Observational Study

Medicine

OPEN

Novel application of the traditional lipid ratios as strong risk predictors of nonsmall-cell lung cancer risk in a Chinese population

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Abstract

Dyslipidemia has been associated with cancer risk, yet the relationship between lipid ratios and nonsmall-cell lung cancer (NSCLC) is still unclear. This study aimed to explore the value of lipid ratios, including total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) and triglyceride/HDL-C (TG/HDL-C) as predictors of NSCLC in a Chinese population. Adult patients with histologically confirmed NSCLC, without a previous history of cancer, concomitant disease associated with lipid metabolism disorders, or usage of lipid-lowering drugs, were enrolled from a single center. Controls without NSCLC, matched for age and sex, were enrolled from the same Center. Lipid profile including TC, TG, HDL-C were measured in all participants. TC/HDL-C and TG/HDL-C were calculated based on the levels of TC, TG, HDL-C. Seven hundred eighty-two NSCLC cases and 599 controls were enrolled. NSCLC patients had significantly higher TG/HDL-C and TC/HDL-C levels than those in the control. After controlling for confounding factors, TG/HDL-C (OR = 4.489, 95% CI: 2.463–6.035, $P < .001$) and TC/HDL-C (OR = 2.396, 95% CI: 2.086–2.752, $P = .001$) were independently associated with NSCLC risk. The incidence of NSCLC was increased with rising tertiles of TG/HDL-C and TC/HDL-C. Moreover, patients with TNM II-IV stage NSCLC had higher TG/HDL-C and TC/HDL-C than those in TNM I and Tis stage. TG/HDL-C and TC/HDL-C are positively correlated with NSCLC risk and TG/HDL-C is more predictive than TC/HDL-C in predicting the risk of NSCLC. The highest AUC was that of TG/HDL (0.898), at a cutoff point of 0.62, with 83.6% sensitivity and 83.5% specificity.

Abbreviations: AUC = area under curve, BMI = body mass index, DBP = diastolic blood pressure, FBG = Fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, NSCLC = nonsmall-cell lung cancer, ROC = receiver operating characteristic, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

Keywords: Lipid ratios, nonsmall-cell lung cancer, Total cholesterol/ high-density lipoprotein cholesterol, Triglycerides/ high-density lipoprotein cholesterol

1. Introduction

The major cause of cancer-related death in China, especially in the male population, is lung cancer.[1] nonsmall-cell lung cancer (NSCLC), which is the most common subtype of lung cancer, has the highest mortality rate of malignant tumors in China. It is a substantial economic burden and a public health concern. Despite improved understanding and treatment of its risk factors (e.g., smoking and environmental pollution), the incidence of NSCLC is still increasing. Considering the paucity of available treatments and the substantial economic burden of NSCLC, understanding its other risk factors is a growing need.

Dyslipidemia plays a pivotal role in the pathophysiological mechanism of diabetes mellitus and coronary heart disease.[2,3] More and more evidence found that dyslipidemia was also an important risk factor for various cancers, including breast cancer, colorectal cancer, and prostate cancer.[4–6] In addition, the association of dyslipidemia with NSCLC has been observed in some studies.[7,8] Recently, circulating lipid ratios, including the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) and triglycerides to high-density lipoprotein cholesterol (TG/HDL-C), have been reported to be the risk factors for some cancers. A prospective study found that TG/HDL-C efficiently and independently predicted 5-year overall survival of gastric cancer patients.[9] A population-based survival study indicated that high TG/HDL-C was a better predictor for adverse clinical outcomes in patients with triple negative breast cancer compared with TG.[10] A meta-analysis of prospective cohort studies showed that TC and HDL-C were negatively associated, and TG was positively associated with lung cancer risk.[11]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors of this work have no conflicts of interest to disclose.

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How to cite this article: Qiu X, Li Y, Ma M, Cao M, Yan X, Cai H. Novel application of the traditional lipid ratios as strong risk predictors of nonsmall-cell lung cancer risk in a Chinese population. Medicine 2022;101:35(e30230).

