4^+$, $CD8^+$ T cells and $CD4^+/CD8^+$ ratio. Complete blood counts were performed using an automated hematology analyzer (Sysmex XN-10, Kobe, Japan).

Follow-up

All patients were followed up every 3–6 months, with a range of 3–28 months and a mean follow-up of 13.3 months. Physical examination, routine blood test and chemistry analysis, chest radiography and abdominal ultrasonography or computed tomography were performed at each follow-up. The study endpoint was patient death. Overall survival (OS) was calculated as the time from the date of enrollment to death or the date of the last follow-up.

Statistical analysis

All statistical analyses were performed using the SPSS, version 19.0 (Chicago, IL, USA). Chi-square test was adopted for the comparisons between groups. Independent predictors of OS were analyzed using the univariate and multivariate Cox proportional hazards regression analyses. Survival analyses of T lymphocyte cell subsets were performed using Kaplan–Meier curve and log-rank test. The Spearman correlation coefficient were used to detect the linear correlations. $P<0.05$ suggested that the difference was statistically significant.

Results

Distribution of T lymphocyte subsets in patients with ccRCC

As reported, cancer patients are often accompanied by decreased $CD3^+$, $CD4^+$, $CD8^+$ T cells and $CD4^+/CD8^+$ ratio (10). In our study, 22 patients were presented with low $CD3^+$ T cells, and low $CD4^+$ T cells, low $CD8^+$ T cells and low $CD4^+/CD8^+$ ratio were found in 33, 15 and 15 patients, respectively. The distribution of T lymphocyte subsets of 80 patients with ccRCC was shown in Table S1.

Clinicopathological characteristics and T lymphocyte subsets of ccRCC patients

Among the 80 patients with ccRCC, 51 (63.8%) patients were male and 29 (36.2%) patients were female, with a mean

age of 54.9 years (range, 26–84 years). The distributions of clinicopathological characteristics in T lymphocyte subset group were shown in *Table 1*.

PLR was significantly higher among the $CD3^+$ low group, the $CD4^+$ low group and the $CD8^+$ low group than those among the $CD3^+$ high group, the $CD4^+$ high group and the $CD8^+$ high group (P=0.002, 0.001 and 0.007, respectively), and NLR was significantly higher in the $CD3^+$ low group and the $CD4^+$ low group than those in the $CD3^+$ high group and the $CD4^+$ high group (P<0.001, for both). Patients in the $CD3^+$ low group and the $CD8^+$ low group were significantly more likely to have higher RENAL score, bigger tumor size and higher Fuhrman grade. Age and sex are significantly associated with the level of $CD4^+/CD8^+$ ratio (P=0.020 and 0.034, respectively). Additionally, larger BMI and a positive history of hypertension were found in patients with high level of $CD8^+$ T cells than those with low level of $CD8^+$ T Cells (P=0.005 and 0.025, respectively), however with no difference among the other three T lymphocyte subgroups.

Survival analysis with T lymphocyte cell subsets

As shown in *Figure 1A*, patients with low $CD3^+$ T cells displayed a worse OS than patients with high $CD3^+$ T cells (P=0.029). Similarly, the survival outcomes for patients in $CD4^+/CD8^+$ low group were also more negative (P=0.002) (*Figure 1B*). However, patients with low $CD4^+$ T cells and low $CD8^+$ T cells showed no significantly difference in OS compared with patients with high $CD4^+$ T cells and high $CD8^+$ T cells (P=0.549 and 0.199, respectively) (*Figure 1C,D*).

$CD3^+$ T cells and $CD4^+/CD8^+$ ratio are independent predictive factors for the OS

On univariate Cox regression analysis, longer OS was noted in patient with younger age (HR =3.438, 95% CI: 1.085–10.894, P=0.036), higher $CD3^+$ T cells (HR =0.302, 95% CI: 0.096–0.951, P=0.041) and higher $CD4^+/CD8^+$ ratio (HR =0.185, 95% CI: 0.055–0.626, P=0.007) (*Table 2*). Then multivariate survival analysis was performed to find out the independent factors affecting OS. The results indicated that $CD3^+$ T cells (HR =0.295, 95% CI: 0.091–0.956, P=0.042) and $CD4^+/CD8^+$ ratio (HR =0.244, 95% CI: 0.065–0.920, P=0.037) were independent prognostic factors for OS (*Table 2*).

