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Impact of Serum Apolipoprotein A-I on Prognosis and Bevacizumab Efficacy in Patients with Metastatic Colorectal Cancer: a Propensity Score-Matched Analysis[1]

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Abstract

PURPOSE: We aimed to investigate the role of apolipoprotein A-I (ApoA-I) as a predictor of prognosis and treatment efficacy of bevacizumab in patients with metastatic colorectal cancer (mCRC) treated with first-line chemotherapy with or without bevacizumab. *METHODS:* We conducted a retrospective study on consecutive patients who were diagnosed with mCRC at Sun Yat-sen University Cancer Center. According to their pretreatment ApoA-I level, patients were divided into low– and high–ApoA-I groups. Propensity score-matched method was performed to balance baseline characteristics between two groups. Based on whether they accepted bevacizumab as a first-line therapy, patients were further divided into the chemo + bevacizumab group and the chemo group. Overall survival (OS) and progression-free survival (PFS) were assessed with Kaplan-Meier method, log-rank test, and Cox regression. *RESULTS:* The optimal cutoff value for the ApoA-I level was determined to be 1.105 g/l. In the propensity-matched cohort of 508 patients, low ApoA-I was significantly associated with inferior OS ($P < .001$) and PFS ($P < .001$) than high ApoA-I. Multivariate analysis showed that ApoA-I level was an independent prognostic maker of OS ($P < .001$) and PFS ($P = .001$). PFS ($P < .001$) in either the high– or low–ApoA-I groups could be extended significantly after the administration of bevacizumab, and patients with a high ApoA-I level also had a better OS in the chemo + bevacizumab group than the chemo group ($P = .049$). *CONCLUSIONS:* Patients with a low ApoA-I level have poor prognoses, and they did not display an OS benefit from bevacizumab.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, resulting in over 690,000 deaths annually. Approximately 25% of patients present with synchronous metastases at the time of diagnosis. Surgical resection is the mainstay curative treatment modality for early-stage colorectal cancer; however, approximately 20% to 45% patients develop metastasis and/or recurrent disease [1]. The use of bevacizumab combined with fluoropyrimidine-based chemotherapy is considered standard first- and second-line treatment for patients with metastatic colorectal cancer (mCRC) [2]. Although several studies have investigated this issue in recent years, no validated predictors of the response and efficacy to antiangiogenic treatment have been identified [3,4].

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As a major protein constituent of high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (ApoA-I) is synthesized in the liver and the small intestine. ApoA-I plays a key role in reverse cholesterol transport by transferring cholesterol and phospholipids from peripheral organs to the liver for excretion. ApoA-I also functions as a cofactor of lecithin cholesterol acyltransferase and participates in the conversion of cholesterol to cholesteryl ester [5,6]. As recently reported, ApoA-I is related to the generation, progression, and prognosis of cancer. ApoA-I has been identified as a potentially useful biomarker for effectively distinguishing cholangiocarcinoma from benign biliary disease and improving the early diagnosis of ovarian cancer [7,8]. Moreover, decreased serum ApoA-I has been shown to be correlated with worse overall survival in lung cancer and metastatic nasopharyngeal carcinoma [9,10]. The role of ApoA-I in patients with mCRC has not yet been reported. We aimed to investigate the role of pretreatment ApoA-I levels as predictors of prognosis and the treatment efficacy of bevacizumab in patients with mCRC treated with first-line chemotherapy with or without bevacizumab.

Patients and Methods

Ethics Statement

The study complied with the standards of the Declaration of Helsinki and was approved by the Research Ethics Committee at the Cancer Center of Sun Yat-sen University. Written informed consent was obtained from each patient.

