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# C-REACTIVE PROTEIN / ALBUMIN RATIO AS A NEW BIOMARKER IN DIAGNOSIS OF POLYCYSTIC OVARIAN SYNDROME

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## ABSTRACT

**Background:** Polycystic ovarian syndrome (PCOS) affects reproductive-aged women. This syndrome causes infertility, insulin resistance, obesity, cardiovascular disease, and other health difficulties. Lifestyle mistakes cause polygenic, polyfactorial, systemic, inflammatory, dysregulated steroid state, autoimmune illness PCOS. The aim of study is to evaluate the role of C- reactive protein / Albumin ratio as a new biomarker in diagnosis of poly cystic ovarian syndrome. **Method**: Babylon Maternity and Pediatric Hospital conducted a case-control research from January to December 2019. 100 women (50 case and 50 control) aged 18–37 were studied. PCOS cases. Age, marital status, parity, occupation, residence, risk factors, gynecological history, past medical history, drug history, family history, BMI, general and local examination, blood test, and ultrasound were examined. Vein puncture was used to acquire 5 ml of blood from each individual, which was placed in a flat tube and centrifuged at 2000x g for 5 minutes. Fasting glucose, insulin, CRP, Albumin, and CRP/Albumin ratio were measured in serum. Sandwich-ELISA (Elabscience/China) assessed CRP and albumin. **Results:** Cases had a significantly higher CRP/Albumin ratio than controls ($P < 0.001$). Cases had greater BMIs than controls (P 0.001). BMI highly positively correlates with CRP (P0.001). Age does not affect CRP/Albumin ratio (P=0.365). Case group CRP/Albumin ratio was negatively correlated with parity ($P < 0.001$). **Conclusion:** The study concluded that CRP /Albumin ratio significantly increase in patients with PCOS.

**KEYWORDS:** C-Reactive, Protein / Albumin Ratio, Biomarker, Diagnosis, Polycystic Ovarian Syndrome.

## INTRODUCTION

Ovarian dysfunction, endocrine problem, hyperinsulinemia, and metabolic disorder are all symptoms of polycystic ovary syndrome (PCOS). Having two of the following three symptoms—amenorrhea, menstrual irregularity, or anovulation; hyperandrogenism; and polycystic ovaries as detected by ultrasound—is diagnostic of this heterogeneous condition.[1] Polycystic ovarian syndrome is one of the most common endocrine disorders of reproductive age women with prevalence of 8-10%, up to 10% diagnosed during gynecologic visits.[2] Polycystic ovarian syndrome (PCOS) is a multifactorial condition with unknown exact causes, but hormonal imbalances, hyperinsulinemia, and insulin resistance are thought to play a role. Genetic factors and obesity have also been associated with an increased risk of PCOS. PCOS is related to disordered insulin metabolism and may be a complex genetic trait disorder. Familial studies suggest a dominant mode of inheritance.[3, 4] C-reactive protein (CRP) is an acute-phase protein that was first described in 1930 by Tillet and Francis. It is named after its ability to interact with phosphorylcholine residues of the C polysaccharide derived from teichoic acid within the cellular wall of Streptococcus pneumoniae and its ability to precipitate with calcium ions.[5] CRP is involved in the regulation of the innate immune system and the acute-phase response, but it has also been associated with chronic inflammatory processes, rheumatologic conditions, cancer, and cardiovascular disease.[6] CRP belongs to the short pentraxin family and is predominantly synthesized in the liver in response to pro-inflammatory cytokines, with IL-6 being a main regulator. IL-6 promotes de novo synthesis of CRP by up-regulating key transcription factors C/EBPβ and C/EBPδ.[7] CRP levels are also influenced by pro-inflammatory cytokines released by visceral adipose tissue, and disturbances in adipokines

