Original Article

Visceral Adiposity Index and Lipid Accumulation Product as diagnostic markers of Metabolic Syndrome in South Indians with Polycystic Ovary Syndrome

Zeinab Naghshband, Lakshmi Kumar, Sonia Mandappa[1], Ashitha S. Niranjana Murthy[2], Suttur S. Malini

Department of Studies in Zoology, University of Mysore, Manasagangotri, [1]Mother's Care Clinic and Ashwini Hospital, [2]Department of Studies in Genetics and Genomics, University of Mysore, Manasagangotri, Mysuru, Karnataka, India

Abstract

Background: Cardiovascular disease (CVD) is one of the debilitating consequences of polycystic ovary syndrome (PCOS). Early diagnosis of metabolic syndrome (MetS) with a simple but accurate method can reduce the risk of progression to CVD in PCOS. **Aims:** This study aimed to determine the accuracy of various anthropometric indices and lipid accumulation product (LAP), in assessing the risk of MetS in PCOS. **Settings and Design:** This is a cross-sectional study including 150 PCOS women and 100 control subjects. **Materials and Methods:** Anthropometric parameters were measured and calculated. Lipid profile, fasting plasma glucose (FPG), and insulin were estimated. MetS was detected according to the International Diabetes Federation criteria. **Statistical Analysis:** Logistic regression and receiver operating characteristic curve analysis were applied to determine the potential association of anthropometric indices such as body mass index, waist circumference (WC), waist-to-hip ratio, waist-to-height ratio, conicity index (CI), visceral adiposity index (VAI), abdominal volume index (AVI), body adiposity index (BAI), and a body shape index (ABSI) and LAP with MetS. **Results:** In our study of PCOS women of the south Indian population, the prevalence of MetS was 59.3%, which was higher than other populations and the cutoff values of VAI and LAP were 6.05 and 53, respectively. VAI showed the strongest association with MetS, followed by diastolic blood pressure BP, FPG, and LAP. **Conclusions:** We recommend VAI and LAP as new indices for MetS diagnosis. As these indices exhibit population specificity, it is imperative that independent cutoffs are determined for every demographic population.

Keywords: *Anthropometric indices, lipid accumulation product, metabolic syndrome, polycystic ovary syndrome, visceral adiposity index*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most frequent causes of infertility in women of childbearing or reproductive age. It is mainly characterised by irregularity in the menstrual cycle, obesity, hyperandrogenism, and polycystic ovary.[1] The worldwide prevalence of PCOS lies between 5% and 26% depending on the population and diagnostic criteria applied.[2,3]

PCOS patients might show metabolic consequences such as insulin resistance, Type 2 diabetes, obesity, dyslipidemia, and hyperinsulinemia. These form the risk factors of metabolic syndrome (MetS) and therefore, increase the susceptibility of those women of developing cardiovascular disease (CVD).[4] Several studies proved

Received: 17-01-2021 **Revised:** 28-04-2021
Accepted: 17-05-2021 **Published:** 25-08-2021

Access this article online

Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/jhrs.jhrs_12_21

Address for correspondence: Prof. Suttur S. Malini, Department of Studies in Zoology, University of Mysore, Manasagangothri, Mysore - 570 006, Karnataka, India. E-mail: sutturmalini@yahoo.com

How to cite this article: Naghshband Z, Kumar L, Mandappa S, Niranjana Murthy AS, Malini SS. Visceral adiposity index and lipid accumulation product as diagnostic markers of metabolic syndrome in South Indians with polycystic ovary syndrome. J Hum Reprod Sci 2021;14:234-43.

that women with PCOS have an increased tendency of developing obesity, especially visceral obesity and lipid abnormalities during reproductive age.[5-7] Adiposity has a significant role in maintaining and generating PCOS.[8]

Body mass index (BMI) assesses the total obesity of PCOS patients,[9] but BMI cannot estimate abdominal fat distribution. It seems intra-abdominal fat has a stronger association with the risk of obesity-related morbidity than overall adiposity.[10] Hence, additional anthropometric indices such as elevated waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are being used to measure central obesity.[11] Related epidemiological studies expressed that these measurements were strongly correlated with MetS [Table 1]. As presented in Table 1, some studies in different populations showed that the visceral adiposity index (VAI) is another index that could be used as an indicator of MetS and cardiometabolic risk. A body shape index (ABSI), abdominal volume index (AVI), conicity index (CI), and body adiposity index (BAI) were the other anthropometric indices which showed correlation with MetS and CVD parameters such as dysfunction of glucose metabolism and central obesity.[11,27] All of the above anthropometric methods are simple, noninvasive, cost-effective, and do not require any special training.[25] However, an inclusive agreement has not been reached regarding the best anthropometric indices to assess the risk of MetS in PCOS patients.

Kahn described lipid accumulation product (LAP) as a better indicator than BMI for identifying the risk of CVD for the first time[28] in the National Health and Nutrition Examination Survey III. LAP is based on the combination of waist measurements and fasting triglycerides levels, considering both the anatomical and physiological changes related to lipid over-accumulation. Several studies have shown that LAP was closely associated with MetS in different diagnostic criteria [Table 1]. Therefore, LAP might be an easy and powerful marker for predicting the risk of MetS.

Early diagnosis of MetS in PCOS patients potentially will prevent further complications of metabolic disturbances such as CVD. MetS diagnosis is based on the combination of anthropometric and laboratory biochemical evaluations. Therefore, there is a necessity for using the simple, cost-effective, precise, and comprehensive indices of MetS risk assessment in PCOS women during the extended period of transition from subclinical to obvious CVD.

This paper analysed the accuracy and association of different anthropometric indices and LAP in PCOS women with MetS in certain geographic area.