Received: 17 January 2022 / Received in final form: 8 July 2022 / Accepted: 12 July 2022

http://dx.doi.org/10.1097/MD.0000000000030230

Despite this, the associations of NSCLC risk with lipid ratios, such as TG/HDL-C and TC/HDL-C have been rarely investigated and remain unclear. In addition, to our knowledge no study has focused on the comparison of predictive value of TG/HDL-C and TC/HDL-C for NSCLC risk. Therefore, this study aimed to evaluate the potential association of NSCLC with TG/HDL-C and TC/HDL-C. Additionally, the predictive values of TG/HDL-C and TC/HDL-C for NSCLC risk were compared.

2. Methods

A total of 782 NSCLC patients who were pathologically confirmed diagnosed and with no previous or coexisting cancer were enrolled at the Department of Respiratory and Critical Care Medicine, Nanjing Drum Tower Hospital from 2016 to 2018. There were 654 patients with adenocarcinoma, 105 patients with squamous cell carcinoma and 23 patients with other types according to the pathological results. In addition, there were 133 patients in the Tis stage, 374 patients in the TNM I stage and 275 patients in the TNM II-IV stage according to TNM stages. 599 adults without NSCLC were enrolled as controls. Written informed consent was obtained from all participants. We excluded individuals with cancer history and concomitant diseases associated with lipid metabolism disorders (i.e., diabetes, hypothyroidism). We also excluded individuals taking lipid-lowering drugs. The study was approved by the Human Research Ethics Committee of Nanjing Drum Tower Hospital.

Detailed clinical and pathological information were obtained from the participants' medical records including age, sex, smoking, tumor stage, pathological type and TNM stage. Weights, heights, systolic blood pressure and diastolic blood pressure of all participants were measured using standardized methods. Fasting blood glucose (FBG), a blood lipid profile including TC, TG, LDL-C, low-density lipoprotein cholesterol (LDL-C), and HDL-C and uric acid were measured in blood samples obtained in the early morning before therapy, and were immediately analyzed (Beckman Coulter AU5400, Olympus Medical Engineering Company, Japan). The TC/HDL-C and TG/HDL-C were calculated based on the levels of TC, TG, and HDL-C.

Differences in continuous variables were analyzed by Student t-tests and 1-way ANOVA. Chi-squared tests were used for categorical variables. Binary logistic regression analysis was used to explore the relationship between NSCLC risk and the lipid ratios. Receiver operating characteristic (ROC) curve analysis was carried out to test the predict values of lipid ratios for NSCLC. All statistical analyses were performed using SPSS18.0 statistical software. All tests were 2-tailed, and a P value of <.05 was considered to be significant.

3. Results

3.1. Baseline characteristics of the study population

Compared with the control group, patients with NSCLC were more likely to smoke, and serum levels of HDL-C, LDL-C, and TC in patients with NSCLC were significantly lower than those in matched controls. However, BMI, the levels of FBG, TG, uric acid, TG/HDL-C, and TC/HDL-C in NSCLC patients were significantly higher than those in the control group. Systolic blood pressure and Diastolic blood pressure were similar in the 2 groups (Table 1).

3.2. Correlation of NSCLC risk with lipid ratios

The correlation of NSCLC risk with lipid ratios was determined by binary logistic regression. Multivariable logistic regression showed that the associations of NSCLC risk with TG/HDL-C (OR = 4.489, 95% CI: 2.463–6.035, P < .001) and TC/HDL-C (OR = 2.396, 95% CI: 2.086–2.752, P = .001) were also significant after adjusting for multiple covariates such as age, sex, smoking, and FBG (Table 2).

3.3. Prevalence of NSCLC across tertiles of TG/HDL-c and TC/HDL-c

Participants were grouped into 3 groups according to the tertiles of TG/HDL-C or TC/HDL-C, respectively. The incidence of NSCLC increased with each increasing tertiles of TG/HDL-C (12.19% vs 64.48% vs 92.34%, P < .01) and TC/HDL-C (36.05% vs 55.14% vs 79.04%, P < .01) (Fig. 1A,B).

3.4. Relationship between lipid ratios and clinical characteristics

Patients with adenocarcinoma had a trend toward increased levels of TG/HDL-C (1.35 ± 0.99 vs 1.27 ± 0.72 vs 1.11 ± 0.49, P = .56) and TC/HDL-C (3.98 ± 1.13 vs 3.96 ± 1.22 vs 3.72 ± 1.10, P = .38), compared with those in the squamous cell carcinoma group and other subtypes group. Patients with TNM II-IV stages had higher TG/HDL-C (4.12 ± 1.27 vs 3.93 ± 1.06 vs 3.74 ± 1.05, P < .01) and TC/HDL-C (1.41 ± 1.03 vs 1.35 ± 0.95 vs 1.12 ± 0.72, P = .01) than those with TNM I and Tis stages.

