BAGHDAD JOURNAL OF BIOCHEMISTRY AND APPLIED BIOLOGICAL SCIENCES
2022, VOL. 3, NO. 04, 286-298, e-ISSN: 2706-9915, p-ISSN: 2706-9907
https://doi.org/10.47419/bjbabs.v3i04.151

ORIGINAL ARTICLE

Estimation of renin and D-dimer levels in women with polycystic ovary disease with or without coronavirus infection

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Received 13-09-2022
Revised 04-11-2022
Accepted 07-11-2022
Published 07-11-2022

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DOI https://doi.org/10.47419/bjbabs.v3i04.151

Pages: 286-298

ABSTRACT

Background and objective: Polycystic ovarian syndrome (PCOS) is a common endocrinological disorder among women of childbearing age. Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The association between PCOS and COVID is yet to be understood. This study aimed to determine the levels of renin, D-dimer, and some relevant biomarkers in patients with PCOS (with and without COVID-19).
Methods: This cross-sectional study included 120 women [80 PCOS women (40 with COVID-19 and 40 without COVID-19) and 40 non-PCOS women (20 with COVID-19 and 20 without)] with age range of 15–40 years old. Blood samples were collected from participants, and biochemical parameters were evaluated by ELISA (renin and D-dimer), VIDAS (sex hormones: LH, FSH and testosterone), and colorimetric methods (serum lipids and glucose concentrations).
Results: Renin and D-dimer levels were significantly higher in PCOS groups compared to non-PCOS groups. In addition, luteinizing hormone, fasting blood glucose, and serum lipid tests (total cholesterol, triglycerides, and low-density lipoprotein) reveal significant elevation in PCOS patients compared to non-PCOS women. While, high-density lipoprotein and follicle-stimulating hormone levels were lower in PCOS patients. The results also showed that a highly significant increase in renin and D-dimer levels can be seen in PCOS patients with COVID-19.
Conclusions: In the present study, we found there is a possible relationship between renin and D-dimer in PCOS patients and SARS-CoV-2 infection.

Keywords COVID-19, follicle-stimulating hormone, D-dimer, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common diseases that affects 5-10% of women of childbearing age.[1] It is characterized by an irregular menstrual cycle, ovulatory dysfunction, and hyperandrogenism as well as metabolic disturbances.[2] PCOS disease increases the risk of developing hypertension, metabolic syndrome, obesity, endometrial cancer, and diabetes.[3] A small percentage of PCOS women have the ability to compensate for their insulin resistance, and a large percentage of them have a defect in the beta function that works on secreting insulin. Thus, the increased level of blood glucose in PCOS women can lead to developing type 2 diabetes mellitus (T2DM), regardless of age and body mass index (BMI).[4] In PCOS, it has been found that there is a strong relationship between hyperandrogenism and hyperinsulinemia, but the underlying mechanism of their relationship with PCOS is not yet clear.[5]

Coronavirus disease (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 (or SARS-CoV-2). It was announced firstly in late 2019.[6] This virus was identified for the first time in Wuhan, China. The number of deaths reached 3,087, or 6% of the total number of patients who were rescued, which was 45,726.[7] According to recent reports, symptoms and complications of PCOS show significant overlap with risk factors for severe COVID-19 infection.[8] The PCOS complications (such as cardiac and metabolic ones) are similar to the main clinical outcomes of COVID-19. Therefore, PCOS women are expected to be more vulnerable to COVID-19.[9] And, the acceptable relationship between androgens and COVID-19 severity can support the hypothesis that anti-androgens may represent a potential additional intervention against COVID-19.[10]

Renin-secreting cells are essential in blood pressure maintenance and fluid-electrolyte balance. In mammals, the main source of renin is the kidney cells, which are known as the juxtaglomerular cells. Renin cells are powerful sensors with a high ability to sense and respond to changes in blood pressure and extracellular fluid volume. When the blood pressure decreases, the cells adjacent to the glomerulus secrete the renin enzyme and release it into the blood circulation, which leads to hypertension. On the other hand, when the blood pressure rises, the secretion of renin decreases, thus maintaining fulfillment of the normal blood pressure in the body.[11]

D-dimer molecules are formed when cross-linked fibrin breaks down during fibrinolysis. D-dimer testing is critical for the diagnosis of many life-threatening events such as deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC).[12] Accumulated evidence suggests the interrelationship between the renin-angiotensin system, coagulation systems, fibrinolysis, and D-dimer formation.[13] The aim of this study is to investigate the relationship between renin and D-dimer in PCOS patients with and without COVID-19.

