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Retrospective Study

Novel parameter based on lipid indicators ratio improves prognostic value of plasma lipid levels in resectable colorectal cancer patients

Jun-Nan Gu, Shuang Yao, Ying-Hao Cao, Sheng-He Deng, Fu-Wei Mao, Hong-Yu Jiang, Yang-Ting He, Xin-Ying Li, Song-Qing Ke, Hui-Li Li, Hang Li, Xing-Hua Liu, Hong-Li Liu, Ji-Liang Wang, Ke Wu, Li Liu, Kai-Lin Cai

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Abstract

BACKGROUND

At present, the value of lipid indicators in evaluating the prognosis of colorectal cancer is still relatively limited.

AIM

To evaluate the value of a novel parameter for colorectal cancer (CRC) prognosis scoring based on preoperative serum lipid levels.

METHODS

Four key serum lipid factors, namely, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB), were detected. Two representative ratios, HDL-C-LDL-C ratio (HLR) and ApoA1-ApoB ratio (ABR) were calculated. The relationship of these parameters with the prognosis of CRC patients including progression-free

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survival (PFS) and overall survival (OS) was analyzed by Kaplan-Meier plot and Cox proportional hazards regression. A novel lipoprotein cholesterol-apolipoprotein (LA) score based on HLR and ABR was established and its value in prognosis evaluation for CRC patients was explored.

RESULTS

Multivariate Cox proportional hazards regression analysis of PFS and OS showed that HDL-C, ApoA1, HLR, and ABR were positively associated with the prognosis of CRC patients. LA score was independently associated with a good prognosis in resectable CRC patients. Data processing of a dummy variable showed that the prognosis of patients with higher LA scores is better than that with lower LA scores.

CONCLUSION

The newly established LA score might serve as a better predictor of the prognosis of resectable CRC patients.

Key Words: Colorectal cancer; High-density lipoprotein cholesterol-low-density lipoprotein cholesterol ratio; Apolipoprotein A1-apolipoprotein B ratio; Lipid cholesterol-apolipoprotein score; Prognosis

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Core Tip: Although the diagnosis and treatment of colorectal cancer are constantly improving, the prognosis of colorectal cancer still needs to be further improved. At present, the methods to evaluate the prognosis of colorectal cancer, whether imaging examination or endoscopic examination, are based on the judgment of tumor stage. Under the background that the relationship between lipid metabolism and cancer has been gradually explored, our research has further studied the relationship between some key lipid indicators and the prognosis of colorectal cancer, and has established a novel prognosis scoring system, namely, lipoprotein cholesterol-apolipoprotein score, based on lipid indicators, which is expected to have more application value in the future clinical work.

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most prevalent and second deadliest type of cancer worldwide[1]. The 5-year survival rates of CRC patients with local and distant metastasis are 71% and 14%, respectively, which remain unsatisfactory[2]. As such, early prediction of tumor progression is important[3-5]. The discovery of new indicators allows the identification and characterization of the initial steps of tumorigenesis and the prediction of disease prognosis[6,7].

At present, the prognostic assessment of CRC patients primarily includes imaging examination, such as computerized tomography/magnetic resonance imaging; endoscopic examination, such as colonoscopy/enteroscopy; and pathological examination[8,9]. These evaluation methods rely on the judgment of the tumor stage to predict the survival of patients[6,8]. To improve the oncology results of CRC patients, we explored prognostic indicators independent of tumor stage to establish a complete prognostic evaluation system for CRC.

Previous studies have shown that abnormal lipid metabolism plays an important role in tumor progression and may be associated with a poor prognosis in esophageal squamous cell carcinoma[10], nasopharyngeal carcinoma[11], and CRC[12]. A lipid

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profile includes lipid molecules [cholesterol (CHO), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB)], and lipid-based biomarkers [namely, HDL-C-LDL-C ratio (HLR) and ApoB-ApoA1 ratio (ABR)]. Epidemiological evidence has indicated an inverse relationship between plasma HDL-C and ApoA1 levels and adenoma risk[13]. Functional studies have revealed important roles of ApoA1 in the development and progression of cancer, such as renal cell carcinoma [14], esophageal squamous cell carcinoma[15], and nasopharyngeal carcinoma[11]. However, the values of lipid molecules in the prognosis of CRC are still under discussion. Hence, the current retrospective cohort study was designed to detect the association of individual lipid molecules and an integrated lipid score with the survival rate of CRC patients.

MATERIALS AND METHODS

Patients

A total of 1696 CRC patients from the Wuhan Union Hospital were enrolled in this study between January 2013 and December 2017. All patients were pathologically identified with primary CRC. The exclusion criteria were as follows: (1) Patients treated with medication or undergoing hormone replacement therapy or curative resection; (2) Patients with concomitant diseases that were associated with increasing serum lipids and proteins levels (*i.e.*, diabetes, hyperlipidemia, or metabolic syndrome); and (3) Other types of malignancy. The present study was approved by the ethics committee of Wuhan Union Hospital and was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

Follow-up

All CRC patients were followed after completion of tumor resection according to clinical guidelines. The patients were generally followed every 3 mo by the outpatient service with ultrasound in the first 2 years and then annually for the next 3 to 5 years when no evidence of recurrence was observed. For the patients who did not visit our hospital as scheduled, telephone interviews were conducted to obtain treatment information and progression status. The end of follow-up was in August 2018. The outcomes of this study were progression-free survival (PFS) and overall survival (OS). PFS was calculated as the interval between cancer diagnosis and the first documentation of disease recurrence, metastasis, death, or end of follow-up, whichever came first. OS was defined as the time from the diagnosis of CRC to the date of death, follow-up, or end of follow-up, whichever came first.

