Association between blood lipid levels and risk of liver cancer: a systematic review and meta-analysis

Zhihui Zhang
Southwest Medical University

Shicong Xu
Southwest Medical University

Meixuan Song
Southwest Medical University

Weirong Huang
Southwest Medical University

Manlin Yan
Southwest Medical University

Xianrong Li
1446319866@qq.com

The Affiliated Hospital of Southwest Medical University

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Abstract

**Purpose:** The association between blood lipid levels and the risk of developing liver cancer remains a subject of ongoing debate. In order to elucidate this association, we conducted a meta-analysis by systematically incorporating data from all relevant prospective cohort studies.

**Method:** We conducted a systematic search in PubMed, Embase, Web of Science, and The Cochrane Library, covering data from the inception of these databases up to July, 2023. This study included prospective cohort studies related to lipid profiles (e.g., total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) that reported hazard ratios (HRs) or relative risks (RRs) with their corresponding 95% confidence intervals (95%CIs) to investigate their association with the risk of liver cancer. During the analysis process, we used fixed-effect or random-effects models based on the level of heterogeneity among the studies and obtained pooled risk ratios using these models. To ensure the robustness and reliability of the study findings, we also conducted sensitivity analyses and publication bias analyses.

**Results:** After conducting a systematic search, we identified 12 studies from a total of 11,904 articles, which were included in the meta-analysis. These studies encompassed a combined population of 10,765,221 participants, including 31,055 cases of liver cancer events. The analysis results revealed that the highest versus lowest pooled risk ratio for serum total cholesterol (TC) concentration was 0.45 (95% CI = 0.35-0.58, $I^2 = 78\%$). For triglycerides (TGs), the risk ratio was 0.67 (95% CI = 0.46-0.96, $I^2 = 86\%$), while for high-density lipoprotein (HDL-C), the risk ratio was 0.72 (95% CI = 0.58-0.90, $I^2 = 65\%$). Regarding low-density lipoprotein (LDL-C), the risk ratio was 0.51 (95% CI = 0.23-1.13, $I^2 = 93\%$).

**Conclusion:** The findings of this study indicate a negative association between serum levels of total cholesterol, triglycerides, and high-density lipoprotein with liver cancer, suggesting that higher concentrations of these lipids are associated with a reduced risk of liver cancer. However, no significant association has been found between low-density lipoprotein and liver cancer at present.

Introduction

Liver cancer ranks as the sixth most common cancer and the third deadliest cancer worldwide (1, 2). According to data from the World Health Organization (WHO), approximately 800,000 people are diagnosed with primary liver cancer globally each year (3). The incidence of liver cancer is particularly high in Asia, with China having the highest rate, accounting for about half of all global cases (4). The main risk factors for liver cancer are related to chronic hepatitis B, hepatitis C, and fatty liver diseases (5, 6). Some studies have suggested that abnormalities in blood lipid levels may be associated with an increased risk of liver cancer (7, 8). Dyslipidemia may lead to the accumulation of fat in the liver and chronic inflammatory responses, thereby promoting the development of liver cancer (9).

Blood lipids refer to lipid or fat substances in the blood. Lipids are a class of biomolecules that mainly include fatty acids, triglycerides, cholesterol, and phospholipids, among others (10, 11). Blood lipids play
essential physiological roles in the body, such as providing energy, constructing cell membranes, synthesizing hormones, and regulating other biological processes (12). The link between blood lipid levels and cardiovascular diseases has been well-established (13, 14), and associations with colorectal cancer (15), prostate cancer (16), and breast cancer (17) have also been firmly established. Moreover, research has indicated that blood lipid levels are associated with prognosis of various cancers (18-20).

The association between blood lipid levels and the risk of liver cancer is a topic of considerable research interest. However, there is currently some controversy regarding this relationship. Some studies suggest that dyslipidemia may be associated with an increased risk of liver cancer (21, 22), while others report no clear association (23). These discrepancies may be attributed to the complex interplay between dyslipidemia and other risk factors, such as obesity, diabetes, and alcohol consumption, collectively influencing the risk of liver cancer. To assess the association between blood lipid levels and the risk of liver cancer, this study conducted a meta-analysis, incorporating all prospective studies relevant to blood lipid components. By employing systematic review and meta-analysis methods, we aim to explore the association between blood lipids and the risk of liver cancer, with the hope of providing further insights into this unclear association.

