

Predictive Value of First-Trimester Serum TREM2 and SIGLEC1 Levels for Adverse Pregnancy Outcomes in Women with PCOS

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Objective: To investigate the predictive value of first-trimester serum triggering receptor expressed on myeloid cells 2 (TREM2) and sialic acid-binding immunoglobulin-like lectin 1 (SIGLEC1) levels for adverse pregnancy outcome (APO) in pregnant women with polycystic ovary syndrome (PCOS), and to provide novel biomarkers for risk stratification management during pregnancy.

Methods: This retrospective cohort study enrolled 380 singleton pregnant women with PCOS diagnosed between August 25, 2022, and January 25, 2025. Serum samples collected at gestational weeks 6–12 were retrieved from the biobank. TREM2 and SIGLEC1 concentrations were measured using ELISA. Participants were stratified into APO (n=117) and non-APO (n=263) groups. Receiver operating characteristic (ROC) curve analysis assessed predictive performance, and multivariable logistic regression identified independent risk factors.

Results: Comparison of clinical data revealed that serum TREM2 and SIGLEC1 levels in the first trimester were significantly higher in the APO group than in the non-APO group ($p < 0.05$). Additionally, waist circumference, fasting plasma glucose (FPG), fasting insulin (FINS), and homeostatic model assessment for insulin resistance (HOMA-IR) were all significantly elevated in the APO group compared with the non-APO group (all $p < 0.001$). ROC analysis showed TREM2 achieved an area under the curve (AUC) of 0.828 (sensitivity 80.23%, specificity 75.21%) and SIGLEC1 yielded an AUC of 0.815 (sensitivity 83.65%, specificity 63.25%). The combined model demonstrated superior predictive accuracy (AUC 0.899, sensitivity 84.79%, specificity 82.05%). Multivariable logistic regression analysis demonstrated that elevated waist circumference (OR = 1.035, 95% CI: 1.010–1.060), HOMA-IR (OR = 2.027, 95% CI: 1.053–3.902), TREM2 (OR = 1.007, 95% CI: 1.005–1.009), and SIGLEC1 (OR = 1.006, 95% CI: 1.004–1.008) were all independent risk factors for APO in pregnant women with PCOS (all $p < 0.05$). TREM2 and SIGLEC1 levels positively correlated with HOMA-IR ($r=0.202$ and 0.231 , respectively; both $p < 0.001$).

Conclusion: Elevated serum TREM2 and SIGLEC1 levels in early pregnancy are associated with overall APO risk in PCOS patients, and their combined detection shows predictive potential; differential predictive values for specific outcome subtypes await further validation.

Keywords: polycystic ovary syndrome, adverse pregnancy outcome, TREM2, SIGLEC1, insulin resistance, biomarker

Introduction

Polycystic ovary syndrome (PCOS) represents one of the most prevalent endocrine and metabolic disorders affecting women of reproductive age worldwide, with an estimated prevalence of 8%–20%.¹ The disease is characterized by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology (PCOM), and is frequently associated with metabolic disturbances including insulin resistance, obesity, and glucose and lipid metabolism disorders, which seriously affect female reproductive health.² Even after successful conception, women with established PCOS remain at heightened risk for adverse pregnancy outcomes (APO), including gestational diabetes mellitus, hypertensive disorders of pregnancy, preterm birth, fetal growth restriction, and miscarriage, with incidence rates significantly higher than those in

normal pregnant women.^{3,4} Therefore, early identification of high-risk populations for APO among pregnant women with PCOS is of important clinical significance for improving maternal and neonatal outcomes.

Recent studies have suggested that chronic subclinical inflammation and immunological-metabolic dysregulation contribute to the etiopathogenesis of PCOS. Research has demonstrated that an imbalance in the immune microenvironment characterized by abnormal macrophage activation exists in patients with PCOS. Dysregulation of the M1/M2 macrophage ratio can exacerbate local inflammatory responses in the ovary, thereby affecting follicular development, ovulation, and pregnancy outcomes.⁵ Additionally, PCOS frequently coexists with autoimmune abnormalities; the interplay between Hashimoto's thyroiditis and insulin resistance can influence ovarian morphology and function,⁶ further supporting the importance of immune-metabolic crosstalk in PCOS pathophysiology. Triggering receptor expressed on myeloid cells 2 (TREM2) and sialic acid-binding immunoglobulin-like lectin 1 (SIGLEC1) play key roles in macrophage activation, inflammatory regulation, and metabolic homeostasis, and are theoretically released into the circulation; however, their expression profiles and predictive value in the serum of pregnant women with PCOS remain to be clinically validated.^{7,8}

TREM2 belongs to the immunoglobulin superfamily and is primarily expressed on the surface of myeloid cells such as macrophages, microglia, and dendritic cells. It transmits signals through binding with the adaptor protein DAP12 and participates in regulating macrophage survival, proliferation, and phagocytic function.^{9,10} Its serum level (sTREM2) is associated with inflammatory status in metabolic diseases such as obesity and diabetes mellitus.^{11–13} SIGLEC1, as a type I interferon-induced marker molecule, can reflect disease activity in autoimmune diseases^{14,15} and represents one of the potential key genes shared between PCOS and atherosclerosis, with close associations to immune-inflammatory pathways.¹⁶

To date, studies on TREM2 and SIGLEC1 in PCOS have been largely confined to ovarian tissue or animal models, with no investigation in pregnant populations. The expression characteristics of SIGLEC1 in serum from patients with PCOS have yet to be reported. Furthermore, no study has evaluated the predictive value of TREM2 and SIGLEC1 for APOs in pregnant women with PCOS, and clinical evidence for combined testing in the first trimester is lacking. This study aims to detect first-trimester serum TREM2 and SIGLEC1 levels in women with PCOS, explore their association with APO, and evaluate their combined predictive value, to provide novel biomarkers for pregnancy risk stratification and management during pregnancy in this population.