Laboratory measurements

Laboratory measurements of lipid-related factors in routine blood tests were collected. Blood samples from each patient were obtained within 1 wk prior to the surgical resection of their primary tumors. On the basis of previous studies on the relationship between lipid metabolism and CRC, we identified four key serum lipid factors, namely, HDL-C, LDL-C, ApoA1, and ApoB.

Statistical analysis

Continuous variables are expressed as the mean $\pm$ SD, and the Student's *t* test was used for comparison between groups. Categorical variables are represented by the number of cases (percentage), and the chi-square test was used for comparison between groups. We used the inflexion value of the receiver operating characteristic (ROC) curve to transform the continuous variables into categorical variables. Kaplan-Meier (KM) method and log-rank test were applied to compare the survival difference between groups. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and the corresponding 95% confidence intervals (95% CIs). In addition, subgroup analyses were conducted by age, sex, tumor node metastasis (TNM) stage, tumor location, tumor size, and pathological differentiation. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina, United States) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All analyses were two-sided, and *P* values < 0.05 were considered statistically significant.

RESULTS

Clinicopathological characteristics of CRC patients

A total of 1696 patients with CRC, 1016 of which were male and 680 were female, were included in the final analysis. Demographic characteristics are described in [Table 1](#). Of the patients included, 979 (57.72%) had tumors located in the colon and 717 (42.28%) in the rectum. TNM stages I, II, III, and IV were observed in 223 (13.15%), 573 (33.79%), 654 (38.56%), and 246 (14.50%) of the patients, respectively. Compared with 1673 (98.64%) CRC patients with a negative circumferential margin, only 23 (1.36%) patients had a positive margin. A total of 367 (21.64%) and 1329 (78.36%) CRC patients were with and without vascular invasion, respectively. In addition, 370 (21.82%) and 1326 (78.18%) patients presented neural invasion and absence of neural invasion, respectively. [Supplementary Table 1](#) shows the baseline clinicopathologic characteristics of patients without serum ApoA1 and ApoB data.

Prognostic association of lipid-related indicators in CRC patients

The areas under the ROC curves of HDL-C, LDL-C, ApoA1, and ApoB for PFS and OS are presented in [Table 2](#). As shown in the KM curve ([Supplementary Figure 1](#)), higher serum levels of HDL-C, ApoA1, and ApoB were associated with a better PFS and OS than those with lower levels. By contrast, the patients with higher serum LDL-C levels showed a worse PFS and OS than those with lower LDL-C levels. Multivariate Cox proportional hazards regression revealed that the HRs of PFS were 0.696 (95%CI: 0.528-0.918) and 0.617 (95%CI: 0.442-0.863) for high levels of HDL-C and ApoA1, respectively. Similarly, HDL-C and ApoA1 were associated with a low risk for OS, with HRs of 0.505 (95%CI: 0.363-0.702) and 0.625 (95%CI: 0.410-0.955), respectively, whereas LDL-C was associated with a high risk for OS (HR: 1.503, 95%CI: 1.001-2.258).

The areas under the ROC curves of two hallmarks comprising the ratio of lipid biomarkers, HLR and ABR, for PFS and OS are shown in [Table 3](#). The KM curves for the two hallmarks are shown in [Figure 1](#), which indicated that higher levels of HLR and ABR were associated with a better PFS and OS than those with lower levels. In the multivariate Cox proportional hazards regression analyses, high levels of HLR and ABR were associated with a decreased risk of disease progression, with HRs of 0.710 (95%CI: 0.528-0.955) and 0.501 (95%CI: 0.324-0.775), respectively. High levels of HLR and ABR were associated with a decreased risk of overall mortality, with HRs of 0.619 (95%CI: 0.434-0.882) and 0.481 (95%CI: 0.271-0.853), respectively. At the same time, we made subgroup analysis of lipid indicators and found some significant results ([Supplementary Tables 2-7](#)).

