

Original Article

# Preoperative serum lipid profile and outcome in nonmetastatic colorectal cancer

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## Abstract

**Objective:** A large portion of non-metastatic colorectal cancers (non-mCRCs) recur after curative surgery. In addition to the traditional tumor-related factors, host-related factors are also required to accurately predict prognosis. A few studies have shown an association between the serum lipid profile and the survival and treatment response of patients with colorectal cancer.

**Methods:** We retrospectively evaluated the prognostic significance of the preoperative serum lipid profile [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)] in patients with non-mCRC treated with curative surgery. The Spearman rank correlation test was used to analyze associations between lipid levels and categorical variables. Lipid levels were modeled as four equal-sized quartiles based on the distribution among the whole cohort. Kaplan-Meier curves were used to estimate survival probabilities, and the log-rank test was used to detect differences between them. Multivariate fractional polynomial (MFP) analysis was used to model any non-linear effects and avoid categorization. To evaluate the added prognostic value of lipids, the predictive power of two models (with and without lipids as covariates) was compared by using Harrell's C-statistic and the Akaike information criterion (AIC).

**Results:** A total of 266 patients with non-mCRC were enrolled in the present study. Spearman rank correlation test showed that TG levels inversely correlated with N stage ( $r = -0.20$ ,  $P = 0.00$ ) and Tumor-Node-Metastasis (TNM) stage ( $r = -0.19$ ,  $P = 0.00$ ). HDL-C levels positively correlated with perineural invasion (PNI) ( $r = 0.15$ ,  $P = 0.02$ ), and LDL-C levels inversely correlated with lymphovascular invasion (LVI) ( $r = -0.12$ ,  $P = 0.04$ ). None of the four lipids predicted overall survival (OS) in univariate or multivariate analyses adjusted for age, gender, T stage, N stage, TNM stage, histological grade, tumor deposits, LVI, PNI, and adjuvant treatment (all  $P > 0.05$ ). In agreement, the Kaplan-Meier curves for OS according to the lipid quartiles were not significantly different, as confirmed by the log-rank test (all  $P > 0.05$ ). MFP analysis also found no significant associations between lipid levels and OS (all  $P > 0.05$ ). A prognostic model that included lipids had a higher Harrell's C-statistic and a lower AIC value than did a model that did not include lipids (for Harrell's C-statistic: 0.82 vs. 0.77; for AIC: 398 vs. 432).

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**Conclusion:** Measuring preoperative serum lipid levels may be a simple and cost-effective way of increasing prognostic accuracy in patients with non-mCRC treated with curative surgery.

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*Keywords:* Serum lipids; Colorectal cancer; Overall survival; Prognostic model

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## Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer-related death worldwide despite a significant decrease in its mortality rate in recent years. Although non-metastatic CRC (non-mCRC) can be potentially cured via radical surgery and adjuvant therapy, this cancer often recurs. Several pathological characteristics of CRC have prognostic significance including Tumor-Node-Metastasis (TNM) staging, histological grade, resection marginal status, perineural invasion (PNI), and lymphovascular invasion (LVI). However, the identification of additional factors is required to fine-tune prognostic accuracy, and both tumor-related and host-related factors should be considered.

The serum lipid profile [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)] is one of the few host-related factors whose relationship with CRC prognosis has been investigated. Lipids, as key components of the cell membrane, are required for tumor growth. Moreover, as an epidemiological observation, statins, a class of drugs that lower LDL-C levels, have been shown to reduce CRC risk<sup>1–4</sup> and mortality rates.<sup>5,6</sup> However, whether these protective effects result from LDL-C depletion<sup>7,8</sup> or other mechanisms<sup>9,10</sup> is unclear.