Patient Selection

This study enrolled 721 patients pathologically diagnosed with mCRC from January 2005 to December 2013 at the Sun Yat-Sen University Cancer Center in Guangzhou, Guangdong, China. Cases were included if they met the following criteria: 1) cytological or histological diagnosis of mCRC, 2) Eastern Cooperative Oncology Group performance status ≤2, 3) complete medical record and follow-up information, and 4) receipt of at least four cycles of treatment of first-line chemotherapy. Patients were excluded if they met the following criteria: 1) they received cetuximab as first-line therapy, or 2) they suffered from other types of malignant tumor or acute illnesses, including stroke, acute infection, surgery, or trauma. Moreover, the propensity score match method was used to adjust for uneven clinical features of high– and low–ApoA-I groups.

Clinical data collection

The clinical data contained the following information: patient demographics, weight, height, serum carcinoembryonic antigen (CEA), serum lipids and lipoproteins (total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol [LDL-C], ApoA-I, and apolipoprotein-B [ApoB]), or computed tomography or magnetic resonance scans or positron emission tomography/computed tomography of the full body. The levels of lipids and lipoproteins in the fasting state were determined by an automatic biochemical analyzer. As no pellucid marginal value for serum lipids or lipoproteins was found to be associated with malignancy outcome, we analyzed the receiver operating characteristic (ROC) curve to provide an optimal critical value for ApoA-I and ApoB. According to the National Cholesterol and Education Program Adult Treatment Panel III criteria, a total cholesterol serum concentration ≥ 200 mg, a triglyceride serum concentration ≥ 150 mg/dl, an HDL-C serum concentration < 40 mg/dl, and an LDL-C serum concentration ≥ 130 mg/dl are defined as hypercholesterolemia, hypertriglyceridemia, categorical low HDL-C, and high LDL-C, respectively [11]. Written informed consent was obtained from each of the patients.

Patient Follow-Up and Statistical Analysis

Tumor responses were assessed by RECIST 1.1 criteria every 6 to 8 weeks. Overall survival (OS) was defined as the interval between the diagnosis date and the time of death for any reason or last follow-up. Propensity score match analysis was performed using R software version 2.15.0 (R Project for Statistical Computing, Vienna, Austria) via one-to-one matching to ensure even distributions. Progression-free survival (PFS) after first-line chemotherapy was defined as the time from the initiation of first-line chemotherapy to disease progression or death. Statistical analyses were conducted using SPSS standard version 22.0 (IBM Corporation, Armonk, NY) for Windows. Categorical characteristics were compared by the chi-square test. Survival curves were analyzed by the Kaplan-Meier method, and the log-rank test was used to compare differences

Table 1. Baseline Characteristics of Patients by Serum ApoA-I Level

Characteristics	Low–ApoA-I Group, *n*	High–ApoA-I Group, *n*	*P* Value
No. of cases			
Age at diagnosis (years)			.786
≤60	149	153	
>60	105	101	
Gender			.845
Male	179	182	
Female	75	72	
Primary tumor site			.537
Right	66	59	
Left	188	195	
Synchronous metastases			.824
Yes	205	201	
No	49	52	
No of metastatic organs			.759
1	188	192	
≥2	66	62	
Primary tumor resection			1.000
Yes	157	158	
No	97	96	
CEA (ng/ml)			.467
≤5	57	65	
>5	197	189	
First-line therapy			.679
Chemo alone	195	190	
Chemo + bevacizumab	59	64	
First-line chemotherapy regimen			.102
Oxaliplatin/irinotecan-containing	228	239	
5-FU alone	26	15	
Cholesterol (mg/dl)			**.001**
≥200	102	140	
<200	152	114	
Triglyceride (mg/dl)			.742
≥150	50	54	
<150	204	200	
HDL-C (mg/dl)			**<.001**
<40	167	216	
≥40	87	38	
LDL-C > 2.75 (mg/dl)			.790
≥130	127	123	
<130	127	131	
ApoB (g/l)			.541
>1.170	68	61	
≤1.170	186	193	

between groups. The multivariate Cox regression model was used to evaluate independent predictive factors associated with survival difference. A two-tailed P value < .05 was considered statistically significant.

