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Association of PTPN22 and PADI4 Polymorphisms with Rheumatoid Arthritis in Aswan

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Abstract

Background: RA is a prevalent autoimmune disease affecting approximately 84,338 individuals in Egypt. Genetic predispositions, such as the PTPN22 and PADI4 genes, are linked to RA risk. PTPN22, a protein tyrosine phosphatase, and PADI4, which are involved in citrullination, have shown varying levels of association with RA across populations. Studies have been inconclusive regarding their roles in RA susceptibility, progression, and activity.

Patients and Methods: A total of 240 participants were included in this study, RA patients and healthy controls from the Aswan governorate. Genomic analysis was conducted to evaluate PTPN22 and PADI4 polymorphisms. Associations with disease activity markers, such as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and the Disease Activity Score (DAS28).

Results: No significant association between PTPN22 and RA. However, PTPN22 significantly correlated with RF and ACPA, with p-value of 0.006 and ≤0.001, respectively, suggesting its diagnostic value in RA. No significant associations were found between PTPN22 and disease activity markers such as the ESR and CRP.

In contrast, PADI4 levels were elevated in the control groups, which conflicts with findings from other studies. Despite this, PADI4 demonstrated greater specificity (73.3%), in RA diagnosis than did PTPN22 (45.3%) , making it a potential diagnostic marker in combination with RF and ACPA.

Conclusion: Our study revealed no significant associations between PTPN22 or PADI4 polymorphisms and RA susceptibility in the Aswan population. However, both genes were correlated with diagnostic markers such as RF and ACPA. The PADI4 has potential as a diagnostic marker with high specificity.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic synovial inflammation that leads to joint destruction and disability in addition to other system effects and manifestations. According to a study titled “The burden of rheumatoid arthritis in the Middle East and North Africa, 1990–2019,” the prevalence of rheumatoid arthritis cases in Egypt was 84,338 cases in 2019, which is considered to be a serious healthcare problem facing the Egyptian community and the whole world [1]. The definitive etiology of RA is not fully understood; however, several genetic and environmental factors have been defined. The first genetic risk factor for RA consists of the human leukocyte antigen (HLA), the strongest of which is genes within the HLA region, particularly the HLA-DRB1 gene[2]. A second, more modest, association has been identified for the protein tyrosine phosphatase on receptor 22 (PTPN22) gene (SNP: rs2476601) [3]. Several studies have focused on the associations of the PTPN22 variant with RA risk and its clinical features, especially in the European population. The PTPN22R620W allele is associated with seropositive diseases [4, 5], anti-citrullinated protein antibodies (ACPAs) [6, 7], erosive diseases [8], and earlier disease onset [9]. In a stratified meta-

analysis, PTPN22C1858T was more common in RF-positive patients than in RF-negative patients and was also more common in patients with anti-CCP antibodies than in those without [10].

Another important genetic variant, the peptidyl arginine deiminase 4 (PADI4) gene, is a member of the PADI family encoding enzymes involved in the posttranslational conversion of arginine within peptides to citrulline, calcium ion binding, and hydrolase activity, which play a role in hemostasis of the epidermis. PAD4 is expressed mainly in the hematological system and is believed to be involved in RA pathogenesis. [11]. The strongest association was observed for an SNP (rs2240340) located in intron 3 of the PADI4_94 gene, which is associated with RA susceptibility and anticitrullinated peptide antibody (ACPA) positivity [12]. The association of this variant with RA susceptibility has been observed in different Asian populations [13, 14]. However, controversial results have been obtained in European Caucasian populations [15–17].

There are limited data concerning the associations of PTPN22 and PADI4 polymorphisms with RA in Egypt. Therefore, this study aimed to investigate whether PTPN22 and PADI4 gene polymorphisms are involved in the genetic predisposition to RA in Aswan and to assess their influence on the clinical and immunological features of the disease in Aswan governorate.

Methods

Study design and participants

We conducted a case–control study at Aswan University Hospital as well as the general and insurance hospitals of the Aswan government. A total of 150 RA patients were enrolled in our study as case groups, and 90 healthy participants in the control group were matched for age, sex, and geographical origin with case subjects.

The inclusion criteria for RA patients were as follows: patients with rheumatoid arthritis who fulfilled the diagnostic criteria (at least four of the seven criteria for the diagnostic classification of RA established by the American College of Rheumatology (ACR 1987) and 6 of the 10 criteria of the 2010 ACR/ EULAR classification criteria of RA), as well as patients above 18 years of age.

The exclusion criteria for RA patients were as follows: patients with autoimmune diseases or arthritis other than rheumatoid arthritis; patients with chronic disease, alcoholism, liver disease, or kidney disease; patients under 18 years of age.

Methods

All patients were subjected to complete medical history, clinical evaluation, and full investigation. Disease activity will be evaluated with a disease activity score for 28 joints (DAS28), and functional disability will be assessed by the health assessment questionnaire (HAQ). Inflammatory activity will be

evaluated via the erythrocyte sedimentation ratio (ESR) and C-reactive protein (CRP) level. Radiographic changes will be assessed. Immunological analysis All patients' sera were tested for the presence of the anti-CCP IgM RF (rheumatoid factor) (ELISA method) according to the manufacturer's protocol.

For PTPN22 and PADI4 analysis, genomic DNA will be extracted from the collected whole blood of RA patients and healthy subjects, via the standard salting out extraction method. All the DNA will be stored at -20°C until testing. The samples will be genotyped for PTPN22 and PADI4 variants via ELISA according to the manufacturer's instructions.

Statistical analysis

Data will be collected and analysed. All the statistics will be performed via IBM SPSS Statistics 27.0. Continuous data such as age and weight are presented as the means ± SDs and ranges.

Results

1. Participant characteristics

A total of 240 participants were enrolled in our study, of which 150 RA patients and 90 healthy participants composed the control group. In terms of sex, the majority of the participants in both groups were female, as the prevalence of RA is greater in females than in males [18] There were slightly more male participants in the control group (22.22%) than in the RA group (15.33%), but this difference was not significant (p = 0.178). The mean age of the RA patients was 44.55 years, whereas the mean age of the controls was 45.4 years. (Table 1)

Table 1
Comparison of the characteristics of the two groups.

		Group		Test of Significance		
		Controls	Cases			
		N (%) Mean ± SD	N (%) Mean ± SD	Value	P Value	Significance
Sex	Male	20 (22.22%)	23 (15.33%)	X^2 =1.815	0.178	NS
	Female	70 (77.78%)	127 (84.67%)			
Age		45.4 ± 13.29	44.55 ± 13.36	t = 0.476	0.634	NS

Chi-square test of significance (X^2)

Student's t test of significance (t)

Table (1) presents a comparison between cases and controls regarding sex and age. In terms of sex distribution, there were slightly more males among the controls (22.22%) than among the cases (15.33%), but this difference was not significant between the groups (p = 0.178). Similarly, for age, the mean ages of the cases and controls were comparable, with no significant difference observed, indicating good matching between the two groups.

