OPEN

Nonalcoholic Fatty Liver Disease

A Negative Risk Factor for Colorectal Cancer Prognosis

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is known to be associated with an increased risk of colorectal cancer (CRC). However, the relationship between NAFLD and the prognosis of CRC remains unclear. The primary objective of this study was to evaluate the overall survival (OS) and disease-free survival (DFS) rates in patients with CRC and the secondary objective was to compare clinicopathologic variables which were stratified by NAFLD.

We performed a large cohort study of 1314 patients who were first diagnosed with CRC between January 2006 and April 2011. Post-operative follow-up data were collected from out-patient medical records, telephone consultations, and social security death indices. The Kaplan–Meier method was used to calculate the cumulative survival rate. Clinicopathologic variables were analyzed by univariate analysis and multivariate analysis through a Cox proportional hazard regression model.

The mean follow-up time was 52.7 ± 25.3 months. Upon baseline comparison, the NAFLD group had significantly higher values of body mass index, triglycerides, and uric acid and significantly lower values of high-density lipoprotein, compared with the non-NAFLD group ($P < 0.05$ for all). There were no significant differences between the 2 groups with regard to tumor location, TNM staging, tumor differentiation, carcinoembryonic antigen, and vascular invasion. The cumulative 1-, 3-, and 5-year OS rates were 96.1%, 85.2%, and 80.6%, respectively, in the NAFLD group, which were statistically significantly higher than the OS rates of 91.6%, 76.2%, and 67.8%, respectively, in the non-NAFLD group ($P = 0.075$, $P = 0.002$, $P = 0.030$, respectively). There was no difference in DFS rates between the CRC patients with and without NAFLD ($P = 0.267$). Multivariate analysis showed that the presence of NAFLD was an independent negative risk factor for OS after adjusting for clinicopathologic covariates (hazard ratio = 0.593; 95% confidence interval 0.442, 0.921; $P = 0.020$), but not for DFS ($P = 0.270$).

NAFLD may play a protective role in OS for CRC patients. Further studies are needed to elucidate the molecular mechanisms of putative protective effects in CRC patients with NAFLD.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CEA = carcinoembryonie antigen, CRC = colorectal cancer, CI = confidence interval, DM = diabetes mellitus, DFS = disease-free survival, HDL = high-density lipoprotein, HR = hazard ratio, IGF = insulin-like growth factor, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, OS = overall survival.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the world and >1.2 million new cases are diagnosed each year.[1,2] It is also the second leading cause of cancer mortality.[3] It has been confirmed that most cases of CRC develop slowly over >10 years through the adenoma-carcinoma sequence.[4] In China, the incidence and mortality from CRC have substantially increased at a higher rate in urban rather than rural areas over the past several decades.[5] Changes in dietary patterns and physical activity may contribute to the increasing risk of CRC. Other risk factors for the development of CRC, which include family history of the disease, inflammatory bowel disease, smoking, excessive alcohol consumption, obesity, and diabetes mellitus (DM), have all been proven to be associated with the development of CRC.[6–10] Therefore, it is necessary to identify risk factors, which may be associated with adverse outcomes in patients with CRC.

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Nonalcoholic fatty liver disease (NAFLD) is a clinical syndrome characterized by predominant macrovesicular steatosis of the liver.[11] It is now recognized to be the most common chronic liver disease worldwide, affecting up to 20% to 40% of the population.[12,13] The common most risk factors for acquiring NAFLD are obesity, DM, and hyperlipidaemia, which have been reported as predictable risks for CRC.[14–16] Recently, several cross-sectional studies have been conducted to understand the potential association of NAFLD with an increased rate of colorectal adenomas and cancer.[17,18] Our previous study further confirmed that NAFLD is an independent risk factor for CRC, even after adjusting for metabolic and other demographic factors.[19]

To date, there have been few studies investigating the potential impact of NAFLD on the prognosis of patients with CRC. Recently, one study found that the presence of NAFLD showed a favorable trend on survival rates in CRC patients, although the data did not reach statistical significance ($P = 0.079$), perhaps in part due to the small number of patients (227 patients) and poor statistical power.[20] Therefore, we aimed to design a large and more statistically robust cohort study to investigate the impact of NAFLD on the prognosis of patients with CRC.