Results

Patient Characteristics

A total of 721 eligible patients were included the study. As shown in the Attached Table, several clinical features including gender, synchronous metastases, number of metastatic organs, and primary tumor resection between high– and low–ApoA-I groups are uneven. After adjusting for these features, a total of 508 patients was retained. The clinical baseline features of the 508 cases are listed in Table 1. The median age at diagnosis was 57 years (range, 18-78 years), and 71.0% of the patients were male. A total of 406 (79.9%) patients presented with synchronous metastases. The majority of the patients (75.9%) exhibited increased CEA. A total of 128 patients (25.2%) had two or more metastatic organs. A total of 125 (24.6%) and 383 (75.4%) patients presented with primary right and left locations, respectively. Chemo + bevacizumab was administered to 123 (24.2%) patients, with chemo alone being administered to the remaining 385 (75.8%) patients. As for the chemo treatments, 467 (91.9%) patients received oxaliplatin/irinotecan-containing regimens. The majority of the patients (62.0%) had received primary tumor resection.

Correlation between Serum ApoA-I and Clinical Features

The median serum ApoA-I level (range) was 1.105 (0.38-2.00 g/l). The optimal cutoff value for serum ApoA-I was 1.105 g/l based on the ROC analysis results (area under the curve: 0.594, 95% confidence interval [CI]: 0.552-0.636, P < .001) (Figure 1). All patients were divided into two groups based on the 1.105 g/l ApoA-I level. As shown in Table 1, 254 patients were categorized into the high–ApoA-I group, of which 64 patients received bevacizumab plus chemo and 190 patients received chemo alone. Among all the 254 patients in the low–ApoA-I group, 59 patients received bevacizumab plus chemo, and 195 patients received chemo alone. The optimal cutoff value for ApoB was 1.170 g/l. Patients in the low–ApoA-I group tended to show a higher rate of low cholesterolemia and low HDL-C levels. Patients' characteristics in the two groups were well balanced for age, primary tumor location, and treatment regimen, among other criteria.

Survival Analysis

The cutoff point for follow-up data collection was December 31, 2015, and the median follow-up duration was 46 months (range, 1-131 months). In the current study, the median OS and PFS of the first line treatment were 24.4 and 6.5 months, respectively (Figure 2, *A* and *B*). The patients from the low–ApoA-I group exhibited shorter OS (20.6 vs 28.3 months; P < .001; Figure 2*C*) and PFS (6.0 vs 6.9 months; P = .012; Figure 2*D*) than the patients in the high–ApoA-I group. As shown in Figure 3, for patients in the high–ApoA-I group, the median OS of the chemo + bevacizumab group of 40.3 months was higher than that of the chemo group of 26.8 months (P = .049; Figure 3*A*). However, for patients in the low–ApoA-I group, the median OS of chemo + bevacizumab and chemo groups was similar (22.6 vs 20.3 months; P = .197; Figure 3*B*). PFS benefits were not affected by the addition of bevacizumab in patients with either high or low ApoA-I levels.

