

Lipid Accumulation Product Better Predicts Metabolic Status in Lean Polycystic Ovary Syndrome than that by Visceral Adiposity Index

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ABSTRACT

Background: Both visceral adiposity index (VAI) and lipid accumulation product (LAP) can be used to assess insulin resistance (IR) and metabolic syndrome (MetS) which are required for management of even lean polycystic ovary syndrome (PCOS) (body mass index [BMI] <23 kg/m²). **Aim:** This study was aimed to see the magnitude of associations of VAI and LAP with cardiometabolic risk factors including IR and MetS in lean PCOS. **Study Setting and Design:** This cross-sectional study was done amongst 62 newly detected lean PCOS patients and 58 age- and BMI-matched healthy controls. **Materials and Methods:** PCOS was diagnosed according to the Revised 2003 Rotterdam Consensus criteria. Along with relevant clinical data, fasting blood was taken to measure glucose, insulin and lipid profile by glucose oxidase, chemiluminescent microparticle immunoassay and by glycerol phosphate dehydrogenase-peroxidase method, respectively. IR was calculated by homeostasis model of IR (HOMA-IR). VAI and LAP were calculated from BMI, waist circumference, triglyceride and high-density lipoprotein cholesterol by using sex-specific formulae. **Statistical Analysis Used:** Linear and binary regression analyses and receiver operating characteristics curve (ROC) analyses were done as appropriate. **Results:** Only LAP had predictive associations with age, systolic and diastolic blood pressure and total and low-density lipoprotein cholesterol. Both VAI and LAP had predictive associations with history of subfertility and MetS. LAP had moderate discriminating index for IR with cut-off of HOMA-IR of 2.3. Both VAI and LAP had excellent discriminating index for MetS in lean PCOS patients. **Conclusions:** LAP had more associations with cardiometabolic risks than VAI and was a moderate discriminator of IR in lean PCOS.

KEYWORDS: *Insulin resistance, lean polycystic ovary syndrome, lipid accumulation product, metabolic syndrome, visceral adiposity index*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting mostly young reproductive aged women with an increasing incidence than assumed.^[1] Besides reproductive and cutaneous manifestations, it can increase the risk of metabolic complications such as insulin resistance (IR), type 2 diabetes mellitus (DM), metabolic syndrome (MetS) and cardiovascular (CV) disease (CVD). Obesity is largely thought to be associated with these metabolic abnormalities, which affect around

half of PCOS women.^[2] On the other hand, the metabolic characteristics of PCOS patients who are not obese, are debatable. After adjusting for body mass index (BMI), some researchers have shown that patients with PCOS are still at risk for metabolic dysfunctions.^[3] In addition, a previous meta-analysis found a higher prevalence of

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Received: 02-08-2021
Accepted: 31-01-2022

Revised: 29-01-2022
Published: 31-03-2022

Access this article online

Quick Response Code:



Website:
www.jhrsonline.org

DOI:
10.4103/jhrs.jhrs_114_21

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How to cite this article: Banu H, Morshed MS, Sultana T, Shah S, Afrine S, Hasanat MA. Lipid accumulation product better predicts metabolic status in lean polycystic ovary syndrome than that by visceral adiposity index. J Hum Reprod Sci 2022;15:27-33.

impaired glucose tolerance and MetS in women with PCOS relative to BMI-matched controls, particularly in lean women (BMI <25 kg/m²).^[4]

CVDs are leading causes of deaths which were approximately 35% of the total deaths in Asia. It is well established that CVD risk depends on several factors such as lifestyle, ethnicity, genetic, intrauterine and environmental factors, but it is debatable whether all PCOS phenotypes are at high CVD risk. Obesity (particularly visceral adiposity) and PCOS jointly increase the early atherosclerosis and CV mortality.^[5] The visceral adiposity is responsible for IR and hyperandrogenaemia, the two most important component in the pathophysiology of PCOS.^[6]