2. Characteristics of the RA patients

After the RA patients were evaluated, their history revealed that the mean duration of illness was 7.35 years, with a minimal duration of illness of 1 year and a maximal duration of 23 years. More than 80% of the patients had an irrelevant family history. Our data, revealed that rheumatoid factor (RF) was positive in 64% of the patients. (Table 2, Fig. 1)

Table 2
Characteristics of the RA patients

		Mean ± SD/N	Median (IQR)/%	Min–Max
family history	Irrelevant	123	82.0%	
	Positive	27	18.0%	
duration of RA		7.35 ± 5.03	6 (3–10)	1–23
RF	Negative	54	36.0%	
	Positive	96	64.0%	

Table (2) shows the characteristics of the RA cases. Approximately 18% of the rheumatic patients had a positive family history. The mean RA duration was 7.35 years (± 5.03). More than half of the patients (64.0%) had positive RFs.

Figure 1

(Fig. 1) shows Our data, revealed that rheumatoid factor (RF) was positive in 64% of the patients.

3. Laboratory investigations in RA patients

The results of the laboratory investigations for RA patients revealed that the mean ESR was 53.09, with a minimum value of 10 and a maximum value of 105, whereas the median CPR was 6, ranging from 6–24. Moreover, the mean DAS28 ESR was 5.14, and the mean PGA was 6.41. In addition, 99 patients were positive for ACPAs. (Table 3, Fig. 2)

Table 3
Laboratory investigations of RA patients

		Mean ± SD/N	Median (IQR)/%	Min–Max
ESR		53.09 ± 20.57	50 (40–65)	10–105
CRP		15.16 ± 16.67	6 (6–24)	0–64
DAS28 ESR		5.14 ± 1.31	5.22 (4.35–6.04)	1.9–7.9
PGA		6.41 ± 2.04	7 (5–8)	2–10
ACPA	Negative	51	34.0%	
	Positive	99	66.0%	

Table (3) shows the results of the laboratory investigations among the RA cases. The mean ESR was 53.09 (± 20.57), with a median CPR of 6 (6–24). Moreover, the mean DAS28 ESR and PGA were 5.14 (± 1.31) and 6.41 (± 2.04), respectively. Approximately 66% of the patients were ACPA positive.
Figure 2

Figure 2 shows that 99 patients were positive for ACPAs with 66% of patients .

4. PTPN22 and PAD4

According to the Mann–Whitney Test of Significance, there is no significant difference between the two groups regarding PTPN22 expression levels with p value ≥ 0.05, while there is a significant difference regarding PAD4 being higher in the control groups compared to RA cases group with p value ≤ 0.001which is against the study hypothesis. (Table 4, Fig. 3)

Table 4
Comparison of PTPN22 & PAD4 expression between the two groups

	Group		Mann–Whitney Test of Significance		
	Controls	Cases			
	Median (IQR)	Median (IQR)	Value	p Value	Significance
PTPN22	0.62 (0.55–0.72)	0.58 (0.49–0.72)	-1.575	0.115	NS
PAD4	0.62 (0.47–0.74)	0.46 (0.36–0.57)	-5.412	≤ 0.001	S

Table (4) shows a statistically significant difference between the two groups in terms of PAD4, which was greater in the control group (0.62) than in the case group (0.46), with a p value ≤ 0.001. However, there were no significant differences between the cases and controls regarding PTPN22, with a p value ≥ 0.05.

(Fig. 3) : shows a statistically significant difference between the two groups in terms of PAD4, which was greater in the control group than in the case group .

5. Correlations between PTPN22 characteristics and laboratory findings

To assess the relationship between PTPN22 and RA patient characteristics, we used the Mann–Whitney test of significance. Our data revealed that there was a significant difference between PTPN22 levels and sex, with a p-value of 0.036 (Fig. 4). RF and ACPA levels were significantly different from PTPN22 levels, with p-values of 0.006 and ≤ 0.001, respectively (Figs. 5, 6). Instead, the data concerning family history were not significantly different from those concerning PTPN22, with a p value of 0.597. (Table 5)

(Fig. 4) :Our data revealed that there was a significant difference between PTPN22 levels and sex.

(Figs. 5, 6):RF and ACPA levels were significantly different from PTPN22 levels, with p-values of 0.006 and ≤ 0.001, respectively.

On the other hand, the correlation between PTPN22 levels and laboratory findings in the RA patient group determined via Spearman's coefficient test revealed a positive significant correlation between PTPN22 levels and the DAS28 ESR, with a p-value = 0.011(Fig. 7). However, our analysis revealed an insignificant relationship between PTPN22 levels and the other laboratory parameters, such as ESR, CRP, and PGA, with p values ≥ 0.05. (Table 6)

(Fig. 7) revealed a positive significant correlation between PTPN22 levels and the DAS28 ESR, with a p-value = 0.011.

Table 5
Correlations between PTPN22 characteristics

		PTPN22	Mann–Whitney Test of Significance		
			Value	p Value	Significance
Sex	Male	0.72 (0.52–0.84)	-2.092	0.036	S
	Female	0.58 (0.48–0.69)			
family history	Irrelevant	0.57 (0.49–0.72)	-0.528	0.597	NS
	Positive	0.6 (0.5–0.72)			
RF	Negative	0.54 (0.49–0.6)	-2.737	0.006	S
	Positive	0.63 (0.5–0.74)			
ACPA	Negative	0.52 (0.47–0.58)	-3.803	≤ 0.001	S
	Positive	0.62 (0.5–0.75)			

Table (5) shows that PTPN22 expression was significantly associated with sex and was lower in females, with a p-value of 0.036. Moreover, PTPN22 expression was greater in patients with positive RFs and positive ACPAs, indicating a statistically significant association between PTPN22, RF and ACPAs. However, there was no significant association with family history, with a p-value ≥ 0.05.

Table 6
Correlations among PTPN22 laboratory investigations

		Age	duration of RA	ESR	CRP	DAS28 ESR	PGA
PTPN22	Spearman's Coefficient	0.058	0.046	0.132	0.079	.208*	0.136
	p Value	0.479	0.574	0.107	0.338	0.011	0.098
	Significance	NS	NS	NS	NS	S	NS

Table (6) shows the correlations among PTPN22, patient characteristics and the results of laboratory investigations. PTPN22 was significantly positively correlated with the DAS28 ESR (p value = 0.011). However, the other variables did not have a statistically significant p value (≥ 0.05).

