Research Article

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Can triglyceride related indices be reliable markers in the assessment of polycystic ovarian syndrome?

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Abstract

Objectives: This study aimed to evaluate the diagnostic utility of the triglyceride glucose (TyG), triglyceride glucose–body mass (TyG-BMI), and lipid accumulation product (LAP) indices for both screening polycystic ovary syndrome (PCOS) and diagnosing insulin resistance (IR) in women diagnosed with PCOS.

Methods: Retrospective data from medical records of 124 women were analyzed, with 71 in the PCOS group and 53 in the non-PCOS group. The PCOS diagnosis followed the 2003 Rotterdam criteria. Basic clinical and biochemical parameters were compared. The TyG index was computed using the formula ln [triglyceride (TG) (mmol/L) × fasting plasma glukose (FPG) (mg/dL)/2]. TyG-BMI value was derived as TyG × BMI. LAP was calculated as (waist circumference (WC-58) × TG (mmol/L). IR was identified if Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was >2.7.

Results: TyG-BMI (AUC=0.62) and LAP indices (AUC=0.61) did not demonstrate statistically significant diagnostic performance for PCOS. Regarding IR in PCOS patients, the highest AUC was for TyG-BMI (0.84, 95 % CI: 0.73–0.93, p<0.001) with a cutoff at 116.15, showing 80 % sensitivity and 86 % specificity. LAP had an AUC of 0.86 with a cutoff of 30.21 (sensitivity 80 %, specificity 81 %), while TyG showed an AUC of 0.78 (95 % CI: 0.67–0.89, p<0.001) with a cutoff of 4.47, demonstrating a sensitivity of 70 % and specificity of 72 %.

Conclusions: Numerous biochemical markers have been explored for PCOS detection, however, many are expensive, not universally available, and necessitate specific test kits. TyG, TyG-BMI, and LAP indices might not serve as reliable markers for PCOS screening but could offer utility in identifying IR in Turkish women diagnosed with PCOS.

Keywords: index; lipid accumulation product; polycystic ovary syndrome; triglyceride glucose; triglyceride glucose-body mass

Introduction

Polycystic ovary syndrome (PCOS) is a common disorder in reproductive-aged women. PCOS is characterized by ovulatory dysfunction, clinical/biochemical signs of elevated androgen levels, and the presence of polycystic ovarian morphology (PCOM) detected through ultrasound [1]. The worldwide incidence of PCOS varies between 5 and 15 % [2]. The underlying metabolic mechanisms contributing to PCOS remain elusive and complicate the development of metabolic interventions [3]. In addition to gynecological conditions such as anovulation and irregular menstruation, PCOS is closely associated with glucose intolerance, type 2 diabetes (T2DM), and cardiovascular morbidity [4, 5]. The increased risk of T2DM and CVD in patients with PCOS is linked to tendencies toward abdominal fat accumulation [6].

In insulin resistance (IR), the clearance of triglyceride-rich lipoproteins from the bloodstream is delayed, leading to the development of hypertriglyceridemia. IR is more commonly detected in women with a diagnosis of PCOS than in healthy women [7]. It is claimed that patients with PCOS have higher levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), as well as TG to HDL-C and low density lipoprotein cholesterol (LDL-C) to HDL-C ratios [8]. Managing PCOS

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effectively requires a multidisciplinary approach involving gynecologists, dermatologists, endocrinologists, psychiatrists, and nutritionists to develop a comprehensive management plan aimed at reducing both the metabolic and psychological damage caused by the syndrome [9]. Traditionally, PCOS is diagnosed by gynecologists following the Rotterdam criteria [10]. However, early detection of PCOS using simple markers by medical professionals other than gynecologists can mitigate the long-term adverse consequences of the disease.

The triglyceride-glucose (TyG) index is a marker of IR and has been shown to be an effective predictor of glycolipid metabolism-related diseases [11]. TyG, calculated from venous blood fasting glucose (FBG) and TG levels, provides a straightforward assay for identifying IR [12]. Despite limited research, the TyG index has shown promise in diagnosing PCOS patients [7, 13].

The triglyceride glucose-body mass index (TyG-BMI) has emerged as a valuable tool for identifying individuals at risk of T2DM, one of common morbidities of PCOS [14]. The TyG-BMI has also been recognized as a practical serum biochemical parameter for distinguishing individuals with and without non-alcohol-related fatty liver disease [15]. Although studies on the TyG-BMI and PCOS incidence are limited, the TyG-BMI holds potential for clinical application [7, 16].

