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Insights into VAI and Liver Function as Predictive Markers of Metabolic Syndrome in PCOS phenotypes.

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Abstract:

Study objective: To correlate between Visceral adiposity index (VAI) and Liver function to predict Metabolic syndrome in Phenotypes of Polycystic Ovarian Syndrome.

Methods: Hundred reproductive-aged women (18–35 years old) diagnosed with PCOS based on the Rotterdam criteria from the outpatient department of Obstetrics &Gynaecology of RRMCH, Bengaluru were included in the study. The subjects were categorized based on the Rotterdam criteria into 4 phenotype groups. For all study participants, VAI was calculated using the anthropometric& biochemical parameters. Liver function test parameters were analyzed. The data was analyzed by Pearson's correlation coefficient for relationship between the variables. Statistical analyses were performed using SPSS software. For all statistical analyses the p value was significant when $p < 0.05$.

Results: Correlation between VAI & Liver function tests parameters in PCOS Phenotype A & Phenotype C showed negative correlation with all Liver function tests parameters. In PCOS Phenotype B samples. The Liver function tests parameters showed negative correlation with VAI except for SGOT which showed positive correlation Pearson's correlation coefficient value(R) of -0.57 with p value of 0.041 showing statistically significant. In PCOS Phenotype D samples:

The Liver function tests parameters showed negative correlation with VAI except for Serum alkaline phosphatase which showed positive correlation with the Pearson's correlation coefficient value(R) of -0.89 with p value of 0.043 showing statistically significant.

Conclusion: In PCOS phenotypes, especially with PCOS Phenotype B there is a correlation between VAI & SGOT. In PCOS Phenotype D samples, VAI & Serum alkaline phosphatase showed positive correlation. Based on the present study results, correlating liver function with VAI can help in the early diagnosis of MetS. The reported results need to be corroborated by additional prospective studies with a bigger sample size.

Key words:

Polycystic ovarian syndrome (PCOS), Visceral adiposity index (VAI), Liver function& Metabolic syndrome/

INTRODUCTION:

Polycystic Ovarian Syndrome (PCOS) is one of the most prevalent endocrine disorders in women of reproductive age. About 7–8% of women who are of reproductive age suffer with polycystic ovarian syndrome, or PCOS. The prevalence of PCOS varies from 6 to 21 percent, depending on the demographic and the Rotterdam criteria used to diagnose it. The majority of female PCOS patients also have elevated BMI, insulin resistance, and cholesterol, all of which contribute to obesity. PCOS is categorized as a heterogeneous condition because of the heterogeneity in its underlying etiology and clinical presentation.Studies by Khulood.et.al 2023 & Aziz U.et.al.2023 have shown that most women with PCOS also typically have elevated levels of cholesterol, insulin resistance and BMI, which results in obesity. Because of the differences in its underlying causes and clinical presentation, PCOS etiology is categorized as a condition with heterogeneity (1,2). PCOS has been linked to a number of illnesses, such as diabetes, hypertension, and cardiovascular disease. Seventy percent of PCOS-affected women have insulin resistance (IR), which can subsequently cause more metabolic and reproductive issues. Therefore, it is critical to find biological and/or clinical indicators of early IR in PCOS patients in order to improve their long-term prognosis, reduce the prevalence of diabetes and other metabolic disorders, and improve their quality of life (3,4).

A joint statement from the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity established a consensus criterion regarding the definition of MS in 2009. In summary, MS is diagnosed when any three of the following five criteria—higher blood pressure (BP), elevated triglycerides (TG), decreased HDL, and elevated waist circumference (WC) (5). Key characteristics of metabolic syndrome (MS) are obesity, insulin resistance, and dyslipidemia. People with PCOS often have abnormal lipid profiles regardless of their BMI (6).

Investigations by Perera, Sajithya et al.2008 & Zhang, Lu et al.2015 have revealed a strong correlation between MS and liver function, namely total bilirubin (TBIL), gamma glutamyltransferase (GGT), and alanine aminotransferase (ALT) (7,8). Currently, a variety of liver enzymes have been extensively studied as markers of MetS and its components in various populations. These include alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), a biomarker for oxidative stress linked to glutathione regulation, and ALT and AST, which are frequently used as indicators of liver damage (9,10,11).

An innovative indicator of fat distribution and function, the visceral adiposity index (VAI) combines laboratory and anthropometric data. VAI has been proposed as a screening tool for metabolic syndrome (MetS) in a study done by Amato, Marco C et al. 2011. It has previously been demonstrated to be linked to irregularities in glucose homeostasis, resistance to insulin action, and an elevated risk of cardiovascular disease in adulthood. Triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), two laboratory parameters, are related to certain anthropometric variables (BMI and WC) in a sex-specific mathematical model that calculates this index (12,13,14).

In this study, we aimed to explore the relationship between VAI and liver function to predict metabolic syndrome in PCOS phenotypes.