Correlation between clinicopathological characteristics and T lymphocyte cell subsets

We further analyzed the correlation between clinicopathological characteristics and T lymphocyte cell subsets. Our results displayed that NLR was both negatively correlated with $CD3^+$ T cells (r=–0.398, P<0.001) and $CD4^+/CD8^+$ ratio (r=–0.280, P =0.012) (*Figure 2*). A positive correlation was observed between BMI and $CD3^+$ T cells (r=0.301, P=0.007) and a negative correlation was observed between PLR and $CD3^+$ T cells (r=–0.483, P<0.0001) (*Figure 2A*), however no significantly correlations were found neither between BMI and $CD4^+$ T cells nor between PLR and $CD4^+$ T cells (*Figure 2B*).

Discussion

Prior studies have indicated that the prognostic and predictive value of T cells infiltrated in formalin-fixed and parrffin-embedded specimens in RCC (11,12). However, to the best of our knowledge, the present study is the first to identify the relationship between peripheral blood T lymphocyte subsets and the prognosis of patients with ccRCC. The current study shows that low $CD3^+$ T cells and low $CD4^+/CD8^+$ ratio in peripheral blood were negatively associated with the OS in ccRCC patients.

One characteristic of most patients with malignant tumor is immune dysfunction, and inhibition of host immune system facilitates tumor progression. Increasing studies have demonstrated a prognostic and predictive role of systemic and local immunological markers in cancer patients (10,13). Clear cell renal cell carcinoma (ccRCC), representing the majority of RCC, is characterized by strong immunogenicity. As a result of it, immunotherapies targeting and blocking immune checkpoint, such as CTLA-4 and PD-1 are newly applied to patients with ccRCC during the last decade. $CD3^+$ tissue infiltrating lymphocytes (TILs) forming memory T-cell and $CD8^+$ TILs forming cytotoxic T-cell play a key role in immune defense (14). Local immune response in ccRCC, such as $CD3^+$ and $CD8^+$ TILs, has been analyzed in recent studies. It was reported that higher density of $CD8^+$ TILs was associated with prolonged progression-free survival in ccRCC (15). In a cohort of 756 patients with ccRCC, the percentage of tumor-infiltrating $CD3^+$ T cells in patients with better response to nivolumab was significantly increased (16). Moreover, lower T cell infiltrate significantly increased the

Table 1 Clinical and pathological characteristics stratified by CD3+ T cell count, CD4+ T cell count and CD4/CD8 ratio in patients with ccRCC