The lipid accumulation product (LAP) was originally identified as a superior indicator of body mass index (BMI) in identifying adults at risk of cardiovascular disease [17]. It offers a straightforward measure of lipid overaccumulation [17]. LAP shows promise for the early detection of IR and cardiometabolic risk, making it a potentially useful tool for assessing hyperandrogenism in lean PCOS patients [13, 18].

The aim of this study was to investigate whether the TyG, TyG-BMI, and LAP indices, which are simple and practical alternatives, could serve as surrogate biochemical markers for screening for PCOS and diagnosing IR in PCOS patients.

Materials and methods

We conducted this retrospective study at the Training and Research Medical Center of Düzce Medical University from December 2018 to March 2023. Women with a diagnosis of Cushing disease, tuberculosis, androgen-secreting ovarian tumors, adrenal hyperplasia, any kind of malignancy, a decreased ovarian reserve, intake of glucocorticoids, any hormonal drug, antidiabetic treatment, or antihyperlipidemic treatment and women with incomplete data were excluded from this study [3]. Women with concurrent systemic conditions such as thyroid dysfunction, diabetes, hepatic dysfunction, renal dysfunction, or hypertension were excluded from the study [13]. Also cigarette smokers and alcohol users were not included. The PCOS diagnosis was performed according to the 2003 Rotterdam criteria and included two out of three following features: (1) irregular cycles, (2) hyperandrogenism (biochemical and/or clinical), and (3) a PCOM described on ultrasound [10]. This study was performed in compliance with the Declaration of Helsinki, and all participants provided informed consent for the data analysis. Retrospective data were collected via the review of patient medical records, and 124 women were included in this study. Included and excluded patients were summarized in the study flowchart (Supplemental Figure 1).

The waist circumference (WC) was measured at the midpoint between the iliac crest and the lowest rib [19]. All biochemical and hormonal parameters were obtained through the analysis of venous blood samples collected from patients after 8 h of overnight fasting on the second or third day of the menstrual cycle [3]. The patients were divided into two main groups based on the diagnosis of PCOS: the PCOS group and the non-PCOS group. The clinical variables, including age, weight, height, diastolic blood pressure (DBP) and systolic blood pressure (SBP), were recorded. Serum biochemical parameters, including LDL-C, HDL-C, TG, TC, fasting insulin (FINS) and FPG, were measured. The Friedewald equation [LDL-C =TC − (HDL-C + TG/5)] was used to calculate LDL-C levels. LDL-C levels of patients with TG≤400 mg/dL (low-TG) are calculated using the Friedewald formula in Turkish routine biochemistry laboratory tests [20]. There was no patient with TG>400 mg/dL in this study. The Friedewald equation calculates the LDL-C value using the patients' TC, HDL-C, and TG test results [3]. The expression profiles of various hormones, including follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), total testosterone (TT) and luteinizing hormone (LH), were analyzed [21]. BMI was defined as weight (kg)/height^2 (m^2) (kg/m^2). The TyG index was calculated using the formula ln [TG (mmol/L) × FPG (mg/dL)/2] [22]. The TyG-BMI was calculated as TyG × BMI [23]. The LAP value was calculated as follows: (WC-58) × TG (mmol/L) [13]. A diagnosis of IR was made if the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) value, calculated as FPG (mmol/L) × FINS (mIU/L)/22.5, was above 2.7 [24].

Statistical analysis

We analyzed all the data by using the IBM Statistical Package for Social Sciences for Windows (SPSS) software package (version 22, SPSS, Inc., Chicago, IL, USA). Normally distributed quantitative variables were assessed with the Kolmogorov–Smirnov test. Continuous variables with a nonnormal distribution were expressed as medians (minimums and medians), while categorical data were expressed as numbers and percentages (%). For comparisons of continuous variables between groups, the nonparametric Mann–Whitney U test was used; for comparisons of categorical data, the Pearson chi–squared test was used. The number of participants in the study was calculated using values from a similar study performed with Minitab 16.0 software (Minitab, Inc., State College, PA, USA). A minimum of 52 participants in each group were determined to achieve a Type 1 error of 5 % and a study power of at least 80 % [7]. Sensitivity and specificity, along with the cutoff value for distinguishing two groups, were evaluated using receiver operating characteristic (ROC) curve analysis. $p<0.05$ was considered statistically significant.

