International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Dynamics of Conventional Metabolic Indices in Relation to Endometriosis Severity: A Retrospective Analysis

Xiaolin Zhong[1,*], Weihong Lu[1,*], Qi Zhang[1], Jie Dong[1], Hongyang Xiao[2], Ruiqin Tu[2]

[1]Department of Gynecology, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 366100, People's Republic of China; [2]Department of Gynecology, Zhongshan Hospital, Fudan University, Shanghai, 200035, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hongyang Xiao; Ruiqin Tu, Department of Gynecology, Zhongshan Hospital, Fudan University, No. 180, Fenglin Road, Xuhui District, Shanghai, 200035, People's Republic of China, Tel +86-592-3568682, Email xhy2024521@163.com; xiao.hongyang@zs-hospital.sh.cn; tu.ruiqin@zs-hospital.sh.cn

Objective: This study aims to investigate the association between the dynamics of routine metabolic markers and endometriosis severity.

Methods: A retrospective analysis was conducted on patients diagnosed with endometriosis at Zhongshan Hospital, Xiamen, affiliated with Fudan University. The collected data encompassed demographic details and biochemical indicators related to lipid, hepatobiliary, renal metabolism, and electrolyte balance. Independent influencing factors were screened by univariate logistic regression and statistically significant variables were included in the model for adjustment. Restricted cubic spline (RCS) models were also plotted to analyze the nonlinear relationship between factors and endometriosis severity. The receiver operating characteristic (ROC) curve was used to validate the discriminative ability of independent influencing factors.

Results: Ninety-four patients were enrolled in the study, including 32 at stage IV as classified by the American Society for Reproductive Medicine (ASRM) staging. Univariate analysis identified fasting blood glucose (FBG), total protein, direct bilirubin, total bilirubin (TBil) and glutamic-pyruvic transaminase (ALT) as significant metabolic indicators. Additionally, carbohydrate antigen 125 (CA125) and human epididymal protein 4 (HE4) emerged as significant covariates. The RCS analysis revealed a nonlinear association between most metabolic indicators and outcome measures. ROC curve analysis showed that the area under the curve (AUC) of the alanine transaminase (ALT) was above 0.6.

Conclusion: ALT had a negative correlation with the severity of endometriosis and was an independent influencing factor with statistical significance. This finding could offer clinicians non-invasive biomarkers for early detection and precise monitoring of disease progression.

Keywords: endometriosis, metabolic, American Society for Reproductive Medicine staging

Introduction

Endometriosis, a chronic inflammatory disorder characterized by the presence of endometrial-like tissue ectopic to the uterus, is linked to pelvic pain and infertility.[1,2] It is estrogen-dependent, prevalent during the reproductive years, and affects 5–15% of women globally.[3,4] This disorder poses a serious public health problem and economic strain.[5] According to Ballweg et al, the average wait time for a final diagnosis of endometriosis is nine years.[6] There is growing evidence that endometriosis raises the risk of several pregnancy-related complications, including premature placental abruption, retained placenta, premature rupture of membranes, pre-eclampsia, pregnancy-induced hypertension, gestational diabetes mellitus, gestational cholestasis, antepartum and postpartum hemorrhages, labor dystocia, stillbirth, neonatal deaths, and uterine congenital abnormalities.[7] In a few cases, endometriosis can undergo malignant transformation, with ovarian cancer being the most frequent malignancy associated with the disease.[8–10]

Received: 22 May 2025
Accepted: 20 August 2025
Published: 4 September 2025

Deep endometriotic lesions have the potential to infiltrate nerves[11] and lymph nodes,[12] causing heightened negative effects on the body. However, research on the severity of endometriosis is currently limited. Existing studies have identified advancing age,[13] concomitant autoimmune diseases, and the frequency of laparoscopic operations as predictors of endometriosis severity.[14] To date, a few studies have explored the correlation between patients' metabolic profiles and the severity of their endometriosis. The liver plays a central role in regulating systemic metabolism, including glucose homeostasis. Dysregulation in liver function can lead to imbalances in metabolic pathways that influence inflammation and immune responses, both of which are implicated in the development and progression of endometriosis.[15] Additionally, altered glucose metabolism can affect energy availability and cellular function in endometrial tissue, potentially contributing to the survival and growth of ectopic endometrial implants.[16] Thus, understanding these metabolic connections may provide insights into the underlying mechanisms of endometriosis.

In this study, we aimed to investigate the correlation between metabolic indicators and the severity of endometriosis using both univariate and multivariate logistic regression analyses. Additionally, restricted cubic spline modeling was applied to examine nonlinear relationships. This research may provide valuable early diagnostic markers and therapeutic strategies for severe endometriosis.

Materials and Methods

Research Cohort and Profile

This study retrospectively collected patients diagnosed with endometriosis by laparoscopy or laparotomy based on histological confirmation in Zhongshan Hospital (Xiamen), Fudan University from January 2018 to August 2022. Patients were excluded from the study if they presented with abnormal metabolic markers, hypertension, diabetes, hyperlipidemia, liver or gallbladder diseases, autoimmune diseases, a history of uterine surgery or pregnancy, hormone therapy, or if there was any missing information. The collected variables included covariates and indicators reflecting patient lipid metabolism, hepatobiliary metabolism, renal metabolism, and electrolyte metabolism. Covariates included age, body mass index (BMI), carbohydrate antigen 125 (CA-125), human epididymis protein 4 (HE4). Metabolic indicators included apolipoprotein A, apolipoprotein B, fasting blood glucose, serum albumin, serum total protein, direct bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase, prealbumin, urea, creatinine, glomerular filtration rate, uric acid, sodium, potassium, chloride, CO2, total cholesterol, triglycerides, HDL, and LDL. All laboratory data were collected within 3 days of the end of the patient's menstrual period. ASRM staging data for endometriosis were collected from patients, with all diagnoses confirmed through pathological examination. This study was performed in accordance with the declaration of Helsinki and was approved by the ethics committee of Xiamen Hospital, Zhongshan Hospital, Fudan University.