Materials and Methods:

Study design: After receiving approval from the institutional ethics committee (reference number RRMCH-IEC/16/2022) the current study was carried out in the Obstetrics and Gynecology Department at Rajarajeswari Medical College and Hospital. Hundred reproductive-aged women (18–35 years old) who met the Rotterdam criteria for PCOS were enrolled in the Gynaecology outpatient department at our hospital and were included in the study. The subjects were categorized based on the Rotterdam criteria into 4 phenotype groups as phenotype-A (hyperandrogenism + ovulatory dysfunction + polycystic ovarian morphology), phenotype-B (hyperandrogenism + ovulatory dysfunction), phenotype-C (hyperandrogenism + polycystic ovarian morphology), and phenotype-D (ovulatory dysfunction + polycystic ovarian morphology). Written informed consent was acquired from each individual participant included in the research.

For all study participants, a thorough clinical history was taken, including information about menstruation (h/o of the onset and duration of symptoms, duration of cycles, amount of flow, and treatment received), acne, hair growth at abnormal sites like the chin, upper lip and breast, weight gain or loss, acanthosis nigricans, galactorrhea and thyroid , as well as general, systemic, and local examination. This was followed by a baseline clinical evaluation, during which the following variables were noted: Height In Cm, Weight In Kg, BMI Kg/m2 & Waist Circumference in Cm.

During the proliferative phase, transabdominal ultrasound was performed to check the presence or absence of polycystic ovarian morphology.

The biochemical parameters like HDL Cholesterol, Triglycerides, liver function parameters: serum total bilirubin, serum direct bilirubin, SGOT (Serum glutamic oxaloacetic transaminase), SGPT (Serum glutamate pyruvate transaminase), serum Alkaline phosphatase, serum total protein, serum albumin & serum globulin were analyzed.

Using the anthropometric & the biochemical parameters, Visceral adipocity index (VAI) was calculated using the formula,

- Female VAI : $\left[\frac{WC\ (cm)}{\left\{36.58+(1.89x\mathrm{BMI}\left(\frac{\mathrm{kg}}{\mathrm{m}^2}\right))\right\}}\right] \mathrm{x} \left[\frac{\mathrm{TG(mmol/l)}}{0.81}\right] \mathrm{x} \left[\frac{1.52}{\mathrm{HDL(mmol/l)}}\right]$

VAI: Visceral Adipose Index, WC: Waist Circumference, BMI: Body Mass Index, TG: Triglyceride, HDL: High Density Lipoprotein (15)

Statistical analysis:

The data was analyzed by Pearson's correlation coefficient for relationship between variables. Statistical analyses were performed with the help of SPSS software. For all statistical analyses the p value was considered to be significant when $p < 0.05$.

RESULTS:

In the present study, Hundred women who met the Rotterdam criteria for PCOS were analyzed. Among the 100 subjects, phenotype-A were 61, phenotype-B were 13, phenotype-C were 21 & phenotype-D were 5. TABLE:1 shows the descriptive statistics of age, anthropometrics, biochemical measures & VISCERAL ADIPOSITY INDEX (VAI) in PCOS phenotypes.

TABLE:1 DESCRIPTIVE STATISTICS OF AGE, ANTHROPOMETRICS, BIOCHEMICAL MEASURES & VISCERAL ADIPOSITY INDEX (VAI) IN PCOS PHENOTYPES.

PARAMETERS	PCOS-PHENOTYPES							
	PHENOTYPE – A N=61		**PHENOTYPE – B N=13**		**PHENOTYPE – C N=21**		**PHENOTYPE – D N=5**	
	MEAN	STD.DEV	MEAN	STD.DEV	MEAN	STD.DEV	MEAN	STD.DEV
AGE	24.84	3.85	25.77	4.34	26.52	4.30	24.00	1.87
HEIGHT IN CM	157.17	7.47	153.38	6.04	154.43	7.05	156.00	1.58
WEIGHT IN KG	69.34	1.69	69.54	0.88	68.98	2.48	65.50	3.35
BMI KG/M2	28.12	2.92	29.68	2.25	29.06	2.43	26.92	1.49
WAIST CIRCUMFERENCE	72.32	8.32	73.46	7.61	72.38	7.45	71.00	9.38
HDL CHOLESTEROL(42-88mg/dl)	58.66	15.85	71.88	13.79	62.57	15.54	61.00	11.14
TRIGLYCERIDES (40-140mg/dl)	130.13	44.95	130.11	40.54	128.68	35.77	108.40	35.40
VAI	3.68	1.85	2.82	1.09	3.27	1.35	2.86	1.33
S. TOTAL BILIRUBIN(UP TO 1.2mg/dl)	0.51	0.32	0.52	0.41	0.48	0.29	0.55	0.39
S.Direct	0.25	0.16	0.23	0.17	0.23	0.16	0.3	0.07

Bilirubin(upto 0.4mg/dl)							7	
SGOT (UPTO 46U/L)	51.69	6.40	48.55	3.88	52.14	8.41	48.98	4.41
SGPT (UPTO 49 U/L)	51.70	6.17	51.40	7.80	53.46	6.26	55.64	4.10
S. ALKALINE PHOSPATASE(30-103U/L)	93.42	14.53	84.57	19.06	74.12	18.83	94.00	15.73
S TOTAL PROTEIN (6.4-8.3gm/dl)	7.97	1.06	8.68	0.54	8.74	1.13	7.02	0.68
S ALBUMIN (3.5-5.5gm/dl)	4.52	0.87	4.67	0.68	4.48	0.86	3.98	0.16
S GLOBULIN(1.3-3.3gm/dl)	1.52	0.74	1.77	0.84	2.04	0.69	1.36	0.48

Table:2 shows the correlation between visceral adiposity index (VAI) & liver function tests (LFT) in phenotypes of PCOS.

