Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies

Liu YuPeng¹, Zhang YuXue², Li PengFei³, Cheng Cheng⁴, Zhao YaShuang¹, Li DaPeng¹, and Du Chen⁵

Abstract

Background: As a neutral lipid and prominent component of the Western diet, cholesterol levels might be a risk factor for prostate cancer. However, current evidence has been inconsistent. This meta-analysis aimed to evaluate the association between blood cholesterol levels and the risk of prostate cancer.

Methods: An extensive search was performed in MEDLINE and EMBASE for prospective studies that have reported the association between total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) levels in blood and risk of prostate cancer. Random-effects models were used to summarize the study-specific results.

Results: Fourteen studies were included in this meta-analysis. In the meta-analysis, the summarized risk ratios (RR) for the highest to lowest cholesterol levels were as follows: 1.05 (95% confidence interval [CI], 0.97–1.14; P = 0.21) for TC, 0.93 (95% CI, 0.80–1.10; P = 0.40) for HDL, and 1.17 (95% CI, 0.88–1.55; P = 0.51) for LDL. When restricting to high-grade prostate cancer, the pooled RR was 1.32 (95% CI, 0.93–1.87; P = 0.13) for TC. In dose–response analyses, a 1 mmol/L increment in blood TC, HDL, and LDL level conferred an RR of 1.01 (95% CI, 0.99–1.02; P = 0.38), 0.98 (95% CI, 0.91–1.07; P = 0.72), and 1.04 (95% CI, 0.98–1.10; P = 0.24), respectively.

Conclusion: In this meta-analysis of 14 large prospective studies, blood TC, HDL, and LDL levels were not associated with the risk of either overall prostate cancer or high-grade prostate cancer.

Impact: Our findings did not appear to support the hypothesis that hypercholesterolemia increases the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev; 1–8. ©2015 AACR.

Introduction

Cholesterol, a modified steroid lipid that makes up about one third of the lipid content of the plasma membrane, is an essential structural component of cell membranes (1). Cholesterol is the principal sterol synthesized in the human liver. Major food sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp (2). Western diets of excess cholesterol may cause hypercholesterolemia in developed countries. Hypercholesterolemia presents with high cholesterol levels in the blood (3). Hypercholesterolemia is not a disease, but a metabolic derangement that can be secondary to many diseases, and can contribute to many types of disease, most notably cardiovascular disease.

Prostate cancer is the second-most frequently diagnosed cancer and the sixth-leading cause of cancer-related death in men (4). Although the causes of prostate cancer are not understood, it is apparent that both genetic factors and environmental factors play important roles in risk of prostate cancer. Geographically, prostate cancer has a high incidence in Western Europe and North America, but a low incidence in Asia (4), which suggests that the Western lifestyle or environment might have a causal role in the incidence of prostate cancer in these areas. In addition, the prevalence of elevated blood total cholesterol (TC) levels was highest in the WHO Region of Europe (54% for both sexes) followed by the WHO Region of the Americas (48% for both sexes); the prevalence of high TC levels was the lowest in the WHO African Region (22.6%) and the WHO South East Asian Region (29.0%; ref. 5). Hence, prostate cancer risk has been suggested to be related to the high levels of circulating cholesterol concentrations.

According to studies of mechanisms and epidemiologic studies, some reviews have proposed that a high blood cholesterol level might be a risk factor for prostate cancer (6–8), and some studies have suggested that high TC level might increase the risk of high-grade or advanced prostate cancer rather than total prostate cancer (6, 9). Some epidemiologic studies and preclinical models also suggest that high levels of cholesterol in blood may be associated with the risk of prostate cancer (6). However, the findings from these epidemiologic studies are inconsistent (10–23), as some studies have reported that high levels of...
cholesterol increased risk of prostate cancer (15, 16, 18), and some studies have reported no association between cholesterol and risk of prostate cancer (10–14, 17, 19, 21–23). Moreover, high cholesterol has been proposed to be closely associated to late-stage prostate cancer, and cholesterol may play a promotional role in late-stage prostate cancer development and progression (11, 15, 18, 19). Therefore, this meta-analysis comprehensively summarized the results of prospective studies that focused on the association between blood cholesterol level and risk of prostate cancer.