such as hypo-adiponectinemia and hyper-leptinemia, which are common in obesity and insulin resistance, can lead to increased hepatic production of CRP.[8] In addition to its hepatic synthesis, CRP can be expressed in various extrahepatic sites, including adipose tissue, lungs, renal cortical tubules, lymphocytes, and atherosclerotic lesions.[9,10] Local production of CRP may contribute to endothelial cell activation and the development of cardiovascular risk.[11] Albumin, on the other hand, is the main protein in human blood and plays a crucial role in regulating the osmotic pressure of blood. It makes up about 60% of the total protein in the blood and is synthesized by liver hepatocytes. Albumin helps prevent fluid leakage from blood vessels, nourishes tissues, and transports hormones, vitamins, drugs, and other substances throughout the body. It is a negative acute-phase protein and is decreased in chronic inflammation.[12] Women with polycystic ovary syndrome (PCOS) often exhibit greater chronic subclinical inflammation, as evidenced by elevated levels of CRP. This suggests that inflammation may play a significant role in the pathophysiology of PCOS. Elevated CRP levels are associated with increased health risk factors in women with PCOS, such as insulin resistance, type 2 diabetes, endothelial dysfunction, and the development of atherosclerosis and coronary artery disease.[13] The ratio of serum CRP to serum albumin (CRP/albumin) has been found to be strongly associated with more severe metabolic disorders in premenopausal women with induced changes in their ovarian hormone status.[13] The aim of study is to evaluate the role of C-reactive protein / Albumin ratio as a new biomarker in diagnosis of poly cystic ovarian syndrome.

## METHOD

This study is a case-control study that was conducted at the Department of Obstetrics and Gynecology at Babylon Maternity and Pediatric Teaching Hospital in Iraq between January 2019 and December 2019. The study was approved by the Iraqi board of medical specialization and informed consent was obtained from patients and control women. The study included 100 women, 50 with polycystic ovary syndrome (PCOS) attending the infertility department at the hospital and 50 healthy women as a control group whose age matched with patients. The participants for the study were chosen based on certain inclusion and exclusion criteria. The inclusion criteria for the study included women aged between 18 and 37 years, 50 of whom had PCOS, and the other 50 were healthy women with a regular menstrual cycle. Additionally, patients were excluded based on several criteria that include, medical diseases such as diabetes mellitus, hypertension, thyroid disease, and other systemic illnesses like rheumatoid arthritis, juvenile chronic arthritis, ankyloses spondylitis and crohns disease. Patients using medication or supplements that affect weight or insulin sensitivity were excluded from the study. Detailed history, examinations, and blood investigations were taken from all the participants in the study to determine their demographic criteria, patient complaints, gynecological history, past medical history, drug history, and family history. The examination included measuring height, weight, Body Mass Index (BMI), blood pressure, and other features. The presence of acne and hirsutism was also documented. Additionally, ultrasound examination was performed, which included trans-vaginal and abdominal ultrasound for cases using a Philips HD 11 XE (Japan) with 5-9 MHZ. Blood investigation tests such as hormonal profile, CRP, albumin, and fasting glucose were conducted for all participants. The collected blood samples were used to measure fasting glucose, CRP, albumin, and CRP/Albumin ratio. The statistical analysis was conducted using SPSS® Software (version 23.0 for Linux®). Qualitative data was represented as numbers and percentages, while continuous numerical data were represented as mean ± standard deviation. The Student's t-test was utilized to compare continuous data between the study groups, and Pearson's correlation was used to assess the correlation between continuous variables within study groups.

## RESULTS

This study is a case-control study that included a total of (100) female individuals, (50) of them were cases of PCOS, while the remaining (50) were controls. Age of participants ranged from (18 – 37) years, with a mean age of (25.79 ± 5.13) years and a median of (25) years. Age group distribution of the study participants by study group is illustrated in Figure (1).