Methods

This cross-sectional study was carried out in women with PCOS based on observation and samples collected from PCOS patients (150) and healthy women, i.e. control (100) in December 2017 to October 2019, from private hospitals of Mysuru, Karnataka, India, namely Ashwini hospital, Santasa IVF Centre, and Mediwave Infertility hospital. According to previous studies,[29,30] we assumed that the prevalence of PCOS in south of India is around 9.13%. The following formula was utilised to calculate the suitable sample size in a prevalence study.[31] Based on the formula, in this study the minimum sample size with a 95% confidence level should be 128 individuals, but we increased the sample size to 150 in order to achieve more precise results.

$$n = Z^2P\ (1 - P)/d^2$$

n: Sample size

Z: Statistic corresponding to the level of confidence

P: Expected prevalence

d: Precision (corresponding to impact size).

In this study, the following inclusion criteria were used: PCOS women aged 18–45 as reproductive age diagnosed by Rotterdam criteria[32] that require the presence of at least two criteria out of the following three:

- Oligo- and/or anovulation – whether oligoamenorrhea or amenorrhea was present.
- Clinical and/or biochemical signs of hyperandrogenemia.
- Polycystic ovaries on ultrasound.

Women with a medical history of Cushing's syndrome, adrenal 21-hydroxylase deficiency, androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia were excluded from the study. Women without any signs of the above criteria were used as a control for the studies.

General information for each patient, such as name, age, personal medical history, and information related to diagnosis and treatment of PCOS, was collected. Systolic and diastolic blood pressures (SBP and DBP) were measured with the subjects in the sitting position on the right hand. Weight, height, hip, and waist were measured precisely. All measurements were performed in a standing position with feet together, relaxed abdomen, and arms at their sides. The WC of subjects was measured by placing a soft tape measure at the midpoint between the lowest rib and iliac crest, and hip circumference (HC) was measured at the widest level of the great trochanters. 2-ml blood samples were drawn from all the subjects after a 12-h overnight fast. Plasma

Table 1: Studies on association of anthropometric indices/lipid accumulation product with metabolic syndrome in different population

Region	Population	Subjects (*n*)	Age (years)	Anthropometric indices and LAP	MetS; Population type (diagnostic criteria)	ROC curve analysis index (gender):AUC	Cut-off
Asia	Japanese population[12]	629 Male: 315 Female: 314	51-75	BMI, WC, WHR, WHtR	MetS-general (IDF)	WC (male): 0.65 WC (female): 0.72	WC (male): 85 WC (female): 90
	Chinese population[13]	2947 Male: 1674 Female: 1273	>20	BMI, WC, WHR, WHtR	MetS-general (CDS IDF, NHLBI/AHA)	WHtR (male): 0.79 WHtR (female): 0.90	WHtR: 0.50
	Jordanian population[14]	500 Male: 212 Female: 288	20-85	BMI, WC, WHR, WHtR	MetS-general population (IDF)	WHR (male): 0.71, WHR (female): 0.76 WHtR (female): 0.75 WC (female): 0.74	WHR (male): 0.89 WHR (female): 0.84 WHtR (female): 0.61 WC (female): 95.6
	Taiwanese adults[15]	513 Male: 266 Female: 247	≥50	BMI, WC, WHR, WHtR, LAP	MetS-general (MS-TW)	LAP: 0.90	LAP: 28.4
	Iranian population[16]	206	>19	BMI, WC, WHR, WHtR	MetS- eldery population (NCEP ATP III)	WC: 0.68 WHtR: 0.68	WC: 94.5 WHtR: 58.6
	Jordanian population[17]	630 Male: 308 Female: 322	20-70	BMI, WC, WHR, WHtR	MetS-general population (IDF)	WC (male): 0.85 WC (female): 0.86 WHtR (male): 0.85 WHtR (female): 0.87	WC (male): 98.5 WC (female): 86.7 WHtR (male): 0.56 WHtR (female): 0.52
	Chinese population[18]	1029	47±13.6	BMI, WC, VAI, LAP, BAI, WHtR	MetS-Low income rural adults (JIS)	LAP: >0.81 VAI, WHtR: >0.7	LAP (male): 34.7 LAP (female): 27.3
	Thai women[19]	441 Patient: 399 Control: 42	25.4±5.6	BMI, WC, WHR, WHtR, VAI	MetS-PCOS (IDF)	BMI: 0.90 VAI: 0.94	BMI: 28 VAI: 5.6
	Chinese adults[11]	379 Male: 198 Female: 181	40-65	BMI, WC, WHR, ABSI, AVI, BAI, BRI, CI, VAI	MetS-general (IDF)	BMI (male): 0.77 AVI (female): 0.72	BMI (male): 24.94 AVI (female): 13.03
	Iranian population[20]	5312 Male: 2972 Female: 2340	18-74	BMI, WC, WHR, WHtR, VAI	MetS-general (NCEP ATP III, AHA/NHLBI, IDF, JIS)	VAI (male): 0.82-0.87* VAI (female): 0.87-0.89*	Nil
Europe	Caucasian sicilian population[21]	1764	20-40	BMI, WC, VAI	MetS-Primery care Patients (NCEP-ATPIII)	VAI: 0.78-0.99†	VAI: 1.92-2.5†
	Caucasian serbian women[22]	267 Patient: 222 Control: 45	25±4.89	BMI, WC, LAP	MetS-PCOS (NCEP ATP III, IDF and JIS)	LAP: 0.97	LAP: 25.9
	Polish women[23]	43	18-38	BMI, WC, WHR, WHtR, VAI	MetS-PCOS (IDF)	Nil	VAI: 1.67
	Polish population[24]	12328 Male: 4094 Female: 8234	37-66	BMI, WC, WHtR, BRI, ABSI, CUN-BAE	MetS-general (IDF)	WHtR (male): 0.76 WHtR (female): 0.75	WHtR (male): 0.56 WHtR (female): 0.54
South America	Brazilian women[25]	Patient: 113	27.2±4.5	WC, WHR, WHtR, CI	MetS-PCOS (NCEP ATP-III)	WC: 0.83 WHtR: 0.82	WC: 95 WHtR: 0.59

Contd...

