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Downregulated Lecithin–Cholesterol Acyltransferase in Polycystic Ovary Syndrome and its potential as a clinical biomarker for ovarian dysfunction:a case-control study

Boqun Xu
Nanjing Women and Children's Healthcare Hospital
Wenxin Chen
Nanjing Women and Children's Healthcare Hospital
Chiyuan Yu
Nanjing Women and Children's Healthcare Hospital
Zhiyi Zhou
Nanjing Women and Children's Healthcare Hospital
Tianzhen Tang
Sir Run Run Hospital
Yuan Lin
Nanjing Medical University
Xiaoyan Ying
Second Affiliated Hospital of Nanjing Medical University
Bing Yao
Nanjing General Hospital of Nanjing Military Command
Bin Xue
xuebin@njmu.edu.cn

Nanjing Children's Hospital

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Abstract

Objective: To investigate the association between lecithin-cholesterol acyltransferase (LCAT) and polycystic ovary syndrome (PCOS).

Methods: Basal serum samples were collected from 156 patients with PCOS and 148 control subjects. Follicular fluid samples were collected from 74 patients with PCOS and 85 controls. LCAT levels in serum and follicular fluid were detected by enzyme-linked immunosorbent assay. Sex hormones, parameters of glucose and lipid metabolism, and indicators of thyroid function were measured in a clinical laboratory.

Results: (1) LCAT expression in both serum and follicular fluid was lower in the PCOS group than in the control group. (2) Serum LCAT concentrations were negatively correlated with luteinizing hormone, testosterone and luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio,while positively correlated with FSH, with statistically significant differences. (3) Follicular fluid LCAT concentrations were negatively correlated with estradiol(E_2) and positively correlated with progesterone(P), with statistically significant differences. (4) Patients with PCOS with higher levels of LH/FSH ratios had lower LCAT concentrations. (5) After adjustment for age, body mass index (BMI), and testosterone, both serum and follicular fluid LCAT levels remained associated with high odds of PCOS in the logistic regression model.(6)Serum LCAT alone showed weak discrimination for PCOS (AUC = 0.655), whereas combining LCAT with age and BMI significantly improved discriminatory ability (AUC = 0.775, DeLong test $P < 0.001$)

Conclusion: LCAT expression significantly decreased in the PCOS group and was negatively correlated with testosterone and LH/FSH ratio, suggesting that LCAT may be involved in the disrupted growth and maturation of follicles in PCOS. Combining LCAT with age and BMI significantly improved discriminatory ability of PCOS suggests that LCAT may serve as an auxiliary rather than standalone biomarker.Within ovarian follicles, the positive association between follicular fluid LCAT levels and progesterone and negative association between follicular fluid LCAT levels and estradiol indicate that LCAT may act locally within the follicle to alleviate excessive estrogen overproduction and optimize the intrafollicular hormonal microenvironment. Overall, LCAT is associated with ovulation dysfunction in PCOS and may serve as a new serological biomarker for its diagnosis.

2. Background

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine and metabolic disorder in women of reproductive age[1]. Its main clinical features include clinical or biochemical hyperandrogenism, persistent anovulation or oligo-ovulation, and polycystic ovarian morphology on ultrasound[2]. PCOS is often accompanied by various complications, such as hormonal disturbances, dysregulated lipid metabolism, and ovulatory dysfunction[3, 4]. The etiology of PCOS is complex and is thought to result from interactions between certain genetic susceptibility and environmental factors[5]. Previous studies have shown that environmental factors include prenatal androgen exposure and poor

fetal growth[6], while obesity is the main postnatal factor[7]. Despite extensive research, the exact pathogenesis of PCOS remains unclear.

Hyperandrogenemia and metabolic abnormalities are typical features of PCOS, with excessive androgens production regarded as a key pathogenic factor[8]. However, PCOS is a heterogeneous disorder, and hyperandrogenemia is not its only pathogenic factor. PCOS is associated with an increased risk of metabolic diseases, including insulin resistance (IR), central obesity, dyslipidemia, and type 2 diabetes mellitus[9–11]. Studies have shown that over 50% of patients with PCOS have IR, which further induces lipid metabolic disturbances. Among these disorders, the imbalance of cholesterol metabolism is one of the key links[4]. Clinical studies have found that patients with PCOS often exhibit reduced levels of high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), and decreased efficiency of reverse cholesterol transport (RCT). These abnormalities not only increase the cardiovascular risk but also contribute to the pathological progression of PCOS by modulating the endocrine microenvironment[12, 13]. However, the mechanism by which cholesterol metabolism disorders specifically affect the development of PCOS requires in-depth exploration, particularly with respect to key regulatory molecules.

Cholesterol is an essential lipid that serves as a core component of cell membranes and a precursor for steroid hormone synthesis, including estrogen and androgens[14, 15]. Under physiological conditions, cholesterol is maintained through a dynamic balance of synthesis, transport, and clearance[16]. RCT is a key pathway for clearing excess cholesterol from peripheral tissues and maintaining cholesterol homeostasis. In this process, HDL acts as a carrier, transporting excess cholesterol from tissues such as blood vessel walls and ovaries to the liver for metabolism and excretion[17]. In PCOS patients, this balance is disrupted. IR can activate cholesterol-synthesizing enzymes, such as HMG-CoA reductase, leading to increased endogenous cholesterol synthesis[18, 19]. Concurrently, structural and functional abnormalities of HDL, including reduced particle size and diminished antioxidant capacity, impair RCT efficiency and promote cholesterol accumulation in peripheral tissues[20]. Notably, the ovary is the main site for steroidogenesis, and disorders of ovarian cholesterol metabolism directly affect androgen synthesis, leading to excessive androgen secretion and further exacerbation of ovulatory dysfunction and hyperandrogenic symptoms[12, 21, 22]. These observations suggest that regulating key links in cholesterol metabolism may become a potential target for PCOS management.

Lecithin-cholesterol acyltransferase (LCAT) is a central enzyme in RCT[23]. It is mainly synthesized in the liver and secreted into the circulation, where it catalyzes the combination of free cholesterol (FC) on the surface of HDL with fatty acids in lecithin molecules to form cholesterol esters (CE). This process promotes the maturation of HDL particles and enhances their ability to bind to free cholesterol in peripheral tissues; on the other hand, it facilitates the transport of excess cholesterol from peripheral tissues to the liver (RCT), which is of great significance for maintaining cholesterol homeostasis[24].

