Submitted: 29 February, 2024 Accepted: 07 May, 2024 Published: 15 December, 2024 DOI:10.22514/ejgo.2024.120

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

The effect of postoperative chemotherapy on serum lipids and prognosis in patients with advanced ovarian cancer

Ting Du[1], Qiuxia Qu[2], Yawen Zhang[1], Qin Huang[1], Zhen Bian[3,*]

[1]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Soochow University, 215006 Suzhou, Jiangsu, China
[2]Clinical Immunology Institute, The First Affiliated Hospital of Soochow University, 215006 Suzhou, Jiangsu, China
[3]Department of Anesthesiology, The First Affiliated Hospital of Soochow University, 215006 Suzhou, Jiangsu, China

***Correspondence**
bianzhen@suda.edu.cn
(Zhen Bian)

Abstract

Recent studies have shown that chemotherapy can cause abnormal blood lipid metabolism in cancer patients. However, little is known about the association between blood lipids and chemotherapy in patients with ovarian cancer. In this study, we investigated the change in blood lipid levels in patients with advanced ovarian cancer before and after adjuvant chemotherapy and its effect on patient prognosis. Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein (HDL) levels and clinical data from 100 patients with advanced (International Federation of Gynecology and Obstetrics, FIGO stage III/IV) ovarian cancer before and after postoperative adjuvant chemotherapy were measured and analyzed, and the correlation of LDL level with overall survival (OS) was evaluated. After chemotherapy, the TG, TC, HDL and LDL levels were significantly greater than those before chemotherapy ($p < 0.01$). A high LDL level in patients with advanced ovarian cancer after chemotherapy was significantly correlated with poor overall survival (OS). Patients with advanced ovarian cancer have abnormal blood lipid metabolism during adjuvant chemotherapy, and elevated LDL levels after chemotherapy are significantly correlated with a poor prognosis.

Keywords

Ovarian cancer; Chemotherapy; Serum lipids; Overall survival

1. Introduction

Ovarian cancer is a malignant tumor of the ovary. Approximately 90%~95% of these cases are primary ovarian cancer, and the other 5%~10% are metastatic to the ovary. Because of the lack of symptoms in the early stage of ovarian cancer and because the symptoms are not specific, early diagnosis is difficult; thus, 60%~70% of cases are already advanced at the time of diagnosis, and the treatment outcomes for advanced cases are not good [1]. Therefore, although the incidence of ovarian cancer is lower than that of cervical cancer and endometrial cancer, the mortality of ovarian cancer is greater than that of cervical cancer and endometrial cancer and it is a more serious threat to women's health.

Chemotherapy is one of the most important treatment methods for ovarian cancer patients and can significantly retard tumor progression and prolong patient survival [2]. However, while chemotherapy drugs exert antitumor effects, they also have many side effects on patients, such as alopecia (which is a well-known condition), functional damage to important organs, functional damage to the blood system, and gastrointestinal reactions such as nausea and vomiting. These side effects have a strong adverse impact on patients, and if they are not treated in time, they may lead to the interruption of chemotherapy, so clinicians attach great importance to symptoms of adverse effects. However, disorders of blood lipid metabolism caused by chemotherapy drugs are asymptomatic and therefore often ignored.

Lipid metabolism plays an important role in tumor cell membrane maintenance, energy metabolism, angiogenesis, cell growth and signal transduction [3–5]. Studies have shown that inhibiting cholesterol synthesis, which is needed for tumor growth, can effectively inhibit tumor cell proliferation, metastasis and invasion [6]. Recent studies based on lipomics have shown that there are obvious lipid metabolism disorders in ovarian cancer patients, which strengthens the view that lipid metabolism may affect ovarian tumor behavior [7–9]. Moreover, some studies have shown that chemotherapy leads to changes in lipids in some types of cancer [10, 11], but there is still a lack of research on the effect of chemotherapy on lipids in ovarian cancer patients. In this study, the changes in blood lipids in 100 patients with advanced ovarian cancer before and after postoperative adjuvant chemotherapy were retrospectively analyzed, and the influence of chemotherapy on blood lipids and its relationship with the prognosis of patients with ovarian cancer were investigated.