Table 1: Contd...

Region	Population	Subjects (*n*)	Age (years)	Anthropometric indices and LAP	MetS; Population type (diagnostic criteria)	ROC curve analysis index (gender):AUC	Cut-off
	Argentinean women[26]	198 Patient: 110 Control: 88	18-35	BMI, WC, VAI, LAP	MetS-PCOS NCEP ATP III	Nil	VAI: 2.19 LAP: 18.24

*AUC range for significant parameters according to different diagnostic criteria as mentioned in the study, †AUC and cutoff range for significant parameters according to age quintile as mentioned in the study. Values are expressed as mean±SD, bold parameters are statistically significant. AUC=Area under the curve, MetS=Metabolic syndrome, IDF=International Diabetes Federation, CDS=Chinese Diabetes Society, NHLBI/AHA=National Heart, Lung, and Blood Institute and the American Heart Association, MS-TW=MS using Taiwanese criteria, NCEP ATP III=The National Cholesterol Education Program Adult Treatment Panel III, JIS=Joint Interim Statement, BMI=Body mass index, WC=Waist circumference, WHR=Waist-to-hip ratio, WHtR=Waist-to-height ratio, CI=Conisity index, AVI=Abdominal volume index, BAI=Body adiposity index, ABSI=A body shape index, VAI=Visceral adiposity index, LAP=Lipid accumulation product, PCOS=Polycystic ovary syndrome, CUN-BAE=Clínica universidad de Navarra-Body adiposity estimator, BRI=Body roundness index

glucose was measured by glucose oxidase-peroxidase assay (ARKRAY kit, Mumbai, Maharashtra, India). Lipid profile including cholesterol, triglycerides, and high-density lipoprotein (HDL) were estimated by enzymatic assay (Meril kit, Vapi, Gujarat, India), and low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were calculated by Friedewald equation.[33,34] Fasting insulin level was determined by ELISA (Prime Biomed, Bangaluru, Karnataka, India).

We applied the International Diabetes Federation criteria (IDF) and South Asian-specific abdominal obesity standards for the diagnosis of MetS in all subjects in this study.[35] Conforming to the new definition, a person assessed as having MetS must have central obesity (in this study, South Asian female WC ≥80 cm), plus any two of the following four factors: (i) elevated triglycerides (triglycerides ≥150 mg/dL); (ii) reduced HDL (HDL <50 mg/dL in female); (iii) raised blood pressure (SBP ≥130 mmHg, DBP ≥85 mmHg); (iv) and high fasting plasma glucose (FPG ≥100 mg/dL).

LAP was measured as follows:[28]

Female LAP [waist (cm) −58] × triglycerides concentration (mmol/l)

BMI, WHR, WHtR, CI, AVI, ABSI, BAI, and VAI were calculated: [27,36,37]

$BMI = Weight\ (kg)/Height^2\ (m)$

$CI = WC\ (m)/0.109\sqrt{[weight\ (kg)/height\ (m)]}$

$AVI = [2\ WC^2\ (cm) + 0.7\ (WC - HC)^2\ (cm)]/1000$

$ABSI = WC\ (cm)/(BMI^{2/3}\ Hight^{1/2})$

$BAI = HC\ (cm)/Height\ (m)^{1.5} - 18$

VAI (Female) =WC (cm)/[36.58+ (1.89 × BMI)] × triglycerides (mmol/l)/0.81 × 1.52/HDL (mmol/l)

The study was approved by the Institutional Human Ethical Committee, University of Mysore, Manasagangothri,, Mysore (No. 151/PhD/2017-18), in accordance with the Helsinki Declaration (as revised in 2013), and written consent was obtained from all the subjects.

Statistical analysis was employed using the Statistical Package for the Social Sciences software SPSS, version 23.0; IBM (IBM Corp. Armonk, NY, USA). Results were expressed as mean ± standard deviation. The normality of data distribution of continuous variables was subjected to the Shapiro–Wilks test. Student's *t*-test and univariate analysis of variance were applied for analysing the differences between groups. Homogeneity of variance was tested using the Leven's test, and to identify any heterogeneity of variance, Games–Howell test was performed. For multiple comparisons, *post hoc* was executed. A $P < 0.05$ was reflected as statistically significant.

Multiple binary logistic regression was applied to analyse the determinants of MetS. Receiver operating characteristic (ROC) curves were created for each continuous variable, which showed a significant association with MetS. The area under curves was calculated to identify the accuracy of determinants of MetS and LAP and anthropometric indices. Optimal new cutoff points were determined by Youden's Index (sensitivity + specificity − 1). The ability of each variable to predict MetS was shown by the area under the curve with the standard error of the mean and 95% confidence intervals (95% CIs). For determinant variables of MetS, their IDF criteria known cutoff values were used to compare their sensitivity and specificity and the sensitivity and specificity of the new cutoff values determined by Yoden's Index in our study population.

Results

Comparing the clinical and anthropometric characteristics between PCOS and control eligible candidates, 150 patients and 100 controls were compared in the present study. The PCOS and control samples' mean age

was 25.78 ± 5.00 and 24.79 ± 4.66 years, respectively. Anthropometric parameters such as WC and WHtR determining central obesity were found significantly increased in PCOS group in comparison to control group. LAP in the PCOS and control were 63.49 ± 48.96 and 43.74 ± 20.85, respectively, that shows a significant difference in PCOS group in comparison to control group. Metabolic and anthropometric characteristics are expressed in Table 2, according to which there was a significant difference in DBP, FPG, fasting insulin, BMI, WC, WHR, WHtR, AVI, BAI, VAI, cholesterol, triglycerides, HDL, LDL, and LAP between PCOS and control group.

