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Original Article

Exploring the Genetic Influence of Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) on Inflammatory Biomarkers in Endometriosis Progression

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Abstract

Objective: Investigating the genetic influence of Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) on key inflammatory biomarkers-Interleukin-1β, Interleukin-6, and high-sensitivity C-reactive protein (hsCRP) and to evaluate their association with disease progression in endometriosis. Specifically, this study aims to (i) assess differential expression of PTPN22 in cases versus controls, (ii) examine correlations between PTPN22 expression and inflammatory markers, and (iii) determine the predictive value of these biomarkers using ROC curve analysis.

Materials and methods: This study involved 150 women with endometriosis and 150 matched controls. Blood samples were analyzed for inflammatory markers (IL-6, IL-1β, hsCRP) using ELISA and PTPN22 gene expression by real-time PCR. Statistical analyses were conducted using Stata 17.0, and ethical approval (01/2022/IECG) and informed consent was obtained.

Results: PTPN22 expression was higher in endometriosis cases ($p = 0.0001$), suggesting a role in disease pathophysiology. ROC analysis showed moderate predictive accuracy (AUC = 0.63). Among the inflammatory markers, hs-CRP was the most diagnostic, followed by IL-6 and IL-1β, with stronger positive correlations observed in the endometriosis group.

Conclusion: These findings highlight the translational relevance of PTPN22 and hsCRP as candidate biomarkers for early detection and risk stratification in endometriosis, underscoring the interplay between genetic susceptibility and inflammatory signaling in its pathogenesis.

Keywords: Endometriosis; Inflammatory Biomarkers; Immune Regulation; Pro-Inflammatory Cytokines; Protein Tyrosine Phosphatase Non-Receptor Type 22

Introduction

Endometriosis is a chronic, estrogen-driven condition where tissue similar to the uterine lining grows

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outside the uterus. It most commonly affects the ovaries, sometimes forming chocolate cysts, but can also involve the Fallopian tubes, ligaments, digestive tract, and rarely, the lungs, heart lining, or nervous system (1). Globally, endometriosis affects approximately 6–10% of women, with around 10% of cases occurring in women of reproductive age. This accounts for an estimated 247 million affected individuals worldwide, including 42 million in India alone (2). Endometriosis develops due to a mix of factors such as hormonal imbalances, immune system issues, genetic risk, surgical scars, and environmental exposures (3). A key gene linked to immune regulation in endometriosis is PTPN22, located on chromosome 1. It encodes the Lyp protein, which helps maintain immune balance by controlling T-cell activation. Variants such as C1858T can disrupt this regulation, increasing susceptibility to autoimmune disorders (4). Studies on the PTPN22 C1858T polymorphism and endometriosis have shown conflicting results. While an Italian study found a positive association with the T allele, research in Australian and Polish populations showed no significant link, suggesting ethnic variations in genetic susceptibility. A meta-analysis confirmed an overall increased risk, emphasizing the need for further investigation (5).While genetic variants like the PTPN22 C1858T polymorphism may influence disease susceptibility, the pro-inflammatory milieu, characterized by elevated cytokines and biomarkers, including Interleukin-6 (IL-6), Interleukin-1β (IL-1β), and high-sensitivity C-reactive protein (hs- CRP) could further drive disease progression. These biomarkers serve as indicators of inflammation and actively drive pathological processes, including tissue adhesion, angiogenesis, and immune evasion, thereby worsening disease outcomes (6). The potential interplay between PTPN22 Gene Expression and inflammatory biomarkers in endometriosis is an area of growing interest. Investigating the genetic impact of PTPN22 on inflammatory biomarkers can enhance our understanding of endometriosis pathogenesis. Further research is needed to clarify how PTPN22 expressions influence cytokine production and inflammation, potentially leading to personalized therapies targeting genetic and immune pathways.

Materials and methods

Study Design & Study Subjects: This case-control study (2022–2024) included 150 women with clinically confirmed endometriosis and 150 age-matched healthy controls, recruited from hospitals across Kerala, India. Cases were confirmed through clinical diagnosis and medical records, while controls were healthy, age-matched women with regular cycles and no hormone therapy in the past six months. The characteristics of the endometriosis group and controls are shown in Table 1.

