Prognostic Effect of Preoperative Apolipoprotein B Level in Surgical Patients with Renal Clear Cell Carcinoma

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Research

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Abstract

Background To assess the prognostic value of preoperative apolipoprotein B level in surgical patients with renal clear cell carcinoma (ccRCC).

Materials and Methods The study included 307 ccRCC patients receiving radical or partial nephrectomy between 2003 and 2012 in our center. The correlations among the preoperative ApoB, clinico-pathological parameters, and overall survival (OS) were evaluated.

Results A total of 193 men (62.9%) and 114 women (37.1%) with ccRCC underwent radical or partial nephrectomy were enrolled in the present study. The OS at five years after operation was 90.6% for all patients, 87.4% for the lower ApoB group, and 97.0% for the higher ApoB group. The CSS at 5 years after surgery was 90.2% for all patients, 86.7% for the lower ApoB group, and 97.0% for the higher ApoB group. A higher ApoB level was related to a better OS and CSS in ccRCC patients ($P = 0.001$ and $P < 0.001$, respectively). In multivariate analysis, age >60 ($P=0.008$ and $P=0.023$), lower Apo B level ($P= 0.019$ and $P= 0.018$), were independent prognostic factors for OS and CSS, respectively.

Conclusions In the Apo apolipoprotein family, the preoperative ApoB level has an important clinical significance for predicting the prognosis survival rate of the ccRCC patients.

Introduction

Renal cell cancer is a common kind of urinary tumor and accounts for 2–3% of all cancers[1]. More than 80% of them are clear cell carcinoma, and other histological types are very rare[2]. Surgery has been the benchmark for the treatment of RCC[3]. However, preoperative judgment of the patient's prognosis is very important for patients and clinicians[4]. Although there are already some indicators that could predict the prognosis[5, 6], such as TNM stage, Fuhrman grade and CRP/Alb ratio, simple biomarkers are still lacking for early diagnosis and the judgment of prognosis in clinical practice.

Apolipoprotein ApoB is a newly discovered potential tumor marker that plays an important role in lipoprotein metabolism and participates in the reverse transport of cholesterol[7]. There are different degrees of ApoB elevation in the patient's serum of liver cancer, breast cancer and ovarian cancer[8, 9]. The changes of ApoB level had an important value for the prognosis of the above tumors. Therefore, in this study we aim to explore the prognostic performance of the preoperative ApoB level in Chinese patients with ccRCC.

Materials And Methods

Patients

The data of 414 CCRCC patients which underwent radical or partial nephrectomy in The Third Affiliated Hospital of Soochow University between 2003 and 2012 were collected in our study. Of all 414 patients,

107 patients were excluded: 37 patients had concomitant chronic diseases, including diabetes, hyperlipidemia and metabolic syndrome; 17 patients had been lost in the follow-up time; 17 patients' information on were incomplete and unclear; 36 patients had received drug therapy previously. Finally, the 307 patients were identified for related analysis.

Clinical and laboratory data

The characteristics and information of each patient included in our study were summarized: age at surgery, gender, TNM stage, Fuhrman grade, tumor necrosis and tumor size, LVI and LDH and AKP. The 2010 renal TNM stage by AJCC was adopt[10]. Fuhrman grade was recommended by WHO in 1997. Tumor necrosis was defined as microscopic coagulative necrosis[11]. The data of LVI, LDH and AKP were obtained within 1 week before surgery. All of the above data above were retrieved from Medical records inquiry system of The Third Affiliated Hospital of Soochow University.

Statistical analyses

For the description of clinical and pathological characteristics of patients, categorical variables were presented as numbers and percentages, continuous variables were allocated in groups according to the optimal cut-off value. Receiver operating characteristics (ROC) analysis was done to identify the cutoff point of continuous variables. OS was calculated from date of surgery to individuals' death of any cause or last follow-up. The OS rates were calculated using the Kaplan-Meier method, and compared using the log-rank test. Univariate analysis of the potential factors related to survival was conducted with the help of Mantel-Cox regression methodology. The Cox proportional hazards model was used for the multivariate analysis to identify independent prognostic factors associated with OS. ROC analysis was also used to measure and compare the areas under the curve (AUC). The Chi square test was used to detect the differences between groups. All statistical tests were two-sided and a P-value < 0.05 was considered statistically significant. All data analyses were performed with SPSS Statistics 17.0.