Subjects and Methods

Study Subjects

Sample size determination was based on documented occurrence rates for preeclampsia, gestational diabetes mellitus, and miscarriage in previously reported PCOS populations.¹⁷ PASS software was used to calculate the sample size for confidence interval estimation of a single proportion based on the exact binomial distribution method (Exact/Clopper-Pearson method). Assuming a two-sided 95% confidence interval, an expected APO incidence of 30.2%, and a margin of error of 5.0%, the minimum required sample size was 342 cases. Accounting for a 10% attrition rate, a total of 380 subjects were finally enrolled.

This was a retrospective observational study. A total of 380 singleton pregnant women with PCOS who were registered at our hospital and diagnosed with PCOS between August 25, 2022, and January 25, 2025, were enrolled. All enrolled pregnant women had fasting venous blood collected during the first trimester (gestational weeks 6–12) at prenatal visits, and baseline clinical data were recorded.

Inclusion criteria: (1) PCOS diagnosed according to the 2023 International Evidence-Based Guideline for the assessment and management of PCOS in adults,¹⁸ specifically: ① exclusion of other similar conditions such as thyroid disorders, hyperprolactinemia, and non-classic congenital adrenal hyperplasia; ② fulfillment of at least two of the following three criteria: clinical and/or biochemical hyperandrogenism; ovulatory dysfunction/oligo-amenorrhea; PCOM: ultrasound showing ≥ 20 follicles per ovary and/or ovarian volume ≥ 10 mL, or elevated serum anti-Müllerian hormone (AMH) levels; ③ if both oligo-amenorrhea and hyperandrogenism were already present, ultrasound or AMH testing was not required for definitive diagnosis; (2) age ≥ 18 years; (3) singleton pregnancy; (4) registration at our hospital at 6–12 weeks of gestation with planned prenatal care and delivery at our institution. Exclusion criteria: (1) presence of dysfunction in critical organs including the

heart, liver, or lung; (2) presence of malignancy; (3) presence of psychiatric disorders or autoimmune diseases; (4) use of insulin sensitizers, anticoagulants, or other medications that may affect insulin resistance or pregnancy outcomes within 3 months prior to enrollment or during pregnancy; (5) presence of active infection; (6) presence of inherited metabolic disorders; (7) presence of other endocrine disorders such as thyroid dysfunction or adrenal cortical dysfunction; (8) history of adverse pregnancy outcomes such as miscarriage or preterm birth; (9) presence of severe malnutrition or extreme obesity (BMI >40 kg/m²); (10) known or subsequently detected factors during prenatal care that may adversely affect pregnancy outcomes, including chromosomal abnormalities, fetal structural anomalies, or placental abnormalities; (11) presence of deleterious lifestyle behaviors including tobacco use or excessive ethanol consumption; (12) conception through assisted reproductive technology; (13) occurrence of early miscarriage or embryonic demise at the time of enrollment; (14) loss to follow-up or voluntary withdrawal during the study period.

Methods

Collection of Clinical Data

Clinical data were retrieved from the electronic medical record (EMR) system of our institution for patients with PCOS, including age, parity, body mass index (BMI), waist circumference, diastolic blood pressure (DBP), systolic blood pressure (SBP), lipid metabolism indices, glucose metabolism indices, and PCOS-specific characteristics. Lipid metabolism indices included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Glucose metabolism indices included fasting plasma glucose (FPG), fasting insulin (FINS), glycated hemoglobin (HbA1c), and homeostatic model assessment for insulin resistance (HOMA-IR). PCOS-specific characteristics included diagnostic phenotypes (phenotype A: hyperandrogenism + oligo-anovulation + PCOM; phenotype B: hyperandrogenism + oligo-anovulation; phenotype C: hyperandrogenism + PCOM; phenotype D: oligo-anovulation + PCOM),¹⁹ modified Ferriman-Gallwey hirsutism score,²⁰ acne grade,²¹ and presence or absence of acanthosis nigricans.²² HOMA-IR was computed using the HOMA method:²³ $\text{HOMA-IR} = \text{FINS (mU/L)} \times \text{FPG (mmol/L)} / 22.5$.

Pregnancy Outcome Assessment

APO refers to clinical events occurring during pregnancy and delivery that adversely affect maternal and/or fetal health, primarily including hypertensive disorders of pregnancy²⁴ (eg., preeclampsia, gestational hypertension, and eclampsia), gestational diabetes mellitus,²⁵ fetal growth restriction,²⁶ preterm birth²⁷ (delivery from 24 weeks to <37 weeks of gestation), placental abruption,²⁸ and pregnancy loss²⁹ (stillbirth or miscarriage). Specifically, the diagnosis of preeclampsia requires hypertension ($\geq 140/90$ mmHg) developing after 20 weeks of gestation, accompanied by proteinuria or maternal end-organ dysfunction. Preterm birth is classified by gestational age into moderate preterm birth (<35 weeks) and mild preterm birth (35–36 weeks). Fetal growth restriction is defined as estimated fetal weight below the 10th percentile for gestational age.³⁰ These outcomes not only result in perinatal complications but are also significantly associated with increased long-term risks of maternal cardiovascular disease, type 2 diabetes mellitus, and chronic kidney disease; therefore, early identification and intervention are critical for improving maternal and neonatal outcomes. Based on the presence or absence of APO, participants were divided into the APO group (n=117) and the non-APO group (n=263).

