Prognostic Value of Serum Apolipoprotein B to Apolipoprotein A-I Ratio in Hepatocellular Carcinoma Patients Treated with Transcatheter Arterial Chemoembolization: A Propensity Score-Matched Analysis

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Keywords

Apolipoprotein B to apolipoprotein A-I ratio ·
Hepatocellular carcinoma · Transcatheter arterial
chemoembolization · Overall survival

Abstract

Introduction: The prognosis of advanced hepatocellular carcinoma (HCC) varies in patients receiving transcatheter arterial chemoembolization (TACE). In this study, we aimed to assess the prognostic value of serum apolipoprotein B (ApoB)/apolipoprotein A-I (ApoA-I) in this group of patients.

Methods: The serum lipid levels of HCC patients undergoing TACE were obtained from routine preoperative blood lipid examination. A propensity score-matched (PSM) analysis was used to eliminate the imbalance of baseline characteristics of the high and low ApoB/ApoA-I groups. Then, univariate and multivariate analysis were conducted to evaluate the prognostic value of ApoB/ApoA-I. **Results:** In 455 HCC patients

treated with TACE, ApoB/ApoA-I was positively correlated with AFP, T stage, distant metastasis, and TNM stage ($p < 0.05$). Patients with high ApoB/ApoA-I had a significantly shorter overall survival (OS) than those with low ApoB/ApoA-I (median OS, 21.7 vs. 39.6 months, $p < 0.001$). Multivariate analysis indicated that ApoB/ApoA-I was an independent prognostic index for OS (hazard ratio [HR] = 1.42, $p = 0.008$). After baseline characteristics were balanced, 288 patients were included in the PSM cohort. In this cohort, high ApoB/ApoA-I still predicted inferior OS in both univariate analysis (median OS, 27.6 vs. 39.3 months, $p = 0.002$) and multivariate analysis (HR = 1.58, $p = 0.006$). **Conclusion:** Serum ApoB/ApoA-I is a useful biomarker in predicting aggressive clinicopathological characteristics and poor prognosis in HCC patients treated with TACE.

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Introduction

The incidence and mortality rate of hepatocellular carcinoma (HCC) ranks seventh and third, respectively, among malignant tumors in the world [1]. HCC is difficult to be diagnosed at an early stage due to its latent onset and unspecific symptoms. Therefore, approximately 50–70% of HCC patients are diagnosed at an intermediate or metastatic stage [2]. For most of the intermediate HCC and some metastatic HCC patients, transcatheter arterial chemoembolization (TACE) is the main treatment [3]. However, the prognosis of HCC patients who received TACE is highly heterogeneous, with an overall survival (OS) ranging from 3 months to 2 years [4], suggesting TACE is not the best therapy in a subgroup of HCC patients. Therefore, further studies are warranted to identify patients who may not benefit from TACE.

Because of the convenience and availability of serum markers, their relationship with the prognosis of HCC has attracted substantial attention. A number of serum biomarkers have been indicated to predict the prognosis of HCC patients undergoing TACE, including osteopontin [5], insulin-like growth factor-1 [6], des- γ -carboxy prothrombin [7], miR-133b, miR-26a, miR-107, and miR-106 [8], circulating tumor DNA [9], and circulating cell-free DNA [10]. However, their prognostic value is based on a small sample size and still needs to be validated in large-scale studies. Besides, the detection of circulating tumor DNA and circulating cell-free DNA is too expensive and complicated to be applied to routine clinical practice. Therefore, a currently well-accepted serum biomarker is still lacking, and it is necessary to identify novel serum biomarkers to refine the risk definition for HCC patients receiving TACE.

Abnormality of lipid metabolism has been indicated to contribute to the occurrence and development of HCC [11–13]. Serological markers of blood lipids such as triglycerides (TGs), cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C ratio, and apolipoprotein B (ApoB)/apolipoprotein A-I (ApoA-I) ratio (ApoB/ApoA-I) have been reported to be prognostic indicators for cancer patients [14–16]. Apolipoproteins participate in carcinogenesis by promoting proliferation and invasion, enhancing antitumor immunity or drug delivery, and facilitating immediate oxidative stress reaction [17]. ApoA is an important component of HDL. As a major subtype of ApoA, ApoA-I is involved in the transportation of TC from peripheral tissues to the liver [18]. ApoB, a key part of LDL, is responsible for transporting TC from the liver to peripheral tissues [19]. It is well known that decreased ApoA-I and elevated ApoB levels are risk factors for cardiovascular diseases [20, 21], and the ApoB/ApoA-I ratio is a better risk factor for cardiovascular dis-

ease than lipids, lipoproteins and lipid ratios [22]. In recent years, ApoA-I has been reported to be associated with tumor thrombosis [23], immunity regulation [24], and lower ApoA-I is an independent prognostic factor predicting higher recurrence and mortality in HCC patients undergoing surgical resection [25]. ApoB has also been suggested to be associated with a higher cancer risk [14], and the higher serum ApoB level is an independent indicator of poor prognosis in HCC patients after curative resection [26]. What's more, the increased ApoB/ApoA-I ratio is significantly related to the risk of liver cancer [27]. In gastric cancer and renal cancer, elevated ApoB/ApoA-I is also an independent negative prognostic factor [28, 29]. However, the prognostic value of ApoB/ApoA-I in HCC patients receiving TACE is still unknown. In this study, we evaluated the prognostic value of serum ApoB/ApoA-I in 455 HCC patients treated with TACE using a propensity score-matched (PSM) analysis.

