

# The Clinical Value of Lipid Abnormalities in Cervical Cancer

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## Research article

**Keywords:** Cervical cancer, lipid profile, triglyceride, cholesterol, Prognosis

**Posted Date:** May 13th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-118805/v2>

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# Abstract

**Background:** To describe the characteristic of plasma lipid profile among cervical cancer and further evaluate the prognostic significance of lipid levels in cervical cancer.

**Methods:** We retrospectively reviewed 1,713 patients with cervical cancer in our hospital. Preoperative plasma lipid profile, including cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL), of 1,713 cervical cancer patients were compared with 10,397 healthy women. Then, we evaluated the impact of lipids on overall survival (OS) and recurrence-free survival (RFS) in cervical cancer using univariate and multivariate Cox model.

**Results:** While plasma TC, TG and LDL were significantly higher, HDL was lower in patients with cervical cancer as compared with healthy women. TG was identified as independent predictors for RFS, and OS among patients with cervical cancer. Further stratified by age, patients with higher TG showed a significantly worse RFS and OS compared with those with lower TG among patients  $\geq 50$  years old, but not among  $< 50$  years old.

**Conclusion:** Cervical cancer was associated with a disordered lipid profile. Hypertriglyceridemia was an independent poor prognostic indicator for cervical cancer, especially for elder patients. Strengthening lipid management may be beneficial for improving postoperative OS and RFS in patients with cervical cancer.

## 1. Background

Cervical cancer is the most common gynecologic malignancy with an estimated 596,847 new cases and 311,365 deaths in 2018 worldwide[1]. High-risk subtypes of the human papillomavirus (HPV) infection has been well established as the main cause for cervical carcinoma. In the past decade, the use of screening programs and HPV vaccination program has dramatically reduced the incidence of cervical cancer in developed countries. However, these diseases remain a heavy health burden and a major public health problem in the developing world because of the high incidence and poor prognosis of recurrent disease. Therefore, it is imperative to identify some simple and valuable predictor that could identify high-risk cervical cancer patients, poor progression and prognosis, further facilitating novel treatment strategy and improving clinical outcome.

A large body of evidence has shown a relationship between lipid abnormalities and cancer initiation[2]. Lipids crucially contribute to cell proliferation and tumorigenesis, due to its influence on chemical-energy storage, cellular signaling, cell membranes, and cell-cell interactions[2]. Pre-clinical studies have revealed the ability of adipocytes providing energy for rapid cancer growth and metastasis[3]. A positive correlation was found between serum triglycerides (TG) and risk of endometrial cancer[4]. High levels of total cholesterol (TC) and low density lipoprotein (LDL) increased colorectal cancer risk[5]. Hypertriglyceridemia increased the risk of prostate cancer and promoted the aggressiveness of these disease[6, 7]. With regard to cervical cancer, triglyceride was reported elevated among cervical cancer patients in an India population[8]. However, no significant difference in any lipid parameters was detected

between cervical cancer group and uterine leiomyomas group in a study by Sun et al[9]. Thus, the alterations of plasma lipid profiles in cervical cancer remains a matter of controversy.

Recently, lipid parameters were described as a prognostic factor in various cancers, with contradictory findings. While increased levels of LDL were reported as a negative prognosis in nasopharyngeal carcinoma[10], higher preoperative LDL was related to an improved 5-year RFS of ovarian cancer[11]. Besides, high density lipoprotein (HDL) was a favorable prognostic indicators of lung cancer and breast cancer [12, 13]. So far, the impact of lipid abnormalities in cervical cancer has been poorly investigated. In the current study, we first evaluated the correlation between lipid parameters and cervical cancer, then further explored the prognostic value of preoperative lipid profile in a large population of cervical cancer patients treated with radical hysterectomy, and thus, identified a reliable and convenient predictor.

## 2. Methods

### 2.1 Study population

This study included 1,713 patients with pathologically confirmed uterine cervical carcinoma, who underwent radical hysterectomy between January 2008 and December 2018 at the First Affiliated Hospital of Wenzhou Medical University, China. The following exclusion Criteria was used: (1) Women who received any drugs that impacted lipid metabolism; (2) Patients with chronic diseases that effected lipid levels (i.e., diabetes); 3) Patients received any treatments before serum collection. Information mentioned above was obtained from the electronic medical records. Besides, the control group included 10,397 healthy women. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and informed consent was signed by the patients before taking part in this study. A detailed review of patient history, general physical examination, pelvic examination (including bimanual pelvic and rectal examinations), preoperative laboratory (plasma lipid profiles, and SCC-Ag ), pathological data (metastasis, stage, and differentiation) of all patients were collected from electronic medical records and reviewed. Detailed clinical data were collected within one week before operation. Preoperative plasma levels of HDL, LDL, TC, TG, and serum squamous cell carcinoma antigen (SCC-Ag) were measured in early morning before surgical operation and immediately measured using a Hitachi 7600-020 automatic biochemical analyzer with the kinetic method [11]. Body mass index (BMI) was calculated as  $\text{body-weight(kg)/height(m)}^2$ .

