Clinical Significance of Kinetics of Low-Density Lipoprotein Cholesterol and Its Prognostic Value in Limited Stage Small Cell Lung Cancer Patients

Tingting Liu, PhD¹, Ting Zhou, PhD¹, Fan Luo, PhD¹, Yunpeng Yang, PhD¹, Shen Zhao, PhD¹, Yan Huang, PhD¹, Hongyun Zhao, PhD², Li Zhang, PhD¹, and Yuanyuan Zhao, PhD¹

Abstract

Objectives: To investigate the clinical significance of dynamic alteration of serum lipids in limited stage small cell lung cancer (LS-SCLC) patients and the risk that different lipid profiles poses to patients' health.

Methods: We retrospectively analyzed the variation trends and prognostic values of serum lipids in 310 LS-SCLC patients who had received standard chemotherapy between 2002 and 2017. In addition to serum lipid level, which were measured at the time of pretreatment, after-chemotherapy and during disease progression and later analyzed, the dynamic lipid alteration trend and its correlation to progression-free survival (PFS) and overall survival (OS) were also statistically analyzed using Log-rank test and COX regression analyses.

Results: A significant decrease in HDL-C level was observed after standard chemotherapy (Post-CT baseline = $-0.08 \pm 0.34$, $P < 0.001$), and this trend of reduction was further enhanced by thoracic radiotherapy ($P = 0.046$). Increase in LDL-C level was also observed to be associated with higher likelihood of disease progression ($P = 0.003$). Moreover, the extent of the increase in LDL-C was also associated with the number of progression sites, as patients with higher increase in LDL-C in exhibiting a progression at more than 2 sites outside thorax ($P = 0.037$). The patients' median PFS and OS were 14.04 months (95%CI: 25.12-33.81) and 22.40 months (95%CI: 33.19-42.13), respectively. For both PFS and OS, LDL-C elevation remained an independent prognostic factor in the multivariate model ($P = 0.007$ and $P = 0.022$, respectively).

Conclusion: Overall, for LS-SCLC patients, standard chemotherapy decreases the level of HDL-C, the level of increase in LDL-C could predict disease progression and even the number of progression sites, and LDL-C elevation could be an independent prognostic factor for poor OS and PFS.

Keywords

small cell lung cancer, limited stage, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, chemotherapy, progression, prognosis

Received June 7, 2020. Received revised January 6, 2021. Accepted for publication April 22, 2021.

1 Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, People’s Republic of China

2 Department of Clinical Laboratory, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, People’s Republic of China

Corresponding Author:
Li Zhang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, People’s Republic of China.
Email: zhangli@sysucc.org.cn
**Introduction**

Small cell lung cancer (SCLC) accounts for 15%-17% of total lung cancer cases and has characters of rapid growth and early widespread metastasis. Among all SCLC cases, approximately 30% are limited-stage SCLC (LS-SCLC). Due to the slow progress in treatment of LS-SCLC over the past few decades, concurrent chemoradiotherapy with etoposide plus platinum (cisplatin or carboplatin) remains the standard-of-care therapy for LS-SCLC patients. Despite the high initial response rate of 60%-70% for patients treated with etoposide-platinum regimen, a high proportion of patients still experience disease progression or relapse, with a low median survival of up to 30 months and a 5-year survival rate of 30%.

Cholesterol plays a novel role in every aspect of tumor development and progression. Emerging evidences have demonstrated that anti-tumor treatment using drugs such as paclitaxel, cisplatin and doxorubicin may affect the serum lipid level by lowering cholesterol synthesis, inhibiting extracellular cholesterol into cells, or enhancing lipids degradation. Recently, chemotherapy-related alterations in the serum level of high-density lipoprotein cholesterol (HDL-C) have been observed in several cancers, such as reduction observed in breast cancer and elevation in colorectal cancer. However, this observation has not been reported in patients with LS-SCLC and its prognostic value is still unknown. Owing to the high rate of relapse in patients with SCLC, it is therefore crucial to explore all the tools for patient selection and various treatment options. Recently, lipid rafts have also been observed to contribute toward cancer cell adhesion and migration. Although we have previously evaluated the value of baseline level of low-density lipoprotein cholesterol (LDL-C) as a prognostic factor in heterogeneous SCLC patients at both extensive and limited stages, the dynamic alterations of these serum lipids in patients with LS-SCLC and their relationship with disease progression have not yet been analyzed.

In this study, we evaluated the dynamic alteration of serum lipid levels in a large cohort of patients with LS-SCLC both at the time of finishing chemotherapy and the oval disease progression, comprehensively investigated its clinical significance in LS-SCLS patients, and analyzed its association with disease progression.