MATERIALS AND METHODS

Study Protocol

In this study, we included 1314 patients who underwent surgical resection of CRC at the First Affiliated Hospital of Wenzhou Medical University between January 2006 and April 2011. Patients with any history of other cancers, adolescents (<18 years' old), those with familial adenomatous polyposis syndrome of hereditary nonpolyposis CRC, viral hepatitis, cirrhosis, liver cancer, or other liver disease, patients who took medications that could cause fatty disease, or men who consumed >30 g of alcohol per day, and women who consumed >20 g/day over a 2-year period prior to diagnosis of NAFLD were excluded.[17,21] Demographic, pre-operative laboratory, and pathologic data of all patients were collected from electronic medical records and reviewed. The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and informed consent was obtained from every patient.

Ultrasound Examination

Hepatic ultrasonography scanning (Siemens, Germany) was performed on all patients by 3 experienced sonographers who were blinded to the clinical details of the patients. The diagnosis of NAFLD was based on specific ultrasonographic features including hepatomegaly, diffusely increased echogenicity of liver parenchyma, and blurring of vasculature.[22] This diagnosis was reached after exclusion of viral hepatitis, cirrhosis, liver cancer or other liver disease, and excess alcohol consumption.

Data Collection

Data collection included history of smoking, alcohol consumption, history of DM and hypertension, surgical outcomes, clinicopathologic variables, chemotherapy administered, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting glucose, total cholesterol, and carcinoembryonic antigen (CEA). Body mass index (BMI) was calculated as weight (kg) in kilograms divided by height (m) in meters squared (kg/m^2). Subjects were defined as obese when their BMI was the same or $>25\,kg/m^2$.

Patients with CRC were primarily treated by surgical resection with adjuvant chemotherapy for node-positive patients and node-negative patients with adverse pathological features according to the National Comprehensive Cancer Network guidelines. CRC tumor stage was defined on the basis of the American Joint Committee on Cancer staging system. Information regarding tumor location, TNM staging and histologic differentiation of tumors, and vascular invasion and treatment options was collected from pathological and colonoscopic sample analyses.

Patients were followed up in a postoperative outpatient schedule for every 3 to 6 months for 2 years, every 6 months thereafter for a total of 5 years and every 1 year thereafter. Colonoscopy and imaging with computed tomography (CT) were obtained at postoperative follow-up appointments in addition to blood analysis including CEA. Tumor recurrence such as suggested by elevated CEA, abnormal findings on colonscopy, or the CT scan was defined as an earlier follow-up event. Information on death was obtained either from the patient's social security death index, outpatient medical records, or notifications from the family of the deceased. The overall survival (OS) rates were calculated as the date of initial visit to the date of death or the date of last follow-up after the initial visit. DFS was defined as the time from surgery to the time of recurrence or date of last follow-up after surgery.

Statistical Analysis

Continuous variables were tested for normality by using the Kolmogorov–Smirnov test. Continuous data with a normal distribution were expressed as the mean ± standard deviation (SD) and compared using a standard *t* test. Otherwise, continuous data with non-normal distribution were compared using the Wilcoxon rank-sum test. Categorical variables were expressed as percentage and compared using the Chi-square test or Fisher exact test as appropriate. Kaplan–Meier survival curves with log-rank tests and Cox proportional hazard regression analyses, recording patients at the time of last follow-up visit, were used to compare the OS and DFS rates. Variables with $P < 0.1$ in the univariate Cox regression analysis were progressed to a multivariate analysis using forward stepwise selection. All *P* values were 2-sided and a *P* value <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL, USA) and MedCalc version 13.0.0.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Baseline Characteristics

A total of 1314 CRC patients were enrolled in this study. Of these, a total of 127 (9.7%) patients had NAFLD. Table 1 shows the baseline characteristics of the CRC patients with and without NAFLD. Upon baseline comparison, there were no statistically significant differences between the 2 groups with respect to sex, age, fasting glucose, total cholesterol, LDL, AST, creatinine, medical history of DM, and smoking habit. However, the NAFLD group had a significantly higher incidence of hypertension and obesity, higher values of BMI, triglyceride, and uric acid and lower values of HDL when compared with the non-NAFLD group ($P < 0.05$ for all, Table 1).