TABLE:2 CORRELATION BETWEEN VISCERAL ADIPOSITY INDEX (VAI) & LIVER FUNCTION TESTS IN PCOS PHENOTYPES.

PCOS PHENOTYPES	CORRELATION	S. TOTAL BILIRUBIN	S. DIRECT BILIRUBIN	SGOT	SGPT	S. ALKALINE PHOSPATASE	S TOTAL PROTEIN	S ALBUMIN	S GLOBULIN
PHENOTYPE – A N=61	VAI	0.01	0.12	-0.05	0.00	-0.04	0.03	-0.05	0.03
	P value (p < .05)	0.93	0.35	0.70	1.00	0.75	0.81	0.70	0.81
PHENOTYPE-B N=13	VAI	-0.20	0.02	-0.57	0.15	-0.26	-0.10	-0.10	-0.32
	P value (p < .05)	0.51	0.94	**0.041**	0.62	0.39	0.74	0.74	0.28
PHENOTYPE-C N=21	VAI	-0.24	0.34	-0.32	-0.23	0.25	-0.08	0.23	-0.05
	P value (p < .05)	0.29	0.13	0.15	0.31	0.27	0.73	0.31	0.82
PHENOTYPE-D N=05	VAI	0.86	0.39	0.64	-0.77	-0.89	0.03	-0.01	-0.80
	P value (p < .05)	0.06	0.51	0.24	0.12	**0.043**	0.96	0.98	0.10

Correlation between VAI & Liver function tests parameters in PCOS Phenotype A & Phenotype C showed negative correlation with all Liver function tests parameters. In PCOS Phenotype B samples: The Liver function tests parameters showed negative correlation with VAI except for SGOT which showed positive correlation Pearson's correlation coefficient value(R) of -0.57 with p value of 0.041 showing statistically significant. In PCOS Phenotype D samples: The Liver

function tests parameters showed negative correlation with VAI except for Serum alkaline phosphatase which showed positive correlation with the Pearson's correlation coefficient value(R) of -0.89 with p value of 0.043 showing statistically significant.

FIGURE 1: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-A

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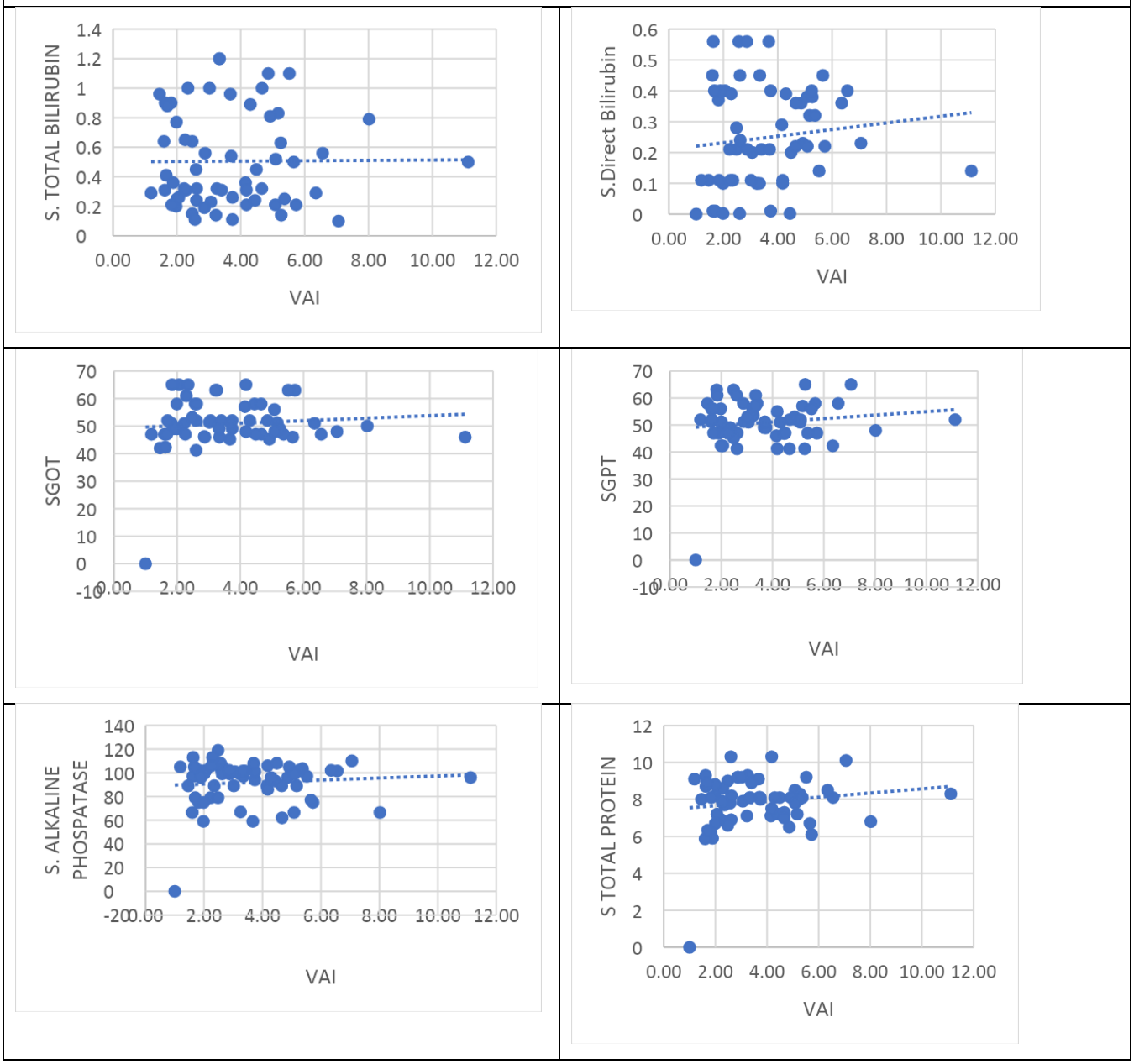