Results

A total of 193 men (62.9%) and 114 women (37.1%) with CCRCC underwent radical or partial nephrectomy were enrolled in the present study. The mean age of the patient group was 56.29 years (SD ± 11.63; range 24–80). The mean postoperative follow-up was 69.17 (range 1–151) months. The mean and median preoperative value of the ApoB was 0.941 ± 0.282 (range 0.41–2.73) and 0.92.

The cutoff value of ApoB divided the patients into two groups (ApoB ≤ 1.015 and ApoB > 1.015). Table 1 showed the relationships between ApoB levels and the clinicopathological characteristics of the all CCRCC patients included in the study. There were no significant differences with regard to age, sex, tumor size, tumor stage, lymph node stage, Fuhrman grade, the presence of Tumor necrosis, lymphovascular invasion, LDH and AKP levels between the two groups. Therefore, we did not conduct the propensity score-matched analysis for ApoB.

Table 1
The clinicopathological characteristics of patients, and correlation of Apo B with the clinicopathological characteristics.

Variable	No. of Patients (%)			
	(n = 307)	Apo B ≤ 1.015 (n = 206)	Apo B > 1.015 (n = 101)	P value
Age (years)				0.603
≤ 60 > 60	179 (58.3) 128 (41.7)	118 (57.3) 88 (42.7)	61 (60.4) 40 (39.6)	
Sex				0.530
Male Female T stage 1 2 3 N stage 0 1	193 (62.9) 114 (37.1) 251 (81.8) 32 (10.4) 24 (7.8) 297 (96.7) 10 (3.3)	132 (64.1) 74 (35.9) 166 (80.6) 20 (9.7) 20 (9.7) 199 (96.9) 7 (3.4)	61 (60.4) 40 (39.6) 85 (84.2) 12 (11.9) 4 (4.0) 98 (97.0) 3 (3.0)	0.194 0.843
Fuhrman grade 1 2 3 4	64 (21.5) 153 (51.5) 63 (21.2) 17 (5.7)	43 (21.6) 101 (50.8) 42 (21.1) 13 (6.5)	21 (21.4) 52 (53.1) 21 (21.4) 4 (4.1)	0.859
Tumor size, cm ≤ 5 > 5	194 (63.6) 111 (36.4)	122 (59.8) 82 (40.2)	72 (71.3) 29 (28.7)	0.050
Tumor necrosis				0.216
Absent Present	280 (91.2) 27 (8.8)	185 (89.8) 21 (10.2)	95 (94.1) 6 (5.9)	
LVI				0.320
Absent Present	289 (94.1) 18 (5.9)	192 (93.2) 14 (6.8)	97 (96.0) 4 (4.0)	
LDH (U/L)				0.542
≤ 245	301 (98.4)	202 (98.1)	99 (99.0)	
245	5 (1.6)	4 (1.9)	1 (1.0)	

* indicates that the difference was statistically significant

Abbreviation: LVI lymphovascular invasion, AKP, alkaline phosphatase, LDH lactate dehydrogenase

Variable	No. of Patients (%)			
	(n = 307)	Apo B ≤ 1.015 (n = 206)	Apo B > 1.015 (n = 101)	P value
AKP (U/L)				0.358
≤ 130	292 (95.4)	195 (94.7)	97 (97.0)	
130	14 (4.6)	11 (5.3)	3 (3.0)	
* indicates that the difference was statistically significant				
Abbreviation: LVI lymphovascular invasion, AKP, alkaline phosphatase, LDH lactate dehydrogenase				

Univariate analysis indicated that age > 60 (P = 0.002 and P = 0.004), higher pathological T stage (P < 0.001 and P < 0.001), higher pathological N stage (P < 0.001 and P < 0.001), higher Fuhrman grade (P < 0.001 and P < 0.001), larger Tumor size (P < 0.001 and P < 0.001), present of Tumor necrosis (P < 0.001 and P < 0.001), present of LVI (P < 0.001 and P < 0.001), lower Apo B level (P = 0.003 and P = 0.002), higher LDH level (P = 0.001 and P < 0.001), higher AKP level (P < 0.001 and P < 0.001) were poor survival for OS (Table 2) and CSS (Table 3), respectively. In multivariate analysis, age > 60 (P = 0.008 and P = 0.023), lower Apo B level (P = 0.019 and P = 0.018), were independent prognostic factors for OS (Table 2) and CSS (Table 3), respectively.