All of 1,713 cervical cancer patients were classified as high-risk, intermediate-risk, and low-risk after postoperative pathological evaluation. High-risk patients defined as the presence of tumor involvement of the parametria, positive margins, or lymph node metastases [14]. Intermediate risk factors included depth of invasion, lymphovascular space invasion, and tumor size [15]. Patients without high and intermediate risk factors are defined as low-risk.

Besides, we collected age, BMI, plasma levels of HDL, LDL, TC, TG from 10,397 healthy women as control. Given that lipid levels were affected by confounders such as age and BMI, we matched the

healthy women group and the cervical cancer group with age, with every 10 years as a subgroup. Then, by randomly matching the healthy control group and the cancer group with a ratio of 2: 1, we obtained 3,426 healthy women. We then controlled the potential confounders (age and BMI) by regression analysis and analyzed the difference of lipid levels between healthy group and cancer group.

Follow-up examinations were performed every 3 months in the first 2 years, and then every 6 months for the next 3 years and every 1 year thereafter. Pelvic examination, cytology, the serum concentration of SCC-Ag, and imaging studies including Computed Tomography, Magnetic Resonance Imaging, or Positron Emission Tomography-Computed Tomography, were performed during routine follow up.

The last follow-up date was July 15, 2019. The end points of this study were overall survival (OS) and recurrence-free survival (RFS). Overall survival was determined from the date of surgery to death or last follow-up. Recurrence-free survival (RFS) was calculated from the date of surgery to the tumor recurrence or distant metastasis.

## 2.2 Statistical analysis

Continuous data were presented as median (Q1-Q3) or mean  $\pm$  standard deviation based on their distribution. and then difference between groups were tested using the Wilcoxon rank-sum test or a standard t test. Categorical data were analyzed using Fisher's exact test or  $\chi^2$  test. The Kaplan-Meier method was used to calculate survival estimates for OS and RFS. Univariate and multivariate Cox regression analyses were used to evaluate the associations between clinical covariates and survival. A two-tailed  $P < 0.05$  was considered statistically significant. Analyses were performed using R(version 3.3).

## 3. Results

### 3.1 Characteristics of cervical cancer

Clinical and pathologic characteristics of cervical cancer were summarized in Table 1. This study included 1,713 cervical cancer patients. The median age at diagnosis was 52 years (range: 22–82 years) and the median BMI was 23.24 (19.95, 26.53). The most common histological type was squamous cell carcinoma (85.9%), followed by adenocarcinoma (9.0%). All of patients were diagnosed with FIGO stage I-II. Tumor sizes in 221 patients (22.9%) were  $\geq 4$ cm, 560 (58.3%) were 2-4cm, and 181 (18.8%) were  $< 2$ cm. In addition, 274 patients showed lymph node metastasis, 342 cases were lymphovascular space invasion and 40 patients were parametrial involvement. Based on pathology after radical hysterectomy, there were 319 (18.6%) patients with high risk factors, 643 (37.5%) patients with intermediate risk factors.

Table 1  
The baseline patients' characteristics

Parameter	No.(%)	Q2(Q1, Q3)
Age (years)	1713	52(45, 60)
Tumor subtype		
Squamous	1472 (85.9%)	
Adenocarcinoma	154(9.0%)	
Other	87(5.1%)	
FIGO stage		
I	987(57.6)	
II	726(42.4)	
Tumor size		
≥ 4cm	221 (23.1%)	
2-4cm	560(58.2%)	
< 2cm	181(18.8%)	
Differentiation		
I-II	1344(93.0%)	
III	101(7.0%)	
Lymph node Metastasis		
No	1397(83.6%)	
Yes	274(16.4%)	
Lymphovascular space invasion		
No	1328(79.5%)	
Yes	342(20.5%)	
Parametrial involvement		
No	1665(97.7%)	
Yes	40(2.3%)	
Infiltration depth		

Abbreviations: No. = number of patients; SCC-Ag = serum squamous cell carcinoma antigen; TC = total cholesterol; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Parameter	No.(%)	Q2(Q1, Q3)
< 1/3	573(33.6%)	
$\geq 1/3 < 2/3$	348(20.4%)	
$\geq 2/3$	783(46.0%)	
SCC(Pre-O) (U/mL)	1434	1.4(0.9, 3.4)
TC (mmol/L)	1502	5.08(4.41, 5.84)
TG (mmol/L)	1500	1.49(1.03, 2.24)
HDL (mmol/L)	1457	1.26(1.08, 1.48)
LDL (mmol/L)	1455	2.92(2.42, 3.52)

