



# Preoperative low-density lipoprotein cholesterol as a predictor of favorable prognosis in patients with clear cell renal cell carcinoma

Yangyang Mei, Zhen Chen, Xiaogang Wang, Renfang Xu, Hao Lu

Department of Urology, The Third Affiliated Hospital of Soochow University, Changzhou, China

**Contributions:** (I) Conception and design: Y Mei, Z Chen; (II) Administrative support: R Xu, H Lu; (III) Provision of study materials or patients: Z Chen, X Wang; (IV) Collection and assembly of data: Z Chen, Y Mei; (V) Data analysis and interpretation: Y Mei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Hao Lu, MM; Renfang Xu, BS. Department of Urology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou, China. Email: luhao202203@163.com; czyyxf@163.com.

**Background:** Studies have shown that dyslipidemia is closely tied to a variety of cancers, and the level of low-density-lipoprotein-cholesterol (LDL-C) is related to the prognosis of cancer patients. However, what remains unclear is the predictive meaning of LDL-C among patients who suffer from renal cell carcinoma, especially clear cell renal cell carcinoma (CCRCC). The aim of this study was to investigate the correlation between the preoperative levels of serum LDL-C and the prognosis of surgical patients who suffer from clear cell renal cell carcinoma.

**Methods:** A total of 308 CCRCC patients that received radical or partial nephrectomy were retrospectively included in this study. The clinical data of each included patient were collected. Overall survival (OS) and cancer-specific survival (CSS) were calculated using Kaplan-Meier method and Cox proportional hazards regression model.

**Results:** Univariate analysis showed that a higher LDL-C level indicated a better OS and CSS in CCRCC patients ( $P=0.002$  and  $P=0.001$ , respectively). The same was shown in the Multivariate analysis that a higher LDL-C level indicated a better OS and CSS in CCRCC patients ( $P<0.001$  and  $P<0.001$ , respectively). Following propensity score matching (PSM) analysis, a higher LDL-C level still existed as an ideal indicator for both OS and CSS.

**Conclusions:** The study indicated that a higher serum level of LDL-C showed clinical significance for predicting better OS and CSS in patients with CCRCC.

**Keywords:** Low-density-lipoprotein-cholesterol (LDL-C); clear cell renal cell carcinoma (CCRCC); prognosis; operation

Submitted Nov 26, 2022. Accepted for publication May 11, 2023. Published online Jun 13, 2023.

doi: 10.21037/tcr-22-2705

**View this article at:** <https://dx.doi.org/10.21037/tcr-22-2705>

## Introduction

Renal cell carcinoma (RCC) is the seventh most common cancer globally. The incidence and mortality of RCC are constantly growing worldwide (1). Clear cell renal cell carcinoma (CCRCC) is the most common pathological subtype of RCC, accounting for more than 70% of all RCC cases (2). Although new treatments for RCC are emerging, such as immunotherapy (3), anti-angiogenesis (4) and HIF2 inhibitor (5), surgical treatment still plays an important role (6).

Therefore, preoperative laboratory indicators are crucial for surgical prognosis, which means a lot to both surgeons and patients. Although many indicators such as tumor-node-metastasis (TNM) stage (7), Fuhrman grade (8), C-reactive protein to albumin ratio (9), albumin to globulin ratio (10), pretreatment neutrophil-to-lymphocyte ratio (11) and positive surgical parenchymal margin (12) have been used to evaluate the risks, it is still necessary to identify simple biomarkers to predict the prognosis in clinical practice.

Lipid metabolism disorders which have been described in previous study are common in cancer (13). Many studies have found the connection between serum lipids and various carcinoma, such as esophageal squamous cell carcinoma (14), small cell lung cancer (15) and gastric cancer (16,17). Jung *et al.* (18) found that patients with a high level of bad lipids [low-density-lipoprotein-cholesterol (LDL-C)] and low level of good lipid [high-density-lipoprotein-cholesterol (HDL-C)] generally demonstrated a good prognosis for breast cancer recurrence, suggesting LDL-C may also be correlated with the prognosis of other tumors. Riscal *et al.* (19) later discovered that elevated circulating HDL-C level was significantly associated with the risk of CCRCC. Coincidentally, the association between serum LDL-C and the outcome of CCRCC have not yet been assessed. This study is aiming to figure out the potential role of the LDL-C on overall survival (OS) and cancer-specific survival (CSS) in CCRCC patients after surgical resections. The application of propensity score matching analysis (PSM) aimed to improve statistical reliability and further confirm the latent prognostic value of LDL-C. We present this article in accordance with the REMARK reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2705/rc>).

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Changzhou No.1 People's Hospital Medical Ethics Committee (2013 No. 14) and informed consent was obtained from all the patients.

## Patients

The data of 414 patients with CCRCC that underwent

surgical treatment in The Third Affiliated Hospital of Soochow University from 2003 to 2012 were collected in this study. The inclusion criteria were: (I) patients with radical nephrectomy; (II) CCRCC was histopathologically diagnosed; (III) patients without cancer history; (IV) patients without preoperative neoadjuvant therapy; and (V) preoperative laboratory tests were acquired before treatment. After the exclusion of 106 patients, the remaining 308 patients were eventually enrolled in the analysis.

## Data collection

The necessary clinical data of each patient in this study included gender, age at surgery, Fuhrman grade, TNM stage, tumor size and tumor necrosis, lymphovascular invasion (LVI), and lactate dehydrogenase (LDH) and alkaline phosphatase (AKP). The required laboratory indicators were collected prior to the operation.

## Follow-up assessment

Review of the medical records and telephone interviews were involved in follow-up assessment. OS defined as the interval between the date of the resection and the last follow-up or death was the primary endpoint. CSS calculated from the date of the resection was the secondary endpoint. If the patients were locally advanced CCRCC, they would undergo physical examinations and laboratory tests every 6 months in the first 3 years, then annually thereafter. If the patients were locally CCRCC, they would perform laboratory tests and physical examinations twice in the first year and annually thereafter.