Materials and Methods

Search strategy

We systematically reviewed MEDLINE and EMBASE through March 2014 to identify all relevant articles. We used the following MeSH terms for exposure: lipid level, cholesterol, high-density lipoprotein, HDL, low-density lipoproteins, LDL. We combined these terms with the following terms using corresponding free-text words for the outcomes: prostate neoplasm, prostate neoplasms, prostatic neoplasm, prostatic neoplasms, prostate cancer, prostate cancers, prostatic cancer, and prostatic cancers. Moreover, we reviewed reference lists from retrieved articles to identify any potentially relevant studies. This systematic review was planned, conducted, and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE; Supplementary Table S1; ref. 24).

Inclusion criteria

We included studies if they met the following criteria: (i) studies published in English; (ii) studies designed as a prospective method (including cohort, case–cohort, and nested case–control); (iii) exposure factors were levels of cholesterol (TC, LDL, or HDL) in blood serum or plasma; (iv) the outcome of interest was prostate cancer; (v) relative risk (RR), odds risk (OR), or HR estimates with 95% confidence intervals (CI, or sufficient information to calculate these data) for more than three categories of cholesterol levels were reported; and (vi) when duplicated reports were published from the same population, we included the most recent or complete publications.

Data extraction

Data abstraction was conducted independently by two authors (D. Chen and Z. YaShuang) according to the standard forms specifically created for this systematic review and meta-analysis, and any disagreement was resolved by consensus. The following information was extracted for each retrieved article: name of the first author, publication year, study design, study period or follow-up time, country, mean age or age range of participants at baseline, number of prostate cancer cases, sample size, variables that were adjusted for or matched in each retrieved article, and effect estimates with corresponding 95% CIs for the highest versus the lowest categories of blood TC, LDL, or HDL cholesterol levels.