TABLE 1. Baseline Characteristics of Colorectal Cancer Patients Stratified by NAFLD (n = 1314)

Variables	NAFLD Group (n = 127)	Non-NAFLD Group (n = 1187)	*P*
Demographic data			
Male sex, n (%)	68 (53.5%)	717 (60.4%)	0.134
Age (years)	67.2 ± 10.1	65.9 ± 12.8	0.340
BMI (kg/m^2)	24.4 ± 3.6	21.6 ± 3.7	0.036
Diabetes, n (%)	12 (9.4%)	119 (10.0%)	0.837
Hypertension, n (%)	59 (46.5%)	328 (27.6%)	0.001
Obesity, n (%)	46 (36.2%)	145 (12.2%)	0.001
Smoking, n (%)	44 (34.6%)	498 (42.0%)	0.112
Preoperative laboratory data			
Fasting glucose (mmol/dL)	6.6 ± 2.3	6.1 ± 2.3	0.263
Total cholesterol (mmol/dL)	4.8 ± 1.0	4.4 ± 1.1	0.282
Triglycerides (mmol/dL)	1.9 ± 0.99	1.4 ± 0.97	0.001
HDL (mmol/dL)	1.11 ± 0.28	1.12 ± 0.35	0.011
LDL (mmol/dL)	2.8 ± 1.0	2.6 ± 0.9	0.512
AST (IU/L)	25.7 ± 17.5	23.7 ± 39.5	0.149
ALT (IU/L)	23.9 ± 10.8	28.3 ± 42.5	0.054
Creatinine (μmol/L)	64.5 ± 25.9	63.3 ± 31.5	0.614
Uric acid (mmol/L)	302.2 ± 88.9	274.4 ± 100.2	0.001
CEA (ng/mL)	15.3 ± 68.5	45.1 ± 443.6	0.450
Pathological data			
Location			
Right side, n (%)	14 (11.0%)	194 (16.3%)	0.242
Sigmoid, n (%)	29 (22.8%)	203 (17.1%)	
Rectal, n (%)	67 (52.8%)	630 (13.1%)	
Stage			
Stage I, n (%)	18 (14.2%)	192 (16.2%)	0.754
Stage II, n (%)	54 (42.5%)	449 (37.8%)	
Stage III, n (%)	46 (36.2%)	449 (37.8%)	
Stage IV, n (%)	9 (7.1%)	97 (8.2%)	
Stage I and II, n (%)	72 (56.7%)	641 (54.0%)	0.563
Stage III and IV, n (%)	55 (43.3%)	546 (46.0%)	
Differentiation			
Well, n (%)	5 (3.9%)	38 (3.2%)	0.168
Moderately, n (%)	94 (74.0%)	829 (69.8%)	
Poorly, n (%)	12 (9.4%)	183 (15.4%)	
Mucinous, n (%)	16 (12.6%)	137 (11.5%)	
Well and Moderately, n (%)	99 (78.0%)	867 (73.0%)	0.295
Poorly and Mucinous, n (%)	28 (22.0%)	320 (27.0%)	
Vascular invasion, n (%)	12 (9.4%)	173 (14.6%)	0.114
Treatment			<0.001
Local treatment, n (%)	7 (5.5%)	163 (13.7%)	
Op alone, n (%)	55 (43.0%)	271 (22.8%)	
OP + CTx and/or RTx, n (%)	60 (47.2%)	726 (61.2%)	
Palliative CTx, n (%)	5 (3.9%)	27 (2.3%)	

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CEA = carcinoembryonic antigen, CTx = chemotherapy, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, Op = operation, RTx = radiotherapy.

Tumor characteristics and Treatment

Table 1 shows the tumor characteristics of the 2 groups according to the presence of NAFLD. There were no significant differences between the 2 groups regarding the location, TNM staging, tumor differentiation, and CEA. The modality of treatment was different between the 2 groups; notably more CRC patients without NAFLD underwent chemotherapy and/or radiotherapy than patients with NAFLD ($P < 0.001$).