Dyslipidemia has been associated with an increased risk for CRC.<sup>11,12</sup> However, whether it increases,<sup>6,8,13–16</sup> decreases,<sup>17–20</sup> or has no effect<sup>21</sup> on mortality rates is still controversial. In patients with metastatic CRC (mCRC) with elevated LDL-C levels, a high LDL-C/HDL-C ratio predicted poor prognosis.<sup>22</sup> In patients with non-mCRC, investigation of the usefulness of serum lipids as prognostic indicators showed that adjuvant chemotherapy-related elevations in HDL-C levels correlated with longer disease free-survival and overall survival (OS) time<sup>23</sup>; TC independently predicted tumor regression after neoadjuvant chemoradiotherapy<sup>24</sup>; dyslipidemia predicted a favorable prognosis in one study<sup>15</sup> and a poor prognosis in another<sup>18</sup>; and low pretreatment serum levels

of C-reactive protein and cholesterol indicated a poor prognosis.<sup>14</sup>

To further clarify the prognostic role of serum lipids in CRC, we conducted a retrospective cohort study that examined the effects of preoperative serum lipid levels on the outcome of patients with non-mCRC after curative surgery.

## Material and methods

### *Patients*

We retrospectively collected, reviewed, and analyzed the medical information of all patients treated with curative surgery for CRC at the Department of Surgical Oncology at the Fourth People's Hospital of Wuxi from January 2009 to December 2014. Patients were excluded if they were diagnosed with other malignancies; died within 1 month after surgery; had a metastatic disease, multiple synchronous CRCs, or a history of diabetes mellitus or hypertension; had received neoadjuvant treatment; or had an unknown survival status. The following information was collected from the medical charts and recorded: the patient's name, age, and gender; the site and histology of the CRC; the depth of the primary tumor invasion; the number of metastatic lymph nodes, total lymph nodes sampled, and tumor deposits; the histology grade; PNI; LVI; tumor necrosis; and adjuvant treatment. Patients were classified according to the guidelines of the 7th edition of American Joint Committee on Cancer TNM Staging Manual. Patients with preoperative measurement of the four lipids (TC, TG, LDL-C, or HDL-C) were eligible for the study. Since the patients in our study were not prospectively followed up, their survival status was determined by consulting the death information registry at the Bureau of Public Security in Wuxi. If the patient was not listed in this registry, we interviewed via telephone either the patient or a close relative.

This study was approved by our hospital's ethics review board.

Further details regarding patient inclusion and exclusion are shown in Fig. 1.

*Lipid measurement*

All lipid levels were measured preoperatively. Serum lipids, including TC, TG, LDL-C, and HDL-C, were routinely tested on the second day of hospital admission in patients fasted for at least 8 h before sampling. Blood (4–5 ml) was collected in ethylene diamine tetraacetic acid (EDTA)-coated tubes. A Roche Modular P800 Automatic Biochemistry Analyzer was used to measure TC and TG levels (the colorimetric method) and LDL-C and HDL-C (turbidimetric immunoassay).

*Statistical analysis*

The Spearman rank correlation test was used to analyze associations among continuous variables (age; TC, TG, HDL-C, and LDL-C levels) and associations between lipid levels and categorical variables including gender (female/male), T stage (T1/T2/T3/T4a/T4b), N stage (N0/N1a/N1b/N1c/N2a/N2b), TNM stage (I/IIA/IIIB/IIC/IIIA/IIIB/IIIC), histological grade (I/II/III), tumor deposits (positive/negative), LVI (positive/negative), PNI (positive/negative), and necrosis (yes/no).

Lipid levels were modeled as four equal-sized quartiles based on the distribution among the whole cohort. Kaplan-Meier curves were used to estimate survival probabilities, and the log-rank test was used to detect differences between them. The assumption of proportionality was checked by including time-dependent covariates in the model. Univariate and multivariate Cox proportional hazards models were used to test the independent prognostic significance of each variable. To achieve better prediction by keeping lipid levels continuous, multivariate fractional polynomial (MFP) analysis was used to model any non-linear effects and avoid categorization.<sup>25</sup> Subgroup analysis based on gender, TNM stage, and disease site was used to identify potential confounding effects. To evaluate the added prognostic value of lipids, the predictive power of two models (with and without lipids as covariates) was compared by using Harrell's C-statistic and the Akaike information criterion (AIC). The higher the Harrell's C-statistic and the lower the AIC value, the better the performance (sensitivity and specificity) of the model.<sup>26</sup>

All hypothesis tests were two-sided with  $P < 0.05$  as statistically significant. All statistical analyses were performed using STATA version 14.0 software (STATA Corp, Texas, USA).