Emerging evidence also indicates that LCAT plays an important role in ovarian folicular development and maturation. Studies have shown that the upregulated expression of LCAT is significantly associated with

high fertilization rates in women[25]. Further studies suggest that LCAT participates in the synthesis of follicular estrogen derivatives and maintains the integrity and repair of oocyte cell membranes by regulating lipid transport and metabolism[25, 26]. These findings imply a potential role for LCAT in the regulation of PCOS.

However, the involvement of LCAT in the pathogenesis PCOS has not been fully established. Our previous observations demonstrated reduced serum LCAT concentrations in the PCOS group. Therefore, we hypothesized that LCAT may be implicated in the development of PCOS and can provide new ideas for the diagnosis and treatment of female reproductive metabolism. This study aims to explore the correlation between LCAT and PCOS and to provide clinical evidence for further research.

3. Methods and materials

3.1. Participants

Two types of biological samples were collected for this study. Serum samples were obtained from 156 patients diagnosed with PCOS and 148 healthy control subjects. Follicular fluid samples were collected from 74 patients with PCOS and 85 healthy controls. All samples were obtained from the Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Nanjing Medical University, and the Reproductive Medicine Center of the General Hospital of the Eastern Theater Command between September 2023 and June 2025. The diagnosis of PCOS was based on the 2003 Rotterdam criteria: 1) oligo-ovulation or anovulation; 2) clinical or biochemical manifestations of hyperandrogenism; and 3) polycystic ovarian morphology on ultrasound. Meanwhile, exclusion criteria were as follows: (1) patients with severe systemic diseases, including chronic liver disease, chronic kidney disease, severe obesity (BMI ≥ 35 kg/m²) accompanied by severe metabolic disorders; (2) presence of other diseases that could cause hyperandrogenism, menstrual irregularities, or ovulatory dysfunction, such as Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, premature ovarian failure, congenital adrenal hyperplasia, or androgen-secreting tumors; (3) use of any medications affecting glucose and lipid metabolism (e.g., hypoglycemic agents, lipid-lowering drugs) within the past six months; (4) receipt of immunosuppressive agents or hormone therapy (e.g., oral contraceptives, glucocorticoids, ovulation induction agents) within the past six months; (5) women who were pregnant or lactating; (6) patients with malignant tumors or severe abnormalities in liver or kidney function tests.

Control group were recruited based on their etiology or medical consultation status and included women seeking medical treatment for male-factor infertility, those undergoing in vitro fertilization-embryo transfer due to tubal-factor infertility, and patients seeking medical treatment for benign cervical diseases.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University (2025-KY-236-01) and General Hospital of the Eastern Theater Command (2023DZKY-009-01).

3.2. Clinical demographic and biochemical information

All participants completed a questionnaire to collect demographic information, including age, height, weight, menstrual cycle characteristics, medication use, and other personal history. BMI was calculated as body weight (kilograms) divided by height squared (meters). Oligo-ovulation was defined as a menstrual cycle length exceeding 35 days for three or more consecutive cycles and anovulation as a complete absence of ovulation for three or more consecutive menstrual cycles.

Fasting blood samples were collected between days 2 and 5 of the menstrual cycle after at least 8 hours of fasting. Blood samples were immediately centrifuged at 4 ℃ and 3500 rpm for 15 minutes. All clinical biochemical indicator tests were performed by the clinical laboratory of The Second Affiliated Hospital of Nanjing Medical University and General Hospital of the Eastern Theater Command. Follicular fluid samples were obtained from the largest follicle aspirated from each ovary, centrifuged at 3000 g for 15 minutes and then stored at − 80°C until analysis.

3.3. Sample preparation and laboratory assays

LCAT concentrations in serum and follicular fluid were determined by ELISA kit according to the manufacturer's recommendations (*Cloudclone, Wuhan*). Absorbance was measured using a microplate reader, and the final concentration value was obtained through calculation.

3.4. Statistical analysis

Baseline characteristics are expressed as medians with interquartile ranges. Data normality was tested using the Shapiro-Wilk test. Comparisons between women with and without PCOS in terms of demographics and laboratory characteristics were performed using independent-samples t tests (two-tailed) or non-parametric test. Correlation analyses were conducted to evaluate the relationship between LCAT levels and demographic and laboratory characteristics. The Mann–Whitney U test was used to compare LCAT concentrations between PCOS subgroups stratified by LH/FSH ratios. To determine the correlation of LCAT concentrations with metabolic or hormone-related indicators, multiple logistic regression analysis was used to calculate the odds ratio, and LCAT concentrations, age, BMI, and testosterone concentrations were added into the model. All reported confidence interval values were calculated at the 95% level. A P-value of < 0.05 was considered to represent a significant difference.Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of serum LCAT for PCOS. The area under the curve (AUC) with 95% confidence interval (CI) was calculated using the DeLong method.To assess whether the combination of LCAT with age and BMI improved discrimination, a multivariable logistic regression model was constructed with PCOS as the dependent variable and LCAT, age, and BMI as independent variables. ROC curves were generated for LCAT alone and for the combined model. The AUCs were compared using the DeLong test for paired ROC curves. A two-sided $P < 0.05$ was considered statistically significantAll statistical analyses were performed using R Studio,version 4.2.1.

4. Results

4.1. Baseline characteristics

The baseline characteristics of women with PCOS and control group are presented in Table 1,2.

Among the study population providing serum samples (Table 1), BMI was significantly higher in the PCOS group compared with the control group (P < 0.001). Serum concentrations of luteinizing hormone (LH), estradiol, testosterone and anti-mullerian hormone (AMH) were markedly elevated in the PCOS group, whereas follicle-stimulating hormone (FSH) were decreased, leading to a notable increase in the LH/FSH ratio. These differences are consistent with the clinical diagnosis of PCOS.

Table 1
Baseline characteristics of participants providing serum samples

Baseline demographics	**control**	**PCOS**	**p-value**
	(n = 148)	**(n = 156)**	
Age***	30.5 ± 4.3	28.0(23.0,32.0)	< 0.001
BMI(kg/m²)***	22.4 ± 3.3	23.5(21.1,26.7)	< 0.001
LH (mIU/ml)***	4.2(3.1,5.9)	8.0(4.9,12.5)	< 0.001
FSH (mIU/ml)***	6.4(5.1,7.8)	5.5(4.5,6.7)	< 0.001
LH/FSH***	0.7(0.4,1.0)	1.5(0.9,2.6)	< 0.001
E_2 (pmol/L)*	150.2(113.5,200.3)	176.2(119.1,251.9)	0.013
P (nmol/L)	1.6(1.0,3.5)	1.5(0.8,2.9)	0.254
TT (nmol/L)***	1.2(0.7,1.7)	1.9 ± 0.9	< 0.001
PRL (mIU/L)	334.4(224.6,479.2)	311.7(219.5,457.6)	0.362
	(n = 95)	**(n = 77)**	
AMH (ng/ml)***	4.1(2.4,6.0)	7.8(5.9,11.7)	< 0.001

Normal distributed data were expressed as mean ± standard deviation; non-normal distributed data were expressed as median and interquartile range.