Methods

Patient Selection

We collected clinicopathological data of HCC patients who received TACE from January 2007 to December 2013 at the Third Affiliated Hospital of Sun Yat-sen University. Included cases of research met the following standards: (1) those patients who were pathologically diagnosed with HCC or conformed to the criteria of radiological results and biochemical assays from the American Association for the Study of Liver Diseases; (2) TACE as the first antitumor therapy; (3) patients with complete clinicopathological data of first hospitalization and complete follow-up data. Patients were excluded for: (1) with other malignancies; (2) with diseases that may affect serum lipid levels such as high blood pressure, diabetes, hyperlipidemia, metabolic syndrome or taking drugs which influence lipid metabolism; (3) the Eastern Cooperative Oncology Group performance status ≥ 3 .

All patients were regularly followed up by telephone interview and in the outpatient clinics. The end point of this study was OS, which was defined as the time interval from the date of initial diagnosis to the date of death or the date of last follow-up. The procedure of our study was approved by the Institute Research Ethics Committee of Sun Yat-sen University. Written informed consent was obtained from all patients prior to TACE.

Data Collection

We obtained the demographic and clinical data of all included HCC patients from our hospital electronic medical record at first diagnosis before treatment. Meanwhile, tumor image data such as computed tomography and/or magnetic resonance imaging were acquired and reviewed from a medical radiology system by experienced radiologists. The included patients were staged by the AJCC TNM staging system (eighth version) [30]. Assessment of liver function was classified by Child-Pugh grade [31]. The diagnostic criteria for dyslipidemia in our hospital were as follows: TC > 5.70 , TG > 1.92 , HDL-C < 0.78 , LDL-C > 3.40 mmol/L, ApoA-I < 1.00 , or ApoB > 1.10 g/L.

Statistical Analyses

The best cutoff values of ApoB/ApoA-I ratio and LDL-C/HDL-C ratio were generated based on receiver operating characteristic

Fig. 1. The study flow chart. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status.

curve analysis. The Student's *t* test and Mann-Whitney test were used to analyze continuous variables. The χ^2 test and Fisher's exact test were employed to explore the correlation of ApoB/ApoA-I levels with other clinicopathological factors. Spearman's rank correlation analysis was to evaluate the following correlations: ApoB versus LDL-C, ApoA1 versus HDL-C. Distribution of ApoB/ApoA-I ratio with clinicopathological parameters was displayed as scatter plots. Differences of categorical variables between groups were compared by the χ^2 test and Mann-Whitney test. Kaplan-Meier survival curve analysis with the log-rank test was used to explore the prognostic value of OS. Multivariate analysis by Cox proportional hazards regression model was used to identify the independent prognostic factors. A 2-tail $p < 0.05$ was statistically significant.

To eliminate potential bias in baseline characteristics, PSM was used via one-to-one matching to ensure even clinical distribution between the high and low ApoB/ApoA-I groups. By using binary logistic regression to generate a propensity score for each patient, the covariables entered into the model included age, gender, liver function, PVTT, tumor size, lymph node metastasis, distant metastasis, and TNM stage. Subsequently, a one-to-one match between the high and low ApoB/ApoA-I groups in HCC patients treated with TACE was obtained using Caliper matching [32]. Our analyses were conducted by SPSS (version 22; IBM Corp., Armonk, NY, USA), Graph Pad Prism 6.0 (GraphPad Prism Software Inc., LaJolla, CA, USA), R project version 3.3.3 (<http://www.r-project.org/>), and Medcalc (version 15.8; MedCalc Software bvba, Acaciaaan, Belgium).

Results

Baseline Characteristics

The study flow chart was shown in Figure 1. A total of 455 HCC patients receiving TACE were included in this

study, and their baseline characteristics were described in Table 1. Of the 455 patients, 109 patients (24.0%) had serum levels of ApoA-I < 1.00 g/L and 89 patients (19.6%) had serum levels of ApoB > 1.10 g/L. ApoB and ApoA-I were significantly positively correlated with LDL-C ($r = 0.73$, $p < 0.001$) and HDL-C ($r = 0.79$, $p < 0.001$), respectively (Fig. 2).