Measurement of Serum TREM2 and SIGLEC1 Levels

Serum samples used in this study were retrieved from -80°C storage. All samples were collected during the first trimester (gestational weeks 6–12) at prenatal visits. To ensure preanalytical standardization, blood was drawn after an overnight fast of at least 8 hours between 08:00 and 10:00 a.m. into clot activator tubes and allowed to clot at room temperature for 30 minutes. Serum was separated by centrifugation within 1 hour of collection and immediately aliquoted into polypropylene tubes to avoid repeated freeze-thaw cycles. At biobank entry, the collection date, centrifugation time, aliquot volume, and storage location were recorded. Samples with visible hemolysis, lipemia, icterus, or abnormal protein content were excluded. The storage duration ranged from 6 to 42 months; all samples were single-use aliquots and had not undergone freeze-thaw cycles prior to analysis.

Prior to analysis, serum samples and all reagent kit components were equilibrated to room temperature (18–25°C). Serum TREM2 and SIGLEC1 levels were measured by enzyme-linked immunosorbent assay (ELISA) using the Human TREM2 ELISA Kit (catalog number ab224881, Abcam, Cambridge, UK) and the Human SIGLEC1 ELISA Kit (catalog number ab213757, Abcam, Cambridge, UK), respectively. All samples were analyzed across four assay batches. Each batch included a complete set of calibration standards and two quality-control (QC) samples (one low-concentration and one high-concentration pooled serum). The inter-batch CVs for QC samples were 7.2% for TREM2 and 8.1% for SIGLEC1. Samples from the APO and non-APO groups were randomized across batches, and laboratory personnel were blinded to clinical outcomes throughout all analytical procedures.

After dilution, serum samples were added to precoated 96-well plates. For the TREM2 assay, the antibody cocktail was added and incubated with shaking at room temperature for 1 hour; after washing, tetramethylbenzidine (TMB) substrate was added for color development for 10 minutes. For the SIGLEC1 assay, biotinylated detection antibody and avidin-biotin-peroxidase complex were added sequentially and incubated at 37°C; after washing, TMB substrate was added for color development for 15–25 minutes. Absorbance was measured at 450 nm for both assays, and concentrations were calculated from standard curves. Both assays employed standard curves and blank controls; all samples were run in duplicate. The intra-assay and inter-assay coefficients of variation (CV) for the TREM2 kit were 6.3% and 4.9%, respectively. For the SIGLEC1 kit, the intra-assay CV ranged from 5.9% to 7.6% and the inter-assay CV ranged from 6.7% to 9.0%. All CV values were below 10%.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 26.0, and figures were created using GraphPad Prism version 10.0. Normality was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean $\pm$ SD, and between-group comparisons were performed using the *t*-test. Non-normally distributed continuous variables were expressed as median (IQR), and comparisons between two groups were performed using the Mann–Whitney *U*-test. Categorical variables were expressed as frequency (n) and percentage (%), and group comparisons were performed using the χ^2 test. Multivariable logistic regression analysis using the forced entry method (ENTER) was performed to identify risk factors affecting pregnancy outcomes in patients with PCOS. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum TREM2 and SIGLEC1 levels for APO in patients with PCOS. To assess the robustness of the predictive model, internal validation was conducted using the Bootstrap method (1000 resamples with replacement), and the optimism was calculated. Optimism was defined as the difference between the apparent area under the curve (AUC) and the bootstrap-validated AUC (Optimism = Apparent AUC – Bootstrap-validated AUC), and the bias-corrected AUC was calculated as Apparent AUC – Optimism. As both TREM2 and HOMA-IR were non-normally distributed, Spearman's rank correlation was used to examine the correlations of serum TREM2 and SIGLEC1 levels with HOMA-IR. $P < 0.05$ was considered statistically significant in this study.

Results

Bioinformatics Analysis Results

Exploratory bioinformatics analysis was performed using the GSE34526 microarray data from the Gene Expression Omnibus (GEO) database. This dataset was derived from granulosa cells of patients with PCOS with or without insulin resistance. Differential expression analysis was conducted using the GEO2R online tool, with screening criteria of adjusted *p*-value < 0.05 and $|\log_2\text{fold change (FC)}| > 1$, yielding a total of 4,045 differentially expressed genes. Among these, both TREM2 and SIGLEC1 were significantly upregulated in patients with PCOS with insulin resistance (Figure 1). To further explore functional associations, 18 highly expressed genes ($\log_2\text{FC} > 4$) were imported into the STRING database to construct a protein-protein interaction (PPI) network. PPI network analysis revealed that both TREM2 and SIGLEC1 were located in the core region of the network, and a direct protein-protein interaction existed between the two. Given that both TREM2 and SIGLEC1 can be released into circulation through shedding or secretion, these findings suggest that both molecules may serve as potential circulating biomarkers for PCOS with insulin

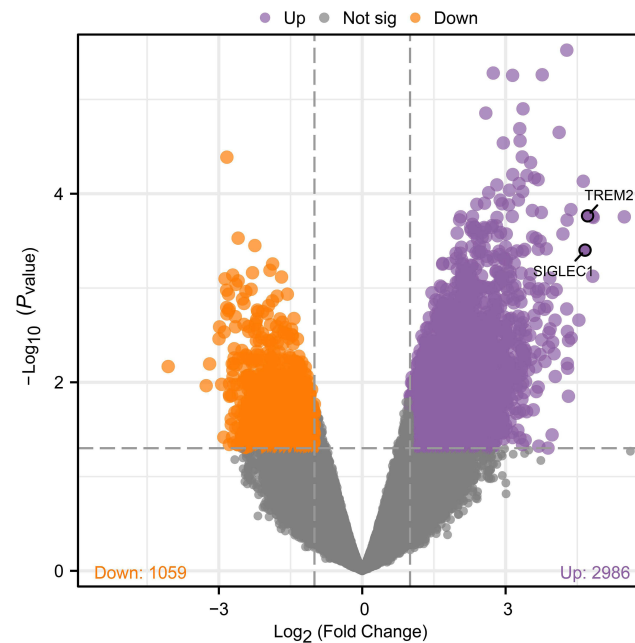


Figure 1 Bioinformatics analysis results of GSE34526 microarray data.

