

Associations of preoperative serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels with the prognosis of ovarian cancer

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Research

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Abstract

Background

The effect of serum lipids on ovarian cancer is controversial. We conduct this study to evaluate the prognostic value of preoperative plasma lipid profile in patients with ovarian cancer.

Methods

The medical records of 156 epithelial ovarian cancer patients who underwent surgical resection in our department were retrospectively reviewed and analyzed. Serum lipids profiles, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), apolipoprotein A- β (apoA- β), apolipoprotein B (apoB) and clinicopathologic data were analyzed. Cox proportional hazards regression analyses and Kaplan-Meier method were performed to evaluate the overall survival (OS) and progression-free survival (PFS).

Results

Multivariable Cox regression analysis found that preoperative higher LDL-C level was significantly associated with worse OS (HR 2.088, 95% CI 1.052–4.147, $p = 0.035$), whereas higher HDL-C level showed significant association with better PFS (HR 0.491, 95% CI 0.247–0.975, $p = 0.042$). Further Kaplan–Meier survival analysis demonstrated that OS was longer for patients with low levels of LDL-C (< 2.76 mmol/L) compared to those with high levels of LDL-C (≥ 2.76 mmol/L) ($P = 0.028$), and PFS was better for patients with high levels of HDL-C (≥ 1.19 mmol/L) compared to those with low levels of HDL-C (< 1.19 mmol/L) ($P = 0.001$).

Conclusions

Preoperative HDL-C and LDL-C levels are significant predictors of clinical outcome in patients with epithelial ovarian cancer.

Background

Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy [1]. Annually worldwide, 230000 women will be diagnosed and 150000 will die [2]. The standard treatment for EOC is primary surgery followed by the combination of platinum and taxane chemotherapy [3]. Recently, weekly paclitaxel therapy, intraperitoneal chemotherapy, and bevacizumab therapy are also considered to be acceptable as primary therapy [4–7]. However, owing to late diagnosis with advanced-stage disease, up to 80% of the patients have a relapse within five years, and the overall survival remains poor [8]. Thus, it is important to search for effective and accessible prognostic factors to identify ovarian cancer.

In the last decade, dysregulation of lipid metabolism has been increasingly recognized as a component of malignant transformation in many different cancers, including ovarian cancer [9, 10]. Lipids, as a kind of vital metabolites, comprise the majority of cellular membranes, play important roles as signaling molecules and contribute significantly to energy [11]. In order to fulfill the increased biochemical demands that accompany increased proliferation, lipid metabolism is often dysregulated in cancer [12]. The metabolic reprogramming is now understood to be linked to rapid growth of tumors, metastatic potential, resistance to chemotherapy, and cancer stemness [11]. Accordingly, altered metabolism has now been added to the list of cancer hallmarks [13].

Variations of plasma lipids and lipoproteins have been observed in ovarian cancer patients. Several studies have investigated whether the unbalanced lipid profile is associated with risk of developing ovarian cancer. Helzlsouer et al. [14] reported that women with a higher serum cholesterol level had an increased risk of ovarian cancer. A study by Delimaris et al. [15] found that oxidized low-density lipoprotein (ox-LDL) in serum was higher in ovarian cancer patients than in control subjects, but total cholesterol (TC) and high-density lipoprotein (HDL) showed no such association. Moreover, a recent study has clarified that elevated triglycerides (TG) was linked with cancer risk in patients with EOC [16]. In addition, it has been suggested that low levels of HDL could be reflective of an unfavorable hormonal profile which, in turn, would increase the risk of ovarian cancer [17].

However, the prognostic significance of lipid components in patients with EOC remains poorly understood. Therefore, in this study, we aimed to investigate the prognostic value of serum lipids and lipoproteins including TC, TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A- I (apoA- I), and apolipoprotein B (apoB) in patients of EOC.