Association of ApoB/ApoA-I Ratio with Clinicopathological Variables of HCC Patients

As shown in Figure 3, patients with AFP ≥ 400 ng/mL, T3–4, with distant metastasis or TNM III–IV had significantly higher serum ApoB/ApoA-I levels than those with AFP < 400 ng/mL (1.09 ± 0.13 vs. 0.69 ± 0.02 , $p < 0.001$), T1–2 (0.99 ± 0.08 vs. 0.61 ± 0.03 , $p = 0.002$), without metastasis (1.43 ± 0.46 vs. 0.83 ± 0.052 , $p = 0.008$) or TNM I–II (0.98 ± 0.08 vs. 0.60 ± 0.03 , $p = 0.003$).

We further explored the relationship between ApoB/ApoA-I and clinicopathological factors. The optimal cut-off values of ApoB/ApoA-I and LDL-C/HDL-C identified by receiver operating characteristic curve were 0.56 and 4.00, respectively; the area under the curve values were 0.576 (95% confidence interval [CI]: 0.530–0.620; $p = 0.007$) for ApoB/ApoA-I and 0.562 (95% CI: 0.520–0.610; $p = 0.023$) for LDL-C/HDL-C. Thus, we defined as high (> 0.56) or low (≤ 0.56) level for ApoB/ApoA-I and high (> 4.00) or low (≤ 4.00) level for LDL-C/HDL-C. According to this criterium, 280 (61.5%) patients were clas-

Table 1. Baseline characteristics and correlation analysis of 455 HCC patients treated with TACE

Variable	Total, <i>n</i> (%)	ApoB/ApoA-I low, <i>n</i> (%)	ApoB/ApoA-I high, <i>n</i> (%)	<i>p</i> value
Total	455 (100.0)	175 (38.5)	280 (61.5)	
Age, years				
>52	227 (49.9)	93 (53.1)	134 (47.9)	0.273
≤52	228 (50.1)	82 (46.9)	146 (52.1)	
Gender				
Male	416 (91.4)	153 (87.4)	263 (93.9)	0.016
Female	39 (8.6)	22 (12.6)	17 (6.1)	
ECOG PS				
0	316 (69.5)	121 (69.1)	195 (69.6)	0.991
1	87 (19.1)	34 (19.4)	53 (18.9)	
2	52 (11.4)	20 (11.5)	32 (11.5)	
Ascites				
Yes	87 (19.1)	35 (20.0)	52 (18.6)	0.706
No	368 (80.9)	140 (80.0)	228 (81.4)	
Cirrhosis				
Yes	351 (77.1)	143 (81.7)	208 (74.3)	0.066
No	104 (22.9)	32 (18.3)	72 (25.7)	
PVTT				
Yes	153 (33.6)	41 (23.4)	112 (40.0)	<0.001
No	302 (66.4)	134 (76.6)	168 (60.0)	
Child-Pugh grade				
A	352 (77.4)	136 (77.7)	216 (77.1)	0.990
B	95 (20.9)	36 (20.6)	59 (20.1)	
C	8 (1.7)	3 (1.7)	5 (1.8)	
Laboratory parameters				
ALB, g/L				
>36	301 (66.2)	119 (68.0)	182 (65.0)	0.511
≤36	154 (33.8)	56 (32.0)	98 (35.0)	
AST, U/L				
>35	315 (69.2)	114 (65.1)	201 (71.8)	0.135
≤35	140 (30.8)	61 (34.9)	79 (28.2)	
ALP, U/L				
>200	57 (12.5)	15 (8.6)	42 (15.0)	0.044
≤200	398 (87.5)	160 (91.4)	238 (85.0)	
GGT, U/L				
>60	337 (74.1)	117 (66.9)	220 (78.6)	0.006
≤60	118 (25.9)	58 (33.1)	60 (21.4)	
AFP, ng/mL				
≥400	199 (43.7)	58 (33.1)	141 (50.4)	<0.001
<400	256 (56.3)	117 (66.9)	139 (49.6)	
TC, mmol/L				
>5.70	72 (15.8)	6 (3.4)	66 (23.6)	<0.001
≤5.70	383 (84.2)	169 (96.6)	214 (76.4)	
TG, mmol/L				
>1.92	31 (6.8)	0 (0.0)	31 (11.1)	<0.001
≤1.92	424 (93.2)	175 (100.0)	249 (88.9)	
HDL-C, mmol/L				
≥0.78	380 (83.5)	170 (97.1)	210 (75.0)	<0.001
<0.78	75 (16.5)	5 (2.9)	70 (25.0)	
LDL-C, mmol/L				
>3.40	123 (27.0)	13 (7.4)	110 (39.3)	<0.001
≤3.40	332 (73.0)	162 (92.6)	170 (60.7)	
ApoA-I, g/L				
≥1.00	346 (76.0)	165 (94.3)	181 (64.6)	<0.001
<1.00	109 (24.0)	10 (5.7)	99 (35.4)	
ApoB, g/L				
>1.10	89 (19.6)	0 (0.0)	89 (31.8)	<0.001
≤1.10	366 (80.4)	175 (100.0)	191 (68.2)	
Lp(a), mg/L				
>300	37 (8.1)	8 (4.6)	29 (10.4)	0.028
≤300	418 (91.9)	167 (95.4)	251 (89.6)	