Variables	$CD3^+$ T cell count			$CD4^+$ T cell count			$CD8^+$ T cell count			$CD4^+/CD8^+$ ratio		
	Low (<770)	High (>770)	P	Low (<500)	High (>500)	P	Low (<238)	High (>238)	P	Low (<1.0)	High (>1.0)	P
Age (y)			0.614			0.994			0.630			0.020
<65	16	47		26	37		13	50		8	55	
>65	6	11		7	10		2	15		7	10	
Sex			0.612			0.624			0.392			0.034
Male	15	36		20	31		11	40		6	45	
Female	7	22		13	16		4	25		9	20	
Hypertension			0.787			0.921			0.025			0.912
Yes	8	23		13	18		2	29		6	25	
No	14	35		20	29		13	36		9	40	
Diabetes mellitus			0.984			1.000			0.865			0.865
Yes	3	6		4	5		1	8		1	8	
No	19	52		29	42		14	57		14	57	
Location			0.291			0.698			0.014			0.031
Left	12	24		14	22		11	25		6	34	
Right	10	34		19	25		4	40		9	31	
Surgical approach			0.075			0.004			0.026			0.519
NSS	14	24		22	16		11	27		6	32	
RN	8	34		11	31		4	38		9	33	
BMI (kg/m^2)			0.358			0.578			0.005			1.000
<25	15	33		21	27		12	36		9	39	
>25	7	25		12	20		3	29		6	26	
NLR			<0.001			<0.001			0.166			0.166
<3	8	49		16	41		8	49		8	49	
>3	14	9		17	6		7	16		7	16	
PLR			0.002			0.001			0.007			0.694
<132	5	36		9	32		3	38		7	34	
>132	17	22		24	15		12	27		8	31	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	$CD3^+$ T cell count			$CD4^+$ T cell count			$CD8^+$ T cell count			$CD4^+/CD8^+$ ratio		
	Low (<770)	High (>770)	P	Low (<500)	High (>500)	P	Low (<238)	High (>238)	P	Low (<1.0)	High (>1.0)	P
$CD3^+$ T cell (cells/μL)			-			<0.001			<0.001			0.128
<770	22	0		22	0		14	8		7	15	
>770	0	58		11	47		1	57		8	50	
$CD4^+$ T cell (cells/μL)			<0.001			–			<0.001			0.102
<500	22	11		33	0		14	19		9	24	
>500	0	47		0	47		1	46		6	41	
$CD8^+$ T cell (cells/μL)			<0.001			<0.001			–			0.035
<238	14	1		14	1		15	0		1	14	
>238	8	57		19	46		0	65		14	51	
$CD4^+/CD8^+$			0.128			0.102			0.335			–
<1.0	7	8		9	6		1	14		15	0	
>1.0	15	50		24	41		14	51		0	65	
MAP score			0.201			0.882			0.519			0.099
0–2	9	33		17	25		9	33		5	37	
3–5	13	25		16	22		6	32		10	28	
RENAL score			0.006			0.403			0.039			0.702
4–6	2	24		9	17		1	25		6	20	
7–12	20	34		24	30		14	40		9	45	
Tumor size (cm)			0.001			0.063			0.002			0.452
<5	4	35		12	27		2	37		6	33	
>5	18	23		21	20		13	28		9	32	
T stage			0.081			0.464			0.509			0.925
T1-2	15	51		26	40		11	55		13	53	
T3-4	7	7		7	7		4	10		2	12	
Fuhrman grade			0.007			0.103			0.047			0.801
1–2	7	38		15	30		5	40		8	37	
3–4	15	20		18	17		10	25		7	28	

BMI, body mass index; MAP, Mayo adhesive probability; NLR, neutrophil to lymphocyte ratio; NSS, nephron sparing surgery; PLR, platelet to lymphocyte ratio; RN, radical nephrectomy.