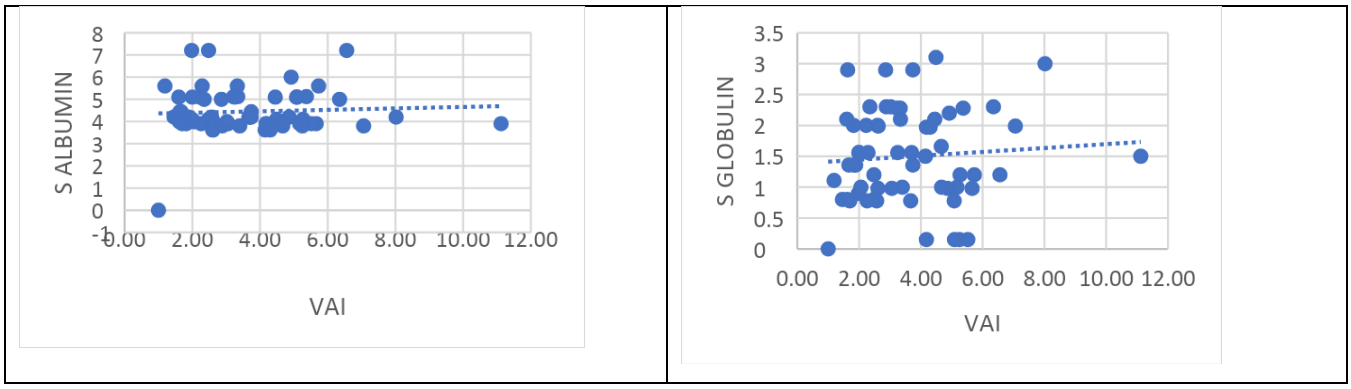

FIGURE 2: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-B

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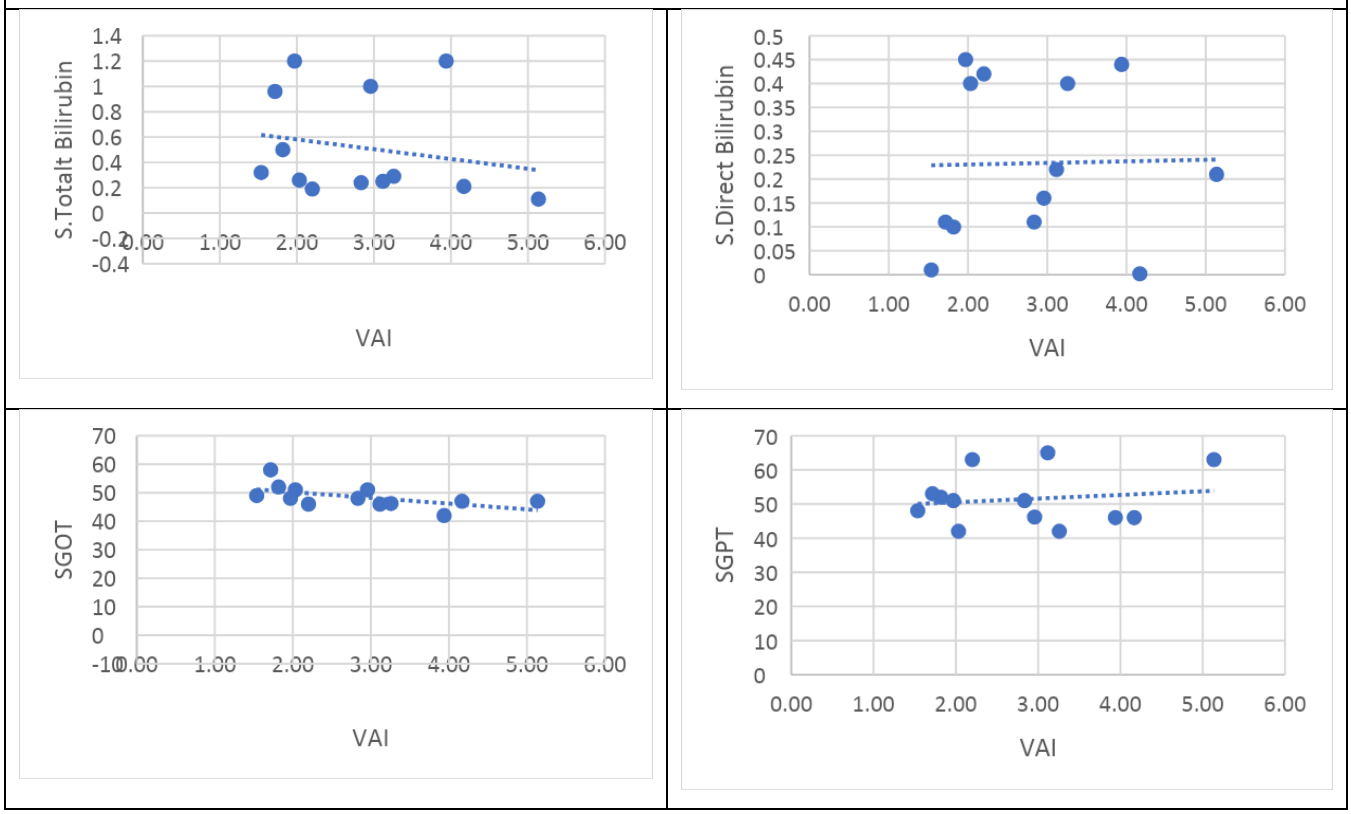