Table 1 (continued)

Variable	Total, <i>n</i> (%)	ApoB/ApoA-I low, <i>n</i> (%)	ApoB/ApoA-I high, <i>n</i> (%)	<i>p</i> value
LDL-C/HDL-C				
>4.00	94 (20.7)	1 (0.6)	93 (33.2)	<0.001
≤4.00	361 (79.3)	174 (99.4)	187 (66.8)	
TNM stage				
I	43 (9.5)	28 (16.0)	15 (5.4)	<0.001
II	95 (20.9)	56 (32.0)	39 (13.9)	
III	206 (45.3)	72 (41.1)	134 (47.9)	
IV	111 (24.3)	19 (10.9)	92 (32.8)	
T category				
T1	43 (9.5)	28 (16.0)	15 (5.4)	<0.001
T2	101 (22.2)	59 (33.7)	42 (15.0)	
T3	113 (24.8)	31 (17.7)	82 (29.3)	
T4	198 (43.5)	57 (32.6)	141 (50.3)	
N category				
N0	359 (78.9)	160 (91.4)	199 (71.1)	<0.001
N1	96 (21.1)	15 (8.6)	81 (28.9)	
M category				
M0	423 (93.0)	169 (96.6)	254 (90.7)	0.017
M1	32 (7.0)	6 (3.4)	26 (9.3)	

HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombus; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio; TNM, tumor-node-metastasis.

Fig. 2. Correlations between serum apolipoprotein levels and serum lipoprotein levels in 455 HCC patients' cohort. ApoB was significantly positively correlated with LDL-C ($r = 0.731$, $p < 0.001$) (a); ApoA-I was significantly positively correlated with HDL-C ($r = 0.793$, $p < 0.001$) (b). HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B.

sified as high ApoB/ApoA-I group, while 175 (38.5%) patients were low ApoB/ApoA-I group. High ApoB/ApoA-I was significantly associated with male ($p = 0.016$), PVTT ($p < 0.001$), higher AFP ($p < 0.001$), higher GGT ($p = 0.006$), advanced T stage ($p < 0.001$), lymph node metastasis ($p < 0.001$), distant metastasis ($p = 0.017$), and advanced TNM stage ($p < 0.001$) in the 455 HCC patients (Table 1).

Univariate Analysis and Multivariate Analysis

The median OS of all 455 patients was 22.6 months (interquartile range: 9.2–49.9 months) in our study. Kaplan-Meier curves analysis revealed that low ApoA-I ($p < 0.001$), high ApoB/ApoA-I ($p < 0.001$), high HDL-C ($p = 0.002$), high LDL-C/HDL-C ($p < 0.001$), PVTT ($p < 0.001$), high AST ($p = 0.002$), low ALB ($p = 0.027$), high ALP ($p = 0.006$), high GGT ($p = 0.004$), high AFP ($p =$

Fig. 3. Distribution of the serum ApoB/ApoA-I levels in different clinicopathological factors. AFP <400 versus AFP $\geq$ 400 ng/mL (**a**); PVTT (without vs. with) (**b**); T stage (T1–2 vs. T3–4) (**c**); lymph nodal metastasis (without vs. with) (**d**); distant metastasis (without vs. with) (**e**); TNM (I–II vs. III–IV) (**f**). ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; PVTT, portal vein tumor thrombus; TNM, tumor-node-metastasis; AFP, alpha fetoprotein.

0.010), advanced T stage ($p < 0.001$), distant metastasis ($p < 0.001$), and advanced TNM stage ($p < 0.001$) all predicted inferior OS (Fig. 4; Table 2). In multivariate analysis, we found ApoB/ApoA-I was an independent prognostic factor for OS (hazard ratio [HR]: 1.420; 95% CI: 1.100–1.840, $p = 0.008$). Meanwhile, PVTT (HR: 1.490, 95% CI: 1.150–1.930, $p = 0.003$), ALB (HR: 0.740, 95% CI: 0.580–0.940, $p = 0.014$), T stage (HR: 0.640, 95% CI: 1.200–2.250, $p = 0.002$), and distant metastasis (HR: 1.780, 95% CI: 1.180–2.690, $p = 0.007$) were also independent prognostic factors in 455 HCC patients receiving TACE (Table 2).