Table 1: The characteristics of endometriosis cases and controls

Variable	Cases (n=150)	Controls (n=150)	p-value
Age (Mean ± SD)	31.4 ± 4.8	29.1 ± 5.2	<0.001
Residence (Rural)	50.7%	37.3%	<0.001
Thyroid Disorder	27.3%	8.0%	<0.001
Psychological Stress	19.3%	5.3%	<0.001
Menorrhagia	56.0%	8.7%	<0.001
Dysmenorrhea	54.7%	8.0%	<0.001
PCOS	28.7%	3.3%	<0.001
Obesity	19.3%	4.0%	<0.001

Data presented as Mean ± SD, Student t-test. Data presented as n (%), Student t-test, and Chi- square test. PCOS: Polycystic ovary syndrome. Participants could have multiple symptoms

Inclusion and exclusion criteria: The study enrolled women aged 18–45 years. Cases had clinically confirmed endometriosis, verified by laparoscopy and histology, while controls had no history of endometriosis, confirmed by clinical assessment and imaging. To reduce the risk of undiagnosed endometriosis, controls with a history of chronic pelvic pain, dysmenorrhea, or dyspareunia were excluded. Individuals with cardiovascular, neurological, psychological, or autoimmune disorders, as well as those with a history of pelvic surgery (except endometriosis cases), were excluded. Participants who withdrew consent at any stage were also not included.

Sample size: The sample size was calculated using the formula Z^2pq/d^2, where Z represents the standard normal deviation, p corresponds to the prevalence derived from published data, q is determined as 1-p, and d denotes the desired margin of error. The prevalence was estimated based on existing literature to ensure an adequate sample size for the study.

Sample collection & processing: After screening, fasting blood samples (8-10 ml) were drawn into plain and EDTA tubes. Serum from plain tubes was used for ELISA tests for markers like IL-6, IL-1 Beta, and hsCRP. RNA isolation, cDNA synthesis, and Real-Time PCR assessed PTPN22 gene expression

using blood from EDTA tubes.

Measurement of inflammatory markers: hs-CRP, IL-6, and IL1Beta present in the sample were measured by sandwich enzyme-linked immunosorbent assay (ELISA) using the Origin Diagnostics & Research, Kerala, India kit according to the manufacturer's instructions.

PTPN22 gene expressions: Total ribonucleic acid (RNA) was extracted from all blood samples using total RNA extraction and first-strand cDNA generation using kits (Origin Diagnostics & Research, Kerala, India). Spectrophotometer was applied to determine RNA concentration, which was adjusted to 1000 ng/µl. cDNA synthesis kit was applied to synthesize cDNA on the same day as guided.

Real-time PCR: Real-time PCR was used to evaluate PTPN22 levels using specific primers (Table 2). The internal control was the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene. Fresh blood was mixed with Buffer RZ in a 3:1 ratio and incubated at 15–30°C for 5 minutes. This was followed by chloroform extraction and centrifugation at 12,000 rpm for 10 minutes at 4°C. The aqueous phase was carefully transferred, mixed with ethanol, and processed through a spin column system. After a series of sequential washes, RNA was eluted using RNase-free water.For cDNA synthesis, 50 µg of RNA was combined with Oligo (dT) 18, random hexamer primers, dNTPs, RT Buffer, and Reverse Transcriptase. The reaction was incubated at 25°C for 5 minutes, followed by 50°C for 60 minutes, then heated to 95°C for 5 minutes to inactivate the enzyme. Real-time PCR was performed in a 20 µL reaction volume containing 2X Real-Time PCR Master Mix, specific primers for the PTPN22 gene, cDNA, and nuclease-free water. The thermal cycling conditions included an initial denaturation at 94°C, followed by 32 cycles of denaturation, annealing at 54°C, and extension at 72°C, each lasting 1 minute. A final extension was performed at 72°C for 10 minutes to ensure complete amplification. Melt curve analysis was conducted to confirm the specificity of the amplified products. Relative expression of the PTPN22 gene was analyzed using the $2^{(-\Delta\Delta Ct)}$ method, and the results were graphically represented.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of Genetika (01/2022/IECG) and performed according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants.

