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Preoperative apolipoprotein B/A1 ratio is an independent prognostic factor in metastatic renal cell carcinoma

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Abstract

Objectives: We aimed to explore the prognostic value of preoperative apolipoprotein B/apolipoprotein A1 (Apo B/A1) ratio in metastatic renal cell carcinoma (mRCC).

Materials and methods: Between January 2006 and December 2016, patients with mRCC who underwent cytoreductive nephrectomy at the Chinese PLA General Hospital were enrolled. The clinical-pathological parameters were collected retrospectively, and the preoperative Apo B/A1 ratios of two different subgroups were compared. The cut-off value was determined with the receiver operating characteristic (ROC) curve. The value of preoperative Apo B/A1 ratio on oncological outcome was determined through Kaplan−Meier survival analysis and Cox regression analysis.

Results: A total of 287 mRCC patients were enrolled in this study. The median postoperative follow-up time was 27.8 months (IQR, 12.5−58.6 months). The Apo B/A1 ratio was higher in the high Fuhrman grade (G3 and G4) group than that in the low Fuhrman grade (G1 and G2) group ($P = 0.010$). The area under the curve values of the ROC curves were 0.613 for progression-free survival (PFS) ($P = 0.005$) and 0.607 for overall survival (OS) ($P = 0.004$). The optimal cut-off values of Apo B/A1 ratio were 0.977 for PFS and 0.847 for OS. A high preoperative Apo B/A1 ratio (PFS ≥ 0.977; OS ≥ 0.847) was significantly associated with poor PFS ($P < 0.0001$) and OS ($P = 0.0005$). Cox regression analyses showed that the Apo B/A1 ratio is an independent prognostic factor for PFS (hazard ratio [HR] = 3.131; 95% confidence interval [CI] = 2.249−4.360; $P < 0.001$) and OS (HR = 2.173; 95% CI = 1.533−3.080; $P < 0.001$).

Conclusion: Preoperative Apo B/A1 ratio is an independent prognostic factor for PFS and OS in patients with mRCC. Preoperative Apo B/A1 ratio can be useful in improving current prognostic evaluation and treatment decision for patients with mRCC. © 2018 Published by Elsevier Inc.

Keywords: Renal cell carcinoma; Metastasis, Prognosis; Apolipoprotein

1. Introduction

Kidney cancer is among the 10 most common human malignancies in men and women [1,2]. According to statistics, approximately 65,340 new cases and 14,970 deaths are related to this malignancy in 2018 in the United States [3]. Renal cell carcinoma (RCC), which is derived from renal tubular epithelial cells, is the most common histological type and accounts for over 80% of all cases [1,2,4,5]. Approximately more than 15% of all RCC patients are diagnosed with metastatic renal cell carcinoma (mRCC) [1,3,6], and over 20% of patients with localized RCCs have metastases after partial or radical nephrectomy [7]. Metastatic RCC is a highly aggressive cancer with poor prognosis and currently have less than 8% 5-year survival rate [5,8]. Moreover, mRCC requires systemic therapy and close follow-up is highly recommended owing to its

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biological characteristics [1,2,5,9-11]. Methods that can accurately predict and evaluate the prognosis of mRCC have attracted considerable interest. For the past few years, an increasing number of valuable models and molecules for the prognosis prediction have been discovered, including the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model [12], Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model [13], and others [14-18]. However, different clinical–pathological features result in different oncological outcomes, and even patients with comparable parameters can have highly different prognosis. Thus, novel easy-to-detect markers that can predict prognosis for patients with metastatic RCCs are needed.

Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) are two predominant components of high-density lipoprotein (HDL) and low-density lipoprotein (LDL), which have long been regarded to have extensive connections with cardiovascular disease [19,20], diabetes [21], and Alzheimer's disease [22,23]. In the field of tumor research, several experimental studies have showed that Apo A1 suppresses tumor cell growth both in vitro and in vivo, these tumors including colorectal cancer [24,25], breast cancer [26], and melanoma [27]. Many studies that based on clinical data have reported that high Apo A1 level is associated with better prognosis in cancers, which including breast cancer [28], esophageal cancer [29], nasopharyngeal cancer [30], colorectal cancer [31,32], bladder cancer [33], and renal cancer [34]. Apo B contains two subtypes, Apo B-48 and Apo B-100. Existing studies have showed that the Apo B and their mRNA editing enzymes are transcriptionally regulated by tumor suppressor gene p53 [35] and are involved in tumorigenesis [36]. For a long time, Apo B/Apo A1 (Apo B/A1) ratio was used as a risk index for cardiovascular disease [37]. Recently, several clinical studies have reported that Apo B/A1 ratio have potential values for the prognosis prediction of some kind of neoplasms, such as gastric cancer [38] and colorectal cancer [32]. However, the value of preoperative Apo B/A1 ratio in the prognostic evaluation of mRCC is still unclear.