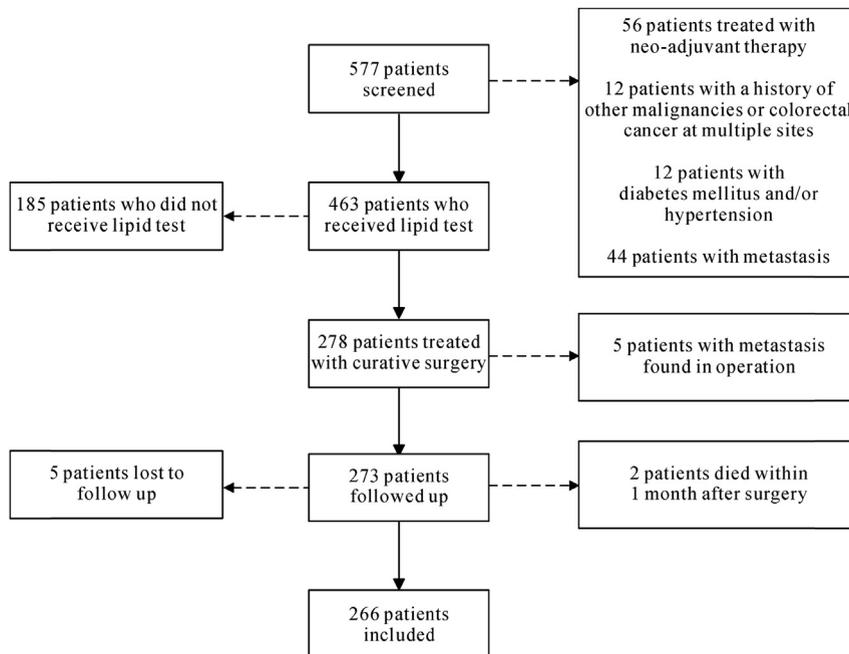


Fig. 1. Flow chart of patient inclusion and exclusion. Ten patients with metastasis also received neoadjuvant therapy. - - - - -> exclusion; ———> inclusion.

## Results

### Patients

We screened 577 patients for study eligibility. Patients who received the neoadjuvant treatment were excluded (56 patients, 55 with rectal cancer and one with colon cancer), including 55 with neoadjuvant chemotherapy, 26 with neoadjuvant radiation, and 1 (rectal cancer) with intra-artery neoadjuvant chemotherapy. Also excluded were patients with a previous history of other malignancies (5 patients, 2 with breast cancer, and one each with cervical cancer, endometrial cancer, and prostate cancer) or CRC at multiple sites (7 patients); diabetes mellitus and/or high blood pressure (12 patients); metastasis found in operation (5 patients) or preoperative metastasis (44 patients), and patients who died within 30 days postoperatively (2 patients). Lipid levels were not measured in 185 patients.

Fifty-two patients had died as of December 2015 according to the death information registry of Wuxi. We attempted to contact the remaining patients via telephone during March 2016. Two additional deaths not yet registered were identified, and five patients were unreachable. Thus, 266 patients (104 with colon cancer and 162 with rectal cancer), including 54 who had died, were included in the present study.

The demographic and pathological characteristics of the 266 patients are listed in [Table 1](#). The study cohort consisted of a roughly equal number of men and women, with a median age of 65 years (range, 27–93 years). TC levels (mean  $\pm$  SD:  $4.34 \pm 0.92$  mmol/L for the entire cohort) were normal in 76.3% (203/266) of the patients, abnormally high in 21.1% (56/266) of the patients, and abnormally low in 2.6% (7/266) of the patients. TG levels (mean  $\pm$  SD:  $1.35 \pm 0.66$  mmol/L for the entire cohort) were normal in 80.5% (214/266) of the patients and abnormally high in 19.5% (52/266) of the patients. HDL-C levels (mean  $\pm$  SD:  $1.11 \pm 0.35$  mmol/L for the entire cohort) were normal in 98.5% (262/266) of the patients and abnormally high in 1.5% (4/266) of the patients. LDL-C levels (mean  $\pm$  SD:  $2.23 \pm 0.66$  mmol/L for the entire cohort) were normal in 74.2% (193/260) of the patients and abnormally high in 15.8% (67/260) of the patients (lack of LDL-C information for 6 patients). Most patients had T3 disease, and more than half had N0 disease. More patients had stage IIIB disease, followed by stage IIA disease. One to five tumor deposits were found in 7.1% (19/266) of the patients, and 71.8% (191/266) of the patients had 12 or more lymph nodes sampled.