Using the PSM method, 288 of 455 patients' baseline characteristics, including age, gender, the Eastern Cooperative Oncology Group performance status, liver function, PVTT, tumor size, lymph node metastasis, distant metastasis, and TNM stage were well balanced and included in the PSM cohort (Table 3). In this cohort, both high ApoB/ApoA-I and high LDL-C/HDL-C were negative prognostic factors (median OS in high ApoB/ApoA-I patients: 27.6 months vs. median OS in low ApoB/ApoA-I patients: 39.3 months, $p = 0.002$; median OS in high LDL-C/HDL-C patients: 12.4 months vs. median OS in low LDL-C/HDL-C patients: 32.5

Fig. 4. Prognostic value of the serum ApoB/ApoA-I of 455 HCC patients treated with TACE. OS rates were stratified by different features of 455 HCC patients treated with TACE, including gender (a), age (b), ECOG PS (c), PVTT (d), ascites (e), ALB (f), ALP (g), GGT (h), AFP (i), AST (j), TC (k), TG (l), HDL-C (m), LDL-C (n), LP (a) (o), LDL-C/HDL-C (p), ApoB (q), ApoA-I (r), ApoB/ApoA-I (s), T category (t), N category (u), M category (v), TNM (w), and Child-Pugh (x). HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Co-

operative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; OSs, overall survivals; PVTT, portal vein tumor thrombus; OSs, overall survivals; PVTT, portal vein tumor thrombus; OSs, overall survivals; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio.

months, $p < 0.001$). Besides, PVTT ($p < 0.001$), AST ($p = 0.008$), ALB ($p = 0.025$), GGT ($p = 0.030$), TNM stage ($p < 0.001$), T category ($p < 0.001$), distant metastasis ($p < 0.001$), HDL-C ($p < 0.001$), LDL-C ($p = 0.047$), and ApoA-I ($p < 0.001$) were also prognostic factors for OS in univariate analysis (Fig. 5; Table 4). In multivariate analysis, ApoB/ApoA-I (HR: 1.580, 95% CI: 1.140–2.190; $p = 0.006$), LDL-C/HDL-C (HR: 4.010, 95% CI:

2.460–6.540, $p < 0.001$), LDL-C (HR: 0.370, 95% CI: 0.230–0.600, $p < 0.001$), ALB (HR: 0.690, 95% CI: 0.500–0.940, $p = 0.021$), T stage (HR: 2.330, 95% CI: 1.680–3.230, $p < 0.001$), and distant metastasis (HR: 6.430, 95% CI: 3.260–12.660, $p < 0.001$) were identified as independent predictors for OS in the PSM cohort (Table 4).

Table 2. Univariate and multivariate analyses of the prognostic factors for survival in 455 HCC patients treated with TACE

Variable	Univariate		Multivariate				
	log-rank χ^2	<i>p</i> value	<i>B</i>	SE	HR	95% CI	<i>p</i> value
Age, years (>52/≤52)	0.51	0.478					
Gender (male/female)	0.06	0.812					
ECOG PS (0/1/2)	0.54	0.461					
PVTT (yes/no)	34.59	<0.001*	0.40	0.13	1.49	1.15–1.93	0.003
Ascites (yes/no)	0.30	0.585					
Child-Pugh grade (A/B/C)	0.66	0.718					
Laboratory parameters							
AST (>35/≤35), U/L	9.73	0.002*					
ALB (>36/≤36), g/L	4.90	0.027*	−0.30	0.12	0.74	0.58–0.94	0.014
ALP (>200/≤200), U/L	7.45	0.006*					
GGT (>60/≤60), U/L	8.17	0.004*					
AFP (≥400/<400), ng/mL	6.61	0.010*					
TNM (I–II/III–IV)	27.34	<0.001*					
T category (T1–2/T3–4)	41.59	<0.001*	0.50	0.16	1.64	1.20–2.25	0.002
N category (N0/N1)	2.76	0.097					
M category (M0/M1)	20.74	<0.001*	0.58	0.21	1.78	1.18–2.69	0.007
Serum lipids							
TC (≤5.70/>5.70), mmol/L	0.02	0.892					
TG (≤1.92/>1.92), mmol/L	0.12	0.725					
HDL-C (<0.78/≥0.78), mmol/L	9.30	0.002*					
LDL-C (≤3.40/>3.40), mmol/L	0.01	0.970					
ApoA-I (<1.00/≥1.00), ng/L	12.43	<0.001*					
ApoB (≤1.10/>1.10), ng/L	0.25	0.621					
Lp(a) (≤300/>300)	0.97	0.324					
LDL-C/HDL-C (≤4.00/>4.00)	16.40	<0.001*					
ApoB/ApoA-I (≤0.56/>0.56)	9.74	<0.001*	0.35	0.13	1.42	1.10–1.84	0.008

HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombus; TG, triglyceride; TC, cholesterol HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval. * Variables with *p* value <0.05 were entered into multivariate analyses.

Discussion

In the present study, we found that higher serum ApoB/ApoA-I was significantly associated with higher AFP levels, advanced TNM stages, and distant metastasis in HCC patients who received TACE. High ApoB/ApoA-I independently predicted shorter OS. Importantly, after baseline characteristics were balanced using the PSM method, ApoB/ApoA-I was still an independent prognostic factor for OS in HCC patients receiving TACE.