2. Methods

2.1 Study design and patients

From January 2013 to December 2016, 206 patients with advanced ovarian high-grade serous cancer were treated in our hospital. All patients were pathologically diagnosed with ovarian cancer. The inclusion criteria were as follows: (1) a definitive diagnosis and a complete set of clinical data, including age, stage, overall survival time and pathological data; (2) normal liver function before chemotherapy and satisfactory tumor cytoreductive surgery (residual lesion $\leq$1 cm after resection is considered satisfactory tumor cytoreductive surgery), followed by a combination of paclitaxel and cisplatin every 3 weeks for a total of 6 cycles; and (3) normal results on the accessory examinations.

The exclusion criteria for patients were as follows: patients lacking a complete blood count, blood pressure, blood glucose, sternum, electrocardiography and hemopathy; (1) previous hepatitis virus infection, hypertension, diabetes or coronary heart disease; (2) previous history of liver disease, alcoholism or liver function damage; (3) a preoperative Body Mass Index (BMI) that exceeded 30 kg/m^2; or (4) dyslipidemia before chemotherapy (regardless of whether they were using lipid-lowering drugs). All patients were diagnosed by routine pathological examination.

According to the above criteria, 100 patients with advanced ovarian cancer were ultimately included. The age of the patients ranged from 32 to 80 years, with an average age of 55.55 years. Patient data were investigated retrospectively, and data relating to age, operation time, and blood lipid levels were acquired from their medical records. The 5-year survival rate after surgery was ascertained by telephone follow-up.

2.2 Data collection

All patients underwent blood tests before the first chemotherapy session and seven days after the end of six cycles of chemotherapy. Blood samples were taken from every patient in the morning on an empty stomach. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were detected by enzymological methods. The changes in blood lipids in each patient before chemotherapy and after the last chemotherapy was compared. According to the serum LDL level after chemotherapy, the patients were divided into two groups: LDL $\geq$3.4 mmol/L (high-LDL) and $<$3.4 mmol/L (low-LDL) [12]. The 5-year survival time of the two groups was followed up.

2.3 Statistical analysis

SPSS version 26.0 (IBM, Inc., New York, NY, USA) was used for statistical analysis, and measurement data were analyzed by paired *t* tests and are expressed as the mean $\pm$ standard deviation. Rate comparisons were evaluated by the chi-squared test. The Kaplan-Meier method was used to calculate OS curves for patients in the high-LDL and low-LDL groups, and the statistical differences between the groups were evaluated with log-rank tests. The Mantel-Cox model was used to evaluate the independent impact of blood lipid levels on OS after chemotherapy. A p value < 0.05 was considered to indicate statistical significance.

3. Results

3.1 Comparison of TC, TG, LDL and HDL levels in patients with ovarian cancer before and after chemotherapy

The blood lipid levels of 100 patients with ovarian cancer were within the normal range before chemotherapy. After 6 cycles of platinum-containing chemotherapy, their blood lipid levels had significantly increased ($p < 0.01$) (Table 1).

3.2 LDL levels and clinical significance in patients with ovarian cancer

For the 100 patients with advanced ovarian cancer included in this study, the average age was 55.55 years (32–80 years). There were 59 patients (59.00%) with FIGO III disease and 41 patients (41.00%) with FIGO IV disease. Forty-nine patients (49.00%) achieved R0 surgical resection, and 51 patients (51.00%) achieved R1 surgical resection. Blood lipid analysis after chemotherapy revealed 55 patients (55.00%) in the high-LDL group and 45 patients (45.00%) in the low-LDL group. There was no significant difference in age, FIGO stage or satisfactory cytoreductive surgery between the high-LDL group and low-LDL group (Table 2).