Table 1

Basic and pathological characteristics of the cohort.

Characteristics	<i>n</i>	%
Gender		
Male	137	51.5
Female	129	48.5
T stage		
T1	3	1.1
T2	72	27.1
T3	107	40.2
T4a	80	30.1
T4b	4	1.5
N stage		
N0	153	57.5
N1a	29	10.9
N1b	45	16.9
N1c	9	3.4
N2a	21	7.9
N2b	9	3.4
TNM stage		
I	58	21.8
IIA	64	24.1
IIB	29	10.9
IIC	2	0.8
IIIA	13	4.9
IIIB	81	30.5
IIIC	19	7.1
Histological grade		
I	80	30.1
II	128	48.1
III	42	15.8
Not determined	16	6.0
Tumor deposits		
Positive	19	7.1
Negative	247	92.9
Number of LN sampled		
$\geq 12$	191	71.8
$< 12$	75	28.2
LVI		
Positive	41	15.4
Negative	215	80.8
Indeterminate	10	3.8
PNI		
Positive	29	10.9
Negative	227	85.3
Indeterminate	10	3.8
Necrosis		
Positive	38	14.3
Negative	228	85.7
Adjuvant treatment		
Yes	152	57.1
No	114	42.9
Disease site		
Colon	105	39.5
Rectum	161	60.5

TNM: Tumor-Node-Metastasis; LN: lymph nodes; LVI: lymphovascular invasion; PNI: perineural invasion.

Relationships of lipid levels with other variables

The levels of the four lipids were interdependent, although HDL-C and LDL-C levels did not correlate with each other ( $r = 0.03$ ,  $P = 0.61$ ). The relationships between lipid levels and other variables are shown in Table 2. Lipid levels were independent of age and gender. TC levels did not correlate with any of the tumor characteristics. TG levels inversely correlated with N stage ( $r = -0.20$ ,  $P = 0.00$ ) and TNM stage ( $r = -0.19$ ,  $P = 0.00$ ). HDL-C levels positively correlated with PNI ( $r = 0.15$ ,  $P = 0.02$ ), and LDL-C levels inversely correlated with LVI ( $r = -0.12$ ,  $P = 0.04$ ).

Prognostic associations

The prognostic effects of the predictor variables were constant over time, and there were linear relationships between OS and the predictor variables (test of the proportional hazards assumption, all  $P > 0.05$ ). Univariate analysis identified T stage ( $P = 0.00$ ), N stage ( $P = 0.00$ ), TNM stage ( $P = 0.00$ ), histological grade ( $P = 0.03$ ), tumor deposit status [hazard ratio (HR) = 2.64, 95% confidence interval (CI): 1.18–5.90,  $P = 0.03$ ], PNI status (HR = 2.39, 95% CI: 1.14–4.99,  $P = 0.03$ ), and LVI status (HR = 2.08, 95% CI: 1.07–4.03,  $P = 0.04$ ) as significant prognostic factors. Necrosis ( $P = 0.75$ ), adjuvant treatment ( $P = 0.23$ ),

and number of lymph nodes sampled ( $P = 0.79$ ) did not predict patient survival. Multivariate analysis showed that only T stage ( $P = 0.01$ ), N stage ( $P = 0.02$ ), and TNM stage ( $P = 0.04$ ) were independent prognostic factors in our cohort.

When included as categorical variables, none of the four lipids predicted OS in univariate or multivariate analyses adjusted for age, gender, T stage, N stage, TNM stage, histological grade, tumor deposits, LVI, PNI, and adjuvant treatment (Tables 3 and 4). In agreement, the Kaplan-Meier curves for OS according to the lipid quartiles were not significantly different, as confirmed by the log-rank test (Figs. 2–5). MFP analysis also found no significant associations between lipid levels and OS (TC:  $P = 0.46$ , TG:  $P = 0.05$ , LDL-C:  $P = 0.73$ , HDL-C:  $P = 0.15$ ).