In this study, we explore the association between preoperative Apo B/A1 ratio and the clinical–pathological features and evaluate the prognostic value of preoperative Apo B/A1 ratio in mRCC.

2. Materials and methods

2.1. Patient population

This study was performed after obtaining the authorization of Ethics Committee of Chinese PLA General Hospital. Patients who conformed to the inclusion criteria between January 2006 and December 2016 were enrolled consecutively. The inclusion criteria for all the mRCC patients were listed below: (1) patients were diagnosed with mRCC, and underwent cytoreductive nephrectomy at the Urology Department of Chinese PLA General Hospital; (2) specimens were pathologically confirmed to be RCC by senior pathologists; (3) no history of other malignancies; (4) no hematological diseases, inflammatory diseases, immune diseases, hepatic insufficiency, hepatitis, and hyperpyrexia; and (5) preoperative blood parameters and clinical-pathological parameters can be fully obtained.

2.2. Data extraction

For each patient, clinical and pathological parameters before operation were collected retrospectively, including age, gender, body mass index (BMI), fatty liver, primary tumor characteristics (histological subtype, pT-stage, N-stage, number of metastases, tumor site, tumor size, tumor hemorrhage, tumor necrosis, tumor cystic degeneration, and Fuhrman grade), and targeted therapy. The TNM stages and Fuhrman grades were determined according to the 2010 UICC/AJCC TNM classification system and the Fuhrman nuclear grading system. The preoperative whole blood of patient was drawn 1 week before operation. Then, the sample was centrifuged, and the serum was collected for the laboratory analysis. The sample was tested automatically with a Cobas 8000 modular analyzer (Roche Diagnostics, USA). Laboratory hematological parameters, including cholesterol, triglyceride, Apo A1, and Apo B were collected. The ratio between Apo B and Apo A1 (Apo B/A1) was calculated with the conventional division method.

2.3. Follow-up

Follow-up was performed by our institution under a standardized procedure. Physical examination, laboratory examinations, abdominal ultrasound and computed tomography, and chest X-ray were performed monthly for the first year after operation, then performed every 3 months in the next 2 years. Since then, these items were performed semiannually. Follow-up was terminated on December 31, 2017. Progression-free survival (PFS) and overall survival (OS) were used as prognostic indexes. PFS was defined as the time from operation to progression, death, or last follow-up. OS was defined as the time from operation to all-cause death.

2.4. Statistical analysis

All statistical analyses were performed by using SPSS 22.0 (IBM Inc.) and Prism 7.0 (GraphPad). The Kolmogorov–Smirnov test was used for the normality test. Abnormal distribution variables were expressed as median with interquartile range (IQR), and the comparison between the groups was performed using nonparametric Kruskal–Wallis or Wilcoxon rank-sum test. The receiver operating characteristic (ROC) curve analysis was applied to determine the optimal cut-off value, which corresponded to the

maximum value of sensitivity plus specificity. Univariate survival analysis was performed using the Kaplan−Meier method with log-rank test. Pearson correlation analysis was used for the identification of the correlation between variables. Univariate and multivariate analyses were performed with the Cox proportional hazards model. Two-tailed tests were used for all the comparisons, and a P value of <0.05 was considered statistically significant.

3. Results

3.1. Patient and clinical−pathological features

This study totally enrolled 287 mRCC patients. The detailed clinical−pathological characteristics are shown in Table 1. All enrolled patients underwent cytoreductive nephrectomy at our hospital. The median age of the 287 mRCC patients was

Table 1
The clinical-pathological characteristics of metastatic renal cell carcinoma patients and the comparison of Apo B/A1 ratios between groups.