Statistical Analysis

Categorical variables were described using frequency and percentage (%), with the chi-square test was used to compare the differences between the two groups. Continuous variables were tested for normality. Continuous variables with normal distribution were described using mean and standard deviation (Mean (SD)), and group differences were compared using a *t*-test. However, non-normally distributed continuous variables were described using medians and quartiles (Median [IQR]), and the differences between the two groups were compared using the rank sum test. Independent factors influencing endometriosis severity were ascertained by univariate logistic regression. Notably, according to the results of univariate regression and stepwise regression combined with factors that were known or suspected to be related to endometriosis severity, we finally determined the variable selection in multivariate models. Moreover, restricted cubic spline models were developed to analyze the nonlinear relationship between metabolic indicators and outcomes. A nomograph was drawn to visualize the independent influencing factors, and the ROC curve was used to verify the discriminative ability of the independent influencing factors. All statistical analyzes were performed using R 4.2.1 (https://www.r-project.org), and a double trailed P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

In accordance with the patient inclusion criteria, this study included a total of 94 endometriosis patients, 32 of whom were diagnosed with ASRM stage IV. The mean age of all patients was 34.85 years old, with the ASRM stage IV patients having a mean age of 36.81 years. Table 1 offers a comprehensive summary of the demographic and clinical characteristics of the patients.

Influence of Metabolic Indicators on the Severity of Endometriosis

To analyze the effect of different levels of metabolic indicators on outcome indicators, we categorized metabolic indicators according to their quartiles and included them in logistic regression for analysis in the form of both continuous and categorical variables. The results of the univariate logistic regression showed that FBG (OR [95% CI]: Q4: 3.5 [1.093, 11.974], continuous: 3.422[1.116, 11.539]), total protein (OR [95% CI]: continuous: 1.094[1.012, 1.198]), direct bilirubin (OR [95% CI]: Q4: 0.176[0.035, 0.683], continuous: 0.645[0.402, 0.972]), TBil (OR [95% CI]: Q4: 0.278 [0.073, 0.933]) and ALT (OR [95% CI]: Q4: 0.239[0.049, 0.888]) were statistically significant in relation to the severity of endometriosis (Table 2).

Table 1 The Characteristics of All Patients

Characteristics	ASRM Staging I/II/III	ASRM Staging IV	P-value
n	62	32	
Age (mean (SD))	34.85 (7.00)	36.81 (8.42)	0.234
CA125	48.78 [31.12, 69.22]	72.94 [35.71, 127.00]	0.020
HE4	47.65 [42.31, 55.56]	47.72 [38.33, 54.10]	0.346
Apolipoprotein A (g/L)	1.32 [1.28, 1.39]	1.37 [1.29, 1.43]	0.094
Apolipoprotein B (g/L)	0.85 [0.74, 0.89]	0.89 [0.77, 0.98]	0.140
FBG	4.88 [4.70, 5.00]	4.95 [4.77, 5.43]	0.100
Albumin (g/L)	45.00 [42.25, 47.00]	45.00 [43.75, 48.00]	0.289
Total protein (g/L)	71.00 [67.25, 74.00]	72.50 [69.00, 77.00]	0.094
Direct bilirubin (μmol/L)	3.40 [2.73, 4.27]	2.75 [2.48, 3.42]	0.022
TBil (μmol/L)	8.40 [6.40, 10.55]	7.25 [5.75, 8.07]	0.022
ALT (U/L)	12.00 [10.00, 16.00]	11.00 [8.00, 12.00]	0.049
AST (U/L)	16.00 [14.00, 18.00]	14.50 [13.00, 17.00]	0.145
ALP (U/L)	53.00 [44.25, 59.00]	52.50 [45.75, 65.50]	0.500
γ-GT (U/L)	13.00 [11.00, 17.00]	13.00 [11.00, 17.25]	0.764
LDH (U/L)	151.50 [138.00, 171.25]	166.00 [148.75, 175.50]	0.063
Prealbumin (g/L)	0.21 [0.19, 0.23]	0.21 [0.18, 0.23]	0.758
Urea (mmol/L)	4.25 [3.23, 4.97]	4.05 [3.45, 5.03]	0.734
Creatinine (μmol/L)	58.40 (8.65)	58.09 (8.38)	0.868
GFR (mL/min/1.73 m^2)	112.66 (11.51)	111.81 (12.80)	0.746
Uric Acid (μmol/L)	279.00 [226.00, 320.25]	266.00 [241.75, 306.25]	0.914
Sodium (mmol/L)	140.00 [139.00, 141.00]	140.00 [139.00, 141.00]	0.607
Potassium (mmol/L)	4.00 [3.80, 4.10]	4.05 [3.90, 4.20]	0.155
Chlorine (mmol/L)	104.00 [102.00, 105.00]	104.00 [102.00, 105.00]	0.955
CO2 (mmol/L)	24.84 (1.79)	24.59 (2.01)	0.548
Total cholesterol (mmol/L)	4.37 [3.95, 4.61]	4.43 [4.01, 4.69]	0.273
Triglyceride (mmol/L)	0.99 [0.82, 1.15]	1.10 [0.85, 1.31]	0.205
HDL (mmol/L)	1.47 [1.36, 1.57]	1.50 [1.44, 1.57]	0.222
LDL (mmol/L)	2.40 [2.25, 2.61]	2.57 [2.21, 2.78]	0.161
BMI	21.02 [19.59, 22.51]	21.39 [19.15, 23.19]	0.658

Notes: The data were presented as mean (standard deviation) or median [interquartile range].
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyltransferase; LDH, lactate dehydrogenase; GFR, Glomerular filtration rate; HDL, high-density lipoprotein; LDL, Low-density lipoprotein; BMI, body mass index.