Note: Differential expression analysis was performed using GEO2R with criteria of adjusted $p < 0.05$ and $|\log_2 \text{fold change}| > 1$. Purple dots indicate upregulated genes (Up: 2,986), orange dots indicate downregulated genes (Down: 1,059), and gray dots indicate non-significant genes.

resistance. It should be emphasized that this analysis was based solely on publicly available transcriptomic data from granulosa cells, which represents a dimension distinct from clinical serum ELISA detection. Therefore, the bioinformatics results cannot serve as direct mechanistic evidence for the predictive value of serum biomarkers, but rather provide preliminary clues for hypothesis generation.

Comparison of TREM2 and SIGLEC1 Levels Between the Two Groups

In pregnant women with PCOS, first-trimester serum TREM2 and SIGLEC1 levels were significantly higher in the APO group than in the non-APO group, and the differences were statistically significant ($p < 0.05$) (Figure 2).

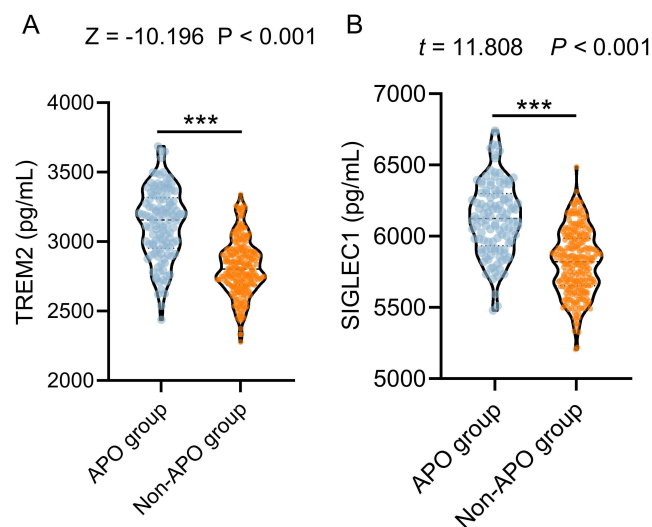


Figure 2 Comparison of serum TREM2 and SIGLEC1 levels between the two groups.

Note: (A) Serum TREM2 levels were significantly higher in the APO group than in the non-APO group (Mann–Whitney U -test, $Z = -10.196$, $p < 0.001$). (B) Serum SIGLEC1 levels were significantly higher in the APO group than in the non-APO group (t -test, $t = 11.808$, $P < 0.001$). *** $p < 0.001$.

Comparison of Clinical Characteristics

No significant differences were detected in age, parity, BMI, blood pressure, TG, HDL-C, or LDL-C between groups (all $p > 0.05$). The APO group exhibited significantly higher waist circumference and FPG, FINS, and HOMA-IR levels compared with the non-APO group (all $p < 0.001$), along with significantly elevated TC levels ($p=0.043$). No significant differences were observed between the two groups in the distribution of PCOS diagnostic phenotypes (phenotypes A/B/C/D), modified Ferriman-Gallwey hirsutism scores, acne grades, or the incidence of acanthosis nigricans (all $p > 0.05$) (Table 1).

Predictive Value of Serum TREM2 and SIGLEC1 for APO in Pregnant Women with PCOS

ROC curve analysis showed that serum TREM2 and SIGLEC1 individually had AUC values of 0.828 and 0.815, respectively, in predicting APO in patients with PCOS, whereas the combined model had an AUC of 0.899, significantly higher than that of either marker alone, with concomitant increases in both sensitivity and specificity. The apparent AUC of the combined prediction model was 0.899. After 1,000 bootstrap resampling iterations, the mean AUC in the bootstrap validation samples was 0.897, with an optimism of 0.002 (0.22%). The bias-corrected AUC was 0.897. These findings

Table 1 Comparison of Clinical Characteristics

Variable	APO Group (n = 117)	Non-APO Group (n = 263)	t/Z/ χ^2	P
Age (years)	27.00 (25.00,29.00)	28.00 (26.00,30.00)	-1.048 [#]	0.294
Parity [n (%)]			0.225 [^]	0.635
Multiparous	38 (32.48)	93 (34.98)		
Nulliparous	79 (67.52)	171 (65.02)		
BMI (kg/m ²)	24.41±2.43	24.38±2.40	0.037*	0.970
Waist circumference (cm)	100.49±18.96	89.94±15.28	5.302*	<0.001
DBP (mmHg)	79.32±6.81	79.04±7.64	0.349*	0.727
SBP (mmHg)	131.00 (127.00,135.00)	131.00 (126.00,135.00)	-0.286 [#]	0.775
TC (mmol/L)	5.10 (4.70,5.50)	5.00 (4.70,5.30)	-2.028 [#]	0.043
TG (mmol/L)	2.30 (1.80,2.60)	2.10 (1.70,2.50)	-1.413 [#]	0.158
HDL-C (mmol/L)	1.26±0.22	1.23±0.31	1.089*	0.277
LDL-C (mmol/L)	2.58±0.90	2.73±0.77	-1.665*	0.097
FPG (mmol/L)	5.25 (5.03,5.52)	4.72 (4.16,5.30)	-7.015 [#]	<0.001
FINS (mU/L)	7.80±0.99	6.88±1.12	7.653*	<0.001
HOMA-IR	2.81 (2.60,3.12)	2.35 (2.04,2.65)	9.381 [#] *	<0.001
PCOS diagnostic phenotype [n (%)]			2.991 [^]	0.405
Phenotype A	78 (66.66)	173 (65.78)		
Phenotype B	12 (10.26)	29 (11.03)		
Phenotype C	15 (12.82)	45 (17.11)		
Phenotype D	12 (10.26)	16 (6.08)		
Modified Ferriman-Gallwey hirsutism score (points)	7.00 (5.00,9.00)	6.00 (4.00,9.00)	-0.276 [#]	0.782
Acne grade [n (%)]			0.279 [^]	0.870
Mild	59 (50.43)	136 (51.71)		
Moderate	41 (35.04)	94 (35.74)		
Severe	17 (14.53)	33 (12.55)		
Acanthosis nigricans [n (%)]			2.925 [^]	0.087
Present	22 (18.80)	32 (12.17)		
Absent	95 (81.20)	231 (87.83)		

