Independent Associations Between Blood Lipid Profiles and Lung Cancer Risk

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Research Article

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Abstract

Introduction: Dyslipidemia is a common intermediate aggravating factor of various cancers, but the relationship between blood lipid profiles and lung cancer remains unclear. This study was performed to assess the non-linear and linear relationships between them.

Material and methods: We enrolled 1593 newly diagnosed lung cancer patients and 1593 age- and sex-matched healthy controls between 2017 and 2019. Biochemical indicators, including lipid profiles and tumor markers, were collected. Odds ratios and 95% confidence intervals were calculated using conditional logistic regression analysis. The restricted cubic spline analysis and multiple linear regression were used to explore the non-linear and linear associations.

Results: Lung cancer patients had lower values for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). After multivariate adjustment, hyper-TC and low-HDL-C were associated with lung cancer risk. In addition, non-linear relationships were identified between lung cancer risk and TC/HDL-C. Multiple linear regression analyses showed that triglycerides were significantly associated with squamous cell carcinoma antigen (SCC). As well, HDL-C was significantly associated with neuron-specific enolase (NSE), cytokeratin 19 fragments (CYFRA21-1), SCC, and tumor-associated antigen 125 (CA-125). Significant linear trends were observed between increasing triglyceride quartiles and hyper-NSE/hyper-CYFRA21-1, and between increasing HDL-C quartiles and hyper-NSE/hyper-CYFRA21-1/hyper-CA-125.

Conclusions: Lipid levels were significantly lower in lung cancer patients, and there were negative non-linear associations of TC and HDL-C with lung cancer risk. In addition, there were negative linear trends across TG and HDL-C quartiles for the risk of abnormal tumor markers among lung cancer patients.

Introduction

Lung cancer is the most common tumor in the world, accounting for 11.6% of total cancer cases, and it is also the leading cause of cancer-related death, accounting for 18.4% of total cancer mortality [1]. Although many epidemiologic studies have suggested that smoking is the major risk factor, the increasing incidence of lung cancer in nonsmokers indicates that other risk factors may exist [2]. As the tumorigenesis in the body is a systemic process, abnormal metabolism, including dyslipidemia, may play a role in the occurrence and deterioration of tumors [3].

Dyslipidemia is a common intermediate aggravating factor in many chronic diseases, including various types of cancer. Elevated triglyceride (TG) levels have been associated with prostate cancer [4], and elevated total cholesterol (TC) levels could increase the risk of prostate and colorectal cancers [4, 5]. Decreased high-density lipoprotein cholesterol (HDL-C) levels were associated with breast cancer and lymphoma [6, 7], and low-density lipoprotein cholesterol (LDL-C) levels were correlated with poor prognosis in pancreatic carcinoma [8]. However, the relationship between blood lipids profile and lung cancer has thus far resulted in contradictory conclusions and remains unclear. Lin et al. [9] demonstrated

that TC and HDL-C were negatively associated with lung cancer risk, while TG was positively associated with lung cancer risk. Hao et al. [10] reported that blood lipid profiles were not associated with lung cancer risk, with the exception of HDL-C. Lyu et al. [11] reported a non-linear relationship between lung cancer risk and both TG and TC, respectively, while low LDL-C was associated with increased lung cancer risk; and there was no significant relationship between HDL-C and lung cancer. Therefore, we performed this study to investigate the linear and non-linear relationships between blood lipid profiles and lung cancer risk.

In addition, much concern has been aroused in recent years regarding the value of molecular-based techniques in cancers. Cytokeratin 19 fragments (CYFRA21-1), squamous cell carcinoma antigen (SCC), serum carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and tumor-associated antigen 125 (CA125) have been the most commonly used in lung cancer because of their excellent sensitivity [12]. To comprehensively evaluate the linear relationship between blood lipid profiles and lung cancer risk, the association between abnormal tumor markers and lipid profiles among lung cancer patients was also explored.