Characteristics	NO. (%)	Apo B/A1, median (IQR)	P value
All patients	287	0.859 (0.686−1.083)	
Age (years), median (IQR)	56 (47−64)		0.057
≤60	175 (61.0)	0.869 (0.691−1.106)	
>60	112 (39.0)	0.837 (0.662−1.047)	
Gender			0.155
Male	221 (77.0)	0.854 (0.690−1.063)	
Female	66 (23.0)	0.901 (0.659−1.214)	
BMI (kg/m^2), median (IQR)	23.8 (21.7−26.1)		0.979
<25	175 (61.0)	0.860 (0.661−1.102)	
≥25	112 (39.0)	0.856 (0.715−1.065)	
Fatty liver			0.202
Absent	212 (73.9)	0.862 (0.687−1.102)	
Present	75 (26.1)	0.839 (0.667−1.058)	
Histological subtype			0.147
Clear cell	266 (92.7)	0.859 (0.685−1.079)	
Nonclear cell	21 (7.3)	0.868 (0.716−1.167)	
pT-stage			0.898
pT1 + pT2	171 (59.6)	0.864 (0.671−1.101)	
pT3 + pT4	116 (40.4)	0.853 (0.690−1.065)	
N-stage			0.513
N0	189 (65.9)	0.866 (0.693−1.059)	
N1	98 (34.1)	0.850 (0.677−1.153)	
Number of metastases			0.062
<2	153 (53.3)	0.859 (0.672−1.053)	
≥2	134 (46.7)	0.857 (0.691−1.152)	
Tumor site			0.811
left	149 (51.9)	0.830 (0.654−1.102)	
Right	138 (48.1)	0.884 (0.725−1.077)	
Tumor diameter, cm			0.226
≤7	145 (50.5)	0.835 (0.676−1.052)	
>7	142 (49.5)	0.896 (0.690−1.143)	
Tumor hemorrhage			0.457
Absent	159 (55.4)	0.868 (0.686−1.102)	
Present	128 (44.6)	0.842 (0.687−1.065)	
Tumor necrosis			0.364
Absent	123 (42.9)	0.835 (0.656−1.040)	
Present	164 (57.1)	0.874 (0.719−1.113)	
Tumor cystic degeneration			0.131
Absent	243 (84.7)	0.868 (0.689−1.095)	
Present	44 (15.3)	0.788 (0.663−0.989)	
Fuhrman grade			0.010
G1+G2	143 (49.8)	0.825 (0.656−1.023)	
G3+G4	144 (50.2)	0.916 (0.706−1.147)	
Targeted therapy			0.086
Absent	162 (56.4)	0.881 (0.725−1.113)	
Present	125 (43.6)	0.810 (0.633−1.060)	
Follow-up, median (IQR)	27.8 (12.5−58.6)		
Progression-free survival	11.6 (4.5−28.6)		
Overall survival	27.0 (12.3−58.0)		

Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; BMI = body mass index; IQR = interquartile range.

56 years (IQR, 47−64 years). The median body mass index (BMI) was 23.8 kg/m^2 (IQR, 21.7−26.1 kg/m^2). The median Apo B/A1 ratio was 0.859 (IQR, 0.686−1.083). Fatty liver was present in 75 (26.1%) patients. Regional lymph node metastasis was present in 98 (34.1%) patients, and more than 2 sites of distant metastasis were found in 134 (46.7%) patients. Exactly 149 (51.9%) patients had tumor on their left renal, and 138 (48.1%) patients had tumor on the right. Postoperative pathological result showed that histological subtype of clear cell RCC was present in 266 (92.7%) specimens, and papillary RCC was present in 21 (7.3%) specimens; tumor hemorrhage was present in 128 (44.6%) specimens; tumor necrosis was present in 164 (57.1%) specimens; and tumor cystic degeneration was present in 44 (15.3%) specimens. Tumors of more than 7 cm in diameter were found in 142 (49.5%) specimens. Exactly 171 (59.6%) specimens were categorized to pT1/T2, and 116 (40.4%) specimens were categorized to pT3/T4. A total of 143 (49.8%) specimens and 144 (50.2%) specimens were classified as low-grade (Fuhrman G1 and G2) and high-grade (Fuhrman G3 and G4), respectively. Targeted therapy (tyrosine kinase inhibitors) was applied to 125 (43.6%) patients after surgery. A total of 221 (77.0%) patients developed tumor progression, and 198 (69.0%) patients died from all causes at the end of follow-up. The median postoperative follow-up time was 27.8 months (IQR, 12.5−58.6 months). The median PFS and OS were 11.6 months (IQR, 4.5−28.6 months) and 27.0 months (IQR, 12.3−58.0 months).