Prospects for the newly established scoring system

Given that HLR and ABR presented inverse associations with CRC mortality, an integrated lipid score, that is, lipoprotein cholesterol-apolipoprotein score (LA score), was developed as a novel prognostic indicator for CRC survival. HLR and ABR were dichotomized with the inflection point of the corresponding ROC curve on OS ([Table 3](#)). This LA score was generated as follows: Score 0: $0 < \text{HLR} < 0.323$ and $0 < \text{ABR} < 0.871$; score 1: $\text{HLR} > 0.323$ and $0 < \text{ABR} < 0.871$, or $0 < \text{HLR} < 0.323$ and $\text{ABR} > 0.871$; and score 2: $\text{HLR} > 0.323$ and $\text{ABR} > 0.871$. As shown in [Figure 2](#), KM log-rank survival analysis suggested that PFS was good for CRC patients at the same survival time point with per point increase in LA score ($P = 0.00058$). According to the multivariate Cox regression analysis, resectable CRC patients with an LA score of 2 had a better PFS than patients with an LA score of 0 through data processing of dummy variable quantification (HR: 0.427, 95%CI: 0.256-0.713, $P = 0.001$, [Table 4](#)). Furthermore, the analysis of continuous variables suggested that LA score had a protective effect on the prognosis of patients with resectable CRC (HR: 0.654, 95%CI: 0.512-0.836, $P = 0.001$, [Table 4](#)).

In further subgroup analysis ([Table 5](#)), for CRC patients with TNM stage III/IV, patients with rectal tumor, or those with a tumor size (cm) of $2 \leq d < 5$, the increased LA score had a stronger protective effect on PFS, with HRs of 0.632 (95%CI: 0.485-0.824), 0.582 (95%CI: 0.411-0.826), and 0.575 (95%CI: 0.435-0.761), respectively. For CRC patients younger than 65 years, female patients, patients with TNM stage III/IV, patients with a tumor size (cm) of $2 \leq d < 5$, or patients with low tumor differentiation, the increased LA score was associated with a decreased risk of OS, with HRs of 0.626 (95%CI: 0.424-0.924), 0.572 (95%CI: 0.333-0.981), 0.676 (95%CI: 0.490-0.932), 0.636 (95%CI: 0.445-0.908), and 0.298 (95%CI: 0.149-0.594), respectively.

Table 1 Baseline patient clinicopathologic characteristics

		Progression-free survival			Overall survival		
		No progression	Progression	¹ P value	Survival	Death	¹ P value
		(n = 1388) (%)	(n = 308) (%)		(n = 1494) (%)	(n = 202) (%)	
Age (yr) (mean ± SD)		58.61 ± 11.71	58.48 ± 12.64	0.861	58.64 ± 11.75	58.19 ± 12.81	0.618
Sex	Male	821 (59.15)	195 (63.31)	0.199	880 (58.90)	136 (67.33)	0.022
	Female	567 (40.85)	113 (36.69)		614 (41.10)	66 (32.67)	
Tumor location	Colon	801 (57.71)	178 (57.79)	0.999	861 (57.63)	118 (58.42)	0.880
	Rectum	587 (42.29)	130 (42.21)		633 (42.37)	84 (41.58)	
TNM stage	I	216 (15.56)	7 (2.27)	< 0.001	219 (14.66)	4 (1.98)	< 0.001
	II	522 (37.61)	51 (16.56)		536 (35.88)	37 (18.32)	
	III	561 (40.42)	93 (30.19)		570 (38.15)	84 (41.58)	
	IV	89 (6.41)	157 (50.97)		169 (11.31)	77 (38.12)	
Tumor size (cm)	d < 2	61 (4.39)	12 (3.90)	0.863	67 (4.48)	6 (2.97)	0.246
	2 ≤ d < 5	886 (63.83)	201 (65.26)		964 (64.52)	123 (60.89)	
	d > 5	441 (31.77)	95 (30.84)		463 (31.00)	73 (36.14)	
Differentiation	Low	186 (13.40)	36 (11.69)	0.586	192 (12.85)	30 (14.85)	0.648
	Medium	1104 (79.54)	253 (82.14)		1197 (80.12)	160 (79.21)	
	High	98 (7.06)	19 (6.17)		105 (7.03)	12 (5.94)	
Circumferential margin	No	1372 (98.85)	301 (97.73)	0.167	1477 (98.86)	196 (97.03)	0.047
	Yes	16 (1.15)	7 (2.27)		17 (1.14)	6 (2.97)	
Vascular tumor thrombus	No	1111 (80.04)	218 (70.78)	0.001	1180 (78.98)	149 (73.76)	0.101
	Yes	277 (19.96)	90 (29.22)		314 (21.02)	53 (26.24)	
Nerve invasion	No	1098 (79.11)	228 (74.03)	0.057	1177 (78.78)	149 (73.76)	0.122
	Yes	290 (20.89)	80 (25.97)		317 (21.22)	53 (26.24)	
Chemotherapy	No	606 (43.66)	87 (28.25)	< 0.001	603 (40.36)	90 (44.55)	0.254
	Yes	782 (56.34)	221 (71.75)		891 (59.64)	112 (55.45)	
Radiotherapy	No	1315 (94.74)	275 (89.29)	0.001	1400 (93.71)	190 (94.06)	0.999
	Yes	73 (5.26)	33 (10.71)		94 (6.29)	12 (5.94)	
ApoA1 (G/L)		1.22 ± 0.25	1.12 ± 0.27	< 0.001	1.20 ± 0.25	1.12 ± 0.28	0.010
ApoB (G/L)		0.94 ± 0.23	0.91 ± 0.24	0.170	0.93 ± 0.23	0.92 ± 0.25	0.628
HDL-C (mmol/L)		1.22 ± 0.33	1.20 ± 0.34	0.208	1.22 ± 0.33	1.20 ± 0.37	0.440
LDL-C (mmol/L)		2.62 ± 0.75	2.60 ± 0.84	0.807	2.61 ± 0.75	2.64 ± 0.90	0.664

¹P value was calculated by the Student's *t*-test for continuous variables and the Chi-square test for categorical variables.

ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; HDL-C: High-density lipoprotein-cholesterol; TNM: Tumor node metastasis; LDL-C: Low-density lipoprotein-cholesterol.

DISCUSSION

Recently, abnormal lipid metabolism has been linked with cancer risk and progression in several malignancies[16,17] and validated to be a vital metabolic reprogramming process in cancer cells[18,19]. However, the role of lipid-related molecules in evaluating the prognosis of resectable CRC is not very clear. Therefore, the establishment of intuitive, sensitive, and specific lipid-derived markers that can be used to clinically predict cancer prognosis is required. In the present study, the prognostic effects of various lipid-related indicators were systematically and comprehensively studied, and several important findings were discovered. First, the

Table 2 Cox proportional hazards regression analyses for basic lipid indicators for progression-free survival and overall survival

	AUC	Cut-point	PFS			
			Univariate	P value	Multivariate ¹	P value
			HR (95%CI)		HR (95%CI)	
HDL-C (mmol/L)	0.519	0.920	0.699 (0.530-0.920)	0.011 ^b	0.696 (0.528-0.918)	0.010 ^a
LDL-C (mmol/L)	0.513	2.160	0.865 (0.679-1.103)	0.242	0.878 (0.689-1.119)	0.295
ApoA1 (G/L)	0.610	1.030	0.520 (0.374-0.725)	< 0.001 ^b	0.617 (0.442-0.863)	0.005 ^a
ApoB (G/L)	0.547	0.860	0.743 (0.537-1.029)	0.074	0.796 (0.574-1.103)	0.170
	AUC	Cut-point	OS			
			Univariate	P value	Multivariate ²	P value
			HR (95%CI)		HR (95%CI)	
HDL-C (mmol/L)	0.519	0.900	0.492 (0.354-0.685)	< 0.001 ^b	0.505 (0.363-0.702)	< 0.001 ^a
LDL-C (mmol/L)	0.499	3.650	1.645 (1.096-2.468)	0.016 ^b	1.503 (1.001-2.258)	0.050
ApoA1 (G/L)	0.578	1.130	0.572 (0.375-0.873)	0.010 ^b	0.625 (0.410-0.955)	0.030 ^a
ApoB (G/L)	0.527	0.860	0.744 (0.487-1.136)	0.171	0.807 (0.528-1.234)	0.323

Binary classification (I/II vs III/IV) of tumor node metastasis (TNM) stage was adopted.

¹(Progression-free survival) Multivariate analysis adjusted for age, TNM stage, vascular tumor thrombus, chemotherapy, and radiotherapy. We used a stepwise regression approach for multivariate analysis.

²(Overall survival) Multivariate analysis adjusted for age, sex, TNM stage, and circumferential margin.

^aStatistical significance is expressed as $P < 0.05$ (for multivariate analysis).

^bStatistical significance is expressed as $P < 0.05$ (for univariate analysis).

HR: Hazard ratio; 95%CI: 95% confidence interval; AUC: Area under the ROC curve; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; TNM: Tumor node metastasis; PFS: Progression-free survival; OS: Overall survival.

protective effects of certain lipid indicators, such as HDL-C, ApoA1, HLR, and ABR, on PFS and OS in patients with resectable CRC were validated. Second, the combination of HLR along with ABR, defined as LA score, was statistically significant in relation to the prognosis of CRC and is more intuitive than other lipid-based indicators. Third, the clinical feasibility of the newly established LA score was evaluated and accordingly confirmed as a prognostic factor.

PFS and OS in CRC patients with a high preoperative serum HDL-C concentration were higher than those with a low serum HDL-C concentration. Previous studies have reported that the levels of HDL-C are inversely related to the risk of CRC[13,20]. Unlike previous studies, a large cohort of CRC patients was included in the present study to further demonstrate the validity of this conclusion. In addition, a total of 1696 patients with CRC after surgical operation from Wuhan Union Hospital were included in this multivariate Cox proportional hazards regression analysis. The primary role of HDL-C, as the only atherosclerotic protective lipid, is to transport excess CHO from the periphery to the liver for excretion. Moreover, HDL-C has been shown to exhibit antioxidant, anti-inflammatory, and antithrombotic effects and is inversely associated with cancer[21-23]. However, the function of HDL-C in carcinogenesis is not fully understood. Cancer is a pro-inflammatory state, including tumor cell proliferation, survival, and migration, and inflammatory cells actively participate in the development of tumors[24]. HDL-C may influence certain pro-inflammatory mediators involved in carcinogenesis[21]. Su *et al*[25] suggested that HDL-C mimetic peptides may considerably reduce colon cancer cell proliferation in BALB/c mice through antioxidant and anti-inflammatory mechanisms. In addition, HDL-C may affect immune cells in the tumor microenvironment rather than directly kill tumor cells[26]. HDL-C inhibits the progression of CRC through anti-inflammatory and immune mechanisms probably *via* the aforementioned mechanisms; hence, CRC patients with a high preoperative serum HDL-C presented a better OS, as shown in the present study (HR: 0.505, 95%CI: 0.363-0.702, $P < 0.001$). Several studies have reported elevated LDL-C levels in several types of cancer, such as breast cancer[27] and CRC [28]. The present study revealed that CRC patients with high blood LDL-C had a worse OS (HR: 1.503, 95%CI: 1.001-2.258, $P = 0.050$), which is consistent with the