Correlation between PAD4, characteristics and laboratory investigations

According to the Mann—Whitney test of significance in measuring the correlation between PAD4 and RA patient group characteristics, the analysis revealed that there was a significant difference between PAD4 levels and ACPA positive cases, with a p-value ≤ 0.001(Fig. 8); however, there was an insignificant difference between PAD4 and sex, family history and RF, with a p-value ≥ 0.05. (Table 7)

(Fig. 8): revealed that there was a significant difference between PAD4 levels and ACPA positive cases, with a p-value ≤ 0.001.

Spearman's coefficient test revealed a positive correlation between PAD4 and DAS28 ESR, with a p-value = 0.025(Fig. 9), whereas the other variables were not correlated with PAD4, ESR, CRP or PGA, with a p value ≥ 0.05. (Table 8)

(Fig. 9) : revealed a positive correlation between PAD4 and DAS28 ESR, with a p-value = 0.025

Table 7
Correlations between PAD4 characteristics

		PAD4	Mann–Whitney Test of Significance		
			Value	p Value	Significance
Sex	Male	0.46 (0.38–0.53)	-0.378	0.705	NS
	Female	0.45 (0.36–0.59)			
family history	Irrelevant	0.45 (0.37–0.55)	-1.304	0.192	NS
	Positive	0.5 (0.34–0.74)			
RF	Negative	0.42 (0.35–0.54)	-1.693	0.090	NS
	Positive	0.47 (0.38–0.58)			
ACPA	Negative	0.4 (0.33–0.5)	-3.424	≤ 0.001	S
	Positive	0.47 (0.4–0.6)			

Table (7) shows that PAD4was more common in patients with positive ACPAs, with a p value ≤ 0.001. However, PAD4 was not significantly associated with sex, family history or RF, with a p value ≥ 0.05.

Table 8
Correlations between PAD4 laboratory investigations

		Age	duration of RA	ESR	CRP	DAS28 ESR	PGA
PAD4	Spearman's Coefficient	0.046	0.097	0.060	-0.009	.183*	0.033
	p Value	0.579	0.23 6	0.466	0.909	0.025	0.686
	Significance	NS	NS	NS	NS	S	NS

Table (8) shows the correlations among PAD4, characteristics and the results of laboratory investigations. PTPN22 was significantly positively correlated with the DAS28 ESR (p value = 0.025). However, the other variables did not have a statistically significant p value (≥ 0.05).

6. Overall sensitivity and specificity of PTPN22 and PAD4

Receiver operating characteristic(ROC) curve analysis revealed that the overall sensitivities and specificities for the tested biomarkers (PTPN22 and PAD4 markers) were different. Compared with the PAD4 test, the PTPN22 test had better sensitivity than did the PAD4 test (75.6%, 64.6%). However, the

PAD4 test had greater specificity (73.3%), making it a good negative test, whereas the specificity of the PTPN22 test was 45.3%.(Fig. 10, 11)

(Fig. 10, 11): the overall sensitivities and specificities for the tested biomarkers (PTPN22 and PAD4 markers) were different. Compared with the PAD4 test, the PTPN22 test had better sensitivity than did the PAD4 test (75.6%, 64.6%). However, the PAD4 test had greater specificity (73.3%), making it a good negative test, whereas the specificity of the PTPN22 test was 45.3%.

The area under the curve (AUC),which represents the overall diagnostic performance of each marker, was 0.56 for PTPN22, with a cut-off value of 0.55, while the PADI4 AUC was 0.708, and the cut-off value was also 0.55, with higher AUC values indicating better diagnostic accuracy.

With respect to PTPN22, the results were not significant, as the P value was greater than 0.1, which indicates that there was no evidence against the null hypothesis; however, the PAD4 results were significant, with P-values less than 0.05. (Table 9)

Table 9
Overall sensitivity and specificity of PTPN22 & PAD4

Markers (Units)	PTPN22	PAD4
Cut-off value	0.553	0.554
AUC	0.56	0.708
S.E.M	0.038	0.034
P value	0.115	≤ 0.001
95% CI	0.485 to 0.635	0.64 to 0.776
Sensitivity %	75.6	64.4
Specificity %	45.3	73.3

Table (9) shows the PTPN22 test had better sensitivity than did the PAD4 test (75.6%, 64.6%). However, the PAD4 test had greater specificity (73.3%), making it a good negative test, whereas the specificity of the PTPN22 test was 45.3%

Discussion

This study aimed to investigate the associations of **PTPN22** and **PADI4** gene polymorphisms with rheumatoid arthritis (RA) susceptibility and disease activity in the Aswan population. Our results did not reveal a significant association between these genes and RA risk, but we observed correlations with disease activity and diagnostic markers, such as **RF** and **ACPA**. These findings are consistent with several studies but also highlight notable differences across populations.

PTPN22 and RA susceptibility

Our study did not reveal significant differences in **PTPN22** expression between RA patients and controls with p-value ≥ 0.05, which aligns with findings from a Turkish study that also revealed no association between PTPN22 gene polymorphisms and RA [18]. Additionally, a meta-analysis confirmed that the **PTPN22 1858C/T** polymorphism is associated with RA in Caucasians but not in Asians[19]. However, studies in Mediterranean populations have reported conflicting results, with some showing a significant association in northern Europe and others, such as Italy, suggesting regional variability[20].

Diagnostic and prognostic value of PTPN22

Our data suggest that PTPN22 is significantly associated with RF and ACPA levels with p-value ≥ 0.006 and ≤ 0.001, respectively, which supports its potential as a diagnostic marker, as noted in previous research [21, 22, 23]. However, its value in disease progression remains unclear. In contrast to our findings, Lie et al. (2007) demonstrated that **PTPN22** is linked to the progression of joint damage in RA patients, suggesting that it could also play a role in disease severity and long-term outcomes[8].

PADI4 and RA Risk

The PADI4 expression levels were lower in our RA patients than in the controls, which contrasts with findings from studies in Iran, Swede ,Japan and Egypt [24, 25, 26, 27]and agreed with other study in Egypt [23].

Despite the lack of association between PADI4 and RA diagnosis in our study, PADI4 showed a significant correlation with ACPA positivity (p ≤ 0.001), similar to [27, 28] study, that demonstrated that PADI4 could serve as a diagnostic marker in RA.

Sensitivity and specificity of PTPN22 and PADI4

Our analysis revealed significant diagnostic potential for **PADI4**, with a sensitivity of 64.4% and a specificity of 73.3%, indicating that it could be a reliable negative test for RA. In contrast, **PTPN22** did not show significant diagnostic value in our study. These findings are consistent with those of [27], who reported similar results in Egyptian cohorts, confirming the diagnostic utility of the PADI4.