Material And Methods

Study population

We enrolled 2390 newly diagnosed lung cancer patients admitted to Qilu Hospital of Shandong University between 2017 and 2019. The exclusion criteria were as follows: 1) history of treatment for lung cancer; 2) use of lipid-lowering drugs; 3) severe chronic diseases, such as chronic kidney disease or hyperparathyroidism; 4) other malignancy; 5) < 18 years of age; 6) undergoing systemic steroid treatment; and 7) missing clinical data. Ultimately, 1593 eligible patients were included in the study. In addition, 1593 age- and sex-matched healthy controls were collected from the Health Examination Center, Qilu Hospital of Shandong University.

Biochemical Indicators

Fasting blood samples were taken in the morning from each participant's anterior cubital vein. Determination of serum lipid profiles, including TC, TG, HDL-C, and LDL-C, and tumor marker profiles, including NSE, CYFRA21-1, SCC, and CA125, were performed using routine procedures in the hospital laboratory. Dyslipidemia was defined as hyper-TC ≥ 5.17 mmol/L, hyper-TG ≥ 1.7 mmol/L, low HDL < 1.03 mmol/L, and high LDL ≥ 3.33 mmol/L, respectively, according to the diagnostic criteria of the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEPIII) [13] and the Joint Committee for Developing Chinese Guidelines on the Prevention and Treatment of Dyslipidemia in Adults (JCDCG) [14]. Hyper-NSE (≥ 20 ng/mL), hyper-CYFRA21-1 (3.3 ng/mL), hyper-SCC (1.5 ng/mL), and hyper-CA-125 (35 ng/mL) levels were defined according to the manufacturer.

Statistical analysis

All data were tested for normality prior to statistical analysis. Data are expressed as medians (interquartile range) for continuous variables with skewed distribution and percentages for categorical variables. Differences in skewed continuous variables were examined using Mann-Whitney U test. Differences in categorical variables were examined using Chi-squared tests. Correlations were estimated using Spearman's correlation analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for lung cancer were calculated for binary or quaternary lipid profiles using conditional logistic regression adjusted for age, sex, smoking status, alcohol consumption, and other lipid profile components. The restricted cubic spline (RCS) analysis was used to explore the non-linear association between blood lipid profiles and lung cancer, and knots for blood lipid profiles were identified at the 5th, 25th, 50th, 75th, and 95th percentiles. Supplementary analyses, including multiple linear regression and logistic regression, were performed among lung cancer patients to estimate the linear association between the blood lipids profile and lung cancer. All statistical analyses were performed using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA) and R software package 3.6.2 (http://www.r-project.org/). Two-tailed P-values < 0.05 were considered significant.

Results

Basic characteristics of the study participants

In total, 3186 participants, including 1593 patients and 1593 controls, were included in this study. The basic characteristics of the two groups are shown in Table 1. Lung cancer patients presented with higher percentages of smoking and drinking, and all tumor markers, including NSE, CYFRA21-1, SCC, and CA-125 were significantly higher in this group. Analysis of lipid profiles revealed that the lung cancer patients had lower TC, HDL-C, and LDL-C values, whereas there were no significant differences in the TG values. Similarly, the percentages of individuals with hyper-TC, low HDL-C, and high LDL-C were significantly higher in lung cancer patients.

Relationship Between lipid profilesand lung cancer risk

As shown in Table 2, hyper-TC, low HDL-C and high LDL-C were all significantly associated with lung cancer risk. However, after adjusting for confounding factors, including age, sex, smoking status, alcohol consumption, and other lipid profile components, only hyper-TC and low HDL-C remained significantly associated with lung cancer risk. In particular, hyper-TC was associated with decreased lung cancer risk, with an OR (95% CI) of 0.632 (0.527, 0.759), while low-HDL-C was associated with increased lung cancer risk, with an OR (95% CI) of 1.992 (1.599, 2.482).