Statistical Analysis: Descriptive statistics (mean, standard deviation, frequency, and percentages) were used to compare cases and controls. Categorical variables were analyzed using the chi-square test, while independent t-tests compared mean values. ROC curve analysis evaluated the predictive accuracy of biochemical parameters, with AUC, sensitivity, specificity, PPV, and NPV calculated. Binary logistic regression assessed the impact of clinical parameters on endometriosis, adjusting for demographic and lifestyle factors. A p-value <0.05 was considered significant. Data analysis was conducted using Stata 17.0.

Results

This study included 150 individuals diagnosed with endometriosis and 150 control subjects to assess the inflammatory and genetic alterations associated with the disease. To better understand the background characteristics of the study population, a comparison was made between 150 control subjects and 150 cases. In Table 3, the Mann-Whitney U test showed a significant increase in PTPN22 gene expression in endometriosis cases compared to controls (p = 0.0001). The case group had a higher median (1.243 vs. 0.978) and wider IQR (0.768–2.010 vs. 0.847–1.120), indicating elevated expression in affected individuals.

Receiver Operating Characteristic (ROC) analysis was performed to evaluate the predictive ability of PTPN22 gene expression for endometriosis (Figure 1).

The Area under the Curve (AUC) was 0.6286, indicating a moderate discriminatory ability. The optimal PTPN22 expression cutpoint was 1.1849, showing 60% sensitivity and 77% specificity.

Table 2: The PTPN22 and GAPDH genes and their Purification

Gene	Primer sequence	Purification
PTPN22	Forward:5'-ACAACTGTGGCTGAGAAGCCCA-3' Reverse: 5'-GTAGCTGGAATCCTCATCAGAGG-3'	HPSF
GAPDH	Forward: 5′-CCATGGAGAAGGCTGGGG-3′ Reverse: 5′-CAAAGTTGTCATGGATGACC-3′	HPSF

PTPN22 – Protein Tyrosine Phosphatase Non-Receptor Type 22; GAPDH –Glyceraldehyde-3-Phosphate Dehydrogenase; bp – Base Pairs

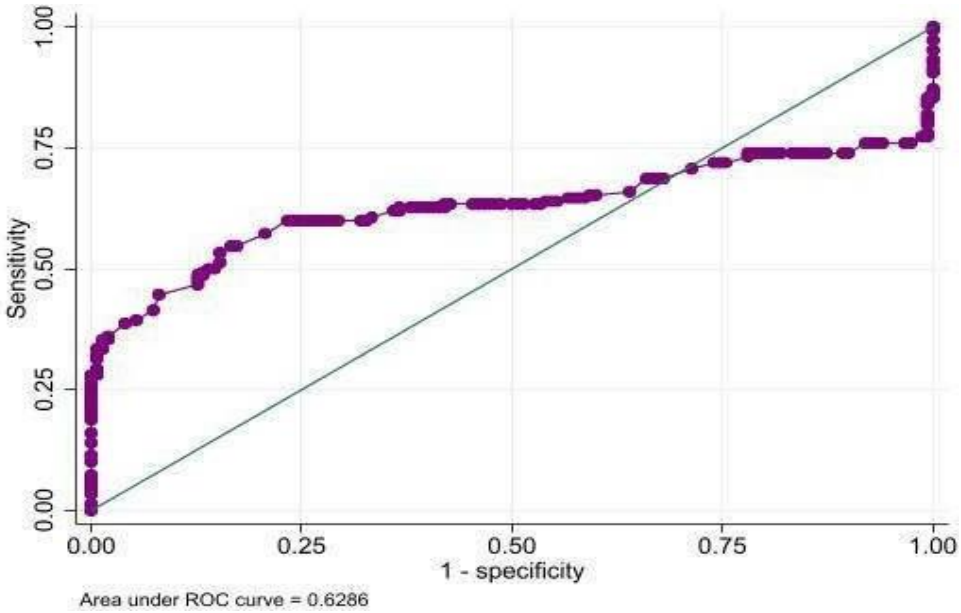

Figure 1: ROC Curve of PTPN22 Gene Expression for Predicting Endometriosis

Table 3: Comparison of PTPN22 Gene Expression Between Control and Cases

Group	Mean ± SD	Median (IQR)	P-value
Controls	1.00 ± 0.20	0.978 (0.847–1.120)	0.0001
Cases	1.44 ± 0.93	1.243 (0.768–2.010)	

Values are presented as Mean ± Standard Deviation (SD) and Median (Interquartile Range, IQR). SD – Standard Deviation; IQR – Interquartile Range; IL-1β – Interleukin 1 Beta; IL-6 – Interleukin 6; hsCRP – High-Sensitivity C-Reactive Protein.