Hyperinsulinaemic euglycaemic clamp method is the gold standard to assess IR.^[7] In spite of its precision, this index is difficult to evaluate in clinical practice because it is expensive and time-consuming to adapt in vast populations. Alternative indexes have recently gained popularity as methods for identifying IR because of their efficiency and low cost. The lipid accumulation product (LAP) and the visceral adiposity index (VAI) have thus been proposed as credible markers of IR and CV risk in general population, as well as for PCOS women.^[8-10] However, their cut-off values are different depending on different study populations. LAP and VAI are also responsive indicators of central visceral obesity and adipocyte function estimators. Besides, the central fat distribution pattern is related to IR and linked to metabolic disorders and dyslipidaemia; it plays an important role in cardiometabolic risk estimation.^[11]

Obese women have a clustering of coexisting risk factors, such as MetS components, that aids in the early detection of metabolic abnormalities; but, risk identification using standard CV risk factors may be challenging in lean patients. LAP and VAI are more effective in predicting IR and MetS compared with traditional anthropometric parameters.^[12] However, these were mostly studied in PCOS population as a whole or with a BMI of <25 kg/m². For Asian population, the lean population should be considered with the BMI cut-off of 23 kg/m². Currently, studies evaluating the cardiometabolic risk factors in lean PCOS are lacking. The objective of the present study was to evaluate the associations of VAI and LAP with metabolic parameters and their utility as markers of IR and MetS in lean PCOS patients.

SUBJECTS AND METHODS

This cross-sectional study was done in the Department of Endocrinology of a university hospital over a period of 2 years. Considering this formula

($n = [Z^2 \times p \times q] \div d^2$), the minimum number of sample size was ~39.^[13] This study included 62 newly detected lean (BMI <23 kg/m²) PCOS patients of 16–30 years and 58 age- and BMI-matched healthy controls. The study was conducted in accordance with the ethical principles mentioned in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (No. BSMMU/2016/2566). Informed written consent was taken from each participant.

PCOS was diagnosed according to the Revised 2003 Rotterdam Consensus criteria (two out of the following three: oligo/anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries by ultrasonography along with exclusion of similar diseases by appropriate clinical and hormonal investigations).^[14] Participants with regular menstrual cycle with insignificant hirsutism (modified Ferriman–Gallwey score <8) and normal total testosterone (≤ 46 ng/dL) were included as healthy control. Relevant history (personal and family history) was taken and physical examinations (height, weight, waist circumference [WC] and blood pressure [BP]) were done for each participant. History of subfertility defined as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles.^[15] Participants taking oral contraceptive within the last 3 months and having BMI ≥ 23 kg/m² were excluded. Fasting blood was taken to measure glucose, insulin and lipid profile. Glucose was measured by glucose oxidase, insulin by chemiluminescent microparticle immunoassay and lipid by glycerol phosphate dehydrogenase-peroxidase method. IR was measured by homeostasis model of IR (HOMA-IR = [fasting insulin in μ IU/ml \times fasting plasma glucose (FPG) in mmol/L] \div 22.5).^[16] IR was considered with HOMA-IR ≥ 2.3 .^[17] MetS was diagnosed by presence of any three of the five following criteria: WC ≥ 80 cm, elevated BP $\geq 130/85$ mmHg, elevated FPG ≥ 5.6 mmol/L, elevated triglyceride (TG) ≥ 150 mg/dl and low high-density lipoprotein cholesterol (HDL-C) <50 mg/dl.^[18] VAI and LAP were calculated from BMI, WC, TG and HDL-C by using sex-specific following formulae:

- VAI for female = (WC in cm \div [39.68 + (1.88 \times BMI)]) \times (TG in mmol/L \div 0.81) \times (1.52 \div HDL-C in mmol/L)^[9]
- LAP for female = (WC in cm – 58) \times TG in mmol/L.^[19]

Statistical analysis

Data were expressed as median (interquartile range), IQR or frequency (percentages, %) as appropriate. Comparison

between groups was done by Mann–Whitney *U*-test or Pearson’s Chi-square/Fisher’s exact test. Multivariate linear regression of the manifestations with VAI and LAP as independent variable was done. Predictive associations of VAI and LAP (independent variables) with manifestations of PCOS (dependent variable) were analysed by binary logistic regression. Receiver operating characteristic (ROC) curve analyses were done to see the discriminating index of VAI, LAP along with BMI and WC for IR and MetS amongst patients with lean PCOS. A two-tailed $P < 0.05$ was set as statistically significant. We used SPSS software 22.0 version for statistical analysis of data (Armonk, NY: IBM Corp).