Genetic variation and SNPs

The variability in results across different populations may be attributed to genetic differences, particularly **single nucleotide polymorphisms (SNPs)**. Studies have shown that specific **PADI4 SNPs** are associated with RA, suggesting that differences in genetic architecture may explain the inconsistencies observed in different regions [29]. This highlights the importance of considering geographic and ethnic diversity in genetic research on RA.

Conclusion

While **PTPN22** and **PADI4** were not significantly associated with RA risk in the Aswan population, their correlation with disease activity markers such as **ACPA** suggests a potential diagnostic role. **PADI4**, in particular, shows promise as a negative diagnostic marker because of its high specificity. However, further studies with larger sample sizes and functional analyses are needed to explore the exact role of these genes in RA susceptibility and disease progression.

Abbreviations

Rheumatoid Arthritis

Genetics

Aswan, Egypt

PADI4

PTPN22

Declarations

Ethical approval and consent to participate :

Verbal and written consent obtained from all patients before they were involved in the study. The steps of the study, the aim of the study, and the potential benefits and hazards will all be discussed with the cases. The confidentiality of all the data will be ensured. The patients had the right to withdraw from the study at any time without giving any reason.

The Institutional Ethics committee (Aswan faculty of medicine ethical committee) (Graduate studies & research office ,Aswan faculty of medicine ,Ethics committee board ,Aswan University) Had Reviewed and Approved to conduct the above mentioned clinical trial and the study in compliance with the Helsinki Declaration.

On IRB Ref NO: Asw.Uni. / 678 / 10 / 22

Site of the study: Aswan Faulty of Medicine

Chairman of ethical committee Board:

- Prof. Mohamed ZaKi Ali Ahmed (Dean of Aswan faulty of medicine)
- Prof. Moustafa Adam Ali (VICE DEAN for Graduate Studies and Research Affairs)

Consent of publication:

All authors have agreed to the publication and the consent for publications of this data was obtained

Availability of data and materials

The data and the material used in our study can be accessed and available in request.

Competing interest :

None

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Declaration :

The author declare that they have no known completing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors contributions :

(Khaled A. A. Abdelgalil) conceived and designed the study, performed the data analysis, and drafted the manuscript.

(Nihal A. Fathi Awad) contributed to the study design, supervised the research process, and critically revised the manuscript for intellectual content.

(Fatma H. Elnoby) provided methodological expertise, contributed to data interpretation, and assisted in drafting specific sections of the manuscript.

(Loay I. Aglan) facilitated data collection and contributed to statistical analysis and manuscript review.

(Nour A. Mohammed) conducted laboratory investigations, interpreted clinical pathology data, and contributed to manuscript preparation.

All authors reviewed the manuscript, provided critical revisions, and approved the final version for submission

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References

1. Mousavi S, Nejadghaderi S, Khabbazi A, et al. The burden of rheumatoid arthritis in the Middle East and North Africa region, 1990–2019. Sci Rep. 2022;12:19297.

2. Padyukov L. Genetics of rheumatoid arthritis. Semin Immunopathol. 2022;44:47–62.
3. Bowes J, Barton A. Recent advances in the genetics of RA susceptibility. Rheumatology. 2008;47:399–402.
4. Hinks A, Barton A, John S, Bruce I, Hawkins C, Griffiths C, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: Further support that PTPN22 is an autoimmunity gene. Arthr Rhuem. 2005;52:1694–9.
5. Gregersen PK. Pathways to gene identification in rheumatoid arthritis: PTPN22 and beyond. Immunol Rev. 2005;204:74–86.
6. Goeb V, Dieude P, Daveau R, Thomas-L'Otellier M, Jouen F, Hau F, et al. Contribution of PTPN22 1858T, TNFRII 196R and HLA-shared epitope alleles with rheumatoid factor and anti-citrullinated protein antibodies to very early rheumatoid arthritis diagnosis. Rheumatology. 2008;47:1208–12.
7. Johansson M, Arlestig L, Hallmans G, Rantapää-Dahlqvist S. PTPN22 polymorphism and anti-cyclic citrullinated peptide antibodies in combination strongly predicts future onset of rheumatoid arthritis and has a specificity of 100% for the disease. Arthritis Res Therapy. 2006;8:R19.
8. Lie BA, Viken MK, Ødegård S, van der Heijde D, Landewé R, Uhlig T, et al. Associations between the PTPN22 1858C->T polymorphism and radiographic joint destruction in patients with rheumatoid arthritis: Results from a 10-year longitudinal study. Ann Rheum Dis. 2007;66:1604–9.
9. Karlson EW, Chibnik LB, Cui J, Plenge RM, Glass RJ, Maher NE, et al. Associations between human leukocyte antigen, PTPN22, CTLA4 genotypes and rheumatoid arthritis phenotypes of autoantibody status, age at diagnosis and erosions in a large cohort study. Ann Rheum Dis. 2008;67:358–63.
10. Zheng J, Ibrahim S, Petersen F, Yu X. Meta-analysis reveals an association of PTPN22 C1858T with autoimmune diseases, which depends on the localization of the affected tissue. Genes Immun. 2012;13:641–52.
11. Chavanas S, Méchin MC, Takahara H, Kawada A, Nachat R, Serre G, et al. Comparative analysis of the mouse and human peptidylarginine deiminase gene clusters reveals highly conserved noncoding segments and a new human gene, PADI6. Gene. 2004;330:19–27.
12. Ikari K, Kuwahara M, Nakamura T, Momohara S, Hara M, Yamanaka H, et al. Association between PADI4 and rheumatoid arthritis: A replication study. Arthr Rhuem. 2005;52:3054–7.
13. Too CL, Murad S, Dhaliwal JS, Larsson P, Jiang X, Ding B, et al. Polymorphisms in peptidylarginine deiminase associate with rheumatoid arthritis in diverse Asian populations: Evidence from MYEIRA study and meta-analysis. Arthritis Res Therapy. 2012;14:R250.
14. Du Y, Liu X, Guo JP, Liu X, Li R, Zhao Y, et al. Association between PADI4 gene polymorphisms and anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis in a large Chinese Han cohort. Clin Experimental Rheumatol. 2014;32:377–82.
15. Burr ML, Naseem H, Hinks A, Eyre S, Gibbons LJ, Bowes J, et al. The PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population. Ann Rheum Dis. 2010;69:666–70.