MATERIALS AND METHODS

Study design and patients

This study is a part of cross-sectional study conducted at the Baghdad University (Baghdad, Iraq), from December 2021 to June 2022. One hundred and twenty (120) women, whose ages ranged from 15–40 years were recruited in the study. The participants were 80 patients with polycystic ovary syndrome (from Kamal Al-Samarai Hospital) and 40 healthy women as a control group. Patients and control groups were subdivided, according to COVID-19 status, each into two subgroups: COVID-19 and non-COVID-19.

The inclusion criteria were: PCOS medical history, $COVID$-19 medical history, and patients ranging from (15-40) years. PCOS women have already been diagnosed with the syndrome according to the American Society for Reproductive Medicine and European Society Standards for Human Reproduction and Fetus.

Menopausal women, women who have had previous surgeries (such as removing one of their ovaries), patients with respiratory disease, heart disease and diabetes were all excluded.

Biochemical analyses

Ten milliliters (ml) of venous blood were withdrawn from each participant and collected into gel-containing tubes (anticoagulant-free) at room temperature for 20 minutes, then serum was separated by centrifugation for 10 minutes, and the serum separated was stored in Eppendorf tubes. Serum was used for evaluating fasting blood sugar (FBS) and lipid profile by applying the enzymatic colorimetric methods with commercial kits from Human (Germany), while the hormonal profile was assayed using VIDAS (Biomerieux, France). The remaining serum was frozen at -20°C for the evaluation of renin and D-dimer by enzyme-linked immune sorbent assay (ELISA) technique (MyBioSource, USA).

Statistical analysis

All statistical analysis data were performed using SPSS statistical software, version 26, and Medcalc software, version 20 which is used in receiver operating characteristic (ROC) curve analysis for the assessment of its value as a marker for discriminating patients with PCOS infected or non-infected with COVID-19. The variables were reported as means$\pm$standard deviation (SD), and the one-way ANOVA is used to determine whether there are statistically significant differences between the means of the studied groups. Non-parametric Kruskal Wallis test was used for testing the difference between means of groups that are non-normally distributed. The post-hoc (Conover) analysis was applied to indicate a pairwise variance between each 2 groups whenever the Kruskal Wallis test was significant.

RESULTS

Serum biomakers of all participants were presented in Table 1, which also shows clinical characteristics of all study groups. In this study, the age of the healthy and patient groups was matched. The result shown no significant differences (p> 0.05) in age between all groups, while high significant difference ($p\leq$0.05) noted among all groups in regards to body mass index (BMI), fasting blood sugar (FBS), follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH, testosterone, insulin, diastolic blood pressure (DBP), systolic blood pressure (SBP).

Table 1 **General characteristics of the study participants.**

Parameters	PCOS with COVID-19 (n=40)	PCOS without COVID-19 (n=40)	Non-PCOS with COVID-19 (n=20)	Non-PCOS without COVID-19 (n=20)	*P*-value
Age (year)	27.25±5.82^{a}	26.37±5.78^{a}	25.90±6.88^{a}	24.10±5.29^{a}	0.393
FBG (mmol/l)	5.17±0.52^{a}	5.05±0.51^{a}	4.29±0.61^{b}	3.75±0.69^{c}	0.0001**
Insulin (μIU/ml)	44.10±16.94	29.45±10^{b}	8.73±2.71^{c}	6.35±2.91^{c}	0.0001**
BMI (Kg/m^2)	2.39±5.80^{a}	29.47±7.01^{a}	25.46±3.98^{b}	21.40±1.92^{c}	0.0001**
SBP (mmHg)	124.10±11.85^{ai}	120.25±12.2^{a}	115.90±5.60^{c}	109.0±6.28^{bc}	0.0001**
DBP (mmHg)	79.05±5.34^{a}	74.6±7.07^{b}	72.95±4.69^{b}	68.20±4.2^{c}	0.0001**
FSH (mIU/ml)	6.22±2.41^{ab}	4.87±2.22^{a}	8.50±2.20^{c}	7.70±2.91^{bc}	0.0001**
LH (mlU/ml)	9.18±3.13^{a}	8.69±5.55^{a}	5.09±2.12^{b}	4.44±1.97^{b}	0.0001**
LH/FSH ratio	1.56±0.46^{a}	1.86±0.98^{a}	0.763±0.76^{b}	0.58±0.16^{b}	0.0001**
Testosterone (ng/ml)	0.78±0.22^{c}	0.67±0.21^{c}	0.45±0.22^{a}	0.30±0.10^{b}	0.0001**

Data were presented as mean±standard deviation (SD). * Statistically significant at p=0.05, ** Significant at p=0.01. Letters (a, b, c, d) are symbols for comparisons between the groups. Different letters (a, b, c, and d) refer to the significant difference in the same row at p<0.001.