3.3 Factors associated with overall survival

The relationship between LDL levels and OS was evaluated by Kaplan-Meier analysis (Fig. 1). The average 5-year OS of the 100 patients in this study was 36.86 months. The average OS of patients with low LDL levels was 39.87 months, while that of patients with high LDL levels was 29.36 months. There was a statistically significant difference between the two groups ($p < 0.01$). Based on Mantel-Cox statistics, there was a significant correlation between the high-LDL group and low OS in ovarian cancer patients after chemotherapy ($p < 0.01$). The Cox regression model indicated that postchemotherapy blood LDL levels exerted an independent impact on OS in OC patients (hazard ratio (HR): 3.351; 95% confidence interval (CI): 2.058–5.456; $p < 0.01$). In addition, FIGO stage and surgical R0 resection also exerted independent effects on the survival of patients with ovarian cancer (Table 3).

4. Discussion

Ovarian cancer is the most malignant tumor in gynecology. As an indispensable part of treatment for ovarian cancer, postoperative adjuvant chemotherapy can help reduce the recurrence of ovarian cancer and prolong patient survival. Paclitaxel combined with carboplatin, as the first-line chemotherapy for ovarian cancer, has been widely recognized and adopted [13]. However, we found in clinical work that patients receiving chemotherapy for ovarian cancer often have dyslipidemia, which is often ignored by clinicians. Lipids are important components of the cell membrane and directly or indirectly participate in signal transduction, inflammatory mediator pro-

TABLE 1. Comparison of serum lipids concentrations pre and postchemotherapy ($\bar{x} \pm s$).

Chemotherapy	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
Pre-Chemotherapy	4.45 ± 0.33	1.41 ± 0.15	1.19 ± 0.11	2.80 ± 0.34
Post-Chemotherapy	4.63 ± 0.37	1.53 ± 0.17	1.29 ± 0.14	3.16 ± 0.38
p	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

TC: total cholesterol; TG: triglyceride; HDL: low-density lipoprotein; LDL: high-density lipoprotein.

TABLE 2. Clinical characteristics of the patients (n (%)).

	LDL-Low	LDL-High	Total	*p*
Number of patients	45	55	100	
Age (yr)	56.18	55.04		0.58
FIGO				
III	29 (64.44)	30 (54.55)	59 (59.00)	0.32
IV	16 (35.56)	25 (44.45)	41 (41.00)	
Residual disease (cm)				
0	26 (57.78)	23 (41.82)	49 (49.00)	0.11
1	19 (42.22)	32 (58.18)	51 (51.00)	

LDL-High/LDL-Low: According to the serum LDL level after chemotherapy, the patients were divided into two groups: LDL ≥3.4 mmol/L (LDL-High) and <3.4 mmol/L (LDL-Low). LDL: high-density lipoprotein; FIGO: International Federation of Gynecology and Obstetrics.