The women with PCOS were subgrouped into MetS and non-MetS according to IDF criteria. The prevalence of the MetS, according to the IDF for the PCOS women, was 59.3% (n = 89). The clinical and anthropometric characteristics of three groups (PCOS with and without MetS and control) are presented in Table 3. Multiple comparisons between PCOS with MetS and without MetS and control were performed. Compared to both control and PCOS without MetS, participants with MetS had a significantly higher level of SBP, DBP, FPG, fasting insulin, lipid profile (cholesterol, triglycerides, LDL, and VLDL), and LAP but the lower level of HDL. Moreover, the anthropometric indices, including BMI, WC, WHR, WHtR, CI, AVI, BAI, and especially VAI, were significantly elevated in the cases of PCOS with MetS. ABSI was increased in PCOS with MetS but not significantly.

Table 2: Clinical and anthropometric characteristics in polycystic ovary syndrome and control groups

Analyses	PCOS (n=150)	Control (n=100)	P
Age (year)	25.78±5.00	24.79±4.66	0.114
SBP (mmHg)	125.26±10.00	123.88±8.56	0.246
DBP (mmHg)	80.55±5.29	78.79±5.36	0.011*
FPG (mg/dL)	94.89±15.26	90.70±12.58	0.024*
Fasting insulin (mU/L)	15.50±5.78	11.84±4.79	<0.001*
BMI (kg/m^2)	26.73±5.28	23.07±3.71	<0.001*
WC (cm)	92.2±12. 61	85.35±9.4	<0.001*
WHR	0.91±0.08	0.89±0.04	0.017*
WHtR	61.33±9.89	54.18±5.79	<0.001*
CI	1.32±0.12	1.29±0.09	0.068
AVI	17.72±4.46	14.8±3.24	<0.001*
BAI	33.98±6.64	29.21±4.52	<0.001*
ABSI	0.09±0.01	0.08±0.006	0.082
VAI	9.17±8.08	6.61±2.25	<0.001*
Cholesterol (mg/dL)	212.83±51.12	184.84±61.76	<0.001*
Triglycerides (mg/dL)	154.08±76.74	140.19±32.43	0.05*
HDL (mg/dL)	39.42±13.56	44.36±9.30	0.001*
LDL (mg/dL)	142.58±44.67	115.74±59.22	<0.001*
VLDL (mg/dL)	30.81±15.34	28.56±5.95	0.106
LAP	63.49±48.96	43.74±20.85	<0.001*

Values are expressed as mean±SD, *P≤0.05 was considered as significant. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FPG=Fasting plasma glucose, BMI=Body mass index, WC=Waist circumference, WHR=Waist-to-hip ratio, WHtR=Waist-to-height ratio, CI=Conisity index, AVI=Abdominal volume index, BAI=Body adiposity index, ABSI=A body shape index, VAI=Visceral adiposity index, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very low-density lipoprotein, LAP=Lipid accumulation product, PCOS=Polycystic ovary syndrome

Multiple binary logistic regression showed that LAP, VAI, DBP, and fasting glucose were significantly associated with MetS. We applied all of the variables in multiple binary logistic regression analysis model. In step 1, DBP was entered in step 2, VAI, then FPG, and in the last stage, LAP. In the final model, VAI, DBP, FPG, and LAP remained significantly associated with MetS defined by IDF [Table 4]. VAI was a more useful indicator than others. The second indicator was DBP, but the model was more robust when all parameters were present.

We analysed the diagnostic test accuracy of the MetS determinants and significantly associated anthropometric parameters with MetS [Table 3] by ROC curve analysis. The following cutoff values were identified for: VAI 6.05, DBP 81.4 mmHg, triglycerides 152.4 mg/dL, LAP 53, FPG 99.75 mg/dL, WHR 0.92, SBP 123.15 mmHg, WC 88.5 cm, WHtR 55.85, CI 1.34, BMI 23.2 kg/m2, AVI 19.48, insulin 11.53 mU/L, BAI 40.25, and HDL 37.90 mg/dL [Table 5].

As presented in Table 5, VAI, DBP, triglycerides, and LAP showed the highest MetS diagnostic accuracy. Other parameters' accuracy for the MetS are presented in Table 5. AVI cutoff value 6.05 showed sensitivity: 0.85 and specificity: 0.85 with higher positive predictive value (0.89) than negative predictive value (NPV: 0.79) for MetS.

ROC curves for determinants of MetS according to the final model of logistic regression are plotted in Figure 1.

Discussion

Our study proposes VAI and LAP as simple and cost-effective indices for assessing the risk of MetS in women with PCOS in certain geographic area. Our study identified that VAI provided the highest diagnostic accuracy among known and associated determinants for MetS. MetS has a variable frequency of up to 50% among PCOS women, which varies between populations and ethnicities.[2,38-40] The prevalence of MetS within our population of PCOS women was 59.3%, with a mean age of 25.78 ± 5.00 years. This was higher than the prevalence of 47.4% identified previously using

Table 3: Clinical and anthropometric characteristics of polycystic ovary syndrome with and without metabolic syndrome according to International Diabetes Federation criteria