BMI=body mass index, FBS= fasting blood sugar, PCOS = polycystic ovary syndrome, COVID-19= coronaviruses ,95% CI= 95% confidence interval of the difference, FSH= follicle stimulating hormone, LH= luteinizing hormone, (DBP) diastolic blood pressure, (SBP) systolic blood pressure, SD = standard deviation.

General characteristics of participants

As shown in Table 2, the mean±standard deviation values of lipid profile for the studied groups showed a highly significant ($p\leq$0.05) differences in cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) levels.

Lipid profile

As shown in Table 3 , the results indicted a statistically significant differences ($p\leq$0.05) in the serum renin (pg/ml) between patient groups (PCOS patients) and healthy participants groups (non-PCOS). In addition, highly significant differences ($p\leq$0.05) in D-dimer levels

Table 2 **Lipid profile of the study participants.**

Parameters	PCOS with COVID-19 (n=40)	PCOS without COVID-19 (n=40)	Non-PCOS with COVID-19 (n=20)	Non-PCOS without COVID-19 (n=20)	*P*-value
Cholesterol (mmol/l)	7.21±1.41^{c}	6.47±1.29^{bc}	5.52±1.67^{a}	3.74±1.14^{b}	0.0001**
Triglycerides (mmol/l)	6.36±2.27^{c}	4.26±1.73^{b}	3.98±1.32^{b}	0.85±0.57^{a}	0.0001**
HDL (mmol/)	1.04±0.59^{a}	1.08±0.45^{b}	1.10±0.82^{a}	1.33±0.39^{a}	0.0001**
LDL (mmol/l)	3.27 ±1.31^{b}	2.89±1.55^{ab}	2.65±1.75^{ab}	2.04±0.94^{a}	0.02*
VLDL (mmol/l)	2.89±1.03^{c}	1.78±0.63^{b}	1.76±0.64^{b}	0.38±0.26^{a}	0.0001**

Data were presented as mean±standard deviation (SD). * Statistically significant at *p*=0.05, ** Significant at *p*=0.01. Letters (a, b, c, d) are symbols for comparisons between the groups. Different letters (a, b, c, and d) refer to the significant difference in the same row at *p*<0.001.
HDL= high-density lipoprotein, LDL= low-density lipoprotein, VLDL= very low-density lipoprotein.

(ng/mL) among the study groups were observed.

Table 3 **Levels of renin and D-dimer between patients and control groups.**

Parameters	PCOS with COVID-19 (n=40)	PCOS without COVID-19 (n=40)	Non-PCOS with COVID-19 (n=20)	Non-PCOS without COVID-19 (n=20)	*P*- value
Renin (pg/ml)	163.93±24.22^{a}	190.95±27.56^{b}	97.079±4.005^{c}	101.80±3.08^{c}	0.0001**
D-dimer (ng/ml)	290.46±83.38^{a}	207.27±75.39^{b}	141.28±60.21^{c}	85.10±20.94^{d}	0.0001**

Data were presented as mean±SD. ANOVA (or Kruskal-Walis) test was used for the statistical evaluation of data. Symbols are used to denote the comparisons and significant differences. for comparisons between the groups. Different letters (a, b, c, and d) refer to a significant difference in the same row at *p*<0.001.
PCOS: polycystic ovary syndrome, COVID-19: coronaviruses.

According to post-hoc analysis (Conover), pairwise comparisons showed significant differences (p≤ 0.05) for serum renin as shown in Figure 1. The box plot reveals an increase in the levels of serum renin in PCOS patients with COVID-19, and PCOS patients without COVID-19 when compared with non-PCOS participants with COVID-19, and non-PCOS without COVID-19. The concentration of serum renin is higher in PCOS with COVID-19 compared with PCOS patients without COVID-19. In addition, serum renin concentration is higher in participants who were non-PCOS but with COVID-19 in comparison with those who are non-PCOS and without COVID-19. Also, post-hoc analysis (Conover) has shown significant differences (p≤ 0.05) in D-dimer between both PCOS patient groups and non-PCOS groups. The levels of D-dimer notably increased in PCOS patients with COVID-19, PCOS patients without COVID-19, and non-PCOS patients with COVID-19 group in comparison with non-PCOS without COVID-19 (Figure 2).