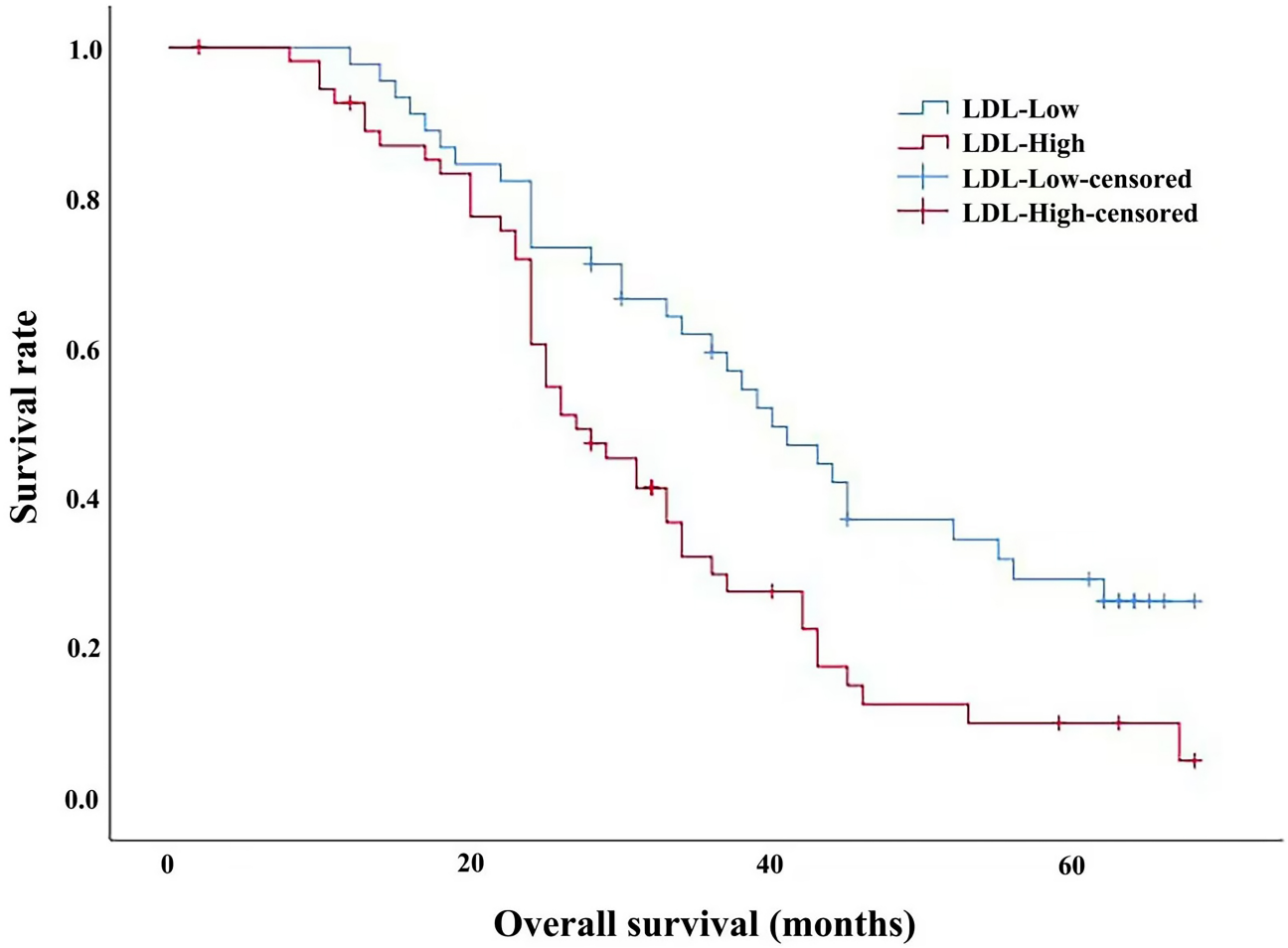

FIGURE 1. Kaplan-Meier survival curves according to LDL level after chemotherapy. LDL: Low-density lipoprotein.

TABLE 3. Factors influencing patient mortality as determined by Cox proportional hazards.

Variables	Regression coefficient	Wald	*p*	HR	95% CI
FIGO	0.952	3.022	0.003	2.590	1.397–4.802
Cytoreduction	1.585	5.233	<0.001	4.877	2.694–8.829
LDL	1.209	4.860	<0.001	3.351	2.058–5.456

HR: Hazard ratio; CI: Confidence interval; FIGO: International Federation of Gynecology and Obstetrics; LDL: low-density lipoprotein.

duction and angiogenesis [14]. Therefore, abnormal lipid metabolism in tumor patients not only induces cardiovascular and cerebrovascular diseases but also affects the occurrence, development, invasion and metastasis of tumors, thus affecting patient prognosis.

Hyperlipidemia is also called dyslipidemia. Excessive fat intake, lipoprotein synthesis and metabolic disorders can all cause dyslipidemia. Generally, increased cholesterol and/or triglycerides, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol are all considered to be hyperlipidemia and usually occur together. The results of this study showed that the plasma cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels in patients with advanced ovarian cancer after chemotherapy were all greater than those before chemotherapy ($p < 0.01$), which is different from the findings in patients with usual hyperlipidemia. The mechanism of this type of dyslipidemia is very complex and has not been fully clarified at present, but it may be related to the following mechanisms: (1) Chemotherapy drugs reduce lipase activity [15]; (2) the synthesis of topoisomerase I is inhibited, causing abnormally high-density lipoprotein cholesterol, leading to high cholesterol and triglyceridemia [16]; (3) the degradation of apolipoprotein B100 is reduced, thus increasing the synthesis of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol [17]; and (4) the chemotherapy drugs cause insulin resistance in patients and reduce the endocytosis of lipid molecules by the cell membrane, thus causing hyperlipidemia [18].