Analyses	PCOS with MetS (*n*=89)	PCOS without MetS (*n*=61)	Control (*n*=100)	*P*
Age (year)	26.35±5.30[a]	24.97±4.46[a]	24.79±4.66[a]	0.067
SBP (mmHg)	128.98±9.60[b]	119.85±7.95[c]	123.89±8.57[a]	<0.001*
DBP (mmHg)	83.11±4.73[b]	76.84±3.62[c]	78.79±5.36[a]	<0.001*
FPG (mg/dL)	99.89±15.42[b]	87.62±11.80[a]	90.71±12.58[a]	<0.001*
Fasting insulin (mU/L)	16.13±5.46[b]	14.60±6.18[b]	11.84±4.79[a]	<0.001*
BMI (kg/m^2)	28.05±5.22[b]	24.81±4.80[c]	23.07±3.72[a]	<0.001*
WC (cm)	95.84±12.51[b]	86.91±10.83[a]	85.35±9.41[a]	<0.001*
WHR	0.95±0.07[b]	0.87±0.07[c]	0.90±0.05[a]	<0.001*
WHtR	63.65±10.18[b]	57.97±8.48[c]	54.19±5.79[a]	<0.001*
CI	1.35±0.14[b]	1.29±0.10[a]	1.30±0.09[a]	0.004*
AVI	18.67±4.74[b]	16.35±3.66[c]	14.81±3.24[a]	<0.001*
BAI	34.57±6.76[b]	33.12±6.43[b]	29.22±4.52[a]	<0.001*
ABSI	0.10±0.12[a]	0.09±0.08[a]	0.08±0.01[a]	0.306
VAI	12.00±9.47[a]	5.04±1.23[b]	6.61±2.25[c]	<0.001*
Cholesterol (mg/dL)	224.47±53.84[b]	195.86±41.79[a]	184.85±61.76[a]	<0.001*
Triglycerides (mg/dL)	182.62±86.05[b]	112.44±28.18[c]	140.19±32.44[a]	<0.001*
HDL (mg/dL)	35.38±12.14[b]	45.34±45.34[a]	44.36±9.31[a]	<0.001*
LDL (mg/dL)	152.56±47.59[b]	128.03±35.68[a]	115.74±59.23[a]	<0.001*
VLDL (mg/dL)	36.52[a]±17.21[b]	22.49[a]±5.64[c]	28.56[a]±5.95[a]	<0.001*
LAP	81.51±55.14[b]	37.20±17.65[a]	43.74±20.86[a]	<0.001*

Values are expressed as mean±SD, Different letters "[a,b,c]" express statistical differences between groups in univariate analysis. *$P \leq 0.05$ was considered as significant. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FPG=Fasting plasma glucose, BMI=Body mass index, WC=Waist circumference, WHR=Waist-to-hip ratio, WHtR=Waist-to-height ratio, CI=Conisity index, AVI=Abdominal volume index, BAI=Body adiposity index, ABSI=A body shape index, VAI=Visceral adiposity index, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very low-density lipoprotein, LAP=Lipid accumulation product, PCOS=Polycystic ovary syndrome, SD=Standard deviation

Table 4: Determinants of metabolic syndrome using International Diabetes Federation criteria

Variable	RR	95% CI	*P*
VAI	4.03	1.86-8.73	0.001
DBS	1.87	1.37-2.56	0.001
FPG	1.13	1.04-1.23	0.002
LAP	1.05	1.00-1.10	0.027

Evaluated by multiple binary logistic regression. RR=Relative risk, CI=Confidence interval, VAI=Visceral adiposity index, FPG=Fasting plasma glucose, LAP=Lipid accumulation product, DBS=Diastolic blood pressure

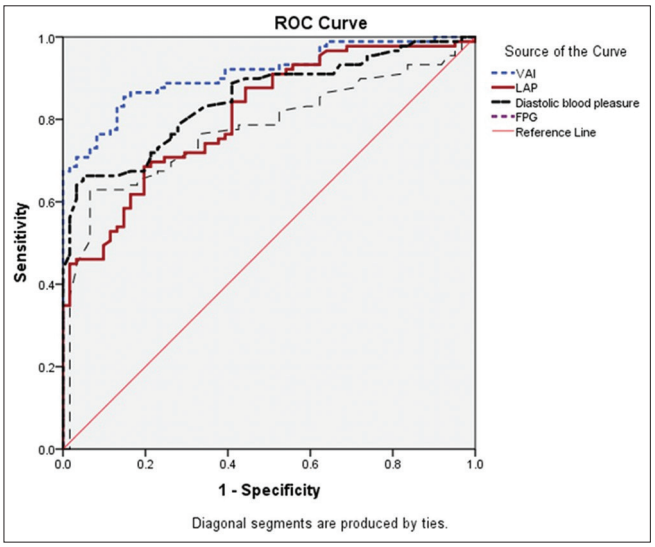

Figure 1: ROC curves for determinants of MetS using IDF criteria: ROC = Receiver-operating characteristic, VAI = Visceral adiposity index, LAP = Lipid accumulation product, FPG = Fasting plasma glucose

IDF criteria by Bhattacharya,[41] as well as the 53.3% and 37.5% prevalence identified on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria[42] and modified NCEP ATP III,[43] respectively, in various Indian studies. This study re-establishes a relationship between obesity and the MetS. The prevalence of obesity is increasing worldwide, and the high prevalence rate of MetS in our study reiterates that obesity is a direct contributing factor of MetS in this population. For the first time, our results established a strong association between VAI with MetS in a selected south Indian population of women with PCOS. The final model obtained from logistic regression shows the strong association of VAI, followed by DBP, FPG, and LAP with MetS, where DBP and FPG were previously defined as determinants of MetS by IDF criteria.