Overall and Disease-free Survival Analysis

The mean follow-up time of the cohort was 52.7 ± 25.3 months. The mean follow-up time was 59.1 ± 23.6 months in the NAFLD group and 52.1 ± 25.4 months in the non-NAFLD patient group ($P = 0.003$). During the follow-up period, observed patient survival was 79.5% (101/127) in the NAFLD group and 67.6% (802/1187) in the non-NAFLD group. As shown in Figure 1A, the difference between the 2 survival curves for the 2 groups was statistically significant ($P = 0.005$). The cumulative 1-, 3-, and 5-year OS rates in the NAFLD group were 96.1%, 85.2%, and 80.6%, respectively, all of which were significant higher than OS rates of 91.6%, 76.2%, and 67.8%, respectively, in the non-NAFLD patient group ($P = 0.075$, $P = 0.002$, $P = 0.030$, respectively).

During the mean follow-up period of 52.3 ± 26.8 months, freedom from recurrence was observed in 87 of 118 (73.7%) patients in the NAFLD group and 759 of 1095 (69.3%) in the non-NAFLD patient group ($P = 0.015$). As shown in Figure 1B, the DFS curve of the NAFLD group was favorable when compared with that of the non-NAFLD group. However, the

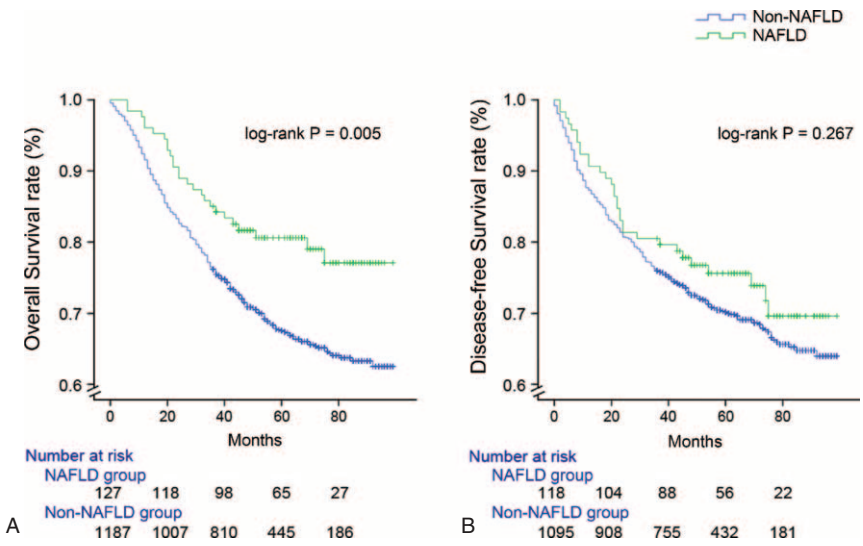

FIGURE 1. Kaplan–Meier survival curves showing overall survival (A) and disease-free survival (B) in colorectal cancer patients with and without nonalcoholic fatty liver disease.

TABLE 2. Cox Proportional Hazards Regression Models of Risk Factors Associated with Overall and Disease-free Survival Among CRC Patients (n = 1314)