Table 3 Cox proportional hazards regression analyses for lipid-based indicators for progression-free survival and overall survival

	AUC	Cut-point	PFS			
			Univariate		Multivariate ¹	
			HR (95%CI)	P value	HR (95%CI)	P value
HDL-C/LDL-C	0.497	0.323	0.672 (0.500-0.904)	0.009 ^b	0.710 (0.528-0.955)	0.024 ^a
ApoA1/ApoB	0.528	0.909	0.465 (0.302-0.715)	0.001 ^b	0.501 (0.324-0.775)	0.002 ^a
	AUC	Cut-point	OS			
			Univariate		Multivariate ²	
			HR (95%CI)	P value	HR (95%CI)	P value
HDL-C/LDL-C	0.506	0.323	0.573 (0.402-0.815)	0.002 ^b	0.619 (0.434-0.882)	0.008 ^a
ApoA1/ApoB	0.527	0.871	0.411 (0.232-0.729)	0.002 ^b	0.481 (0.271-0.853)	0.012 ^a

Binary classification (I/II vs III/IV) of tumor node metastasis (TNM) stage was adopted.

¹(Progression-free survival) Multivariate analysis adjusted for age, TNM stage, vascular tumor thrombus, chemotherapy, and radiotherapy. We used a stepwise regression approach for multivariate analysis.

²(Overall survival) Multivariate analysis adjusted for age, sex, TNM stage, and circumferential margin.

^aStatistical significance is expressed as $P < 0.05$ (for multivariate analysis).

^bStatistical significance is expressed as $P < 0.05$ (for univariate analysis).

HR: Hazard ratio; 95%CI: 95% confidence interval; AUC: Area under the ROC Curve; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; PFS: Progression-free survival; OS: Overall survival.

findings reported in the literature. This result indicates that LDL-C might be an independent predictor of CRC prognosis. Montel *et al*[29] and Song *et al*[30] reported that cancer cells can express an LDL receptor-related protein that can promote the growth and invasion of cancer cells. This process may be one of the mechanisms by which LDL-C in blood affects cancer progression. On the basis of this evidence, we proposed that HLR, a lipid-based hallmark, is linked to the prognosis of CRC. This retrospective cohort study confirmed that high levels of HLR were associated with a better postoperative OS (HR: 0.619, 95%CI: 0.434-0.882, $P = 0.008$). Although previous work has clarified the role of LDL-C-to-HDL-C ratio in the evaluation of cardiovascular disease[31,32], few have linked a similar ratio to the prognosis of CRC. The present study confirmed that HLR is helpful in assessing the prognosis of patients with resectable CRC. Furthermore, HLR is worthy of further study and may be clinically applied in the future.

Serum ApoA1 also exhibited protective effects on PFS and OS in CRC patients according to multivariate Cox proportional hazards regression analysis. Among the 522 CRC patients who had been measured for preoperative serum ApoA1, those with high serum ApoA1 levels showed a better prognosis after surgical operation. Apolipoprotein A1, which is encoded by a gene located on chromosome 11q23-q24, is a member of the apolipoprotein family[33,34]. As a major protein constituent of high-density lipoproteins, ApoA1 is synthesized predominantly in the liver and small intestine and is part of the apolipoprotein A1/A4/E family[35]. ApoA1 is widely recognized and validated in various cancers as a prognostic factor[36,37]. However, researchers have different opinions on how ApoA1 plays a role in cancer patients, and the pathogenesis is still under exploration. Recent studies have found that ApoA1 has a negative effect on tumor microenvironment in terms of overall metastasis reduction and accumulation of tumor-associated macrophages[38]. Moreover, ApoA1 can inhibit tumor-associated angiogenesis and then decrease protein expression of MMP9, which is a critical matrix-degrading enzyme needed for metastasis[36]. Georgila *et al*[36] demonstrated that ApoA1 may function as a potent immunomodulator in tumor microenvironment, transforming tumor-related macrophages from pro-tumor into antitumor phenotypes. These findings imply that ApoA1 may play an important role in the tumorigenesis and progression of CRC. Consistent with previous studies, the present study showed that a low ApoA1 level was correlated with a poor OS and may act as an independent prognostic factor for survival (HR: 0.625, 95%CI: 0.410-0.955, $P = 0.030$). However, further research is required to clarify the underlying mechanisms. Furthermore, consistent with some previous studies[39,40], the present study found no statistically significant association between serum ApoB levels and CRC prognosis. Therefore, the predictive importance of ABR is positive. Previous studies have found

Table 4 Cox proportional hazards regression analyses for lipoprotein-cholesterol-apolipoprotein score for progression-free survival and overall survival