WC as a primary clinical parameter for estimating increased visceral fat does not help differentiate between subcutaneous and visceral fat, especially additional fat, and subsequent dysfunctions associated with

Table 5: Area under the ROC Curve for identification of accuracy and cutoff value for determinant of metabolic syndrome

Variable	AUC	*P*	95% CI	Cut-off	SEN (%)	SP (%)
VAI	0.91±0.02	<0.001	0.86-0.95	6.05	0.85	0.85
DBP	0.85±0.03	<0.001	0.79-0.91	81.4	0.66	0.95
Triglycerides	0.81±0.03	<0.001	0.74-0.88	152.4	0.51	0.96
LAP	0.81±0.03	<0.001	0.74-0.87	53	0.68	0.80
FPG	0.77±0.03	<0.001	0.70-0.85	99.75	0.62	0.93
WHR	0.77±0.04	<0.001	0.69-0.85	0.92	0.64	0.78
SBP	0.76±0.03	<0.001	0.68-0.83	123.15	0.71	0.80
WC	0.70±0.04	<0.001	0.61-0.78	88.5	0.71	0.60
WHtR	0.65±0.04	0.001	0.56-0.74	55.85	0.83	0.44
CI	0.64±0.04	0.003	0.55-0.73	1.34	0.56	0.70
BMI	0.64±0.04	0.003	0.55-0.73	23.2	0.93	0.41
AVI	0.64±0.04	0.004	0.55-0.72	19.48	0.39	0.85
Insulin	0.57±0.04	0.137	0.47-0.66	11.53	0.84	0.34
BAI	0.54±0.04	0.326	0.45-0.64	40.25	0.24	0.90
HDL	0.27±0.04	0.001	0.19-0.35	37.90	0.31	0.34

ROC= Receiver operating characteristic curve, AUC=Area under the curve, SEN=Sensitivity, SP=Specificity, VAI=Visceral adiposity index, DBP=Diastolic blood pressures, FPG=Fasting plasma glucose, LAP=Lipid accumulation product, WHR=Waist-to-hip ratio, WHtR=Waist-to-height ratio, CI=Conisity index, SBP=Systolic blood pressure, WC=Waist circumference, AVI=Abdominal volume index, BMI=Body mass index, BAI=Body adiposity index, HDL=High-density lipoprotein, CI=Confidence interval

different structures of the body.[44] A study by Amato *et al*. in 2010 proposed VAI as a substitute marker of "adipose tissue dysfunction." VAI showed a significant association with all MetS factors and cardiovascular events, which may be justified since VAI assessment includes physical and metabolic parameters. On the other hand, possibly, VAI indirectly indicates other risk factors, such as increased lipolysis, modified production of adipocytokines, and plasma free fatty acids, which are not indicated by BMI, WC, triglycerides, and HDL parameters independently. Consequently, VAI might be a superior index of fat distribution and function.[45] As represented in Table 1, several studies have shown that VAI has a strong association with MetS risk factors and suggested it as a good predictor for MetS.[18-20] In another study, VAI, WC, and WHtR were proposed as the best predictors for individual MetS components in a Peruvian population.[46] Our findings established a new VAI cut point >6.05, which is higher than previously reported cut point values in other populations investigated.[19,21-23,26] This observation can be explained by the fact that south Indian PCOS patients in this study have shown more central obesity than BMI, and the mean baseline of WC and triglycerides was remarkably elevated with significantly reduced HDL in the MetS group.

The second highest test accuracy was DBP, a recognized clinical marker for diagnosing MetS in the general population.[35,47] Raised blood pressure associates with obesity and glucose intolerance and frequently occurs in insulin-resistant persons. The association's impact differs significantly from one population to another.[47] Our findings show the strong effect of DBP in MetS. It might be due to DBP being a more potent cardiovascular risk factor than SBP until the age of 50.[48] In this study, the mean age of patients was 25.78 ± 5.00 years.

FPG shows a significant association with MetS in agreement with several earlier studies conducted globally.[49,50] An elevated level of blood glucose is a severe risk factor for a person diagnosed with diabetes and hyperglycemia. It might be due to the increasing triglycerides and decreasing HDL that increase CVD risk.[47]

Another significant predictive marker identified in this study was previously proposed by Henry Kahn, in 2005, based on the measurement of WC. Lipid overaccumulation, associated with metabolic and cardiovascular risk factors, can be assessed through LAP in adults.[28] One study confirmed the diagnostic accuracy of LAP in predicting metabolic disturbances associated with insulin resistance among young Argentinian PCOS patients.[50] Furthermore, this index was associated with the homeostatic model assessment in 51 Brazilian PCOS patients[51] and impaired glucose tolerance in Caucasian women.[52] Macut *et al*. in 2016 have shown that LAP is an independent and straightforward indicator for the assessment of MetS among PCOS women of Caucasian origin.[22] One study on the Chinese population has demonstrated the relation between LAP and MetS in PCOS as well.[53]

Our analysis showed that the LAP optimal cutoff value for determining MetS was >53. We support the proposal that each population should establish its own cutoff values.[28] Our data showed that LAP and triglycerides shared the same level of accuracy. However, in the final model of logistic regression, LAP displayed a significant association with MetS in south Indian women with PCOS. It might be justified by the fact that LAP, including the combination of triglycerides and WC, increases the chance of MetS than triglycerides independently.

Some limitations in the current study should be contemplated. This study was limited to the PCOS women from certain geographic area and indicates two new indexes VAI and LAP, as statistically significant determinants of MetS in women with PCOS. Similar studies need to be carried out in other populations to infer if these new indexes exhibit population specificity. IDF criteria were used in the current study to define MetS. Therefore, further studies are required to determine whether the results are applicable under other well-known criteria.

Conclusions

The present study suggests two new indexes VAI and LAP, as statistically significant determinants of MetS in south Indian women with PCOS, in addition to the prevalently used predictors DBP and FPG. The high diagnostic accuracy of VAI indicates the strength of the combination of WC, BMI, serum triglycerides, and HDL as a simple index instead of utilising them independently for determining the MetS and in the subsequent prediction of CVD in PCOS women.