The marker had a positive likelihood ratio of 2.61, a negative likelihood ratio of 0.52, with predictive values of 72% (PPV) and 65.7% (NPV) suggesting that while PTPN22 gene expression provides moderate predictive value, it may not be highly accurate on its own (Table 4).

The Mann-Whitney U test confirmed that all inflammatory markers were statistically significant ($p < 0.05$). ROC analysis (Figure 2) showed that hs-CRP, IL-6, and IL-1β are important markers in endometriosis. Among them, hs-CRP had the strongest predictive ability, with a significantly higher AUC than both IL-6 ($p < 0.001$) and IL-1β ($p = 0.0005$). IL-1β ranked next, outperforming IL-6 ($p < 0.001$), while IL-6 showed the weakest predictive value.

The association between PTPN22 gene expression and inflammatory markers (hs-CRP, IL-6, and IL-1β) was analyzed using scatter plots, as shown in Figures 3-5.

Figure 3 illustrates the scatter plots showing the relationship between PTPN22 gene expression and hs-CRP levels showed a positive association in cases, though with considerable variability. In controls, the relationship was more consistent, indicating a stronger correlation with PTPN22 expression.

Table 4: Results of ROC analysis of PTPN22 Gene Expression for predicting Endometriosis

Metric	Value
Area Under ROC Curve	0.6286
Z statistic	3.63
Significance level P (Area=0.5)	<0.001
Youden Index J	0.37
Optimal Cutpoint	1.1849
Sensitivity	60%
Specificity	77%
+LR	2.61
-LR	0.52
+PV	72%
-PV	65.7%

ROC: Receiver Operating Characteristic, AUC: Area Under Curve, Z statistic: Standard score, P: Significance level, Youden Index J: Test effectiveness, Optimal Cutpoint: Best threshold, +LR: Positive Likelihood Ratio, -LR: Negative Likelihood Ratio, +PV: Positive Predictive Value, -PV: Negative Predictive Value

Figure 4 depicts the correlation between PTPN22 expression and IL-1β levels in cases and controls. While cases show a positive but variable association, controls demonstrate a clearer upward trend, indicating a stronger and more consistent relationship.