16. Barton A, Bowes J, Eyre S, Spreckley K, Hinks A, John S, et al. A functional haplotype of the PADI4 gene associated with rheumatoid arthritis in a Japanese population is not associated United Kingdom population. Arthr Rhuem. 2004;50:1117–21.
17. Eyre S, Bowes J, Diogo D, Lee A, Barton A, Martin P, et al. High-density genetic mapping identifies new susceptibility loci for rheumatoid arthritis. Nat Genet. 2012;44:1336–40.
18. Sahin N, Gunduz F, Inanc N, et al. No association of PTPN22 gene polymorphism with rheumatoid arthritis in Turkey. Rheumatol Int. 2009;30:81–3.
19. Nabi G, Akhter N, Wahid M, Bhatia K, Mandal RK, Dar SA, Jawed A, Haque S. Meta-analysis reveals PTPN22 1858C/T polymorphism confers susceptibility to rheumatoid arthritis in Caucasian but not in Asian population. Autoimmunity. 2016;49(3):197–210. https://doi.org/10.3109/08916934.2015.1134514.
20. Totaro MC et al. (2011). PTPN22 1858C > T polymorphism distribution in Europe and association with rheumatoid arthritis: Case–control study and meta-analysis. PLoS ONE, 6(9), e24292.
21. Majorczyk E, Pawlik A, Kuśnierczyk P. PTPN22 1858C > T polymorphism is strongly associated with rheumatoid arthritis but not with a response to methotrexate therapy. Int Immunopharmacol. 2010;10(12):1626–9. https://doi.org/10.1016/j.intimp.2010.09.008.
22. Salama A, et al. Protein tyrosine phosphatase nonreceptor type 22 (PTPN22) + 1858 C > T gene polymorphism in Egyptian cases with rheumatoid arthritis. Cell Immunol. 2014;290(1):62–5. 10.1016/j.cellimm.2014.05.003.
23. Hegab MM, et al. CD28 and PTPN22 are associated with susceptibility to rheumatoid arthritis in Egyptians. Hum Immunol. 2016;77(6):522–6. 10.1016/j.humimm.2016.04.018.
24. Bagheri-Hosseinabadi Z, Mirzaei MR, Esmaeili O, Asadi F, Ahmadinia H, Shamsoddini B, Abbasifard M. Implications of Peptidyl Arginine Deiminase 4 gene transcription and polymorphisms in susceptibility to rheumatoid arthritis in an Iranian population. BMC Med Genom. 2023;16(1):104. https://doi.org/10.1186/s12920-023-01532-9IF:. 2.1 Q3.
25. Kokkonen H, Johansson M, Innala L, Jidell E, Rantapaa-Dahlqvist S. The PTPN22 1858C/T polymorphism is associated with anti-cyclic citrullinated peptide antibody-positive early rheumatoid arthritis in northern Sweden. Arthritis Res Ther. 2007;9(3):R56.
26. Umeda N, Matsumoto I, Kawaguchi H, Kurashima Y, Kondo Y, Tsuboi H, et al. Prevalence of soluble peptidylarginine deiminase 4 (PAD4) and anti-PAD4 antibodies in autoimmune diseases. Clin Rheumatol. 2016;35(5):1181–8. 10.1007/s10067-015-3082-z.
27. Ahmed A, El-Gawish M, Esh A, Makram W. Serum peptidyl Arginine Deiminase-4 (PADI4) antibodies in rheumatoid arthritis and their correlation with disease activity. Zagazig Univ Med J. 2023;29(21):80–6. 10.21608/zumj.2021.48120.198.
28. Hussein N, et al. Peptidyl-arginine deiminase-type IV as a diagnostic and prognostic marker in rheumatoid arthritis patients. Egypt Rheumatologist. 2019;41:87–91.
29. Abd-Allah SH, et al. PADI4 polymorphisms and related haplotypes in rheumatoid arthritis patients. Joint Bone Spine. 2012;79(2):124–8. 10.1016/j.jbspin.2011.07.006.