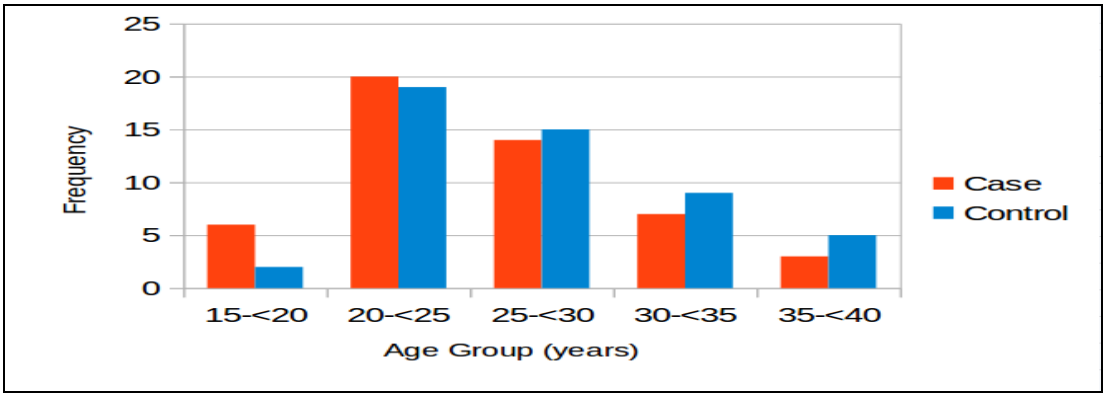


**Figure (1): Age group distribution of study participants by study group.**

Comparison between cases and controls regarding age was done using Student's t-test. No significant difference was observed between the two groups, t-test = 1.47, P-value = 0.145, as detailed in Table (1). Body-mass index (BMI) of the study participants ranged from (16) kg/m$^2$ to (40) kg/m$^2$, with a mean BMI of (26.92 ± 5.58) kg/m$^2$. Student's t-test was used to compare BMI between the two study groups; BMI was found to be significantly higher among cases of PCOS compared to controls, with a mean difference of (5.32) kg/m$^2$, t-test = 5.41, d.f. = 98, P-value < 0.001. Details are provided in Table (1). No statistically significant relationship was observed between the presence of PCOS and residence, chi-square = 0.17, P-value = 0.677 (Table 1). No significant difference in CRP/Albumin ratio was observed between urban residents (0.548 ± 0.148) and rural residents (0.602 ± 0.167), t-test = 1.179, P-value = 0.244. Comparison between cases and controls regarding marital status was performed using chi-square test. Presence of PCOS was higher among unmarried females (55.56%) compared to married females (45.45%). However, this difference was not statistically significant (P=0.315). No statistically significant difference in CRP/Albumin ratio was observed between married participants (0.30 ± 0.27) and unmarried participants (0.35 ± 0.27), Student's t-test = 1.09, P-value = 0.277. Parity was significantly lower among cases (0.30 ± 0.61) compared to controls (1.12 ± 1.38), Student's t-test = 3.84, P-value < 0.001. Additionally, chi-square test of the relationship between parity category and study group had also shown significant relationship, chi-square = 13.63, P-value = 0.003 (Table 1). It was noticeable that no cases with PCOS had a parity higher than P2, unlike controls who had up to P5 parity. Nulliparous females formed (78%) of cases and (50%) of controls.

**Table (1): Demographic characteristics of the study groups.**

| Characteristics | | Frequency No (%) | | | P-value |
|---|---|---|---|---|---|
| | | Cases (n=50) | Controls (n=50) | Total (n=100) | |
| Age (mean±SD) | | 25.04 ± 4.98 | 26.54 ± 5.22 | 25.79 ± 5.13 | 0.145 |
| BMI (mean±SD) | | 29.58 ± 4.51 | 24.26 ± 5.29 | 26.92 ± 5.58 | **< 0.001*** |
| Residence | Urban | 33 (51.56%) | 31 (48.44%) | 64 (100%) | 0.677 |
| | Rural | 50 (50.00%) | 50 (50.00%) | 100 (100%) | |
| Marital Status | Married | 25 (45.45%) | 30 (54.55%) | 55 (100%) | 0.315 |
| | Unmarried | 25 (55.56%) | 20 (44.44%) | 45 (100%) | |
| Parity | Nullipara | 39 (60.94%) | 25 (39.06%) | 64 (100%) | **0.003*** |
| | P1 | 7 (50.00%) | 7 (50.00%) | 14 (100%) | |
| | P2 | 4 (28.57%) | 10 (71.43%) | 14 (100%) | |
| | P3 or more | - | 8 (100%) | 8 (100%) | |

