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

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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 pre-treatment, 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

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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.[1,2] Among all SCLC cases, approximately 30% are limited-stage SCLC (LS-SCLC).[3] 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.[3] 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%.[4]

Cholesterol plays a novel role in every aspect of tumor development and progression.[5,6] 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.[7-9] 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[10] and elevation in colorectal cancer.[11] 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.[12] Although we have previously evaluated the value of baseline level of low-density lipoprotein cholesterol (LDL-C) as a prognostic factor[13] in heterogeneous SCLC patients at both extensive and limited stages, the dynamic alterations of these serum lipids in patients with LS-SCLC patients 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 $\geq$ 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.[14,15]

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.

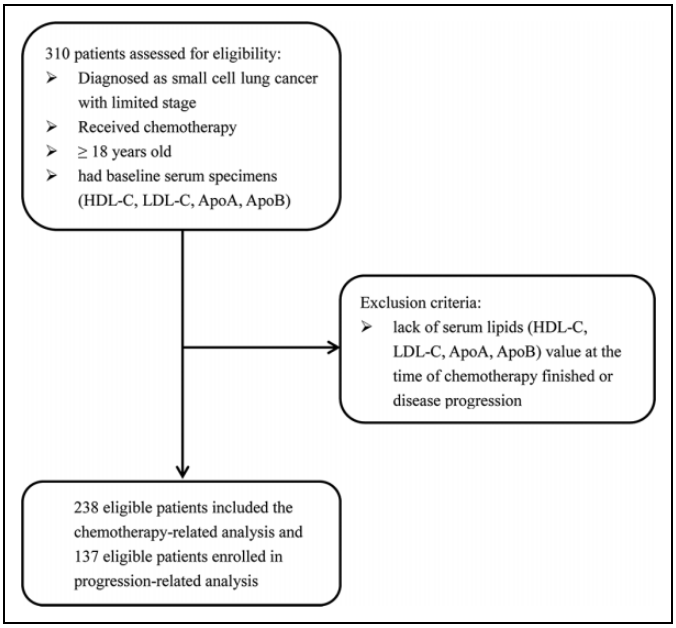

Figure 1. Screening flow chart.

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

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

			Univariate analysis (progress-free survival)			Univariate analysis (overall survival)		
		N (%)	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 (Referent)	-	0.943	1 (Referent)	-	0.055
	>59	151 (48.71)	1.01	0.74-1.39		0.76	0.58-1.01	
Gender	Female	38 (12.26)	1 (Referent)	-	0.709	1 (Referent)	-	0.382
	Male	272 (87.74)	0.92	0.58-1.45		1.21	0.79-1.86	
Smokers	Yes	255 (82.26)	1 (Referent)	-	0.961	1 (Referent)	-	0.358
	No	55 (17.74)	1.01	0.67-1.53		0.84	0.57-1.22	
PS	0	200 (64.52)	1 (Referent)	-	**0.009**	1 (Referent)	-	**<0.001**
	1	95 (30.61)	0.35	0.18-0.70		0.24	0.13-0.45	
	2	15 (4.87)	0.33	0.16-0.68		0.25	0.13-0.47	
Progression site	Intrathoracic	58 (39.19)	1 (Referent)	-	0.283	1 (Referent)	-	**0.013**
	Only one site outside thorax	85 (57.43)	0.73	0.29-1.83		0.25	0.10-0.65	
	≥2 sites outside thorax	5 (3.38)	0.95	0.39-2.36		0.25	0.10-0.64	
Radical operation	Yes	45 (14.52)	1 (Referent)	-	**0.014**	1 (Referent)	-	**0.001**
	No	265 (85.48)	1.96	1.15-3.34		2.25	1.38-3.65	
Thoracic radiotherapy	Yes	239 (77.10)	1 (Referent)	-	0.849	1 (Referent)	-	0.608
	No	71 (22.90)	0.85	0.65-1.42		1.09	0.78-1.52	
Chemotherapy cycles	<4	89 (28.71)	1 (Referent)	-	0.098	1 (Referent)	-	**0.026**
	≥4	221 (71.29)	1.33	0.95-1.88		1.40	1.04-1.88	

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.