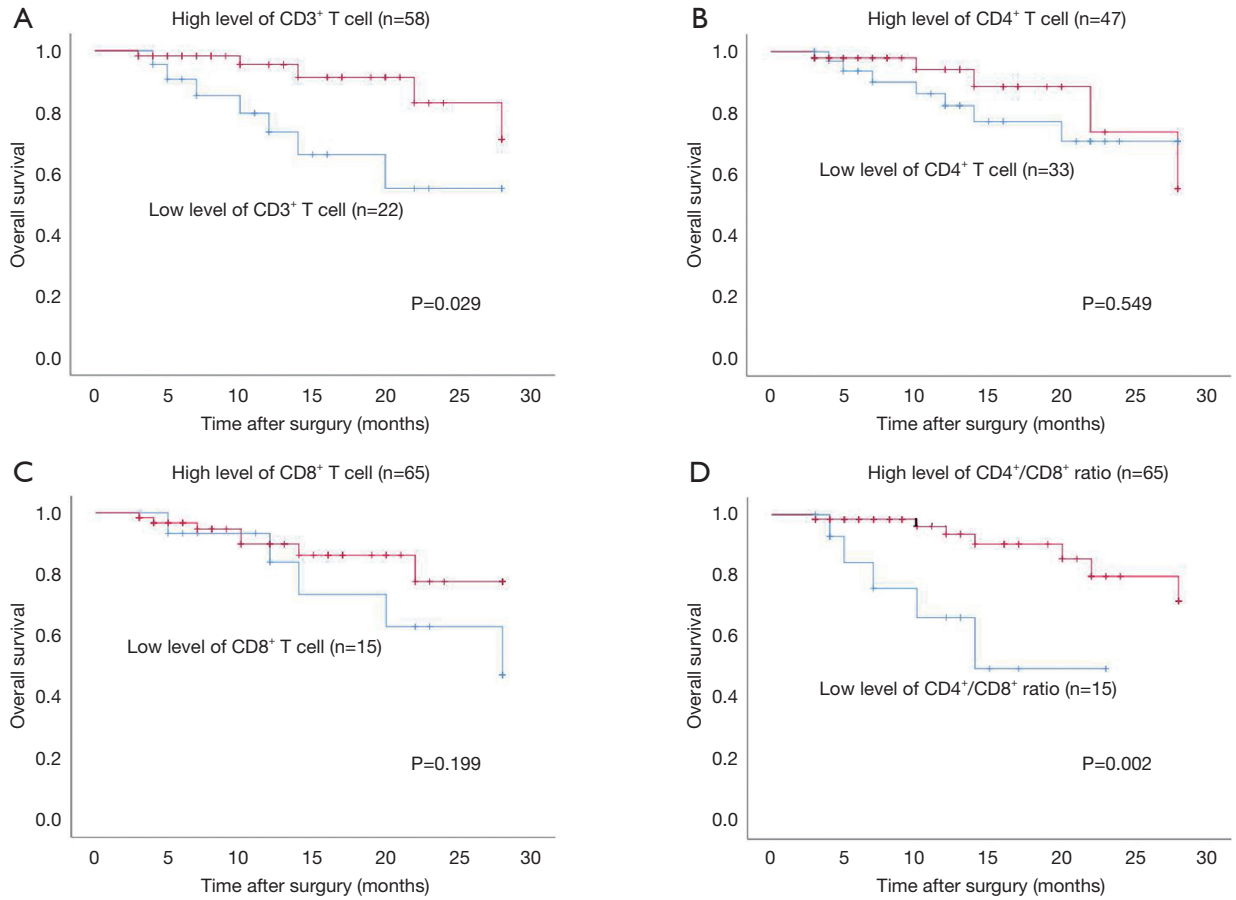

Figure 1 Kaplan-Meier analysis for overall survival (OS) in patients with ccRCC. (A) OS for patients with $CD3^+$ T cells; (B) OS for patients with $CD4^+$ T cells; (C) OS for patients with $CD8^+$ T cells; (D) OS for patients with $CD4^+/CD8^+$ ratio.

recurrence of localized ccRCC following surgery (12).

Compared to local immunological markers by detecting tumor tissues, peripheral blood T lymphocyte subsets are indicators of systemic immune response and can be conveniently acquired. Changes of the peripheral blood T lymphocyte subsets response to various treatment and clinical outcomes are observed. For patients with various types of cancers after hyperthermia treatment, such as ovarian, gastric or endometrial cancer, the proportion of $CD8^+/CD28^+$ T cells was increased, while that of $CD4^+/CD25^+/CD127^+$ cells was decreased (17). Excitingly, the prognostic role of the peripheral blood T lymphocyte subsets was also noted. The correlation between increased peripheral blood $CD3^+$ and $CD8^+$ T cells and improved survival was significantly positive in patients with pancreatic cancer after chemotherapy with 5FU (18). Similarly, for patient with small cell lung cancer, higher $CD8^+$ T cells demonstrated better progression free survival (7).

The available evidence regarding the possible role of $CD4^+/CD8^+$ ratio in different cancer patients is conflicting. On one hand, the declined in $CD4^+/CD8^+$ ratio was associated with the progression of lung cancer patients, as the percentage of $CD4^+/CD8^+$ in high stage was lower than that in low stage (19). On the other hand, ovarian cancer patients with a decreased $CD4^+/CD8^+$ ratio were found to have a better OS than those with an increased ratio (20). In the present study, our results showed that declined $CD3^+$ T cells and $CD4^+/CD8^+$ ratio were correlated with shorter OS in patients with ccRCC. To further explore the reduction of $CD3^+$ T cells and $CD4^+/CD8^+$ ratio in patients with worse prognosis, their correlation with clinicopathological characteristics were detected. Our results showed that patients who were immunosuppressive were more likely to have an activated inflammatory response, such as a high

