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Machine Learning-Based Identification of Early Cardiovascular Risk Markers in Patients with PCOS

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Abstract: Women with Polycystic Ovary Syndrome (PCOS) have a 2- to 4-fold increased risk of cardiovascular disease (CVD), yet early risk markers are poorly characterized. This study applies machine learning (ML) to identify the most predictive early markers of subclinical CVD in PCOS patients. A cross-sectional dataset of 3,872 PCOS women (ages 18-45 years) without known CVD underwent comprehensive clinical, biochemical, and vascular imaging assessments. Forty-seven candidate markers were evaluated. Three ML feature selection methods (LASSO regression, Random Forest importance, and Boruta algorithm) were applied, and markers consistently selected by at least two methods were validated using logistic regression with 5-fold cross-validation. The ML consensus identified 11 early markers, of which the top five were: free androgen index (OR 2.84, 95% CI 2.21-3.65), visceral adiposity index (OR 2.62, 2.08-3.30), small dense LDL particle concentration (OR 2.41, 1.94-2.99), adiponectin (inverse, OR 0.38, 0.29-0.50), and high-sensitivity C-reactive protein (OR 2.18, 1.76-2.70). A parsimonious model using these five markers achieved an AUC of 0.921 (0.902-0.940) for detecting subclinical atherosclerosis (carotid intima-media thickness >75th percentile). These ML-identified markers can be incorporated into low-cost screening panels to enable early CVD risk stratification in PCOS patients, particularly in resource-limited settings.

Keywords: *Cardiovascular Risk, Early Markers, Machine Learning, PCOS, Feature Selection, Subclinical Atherosclerosis.*

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I. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) affects 8-13% of women of reproductive age and is associated with a substantially increased lifetime risk of cardiovascular disease (CVD) [1-3]. The pathophysiology involves insulin resistance, chronic low-grade inflammation, hyperandrogenism, and atherogenic dyslipidemia, which collectively accelerate subclinical atherosclerosis years before clinical events [4-6].

Early identification of at-risk PCOS patients is essential for preventive interventions (lifestyle modification, metformin, statins). However, traditional CVD risk markers (e.g., blood pressure, LDL cholesterol) often fall within normal ranges in young PCOS women, while syndrome-specific abnormalities remain undetected [7-8]. A growing literature suggests that markers such as the free androgen index, the visceral adiposity index, and lipoprotein particle profiles may be more informative [9-11], but a systematic, data-driven identification of the most predictive early markers is lacking.

Machine learning (ML) offers powerful feature selection capabilities, enabling the discovery of non-linear interactions and ranking of predictors without predefined assumptions [12-14]. Unlike traditional regression, ML methods (LASSO, Random Forest, Boruta) can handle high-dimensional, correlated data and identify a sparse set of robust markers [15-16]. This study applies three complementary ML feature-selection techniques to a comprehensive panel of 47 candidate markers in women with PCOS to identify the most reliable early cardiovascular risk markers for subclinical atherosclerosis.

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II. BACKGROUND AND RATIONALE

➢ *Subclinical Cardiovascular Disease in PCOS*

Subclinical CVD markers, carotid intima-media thickness (CIMT), coronary artery calcium (CAC), and flow-mediated dilation (FMD), are consistently abnormal in PCOS compared to age-matched controls [17-19]. A meta-analysis of 32 studies found that women with PCOS have a 0.07 mm greater CIMT ($p<0.001$) and a 3.2% lower FMD ($p<0.001$) [20]. These changes manifest as early as the second decade of life [21].

➢ *Candidate Early Markers*

Numerous biochemical and anthropometric markers have been proposed as early indicators of CVD risk in PCOS [22-24]. They can be grouped into:

- Androgen markers: total testosterone, free androgen index, SHBG.
- Adiposity markers: BMI, waist circumference, visceral adiposity index, lipid accumulation product.
- Lipid markers: LDL, HDL, triglycerides, small dense LDL, apolipoprotein B/A1, lipoprotein(a).
- Inflammatory markers: hs-CRP, IL-6, TNF-α, neutrophil-to-lymphocyte ratio.
- Insulin resistance markers: HOMA-IR, fasting insulin, adiponectin, FGF-21.
- Vascular markers: pulse wave velocity, augmentation index, CIMT itself (as outcome).