Results

The mean age was 26.5±6.3 years. Seventy-one (57.3 %) women were diagnosed with PCOS in our study, while 53

(42.7 %) were classified as non-PCOS patients. Significantly higher rates of nulliparity and nulligravidity were detected in women with a diagnosis of PCOS (p=0.032; p=0.03). No statistically significant difference was found between the PCOS group and the non-PCOS group in terms of abortion frequency (p=0.10).

The PCOS group exhibited significantly greater BMIs (p=0.02), hirsutism scores (p<0.001 and p<0.05), FPG (p=0.27), HbA_{1c} (p=0.57), LH levels (p=0.03 and p<0.05), LH/FSH ratios (p<0.001 and p<0.05), and total testosterone levels (p=0.001) than did the non-PCOS group. We did not find any statistically significant difference between the PCOS group and the non-PCOS group in terms of IR (p=0.068). An overview of all the laboratory values for the patients can be found in the first table.

The TyG index did not significantly differ between the two groups (p=0.26). However, the mean TyG-BMI and LAP indices were significantly lower in the non-PCOS group (p=0.02 and p=0.03, respectively) (Table 1).

The ideal cutoff value for the TyG-BMI for predicting the diagnosis of PCOS was 93.77, the sensitivity was 73 %, and the specificity was 44 %. The AUC for the TyG-BMI was 0.62 (95 % confidence interval [CI]: 0.52–0.71, p=0.022). Similarly, for the LAP index, a cutoff of 14.25 was chosen, resulting in a sensitivity of 70 % and a specificity of 48 %. The AUC of the LAP index was 0.61 (95 % CI: 0.51–0.71, p=0.033). It should be noted that the TyG-BMI and LAP indices for diagnosing PCOS were not statistically acceptable (Figure 1).

The mean TyG index (p<0.001), TyG-BMI (p<0.001), and LAP index (p<0.001) were significantly greater in PCOS patients with IR (IR+) (Table 2.). Similarly, in the non-PCOS group, the TyG, TyG-BMI, and LAP indices were significantly greater in individuals with IR (+) than in those without IR (p=0.004, p=0.01, p=0.004, respectively) (Table 2).

The ROC curve of IR (+) in PCOS patients showed that the AUC of the TyG-BMI was the best at 0.84 (95 % CI: 0.73–0.93, p<0.001) when the cutoff point was 116.15. The ideal TyG-BMI had 80 % sensitivity and 86 % specificity. ROC analysis revealed that the optimal cutoff value for the LAP index for defining IR (+) in women with PCOS was 30.21 (sensitivity 80 %, specificity 81 %), and the AUC was 0.86. The AUC of the TyG index for determining IR (+) in PCOS patients was 0.78 (95 % CI: 0.67–0.89, p<0.001) with a best cutoff point of 4.47, which had a sensitivity of 70 % and specificity of 72 %. The cutoff points, sensitivities, specificities, and standard errors of the abovementioned serum TG-related parameters are shown in Table 3 and Figure 2.

Table 1: Table depicting the basic clinical data of the two groups.

Variables	Non-PCOS group Median (min–max)	PCOS group Median (min–max)	p-Value[a,b]
BMI, kg/m^2	22.1 (16.6–36.9)	25.0 (17.3–40.0)	**0.02**[a]
Waist circumference, cm	81.0 (60–133)	85.0 (60–130)	0.10
Hirsutismus score-MFGS	3.0 (0–7)	11.0 (0–28)	**<0.001**[a]
FSH, mIU/mL	6.8 (3.1–18.4)	5.6 (0.5–49.3)	**<0.001**[a]
LH, mIU/mL	6.0 (1.5–13.2)	7.1 (0.4–35.6)	**0.03**[a]
LH/FSH	0.8 (0.3–1.9)	1.2 (0.1–4.3)	**<0.001**[a]
E2, pg/mL	50.8 (5.0–292.4)	37.6 (5.0–182.4)	**0.01**[a]
Total testosterone, ng/dL	0.2 (0.03–0.49)	0.3 (0.03–0.67)	**0.001**[a]
Prolactin, mIU/L	16.5 (8.2–52.9)	20.0 (8.0–72.4)	0.07
TSH, mIU/L	1.9 (0.02–7.02)	2.1 (0.4–6.45)	0.23
FPG, mmol/L	93.4 (82.2–129.4)	91.6 (68.1–121.3)	0.27
HbA_{1c}, mmol/mol	5.1 (4.2–8.0)	5.1 (4.5–5.8)	0.57
HOMA-IR (unit)	1.8 (0.3–11.7)	2.3 (0.09–15.2)	0.10
TC, mg/dL	165.0 (115.1–237.2)	166.0 (93.3–247.6)	0.98
TG, Mmol/L	0.8 (0.3–2.6)	0.9 (0.4–3.1)	0.07
LDL-C, mg/dL	91.9 (39.3–151.0)	88.9 (33.2–184.4)	0.74
HDL-C, mg/dL	55.2 (28.6–90.4)	50.5 (26.9–88.7)	0.12
TyG index (unit)	4.3 (4.0–5.0)	4.4 (3.0–5.2)	0.26
TyG-BMI index (unit)	99.6 (70.5–183.4)	107.7 (76.1–218.8)	**0.02**[a]
LAP index (unit)	18.3 (1.6–196.4)	23.5 (1.4–144.9)	**0.03**[a]