Quality assessment

We chose to use the 9-star Newcastle-Ottawa Scale (NOS) to assess the studies' quality (Supplementary Table S2; ref. 25). The NOS consists of three parts of quality: selection, comparability, and outcome. The maximum points for four points for selection, two points for comparability, and three points for outcome were assigned, respectively. Quality assessment was conducted inde-
Table 1. Characteristics of prospective studies on serum cholesterol and prostate cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Study design</th>
<th>Location</th>
<th>Name of cohort</th>
<th>Follow-up years</th>
<th>Sample size</th>
<th>Age, y</th>
<th>Exposure Range of exposure</th>
<th>Outcome (no. of cases)</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>His et al. (10)</td>
<td>Randomized intervention trial</td>
<td>France</td>
<td>SU.VI.MAX Cohort</td>
<td>8–15</td>
<td>3,148</td>
<td>49.00 (mean)</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>TC: Q1 (&lt;5.53), Q4 (&gt;6.80) mmol/L&lt;br&gt;HDL: Q1 (&lt;1.5), Q4 (&gt;1.91) mmol/L&lt;br&gt;LDL: Q1 (&gt;3.39), Q4 (&gt;4.35) mmol/L</td>
<td>PCa (128)</td>
</tr>
<tr>
<td>Haggström et al. (13)</td>
<td>Cohort study</td>
<td>Norway, Sweden, and Austria</td>
<td>the Metabolic Syndrome and Cancer (Me-Can) project</td>
<td>12 (mean)</td>
<td>2,89,886</td>
<td>43.9 (mean)</td>
<td>TC</td>
<td>TC: Q1 (=165), Q4 (&gt;207) mg/dL&lt;br&gt;HDL: Q1 (&lt;36), Q4 (&gt;51) mg/dL&lt;br&gt;LDL: Q1 (&gt;188), Q4 (&gt;28) mg/dL</td>
<td>PCa (6,673)</td>
</tr>
<tr>
<td>Jacobs et al. (12)</td>
<td>Nest case-control study</td>
<td>USA</td>
<td>the Cancer Prevention Study II Nutrition Cohort</td>
<td>6–9</td>
<td>14,241</td>
<td>50–79</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>PCa (650)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Shafique et al. (11)</td>
<td>Cohort study</td>
<td>Scotland, UK</td>
<td>The Midspan studies</td>
<td>37</td>
<td>12,276</td>
<td>45–64</td>
<td>TC</td>
<td>PCa (208)</td>
<td>High grade (231)</td>
</tr>
<tr>
<td>Farwell et al. (18)</td>
<td>Retrospective cohort study</td>
<td>USA</td>
<td>the Statins user of Veterans Affairs (VA) New England Healthcare System</td>
<td>2–11</td>
<td>55,875</td>
<td>(mean)</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>PCa (2,041)</td>
<td>High grade (650)</td>
</tr>
<tr>
<td>Grundmark et al. (17)</td>
<td>Cohort study</td>
<td>Sweden</td>
<td>ULSAM</td>
<td>34</td>
<td>2,322</td>
<td>50 (mean)</td>
<td>TC</td>
<td>PCa (208)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Mondul et al. (2)</td>
<td>Randomized intervention trial</td>
<td>Finland</td>
<td>ATBC</td>
<td>21 (mean)</td>
<td>29,093</td>
<td>50–69</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>PCa (2,041)</td>
<td>High grade (650)</td>
</tr>
<tr>
<td>Van Hemelrijck et al. (2)</td>
<td>Cohort study</td>
<td>Sweden</td>
<td>AMORIS</td>
<td>8.23 (mean)</td>
<td>2,00,660</td>
<td>&gt;35</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>PCa (5,112)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Kitahara et al. (2)</td>
<td>Cohort study</td>
<td>Korea</td>
<td>Korean NHIC</td>
<td>11–14</td>
<td>53,944</td>
<td>45.08 (mean)</td>
<td>TC</td>
<td>PCa (2,480)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Mondul et al. (19)</td>
<td>Cohort study</td>
<td>USA</td>
<td>CLUE II cohort</td>
<td>11.9 (mean)</td>
<td>6,816</td>
<td>≥35</td>
<td>TC</td>
<td>PCa (443)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Iso et al. (22)</td>
<td>Cohort study</td>
<td>Japan</td>
<td>JPHC</td>
<td>10–14</td>
<td>33,368</td>
<td>40–69</td>
<td>TC</td>
<td>PCa (2,728)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Platz et al. (20)</td>
<td>Randomized intervention trial</td>
<td>USA</td>
<td>PCPT</td>
<td>6–9</td>
<td>5,586</td>
<td>≥55</td>
<td>TC</td>
<td>PCa (1,251)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Martin et al. (22)</td>
<td>Cohort study</td>
<td>Norway</td>
<td>HUNT2</td>
<td>8–10</td>
<td>29,364</td>
<td>≥20</td>
<td>TC&amp;HDL&amp;LDL</td>
<td>PCa (687)</td>
<td>High grade (176)</td>
</tr>
<tr>
<td>Steenland et al. (23)</td>
<td>Cohort study</td>
<td>USA</td>
<td>NHANES1</td>
<td>12–16</td>
<td>14,407</td>
<td>25–74</td>
<td>TC</td>
<td>PCa (156)</td>
<td>High grade (176)</td>
</tr>
</tbody>
</table>

Abbreviations: Q, quartile or quintile; PCa, prostate cancer.

*High-grade, Gleason score of prostate cancer ≥7.

Study quality was judged on the basis of the Newcastle-Ottawa Scale (range, 1–9 stars).
and 10 cohort studies) were included in this analysis (10–23). In the 14 included studies, the retrospective cohort study by Farwell and colleagues (18) was also included because it prospectively measured serum cholesterol levels.

Study characteristics and quality assessment

The characteristics of the 14 included studies are summarized in Table 1. The additional information (levels of HDL and LDL, adjusted variables) are shown in Supplementary Table S3. The 14 included studies were published between 1995 and 2014. The follow-up duration ranged from 6 years up to 36 years. In the 14 included studies, 5 studies were conducted in the American population, 7 in the European population, and 2 in the Asian population. Most studies adjusted or controlled risk estimates by age (12 studies) or BMI (8 studies).