Differences between the PCOS group and control group were analyzed by Man-Whitney U-test.

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E_2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

Among the study population providing follicular fluid samples(Table 2), BMI was also significantly higher in the PCOS group compared with the control group ($P < 0.05$). Similarly, serum concentrations of luteinizing hormone (LH), testosterone and anti-mullerian hormone (AMH) were markedly elevated in the PCOS group, whereas follicle-stimulating hormone (FSH) were decreased, leading to a notable increase in the LH/FSH ratio. These differences are still consistent with the clinical diagnosis of PCOS.

Table 2
Baseline characteristics of participants providing follicular fluid samples

Baseline demographics	**control**	**PCOS**	**p-value**
	n = 85	**n = 74**	
Age	31.3 ± 3.4	30.4 ± 3.1	0.072[a]
BMI*	22.4(20.2,24.8)	23.5(21.3,26.2)	0.021[b]
LH (mIU/ml)***	3.7(2.6,5.4)	6.2(4.0,10.2)	< 0.001[b]
FSH (mIU/ml)*	7.2(5.8,8.5)	6.4(5.4,7.5)	0.012[b]
LH/FSH***	0.5(0.3,0.8)	0.9(0.6,1.4)	< 0.001[b]
E_2 (pmol/L)	145.0(104.4,178.9)	154.5(112.7,193.9)	0.374[b]
P (nmol/L)	1.5(0.9,3.9)	1.5(0.6,4.0)	0.939[b]
TT (nmol/L)***	1.3(0.9,1.7)	1.8 ± 0.6	< 0.001[b]
PRL (mIU/L)	342.6(241.9,455.0)	353.5(266.9,465.4)	0.619[b]
AMH (ng/ml)***	3.3(1.9,5.4)	8.1(6.2,11.7)	< 0.001[b]

Normal distributed data were expressed as mean ± standard deviation; non-normal distributed data were expressed as median and interquartile range.

[a]Differences between the PCOS group and control group were analyzed by independent samples t-test.

[b]Differences between the PCOS group and control group were analyzed by Man-Whitney U-test.

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

4.2. Expression of LCAT in serum and follicular fluid

LCAT concentrations were measured in both serum and follicular fluid. As shown in Fig. 1A and 1B, serum and follicular fluid LCAT were significantly lower in the PCOS group compared with the control

group, with reductions of approximately 24.08% in serum ($P < 0.0001$) and approximately 21.4% in follicular fluid ($P = 0.014$).

4.3. Localization and distribution of LCAT in ovarian follicles

Three ovarian tissue samples were obtained from patients undergoing bilateral adnexectomy in the Department of Gynecology. Immunohistochemical staining results (Fig. 2A) revealed strong LCAT expression in granulosa cells, weak expression in theca cells, and no obvious positive staining in stromal cells. Consistent with these findings, immunofluorescence analysis (Fig. 2B) confirmed that LCAT was significantly highly expressed in ovarian granulosa cells.

4.4. Correlation between LCAT and other biochemical indicators

Correlation analyses were performed to examine the associations between serum and follicular fluid LCAT levels and clinical demographic or biochemical characteristics.

Spearman analysis demonstrated that serum LCAT concentrations were significantly positively correlated with FSH ($r = 0.144$; $P = 0.012$) and negatively correlated with serum testosterone($r = -0.137$; $P = 0.017$) and LH($r = -0.147$; $P = 0.01$). Consequently, serum LCAT levels were significantly negatively correlated with LH/FSH ratio ($r = -0.207$; $P < 0.001$). No significant correlations were observed between serum LCAT and other PCOS parameters, such as AMH (Table 3).

In follicular fluid, LCAT concentrations were negatively correlated with serum estradiol levels($r = -0.184$, $P = 0.02$) and strongly positively correlated with progesterone($r = 0.308$, $P < 0.001$) (Table 4).

Table 3
Correlation between serum lecithin–cholesterol acyltransferase (LCAT) and clinical parameters in all participants

Variables	LCAT	p-value
	R	
Age	0.006	0.915
BMI	-0.073	0.203
LH*	-0.147	0.01
FSH*	0.144	0.012
LH/FSH***	-0.207	< 0.001
E2	0.02	0.728
P	0.043	0.452
TT*	-0.137	0.017
PRL	0.045	0.433
AMH	-0.088	0.251

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

Table 4
Correlation between follicle fluid lecithin–cholesterol acyltransferase (LCAT) and clinical parameters in all participants

Variables	LCAT	p-value
	r	
Age	-0.124	0.12
BMI	-0.048	0.547
LH	-0.04	0.612
FSH	0.031	0.696
LH/FSH	-0.018	0.826
E2*	-0.184	0.02
P***	0.308	< 0.001
TT	-0.001	0.991
PRL	-0.107	0.181
AMH	-0.057	0.477

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

4.5. Serum LCAT concentrations stratified by LH/FSH ratios in the PCOS group

Given the clinical relevance of LH/FSH ratio in the pathophysiology and clinical assessment of PCOS, PCOS patients (n = 156) were stratified into two subgroups based on baseline serum LH/FSH ratios (Table 5):

1. High LH/FSH ratio subgroup (n = 54): LH/FSH ≥ 2

2. Relatively low LH/FSH ratio subgroup (n = 102): LH/FSH <2

As defined, the high LH/FSH ratio subgroup exhibited a significantly higher serum LH level (P < 0.001) and lower FSH level (P < 0.001) compared to the relatively low LH/FSH ratio group (Table 5).

Regarding the other sex hormone levels, patients in the high LH/FSH ratio subgroup had significantly higher serum testosterone (P = 0.004) and estradiol levels (P < 0.001). Notably, after comparing LCAT

concentration between these two groups, it was significantly lower in patients with a higher level of LH/FSH ratio (P = 0.014)(Fig. 3).