RESULTS

Figure 1 shows the diagnostic characteristics and phenotypes of lean PCOS patients. The frequency of phenotype A was 33.9%, followed by phenotype C (29.0%), then phenotype B (21.0%) and at last phenotype D (16.1%).

The characteristics of the study population are shown in Table 1. History of subfertility ($P = 0.034$) history of PCOS ($P < 0.001$), obesity ($P < 0.001$) and DM ($P < 0.001$) were significantly higher in the lean PCOS group than control. The PCOS group had significantly more metabolic abnormalities than the control group (central obesity: $P = 0.021$; high BP: $P = 0.033$; impaired fasting glucose: $P = 0.006$; hypertriglyceridaemia: $P = 0.017$; MetS: $P = 0.009$; IR: $P < 0.001$) except for low HDL-C. Similarly, total cholesterol (TC) (mg/dl) ($P = 0.001$), low-density lipoprotein cholesterol (LDL-C) (mg/dl) ($P = 0.001$), FPG (mmol/L) ($P = 0.001$), fasting insulin ($\mu\text{IU/ml}$) ($P < 0.001$) and HOMA-IR ($P < 0.001$) all were significantly higher in the PCOS group than control. Other variables including VAI and LAP were statistically similar between the groups ($P = \text{NS}$ for all).

In the lean PCOS group, age ($P = 0.027$), diastolic BP ($P = 0.022$), TC ($P = 0.006$), LDL-C ($P = 0.039$)

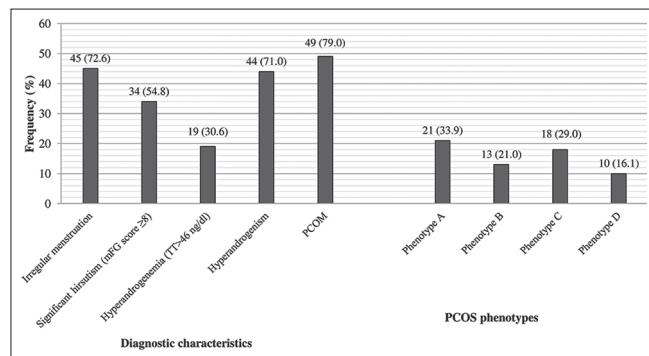


Figure 1: Diagnostic characteristics and phenotypes of lean polycystic ovary syndrome patients

and HOMA-IR ($P = 0.002$) were only weakly correlated with LAP. Only systolic BP was significantly and weakly correlated with both VAI ($P = 0.029$) and LAP ($P = 0.001$). All correlations were in positive direction. Multivariate linear regression analysis showed that age ($P = 0.004$), systolic ($P = 0.001$) as well as diastolic BP ($P = 0.046$), TC ($P = 0.002$) and LDL-C ($P = 0.029$) had predictive association only with LAP [Table 2].

Amongst the characteristics, both VAI and LAP had predictive associations with only history of subfertility (odds ratio, OR [95% confidence interval, CI] – VAI: 2.053 [1.083, 3.893], $P = 0.028$; LAP: 1.083 [1.019, 1.151], $P = 0.010$) and MetS (OR [95% CI] – VAI: 4.781 [1.947, 11.741], $P = 0.001$; LAP: 1.124 [1.050, 1.202], $P = 0.001$) in PCOS participants [Table 3].

ROC curve analysis showed that with a cut-off of HOMA-IR of 2.3, BMI, WC and LAP were moderate discriminators of IR in lean PCOS [Figure 2]. Another ROC curve analysis showed that WC (area under the curve [AUC] = 0.795) was a fair discriminator of MetS in lean PCOS. Both VAI (AUC = 0.915) and LAP (AUC = 0.912) had excellent discriminating index for MetS in lean PCOS patients [Figure 3].

DISCUSSION

Our study shows that patients with lean PCOS had significantly more adverse cardiometabolic risk factors including IR and MetS than their BMI-matched controls.