Note: [^] indicates χ^2 value; [#] indicates Z value; * indicates t value.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostatic model assessment for insulin resistance.

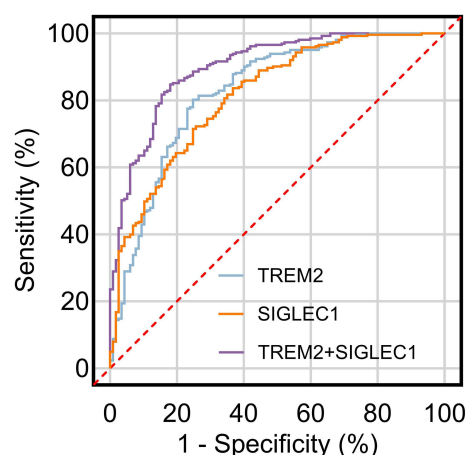


Figure 3 ROC curves of serum TREM2 and SIGLEC1 for predicting pregnancy outcomes in patients with PCOS.

Note: TREM2: AUC = 0.828 (95% CI: 0.780–0.875); SIGLEC1: AUC = 0.815 (95% CI: 0.768–0.861); TREM2 + SIGLEC1 combined: AUC = 0.899 (95% CI: 0.866–0.933). The AUC of the combined model was significantly superior to that of either single marker (DeLong test, $p < 0.05$).

indicate that the model has minimal overfitting and that the bias-corrected model retains favorable discriminatory performance and internal stability (Figure 3 and Table 2).

Multivariable Analysis of APO Predictors in PCOS Pregnancies

Clinically important indicators (age, BMI, waist circumference, SBP, DBP, TC, TG, HDL-C, LDL-C, PCOS diagnostic subtype, modified Ferriman-Gallwey hirsutism score, acne grade, acanthosis nigricans, HOMA-IR, TREM2, and SIGLEC1) were all incorporated into a multivariable logistic regression model using ENTER. Due to severe collinearity among FPG, FINS, and HOMA-IR (variance inflation factor [VIF] >40), and because HOMA-IR is a clinically recognized comprehensive indicator of insulin resistance, only HOMA-IR was retained to ensure model stability and interpretability. Multivariable logistic regression analysis was performed with pregnancy outcomes in women with PCOS (APO = 1, non-APO = 0) as the dependent variable and waist circumference, HOMA-IR, TREM2, and SIGLEC1 as independent variables. The results showed that elevated waist circumference (OR=1.035, 95% CI: 1.010–1.060), elevated HOMA-IR (OR=2.027, 95% CI: 1.053–3.902), elevated TREM2 (OR=1.007, 95% CI: 1.005–1.009), and elevated SIGLEC1 (OR=1.006, 95% CI: 1.004–1.008) were all risk factors for APO in pregnant women with PCOS (all $p < 0.05$). Although age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, PCOS diagnostic subtype, modified Ferriman-Gallwey hirsutism score, acne grade, and acanthosis nigricans were included in the model, none were statistically significant (all $p > 0.05$) (Table 3).

Correlation Analysis of Serum TREM2 and SIGLEC1 Levels with HOMA-IR

Spearman correlation analysis revealed that serum TREM2 and SIGLEC1 levels were both positively associated with HOMA-IR ($r = 0.202$, $p < 0.001$; $r = 0.231$, $p < 0.001$) (Figure 4).

Table 2 Predictive Value of Serum TREM2 and SIGLEC1 for APO in Pregnant Women with PCOS

Variable	Cut-off	Sensitivity%	Specificity%	AUC	95% CI
TREM2	2960.00 pg/mL	80.23	75.21	0.828	0.780–0.875
SIGLEC1	6049.00 pg/mL	83.65	63.25	0.815	0.768–0.861
TREM2+ SIGLEC1	–	84.79	82.05	0.899	0.866–0.933

Table 3 Multivariable Logistic Regression Analysis of Factors Influencing APO in Pregnant Women with PCOS

Variable	β	S.E	Walds	P	OR	95% CI	Tolerance	VIF
Waist circumference	0.034	0.012	7.588	0.006	1.035	1.010–1.060	0.876	1.142
HOMA-IR	0.706	0.334	4.470	0.034	2.027	1.053–3.902	0.882	1.133
TREM2	0.007	0.001	63.032	<0.001	1.007	1.005–1.009	0.866	1.155
SIGLEC1	0.006	0.001	38.308	<0.001	1.006	1.004–1.008	0.862	1.160

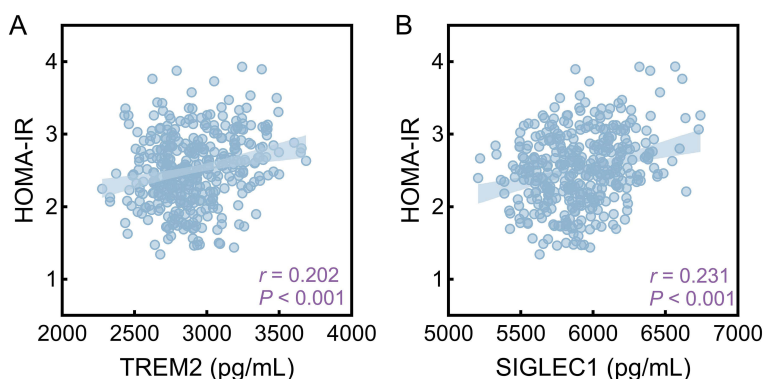
Note: Only statistically significant variables are shown in the table above.