Table 5
Comparisons of lecithin–cholesterol acyltransferase (LCAT) and other laboratory characteristics in different subgroups

Variables	PCOS		p-value
	LH/FSH<2(n = 102)	LH/FSH ≥ 2(n = 54)	
LCAT (ug/ml)*	13.1(10.1,16.0)	10.7 ± 5.1	0.014[b]
Age**	28.0 ± 5.4	25.0(22.0,30.3)	0.007[b]
BMI	23.5(20.9,26.1)	24.6 ± 4.7	0.536[b]
LH (mIU/ml)***	6.0(4.1,8.4)	15.6 ± 6.0	< 0.001[b]
FSH (mIU/ml)***	6.0(4.7,6.9)	4.8 ± 1.6	< 0.001[b]
E_2 (pmol/L)***	160.8(114.9,210.1)	229.0(135.8,548.4)	< 0.001[b]
P (nmol/L)	1.5(0.8,2.7)	1.6(1.0,3.3)	0.324[b]
TT (nmol/L)**	1.7 ± 0.8	2.1 ± 0.9	0.004[a]
PRL (mIU/L)	348.6(228.3,464.7)	277.5(195.1,445.4)	0.088[b]

Normal distributed data were expressed as mean ± standard deviation; non-normal distributed data were expressed as median and interquartile range.

[a]Differences between the PCOS group and control group were analyzed by independent samples t-test.

[b]Differences between the PCOS group and control group were analyzed by Man-Whitney U-test.

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

4.6. Binary logistic regression analysis

Binary logistic regression analyses were performed on all participants to assess independent association between LCAT expression and the occurrence of PCOS (dependent variables) (Table 6). In univariate logistic regression analysis, serum LCAT levels were negatively associated with PCOS risk (OR = 0.879; 95% CI = 0.837–0.924; P < 0.001), whereas BMI, LH, LH/FSH ratio, testosterone, estradiol, and AMH were positively associated with PCOS risk. To account for confounding effects, multivariate logistic regression analyses were conducted with adjustment for age, BMI, and testosterone. In the

adjusted model, the negative association between LCAT levels and PCOS remained statistically significant (OR = 0.868; 95% CI = 0.820–0.919; P < 0.001), indicating that decreased LCAT levels were associated with high odds of developing PCOS, suggesting that LCAT protein may play a protective role in the development and progression of PCOS.

A similar approach was applied to follicular fluid LCAT levels (Table 7). In the unadjusted model, follicular fluid LCAT levels were negatively associated with PCOS risk (OR = 0.960; 95% CI = 0.929–0.992; P = 0.014). After adjustment for age, BMI, and testosterone, reduced follicular fluid LCAT levels remained significantly associated with high odds in the PCOS group (OR = 0.955; 95% CI = 0.922–0.988; P = 0.009).

Table 6
Binary Logistic regression on the association between serum lecithin–cholesterol acyltransferase (LCAT) and polycystic ovarian syndrome (PCOS)

Variables	**Univariate Analysis**		**Multivariate Analysis**	
	p-value	**OR(95%CI)**	**p-value**	**OR(95%CI)**
LCAT	< 0.001	0.879(0.837–0.924)	< 0.001	0.868(0.820–0.919)
Age	< 0.001	0.872(0.829–0.917)	< 0.001	0.861(0.814–0.912)
BMI	< 0.001	1.131(1.062–1.205)	0.005	1.113(1.032-1.200)
LH	< 0.001	1.360(1.245–1.486)		
FSH	0.004	0.842(0.749–0.946)		
LH/FSH	< 0.001	7.520(4.360-12.969)		
E2	0.003	1.003(1.001–1.005)		
P	0.964	0.999(0.949–1.051)		
TT	< 0.001	2.165(1.564–2.997)	< 0.001	1.882(1.351–2.622)
PRL	0.134	0.999(0.998-1.000)		
AMH	< 0.001	1.329(1.191–1.482)		

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

Table 7
Binary logistic regression on the association between follicle fluid lecithin–cholesterol acyltransferase (LCAT) and polycystic ovarian syndrome (PCOS)

Variables	Univariate Analysis		Multivariate Analysis	
	p-value	OR(95%CI)	p-value	OR(95%CI)
LCAT	0.014	0.96(0.929–0.992)	0.009	0.955(0.922–0.988)
Age	0.074	0.916(0.832–1.009)	0.02	0.883(0.796–0.980)
BMI	0.053	1.087(0.999–1.184)	0.032	1.103(1.009–1.206)
LH	< 0.001	1.331(1.176–1.507)		
FSH	0.029	0.837(0.713–0.982)		
LH/FSH	< 0.001	9.969(3.916–25.376)		
E2	0.41	1.001(0.998–1.004)		
P	0.285	1.049(0.961–1.146)		
TT	0.043	1.496(1.012–2.212)	0.036	1.548(1.028–2.332)
PRL	0.913	1.000(0.999–1.001)		
AMH	< 0.001	1.464(1.281–1.674)		
AST	0.067	1.055(0.996–1.117)		

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; P, progesterone; TT, testosterone; PRL, prolactin; AMH, anti-mullerian hormone.

4.7. ROC curve analysis

The ROC curve for LCAT alone in discriminating PCOS from controls is shown in Fig. 4. The AUC was 0.655 (95% CI: 0.599–0.708, P < 0.0001), indicating a weak discriminatory ability. The optimal cutoff value determined by the Youden index was ≤ 19.85 ng/mL, yielding a sensitivity of 100.0% and a specificity of 24.3%(Table 8). Because this cutoff had limited clinical utility due to a high false-positive rate, an alternative cutoff of ≤ 15.30 ng/mL was selected to achieve a specificity of at least 40% while maximizing sensitivity, yielding a sensitivity of 72.44% and a specificity of 43.24%.

When age and BMI were added to LCAT, the combined model yielded an AUC of 0.775 (95% CI: 0.724–0.821). The DeLong test showed that the difference between the two AUCs was statistically significant (difference = 0.120, 95% CI: 0.067–0.174, P < 0.0001).

Table 8
ROC analysis for discriminating PCOS using serum LCAT alone and the combined model

Model	AUC (95% CI)	p-value	Optimal cutoff	Sensitivity (%)	Specificity (%)	Youden index
LCAT alone	0.655 (0.599–0.708)	< 0.001	≤ 19.85μg/mL	100.0	24.3	0.243
LCAT + age + BMI	0.775 (0.724–0.821)	< 0.001	—	—	—	—
Alternative cutoff for LCAT alone	0.655 (0.599–0.708)	< 0.001	≤ 15.30μg/mL	72.4	43.2	0.156

Note: AUCs were compared using the DeLong test. The difference between the two AUCs was 0.120 (95% CI: 0.067–0.174, P < 0.0001).