Subject terms: Liver neoplasms, blood lipids, meta-analysis

**Materials and methods**

This study strictly adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (24) (Supplementary Table S1) and has been registered in PROSPERO (CRD42023442073).

**Inclusion Criteria**

The inclusion criteria were as follows: (1) Cohort studies; (2) Studies involving adult participants (age ≥ 18 years); (3) Clearly stating liver cancer as the outcome of interest; (4) Providing explicit reports on the effect size of serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), or low-density lipoprotein cholesterol (LDL-C); (5) Reporting effect size measurements as hazard ratios (HR) or relative risks (RR) with their corresponding 95% confidence intervals (95%CI).

**Exclusion Criteria**

The exclusion criteria were as follows: (1) Study designs: Excluding studies with small sample sizes or significant selection bias; (2) Age range: Excluding studies that did not cover the age range of the target participants; (3) Outcome clarity: Excluding studies that did not explicitly state the study outcome or relevant indicators; (4) Missing data: Excluding studies with severe data missing or inability to obtain valid data; (5) Duplicate publications: Excluding studies that have been previously published in other literature.

**Search strategy**
Using a combination of subject terms and free-text words, all search terms were used in both singular and plural forms. Two researchers (ZHZ and SCX) independently conducted searches in the Embase, PubMed, Web of Science, and Cochrane Library databases to identify studies investigating the association between blood lipid levels and liver cancer. The search was limited from the inception of the databases up to July 12, 2023. Our search terms included serum lipids, total cholesterol, TC, triglycerides, TG, high-density lipoprotein, HDL-C, low-density lipoprotein, LDL-C, and liver cancer. To ensure the inclusion of all relevant cohort studies, the researchers also manually searched other relevant journal articles, reviews, and other sources, as well as thoroughly reviewed the reference lists of the included studies. In cases where multiple articles were published from the same cohort, we prioritized the study with the longest and most recent follow-up duration.

Data extraction

We extracted the following information from each study: the first author's name, publication year, study location, sample size, duration of follow-up, as well as the Hazard Risk (HR) or Relative Risk (RR) and their corresponding 95% confidence intervals (CIs) between the highest and lowest serum concentrations. Two researchers (ZHZ and SCX) independently extracted data from eligible studies. In case of disagreements, the entire team resolved the issue through consensus. When multiple risk estimates were reported in a single study, we selected the estimate that provided the most comprehensive adjustment for confounding factors.

Quality assessment

The quality assessment of each study was independently conducted by two researchers (MXS and WRH) using the Newcastle-Ottawa Scale (NOS) for quality assessment (25). Based on the NOS scores, the quality of each study was categorized into three groups: low quality (< 5 points), medium quality (5–7 points), and high quality (≥ 8 points).

Statistical analysis

Data analysis was conducted using Review Manager software (Version 5.4.1) and Stata software (Version 17.0). We extracted risk estimates from each study and calculated Hazard Risk (HR) and its corresponding 95% confidence intervals (95% CIs) using either the fixed-effects or random-effects model based on the degree of heterogeneity observed. Heterogeneity was assessed using the $I^2$ statistic, where $I^2 > 50\%$ indicated significant heterogeneity, $I^2$ values between 30\% and 50\% indicated moderate heterogeneity, and $I^2 < 30\%$ suggested the absence of significant heterogeneity. If $I^2 < 50\%$, we used the fixed-effects model; otherwise, the random-effects model was applied. Additionally, we employed the Meta-regression method to assess the variability between subgroups and explored the potential for publication bias through the symmetry of funnel plots and the Begg and Egger tests. The statistical significance was set at a $p$-value less than 0.05, and to evaluate the stability of the results, sensitivity analysis was performed.

Results
Study characteristics

After conducting a systematic search, a total of 11,904 articles were identified. Following the removal of 758 duplicates, the titles and abstracts of the remaining 11,146 articles were reviewed, leading to the selection of 70 articles for full-text screening. After excluding studies unrelated to blood lipid levels and liver cancer risk, a total of 12 articles were included in the meta-analysis (Fig. 1), involving 10,765,221 participants, among whom 31,055 cases of liver cancer were reported. These studies were published between 2009 and 2022, with 8 studies from Asia (26–33) and 4 from Europe (34–37). The NOS scores of the included studies ranged from 7 to 9, with 5 studies obtaining a score of 7 and 7 studies scoring 8 to 9 (Supplementary Table S3).