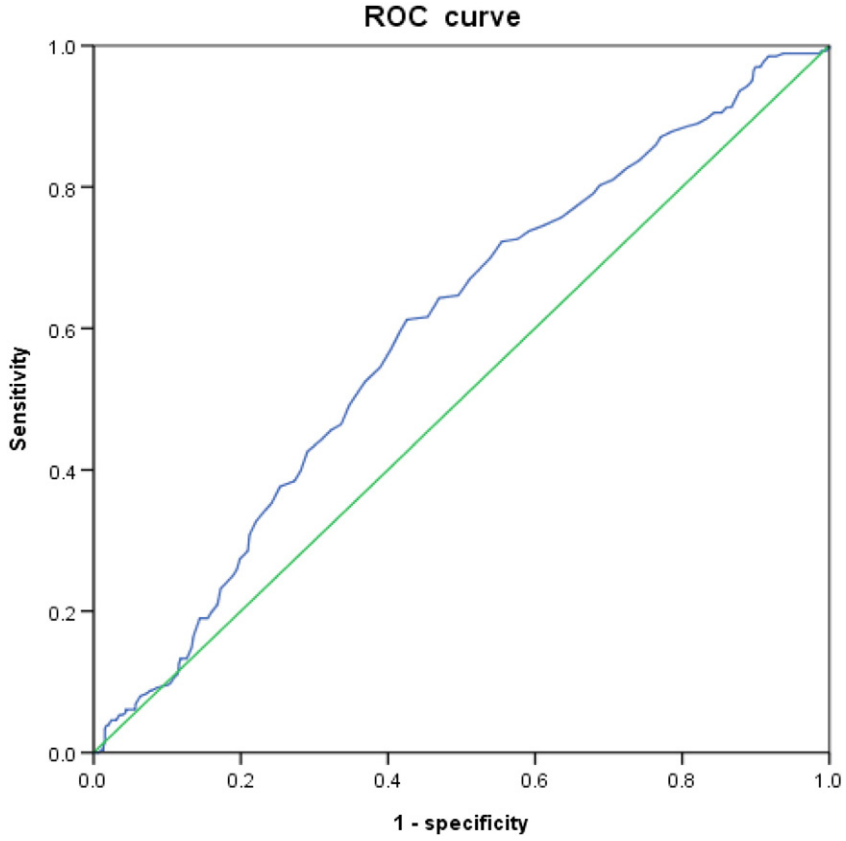

Figure 1. ROC of pretreatment ApoA-I level for outcome prediction.Notes: Area under the ROC curve: 0.594 (95% CI: 0.552-0.636). The sensitivity and specificity of the point with highest accuracy were 61.4% and 57.4%, respectively.