* Significant at P < 0.05

The ratio of C-reactive protein / Albumin of the study participants was compared between the two study groups using Student's t-test. There was a strongly significant difference in C-reactive protein / Albumin ratio between cases (0.57 ± 0.16) and controls (0.08 ± 0.01), with a mean difference of 0.49 and P-value of < 0.001. Figure (2)

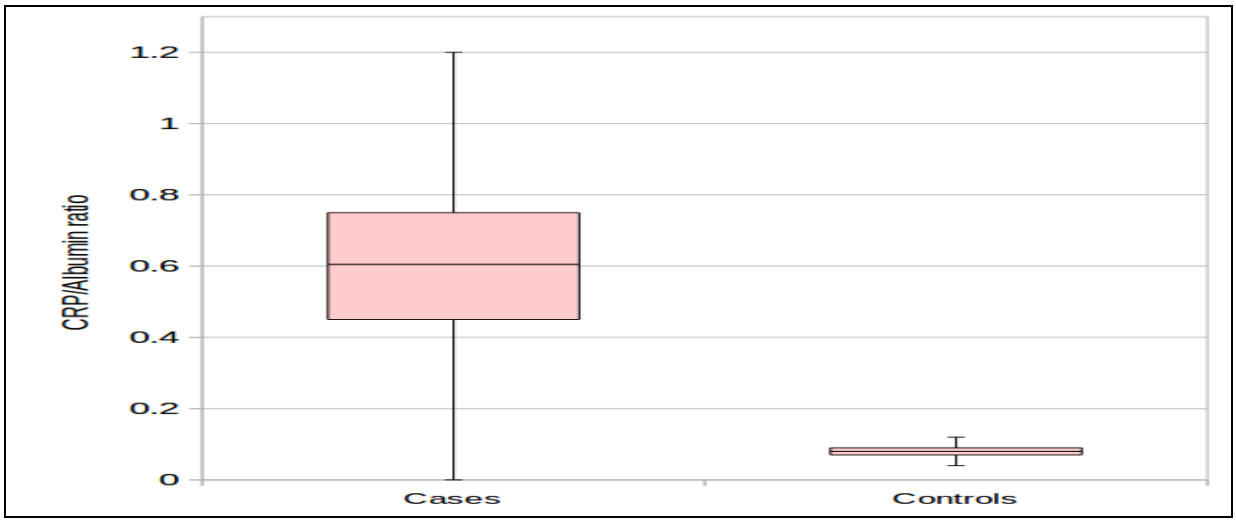


**Figure (2): Whisker boxplot showing the difference of CRP/Albumin ratio between cases and controls.**

Receiver operating characteristics (ROC) curve was calculated to assess the most reliable cut-off value for C-reactive protein/Albumin ratio to distinguish cases of PCOS and healthy individuals. The best cut-off value was 0.31 with 100% sensitivity and 100% specificity, as in Figure (3).