Figure 3 shows ROC curve of renin and and Figure 4 shows ROC curve of D-dimer, for PCOS women patients. The ROC curve analysis revealed that the cut off point for renin and dimer are (> 106.35), (> 130), respectively. The sensitivities, specificities, and area under curve (AUC) of renin and D-dimer are: 80.8% and 78.8%, 100% and 100%, and 0.923 and

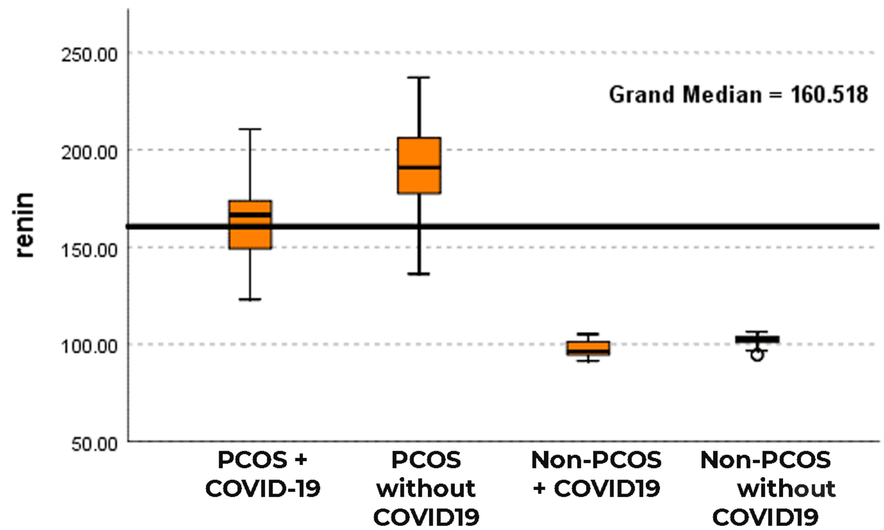

Figure 1 Box plot of renin of PCOS patient and non-PCOS groups. The figure shows the post-hoc analysis (Conover), pairwise comparisons. PCOS= polycystic ovary syndrome, COVID-19= coronaviruses.

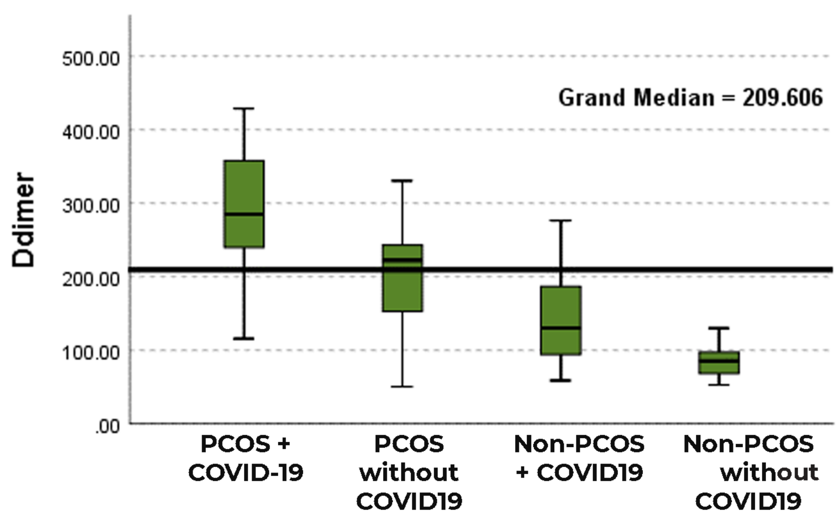

Figure 2 Box plot of D-dimer of PCOS patient and non-PCOS groups. The figure shows the post-hoc analysis (Conover), pairwise comparisons. PCOS= polycystic ovary syndrome, COVID-19= coronaviruses.

0.918, respectively.