[a]p-Value<0.05 was considered to indicate statistical significance.
[b]Mann–Whitney U test was used. BMI, body mass index; WC, waist circumference; MFGS, modified Ferriman–Galley score; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c;E2, estradiol; LH, luteinizing hormone; TC, total cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride–glucose; TyG-BMI, triglyceride glucose body mass index; LAP, lipid accumulation product.

Discussion

In this study, our objective was to diagnose PCOS exclusively through TG-related indices, thereby obviating the need for biochemical assessments such as androgen level evaluations or transvaginal ultrasonography. The PCOS group exhibited significantly greater BMIs, hirsutism scores, FPG, HbA_{1c}, LH levels, LH/FSH ratios, and total testosterone levels than non-PCOS group in our study. However, within our study's homogenous population, we observed that the TyG index did not significantly differ between PCOS patients and healthy women within the Turkish population. Based on our study findings, despite the elevation of TyG-BMI and LAP indices

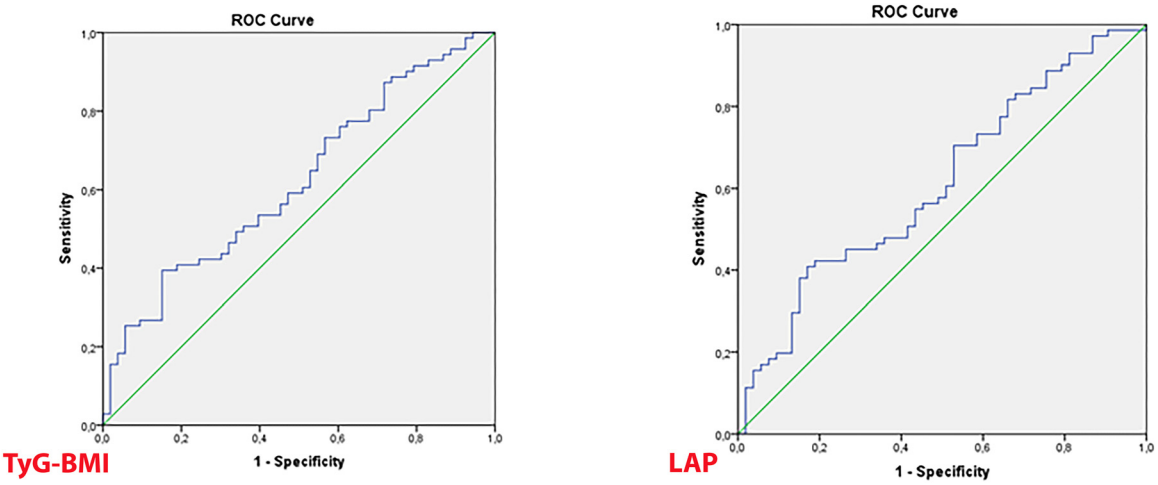

Figure 1: The power of the TyG-BMI and LAP indices to distinguish women with PCOS from healthy individuals.

Table 2: Associations between IR and TyG, TyG-BMI, and LAP indices in women with PCOS.