Meta analysis

Serum total cholesterol

A total of 7 studies reported the association between serum total cholesterol and liver cancer, published between 2009 and 2021, involving 9,812,439 participants, including 28,586 cases of liver cancer. Among these studies, 4 were conducted in Asia (27, 29, 30, 33) and 3 in Europe (34–36). The meta-analysis of the 7 studies demonstrated a significant negative association between serum total cholesterol and liver cancer risk (HR = 0.45, 95% CI = 0.35–0.58, P < 0.01). Significant heterogeneity was detected (I² = 78%, P < 0.01) (Fig. 2). The Egger’s test (P = 0.14) and Begg’s Test (P = 1.00) did not provide evidence of publication bias. Furthermore, a visual inspection of the funnel plot did not reveal any asymmetry (Supplementary Fig. S5).

Serum triglyceride

A total of 8 studies reported the association between serum triglycerides and liver cancer, published between 2009 and 2022, involving 10,199,390 participants, including 28,706 cases of liver cancer. Among these studies, 5 were conducted in Asia (26–28, 31, 32) and 3 in Europe (34, 35, 37). The meta-analysis of the 8 studies demonstrated a significant negative association between serum triglycerides and liver cancer risk (HR = 0.67, 95% CI = 0.46–0.96, P < 0.01) (Fig. 3). Significant heterogeneity was detected (I² = 86%, P < 0.01). The Egger’s test (P = 0.79) and Begg’s Test (P = 0.21) did not provide evidence of publication bias. Furthermore, a visual inspection of the funnel plot did not reveal any asymmetry (Supplementary Fig. S5).

Serum high-density lipoprotein cholesterol

A total of 6 studies reported the association between serum high-density lipoprotein (HDL-C) and liver cancer, published between 2009 and 2021, involving 9,593,597 participants, including 28,367 cases of liver cancer. Among these studies, 3 were conducted in Asia (27, 28, 31) and 3 in Europe (34, 36, 37). The meta-analysis of the 6 studies demonstrated a significant negative association between serum high-
density lipoprotein and liver cancer risk (HR = 0.72, 95% CI = 0.58–0.90, P < 0.01). Significant heterogeneity was detected (I² = 65%, P < 0.01) (Fig. 4). The Egger's test (P = 0.13) and Begg's Test (P = 0.54) did not provide evidence of publication bias. Furthermore, a visual inspection of the funnel plot did not reveal any asymmetry (Supplementary Fig. S5).

**Serum low-density lipoprotein cholesterol**

A total of 2 studies reported the association between serum high-density lipoprotein (HDL-C) and liver cancer, published between 2017 and 2021, involving 9,038,226 participants, including 27,657 cases of liver cancer. Among these studies, 1 was conducted in Asia (27) and 1 in Europe (36). The meta-analysis of the 2 studies showed no significant association between serum high-density lipoprotein and liver cancer risk (HR = 0.51, 95% CI = 0.23–1.13, P < 0.01). Significant heterogeneity was detected (I² = 93%, P < 0.01) (Fig. 5). Due to the limited number of studies, Egger's test and Begg's Test could not be performed. However, a visual inspection of the funnel plot did not reveal any asymmetry.

**Sensitivity analysis and subgroup analysis**

Sensitivity analysis was conducted to explore the stability of the association between blood lipid levels and liver cancer risk in the included studies. Excluding the studies investigating LDL-C and liver cancer risk, the results remained consistent for TC, TG, and HDL-C when each individual study was excluded separately.