Acknowledgments

We acknowledge all participants of our study for their valuable samples. We thank Dr. N.B. Ramachandra for his help and support during the research work. We especially thank Dr. Yogitha Sanjay director of Santasa IVF and Endosurgery institute as well as Ashwini and Mediwave hospital lab staff for helping in sample collection. We thank the Department of Studies in Genetics and Genomics, University of Mysore, Manasagangothri, Mysuru, India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

1. Thathapudi S, Kodati V, Erukkambattu J, Katragadda A, Addepally U, Hasan Q. Anthropometric and biochemical characteristics of polycystic ovarian syndrome in south Indian women using AES-2006 criteria. Int J Endocrinol Metab 2014;12:e12470.
2. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, *et al.* Positions statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237-45.
3. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clini Epidemiol 2014;6:1.
4. Mani H, Levy MJ, Davies MJ, Morris DH, Gray LJ, Bankart J, *et al*. Diabetes and cardiovascular events in women with polycystic ovary syndrome: A 20-year retrospective cohort study. Clin Endocrinol 2013;78:926-34.
5. Gateva A, Kamenov Z. Cardiovascular risk factors in Bulgarian patients with polycystic ovary syndrome and/or obesity. Obstet Gynecol Int 2012;2012:306347.
6. Couto Alves A, Valcarcel B, Mäkinen VP, Morin-Papunen L, Sebert S, Kangas AJ, *et al.* Metabolic profiling of polycystic ovary syndrome reveals interactions with abdominal obesity. Int J Obes (Lond) 2017;41:1331-40.
7. Franik G, Bizoń A, Włoch S, Pluta D, Blukacz Ł, Milnerowicz H, *et al.* The effect of abdominal obesity in patients with polycystic ovary syndrome on metabolic parameters. Eur Rev Med Pharmacol Sci 2017;21:4755-61.
8. Barber TM, McCarthy MI, Wass JA, Franks S. Obesity and polycystic ovary syndrome. Clin Endocrinol (Oxf) 2006;65:137-45.
9. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of the WHO Consultation of Obesity; 2000.
10. Ho SC, Chen YM, Woo JL, Leung SS, Lam TH, Janus ED. Association between simple anthropometric indices and cardiovascular risk factors. Int J Obes Relat Metab Disord 2001;25:1689-97.
11. Wang H, Liu A, Zhao T, Gong X, Pang T, Zhou Y, *et al.* Comparison of anthropometric indices for predicting the risk of metabolic syndrome and its components in Chinese adults: A prospective, longitudinal study. BMJ Open 2017;7:e016062.
12. Kato M, Takahashi Y, Inoue M, Tsugane S, Kadowaki T, Noda M. Comparisons between anthropometric indices for predicting the metabolic syndrome in Japanese. Asia Pac J Clin Nutr 2008;17:223-8.
13. Shao J, Yu L, Shen X, Li D, Wang K. Waist-to-height ratio, an optimal predictor for obesity and metabolic syndrome in Chinese adults. J Nutr Health Aging 2010;14:782-5.
14. Al-Odat AZ, Ahmad MN, Haddad FH. References of anthropometric indices of central obesity and metabolic syndrome in Jordanian men and women. Diabetes Metab Syndr 2012;6:15-21.
15. Chiang JK, Koo M. Lipid accumulation product: A simple and accurate index for predicting metabolic syndrome in Taiwanese people aged 50 and over. BMC Cardiovasc Disord 2012;12:78.
16. Gharipour M, Sadeghi M, Dianatkhah M, Bidmeshgi S, Ahmadi A, Tahri M, *et al.* The cut-off values of anthropometric indices for identifying subjects at risk for metabolic syndrome in Iranian elderly men. J Obes 2014;2014:907149.
17. Obeidat AA, Ahmad MN, Haddad FH, Azzeh FS. Evaluation of several anthropometric indices of obesity as predictors