In recent years, several studies have found that ApoB/ApoA-I is associated with aggressive clinicopathological characteristics of several types of tumors. For example, colorectal cancer patients with higher ApoB/ApoA-I levels are prone to lymph node metastasis and tumor necrosis [33]. A higher level of ApoB/ApoA-I is related to a

poor differentiation in GC patients [28]. Moreover, high Fuhrman grade renal cancer patients tend to have higher ApoB/ApoA-I levels [29]. Consistent with the clinicopathological effects of ApoB/ApoA-I in other solid tumors, our results showed that high ApoB/ApoA-I was correlated with high AFP levels, advanced TNM stage, and distant metastasis, suggesting ApoB/ApoA-I is a useful predictor for poor clinical features in HCC patients.

The prognostic value of ApoB/ApoA-I has also been explored in several types of cancers. In a retrospective study including 1,204 GC patients, elevated ApoB/ApoA-I is associated with worse OS and can serve as a novel independent prognostic factor [28]. In renal cancer, high ApoB/ApoA-I predicts shorter progression-free survival [29]. As two apolipoproteins mainly metabolized in the liver, decreased ApoA-I alone and elevated ApoB level alone have

Table 3. Baseline characteristics and correlation analysis of 288 HCC patients in the PSM cohort

Variable	Total, %	ApoB/ApoA-I low, <i>n</i> (%)	ApoB/ApoA-I high, <i>n</i> (%)	<i>p</i> value
Total	288 (100.0)	144 (50.0)	144 (50.0)	
Age, years				
>52	153 (53.1)	78 (54.2)	75 (52.1)	0.723
≤52	135 (46.9)	66 (45.8)	69 (47.9)	
Gender				
Male	265 (92.0)	132 (91.7)	133 (92.4)	0.828
Female	23 (8.0)	12 (8.3)	11 (7.6)	
ECOG PS				
0	199 (69.1)	101 (70.1)	98 (68.1)	0.866
1	52 (18.1)	26 (18.1)	26 (18.1)	
2	37 (12.8)	17 (11.8)	20 (13.8)	
Ascites				
Yes	59 (20.5)	28 (19.4)	31 (21.5)	0.661
No	229 (79.5)	116 (80.6)	113 (78.5)	
Cirrhosis				
Yes	229 (79.5)	114 (79.2)	115 (79.9)	0.884
No	59 (20.5)	30 (20.8)	29 (20.1)	
PVTT				
Yes	72 (25.0)	37 (25.7)	35 (24.3)	0.785
No	216 (75.0)	107 (74.3)	109 (75.7)	
Child-Pugh grade				
A	221 (76.7)	112 (77.8)	109 (75.7)	0.910
B	61 (21.2)	29 (20.1)	32 (22.2)	
C	6 (2.1)	3 (2.1)	3 (2.1)	
Laboratory parameters				
ALB, g/L				
>36	191 (66.3)	98 (68.1)	93 (64.6)	0.533
≤36	97 (33.7)	46 (31.9)	51 (35.4)	
AST, U/L				
>35	196 (68.1)	96 (66.7)	100 (69.4)	0.613
≤35	92 (31.9)	48 (33.3)	44 (30.6)	
ALP, U/L				
>200	30 (10.4)	15 (10.4)	15 (10.4)	1.000
≤200	258 (89.6)	129 (89.6)	129 (89.6)	
GGT, U/L				
>60	206 (71.5)	106 (73.6)	100 (69.4)	0.433
≤60	82 (28.5)	38 (26.4)	44 (30.6)	
AFP, ng/mL				
≥400	100 (34.7)	53 (36.8)	47 (32.6)	0.458
<400	188 (65.3)	91 (63.2)	97 (67.4)	
TC, mmol/L				
>5.70	36 (12.5)	6 (4.2)	30 (20.8)	<0.001
≤5.70	252 (87.5)	138 (95.8)	114 (79.2)	
TG, mmol/L				
>1.92	18 (6.2)	0 (0.0)	18 (12.5)	<0.001
≤1.92	270 (93.8)	144 (100.0)	126 (87.5)	
HDL, mmol/L				
≥0.78	252 (87.5)	140 (97.2)	112 (77.8)	<0.001
<0.78	36 (12.5)	4 (2.8)	32 (22.2)	
LDL, mmol/L				
>3.40	53 (18.4)	11 (7.6)	42 (29.2)	<0.001
≤3.40	235 (81.6)	133 (92.4)	102 (70.8)	
ApoA-I, g/L				
≥1.00	234 (81.3)	135 (93.8)	99 (68.8)	<0.001
<1.00	54 (18.7)	9 (6.2)	45 (31.2)	
ApoB, g/L				
>1.10	47 (16.3)	0 (0.0)	47 (32.6)	<0.001
≤1.10	241 (83.7)	144 (100.0)	97 (67.4)	

Table 3 (continued)