5. Discussion

In the present study, we demonstrated that LCAT concentrations in both serum and follicular fluid were significantly decreased in the PCOS group, a finding that has not been previously reported. Furthermore, Spearman's rank correlation test demonstrated a strong negative correlation between LCAT levels and the LH/FSH ratio, also between LCAT levels and testosterone. We further analyzed the expression of LCAT in different subgroups established based on the ratio of LH/FSH and found that the concentration of LCAT in the group with a high LH/FSH ratio was significantly higher than that in the group with a low LH/FSH ratio.

Previous studies have confirmed that patients with PCOS exhibit significant lipid metabolism disturbances, characterized by high triglycerides, low HDL-C, and impaired RCT efficiency[20]. These metabolic abnormalities are closely associated with the core pathological features of PCOS, including IR and hyperandrogenism[27, 28]. As a key enzyme in catalyzing cholesterol esterification, LCAT plays a critical role in cholesterol metabolism[29]. Reduced LCAT activity or expression has been shown to impair HDL maturation and RCT[30]. In the present study, we found a significant reduction in LCAT concentrations in the PCOS group. Referring to the metabolic abnormalities in patients with PCOS[31], this alteration suggests that LCAT may be involved in the pathogenesis and development of PCOS by regulating cholesterol metabolism. Although lipid metabolism disorders in patients with PCOS have received widespread attention and in-depth discussion, their specific pathological causes and molecular regulatory mechanisms have not been systematically elucidated. Notably, the association between LCAT and PCOS pathogenesis as well as abnormal lipid metabolism has not been reported in any existing literature, and the related mechanism of action remains a research gap. This study is the first to find the correlation between LCAT and PCOS, providing novel insights for understanding the mechanism of metabolic disorders in PCOS.

FSH is a key gonadotropin that regulates ovarian folliculogenesis[32], and abnormalities in FSH levels, such as relatively decreased FSH and elevated LH/FSH ratio commonly observed in PCOS patients, are important indicators of ovarian dysfunction[33]. In the present study, a significant positive correlation between LCAT and FSH was observed, suggesting that LCAT may synergistically participate in the process of follicle development and maturation. However, FSH may influence the expression of LCAT by regulating the function of ovarian granulosa cells. LCAT may utilize the RCT mechanism to directionally transport excess cholesterol accumulated in the ovaries to the liver for metabolic clearance[34, 35], reducing the substrate source for cholesterol conversion to testosterone in the ovaries, thereby optimizing the local ovarian microenvironment[14, 36]. Furthermore, LCAT may synergize with FSH to jointly activate signaling pathways related to follicular development, further promoting follicle growth and maturation and providing potential support for improving ovarian function in disease states[37]. This association provides new insights into unraveling the metabolic basis of follicle development disorders in patients with PCOS. We hypothesize that the decrease in LCAT in PCOS may exert its effects through the following pathways: 1) Metabolic pathway: Reduced LCAT leads to impaired cholesterol esterification, hindered HDL maturation, and decreased efficiency of RCT, which in turn causes lipid accumulation in peripheral tissues and IR, exacerbating metabolic abnormalities in PCOS[38, 39] and 2) Local ovarian regulation: The synthesis of steroid hormones in both ovarian granulosa cells and theca cells originate from cholesterol as the substrate[40]. LCAT may influence estrogen synthesis by regulating local cholesterol homeostasis in the ovary. Given that estrogen and FSH have a feedback regulatory relationship, changes in LCAT may indirectly affect FSH secretion or action[41]. The above mechanisms require verification in subsequent cell experiments or animal models.

Additionally, the present study revealed that follicle fluid LCAT was significantly associated with serum estradiol and progesterone, whereas no such statistical association was observed for serum LCAT. This finding suggests that the regulatory logic underlying LCAT expression differs between the systemic circulation (serum) and the reproductive compartment (follicular fluid). In another word, LCAT may exert tissue-specific modulation on the hypothalamic-pituitary-ovarian axis and intrafollicular steroid synthesis.

Further stratified analysis of PCOS patients based on an LH/FSH ratio cutoff of 2 showed that patients with LH/FSH ≥ 2 exhibited significantly lower serum LCAT levels than those with LH/FSH < 2. Since an elevated LH/FSH ratio is a typical clinical hallmark of severe endocrine dysfunction in PCOS, this finding further confirms that reduced LCAT expression is closely correlated with aggravated HPO axis disorder, reflecting a potential link between LCAT deficiency and the severity of PCOS endocrine abnormalities.

Notably, binary logistic regression analysis further validated the independent clinical value of LCAT in PCOS. Univariate regression identified LCAT as a significant influencing factor for PCOS. After adjusting for confounding factors including age, BMI, and total testosterone, LCAT remained an independent protective factor for PCOS. Collectively, these clinical findings consistently demonstrate that LCAT downregulation is an independent risk indicator for PCOS, and LCAT deficiency is tightly involved in the

core reproductive endocrine disturbances of PCOS, providing novel evidence for LCAT as a promising biomarker and potential therapeutic target for PCOS.

In the present study, serum LCAT alone showed a weak ability to discriminate PCOS from controls, with an AUC of 0.655. This is consistent with the heterogeneous nature of PCOS and suggests that a single biomarker may not be sufficient for classification[42]. LCAT is a key enzyme in HDL maturation and reverse cholesterol transport, catalyzing the esterification of free cholesterol on the surface of HDL particles to form mature spherical HDL[43]. Given that PCOS is frequently accompanied by dyslipidemia, insulin resistance, and impaired HDL function[44], it is biologically plausible that LCAT levels are altered in this population. When LCAT was combined with age and BMI, the AUC increased to 0.775, indicating a moderate improvement in discrimination. This finding implies that the clinical relevance of LCAT may be better captured in the context of other readily available demographic and anthropometric variables.

The findings of this study may have the following certain clinical implications: 1) Potential as a biomarker: The decreased LCAT concentration and its correlation with FSH may serve as a combined indicator for evaluating metabolic status and ovarian function in PCOS patients, especially with discriminative value for PCOS subtypes complicated with metabolic abnormalities and 2) Implications for therapeutic targets: If subsequent studies confirm that the downregulation of LCAT is a key link in the pathological progression of PCOS, regulating LCAT activity (e.g., improving its expression or function) may provide new therapeutic strategies for metabolic disorders and ovarian dysfunction in PCOS.