Table 2

Univariate and Multivariate Cox Proportional Analysis with Overall Survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)		0.002*		0.008*
> 60 VS ≤ 60	2.81 (1.46–5.41)		2.87 (1.32–6.25)	
Sex		0.109		
Male VS Female	1.80 (0.88–3.67)			
T stage		< 0.001*		0.081
1 2 3	reference 4.67 (2.06–10.57) 18.50 (9.03–37.87)	< 0.001* < 0.001*	reference 1.792 (0.66–4.85) 3.50 (1.16–10.59)	0.251 0.026*
N stage		< 0.001*		0.060
1 VS 0	7.83 (3.25–18.86)		3.91 (0.94–16.21)	
Fuhrman grade		< 0.001*		0.251
1 2 3 4	reference 6.39 (0.85–48.23) 12.66 (1.65–97.16) 35.39 (4.42- 283.19)	0.072 0.015* 0.001*	reference 6.02 (0.78–46.34) 8.22 (1.01–66.94) 4.33 (0.43–43.68)	0.085 0.049* 0.214
Tumor size, cm > 5 VS ≤ 5	4.98 (2.47–10.04)	< 0.001*	1.78 (0.70–4.55)	0.227
Tumor necrosis		< 0.001*		0.343
Present VS Absent	3.95 (1.96–7.97)		1.50 (0.65–3.51)	
LVI		< 0.001*		0.263
Present VS Absent	7.62 (3.59–16.17)		1.95 (0.61–6.15)	
Apo B		0.003*		0.019*
≤ 1.015 VS > 1.015	4.89 (1.73–13.81)		4.30 (1.27–14.59)	
LDH (U/L)		0.001*		0.201
> 245 VS ≤ 245	7.28 (2.22–23.89)		2.83 (0.57–13.91)	
AKP (U/L)		< 0.001*		0.376

* indicates that the difference was statistically significant

Abbreviation: LVI lymphovascular invasion, AKP alkaline phosphatase, LDH lactate dehydrogenase.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
> 130 VS ≤ 130	7.38 (3.19–17.09)		1.75 (0.50–6.04)	
* indicates that the difference was statistically significant				
Abbreviation: LVI lymphovascular invasion, AKP alkaline phosphatase, LDH lactate dehydrogenase.				

Table 3

Univariate and Multivariate Cox Proportional Analysis with Cancer-Specific Survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age(years)		0.004*		0.023*
> 60 VS ≤ 60	2.72 (1.38–5.38)		2.59 (1.14–5.88)	
Sex		0.223		
Male VS Female	1.55 (0.82–2.95)			
T stage		< 0.001*		0.062
1 2 3	reference 6.16 (2.80-13.56) 28.32 (14.30- 56.08)	< 0.001* < 0.001*	reference 2.03 (0.72–5.76) 3.85 (1.24–11.99)	0.183 0.020*
N stage		< 0.001*		0.063*
1 VS 0	7.83 (3.25–18.87)		4.53 (1.25–16.43)	
Fuhrman grade		< 0.001*		0.331
1 2 3 4	reference 2.34 (0.68–8.02) 4.70 (1.36–16.24) 13.07 (3.54–48.31)	0.177 0.014* < 0.001*	reference 5.18 (0.66–40.47) 6.98 (0.84–58.01) 3.82 (0.38–38.54)	0.117 0.072 0.256
Tumor size, cm > 5 VS ≤ 5	6.35 (2.88–13.98)	< 0.001*	2.11 (0.76–5.90)	0.154
Tumor necrosis		< 0.001*		0.182
Present VS Absent	4.71 (2.31–9.58)		1.78 (0.76–4.14)	
LVI		< 0.001*		0.229
Present VS Absent	8.35 (3.89–17.89)		2.04 (0.64–6.51)	
Apo B		0.002*		0.018*
≤ 1.015 VS > 1.015	6.47 (1.98–21.12)		5.92 (1.36–25.74)	
LDH(U/L)		< 0.001*		0.227
> 245VS ≤ 245	8.29 (2.53–27.20)		2.66 (0.54–13.06)	
AKP(U/L)		< 0.001*		0.146

* indicates that the difference was statistically significant

Abbreviation: LVI lymphovascular invasion, AKP alkaline phosphatase, LDH lactate dehydrogenase,

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
> 130 VS ≤ 130	7.38 (3.19–17.09)		2.17 (0.76–6.18)	
* indicates that the difference was statistically significant				
Abbreviation: LVI lymphovascular invasion, AKP alkaline phosphatase, LDH lactate dehydrogenase,				

Discussion

For renal clear cell carcinoma, a simple biomarker for early diagnosis and prognosis is still lacking in clinical practice. Through our research, it is found that apolipoprotein ApoB is of great significance.

