Original Study

Preoperative Cholesterol Level Is Associated With Worse Pathological Outcomes and Postoperative Survival in Localized Renal Cell Carcinoma Patients: A Propensity Score–Matched Study

Hakmin Lee,[1] Chang Wook Jeong,[2] Cheol Kwak,[2] Hyeon Hoe Kim,[2] Seong Il Seo,[3] Hyun Moo Lee,[3] Jong Jin Oh,[1] Sang Chul Lee,[1] Sung Kyu Hong,[1] Sang Eun Lee,[1] Seok-Soo Byun[1]

Abstract

In patients with localized renal cell carcinoma, those with low cholesterol level showed worse pathologic outcomes and inferior postoperative survival. We found that those relationships were related to the clear cell subtype. Further basic research focusing on the underlying mechanism is required.

Introduction: Lipid metabolism has been suggested to be associated with clinical outcomes of renal cell carcinoma (RCC). In this study, we aimed to investigate the relationship between preoperative cholesterol level (PCL) and postoperative outcomes of patients with localized RCC. **Materials and Methods:** We retrospectively analyzed the data of 5022 patients surgically treated for nonmetastatic RCC. According to the receiver operating curve of PCL for cancer-specific mortality, we stratified the patients into 2 groups by using a cutoff value of 161 mg/dL. The propensity scores for having low PCL were calculated, and the low PCL group was matched with the high PCL group at a 1:2 ratio. The oncological profiles and postoperative survival of patients were compared. **Results:** A low cholesterol level was significantly associated with adverse pathologic findings, such as higher pathologic stage ($P < .001$) and large tumor size ($P = .002$). Furthermore, the low cholesterol group showed significantly worse progression-free, cancer-specific, and overall survival (all P values $< .001$) compared with the high cholesterol group. Multivariate analysis exhibited a higher PCL as an independent predictor of better progression-free ($P < .001$), cancer-specific ($P = .018$), and overall survival ($P = .001$) after matching. Subgroup analysis according to tumor histology revealed that PCL had a significant relationship with patients' survival in clear cell RCC, but not in non–clear cell RCC. **Conclusion:** Decreased PCL was significantly associated with worse pathologic outcomes and also inferior postoperative survival in patients with localized RCC; however, those relationships were significant only in clear cell subtypes.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■ © 2017 Published by Elsevier Inc.
Keywords: Cancer, Cholesterol, Hypercholesterolemia, Kidney, Lipid, Obesity, RCC, Survival

Introduction

Advanced modern imaging technologies allow for a diagnosis of more than 300,000 patients with renal cell carcinoma (RCC) worldwide.[1] RCC is the third most common malignancy in Europe[2] and seventh in the Unites States.[3] Several risk factors, such as older age, obesity, smoking status, high blood pressure, and chronic kidney failure, are associated with the increased incidence of RCC.[4]

Obesity is known to be related to higher incidence of RCC; however, increasing evidence suggests an inverse relationship between obesity and clinical outcomes of RCC. This phenomenon was previously termed as the "obesity paradox."[5,6] Lipid metabolism or neoplastic lipogenesis is speculated to be the key mechanism underlying this peculiar phenomenon.[7] Choi et al[5] showed that obese people with a higher body mass index (BMI) have better

[1]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[2]Department of Urology, Seoul National University Hospital, Seoul, Republic of Korea
[3]Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Submitted: Feb 10, 2017; Revised: Apr 17, 2017; Accepted: May 1, 2017

Address for correspondence: Seok-Soo Byun, MD, PhD, Department of Urology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
E-mail contact: ssbyun@snubh.org

1558-7673/$ - see frontmatter © 2017 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.clgc.2017.05.008

postoperative survival after surgical treatment of localized RCC. They also performed a meta-analysis of BMI on progression-free (PFS), overall (OS), and cancer-specific survival (CSS) with 22 studies and found an inverse relationship between BMI and postoperative survival. Recently, a large multicenter study also reported that a low BMI is significantly associated with worse survival in patients treated for metastatic RCC.[6]

Cholesterol is an essential structural component of all human cells and also a crucial part of lipid metabolism.[8] However, only a few studies have focused on the relationship between serum cholesterol and RCC biology. Therefore, we investigated the relationship between preoperative serum total cholesterol level (PCL) and clinical and pathological outcomes of patients with localized RCC after surgery in a relatively large cohort. We also eliminated the possible influence of preoperative characteristic differences on patient survival by performing propensity score matching.

Materials and Methods

After the approval of the institutional Ethical Review Board, we retrospectively analyzed the data of 5493 patients surgically treated for localized RCC from September 1999 to May 2016 in 3 tertiary centers in South Korea. After excluding 471 patients with bilateral disease (n = 54), metastatic disease (n = 194), other malignancy (n = 42), benign pathology (n = 139), or incomplete information (n = 42), a total of 5022 patients were finally included in the study. The clinical and pathologic data were collected from prospectively managed databases of the 3 institutions. All patients initially underwent preoperative evaluations, including abdominal computed tomography (CT), chest CT (or simple radiography), and bone scan. A routine preoperative check-up included PCL (total cholesterol level) measurement at all institutions within 4 weeks preceding surgery. If multiple measurements were conducted during the period, the mean value was considered the representative value.

