

## Original Article

# Preoperative serum lipid profile is associated with the aggressiveness of renal cell carcinoma

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**Abstract:** In order to investigate the potential relationship between serum lipid profile and renal cell carcinoma (RCC), we measured the levels of preoperative serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and correlated them with histopathological characteristics of RCC. The medical records of 382 patients with RCC who had underwent nephrectomy were retrospectively reviewed. The associations among preoperative TC, TG, HDL-C and LDL-C levels and histopathological characteristics such as tumor grade, stage and size were analyzed using logistic regression analysis. HDL-C was lower in the group with high-grade disease than in that with low-grade disease ( $P=0.015$ ). Both HDL-C and TC were lower in the patients with advanced disease compared to those with localized disease ( $P=0.006$  and  $P=0.005$ , respectively). LDL-C was lower in larger tumors ( $P=0.030$ ). Logistic regression analysis indicated that high HDL-C levels were significantly associated with low-grade tumors (OR: 0.293,  $P=0.016$ ) and localized disease (OR: 0.204,  $P=0.006$ ). Furthermore, high TC levels were significantly associated with less advanced disease (OR: 0.660,  $P=0.005$ ), and high LDL-C levels were significantly associated with smaller tumors (OR: 0.756,  $P=0.031$ ). In conclusion, the results of this study indicate that serum lipid profile is associated with the histopathological characteristics of RCC.

**Keywords:** Renal cell carcinoma, cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol

## Introduction

Renal cell carcinoma (RCC) derives from proximal tubular epithelial cells and accounts for 2% to 3% of all malignancies. Recently, the incidence and mortality rates of RCC have been showing an upward trend [1-3]. During the last two decades, there has been an annual increase of approximately 2% in the incidence of RCC worldwide [4]. Additionally, from 2005 to 2012, the incidence of RCC in China has increased from 3.96 to 9.47 per 100,000 [5].

These increases can partially be explained by recent improvements in imaging examination techniques [6]; however, increasing prevalence of risk factors also play an important role [7]. Although the exact etiology of RCC are unknown, accumulating evidence suggests that lipid metabolism is crucially involved in the establishment and progression of RCC. Zhang et al. [8] conducted a 1:2 matched case-control

analysis and found that elevated levels of serum cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) may be associated with a decreased risk of RCC. From a study of 364 patients with clear cell RCC, Ohno et al. [9] concluded that higher preoperative levels of blood cholesterol may be associated with better cancer-specific survival (CSS). We conducted the present study to investigate whether serum lipid profile is associated with the histopathological characteristics of RCC.

## Patients and methods

### Patients

After institutional review board approval, the medical records of 382 consecutive patients who underwent radical or partial nephrectomy at Peking University People's Hospital from January 2010 to September 2015 were retro-

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**Table 1.** Comparison of clinical and biochemical characteristics according to Fuhrman grade

|                                    | High grade  | Low grade    | p value |
|------------------------------------|-------------|--------------|---------|
| No. pts (%)                        | 80 (20.94%) | 302 (79.06%) |         |
| Mean ± SD age                      | 57.26±14.41 | 57.99±12.78  | 0.658   |
| No. gender (%)                     |             |              | 0.354   |
| Male                               | 57 (71.25%) | 198 (65.56%) |         |
| Female                             | 23 (28.75%) | 104 (34.44%) |         |
| Mean ± SD BMI (kg/m <sup>2</sup> ) | 24.55±3.15  | 25.11±3.62   | 0.230   |
| Mean ± SD TG (mmol/L)              | 1.23±0.58   | 1.29±1.23    | 0.449   |
| Mean ± SD TC (mmol/L)              | 3.88±0.90   | 4.02±1.05    | 0.276   |
| Mean ± SD LDL-C (mmol/L)           | 2.69±0.84   | 2.72±0.84    | 0.817   |
| Mean ± SD HDL-C (mmol/L)           | 0.90±0.26   | 0.98±0.27    | 0.015   |

**Table 2.** Comparison of clinical and biochemical characteristics according to AJCC stage

|                                    | Advanced cancer | Local cancer | p value |
|------------------------------------|-----------------|--------------|---------|
| No. pts (%)                        | 63 (16.49%)     | 319 (83.51%) |         |
| Mean ± SD age                      | 55.81±13.95     | 58.24±12.94  | 0.179   |
| No. gender (%)                     |                 |              | 0.056   |
| Male                               | 49 (77.78%)     | 206 (64.58%) |         |
| Female                             | 14 (22.22%)     | 113 (35.42%) |         |
| Mean ± SD BMI (kg/m <sup>2</sup> ) | 24.04±3.41      | 25.19±3.53   | 0.022   |
| Mean ± SD TG (mmol/L)              | 1.11±0.59       | 1.31±1.20    | 0.085   |
| Mean ± SD TC (mmol/L)              | 3.66±0.96       | 4.06±1.02    | 0.005   |
| Mean ± SD LDL-C (mmol/L)           | 2.59±0.84       | 2.74±0.84    | 0.201   |
| Mean ± SD HDL-C (mmol/L)           | 0.88±0.30       | 0.98±0.26    | 0.006   |

spectively reviewed. The inclusion criteria were histologically proven RCC and no previous renal surgery, ablative therapies or immunotherapy for RCC.