## Statistical analysis

The Kaplan-Meier method were used to establish the survival curves, and the optimal cutoff point which allowed the predictive outcome with the best specificity and sensitivity was decided by receiver-operating characteristics (ROC) analysis. Continuous variables were divided into different groups owing to the optimal cutoff value. The  $\chi^2$  test was performed to detect differences between the groups. The Cox proportional hazards model was used for univariate analysis and multivariate analysis. A P value <0.05 was considered statistically significant in all statistical tests. All statistical analysis were performed with SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). Aiming to control the differences between the two different LDL-C

### Highlight box

#### Key findings

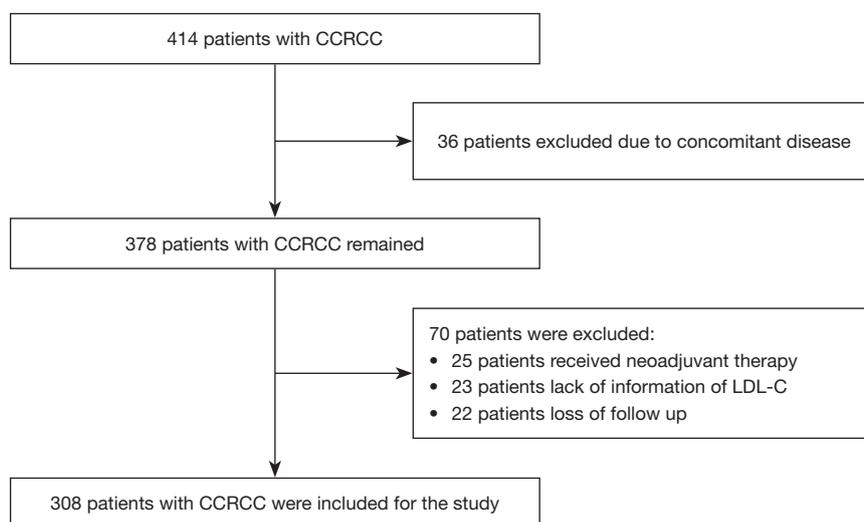
- LDL is a good renal tumor prognostic marker.

#### What is known and what is new?

- LDL is generally connected with poor prognosis.
- LDL indicates good prognosis in CCRCC.

#### What is the implication, and what should change now?

- LDL shouldn't be regarded as an adverse prognostic indicator.



**Figure 1** Flow diagram of the study selection process. LDL-C, low-density-lipoprotein-cholesterol; CCRCC, clear cell renal cell carcinoma.

groups, a 1:1 propensity score matching was performed. Covariates, such as age, sex, tumor size, Fuhrman grade, tumor stage, lymph node stage, lymphovascular invasion, the presence of Tumor necrosis and AKP levels were included in matching. All of the covariates' absolute standardized mean difference was less than 0.1, arriving at a good balance.

## Results

### Patient characteristics

After the eligibility review, 308 patients with CCRCC who underwent radical nephrectomy were enrolled in the present study. *Figure 1* shows the screening process and detailed information. The clinicopathologic information of the 308 included patients is presented in *Table 1*. Of the patients, 193 were male and 115 were female; 128 were older than 60 years old, and 180 were younger; the median follow-up time was 60 months (range, 1–149 months); by the last follow-up date, 40 patients had died, and 268 were alive. On the basis of ROC analysis, 2.315 mmol/L acted as the cut-off value for LDL-C (*Figure 2*). The cut-off value for alkaline phosphatase (AKP) and lactate dehydrogenase (LDH) was 125 U/L and 245 U/L respectively.

### Relationship between the LDL-C levels and other clinical characteristics

*Table 1* shows the connection between LDL-C levels and

clinicopathological characteristics of the enrolled patients. The higher LDL-C level was not significantly associated with the clinicopathological indicators, including age, sex, tumor size, Fuhrman grade, tumor stage, lymph node stage, lymphovascular invasion, the presence of Tumor necrosis and AKP levels (*Table 1*). The differences that existed in clinicopathological characteristics between low LDL-C group and high LDL-C group were well balanced depending on the PSM analysis. The results after PSM analysis were the same as those before PSM analysis. The LDH groups after PSM analysis were all larger than 245 U/L, so the LDH groups after PSM analysis were not discussed.

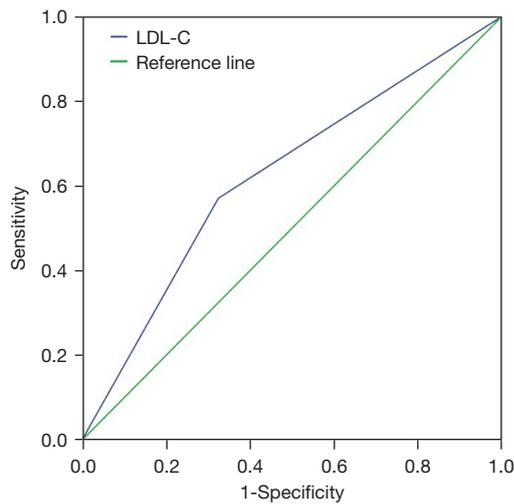
### Prognostic value of LDL-C and clinical characteristics for OS before and after PSM analysis

*Table 2* illustrates that a higher LDL-C level is significantly associated with a better OS [hazard ratio (HR) 2.843; 95% confidence interval (CI): 1.463, 5.525;  $P=0.002$ ; *Table 2*). The Kaplan-Meier survival analysis demonstrated that patients who had a high LDL level had a better OS ( $P<0.001$ ) (*Figure 3*). On the basis of univariate analysis, *Table 2* also shows that other clinicopathological factors, such as an older age than 60 years old ( $P=0.001$ ), a higher pathological T stage ( $P<0.001$ ), an advanced lymph node stage ( $P<0.001$ ), a larger tumor size ( $P<0.001$ ), a higher Fuhrman grade ( $P<0.001$ ), the presence of lymphovascular invasion ( $P<0.001$ ), a high LDH level ( $>245$  U/L) ( $P=0.025$ ), and a high AKP level ( $>130$  U/L) ( $P<0.001$ ),