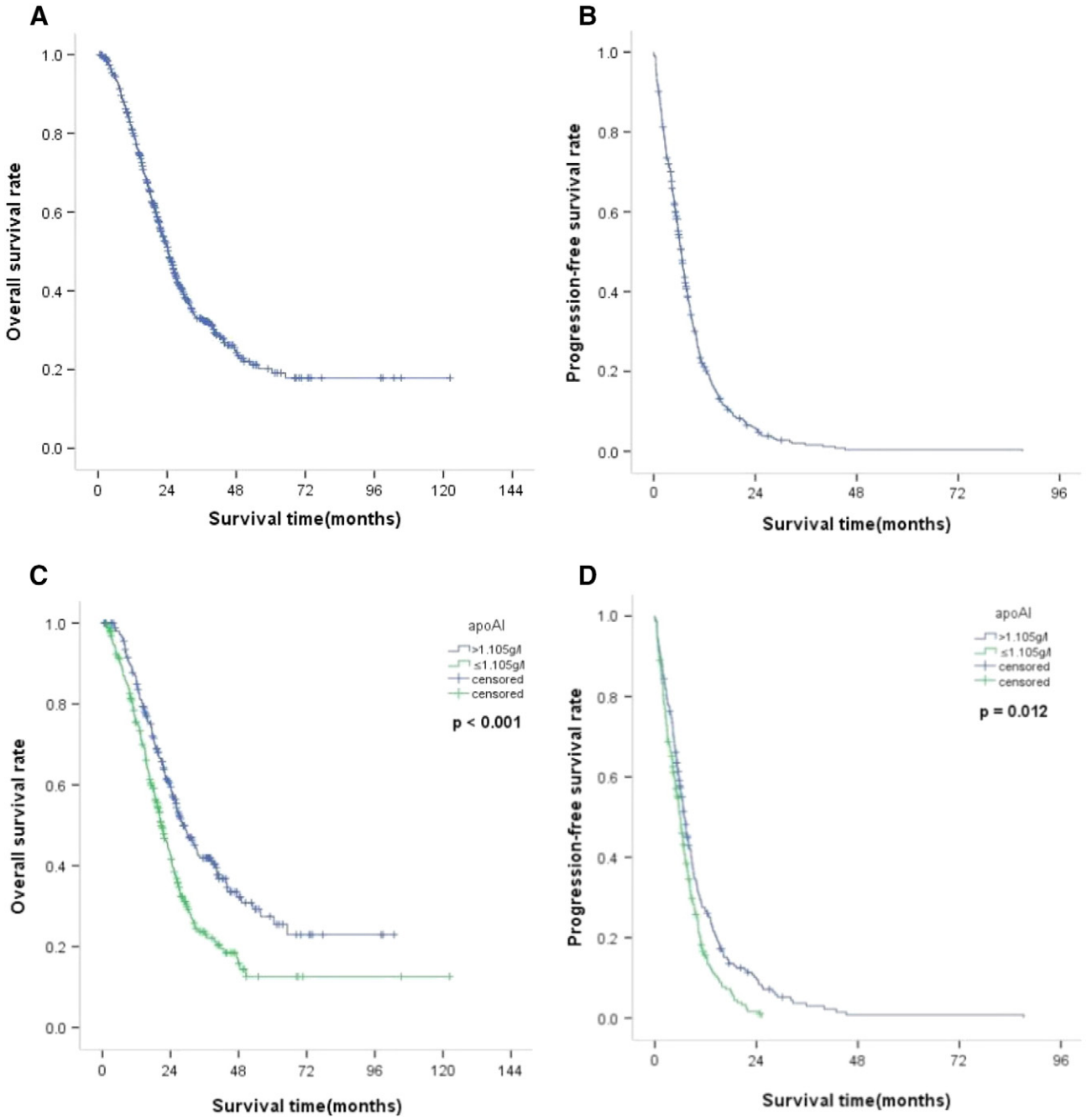

Figure 2. OS and PFS for patients with mCRC. Kaplan-Meier plots of OS (A) and PFS (B) for all patients. Kaplan-Meier plots of OS (C) and PFS (D) according to ApoA-I level (≤1.105 g/l vs >1.105 g/l).

Univariate and Multivariate Analysis

As shown in Table 2, first-line therapy (with bevacizumab) (P = .018), chemo regimen (5-FU alone; P = .011), HDL-C (P < .001), ApoA-I (P = .001), and ApoB were significantly associated with OS and PFS by univariate analyses. Synchronous metastases and primary tumor resection showed statistical significance with OS (P = .026 and P < .001, respectively) but failed to show prognostic significance for PFS. In the multivariate analyses, shown in Table 3, ApoA-I was an independent prognostic indicators of OS (relative risk: 1.636, 95% CI: 1.206-2.050, P < .001) and PFS (relative risk: 1.397, 95% CI: 1.148-1.700, P = .001). In addition, the CEA level was also considered an independent prognostic factor of OS and PFS.

Discussion

The current study showed that low level serum ApoA-I significantly correlated with inferior OS and PFS in patients with mCRC. The addition of bevacizumab to chemotherapy for patients with ApoA-I ≤ 1.105 g/l did not lead to any significant difference in OS, whereas patients with ApoA-I > 1.105 g/l gained significant OS benefit from bevacizumab.

The level of ApoA-I for prognosis in a range of malignancies has been previously investigated and has demonstrated an inverse relationship between the ApoA-I level and the length of survival time in ovarian cancer, lung cancer, and metastatic nasopharyngeal carcinoma [8–10]. To the best of our knowledge, this retrospective study is the first to describe the impact of the ApoA-I level on the