This study has several limitations. First, the cross-sectional design precludes conclusions regarding causality between decreased LCAT levels and the development of PCOS. Second, the limited sample size may introduce selection bias, and subsequent validation with a larger sample size is therefore essential. Third, the molecular mechanism underlying the association between LCAT and FSH has not been explored in depth, and it remains unclear whether it is mediated through the hypothalamic-pituitary-ovarian axis or metabolic pathways. Finally, potential confounding factors, such as dietary habits and detailed glucose and lipid metabolic indices, were not fully controlled and require further stratified analysis.

6.Conclusions

We demonstrated a novel expression pattern that LCAT concentrations in both serum and follicular fluid were decreased in the PCOS patients.We also found that LCAT level was negatively correlated with LH/FSH ratio,suggesting that LCAT may be involved in the disrupted growth and maturation of follicles in PCOS. Meanwhile, serum LCAT alone had limited discriminatory ability for PCOS, while combining LCAT with age and BMI improved the AUC to 0.775. These results suggest that LCAT may serve as a potential auxiliary biomarker for PCOS-related metabolic-endocrine dysfunction. In addition, the significant association between follicular fluid LCAT levels and serum sex hormones indicates that LCAT may act locally within the follicle to alleviate excessive estrogen overproduction and optimize the intrafollicular

hormonal microenvironment. Overall, LCAT is associated with ovulation dysfunction in PCOS and may serve as a new serological biomarker for its diagnosis.

Abbreviations

Abbreviation	Full Term
LCAT	Lecithin–Cholesterol Acyltransferase in
PCOS	Polycystic Ovary Syndrome
BMI	body mass index
LH	luteinizing hormone
FSH	follicle stimulating hormone
TT	testosterone
E2	estradiol
P	progesterone
PRL	prolactin
AMH	anti-mullerian hormone
ROC	receiver operating characteristic
AUC	area under the curve

Declarations

Ethics approval and consent to participate

All procedures performed in accordance with the Declaration of Helsinki.

This study was approved by the Institutional Ethics Committee (IEC) for Clinical Research of the Second Affiliated Hospital of Nanjing Medical University (Ethical Approval Number:2025-KY-

236-01) and General Hospital of the Eastern Theater Command (Ethical Approval Number:

2023DZKY-009-01). Informed consent was obtained from all individual participants included in the study. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors's contributions

BQ.X: Data collection and systematic organization,formal statistical analysis execution,design and operation of experiments,drafting of the manuscript;

WX.C: Data collection and systematic organization,formal statistical analysis execution,design and operation of experiments,drafting of the manuscript;

CY.Y: Data collection and systematic organization,formal statistical analysis execution,design and operation of experiments,drafting of the manuscript;

ZY.Z: Oversight of experimental design rationale and primary data interpretation;

TZ.T:Oversight of experimental design rationale and primary data interpretation;

Y. L: Project daily coordination,management of subject recruitment and follow-up procedures;

XY.Y: Provision of clinical cohort samples and associated clinical data;

B.Y: Provision of clinical cohort samples and associated clinical data,management of subject recruitment and follow-up procedures;

B.X: overall project administration,refinement of study design,final editing of the manuscript.

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Figures

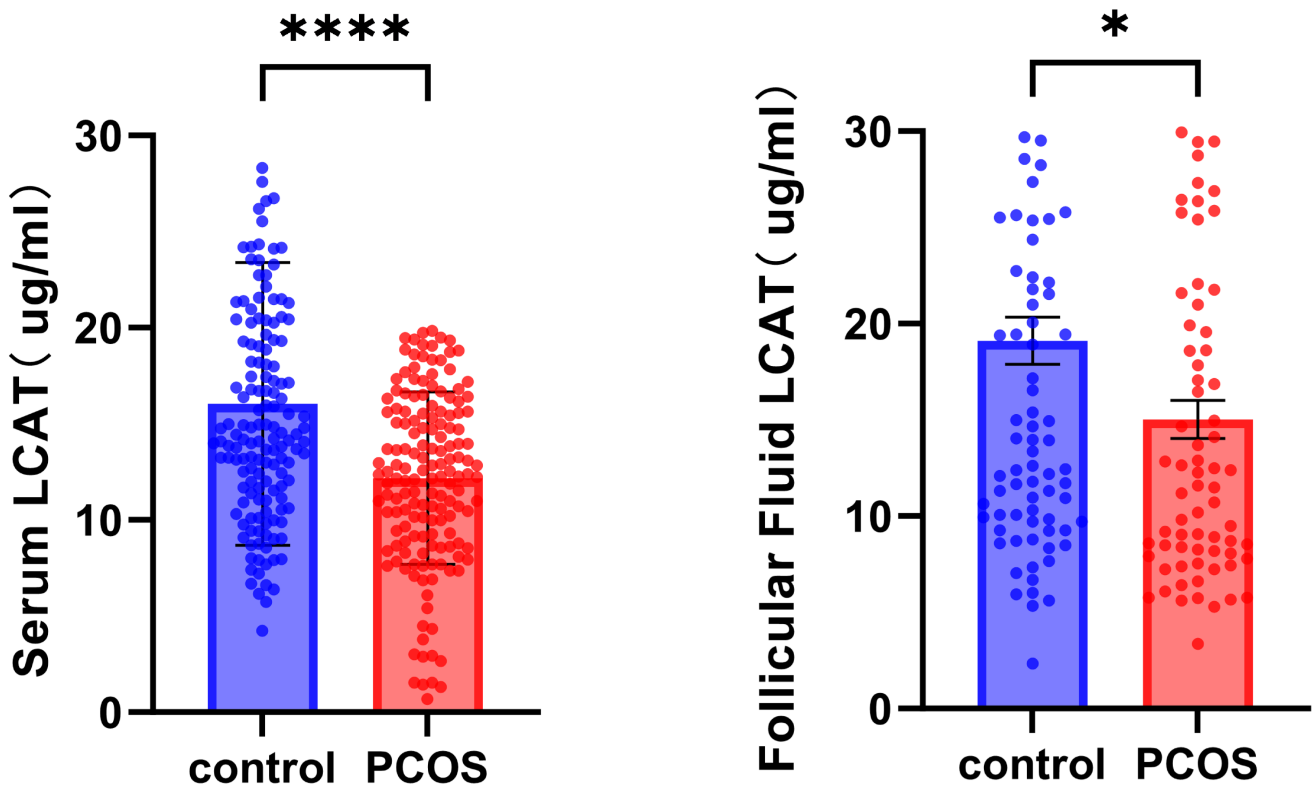


Figure 1

Expression of lecithin–cholesterol acyltransferase (LCAT) in serum and follicular fluid of controls and women with PCOS. Histograms showing the expression of LCAT protein in (A) serum of 156 women with PCOS and 148 controls and (B) follicular fluid of 74 women with PCOS and 85 controls were detected by enzyme-linked immunosorbent assay (ELISA). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