Methods

Patient selection and clinical data collection

This was a retrospective study of 156 patients with primary epithelial ovarian cancer treated at Hangzhou First People's Hospital between January 2009 and November 2015. The study was approved by the ethics committee of our hospital. All patients were eligible for inclusion in the study: (1) had undergone primary surgery aimed at complete resection of all visible tumor followed by at least six cycles of platinum-taxane combination chemotherapy; (2) had a histologically confirmed diagnosis of epithelial ovarian cancer; (3) without hormone replacement therapy or any other drugs known to affect lipid metabolism; (4) without cancer history; (5) serum samples (including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A- I (apoA- I), and apolipoprotein B (apoB)) were collected before treatment. Meanwhile, patient clinical characteristics including age, menopausal status, FIGO (International Federation of Gynecology and Obstetrics) stage, tumor histology and grade, lymph node metastatic status, initial level of cancer antigen 125 (CA-125), treatment (surgery, chemotherapy), recurrence, and death were collected. Optimal surgery was defined as residual tumor < 1 cm.

Follow up

All patients were followed up by medical records review and telephone interview. Data were collected until death or November 2020. Overall survival (OS), the primary endpoint of this study, was defined as the time from the date of primary cytoreductive surgery to the date of the last recorded clinical visit or death from any cause. Progression-free survival (PFS) was the secondary end point which was defined as the time interval from surgery to the date of disease recurrence or progression or the last follow-up.

Statistical analysis

Baseline characteristics of patient data were expressed as numbers and percentages for categorical variables. The cutoff value to stratify patients at high risk of death for serum TC, TG, HDL-C, LDL-C, apoA- ω , apoB and CA-125 was established by receiver operating characteristic (ROC) curves. To evaluate prognostic factors for PFS and OS, we did univariate and multivariate Cox proportional hazards regression analyses. All factors with p-value of < 0.1 at univariate analyses were entered into a multivariate model, and hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). The survival curves were explored through the Kaplan–Meier method with a log-rank test. All statistical analyses were performed using SPSS Statistics software (Version 20.0, Chicago, IL), and a p-value of less than 0.05 was considered statistically significant.

Results

Characteristics of study patients

A total of 156 patients were included in the analysis, and the median follow-up period was 82.2 months (range, 0.5 to 141.6 months). The baseline characteristics of these patients are summarized in Table 1. Their median age at diagnosis was 53 years (range, 15 to 87 years), and 69 (44.2%) patients were premenopausal. Regarding the FIGO stage of disease, 46 (29.5%), 19 (12.2%), 79 (50.6) and 12 (7.7%) were staged in I, II, III, IV respectively. The majority of patients had grade 3 disease (92, or 59.0%) with papillary serous histology (89, or 57.1%). Median CA-125 level was 275.3 kU/L (range, 5.3 to 10000 kU/L) in all patients, and 68 (43.6%) of them had lymph node metastasis. One hundred and thirty-seven patients (87.8%) underwent optimal cytoreductive surgery at initial exploration to residual disease less than 1 cm. Further descriptive data were shown in Table 1.

Table 1
 Characteristics of all patients (n = 156)

Characteristic	Patients	%
Age (years)		
<50	66	42.3
≥50	90	57.7
Menopausal status		
Premenopause	69	44.2
Menopause	87	55.8
Stage		
I	46	29.5
II	19	12.2
III	79	50.6
IV	12	7.7
Grade		
1	31	19.9
2	33	21.2
3	92	59.0
Histology		
Serous	89	57.1
Non-serous	67	42.9
Lymph node metastasis		
Present	68	43.6
Absent	88	56.4
Debulking operation		
Optimal	137	87.8
Suboptimal	19	12.2
CA-125 (kU/L)		

CA-125: cancer antigen 125; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA: apolipoprotein A; ApoB: apolipoprotein B.

Characteristic	Patients	%
< 95.2	65	41.7
≥ 95.2	91	58.3
Total cholesterol (mmol/L)		
< 4.86	86	55.1
≥ 4.86	70	44.9
Triglycerides (mmol/L)		
< 1.36	94	60.3
≥ 1.36	62	39.7
HDL-C (mmol/L)		
< 1.19	76	48.7
≥ 1.19	80	51.3
LDL-C (mmol/L)		
< 2.76	96	61.5
≥ 2.76	60	38.5
ApoA \square (g/L)		
<1.51	101	64.7
≥1.51	55	35.3
ApoB (g/L)		
<1.01	78	50.0
≥1.01	78	50.0
CA-125: cancer antigen 125; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA \square : apolipoprotein A- \square ; ApoB: apolipoprotein B.		