**Material and Methods**

**Patients**

LD-SCLC patients who received chemotherapy at Sun Yat-sen University Cancer Center between June 2002 and February 2017 were enrolled in this retrospective, observational study if they met the following eligible criteria: 1) at age ≥ 18 years old; 2) histologically diagnosed with LD-SCLC according to the 7th edition of American Joint Committee on Cancer staging manual and the Veteran Affairs Lung Study Group (VALG) staging system; 3) received initial chemotherapy; 4) had serum HDL-C, LDL-C, apolipoprotein A (ApoA), apolipoprotein B (ApoB) collected at baseline, within 2 weeks after chemotherapy (Post-CT) and within 2 weeks after disease progression. All clinical data were extracted from the electronic medical records. The study was approved by Sun Yat-sen University Cancer Center Institutional Review Board.

**Information Extraction**

The following clinical and pathological data were obtained: age, gender, smoking history, Eastern Cooperative Oncology Group performance status (ECOG-PS), and treatment information (operation, radiotherapy and chemotherapy). Current or ever smoker is defined as having smoked more than 100 cigarettes. The serum HDL-C, LDL-C, ApoA and ApoB levels were collected at different time points as baseline, within 2 weeks after chemotherapy (Post-CT) and within 2 weeks after disease progression (PD).

**Follow Up**

All enrolled patients were followed up either via review of medical records or by telephone. The last date of follow up was January 14, 2020. Tumor assessment was regularly conducted by CT scans after every 2 cycles of chemotherapy or every 2 months after the completion of therapy. Treatment efficacy was evaluated based on Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

**Statistical Analysis**

Paired samples T test was used to evaluate the differences between serum baseline lipid and lipid after chemotherapy or at the time of disease progression. Independent samples T test was used to evaluate the effects of different chemotherapy regimens and radiotherapy on blood lipid. Bivariate correlations analysis was used to evaluate correlation of serum lipid levels with clinicopathological features. The optimal cut-off value of HDL-C fluctuation was determined using Medcalc. Progression-free survival (PFS) was defined as the date from initiation of treatment to PD or death from any reasons. Overall survival (OS) was calculated from the initiation of treatment to death from any causes. Patients who had not progressed or did not die were censored at the time of the last follow up. PFS and OS were assessed by using Kaplan-Meier methodology and unstratified log-rank test. Variables with significant significance (P < 0.05) in the univariate analysis were assessed by multivariate Cox proportional hazards model. Hazard ratio (HR) was presented as relative risks with 95% confidence interval (CI). All significance tests were 2 sided with a P value < 0.05 was regarded as statistically significant. All above data analyses were performed with SPSS 25.0 software (IBM, Armonk, NY).

**Results**

**Patient Characteristics**

Data of 310 patients diagnosed with LS-SCLC in our cancer center between June 11, 2002 and May 18, 2017 were
retrospectively collected and listed in Figure 1. These patients were aged at 33 to 86 years old with median of 59 years. Among the 310 patients, 272 (87.74%) were male, 255 (82.26%) were current or ever smokers, 295 (95.13%) had an ECOG-PS of 0 to 1, 292 (94.19%) received etoposide platinum regimen, 221 (71.29%) completed at least 4 cycles of chemotherapy, 45 (14.52%) received radical operation, and 252 (81.29%) accepted radiotherapy. Among the latter 252 patients, 239 (77.10%) accepted thoracic radiotherapy and 105 (33.87%) accepted prophylactic cranial irradiation. The minimum and median follow-up time of all patients was 2.96 months and 36.71 months, respectively. At the time of data collection, 73 (23.55%) patients were alive, 203 (65.48%) died, and 34 (10.97%) were lost to follow up.

**Baseline Serum Lipid Levels and Their Correlation With Clinicopathological Characteristics**

Table 1 shows the baseline characteristics and univariate analysis of their relationships to PFS and OS of patients with LS-SCLC. The HDL-C, LDL-C, ApoA and ApoB levels were in the range of 0.51-2.55 mmol/L with a mean ± standard deviation (SD) of 1.25 ± 0.33, 1.33-6.56 mmol/L with a mean ± SD of 3.13 ± 0.93, 0.20-2.08 g/L with a mean ± SD of 1.30 ± 0.26, and 0.41-1.83 g/L with a mean ± SD of 0.98 ± 0.26, respectively.

The statistical analysis of the correlation of serum lipid levels with clinicopathological characteristics presented that 1) the baseline HDL-C level was significantly correlated with gender (R = 0.17, P = 0.002) and smoking status (Figure 1).