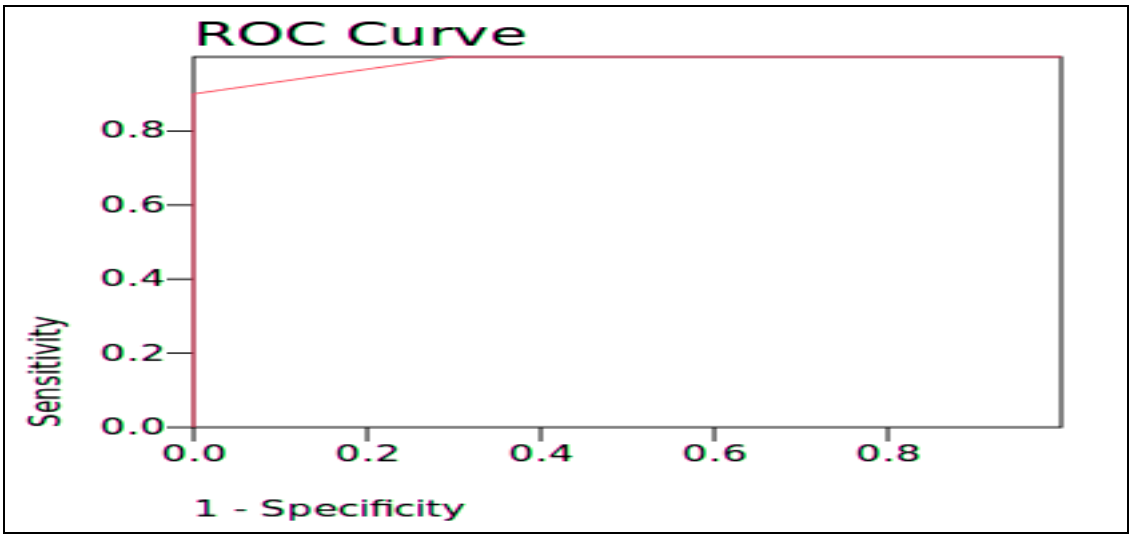


**Figure (3): Receiver operating characteristics (ROC) curve showing the reliability of CRP/Albumin ratio to distinguish between cases of PCOS and healthy individuals.**

Pearson's product-moment correlation coefficient was calculated so as to assess the correlation between C-reactive protein/Albumin ratio and age for each of the two study groups. Within cases group, no significant correlation was observed between age and C-reactive protein/Albumin ratio, with correlation coefficient (R) = -0.137, P-value = 0.342, as illustrated in Figure (4).

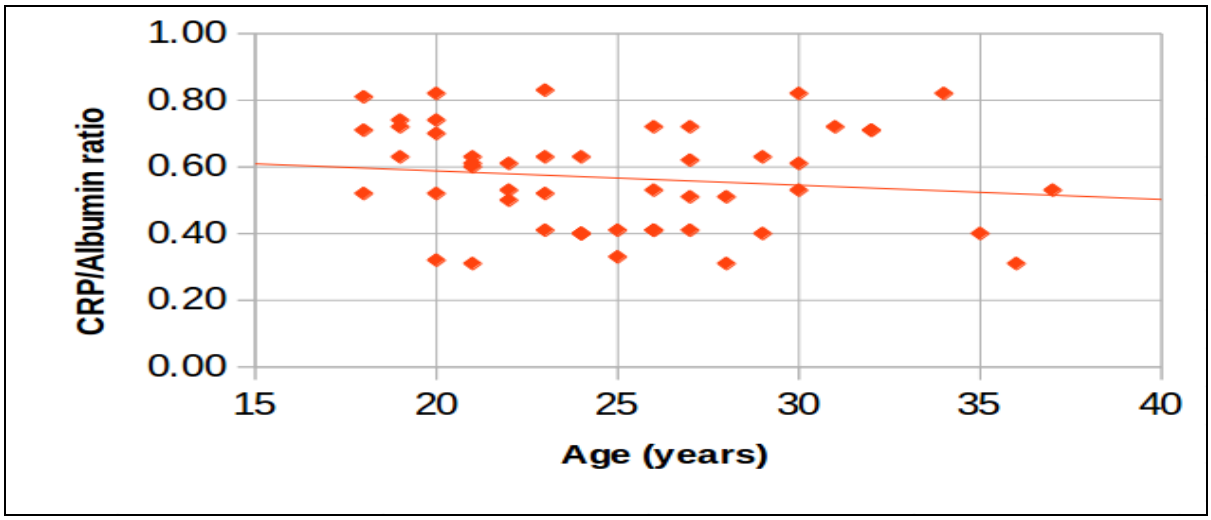


**Figure (4): Correlation between age and CRP/Albumin ratio within cases group.**

Pearson's product-moment correlation coefficient was utilized in order to assess the correlation between BMI and CRP/Albumin ratio. There was a strongly significant positive correlation of medium strength between the two variables, correlation coefficient (R) = 0.438, P-value < 0.001. This correlation is illustrated in Figure (5).