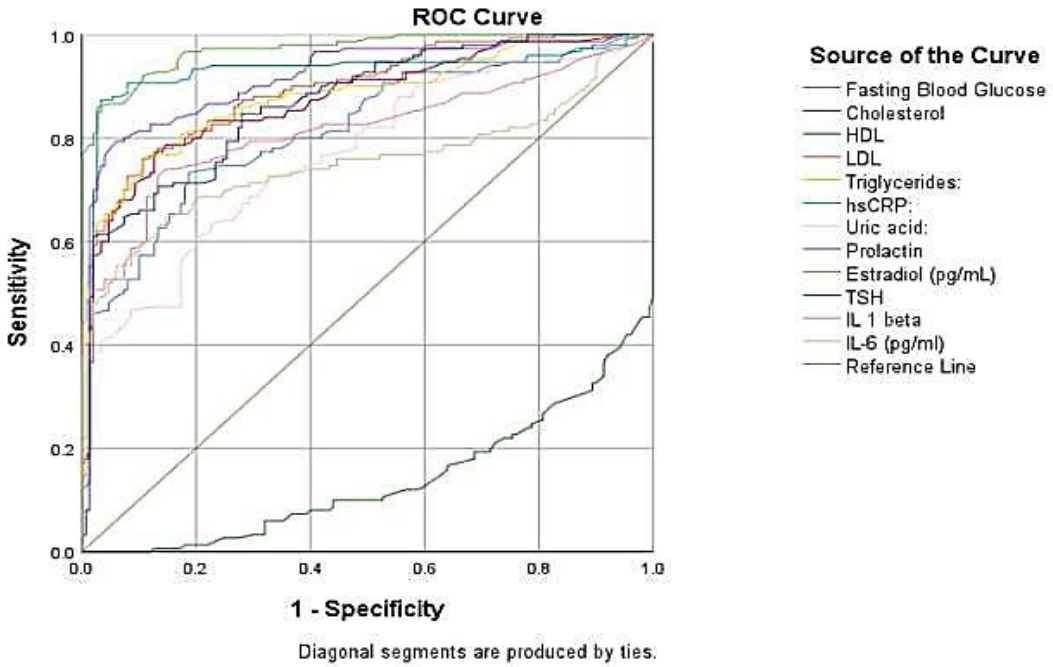

Figure 2: Comparison of ROC curves for Biomarker Predictive Performance

Figure 5 shows a positive correlation between PTPN22 gene expression and IL-6 levels in both cases and controls. The association appears stronger in cases due to more significant variability in IL-6 levels, while controls show a more clustered distribution.

Discussion

Genetic factors are increasingly recognized as important in endometriosis, with certain genes potentially influencing its development. PTPN22, in particular, is being explored as a biomarker to improve diagnosis and treatment.