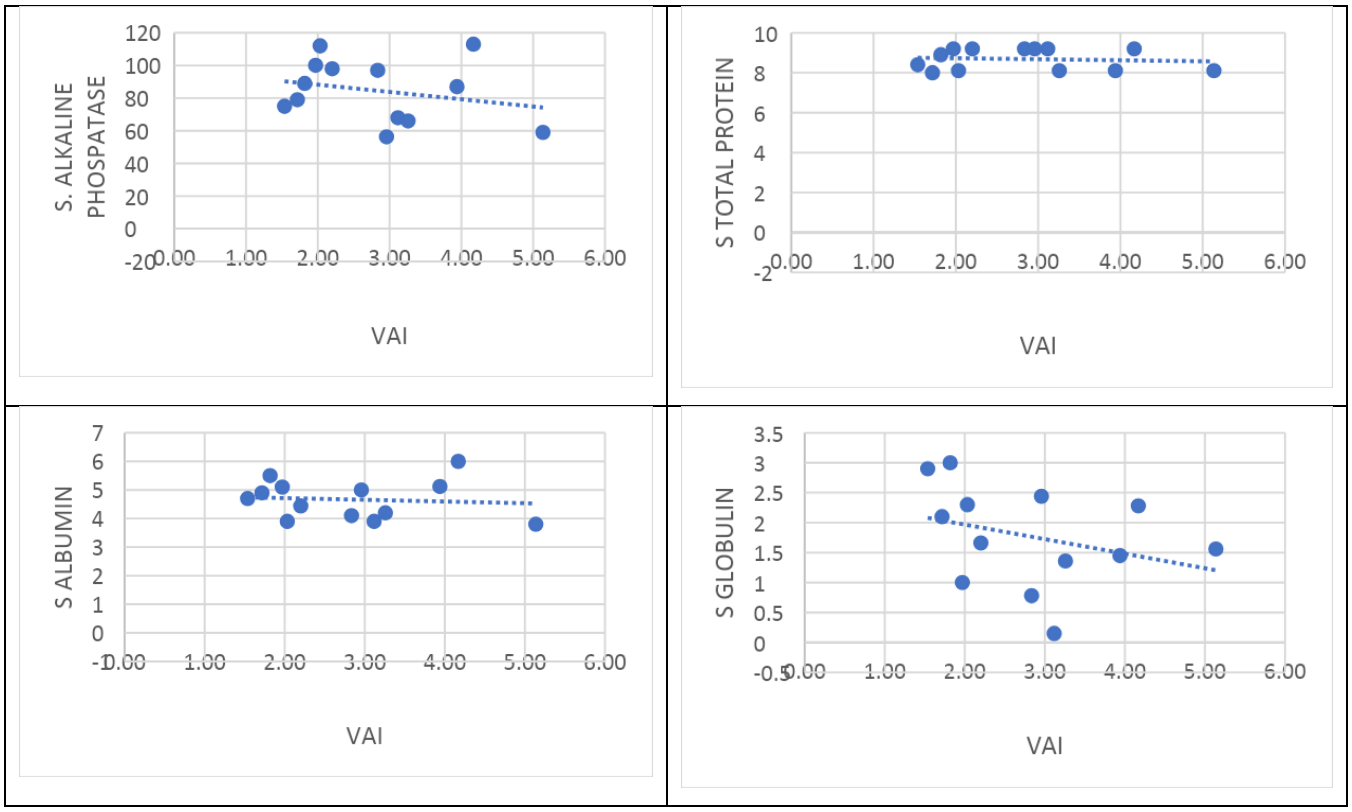
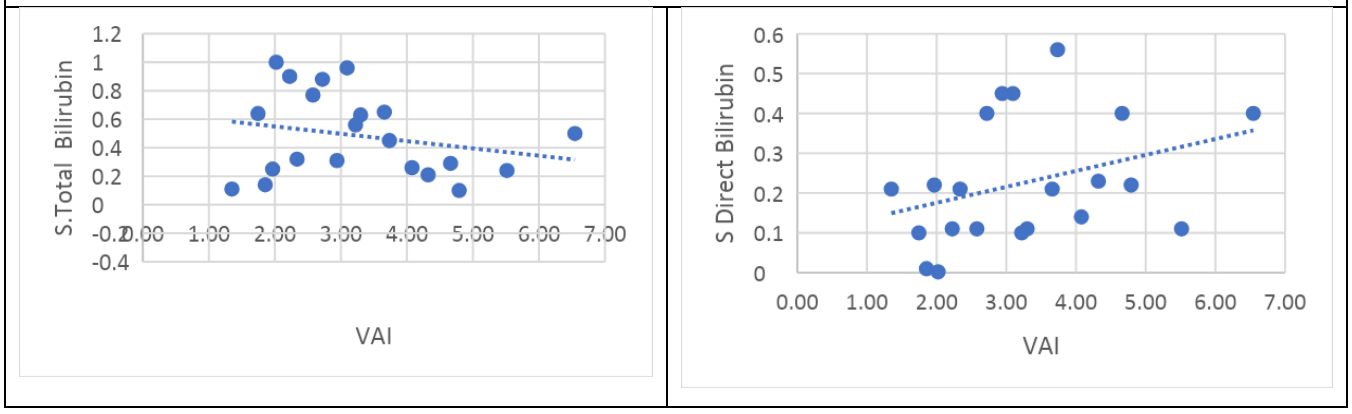