of metabolic syndrome in Jordanian adults. Nutr Hosp 2015;32:667-77.
18. Guo SX, Zhang XH, Zhang JY, He J, Yan YZ, Ma JL, *et al*. Visceral adiposity and anthropometric indicators as screening tools of metabolic syndrome among low income rural adults in Xinjiang. Sci Rep 2016;6:36091.
19. Techatraisak K, Wongmeerit K, Dangrat C, Wongwananuruk T, Indhavivadhana S. Measures of body adiposity and visceral adiposity index as predictors of metabolic syndrome among Thai women with PCOS. Gynecol Endocrinol 2016;32:276-80.
20. Motamed N, Khonsari MR, Rabiee B, Ajdarkosh H, Hemasi GR, Sohrabi MR, *et al.* Discriminatory ability of visceral adiposity index (VAI) in diagnosis of metabolic syndrome: A population based study. Exp Clin Endocrinol Diabetes 2017;125:202-7.
21. Amato MC, Giordano C, Pitrone M, Galluzzo A. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis 2011;10:183.
22. Macut D, Antić IB, Bjekić-Macut J, Panidis D, Tziomalos K, Milutinović DV, *et al*. Lipid accumulation product is associated with metabolic syndrome in women with polycystic ovary syndrome. Hormones 2016;15:35-44.
23. Brończyk-Puzoń A, Jagielski P, Kulik-Kupka K, Koszowska A, Nowak J, Zubelewicz-Szkodzińska B. Usefulness of a new anthropometric indicator-VAI (Visceral Adiposity Index) in the evaluation of metabolic and hormonal disorders in women with polycystic ovary syndrome. Adv Clin Exp Med 2017;26:825-8.
24. Suliga E, Ciesla E, Głuszek-Osuch M, Rogula T, Głuszek S, Kozieł D. The usefulness of anthropometric indices to identify the risk of metabolic syndrome. Nutrients 2019;11:2598.
25. Costa EC, Sá JC, Soares EM, Lemos TM, Maranhão TM, Azevedo GD. Anthropometric indices of central obesity how discriminators of metabolic syndrome in Brazilian women with polycystic ovary syndrome. Gynecol Endocrinol 2012;28:12-5.
26. Abruzzese GA, Cerrrone GE, Gamez JM, Graffigna MN, Belli S, Lioy G, *et al*. Lipid accumulation product (LAP) and visceral adiposity index (VAI) as markers of insulin resistance and metabolic associated disturbances in young argentine women with polycystic ovary syndrome. Horm Metab Res 2017;49:23-9.
27. Guerrero-Romero F, Rodríguez-Morán M. Abdominal volume index. An anthropometry-based index for estimation of obesity is strongly related to impaired glucose tolerance and type 2 diabetes mellitus. Arch Med Res 2003;34:428-32.
28. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: A population-based comparison. BMC Cardiovasc Disord 2005;5:26.
29. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. J Pediatr Adolesc Gynecol 2011;24:223-7.
30. Bharathi RV, Swetha S, Neerajaa J, Madhavica JV, Janani DM, Rekha SN, *et al*. An epidemiological survey: Effect of predisposing factors for PCOS in Indian urban and rural population. Middle East Fertil Soc J 2017;22:313-6.
31. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol Bed Bench 2013;6:14.
32. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
33. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
34. Cleeman JI, Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA, *et al*. Cholesterol Educ program, executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486-97.
35. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al.* Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
36. Farzad S, Fatemeh A, Salehi M, Nojomi M. Association of waist circumference, body mass index and conicity index with cardiovascular risk factors in postmenopausal women. Cardiovasc J Afr 2012;23:442.
37. Freedman DS, Thornton JC, Pi-Sunyer FX, Heymsfield SB, Wang J, Pierson RN Jr., *et al*. The body adiposity index (hip circumference ÷ height1. 5) is not a more accurate measure of adiposity than is BMI, waist circumference, or hip circumference. Obesity 2012;20:2438-44.
38. Gambineri A, Repaci A, Patton L, Grassi I, Pocognoli P, Cognigni GE, *et al*. Prominent role of low HDL-cholesterol in explaining the high prevalence of the metabolic syndrome in polycystic ovary syndrome. Nutr Metab Cardiovasc Dis 2009;19:797-804.
39. Wijeyaratne CN, Seneviratne Rde A, Dahanayake S, Kumarapeli V, Palipane E, Kuruppu N, *et al.* Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS): Results of a large database from a specialist Endocrine Clinic. Hum Reprod 2011;26:202-13.
40. Panidis D, Tziomalos K, Papadakis E. Metabolic syndrome in patients with the polycystic ovary syndrome. Exp Rev Endocrinol Metab 2013;8:559-68.
41. Bhattacharya SM. Metabolic syndrome in females with polycystic ovary syndrome and International Diabetes Federation criteria. J Obstet Gynaecol Res 2008;34:62-6.
42. Varghese J, Supriya K, Thunga S, Joseph N, Singh PK. Prevalence and predictors of metabolic syndrome in women with polycystic ovarian syndrome: A study from Southern India. Int J Reprod Contracept Obstet Gynecol 2015;4:113-8.
43. Mandrelle K, Kamath MS, Bondu DJ, Chandy A, Aleyamma T, George K. Prevalence of metabolic syndrome in women with polycystic ovary syndrome attending an infertility clinic in a tertiary care hospital in south India. J Hum Reprod Sci 2012;5:26-31.
44. Mathieu P, Pibarot P, Larose É, Poirier P, Marette A, Després JP. Visceral obesity and the heart. Int J Biochem Cell Biol 2008;40:821-36.
45. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, *et al.* Visceral Adiposity Index: A reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 2010;33:920-2.
46. Knowles KM, Paiva LL, Sanchez SE, Revilla L, Lopez T, Yasuda MB, *et al.* Waist circumference, body mass index, and other measures of adiposity in predicting cardiovascular disease risk factors among peruvian adults. Int J Hypertens 2011;24:2011.
47. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – A new world-wide definition. A consensus statement from the international diabetes federation. Diabetic Med 2006;23:469-80.

48. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., *et al*. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42:1206-52.
49. Liu CS, Hsu HS, Li CI, Jan CI, Li TC, Lin WY, *et al.* Central obesity and atherogenic dyslipidemia in metabolic syndrome are associated with increased risk for colorectal adenoma in a Chinese population. BMC Gastroenterol 2010;10:51.
50. Kurotani K, Miyamoto T, Kochi T, Eguchi M, Imai T, Nishihara A, *et al.* Metabolic syndrome components and diabetes incidence according to the presence or absence of impaired fasting glucose: The Japan Epidemiology Collaboration on Occupational Health Study. J Epidemiol 2017;27:408-12.
51. Wiltgen D, Benedetto IG, Mastella LS, Spritzer PM. Lipid accumulation product index: A reliable marker of cardiovascular risk in polycystic ovary syndrome. Hum Reprod 2009;24:1726-31.
52. Wehr E, Gruber HJ, Giuliani A, Möller R, Pieber TR, Obermayer-Pietsch B. The lipid accumulation product is associated with impaired glucose tolerance in PCOS women. J Clin Endocrinol Metab 2011;96:E986-90.
53. Xiang S, Hua F, Chen L, Tang Y, Jiang X, Liu Z. Lipid accumulation product is related to metabolic syndrome in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2013;121:115-8.