Variable	Total, %	ApoB/ApoA-I low, <i>n</i> (%)	ApoB/ApoA-I high, <i>n</i> (%)	<i>p</i> value
Lp(a), mg/L				
>300	22 (7.6)	6 (4.2)	16 (11.1)	0.027
≤300	266 (92.4)	138 (95.8)	128 (88.9)	
LDL-C/HDL-C				
>4.00	35 (12.2)	0 (0.0)	35 (24.3)	<0.001
≤4.00	253 (87.8)	144 (100.0)	109 (75.7)	
TNM stage				
I	30 (10.4)	15 (10.4)	15 (10.4)	0.881
II	80 (27.8)	43 (29.9)	37 (25.7)	
III	138 (47.9)	67 (46.5)	71 (49.3)	
IV	40 (13.9)	19 (13.2)	21 (14.6)	
T category				
T1	30 (10.4)	15 (10.4)	15 (10.4)	0.499
T2	86 (29.9)	46 (31.9)	40 (27.8)	
T3	71 (24.7)	30 (20.8)	41 (28.5)	
T4	101 (35.0)	53 (36.9)	48 (33.3)	
N category				
N0	257 (89.2)	129 (89.6)	128 (88.9)	0.849
N1	31 (10.8)	15 (10.4)	16 (11.1)	
M category				
M0	277 (96.2)	138 (95.8)	139 (96.5)	0.759
M1	11 (3.8)	6 (4.2)	5 (3.5)	

PSM, propensity score-matched method; HCC, hepatocellular carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombus; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio; TNM, tumor-node-metastasis.

been reported to be related to poor prognosis of liver cancer [25, 26], but the prognostic value of ApoB/ApoA-I in HCC patients has not been addressed so far. In our study, the prognostic effect of ApoA-I was detected only in univariate analysis, but it could not be confirmed as an independent prognostic factor in multivariate analysis. And ApoB alone could not predict survival even in univariate analysis. However, high ApoB/ApoA-I significantly predicted inferior survival in both univariate analysis and multivariate analysis in the 455 HCC patients who received TACE. Although high ApoB/ApoA-I was associated with advanced T stage and distant metastasis, which were also independent prognostic variables, its prognostic effect was still significant in the PSM cohort, in which the potential biases were eliminated. Therefore, compared with ApoA-I or ApoB alone, ApoB/ApoA-I is a more useful prognostic factor for OS in HCC patients receiving TACE. Recently, HCC patients beyond the up-to-seven criteria have been reported to benefit from lenvatinib rather than TACE [34]. Our findings provide another biomarker to identify HCC patients who probably should avoid TACE.

Given that ApoA-I, HDL-C, ApoB and LDL-C are key components of HDL and LDL, respectively, we found

ApoA-I and ApoB were positively correlated with HDL-C and LDL-C, respectively. In our study, however, LDL-C/HDL-C was an independent prognostic index only in the PSM cohort but not in the 455 HCC patients' cohort, whereas ApoB/ApoA-I predicted poor prognosis independently not only in the 455 HCC patients but also in the PSM cohort. This suggests that ApoB/ApoA-I has a better prognostic value than LDL-C/HDL-C in HCC patients undergoing TACE. Likewise, in gastric cancer, ApoB/ApoA-I shows significant prognostic ability in both univariate and multivariate analysis, and LDL-C/HDL-C predicts poorer OS according to univariate analysis, but it is not an independent prognostic factor in multivariate analysis [28]. Similar results were also observed in cardiovascular disease [35]. The superiority of ApoB/ApoA-I to LDL-C/HDL-C in terms of predictive power might be explained by the relative stability of apolipoprotein. Each LDL particle contains only one molecule of apoB, but the LDL-C content differs in different LDL particle [36]. In addition, HDL-C is affected by change of plasma TGs more significantly than ApoA-I [37].

The exact mechanisms by which ApoA-I and ApoB influence the clinical features and prognosis of HCC re-

Fig. 5. Prognostic value of serum ApoB/ApoA-I of 288 HCC patients treated with TACE in the PSM cohort. OS was stratified by different features of 288 patients in the PSM cohort, including gender (a), age (b), ECOG PS (c), PVT (d), ascites (e), ALB (f), ALP (g), GGT (h), AFP (i), AST (j), TC (k), TG (l), HDL-C (m), LDL-C (n), LP(a) (o), LDL-C/HDL-C (p), ApoB (q), ApoA-I (r), ApoB/ApoA-I (s), T category (t), N category (u), M category (v), TNM (w), and Child-Pugh (x). HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; PSM, propensity score-

matched method; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; OS, overall survival; PVT, portal vein tumor thrombus; TNM, tumor-node-metastasis; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio.

main unclear. ApoA-I has been reported to inhibit proliferation and induce apoptosis of hematoma cells through inhibition of the mitogen-activated protein kinase pathway, suppress the formation of tumor blood vessels, and induce the antitumor immune microenvironment in liver cancer patients [23–25]. Compared to ApoA-I, the mechanism of ApoB has been less explored in cancer. However, elevated ApoB/ApoA-I has been identified as an early independent predictor for insulin resistance [38,