The determination of pathologic stage and histologic subtype was performed according to the seventh TNM classification of the American Joint Committee cancer guidelines and the Heidelberg recommendations.[9,10] Grading of tumor cells was done according to the Fuhrman grading system.[11] Disease progression was defined when there was a definite evidence of recurrence, distant metastasis, and/or mortality from RCC. The survival data of the subjects, including the cause of death, were obtained from the database of the Korean National Statistical Office and by a rigorous review of medical records. The follow-up protocols after surgery were slightly different for each surgeon or institution but usually performed at 3- to 6-month intervals for the first 2 years and annually thereafter.

The receiver operating curve of PCL for cancer-specific mortality (CSM) was analyzed to determine the optimal cutoff level. The cutoff value of PCL was set to 161 mg/dL, at which the Youden index was maximum. Patients with PCL $\geq$ 161 mg/dL were assigned to the high PCL group, whereas those with PCL $<$ 161 mg/dL were assigned to the low PCL group. There were 3664 patients in the high PCL group and 1358 patients in the low PCL group. To reduce the possible influences of baseline characteristic differences, we performed propensity score matching according to the propensity to have low PCL. The propensity scores were calculated using nonparsimonious multiple logistic regression of preoperative characteristics including patients' age, BMI, sex, American Society of Anesthesiologists (ASA) score, history of diabetes mellitus and hypertension, surgical approach (open vs. laparoscopic and robotic surgery), type of nephrectomy (partial vs. radical nephrectomy), and tumor size. Given that postoperative variables cannot influence the determination of preoperative condition, postoperative pathological outcomes were excluded from the calculations of the propensity score. Except for 37 subjects without an appropriate pair, 1321 patients with low PCL were successfully matched to 2425 patients with high PCL at a 1:2 ratio by nearest-neighbor matching with a caliber of 0.02. When we validated the balance of the involved variables after propensity score matching, our matched cohorts were well calibrated and discriminated with mean standardized differences less than 0.05 in all variables (Table 1).

To compare the clinico-pathological characteristics of the high and low PCL groups, we performed independent t and χ^2 tests. The survival outcomes of the 2 groups were compared using the Kaplan-Meier analysis. Multivariate Cox proportional-hazard models were used to identify the independent predictors of PFS, OS, and CSS. All statistical analyses were performed using SPSS software package (version 19.0; IBM Corp, Chicago, IL) and R software (The R Foundation for Statistical Computing, Vienna, Austria). All P values were 2-sided, and P values less than .05 were considered to be statistically significant.

Results

The overall characteristics of the patients and by subgroups according to PCL are summarized in Table 1. The median age, median tumor diameter, median PCL, and median follow-up time were 55.0 years (interquartile range [IQR] 46.0-65.0), 3.5 cm (IQR 2.2-5.5), 181.0 months (IQR 158.0-205.0), and 49.0 months (IQR 25.0-77.0), respectively. Significant differences were found between the 2 groups in all preoperative clinical profiles. The low PCL group was significantly older ($P < .001$), showed significantly large tumor diameter ($P < .001$) with higher clinical stage ($P < .001$), and had lower BMI ($P < .001$). This group also had a male predominance ($P < .001$), positive history of hypertension ($P < .001$) and diabetes mellitus ($P < .001$), higher ASA score ($P < .001$), and tended to be treated less by a laparoscopic or robotic approach ($P < .001$) and by partial nephrectomy ($P = .001$). The low PCL group showed worse pathologic outcomes evidenced by higher cellular grade ($P < .001$) and higher pathologic stage ($P < .001$). Multivariate multiple regression tests showed that every 10 mg/dL increase of PCL was significantly related to a 7% decreased risk of having high pathologic stages (hazard ratio [HR] 0.932; 95% confidence interval [CI], 0.904-0.960, $P < .001$) and a 4% decreased risk of having a large tumor (HR 0.961; 95% CI, 0.937-0.986, $P < .002$) (Table 2).

Survival Outcomes for the Entire Cohort

Before the propensity score matching, 487 patients showed disease progression after a median of 22.0 months (IQR 7.0-47.1) postoperatively. There were 260 CSMs after a median of 41.8 months (IQR 18.2-78.9) and 397 all-cause mortalities (AMs) after a median of 44.1 months (IQR 21.5-82.4). The low PCL group showed significantly inferior survival in PFS ($P < .001$), OS ($P = .005$), and CSS ($P < .001$) (Figure 1). Subsequent multivariate Cox-regression tests revealed that higher PCL was a significant