Discussion

This study assessed the predictive value of first-trimester serum TREM2 and SIGLEC1 levels for APO in pregnant women with PCOS. The results revealed significantly higher serum TREM2 and SIGLEC1 levels in the APO group of pregnant women with PCOS. ROC curve analysis showed that the combined assessment of TREM2 and SIGLEC1 exhibited favorable predictive performance for APO and outperformed individual markers. These findings suggest that serum TREM2 and SIGLEC1 may serve as potential predictive biomarkers for APO in pregnant women with PCOS.

Pregnant women with PCOS frequently exhibit insulin resistance and lipid metabolism disorders. These metabolic abnormalities can activate inflammasomes (eg., NLRP3), thereby promoting the release of pro-inflammatory cytokines such as IL-1 β and exacerbating systemic inflammatory responses.^{31,32} Elevated TREM2 expression in PCOS is closely associated with macrophage polarization imbalance. Studies have demonstrated that TREM2 is significantly upregulated in the ovarian tissue of patients with PCOS and is closely related to M2-type macrophage polarization, potentially affecting ovarian function by modulating the local immune microenvironment.³³ Furthermore, TREM2 may serve as a sensor of metabolic stress, with its expression upregulated in lipid overload and inflammatory microenvironments.^{34,35} Elevated serum TREM2 levels may reflect the severity of metabolic-immune disturbances; however, comprehensive assessment incorporating additional indicators is required to evaluate APO risk. SIGLEC1, as a type I interferon-inducible gene, was identified by Zhang et al through bioinformatics analysis as a key gene underlying the comorbidity of PCOS and atherosclerosis, a finding that further supports the important role of interferon signaling pathways in PCOS.¹⁶ The present study found elevated serum SIGLEC1 levels in pregnant women with PCOS, providing preliminary evidence for aberrant activation of the type I interferon system in PCOS. However, the weak correlation between SIGLEC1 and HOMA-IR suggests that its elevation may not be entirely driven by insulin resistance.

Multivariable logistic regression analysis demonstrated that both TREM2 and SIGLEC1 were independent risk factors for APO, indicating that elevated serum TREM2 and SIGLEC1 levels were independently associated with increased APO risk. Logistic regression analysis also identified waist circumference and HOMA-IR as independent

**Figure 4** Spearman correlation of serum TREM2 and SIGLEC1 levels with HOMA-IR in pregnant women with PCOS.

Note: (A) Serum TREM2 levels were positively correlated with HOMA-IR ($r = 0.202$, $p < 0.001$). (B) Serum SIGLEC1 levels were positively correlated with HOMA-IR ($r = 0.231$, $p < 0.001$).

risk factors, suggesting that central obesity is an important metabolic risk factor for APO³⁶ and that insulin resistance is also closely related to pregnancy outcomes.^{37,38}

In this study, the combination of TREM2 and SIGLEC1 demonstrated superior predictive performance compared with either marker alone. This may be attributed to their distinct biological functions: TREM2 primarily regulates macrophage phagocytosis and polarization, whereas SIGLEC1 mediates intercellular adhesion and antigen presentation. Together, they may act synergistically in innate immunity. Correlation analysis revealed that both TREM2 and SIGLEC1 were positively correlated with HOMA-IR; however, the correlation coefficients were relatively low ($r = 0.202$ and 0.231 , respectively), suggesting a limited association between these markers and insulin resistance. The predictive value of TREM2 and SIGLEC1 for APO may not primarily lie in reflecting the degree of insulin resistance, but may instead involve other immune-metabolic interactive mechanisms. This weak correlation may also be attributable to sample heterogeneity, the timing of measurement (a single assessment during early pregnancy), or the inherent limitations of HOMA-IR as a surrogate marker for insulin resistance.

These findings provide novel insights into pregnancy management in women with PCOS. Measurement of serum TREM2 and SIGLEC1 levels in the first trimester (6–12 weeks) may facilitate early identification of women at high risk for APO, thereby enabling individualized monitoring and intervention. For those with elevated levels, increased frequency of prenatal surveillance, early screening for gestational diabetes mellitus and hypertensive disorders of pregnancy, and investigation of the potential benefits of anti-inflammatory or immunomodulatory therapies may be considered. Bioinformatics analysis failed to provide direct mechanistic evidence for a causal association between these serum biomarkers and APO; future studies incorporating animal models and in vitro experiments are warranted to further elucidate the underlying mechanisms.