https://doi.org/10.2147/IJGM.S537848

Table 2 The Results of the Univariate Analysis

Characteristics			OR [95% CI]	P-value
Metabolic markers	Apolipoprotein A (continuous)		10.696[0.426, 468.785]	0.1789
	Apolipoprotein A	Q1	–	–
		Q2	0.675[0.170, 2.521]	0.5605
		Q3	1.295[0.377, 4.533]	0.6800
		Q4	2.429[0.754, 8.311]	0.1437
	Apolipoprotein B (continuous)		5.096[0.413, 82.358]	0.2145
	Apolipoprotein B	Q1	–	–
		Q2	1.295[0.377, 4.533]	0.6800
		Q3	0.511[0.117, 2.000]	0.3448
		Q4	2.870[0.893, 9.876]	0.0828
	FBG (continuous)		3.422[1.116, 11.539]	**0.0372**
	FBG	Q1	–	–
		Q2	1.105[0.342, 3.574]	0.8657
		Q3	0.808[0.185, 3.130]	0.7625
		Q4	3.500[1.093, 11.974]	**0.0387**
	Albumin (continuous)		1.083[0.959, 1.233]	0.2107
	Albumin	Q1	–	–
		Q2	2.352[0.717, 7.974]	0.1599
		Q3	1.327[0.366, 4.684]	0.6595
		Q4	1.725[0.544, 5.589]	0.3541
	Total protein (continuous)		1.094[1.012, 1.198]	**0.0399**
	Total protein	Q1	–	–
		Q2	1.150[0.324, 3.907]	0.8237
		Q3	0.863[0.249, 2.817]	0.8085
		Q4	2.091[0.675, 6.633]	0.2021
	Direct bilirubin (continuous)		0.645[0.402, 0.972]	**0.0492**
	Direct bilirubin	Q1	–	–
		Q2	0.571[0.174, 1.804]	0.3444
		Q3	0.444[0.138, 1.359]	0.1608
		Q4	0.176[0.035, 0.683]	**0.0189**
	TBil (continuous)		0.853[0.718, 0.991]	0.0513
	TBil	Q1	–	–
		Q2	0.769[0.245, 2.374]	0.6483
		Q3	0.222[0.053, 0.788]	0.0265
		Q4	0.278[0.073, 0.933]	**0.0453**
	ALT (continuous)		0.918[0.826, 1.001]	0.0756
	ALT	Q1	–	–
		Q2	1.163[0.411, 3.298]	0.7746
		Q3	0.339[0.068, 1.314]	0.1416
		Q4	0.239[0.049, 0.888]	**0.0467**
	AST (continuous)		0.941[0.826, 1.056]	0.3234
	AST	Q1	–	–
		Q2	0.412[0.12, 1.327]	0.1437
		Q3	0.350[0.104, 1.109]	0.0800
		Q4	0.462[0.125, 1.585]	0.2274
	ALP (continuous)		1.020[0.988, 1.055]	0.2284
	ALP	Q1	–	–
		Q2	1.195[0.369, 3.928]	0.7654
		Q3	0.664[0.169, 2.422]	0.5400
		Q4	1.635[0.506, 5.438]	0.4133

(*Continued*)

Table 2 (Continued).

Characteristics			OR [95% CI]	P-value
	γ-GT (continuous)		1.004[0.961, 1.045]	0.8347
	γ-GT	Q1	–	–
		Q2	2.100[0.593, 7.503]	0.2463
		Q3	0.988[0.304, 3.103]	0.9839
		Q4	1.477[0.462, 4.695]	0.5059
	LDH (continuous)		1.013[0.997, 1.029]	0.1085
	LDH	Q1	–	–
		Q2	0.463[0.106, 1.796]	0.2753
		Q3	2.870[0.893, 9.876]	0.0828
		Q4	1.495[0.429, 5.324]	0.5271
	Prealbumin (continuous)		5.877[0, 361,026.273]	0.7498
	Prealbumin	Q1	–	–
		Q2	0.844[0.268, 2.581]	0.7677
		Q3	0.565[0.151, 1.913]	0.3718
		Q4	0.792[0.240, 2.501]	0.6930
	Urea (continuous)		1.051[0.702, 1.575]	0.8078
	Urea	Q1	–	–
		Q2	1.558[0.474, 5.232]	0.4654
		Q3	0.875[0.256, 2.941]	0.8283
		Q4	1.385[0.409, 4.732]	0.5988
	Creatinine (continuous)		0.996[0.946, 1.047]	0.8667
	Creatinine	Q1	–	–
		Q2	1.446[0.443, 4.810]	0.5402
		Q3	1.385[0.409, 4.732]	0.5988
		Q4	0.926[0.270, 3.132]	0.9017
	GFR (continuous)		0.994[0.959, 1.031]	0.7428
	GFR	Q1	–	–
		Q2	1.071[0.327, 3.514]	0.9085
		Q3	0.889[0.266, 2.941]	0.8463
		Q4	0.556[0.154, 1.895]	0.3527
	Uric Acid (continuous)		1.001[0.994, 1.008]	0.7581
	Uric Acid	Q1	–	–
		Q2	2.226[0.680, 7.692]	0.1918
		Q3	1.062[0.300, 3.771]	0.9243
		Q4	1.000[0.284, 3.527]	1.0000
	Sodium (continuous)		1.056[0.834, 1.344]	0.6520
	Sodium	Q1	–	–
		Q2	0.481[0.135, 1.512]	0.2266
		Q3	3.846[1.015, 16.755]	0.0548
		Q4	0.888[0.261, 2.828]	0.8426
	Potassium (continuous)		3.534[0.916, 16.839]	0.0897
	Potassium	Q1	–	–
		Q2	2.787[0.823, 10.511]	0.1096
		Q3	2.235[0.656, 8.419]	0.2098
		Q4	2.073[0.511, 8.799]	0.3075
	Chlorine (continuous)		0.959[0.777, 1.183]	0.6963
	Chlorine	Q1	–	–
		Q2	0.871[0.304, 2.505]	0.7957
		Q3	1.330[0.381, 4.594]	0.6502
		Q4	0.844[0.190, 3.340]	0.8135

(*Continued*)

https://doi.org/10.2147/IJGM.S537848

Table 2 (Continued).