Abbreviations: No. = number of patients; SCC-Ag = serum squamous cell carcinoma antigen; TC = total cholesterol; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density lipoprotein

## 3.2 Lipid profile in healthy women and patients with cervical cancer

In 1,713 patients with cervical cancer, the median preoperative levels of TC, TG, LDL and HDL were 5.08(4.41, 5.84), 1.49(1.03, 2.24), 2.92(2.42, 3.52), and 1.26(1.08, 1.48) mmol/L, respectively. Figure 1 showed the comparisons of plasma lipid levels between healthy women and patients with cervical cancer. While plasma levels of TC, TG, and LDL were significantly higher, plasma HDL levels were significantly lower among patients with cervical cancer as compared with healthy women (Fig. 1A).

Given that age may influence lipid levels, all the individuals were further divided into young (< 50 years) and old groups ( $\geq 50$  years). Similarly, patients with cervical cancer showed higher TC, TG, and LDL levels, and lower HDL as compared with healthy women both in young and old groups (Fig. 1B). Subsequently, we matched the healthy group and the cancer group with age, with every 10 years as a subgroup. Then, by randomly matching the healthy group and the cancer group with a ratio of 2: 1, we obtained 3,426 healthy women. Patients with cervical cancer showed higher TC, TG, and LDL levels, and lower HDL levels than healthy women (Supplementary Fig. 1). The difference of lipid levels, including TC, TG, LDL and HDL, between healthy group and cancer group remained statistically significant after further adjustment for age and BMI ( $P < 0.001$ ,  $P = 0.001$ ,  $P < 0.001$ ,  $P = 0.008$ , respectively). Thus, compared with healthy women, patients with cervical cancer were coupled to a disordered lipid profile characterized by higher TG, TC and LDL levels, and lower HDL levels.

## 3.3 Lipid Profile Levels and survival

Following-up was available for 1,499 cervical cancer patients. With a median follow-up of 4.76 (2.40, 8.21) years, 156 patients (10.41%) suffered relapse and 102 patients (6.80%) deceased.

Initially, univariate analyses were employed to depict the prognostic value of clinicopathological features among patients with cervical cancer. As expected, the factors that were statistically significant in predicting poor RFS as well as OS were positive lymph node metastasis, parametrial involvement, late FIGO stage, positive lymphovascular space invasion, deeper infiltration depth, large tumor size and increased pre-operative level of SCC-Ag (Table 2).

Table 2  
Univariate Cox regression analysis of clinical characteristics regarding RFS and OS

Parameter	Classify	RFS	P	OS	P
		HR (95%CI)		HR (95%CI)	
Age	≥50year vs. <50year	1.17(0.84–1.62)	0.355	1.75(1.15–2.66)	0.008*
Tumor size	≥ 2cm vs. <2cm	1.85(0.99–3.47)	0.056	2.98(1.07–8.26)	0.036*
	≥ 4cm vs. <4cm	1.8(1.16–2.82)	0.009*	1.81(1.01–3.26)	0.048*
FIGO stage	II vs. I	2(1.44–2.79)	< 0.001*	2.23(1.48–3.36)	< 0.001*
Lymph node Metastasis	Yes vs. No	3.75(2.69–5.24)	< 0.001*	4.21(2.81–6.32)	< 0.001*
Lymphovascular space invasion	Yes vs. No	2.36(1.67–3.33)	< 0.001*	2.16(1.41–3.3)	< 0.001*
Differentiation	III vs. I-II	0.44(0.16–1.18)	0.101	0.5(0.16–1.57)	0.235
Tumor subtype	Adenocarcinoma vs. Squamous	1.28(0.74–2.24)	0.378	1.51(0.8–2.84)	0.205
Parametrial involvement	Yes vs. No	3.96(2.19–7.16)	< 0.001*	4.55(2.21–9.39)	< 0.001*
Depth of cervical stromal invasion	≥ 1/3 vs. <1/3	3.01(1.94–4.68)	< 0.001*	2.78(1.65–4.7)	< 0.001*
SCC-Ag	> 1.5 ug/L vs. ≤1.5 ug/L	2.02(1.43–2.85)	< 0.001*	1.9(1.22–2.96)	0.004*
Abbreviations: RFS = recurrence-free survival; OS = overall survival; SCC-Ag = serum squamous cell carcinoma antigen					
*:P<0.05					

Next, we explored the prognostic value of the lipid profile among patients with cervical cancer. Cut-off was determined according to the medium lipid levels of 1,499 cervical cancer patients. Patients were

divided into “low” and “high” according to the comparisons between lipid profile levels with established cut-offs. Table 3 showed the RFS and OS of the patients included in the study according to TC, TG, LDL and HDL levels. As shown in Table 3, patients with high TG levels had a significantly worse RFS than those with low TG levels both in univariate and multivariate Cox model. However, null association was detected between TC/LDL/HDL and RFS of cervical cancer.