3.5. Diagnostic value of TG/HDL-c and TC/HDL-c for predicting NSCLC incidence

The area under curve (AUC) values for evaluating the discriminate validity of TG/HDL-C and TC/HDL-C as predictors of NSCLC

Table 1

Demographic and clinical characteristics of all participants.

	Controls (n = 599)	NSCLC (n = 782)	P
Age (yrs)	60.96 ± 12.97	61.52 ± 10.85	.58
Sex (male/female)	310/289	407/375	.43
Smoking (n, %)	42 (7.01)	181 (23.14)	<.01
SBP (mm Hg)	131.74 ± 8.31	130.05 ± 9.17	.37
DBP (mm Hg)	84.25 ± 9.06	85.22 ± 8.88	.29
BMI (kg/m2)	22.36 ± 2.77	23.62 ± 3.04	.03
FBG (mmol/L)	4.96 ± 0.52	5.44 ± 1.26	.02
TC (mmol/L)	5.00 ± 0.93	4.07 ± 0.87	<.01
TG (mmol/L)	0.75 ± 0.24	1.29 ± 0.70	<.01
LDL-C (mmol/L)	2.96 ± 0.69	2.37 ± 0.71	<.01
HDL-C (mmol/L)	1.59 ± 0.32	1.08 ± 0.30	<.01
Uric acid (mmol/L)	282.44 ± 72.79	328.39 ± 86.47	<.01
TG/HDL-C	0.49 ± 0.23	1.33 ± 0.95	<.01
TC/HDL-C	3.21 ± 0.71	3.97 ± 1.14	<.01

Values are presented as mean ± standard deviation.

BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triacylglyceride.

Table 2

Logistic regression analysis of lipid ratios and NSCLC risk.

	TG/HDL-C		TC/HDL-C	
Model	OR (95% CI)	P	OR (95% CI)	P
1	4.722 (2.894–5.998)	<.001	2.637 (1.837–3.740)	<.001
2	4.489 (2.463–6.035)	<.001	2.396 (2.086–2.752)	.001

Model 1: unadjusted

Model 2: adjustment for age, sex, smoking, SBP, DBP, BMI, FBG, TC, TG, LDL-C, HDL-C, Uric acid.

BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triacylglyceride.

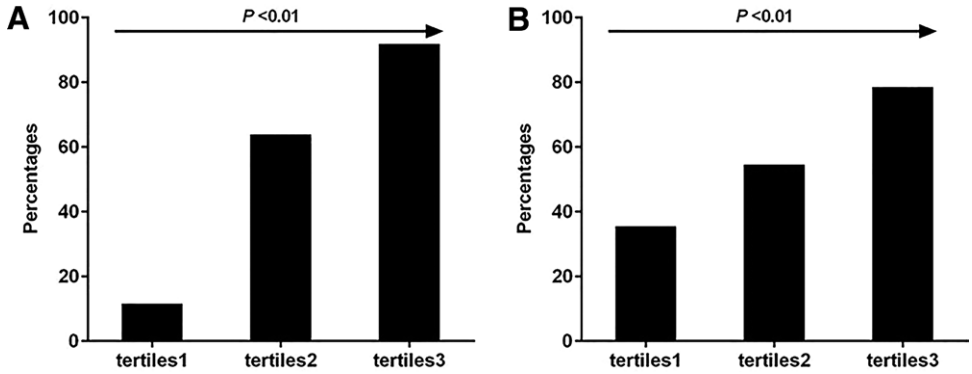

Figure 1. The incidence of NSCLC compared across the tertiles of lipid ratios, (A) the incidence of NSCLC compared across the tertiles of TG/HDL-C; (B) the incidence of NSCLC compared across the tertiles of TC/HDL-C. NSCLC = nonsmall-cell lung cancer, TC/HDL-C = total cholesterol/high-density lipoprotein cholesterol, TG/HDL-C = triglyceride//high-density lipoprotein cholesterol.