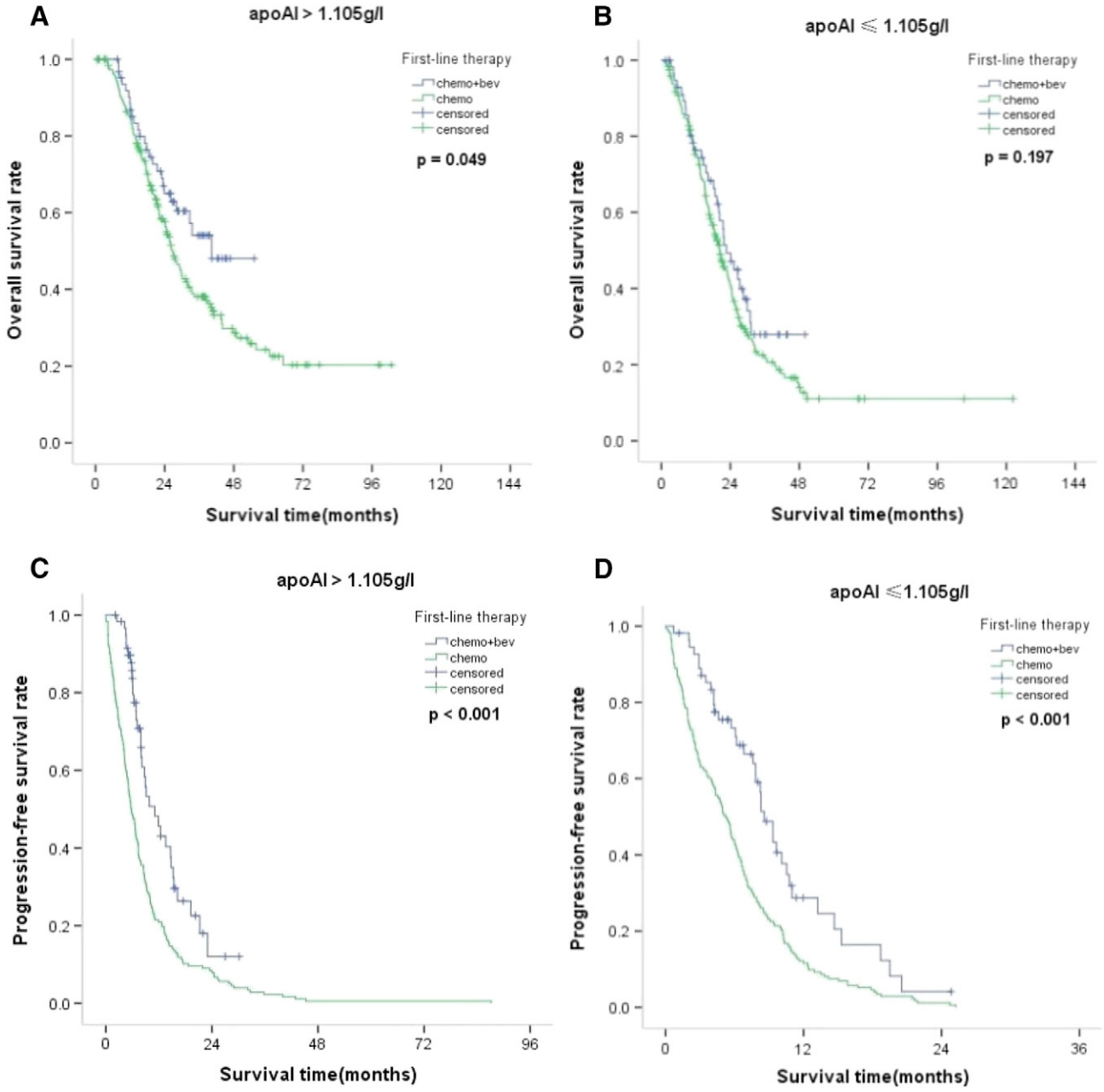

Figure 3. OS and PFS according to first-line therapy (chemo + bev versus chemo) in the subgroups. Kaplan-Meier plots of OS (A) and PFS (C) according to first-line therapy (chemo + bev versus chemo) in the subgroups of ApoA-I >1.105 g/l. Kaplan-Meier plots of OS (B) and PFS (D) according to first-line therapy (chemo + bev versus chemo) in the subgroups of ApoA-I ≤1.105 g/l. *bev*, bevacizumab.

survival of patients with mCRC. In this study, we divided patients into two groups using a cutoff value of 1.105 g/l based on the ROC curve. Regardless of the association between ApoA-I and other prognostic factors, multivariate analysis showed that baseline serum ApoA-I was a powerful predictor of OS and PFS in patients with mCRC.