### Table 1. Baseline Characteristics and Univariate Analysis of Their Relationships to PFS and OS of Patients With LS-SCLC.

| Characteristic                  | N (%) | Univariate analysis (progress-free survival) | Univariate analysis (overall survival) |
|--------------------------------|-------|---------------------------------------------|---------------------------------------|
|                                |       | HR  | 95%CI | P value  | HR  | 95%CI | P value  |
| **Baseline serum lipid**       |       |     |       |          |     |       |          |
| (Mean ± SD)                    |       |     |       |          |     |       |          |
| HDL-C level (mmol/L)           | 1.25 ± 0.33 | 0.94 | 0.57-1.57 | 0.825 | 1.11 | 0.71-1.73 | 0.652 |
| LDL-C level (mmol/L)           | 3.13 ± 0.93 | 0.99 | 0.84-1.17 | 0.897 | 0.94 | 0.81-1.09 | 0.415 |
| ApoA level (g/L)               | 1.30 ± 0.26 | 0.77 | 0.43-1.39 | 0.388 | 1.20 | 0.72-2.00 | 0.480 |
| ApoB level (g/L)               | 0.98 ± 0.26 | 0.92 | 0.50-1.69 | 0.787 | 1.03 | 0.60-1.77 | 0.917 |
| **Age**                        |       |     |       |          |     |       |          |
| ≤59                            | 159 (51.29) | 1   | 0.74-1.39 | 0.943 | 1   | 0.74-1.39 | 0.917 |
| >59                            | 151 (48.71) | 1.01 | 0.92-1.45 | 0.709 | 0.76 | 0.58-1.01 | 0.482 |
| **Gender**                     |       |     |       |          |     |       |          |
| Female                         | 38 (12.26) | 1   | 0.92-1.45 | 1.21 | 1.13 | 0.57-1.22 | <0.001 |
| Male                           | 272 (87.74) | 1.01 | 0.74-1.45 | 0.961 | 1.03 | 0.81-1.39 | 0.038 |
| **Smokers**                    |       |     |       |          |     |       |          |
| Yes                            | 255 (82.62) | 1   | 0.67-1.53 | 0.91 | 0.84 | 0.67-1.66 | <0.001 |
| No                             | 55 (17.4)  | 1.01 | 1.00-1.45 | 0.91 | 1.21 | 0.79-1.86 | 0.038 |
| **PS**                         |       |     |       |          |     |       |          |
| 0                              | 200 (64.52) | 1   | 0.58-1.45 | 0.24 | 0.25 | 0.13-0.47 | <0.001 |
| 1                              | 95 (30.61)  | 0.35 | 0.18-0.70 | 0.73 | 0.25 | 0.10-0.65 | 0.013 |
| 2                              | 15 (4.87)   | 0.33 | 0.16-0.68 | 0.39 | 0.25 | 0.10-0.64 | <0.001 |
| **Progression site**           |       |     |       |          |     |       |          |
| Intrathoracic                  | 58 (39.19) | 1   | 0.283 | 0.14 | 0.25 | 0.10-0.65 | 0.001 |
| Only one site outside thorax   | 85 (54.73) | 0.73 | 0.29-1.83 | 0.25 | 0.25 | 0.10-0.64 | 0.001 |
| ≥2 sites outside thorax        | 5 (3.38)   | 0.95 | 0.39-2.36 | 0.014 | 1    | 0.78-1.52 | 0.026 |
| **Radical operation**          |       |     |       |          |     |       |          |
| Yes                            | 45 (14.52) | 1   | 0.14 | 0.098 | 1   | 0.84 | 0.65-1.42 | 0.026 |
| No                             | 265 (85.48) | 1.96 | 1.15-3.34 | 0.25 | 0.25 | 0.10-0.64 | 0.001 |
| **Thoracic radiotherapy**      |       |     |       |          |     |       |          |
| Yes                            | 239 (77.1) | 1   | 0.84 | 1.09 | 1.09 | 0.78-1.52 | 0.608 |
| No                             | 71 (22.9)  | 0.85 | 0.65-1.42 | 0.09 | 0.25 | 0.10-0.64 | 0.001 |
| **Chemotherapy cycles**        |       |     |       |          |     |       |          |
| <4                             | 89 (28.71) | 1   | 0.95 | 0.84 | 1.40 | 1.04-1.88 | 0.026 |
| ≥4                             | 221 (71.3) | 1.33 | 0.95-1.88 | 0.91 | 1.40 | 1.04-1.88 | 0.026 |

Abbreviations: HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; ApoA, Apolipoprotein A; ApoB, Apolipoprotein B; PFS, Progress-free survival; OS, overall survival; PS, performance status.

*Data shown are the mean ± standard deviation (SD). Values in boldface indicate P values <0.05.
(R = –0.16, P = 0.004), 2) the baseline ApoA level was positively correlated with gender (R = 0.17, P = 0.002) and negatively correlated with smoking status (R = –0.14, P = 0.017), and 3) there was no link between the HDL-C level as well as the ApoA level and other parameters. In addition, the LDL-C and ApoB levels were not correlated with clinicopathological features (Table 2).