Table 3  
Univariate Cox regression analysis and Multivariate Cox regression analysis of lipid profile regarding Recurrence-Free Survival and Overall survival

Parameter	Univariate analysis		Multivariate analysis <sup>#</sup>	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
RFS	1.24(1.00-1.30)	0.058		
TC	1.15(1.04–1.26)	0.005*	1.12(1.02–1.31)	0.033*
TG	0.75(0.43–1.29)	0.293		
HDL	1.02(0.86–1.17)	0.964		
LDL				
OS	1.21(1.03–1.42)	0.024*	1.12(0.83–1.50)	0.462
TC	1.18(1.06–1.31)	0.002*	1.23(1.08–1.40)	0.025*
TG	0.86(0.44–1.69)	0.67		
HDL	1.04(0.88–1.23)	0.624		
LDL	1.24(1.00-1.30)	0.058		
Abbreviations: RFS: recurrence-free survival; OS: overall survival; TC = total cholesterol; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density lipoprotein				
<sup>#</sup> : Adjusted for age, FIGO stage, lymph node metastasis, parametrial involvement, lymphovascular space invasion, infiltration depth, tumor size and increased pre-operative level of SCC-Ag.				
*: <i>P</i> < 0.05				

With regard to OS, the univariate analysis revealed that increased TC and TG levels were significant correlation with a poor OS of cervical cancer. Further multivariate analysis showed increased levels of TG related to a significantly unfavorable OS of cervical cancer. Higher TC group had a trend towards higher HRs for OS compared with the lower group; however, *P*-values were 0.462. Nevertheless, HDL and LDL levels have no effect on OS (HR: 0.86; 95%CI: 0.44–1.69; *P*: 0.67; HR: 1.04; 95%CI: 0.88–1.23; *P*: 0.624, respectively) (Table 3). The Kaplan–Meier curves for RFS and OS of the two groups (high TG levels vs low TG levels) were further illustrated in Fig. 2.

Since lipid levels were commonly associated with age, all the individuals were further divided into two groups according to age (< 50 years vs. ≥50 years). Stratified by age, interestingly, no significant association was detected between lipid profile and RFS/OS of cervical cancer among patients < 50 years old. Nevertheless, patients with higher TG had a significantly worse RFS and OS than those with lower TG among patients ≥ 50 years old (Table 4).

Table 4

**Univariate Cox regression analysis of lipid profile regarding Recurrence-Free Survival and Overall survival stratified by age**

Parameter	RFS		OS	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
Young group (< 50 years)				
TC	1.14(0.89–1.47)	0.306	1.24(0.88–1.76)	0.218
TG	1.02(0.80–1.30)	0.863	1.14(0.85–1.53)	0.380
HDL	1.31(0.62–2.76)	0.485	1.34(0.46–3.88)	0.595
LDL	0.99(0.79–1.24)	0.913	1.03(0.80–1.33)	0.808
Old groups (≥ 50years)				
TC	1.13(0.95–1.35)	0.169	1.12(0.92–1.37)	0.252
TG	1.17(1.05–1.29)	0.003*	1.15(1.02–1.30)	0.026*
HDL	0.46(0.21-1.00)	0.050	0.71(0.30–1.66)	0.426
LDL	1.01(0.80–1.28)	0.930	1.01(0.78–1.32)	0.929
Abbreviations: RFS: recurrence-free survival; OS: overall survival; TC = total cholesterol; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density lipoprotein				
*: <i>P</i> < 0.05				

Cervical cancer patients with high-risk factors showed worse prognosis as comparing with patients with intermediate-risk or low-risk factor, we further analyzed patients with high-risk factors. As shown in Fig. 3 and Fig. 4, higher level of TG was an independent poor prognostic factor among cervical cancer patients with high risk (Fig. 3, Fig. 4).

## 4. Discussion

In this study, we explored the clinical signification of lipids profile among cervical cancer patients, and made several important discoveries. Firstly, we comprehensively investigated the difference in serum lipid levels between healthy women and patients with cervical cancer using a relative large number of population, and demonstrated that TC/TG/LDL were elevated, and HDL were decreased in patients with

cervical cancer. These results suggest dyslipidemia could be correlation with cervical cancer. Secondly, to our knowledge, this is the first report to evaluate the prognostic value of lipids profile in cervical cancer. Our study showed that hyperlipidemia was an independent prognostic factor for both RFS and OS among patients with cervical cancer.