	Overall Survival						Disease-free Survival					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
NAFLD	0.571	0.384–0.849	0.006	0.593	0.442–0.921	0.020	0.813	0.562–1.175	0.270			
Sex	1.389	1.133–1.704	0.002	1.501	1.188–1.897	0.001	0.729	0.588–0.904	0.004	0.682	0.534–0.872	0.002
Age	1.011	1.003–1.019	0.009	1.011	1.003–1.019	0.010	1.007	0.998–1.015	0.111			
BMI (kg/m^2)	0.968	0.939–0.998	0.035				0.984	0.954–1.016	0.328			
<18.5	1.000	–	–				1.000	–	–			
18.5–24.9	0.687	0.540–0.875	0.002				0.841	0.457–1.549	0.578			
25–30	0.782	0.580–1.053	0.105				0.695	0.389–1.244	0.221			
>30	0.764	0.409–1.427	0.399				0.760	0.412–1.401	0.379			
Fasting glucose	1.025	0.988–1.064	0.194				1.022	0.983–1.062	0.276			
TNM staging	0.220	0.176–0.275	<0.001	0.244	0.192–0.310	<0.001	0.322	0.260–0.398	<0.001	2.904	2.306–3.657	<0.001
Stage I	1.000	–	–	1.000	–		1.000	–	–	1.000	–	–
Stage II	1.009	0.6640–1.533	0.967	0.671	0.378–1.191	0.173	1.022	0.805–1.484	0.907	0.970	0.658–1.429	0.877
Stage III	3.438	2.356–5.016	<0.001	2.657	1.600–4.413	<0.001	3.119	2.220–4.381	<0.001	2.840	1.982–4.070	<0.001
Stage IV	17.431	11.575–26.248	<0.001	10.029	5.763–17.453	<0.001	11.790	4.199–33.102	<0.001	9.905	3.366–29.151	<0.001
Differentiation	0.580	0.474–0.711	<0.001	0.749	0.601–0.933	0.010	0.604	0.486–0.750	<0.001	1.379	1.092–1.743	0.007
Total cholesterol	0.951	0.894–1.013	0.117				0.939	0.880–1.003	0.061			
Triglycerides	0.882	0.791–0.984	0.024				0.947	0.851–1.053	0.312			
HDL	0.502	0.363–0.693	<0.001	0.637	0.451–0.899	0.010	0.481	0.34–0.682	<0.001	0.581	0.393–0.858	0.006
LDL	1.125	1.054–1.200	<0.001	1.148	1.068–1.234	<0.001	1.103	1.029–1.182	0.006	1.116	1.029–1.211	0.008
AST	1.003	1.001–1.006	0.065				1.002	0.998–1.006	0.227			
ALT	1.005	1.002–1.007	<0.001				1.005	1.001–1.009	0.011	1.005	1.001–1.009	0.023
Creatinine	1.000	0.997–1.003	0.958				1.001	0.998–1.004	0.536			
Uric acid	0.998	0.997–0.999	<0.001	0.998	0.997–1.000	0.006	0.999	0.998–1.000	0.016	0.999	0.998–1.000	0.032
Diabetes	0.980	0.707–1.358	0.905				0.948	0.672–1.338	0.763			
Hypertension	0.873	0.707–1.078	0.206				0.837	0.670–1.046	0.117			
Location	1.188	0.979–1.441	0.081				1.086	0.885–1.333	0.428			
Obesity	0.938	0.717–1.227	0.641				1.159	0.876–1.535	0.301			
Vascular invasion	0.528	0.416–0.669	<0.001				0.608	0.465–0.795	<0.001			
CEA	1.000	1.000–1.001	<0.001	1.000	1.000–1.001	<0.001	1.000	1.000–1.001	<0.001			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, HDL = high–density lipoprotein, HR = hazard ratio, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease.

difference between the 2 curves was not statistically significant ($P = 0.267$). The cumulative 1-, 3-, and 5-year DFS rates in the NAFLD group were 90.7%, 79.7%, and 75.6%, respectively, all of which were not statistically higher than the DFS rates of 87.3%, 76.0%, and 69.8%, respectively, observed in the non-NAFLD group.

Univariable and multivariate Cox proportional hazard models were used to identify variables associated with OS and DFS in the study population and are presented in Table 2. Fasting glucose, total cholesterol, creatinine, history of DM, hypertension, and obesity were not significant predictive factors for the prognosis of CRC patients as determined by univariate analysis. In the multivariate Cox analysis of OS, the presence of NAFLD, sex, age, TNM staging, tumor differentiation, HDL, LDL, and uric acid were independent predictive risk factors for the prognosis of CRC patients after adjustment for BMI, AST, ALT, tumor location, and vascular invasion ($P < 0.05$ for all, Table 2).

The presence of NAFLD, age, BMI, fasting glucose, triglycerides, AST, creatinine, the history of DM, and hypertension and obesity were not significant predictive factors for DFS of CRC patients as determined by univariate analysis. In the multivariate Cox analysis of DFS, sex, TNM staging, tumor differentiation, HDL, LDL, ALT, and uric acid were independent predictive risk factors for the prognosis of CRC patients after adjusting for total cholesterol and vascular invasion ($P < 0.05$ for all, Table 2).