**Table 1** Correlation of LDL-C with the clinicopathological characteristics of CCRCC patients

Variables	Pre-PSM, n (%)			Post-PSM, n (%)		
	LDL-C $\leq$ 2.315 mmol/L (n=142)	LDL-C >2.315 mmol/L (n=166)	P value	LDL-C $\leq$ 2.315 mmol/L (n=124)	LDL-C >2.315 mmol/L (n=124)	P value
Age (years)			0.645			0.897
$\leq$ 60	85 (59.9)	95 (57.2)		73 (58.9)	74 (59.7)	
>60	57 (40.1)	71 (42.8)		51 (41.1)	50 (40.3)	
Sex			0.723			0.538
Male	87 (61.3)	106 (63.9)		75 (60.5)	74 (59.7)	
Female	55 (38.7)	60 (36.1)		49 (39.5)	50 (40.3)	
Tumor size (cm) <sup>#</sup>			0.905			0.791
$\leq$ 5	89 (63.1)	106 (64.2)		81 (65.3)	78 (62.9)	
>5	52 (36.9)	59 (35.8)		43 (34.7)	46 (37.1)	
T stage			0.701			0.806
T1	114 (80.3)	138 (83.1)		103 (83.1)	101 (81.5)	
T2	15 (10.6)	17 (10.2)		11 (8.9)	14 (11.3)	
T3	13 (9.2)	11 (6.6)		10 (8.1)	9 (7.3)	
N stage			1.000			0.734
N0	137 (96.5)	161 (97.0)		120 (96.8)	119 (96.0)	
N1	5 (3.5)	5 (3.0)		4 (3.2)	5 (4.0)	
Fuhrman grade			0.416			0.841
1	24 (17.4)	40 (25.0)		21 (16.9)	19 (15.3)	
2	77 (55.8)	77 (48.1)		72 (58.1)	68 (54.8)	
3	29 (21.0)	34 (21.3)		26 (21.0)	30 (24.2)	
4	8 (5.8)	9 (5.6)		5 (4.0)	7 (5.6)	
LVI			0.629			0.571
Absent	135 (95.1)	155 (93.4)		119 (96.0)	116 (93.5)	
Present	7 (4.9)	11 (6.6)		5 (4.0)	8 (6.5)	
Tumor necrosis			0.072			0.811
Absent	125 (88.0)	156 (94.0)		114 (91.9)	115 (92.7)	
Present	17 (12.0)	10 (6.0)		10 (8.1)	9 (7.3)	
AKP (U/L)			0.180			0.701
$\leq$ 130	132 (93.6)	160 (97.0)		121 (97.6)	120 (96.8)	
>130	9 (6.4)	5 (3.0)		3 (2.4)	4 (3.2)	
LDH (U/L)			0.185			
$\leq$ 245	137 (97.2)	164 (99.4)		–	–	
>245	4 (2.8)	1 (0.6)		–	–	

On the basis of the *Table 1*, the clinicopathological indicators, such as age, sex, tumor size, Fuhrman grade, tumor stage, lymph node stage, lymphovascular invasion, the presence of tumor necrosis, LDH and AKP levels, were not significantly associated with the higher LDL-C level before PSM analysis. It remains the same after PSM analysis. <sup>#</sup>, tumor size was defined as the largest diameter of the tumor mass. T, tumor; N, node; LVI, lymphovascular invasion; LDL-C, low-density-lipoprotein-cholesterol; CCRCC, clear cell renal cell carcinoma; LDH, lactate dehydrogenase; AKP, alkaline phosphatase; PSM, propensity score matching.



**Figure 2** According to the ROC analysis, the cut-off value for LDL-C was 2.315 mmol/L. ROC, receiver-operating characteristics; LDL-C, low-density-lipoprotein-cholesterol.

are significantly associated with poor OS. On the basis of multivariate analysis, the level of LDL-C was found to exist as an independent prognostic factor in patients who suffered from CCRCC (HR 4.315; 95% CI: 1.962, 9.489;  $P < 0.001$ ; *Table 2*). Moreover, age was found to be of significant associations with OS. After PSM analysis, LDL-C remained associated with better OS on univariate analysis with HR 2.292, 95% CI: 1.102, 4.767;  $P = 0.026$ ; *Table 3*). The same held true for Kaplan-Meier survival analysis ( $P = 0.022$ ; *Figure 4*). While in multivariate analysis, a higher pathological T stage ( $P = 0.016$ ) was also strongly associated with OS, which was different from previous suggestions. In addition, lower age ( $P = 0.003$ ) and higher LDL-C (HR 3.545; 95% CI: 1.603, 7.837;  $P = 0.002$ ; *Table 3*) also predicted better OS.

