Original Article

Association between surrogate indices of fatty liver and the risk of colorectal cancer: a cross-sectional United States study

Chenyuan Shi[1#], Chao Yuan[1#], Yifei Hao[2#], Zheng Zhou[1], Yigang Zhang[2]

[1]Department of Emergency Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Contributions: (I) Conception and design: C Shi, Y Zhang; (II) Administrative support: Z Zhou; (III) Provision of study materials or patients: C Yuan; (IV) Collection and assembly of data: Y Hao; (V) Data analysis and interpretation: Y Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zheng Zhou, MD, PhD. Department of Emergency Medicine, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China. Email: zhouzheng@njmu.edu.cn; Yigang Zhang, MD, PhD. Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China. Email: zhangyg0021@163.com.

Background: The presence of fatty liver (FL) has been suggested to influence the incidence of colorectal cancer (CRC). This study aimed to evaluate the predictive utility of six alternative indices of FL—namely, liver fat percentage (PLF), lipid accumulation product (LAP), hepatic steatosis index (HSI), United States fatty liver index (USFLI), fatty liver index (FLI), and Zhejiang University index (ZJU)—in assessing the risk of CRC. We aimed to determine their effectiveness in predicting CRC risk by comparing these surrogate indices.

Methods: Data for this study were derived from the National Health and Nutrition Examination Survey (NHANES) conducted between 2003 and 2018, focusing on adults over 20 years old. The six FLIs were calculated using established methodologies outlined in prior research. To identify key variables, the Boruta algorithm was employed. The relationships between FLIs and CRC risk were assessed using multivariable logistic regression, generalized linear models (GLMs), and restricted cubic spline (RCS) models. Additionally, subgroup analyses were performed to investigate the effects of potential confounders.

Results: Among the 16,250 individuals surveyed, 96 were diagnosed with CRC. Those with CRC exhibited significantly higher levels of PLF (4.65 *vs.* 3.31, P=0.004), LAP (55.63 *vs.* 42.34, P=0.04), USFLI (23.22 *vs.* 17.83, P<0.001), and FLI (58.16 *vs.* 50.86, P=0.048) compared to individuals without CRC. Multivariate logistic regression and RCS analyses indicated that, of the six indices, only USFLI was significantly associated with an increased risk of CRC. Notably, further stratification of USFLI revealed that this association was consistently stronger in individuals aged over 65 years [odds ratio (OR) =1.023; 95% confidence interval (CI): 1.005–1.041; P=0.01] and among non-smokers (OR =1.018; 95% CI: 1.003–1.033; P=0.02) after adjusting for multiple confounders.

Conclusions: The USFLI index demonstrated a more significant association with the risk of CRC compared to the other five alternative FLIs, highlighting its potential utility in predicting CRC risk in clinical settings.

Keywords: Colorectal cancer (CRC); fatty liver (FL); United States fatty liver index (USFLI); Boruta algorithm; National Health and Nutrition Examination Survey (NHANES)

Submitted Aug 17, 2024. Accepted for publication Oct 31, 2024. Published online Jan 23, 2025.
doi: 10.21037/tcr-24-1444
View this article at: https://dx.doi.org/10.21037/tcr-24-1444

Introduction

According to the latest statistics, colorectal cancer (CRC) ranks as the third most commonly diagnosed cancer in both genders (1). Despite the improvement of endoscopic screening increased the detection rate of early-stage CRC, while advances in surgery have increased the overall survival of patients with resectable CRC, patients with advanced disease still face a poor prognosis, and CRC is estimated to be the third highest cause of cancer-related death worldwide (1,2). This underscores the necessity of identifying risk factors and implementing preventive measures, particularly within high-risk populations. Previous research has identified several established risk factors for CRC, including a family history of the disease, hereditary conditions such as Lynch syndrome and familial adenomatous polyposis, inflammatory bowel disease, smoking, alcohol consumption, and the intake of processed meats (3). However, the potential impact of emerging factors, such as fatty liver (FL), on CRC risk has been relatively overlooked and remains largely unexamined. Therefore, investigating the influence of FL on CRC risk is essential for effectively mitigating the disease burden associated with CRC.

FL is characterized by the accumulation of fat in the liver and encompasses a spectrum of conditions ranging from initial steatohepatitis to advanced fibrosis and cirrhosis (4,5). As the most prevalent liver disease globally, FL is traditionally categorized into non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) (6). Recently, a more inclusive definition known as metabolic dysfunction-associated fatty liver disease (MAFLD) has gained traction as a potential replacement for the NAFLD classification (7-9). Despite ongoing debates regarding these definitions, there is a consensus among researchers that FL is a multi-systemic disease that extends beyond the liver and may contribute to various extrahepatic disorders, including tumorigenesis (10-12). Recent studies have suggested that FL could be a significant risk factor for CRC, as it shares metabolic disturbances and elevated systemic inflammation with conditions such as diabetes and obesity (13,14). Additionally, research has indicated that liver fat accumulation in FL may disrupt gut microbiota, which plays a critical role in the tumorigenesis of CRC (15,16). Nevertheless, the precise relationship between FL, liver fat accumulation, and CRC risk has yet to be fully clarified.

In clinical practice, liver ultrasonography (LUS) is the most common method for diagnosing FL. In instances where LUS is unavailable, non-invasive and non-imaging surrogate indices of FL are recommended for diagnosis (17-19). Various indices, including liver fat percentage (PLF), lipid accumulation product (LAP), hepatic steatosis index (HSI), United States fatty liver index (USFLI), fatty liver index (FLI), and Zhejiang University index (ZJU), have been developed as assessment tools to quantify liver fat accumulation (20-22). This study employs these FLIs to evaluate the degree of hepatic fat accumulation. Data from the National Health and Nutrition Examination Survey (NHANES) was used to investigate the association between FLIs and CRC among adults from the United States (US). The ultimate objective of this study was to assess the effectiveness of FLIs in predicting CRC risk, thereby providing a theoretical foundation for CRC prevention from a public health perspective. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1444/rc).

Highlight box

Key findings

- This study identifies a significant association between United States fatty liver index (USFLI) and the risk of developing colorectal cancer (CRC). Of the six fatty liver (FL) indices examined, USFLI demonstrated the strongest correlation with CRC risk, especially among individuals over 65 years of age and non-smokers.

What is known and what is new?

- Existing knowledge highlights FL as a potential risk factor for CRC, but comprehensive studies using surrogate indices such as USFLI in assessing CRC risk are limited.
- This study adds a new dimension by demonstrating the predictive utility of USFLI for CRC risk in a cross-sectional analysis of the United States adult population. It offers comparative insights into six surrogate indices, with USFLI standing out as a significant predictor.

What is the implication, and what should change now?

- The findings suggest that USFLI could serve as a practical tool in clinical settings to identify individuals at higher risk of CRC, potentially guiding early screening strategies such as colonoscopy. Proactive monitoring and prevention efforts could be tailored based on FL-related risk assessments.