Subgroup Analyses Associated With NAFLD

In the subgroup analyses, the treatment options had no direct impact on patient prognosis adjusting for NAFLD (Table 3). However, the presence of NAFLD had a significant impact on OS in patients with stage II and stage III CRC ($P = 0.048$, $P = 0.057$, respectively), when stratified by TNM staging (Table 3). On consideration of the impact of BMI in the different ranges, multivariate analysis showed that BMI in the abnormal ranges (BMI $<18.5\,kg/m^2$ and BMI $\geq 25\,kg/m^2$) had no impact on the prognosis of CRC patients after adjustment for NAFLD for all above covariates. However, the presence of NAFLD had a significant impact on the prognosis for patients with BMI in the normal range ($18.5–24.9\,kg/m^2$) ($P < 0.05$) (Table 4). In the NAFLD subgroup, the patients were stratified according to sex, TNM stage, tumor differentiation, age (<60 vs ≥60 years), HDL (<1.2 vs ≥1.2 mmol/dL), LDL (<3.0 vs ≥3 mmol/dL), uric acid (<300 vs ≥300 mmol/L), and CEA (<5 vs ≥5 ng/mL), respectively (Figure 2). Analysis of the risk factors of OS showed that there was only a significant difference in TNM staging ($P = 0.001$) (Figure 2C).

DISCUSSION

This study shows for the first time that the presence of NAFLD may be an independent prognostic factor for the OS of CRC patients (hazard ratio [HR]0.593, $P = 0.020$), but not for DFS. The presence of DM and BMI failed to show prognostic value in the multivariate analyses of OS and DFS. However, in patients stratified by quartiles of BMI, the subgroup analyses showed significant association between NAFLD and the prognosis in patients within the normal BMI range ($18.5–24.9\,kg/m^2$).

To date, the prognostic effects of obesity in CRC remain unclear and recent studies have failed to find a significant association between BMI and CRC prognosis.[23–25] In a study of Asian populations, even among men with BMI 18.5 to $22.9\,kg/m^2$, mild weight gains of 0.6 to 2.3 kg were associated with 38% to 73% increase in the risk for fatty liver disease.[26] This observation could, to some extent, explain the results of our study in patients within the normal BMI range. Contrary to the results from the previous studies suggesting a role for DM on CRC prognosis,[27–29] the present study failed to confirm that DM negatively impacted survival outcomes of CRC patients. When the patients were stratified by TNM staging, we found that the presence of NAFLD had a significant correlation with OS in tumor stage II and stage III. Taken together, this may imply that there was a tendency for protective power of NAFLD to decrease with an increase in TNM staging.

NAFLD is known to be associated with a higher risk of many extrahepatic cancers, including CRC. Several studies focused on different cancers have reported disparate findings.[30,31] Recent studies have demonstrated that NAFLD was a risk factor for colorectal adenomas and advanced neoplasm[17–19]; however, few studies have specifically focused on the impact of NAFLD on the outcomes of CRC patients. Until now, only 1 published study has examined the impact of NAFLD on the prognosis for CRC patients.[20] The results show that there was a

TABLE 3. Cox Proportional Hazard Regression Analysis of Overall and Disease-free Survival Stratified by TNM Staging and Treatment Options in CRC Patients Adjusting for NAFLD (n = 1314)

	Overall Survival			Disease-free Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
TNM Staging						
Stage I	1.000	0.303–3.297	1.000	0.783	0.241–2.548	0.684
Stage II	0.312	0.098–0.991	0.048	0.598	0.277–1.290	0.190
Stage III	0.580	0.331–1.017	0.057	0.974	0.621–1.525	0.907
Stage IV	0.635	0.290–1.388	0.255	–	–	–
Treatment options						
Local treatment	0.932	0.343–2.530	0.889	1.565	0.378–6.484	0.535
Op alone	0.497	0.177–1.398	0.185	0.689	0.311–1.527	0.359
OP + CTx and/or RTx	0.730	0.425–1.253	0.254	1.118	0.723–1.730	0.616
Palliative CTx *	0.686	0.235–2.002	0.491	–	–	–

CI = confidence interval, CRC = colorectal cancer, CTx = chemotherapy, HR = hazard ratio, NAFLD = nonalcoholic fatty liver disease, Op = operation, RTx = radiotherapy.