Table 2 Univariate and multivariate analysis regarding overall survival in patients with ccRCC

Variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age (y)						
<65 *vs.* >65	3.438	1.085–10.894	0.036	2.871	0.817–10.082	0.100
Sex						
Male *vs.* female	1.352	0.427–4.277	0.608			
Hypertension						
Yes *vs.* no	0.806	0.259–2.522	0.709			
Diabetes mellitus						
Yes *vs.* no	25.613	0.020–32,358.570	0.373			
Location						
Left *vs.* right	3.086	0.829–11.487	0.093			
Surgical approach						
NSS *vs.* RN	3.172	0.854–11.782	0.085			
BMI (kg/m^2)						
<25 *vs.* >25	0.315	0.069–1.445	0.137			
NLR						
<3 *vs.* >3	1.936	0.621–6.032	0.255			
PLR						
<132 *vs.* >132	1.018	0.321–3.231	0.975			
CD3$^+$ T cell (cells/μL)						
<770 *vs.* >770	0.302	0.096–0.951	0.041	0.295	0.091–0.956	0.042
CD4$^+$ T cell (cells/μL)						
<500 *vs.* >500	0.704	0.221–2.241	0.553			
CD8$^+$ T cell (cells/μL)						
<238 *vs.* >238	0.475	0.148–1.523	0.211			
CD4$^+$/CD8$^+$ ratio						
<1.0 *vs.* >1.0	0.185	0.055–0.626	0.007	0.244	0.065–0.920	0.037
MAP score						
0–2 *vs.* 3–5	1.622	0.511–5.147	0.412			
RENAL score						
4–6 *vs.* 7–12	4.475	0.576–34.770	0.152			
Tumor size (cm)						
<5 *vs.* >5	4.431	0.965–20.353	0.056			
T stage						
T1–2 *vs.* T3–4	1.779	0.475–6.665	0.392			
Fuhrman grade						
1–2 *vs.* 3–4	1.259	0.403–3.928	0.692			

BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MAP, Mayo adhesive probability.