3.2. Relationship between preoperative Apo B/A1 ratio and clinical−pathological parameters of mRCC patients

To tease out the relationship between the Apo B/A1 ratio and the clinical−pathological parameters, we compared the Apo B/A1 ratios of two different subgroups, which were divided according to the clinical−pathological parameters (Table 1). As a continuous variable, the Apo B/A1 ratio in high Fuhrman grade (G3 and G4) group was higher than that in the low Fuhrman grade (G1 and G2) group ($P = 0.010$), but no statistically significant differences were found between the Apo B/A1 ratios in the subgroups by age ($P = 0.057$), gender ($P = 0.155$), BMI ($P = 0.979$), fatty liver ($P = 0.202$), histological subtype ($P = 0.147$), pT-stage ($P = 0.898$), N-stage ($P = 0.513$), number of metastases ($P = 0.062$), tumor site ($P = 0.811$), tumor diameter ($P = 0.226$), tumor hemorrhage ($P = 0.457$), tumor necrosis ($P = 0.364$), tumor cystic degeneration ($P = 0.131$), and targeted therapy ($P = 0.086$).

3.3. Determination of the optimal cut-off values for preoperative Apo B/A1 ratio

By using PFS and OS as the end-point indexes, we drew ROC curves for the preoperative Apo B/A1 ratio (Figs. 1A and 1B). The area under the curve (AUC) values were 0.613 ($P = 0.005$; 95% CI = 0.539−0.687) for the PFS curve and 0.607 ($P = 0.004$; 95% CI = 0.538−0.676) for the OS curve. By using the maximum value of sensitivity plus specificity, which obtained from ROC curves, we determined the value of 0.977 as the optimal cut-off value for PFS, and the value of 0.847 as the optimal cut-off value for OS.

3.4. Association of preoperative Apo B/A1 ratio with mRCC prognosis

By using PFS and OS as the end-point indexes, we performed Kaplan−Meier survival analysis with log-rank test. All the patients were divided into high or low preoperative

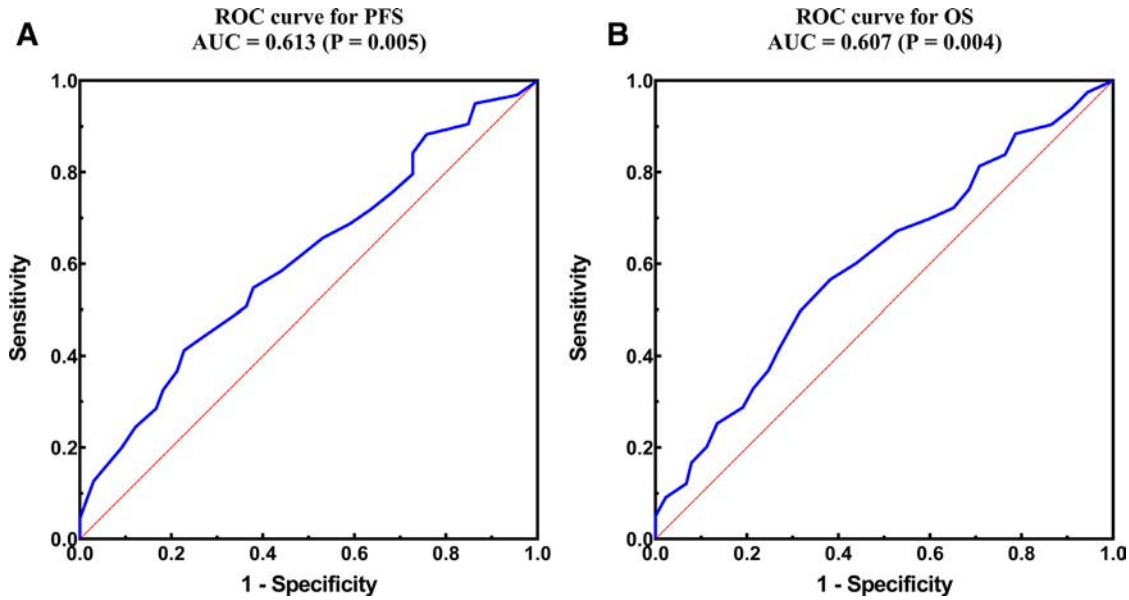

Fig. 1. ROC curves of preoperative Apo B/A1 ratio and the determination of optimal cut-off values for PFS and OS. (A) ROC curve for PFS gives the AUC value of 0.613 and the optimal cut-off value of 0.977. (B) ROC curve for OS gives the AUC value of 0.607 and the optimal cut-off value of 0.847. AUC = area under the curve; OS = overall survival; PFS = progression-free survival; ROC = receiver operating characteristic.