In this study, the levels of cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol after chemotherapy were significantly greater than those before chemotherapy, which was consistent with previous reports [19]. Additionally, some studies have indicated that increases in LDL-C are positively associated with tumor size and lymph node metastasis [20], and high blood cholesterol is associated with an increased ovarian cancer risk [9]. Overall, high serum cholesterol levels are strongly associated with all stages of cancer development [21]. In addition, this study revealed that when the low-density lipoprotein cholesterol level of chemotherapy patients increased, their overall survival rate decreased. Lin *et al.* [22] also showed that the level of low-density lipoprotein cholesterol was related to the progression-free survival of ovarian cancer patients. Some studies have shown that patients with hyperlipidemia have a significantly increased risk of prostate cancer, colon cancer and breast cancer, and the treatment effect is worse [23]. These findings indicate that dyslipidemia increases the probability of tumor occurrence; promotes tumor proliferation, invasion and drug resistance; and ultimately forms a vicious cycle, resulting in a poor prognosis for patients with tumors.

At present, dyslipidemia is common and easily overlooked in patients with ovarian cancer who are receiving adjuvant chemotherapy after surgery. If dyslipidemia is not corrected in time, it will promote the progression of the disease and adversely affect patient prognosis. Therefore, during chemotherapy, patients' blood lipid changes should be closely monitored, and lipid-regulating drugs should be administered when necessary to alleviate the probability of adverse cardiovascular and cerebrovascular events caused by dyslipidemia to a certain extent and improve the prognosis of these patients.

This study has several limitations that need to be considered. First, this was a cross-sectional study, which precluded the determination of causal relationships. Second, the sample size was small, and the patients were from a single center; this may have introduced bias. Finally, this was a retrospective study and it was only possible to analyze a limited body of information found in patient charts. However, some pathological parameters, such as tumor type, tumor grade, and lymphatic vessel infiltration, have a significant impact on prognosis and survival. Finally, we discussed only advanced high-grade serous ovarian carcinoma.

5. Conclusions

In summary, chemotherapy drugs can cause blood lipid metabolism disorders in patients and can affect patient prognosis. During chemotherapy, attention should be given to monitoring patients for a range of physical and chemical indicators. For those with abnormalities, timely intervention must be performed to improve the final prognosis of the patients.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

TD—conducted the research and drafted the manuscript. YWZ and ZB—analyzed the data. QH and ZB—reviewed and revised the manuscript. TD and QXQ—designed the study, verified the authenticity of the raw data, and conceptualized the study. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University (approval no. (2024), Ethical Research No. 037). Informed consent was obtained from all patients or their legal surrogates.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Wu SG, Li FY, Lei J, Hua L, He ZY, Zhou J. Histological tumor type is associated with one-year cause-specific survival in women with stage III–IV epithelial ovarian cancer: a surveillance, epidemiology, and end results (SEER) database population study, 2004–2014. Medical Science Monitor. 2020; 26: e920531.

[2] Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. CA: A Cancer Journal for Clinicians. 2019; 69: 280–304.

[3] Vasseur S, Guillaumond F. Lipids in cancer: a global view of the contribution of lipid pathways to metastatic formation and treatment resistance. Oncogenesis. 2022; 11: 46.

[4] Fang Z, He M, Song M. Serum lipid profiles and risk of colorectal cancer: a prospective cohort study in the UK Biobank. British Journal of Cancer. 2021; 124: 663–670.

[5] Li Y, Shang C, Liang H, Zhang K, Wu Y, Guo H. Associations of novel serum lipid index with epithelial ovarian cancer chemoresistance and prognosis. Frontiers in Oncology. 2023; 13: 1052760.

[6] Dong J, Kong L, Wang S, Xia M, Zhang Y, Wu J, *et al.* Oncolytic adenovirus encoding apolipoprotein A1 suppresses metastasis of triple-negative breast cancer in mice. Journal of Experimental & Clinical Cancer Research. 2024; 43: 102.

[7] Wang Y, Wang Y, Chen C, Ren F, Cao R, Wang Y, *et al.* Serum lipid profiling analysis and potential marker discovery for ovarian cancer based on liquid chromatography—mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis. 2021; 199: 114048.