Subgroup analyses based on gender, disease site, and TNM stage were performed. The results of these analyses showed no significant correlation between lipid levels and OS in these subgroups (all  $P > 0.05$ ) (Table 5).

Comparison of models

The predictive power of two models (one with and one without lipid levels as variables) was compared using Harrell's C-statistic and the AIC. A model with

Table 2  
Correlations between TC, TG, HDL-C and LDL-C levels and patients' characteristics.

Characteristics	TC		TG		HDL-C		LDL-C	
	r	P	r	P	r	P	r	P
Age	0.08	0.21	-0.05	0.46	0.08	0.20	0.10	0.11
Gender	0.10	0.10	-0.01	0.87	0.10	0.11	0.04	0.47
T stage	-0.03	0.62	-0.10	0.12	-0.02	0.69	0.00	0.96
N stage	-0.02	0.75	-0.20	0.00	0.09	0.14	-0.04	0.49
TNM stage	-0.03	0.60	-0.19	0.00	0.06	0.29	-0.04	0.51
Histological grade	0.02	0.78	-0.04	0.53	0.01	0.84	0.03	0.69
Tumor deposits	0.09	0.13	-0.12	0.04	0.09	0.13	0.11	0.07
LVI	-0.07	0.24	-0.08	0.22	0.11	0.09	-0.12	0.04
PNI	0.02	0.72	-0.04	0.48	0.15	0.02	-0.04	0.50
Necrosis	-0.07	0.24	-0.05	0.45	0.05	0.45	-0.05	0.42

Spearman's rank correlation test was used to detect the associations between variables.

TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TNM: Tumor-Node-Metastasis; LVI: lymphovascular invasion; PNI: perineural invasion.

Table 3  
Univariate prognostic analysis of TC, TG, HDL-C and LDL-C.

Lipids	HR (95% CI)	P
TC (mmol/L)		
Q1 (2.42–3.69)	1.00	
Q2 (3.70–4.24)	0.94 (0.42–2.09)	0.88
Q3 (4.25–4.84)	0.93 (0.42–2.07)	0.86
Q4 (4.85–7.25)	0.67 (0.28–1.60)	0.37
TG (mmol/L)		
Q1 (0.45–0.90)	1.00	
Q2 (0.91–1.18)	0.68 (0.30–1.50)	0.34
Q3 (1.19–1.56)	0.71 (0.32–1.58)	0.40
Q4 (1.57–4.73)	0.66 (0.30–1.47)	0.31
HDL-C (mmol/L)		
Q1 (0.43–0.85)	1.00	
Q2 (0.86–1.06)	0.74 (0.29–1.88)	0.53
Q3 (1.07–1.31)	1.32 (0.58–3.01)	0.51
Q4 (1.32–2.78)	1.32 (0.58–3.01)	0.51
LDL-C (mmol/L)		
Q1 (0.85–1.70)	1.00	
Q2 (1.71–2.18)	1.11 (0.50–2.48)	0.80
Q3 (2.19–2.63)	0.50 (0.18–1.34)	0.17
Q4 (2.64–4.29)	1.12 (0.50–2.49)	0.79

TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HR: hazard ratio; CI: confidence interval.

Table 4  
Multivariate prognostic analysis of TC, TG, HDL-C and LDL-C.