**Impacts of Serum Lipid Fluctuations After Chemotherapy**

To explore the association between serum lipid fluctuations and chemotherapy, the analysis of differences in lipids alteration before and after chemotherapy was performed. Of the 310 patients, 238 (76.77%) underwent chemotherapy and had available lipid information. Table 3 shows the variation trends of lipids and the univariate analysis of their relationship with PFS and OS. The mean levels of HDL-C, LDL-C, ApoA and ApoB after chemotherapy were 1.17 mmol/L, 3.14 mmol/L, 1.27 g/L and 1.02 g/L, respectively. Compared with the baseline levels, the level of HDL-C after chemotherapy was significantly decreased and related to chemotherapy regimens (Post-CT-baseline = –0.08 ± 0.34, P < 0.001), while the levels of LDL-C, ApoA and ApoB were not statistically different after chemotherapy (P = 0.913 for LDL-C; P = 0.185 for ApoA, and P = 0.053 for ApoB).

**Table 2.** Correlation Analysis of Lipids Levels With Clinicopathological Features.a

| Variables          | HDL-C | LDL-C | ApoA | ApoB | HDL-C | LDL-C | ApoA | ApoB |
|--------------------|-------|-------|------|------|-------|-------|------|------|
| Baseline lipid level | R     | P value | R     | P value | R     | P value | R     | P value |
| Age ≤ 59 vs. >59   | 0.09  | 0.107 | 0.01 | 0.886 | 0.05 | 0.425 | –0.01 | 0.882 |
| Gender Male vs. Female | 0.17  | **0.002** | 0.06 | 0.264 | 0.17 | **0.002** | 0.05 | 0.423 |
| Smokers Yes vs. No | –0.16 | **0.004** | –0.04 | 0.494 | –0.14 | **0.017** | –0.02 | 0.784 |
| PS 0 vs. 1 vs. 2   | –0.06 | 0.325 | 0.05 | 0.376 | –0.04 | 0.470 | 0.10 | 0.070 |
| Operation Yes vs. No | –0.03 | 0.579 | 0.01 | 0.825 | 0.02 | 0.707 | 0.05 | 0.339 |
| Radiotherapy Yes vs. No | –0.02 | 0.700 | 0.04 | 0.475 | –0.06 | 0.328 | 0.01 | 0.805 |
| Chemotherapy cycles <4 vs. ≥4 | –0.02 | 0.725 | 0.01 | 0.894 | 0.02 | 0.764 | 0.01 | 0.889 |
| Progression site Intrathoracic vs. Only one site outside thorax vs. ≥2 sites outside thorax | 0.18 | **0.037** |

**Table 3.** Changes of Lipid Levels and Univariate Analysis of Their Relationship With PFS and OS.a

| Lipids               | Post-CT | Difference (Lipid<sub>Post-CT</sub> – Lipid<sub>Baseline</sub>) | P value | PFS | OS |
|----------------------|---------|------------------------------------------------------------------|---------|-----|----|
| HDL-C (mmol/L)       | 1.17 ± 0.34 | –0.08 ± 0.34                                                      | **< 0.001** | 1.54 | 1.42 |
| LDL-C (mmol/L)       | 3.14 ± 1.03 | 0.01 ± 1.01                                                      | 0.913 | 0.94 | 1.31 |
| ApoA (g/L)           | 1.27 ± 0.28 | –0.03 ± 0.32                                                      | 0.185 | 1.17 | 1.27 |
| ApoB (g/L)           | 1.02 ± 0.34 | 0.04 ± 0.35                                                      | 0.053 | 1.12 | 1.58 |

**Table 3.** Changes of Lipid Levels and Univariate Analysis of Their Relationship With PFS and OS.a

| Lipids               | PD | Difference (Lipid<sub>PD</sub> – Lipid<sub>Baseline</sub>) | P value | PFS | OS |
|----------------------|----|------------------------------------------------------------------|---------|-----|----|
| HDL-C (mmol/L)       | 1.21 ± 0.35 | –0.04 ± 0.30                                                      | 0.141 | 0.93 | 1.13 |
| LDL-C (mmol/L)       | 3.34 ± 0.88 | 0.22 ± 0.80                                                      | **0.002** | 0.57 | 0.60 |
| ApoA (g/L)           | 1.31 ± 0.26 | 0.03 ± 0.32                                                      | 0.336 | 0.98 | 1.28 |
| ApoB (g/L)           | 1.05 ± 0.26 | 0.09 ± 0.24                                                      | **< 0.001** | 0.85 | 0.92 |

Abbreviations: CT, chemotherapy; PD, disease progression.