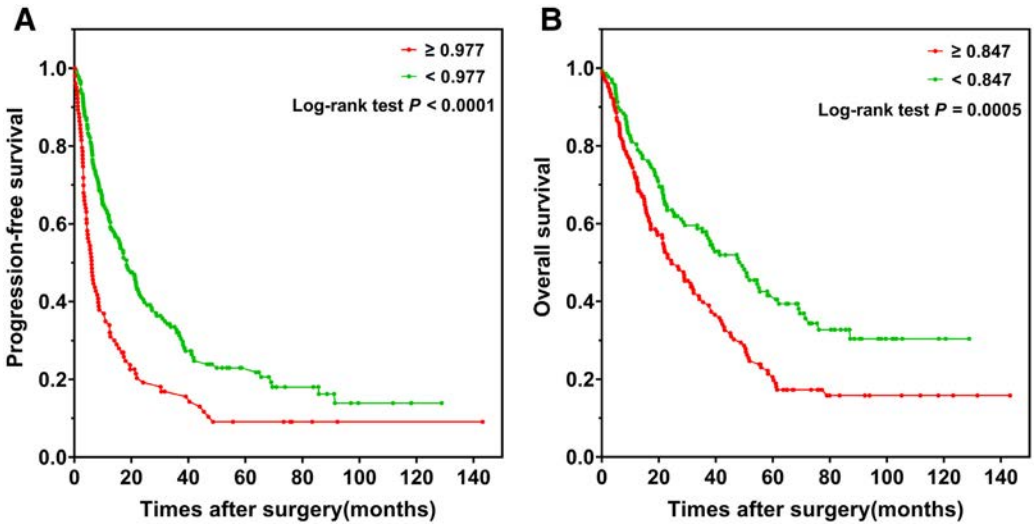

Fig. 2. Kaplan-Meier survival analysis for PFS and OS according to preoperative Apo B/A1 ratio. (A) Kaplan-Meier curve for PFS. (B) Kaplan-Meier curve for OS. OS = overall survival; PFS = progression-free survival.

Apo B/A1 ratio groups according to the optimal cut-off values. The patients with higher preoperative Apo B/A1 ratios (≥0.977) had significantly poorer PFS ($P < 0.0001$, Fig. 2A) than the patients with lower ratios. Similarly, the patients with higher preoperative Apo B/A1 ratios (≥0.847) had significantly poorer OS ($P = 0.0005$, Fig. 2B) than the patients with lower ratios.

Next, we performed Cox regression analyses for PFS and OS to determine whether preoperative Apo B/A1 ratio can be a prognostic factor of mRCC. Before this step, we checked the correlations between variables and found that the levels of serum high-density lipoprotein−cholesterol (HDL-C) and low-density lipoprotein−cholesterol (LDL-C) showed statistically moderate ($0.5 \leq r < 0.8$) correlations with the levels of Apo A1 ($r = 0.541$, $P < 0.001$) and Apo B ($r = 0.602$, $P < 0.001$). Considering the interaction between them, we did not introduce HDL-C and LDL-C as variables into the Cox regression analyses. Univariate Cox regression analysis for PFS showed the following values: pT-stage (hazard ratio [HR] = 1.483; 95% confidence interval [CI] = 1.133−1.942; $P = 0.004$), N-stage (HR = 1.369; 95% CI = 1.036−1.810; $P = 0.027$), number of metastases (HR = 1.483; 95% CI = 1.138−1.933; $P = 0.004$), tumor size (HR = 1.260; 95% CI = 0.967−1.641; $P = 0.087$), Fuhrman grade (HR = 2.256; 95% CI = 1.716−2.966; $P < 0.001$), targeted therapy (HR = 0.738; 95% CI = 0.564−0.966; $P = 0.027$), triglyceride (continuous) (HR = 0.814; 95% CI = 0.680−0.974; $P = 0.025$), and Apo B/A1 ratio (continuous) (HR = 3.432; 95% CI = 2.465−4.777; $P < 0.001$) were statistically significant prognostic factors. The further multivariate analysis revealed that preoperative Apo B/A1 ratio (continuous) (HR = 3.131; 95% CI = 2.249−4.360; $P < 0.001$), together with Fuhrman grade (HR = 1.906; 95% CI = 1.423−2.552; $P < 0.001$), were independent prognostic factors for PFS (Table 2).