Lipids are essential components of cell membranes, lipid metabolism essentially contributes to tumor cell bioenergetics and biomass formation[16]. Cholesterol and triglycerides are the two main lipids in plasma[17]. LDL and HDL are lipoproteins responsible for cholesterol transportation. While the LDL lead cholesterol to the cells and facilitate the deposition of fat in the vessel, the HDL is on the opposite promotes the removal of excess cholesterol[17]. Epidemiological studies, despite being controversial, reported the correlation between plasma triglyceride levels and the risk for cancer. Higher levels of triglyceride was associated with increased risk of lung, thyroid cancer, renal cancer, prostate cancer, gynecological cancer in a large cohort study in Austria[18]. Similarly, triglycerides were reported to increase the risk for cervix cancer in females, and colon and thyroid cancer in males in a cohort of 22,946 Icelanders[19]. Conversely, lower triglyceride (< 1.70 mmol/L) was related to an evaluated cancer risk in Chinese type 2 diabetes mellitus patients[20]. Our observation of higher lipid prolife in cervical cancer was similar to a previous cohort study among Icelanders, which regarded triglycerides as a positive risk factor for cervix cancer[19]. Further evidence for a relationship with triglyceride comes from India[8]. Raju et al reported TG was elevated in cervical cancer as comparing to healthy control[8]. Therefore, cervical cancer are coupled to a disordered lipid profile characterized by higher TG, TC and LDL levels, and lower HDL levels. Dyslipidemia could be associated with cervical cancer.

Our current study further explored the prognostic value of hyperlipidemia at diagnosis in cervical cancer. We provided first evidence that higher plasma triglyceride levels correlated to a worse RFS as well as OS among patients with cervical cancer. This observation was consistent with previous studies in prostate cancer and breast cancer. Elevated serum triglycerides increased the risk of prostate cancer recurrence [21]. Hypertriglyceridemia was correlation with a decreased 5-year OS among patients with triple negative breast cancer [22]. In a recently published, monocentric, retrospective study, Vernieri et al reported higher plasma triglyceride levels correlated with lower progression-free survival in everolimus-treated patients with advanced pancreatic neuroendocrine tumors[23]. These findings, coupled with evidence that adipocytes provided energy for rapid cancer growth and metastasis in vivo and in vitro[3], indicate that increased utilize of extracellular lipids, or their de novo synthesis, could increase the recurrence risk and result into poor clinical outcomes among cervical cancer. Therefore, we recommend lipid management for patients with cervical cancer, especially those have hyperlipidemia. Accordingly, lipid profile was recommended routinely evaluated during follow-up

Stratification by age revealed a negative association between hypertriglyceridemia and prognosis in patients  $\geq 50$  years old rather than in patients < 50 years old, suggesting hypertriglyceridemia was associated with poor outcomes of cervical cancer patients, especially for elder patients. Sub-analysis for cervical cancer patients with high-risk factor, showed that higher level of TG was an independent poor

prognostic factor for this population. These sub-analysis further supported preoperative lipid profile as a promising prognostic predictor in cervical cancer by controlling the confounding data.

Our study has some limitations. As a retrospective study, it was limited availability of collecting the change of lipid profile during follow-up. This is because serum lipid profile was not routinely evaluated in all patients during follow-up. A prospective randomized study evaluating the survival benefits of controlling lipids in primary cervical cancer is warranted.

## **5. Conclusions**

In conclusion, a disordered lipid profile characterized by higher TG, TC and LDL levels, and lower HDL levels could be associated with cervical cancer. TG exerted unfavorable influence either on RFS or on OS of cervical cancer. Hypertriglyceridemia was an independent negative prognostic predictor for cervical cancer. This simple and routinely tested parameters may be a convenient prognostic candidate for cervical cancer in clinic. Strengthening lipid management may be beneficial for improving postoperative OS and RFS in patients with cervical cancer.

## **Abbreviations**

HPV: human papillomavirus; TG: triglycerides; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; SCC-Ag: serum squamous cell carcinoma antigen; OS: overall survival; RFS: recurrence-free survival; BMI: body mass index.

## **Declarations**

### **–Acknowledgments**

We would like to thank all doctors, nurses, patients, and their family members for their kindness to support our study.

### **–Consent for publication**

Not Applicable.

### **–Ethics approval and consent to participate**

This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and informed consent was signed by the patients before taking part in this study. All patients agreed to use their clinical data for clinical research before being hospitalized.

### **–Competing interests**

The authors declare that they have no competing interests.

## -Availability of data and materials

Available under request.