Methods

Study design and population

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data for this study were

collected from NHANES, a multistage stratified composite design survey on the health and nutritional information of a representative selection of the US population. Eight consecutive NHANES surveys (2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018) were combined into a single analytic sample. Participants who had incomplete information were excluded and eventually a total of 16,250 eligible participants aged over 20 years were included.

NAFLD indices and other variable selection

PLF (22), LAP (21), HSI (23), USFLI (20), FLI (24), and ZJU (25) were calculated separately by published formula. Participants who lacked a calculated index related to FLIs were excluded from this study.

The diagnoses of CRC were defined using items on the Medical Status Questionnaire: "Have you ever been told by a doctor or other health professional that you had cancer or malignancy?" and "What kind of cancer was it?". Answerers which indicated only "colon cancer" or "rectum (rectal) cancer" were classified as outcome variables.

We assessed demographic covariates including age, race, education, family poverty-to-income ratio (PIR), smoking state, and body measurement data such as weight (kg) and body mass index (BMI; kg/m^2).

Statistical analysis

The data in the current study were obtained and statistically evaluated by the R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance level was set at 0.05. The NHANES study population was divided into two groups according to the presence or absence of CRC, characteristics were performed for comparison between groups. Continuous variables were expressed as the median with interquartile range (IQR) for they did not obey normal distribution. Significance difference between the two groups was appraised by Wilcoxon rank-sum test. Frequency and percentage were used to describe categorical variables. The distribution of categorical variables was appropriately compared by Pearson Chi-squared test.

In this study, we employed the Boruta algorithm, a supervised categorical feature selection method that utilizes random forests, to identify all relevant features. This algorithm operates by calculating the Z-value for each attribute during each iteration of the random forest model. A feature is deemed "significant" if its Z-value exceeds the maximum Z-value of the corresponding shaded feature. Through this rigorous process, we aimed to ensure a comprehensive selection of features that are pertinent to our analysis.

Considering the stratified, multi-stage probabilistic sampling approach of NHANES, we used the "survey" package to adjust complex sampling weights for the current study. Two-year cycle weights were divided by eight to reflect 16 survey years. Then, the "effects" package was used to conduct generalized linear model (GLM). We used the "rms" package to conduct restricted cubic spline (RCS) logistic analysis and calculate P value for nonlinearity. Weighted logistic multivariate analysis was utilized to explore the association between USFLI and CRC. Three different models were used to decrease the influence of confounders. Model 1 was the crude model; Model 2 was adjusted for gender and age; Model 3 was adjusted for gender, age, race, PIR, education, and BMI. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the association.

We further stratified the analysis of significant covariates according to age (<65 or ≥65 years old), gender, ethnicity, smoking status, and BMI.

Results

Characteristics of included participants

A total of 16,250 individuals, representing 87,892,702 people aged 20 years and older, were included in our study utilizing the NHANES database (*Figure 1*). Of these participants, 96 (which represented 387,440 individuals) were diagnosed with CRC. Characteristics of individuals stratified by the presence or absence of CRC are shown in *Table 1*. Notably, individuals with CRC were significantly older than those without CRC, with median ages of 72 and 47 years, respectively (P<0.001). However, no significant differences of gender, race, education, smoking status, PIR, weight, and BMI were observed between the two groups (*Table 1*).

FLIs and the risk of CRC

Six FLIs were calculated separately. We found that individuals diagnosed with CRC exhibited significantly higher levels of PLF (4.65 *vs.* 3.31, P=0.004), LAP (55.63 *vs.* 42.34, P=0.04), USFLI (23.22 *vs.* 17.83, P<0.001), and

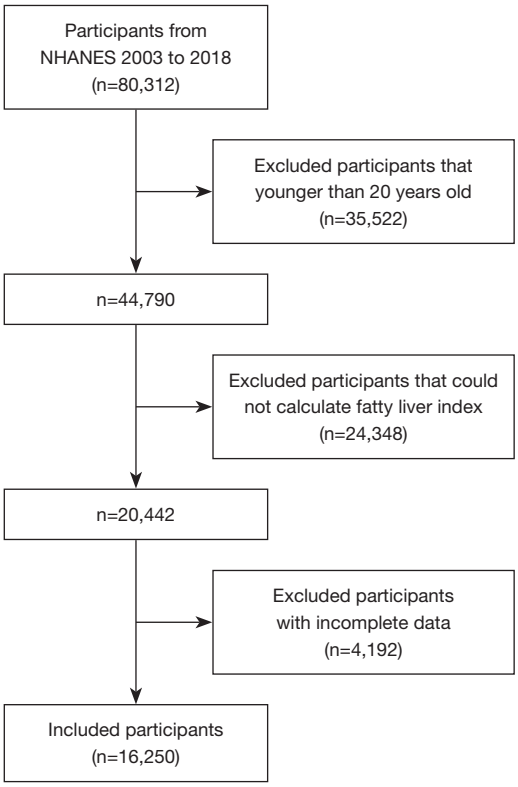

Figure 1 Flowchart of study participants. NHANES, National Health and Nutrition Examination Survey.

FLI (58.16 *vs.* 50.86, P=0.048), However, no significant differences were found in HSI and ZJU between the two groups (*Table 1*).

The results of feature selection based on Boruta's algorithm are shown in order of Z-value in *Figure 2*. After 500 iterations, it was determined that all six FLIs were closely associated with CRC and the six variables most strongly correlated with CRC were weight, age, PLF, LAP, HSI, and USFLI. Further analysis indicated a robust association among all indices (Figure S1), which could be partially attributed to the use of the same or highly correlated predictors.

The GLM results further demonstrated a positive association between all FLIs and CRC across different genders and ethnicities (*Figures 3,4*). Specifically, a positive linear association was observed between CRC risk and PLF (P for nonlinearity =0.62), LAP (P for nonlinearity =0.86), USFLI (P for nonlinearity =0.28), FLI (P for nonlinearity =0.89), and ZJU (P for nonlinearity =0.51) after adjusting for potential confounders through RCS logistic analysis (*Figures 5,6*). Conversely, HSI exhibited a negative linear association with CRC in the model adjusted for multiple confounders (P for nonlinearity =0.56) (*Figure 5F*).

To further investigate the relationship between FLIs and the risk of CRC, we evaluated the odds of CRC across the quartiles of six indices (Q1: PLF <2.056, LAP <24.041, HSI <32.438, USFLI <7.944, FLI <21.150, ZJU <34.695; Q2: PLF: 2.056–3.592, LAP: 24.041–43.072, HSI: 32.438–37.081, USFLI: 7.944–18.919, FLI: 21.150–52.501, ZJU: 34.695–39.260; Q3: PLF: 3.593–6.659, LAP: 43.073–74.307, HSI: 37.082–42.567, USFLI: 18.920–39.391, FLI: 52.502–82.720, ZJU: 39.261–44.774; Q4: PLF >6.659, LAP >74.307, HSI >42.567, USFLI >39.391, FLI >82.720, ZJU >44.774) by conducting logistic regression analysis after adjustment for multiple potential confounders, as detailed in *Table 2*. In the crude model, the top quartile of the LAP demonstrated a significant positive association with CRC (OR =3.00; 95% CI: 1.30–6.93; P=0.01). However, it was only the USFLI that consistently exhibited a positive association with CRC risk across both the top (Model 1: OR =6.26, 95% CI: 2.63–14.90, P<0.001; Model 2: OR =3.37, 95% CI: 1.33–8.52, P=0.01; Model 3: OR =3.22, 95% CI: 1.02–10.15, P=0.047) and second (Model 1: OR =6.29, 95% CI: 2.16–18.31, P<0.001; Model 2: OR =3.88, 95% CI: 1.24–12.10, P=0.02; Model 3: OR =3.81, 95% CI: 1.21–12.06, P=0.02) quartiles in all three models analyzed. These findings suggest that among the six indices evaluated, only the USFLI was significantly associated with an increased risk of CRC.