Characteristics			OR [95% CI]	P-value
	CO2 (continuous)		0.931[0.735, 1.173]	0.5435
	CO2	Q1	–	–
		Q2	0.688[0.233, 2.021]	0.4934
		Q3	0.682[0.171, 2.517]	0.5713
		Q4	0.750[0.204, 2.631]	0.6558
	Total cholesterol (continuous)		1.846[0.833, 4.391]	0.1425
	Total cholesterol	Q1	–	–
		Q2	0.992[0.284, 3.415]	0.9894
		Q3	0.750[0.206, 2.619]	0.6530
		Q4	1.798[0.567, 5.911]	0.3225
	Triglyceride (continuous)		1.627[0.567, 4.815]	0.3578
	Triglyceride	Q1	–	–
		Q2	0.421[0.097, 1.598]	0.2166
		Q3	1.286[0.389, 4.317]	0.6795
		Q4	1.692[0.530, 5.592]	0.3775
	HDL (continuous)		2.115[0.270, 20.622]	0.4862
	HDL	Q1	–	–
		Q2	2.027[0.559, 7.943]	0.2893
		Q3	3.483[1.006, 13.482]	0.0561
		Q4	1.900[0.527, 7.400]	0.3333
	LDL (continuous)		2.291[0.869, 6.816]	0.1092
	LDL	Q1	–	–
		Q2	0.706[0.193, 2.478]	0.5878
		Q3	0.706[0.193, 2.478]	0.5878
		Q4	2.000[0.631, 6.622]	0.2441
Covariates	Age (continuous)		1.035[0.978, 1.098]	0.2330
	Age	Q1	–	–
		Q2	1.490[0.431, 5.372]	0.5298
		Q3	1.705[0.464, 6.460]	0.4206
		Q4	2.679[0.812, 9.556]	0.1132
	CA125 (continuous)		1.009[1.003, 1.018]	**0.0167**
	CA125	Q1	–	–
		Q2	0.675[0.170, 2.521]	0.5605
		Q3	1.062[0.300, 3.771]	0.9243
		Q4	2.870[0.893, 9.876]	0.0828
	HE4 (continuous)		0.987[0.947, 1.026]	0.5174
	HE4	Q1	–	–
		Q2	0.211[0.049, 0.758]	**0.0229**
		Q3	0.533[0.160, 1.705]	0.2937
		Q4	0.500[0.151, 1.586]	0.2441
	BMI (continuous)		1.053[0.908, 1.223]	0.4888
	BMI	Q1	–	–
		Q2	0.588[0.162, 2.018]	0.4034
		Q3	0.729[0.211, 2.448]	0.6099
		Q4	1.190[0.372, 3.848]	0.7680

Notes: Q1, 0%–25% quantile; Q2, 25%–50% quantile; Q3, 50%–75% quantile; Q4, 75%–100% quantile. Bolded values indicate statistical significance.

For the above variables, we included covariates for adjustment (Model 1: unadjusted; Model 2: adjusted for age, BMI; Model 3: adjusted for age, BMI, CA125, HE4). The results showed that FBG and total protein were not statistically significant associated with endometriosis severity after adjustment for age and BMI. However, TBil (OR [95% CI]: 0.28 [0.073, 0.957], P: 0.0499) and direct bilirubin (OR [95% CI]: 0.18[0.035, 0.702], P: 0.0209) remained significantly

associated with endometriosis severity after adjustment for age and BMI. Additionally, ALT (Model 2: OR [95% CI]: 0.194[0.037, 0.768], P: 0.03, Model 3: OR [95% CI]: 0.138[0.019, 0.67], P: 0.0247) remained significantly associated with endometriosis severity after adjustment for age, BMI, CA125, and HE4 (Table 3).

Nonlinear Relationship Between Metabolic and Outcome Indicators

Restricted cubic spline models were constructed to analyze the potential nonlinear relationship between metabolic indicators and endometriosis severity. The results showed that, with the exception of FBG which showed a significant nonlinear relationship (P-nonlinear: 0.0362), the remaining metabolic markers did not exhibit a significant nonlinear association with the outcome measures (P-nonlinear > 0.05) (Figures 1 and 2).