Continuous variable				
PFS				
	Univariate	P value	Multivariate ¹	P value
	HR (95%CI)		HR (95%CI)	
LA score ³	0.625 (0.490-0.797)	< 0.001 ^b	0.654 (0.512-0.836)	0.001 ^a
OS				
	Univariate	P value	Multivariate ²	P value
	HR (95%CI)		HR (95%CI)	
LA score ³	0.616 (0.453-0.838)	0.002 ^b	0.677 (0.500-0.917)	0.012 ^a
Dummy variable				
PFS				
	Univariate	P value	Multivariate ¹	P value
	HR (95%CI)		HR (95%CI)	
LA score ³ 1	0.598 (0.280-1.277)	0.184	0.646 (0.302-1.383)	0.261
LA score ³ 2	0.387 (0.233-0.643)	< 0.001 ^b	0.427 (0.256-0.713)	0.001 ^a
OS				
	Univariate	P value	Multivariate ²	P value
	HR (95%CI)		HR (95%CI)	
LA score ³ 1	0.973 (0.370-2.561)	0.956	1.508 (0.507-3.992)	0.408
LA score ³ 2	0.413 (0.213-0.802)	0.009 ^b	0.524 (0.269-1.019)	0.057

Binary classification (I/II vs III/IV) of tumor node metastasis (TNM) stage was adopted.

¹(Progression-free survival) Multivariate analysis adjusted for age, TNM stage, vascular tumor thrombus, chemotherapy, and radiotherapy. We used a stepwise regression approach for multivariate analysis.

²(Overall survival) Multivariate analysis adjusted for age, sex, TNM stage, and circumferential margin.

³This indicator combined ApoA1/ApoB and HDL-C/LDL-C. Per additional score was associated with a decreased risk of progression-free survival and overall survival in colorectal cancer patient.

^aStatistical significance is expressed as $P < 0.05$ (for multivariate analysis).

^bStatistical significance is expressed as $P < 0.05$ (for univariate analysis).

HR: Hazard ratio; 95%CI: 95% confidence interval; AUC: Area under the ROC curve; PFS: Progression-free survival; OS: Overall survival; LA: Lipoprotein cholesterol-apolipoprotein.

that the ratio of ApoB to ApoA1 is useful for assessing not only cardiovascular diseases[41,42] but also the risk of osteonecrosis[43]. By contrast, few studies have reported that the ratio may be associated with the prognosis of CRC. In this retrospective cohort study, the CRC patients with low preoperative ABR had a worse OS than those with high ABR (HR: 0.481, 95%CI: 0.271-0.853, $P = 0.012$). Therefore, preoperative measurement of ABR may provide pivotal information for the stratified assessment of prognostic risk in patients who had undergone CRC radical correction.

According to the results of the above study, this cohort study supports the conclusion that HLR and ABR are independent prognostic factors for CRC patients. In the past decade, the Glasgow prognostic score has been widely used in assessing the inflammatory state and risk of cancer prognosis[44-47]. A lipid-related scoring system similar to the GPS was built considering the evidence reported in the literature. This novel CRC prognostic scoring system, called "LA score", is achieved by combining dichotomized HLR and ABR based on the optimal cut-off threshold from the corresponding RUC curves. Moreover, LA score remarkably correlated with the prognosis of CRC patients. Multivariate Cox proportional hazards regression analysis showed that LA score was an independent prognostic factor for patients with resectable CRC. Patients with an LA score of 2 had a better PFS than those with an LA score of 0 based on data processing of dummy variable quantification (HR: 0.427, 95%CI: 0.256-0.713, $P = 0.001$, Table 4). As a newly established scoring system, the combination of HLR and

Table 5 Association between lipoprotein-cholesterol-apolipoprotein score with overall survival and progression-free survival in patients with colorectal cancer among different subgroups

		LA score					
		PFS			OS		
		<i>n</i>	Progression	HR (95%CI)	<i>n</i>	Death	HR (95%CI)
Age (yr)	< 65	330	90	0.725 (0.532-0.987)	330	49	0.626 (0.424-0.924)
	≥ 65	191	58	0.540 (0.358-0.814)	191	38	0.724 (0.437-1.199)
Sex	Male	321	97	0.671 (0.500-0.901)	321	58	0.756 (0.520-1.101)
	Female	200	51	0.592 (0.366-0.956)	200	29	0.572 (0.333-0.981)
TNM stage	I/II	243	35	0.805 (0.421-1.538)	243	15	0.678 (0.265-1.735)
	III/IV	278	113	0.632 (0.485-0.824)	278	72	0.676 (0.490-0.932)
Tumor location	Colon	320	91	0.793 (0.557-1.128)	320	53	0.686 (0.454-1.036)
	Rectum	201	57	0.582 (0.411-0.826)	201	34	0.710 (0.450-1.121)
Tumor size (cm)	d < 2	12	2	0	12	2	0
	2 ≤ d < 5	374	108	0.575 (0.435-0.761)	374	61	0.636 (0.445-0.908)
	d ≥ 5	135	38	0.792 (0.485-1.294)	135	24	0.634 (0.354-1.137)
Differentiation	Low	56	18	0.504 (0.286-0.890)	56	11	0.298 (0.149-0.594)
	Medium	415	118	0.722 (0.534-0.977)	415	68	0.781 (0.528-1.155)
	High	50	12	0.534 (0.261-1.093)	50	8	0.704 (0.313-1.586)

LA: Lipoprotein cholesterol-apolipoprotein; PFS: Progression-free survival; OS: Overall survival; HR: Hazard Ratio; CI: Confidence interval.