#### ***Prognostic value of LDL-C and clinical characteristics for CSS before and after PSM analysis***

Regarding CSS, univariate analysis before PSM analysis illustrated that a high LDL-C level was significantly associated with a better CSS (HR 3.649; 95% CI: 1.756, 7.585;  $P = 0.001$ ; *Table 4*). The Kaplan-Meier survival analysis before PSM analysis indicated that an increased LDL level had a better CSS in patients enrolled in this study ( $P < 0.001$ ) (*Figure 5*). On the basis of univariate analysis, clinicopathological factors, such as an older age than 60 years old ( $P = 0.004$ ), a higher lymph node stage ( $P < 0.001$ ),

a higher pathological T stage ( $P < 0.001$ ), the presence of tumor necrosis ( $P < 0.001$ ), a larger tumor size ( $P < 0.001$ ), a high AKP level ( $> 130$  U/L) ( $P < 0.001$ ), the presence of lymphovascular invasion ( $P < 0.001$ ) and a high LDH level ( $> 245$  U/L) ( $P = 0.010$ ), were connected with worse CSS. On the basis of multivariate analysis, an increased LDL-C level was found to be of significant association with increased CSS (HR 5.766; 95% CI: 2.370, 14.030;  $P < 0.001$ ; *Table 4*). In addition, age, T stage, N stage and the presence of lymphovascular invasion were independent risk factors for CSS (*Table 4*). Compared with the univariate analysis before PSM analysis, the univariate analysis after PSM analysis indicated that a younger age ( $P = 0.019$ ; *Table 5*), a lower lymph node stage ( $P < 0.001$ ; *Table 5*), a lower pathological T stage ( $P < 0.001$ ; *Table 5*), the presence of tumor necrosis ( $P = 0.019$ ; *Table 5*), a smaller tumor size ( $P < 0.001$ ; *Table 5*), a lower AKP level ( $\leq 130$  U/L) ( $P < 0.001$ ; *Table 5*) and the absence of lymphovascular invasion ( $P < 0.001$ ; *Table 5*), were related to better CSS. What was expressed by the Kaplan-Meier survival analysis before and after PSM analysis was consistent, indicating that a depressed LDL-C level had a worse CSS in CCRCC patients ( $P = 0.005$ ; *Figure 6*). During the multivariate analysis after PSM analysis, except the lymphovascular invasion, other indicators associated with CSS were found to be still valid, such as age ( $P = 0.008$ ; *Table 5*), T stage ( $P = 0.009$ ; *Table 5*), lymph node stage ( $P = 0.014$ ; *Table 5*).

#### **Discussion**

Recent study shows that the role of lipids among the development of tumor has been a center of interest. However, the roles of various lipids in different tumor types are often contradictory (20). An association between blood cholesterol levels and the risk of different cancers that includes colorectal (21), lung (22), prostate (23-25), breast (26), pancreatic (27), endometrial (28) and gastric (17) cancer has been shown by previous studies, and this connection would change as per the different types of cancer. Nowadays, traditional clinicopathological prognostic variables and pathological factors are still the basis of the prognostic evaluation of CCRCC (29) even though the progress has already been made in the epigenetic changes and genetic identification (30). Hence, the need to figure out a simple biomarker that could predict the early diagnosis and prognosis of CCRCC is very crucial for not only clinicians but also patients and their family.

On the basis of the cut-off value of serum LDL-C before

**Table 2** Univariate and multivariate Cox proportional analysis with overall survival before PSM analysis

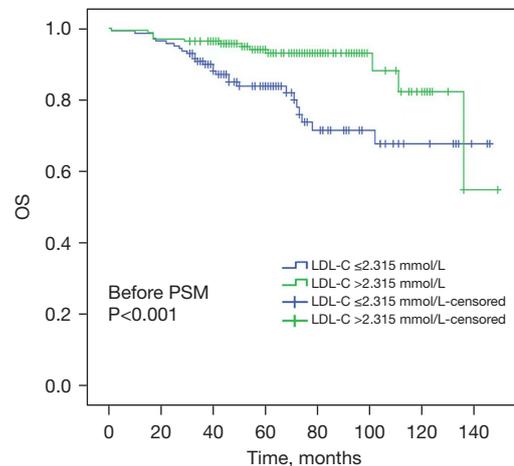
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.001*		0.003*
>60 vs. ≤60	2.82 (1.46, 5.42)		3.436 (1.539, 7.674)	
Sex		0.109		
Male vs. female	1.80 (0.88, 3.67)			
Tumor size (cm) <sup>#</sup>		<0.001*		0.240
≤5	Reference		Reference	
>5	4.99 (2.48, 10.06)		2.027 (0.794, 5.171)	
T stage		<0.001*		0.296
1	Reference		Reference	
2	4.67 (2.06, 10.59)	<0.001*	1.944 (0.714, 5.293)	0.193
3	18.53 (9.05, 37.94)	<0.001*	4.722 (1.641, 13.593)	0.004*
N stage		<0.001*		0.009*
1 vs. 0	7.84 (3.26, 18.90)		5.771 (1.535, 21.699)	
Fuhrman grade		<0.001*		0.262
1	Reference		Reference	
2	6.37 (0.84, 48.09)	0.073	5.935 (0.765, 46.065)	
3	12.66 (1.65, 97.15)	0.015*	7.651 (0.901, 64.967)	
4	16.70 (4.42, 283.20)	0.001*	3.533 (0.364, 34.252)	
LVI		<0.001*		0.073
Absent	Reference	Reference	Reference	
Present	7.64 (3.60, 16.20)		2.974 (0.904, 9.789)	
LDL-C (mmol/L)		0.002*		<0.001*
≤2.315 vs. >2.315	2.843 (1.463, 5.525)		4.315 (1.962, 9.489)	
LDH (U/L)		0.025*		0.628
>245 vs. ≤245	3.87 (1.18, 12.68)		1.519 (0.281, 8.222)	

**Table 2** (continued)

**Table 2** (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AKP (U/L)		<0.001*		0.426
>130 vs. ≤130	10.28 (4.23, 24.99)		1.556 (0.524, 4.619)	

The variables (age, sex, tumor size, TNM stage, Fuhrman grade, LVI, LDL-C) were tested in a multivariate analysis. The univariate analysis of *Table 2* indicated that a higher LDL-C level was significantly associated with a better OS (HR 2.843; 95% CI: 1.463, 5.525; P=0.002). While the multivariate analysis of *Table 2* illustrated that except age, only the LDL-C level existed as an independent prognostic factor in patients with CCRCC. \*, the difference was statistically significant; #, tumor size was defined as the largest diameter of the tumor mass. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; OS, overall survival; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis; LDH, lactate dehydrogenase; AKP, alkaline phosphatase; CCRCC, clear cell renal cell carcinoma.