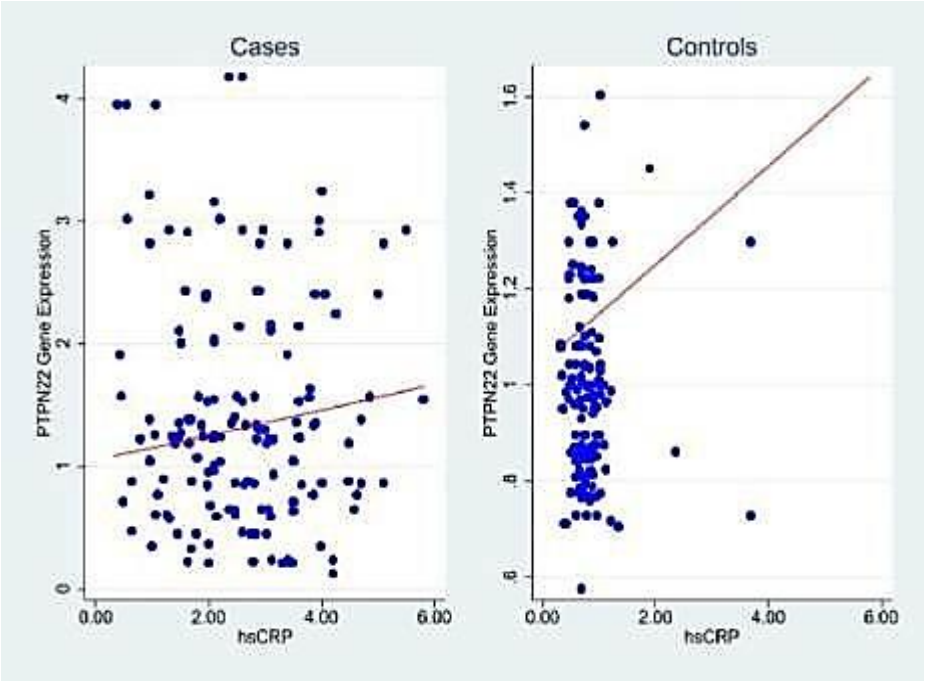

Figure 3: Scatter Plot of PTPN22 Gene Expression and hs-CRP

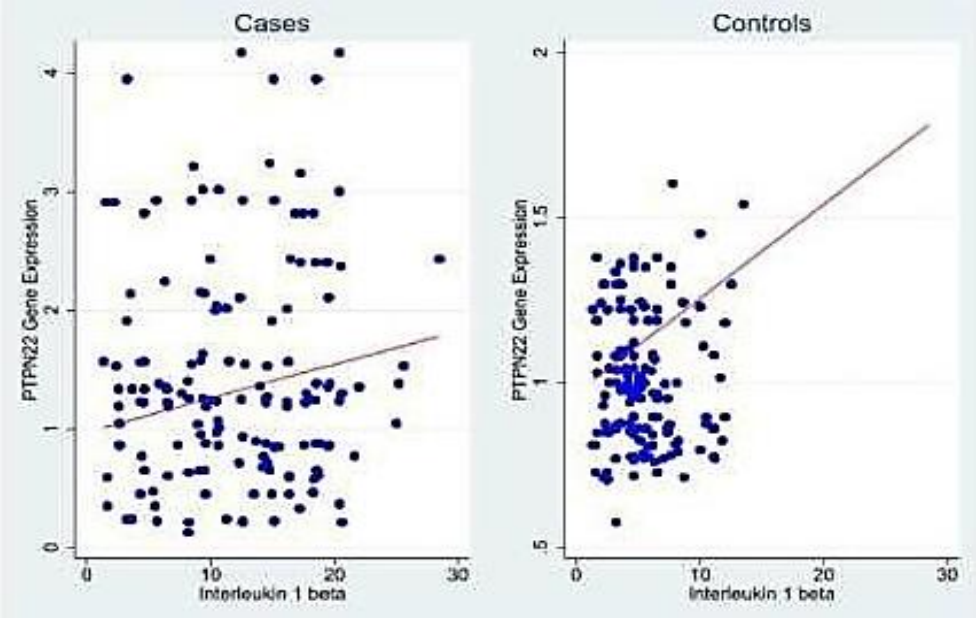

Figure 4: Scatter Plot of PTPN22 Gene Expression and Interleukin-1 beta

This study focuses on evaluating PTPN22 gene expression in individuals with endometriosis. According to the results, there is a significant increase in PTPN22 gene expression in endometriosis cases ($p = 0.0001$), with higher median values than controls (Table 3). ROC analysis showed a moderate predictive ability (AUC = 0.6286), with 60% sensitivity and 77% specificity at an optimal cutpoint of 1.1849 (Figure 1) (7), point to a possible association of the PTPN22 C1858T polymorphism with endometriosis in the Italian population. Compared with other studies (8, 9) all found an association between PTPN22 gene polymorphism and endometriosis conditions. A study by (10, 11) found that PTPN22 was associated with endometriosis (OR=1.39, CI= 1.0097 < OR < 1.9136, p= 0.04) in Caucasians. A lack of studies investigating PTPN22 gene expression in endometriosis was noted, highlighting the need to explore this aspect further.

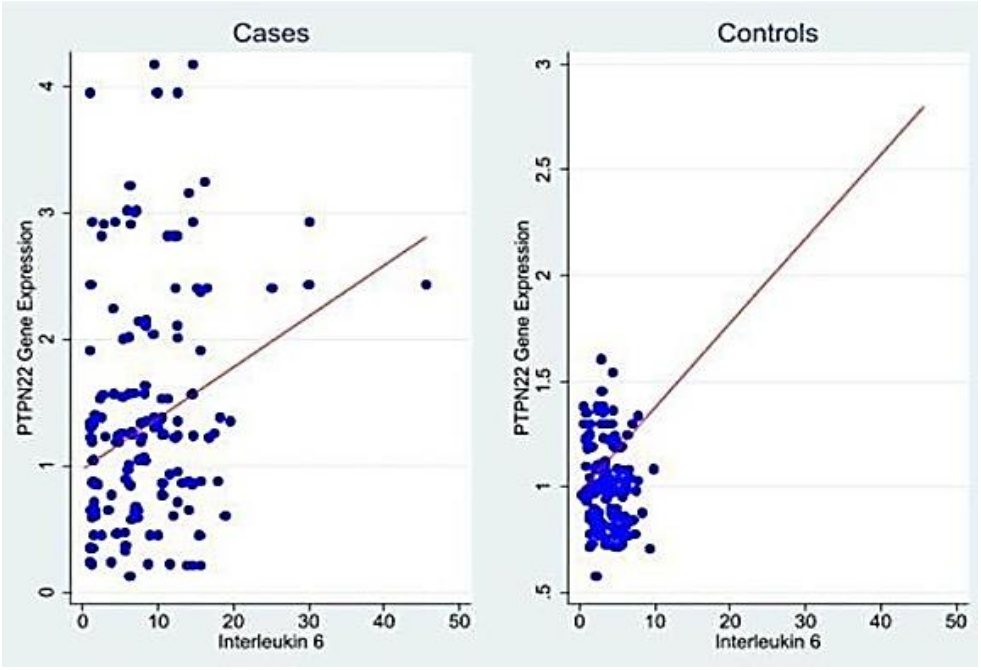

Figure 5: Scatter Plot of PTPN22 Gene Expression and Interleukin 6

This absence of related research guided the present study's focus, aiming to investigate this relationship in greater detail.