ABR reduces the deviation that might be caused by a single ratio hallmark as a predictor and reflects a better prediction effect than either of the two ratios alone (HRs: 0.427 *vs* 0.710 and 0.501). Such a combination leads to intuitive and convenient evaluation of the prognosis. Notably, the relative stability of lipid indicators in the human body would result in stronger clinical application value of LA score than that of markers or scores composed of inflammatory indicators that considerably vary during the perioperative period. As treatment plans are becoming individualized for each patient, a prognostic scoring system, such as LA score, can be of great help in identifying high-risk populations that require close follow-up surveillance or postoperative adjuvant radiotherapy and chemotherapy to prevent disease recurrence and improve oncological outcomes.

Subgroup analyses provided additional information for the prognostic value of lipid hallmarks. For patients with TNM stage III/IV CRC, high preoperative HLR, ABR levels, and LA scores had protective effects on PFS and OS (Table 5; Supplementary Tables 4 and 7). These findings suggest that HLR, ABR, and LA scores were prognostic indicators independent of TNM stage for postoperative CRC patients. For example, based on the protective effect of LA scores, the preoperative or postoperative LA scores can be increased to improve the prognosis of TNM stage III CRC patients who plan to undergo surgical operations. These clinically important hypotheses deserve further study. Furthermore, these issues require retrospective, multicenter research. Subgroup analysis may be useful and important when used properly despite of data misjudgments. In conclusion, the subgroup analysis also supports the statistical results reported by previous studies.

However, the current research has several limitations. Although the clinical feasibility of lipid-related research factors had been verified as prognostic factors, the quantification and clinical application of such factors still require further research. The results must be validated in a large-scale and multicenter retrospective study because the number of patients included in this cohort study was not sufficiently large and the patients came from a single source. Detailed and definitive mechanisms and the biological importance of HDL-C and ApoA1 in CRC should be elucidated.