Cut-off determination of serum lipid and lipoproteins

ROC curves analysis showed that the optimal cutoff value of joint maximum sensitivity and specificity were for TC 4.86 mmol/L (AUC: 0.563, 95% CI: 0.468–0.658), 1.36 mmol/L for TG (AUC: 0.538, 95% CI: 0.447–0.629), 1.19 mmol/L for HDL-C (AUC: 0.624, 95% CI: 0.533–0.716), and 2.76 mmol/L for LDL-C (AUC: 0.597, 95% CI: 0.503–0.681), 1.51 g/L for apoA \square (AUC: 0.554, 95% CI: 0.458–0.649), 1.01 g/L for apoB (AUC: 0.508, 95% CI: 0.413–0.602), respectively.

The prognostic impact of serum lipids on OS and PFS

In univariate analyses, early-stage (I, II), low grade tumors, non-serous histology, without lymph node metastasis, preoperative lower CA125 and optimal debulking (residual disease < 1 cm) were favorable prognostic factors for OS and PFS. Moreover, according to the recommended cutoff levels of preoperative serum lipids and lipoproteins, the preoperative higher TC, HDL-C, apoA-I and lower LDL-C level were significantly associated with better OS and PFS (Tables 2 and 3).

Table 2

Univariable and multivariable Cox proportional hazards regression analyses of prognostic factors for OS

Factors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥ 50 year vs. <50 year)	1.225 (0.698–2.149)	0.480		
Menopause (yes vs. no)	1.225 (0.701–2.140)	0.476		
Stage (III, IV vs. I, II)	3.693 (2.436–5.601)	< 0.001	2.005 (1.057–3.805)	0.033
Grade (1, 2 vs. 3)	0.445 (0.275–0.718)	0.001	0.738 (0.428–1.272)	0.274
Histology (Non-serous vs. Serous)	0.281 (0.140–0.562)	< 0.001	0.593 (0.262–1.342)	0.210
Lymph node metastasis (yes vs. no)	8.959 (4.342–18.484)	< 0.001	2.515 (1.078–5.871)	0.033
Optimal debulking (no vs. yes)	9.810 (5.294–18.178)	< 0.001	3.913 (1.925–7.956)	< 0.001
CA125 ≥ 95.2 kU/L	4.694 (2.204–9.997)	< 0.001	1.139 (0.496–2.612)	0.759
Total cholesterol ≥ 4.86 mmol/L	0.526 (0.293–0.943)	0.031	0.556 (0.266–1.164)	0.119
Triglycerides ≥ 1.36 mmol/L	1.052 (0.602–1.838)	0.860		
HDL-C ≥ 1.19 mmol/L	0.298 (0.161–0.551)	< 0.001	0.586 (0.257–1.339)	0.205
LDL-C ≥ 2.76 mmol/L	1.835 (1.059–3.180)	0.030	2.088 (1.052–4.147)	0.035
ApoA I ≥ 1.51 g/L	0.515 (0.270–0.985)	0.045	1.282 (0.550–2.988)	0.566
ApoB ≥ 1.01 g/L	0.747 (0.430–1.298)	0.301		
OS: overall survival; CA-125: cancer antigen 125; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B.				

Table 3

Univariable and Multivariable Cox proportional hazards regression analyses of prognostic factors for PFS

Factors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥ 50 year vs. <50 year)	1.471 (0.902-2.400)	0.122		
Menopause (yes vs. no)	1.417(0.876–2.294)	0.156		
Stage (I, II vs. III, IV)	3.315(2.398–4.583)	< 0.001	1.939(1.209–3.111)	0.006
Grade (1, 2 vs. 3)	0.459(0.310–0.679)	0.001	0.795(0.510–1.239)	0.311
Histology (Non-serous vs. Serous)	0.314(0.179–0.550)	< 0.001	0.577(0.306–1.090)	0.090
Lymph node metastasis (yes vs. no)	6.814(3.914–11.864)	< 0.001	1.726 (0.866–3.439)	0.121
Optimal debulking (no vs. yes)	12.431(6.916–22.343)	< 0.001	4.465(2.206–9.037)	< 0.001
CA125 ≥ 95.2 kU/L	4.225(2.308–7.736)	< 0.001	1.233(0.625–2.434)	0.546
Total cholesterol ≥ 4.86 mmol/L	0.536(0.327–0.878)	0.013	0.768(0.399–1.481)	0.431
Triglycerides ≥ 1.36 mmol/L	1.068(0.664–1.720)	0.786		
HDL-C ≥ 1.19 mmol/L	0.279(0.165–0.470)	< 0.001	0.491(0.247–0.975)	0.042
LDL-C ≥ 2.76 mmol/L	1.624(1.015–2.597)	0.043	1.805(0.991–3.288)	0.054
ApoA ≥ 1.51 g/L	0.471(0.270–0.824)	0.008	1.053 (0.520–2.133)	0.886
ApoB ≥ 1.01 g/L	0.916(0.573–1.465)	0.715		
PFS: progression-free survival; CA-125: cancer antigen 125; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA: apolipoprotein A; ApoB: apolipoprotein B.				