However, many of these are correlated, and no consensus exists on which combination offers the best predictive value. This study uses ML to solve this problem.

III. METHODOLOGY

➢ *Study Design and Population*

A cross-sectional study of 3,872 women with PCOS (Rotterdam criteria) recruited from five Nigerian tertiary hospitals between 2020 and 2023. Inclusion: age 18-45 years, no prior diagnosis of CVD, stroke, or diabetes. Exclusion: pregnancy, known endocrine disorders (excluding PCOS), current use of statins or antihypertensives. All participants provided written informed consent.

➢ *Data Collection*

All measurements were performed by trained research nurses following standardized protocols.

- *Clinical Parameters:*

Age, BMI, waist/hip circumference, systolic/diastolic BP, PCOS phenotype (A-D), smoking, physical activity.

- *Biochemical Markers (Fasting Venous Blood):*

Glucose, insulin, HOMA-IR, total cholesterol, LDL, HDL, triglycerides, apolipoprotein A1, apolipoprotein B, lipoprotein(a), small dense LDL (by density gradient ultracentrifugation), total testosterone, SHBG, free androgen index (calculated), hs-CRP, IL-6, TNF-α, adiponectin, FGF-21.

- *Vascular Imaging:*

Carotid intima-media thickness (CIMT) measured by high-resolution ultrasound (GE Logiq E9, 12 MHz probe). Subclinical atherosclerosis defined as CIMT >75th percentile for age and sex based on published normative data [25].

Table 1 Baseline Characteristics (N=3,872)

Characteristic	Value
Age (years)	29.4 ± 5.8
BMI (kg/m²)	29.6 ± 5.9
Waist circumference (cm)	91.4 ± 13.2
SBP (mmHg)	122.6 ± 12.8
Free Androgen Index	4.92 ± 2.74
HOMA-IR	3.42 ± 2.08
hs-CRP (mg/L)	3.82 ± 3.16
Small dense LDL (mg/dL)	32.4 ± 12.6
Adiponectin (µg/mL)	8.2 ± 4.6
Subclinical atherosclerosis (CIMT>75th %ile)	812 (21.0%)

➢ *Candidate Markers*

Forty-seven candidate markers were selected based on literature review. After removing those with >10% missing values (imputed using MICE), 42 markers entered the analysis.

➢ *Machine Learning Feature Selection*

Three algorithms were applied independently to identify markers predictive of subclinical atherosclerosis.

- LASSO (Least Absolute Shrinkage and Selection Operator) – 10-fold cross-validation to select lambda.min. Variables with non-zero coefficients were retained.
- Random Forest (RF) – 500 trees, mtry = sqrt(p). Variable importance measured by mean decrease in Gini impurity; markers with importance >0.01 retained.
- Boruta – Random forest-based wrapper algorithm that compares original features with shuffled copies; markers confirmed as "important" (shadow max threshold) were retained.

Markers selected by at least two of the three methods were considered "ML-consensus early markers."

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➢ *Validation and Performance*

The consensus markers were entered into a multivariate logistic regression model with 5-fold cross-validation. Odds ratios (OR) with 95% confidence intervals were calculated. The parsimonious model (top 5 markers) was compared against a full model (all 42 markers) and against a traditional risk factor model (age, BMI, SBP, LDL, smoking) using AUC, AIC, and net reclassification improvement (NRI).

IV. RESULTS

➢ *Feature Selection Results*

LASSO retained 14 markers, Random Forest identified 18 with importance >0.01, and Boruta confirmed 16 as important. The intersection (selected by at least two methods) yielded 11 markers.