Lipids	HR (95% CI)	P
TC (mmol/L)		
Q1 (2.42–3.69)	1.00	
Q2 (3.70–4.24)	0.83 (0.32–2.18)	0.70
Q3 (4.25–4.84)	1.02 (0.41–2.53)	0.97
Q4 (4.85–7.25)	0.44 (0.16–1.21)	0.11
TG (mmol/L)		
Q1 (0.45–0.90)	1.00	
Q2 (0.91–1.18)	0.61 (0.24–1.57)	0.31
Q3 (1.19–1.56)	0.76 (0.30–1.95)	0.57
Q4 (1.57–4.73)	1.06 (0.43–2.57)	0.90
HDL-C (mmol/L)		
Q1 (0.43–0.85)	1.00	
Q2 (0.86–1.06)	0.69 (0.21–2.24)	0.54
Q3 (1.07–1.31)	1.67 (0.61–4.59)	0.32
Q4 (1.32–2.78)	1.39 (0.48–4.07)	0.54
LDL-C (mmol/L)		
Q1 (0.85–1.70)	1.00	
Q2 (1.71–2.18)	0.62 (0.24–1.60)	0.32
Q3 (2.19–2.63)	0.38 (0.13–1.12)	0.08
Q4 (2.64–4.29)	0.81 (0.32–2.03)	0.65

Multivariate Cox proportional hazards regression analysis adjusted by age, gender, T stage, N stage, TNM stage, histological grade, tumor deposits, lymphovascular invasion, perineural invasion, and adjuvant treatment. TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HR: hazard ratio; CI: confidence interval; TNM: Tumor-Node-Metastasis.

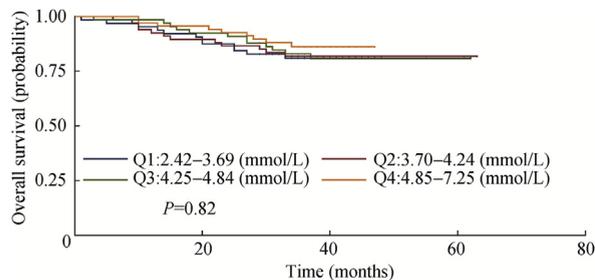


Fig. 2. Kaplan-Meier curve for overall survival according to quartiles of total cholesterol level.

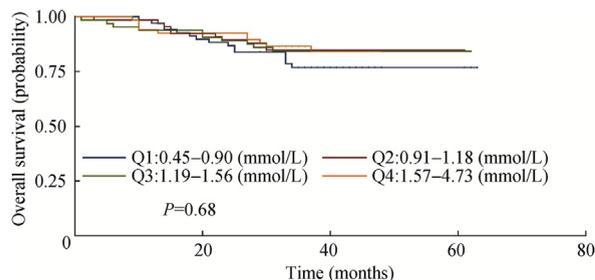


Fig. 3. Kaplan-Meier curve for overall survival according to quartiles of triglyceride level.

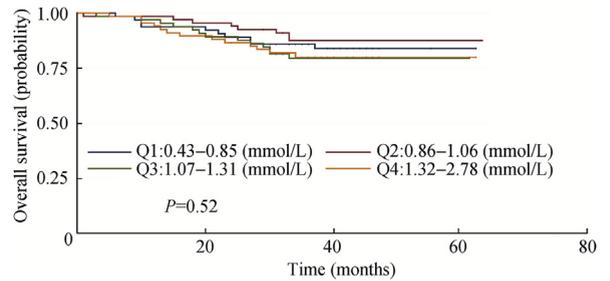


Fig. 4. Kaplan-Meier curve for overall survival according to quartiles of high-density lipoprotein cholesterol level.

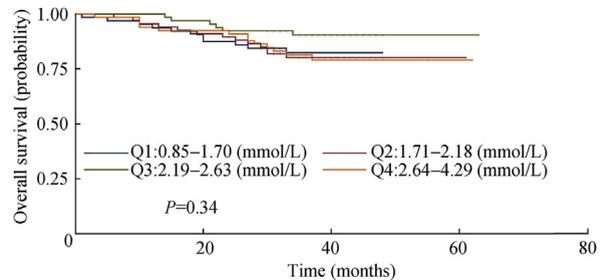


Fig. 5. Kaplan-Meier curve for overall survival according to quartiles of low-density lipoprotein cholesterol level.

perfect predictive capacity (100% sensitivity and specificity) would have a Harrell's C-statistic of 1.00; hence, the higher the value, the better the model. The AIC assesses how well the model fits the data and the complexity of the model. The lower the AIC value, the lower the loss of information for predicting survival outcome. In our comparison, the model with lipids had a higher Harrell's C-statistic (model with lipids vs. model without lipids: 0.82 vs. 0.77) and a lower AIC value (model with lipids vs. model without lipids: 398 vs. 432) than did the model without lipids, and thus was the better model.