**Figure 3** On the basis of the Kaplan-Meier survival analysis, we could calculate those patients with a high LDL-C level that higher than 2.315 mmol/L had better OS. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; OS, overall survival.

operation, not only the univariate analysis but also the multivariate analysis showed that the high serum LDL-C was associated with better OS. In this way, a conclusion that high serum LDL-C levels may exist as a favorable predictor for CSS in patients with CCRCC was made. In some other

**Table 3** Univariate and multivariate Cox proportional analysis with overall survival after PSM analysis

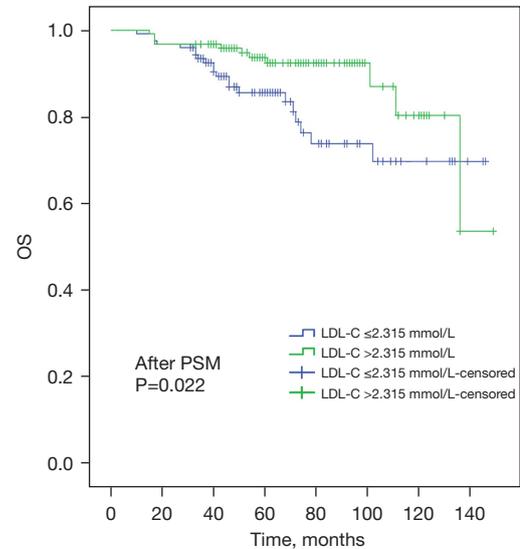
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.009*		0.003*
>60 vs. ≤60	2.614 (1.267, 5.391)		3.601 (1.528, 8.483)	
Sex		0.199		
Male vs. female	1.657 (0.767, 3.584)			
Tumor size (cm) <sup>#</sup>		<0.001*		0.129
≤5	Reference		Reference	
>5	4.353 (2.054, 9.226)		2.103 (0.807, 5.488)	
T stage		<0.001*		0.016*
1	Reference		Reference	
2	3.106 (1.234, 8.094)	0.016*	2.080 (0.705, 6.137)	0.185
3	11.159 (5.006, 24.877)	<0.001*	5.145 (1.652, 16.025)	0.005*
N stage		<0.001*		0.014*
1 vs. 0	7.138 (2.707, 18.824)		5.794 (1.418, 23.671)	
Fuhrman grade		0.014*		0.334
1	Reference		Reference	
2	3.963 (0.523, 30.056)	0.183	5.229 (0.663, 41.256)	0.117
3	6.943 (0.892, 54.058)	0.064	5.647 (0.665, 48.433)	0.113
4	15.764 (1.839, 135.148)	0.012*	2.561 (0.244, 26.845)	0.433
LVI		<0.001*		0.298
Absent	Reference		Reference	
Present	8.540 (3.645, 20.010)		2.135 (0.512, 8.897)	
LDL-C (mmol/L)		0.026*		0.002*
≤2.315 vs. >2.315	2.292 (1.102, 4.767)		3.545 (1.603, 7.837)	

**Table 3** (continued)

**Table 3** (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AKP (U/L)		<0.001*		0.201
>130 vs. ≤130	7.874 (2.677, 23.158)		2.548 (0.608, 10.675)	

The variables (age, sex, tumor size, TNM stage, Fuhrman grade, LVI, LDL-C) were tested in a multivariate analysis. The univariate analysis of *Table 3* indicated that a higher LDL-C level was significantly related to a better OS (HR 2.292; 95% CI: 1.102, 4.767; P=0.026). The multivariate analysis of *Table 3* illustrated that except age and T stage, the LDL-C level still existed as an independent prognostic factor in patients with CCRCC. \*, the difference was statistically significant; #, tumor size was defined as the largest diameter of the tumor mass. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; OS, overall survival; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis; LVI, lymphovascular invasion; AKP, alkaline phosphatase; CCRCC, clear cell renal cell carcinoma.



**Figure 4** After PSM analysis, higher LDL-C resulted in better OS, which was also true for Kaplan-Meier survival analysis. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; OS, overall survival.

studies, the conclusions were consistent with that of this current study in which a high serum LDL-C may function as a favorable predictor in the corresponding cancers, such as non-esophageal squamous cell carcinoma (31), squamous

**Table 4** Univariate and multivariate Cox proportional analysis with cancer-specific survival before PSM analysis

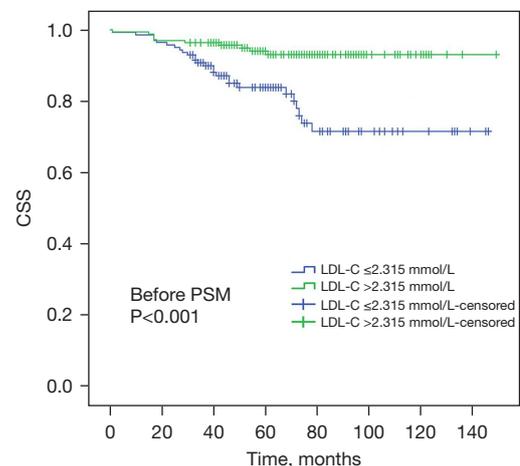
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.004*		0.006*
>60 vs. ≤60	2.73 (1.38, 5.39)		3.299 (1.404, 7.754)	
Sex		0.223		
Male vs. female	1.55 (0.82, 2.95)			
T stage		<0.001*		0.009*
1	Reference		Reference	
2	6.35 (2.67, 15.07)	<0.001*	2.173 (0.764, 6.174)	0.145
3	23.27 (10.80, 50.17)	<0.001*	5.565 (1.850, 16.737)	0.002*
N stage		<0.001*		0.009*
1 vs. 0	7.84 (3.26, 18.90)		5.632 (1.542, 20.574)	
Tumor size <sup>#</sup> , cm		<0.001*		0.173
≤5	Reference		Reference	
>5	6.37 (2.89, 14.02)		2.338 (0.841, 6.500)	
Tumor necrosis		<0.001*		0.251
Present vs. absent	4.71 (2.32, 9.60)		1.710 (0.684, 4.279)	
Fuhrman grade		<0.001*		0.419
1	Reference		Reference	
2	5.95 (0.78, 45.27)	0.085	4.828 (0.621, 37.550)	
3	11.96 (1.54, 92.64)	0.018*	5.176 (0.587, 45.611)	
4	36.76 (4.60, 293.98)	0.001*	2.903 (0.304, 27.752)	
LVI		<0.001*		0.037*
Absent	Reference		Reference	
Present	8.36 (3.90, 17.92)		3.684 (1.084, 112.524)	
LDL-C (mmol/L)		0.001*		<0.001*
≤2.315 vs. >2.315	3.649 (1.756, 7.585)		5.766 (2.370, 14.030)	