For TC, there were 23,142 prostate cancer cases from the 14 included studies across 737,217 total participants. As for HDL, 6 studies reported the association between blood HDL levels and the risk of prostate cancer. Only 4 studies reported the RRs of blood LDL levels relating to the prostate cancer risk.

Total cholesterol

**Highest versus lowest of TC.** The pooled results combined for the highest versus lowest TC levels are shown in Fig. 1. For the association between TC levels and risk of prostate cancer, the general studies reported null results with the exception of the two Asian studies. The overall pooled RR for the highest versus lowest levels of TC was 1.05 (95% CI, 0.97–1.07) (P = 0.13). There was moderate heterogeneity in the results of the association between TC (I² = 45.44%, P for heterogeneity = 0.05) and the risk of prostate cancer. When restricting to patients with prostate cancer of a high grade, there was still no obvious association between TC and risk of prostate cancer with a high cancer grade (RR, 1.32; 95% CI, 0.93–1.87; P = 0.13; Table 2).

**Dose–response analysis.** For the dose–response analysis, 12 studies were included to assess the dose–response relationship between TC and the risk of prostate cancer. The summary RR was 1.01 (95% CI, 0.99–1.02; P = 0.38; Supplementary Table S4) using two-stage random-effects dose–response model with heterogeneity (P = 0.001). We did not detect the potentially nonlinear dose–response relationship (P = 0.19; Fig. 2 and Supplementary Table S4).

**Subgroup analyses.** The stratified analyses were defined by the study population, study design, follow-up times, number of patients with prostate cancer, and adjustment for BMI (Table 2). The effects of TC on the risk of prostate cancer differed across different populations (Table 2). TC was not related to the risk of prostate cancer in the European population (RR, 1.01; 95% CI, 0.94–1.07; Table 2) and the American population (RR, 1.06; 95% CI, 0.88–1.29; Table 2), whereas TC significantly increased the risk of prostate cancer in the Asian population (RR, 1.25; 95% CI, 1.05–1.49; Table 2). For the heterogeneity of pooled results of TC, the subgroup analysis by study population showed that the heterogeneity was substantially reduced in different study populations (Table 2).

**HDL and LDL cholesterol**

**Highest versus lowest of HDL and LDL.** The pooled RRs of prostate cancer for the highest versus lowest of HDL and LDL levels were 0.93 (95% CI, 0.80–1.10; P = 0.40; Fig. 3) and 1.17 (95% CI, 0.88–1.55; P = 0.51; Fig. 3), respectively. There was statistically significant moderate heterogeneity among studies of HDL (I² = 61.00%, P for heterogeneity = 0.03) and LDL (I² = 63.88%, P for heterogeneity = 0.04). Neither HDL (RR, 1.21; 95% CI, 0.63–2.30; P = 0.57) and LDL (RR, 1.30; 95% CI, 0.35–4.80; P = 0.69) were related to the risk of high-grade prostate cancer. Because a relatively small number of studies reported the association between HDL, LDL, and the risk of prostate cancer, we did not perform subgroup analyses of HDL and LDL.

**Dose–response analysis.** For the dose–response analysis between HDL and prostate cancer risk, 6 studies that reported on ≥3 categories of HDL levels were included. The summary RR associated with a 1 mmol/L increase in HDL levels was 0.99 (95% CI, 0.91–1.07; P = 0.72; Supplementary Table S4) using a two-stage random-effects dose–response model with heterogeneity (P = 0.001).
We did not detect a potentially nonlinear dose–response relationship ($P = 0.06$; Fig. 4 and Supplementary Table S4). When examining LDL, 4 studies were included to assess the dose–response relationship between LDL and risk of prostate cancer. A 1 mmol/L increment in LDL level conferred an RR of 1.04 (95% CI, 0.98–1.10; $P = 0.24$; Supplementary Table S4) using the two-stage random-effects dose–response model with heterogeneity ($P = 0.03$). We found no evidence of a statistically significant departure from a nonlinear dose–response relationship ($P = 0.49$; Fig. 4 and Supplementary Table S4).