Table 3 Impact of Metabolic Indicators on Outcome

Levels		Model 1		Model 2		Model 3	
		OR [95% CI]	**P-value**	**OR [95% CI]**	**P-value**	**OR [95% CI]**	**P-value**
TBil (continuous)		0.853 [0.718, 0.991]	0.051	0.860 [0.723, 1.000]	0.065	0.883 [0.740, 1.030]	0.130
		P of trend: 0.013*		P of trend: 0.012*		P of trend: 0.016*	
TBil (categorical)	Q1	–	–	–	–	–	–
	Q2	0.769[0.245, 2.374]	0.6483	0.739[0.231, 2.317]	0.6048	0.823[0.235, 2.827]	0.7574
	Q3	0.222[0.053, 0.788]	0.0265*	0.220[0.05, 0.817]	0.0308*	0.281[0.058, 1.155]	0.0898
	Q4	0.278[0.073, 0.933]	0.0453*	0.280[0.073, 0.957]	0.0499*	0.334[0.08, 1.251]	0.1131
Direct bilirubin (continuous)		0.645[0.402, 0.972]	0.049*	0.661[0.410, 0.999]	0.065	0.725[0.448, 1.106]	0.2
		P of trend: 0.018*		P of trend: 0.024*		P of trend: 0.093	
Direct bilirubin (categorical)	Q1	–	–	–	–	–	–
	Q2	0.571[0.174, 1.804]	0.3444	0.523[0.155, 1.683]	0.2832	0.588[0.16, 2.074]	0.4123
	Q3	0.444[0.138, 1.359]	0.1608	0.474[0.142, 1.511]	0.2119	0.649[0.179, 2.292]	0.5024
	Q4	0.176[0.035, 0.683]	0.0189*	0.18[0.035, 0.702]	0.0209*	0.25[0.047, 1.045]	0.0715
FBG (continuous)		3.422[1.116, 11.539]	0.0370*	3.099[0.984, 10.647]	0.0600	3.132[0.897, 12.002]	0.081
		P of trend: 0.078		P of trend: 0.110		P of trend: 0.120	
FBG (categorical)	Q1	–	–	–	–	–	–
	Q2	1.105[0.342, 3.574]	0.8657	1.035[0.312, 3.426]	0.9541	1.28[0.347, 4.872]	0.7103
	Q3	0.808[0.185, 3.13]	0.7625	0.779[0.177, 3.046]	0.7257	0.87[0.18, 3.826]	0.8554
	Q4	3.5[1.093, 11.974]	0.0387*	3.134[0.943, 11.043]	0.0665	3.482[0.948, 13.86]	0.0653
Total protein (continuous)		1.094[1.012, 1.198]	0.040*	1.087[1.008, 1.192]	0.057	1.055[0.984, 1.163]	0.2
		P of trend: 0.300		P of trend: 0.400		P of trend: 0.800	
Total protein (categorical)	Q1	–	–	–	–	–	–
	Q2	1.15[0.324, 3.907]	0.8237	1.008[0.273, 3.526]	0.9904	0.478[0.103, 1.958]	0.3199
	Q3	0.863[0.249, 2.817]	0.8085	0.837[0.237, 2.785]	0.7745	0.446[0.108, 1.67]	0.243
	Q4	2.091[0.675, 6.633]	0.2021	1.911[0.597, 6.22]	0.2748	0.881[0.217, 3.404]	0.8552
ALT (continuous)		0.918[0.826, 1.001]	0.076	0.907[0.814, 0.992]	0.050	0.898[0.796, 0.993]	0.055
		P of trend: 0.016*		P of trend: 0.010*		P of trend: 0.012*	
ALT (categorical)	Q1	–	–	–	–	–	–
	Q2	1.163[0.411, 3.298]	0.7746	1.072[0.361, 3.165]	0.8989	0.976[0.301, 3.121]	0.9672
	Q3	0.339[0.068, 1.314]	0.1416	0.317[0.062, 1.255]	0.1241	0.356[0.065, 1.541]	0.1912
	Q4	0.239[0.049, 0.888]	0.0467*	0.194[0.037, 0.768]	0.03*	0.138[0.019, 0.67]	0.0247*

Notes: Q1, 0%-25% quantile; Q2, 25%-50% quantile; Q3, 50%-75% quantile; Q4, 75%-100% quantile. Model 1: unadjusted; Model 2: adjusted for age, BMI; Model 3: adjusted for age, BMI, CA125, HE4. * P < 0.05.

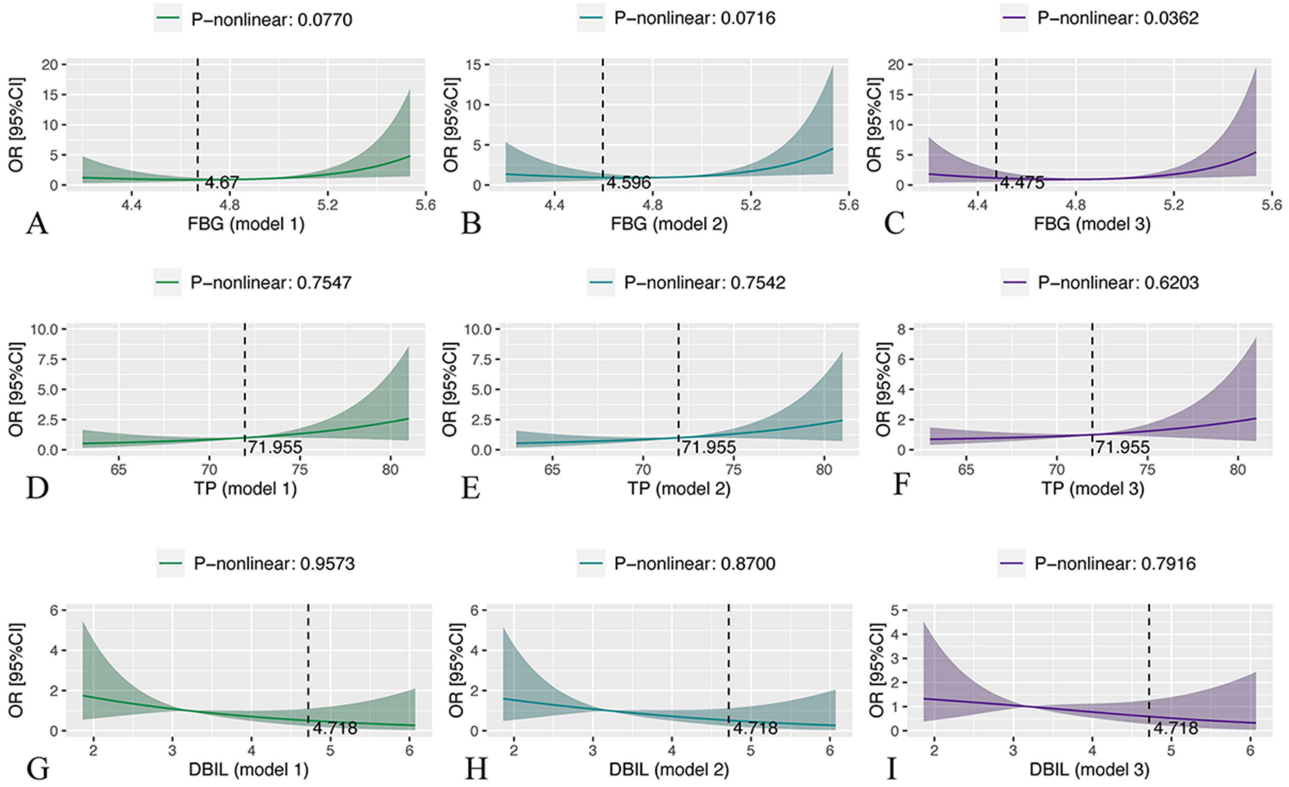

Figure 1 RCS cubic spline plots of FBG (**A**–**C**), TP (**D**–**F**), and DBIL (**G**–**I**) in different models. The vertical dotted line indicates the value of the metabolic indicator when the OR is equal to 1.
Abbreviations: TP, total protein; DBIL, direct bilirubin.