**Table 4** (continued)

**Table 4** (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
LDH (U/L)		0.010*		1.306
>245 vs. ≤245	4.72 (1.44, 15.43)		1.306 (0.238, 7.171)	
AKP (U/L)		<0.001*		0.670
>130 vs. ≤130	10.28 (4.23, 24.99)		1.267 (0.427, 3.760)	

The variables (age, sex, tumor size, Fuhrman grade, LDL-C) were tested in a multivariate analysis. The univariate analysis of *Table 4* illustrated that a high LDL-C level was significantly associated with a better CSS (HR 3.649; 95% CI: 1.756, 7.585; P=0.001), which was contrast with an order age than 60 years (P=0.004), a higher lymph node stage (P<0.001), a higher pathological T stage (P<0.001), the presence of tumor necrosis (P<0.001), a larger tumor size (P<0.001), a high AKP level (>130 U/L) (P<0.001), the presence of lymphovascular invasion (P<0.001) and a high LDH level (>245 U/L) (P=0.010). Through the multivariate analysis, we found a significant association of increased LDL-C level with increased CSS. \*, the difference was statistically significant; <sup>#</sup>, tumor size was defined as the largest diameter of the tumor mass. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis; LVI, lymphovascular invasion; AKP, alkaline phosphatase; LDH, lactate dehydrogenase.



**Figure 5** Before PSM analysis, the CSS of patients with LDL-C >2.315 mmol/L was significantly higher than that of the other group. PSM, propensity score matching; CSS, cancer-specific survival; LDL-C, low-density-lipoprotein-cholesterol.

**Table 5** Univariate and multivariate Cox proportional analysis with cancer-specific survival after PSM analysis

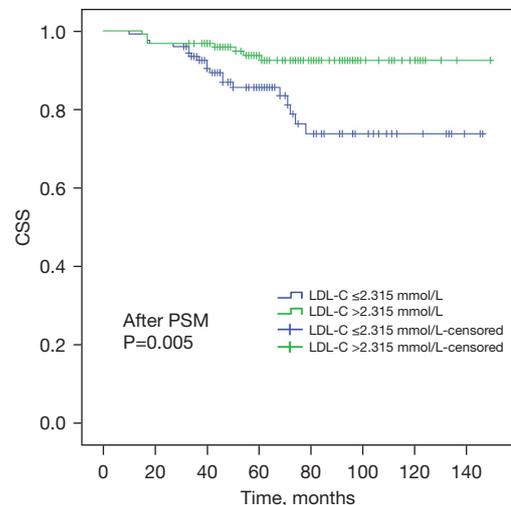
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.019*		0.008*
>60 vs. ≤60	2.486 (1.164, 5.310)		3.494 (1.381, 8.840)	
Sex		0.221		
Male vs. female	1.668 (0.735, 3.788)			
T stage		<0.001*		0.009*
1	Reference		Reference	
2	4.375 (1.641, 11.665)	0.003*	2.119 (0.670, 6.700)	0.201
3	13.814 (5.924, 32.214)	<0.001*	6.328 (1.908, 20.988)	0.003*
N stage		<0.001*		0.014*
1 vs. 0	7.138 (2.707, 18.824)		5.442 (1.407, 21.046)	
Tumor size <sup>#</sup> , cm		<0.001*		0.173
≤5	Reference		Reference	
>5	5.665 (2.407, 13.331)		2.338 (0.841, 6.500)	
Tumor necrosis		0.019*		0.106
Present vs. absent	2.968 (1.199, 7.342)		2.359 (0.834, 6.670)	
Fuhrman grade		0.010*		0.367
1	Reference		Reference	
2	3.727 (0.487, 28.492)	0.205	5.004 (0.613, 40.866)	0.133
3	6.507 (0.824, 51.373)	0.076	4.117 (0.446, 37.994)	0.212
4	16.760 (1.957, 143.523)	0.010*	2.170 (0.217, 21.738)	0.510
LVI		<0.001*		0.265
Present	Reference		Reference	
Absent	9.811 (4.124, 23.343)		2.342 (0.524, 10.470)	
LDL-C (mmol/L)		0.007*		0.001*
>2.315 vs. ≤2.315	3.074 (1.350, 6.998)		4.720 (1.901, 11.720)	

**Table 5** (continued)

**Table 5** (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AKP (U/L)		<0.001*		0.218
>130 vs. ≤130	7.874 (2.677, 23.158)		2.561 (0.573, 11.438)	

The variables (age, sex, tumor size, Fuhrman grade, LDL-C) were tested in a multivariate analysis. The univariate analysis of *Table 5* showed that a low LDL-C level was significantly associated with a worse CSS (HR 3.074; 95% CI: 1.350, 6.998; P=0.007). Through the multivariate analysis, LDL-C level remained to be an important index of CCRCC prognosis. \*, the difference was statistically significant; #, tumor size was defined as the largest diameter of the tumor mass. PSM, propensity score matching; LDL-C, low-density-lipoprotein-cholesterol; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis; LVI, lymphovascular invasion; AKP, alkaline phosphatase.