We conducted several targeted subgroup analyses based on the characteristics of the studies to investigate the sources of heterogeneity. Due to insufficient research on the association between LDL-C and liver cancer, we only conducted subgroup analyses for TC, TG, and HDL-C. Regarding study quality, in high-quality studies, both TC (HR = 0.43, 95% CI = 0.33–0.55) and HDL (HR = 0.68, 95% CI = 0.47–0.99) showed significant associations with liver cancer risk, while there was no significant correlation between TG (HR = 0.83, 95% CI = 0.55–1.25) and liver cancer risk. In the subgroup analysis based on the geographic region of the study population, the association between TC and liver cancer risk was similar in the European group (HR = 0.45, 95% CI = 0.35–0.59) and the Asian group (HR = 0.47, 95% CI = 0.33–0.69). In the Asian group, a significant correlation was observed between TG (HR = 0.59, 95% CI = 0.54–0.64) and liver cancer risk, while there was no association between HDL (HR = 0.75, 95% CI = 0.54–1.02) and liver cancer risk. In the European group, a significant correlation was also observed between HDL (HR = 0.68, 95% CI = 0.47–0.99) and liver cancer risk, but no significant association was found between TG (HR = 0.94, 95% CI = 0.58–1.53) and liver cancer risk. Additionally, in studies with a case number ≥ 266, TC (HR = 0.41, 95% CI = 0.31–0.54) showed a significant correlation with liver cancer risk. Lastly, we observed significant associations between TC (HR = 0.49, 95% CI = 0.37–0.65) and HDL (HR = 0.56, 95% CI = 0.43–0.72) and liver cancer risk in studies with a follow-up duration of ≥ 10 years (Table 1 and Supplementary Table. S4).
Table 1
Subgroup analysis of the association between total cholesterol and liver cancer risk.

<table>
<thead>
<tr>
<th>Areas</th>
<th>Number of studies</th>
<th>HR (95%CI)</th>
<th>( I^2 )</th>
<th>( p^a )</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>4</td>
<td>0.47(0.33, 0.69)</td>
<td>76.5%</td>
<td>0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>0.45(0.35, 0.59)</td>
<td>78.1%</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study quality</th>
<th>Number of studies</th>
<th>HR (95%CI)</th>
<th>( I^2 )</th>
<th>( p^a )</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td>5</td>
<td>0.43(0.33, 0.55)</td>
<td>79.3%</td>
<td>0.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Medium quality</td>
<td>2</td>
<td>0.61(0.41, 0.90)</td>
<td>0.0%</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up years</th>
<th>Number of studies</th>
<th>HR (95%CI)</th>
<th>( I^2 )</th>
<th>( p^a )</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10</td>
<td>5</td>
<td>0.49(0.37, 0.65)</td>
<td>60.2%</td>
<td>0.03</td>
<td>0.16</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0.37(0.35, 0.38)</td>
<td>0.0%</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Number of studies</th>
<th>HR (95%CI)</th>
<th>( I^2 )</th>
<th>( p^a )</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 266</td>
<td>4</td>
<td>0.41(0.31, 0.54)</td>
<td>86.2%</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>266</td>
<td>3</td>
<td>0.62(0.44, 0.88)</td>
<td>0.0%</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

**Adjustment for confounders**

<table>
<thead>
<tr>
<th>Confounder</th>
<th>Number of studies</th>
<th>HR (95%CI)</th>
<th>( I^2 )</th>
<th>( p^a )</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI YES</td>
<td>5</td>
<td>0.46(0.33, 0.64)</td>
<td>81.6%</td>
<td>0.01</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI NO</td>
<td>2</td>
<td>0.46(0.37, 0.57)</td>
<td>0.0%</td>
<td>0.826</td>
<td></td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>YES</td>
<td>4</td>
<td>0.52(0.36, 0.76)</td>
<td>83.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>NO</td>
<td>3</td>
<td>0.36(0.22, 0.59)</td>
<td>63.7%</td>
<td>0.06</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>YES</td>
<td>5</td>
<td>0.46(0.33, 0.64)</td>
<td>81.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>NO</td>
<td>2</td>
<td>0.46(0.37, 0.57)</td>
<td>0.0%</td>
<td>0.826</td>
</tr>
<tr>
<td>Physical activity</td>
<td>YES</td>
<td>3</td>
<td>0.50(0.33, 0.77)</td>
<td>90.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Physical activity</td>
<td>NO</td>
<td>4</td>
<td>0.43(0.35, 0.52)</td>
<td>42.8%</td>
<td>0.136</td>
</tr>
<tr>
<td>Dietary factors</td>
<td>YES</td>
<td>2</td>
<td>0.65(0.45, 0.65)</td>
<td>0.0%</td>
<td>0.815</td>
</tr>
</tbody>
</table>
Discussion