*aValues in boldface indicate P values <0.05.*

*aValues in boldface indicate P values <0.05.*

(©2019 American Society for Clinical Oncology)
To investigate the correlation of chemotherapy-related HDL-C reduction with chemotherapy regimens and thoracic radiotherapy, patients were further categorized according to the chemotherapy regimens they received into etoposide-based group (n = 292, 94.19%) and non-etoposide-based group (n = 18, 5.81%). There was no significant difference in HDL-C reduction between the 2 treatment groups (P = 0.428, Supplementary Table 1). Moreover, the cycles of chemotherapy patients received also presented no disparity in chemotherapy-related HDL-C reduction (P = 0.707, Table 2). Among these patients, 239 (77.10%) had thoracic radiotherapy concurrent with chemotherapy. The relationship between the chemotherapy-related HDL-reduction and thoracic radiotherapy was strong, with more frequently reduced HDL in patients treated with thoracic radiotherapy (P = 0.046, Supplementary Table 1).

Based on the alteration trend of HDL-C level, patients were further divided into 2 groups: Group 1 consisted of 150 (63.03%) patients with chemotherapy-related HDL-C reduction and Group 2 consisted of 88 (36.97%) patients with chemotherapy-related HDL-C elevation. The median and mean PFS of the 310 patients were 14.04 months and 29.46 months, respectively (95% CI: 25.12-33.81). In addition, patients in Group 1 achieved significantly lower median PFS of 13.83 months than patients in Group 2, who had a median PFS of 22.18 (P = 0.041, Figure 2A).

By the last time of follow-up, the median and mean OS of all patients was 22.40 months and 37.66 months, respectively (95% CI: 33.19-42.13). Among them, the median OS for patients with HDL-C reduction and HDL-C elevation was 22.88 months (95% CI: 15.07-30.67) and 42.38 months (95% CI: 15.70-69.07), respectively, showing significant difference between the 2 groups (P = 0.045, Figure 3A).

Impact of Serum Lipid Fluctuations After Disease Progression

During the treatment, 152 (49.03%) patients suffered from disease progression. The mean value of HDL-C, LDL-C, ApoA and ApoB after disease progression was 1.21 mmol/L, 3.34 mmol/L, 1.31 g/L and 1.05 g/L, respectively. In addition, compared to those at the baseline, the levels of LDL-C and ApoB were significantly elevated at disease progression by 0.22 ± 0.80 (P = 0.002) and 0.09 ± 0.24 (P < 0.001), respectively, but the levels of HDL-C and ApoA were not significantly different (P = 0.141 and P = 0.336, respectively). Table 3 shows the detailed information, indicating that the disease progression is significantly related to LDL-C alteration. To further investigate the power of LDL-C to predict the precise site of disease progression, the disease progression was divided into 1) intrathoracic progression, 2) progression at only one site outside thorax and 3) progression at ≥2 sites outside thorax. Patients with disease progression at ≥2 sites outside thorax had significantly higher LDL-C increment at the time of disease progression (P = 0.037). Moreover, patients with disease progression were further stratified into 2 subgroups according to the alteration of their LDL-C level: LDL-C elevation group (n = 92, 67.15%) and no LDL elevation group (n = 45, 32.85%). Further investigation indicated that compared with patients in the no LDL elevation group, patients in the LDL-C elevation group had significantly worsened PFS [median of 8.08 months (95% CI, 6.88-9.29) vs. median of 10.19 months (95% CI, 8.69-13.68), HR = 0.57, (95% CI, 0.39-0.83), P = 0.003; Figure 2B] and OS [median of 20.73 months (95% CI: 17.38-24.08) vs. 30.88 months (95% CI: 24.72-37.05), P = 0.021, Figure 3B] at the time of disease progression.

Prognostic Factors for PFS and OS

Furthermore, we comprehensively explored the prognostic power of main pathological and clinical factors for PFS and OS.

For PFS, we performed univariate analysis and identified the prognostic value of ECOG-PS (P = 0.009), radical operation (P = 0.014), chemotherapy-related HDL-C reduction (P = 0.043), and progression-related LDL-C elevation (P =

Figure 2. Kaplan-Meier curves for PFS. (A) PFS of patients with or without chemotherapy-related HDL-C decrease; (B) PFS of patients with or without LDL-C increase at the time of disease progression.
Further multivariate analysis indicated that ECOG-PS ($P = 0.001$), radical operation ($P = 0.010$), and progression-related LDL-C elevation ($P = 0.007$) remained independent predictive factors for longer PFS.

Similarly, we also performed univariate analysis for OS and identified the prognostic value of ECOG-PS ($P < 0.001$), cycles of chemotherapy ($P = 0.005$), radical operation ($P = 0.001$), progression site ($P = 0.013$), chemotherapy-related HDL-C reduction ($P = 0.046$), chemotherapy-related ApoB elevation ($P = 0.006$) and progression-related LDL-C elevation ($P = 0.022$). Further multivariate analysis showed that a PS of 0-1 ($P = 0.002$), cycles of chemotherapy ($P = 0.005$), progression site ($P = 0.015$), chemotherapy-related ApoB reduction ($P = 0.028$) and progression-related LDL-C reduction ($P = 0.022$) remained as independent predictive factors for better OS (Table 4).