**Figure 6** After PSM analysis, the CSS of the higher LDL-C group of patients was still higher than that of the group with lower LDL-C. PSM, propensity score matching; CSS, cancer-specific survival; LDL-C, low-density-lipoprotein-cholesterol.

cell carcinoma of the head and neck (32) and peripheral T-cell lymphoma (33).

Therefore, the mechanisms behind the role that LDL-C plays in the progress of tumors remain indistinct, because the influences of LDL-C on different tumors may be different as per the receptors expressed by the tumors. First,

although the conclusions are debatable, there have been several studies on the protective effects of statins among patients with RCC (34-36). Therefore, considering the effect of statins on blood lipids, the patients included in the study were based on their specific past medical history and medication history. The patients included were not only non-statin taken before surgery, but also did not take statins during postoperative follow-up. As a result, the effect of statins was able to be ruled out in the study, making the findings more reliable. Besides, the LDL-C level analyzed in the current study was preoperative level, therefore, the group of patients with dyslipidemia may have already taken statins during the recovery period, which helped with a good prognosis. In this case, the prognostic effect of using statins after CCRCC surgery would affect the results. Second, the results can be explained from a nutritional point of view. The amount of food intake and the dietary pattern can influence the lipid level to some degree. A study has shown that a great reduction in total cholesterol (TC) and LDL-C resulted from a low-fat diet and that would affect HDL-C and triglyceride (TG) levels (37). Another study indicates that a high-fat diet promotes tumor growth (19). In other words, nutritional status could be indirectly indicated by the serum lipid profile and have connections with tumor growth. Like statins, the indicators used in the study were preoperative indicators, and whether patients had significant weight changes after surgery was difficult to be found in the study. As obesity is a prognostic indicator of renal tumors, once the nutritional status of patients changes, the results would be affected (38). There are other possible mechanisms for this result explanation. Tumor growth, duplication, invasion and metastatic development are directly stimulated by angiogenesis. CCRCC belongs to the angiogenesis-dependent tumor. And Ozdemir *et al.* (39) indicated that angiogenesis is impaired by hypercholesterolemia by suppressing the expression of bFGF and VEGF. This could help to explain the good prognosis of hypercholesterolemia in the current study. Among other studies, the researchers (40) reported that low levels of low-density lipoprotein (LDL) in leukemia and other tumor diseases may be due to increased LDL receptor activity in malignant cells. And low-density lipoprotein receptors are low in suppressed cells, while actively dividing cells usually express an increased number of low-density lipoprotein receptors, which may lead to a decrease of low-density lipoprotein levels (41). In this case, low lipid levels may be a reflection of tumor recurrence and lead to a poor prognosis for these patients.

There are some limitations in the present study. First, the number of patients enrolled in the study was relatively small; second, the research was a single center retrospective study; third, the findings need to be further validated in future studies involving more centers.

## Conclusions

On the basis of our existing results, the presence of higher LDL among CCRCC patients indicates a better OS and CSS no matter before and after PSM analysis. This means that LDL exists as a significant prognostic factor.

## Acknowledgments

*Funding:* This study was supported by the Youth Talent Science and Technology Project of Changzhou Health Commission (No. QN202010) and Changzhou Applied Basic Research Project (No. CJ20200093).

## Footnote

*Reporting Checklist:* The authors have completed the REMARK reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2705/rc>

*Data Sharing Statement:* Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2705/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2705/coif>). The authors have no 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Changzhou No.1 People's Hospital Medical Ethics Committee (2013 No. 14) and informed consent was obtained from all the patients.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-

commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Rysz J, Konecki T, Franczyk B, et al. The Role of Long Noncoding RNA (lncRNAs) Biomarkers in Renal Cell Carcinoma. *Int J Mol Sci* 2022;24:643.
- Prochazkova K, Ptakova N, Alaghehbandan R, et al. Mutation Profile Variability in the Primary Tumor and Multiple Pulmonary Metastases of Clear Cell Renal Cell Carcinoma. A Review of the Literature and Analysis of Four Metastatic Cases. *Cancers (Basel)* 2021;13:5906.
- Zhang T, George DJ. Immunotherapy and targeted-therapy combinations mark a new era of kidney cancer treatment. *Nat Med* 2021;27:586-8.
- Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev* 2020;86:102017.
- Choueiri TK, Kaelin WG Jr. Targeting the HIF2-VEGF axis in renal cell carcinoma. *Nat Med* 2020;26:1519-30.
- Kunath F, Schmidt S, Krabbe LM, et al. Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. *Cochrane Database Syst Rev* 2017;5:CD012045.
- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471-4.
- Erdoğan F, Demirel A, Polat O. Prognostic significance of morphologic parameters in renal cell carcinoma. *Int J Clin Pract* 2004;58:333-6.
- Chen Z, Shao Y, Fan M, et al. Prognostic significance of preoperative C-reactive protein: albumin ratio in patients with clear cell renal cell carcinoma. *Int J Clin Exp Pathol* 2015;8:14893-900.
- Chen Z, Shao Y, Yao H, et al. Preoperative albumin to globulin ratio predicts survival in clear cell renal cell carcinoma patients. *Oncotarget* 2017;8:48291-302.
- Ohno Y, Nakashima J, Ohori M, et al. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol* 2010;184:873-8.
- Permpongkosol S, Colombo JR Jr, Gill IS, et al. Positive surgical parenchymal margin after laparoscopic partial nephrectomy for renal cell carcinoma: oncological outcomes. *J Urol* 2006;176:2401-4.
- Rozeveld CN, Johnson KM, Zhang L, et al. KRAS Controls Pancreatic Cancer Cell Lipid Metabolism and Invasive Potential through the Lipase HSL. *Cancer Res* 2020;80:4932-45.
- Deng H, Zhou T, Mo X, et al. Low-density lipoprotein promotes lymphatic metastasis of esophageal squamous cell carcinoma and is an adverse prognostic factor. *Oncol Lett* 2019;17:1053-61.
- Liu T, Zhou T, Luo F, et al. Clinical Significance of Kinetics of Low-Density Lipoprotein Cholesterol and Its Prognostic Value in Limited Stage Small Cell Lung Cancer Patients. *Cancer Control* 2021;28:10732748211028257.
- Pih GY, Gong EJ, Choi JY, et al. Associations of Serum Lipid Level with Gastric Cancer Risk, Pathology, and Prognosis. *Cancer Res Treat* 2021;53:445-56.
- Lim JH, Shin CM, Han K, et al. Nationwide cohort study: cholesterol level is inversely related with the risk of gastric cancer among postmenopausal women. *Gastric Cancer* 2022;25:11-21.
- Jung SM, Kang D, Guallar E, et al. Impact of Serum Lipid on Breast Cancer Recurrence. *J Clin Med* 2020;9:2846.
- Riscal R, Bull CJ, Mesaros C, et al. Cholesterol Auxotrophy as a Targetable Vulnerability in Clear Cell Renal Cell Carcinoma. *Cancer Discov* 2021;11:3106-25.
- Ganjali S, Ricciuti B, Pirro M, et al. High-Density Lipoprotein Components and Functionality in Cancer: State-of-the-Art. *Trends Endocrinol Metab* 2019;30:12-24.
- Cornish AJ, Law PJ, Timofeeva M, et al. Modifiable pathways for colorectal cancer: a mendelian randomisation analysis. *Lancet Gastroenterol Hepatol* 2020;5:55-62.
- Lyu Z, Li N, Wang G, et al. Independent and joint associations of blood lipids and lipoproteins with lung cancer risk in Chinese males: A prospective cohort study. *Int J Cancer* 2019;144:2972-84.
- Magura L, Blanchard R, Hope B, et al. Hypercholesterolemia and prostate cancer: a hospital-based case-control study. *Cancer Causes Control* 2008;19:1259-66.
- Tewari R, Chhabra M, Natsu SM, et al. Significant association of metabolic indices, lipid profile, and androgen levels with prostate cancer. *Asian Pac J Cancer Prev* 2014;15:9841-6.
- Zhang JQ, Geng H, Ma M, et al. Metabolic Syndrome Components are Associated with Increased Prostate Cancer Risk. *Med Sci Monit* 2015;21:2387-96.

26. Nowak C, Ärnlöv J. A Mendelian randomization study of the effects of blood lipids on breast cancer risk. *Nat Commun* 2018;9:3957.
27. Lu Y, Gentiluomo M, Lorenzo-Bermejo J, et al. Mendelian randomisation study of the effects of known and putative risk factors on pancreatic cancer. *J Med Genet* 2020;57:820-8.
28. Kho PF, Amant F, Annibaldi D, et al. Mendelian randomization analyses suggest a role for cholesterol in the development of endometrial cancer. *Int J Cancer* 2021;148:307-19.
29. Ficarra V, Brunelli M, Cheng L, et al. Prognostic and therapeutic impact of the histopathologic definition of parenchymal epithelial renal tumors. *Eur Urol* 2010;58:655-68.
30. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012;366:883-92.
31. Chen S, Li X, Wen X, et al. Prognostic nomogram integrated baseline serum lipids for patients with non-esophageal squamous cell carcinoma. *Ann Transl Med* 2019;7:548.
32. Wilms T, Boldrup L, Gu X, et al. High Levels of Low-Density Lipoproteins Correlate with Improved Survival in Patients with Squamous Cell Carcinoma of the Head and Neck. *Biomedicines* 2021;9:506.
33. Tang J, Yin H, Wu JZ, et al. Low serum cholesterol levels predict inferior prognosis and improve prognostic index scoring for peripheral T-cell lymphoma, unspecified. *Leuk Res* 2021;103:106534.
34. Graaf MR, Beiderbeck AB, Egberts AC, et al. The risk of cancer in users of statins. *J Clin Oncol* 2004;22:2388-94.
35. Khurana V, Caldito G, Ankem M. Statins might reduce risk of renal cell carcinoma in humans: case-control study of 500,000 veterans. *Urology* 2008;71:118-22.
36. Liu W, Choueiri TK, Cho E. Statin use and the risk of renal cell carcinoma in 2 prospective US cohorts. *Cancer* 2012;118:797-803.
37. Thompson HJ, Sedlacek SM, Paul D, et al. Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight-loss success of breast-cancer survivors. *Breast Cancer Res* 2012;14:R1.
38. Turco F, Tucci M, Di Stefano RF, et al. Renal cell carcinoma (RCC): fatter is better? A review on the role of obesity in RCC. *Endocr Relat Cancer* 2021;28:R207-16.
39. Ozdemir BH, Akcali Z, Haberal M. Hypercholesterolemia impairs angiogenesis in patients with breast carcinoma and, therefore, lowers the risk of metastases. *Am J Clin Pathol* 2004;122:696-703.
40. Vitols S, Gahrton G, Ost A, et al. Elevated low density lipoprotein receptor activity in leukemic cells with monocytic differentiation. *Blood* 1984;63:1186-93.
41. Peterson C, Vitols S, Rudling M, et al. Hypocholesterolemia in cancer patients may be caused by elevated LDL receptor activities in malignant cells. *Med Oncol Tumor Pharmacother* 1985;2:143-7.

**Cite this article as:** Mei Y, Chen Z, Wang X, Xu R, Lu H. Preoperative low-density lipoprotein cholesterol as a predictor of favorable prognosis in patients with clear cell renal cell carcinoma. *Transl Cancer Res* 2023;12(6):1380-1391. doi: 10.21037/tcr-22-2705