The other univariate Cox regression analysis for OS revealed that fatty liver (HR = 0.731; 95% CI = 0.524−1.020; $P = 0.065$), pT-stage (HR = 1.515; 95% CI = 1.145−2.005; $P = 0.004$), N-stage (HR = 1.475; 95% CI = 1.104−1.973; $P = 0.009$), number of metastases (HR = 1.739; 95% CI = 1.313−2.304; $P < 0.001$), tumor size (HR = 1.380; 95% CI = 1.043−1.826; $P = 0.024$), tumor necrosis (HR = 1.550; 95% CI = 1.164−2.065; $P = 0.003$), Fuhrman grade (HR = 3.070; 95% CI = 2.285−4.125; $P < 0.001$), targeted therapy (HR = 0.639; 95% CI = 0.479−0.852; $P = 0.002$), cholesterol (continuous) (HR = 0.788; 95% CI = 0.665−0.934; $P = 0.006$), triglyceride (continuous) (HR = 0.727; 95% CI = 0.585−0.903; $P = 0.004$), and Apo B/A1 ratio (continuous) (HR = 2.487; 95% CI = 1.771−3.491; $P < 0.001$) were statistically significant prognostic factors. The multivariate analysis using these variates revealed that preoperative Apo B/A1 ratio (continuous) (HR = 2.173; 95% CI = 1.533−3.080; $P < 0.001$), tumor necrosis (HR = 1.361; 95% CI = 1.005−1.842; $P = 0.046$), Fuhrman grade (HR = 2.368; 95% CI = 1.734−3.232; $P < 0.001$), and targeted therapy (HR = 0.712; 95% CI = 0.529−0.958; $P = 0.025$) were independent prognostic factors for OS (Table 3).

4. Discussion

Despite the latest achievements in genetic and molecular biological research, the prognostic evaluation of RCC is still dependent on anatomical, histological, clinical, and molecular factors [11,39-42]. The biological association between circulating lipid levels and cancer risk has been confirmed [43,44]. The two most common circulating lipids, namely, Apo A1 and Apo B, are identified as novel hematological biomarkers for the prognosis of many cancer types.

Table 2
Univariate and multivariate Cox regression analyses of clinical-pathological parameters for progression-free survival

Variables	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, years			0.880			
≤60	1 (Reference)					
>60	1.021	0.780−1.336				
Gender			0.100			
Male	1 (Reference)					
Female	1.294	0.952−1.760				
BMI, kg/m^2			0.250			
<25	1 (Reference)					
≥25	0.853	0.650−1.119				
Fatty liver			0.884			
Absent	1 (Reference)					
Present	1.022	0.760−1.376				
Histological subtype			0.744			
Clear cell	1 (Reference)					
Nonclear cell	1.092	0.646−1.846				
pT-stage			0.004			0.330
pT1 + pT2	1 (Reference)			1 (Reference)		
pT3 + pT4	1.483	1.133−1.942		1.172	0.851−1.614	
N-stage			0.027			0.067
N0	1 (Reference)			1 (Reference)		
N1	1.369	1.036−1.810		1.332	0.980−1.811	
Number of metastases			0.004			0.767
<2	1 (Reference)			1 (Reference)		
≥2	1.483	1.138−1.933		1.053	0.750−1.477	
Tumor site			0.674			
left	1 (Reference)					
Right	1.058	0.813−1.378				
Tumor size, cm			0.087			0.966
≤7	1 (Reference)			1 (Reference)		
>7	1.260	0.967−1.641		1.006	0.765−1.323	
Tumor hemorrhage			0.204			
Absent	1 (Reference)					
Present	0.841	0.644−1.099				
Tumor necrosis			0.151			
Absent	1 (Reference)					
Present	1.216	0.931−1.590				
Tumor cystic degeneration			0.642			
Absent	1 (Reference)					
Present	1.091	0.756−1.574				
Fuhrman grade			<0.001			<0.001
G1+G2	1 (Reference)			1 (Reference)		
G3+G4	2.256	1.716−2.966		1.906	1.423−2.552	
Targeted therapy			0.027			0.081
Absent	1 (Reference)			1 (Reference)		
Present	0.738	0.564−0.966		0.784	0.597−1.030	
Cholesterol (continuous)	0.926	0.799−1.074	0.309			
Triglyceride (continuous)	0.814	0.680−0.974	0.025	0.884	0.737−1.058	0.179
Apo B/A1 (continuous)	3.432	2.465−4.777	<0.001	3.131	2.249−4.360	<0.001

Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; BMI = body mass index; CI = confidence interval; HR = hazard ratio.