We propose that the potential mechanisms of action underlying the association between low ApoA-I level and increased mortality risk of cancer patients may be due to tumor cells having an enhanced ability to grow and metastasize in patients with low ApoA-I levels. Accumulating studies have indicated that ApoA-I can powerfully inhibit tumor development through an expansive repertoire of activities including the following: 1) anti-inflammatory activity, as a common mechanism of action of the anti-inflammatory effect of ApoA-I is its ability to bind to proinflammatory phospholipids; 2) antiangiogenic activity, as ApoA-I inhibits tumor angiogenesis through inhibiting the vascular endothelial growth factor (VEGF)/basic FGF signaling pathway [12]; 3) immunoregulatory activity, as a recent study has indicated a significant immunomodulatory role for ApoA-I in the tumor microenvironment, altering tumor-associated macrophages from a protumor phenotype to an antitumor phenotype [13,14]; and 4) antithrombotic activity, as when the ApoA-I level is reduced, the availability of prostacyclin (PGI2) at the location of vascular endothelial injury can be reduced, thereby decreasing the protection against thrombocyte aggregation and thrombosis, which is strongly related to tumor cell growth and metastasis [6,15].

Table 2. Results of Univariate Analyses of Prognostic Factors for PFS and OS

Variables	Median OS, Months (95% CI)	*P* Value	Median PFS, Months (95% CI)	*P* Value
Age				
≤60	25.1 (22.37-27.89)	.108	6.4 (5.61-7.12)	.981
>60	23.4 (20.77-26.08)		6.5 (5.51-7.49)	
Gender		.692		.317
Male	24.5 (21.87-27.14)		6.2 (5.58-6.82)	
Female	23.0 (19.02-27.04)		6.8 (5.95-7.71)	
Primary tumor site		.752		.126
Right	21.5 (16.27-26.71)		7.3 (6.08-8.58)	
Left	24.5 (22.51-26.51)		6.2 (5.60-6.80)	
Synchronous metastases		**.026**		.572
Yes	23.0 (20.47-25.59)		6.0 (5.12-6.88)	
No	26.9 (23.36-30.46)		6.6 (5.98-7.28)	
No of metastatic organs		.817		.960
1	24.2 (21.41-27.09)		6.5 (5.77-7.23)	
≥2	24.5 (21.32-27.70)		6.5 (5.80-7.33)	
Primary tumor resection		**<.001**		.054
Yes	26.8 (23.43-30.25)		6.8 (6.01-7.66)	
No	20.0 (16.41-23.54)		5.5 (4.17-6.76)	
CEA (ng/ml)		**<.001**		**.021**
≤5	34.2 (20.16-48.37)		6.2 (5.63-6.77)	
>5	21.6 (19.61-23.63)		7.8 (6.68-8.99)	
First-line therapy		**.018**		**<.001**
Chemo	23.6 (21.34-25.90)		5.5 (4.91-6.16)	
Chemo + bevacizumab	28.6 (23.06-34.15)		9.3 (7.72-10.94)	
First-line chemo regimen		**.011**		.061
Oxaliplatin/irinotecan-containing	24.7 (22.38-26.96)		6.6 (6.05-7.22)	
5-FU alone	20.6 (13.83-27.44)		4.0 (1.11-6.95)	
Cholesterol (mg/dl)		.393		.485
≥200	24.6 (22.04-27.31)		6.7 (5.85-7.49)	
<200	24.1 (21.30-27.00)		6.3 (5.46-7.07)	
Triglyceride (mg/dl)		.129		.660
≥150	27.4 (20.70-34.04)		6.5 (5.86-7.13)	
<150	23.9 (21.70-26.00)		6.7 (5.13-8.21)	
HDL-C (mg/dl)		**<.001**		**<.001**
<40	20.2 (18.01-22.47)		5.6 (4.78-6.42)	
≥40	27.5 (24.50-30.50)		7.2 (6.35-8.11)	
LDL-C > 2.75 (mg/dl)		.081		.104
≥130	23.0 (20.72-25.34)		6.1 (5.39-6.81)	
<130	25.7 (21.89-29.56)		6.9 (5.95-7.85)	
ApoA-I (g/l)		**<.001**		**<.001**
≤1.105	20.6 (18.27-23.06)		6.0 (5.28-6.73)	
>1.105	28.3 (24.05-32.53)		6.9 (6.07-7.73)	
ApoB (g/l)		**.001**		**.034**
>1.170	19.8 (16.81-22.75)		5.5 (4.63-6.43)	
≤1.170	26.2 (23.34-29.03)		6.8 (6.06-7.53)	