To further explore the non-linear relationship between plasma lipid levels and the risk of lung cancer, RCS was performed with adjustments for age, sex, smoking status, and alcohol consumption. The results showed that there was a non-linear relationship between lung cancer risk and both TC and HDL-C levels

(both P-overall<0.001, P-non-linear<0.001, Figure 1). However, the non-linear relationship was not significant for TG and LDL-C (P-non-linear>0.05, Figure 1).

Relationship between lipid profiles and tumor markers among lung cancer patients

Supplementary analyses, including multiple linear regression and logistic regression, were performed to estimate the linear relationship between blood lipid profiles and tumor markers among lung cancer patients. Multiple linear regression revealed that TG was significantly associated with SCC (β=-0.241, P=0.017), while HDL-C was significantly associated with NSE, CYFRA21-1, SCC, and CA-125 (P<0.05), following adjustment for age, sex, smoking status, and alcohol consumption (Table 3). We then performed logistic regression between the ORs (95% CI) for abnormal tumor markers and increasing TG/HDL-C quartiles. Significant negative linear trends were observed for hyper-NSE and hyper-CYFRA21-1 with increasing TG quartiles, with the ORs (95% CI) for hyper-NSE being 1 (reference), 1.104 (0.758, 1.606) 0.785 (0.518, 1.188), and 0.448 (0.283, 0.709), and the ORs (95% CI) for hyper CYFRA21-1 being 1 (reference), 0.977 (0.687, 1.390), 1.006 (0.697, 1.453), and 0.640(0.433, 0.946) (P for linear trends < 0.05) (Table 4). In addition, hyper-NSE, hyper-CYFRA21-1, and hyper-CA-125 were also significant in the linear trend test for HDL-C quartiles, with ORs (95% CI) for hyper-NSE of 1 (reference), 0.672 (0.457, 0.987), 0.714 (0.484, 1.053), and 0.472 (0.297, 0.752), while the ORs (95% CI) for hyper-CYFRA21-1 were 1 (reference), 0.664 (0.474, 0.929), 0.549 (0.387, 0.780), and 0.342 (0.224, 0.521), and the ORs (95% CI) for hyper CA-125 were 1 (reference), 0.578 (0.420, 0.795), 0.536 (0.386, 0.744), and 0.542 (0.379, 0.776), respectively (all P for linear trend < 0.01) (Table 4).

Discussion

The present study demonstrated that the levels of TC, HDL-C, and LDL-C were significantly lower in lung cancer patients. Notably, significant non-linear and negative associations between TC and HDL-C and lung cancer risk were found after multivariate adjustment. Furthermore, we identified negative linear trends for the risk of abnormal tumor markers across TG and HDL-C quartiles among lung cancer patients when all four lipid indicators were considered jointly.

Several previous studies have demonstrated a relationship between lipid profiles and risk for various types of cancer, including prostate, breast, and colorectal cancers [4–8]; however, the relationship between blood lipid profiles and lung cancer remains unclear. Studies aiming to evaluate the association between TC and non-small cell lung cancer have drawn inconsistent conclusions. Lin et al. [9] and Lyu et al. [11] demonstrated that low TC levels were associated with lung cancer risk. In contrast, Chandler et al. [15] found that high TC levels were associated with increased incidence of lung cancer, although the significance disappeared after multivariable adjustment. In the present study, we demonstrated that hyper-TC was associated with decreased lung cancer risk after adjusting for age, sex, smoking status, alcohol consumption, and other lipid profile components, consistent with the findings of Lin et al. and Lyu et al. However, it remains to be determined whether the observed relationship is causal or due to the effect of pre-diagnosed cancer on serum cholesterol levels. There are several underlying mechanisms that could