Stratified analyses for USFLI

The stability of the correlation between USFLI and CRC risk was further validated across diverse populations using two analytical models: Model 1 (the crude model) and Model 2 (adjusted for gender and age) (*Figure 7*). In the crude model, a positive association was observed between USFLI and CRC risk in individuals aged over 65 years (P=0.03). Gender stratification revealed that USFLI was significantly linked to an increased risk of CRC in both male (P=0.02) and female (P=0.02) populations. Additionally, race-based analyses indicated that higher USFLI levels were associated with CRC risk among white individuals (P=0.01) and Mexican Americans (P=0.03). When stratified by smoking status, a significant correlation between USFLI and CRC risk was found in non-smokers (P<0.001). Furthermore, stratification by BMI demonstrated that USFLI was significantly associated with elevated CRC risk in both healthy weight (P<0.001) and overweight (P=0.04)

Table 1 General characteristics of participants included in this study stratified by the presence or absence of CRC

Variables	Total (unweighted n=16,250, weighted n=87,892,702)	CRC (unweighted n=96, weighted n=387,440)	No CRC (unweighted n=16,154, weighted n=87,505,262)	P value
Age (years)	47 [34, 60]	72 [61, 78]	47 [34, 60]	<0.001*
Gender				0.43
Male	49.42	44.4	49.44	
Female	50.58	55.6	50.56	
Race				0.10
Non-Hispanic Black	10.14	6.67	10.15	
Non-Hispanic White	69.48	81.6	69.42	
Mexican American	8.13	5.51	8.14	
Other Hispanic	4.98	2.99	4.99	
Other race	7.28	3.23	7.29	
Education				0.12
Less than high school	16.05	19.22	16.03	
High school graduate	23.39	33.43	23.35	
Some college	31.09	29.63	31.1	
College graduate or above	29.47	17.71	29.53	
Smoker				0.50
No	79.3	83.17	79.29	
Yes	20.7	16.83	20.71	
PIR	3.00 [1.51, 5.00]	3.00 [1.51, 5.00]	2.82 [1.45, 4.12]	0.27
Weight (kg)	80.00 [67.60, 94.80]	80.00 [67.60, 94.80]	75.60 [65.70, 100.80]	0.76
BMI (kg/m^2)	27.80 [24.10, 32.35]	27.80 [24.10, 32.34]	27.90 [24.86, 33.20]	0.50
PLF	3.31 [1.96, 6.33]	4.65 [2.78, 8.73]	3.31 [1.95, 6.33]	0.004*
LAP	42.37 [23.47, 74.54]	55.63 [26.54, 83.74]	42.34 [23.42, 74.49]	0.04*
HSI	36.89 [32.33, 42.61]	36.33 [32.95, 41.25]	36.89 [32.33, 42.61]	0.83
USFLI	17.84 [7.44, 37.98]	23.22 [12.49, 55.29]	17.83 [7.43, 37.95]	<0.001*
FLI	50.92 [18.95, 82.54]	58.16 [33.05, 85.33]	50.86 [18.94, 82.53]	0.048*
ZJU	38.94 [34.47, 44.50]	39.40 [36.49, 45.15]	38.94 [34.47, 44.50]	0.24

Data are expressed as median [IQR] for skewed variables and percentage (%) for categorical variables. P value was tested by Wilcoxon rank-sum test for skewed variables was tested and Pearson Chi-square test for categorical variables. *, P<0.05. CRC, colorectal cancer; PIR, poverty-to-income ratio; BMI, body mass index; PLF, liver fat percentage; LAP, lipid accumulation product; HSI, hepatic steatosis index; USFLI, United States fatty liver index; FLI, fatty liver index; ZJU, Zhejiang University index; IQR, interquartile range.

individuals. After adjusting for multiple confounders, USFLI maintained a significant association with CRC risk solely in the population aged over 65 years (OR =1.023; 95% CI: 1.005–1.041; P=0.01) and among non-smokers (OR =1.018; 95% CI: 1.003–1.033; P=0.02). Overall, our study demonstrates that high USFLI is a significant risk factor for CRC, suggesting a potential link between NAFLD and CRC.

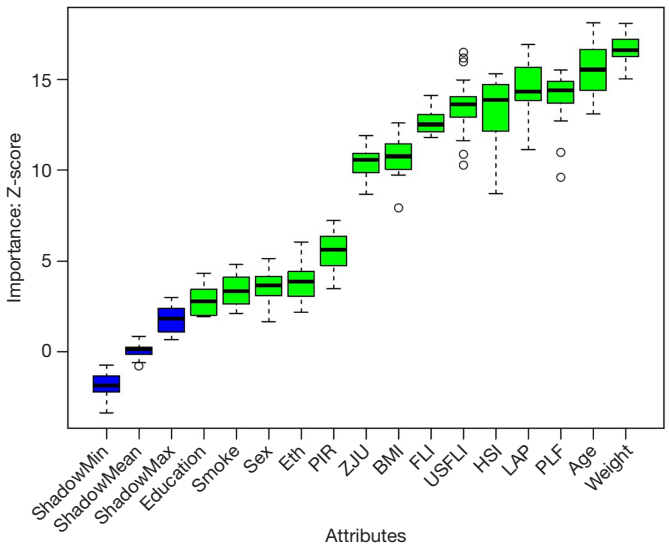

Figure 2 Feature selection process for CRC risk based on Boruta algorithm. The horizontal axis represents the variable name and the vertical axis represents the Z-values of each variable. The blue boxes and lines indicate the minimum, average, and maximum Z-scores for a shadow feature. The green boxes and lines denote the confirmed variables that are associated with CRC risk. PIR, poverty-to-income ratio; ZJU, Zhejiang University index; BMI, body mass index; FLI, fatty liver index; USFLI, United States fatty liver index; HSI, hepatic steatosis index, LAP, lipid accumulation product; PLF, liver fat percent; CRC, colorectal cancer.