Apo A1, which is synthesized in the liver and small intestine, is the dominant component of high-density lipoprotein. By stabilizing the structure of HDL and activating the lecithin-cholesterol acyltransferase, Apo A1 plays a vital function in reverse cholesterol transport. Sirniö et al. [32] reported that high Apo A1 level is associated with better cancer specific survival and overall survival in colorectal cancer. Quan et al. [31] also revealed the similar outcome in metastatic colorectal cancer. His et al. [45] found that Apo A1 is associated with decreased breast cancer risk. Chang et al. [46] demonstrated that low Apo A1 level can predict poor overall survival, disease-free survival, and distant-metastasis-free survival in nasopharyngeal carcinoma. Jiang et al. [30] also found that higher Apo

Table 3
Univariate and multivariate Cox regression analyses of clinical-pathological parameters for overall survival

Variables	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, years			0.228			
≤60	1 (Reference)					
>60	1.190	0.897−1.578				
Gender			0.189			
Male	1 (Reference)					
Female	1.240	0.900−1.709				
BMI, kg/m^2			0.118			
<25	1 (Reference)					
≥25	0.793	0.593−1.060				
Fatty liver			0.065			0.450
Absent	1 (Reference)			1 (Reference)		
Present	0.731	0.524−1.020		0.871	0.608−1.247	
Histological subtype			0.303			
Clear cell	1 (Reference)					
Nonclear cell	1.319	0.778−2.236				
pT-stage			0.004			0.369
pT1+ pT2	1 (Reference)			1 (Reference)		
pT3+ pT4	1.515	1.145−2.005		1.156	0.842−1.588	
N-stage			0.009			0.379
N0	1 (Reference)			1 (Reference)		
N1	1.475	1.104−1.973		1.163	0.831−1.628	
Number of metastases			<0.001			0.331
<2	1 (Reference)			1 (Reference)		
≥2	1.739	1.313−2.304		1.191	0.838−1.692	
Tumor site			0.843			
Left	1 (Reference)					
Right	0.972	0.735−1.285				
Tumor size, cm			0.024			0.891
≤7	1 (Reference)			1 (Reference)		
>7	1.380	1.043−1.826		1.021	0.761−1.370	
Tumor hemorrhage			0.813			
Absent	1 (Reference)					
Present	1.034	0.781−1.369				
Tumor necrosis			0.003			0.046
Absent	1 (Reference)			1 (Reference)		
Present	1.550	1.164−2.065		1.361	1.005−1.842	
Tumor cystic degeneration			0.516			
Absent	1 (Reference)					
Present	0.874	0.582−1.312				
Fuhrman grade			<0.001			<0.001
G1+G2	1 (Reference)			1 (Reference)		
G3+G4	3.070	2.285−4.125		2.368	1.734−3.232	
Targeted therapy			0.002			0.025
Absent	1 (Reference)			1 (Reference)		
Present	0.639	0.479−0.852		0.712	0.529−0.958	
Cholesterol (continuous)	0.788	0.665−0.934	0.006	0.920	0.758−1.116	0.396
Triglyceride (continuous)	0.727	0.585−0.903	0.004	0.894	0.686−1.164	0.404
Apo B/A1 (continuous)	2.487	1.771−3.491	<0.001	2.173	1.533−3.080	<0.001

Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; BMI = body mass index; CI = confidence interval; HR = hazard ratio.

A1 level is an independent protective factor against progression of metastatic nasopharyngeal carcinoma. Shang et al. [33] discovered that patients with high Apo A1 level have greater overall survival and cancer-specific survival (CSS) in non-muscle-invasive bladder cancer. Guo et al. [34] reported that elevated level of preoperative Apo A1 is related with better survival in patients with RCC. Apo B is the major structural protein of low-density lipoprotein and is also synthesized in the liver. Borgquist et al. [43] reported that high Apo B levels are closely related to high risk of colorectal cancer and lung cancer. Chandler et al. [47] also drew the similar conclusion that Apo B-100, which is the major subtype of Apo B, is higher in the female patients with increased colorectal cancer risk.