**Discussion**

In this study, we assessed the dynamic changes of serum lipids at different time points in a large cohort of patients with LS-SCLC. Our results demonstrated that standard chemotherapy would induce a significant decrease in HDL-C level, and the descending range was greater in patients received thoracic radiotherapy. Furthermore, significant increases in LDL-C and ApoB levels at the time of disease progression were also observed. Besides, we further revealed that change in progression-related LDL-C level was statistically different among patients with specific progression site after chemotherapy, and higher LDL-C increase was seen in those with progression at more than 2 sites outside thorax. More importantly, our study demonstrated that progression-related LDL-C increase is a key prognostic factor for both PFS and OS in LS-SCLC patients. To our best knowledge, this is the first study with the largest dataset to evaluate the dynamic changes of serum lipids, demonstrating the prognostic significance of these alterations specific to LS-SCLC patients.

The accumulation of cholesterol is a general feature of cancer tissues. Recent evidences suggest that cholesterol plays an important role in tumorigenesis and tumor progression.\(^\text{16-18}\) However, chemotherapy-related lipid alterations remain controversial. Xin et al and Basani et al showed that under the influence of chemotherapy, the level of HDL-C was reduced while the levels of total cholesterol, triglycerides, LDL-C and ApoB were increased.\(^\text{19,20}\) On the contrary, Wang et al reported that plasma HDL-C level was increased in colorectal cancer patients who completed fluoropyrimidine-based adjuvant chemotherapy.\(^\text{11}\) In this study, we found that HDL-C reduction in LS-SCLC patients was significantly associated with the acceptance of standard chemotherapy (Post-CT-baseline $= C_0 0.08 + 0.34$, $P < 0.001$). The chemotherapy-induced HDL-C reduction may be as following: 1) endothelial cell injury mediated by chemotherapy might lead to lipid metabolism disorders;\(^\text{8,21}\) 2) inhibition of ATP binding cassette transporter A1 (ABCA1), which is crucial for HDL-C production from the liver, down-regulates the peroxisomal proliferator activated receptor $\gamma$ (PPAR$\gamma$) and liver X receptor $\alpha$ (LXR$\alpha$) transcription factors;\(^\text{7}\) and 3) cholesterol ester transfer protein (CETP) activity could contribute to HDL-C decline in patients with cancer.\(^\text{20}\)

Furthermore, we investigated the impact of chemotherapy regimens on chemotherapy-induced HDL-C reduction, but found there was no significant difference in chemotherapy-induced HDL-C alteration among various chemotherapy regimens. Interestingly, we observed that the trend of HDL-C reduction could be enhanced by concurrent thoracic radiotherapy ($\text{Mean} \pm \text{SD}: -0.11 \pm 0.32$ vs. $0.00 \pm 0.39$, $P = 0.046$), in consistence with a previous study showing that irradiation-induced dyslipidemia may ascribe to radiotherapy-induced abnormal metabolism of liver lipids and release of different inflammatory mediators.\(^\text{22}\) Recent studies have suggested that statins may be potential anticancer agents\(^\text{23}\) by lowering protein
prenylation\textsuperscript{24} and inhibiting tumor cell proliferation.\textsuperscript{25,26} However, our study indicated that chemotherapy could interfere cholesterol metabolism in LS-SCLC patients, and subsequently influence the anticancer power of stains to some extent. Therefore, it should be cautious to use statins as anticancer agents alone and together with other regimens such as chemotherapy for treatment of patients with LS-SCLC. As suggested by Emilsson et al, a strict selection criteria should be established to identify optimal patients who may benefit from statins treatment.\textsuperscript{27}

As the major cholesterol type in plasma, LDL is well known for its modulatory effects on proliferation, migration and differentiation of cancer cells.\textsuperscript{24,28,29} But little is known about the potential power of LDL-C in predicting disease progression. Significant increases in LDL-C and ApoB levels were found in LS-SCLC patients at disease progression (LDL-C, PD-baseline = 0.22 $\pm$ 0.80, $P = 0.002$; ApoB, PD-baseline = 0.09 $\pm$ 0.24, $P < 0.001$, respectively). Moreover, our study indicated the increase in LDL-C was significantly different among patients with different extent of disease progression, especially at various sites. Patients with progression at sites outside thorax are more likely to have LDL-C increment ($P = 0.037$). To our best knowledge, this study is the first analysis focusing on the relationship between LDL-C elevation and disease progression, or even disparate progression sites. These results imply that alteration of LDL-C level could be an important tool to identify patients with high-risk for disease progression in LS-SCLC. What's more, patients with frequent increase in LDL-C may be candidates for more frequent follow-up and more aggressive approaches to delay the disease progression.