[a]Data shown are the mean ± standard deviation (SD). Values in boldface indicate *P* values <0.05.

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

		Baseline lipid level								Post-CT		PD	
		HDL-C		LDL-C		ApoA		ApoB		HDL-C reduction		LDL-C elevation	
Variables		R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value
Age	≤ 59 vs. >59	0.09	0.107	0.01	0.868	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	−0.04	0.707		–
Progression site	Intrathoracic vs. Only one site outside thorax vs. ≥2 sites outside thorax											0.18	**0.037**

Abbreviations: CT, chemotherapy; PD, disease progression.
[a]Values in boldface indicate P values <0.05.

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

The alteration of lipids after chemotherapy and univariate analysis of their relationship with PFS and OS									
				Univariate analysis					
				PFS			OS		
Lipids	Post-CT	Difference ($Lipid_{Post\text{-}CT} - Lipid_{Baseline}$)	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
HDL-C (mmol/L)	1.17 ± 0.34	−0.08 ± 0.34	**< 0.001**	1.54	1.01-2.34	**0.043**	1.42	1.01-2.01	**0.046**
LDL-C (mmol/L)	3.14 ± 1.03	0.01 ± 1.01	0.913	0.94	0.64-1.39	0.756	1.31	0.95-1.81	0.104
ApoA (g/L)	1.27 ± 0.28	−0.03 ± 0.32	0.185	1.17	0.79-1.72	0.437	1.27	0.92-1.75	0.154
ApoB (g/L)	1.02 ± 0.34	0.04 ± 0.35	0.053	1.12	0.76-1.67	0.562	1.58	1.14-2.18	**0.006**
The alteration of lipids at the time of disease progression and univariate analysis of their relationship with PFS and OS									
				Univariate analysis					
				PFS			OS		
Lipids	PD	Difference ($Lipid_{PD} - Lipid_{Baseline}$)	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
HDL-C (mmol/L)	1.21 ± 0.35	−0.04 ± 0.30	0.141	0.93	0.66-1.31	0.668	1.13	0.76-1.68	0.551
LDL-C (mmol/L)	3.34 ± 0.88	0.22 ± 0.80	**0.002**	0.57	0.39-0.83	**0.003**	0.60	0.38-0.93	0.022
ApoA (g/L)	1.31 ± 0.26	0.03 ± 0.32	0.336	0.98	0.70-1.37	0.890	1.28	0.87-1.90	0.213
ApoB (g/L)	1.05 ± 0.26	0.09 ± 0.24	**<0.001**	0.85	0.59-1.22	0.372	0.92	0.60-1.40	0.684

[a]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).