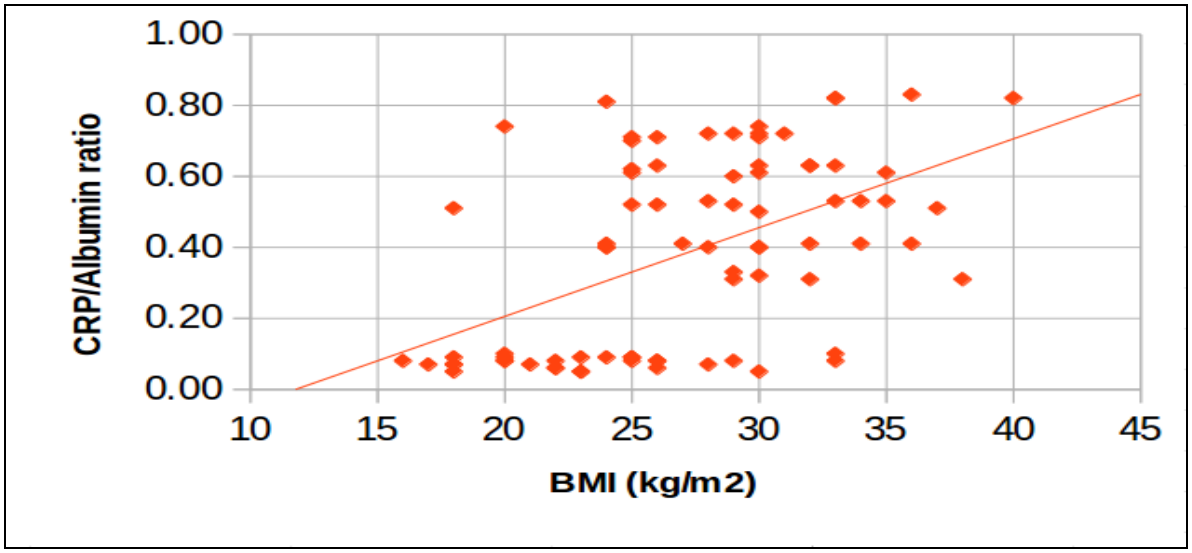


**Figure (5): Correlation between BMI and CRP/Albumin ratio among study participants.**

Spearman's rank-order correlation coefficient was computed to estimate the correlation between parity and CRP/Albumin ratio. There was a statistically significant negative correlation of medium strength between the two variables, correlation coefficient (R) = -0.339, P-value < 0.001 (Fig 6).