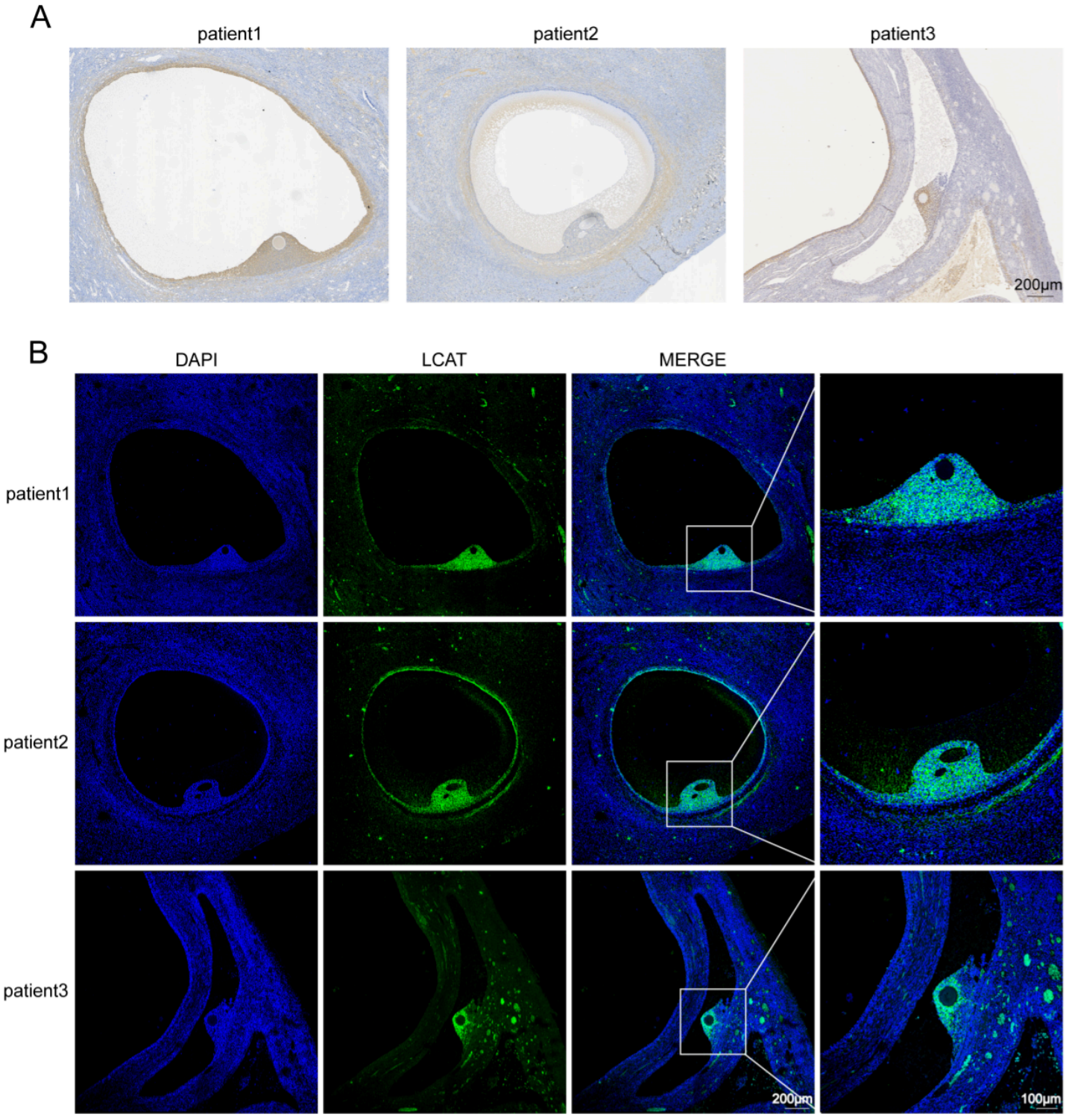


Figure 2

The expression and location of lecithin–cholesterol acyltransferase(LCAT) in the follicles of three human ovaries. (A) Immunohistochemical staining and (B) Immunofluorescence staining from representative ovarian follicle of three women, bar = 200μm, 100μm.