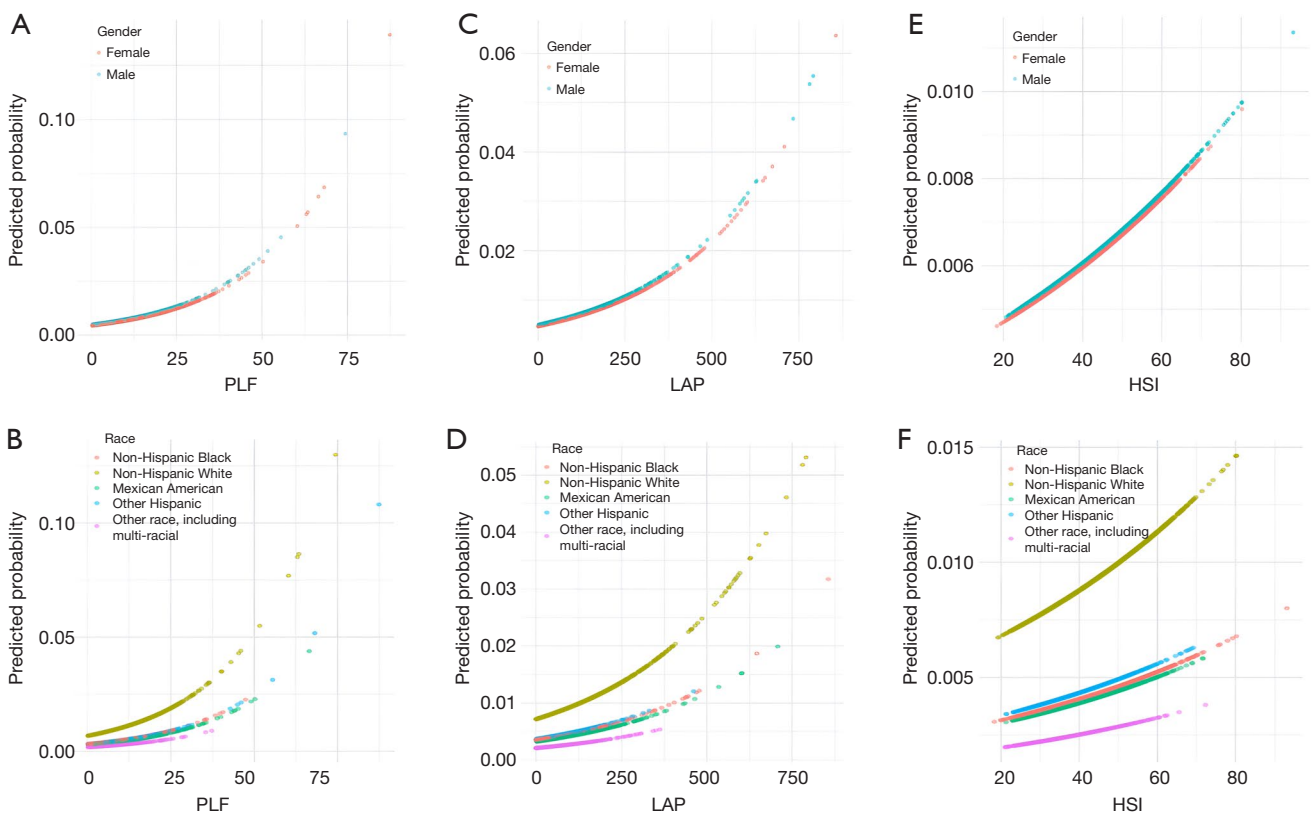

Figure 3 GLMs showed the association between PLF, LAP, and HSI with CRC that stratified by gender (A,C,E) and ethnicity (B,D,F). PLF, liver fat percent; LAP, lipid accumulation product; HSI, hepatic steatosis index; GLM, generalized linear model; CRC, colorectal cancer.

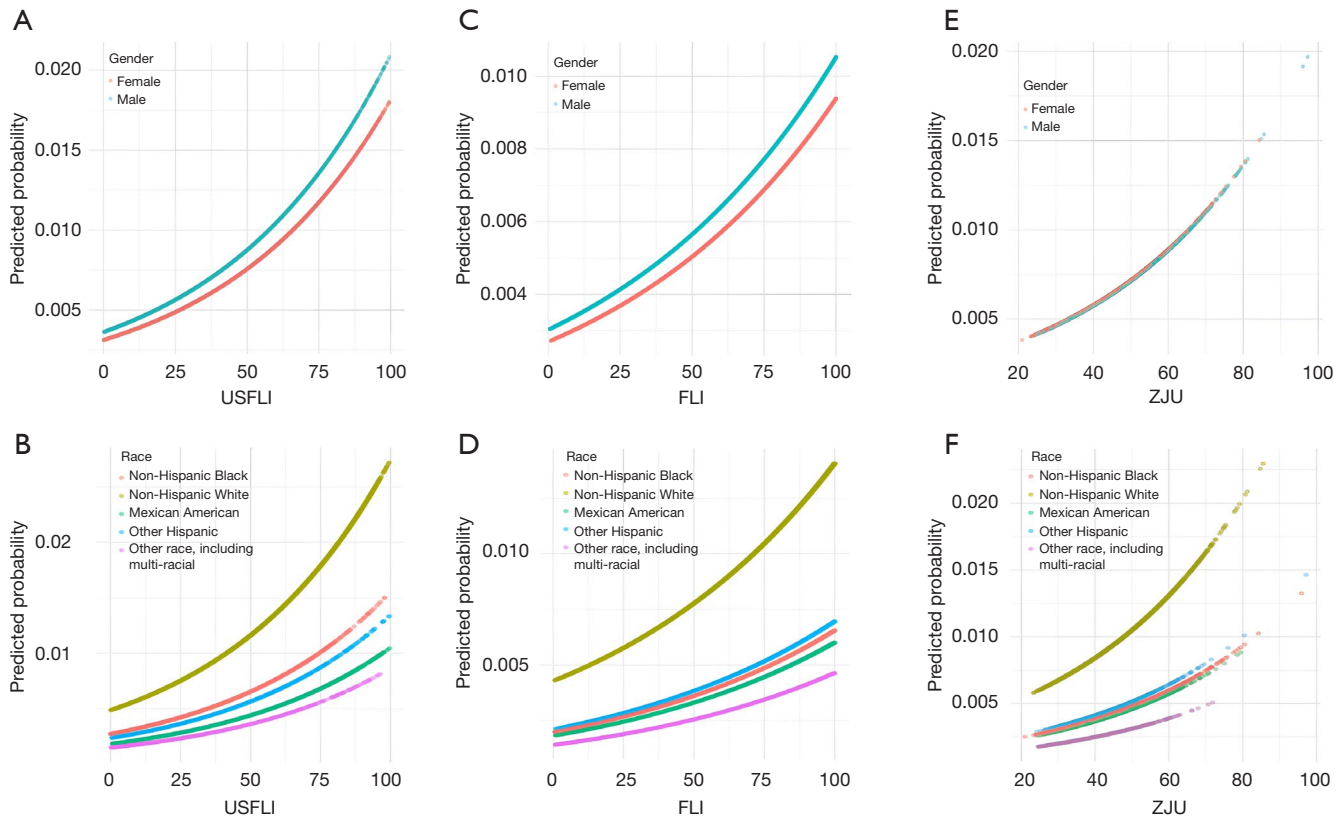

Figure 4 GLMs showed the association between USFLI, FLI, and ZJU with CRC stratified by gender (A,C,E) and ethnicity (B,D,F). USFLI, United States fatty liver index; FLI, fatty liver index; ZJU, Zhejiang University index; GLM, generalized linear model; CRC, colorectal cancer.