This study conducted a comprehensive analysis by systematically integrating all relevant prospective research to further explore the association between blood lipid levels and liver cancer risk. The study covered a large number of participants from multiple countries, ensuring high reliability of the results. The findings revealed that higher levels of total cholesterol (TC), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were associated with a reduced risk of liver cancer, whereas there was no correlation between serum low-density lipoprotein cholesterol (LDL-C) and liver cancer risk. These study results contribute to clarifying the link between blood lipid levels and liver cancer risk. Moreover, this discovery aids in using blood spectrum analysis to predict liver cancer risk in high-risk populations.

Metabolic alterations are widely recognized as hallmarks of cancer (38), and there is a close association between dyslipidemia and the development of liver cancer (22). Previous research has indicated that elevated levels of total cholesterol (TC) increase the risk of cardiovascular diseases (39–41). However, this current study reveals a paradoxical finding where higher TC levels are actually associated with a reduced risk of liver cancer. This association may be attributed to the diverse functions of TC in different organs within the human body. In the liver, cholesterol is involved in bile acid synthesis, and bile acids have been shown to slow down liver damage and the progression of hepatocellular carcinoma (42, 43). Furthermore, studies suggest that receptor tyrosine kinases (RTKs) play a critical role in tumor malignant transformation and cancer metastasis (44), and cholesterol inhibits RTK autophagic degradation in a GOLM1-dependent manner (45, 46). Similarly, research has demonstrated that estrogen exerts a significant protective effect against hepatocellular carcinoma (47), and as cholesterol serves as a precursor for steroid hormones, epidemiological studies have shown an increased incidence of liver cancer in postmenopausal women (48). Nevertheless, further research is warranted to elucidate these potential mechanisms fully.

Previous studies have indicated an association between TG and various cancers (40), such as an increased risk of colorectal (49), prostate (50), and breast cancer(51) with higher triglyceride levels. This meta-analysis combines the results of 8 prospective cohort studies and demonstrates a significant inverse association between TG and liver cancer. The potential mechanism underlying triglycerides as a protective factor against liver cancer in this study may be linked to the expression level of diacylglycerol acyltransferase (DGAT) (52), as confirmed in previous research. High DGAT2 expression is associated
with prolonged overall survival in cancer patients (52, 53), and these findings have been validated in in vitro and in vivo experiments, indicating that DGAT2 overexpression can inhibit cell proliferation and reduce tumor growth (52). DGAT is a key enzyme that facilitates the conversion of diacylglycerol (DAG) to triglycerides (TAG) (54), which is an essential step in fatty acid synthesis and storage. Normal triglyceride metabolism is crucial for maintaining lipid balance in the liver and the whole body. Moreover, some studies have suggested that lower triglyceride levels may be related to excessive fat accumulation and the development of fatty liver in the liver (55). However, this remains a hypothesis, and further research is needed to explore the potential benefits of triglycerides in anti-tumor aspects.

A meta-analysis investigating the association between HDL-C and gastric cancer risk has also reported similar findings (56). In this current study, a link was revealed between higher levels of HDL-C and a reduced risk of liver cancer. However, the specific mechanisms underlying HDL's role in lowering liver cancer risk remain unclear. Firstly, HDL-C may act as a reverse transporter of cholesterol in the body, collecting excess cholesterol and aiding in its clearance (57, 58), thus maintaining cholesterol balance. Secondly, HDL-C also exhibits antioxidant and anti-inflammatory properties, reducing intracellular oxidative stress and inflammation (59, 60), which are closely associated with the occurrence and development of cancer (61). Reports have shown that HBV and HCV are independent risk factors for liver cancer (62, 63), and a case-control study indicated lower levels of cholesterol, triglycerides, and high-density lipoprotein in the serum of HCV patients compared to the control group (64). Although these observed phenomena are intriguing, direct evidence supporting the hypothesized negative correlation between HDL and liver cancer is currently lacking. Therefore, future research should further explore the physiological mechanisms underlying the association between HDL-C and liver cancer to better understand its role in the development of the disease.