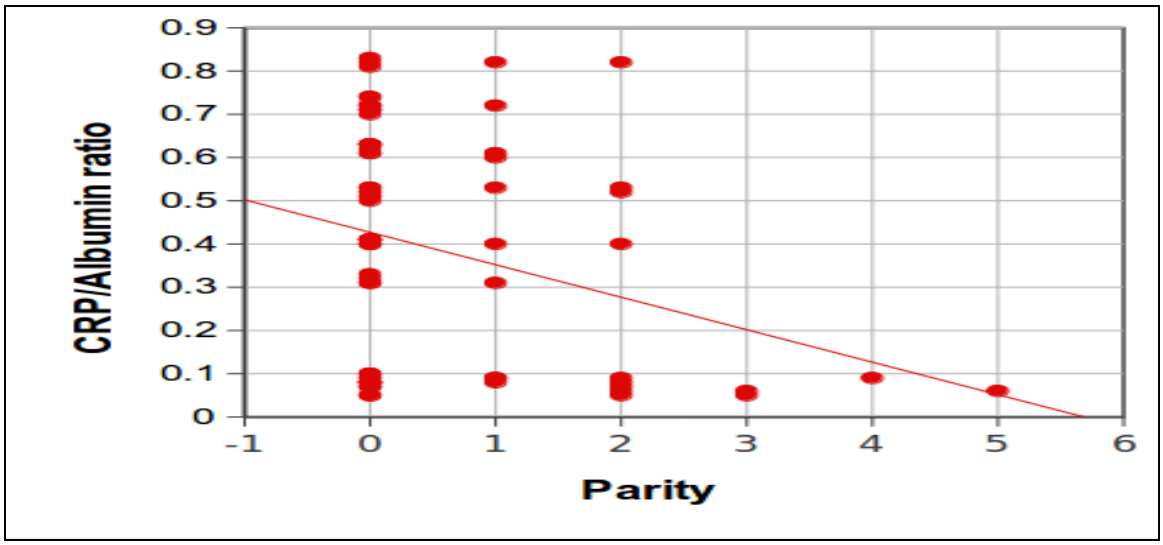


**Figure (6): Scatterplot diagram showing correlation between parity and CRP/Albumin.**

## DISCUSSION

In this study involving Iraqi females of reproductive age, two groups of PCOS patients and control patients were compared, with similar age characteristics. The study found a significantly higher ratio of C-reactive protein (CRP)/Albumin among PCOS patients, with a mean difference of 0.49. This finding was slightly higher than a previous study by Kalyan et al. conducted in Vancouver, Canada, which involved 66 females (mean difference of 0.39).[14] However, the present study found lower CRP/Albumin ratio values in both cases and controls (0.57 and 0.08, respectively) compared to those found by Kalyan et al. (0.77 and 0.38, respectively).[1] This difference may be attributed to the age difference between the two studies, as the participants in the present study were younger. Another more recent study by Kalyan, Goshtesabi et al. conducted in Manama, Bahrain, demonstrated findings that were more closely related to the present study, with a mean difference of 0.45. The CRP/Albumin ratio values were also similar between the present study and the Bahrain study in both cases (0.57 vs. 0.53) and controls (0.08 vs. 0.08). This similarity is likely due to the similar age of the participants in the two studies, with a mean age of 25.8 years in the present study and 27.9 years in the Bahrain study.[15] Receiver operating characteristics (ROC) curve analysis demonstrated an excellent sensitivity and specificity of the CRP/Albumin ratio in detecting PCOS, with a value of 100% for both. This finding was higher than the values demonstrated by Kalyan, Goshtesabi et al., who found a sensitivity of 75% and specificity of 85%.[16] There was no correlation between the CRP/Albumin ratio and age in either the cases or

controls, as determined by Pearson's correlation. Similarly, no correlation was found between the CRP/Albumin ratio and marital status, as determined by Student's t-test. Residence was also found to be unrelated to PCOS, as determined by the chi-square test. BMI was significantly higher among patients with PCOS compared to controls. Obesity is a common finding in PCOS cases, and the relationship between PCOS and obesity involves various interactions of genetic and environmental factors.[17,18] The fundamental link between PCOS and obesity is insulin resistance, which can be present in PCOS patients irrespective of their obesity status. Insulin resistance contributes to the development of diabetes in a large proportion of females with PCOS.[18] The CRP/Albumin ratio was strongly correlated with BMI, possibly due to the association between obesity and CRP levels, which is reported to have a stronger correlation among females. This correlation is linked to the role of adipose tissue as an endocrine organ that secretes cytokines and hormones, triggering hepatic synthesis of CRP.[19] However, a study by Bayrak M. demonstrated no significant relationship between the CRP/Albumin ratio and BMI.[20] Parity was significantly lower among females with PCOS, consistent with previous findings that PCOS is a common cause of infertility in women of reproductive age. Nulliparous women formed 78% of cases in the present study compared to 50% of controls. PCOS has been reported as an important and common cause of infertility.[21, 22]

## CONCLUSION

The study found that women with polycystic ovary syndrome (PCOS) have a significantly higher CRP/albumin ratio compared to healthy women. This indicates that there is a correlation between PCOS and increased inflammation in the body. Furthermore, the study showed that women with PCOS are more likely to be overweight or obese, and the higher their BMI, the higher their CRP/albumin ratio. This association suggests that overweight and obesity may contribute to the increased inflammation observed in women with PCOS.