## -Authors' contributions:

HZ conception and design the study;. AL, WW, LW acquisition of data, AL, MJ and YS analysis of data; AL drafting the manuscript; HZ revising this manuscript. All authors read and approved the final manuscript.

## -Funding information:

Not Applicable.

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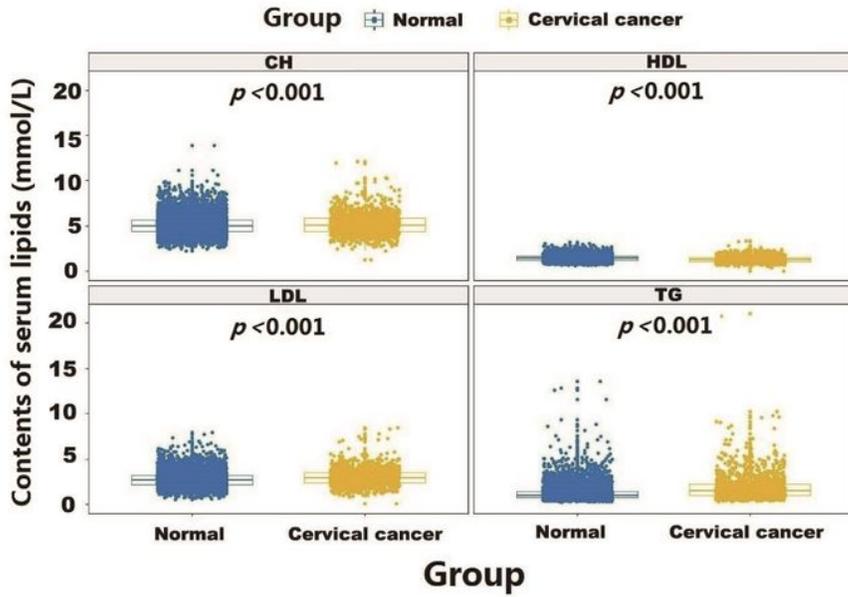
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## Figures

A



B

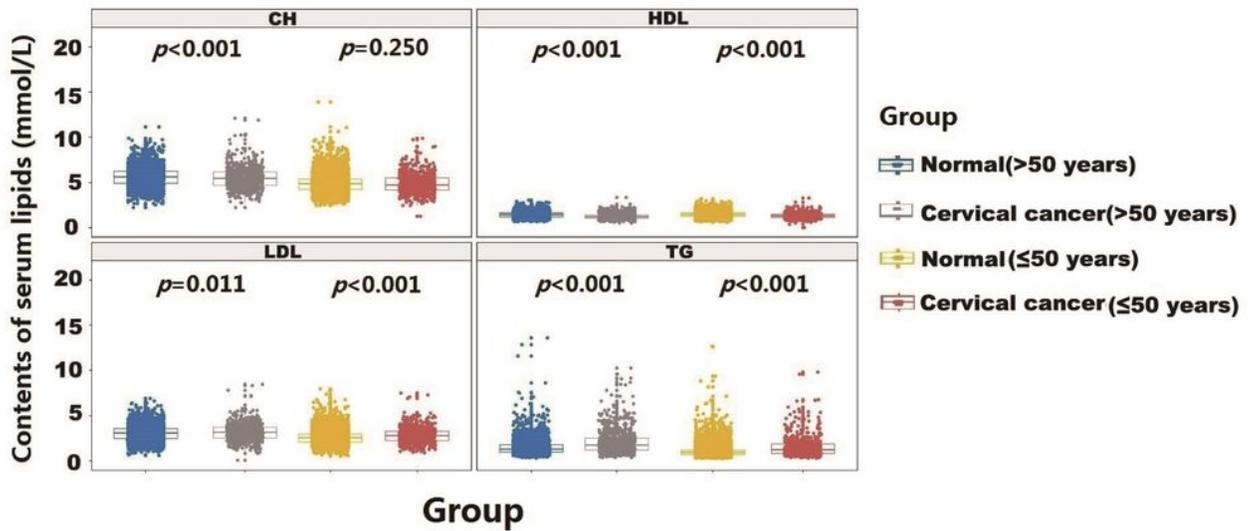
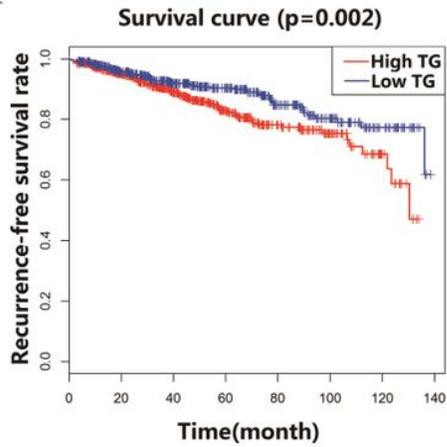