DISCUSSION

In the current study, fasting blood glucose (FBS), BMI, and insulin were higher in both PCOS groups compared with non-PCOS groups. This is in agreement with previous find-

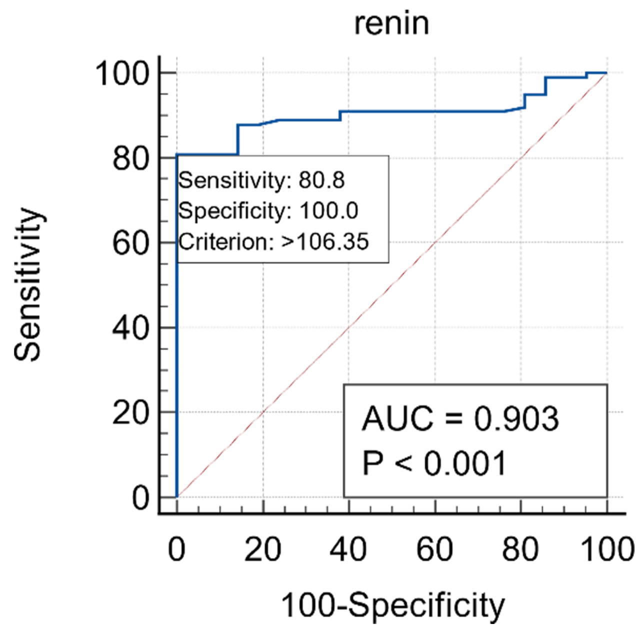

Figure 3 ROC curve of renin in PCOS patients.

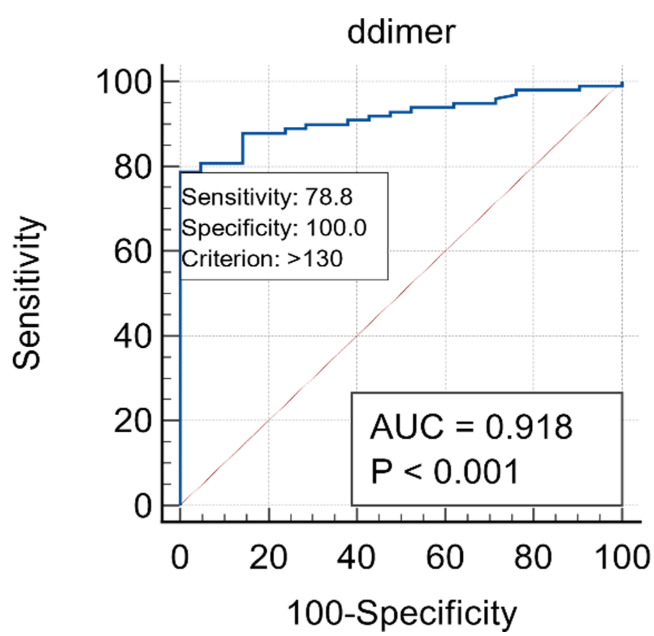

Figure 4 ROC curve of D-dimer in PCOS patients.

ings of M. Ollila,[14] that indicated a strong positive association of the level of blood sugar among PCOS patients. Such findings were also reported by Kyrou, et al.[15] who observed PCOS patients have a higher prevalence of glucose metabolism problems. *In vitro* investigations on adipocytes and skeletal muscle revealed that both under and overweight PCOS individuals had an increase in subcutaneous adipocytes.[16] Although the quantity and affinity of adipocyte insulin receptors were equivalent in both controls and PCOS patients. It has been observed that the abundance of insulin receptors-subunit tyrosine phosphorylation in visceral adipose tissue has reduced in PCOS patients.[16] A decrease in the insulin sensitivity can be understood by a rise in insulin levels that facilitate glucose absorption. This phenomenon was identified as the most persistent adipocyte insulin action deficit in polycystic ovarian syndrome, accompanied by a decrease in insulin-stimulated glucose transport and insulin responsiveness. As a result, the level of glucose in the blood increased.[17] In metabolic tissues, insulin enhances glucose take-up and approves its conversion into glycogen and lipids for storage. Resistance to insulin and the related hyperinsulinemia are factors that improve steroidogenesis in PCOS women. Weight-gain and obesity, through their destroy outcomes for insulin resistance, accordingly drive improved steroidogenesis and hyperandrogenism. This multitude of elements points to central issues and gives clarification to the possible relationship among PCOS and COVID-19. Without a doubt, androgens might lead to clinical outcomes in COVID-19.[18]