In this meta-analysis, no significant association between LDL-C and liver cancer risk was observed. While other studies have suggested that lowering LDL-C levels can enhance the effectiveness of statin therapy for stroke (65) and that elevated LDL-C increases the risk of cardiovascular diseases (66, 67), similar results related to liver cancer were not observed in this study. Additionally, numerous studies have shown that high LDL-C levels are risk factors for various cancers, such as lung (68) and breast cancer (69). However, the lack of association in this study may be attributed to the fact that elevated LDL-C levels are often associated with dyslipidemia (70), and the observed link between LDL-C and cancer risk might be a secondary effect. It is also possible that the impact of LDL-C on cancer risk appears to vary depending on the site of cancer. Furthermore, this study only included two prospective cohort studies, leading to a high level of heterogeneity ($I^2 = 93\%, P < 0.01$). In the future, improvements in study design and increased sample size would be beneficial in gaining a deeper understanding of the potential association between LDL-C and liver cancer.

**Advantages and limitations**

The strength of this meta-analysis lies in its comprehensive inclusion of large-scale, prospective studies with extended follow-up periods, rather than relying on case-control studies, thus reducing potential
limitations associated with case-control designs that could affect result accuracy. Additionally, the substantial number of participants and case data ensures the validity and reliability of the findings. Furthermore, the results of sensitivity analyses indicate stability, and no evidence suggests publication bias in any of the included studies. Taken together, these factors contribute to enhancing the reliability of the research findings. Despite conducting numerous subgroup and sensitivity analyses, the statistical significance of the sources of heterogeneity in these variations has not been definitively determined. However, the study results still demonstrate significant heterogeneity, which may impact the overall reliability of the pooled outcomes. This heterogeneity could stem from factors not accounted for in the analysis, such as lifestyle behaviors, individual differences, dietary habits, comorbidities, and psychological factors, which could potentially influence disease incidence rates. Therefore, when interpreting the results, it is crucial to cautiously consider these potential confounding factors and comprehensively assess their potential impact on the study outcomes. Additionally, while we employed explicit inclusion criteria, differences in comparison methods could contribute to heterogeneity. For instance, comparing the highest reading of serum lipid profiles with the lowest group may yield different estimates, as some studies may categorize groups based on quartiles of serum concentrations, while others may use normal ranges as the basis for categorization. As a result, to gain a more accurate understanding of the research findings, it is essential to integrate and fully comprehend the implications of these diverse measurement criteria on the study conclusions.

Conclusion

The comprehensive analysis of the results indicates a significant negative association between liver cancer risk and serum levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). However, there is no significant association between serum low-density lipoprotein cholesterol (LDL-C) levels and liver cancer risk. Considering these findings, it is necessary to gain a thorough understanding of the potential underlying mechanisms. Moreover, further clinical research is needed to validate whether intervention to lower lipid component concentrations can effectively reduce the incidence of liver cancer.

Declarations

Author contributions

ZH, SCX, and XRL conceived and designed this study. ZHZ and MLY devised the inclusion and exclusion criteria and the literature search strategy. ZHZ and SCX conducted the literature screening and data extraction. MXS and WRH assessed the quality of the included studies. ZHZ and SCX performed the data analysis and data visualization. ZHZ and SCX drafted the original manuscript. All authors made necessary revisions to the original draft and unanimously approved the final version of the manuscript. XRL supervised this study.

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**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

**Data Availability**

All data and analysis processes have been presented in detail in this manuscript and the Supplementary Information section.

**References**

10. Wilkins J, Rohatgi A (2023) Higher High-Density Lipoprotein Cholesterol-Good Omen, Bad Omen, or Not an Omen at All. JAMA Cardiol 8:273–274


64. Arain SQ, Talpur FN, Channa NA, Ali MS, Afridi Hl (2018) Serum lipids as an indicator for the alteration of liver function in patients with hepatitis B. Lipids Health Dis 17:36