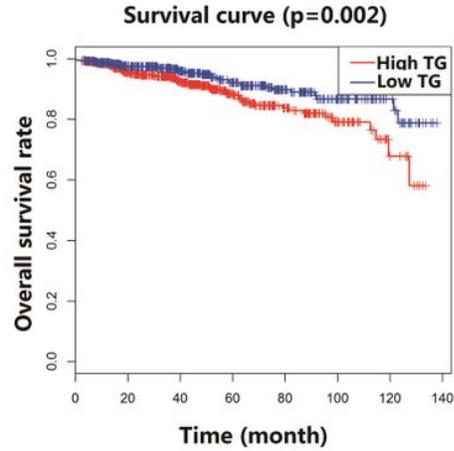
Figure 1

(A) Comparison of plasma lipid profile levels between healthy women and cervical cancer patients. (B) Comparison of plasma lipid profile levels between healthy women and cervical cancer patients stratified by age. Normal: healthy women.

A

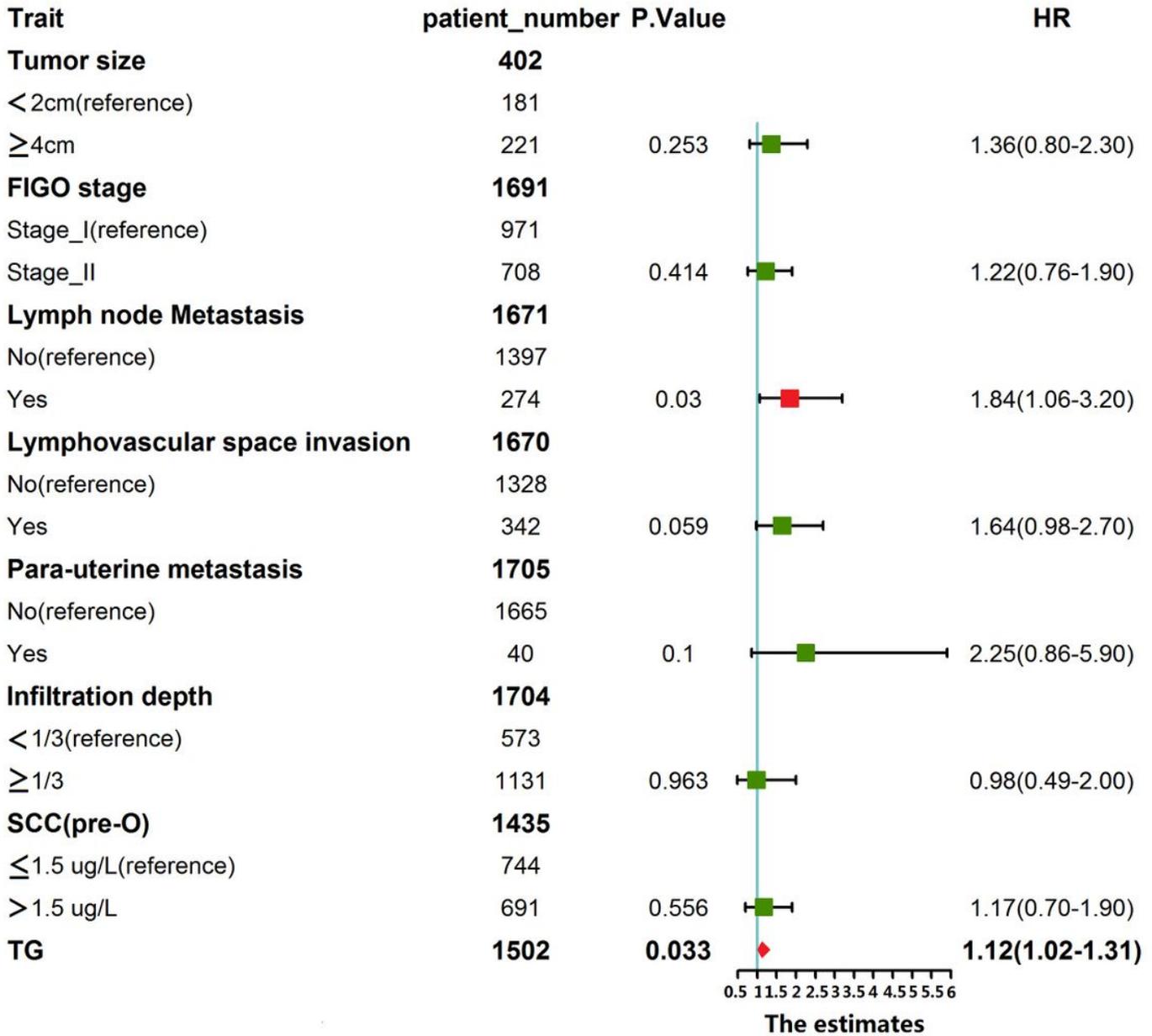


B



**Figure 2**

Kaplan-Meier curves for recurrence-free survival (A) and overall survival (B) of patients with cervical cancer according to TG levels. Patients were stratified into high and low groups according to the cut-off value of 1.49 mmol/L. High TG levels are associated with a poor RFS as well as OS of cervical cancer. P values were estimated using log-rank test.