ROC curve analysis in this study highlighted that in endometriosis, hs-CRP, IL-6, and IL-1β emerged as key inflammatory markers. Among them, hs-CRP showed the strongest predictive value, with a higher accuracy than IL-6 and IL-1β, making it a particularly reliable biomarker. All three markers were statistically significant ($p < 0.05$) underscoring the role of systemic inflammation and supporting hs-CRP's potential utility in diagnosis and monitoring disease progression.

Our findings align with previous studies demonstrating the importance of inflammatory markers in endometriosis. Specifically, hsCRP has been shown to have strong diagnostic potential, with several studies reporting its elevated levels in patients with endometriosis (12, 13). Additionally, the moderate predictive ability of IL-1β, & IL-6 is consistent with findings by (14, 15) who identified IL-1β & IL-6 as a significant marker of inflammation in endometriosis. The markers' statistical significance further supports systemic inflammation's role in the disease. These findings highlight the need for further investigation into the mechanistic role of PTPN22 expression in conjunction with inflammatory markers, which may provide insights into novel therapeutic targets for endometriosis. In the present study, we further explored the relationship between PTPN22 gene expression and inflammatory markers using scatter plot analysis (Figures 3-5). Our results showed that hsCRP, IL-6, and IL-1β levels were significantly elevated alongside increased PTPN22 expression. This positive correlation suggests that PTPN22 may influence inflammatory pathways in endometriosis, potentially enhancing the systemic inflammatory response and contributing to disease pathogenesis. These findings are consistent with earlier research linking PTPN22 to autoimmune diseases that affect immune function. Its correlation with elevated inflammatory markers highlights PTPN22's potential role as a genetic modulator of inflammation, with possible value in disease diagnosis and monitoring progression. The observed positive correlation between PTPN22 and inflammatory markers lays the groundwork for future studies to clarify its role in inflammation-driven conditions like endometriosis. Given its ability to modulate inflammatory pathways, PTPN22 may represent a promising therapeutic target (16). In conclusion, this study shows that PTPN22 expression is significantly elevated in endometriosis and correlates positively with hs-CRP, IL-6, and IL-1β. These findings indicate that PTPN22 may play a central role in driving inflammation and could serve as a potential biomarker for the disease. ROC analysis indicates that PTPN22 has moderate predictive value, supporting its potential clinical relevance. With limited existing research on PTPN22 in endometriosis, these findings provide a basis for future studies on its mechanisms and therapeutic potential. The case-control design is a key strength, allowing direct comparison between patients and healthy controls to identify meaningful associations. A comprehensive analysis incorporating both genetic and demographic factors enhances the study's multidimensional approach in understanding disease pathology. The methodology is robust, with standardized protocols for sample collection, biomarker assessment, and statistical analysis ensuring reliability and validity. Furthermore, the well-defined study population, consisting of the use of carefully selected cases and controls reduced variability and strengthened the reliability of our findings. Combining inflammatory biomarkers with gene expression data also offers fresh insight into disease mechanisms. However, as a case–control study, certain limitations remain, the findings may be influenced by selection bias, limiting generalizability. Self-reported demographic and lifestyle data could be affected by recall bias, and unmeasured factors like environmental exposures may impact associations. While genetic markers were analyzed, gene-gene and gene-environment interactions were not fully explored. Additionally, the sample size, though adequate, may limit detection of weaker associations. These limitations should be considered when interpreting the results.

Conclusion

This study highlights the importance of PTPN22 expression and inflammatory markers in endometriosis. Elevated PTPN22 and its moderate predictive value suggest its potential as a biomarker for early detection, though further research is needed to improve diagnostic accuracy. hsCRP showed the strongest predictive ability, reinforcing its role as a key inflammatory marker. The observed correlation between PTPN22 and inflammatory markers underscores the interplay between genetic and inflammatory mechanisms, offering insights that may inform future targeted therapies.

Conflict of Interests

Authors declare no conflict of interests.

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Ethical approval (01/2022/IECG) was secured from the Institutional Ethics Committee of Genetika. Written Informed consent was obtained from all the participants included in this study.

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