Previous literature[12] reported that ApoB, SLC3A1, SCD5, and AQP1 genes could be used as prognostic biomarkers for renal clear cell carcinoma, and the four genes had different powers that judged the prognosis. However, the specific effect of ApoB was not illuminated.

Renal clear cell carcinoma is a malignant tumor composed of cells whose cytoplasm is transparent[13]. And cancer cells are rich in cholesterol and cholesterol esters[14, 15]. In 1987, it was firstly reported by Gcbhard et al[15]. that the levels of cholesterol and cholesterol esters in renal cell carcinoma were higher than those in normal kidney tissues. Subsequently, some experimental studies also confirmed the above result and further found that the level of cholesterol was positively associated with the malignant degree of cancer cells[16, 17]. However, the cholesterol levels in advanced biological cells are maintained in a fairly narrow range, and the negative feedback regulation of endogenous cholesterol synthesis play an important role in maintaining the cholesterol metabolic balance[18, 19]. And the biological effect of serum cholesterol was related with low-density lipoprotein (LDL)[20]. It was manifested by the fact that about two-thirds of endogenous cholesterol were transported by LDL[21]. Therefore, we concluded that if the cholesterol level in renal cancer tissues increased significantly with the malignant degree elevating, the negative feedback regulation could inhibit the synthesis and transport of endogenous cholesterol, and this indirectly resulted that the level of LDL decreased.

In our study, patients with the high level of preoperative ApoB had a higher survival rate than those with the low level of preoperative ApoB. We considered this was mainly related with the level of LDL metabolism. ApoB is an important structural component of LDL[22]. According to the above analysis, the negative feedback regulation caused by the increasing cholesterol level of renal clear cell carcinoma tissue with the malignant degree elevating indirectly leaded to a decrease in LDL levels, which inevitably resulted in a decrease in serum ApoB levels. In other words, the level of ApoB ultimately reflected the overall prognosis of tumor patients by indirectly reflecting the malignant degree of the tumor.

Apolipoprotein ApoB acts indirectly by reflecting the LDL levels, so why not to directly adopt the LDL levels as the prognostic index? The reasons maybe are as followings: the small, dense low-density

lipoprotein (sd-LDL) is difficult to detect in the blood[23], but as its structural component ApoB can be simply detected in the blood. Thus, apolipoprotein ApoB has become a more advantageous detection index by more comprehensively reflecting the LDL level.

In addition, we considered that in a nutritional perspective patients with the high level of preoperative ApoB should also have a higher survival rate. The reasons were as followings: the level of ApoB represented the nutritional level of the patient to some extent[24]. And the nutritional level of the patient determined the body resistance[25]. When the body resistance increased, the capability of tumor tolerance and the prognosis survival rate also elevated.

Some trials documented that in the apolipoprotein family Apo A-I and ApoL1 had an anti-tumor effect[26]. But the mechanism of the two were different. Recently, researchers used ApoA-I mimetic peptides to observe the association between ApoA-I and ovarian cancer cells[27]. ApoA-I mimetic peptides reduced viability and proliferation of ID8 cells and cis-platinum -resistant human ovarian cancer cells, and decreased ID-8 cell-mediated tumor burden in C57BL/6J mice when administered subcutaneously or orally. However, ApoL1 could play an anti-tumor role by the p53-associated autophagy in the Apo apolipoprotein family[28]. The Study had shown that p53 could stimulate the expression of ApoL1. Then the high level of intracellular ApoL1 activate the transcription of LC3-II which induces the autophagy of cancer cells.

Compared with the ApoB, though Apo A-I and ApoL1 had an anti-tumor effect, there were no related experiment studies confirm their effect in renal clear cell carcinoma. Moreover, no clinical trials revealed the high level of Apo A-I and ApoL1 was associated with the high survival rate of renal cancer. However, the relation between the two and the prognosis of renal clear cell carcinoma could be researched in the future.