Table 3. Results of Multivariate Analyses of Prognostic Factors for PFS and OS

Parameter	OS		PFS	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Primary tumor resection (no)	1.517 (1.204-1.913)	**<.001**	–	–
First-line therapy (chemo alone)	1.312 (0.978-1.760)	.070	2.033 (1.574-2.624)	**<.001**
CEA (>5 ng/ml)	1.306 (1.080-1.579)	**<.001**	1.429 (1.143-1.787)	**.002**
ApoA-I (≤1.105 g/l)	1.636 (1.306-2.050)	**<.001**	1.397 (1.148-1.700)	**.001**

Bevacizumab is a humanized monoclonal antibody targeting VEGFA [16], which has shown excellent efficacy in both first- and second-line settings in combination with either irinotecan- or oxaliplatin-based chemotherapy in mCRC. There is a necessity to search for biomarkers that are able to identify patients who are more likely to benefit from bevacizumab, given its side effects and financial cost. A high serum LDH value was considered a marker of treatment efficacy of bevacizumab in patients with mCRC. In patients with high LDH levels, the addition of bevacizumab to chemotherapy led to a prolonged PFS [17,18]. Passardi et al reported that low NLR was also a useful predictive marker for mCRC patients who are candidates for CT plus bevacizumab [19]. Our results showed that although PFS benefits were not affected by the addition of bevacizumab in patients with either high or low ApoA-I levels, the high–ApoA-I group seemed capable of obtaining long-term benefits. VEGF has also been shown to exert immunosuppressive functions through pathways other than stimulating angiogenesis, mostly regulated by myeloid-derived suppressor cells [20]. Bevacizumab thus induces immune responses by increasing the number of CD8+ and CD4+ memory T cells, increasing the transport of T cells into tumors, decreasing suppressive cytokines, and decreasing the frequency of myeloid-derived suppressor cells [21,22]. As mentioned earlier, decreased levels of ApoA-I may indicate cancer-related inflammation, and decreased levels of ApoA-I may be correlated with a detrimental immunological effect of bevacizumab. Moreover, patients with low ApoA-I may be less tolerant of later-line aggressive management and consequently do not obtain significant OS benefits.

In recent years, some experimental studies have suggested that the pharmacological administration of ApoA-I may have a therapeutic benefit as an antitumor strategy in melanoma. ApoA-I mimetic peptides engineered to mimic the anti-inflammatory functionalities of ApoA-I have recently been reported to suppress ovarian cancer cell growth [23,24]. Although these findings have not yet been successfully confirmed in the clinical context, we expect that ApoA-I and its mimetic peptides will be valuable therapeutic agents to complement antitumor strategies in mCRC in the near future.

We acknowledge that the present study is limited because of its retrospective, single-center design. Some patients with cardiovascular complaints or hepatic illnesses, such as coronary heart disease, hypertension, and chronic hepatitis, were included in this study, and the effects of those diseases on lipid metabolism were not considered.

Conclusion

Our study is the first to demonstrate that pretreatment ApoA-I level can function as an independent indicator of survival outcomes in mCRC and that this biomarker is able to predict the benefits of bevacizumab in patients with higher ApoA-I levels.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.tranon.2017.01.006.

Conflicts of Interest

None.

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