[8] Zhang D, Xi Y, Feng Y. Ovarian cancer risk in relation to blood lipid levels and hyperlipidemia: a systematic review and meta-analysis of observational epidemiologic studies. European Journal of Cancer Prevention. 2021; 30: 161–170.

[9] Onwuka JU, Okekunle AP, Olutola OM, Akpa OM, Feng R. Lipid profile and risk of ovarian tumours: a meta-analysis. BMC Cancer. 2020; 20: 200.

[10] He T, Wang C, Tan Q, Wang Z, Li J, Chen T, *et al*. Adjuvant chemotherapy-associated lipid changes in breast cancer patients: a real-word retrospective analysis. Medicine. 2020; 99: e21498.

[11] Zhao J, Li G, Zhao G, Wang W, Shen Z, Yang Y, *et al*. Prognostic signature of lipid metabolism associated LncRNAs predict prognosis and treatment of lung adenocarcinoma. Frontiers in Oncology. 2022; 12: 986367.

[12] Expert Group of Integrated Cancer Cardiology Branch of National Anti-Cancer Association. Chinese expert consensus on blood lipid management of patients with malignant tumors. Chinese Journal of Oncology. 2021; 43: 1043–1053. (In Chinese)

[13] Markowska A, Kojs Z, Twardawa D, Pietras J, Markowska J. Selected markers of ovarian cancer and their relation to targeted therapy (Review). Experimental and Therapeutic Medicine. 2024; 27: 236.

[14] Goto W, Kashiwagi S, Kamei Y, Watanabe C, Aomatsu N, Ikeda K, *et al*. Relationship between serum lipid levels and the immune microenvironment in breast cancer patients: a retrospective study. BMC Cancer. 2022; 22: 167.

[15] Garg R, Angus E, Fincher S. Capecitabine-induced severe hypertriglyceridaemia and diabetes: a case report and review of the literature. Diabetic Medicine. 2009; 26: 1308–1309.

[16] Saunders RA, Fujii K, Alabanza L, Ravatn R, Kita T, Kudoh K, *et al*. Altered phospholipid transfer protein gene expression and serum lipid profile by topotecan. Biochemical Pharmacology. 2010; 80: 362–369.

[17] Kasiske BL, de Mattos A, Flechner SM, Gallon L, Meier-Kriesche HU, Weir MR, *et al*. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. American Journal of Transplantation. 2008; 8: 1384–1392.

[18] Willemse PM, van der Meer RW, Burggraaf J, van Elderen SG, de Kam ML, de Roos A, *et al*. Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy. Acta Oncologica. 2014; 53: 351–360.

[19] Huang XY, Huang Y, Li P. How do serum lipid levels change and influence progression-free survival in epithelial ovarian cancer patients receiving bevacizumab treatment? Frontiers in Oncology. 2023; 13: 1168996.

[20] Lin F, Zheng R, Yu C, Su Y, Yan X, Qu F. Predictive role of serum cholesterol and triglycerides in cervical cancer survival. International Journal of Gynecological Cancer. 2021; 31: 171–176.

[21] Patel KK, Ksahfi K. Lipoproteins and cancer: the role of HDL-C, LDL-C, and cholesterol-lowering drugs. Biochemical Pharmacology. 2021; 196: 114654.

[22] Lin Q, Liu W, Xu S, Sun L. Associations of preoperative serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels with the prognosis of ovarian cancer. Archives of Gynecology and Obstetrics. 2022; 305: 683–691.

[23] Garrido MM, Marta JC, Ribeiro RM, Pinheiro LC, Guimarães JT. Serum lipids and prostate cancer. Journal of Clinical Laboratory Analysis. 2021; 35: e23705.

How to cite this article: Ting Du, Qiuxia Qu, Yawen Zhang, Qin Huang, Zhen Bian. The effect of postoperative chemotherapy on serum lipids and prognosis in patients with advanced ovarian cancer. European Journal of Gynaecological Oncology. 2024; 45(6): 90-94. doi: 10.22514/ejgo.2024.120.