In multivariate analyses, early-stage, without lymph node metastasis and optimal debulking remained as favorable prognostic factors for OS. Early-stage and optimal debulking predicted longer PFS. The HRs of OS were 2.005 (95% CI 1.057–3.805, $p = 0.033$) for advanced FIGO stage, 2.515 (95% CI 1.078–5.871, $p = 0.033$) for lymph node metastasis, and 3.913 (95% CI 1.925–7.956, $p < 0.001$) for suboptimal debulking, while the HRs of PFS were 1.939 (95% CI 1.209–3.111, $p = 0.006$) for advanced FIGO stage and 4.465

(95% CI 2.206–9.037, $p < 0.001$) for suboptimal debulking. Furthermore, the results revealed that preoperative higher LDL-C level was significantly associated with worse OS (HR 2.088, 95% CI 1.052–4.147, $p = 0.035$), whereas higher HDL-C level showed significant association with better PFS (HR 0.491, 95% CI 0.247–0.975, $p = 0.042$) (Tables 2 and 3).

Kaplan–Meier curves analyses of HDL-C and LDL-C

Kaplan–Meier curves with log-rank tests stratified by the cutoff value level of LDL-C and HDL-C were performed to assess the prognostic significance of the serum lipid profile in ovarian cancer. It demonstrated that the patients with high levels of HDL-C (≥ 1.19 mmol/L) had a better PFS compared with those with low levels of HDL-C (< 1.19 mmol/L) ($P = 0.001$) (Fig. 1), whereas the patients with low levels of LDL-C (< 2.76 mmol/L) had a better OS compared with those with high levels of LDL-C (≥ 2.76 mmol/L) ($P = 0.028$) (Fig. 2).

Discussion

Study of the relationship between ovarian cancer and serum lipid levels, including TC, TG, HDL-C, LDL-C, and apolipoproteins, is of special interest and has sparked debate, and no consensus of their significance has been established. The aim of the present study was to evaluate the association between lipid profiles and ovarian cancer. We found that high level of preoperative HDL-C was a significant independent predictor of better PFS in ovarian cancer patients, whereas high level of LDL-C showed significant association with worse OS.

Cancer cells show specific alterations in different aspects of lipid metabolism, which are related to important cellular processes, including cell growth, proliferation, differentiation, and motility [18]. As the primary mediators of cholesterol and lipid transport, lipoproteins are essential components of energy and lipid metabolism in the body, which may have direct effects on carcinogenesis. Some observational studies have indicated a relationship between HDL-C levels with some cancer types [19–23]. Epidemiological data have shown levels of HDL-C are significantly inversely associated with risk for multiple cancers [24–26]. The meta-analysis conducted by D. Zhang et al. [27] revealed an association between high HDL-C levels and lower ovarian cancer risk. Two retrospective studies also showed that low HDL-C levels were strongly correlated with severity of epithelial ovarian cancer [20, 28]. Although a meta-analysis including 25 studies with a total of 13,140 patients indicated that high serum HDL-C levels were associated with better OS and PFS in most of tumor types [29], the association between HDL-C and ovarian cancer still remains unclear. In our study, we have observed that patients with HDL-C level ≥ 1.19 mmol/L had a better PFS than patients with HDL-C level < 1.19 mmol/L ($p = 0.001$). HDLs play a key role in the reverse cholesterol transport (RCT), which can promote cholesterol removal from cancer cells, thus altering their homeostasis [30]. In addition, HDLs are able to affect several other pathways, including oxidation, inflammation, apoptosis, angiogenesis and immunomodulatory activities which may be also relevant for cancer biology. The anti-oxidative properties of HDLs have been linked to their capacity to protect LDL from oxidative modification, which might be facilitated by HDL-associated apolipoproteins and enzymes, such as apoA \AA , apoE2, apoA $\text{\textcircled{A}}$, apoJ, PON1 and LCAT [31–33]. Besides, HDLs are able to