* All patients who underwent Palliative CTx belonged to stage IV.

TABLE 4. Cox Proportional Hazards Regression Analysis of Overall and Disease-free Survival from Any Cause Associated with BMI among CRC Patients (n = 1314)

	Overall Survival						Disease-free Survival					
	Multivariable*			Multivariable†			Multivariable*			Multivariable†		
BMI (kg/m^2)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
<18.5	1.211	0.383–3.827	0.744	0.809	0.628–1.040	0.099	0.939	0.794–1.111	0.465	0.868	0.633–1.190	0.397
18.5–24.9	0.902	0.820–0.991	0.031	0.509	0.273–0.948	0.033	0.871	0.789–0.962	0.006	0.919	0.800–1.057	0.239
25–30	1.107	0.931–1.315	0.250	1.103	0.876–1.389	0.406	1.113	0.924–1.340	0.260	1.059	0.804–1.395	0.684
>30	0.872	0.680–1.119	0.283	1.477	0.084–25.839	0.789	0.919	0.752–1.123	0.409	1.030	0.736–1.441	0.865

CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, NAFLD = nonalcoholic fatty liver disease.
* Adjusted for NAFLD.
† Adjusted for all covariates (age, sex, NAFLD, TNM staging, differentiation, high-density lipoprotein, low-density lipoprotein, uric acid, carcinoembryonie antigen).

favorable tendency for association in the CRC patients with NAFLD, although the presence of NAFLD had no statistically significant impact on the prognosis of CRC during follow-up ($P = 0.079$). A further study suggested that NAFLD may play a protective role against biochemical recurrence after radical prostatectomy for prostate cancer (HR = 0.36, $P = 0.004$).[31]

The possible molecular mechanisms underlying the effects of NAFLD on CRC are not completely understood, although there are some plausible hypotheses. First, insulin and insulin-like growth factors (IGFs), especially IGF-1, may play a key role in CRC carcinogenesis through their proliferative and anti-apoptotic effects. A meta-analysis of 19 studies demonstrated that elevated circulating IGF-1 levels were significantly associated with CRC risk (odds ratio = 1.25, 95% CI 1.08–1.45 for IGF-1).[32] Furthermore, multivariate analyses indicated that expression of IGF-1, detected as either IGF-1 mRNA in cancer tissue or by measurement of serum concentrations of IGF-1 protein (after adjusting for clinicopathologic factors, $P < 0.05$),[33] was a risk factor for prognosis in CRC patients[34]. In support of these findings, it is recognized that the liver is the main site of circulating IGF-1 in humans and that several studies have suggested that NAFLD is associated with low circulating levels of IGF-1.[35,36] These observations may explain, at least to some extent, why NAFLD is negatively associated with poor prognosis of CRC patients. Second, adiponectin and leptin, which are potential key mediators of many biochemical mechanisms, were significantly decreased and increased respectively in NAFLD patients and also in CRC patients.[37–40] Different