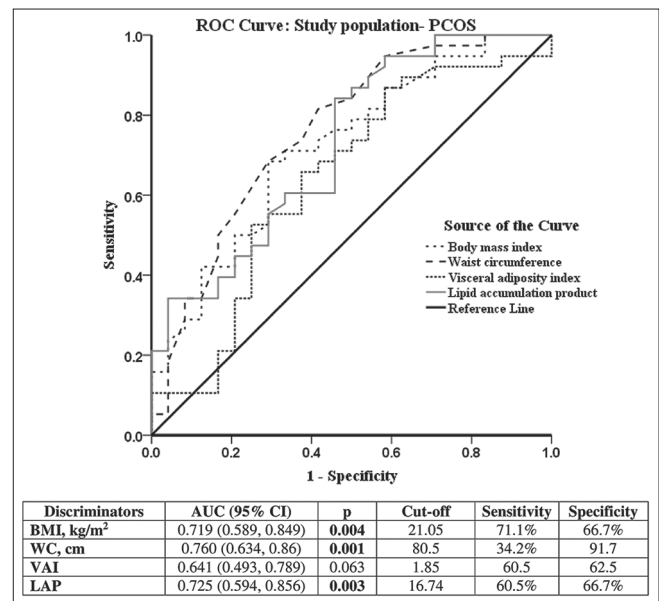


Figure 2: ROC curve analysis of visceral adiposity index and lipid accumulation product as discriminator of insulin resistance (cut-off of 2.3) in lean polycystic ovary syndrome

Table 1: Characteristics of patients with lean polycystic ovary syndrome

Variables	Frequency (%)		P*
	PCOS (n=62)	Control (n=58)	
Menstrual regulation/abortion	2 (3.2)	2 (3.4)	0.665
Subfertility	5 (12.2) [41]	0 (0.0) [47]	0.019
F/H of PCOS	18 (29.0)	0 (0.0)	<0.001
F/H of subfertility	15 (24.2)	4 (6.9)	0.008
F/H of obesity	29 (46.8)	9 (15.5)	<0.001
F/H of DM	37 (59.7)	16 (27.6)	<0.001
Centrally obese (WC ≥80 cm)	14 (22.6)	4 (6.9)	0.021
High blood pressure (≥130/85 mmHg)	8 (12.9)	1 (1.7)	0.033
Impaired fasting glucose (≥5.6 mmol/L)	8 (12.9)	0 (0.0)	0.006
Hypertriglyceridaemia (≥150 mg/dl)	11 (17.7)	2 (3.4)	0.017
Low HDL-C (<50 mg/dl)	47 (75.8)	43 (74.1)	1.00
MetS	10 (16.1)	1 (1.7)	0.009
Insulin resistance (HOMA-IR ≥2.6)	31 (50.0)	3 (5.2)	<0.001
Variables	Median (IQR)		P**
Age (years)	21.0 (18.0-24.0)	21.0 (20.75-24.25)	0.073
BMI (kg/m ²)	21.38 (20.18-22.61)	20.73 (19.49-21.90)	0.057
WC (cm)	74.0 (70.0-80.25)	72.0 (69.0-76.0)	0.081
Systolic blood pressure (mmHg)	110.0 (100.0-120.0)	110.0 (100.0-110.0)	0.559
Diastolic blood pressure (mmHg)	70.0 (60.0-80.0)	70.0 (60.0-76.25)	0.091
Serum TC (mg/dl)	167.0 (152.0-192.0)	150.5 (137.0-176.50)	0.001
Serum LDL-C (mg/dl)	107.0 (92.75-124.40)	90.50 (79.10-109.10)	0.001
Serum HDL-C (mg/dl)	44.0 (36.0-49.25)	44.50 (39.0-51.0)	0.358
Serum TG (mg/dl)	97.0 (66.75-132.0)	85.0 (62.75-115.25)	0.112
TG/HDL-C ratio	2.36 (1.47-3.19)	1.94 (1.43-2.67)	0.126
VAI	1.93 (1.16-2.58)	1.56 (1.10-2.16)	0.109
LAP	16.74 (9.64-30.34)	13.01 (9.23-19.20)	0.078
FPG (mmol/L)	4.75 (4.38-5.37)	4.05 (3.67-4.80)	0.001
TT (ng/dl)	33.37 (23.76-55.40)	27.38 (21.95-36.56)	0.066
LH/FSH ratio	1.58 (1.04-2.72)	Not done	
Fasting insulin (μIU/ml)	13.04 (9.08-17.95)	8.0 (6.28-9.85)	<0.001
HOMA-IR	2.89 (1.87-3.96)	1.50 (1.08-2.02)	<0.001