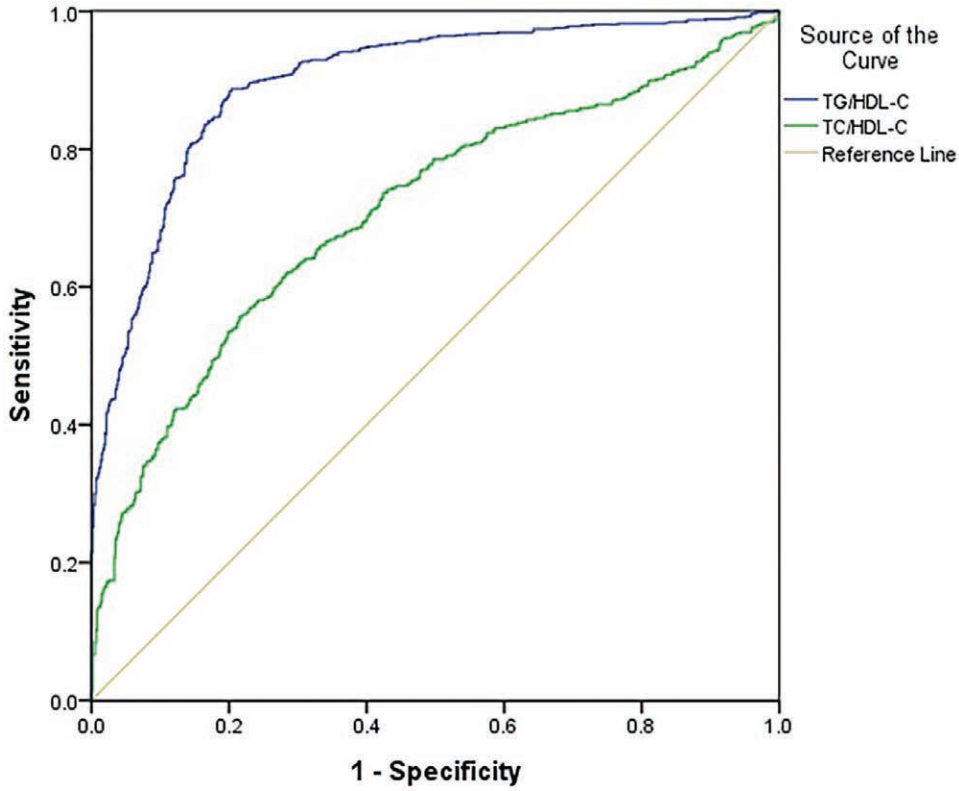

Figure 2. ROC curves of lipid ratios for predicting the incident of NSCLC. NSCLC = nonsmall-cell lung cancer, ROC = receiver operative characteristic.

were shown in Figure 2. The AUC of TG/HDL-C (0.898, 95% CI: 0.881–0.915, $P < .001$) was larger than that of TC/HDL-C (0.709, 95% CI: 0.682–0.736, $P < .001$). The optimal TG/HDL-C and TC/HDL-C cutoff points for predicting the incident of NSCLC were 0.62 (sensitivity: 83.60%, specificity: 83.50%) and 3.48 (sensitivity: 62.10%, specificity: 71.50%), respectively.

4. Discussion

The current study revealed that lipid ratios including TG/HDL-C and TC/HDL-C were significantly higher in patients with NSCLC compared with the control group. In addition, following adjustment for confounding factors, NSCLC was independently correlated with TG/HDL-C and TC/HDL-C. Furthermore, our study revealed that TG/HDL-C might be an effective marker for the incidence of NSCLC.

Lung cancer is the major cause of cancer-related death in China and the standardized mortality rate of lung cancer has consistently increased.[12] This malignancy can be broadly categorized as small cell carcinoma or NSCLC. Epidemiologic studies suggest that tobacco use, environmental pollution and obesity are risk factors for lung cancer, and the related interventions are actions taken to address these factors.[13,14] However, lung cancer incidence is still increasing in China. Hence, further efforts should be concentrated on exploring additional risk factors of lung cancer and early prevention.