Figures

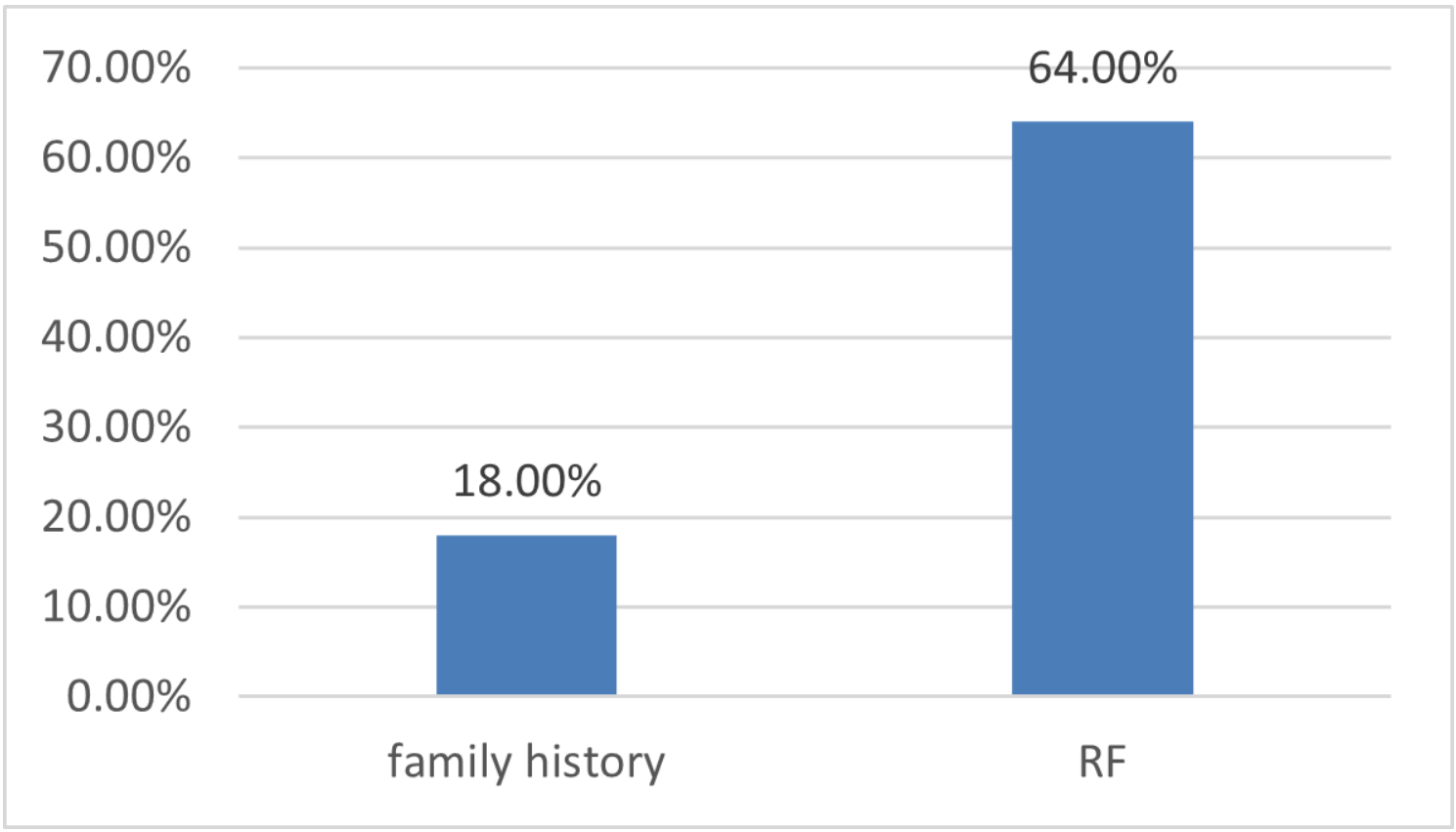


Figure 1

The percnetage of postive family history and postive RF among patinets

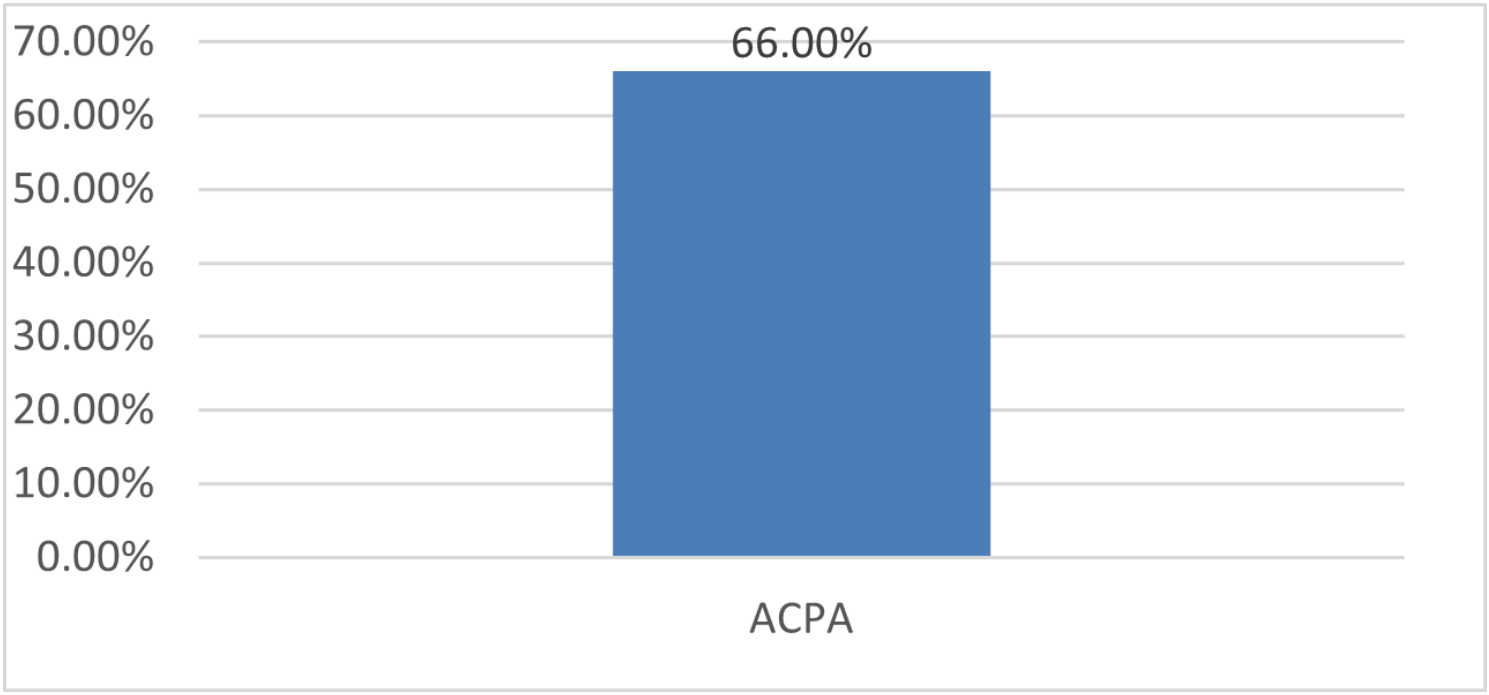


Figure 2

the percntage of postive ACPAs among patients