Discussion

This study aimed to evaluate the effectiveness of six surrogate indices of FL in predicting CRC risk among representative sample of US adults through a cross-sectional analysis. In contrast to the previous methodologies that relied solely on clinical observations for screening variables, our approach integrates the findings from the Boruta algorithm, which indicated a strong association between all six FLIs and CRC risk. Notably, the results from multivariate logistic regression, GLM, and RCS analyses demonstrated that individuals with high USFLI, but not the other five FLIs, have an increased risk of CRC. Furthermore, subgroup analyses demonstrated a significant robust positive correlation between USFLI and CRC risk in individuals aged over 65 years, encompassing both genders, as well as White and Mexican American populations, non-smokers, and individuals with healthy weight and overweight. After controlling for multiple confounding factors, the significant association between USFLI and CRC risk persisted exclusively in the population aged over 65 years and among non-smokers. These findings suggest that USFLI may serve as a valuable predictor of CRC risk, and that interventions aimed at reducing liver fat accumulation could potentially mitigate CRC risk.

Increasing evidence has linked FL or NAFLD, considered as a systemic disease that influence metabolism and inflammatory response, to the incidence of several tumors including CRC (26). A meta-analysis including 11 observational studies revealed that FL significantly increased incidence of colorectal adenomas [hazard ratio (HR) =1.42; 95% CI: 1.118–1.72] and CRC (HR =3.08; 95% CI: 1.02–9.03) (27). Due to the lack of in-depth research, the biological mechanisms underlying such associations remains unknown. Studies have indicated that metabolic disorder, elevated inflammation, and gut microbiota dysbiosis might be the underlying mechanism of FL-related CRC tumorigenesis (13,28).

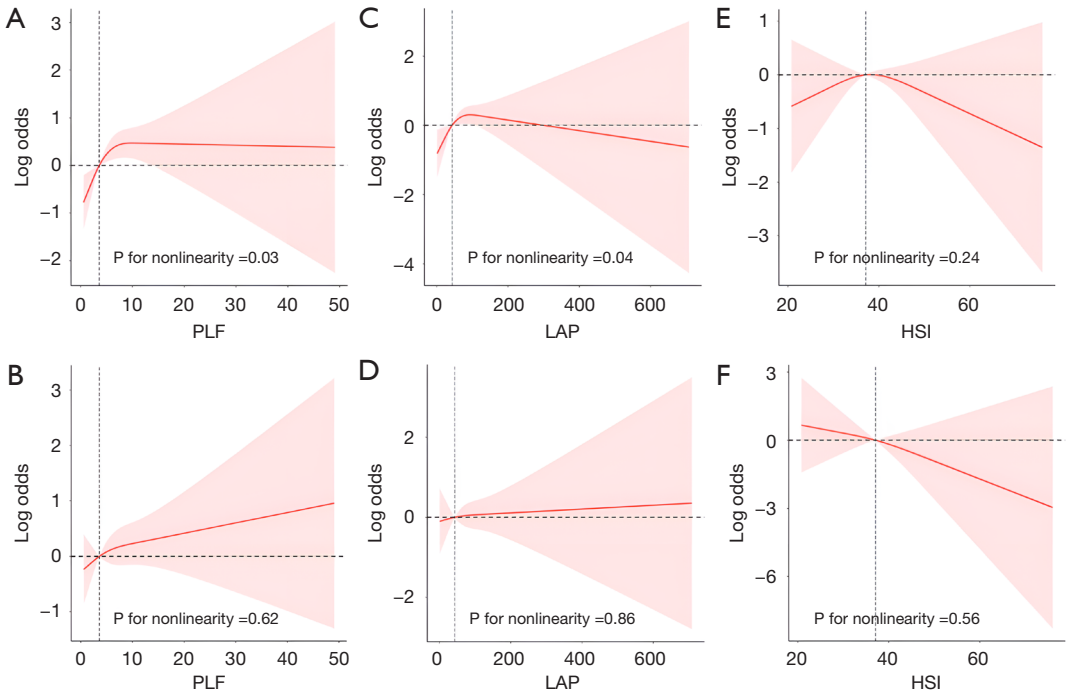

Figure 5 Association of PLF, LAP, and HSI with CRC in a crude (A,C,E) and age, gender, race, PIR, education, and BMI adjusted (B,D,F) RCS model. PLF, liver fat percent; LAP, lipid accumulation product; HSI, hepatic steatosis index; CRC, colorectal cancer; PIR, poverty-to-income ratio; BMI, body mass index; RCS, restricted cubic spline.

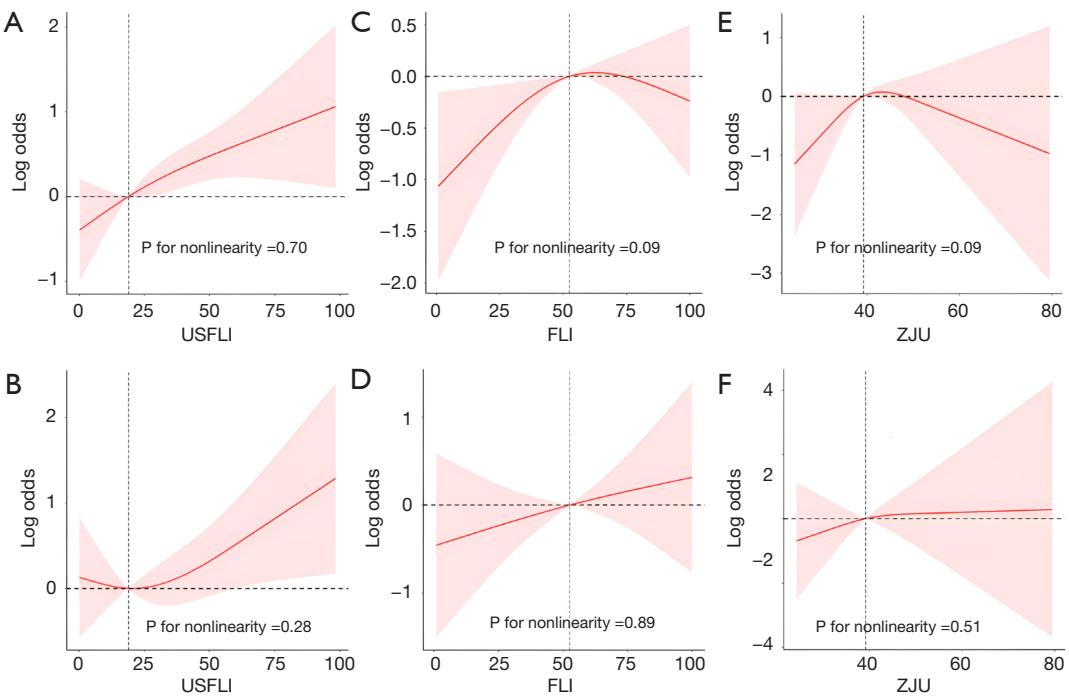

Figure 6 Association of USFLI, FLI, and ZJU with CRC in a crude (A,C,E) and age, gender, race, PIR, education, and BMI adjusted (B,D,F) RCS model. USFLI, United States fatty liver index; FLI, fatty liver index; ZJU, Zhejiang University index; CRC, colorectal cancer; PIR, poverty-to-income ratio; BMI, body mass index; RCS, restricted cubic spline.