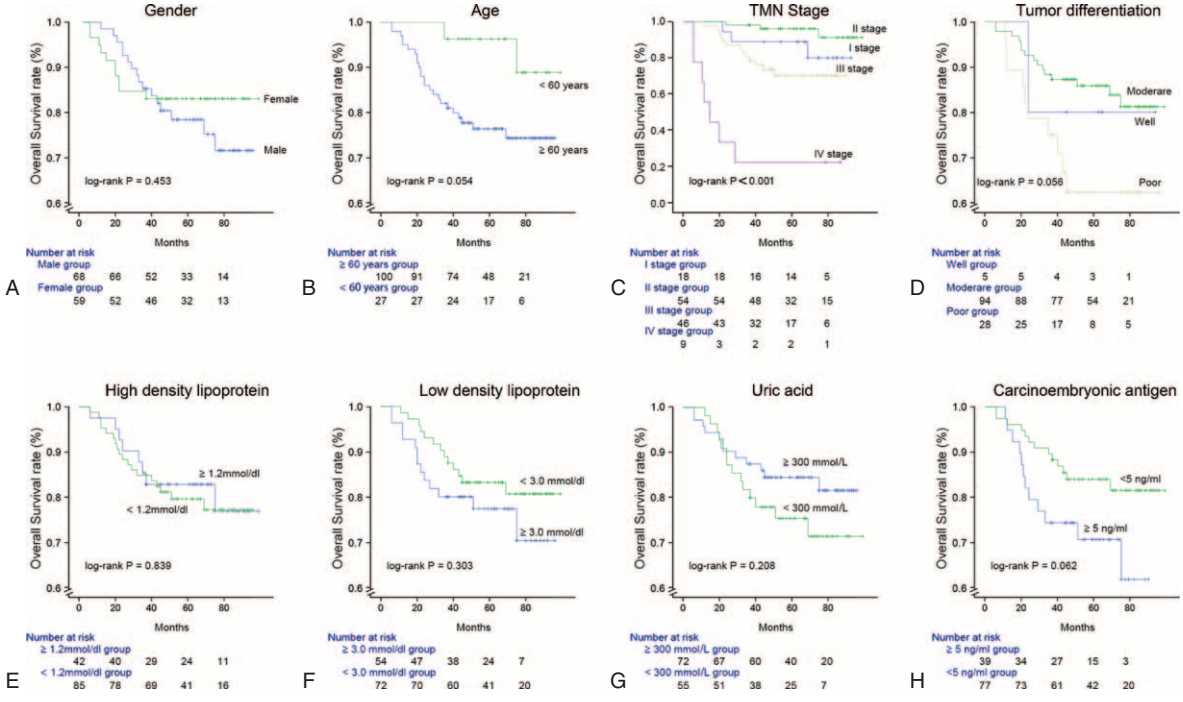

FIGURE 2. Overall survival of NAFLD group following surgical resection, stratified by sex (A), age (B), TNM staging (C), tumor differentiation (D), HDL (E), LDL (F), uric acid (G), and CEA (H). CEA = carcinoembryonic antigen, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease.

functional adiponectin polymorphisms may lead to a different outcome and 1 meta-analysis has indicated that the adiponectin polymorphism rs2241766T/G rather than rs1501299G/T, rs266729C/G, rs822395A/C, and rs822396A/G polymorphisms was associated with the risk of developing CRC.[41] A further meta-analysis has suggested that adiponectin +45T > G and −11377C > G polymorphisms may be a risk factor for NAFLD, whereas +276G > T polymorphism may be a protective factor for NAFLD among Asians.[42] With respect to the potential impact of adiponectin and leptin on the prognosis of colorectal cancer, low serum adiponectin may represent an exploratory biomarker in risk prediction for CRC recurrence and the leptin/adiponectin ratio may be an important independent predictor for adverse outcome in CRC.[43,44] Interestingly, the levels of adiponectin and leptin both increased significantly after patients with advanced CRC received chemotherapy.[45] Furthermore, patients with NAFLD may have had more opportunities for therapeutic intervention and had to adjust their level of adipose tissue function, an essential factor for patients to achieve a good survival prognosis. In summary, further studies are needed to confirm the effects of different levels of adiponectin and leptin on the prognosis of CRC patients with NAFLD, especially in Asian populations.

The present study has several limitations. First, we used abdominal ultrasonography as a noninvasive mode for the diagnosis of NAFLD, whereas liver biopsy as an invasive procedure is regarded as the gold standard. However, mean sensitivity estimates for ultrasonography ranged from 73.3% to 90.5%, and the mean specificity range was 69.6% to 85.2%, suggesting that the use of this noninvasive modality may have the potential to become the diagnostic test of choice for NAFLD rather than liver biopsy.[46] Secondly, the retrospective design and relatively small number of NAFLD patients (n = 127) may represent a further limitation of our study. However, this limitation may be negated by our analyses of the patient subgroups, which are based on BMI, treatment options, and tumor stages. A further limitation may be the retrospective design, which could introduce selection bias, and our conclusions may only be applied to an Asian population. Future studies are needed to prospectively address the influence of different ethnic groups on the conclusions of our study.

In summary, the results of this study show that the presence of NAFLD may play a protective role against the prognosis of OS in CRC patients. Further studies are needed to understand the biochemical mechanisms, which may explain this protective effect against CRC in patients with NAFLD.

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