## Discussion

The finding that lipid metabolism is abnormal in CRC is somewhat paradoxical. On one hand, reductions in serum cholesterol levels prior to CRC diagnosis have been observed.<sup>27</sup> On the other hand, the levels of TC and LDL-C and the LDL-C/HDL-C ratio are significantly higher in patients with CRC with distant metastases than in those without metastases.<sup>28</sup> It appears that host serum lipid levels vary as the CRC evolves.

To the best of our knowledge, this is one of the few studies that focus on the prognostic role of the pre-treatment lipid profile in patients with non-mCRC. The three other studies that addressed this issue were not

Table 5  
Subgroup analysis of TC, TG, HDL-C and LDL-C based on gender, disease site and TNM stage in univariate Cox proportional hazards regression model.

Lipids	Gender		Disease site		TNM stage	
	Male <i>HR (95% CI)</i>	Female <i>HR (95% CI)</i>	Colon cancer <i>HR (95% CI)</i>	Rectal cancer <i>HR (95% CI)</i>	Stage I, II <i>HR (95% CI)</i>	Stage III <i>HR (95% CI)</i>
TC (mmol/L)						
Q1 (2.42–3.69)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (3.70–4.24)	0.78 (0.28–2.20)	1.45 (0.36–5.80)	1.26 (0.32–5.05)	0.74 (0.28–1.99)	0.92 (0.23–3.70)	0.96 (0.36–2.57)
Q3 (4.25–4.84)	0.47 (0.14–1.52)	2.00 (0.53–7.55)	1.59 (0.45–5.65)	0.61 (0.21–1.76)	1.10 (0.30–4.11)	0.87 (0.31–2.39)
Q4 (4.85–7.25)	0.72 (0.24–2.15)	0.79 (0.18–3.53)	1.13 (0.25–5.05)	0.48 (0.16–1.38)	0.45 (0.82–2.44)	0.81 (0.29–2.23)
TG (mmol/L)						
Q1 (0.45–0.90)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (0.91–1.18)	0.65 (0.22–1.89)	0.78 (0.23–2.72)	0.68 (0.21–2.23)	0.65 (0.22–1.93)	5.65 (0.68–46.90)	0.33 (0.11–0.99)
Q3 (1.19–1.56)	0.60 (0.20–1.74)	0.94 (2.71–3.24)	0.36 (0.09–1.45)	1.10 (0.41–2.96)	3.49 (0.41–29.83)	0.74 (0.27–2.06)
Q4 (1.57–4.73)	0.42 (0.13–1.35)	1.12 (0.34–3.69)	0.50 (0.12–2.00)	0.76 (0.28–2.04)	2.08 (0.22–20.02)	0.83 (0.33–2.05)
HDL-C (mmol/L)						
Q1 (0.43–0.85)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (0.86–1.06)	0.78 (0.21–2.90)	0.71 (0.19–2.66)	1.33 (0.36–4.96)	0.41 (0.10–1.63)	0.59 (0.11–3.21)	0.57 (0.18–1.76)
Q3 (1.07–1.31)	0.97 (0.15–4.01)	0.42 (0.10–1.76)	0.99 (0.22–4.42)	1.39 (0.50–3.83)	1.40 (0.35–5.60)	0.84 (0.30–2.37)
Q4 (1.32–2.78)	0.92 (0.25–3.44)	1.48 (0.49–4.42)	2.93 (0.79–10.92)	0.85 (0.30–2.46)	1.82 (0.49–6.80)	0.72 (0.25–2.06)
LDL-C (mmol/L)						
Q1 (0.85–1.70)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (1.71–2.18)	0.88 (0.29–2.61)	1.52 (0.44–5.19)	1.16 (0.31–4.32)	1.08 (0.39–2.99)	0.76 (0.19–3.04)	1.58 (0.59–4.24)
Q3 (2.19–2.63)	0.37 (0.10–1.42)	0.72 (0.16–3.21)	0.48 (0.09–2.63)	0.50 (0.15–1.72)	0.57 (0.13–2.54)	0.50 (0.13–1.94)
Q4 (2.64–4.29)	1.00 (0.34–3.00)	1.32 (0.39–4.62)	1.30 (0.35–4.83)	1.02 (0.3–2.82)	0.82 (0.21–3.28)	1.45 (0.54–3.91)

TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein; TNM: Tumor-Node-Metastasis; *HR*: hazard ratio; *CI*: confidence interval.

designed specifically for lipid analysis. One of these studies investigated both serum albumin and cholesterol, in which although not statistically significant for cholesterol levels, patients with low serum albumin and low cholesterol levels had shorter OS than patients with normal serum albumin and normal cholesterol levels.<sup>14</sup> That study had a small sample size (only 99 patients). The other two studies did not examine the four lipids separately, but instead focused on dyslipidemia as a whole, and had conflicting results regarding the prognostic role of dyslipidemia.<sup>15,18</sup> Although univariate or multivariate analyses showed that none of the four lipids predicted OS in our study, the inverse correlation of TG level with N stage and TNM stage and LDL-C with LVI indicates a less advanced tumor in patients with higher TG and LDL-C levels, whereas the positive correlation between HDL-C and PNI indicates a more advanced tumor in patients with higher HDL-C level.

The biological mechanism underlying the protective effects of dyslipidemia in non-mCRC has not been well elucidated. In the metastatic setting where the tumor load is high, excessive tumor lipogenesis may account for increased serum lipid levels, as suggested by previous observations.<sup>28</sup> However, in non-metastatic disease where the tumor load is fairly low, dyslipidemia is

most likely host-related. A previous study showed that oxidized LDL-C receptor 1 (OLR1) stimulated proliferation, migration, de novo lipogenesis and inhibited apoptosis by activating nuclear factor- $\kappa$ B (NF- $\kappa$ B) target genes.<sup>29</sup> We suggest that host-related dyslipidemia reduces the malignant potential of tumors by downregulating OLR1-mediated signaling.<sup>30</sup> Future studies are needed to test this hypothesis.

The present study included established prognostic factors routinely used in clinical practice, such as TNM stage, histological grade, tumor deposit status, LVI, and PNI. The prognostic significance of these factors in our study and previous studies was similar. With the inclusion of lipids, the performance of the new prognostic model was improved statistically. Although this finding shows that serum lipids add prognostic value, questions regarding the clinical significance of such added value remain. Nevertheless, the simplicity and cost-effectiveness of serum lipid measurement make it an appealing potential prognostic tool.

Several limitations of our study should be noted. First, because the sample size was relatively small, the study may not have had sufficient power to detect meaningful associations between lipid profiles and clinical outcomes. Hence, the effects observed may be weak but true effect or a mere artifact. Second,

recurrence information was lacking. In postoperative cancer patients, prognostic factors tend to better predict recurrence than OS. Third, confounding factors such as use of statins were not examined. Some studies suggest that the administration of statins to patients with dyslipidemia accounts for the antineoplastic effects of dyslipidemia.<sup>7,8</sup> Statins may combat cancer not by lowering LDL-C levels, but by inhibiting protein prenylation in cancer cells.<sup>31</sup> In our hospital, as in many hospitals throughout China, simple dyslipidemia is difficult to diagnose and is rarely treated. The majority of patients in our cohort had normal or slightly abnormal lipid levels, and the number of patients who received statins was probably negligible. Dyslipidemia often accompanies other metabolic syndrome disorders such as diabetes mellitus, hypertension, and central obesity, all of which are associated with poor prognosis. Confounding of our results by metabolic syndrome disorders is unlikely, since we excluded patients with a history of diabetes mellitus or hypertension.

## Conclusions

In summary, our results corroborate those of previous studies showing positive effects of dyslipidemia on the survival of patients with cancer. Although the lipid profile appears to provide additional information about the non-mCRC mortality risk, questions regarding the clinical significance of this information remain. We recommend further investigation of the prognostic value of the lipid profile as measurement of serum lipids is both simple and cost-effective.

## Conflicts of interest

All authors declare no conflicts of interests.

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