be involved in this relationship. Plasma polyunsaturated fatty acids, which can decrease TC levels, were found to be higher in lung cancer patients [16]. As well, low cell cholesterol has been associated with increased NF-κB activity, upregulated mevalonate pathway activity, and suppressed immunity [17, 18]. Finally, due to the rapid growth and high rate of division, malignant cells require far more cholesterol, which could lead to lower levels of blood cholesterol, including TC levels. We additionally found that there was a negative non-linear relationship between TG/TC and lung cancer risk. The identification of this non-linear pattern revealed the complexity of the relationship arising from interactions between multiple risk factors and suggests that lung cancer risk cannot be reduced simply by lowering blood lipids. This was demonstrated by the U-shaped association, which indicated that adjusting TC levels as low as possible did not reduce lung cancer risk.

HDL-C plays an important role in the reverse transport process of cholesterol, which facilitates the removal of excess cholesterol from peripheral tissues, and it is widely recognized as a protective factor in cardiovascular disease [19]. However, the role of HDL-C in the occurrence and progression of cancer, especially lung cancer, has not been determined. A meta-analysis of randomized controlled trials concluded that there was a significant inverse association between HDL-C and the risk of cancer [20], although this conclusion contradicts those of other studies [21, 22]. Some researchers have demonstrated that HDL-C was negatively associated with a risk of lung cancer [10], while Lyu et al. [11] found that no significant relationship existed. Our present results indicate that low HDL-C was associated with increased lung cancer risk, and there exists a significant non-linear and negative association between HDL-C and lung cancer risk after multivariate adjustment. There are numerous underlying mechanisms that may account for these findings. First, HDL-C could confer anti-inflammatory effects and organ protection through leukocyte adhesion and cytokine production; thus, the decrease in HDL-C level may lead to inflammation, which plays a role in the development of neoplasms [23, 24]. Second, lower HDL may have induced a reduction in antioxidant activity, which is associated with lung cancer [25]. Third, a decrease in the ability of HDL-C to inhibit apoptosis, resulting from decreased HDL-C levels, may contribute to the development of cancer [26, 27].

Research to evaluate the relationship between TG and lung cancer risk has drawn inconsistent conclusions as well. Some researchers demonstrated that TG was positively associated with increased lung cancer risk [9, 28], while Siemianowicz et al. [29] found that TG levels were lower in lung cancer patients. In our study, there was no significant difference in TG levels between lung cancer patients and healthy controls, and hyper-TG was not associated with lung cancer risk after multivariable adjustment. LDL-C, another component of cholesterol, was found to be associated with various cancers [30–33], while the relationship between LDL-C levels and lung cancer risk has not been clarified [10, 11]. The present study indicated that LDL-C levels were lower in lung cancer patients, and that high LDL-C was associated with decreased lung cancer risk. Of note, the association disappeared after multivariable adjustment. We speculate that interactions between the confounding factors may exist, and that this relationship requires further investigation. In addition, large-scale prospective studies are needed to clarify these relationships.

The association between biomarkers and tumors has aroused much attention [34, 35]. In order to comprehensively evaluate the linear relationship between blood lipid profiles and lung cancer risk, we explored the association between abnormal tumor markers and lipid profiles among lung cancer patients. Tumor markers, including CYFRA21-1, SCC, CEA, NSE, and CA125 have been commonly used to predict lung cancer because of their excellent sensitivity [12, 36]. We found that TG was associated with a decreased risk of hyper-NSE and hyper-CYFRA21-1, and that HDL-C was associated with a decreased risk of hyper-NSE, hyper-CYFRA21-1, and hyper CA-125, after multivariable adjustment. To our best knowledge, there is no research to explore the relationship between blood lipids and tumor markers of lung cancer, and the involved mechanisms were not clarified. One possible mechanism relating TG with abnormal tumor markers was that hyper TG was associated with the production of reactive oxygen species, which could affect normal cell proliferation [37]. However, hyper TG was not associated with lung cancer risk in aforementioned study. As to HDL-C, the involved mechanism may be related to inflammation, reduced antioxidant activity and disability to inhibit apoptosis [23–27]. In order to clarify the biological mechanism, large-scale prospective cohort studies taking tumor markers as primary target need to be performed.