Our research has several shortcomings. Firstly, it is only a single-center study. In the future, we would collect more samples by multi-centers cooperation to carry out related research. Secondly, we only include renal clear cell carcinoma, and we would further explore the predictive significance of ApoB in other types of kidney cancer in the future.

Conclusions

Conclusively, in the Apo apolipoprotein family, the preoperative ApoB level has an important clinical significance for predicting the prognosis survival rate of the ccRCC patients.

Declarations

Ethics approval and consent: We confirm that the study protocol has been approved by the institute's committee on human research(the Third Affiliated Hospital of Soochow University).

Availability of Data and Materials: We declare that we wish to share their data.

The Authors' contributions section: We confirm that all authors meet the criteria for authorship. WK and CZ conceived and designed the study. CZ and WK performed the study and prepared figure 1. WK and W TC wrote the main manuscript text. W TC and CZ reviewed and edited the manuscript. All authors read and approved the manuscript.

The Consent for publication section: We declared that the consent to publish has be obtained from the patients.

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Conflict of Interest: We declare that we have no conflict of interest.

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Figures

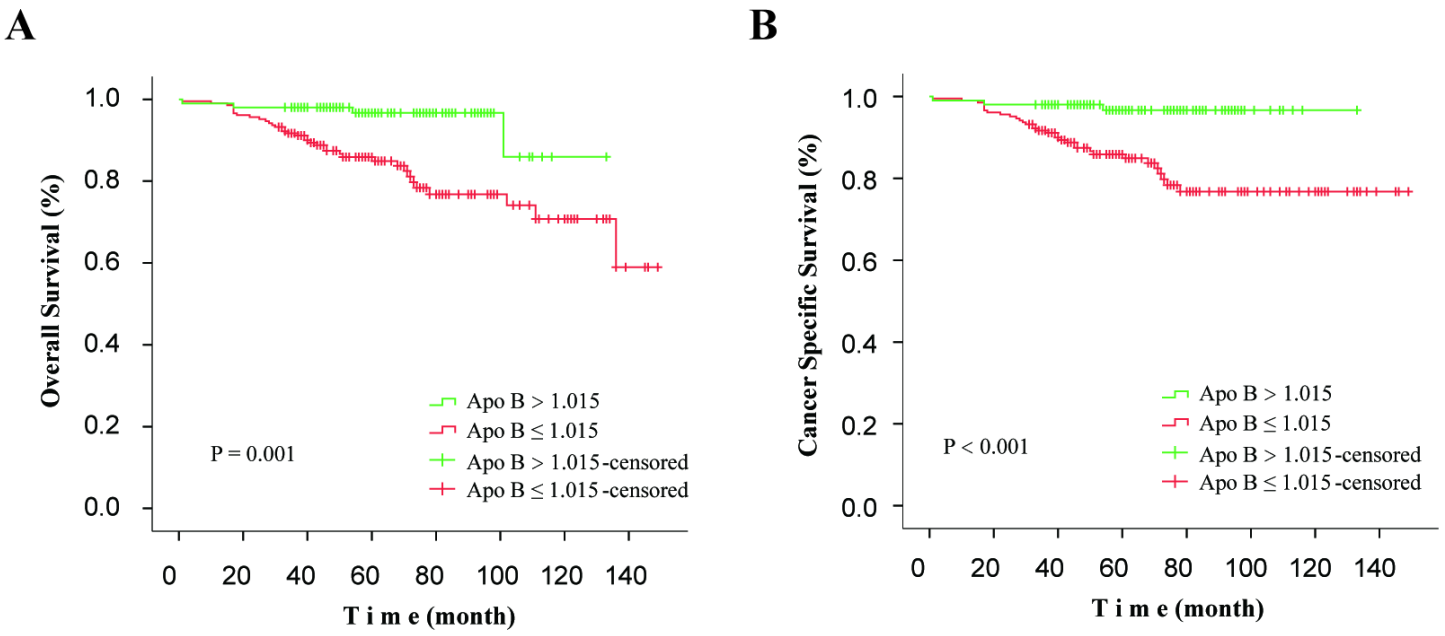

Figure 1

The Kaplan-Meier survival curves according to the preoperative apolipoprotein B level. The OS and CSS rates were significantly higher in the high Apo B level group compared with the low group (P = 0.001 and P < 0.001, respectively).