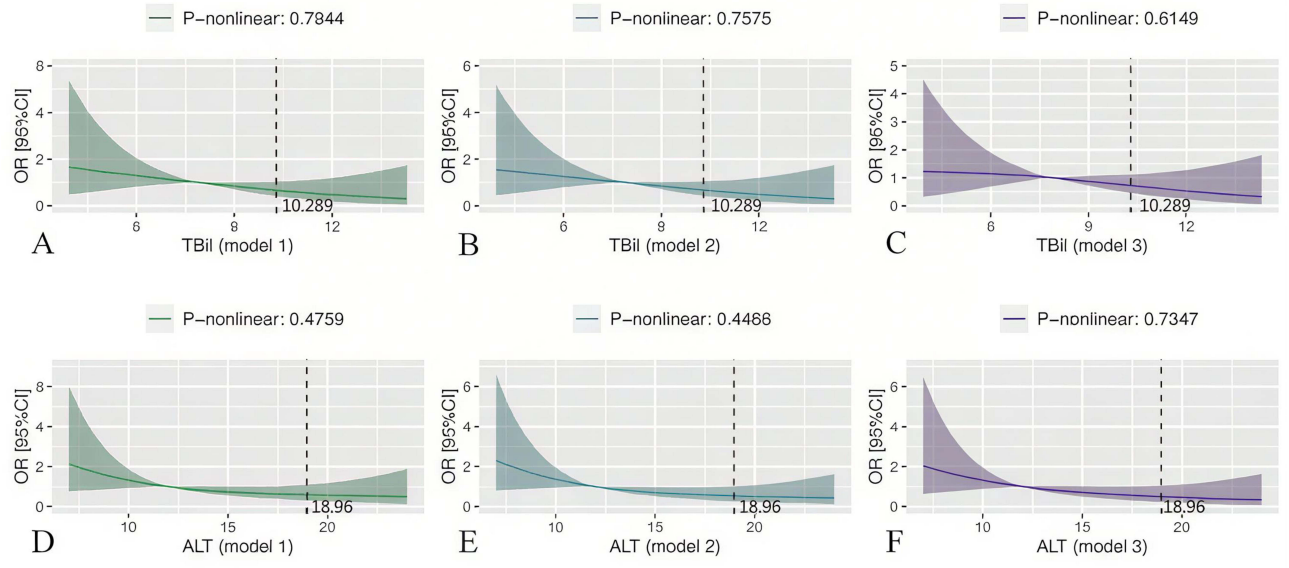

Figure 2 RCS cubic spline plots of TBil (**A**–**C**) and ALT (**D**–**F**) in different models. The vertical dotted line indicates the value of the metabolic indicator when the OR is equal to 1.

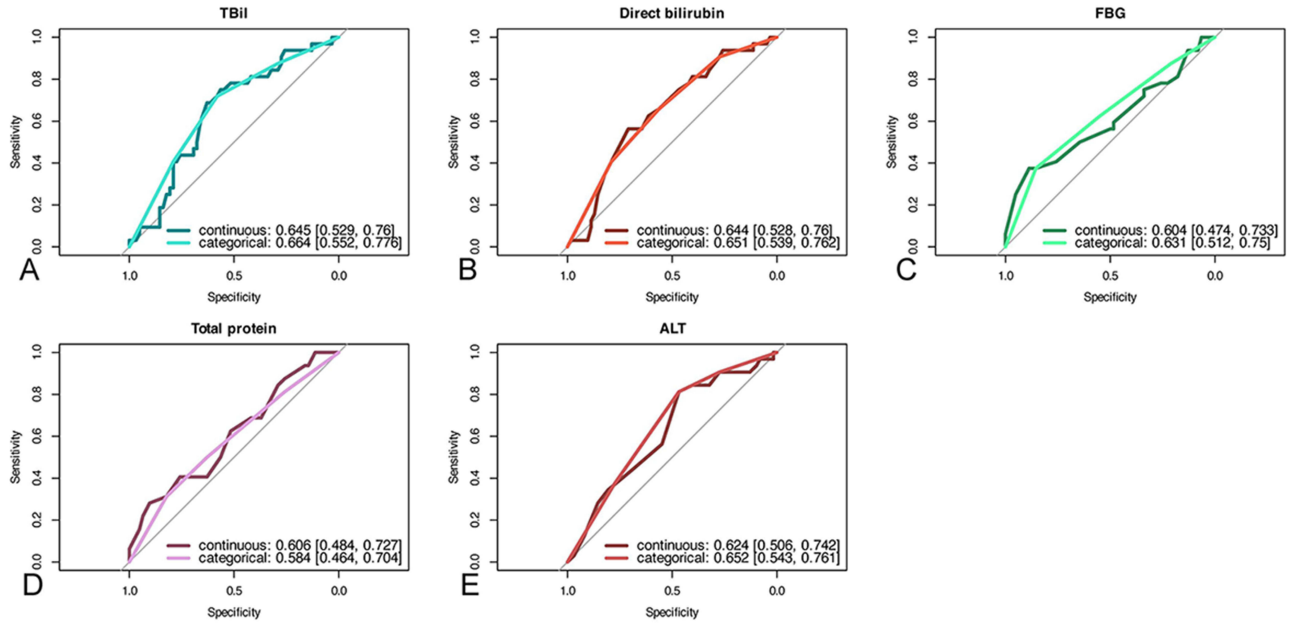

Figure 3 Results of ROC analysis of metabolic indicators. (**A**) TBil; (**B**) Direct bilirubin; (**C**) FBG; (**D**) Total protein; (**E**) ALT.