FIGURE 3: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-C

FIGURE 3: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-C



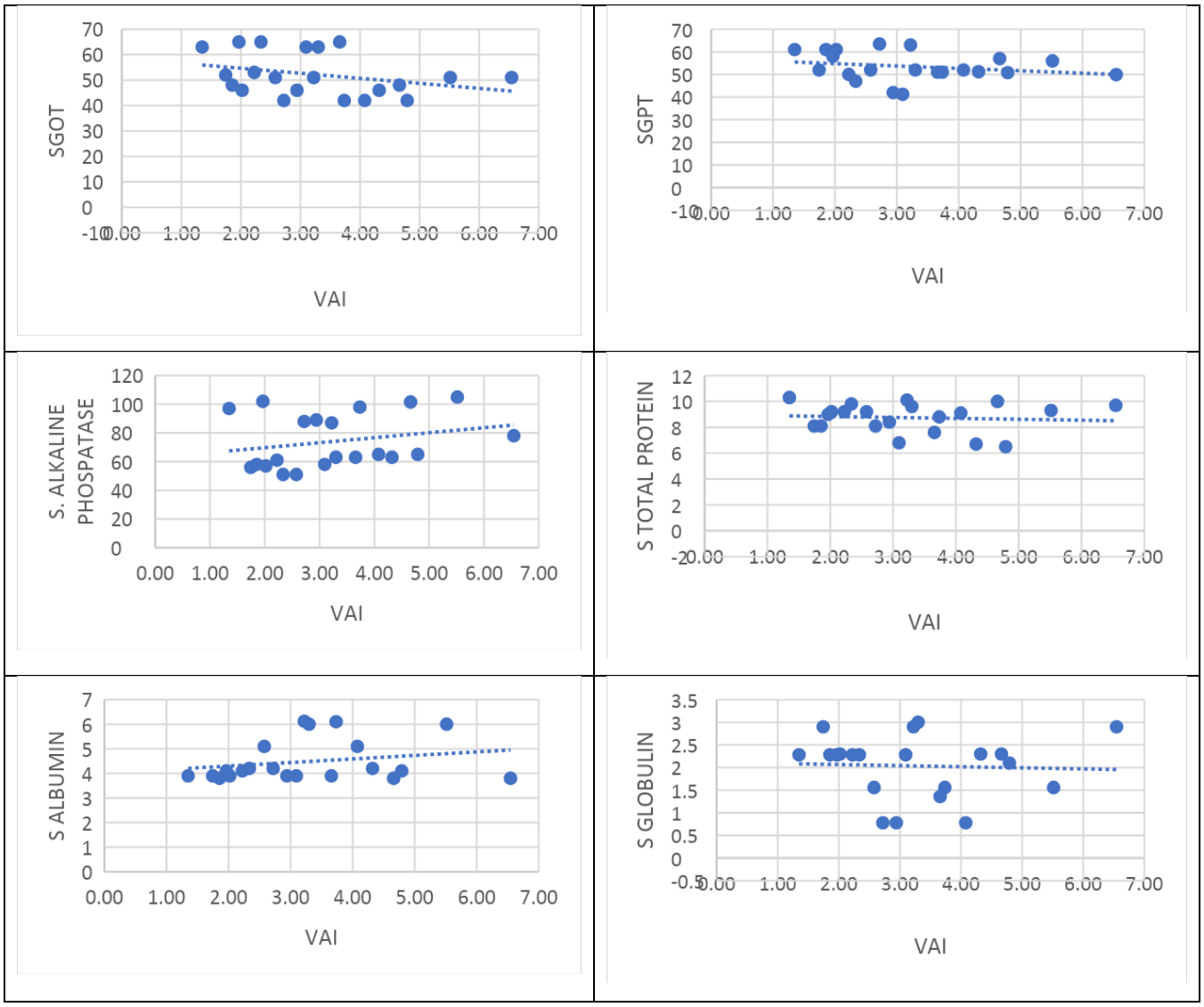
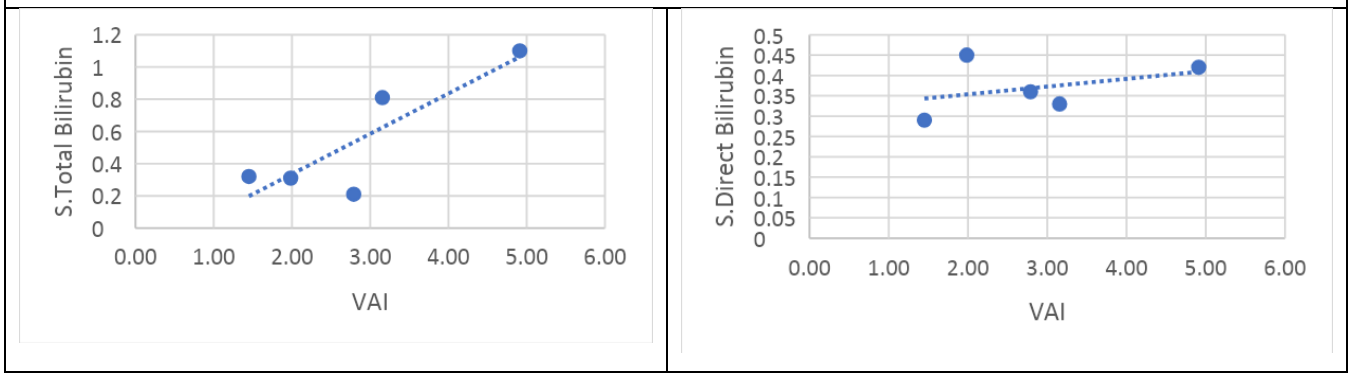
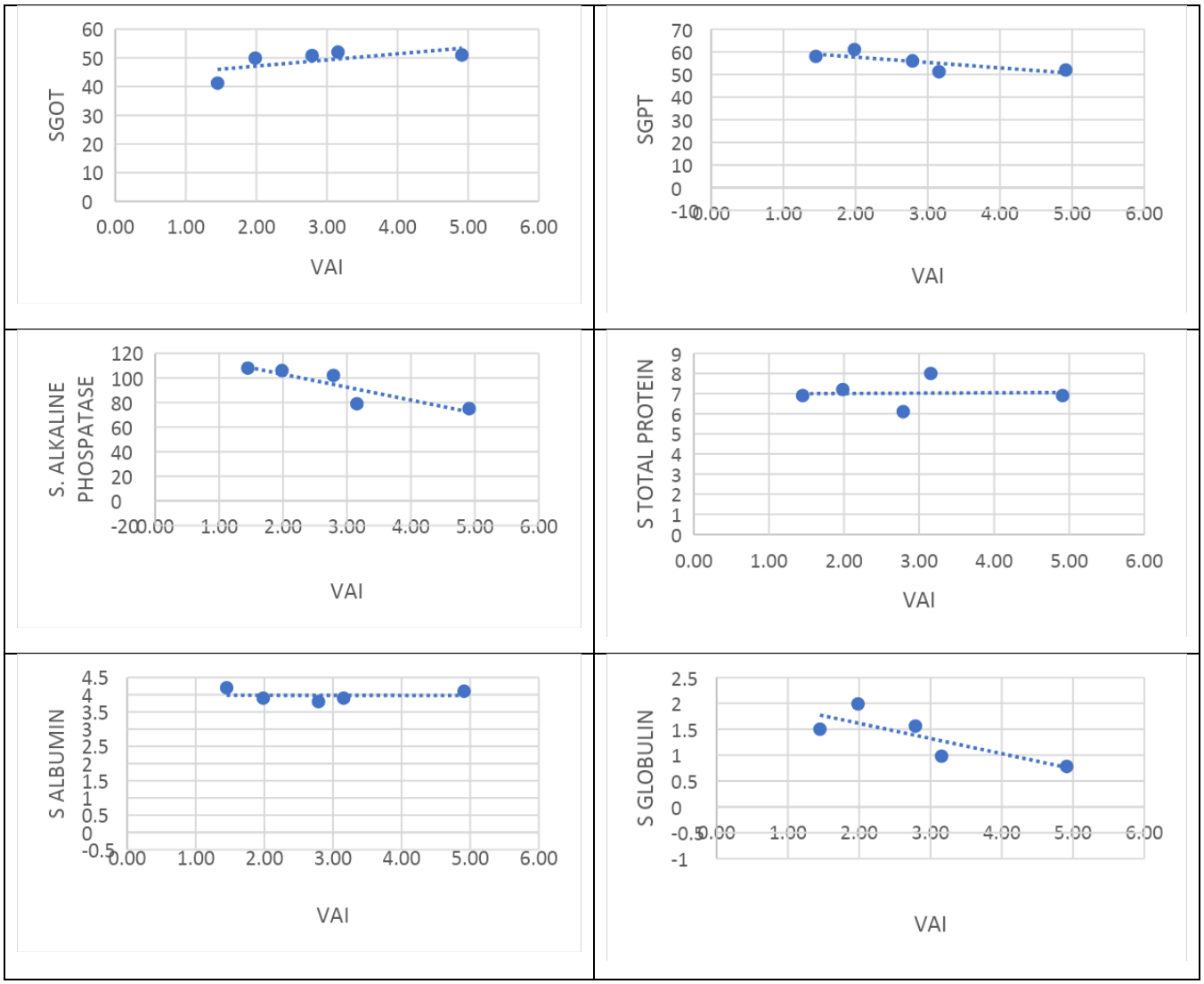