Table 2 ORs and 95% CIs for CRC according to FLI level

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
PLF						
Continuous	1.04 (1.02, 1.06)	<0.001*	1.03 (1.00, 1.06)	0.052	1.03 (0.99, 1.07)	0.18
Q1	Ref.		Ref.		Ref.	
Q2	0.75 (0.31, 1.80)	0.51	0.65 (0.27, 1.57)	0.33	0.64 (0.25, 1.64)	0.35
Q3	2.42 (0.98, 5.99)	0.06	1.35 (0.54, 3.36)	0.51	1.29 (0.44, 3.78)	0.64
Q4	2.15 (0.99, 4.68)	0.06	1.37 (0.63, 3.00)	0.43	1.30 (0.45, 3.73)	0.63
P for trend		0.01*		0.2		0.39
LAP						
Continuous	1.00 (1.00, 1.00)	0.03*	1.00 (1.00, 1.00)	0.23	1.00 (1.00, 1.00)	0.75
Q1	Ref.		Ref.		Ref.	
Q2	2.42 (0.88, 6.67)	0.09	1.55 (0.52, 4.55)	0.43	1.47 (0.50, 4.37)	0.48
Q3	1.96 (0.85, 4.52)	0.11	1.13 (0.47, 2.72)	0.78	1.05 (0.40, 2.74)	0.92
Q4	3.00 (1.30, 6.93)	0.01*	1.83 (0.78, 4.30)	0.16	1.64 (0.57, 4.71)	0.36
P for trend		0.02*		0.28		0.54
HSI						
Continuous	0.99 (0.97, 1.02)	0.68	1.01 (0.98, 1.04)	0.61	0.95 (0.83, 1.08)	0.41
Q1	Ref.		Ref.		Ref.	
Q2	1.68 (0.77, 3.66)	0.19	1.45 (0.67, 3.14)	0.34	1.30 (0.56, 3.05)	0.54
Q3	1.31 (0.54, 3.18)	0.55	1.26 (0.53, 2.98)	0.6	1.01 (0.36, 2.85)	0.98
Q4	1.10 (0.53, 2.27)	0.79	1.34 (0.64, 2.80)	0.43	0.90 (0.23, 3.58)	0.88
P for trend		0.96		0.56		0.83
USFLI						
Continuous	1.02 (1.01, 1.02)	0.001*	1.01 (1.00, 1.02)	0.049*	1.01 (1.00, 1.03)	0.13
Q1	Ref.		Ref.		Ref.	
Q2	6.29 (2.16, 18.31)	<0.001*	3.88 (1.24, 12.10)	0.02*	3.81 (1.21, 12.06)	0.02*
Q3	4.29 (1.73, 10.62)	0.002*	2.34 (0.90, 6.03)	0.08	2.24 (0.80, 6.26)	0.12
Q4	6.26 (2.63, 14.90)	<0.001*	3.37 (1.33, 8.52)	0.01*	3.22 (1.02, 10.15)	0.047*
P for trend		<0.001*		0.13		0.34
FLI						
Continuous	1.01 (1.00, 1.02)	0.09	1.01 (1.00, 1.01)	0.23	1.01 (0.99, 1.03)	0.39
Q1	Ref.		Ref.		Ref.	
Q2	1.61 (0.61, 4.25)	0.33	1.01 (0.38, 2.68)	0.98	0.96 (0.32, 2.86)	0.93
Q3	1.48 (0.56, 3.90)	0.42	0.99 (0.38, 2.54)	0.98	0.88 (0.28, 2.82)	0.83
Q4	1.71 (0.67, 4.35)	0.26	1.33 (0.53, 3.36)	0.54	1.13 (0.23, 5.60)	0.88
P for trend		0.26		0.51		0.95

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
ZJU						
Continuous	1.01 (0.99, 1.04)	0.34	1.02 (0.99, 1.05)	0.32	1.02 (0.91, 1.15)	0.74
Q1	Ref.		Ref.		Ref.	
Q2	2.13 (0.97, 4.69)	0.06	1.65 (0.75, 3.63)	0.21	1.57 (0.65, 3.80)	0.32
Q3	1.73 (0.72, 4.16)	0.22	1.35 (0.56, 3.26)	0.5	1.24 (0.42, 3.71)	0.69
Q4	1.71 (0.81, 3.61)	0.16	1.61 (0.75, 3.41)	0.22	1.41 (0.26, 7.48)	0.69
P for trend		0.30		0.39		0.81

*, P<0.05. Model 1: the crude model. Model 2: adjusted for gender and age. Model 3: adjusted for gender, age, race, PIR, education, and BMI. OR, odds ratio; CI, confidence interval; CRC, colorectal cancer; FLI, fatty liver index; PLF, liver fat percentage; ref., reference; LAP, lipid accumulation product; HSI, hepatic steatosis index; USFLI, United States fatty liver index; ZJU, Zhejiang University index; PIR, poverty-to-income ratio; BMI, body mass index.

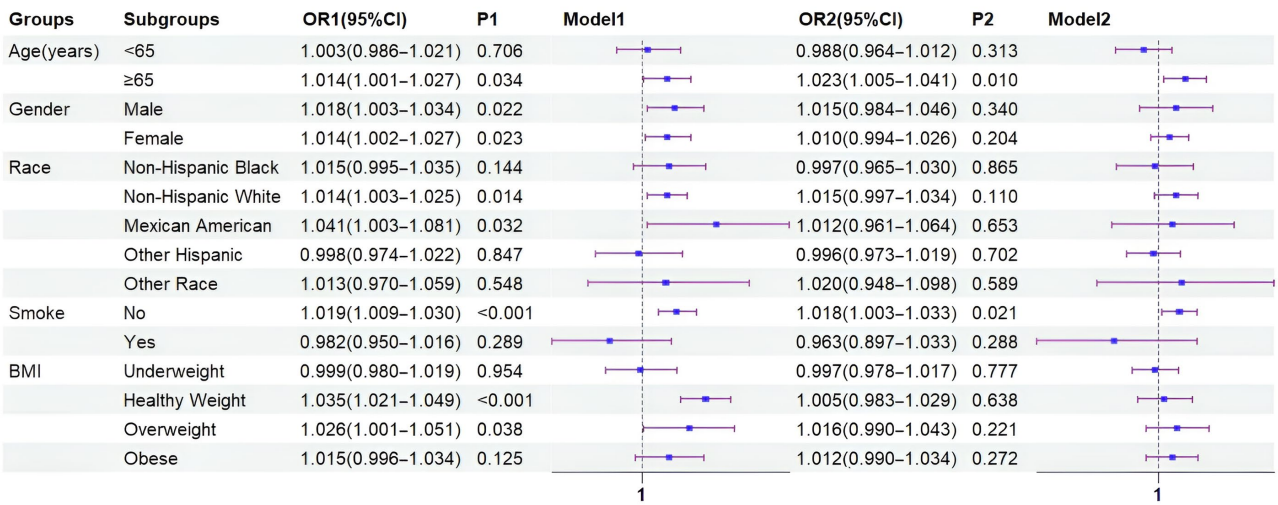

Figure 7 Subgroup analysis of the association between USFLI and CRC risk. Model 1: represents crude model. Model 2: adjusted for gender and age. A value of 1 on the X-axis indicates no difference between the groups being compared. OR, odds ratio; CI, confidence interval; BMI, body mass index; USFLI, United States fatty liver index; CRC, colorectal cancer.