Sensitivity analyses and published bias

The sensitivity analyses by repeating the analysis with fixed-effect models showed that all of the pooled results were consistent (Supplementary Table S5) with the exception of the subgroup of TC by high-grade prostate cancer and the pooled results between HDL and the risk of prostate cancer. In addition, the sensitivity analyses showed that none of the individual studies substantially affected the pooled results for any of the outcomes (Supplementary Table S5). No evidence of publication bias was found by using funnel plots (Supplementary Fig. S2), the Begg’s rank correlation test, or the Egger’s regression test (Table 2).

Discussion

In this meta-analysis of 23,142 prostate cancer cases, we did not observe any association between risk of prostate cancer and blood levels of TC, HDL, or LDL. When restricting to those patients with a high-grade of prostate cancer, blood TC, HDL, and LDL levels were not associated with the risk of high-grade prostate cancer. All of the subgroup analyses also showed no association between blood TC levels and risk of prostate cancer, with exception of a subgroup of Asian participants from only 2 studies.

This meta-analysis showed that higher levels of TC, HDL, or LDL in the blood were not associated with the risk of prostate cancer or high-grade prostate cancer. However, some retrospective studies and preclinical studies have recently proposed that blood cholesterol might play an important role in the progression of prostate cancer. A range of different biologic mechanisms have been proposed, including effects on cell proliferation, inflammation, membrane organization, and steroidogenesis, and it has been proposed that high cholesterol increases the risk of prostate cancer. Some preclinical studies reported that cholesterol levels might affect prostate cell growth and/or survival. Using a xenograft model, Zhuang and colleagues (27) and Solomon and colleagues (28) found that hypercholesterolemia accelerated the growth of prostatic tumors, whereas hypocholesterolemia had the opposite effect and retarded tumor growth. Using the TRAMP mouse model, an autochthonous model of prostate cancer, hypercholesterolemia was shown to result in increased tumor volume and progression as well as increased tumor incidence and metastases to the lung (29). Some experimental studies also...
showed that cholesterol was an important element controlling signaling events in prostate cancer cells (27, 30, 31). Some case–control studies were conducted to assess the role of cholesterol in prostate cancer incidence and progression. A hospital-based case–control study involving 312 prostate cancer patients found a significant association between TC and prostate cancer risk (OR, 1.58; 95% CI, 1.11–2.24; ref. 32). In another case–control study that included 1,294 prostate cancer cases using self-reported history, Bravi and colleagues (33) reported that men with hypercholesterolemia had a higher risk of prostate cancer (OR, 1.51; 95% CI, 1.23–1.85). Nevertheless, case–control studies have some obvious limitations, such as recall bias, selection bias, or survivor bias. In contrast, prospective studies, which have a clear time sequence from causes to diseases, start from exposures and observe the occurrence of the outcome prospectively over time. Moreover, the results from the 14 included prospective studies with large sample sizes have notable clinical and public health implications to general population. Taken together, prospective studies provide stronger statistical power and demonstrability for causality than retrospective studies to detect a potential relationship between blood cholesterol levels and risk of prostate cancer. However, further study is still needed to explore why the results of retrospective studies and preclinical models differed from the null results of our meta-analysis based on prospective studies. Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), as a type of cholesterol-lowering drug, have contrasting effects (including reduced intratumoral steroidogenesis, reduced inflammation, reduced proliferation, and changes in lipid rafts) to cholesterol on prostate cancer progression. In addition, the association between use of statins and the risk of prostate cancer has been assessed in several epidemiologic studies. In a recent meta-analysis of 27 observational studies by Bansal and colleagues (34), statin use significantly reduced the risk of both total prostate cancer by 7% (RR, 0.93; 95% CI, 0.87–0.99) and clinically important advanced prostate cancer by 20% (RR, 0.80; 95% CI, 0.70–0.90). In fact, in the subgroup analysis of cohort studies (RR, 0.93; 95% CI, 0.87–1.01) and case–control studies (RR, 0.87; 95% CI, 0.72–1.05), there was no significant association between cholesterol and prostate cancer risk.
statin use and prostate cancer risk. Moreover, long-term statin use
did not significantly affect the risk of total prostate cancer (RR,
0.94; 95% CI, 0.84–1.05). Hence, those findings from Bansal and
colleagues meta-analysis (34) provided evidence that partly sup-
ported our results. In addition, a meta-analysis of 27 randomized
controlled trials published in the Lancet in 2012 reported that
there was no association between lowering LDL-C with statins
compared with lowering LDL-C with control therapy and total
cancer incidence risk (35).