Predictive Power of Metabolic Indicators

We conducted ROC curve analysis for metabolic indicators that were statistically significant in univariate analyses, including TBil, direct bilirubin, FBG, total protein, and ALT, and computed the AUC values (Figure 3). The AUC ranges from 0 to 1, with 0.5 indicating a random classifier and 1 representing a perfect classifier. The AUC results were as follows: TBil (continuous: 0.645 [0.529, 0.76]; categorical: 0.664 [0.552, 0.776]), direct bilirubin (continuous: 0.644 [0.528, 0.76]; categorical: 0.651 [0.539, 0.762]), FBG (continuous: 0.604 [0.474, 0.733]; categorical: 0.631 [0.512, 0.75]), ALT (continuous: 0.624 [0.506, 0.742]; categorical: 0.652 [0.543, 0.761]). All AUC values were above 0.6, suggesting these indicators possess a high level of predictive capability.

Discussion

This study explored the relationship between standard metabolic indices and the severity of endometriosis. Findings indicated that ALT exhibited a negative association with endometriosis severity. The RCS analysis showed that the majority of these metabolic indicators bore a substantially nonlinear relationship with outcomes.

The present study showed that CA-125 was positively correlated with the severity of endometriosis. Izabela Kokot et al compared serum inflammatory markers between patients with endometriosis and those without and found that CA-125 concentration was significantly elevated in individuals with endometriosis when compared to the non-endometriosis group ($p < 0.001$). Another study showed that the AUC for the diagnostic ability of serum IL-32 for endometriosis was 0.638; however, when the serum IL-32 level was combined with the serum CA-125 level, the AUC increased to 0.749, suggesting that CA-125 may improve the accuracy of diagnosing endometriosis.[17] It has also been shown that increased CA-125 is a marker of severe and deep infiltrating endometriosis. In addition, many studies reported similar results to our research outcomes.[18–21] In addition, HE4 (continuous) was not significantly correlated with endometriosis severity. However, HE4 within the Q2 (25%–50% quantile) range was associated with lower severity compared with Q1 (0%–25% quantile). Previous studies have reported that HE4 alone has limited correlation with endometriosis severity, future studies with larger sample sizes are needed to further explore this relationship.

In terms of hepatobiliary metabolic indicators, our results showed that direct bilirubin, TBil and ALT were significantly associated with endometriosis severity. Bilirubin is a breakdown product of heme, released from the lysis of red blood cells. Slightly elevated plasma bilirubin levels have been associated with protective effects against a range of pathologies, and slight decreases in serum bilirubin concentrations have been linked to an increased risk of cardiovascular and metabolic diseases.[22,23]

https://doi.org/10.2147/IJGM.S537848

However, few studies have directly elucidated the association between direct bilirubin and endometriosis severity. Shogo Imanaka et al reported higher blood bilirubin levels in endometriotic patients compared to non-endometriotic individuals,[24] but the study did not correlate bilirubin levels with the severity of endometriosis. Concurrently, a study by the same agency investigated the effects of iron-related compounds and bilirubin on redox homeostasis in endometriosis and its potential for malignant transformation, revealing higher levels of total iron, heme iron, free iron, and bilirubin in endometriosis patients compared to those with endometriosis-associated ovarian cancer.[25] This suggests that low bilirubin may indicate disease progression and malignancy in endometriosis, although further high-quality research is needed to confirm this association. In addition to CA-125 and bilirubin, ALT is also an independent factor. ALT is regarded as a marker of liver injury, and its decreased concentration is generally considered to be of no clinical significance. However, no study has analyzed the relationship between ALT and the severity of endometriosis; therefore, further studies are needed.

Analyzing the correlation between metabolic indices and endometriosis severity could provide clinicians with non-invasive biomarkers for early detection and more accurate monitoring of disease progression. This would enable more timely identification of patients at risk for severe manifestations. Additionally, understanding these metabolic associations may facilitate the development of targeted therapies tailored to specific metabolic profiles, enhancing treatment efficacy and personalization. Ultimately, such insights could improve diagnostic accuracy and guide more effective management strategies, offering significant benefits in the clinical care of endometriosis patients.

The present study explored the relationship between standard metabolic indices and the severity of endometriosis. It was found that ALT was statistically associated with endometriosis severity. The ROC curve analysis showed that these indicators have a robust discriminatory capacity. Nevertheless, this study has some limitations. First, the retrospective design limited the types of data that could be collected, and certain elusive endogenous metabolites were beyond the scope of this study. Second, the inability to capture data across all menstrual cycle phases (proliferative, secretory, and menstrual) is a constraint of this retrospective approach. Third, the sample size of this study is relatively small. Future studies with larger sample sizes are needed to further validate these findings. These limitations are exactly what our next research intends to remedy.

Conclusion

CA-125 and HE4 were identified as significant independent factors affecting the severity of endometriosis. ALT demonstrated a negative correlation with endometriosis severity and emerged as an independent factor with statistical significance. In contrast, FBG, total protein, direct bilirubin and TBil were not found to be independent factors influencing the severity of endometriosis. The logistic regression model incorporating the aforementioned indicators exhibited strong discriminatory power. Future prospective studies with larger samples and more refined designs are needed to further validate these findings.

Data Sharing Statement

The data that support the findings of this study are available from either corresponding author, Hongyang Xiao or Ruiqin Tu, upon reasonable request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Zhongshan Hospital (Xiamen), Fudan University (No. B2022-046).Written informed consent was obtained from the participants.