	PCOS IR (−) (n:41)	PCOS IR (+) (n:30)	p-Value[a,b]
TyG index	4.3 (3.0–5.0)	4.6 (4.1–5.2)	**<0.001**
TyG-BMI index	96.6 (76.1–218.8)	144.8 (83.4–184.0)	**<0.001**
LAP index	15.2 (3.2–98.0)	52.2 (1.4–144.9)	**<0.001**

[a]p-Value<0.05 was considered to indicate statistical significance.
[b]Mann–Whitney U test. TyG, triglyceride-glucose; TyG-BMI, triglyceride-body mass index; LAP, lipid accumulation product.

Consequently, healthcare providers should endeavor to accurately, easily, and promptly diagnose PCOS [27]. Therefore, extensive research has investigated various biochemical markers for the diagnosis of PCOS, including irisin, betatrophin, endotrophin, X-box-binding protein 1, kisspeptin, and the anti-Mullerian hormone [28–31]. Among these serum parameters, both endotrophin and X-box-binding protein 1 have shown potential as robust screening markers for the future assessment of IR and metabolic

Table 3: Serum triglyceride-related parameters for differentiating women with IR (+) PCOS from those with IR (−) PCOS.

	Cutoff value	Sensitivity %	Specificity %	AUC[a]	SE[b]	p-Value[d]	95 % CI[c]
TyG index	4.37	83	52	0.78	0.055	<0.001	0.67–0.89
	4.47	**70**	**72**				
	4.64	60	86				
TyG-BMI index	96.88	87	55	0.84	0.052	<0.001	0.73–0.93
	116.15	**80**	**86**				
	129.54	63	93				
LAP index	17.01	90	64	0.86	0.048	<0.001	0.76–0.95
	30.21	**80**	**81**				
	40.71	73	89				

[a]Area under the curve. [b]Standard error. [c]95 % confidence interval. [d]ROC curve analysis was used; TyG, triglyceride-glucose; TyG-BMI, triglyceride glucose body mass index; LAP, lipid accumulation product.

in PCOS patients, these indices did not exhibit statistically robust characteristics as reliable biochemical markers for PCOS diagnosis.

A report published in 2022 stated that up to 75 % of PCOS patients in the United States were undiagnosed [25]. Approximately one in four women experience a delay in receiving a PCOS diagnosis for two years or longer [26].

syndrome (MetS) [30, 31]. However, most of these biochemical markers are expensive, unavailable in every laboratory, and require specific test kits. Beyond gynecology, other medical disciplines can achieve early PCOS diagnosis using simple biochemical markers, which may help prevent potential metabolic issues [32]. The PCOS group showed significantly higher BMI, modified Ferriman-

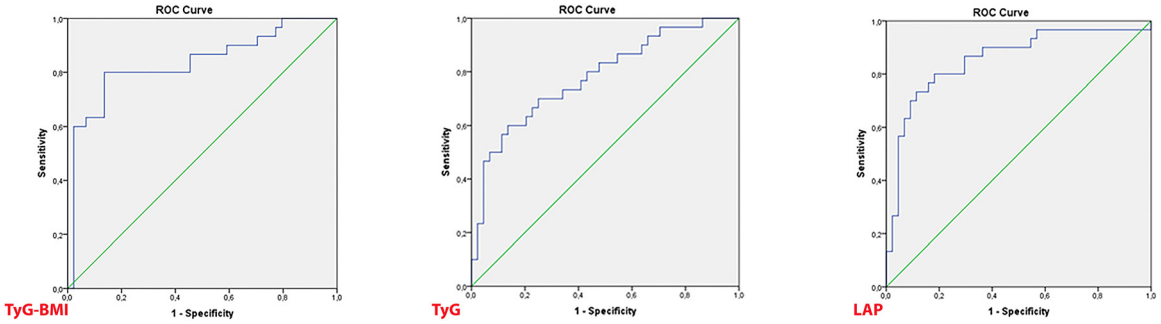

Figure 2: The power of the TyG-BMI, TyG and LAP indices for differentiating women with IR (+) PCOS from those with IR (–) PCOS.