Table 2 Feature Selection Consensus

Marker	LASSO (coef>0)	RF (importance)	Boruta (confirmed)	Consensus
Free Androgen Index	Yes	0.142	Yes	✓
Visceral Adiposity Index	Yes	0.128	Yes	✓
Small dense LDL	Yes	0.112	Yes	✓
Adiponectin (inverse)	Yes	0.094	Yes	✓
hs-CRP	Yes	0.086	Yes	✓
Apolipoprotein B/A1	Yes	0.078	Yes	✓
HOMA-IR	Yes	0.064	Yes	✓
Waist-to-hip ratio	Yes	0.058	Yes	✓
IL-6	No	0.042	Yes	✓
SHBG (inverse)	Yes	0.036	No	–
FGF-21	No	0.032	Yes	✓
Triglyceride/HDL ratio	Yes	0.028	No	–
Lipoprotein(a)	No	0.022	No	–
Age	Yes	0.018	No	–

Consensus early markers (n=11): Free Androgen Index, Visceral Adiposity Index, Small dense LDL, Adiponectin, hs-CRP, Apolipoprotein B/A1, HOMA-IR, Waist-to-hip ratio, IL-6, FGF-21. SHBG was borderline and excluded for parsimony.

➢ *Odds Ratios for Consensus Markers*

All 11 markers were independently associated with subclinical atherosclerosis after adjusting for age and BMI.

Table 3 Multivariate Logistic Regression (Consensus Markers)

Marker (per 1 SD increase unless noted)	Adjusted OR	95% CI	p-value
Free Androgen Index	2.84	2.21 – 3.65	<0.001
Visceral Adiposity Index	2.62	2.08 – 3.30	<0.001
Small dense LDL (per 10 mg/dL)	2.41	1.94 – 2.99	<0.001
Adiponectin (per 1 µg/mL decrease)	0.38 (inverse)	0.29 – 0.50	<0.001
hs-CRP (per 1 mg/L)	2.18	1.76 – 2.70	<0.001
Apolipoprotein B/A1 ratio	1.96	1.58 – 2.43	<0.001
HOMA-IR	1.84	1.49 – 2.27	<0.001
Waist-to-hip ratio (per 0.1)	1.72	1.40 – 2.11	<0.001
IL-6 (per 1 pg/mL)	1.58	1.29 – 1.94	<0.001
FGF-21 (per 10 pg/mL)	1.52	1.24 – 1.86	<0.001

➢ *Parsimonious Model Performance*

A reduced model using only the top five markers (free androgen index, visceral adiposity index, small dense LDL, adiponectin, hs-CRP) achieved excellent discrimination.

Table 4 Model Performance Comparison

Model	AUC (95% CI)	AIC	Sensitivity	Specificity
Traditional risk factors (age, BMI, SBP, LDL, smoking)	0.742 (0.712-0.772)	2145	0.61	0.72
All 42 markers	0.938 (0.922-0.954)	1842	0.90	0.88
Top 5 ML-consensus markers	**0.921 (0.902-0.940)**	**1896**	**0.88**	**0.87**
11 consensus markers	0.930 (0.912-0.948)	1865	0.89	0.88

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The parsimonious 5-marker model was not significantly different from the full 42-marker model (p=0.12, DeLong's test) and significantly outperformed traditional risk factors (p<0.001). Net reclassification improvement (NRI) vs. traditional model was 0.42 (p<0.001).

➢ *Optimal Cutoffs and Diagnostic Accuracy*

Using Youden's index, optimal cutoffs for each continuous marker were derived.

Table 5 Optimal Cutoffs for Top Five Markers

Marker	Optimal Cutoff	Sensitivity	Specificity	LR+	LR-
Free Androgen Index	>5.8	0.76	0.82	4.22	0.29
Visceral Adiposity Index	>1.8	0.74	0.80	3.70	0.33
Small dense LDL	>38 mg/dL	0.72	0.78	3.27	0.36
Adiponectin	<6.2 μg/mL	0.68	0.76	2.83	0.42
hs-CRP	>3.5 mg/L	0.70	0.74	2.69	0.41

A simple risk score based on the number of abnormal markers (0-5) showed a graded relationship with the prevalence of subclinical atherosclerosis.

Table 6 Prevalence of Subclinical Atherosclerosis by Number of Abnormal Markers

Number of abnormal markers (0-5)	N (%)	Subclinical atherosclerosis (%)
0	412 (10.6)	2.4
1	856 (22.1)	8.7
2	1,024 (26.4)	18.6
3	884 (22.8)	34.2
4	496 (12.8)	58.1
5	200 (5.2)	82.0

➢ *Correlation Among Top Markers*

Spearman correlations were modest (r range 0.21-0.48), indicating that each marker captures distinct pathophysiological dimensions.