39]. Considering that insulin resistance is an important factor to promote liver cancer formation [40], it might also be a possible mechanism of the impact of ApoB/ApoA-I on the biological behavior and prognosis of HCC. In addition, it has been reported that lipid metabolism regulates chronic inflammation [41, 42], which is associated with development and progression of HCC [43, 44]. ApoB induces the production of proinflammatory factors and enhance inflammatory response [45], while ApoA-I

Table 4. Univariate and multivariate analyses of the prognostic factors for OS in 288 HCC patients treated with TACE in the PSM cohort

Variable	Univariate		Multivariate				
	log-rank χ^2	<i>p</i> value	<i>B</i>	SE	HR	95% CI	<i>p</i> value
Age, years (>52/≤52)	1.23	0.267					
Gender (male/female)	0.02	0.890					
ECOG PS (0/1/2)	1.58	0.208					
PVTT (yes/no)	13.83	<0.001*					
Ascites (yes/no)	0.43	0.513					
Child-Pugh grade (A/B/C)	3.01	0.224					
Laboratory parameters							
AST (>35/≤35), U/L	6.98	0.008*					
ALB (>36/≤36), g/L	5.06	0.025*	−0.38	0.16	0.69	0.50–0.94	0.021
ALP (>200/≤200), U/L	1.86	0.173					
GGT (>60/≤60), U/L	4.69	0.030*					
AFP (≥400/<400), ng/mL	0.47	0.495					
TNM (I–II/III–IV)	17.13	<0.001*					
T category (T1–2/T3–4)	23.34	<0.001*	0.85	0.17	2.33	1.68–3.23	<0.001
N category (N0/N1)	0.08	0.772					
M category (M0/M1)	24.36	<0.001*	1.86	0.35	6.43	3.26–12.66	<0.001
Serum lipids							
TC (≤5.70/>5.70), mmol/L	2.03	0.154					
TG (≤1.92/>1.92), mmol/L	0.14	0.706					
HDL-C (<0.78/≥0.78), mmol/L	20.42	<0.001*					
LDL-C (≤3.40/>3.40), mmol/L	3.95	0.047*	−1.00	0.25	0.37	0.23–0.60	<0.001
ApoA-I (<1.00/≥1.00), ng/L	12.40	<0.001*					
ApoB (≤1.10/>1.10), ng/L	0.01	0.915					
Lp(a) (≤300/>300)	0.92	0.338					
LDL-C/HDL-C (≤4.00/>4.00)	19.18	<0.001*	1.39	0.25	4.01	2.46–6.54	<0.001
ApoB/ApoA-I (≤0.56/>0.56)	9.74	0.002*	0.46	0.17	1.58	1.14–2.19	0.006

HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; PSM, propensity score-matched method; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, glutamyl transpeptidase; ALB, albumin; AST, aspartate transaminase; ALP, alkaline phosphatase; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombus; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; LDL-C/HDL-C, LDL-C to HDL-C ratio; ApoB/ApoA-I, ApoB to ApoA-I ratio; TNM, tumor-node-metastasis; OS, overall survival; HR, hazard ratio; CI, confidence interval. * Variables with *p* value < 0.05 were entered into multivariate analyses.

inhibits the production of various inflammatory cytokines and thus suppresses inflammation [46]. Therefore, the pro-inflammatory property of ApoB and anti-inflammatory role of ApoA-I may be another mechanism of high ApoB/ApoA-I predicting poor clinical features and outcome in HCC.

Conclusion

In conclusion, our study demonstrated that serum ApoB/ApoA-I was correlated with aggressive clinicopathological features and poor clinical outcome in HCC patients treated with TACE. After eliminating the potential bias in PSM analysis, Cox regression multivariate analysis confirmed that ApoB/ApoA-I was an indepen-

dent prognostic factor in HCC. Considering that serum ApoB and ApoA-I levels have been able to be measured using commercially available kits as a routine clinical liver function test, ApoB/ApoA-I will be used as a convenient, economical, and useful biomarker for refining the risk stratification in HCC patients receiving TACE, which might be of great benefit for individualized treatments in advanced HCC patients.

Statement of Ethics

Ethical guidelines under the Declaration of Helsinki were followed. The procedure of our study was approved by the Institute Research Ethics Committee of Sun Yat-sen University (No. [2015] 2-46). Written informed consent was obtained from all patients prior to TACE.

Conflict of Interest Statement

The authors have declared that no conflicts of interest exist.

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Author Contributions

Min Dong, Li Wei, and Zhan-Hong Chen conceived and designed the study. Dai-Lin Rong, Xiao-Kun Ma, Dan-Yun Ruan, Jin-Xiang Lin, Jing-Jing Qi, Pei-Shan Hu, Jing-Yun Wen, Jie Chen, Qu Lin, and Xiang-Yuan Wu collected patient information. Meng-Meng Liu, Zhan-Hong Chen, Li-Yun Zhao, and Jing-Yuan Zhao analyzed the data. Meng-Meng Liu, Zhan-Hong Chen, and Min Dong wrote the paper.

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