Figures
Figure 1

Flowchart of literature selection process
### Figure 2

Forest plot of the association between total cholesterol and liver cancer risk

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn 2009</td>
<td>-0.41552</td>
<td>0.21784</td>
<td>13.7%</td>
<td>0.68 [0.43, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Borena 2012</td>
<td>-1.46068</td>
<td>0.27411</td>
<td>11.0%</td>
<td>0.23 [0.13, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Cho 2021</td>
<td>-1.02185</td>
<td>0.02157</td>
<td>23.2%</td>
<td>0.36 [0.25, 0.50]</td>
<td></td>
</tr>
<tr>
<td>Iso(F) 2009</td>
<td>-0.22314</td>
<td>0.53386</td>
<td>4.5%</td>
<td>0.80 [0.28, 2.68]</td>
<td></td>
</tr>
<tr>
<td>Iso(M) 2009</td>
<td>-0.71335</td>
<td>0.56052</td>
<td>4.1%</td>
<td>0.49 [0.16, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Lee 2017</td>
<td>-0.89160</td>
<td>0.51059</td>
<td>4.9%</td>
<td>0.41 [0.15, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Nderitu 2017</td>
<td>-0.77653</td>
<td>0.11024</td>
<td>19.8%</td>
<td>0.46 [0.37, 0.57]</td>
<td></td>
</tr>
<tr>
<td>Sun 2021</td>
<td>-0.53649</td>
<td>0.12531</td>
<td>18.9%</td>
<td>0.58 [0.46, 0.75]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.45 [0.35, 0.58]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.07; \chi^2 = 31.30, df = 7 (P < 0.0001); \chi^2 = 78$

Test for overall effect: $Z = 6.33 (P < 0.00001)$

### Figure 3

Forest plot of the association between triglyceride and liver cancer risk

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borena 2012</td>
<td>-0.52763</td>
<td>0.4553</td>
<td>7.8%</td>
<td>0.59 [0.24, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Chang 2022</td>
<td>-1.53248</td>
<td>0.54431</td>
<td>6.5%</td>
<td>0.22 [0.07, 0.63]</td>
<td></td>
</tr>
<tr>
<td>Cho 2021</td>
<td>-0.52763</td>
<td>0.0473</td>
<td>14.7%</td>
<td>0.59 [0.54, 0.65]</td>
<td></td>
</tr>
<tr>
<td>Inoue(F) 2009</td>
<td>-0.54473</td>
<td>0.54252</td>
<td>6.5%</td>
<td>0.58 [0.20, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Inoue(M) 2009</td>
<td>-0.02022</td>
<td>0.30429</td>
<td>10.8%</td>
<td>0.96 [0.54, 1.79]</td>
<td></td>
</tr>
<tr>
<td>Nderitu 2017</td>
<td>0.46859</td>
<td>0.13586</td>
<td>13.6%</td>
<td>1.63 [1.25, 2.13]</td>
<td></td>
</tr>
<tr>
<td>Osaki 2012</td>
<td>-0.85393</td>
<td>0.27453</td>
<td>11.2%</td>
<td>0.52 [0.30, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Si 2018</td>
<td>-1.90569</td>
<td>0.76473</td>
<td>4.2%</td>
<td>0.16 [0.03, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Xia(F) 2021</td>
<td>-0.35687</td>
<td>0.24872</td>
<td>11.7%</td>
<td>0.70 [0.43, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Xia(M) 2021</td>
<td>-0.13926</td>
<td>0.19129</td>
<td>12.8%</td>
<td>0.87 [0.60, 1.27]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.67 [0.46, 0.96]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.23; \chi^2 = 62.62, df = 9 (P < 0.00001); \chi^2 = 86$

Test for overall effect: $Z = 2.17 (P = 0.03)$
Figure 4

Forest plot of the association between high-density lipoprotein cholesterol and liver cancer risk.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log Hazard Ratio</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2021</td>
<td>-1.04982</td>
<td>0.01458</td>
<td>53.5%</td>
<td>0.36 [0.34, 0.38]</td>
</tr>
<tr>
<td>Ndertu 2017</td>
<td>-0.23572</td>
<td>0.21545</td>
<td>46.5%</td>
<td>0.79 [0.52, 1.21]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.51 [0.23, 1.13]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.31; Ch² = 14.21, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 1.65 (P = 0.10)

Figure 5

Forest plot of the association between low-density lipoprotein cholesterol and liver cancer risk.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.docx
- SupplementaryTableS2.docx
- SupplementaryTableS3.docx
- SupplementaryTableS4.docx
- SupplementaryFigureS5.zip