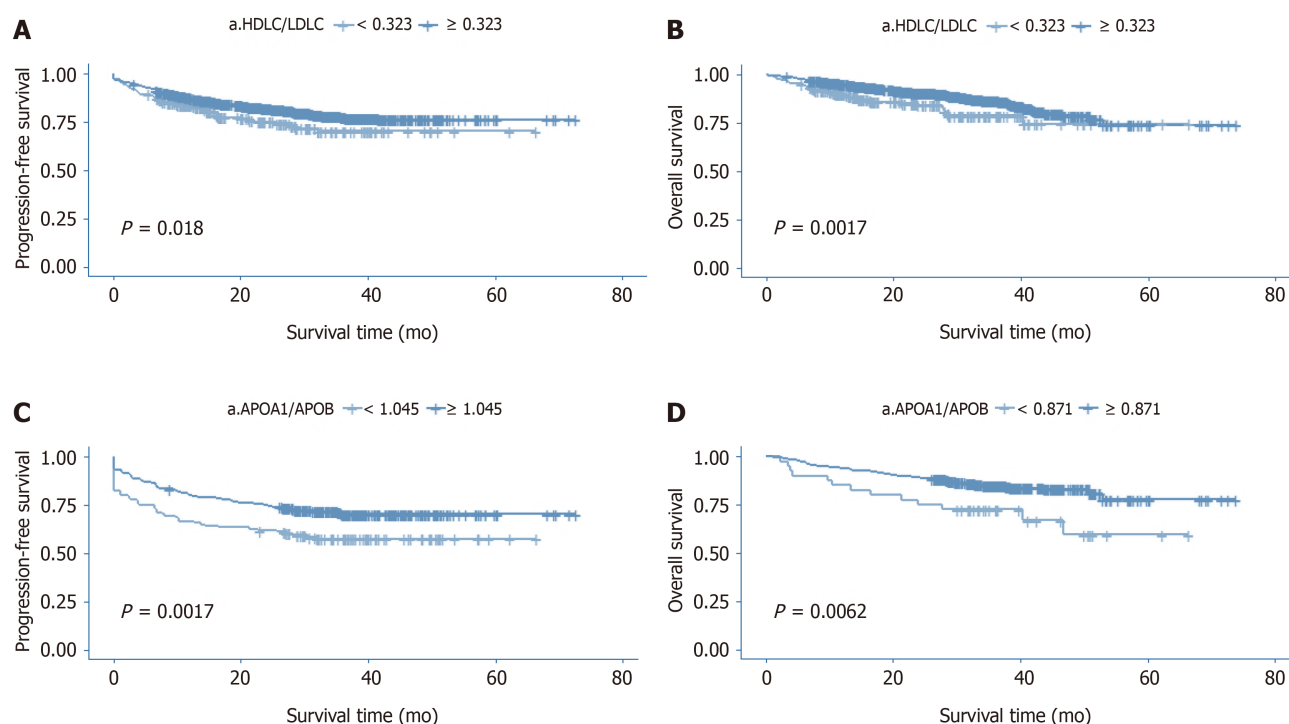


Figure 1 Kaplan-Meier curves for progression-free survival and overall survival of colorectal cancer patients according to two hallmarks consisting of the ratio of lipid biomarkers (high-density lipoprotein cholesterol/low-density lipoprotein cholesterol ratio and apolipoprotein A1/apolipoprotein B ratio). A: Kaplan-Meier curves for progression-free survival (PFS) of colorectal cancer patients according to high-density lipoprotein cholesterol/low-density lipoprotein cholesterol (HDL-C/LDL-C) ratio; B: Kaplan-Meier curves for overall survival (OS) of colorectal cancer patients according to HDL-C/LDL-C ratio; C: Kaplan-Meier curves for PFS of colorectal cancer patients according to ApoA1/ApoB ratio; and D: The Kaplan-Meier curves for OS of colorectal cancer patients according to ApoA1/ApoB ratio.

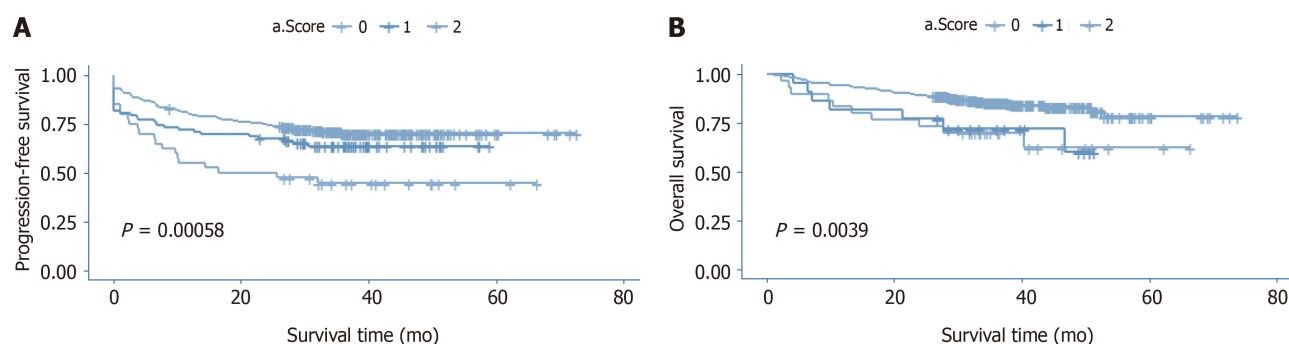


Figure 2 Kaplan-Meier curves for progression-free survival and overall survival of colorectal cancer patients according to lipoprotein cholesterol-apolipoprotein score. A: Kaplan-Meier curves for progression-free survival of colorectal cancer patients according to lipoprotein cholesterol-apolipoprotein (LA) score; B: Kaplan-Meier curves for overall survival of colorectal cancer patients according to LA score.

CONCLUSION

Through a systematic and comprehensive analysis, HDL-C, HLR, ApoA1, and ABR were demonstrated to be protective factors for the prognosis in patients with resectable CRC. Moreover, a novel prognostic scoring system, namely, LA score, for CRC was established. The high correlation between the novel scoring system and the prognosis of CRC patients and its intuitiveness and convenience make it a promising prognostic marker, but its specific clinical value remains to be further explored. Lipid indicators are feasible and promising prognostic biomarkers for CRC, and their quantification may be helpful in the diagnosis and treatment of CRC.

ARTICLE HIGHLIGHTS

Research background

Abnormal lipid metabolism has been considered to be associated with the oncogenesis, development, and prognosis in cancer.

Research motivation

Although the association between abnormal lipid metabolism and cancer progression is widely recognized, the value of lipid indicators in evaluating the prognosis of colorectal cancer (CRC) is still relatively limited.

Research objectives

The present study aimed to evaluate the association between preoperative serum lipid conditions and the prognosis in patients with CRC.

Research methods

This study included 1696 colorectal cancer patients. Four key lipid factors and two lipid ratio indicators were calculated to analyze the association between these parameters and prognosis of CRC by Kaplan-Meier plot and Cox proportional hazards regression.

Research results

High-density lipoprotein cholesterol (HDL-C), apolipoprotein A1, HDL-C-low-density lipoprotein cholesterol ratio, and ApoA1-apolipoprotein B ratio were positively associated with the prognosis of CRC patients. Lipoprotein cholesterol-apolipoprotein (LA) score was independently associated with a good prognosis in resectable CRC patients.

Research conclusions

The current study indicated that serum lipid parameters, particularly the newly established LA score, might serve as candidate predictors of the prognosis of resectable CRC patients.

Research perspectives

We have identified the value of several lipid parameters and a newly constructed score in assessing the prognosis of resectable CRC patients in a retrospective study. Compared with more volatile inflammatory factors, these more stable lipid parameters can provide a great help to improve the prognostic evaluation of CRC.

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