All these results suggested that high Apo A1 level exerts a positive effect on cancer prognosis, whereas Apo B has a negative effect. Nevertheless, a single index may generate bias and fail to predict the prognosis accurately. Therefore, the Apo B/Apo A1 ratio may balance these effects in predicting cancer prognosis. Ma et al. [38] conducted a large-scale retrospective analysis of 1201 gastric cancer patients, they found that high Apo B/A1 ratio is connected with decreased overall survival and preoperative serum Apo B/A1 ratio might be used as a novel prognostic indicator of gastric cancer. Similarly, by retrospectively analyzing 144 colorectal cancer patients, Sirniö et al. [32] drew the conclusion that low Apo B/A1 ratio is directly linked to improved cancer-specific survival and overall survival.

In our study, we found that high preoperative Apo B/A1 ratio is significantly correlated with poor PFS and OS in mRCC patients. These findings may be explained by two possible explanations. First, we found previously that high Fuhrman grade (G3 and G4) tumors had significantly higher Apo B/A1 ratios than low Fuhrman grade (G1 and G2) tumors, and large numbers of studies have proven that high Fuhrman grade is directly linked to poor prognosis in RCC. Second, elevated level of preoperative Apo A1 is closely related to preferable survival in many kinds of cancer, including RCC [34], and Apo B/Apo A1 ratio depends on the values of these two variables, that is, the ratio increases when Apo A1 level decreases. These results coincide with those of Ma [38] and Sirniö [32]. The cut-off value in our study (0.977 for PFS and 0.847 for OS) were different from that in Ma's (1 for OS) and Sirniö's (0.521 for CSS and OS) studies. The different cancer types included in these studies may account for the difference. It is worth mentioning that the AUC values determined by ROC curve analyses in our study were close to 0.5 (0.613 for PFS and 0.607 for OS), this might be due to the relatively smaller number of enrolled patients and shorter postoperative follow-up time. Serum apolipoprotein levels may be influenced by obesity. Thus, in the Cox regression analyses, we introduced some obesity-related-variables to avoid bias. Due to the moderate correlations, HDL-C and LDL-C were excluded. Variables including BMI, fatty liver, serum cholesterol, and serum triglyceride were finally included. Adjustments were made by using these variables. The results of the multivariate analyses demonstrated that the preoperative Apo B/A1 ratio and the Fuhrman grade are independent prognostic factors for PFS; the Apo B/A1 ratio, tumor necrosis, Fuhrman grade, and targeted therapy are independent prognostic factors for OS.

Guo et al. [31] performed a research similar to our research, focusing on the relationship between apolipoprotein and prognosis of renal cell carcinoma, but differing in some aspects. In particular, all the patients included in our study have mRCC, whereas most cases in the study of Guo et al. are localized renal cell carcinoma (86% in pT1+T2, 92.7% in pN0, 96.1% in pM0). Another difference is that we used Apo B/A1 ratio as the prognostic factor, whereas they used Apo A1.

Our study has some limitations. First, our study has a retrospective clinical trial design and is restricted by a single center with relatively small samples and relatively short postoperative follow-up time. Second, the prognostic value of preoperative Apo B/A1 ratio in patients with mRCC needs verifications from other studies. Third, the AUC values given by ROC curves are close to 0.5, and the method that uses ROC curve to determine cut-off value may not be well-accepted by other researchers. Fourth, the specific mechanism of Apo A1 and Apo B in the carcinogenesis and development of mRCC needs further investigation. Finally, peripheral blood biomarkers only provide a supplement to the traditional prognostic factors in the prediction of the prognosis for patients with mRCC and still unable to replace it. A subsequent study will include expanded sample size and extended follow-up time for the validation of the present results.

5. Conclusion

Our study demonstrated that high preoperative Apo B/A1 ratio is significantly connected with poor PFS and OS in patients with mRCC. The preoperative Apo B/A1 ratio is an independent prognostic factor for both PFS and OS in mRCC. Metastatic RCC patients with high levels of preoperative Apo B/A1 ratio must receive considerable attention and must be subjected to consistent follow-up. As a novel prognostic factor, the preoperative Apo B/A1 ratio can be utilized as a supplement to improve the current prognostic evaluation and treatment decision for patients with mRCC.

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