### Data collection

Preoperative demographic and clinical characteristics, including age, gender, height, weight, BMI (calculated by dividing body weight by the square of height), tumor size and concentrations of serum lipids (total cholesterol (TC), triglyceride (TG), HDL-C and LDL-C), were collected from medical records. Fasting blood samples were taken at the time of admission for surgery to measure serum lipid profiles (TC, TC, HDL-C, and calculated LDL-C) within 1-7 days preoperatively. All measurements were performed by skilled clinical laboratory examiners at our hospital. After surgery, tumor size, stage and grade were evaluated by at least two pathologists,

according to the 2009 American Joint Committee on Cancer guidelines (AJCC) TNM classification and the World Health Organization (WHO) Fuhrman grading system, respectively.

### Statistical analysis

Continuous variables were reported in terms of the mean ± standard deviation (SD), and categorical variables were presented as proportions. Serum lipid profile was evaluated as a continuous variable. All patients were stratified into 2 groups based on the following criteria: 1) high-grade disease (Fuhrman grade III or IV) versus low-grade disease (Fuhrman grade I or II), 2) advanced disease (AJCC stage III or IV) versus localized disease (AJCC stage I or II), and 3) larger tumor (tumor size > 4 cm) versus smaller tumor (tumor size ≤ 4 cm). First, we compared demographic and clinical variables between the different groups using Student's *t* test for continuous normally distributed variables, the Mann-Whitney U-test for continuous non-normal distributed variables and the chi-square test for categorical variables. Following this, logistic regression analysis was used to identify risk factors for adverse histopathological outcomes. All statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc, Chicago, IL, USA). All *p* values were 2-tailed, and *P* < 0.05 was considered statistically significant.

## Results

### Patient characteristics

In total, 382 patients' medical records were retrospectively reviewed. The mean age of the patients was 57.84±13.12 years, and the gender split was 255 men (66.8%) and 127 women (33.2%). The mean BMI, TG, TC, LDL-C and HDL-C were 25.00±3.53 kg/m<sup>2</sup>, 1.28±1.12 mmol/L, 3.99±1.02 mmol/L, 2.71±0.84 mmol/L, and 0.97±0.27 mmol/L, respectively. The mean tumor size was 4.39±2.70 cm. Sixty-

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**Table 3.** Comparison of clinical and biochemical characteristics according to tumor diameter

|                                    | Diameter > 4 cm | Diameter ≤ 4 cm | p value |
|------------------------------------|-----------------|-----------------|---------|
| No. pts (%)                        | 153 (40.05%)    | 229 (59.95%)    |         |
| Mean ± SD age                      | 58.57±12.40     | 57.35±13.59     | 0.376   |
| No. gender (%)                     |                 |                 | 0.438   |
| Male                               | 106 (69.28%)    | 149 (65.07%)    |         |
| Female                             | 47 (30.72%)     | 80 (34.93%)     |         |
| Mean ± SD BMI (kg/m <sup>2</sup> ) | 24.86±3.34      | 25.09±3.66      | 0.543   |
| Mean ± SD TG (mmol/L)              | 1.23±0.72       | 1.31±1.33       | 0.438   |
| Mean ± SD TC (mmol/L)              | 3.88±1.03       | 4.07±1.01       | 0.085   |
| Mean ± SD LDL-C (mmol/L)           | 2.60±0.86       | 2.79±0.82       | 0.030   |
| Mean ± SD HDL-C (mmol/L)           | 0.94±0.27       | 0.99±0.27       | 0.066   |

**Table 4.** Logistic regression analyses of the relationships between serum lipids and demographic characteristics, Fuhrman grade, AJCC stage and tumor size

| Variable                 | High grade |         | Advanced RCC |         | Diameter > 4 cm |         |
|--------------------------|------------|---------|--------------|---------|-----------------|---------|
|                          | OR         | p value | OR           | p value | OR              | p value |
| Age                      | 0.996      | 0.658   | 0.986        | 0.180   | 1.007           | 0.375   |
| Sex (referent male)      | 1.302      | 0.338   | 1.920        | 0.045   | 1.211           | 0.392   |
| BMI (kg/m <sup>2</sup> ) | 0.955      | 0.230   | 0.906        | 0.023   | 0.981           | 0.541   |
| TG (mmol/L)              | 0.938      | 0.653   | 0.677        | 0.108   | 0.932           | 0.526   |
| TC (mmol/L)              | 0.871      | 0.275   | 0.660        | 0.005   | 0.835           | 0.086   |
| LDL-C (mmol/L)           | 0.966      | 0.817   | 0.801        | 0.201   | 0.756           | 0.031   |
| HDL-C (mmol/L)           | 0.293      | 0.016   | 0.204        | 0.006   | 0.481           | 0.067   |

three (16.49%) of the patients had advanced RCC, and 80 (20.94%) of the tumors were classified as high-grade disease.