**Figure 3**

Multivariate analyses of recurrence-free survival of cervical cancer patients with high-risk factor. P values were estimated using log-rank test.

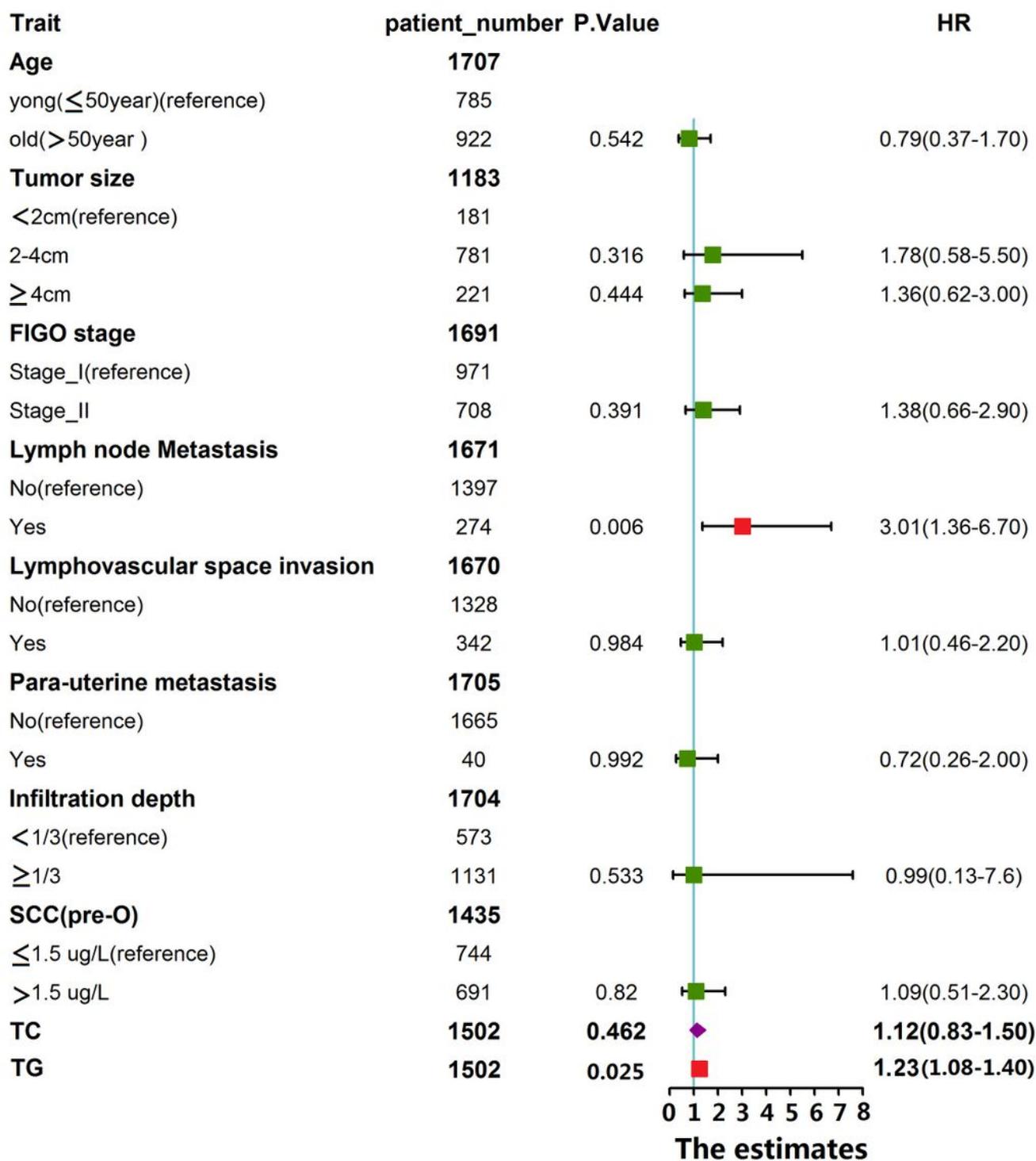


Figure 4

Multivariate analyses of overall survival of cervical cancer patients with high-risk factor. P values were estimated using log-rank test.

## Supplementary Files

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