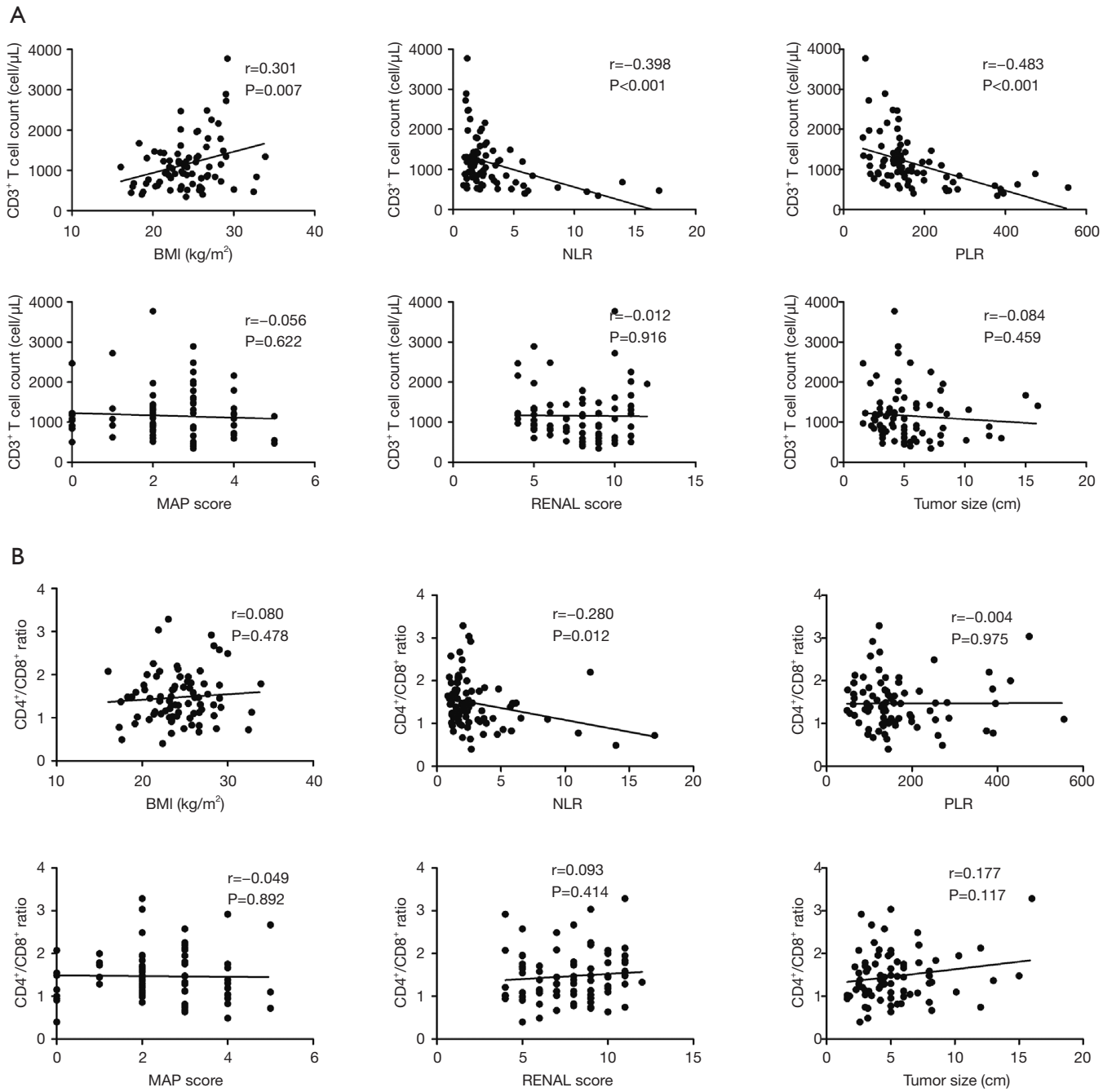

Figure 2 Correlation between clinicopathological characteristics and T lymphocyte cell subsets. (A) Correlation between clinicopathological characteristics and levels of $CD3^+$ T cells. (B) Correlation between clinicopathological characteristics and levels of $CD4^+/CD8^+$ ratio.

level of NLR and PLR.

NLR and PLR are widely used as inflammation-associated indexes. Recent studies have demonstrated their prognostic role in various types of cancers, including RCC (21,22). Moreover, higher NLR and PLR are associated with worse prognosis in immunotherapy for patients with RCC (23,24). High activity of inflammatory response is noted with elevated NLR and PLR, while chronic inflammation usually leads to tumor development by suppressing the immune system. Our data suggested that

$CD3^+$ T cells and $CD4^+/CD8^+$ ratio were correlated with NLR and PLR levels, which is consistent with the above studies (23,24).

The present study also has certain limitations. Firstly, our study was conducted in a single institution with a small sample size of 80 patients and a short-term follow-up of 3–28 months. To provide a better evidence, our results require larger samples and longer follow-up in a multi-center cohorts. Secondly, our study only focused on the T lymphocyte subsets in peripheral blood to reflect the immune status. Our results should combine the B lymphocyte cell and natural killer cell to monitor systemic immune function. Besides, TILs were not detected in our study. A better understanding of the correlation between peripheral blood T lymphocyte subsets and TILs will help to explain the prognostic role of T lymphocyte subsets in ccRCC patients.

Conclusions

In conclusion, our study indicates that $CD3^+$ T cells and $CD4^+/CD8^+$ ratio in peripheral blood are independent predictors for patients with ccRCC. With a low cost and conveniently acquire, $CD3^+$ T cells and $CD4^+/CD8^+$ ratio are promising biomarkers that facilitate the clinical application in ccRCC. Therefore, the value of $CD3^+$ T cells and $CD4^+/CD8^+$ ratio as prognostic indicators is worthy of further exploration in future clinical studies.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-1066

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tau-20-1066

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-1066). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Ethics Committee of the fifth affiliated hospital of Sun Yat-sen University (No.: 2020#L101-1). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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