## REFERENCES


1. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Human reproduction update, 2014 May 1; 20(3): 334-52.
2. Boyle, J., Cunningham J, O'Dea K, Dunbar T, Norman RJ., Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia. Med J Aust, 2012; 196(1): 62-6.
3. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. The Journal of Clinical Endocrinology & Metabolism, 2000; Jul 1; 85(7): 2434-8.
4. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escober-Morreala HF, Futterweit W. Criteria for denying polycystic ovary syndrome as predominatly hyperandrogenic syndrome: an androgen excess society guideline. The Journal of Clinical Endocrinology & Metabolism, 2006. Dec 91; 4237-4245.
5. Ridker PM. C-reactive protein: eighty years from discovery to emergence as a major risk marker for cardiovascular disease. Clinical chemistry, 2009 Feb 1; 55(2): 209-15.
6. Dhingra R, Gona P, Nam BH, D'Agostino Sr RB, Wilson PW, Benjamin EJ, O'Donnell CJ. C-reactive protein, inflammatory conditions, and cardiovascular disease risk. The American journal of medicine, 2007 Dec 1; 120(12): 1054-62.
7. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. The Journal of clinical investigation, 2003 Jun 15; 111(12): 1805-12.
8. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. The American journal of cardiology, 2010 Jul 1; 106(1): 56-61.
9. Semple SJ. C-reactive protein-biological functions, cardiovascular disease and physical exercise. South African Journal of Sports Medicine, 2006; 18(1): 24-8.
10. Agassandian M, Shurin GV, Ma Y, Shurin MR. C-reactive protein and lung diseases. The international journal of biochemistry & cell biology, 2014 Aug 1; 53: 77-88.
11. Calabró P, Willerson JT, Yeh ET. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation, 2003 Oct 21; 108(16): 1930-2.
12. Yuwen P, Chen W, Lv H, Feng C, Li Y, Zhang T, Hu P, Guo J, Tian Y, Liu L, Sun J. Albumin and surgical site infection risk in orthopaedics: a meta-analysis. BMC surgery, 2017 Dec 1; 17(1): 7.
13. Shorakae S, Teede H, de Courten B, Lambert G, Boyle J, Moran LJ. The emerging role of chronic low-grade inflammation in the pathophysiology of polycystic ovary syndrome. InSeminars in reproductive medicine, 2015 Jul 33; 04: 257-269.
14. Kalyan Sh, Patel M, Kingwell E, Cote H, Liu D, Prior J. Competing Factors Link to Bone Health in Polycystic Ovary Syndrome: Chronic Low-Grade Inflammation Takes a Toll. Scientific Reports, 2017; 7: 3432.
15. Kalyan Sh, Goshtesabi A, Sarray S, Joannou A, Almawi W. Assessing C reactive protein/albumin ratio as a new biomarker for polycystic ovary syndrome: a case–control study of women from Bahraini medical clinics. BMJ Open, 2018; 8: e021860.
16. Sam S. Obesity and Polycystic Ovary Syndrome. Obesity Management, 2007; 3(2): 69-73.

17. Li Y, Lin H, Pan P, Yang D, Zhang Q. Impact of Central Obesity on Women with Polycystic Ovary Syndrome Undergoing In Vitro Fertilization. BioResearch Open Access, 2018; 7(1): 116-122.
18. Rojas J, Chavez M, Olivar L, Rojas M, Morillo J, Mejias J et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. International Journal of Reproductive Medicine, 2014; 2014: 71950.
19. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obesity Reviews, 2012; 14: 232-244.
20. Bayrak M. Predictive value of C-Reactive Protein/Albumin ratio in patients with chronic complicated diabetes mellitus. Pakistan Journal of Medical Sciences, 2019; 35(6): 1616-1621.
21. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. Human Reproduction, 2001; 16(2): 226-229.
22. Sterling L, Liu J, Okun N, Sakhuja A, Sierra S, Greenblatt E. Pregnancy outcomes in women with polycystic ovary syndrome undergoing in vitro fertilization. Fertility and Sterility, 2016; 105(3): 791-797.