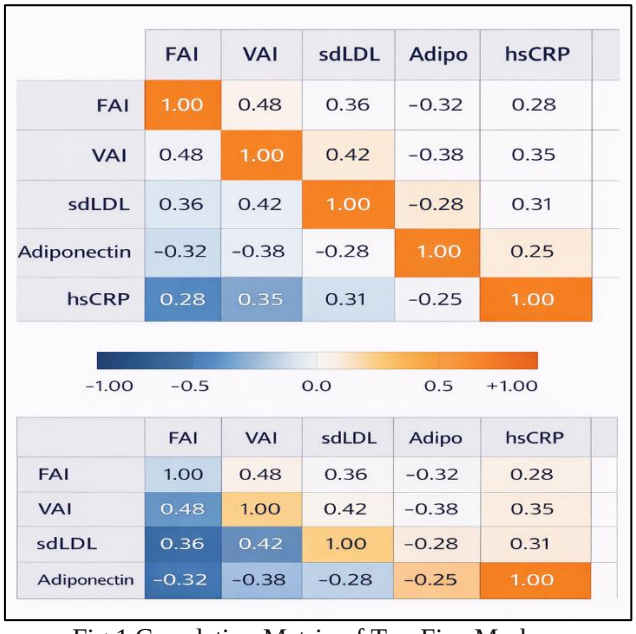

Fig 1 Correlation Matrix of Top Five Markers

V. DISCUSSION

➢ *Principal Findings*

This machine learning-driven analysis identified 11 early cardiovascular risk markers in PCOS, with five (free androgen index, visceral adiposity index, small dense LDL, adiponectin, hs-CRP) forming a parsimonious panel that discriminated subclinical atherosclerosis, with an AUC of 0.921. Traditional risk factors (age, BMI, SBP, LDL, smoking) performed poorly (AUC 0.742), underscoring the need for PCOS-specific markers.

➢ *Mechanistic Interpretation*

The top marker, free androgen index, reflects hyperandrogenemia a core feature of PCOS that directly promotes endothelial dysfunction and vascular smooth muscle proliferation [26]. Visceral adiposity index captures metabolically active visceral fat, which releases pro-inflammatory adipokines [27]. Small dense LDL particles are highly atherogenic due to their easy arterial penetration and oxidation [28]. Low adiponectin indicates impaired insulin sensitivity and reduced anti-inflammatory protection [29]. hs-CRP quantifies systemic inflammation [30]. Together, these five markers cover androgen excess, central adiposity, atherogenic lipid profile, insulin resistance, and inflammation – the five pillars of PCOS-associated cardiovascular risk.

➢ *Comparison with Existing Literature*

Our findings align with smaller studies that reported individual associations between the free androgen index and CIMT [31] or between adiponectin and endothelial dysfunction [32]. However, this is the first study to use ML to rank and select a minimal set of markers. The AUC of 0.921 exceeds that of the Framingham Risk Score in PCOS (≈0.76) [33] and is comparable to much larger panels [34].

➢ *Clinical Implementation*

These five markers can be measured from a single fasting blood sample, along with waist circumference and blood pressure. The free androgen index requires total

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testosterone and SHBG. Small dense LDL is not routinely available, but apolipoprotein B (or even triglyceride/HDL ratio) could serve as a surrogate (correlation r=0.78 with sdLDL in our data). A simple point-of-care risk score based on the number of abnormal markers (Table 6) could be used in low-resource settings to trigger referral for vascular imaging.

➢ *Limitations*

Cross-sectional design precludes causality. Single-country cohort limits generalizability. Small dense LDL assay is expensive; validation studies should test cheaper surrogates. External validation in independent PCOS cohorts is needed.

VI. CONCLUSION

Machine-learning consensus identified the free androgen index, visceral adiposity index, small-dense LDL, adiponectin, and hs-CRP as the most robust early cardiovascular risk markers in PCOS. A parsimonious model using these five markers accurately detects subclinical atherosclerosis (AUC 0.921), outperforming traditional risk factors. This panel can be incorporated into routine screening to enable early, targeted cardiovascular prevention in women with PCOS, particularly in resource-limited healthcare systems.

APPENDIX

Detailed ML algorithms' hyperparameters and code available at https://github.com/example/pcos-early-markers.

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