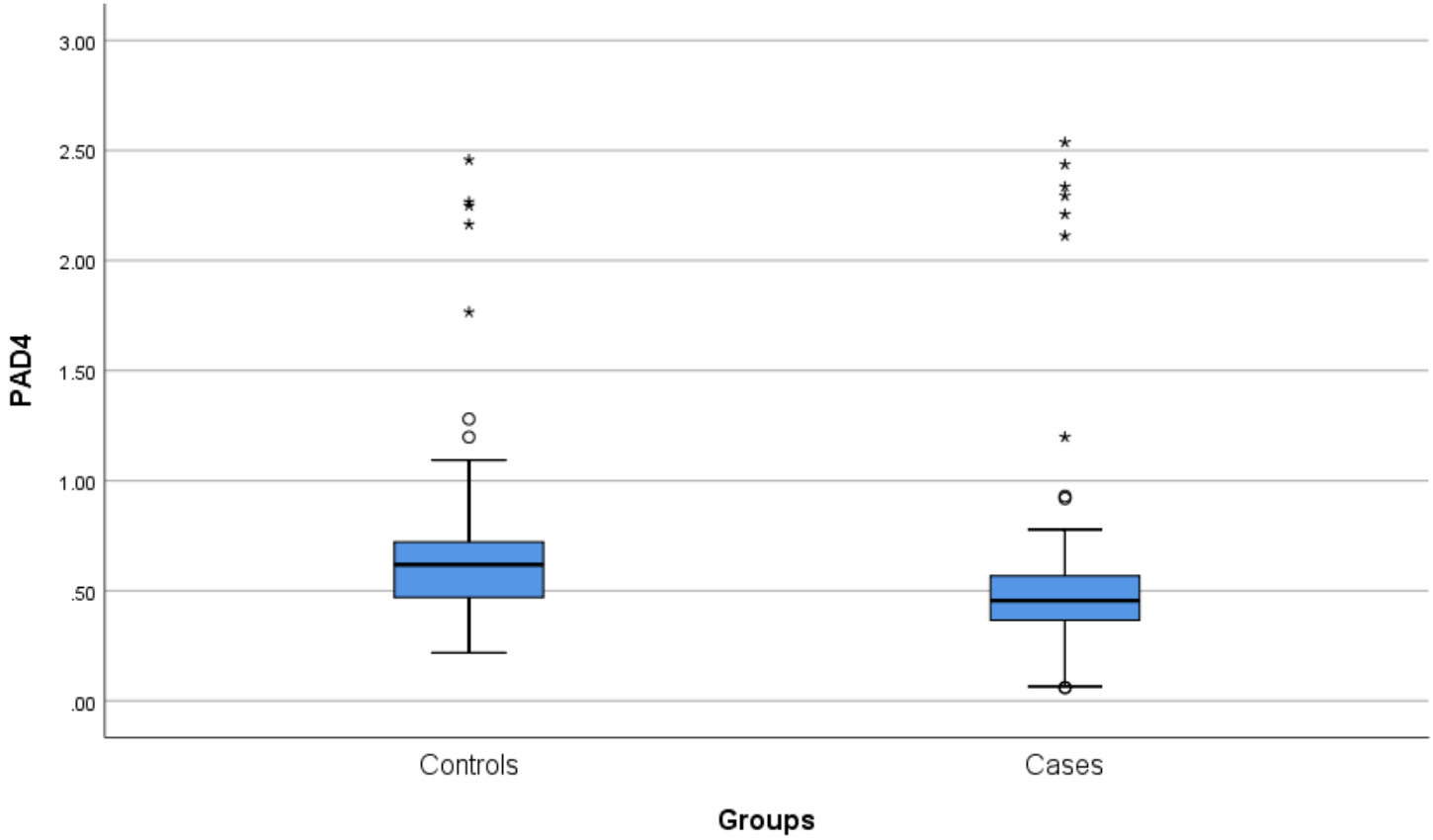


Figure 3

Comparison of PAD4 expression between the two groups

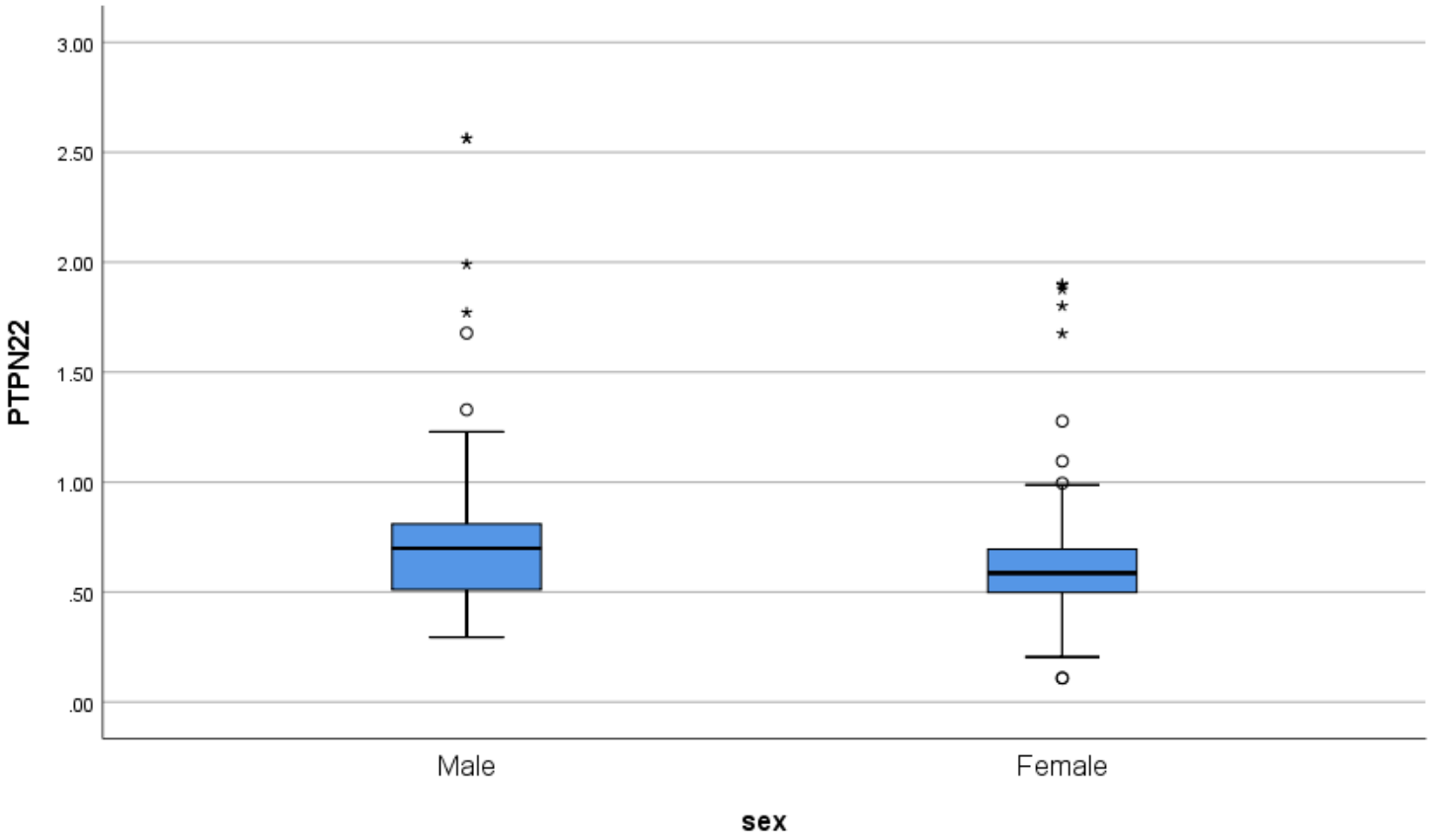


Figure 4

Correlations between PTPN22 and sex .