The role of lipid metabolism in the development and progression of cancer has been investigated.[15,16] Several studies have evaluated the association of lung cancer with lipid profiles, with inconsistent conclusions. A retrospective cohort study in a Chinese population found that normal and raised levels of HDL-C were independently correlated with reduced risk of

NSCLC, while the relationship between NSCLC and high TG levels was not statistically significant after adjusting for confounding factors.[7] Another study in a Chinese population clarified that there was a significant correlation between HDL-C and the worse survival in patients with NSCLC, whereas TC, TG, and LDL-C were not independent prognostic factors for NSCLC.[17] Lyu et al[18] found U-shaped associations between lung cancer risk with TC and TG, while low LDL-C was correlated with an increased risk of lung cancer. However, for HDL-C, no significant association with incident of lung cancer was observed. In the present study, we found that patients with NSCLC had significantly lower levels of HDL-C, LDL-C, and TC, while higher levels of TG, which was consistent with previous findings.[17]

The TG/HDL-C ratio has been confirmed as a reproducible and inexpensive indicator for clinical diseases. Several epidemiological studies have reported that the TG/HDL-C ratio is applicable to predict nonalcoholic fatty liver disease (NAFLD), diabetes, and cardiovascular disease,[19,20] which are all related to NSCLC.[21,22] In addition, the TG/HDL-C ratio is positively linked to increased insulin resistance,[23] which has been emerged as an independent predictor of NSCLC.[24] To our knowledge, the present study is the first to analyze the relationship between the TG/HDL-C ratio and NSCLC in a Chinese population. We found that levels of TG/HDL-C were significantly higher in patients with NSCLC than those in the controls. In logistic regression analysis, TG/HDL-C was independently correlation with NSCLC risk, even after adjustment for confounding factors. In addition, the incidence of NSCLC increased along with elevated TG/HDL-C. We also found that patients with TNM II-IV stages had higher TG/HDL-C than those with TNM I and Tis stages. However, patients with adenocarcinoma had a trend toward increased level of TG/HDL-C compared with those with squamous cell carcinoma and other subtypes. Our study also found the potential of TG/HDL-C for detecting the risk of NSCLC with an AUC of 0.898, at a criterion of 0.62 with 83.6% sensitivity and 83.5% specificity. These results indicated that TG/HDL-C might serve as a potential prognostic biomarker for NSCLC risk.

Similar to TG/HDL-C, TC/HDL-C has also been demonstrated to be correlated with insulin resistance-related diseases, including diabetes, metabolic syndrome, and NAFLD.[25–27] In addition, high-sensitivity C-reactive protein (hs-CRP), which is a biomarker of NSCLC,[28,29] is strongly influenced by TC/HDL-C. Therefore, we hypothesized that TC/HDL-C might have connections with NSCLC. The present study indicated that levels of TC/HDL-C were significantly higher in patients with NSCLC than those in the control group. TC/HDL-C was independently correlated with NSCLC risk by logistic regression analysis. Moreover, raised TC/HDL-C was associated with increased incidence of NSCLC. We also found that patients with TNM II-IV stages had higher TC/HDL-C than those in TNM I and Tis stages. However, our study did not demonstrate a relationship between TC/HDL-C and pathological types of NSCLC. Through ROC analysis, we found that TC/HDL-C could also predict NSCLC, although TG/HDL-C was more accurate than TC/HDL-C. In addition, the incidence of NSCLC increased with each increasing tertiles of TG/HDL-C and TC/HDL-C. It indicated that modulating the lipid ratios may have a potential role in decreasing the incidence of NSCLC, similar to other lipid metabolism disorders. And this hypothesis should be confirmed in further studies.

The following limitations should be considered in the present study. First, because of the cross-sectional design, it was difficult to infer the causality between lipid ratios and NSCLC risk in our study. Further prospective research and in vitro experiments are warranted to elucidate these positive correlations. Second, we did not assess inflammatory factors such as hs-CRP, so the potential role of lipid ratios in NSCLC risk via inflammation needs to be explored in our further research. Third, since the study participants came from a single hospital, it is uncertain whether these results are representative of the general population and other ethnic groups.

5. Conclusion

We report the independent association of NSCLC risk with TG/HDL-C and TC/HDL-C for the first time. We also find that TG/HDL-C is more significant than TC/HDL-C in predicting the presence of NSCLC. Future prospective studies should review whether reduced TG/HDL-C and TC/HDL-C can reduce the prevalence of NSCLC in a large population.

Author contributions

XQ: Provision of study materials, reagents and patients, methodology, validation, investigation, writing-original draft preparation. YL and MM: data curation, formal and date analysis, validation. MC: provision of study patients, supervision. XY and HC: conceptualization, writing-reviewing and editing. All authors read and approved the final article.

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital of Medical School of Nanjing University. Written informed consent was obtained from all subjects in the study protocol.

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