*Pearson's Chi-Square test/Fisher's exact test was done as appropriate, **Mann-Whitney U test was done. Within parentheses are percentages over column total for qualitative variables. [eligible number]. DM: Diabetes mellitus, F/H: Family history, PCOS: Polycystic ovary syndrome, MetS: Metabolic syndrome, BMI: Body mass index, WC: Waist circumference, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, VAI: Visceral adiposity index, LAP: Lipid accumulation product, FPG: Fasting plasma glucose, TT: Total testosterone, LH: Luteinising hormone, FSH: Follicle-stimulating hormone, HOMA-IR: Homeostasis model assessment of insulin resistance, IQR: Interquartile range

LAP had higher associations with several risk factors than VAI. Amongst different body fat indices, WC had the highest discriminating index for IR. On the other hand, both VAI and LAP had excellent discriminating indices for MetS in lean PCOS patients.

The incidence of IR (50%) in our study is similar to that observed in previous studies.^[20,21] In an Indian study, Gupta *et al.* noticed a lower (36%) frequency of IR in lean PCOS subjects and it was significantly more than their healthy counterpart as observed in our study.^[22] We did not find any significant difference of LAP and VAI indices in between cases and controls which is expected as BMI, WC and TG level were similar in both the groups. Rashidi *et al.* found results in agreement with us.^[23]

Whereas another study found significant differences of these markers when compared with obese counterpart.^[24]

We found significant associations of LAP than VAI with different cardiometabolic risk factors. Previous studies also showed that LAP better correlated with hepatic steatosis, IR and other metabolic parameters than VAI.^[25-27] Hence, LAP may be chosen first to screen cardiometabolic risk factors in lean PCOS patients. Association of VAI and LAP with subfertility may indicate the negative impact of metabolic factors on fertility.^[28]

Different adiposity markers were investigated (WC, BMI, VAI and LAP) and their potentials to predict MetS in women with PCOS were assessed. When ROC curve

for markers – WC, BMI, VAI and LAP – was plotted, LAP and VAI were found to possess the highest AUC value (0.91) with a cut-off value of 23.2 cm. mmol/L and 2.32, respectively, which was similar to another study.^[29] LAP has earlier been reported to be a strong predictor of CVD with cut-off of 37.9 cm. mmol/L (sensitivity: 85.19%, specificity: 81.35%) by Nascimento *et al.* and 34.5 cm. mmol/L (sensitivity: 84%; specificity 79%) by Wiltgen *et al.* in women with PCOS which were more than our cut-off level as they included all BMI categories.^[30,31] WC was also found to have

significant ability to predict MetS in the present study with 84.7% specificity and 70% sensitivity, but AUC value (0.79) was less than LAP and VAI. In a Spanish adolescent population, waist-hip ratio was found to have the highest predictive value for MetS whereas WC was found to best predict MetS.^[32] Our study also suggests WC (80.5 cm) with AUC value of 0.76, to be the second best predictor of MetS in PCOS women amongst all the adiposity markers studied.

IR is a prevalent finding women with PCOS and is thought to be an independent risk factor for CVD. In

Table 2: Correlation and multivariate linear regression analysis of manifestations of polycystic ovary syndrome with visceral adiposity index and lipid accumulation product (independent variables)