prevent the release of proinflammatory cytokines and to upregulate the expression of endothelial and leukocyte adhesion molecules, thus exerting anti-inflammatory effects. In addition, the anti-apoptotic effects of HDLs can be attributed to their ability to interact with caspase-3, a key factor of apoptotic pathway, or to induce upregulation of the anti-apoptotic Bcl-2 protein Bcl-xL [34, 35]. The pleiotropic activities of HDLs result into an overall anti-tumorigenesis effects.

Concerning LDL-C, discordant results were also found. One retrospective study from the United States showed that OS and PFS were longer for patients with normal LDL levels compared to those with elevated LDL, and LDL was suggested as a predictor of clinical outcome [36]. In contrast, another retrospective study by Zhu et al [37] found that high levels of LDL was associated with a better recurrence-free survival in women with ovarian cancer. It should also be noted that a Mendelian randomization study of 22,406 women with ovarian cancer did not find any association between genetic variation in controlling LDL-C and risk of epithelial ovarian cancer [38]. In this study, we found that patients with LDL-C level < 2.76 mmol/L had better OS than patients with LDL-C level ≥ 2.76 mmol/L ($P = 0.028$). As a main cholesterol transporter, LDL-C can provide cancer cells with lipids and cholesterol as a component for their proliferation. It was demonstrated that increased LDL receptor expressed in breast cancer tissue to increase the uptake of LDL-C from the bloodstream [39], and LDL promotes breast cancer progression by inducing cell proliferation, migration and loss of adhesion [40, 41]. However, the proliferation rates of ovarian carcinoma cell lines CAOV3 and SKOV3 remained unchanged when they were treated with LDL, which was stimulated by oxidized low-density lipoprotein (ox-LDL), accompanied by an induction of the expression of the antiapoptotic cytokine cardiotrophin 1 [42]. Besides, it was found that ovarian cancer patients possessed high levels of ox-LDL compared with control subjects [15], which indicated that ox-LDL has an important role in ovarian cancer development. The oxidation of LDL results in the formation of peroxidation metabolites which cause structural alterations in DNA and decrease DNA repair capacity through their direct interaction with repair enzymes [43]. Studies have showed a positive correlation between increased serum ox-LDL levels and an increased risk of colon, breast, and ovarian cancer [44–46]. Ox-LDL and its receptor LOX-1 activate the inflammatory pathway through nuclear factor-kappa B, leading to cell transformation. LOX-1 is important for maintaining the transformed state in developmentally diverse cancer cell lines and for tumor growth [49]. However, the studies remained limited, detailed mechanisms of LDL need further investigation.

Several limitations of our study should be considered. Firstly, this was a retrospective study, and patients were excluded if data on serum lipid levels were not available. This may have caused selection bias. Secondly, serum lipid levels were measured only once before treatment, but they may change over time depending on the patient's clinical course and disease status. Thirdly, the cohort of our study was relatively small and from a single center, further multi-center studies with more cases may be needed to minimize selection bias and potential confounding factors such as difference in geographic distribution. Despite these limitations, the use of Cox proportional hazards regression to perform a multivariate analysis is relative strengths of our study.

Conclusion

In conclusion, our results provide evidence that HDL-C and LDL-C levels at diagnosis may be independent prognostic factors for epithelial ovarian cancer, suggesting that serum lipid levels may be used as predictive factors for screening and follow-up of ovarian cancer. In addition, it may be beneficial to adjust these parameters with appropriate therapies in addition to routine cancer therapies. More multiple center and prospective studies are needed.