In the recent study, LH and testosterone levels were higher in patient groups compared with non-PCOS groups; such findings were also seen in previous studies. A study by Hashemi et al.[19] found that the activity of LH and testosterone are significantly increased in PCOS. Furthermore, an increase in LH levels stimulates ovarian androgen production. In the present study, PCOS patients with COVID-19 had a significantly higher difference ($p \leq 0.05$) in concentration of LH, FSH, and testosterone when compared to non-COVID-19 groups. These results are in line with that of Ding et al.[20] That reported COVID-19 illness was thought to be a higher risk factor for ovarian function, which accounted for 14.3% of the rise in testosterone, and the serum FSH level was very different between the COVID-19 group and the non-PCOS group; despite its higher level, COVID-19 women had a higher FSH than the control group. Currently, testosterone is the most widely recognized estimation in routine clinical practice for the examination of females and can be delivered either directly by the ovaries or created by the digestion of its antecedent in fat or limited tissues. Disorders in the metabolism of lipids are metabolic abnormalities that are fairly common in PCOS patients.[21] In the present study, the concentration of serum lipids except HDL were higher in all the groups, except non-PCOS without COVID-19 group. This agreed with recent studies by Eqbal et al.[22] and Ali et al.[2]. Lipid metabolism plays an important role in viral infection cycle. Further, our results are in agreement with the study by Julius et al.,[23] which showed significant elevation in the levels of triglycerides (TGs), HDL, and cholesterol in PCOS patients compared with healthy controls. An elevated cholesterol concentration has been suspected to increase the susceptibility to COVID-19 infection. Cholesterol plays a central role in the mechanisms of COVID-19 infection. In addition, its serum concentration was higher in PCOS patients compared with non-PCOS groups, in the current study. This is in agreement with the findings of Moin et al.[24] that found higher levels of serum renin in PCOS patients rather than that of non-PCOS groups, and seen over activated renin-angiotensin system (RAS) prompting high levels of angiotensin II (Ang II). Overabundance in Ang II makes angiotensin-converting enzyme (ACE2) separate from the angiotensin receptor 1 (AT1R) and bind to AT1R. The binding of Ang II to AT1R causes vasoconstriction, expanded vascular porousness, pneumonic edema, and an intense respiratory trouble disorder. The current study also found that the D-dimer levels of PCOS patients were much higher than those of women without PCOS ($P<0.05$). The results are in agreement with the study by Kebapcilar et al.,[25] which find high level of D-dimer in PCOS groups compared with control group. Moreover, they found PCOS patients had fibrinolytic activation evidenced by elevated D-dimer which could be potentially be used as indicator of risk factor for atherosclerosis in PCOS women. Furthermore, our findings also agreed with Lehmann et al. ones.[26] Finally, the present study suggests a possible relationship between renin and d-dimer in PCOS and COVID-19 disease.

The limitations of this study were the small sample size and cross-sectional design of the study. Future studies should consider these limitations and more studies are required to suggest molecular underlying mechanism.

CONCLUSIONS

In conclusion, higher levels of renin and D-dimer found in PCOS patients' groups and also in non-PCOS participants with COVID-19. Therefore, the assessment of renin and D-dimer may provide a helpful information to physician in PCOS, and to attract the attention to a higher possibility of forming clots in the patients' blood, especially after infection with coronavirus (SARS-CoV-2).

LIST OF ABBREVIATIONS

ACE2, angiotensin-converting enzyme 2; AUC, area under the curve; AT1R, angiotensin receptor 1; BMI, body mass index; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DBP, diastolic blood pressure; DVT, deep vein thrombosis; ELISA, enzyme-linked immune sorbent assay; FSH, follicle-stimulating hormone; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; PE, pulmonary embolism; RAS, renin-angiotensin system; ROC, receiver operator characteristics curve; SBP, systolic blood pressure; SD, standard deviation; T, testosterone; T2DM, type 2 diabetes mellitus; TMPRSS2, transmembrane serine protease 2; TGs, triglycerides; VLDL, very-low-density lipoprotein.

ACKNOWLEDGMENTS

The authors extend their thanks to the staff of Kamal Al-Samara Hospital for their assistance in the practical part of the study and for the facilities that helped in the completion of this study.

DECLARATIONS

Authors' contributions

Conceptualization, data curation, formal analysis, investigation, methodology, software, validation: SEA, FMK, FEA. Funding acquisition: N/A. Supervision: FMK and FEA. Writing-original draft, review, and editing: SEA, FMK, FEA. All the authors have reviewed and approved the final draft before publishing.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This study was approved by the Ethical Committee at the College of Science for Women, Department of Chemistry, University of Baghdad (No.: 4618/22, Date: 2021/9/29). The verbal consent was obtained for all the participants. A structured questionnaire was used to obtain detailed information about PCOS, age, weight, historical disease, whether the patient was infected or not with coronavirus, regularity of the menstrual cycle, etc.

Data availability

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

Funding resources

No external fund was received.

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