Although our investigations were performed on a large sample that adjusted for multiple potential confounding factors, there were still several limitations. First, this observational study had a case-control rather than a prospective design; thus, the cause-consequence relationship cannot be evaluated. Second, although many common confounding factors were adjusted for, other potential confounding factors such as dietary habits, obesity, and physical activity were not considered. Therefore, further research is warranted to clarify the causal relationship and to enhance credibility.

Conclusion

The present study investigated the non-linear and linear relationships between lipid profiles and lung cancer risk after multivariate adjustment. We found that lipid levels were significantly lower in lung cancer patients, and that hyper-TC and low HDL-C were associated with lung cancer risk. In addition, there were negative non-linear associations between both TC and HDL-C and lung cancer risk. We also found negative linear trends among lung cancer patients for the risk of abnormal tumor markers across TG and HDL-C quartiles. These results suggest that it is important to consider lipid levels in populations at high-risk of lung cancer, and that dyslipidemia may be a potential modifiable factor for lung cancer prevention. Therefore, good lipid control may be a new and promising therapeutic strategy for the personalized treatment of lung cancer.

Abbreviations

TC
Total cholesterol; HDL-C:High-density lipoprotein cholesterol; LDL-C:Low-density lipoprotein cholesterol; SCC:Squamous cell carcinoma antigen; NSE:Neuron-specific enolase; CYFRA21-1:Cytokeratin 19 fragments; CA-125:Tumor-associated antigen125; TG:Triglyceride; CEA:Serum carcinoembryonic antigen;

NECPIII:National Cholesterol Education Program Adult Treatment Panel III; JCDCG:Joint Committee for Developing Chinese Guidelines; ORs:Odds ratios; 95%CIs:95% Confidence intervals; RCS:Restricted cubic spline.

Declarations

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Authors' contributions:

Chao Zhao and Hui Tian designed the overall study. Hui Zhao collected and analyzed the data. Chao Zhao wrote the manuscript. Hui Tian revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The clinical data used to support the findings of this study are available from the corresponding authors upon request.

Declarations

Ethics approval and consent to participate

This study was approved by the Internal Review Board of the Institutional Ethics Committee of Qilu Hospital of Shandong University (No.KYLL-2016(KS)-097), and written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

None of the authors has potential conflict of interests related to the content of the manuscript.

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Tables

Table 1. Basic characteristics of controls and lung cancer patients.

	Controls (n = 1593)	Patients (n = 1593)	P-value
Basic characteristics			
Age, y	57.0(52.0, 64.0)	57.0(52.0, 64.0)	-
Female, %	669, 42	669, 42	-
Current smoker, %	132, 8.7	723, 75.4	<0.001
Current drinker, %	371, 24.2	659, 41.4	<0.001
Tumor markers			
NSE, ng/ml	15.47(12.50, 18.91)	16.25(13.58, 20.81)	0.002
CYFRA21-1, ng/ml	1.71(1.23, 2.42)	2.42(1.63, 4.25)	<0.001
SCC, ng/ml	0.33(0.20, 0.45)	0.90(0.60, 1.20)	<0.001
CA-125, U/ml	9.38(7.21, 12.86)	17.14(10.50, 36.02)	<0.001
Lipid profiles			
TG, mmol/L	1.32(0.95, 1.88)	1.29(0.96, 1.78)	0.199
TC, mmol/L	4.91(4.33, 5.54)	4.61(3.97, 5.32)	<0.001
HDL-C, mmol/L	1.30(1.12, 1.51)	1.20(1.02, 1.43)	<0.001
LDL-C, mmol/L	2.92(2.41, 3.44)	2.78(2.26, 3.28)	<0.001
Hyper-TG, %	487, 30.6	449, 28.2	0.139
Hyper-TC, %	626, 39.3	468, 29.4	<0.001
Low HDL-C, %	249, 15.6	424, 26.6	<0.001
High LDL-C, %	440, 27.6	347, 21.8	<0.001

NSE, neuron-specific enolase; CYFRA21-1, cytokeratin 19 fragments; SCC, squamous cell carcinoma antigen; CA-125, tumor-associated antigen 125; TG, triglyceride; TC, elevated total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Odds ratios for lung cancer by binary or quaternary lipid profiles.