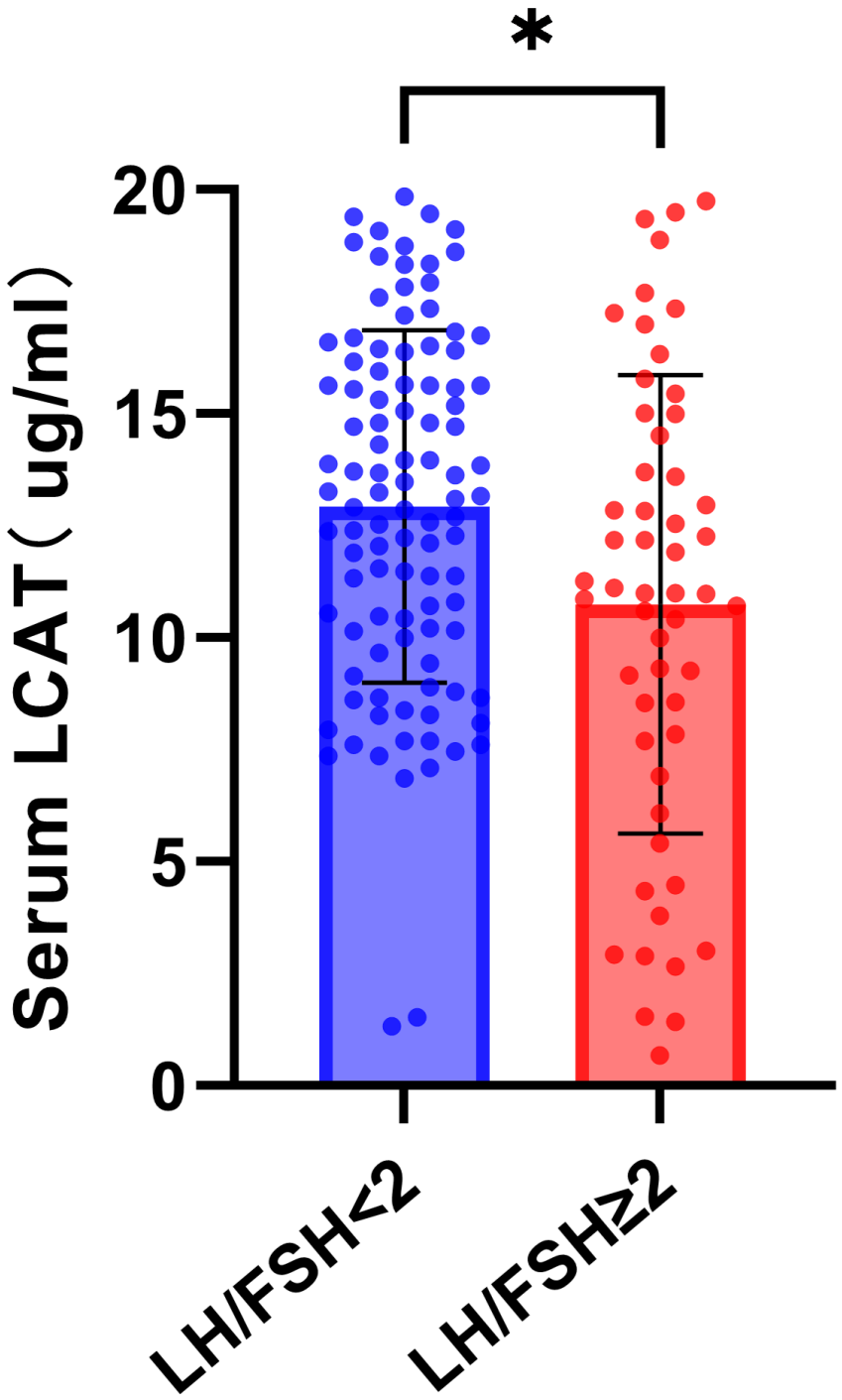


Figure 3

Comparison of LCAT concentrations among PCOS patients with different LH/FSH ratios. Serum of 102 patients with LH/FSH < 2 and 54 patients with LH/FSH ≥2. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

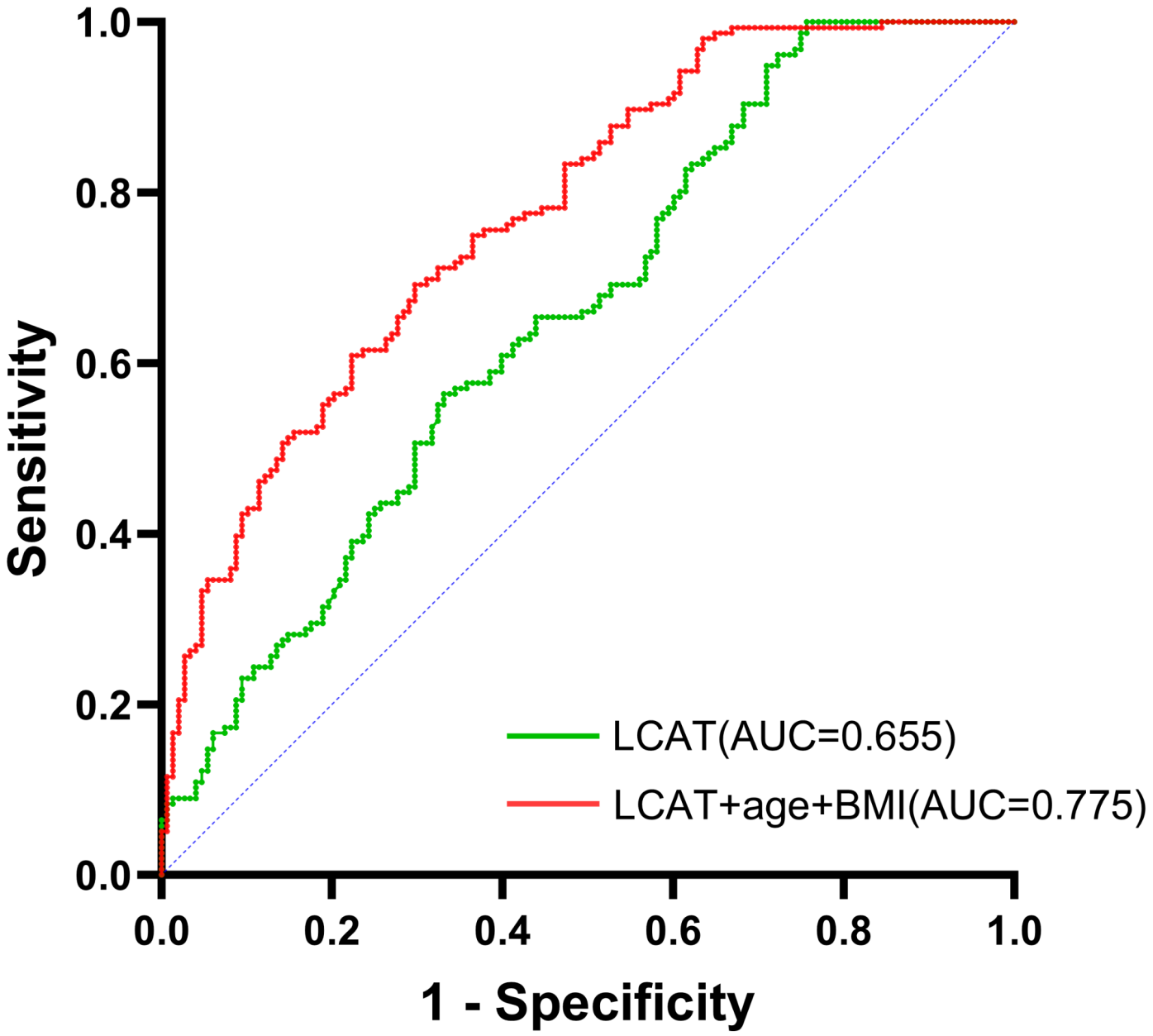


Figure 4

ROC curves for serum LCAT alone and the combined model in discriminating PCOS from controls The solid line represents LCAT alone (AUC = 0.655, 95% CI: 0.599–0.708). The dashed line represents the combined model of LCAT + age + BMI (AUC = 0.775, 95% CI: 0.724–0.821). The diagonal line indicates no discrimination.AUC, area under the curve; CI, confidence interval.