### *Associations between lipid profile and histopathological characteristics of RCC*

We divided the patients into two groups according to Fuhrman grade, AJCC stage or tumor size and compared variables between them. As shown in **Table 1**, the patients with high-grade tumors had lower HDL-C levels compared to the patients with low-grade tumors ( $P=0.015$ ). Additionally, serum TC and HDL-C levels were shown to be significantly decreased in patients with advanced tumors compared to those with localized tumors ( $P=0.005$  and  $0.006$ , respectively) (**Table 2**). Furthermore, LDL-C levels were also lower in patients with tumors larger than 4 cm compared to those with tumors smaller than 4 cm ( $p=0.030$ ) (**Table 3**).

Logistic regression analysis showed that serum HDL-C level was associated with tumor grade and stage. Patients with a relatively high preop-

erative serum HDL-C level had a lower risk of high-grade and advanced RCC. Higher levels of TC were associated with a lower likelihood of advanced RCC, and higher levels of LDL-C were associated with a lower risk of larger tumors (**Table 4**).

### **Discussion**

Same with the colorectal, endometrial and breast cancers, RCC is an obesity-related cancer [10]. Clear cell RCC, the most common type of renal malignancy, is characterized by sterol storage in tumor cytoplasm, which indicates abnormalities in lipid metabolism that may play an important role in the formation and progression of RCC. Thus, the relationship between lipid profile and RCC has drawn increasing attention. Recently, several studies have focused on this topic by evaluating TG, TC, LDL-C and HDL-C levels in RCC.

The impact of serum TC on RCC incidence is inconsistent. Ahn et al. and Van Hemelrijck et al. [11, 12] found a significant association between higher serum TC and a decreased risk of RCC. However, additional research evaluating Asian and European cohorts did not confirm this association [13, 14]. For the prognosis of RCC, Lee et al. [15] concluded that a higher baseline serum TC level and an increase in serum TC level during treatment were significantly associated with improved overall survival in patients with RCC treated with temsirolimus or interferon alpha. Furthermore, Ko et al. [16] reported that patients with cholesterol levels  $\geq 220$  mg/dL had significantly better 5-year progression-free survival rates than those with cholesterol levels  $< 220$  mg/dL (86.8% vs. 73.9%). Our current study demonstrated that a low baseline serum TC level is associated with advanced stage RCC.

Van Hemelrijck et al. [12] reported a significant association between serum TG and risk of RCC; however, this association was not confirmed in

Ulmer et al.'s study [14]. A link between TG and the histopathological characteristics of RCC was not observed in our current study.

Only limited studies have investigated the relationship between LDL-C levels and RCC risk, and the findings remain controversial. One study conducted in Denmark and China reported that plasma levels of LDL-C were inversely associated with risk of RCC [8, 17]. However, no association between serum LDL-C and risk of RCC was found in Van Hemelrijck et al.'s study [12]. In the current study, we found that lower preoperative serum LDL-C levels are associated with larger tumors in patients with RCC.

Few studies have reported on the role of HDL-C in carcinogenesis, especially in the context of RCC. However, an inverse association between high HDL-C levels and the epidemiology of breast cancer, lung cancer, non-Hodgkin's lymphoma, and overall cancer risk [11, 18-21] has been reported. Zhang et al. [8] suggested that the risk of RCC increased by 165% among patients with low HDL-C levels. Our current results indicate that lower serum levels of HDL-C are inversely associated with RCC aggressiveness based on tumor grade and presence of metastatic disease.

To the best of our knowledge, our current study is the first to investigate the association between preoperative serum lipid profile and the risk of aggressive RCC. Despite this, several limitations of the present study should be acknowledged. First, RCC can cause dyslipidemia (decreased serum TC, decreased HDL-C, and elevated LDL-C), which may affect cholesterol absorption, transport, metabolism, or utilization. Second, the study population was relatively small and limited to patients at a single hospital. Thus, a larger confirmatory study is needed to more precisely estimate the effect of lipid profile on RCC. Third, the retrospective design of the present study only allowed us to examine the temporal coexistence of dyslipidemia and RCC, but not causal inferences. The final limitation of this study was that all participants were Chinese; therefore, our results may not necessarily apply to other ethnicities.

In conclusion, the results of the current study indicated that serum lipid profile is associated with the histopathological characteristics of

RCC. In particular, lower levels of serum TC, LDL-C and HDL-C are positively associated with RCC aggressiveness based on tumor grade, stage and size.

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### Disclosure of conflict of interest

None.

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