Gallwey hirsutism score (MFGS), LH levels, total testosterone levels, and LH/FSH ratio in our study. These clinical and laboratory findings are anticipated in individuals with PCOS. Our results align with previous studies [9, 13, 16]. However, mean TG levels were similar between the two groups, and no statistically significant differences were found in terms of TC, LDL-C, or HDL-C between the PCOS and non-PCOS groups in our study. Consequently, it appears that TG-related indices were inadequate for diagnosing PCOS in our study. Liu et al. claimed that dyslipidemia, defined as elevated LDL-C and TG levels and decreased HDL-C levels, is often observed in women diagnosed with PCOS [33]. However, a recent meta-analysis supporting our findings revealed that TG concentrations did not significantly differ between PCOS patients and healthy individuals [34]. Currently, there is limited evidence regarding the utilization of TyG, TyG-BMI, and LAP indices for diagnosing PCOS [35]. Nevertheless, emerging evidence highlights the potential utility of biochemical parameters related to serum TG levels, such as the TyG, TyG-BMI, and LAP indices, in predicting IR among women with PCOS [3, 8, 13].

In our research, we additionally explored the predictive significance of the TyG, TyG-BMI, and LAP indices concerning IR in patients with PCOS. Our findings indicated that the TyG-BMI was the most robust marker, while the TyG and LAP indices proved practical and easily applicable as biochemical serum markers for detecting IR in Turkish women diagnosed with PCOS.

Insulin is believed to influence lipogenesis [36]. Insulin increases glucose uptake by fat cells. Insulin activates lipogenic and glycolytic enzymes through covalent modification, ultimately stimulating lipogenesis [36]. Elevated serum TG-related indices such as TyG-BMI, TyG, and LAP are associated with IR [12, 14, 15]. In our non-PCOS controls, the TyG, TyG-BMI, and LAP indices were notably greater in individuals with IR. β-cell dysfunction and IR are potential mechanisms involved in the development of T2DM [37]. IR plays a fundamental role in the pathophysiology and comorbidities of PCOS [38]. IR and compensatory hyperinsulinemia lead to a significant reduction in the myo-inositol (MI) and d-chiro-inositol (DCI) ratio within the ovaries, contributing to gynecological disorders characterized by hyperandrogenism, altered menstrual cycles, and infertility [39]. Traub et al. emphasized that addressing IR is pivotal in PCOS treatment [40]. However, laboratory measurements for detecting IR, such as QUICKI, Matsuda, HOMA-IR, and FG-IR, are complex, expensive, and challenging to implement [36]. Thus, there is a need for the development of easily applicable, patient-friendly, and cost-effective biochemical markers to diagnose IR in PCOS patients [1].

When evaluating the ability of TyG, TyG-BMI, and LAP to predict IR in patients with PCOS, it is crucial to consider biochemical detection methods and average values specific to each population [8]. Moreover, the TyG and TyG-BMI indices have demonstrated their potential as beneficial biochemical markers for early MetS diagnosis in PCOS patients [3, 20]. Zheng et al. reported a correlation between IR and two TG-related indices, the TyG and TyG-BMI, in women diagnosed with PCOS [7]. In line with our study, IR was defined using HOMA-IR in that study, and the TyG-BMI, with a cutoff point of 191.53, exhibited the highest AUC value of 0.796, with a sensitivity of 85.3 % and specificity of 73.9 % [7]. Kwon et al. recently reported that the TyG index is an appropriate surrogate marker for predicting insulin sensitivity/resistance in women with PCOS [41]. Wehr et al. were the first to show that LAP was a clinically useful marker for the detection of IGT [19]. LAP appears to be a simple, reliable biochemical marker for detecting IR-positive PCOS patients [19]. Hosseinpanah et al. reported that among individuals with PCOS, the LAP index demonstrated the highest diagnostic accuracy in detecting IR [42]. It can confidently screen for IR in PCOS patients without necessitating time-consuming tests such as OGTT or

consecutive venous blood samples [19]. Anik Ilhan et al. suggested that LAP can be used for the early detection of IR and for the risk of CVD in Turkish women diagnosed with PCOS [13].

Limitations

This study was conducted retrospectively. We would have preferred to have a larger number of patients in our study. Additionally, in similar studies conducted in different countries, distinct cut-off values for the TyG, TyG-BMI, and LAP indices in diagnosing IR among PCOS patients have been identified. In order for these markers to be globally utilized, studies involving women from diverse populations will be beneficial. Therefore, there is a necessity for prospective, randomized, and controlled trails encompassing multiple centers across various populations to establish their universal routine use.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki. The Clinical Research Ethics Committee of Düzce University approved this study.
Informed consent: Informed consent was obtained from all individuals included in this study.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
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Data availability: The raw data can be obtained on request from the corresponding author.

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