In subgroup analyses of TC, we noted that high TC concentra-
tions only significantly increased the risk of prostate cancer in the
Asian population. Explaining the different effects of TC on the risk
of prostate cancer in different populations is difficult. However,
the incidence of prostate cancer in Asians was significantly lower
than the population in developed countries, and there are obvious
differences in the diets between Asians and populations in devel-
oped countries. Specifically, Western diets have more excess
cholesterol than Asian diets. Moreover, there are differences in
genetic susceptibility, culture, and lifestyles. Taken together, these
reasons may partly explain the inconsistent results. It cannot be
ruled out that the reason for the significant effect of TC on risk of
prostate cancer was caused by the limited numbers of included
studies (only 2 studies).

Regarding HDL, we could not draw a definite conclusion for
the nonsignificant association between HDL and prostate
cancer risk, based on the currently available evidence in this
meta-analysis. The sensitivity analysis showed an inverse asso-
ciation using a fixed-effect model (RR, 0.90; 95% CI, 0.83–0.98;
Supplementary Table S5). Meanwhile, there was an inverse
association (RR, 0.95; 95% CI, 0.91–0.99; Supplementary
Table S4) between HDL levels and prostate cancer risk using
linear fixed-effect dose–response analysis and the result (P =
0.06; Supplementary Table S4) of nonlinear dose–response
analysis was close to the artificial threshold for statistical
significance. More relevant studies are warranted to assess the
potential effect of HDL on prostate cancer risk.

Strengths and limitations
This meta-analysis had several strengths. First, this meta-anal-
ysis is designed to quantitatively summarize the results from only
quantitative prospective studies, which could partly eliminate
selection bias and recall bias. Second, we included a large sample
size of participants (23,142 prostate cancer cases from a total of
737,217 participants) involving different general populations
throughout the world. However, this study also has several
limitations. First, although the included studies adjusted or con-
trolled for various risk factors (e.g., age, BMI, and physical activity),
the unmeasured residual confounders cannot be excluded.
Second, blood cholesterol levels were only assessed at baseline in
the 14 included studies, which could lead to the loss of informa-
tion about the change in blood cholesterol levels on the devel-
opment and progression of prostate cancer. In addition, because
of the limited number of included studies that focused on HDL
and LDL, we could not use subgroup analyses to evaluate the effect
of HDL and LDL on risk of prostate cancer in different subgroups.
In addition, we summarized the effect estimates and 95% CIs for
the highest versus lowest levels of cholesterol in this meta-anal-
ysis, in which different groups were pooled together. Finally,
cautions is required that the nonsignificant association for high-
grade prostate cancer may be due to the limited studies and future
well-designed studies are required to clarify this issue.

Conclusion
In conclusion, findings from this meta-analysis of 14 prospec-
tive studies suggest that higher levels of TC, HDL, or LDL were not
associated with the risk of prostate cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Disclaimer
The funding source had no involvement in study design, data collection,
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The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

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Development of methodology: L. YuPeng, L. DaPeng, D. Chen
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. YuPeng, L. PengFei, C. Cheng, Z. YaShuang, D. Chen
Writing, review, and/or revision of the manuscript: L. YuPeng, L. DaPeng, D. Chen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Chen
Study supervision: Z. YaShuang, D. Chen

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