This study has several limitations. First, it was a single-center retrospective study with a relatively limited sample size. Serum samples were stored at -80°C for 6 to 42 months as single-use aliquots without freeze-thaw cycles; however, the direct impact of such long-term cryopreservation on TREM2 and SIGLEC1 stability was not internally validated. Although bootstrap internal validation demonstrated good stability of the combined prediction model, independent external validation is still lacking, and the reported performance requires further validation in multicenter prospective cohorts. Second, as an observational study, causal relationships of TREM2 and SIGLEC1 with APO could not be established, and their underlying mechanisms remain to be elucidated through animal studies and in vitro experiments. Third, APO was a composite endpoint encompassing heterogeneous outcomes including gestational diabetes mellitus, hypertensive disorders of pregnancy, preterm birth, fetal growth restriction, and pregnancy loss. Stratified analyses by specific APO subtypes were not performed, making it difficult to clarify the strength of association of TREM2 and SIGLEC1 with individual outcomes. Fourth, dynamic monitoring of TREM2 and SIGLEC1 levels throughout gestation was not conducted, precluding assessment of their value as biomarkers for treatment response. Fifth, bioinformatics analyses did not provide direct mechanistic evidence for a causal association between these serum biomarkers and APO. Sixth, other previously reported PCOS-related APO predictors (such as AMH, adiponectin, IL-6, TNF- α , CRP, VEGF, PlGF, and sFlt-1) were not included for multi-marker comparison; therefore, the incremental predictive value of TREM2 and SIGLEC1 could not be quantified using net reclassification improvement (NRI), integrated discrimination improvement (IDI), or decision curve analysis. Their clinical incremental contribution remains to be confirmed in prospective studies. Future research should construct a base model incorporating routine clinical indicators and systematically evaluate the incremental contribution and cost-effectiveness ratio of novel biomarkers. Seventh, potential confounding factors were not adequately controlled, including visceral adipose tissue area, gestational weight gain, glycemic variability, ambulatory blood pressure, medication use during pregnancy, assisted reproductive technology-related factors, and genetic susceptibility.

In summary, this study demonstrated that elevated serum levels of TREM2 and SIGLEC1 in the first trimester are associated with APO in pregnant women with PCOS, and combined assessment of these biomarkers confers modest predictive potential. However, given the single-center retrospective design, these findings should be considered preliminary and exploratory. TREM2 and SIGLEC1 hold promise as biomarkers for risk stratification of APO in this population, yet their definitive clinical utility warrants further validation through multicenter prospective studies and comparison with existing prediction models. Should future studies confirm their incremental predictive value, these biomarkers may serve as a novel adjunctive tool for pregnancy risk stratification in women with PCOS.

Data Sharing Statement

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

Ethical Statement

This study was reviewed and approved by the Ethics Committee of Qinhuangdao Maternal and Child Health Hospital (approval number: QHDFY-2025061801). Given the retrospective nature of this study, the requirement for informed consent was waived by the Ethics Committee. All patient data were anonymized and handled in strict confidentiality. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests.

References

1. Singh S, Pal N, Shubham S, et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. *J Clin Med*. 2023;12(4):1454. doi:10.3390/jcm12041454
2. Shrivastava S, Conigliaro RL. Polycystic ovarian syndrome. *Med Clin North Am*. 2023;107(2):227–234. doi:10.1016/j.mcna.2022.10.004
3. Bahri Khomami M, Teede HJ. Addressing polycystic ovary syndrome in pregnancy care to improve outcomes. *JAMA Netw Open*. 2024;7(8):e2430549. doi:10.1001/jamanetworkopen.2024.30549
4. Slouha E, Alvarez VC, Gates KM, Ankras NMN, Clunes LA, Kollias TF. Gestational diabetes mellitus in the setting of polycystic ovarian syndrome: a systematic review. *Cureus*. 2023;15(12):e50725. doi:10.7759/cureus.50725
5. Li L, Xiao Y, Wen W, et al. The role of macrophages in polycystic ovary syndrome: a review. *Medicine*. 2025;104(17):e42228. doi:10.1097/md.00000000000042228
6. Gencer G, Serin AN, Gencer K. Analysis of the effect of hashimoto's thyroiditis and insulin resistance on ovarian volume in patients with polycystic ovary syndrome. *BMC Womens Health*. 2023;23(1):86. doi:10.1186/s12905-023-02200-x
7. Colmenares MT, de Oliveira Matos A, dos Santos Dantas PH, et al. Unveiling the impact of TREM-2(+) Macrophages in metabolic disorders. *Cell Immunol*. 2024;405–406:104882. doi:10.1016/j.cellimm.2024.104882
8. Qi W, Liu C, Shi L, et al. CD169+ Macrophages Mediate the Immune Response of Allergic Rhinitis Through the Keap1/Nrf2/HO-1 Axis. *Adv Sci*. 2024;11(45):e2309331. doi:10.1002/advs.202309331
9. Xing J, Titus AR, Humphrey MB. The TREM2-DAP12 signaling pathway in Nasu-Hakola disease: a molecular genetics perspective. *Res Rep Biochem*. 2015;5:89–100. doi:10.2147/rrbc.S58057
10. Zhong L, Zhang ZL, Li X, et al. TREM2/DAP12 complex regulates inflammatory responses in microglia via the jnk signaling pathway. *Front Aging Neurosci*. 2017;9:204. doi:10.3389/fnagi.2017.00204
11. Tanaka M, Yamakage H, Muranaka K, et al. Higher Serum Soluble TREM2 as a Potential Indicative Biomarker for Cognitive Impairment in Inadequately Controlled Type 2 Diabetes Without Obesity: the DOR-KyotoJ-1. *Front Endocrinol*. 2022;13:880148. doi:10.3389/fendo.2022.880148
12. Choi C, Lee J, Park G, Namgoong S, Lee YH. Obesity-induced pyroptotic adipocyte death leads to TREM2-dependent macrophage dysfunction and adipose tissue inflammation. *iScience*. 2026;29(1):114358. doi:10.1016/j.isci.2025.114358
13. Lu Y, Zhao Y, Zhang Q, et al. Soluble TREM2 is associated with death and cardiovascular events after acute ischemic stroke: an observational study from CATIS. *J Neuroinflammation*. 2022;19(1):88. doi:10.1186/s12974-022-02440-y
14. Ishihara R, Watanabe R, Shiomi M, et al. The type I interferon axis in systemic autoimmune diseases: from molecular pathways to targeted therapy. *Biomolecules*. 2025;15(11). doi:10.3390/biom15111586
15. Oliveira JJ, Karrar S, Rainbow DB, et al. The plasma biomarker soluble SIGLEC-1 is associated with the type I interferon transcriptional signature, ethnic background and renal disease in systemic lupus erythematosus. *Arthritis Res Ther*. 2018;20(1):152. doi:10.1186/s13075-018-1649-1
16. Wang L, Zhang Y, Ji F, et al. Identification of crucial genes for polycystic ovary syndrome and atherosclerosis through comprehensive bioinformatics analysis and machine learning. *Int J Gynaecol Obstet*. 2025;170(1):312–325. doi:10.1002/ijgo.70014
17. Foroozanfar F, Asemi Z, Bazarganipour F, Taghavi SA, Allan H, Aramesh S. Comparing pregnancy, childbirth, and neonatal outcomes in women with different phenotypes of polycystic ovary syndrome and healthy women: a prospective cohort study. *Gynecol Endocrinol*. 2020;36(1):61–65. doi:10.1080/09513590.2019.1631278
18. Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Eur J Endocrinol*. 2023;189(2):G43–g64. doi:10.1093/ejendo/lvad096
19. Sachdeva G, Gainder S, Suri V, Sachdeva N, Chopra S. Comparison of the different pcso phenotypes based on clinical metabolic, and hormonal profile, and their response to clomiphene. *Indian J Endocrinol Metab*. 2019;23(3):326–331. doi:10.4103/ijem.IJEM_30_19
20. Ilagan M, Paz-Pacheco E, Totesora DZ, Clemente-Chua LR, Jalique JRK. The modified ferriman-gallwey score and hirsutism among filipino women. *Endocrinol Metab*. 2019;34(4):374–381. doi:10.3803/EnM.2019.34.4.374
21. Bae IH, Kwak JH, Na CH, Kim MS, Shin BS, Choi H. A comprehensive review of the acne grading scale in 2023. *Ann Dermatol*. 2024;36(2):65–73. doi:10.5021/ad.23.094