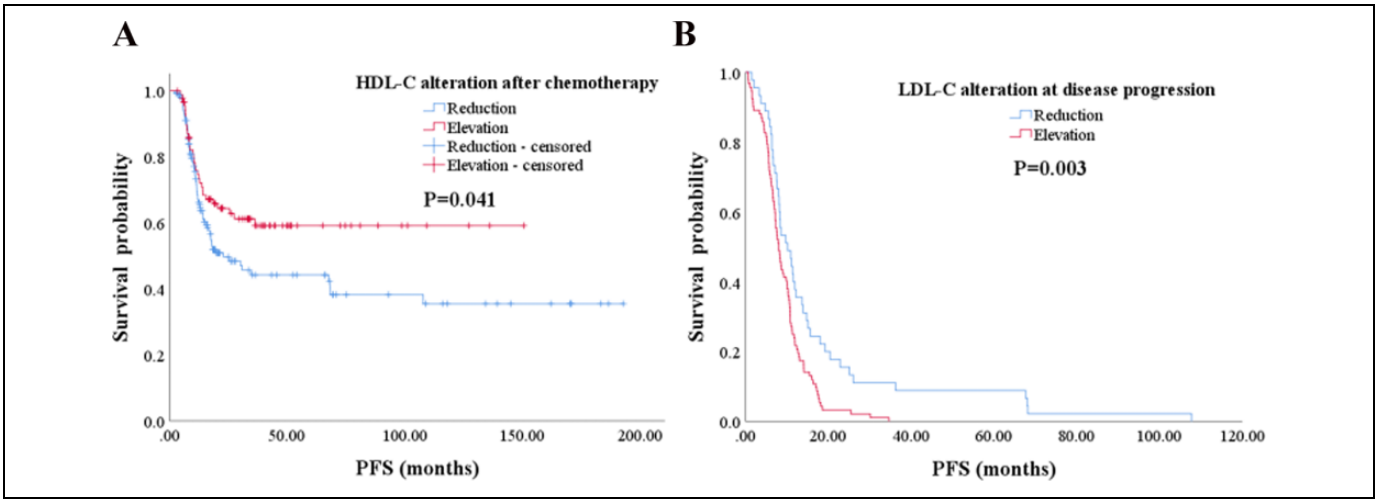

Figure 2. Kaplan-Meier curves for PFS. (A) PFS of patients with or without chemotherapy-related HDL-C decrease; (B) PFS of patients with or without LDL-C increase at the time of disease progression.

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 $\geq$2 sites outside thorax. Patients with disease progression at $\geq$2 sites outside thorax had significantly higher LDL-C increment at the time of disease progression ($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, 6.69-13.68), 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 ($P =$

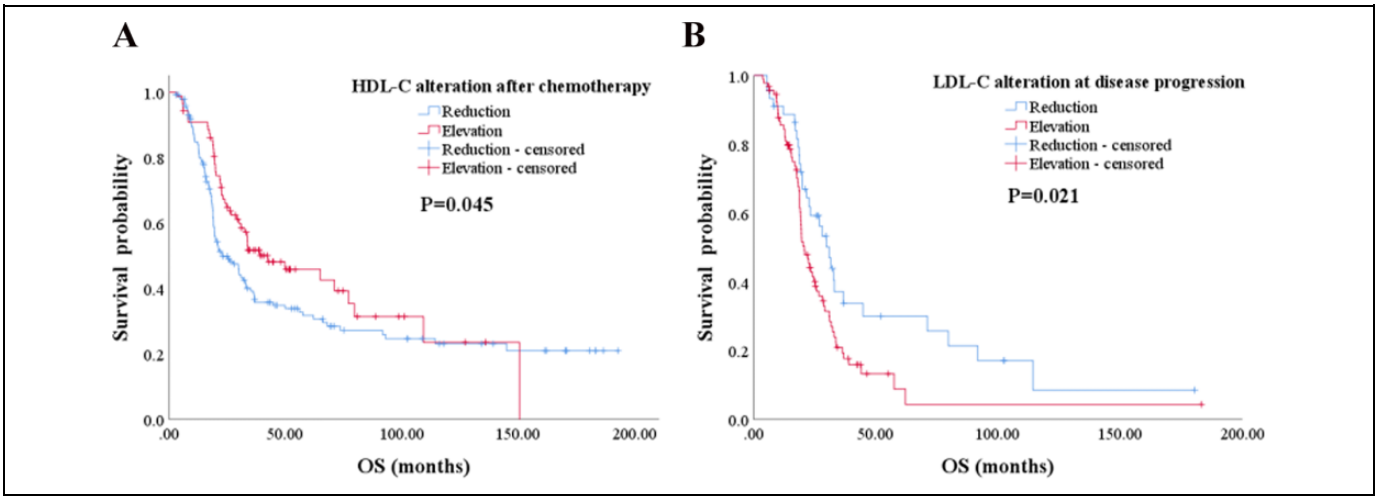

Figure 3. Kaplan-Meier curves for OS. (A) OS according of patients with or without chemotherapy-related HDL-C decrease; (B) OS of patients with or without LDL-C increase at the time of disease progression.