	Unadjusted			Multivariable adjusted*		
	OR	95%CI	P-value	OR	95%CI	P-value
Hyper-TG	0.922	(0.811, 1.048)	0.214	0.886	(0.737, 1.064)	0.194
Hyper-TC	0.748	(0.663, 0.843)	<0.001	0.632	(0.527, 0.759)	<0.001
Low HDL-C	1.703	(1.456, 1.991)	<0.001	1.992	(1.599, 2.482)	<0.001
High LDL-C	0.789	(0.685, 0.908)	0.001	0.922	(0.752, 1.129)	0.432

*Adjusted for age, sex, smoking status, alcohol consumption, and other lipid profiles components.

Table 3. Linear associations of lipid profiles with tumor markers among lung cancer cases.

	NSE, mmol/L		CYFRA21-1, mmol/L		SCC, mmol/L		CA-125, mmol/L	
	β	P	β	P	β	P	β	P
TG	-0.801	0.266	-0.559	0.180	-0.241	**0.017**	-13.971	0.059
TC	1.179	0.061	0.367	0.314	0.073	0.408	9.512	0.140
HDL	-5.895	**0.020**	-3.644	**0.013**	-0.974	**0.006**	-96.190	**<0.001**
LDL	-0.335	0.714	-0.456	0.389	-0.203	0.113	-2.189	0.815

Adjusted for age, sex, smoking status, alcohol consumption, and other lipid profiles components.

Table 4. Odds ratios for abnormal tumor markers by quaternary lipid profiles among lung cancer cases.

	Hyper-NSE	Hyper-CYFRA21-1	Hyper-SCC	Hyper-CA-125
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
TG				
≤0.95	1	1	1	1
0.95<TG≤1.31	1.104(0.758, 1.606)	0.977(0.687, 1.390)	1.115(0.769, 1.615)	1.022(0.738, 1.417)
1.31<TG≤1.82	0.785(0.518, 1.188)	1.006(0.697, 1.453)	0.904(0.600, 1.362)	1.098(0.783, 1.538)
>1.82	0.448(0.283, 0.709)	0.640(0.433, 0.946)	0.780(0.509, 1.195)	0.892(0.629, 1.266)
P for linear trend	**<0.001**	**0.038**	0.143	0.633
HDL				
≤1.07	1	1	1	1
1.07<TG≤1.25	0.672(0.457, 0.987)	0.664(0.474, 0.929)	0.836(0.576, 1.214)	0.578(0.420, 0.795)
1.25<TG≤1.48	0.714(0.484, 1.053)	0.549(0.387, 0.780)	0.786(0.534, 1.155)	0.536(0.386, 0.744)
>1.48	0.472(0.297, 0.752)	0.342(0.224, 0.521)	0.664(0.425, 1.036)	0.542(0.379, 0.776)
P for linear trend	**0.003**	**<0.001**	0.074	**0.001**

Adjusted for age, sex, smoking status, alcohol consumption, and other lipid profiles components.