Abbreviations

TC

total cholesterol

HDL-C

high-density lipoprotein cholesterol

LDL-C

low-density lipoprotein cholesterol

TG

triglyceride

ApoA-I

apolipoprotein A-I

ApoB

apolipoprotein B

OS

overall survival

PFS

progression-free survival

EOC

epithelial ovarian cancer

Ox-LDL

oxidized low-density lipoprotein

HDL

high-density lipoprotein

FIGO

International Federation of Gynecology and Obstetrics

CA-125

cancer antigen 125

ROC

receiver operating characteristic

HR

hazard ratio

CI

confidence intervals

RCT

reverse cholesterol transport

Declarations

Ethics approval and consent to participate

The study was compliant with the Declaration of Helsinki, and approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital of Zhejiang University. Informed consent was waived due to its retrospective nature.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

LPS and QQL conceived and designed the experiments. QQL and SX extracted and analyzed data. QQL and WCL were the statisticians who confirmed the analysis of this study. QQL and WCL wrote the manuscript. All authors read and approved the final manuscript.

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Figures

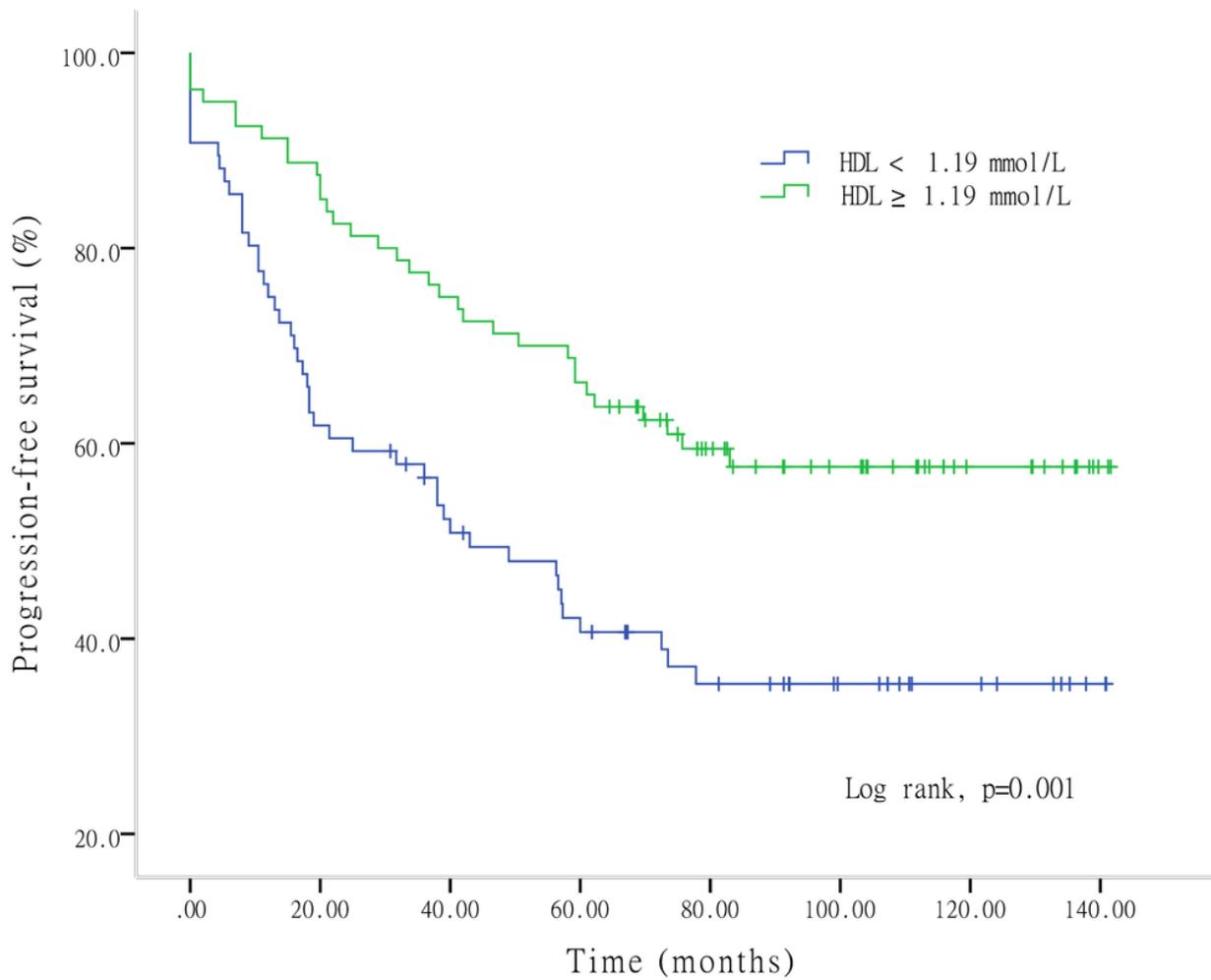


Figure 1

Kaplan-Meier curve of progression-free survival (PFS) according to low vs high HDL-C levels.