Dependent variables	Spearman's correlation test				Linear regression analysis					
	VAI		LAP		VAI			LAP		
	r	P	r	P	B	β	P	B	β	P
Age (years)	-0.02	0.879	0.280	0.027	0.184	0.061	0.638	0.07	0.358	0.004
mFG score	0.134	0.298	0.126	0.327	0.236	0.062	0.632	0.030	0.122	0.345
Systolic blood pressure (mmHg)	0.278	0.029	0.412	0.001	1.872	0.178	0.166	0.280	0.414	0.001
Diastolic blood pressure (mmHg)	0.134	0.300	0.290	0.022	0.323	0.041	0.753	0.129	0.254	0.046
FPG (mmol/L)	-0.138	0.283	0.01	0.940	-0.152	-0.118	0.361	0.005	0.060	0.645
TC (mg/dl)	0.114	0.379	0.343	0.006	1.550	0.045	0.727	0.837	0.379	0.002
LDL-C (mg/dl)	0.098	0.450	0.263	0.039	0.341	0.011	0.933	0.559	0.277	0.029
LH/FSH ratio	0.126	0.328	-0.029	0.824	-0.060	-0.046	0.720	-0.013	-0.159	0.218
TT (ng/dl)	-0.106	0.414	-0.008	0.953	-0.685	-0.259	0.796	0.150	0.113	0.380
HOMA-IR	0.176	0.172	0.377	0.002	0.163	0.094	0.469	0.027	0.237	0.063

TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, VAI: Visceral adiposity index, LAP: Lipid accumulation product, FPG: Fasting plasma glucose, TT: Total testosterone, LH: Luteinising hormone, FSH: Follicle-stimulating hormone, HOMA-IR: Homeostasis model assessment of insulin resistance, mFG: modified Ferriman–Gallwey

Table 3: Characteristics of the polycystic ovary syndrome population in relation to visceral adiposity index and lipid accumulation product (n=62)

Variables	Groups, n (%)	VAI			LAP		
		Median (IQR)	OR (95% CI)	P [†]	Median (IQR)	OR (95% CI)	P [†]
Menstrual cycle	Irregular, 45 (72.58)	1.98 (1.20-2.55)	0.815 (0.529-1.255)	0.352	16.75 (9.57-29.85)	1.007 (0.976-1.040)	0.648
	Regular, 17 (27.42)	1.89 (1.09-3.31)			16.62 (8.81-31.55)		
Infertility (41)	Present, 5 (12.2)	3.40 (1.33-5.86)	1.960 (1.008-3.808)	0.047	44.71 (27.17-92.86)	1.072 (1.010-1.137)	0.021
	Absent, 36 (87.8)	1.98 (1.14-2.52)			17.95 (11.31-29.72)		
Significant hirsutism (mFG score ≥8)	Present, 34 (54.84)	1.98 (1.25-2.61)	1.169 (0.766-1.785)	0.469	17.31 (10.72-30.70)	1.010 (0.982-1.038)	0.482
	Absent, 28 (45.16)	1.78 (1.02-2.65)			16.33 (8.60-30.59)		
Polycystic ovary morphology	Present, 49 (79.03)	1.89 (1.15-2.74)	1.143 (0.665-1.962)	0.629	16.12 (9.44-31.55)	1.005 (0.971-1.040)	0.769
	Absent, 13 (20.97)	1.98 (1.13-2.34)			18.74 (13.11-27.17)		
Hyperandrogenaemia TT >46 ng/dl	Present, 19 (30.65)	1.25 (0.98-2.38)	0.611 (0.339-1.100)	0.100	12.42 (7.93-26.49)	0.973 (0.937-1.011)	0.167
	Absent, 43 (69.35)	2.01 (1.26-2.91)			18.74 (10.91-30.94)		
Altered LH/FSH ratio (>2.0)	Altered, 24 (38.71)	1.93 (1.11-2.78)	0.994 (0.657-1.505)	0.978	16.68 (9.42-30.65)	0.996 (0.970-1.024)	0.796
	Normal, 38 (61.29)	1.85 (1.18-2.51)			17.31 (10.03-30.32)		
MetS	Unhealthy, 10 (16.13)	3.45 (2.78-4.53)	4.781 (1.947-11.741)	0.001	48.05 (30.90-58.82)	1.124 (1.050-1.202)	0.001
	Healthy, 52 (83.87)	1.56 (1.03-2.25)			14.42 (8.76-24.18)		
Insulin resistance (HOMA-IR ≥2.3)	High, 31 (50.0)	1.89 (1.02-2.78)	0.906 (0.602-1.363)	0.636	16.62 (5.96-29.56)	0.992 (0.966-1.019)	0.578
	Normal, 31 (50.0)	1.98 (1.24-2.43)			18.74 (12.42-32.37)		