To optimize personalized therapy for patients with LS-SCLC, an optimal prognostic factor was warranted. Worthy of note, in this study, we also showed the powerful prognostic value of LDL-C alteration at the time of disease progression. Both progression-free survival and overall survival were better in patients with less increase in LDL-C (median PFS, 8.08 vs.

### Table 4. COX Multivariate Regression Analysis.\textsuperscript{a}

| Variables               | PFS                                | OS                                |
|-------------------------|------------------------------------|-----------------------------------|
|                         | HR (95%CI)                         | P value                           | HR (95%CI)                         | P value                           |
| PS                      |                                    |                                   |                                   |                                   |
| 0                       | 1 (Referent)                       | 0.001                             | 1 (Referent)                       | 0.110                             |
| 1                       | 0.27 (0.12-0.60)                   | 0.35 (0.13-0.95)                  | 0.35 (0.12-0.99)                   |                                   |
| 2                       | 0.18 (0.08-0.43)                   |                                   |                                   |                                   |
| Radical operation       |                                    |                                   |                                   |                                   |
| Yes                     | 1 (Referent)                       | 0.10                              | 1 (Referent)                       | 0.746                             |
| No                      | 2.80 (1.27-6.15)                   | 1.19 (0.42-3.41)                  |                                   |                                   |
| Chemotherapy cycles     |                                    |                                   |                                   |                                   |
| $<4$                    |                                    |                                   |                                   |                                   |
| $\geq 4$                |                                    |                                   |                                   |                                   |
| Progression site        |                                    |                                   |                                   |                                   |
| Intrathoracic           |                                    |                                   |                                   |                                   |
| One site outside thorax |                                    |                                   |                                   |                                   |
| $\geq 2$ sites outside thorax |                    |                                   |                                   |                                   |
| HDL-C reduction         |                                    |                                   |                                   |                                   |
| Yes                     | 1 (Referent)                       | 0.20                              | 1 (Referent)                       | 0.955                             |
| No                      | 1.33 (0.86-2.04)                   | 1.02 (0.57-1.82)                  |                                   |                                   |
| ApoB elevation          |                                    |                                   |                                   |                                   |
| Yes                     |                                    |                                   |                                   |                                   |
| No                      |                                    |                                   |                                   |                                   |

\textsuperscript{a}Values in boldface indicate $P$ values <0.05.

\[\text{Liu et al.}\]
Conclusion

In summary, our study explored the clinical value of serum lipid alterations in patients with LS-SCLC. Significant increase in LDL-C was found in patients with high-risk of disease progression, and could even be used to predict the progression sites. To better differentiate patients with good from poor survival outcome, LDL-C alteration trend should be considered based on its prognostic power in both PFS and OS. These findings provide important information for clinical practice based on kinetics of LDL-C.

Abbreviations

Limited stage small cell lung cancer (LS-SCLC); progression-free survival (PFS); overall survival (OS); Small cell lung cancer (SCLC); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); Veteran Affairs Lung Study Group (VALG); apolipoprotein A (ApoA); apolipoprotein B (ApoB); Eastern Cooperative Oncology Group performance status (ECOG-PS); Response Evaluation Criteria in Solid Tumor (RECIST); complete response (CR); partial response (PR); stable disease (SD); progression disease (PD); Progression-free survival (PFS); Time to progression (TTP); Hazard ratio (HR); confidence interval (CI); standard deviation (SD).

Authors’ Note

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. Our study was approved by Sun Yat-sen University Cancer Center Institutional Review Board (ID: B2019-140-01). All patients provided written informed consent before enrollment in this study. Conception and design: Tingting Liu, Ting Zhou, Fan Luo; Development of methodology: Yumpeng Yang, Li Zhang; Acquisition of data: Li Zhang, Ting Zhou; Analysis and interpretation of data: Tingting Liu, Ting Zhou, Fan Luo; Writing, review, and/or revision of the manuscript: Ting Zhou, Tingting Liu; Study supervision: Shen Zhao, Yan Huang, Hongyun Zhao.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by National Key R&D Program of China (2016YFC0905500 and 2016YFC0905503), Science and Technology Program of Guangdong (2017B020227001), Science and Technology Program of Guangzhou (201607020031), Chinese National Natural Science Foundation Project (81772476), the Natural Science Foundation of Guangdong Province of China (2018A030313838), and The 5010 Clinical Research Foundation of Sun Yat-sen University (2016001). All these agencies have no roles in study design, data collection and analysis, and manuscript preparation.

ORCID iD

Li Zhang, PhD https://orcid.org/0000-0001-9417-4201

Supplemental Material

Supplemental material for this article is available online.