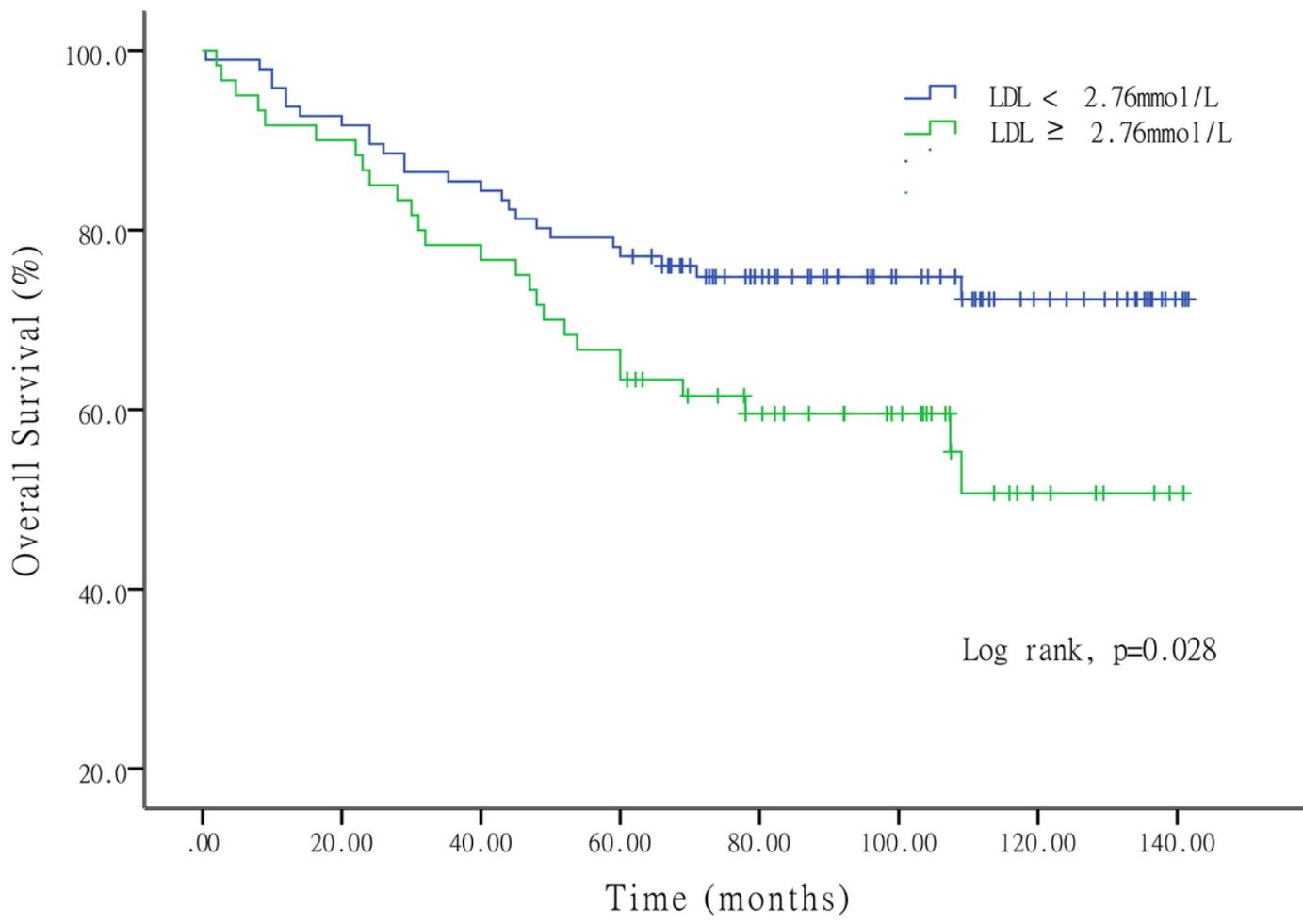


Figure 2

Kaplan-Meier curve of overall survival (OS) according to low vs high LDL-C levels.