FL is regarded as hepatic manifestation of metabolic syndrome (MetS) which leads to CRC risk factors such as dyslipidemia, insulin resistance (IR), and obesity (29-31). Elevated levels of total and low-density lipoprotein (LDL) cholesterol increased CRC risk, particularly in men and postmenopausal women, was observed in an Italian multicenter cohort with 34,148 people (32). A meta-analysis which contained 1,987,753 individuals with 10,876 CRC patients indicated that high levels of serum triglyceride and total cholesterol are associated with an increased risk of CRC (33). Increased leptin and decreased adiponectin were considered the underlying mechanism of CRC tumorigenesis via FL-related dyslipidemia (34,35). Lower systemic adiponectin was found in CRC patients compared with healthy controls by combining analysis of 32 observational studies (36). A study showed that adiponectin has anticarcinogenic effects by repressing tumor cell growth via AMP-activated protein kinase and inducing

apoptosis through a caspase-dependent pathway (29). Moreover, statins, as a treatment for FL and which have a beneficial effect on leptin and adiponectin levels, may play a role in CRC prevention and treatment (37-39). The accumulation of hepatic fat resulted in lower insulin-stimulated glucose uptake and altered insulin signaling that trigger IR (40). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, which is used for IR diagnosis, was found to be more elevated in the CRC cohort than in the controls (1.8±0.4 *vs.* 1.4±0.3, P<0.001) in a case-control study (41). Another prospective cohort study revealed that increased fasting triglyceride-glucose (TyG) index, another IR index, was associated with a higher risk of developing CRC among Chinese adults (42). The most likely mechanism linking FL-related IR with CRC is due to insulin-like growth factor-1 axis and hyperinsulinemia which results in anti-apoptotic and proliferative effects which act as a precursor of developing CRC (29,43). Obesity is the common risk factor for both FL and CRC (15). Although in our study, no significant differences were observed between CRC cohort and the controls (27.90 *vs.* 27.80, P=0.57), obese individuals are encouraged to undergo colonoscopy at a younger age (44,45).

Systemic inflammatory disturbance during the FL development and progression was considered as another mechanism of CRC development. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8, and plasminogen activator inhibitor-1 (PAI-1), play central roles in the promotion of cellular proliferation, inhibition of apoptosis, and angiogenesis which finally lead to colorectal carcinogenesis (46,47). Chronic low-grade inflammation of visceral adipose tissue, another predictor of FL, could promote IR via adipokines release and enhance CRC development (48). Moreover, the effect of FL-induced inflammation on altered gut microbiota has also been linked to the development of CRC (49,50). The hypothesis of the potential mechanism is the activation of toll-like receptors (TLRs) triggered by disruption bacterial metabolites (51). Clearly, more in-depth research is needed to reveal the mechanisms behind this association.

Recent research highlights a lean phenotype among patients with FL disease, challenging traditional associations between FL and obesity. As discussed in a recent research, individuals with lean NAFLD may present unique metabolic profiles that increase CRC risk, independent of BMI (52). This phenotype underscores the complexity of metabolic health issues and their influence on CRC risk factors. Our findings of increased CRC risk in individuals who are lean or overweight align with this paradigm, suggesting that factors beyond obesity contribute significantly to FL-related colorectal carcinogenesis. Further research into lean NAFLD is warranted to elucidate these mechanisms.

Our study represents the first investigation into the association between the FLI and the risk of CRC within a large population-based cross-sectional framework. This adds another important piece of evidence for the association between FL and CRC, indicating that individuals with a high USFLI may constitute a high-risk population for CRC and therefore warrant closer monitoring, including the consideration of early colonoscopy. This finding offers a potential strategy for mitigating the burden of CRC. However, it is essential to acknowledge the limitations inherent in the cross-sectional design of this study; thus, it would be premature to recommend that patients with a high USFLI or those diagnosed with FL automatically undergo colonoscopy. Further in-depth research is necessary to elucidate the underlying mechanisms linking FL and CRC.

This study has several limitations that cannot be ignored. Firstly, the staging, histologic findings, surgery status, and fatal information of CRC were unknown, preventing subgroup analysis based on these factors in the present study. Secondly, the study mainly focused on the Western population, and USFLI has not been shown to be as effective in other regions, such as Asian populations. Further analysis of populations in other areas could enhance the robustness of the results. Thirdly, CRC cases were identified through self-reported questionnaires, which may have led to an underestimation of CRC incidence and potentially affect the reliability of our findings. This limitation should be considered when interpreting the results, as self-reported data might not capture all cases accurately. Finally, as a cross-sectional observational study, it was difficult to establish a causal relationship between USFLI or FL accumulation and the risk of CRC.

Conclusions

The findings indicate that USFLI exhibits a stronger association with the risk of CRC than the other five alternative FLIs. This underscores the potential utility of USFLI in clinical settings for predicting CRC. Furthermore, these results suggest a possible link between FL and CRC, indicating that individuals with FL should be monitored more closely to prevent CRC.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1444/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1444/prf

Funding: This work was partially supported by the National Natural Science Foundation of China (No. 82302794), the China Postdoctoral Science Foundation (No. 2023M741469), the Natural Science Foundation of Jiangsu Basic Research Program-Youth Fund Project (No. BK20220734), and the Young Scholars Fostering Fund of the First Affiliated Hospital of Nanjing Medical University.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1444/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Sato Y, Tsujinaka S, Miura T, et al. Inflammatory Bowel Disease and Colorectal Cancer: Epidemiology, Etiology, Surveillance, and Management. Cancers (Basel) 2023;15:4154.
3. Li N, Lu B, Luo C, et al. Incidence, mortality, survival, risk factor and screening of colorectal cancer: A comparison among China, Europe, and northern America. Cancer Lett 2021;522:255-68.
4. Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Semin Liver Dis 2012;32:3-13.
5. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019;7:313-24.
6. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int 2020;40:1254-61.
7. Gofton C, Upendran Y, Zheng MH, et al. MAFLD: How is it different from NAFLD? Clin Mol Hepatol 2023;29:S17-31.
8. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020;158:1999-2014.e1.
9. Yang A, Zhu X, Zhang L, et al. Transitioning from NAFLD to MAFLD and MASLD: Consistent prevalence and risk factors in a Chinese cohort. J Hepatol 2024;80:e154-5.
10. Kaya E, Yilmaz Y. Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver. J Clin Transl Hepatol 2022;10:329-38.
11. Zhao J, Liu L, Cao YY, et al. MAFLD as part of systemic metabolic dysregulation. Hepatol Int 2024;18:834-47.
12. Yuan X, Wang X, Wu S, et al. Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China. Hepatobiliary Surg Nutr 2023;12:671-81.
13. Mikolasevic I, Orlic L, Stimac D, et al. Non-alcoholic fatty liver disease and colorectal cancer. Postgrad Med J 2017;93:153-8.
14. Brown GT, Kleiner DE. Histopathology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Metabolism 2016;65:1080-6.
15. Lau LHS, Wong SH. Microbiota, Obesity and NAFLD. Adv Exp Med Biol 2018;1061:111-25.
16. Park CH, Eun CS, Han DS. Intestinal microbiota, chronic inflammation, and colorectal cancer. Intest Res 2018;16:338-45.

17. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492-542.
18. Foschi FG, Conti F, Domenicali M, et al. External Validation of Surrogate Indices of Fatty Liver in the General Population: the Bagnacavallo Study. J Clin Med 2021;10:520.
19. Murayama K, Okada M, Tanaka K, et al. Prediction of Nonalcoholic Fatty Liver Disease Using Noninvasive and Non-Imaging Procedures in Japanese Health Checkup Examinees. Diagnostics (Basel) 2021;11:132.
20. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 2015;41:65-76.
21. Li H, Zhang Y, Luo H, et al. The lipid accumulation product is a powerful tool to diagnose metabolic dysfunction-associated fatty liver disease in the United States adults. Front Endocrinol (Lausanne) 2022;13:977625.
22. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology 2009;137:865-72.
23. Kaneva AM, Bojko ER. Fatty liver index (FLI): more than a marker of hepatic steatosis. J Physiol Biochem 2024;80:11-26.
24. Carli F, Sabatini S, Gaggini M, et al. Fatty Liver Index (FLI) Identifies Not Only Individuals with Liver Steatosis but Also at High Cardiometabolic Risk. Int J Mol Sci 2023;24:14651.
25. Wang J, Xu C, Xun Y, et al. ZJU index: a novel model for predicting nonalcoholic fatty liver disease in a Chinese population. Sci Rep 2015;5:16494.
26. Lindenmeyer CC, McCullough AJ. The Natural History of Nonalcoholic Fatty Liver Disease-An Evolving View. Clin Liver Dis 2018;22:11-21.
27. Mantovani A, Dauriz M, Byrne CD, et al. Association between nonalcoholic fatty liver disease and colorectal tumours in asymptomatic adults undergoing screening colonoscopy: a systematic review and meta-analysis. Metabolism 2018;87:1-12.
28. Zoller H, Tilg H. Nonalcoholic fatty liver disease and hepatocellular carcinoma. Metabolism 2016;65:1151-60.
29. Sanna C, Rosso C, Marietti M, et al. Non-Alcoholic Fatty Liver Disease and Extra-Hepatic Cancers. Int J Mol Sci 2016;17:717.
30. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: An update. Metabolism 2016;65:1109-23.
31. Polyzos SA, Bugianesi E, Kountouras J, et al. Nonalcoholic fatty liver disease: Updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPAR-γ agonists. Metabolism 2017;66:64-8.
32. Agnoli C, Grioni S, Sieri S, et al. Colorectal cancer risk and dyslipidemia: a case-cohort study nested in an Italian multicentre cohort. Cancer Epidemiol 2014;38:144-51.
33. Yao X, Tian Z. Dyslipidemia and colorectal cancer risk: a meta-analysis of prospective studies. Cancer Causes Control 2015;26:257-68.
34. Polyzos SA, Aronis KN, Kountouras J, et al. Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 2016;59:30-43.
35. Katsiki N, Mantzoros C, Mikhailidis DP. Adiponectin, lipids and atherosclerosis. Curr Opin Lipidol 2017;28:347-54.
36. Macleod A, Scheurlen KM, Burton JF, et al. Systemic adiponectin levels in colorectal cancer and adenoma: a systematic review and meta-analysis. Int J Obes (Lond) 2023;47:911-21.
37. Gray RT, Coleman HG, Hughes C, et al. Statin use and survival in colorectal cancer: Results from a population-based cohort study and an updated systematic review and meta-analysis. Cancer Epidemiol 2016;45:71-81.
38. Dobrzycka M, Spychalski P, Łachiński AJ, et al. Statins and Colorectal Cancer - A Systematic Review. Exp Clin Endocrinol Diabetes 2020;128:255-62.
39. Li L, Cui N, Hao T, et al. Statins use and the prognosis of colorectal cancer: a meta-analysis. Clin Res Hepatol Gastroenterol 2021;45:101588.
40. Hossain IA, Rahman Shah MM, Rahman MK, et al. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: Association of GGT and HOMA-IR with NAFLD. Diabetes Metab Syndr 2016;10:S25-9.
41. Farahani H, Mahmoudi T, Asadi A, et al. Insulin Resistance and Colorectal Cancer Risk: the Role of Elevated Plasma Resistin Levels. J Gastrointest Cancer 2020;51:478-83.
42. Liu T, Zhang Q, Wang Y, et al. Association between the TyG index and TG/HDL-C ratio as insulin resistance markers and the risk of colorectal cancer. BMC Cancer

2022;22:1007.
43. Alam S, Mustafa G, Alam M, et al. Insulin resistance in development and progression of nonalcoholic fatty liver disease. World J Gastrointest Pathophysiol 2016;7:211-7.
44. Muhidin SO, Magan AA, Osman KA, et al. The relationship between nonalcoholic fatty liver disease and colorectal cancer: the future challenges and outcomes of the metabolic syndrome. J Obes 2012;2012:637538.
45. Lin XF, Shi KQ, You J, et al. Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study. Mol Biol Rep 2014;41:2989-97.
46. Kim S, Keku TO, Martin C, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer Res 2008;68:323-8.
47. Hwang ST, Cho YK, Park JH, et al. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. J Gastroenterol Hepatol 2010;25:562-7.
48. Milić S, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. World J Gastroenterol 2014;20:9330-7.
49. Bibbò S, Ianiro G, Dore MP, et al. Gut Microbiota as a Driver of Inflammation in Nonalcoholic Fatty Liver Disease. Mediators Inflamm 2018;2018:9321643.
50. Yu LC, Wei SC, Ni YH. Impact of microbiota in colorectal carcinogenesis: lessons from experimental models. Intest Res 2018;16:346-57.
51. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 2014;12:661-72.
52. Souza M, Diaz I, Barchetta I, et al. Gastrointestinal cancers in lean individuals with non-alcoholic fatty liver disease: A systematic review and meta-analysis. Liver Int 2024;44:6-14.

Cite this article as: Shi C, Yuan C, Hao Y, Zhou Z, Zhang Y. Association between surrogate indices of fatty liver and the risk of colorectal cancer: a cross-sectional United States study. Transl Cancer Res 2025;14(1):313-326. doi: 10.21037/tcr-24-1444