0.003) (Table 1). 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.[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.[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.[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 $= -0.08 \pm 0.34$, $P < 0.001$). The chemotherapy-induced HDL-C reduction may be as following: 1) endothelial cell injury mediated by chemotherapy might lead to lipid metabolism disorders[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 γ (PPARγ) and liver X receptor α (LXRα) transcription factors;[7]and 3) cholesterol ester transfer protein (CETP) activity could contribute to HDL-C decline in patients with cancer.[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 would be enhanced by concurrent thoracic radiotherapy (Mean ± SD: -0.11 ± 0.32 vs. 0.00 ± 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.[22] Recent studies have suggested that statins may be potential anticancer agents[23] by lowering protein

Table 4. COX Multivariate Regression Analysis.[a]

COX multivariate regression analysis for PFS and OS after chemotherapy					
		PFS		OS	
Variables		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)	
	2	0.18 (0.08-0.43)		0.35 (0.12-0.99)	
Radical operation	Yes	1 (Referent)	**0.010**	1 (Referent)	0.746
	No	2.80 (1.27-6.15)		1.19 (0.42-3.41)	
Chemotherapy cycles	<4		–	1 (Referent)	0.308
	≥4			1.33 (0.77-2.32)	
Progression site	Intrathoracic		–	1 (Referent)	**0.015**
	One site outside thorax			0.19 (0.06-0.59)	
	≥2 sites outside thorax			0.22 (0.07-0.66)	
HDL-C reduction	Yes	1 (Referent)	0.200	1 (Referent)	0.955
	No	1.33 (0.86-2.04)		1.02 (0.57-1.82)	
ApoB elevation	Yes		–	1 (Referent)	**0.028**
	No			1.76 (1.06-2.88)	
COX multivariate regression analysis for PFS and OS at the time of disease progression					
		PFS		OS	
variables		HR (95%CI)	*P* value	HR (95%CI)	*P* value
PS	0	1 (Referent)	0.307	1 (Referent)	**0.002**
	1	0.57 (0.28-1.19)		0.20 (0.08-0.49)	
	2	0.55 (0.25-1.21)		0.25 (0.10-0.64)	
Radical operation	Yes	1 (Referent)	0.858	1 (Referent)	0.988
	No	1.05 (0.60-1.85)		1.01 (0.49-2.06)	
Chemotherapy cycles	<4		–	1 (Referent)	**0.005**
	≥4			1.84 (1.20-2.83)	
Progression site	Intrathoracic		–	1 (Referent)	0.162
	One site outside thorax			0.31 (0.09-1.06)	
	≥2 sites outside thorax			0.32 (0.10-1.05)	
LDL-C elevation	Yes	1 (Referent)	**0.007**	1 (Referent)	**0.022**
	No	0.59 (0.40-0.86)		0.57 (0.36-0.92)	

[a]Values in boldface indicate *P* values <0.05.

prenylation[24] and inhibiting tumor cell proliferation.[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.[27]

As the major cholesterol type in plasma, LDL is well known for its modulatory effects on proliferation, migration and differentiation of cancer cells.[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, especial 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.

10.19 months, $P = 0.003$; median OS, 20.73 vs. 30.88 months, $P = 0.021$, respectively). These findings could help to estimate patients' survival and should be considered as stratification index to select patients receiving more intensive treatment so as to improve clinical outcome.

Several limitations should be considered in our study. Firstly, the study is retrospective and from a single center in nature. Further prospective and multicenter studies should be conducted. Secondly, no direct comparison with other prognosis factors was performed, and further analyses on the differences among these prognostic factors are urgently needed.

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: Yunpeng 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, Yuanyuan Zhao.

Declaration of Conflicting Interests

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Supplemental Material

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