References

1. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017;17(12):765.
2. Yang S, Zhang Z, Wang Q, et al. Emerging therapies for small cell lung cancer. J Hematol Oncol. 2019;12(1):47.
3. Oronsky B, Reid TR, Oronsky A, Carter CA. What’s new in SCLC? A review. Neoplasia. 2017;19(10):842-847.
4. Faiivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18(8):1116-1125.
5. Wang B, Rong X, Palladino E, et al. Phospholipid remodeling and cholesterol availability regulate intestinal stemness and tumorigenesis. Cell Stem Cell. 2018;22(2):206-220.e4
6. Sharma B, Agnihotri N. Role of cholesterol homeostasis and its efflux pathways in cancer progression. J Steroid Biochem Mol Biol. 2019;191:105377.
7. Sharma M, Tuaine J, McLaren B, et al. Chemotherapy agents alter plasma lipids in breast cancer patients and show differential effects on lipid metabolism genes in liver cells. PLoS One. 2016;11(1):e0148049.
8. Willemsen PM, van der Meer RW, Burggraaf J, et al. Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy. Acta Oncol. 2014;53(3):351-360.
9. Panis C, Binato R, Correa S, et al. Short infusion of paclitaxel imbalances plasmatic lipid metabolism and correlates with cardiac markers of acute damage in patients with breast cancer. Cancer Chemother Pharmacol. 2017;80(3):469-478.
10. Lu Q, Wu X, Zhu Y, et al. Effects of chemotherapy on serum lipids in Chinese postoperative breast cancer patients. Cancer Manag Res. 2020;12:8397-8408.
11. Wang Y, Wang ZQ, Wang FH, et al. Predictive value of chemotherapy-related high-density lipoprotein cholesterol (HDL) elevation in patients with colorectal cancer receiving adjuvant chemotherapy: an exploratory analysis of 851 cases. Oncotarget. 2016;7(35):57290-57300.
12. Bovenga F, Sabbà C, Moschetta A. Uncoupling nuclear receptor LXR and cholesterol metabolism in cancer. *Cell Metab*. 2015; 21(4):517-526.
13. Zhou T, Zhan J, Fang W, et al. Serum low-density lipoprotein and low-density lipoprotein expression level at diagnosis are favorable prognostic factors in patients with small-cell lung cancer (SCLC). *BMC Cancer*. 2017;17(1):269.
14. Schwartz LH, Seymour L, Litière S, et al. RECIST 1.1—Standardisation and disease-specific adaptations: perspectives from the RECIST working group. *Eur J Cancer*. 2016;62:138-145.
15. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1—Update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132-137.
16. Goossens P, Rodriguez-Vita J, Etzerodt A, et al. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. *Cell Metab*. 2019;29(6):1376-1389.
17. Voisin M, de Medina P, Mallinger A, et al. Identification of a tumor-promoter cholesterol metabolite in human breast cancers acting through the glucocorticoid receptor. *Proc Natl Acad Sci U S A*. 2017;114(44):E9346-E9355.
18. Baek AE, Yu YA, He S, et al. The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. *Nat Commun*. 2017;8(1):864.
19. Li X, Liu ZL, Wu YT, et al. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. *Lipids Health Dis*. 2018;17(1):91.
20. Basani S, Garg A. Marked lowering of high-density lipoprotein cholesterol levels due to high dose bexarotene therapy. *J Clin Lipidol*. 2015;9(6):832-836.
21. Li M, Zhai G, Gu X, Sun K. ATF3 and PRAP1 play important roles in cisplatin-induced damages in microvascular endothelial cells. *Gene*. 2018;672:93-105.
22. Abou- Zeid SM, El- Bialy BE, El-Borai NB, AbuBakr HO, Elhadary AMA. Radioprotective effect of date syrup on radiation-induced damage in rats. *Sci Rep*. 2018;8(1):7423.
23. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606.
24. Kuzu OF, Noory MA, Robertson GP. The role of cholesterol in cancer. *Cancer Res*. 2016;76(6):2063-2070.
25. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after diagnosis of breast cancer and survival: a population-based cohort study. *Epidemiology (Cambridge, Mass.)* 2015;26(1):68-78.
26. Beckwitt CH, Clark AM, Ma B, Whaley D, OltvaiZN, Wells A. Statins attenuate outgrowth of breast cancer metastases. *Br J Cancer*. 2018;119(9):1094-1105.
27. Emilsson L, García-Albéniz X, Logan RW, Caniglia EC, Kalager M, Hernán MA. Examining bias in studies of statin treatment and survival in patients with cancer. *JAMA Oncol*. 2018;4(1):63-70.
28. Lu CW, Lo YH, Chen CH, et al. VLDL and LDL, but not HDL, promote breast cancer cell proliferation, metastasis and angiogenesis. *Cancer Lett*. 2017;388:130-138.
29. Gallagher EJ, Zelenko Z, Neel BA, et al. Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia. *Oncogene*. 2017;36(46):6462-6471.