Consent to Participate

Written informed consent was obtained from the participants.

Funding

No funding was received for this research.

Disclosure

The authors report there are no competing interests to declare for this work.

References

1. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet*. 2021;397 (10276):839–852. doi:10.1016/S0140-6736(21)00389-5
2. Koninckx PR, Fernandes R, Ussia A, et al. Pathogenesis Based Diagnosis and Treatment of Endometriosis. *Front Endocrinol*. 2021;12:745548. doi:10.3389/fendo.2021.745548
3. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29(3):400–412. doi:10.1093/humrep/det457
4. Falcone T, Flyckt R. Clinical Management of Endometriosis. *Obstet Gynecol*. 2018;131(3):557–571. doi:10.1097/AOG.0000000000002469
5. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol*. 2019;15(11):666–682. doi:10.1038/s41574-019-0245-z
6. Ballweg ML. Treating endometriosis in adolescents: does it matter? *J Pediatr Adolesc Gynecol*. 2011;24(5 Suppl):S2–6. doi:10.1016/j.jpag.2011.07.003
7. Kobayashi H, Kawahara N, Ogawa K, Yoshimoto C. A relationship between endometriosis and obstetric complications. *Reprod Sci*. 2020;27 (3):771–778. doi:10.1007/s43032-019-00118-0
8. Guidozzi F. Endometriosis-associated cancer. *Climacteric*. 2021;24(6):587–592. doi:10.1080/13697137.2021.1948994
9. Bulun SE, Wan Y, Matei D. Epithelial Mutations in Endometriosis: link to Ovarian Cancer. *Endocrinology*. 2019;160(3):626–638. doi:10.1210/en.2018-00794
10. Hermens M, van Altena AM, Bulten J, van Vliet H, Siebers AG, Bekkers RLM. Increased incidence of ovarian cancer in both endometriosis and adenomyosis. *Gynecol Oncol*. 2021;162(3):735–740. doi:10.1016/j.ygyno.2021.07.006
11. Ac SDS, Capek S, Amrami KK, Spinner RJ. Neural involvement in endometriosis: review of anatomic distribution and mechanisms. *Clin Anat*. 2015;28(8):1029–1038. doi:10.1002/ca.22617
12. Jerman LF, Hey-Cunningham AJ. The role of the lymphatic system in endometriosis: a comprehensive review of the literature. *Biol Reprod*. 2015;92(3):64. doi:10.1095/biolreprod.114.124313
13. Conroy I, Mooney SS, Kavanagh S, et al. Pelvic pain: what are the symptoms and predictors for surgery, endometriosis and endometriosis severity. *Aust N Z J Obstet Gynaecol*. 2021;61(5):765–772. doi:10.1111/ajo.13379
14. Vanni VS, Villanacci R, Salmeri N, et al. Publisher Correction: concomitant autoimmunity may be a predictor of more severe stages of endometriosis. *Sci Rep*. 2021;11(1):17715. doi:10.1038/s41598-021-97506-x
15. Kim B-S, Kim B, Yoon S, et al. Warburg-like Metabolic Reprogramming in Endometriosis: from Molecular Mechanisms to Therapeutic Approaches. *Pharmaceuticals*. 2025;18(6):813. doi:10.3390/ph18060813
16. Datkhayeva Z, Iskakova A, Mireeva A, et al. The Multifactorial Pathogenesis of Endometriosis: a Narrative Review Integrating Hormonal, Immune, and Microbiome Aspects. *Medicina*. 2025;61(5):811. doi:10.3390/medicina61050811
17. Choi YS, Kim S, Ys O, Cho S, Hoon KS. Elevated serum interleukin-32 levels in patients with endometriosis: a cross-sectional study. *Am J Reprod Immunol*. 2019;82(2):e13149. doi:10.1111/aji.13149
18. Fiala L, Bob P, Raboch J. Oncological markers CA-125, CA 19-9 and endometriosis. *Medicine*. 2018;97(51):e13759. doi:10.1097/MD.0000000000013759
19. Oliveira MAP, Raymundo TS, Soares LC, Pereira TRD, Demoro AVE. How to Use CA-125 More Effectively in the Diagnosis of Deep Endometriosis. *Biomed Res Int*. 2017;2017:9857196. doi:10.1155/2017/9857196
20. Shin KH, Kim HH, Kwon BS, Suh DS, Joo JK, Kim KH. Clinical Usefulness of Cancer Antigen (CA) 125, Human Epididymis 4, and CA72-4 Levels and Risk of Ovarian Malignancy Algorithm Values for Diagnosing Ovarian Tumors in Korean Patients With and Without Endometriosis. *Ann Lab Med*. 2020;40(1):40–47. doi:10.3343/alm.2020.40.1.40
21. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res*. 2019;12(1):28. doi:10.1186/s13048-019-0503-7
22. Hinds Jr TD, Stec DE. Bilirubin Safeguards Cardiorenal and Metabolic Diseases: a Protective Role in Health. *Curr Hypertens Rep*. 2019;21(11):87. doi:10.1007/s11906-019-0994-z
23. Hinds Jr TD, Stec DE. Bilirubin, a Cardiometabolic Signaling Molecule. *Hypertension*. 2018;72(4):788–795. doi:10.1161/HYPERTENSIONAHA.118.11130
24. Imanaka S, Yamada Y, Kawahara N, Kobayashi H. A delicate redox balance between iron and heme oxygenase-1 as an essential biological feature of endometriosis. *Arch Med Res*. 2021;52(6):641–647. doi:10.1016/j.arcmed.2021.03.006
25. Shigetomi H, Imanaka S, Kobayashi H. Effects of iron-related compounds and bilirubin on redox homeostasis in endometriosis and its malignant transformations. *Horm Mol Biol Clin Investig*. 2021;43(2):187–192. doi:10.1515/hmbci-2021-0065