22. Agrawal K, Mathur R, Purwar N, Mathur SK, Hyperandrogenism MDK. Insulin Resistance, and Acanthosis Nigricans (HAIR-AN) Syndrome Reflects Adipose Tissue Dysfunction (“Adiposopathy” or “Sick Fat”) in Asian Indian Girls. *Dermatology*. 2021;237(5):797–805. doi:10.1159/000512918
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419. doi:10.1007/bf00280883
24. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291–310. doi:10.1016/j.preghy.2018.05.004
25. ACOG Practice Bulletin No. 190. Gestational Diabetes Mellitus. *Obstet Gynecol*. 2018;131(2):e49–e64. doi:10.1097/AOG.0000000000002501.
26. Restriction FG. Fetal Growth Restriction: ACOG Practice Bulletin, Number 227. *Obstet Gynecol*. 2021;137(2):e16–e28. doi:10.1097/aog.0000000000004251
27. Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine*. 2016;34(49):6047–6056. doi:10.1016/j.vaccine.2016.03.045
28. Oyelese Y, Ananth CV. Placental abruption. *Obstet Gynecol*. 2006;108(4):1005–1016. doi:10.1097/01.AOG.0000239439.04364.9a
29. ACOG Practice Bulletin No. 200: early Pregnancy Loss. *Obstet Gynecol*. 2018;132(5):e197–e207. doi:10.1097/aog.0000000000002899.
30. Garr Barry V, Johnson TN, Herrick C, Lindley K, Carter EB. Adverse pregnancy outcomes and postpartum care as a pathway to future health. *Clin Obstet Gynecol*. 2022;65(3):632–647. doi:10.1097/grf.0000000000000724
31. Alenezi SA, Alshammari K, Khan R, Amer S. NLRP3 inflammasome and polycystic ovary syndrome (pcos): a novel profile in adipose tissue. *Int J Mol Sci*. 2026;27(2). doi:10.3390/ijms27020699
32. Bansal B, Thazhuthadath Kishore A, Kathiresan S, et al. A systematic review of inflammatory markers in polycystic ovary syndrome (PCOS) and meta-analysis of interleukin-6 (il-6) in case-control studies. *Cureus*. 2025;17(4):e82350. doi:10.7759/cureus.82350
33. Yuan Y, Mao Y, Yang L, Wang Y, Zhang X. Analysis of macrophage polarization and regulation characteristics in ovarian tissues of polycystic ovary syndrome. *Front Med Lausanne*. 2024;11:1417983. doi:10.3389/fmed.2024.1417983
34. Shi S, Zhou Y, Zhang H, Zhang J. TREM2 in MASH: integrating lipid metabolism and immune response. *Front Immunol*. 2025;16:1604837. doi:10.3389/fimmu.2025.1604837
35. Jaitin DA, Adlung L, Thaïs CA, et al. Lipid-associated macrophages control metabolic homeostasis in a trem2-dependent manner. *Cell*. 2019;178(3):686–698.e14. doi:10.1016/j.cell.2019.05.054
36. Brenes-Martín F, Melero-Jiménez V, López-Guerrero M, et al. First trimester evaluation of maternal visceral fat and its relationship with adverse pregnancy outcomes. *Biology*. 2023;12(2). doi:10.3390/biology12020144
37. Hu G. Are insulin sensitivity and β -cell function associated with adverse pregnancy outcomes among women with gestational diabetes? *Chin Med J*. 2022;135(21):2521–2524. doi:10.1097/cm9.0000000000002383
38. Bano S, Agrawal A, Asnani M, et al. Correlation of Insulin Resistance in Pregnancy with Obstetric Outcome. *J Obstet Gynaecol India*. 2021;71(5):495–500. doi:10.1007/s13224-021-01426-9

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