[†]Univariate binary logistic regression analysis of VAI and LAP as covariates [Eligible number]. VAI: Visceral adiposity index, LAP: Lipid accumulation product, TT: Total testosterone, LH: Luteinising hormone, FSH: Follicle-stimulating hormone, HOMA-IR: Homeostasis model assessment of insulin resistance, mFG: modified Ferriman–Gallwey, IQR: Interquartile range, OR: Odds ratio, CI: Confidence interval, MetS: Metabolic syndrome

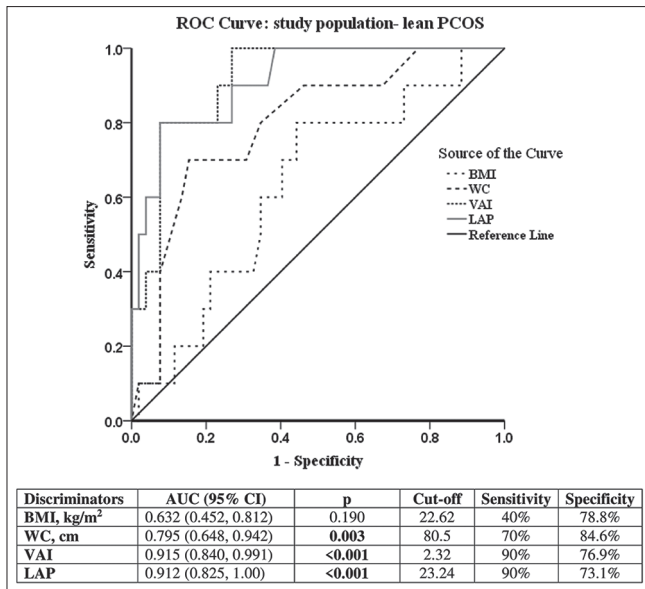


Figure 3: ROC curve analysis of visceral adiposity index and lipid accumulation product as discriminator of metabolic syndrome in lean polycystic ovary syndrome

order to prevent CVD in young women with PCOS, early detection of the IR phenotype is required. IR is assessed using a variety of surrogate markers such as HOMA-IR, LAP, TG/HDL and others because the gold standard approach is not a feasible or cost-effective tool for epidemiological research. LAP and VAI have been proposed as two indicators that best predict IR and as effective markers for detecting cardiometabolic risk in women with PCOS in order to implement early intervention methods in clinical practice.^[17] With IR cut-off of 2.3, BMI, WC and LAP were found moderate discriminator of IR, and amongst the three, WC was found to have significant relation to predict IR with a specificity of more than 90%. The cut-off of HOMA-IR may vary according to the body weight, and it is not yet well established in PCOS.^[27] In a recent Indian study, Rashid *et al.* suggested that LAP can serve as a significant marker to predict IR in PCOS women where their cut-off was >2.0 where they included young PCOS women irrespective of BMI.^[29] A large population-based study of Iran demonstrated that the LAP index and VAI were two indicators that best predict IR in women with PCOS, and amongst the healthy control, the two most reliable indicators were the LAP index and WC that had the optimum sensitivity of 78% and 75% and positive predictive value of 82% and 81%, respectively, where they used the HOMA cut-off at 2.3.^[17] In our study, LAP was found to positively correlate with HOMA-IR. This indicates that LAP can serve as a reliable marker for assessing IR in PCOS women than other indices in lean phenotype. There are some limitations of this study. Our study population was recruited from a referral centre.

We also could not measure serum progesterone and polycystic ovarian morphology in the control group.

In conclusion, lean PCOS patients have significantly more adverse cardiometabolic risk factors than their BMI-matched controls. These cardiometabolic risk factors had significant associations with LAP rather than VAI. The optimal adiposity markers and their optimal cut-off values may differ. However, the LAP index is a simpler metric than VAI and might be used to screen for cardiometabolic risks, especially IR and MetS in lean PCOS women.

Acknowledgement

We would like to thank the Department of Microbiology and Immunology, BSMMU, for hormone analysis and Department of Biochemistry and Molecular Biology, BSMMU, for biochemical analysis.

Financial support and sponsorship

Partial funding from Research and Development, BSMMU, was used for the investigations of the study participants.

Conflicts of interest

There are no conflicts of interest.

Data Availability:

The data used for this study is available with and the authors are willind to share it upon reasonable request.

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