Figures

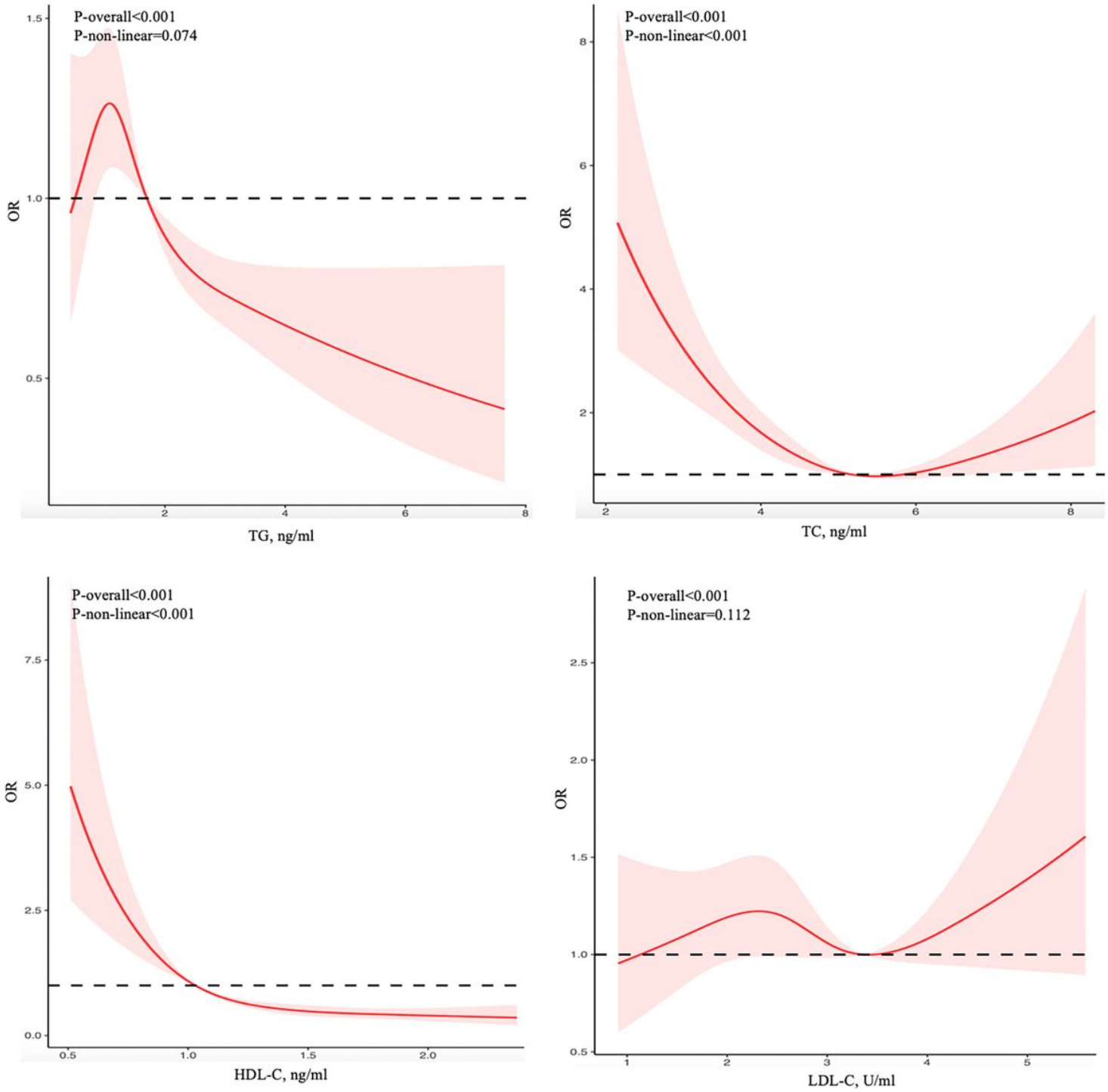

Figure 1

Restricted cubic spline regression of the non-linear relationship between lipid profiles [triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)] and lung cancer risk. There was a non-linear relationship between lung cancer risk and both TC and HDL-C levels (both P-overall<0.001, P-non-linear<0.001). However, the non-linear relationship was not significant for TG and LDL-C (P-non-linear>0.05).