FIGURE 4: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-D

FIGURE 4: CORRELATION OF VAI & LIVER FUNCTION TESTS OF PCOS PHENOTYPE-D





DISCUSSION:

Key characteristics of metabolic syndrome (MS) are obesity, insulin resistance, and dyslipidemia. People with PCOS often have abnormal lipid profiles regardless of their BMI. The current method for assessing this risk is still not optimal, despite the fact that PCOS patients have a higher risk of metabolic syndrome and cardiovascular disease (CVD). The estimation of MS, CVD, and ovarian risk in PCOS would be considerably simplified by the discovery of an affordable MS predictor. Female MS-PCOS patients are more likely to have hyperandrogenism, dyslipidemia and other metabolic disorders (16). One of the hypothesized causes of systemic metabolic disorders, including low-grade inflammation, insulin resistance (IR), dyslipidemia, and dysglycemia, is dysfunction of the adipose tissue. It has been identified as a risk factor for morbidity and mortality in both normal weight and obese persons, and it has been linked to an

increase in the incidence of obesity (especially central obesity) and Metabolic Syndrome (MetS) in the general population (17,18,19).

Compared to WC and BMI, which indicate general obesity, the VAI, which measures the degree of fat distribution and accumulation, is a more significant and useful form of adipose tissue index.Studies done by Tian, Tian et al.2020, Anoop S, Shajith et al.,2021 & Motamed, N et al.2016 have shown a high correlation between the use of VAI and hyperglycemia and insulin resistance in type 2 diabetes (20,21,22).

Finding and correlating easy-to-use and reasonably priced markers to evaluate MS risk in PCOS phenotypes was the purpose of our research.

In the present study VAI was correlated with various liver function parameters like serum total bilirubin, serum direct bilirubin, SGOT (Serum glutamic oxaloacetic transaminase), SGPT (Serum glutamate pyruvate transaminase), serum Alkaline phosphatase, serum total protein, serum albumin & serum globulin. In PCOS Phenotype A & Phenotype C, VAI showed negative correlation with all Liver function tests parameters. In PCOS Phenotype B samples: The Liver function tests parameters showed negative correlation with VAI except for SGOT which showed positive correlation. In PCOS Phenotype D samples: The Liver function tests parameters showed negative correlation with VAI except for Serum alkaline phosphatase which showed positive correlation. Increased liver markers and MetS are linked, however the precise pathophysiological mechanism is still unknown. Furthermore, our study does not allow us to draw any directionality regarding the relationship between liver enzymes and other elements of MetS, including insulin resistance. Elevated liver markers may be a sign of increased fat accumulation in the liver, as proposed by Hanley et al. (23). Another theory is that, as Nakanishi et al. (24) have proposed, increased liver enzymes are a sign of inflammation in the liver. In addition to increased visceral adiposity, Patel et al. (25) also suggested that MetS risk and liver enzymes may be associated with hepatic insulin resistance. Numerous disorders have been linked to elevated serum levels of liver enzymes such as SGOT and SGPT, and individuals who are obese are often found to have these elevated levels (26,27). Through elevated levels of SGOT and SGPT enzymes, obesity has been linked to metabolic problems such high fasting blood glucose and insulin resistance, according to another study by Xu, Lin et al. 2017.& this relationship is stronger in women than in men (28). Given the importance of liver enzymes in the body's metabolism (29,30,31), if the connection between adipose dysfunction and serum liver enzyme levels is established, this

discovery could provide insight into one potential mechanism through which adipose dysfunction contributes to the risk of numerous diseases impacted by MetS. Furthermore, a number of substances secreted by visceral adipose tissues, including adipokines, resistin, leptin, visfatin, and tumour necrosis factor α, might affect liver function and cause cirrhosis, hepatocellular carcinoma, and inflammation. But there are also a number of other variables, like dietary intake, that may have a reciprocal effect on liver function and obesity (32,33,34).

To the best of our knowledge, this is the first time to investigate the association between VAI & LFT parameters in PCOS phenotypes to predict MetS. However, our study had some limitations, as all the parameters & indices of Metabolic syndrome could not be assessed. Future large-scale prospective studies are needed to reveal the association between VAI & Liver function.

CONCLUSION:

In PCOS phenotypes, especially with PCOS Phenotype B there is a substantial correlation between VAI & SGOT. In PCOS Phenotype D samples, VAI & Serum alkaline phosphatase showed positive correlation. Accordingly, based on the present study results, correlating liver function with VAI can help in the early diagnosis of MetS. The reported results need to be corroborated by additional prospective studies with a bigger sample size.

Availability of data and materials

All data supporting the findings of this study are available within the paper.

Abbreviations:

- VAI: Visceral adiposity index.
- PCOS: Polycystic Ovarian Syndrome.
- IR: Insulin Resistance.
- BMI: Body mass index.
- MS/ MetS: Metabolic syndrome.
- SGOT: Serum glutamic oxaloacetic transaminase.
- SGPT: Serum glutamate pyruvate transaminase.
- ALP: alkaline phosphatase.
- GGT: gamma glutamyltransferase.
- ALT : alanine aminotransferase.
- BP: blood pressure.

- TG: triglycerides.
- WC: waist circumference.
- HDL-C: High density lipoprotein- cholesterol.

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