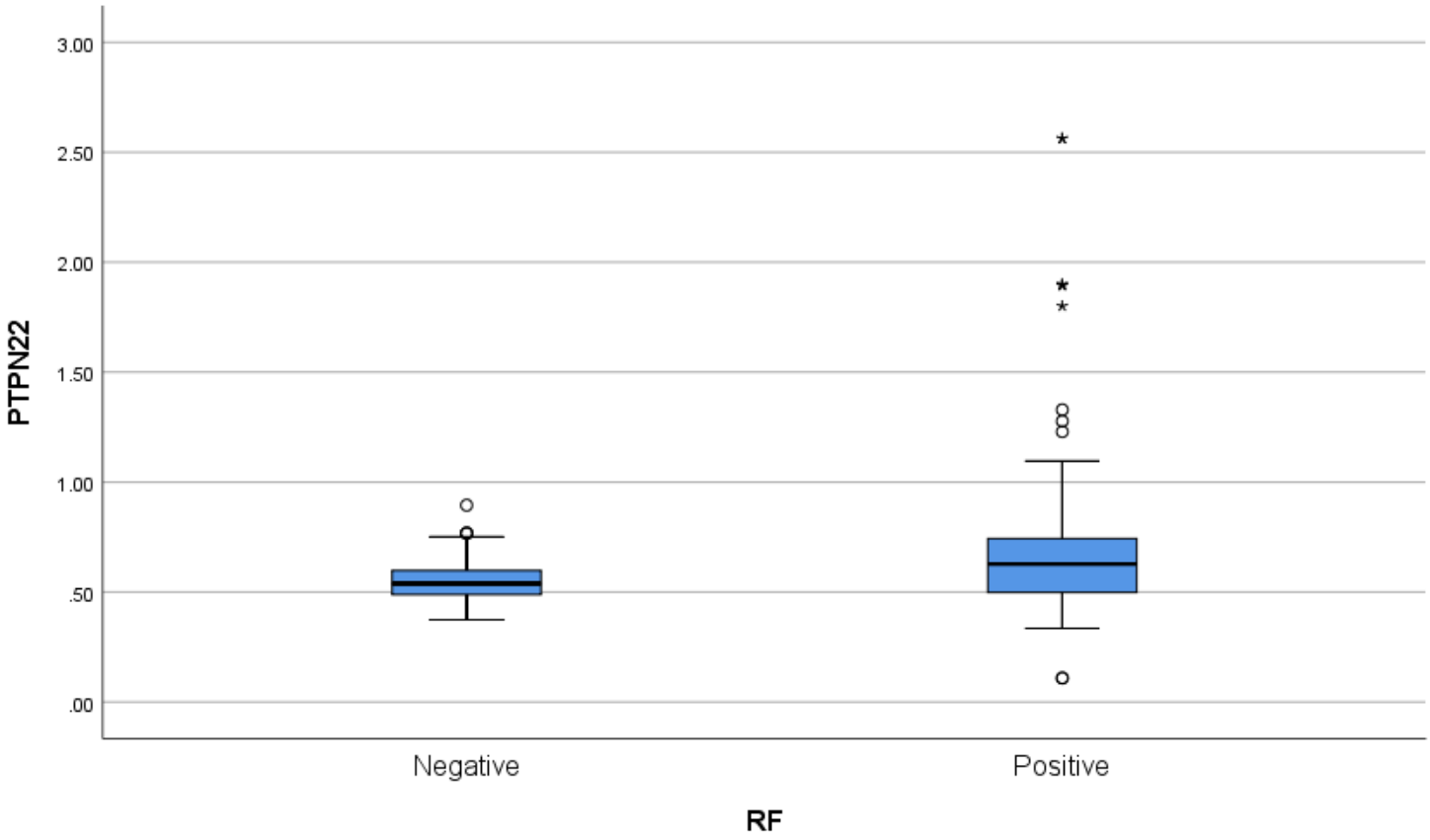


Figure 5

Correlations between PTPN22 and RF

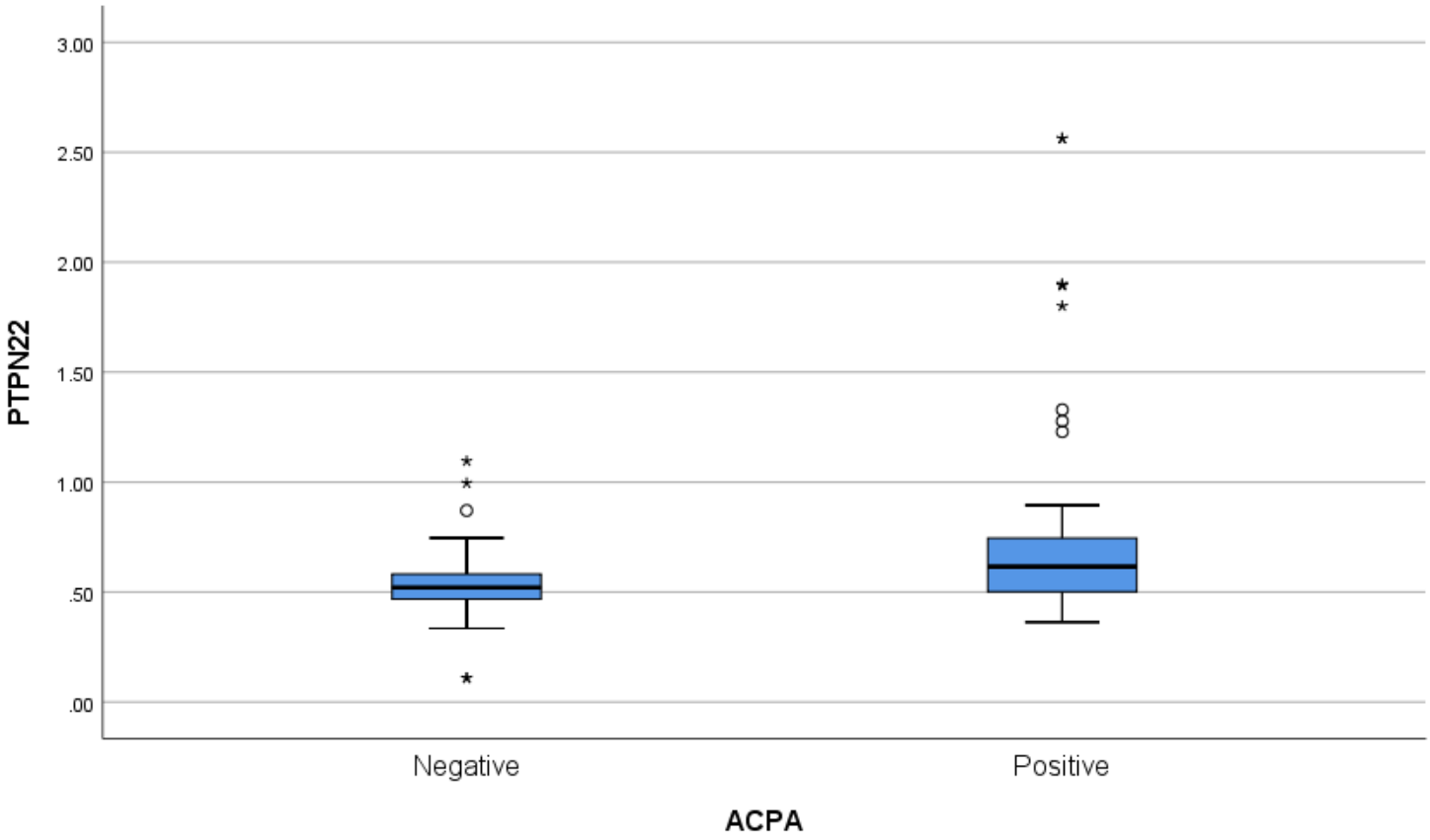


Figure 6

Correlations between PTPN22 and ACPA

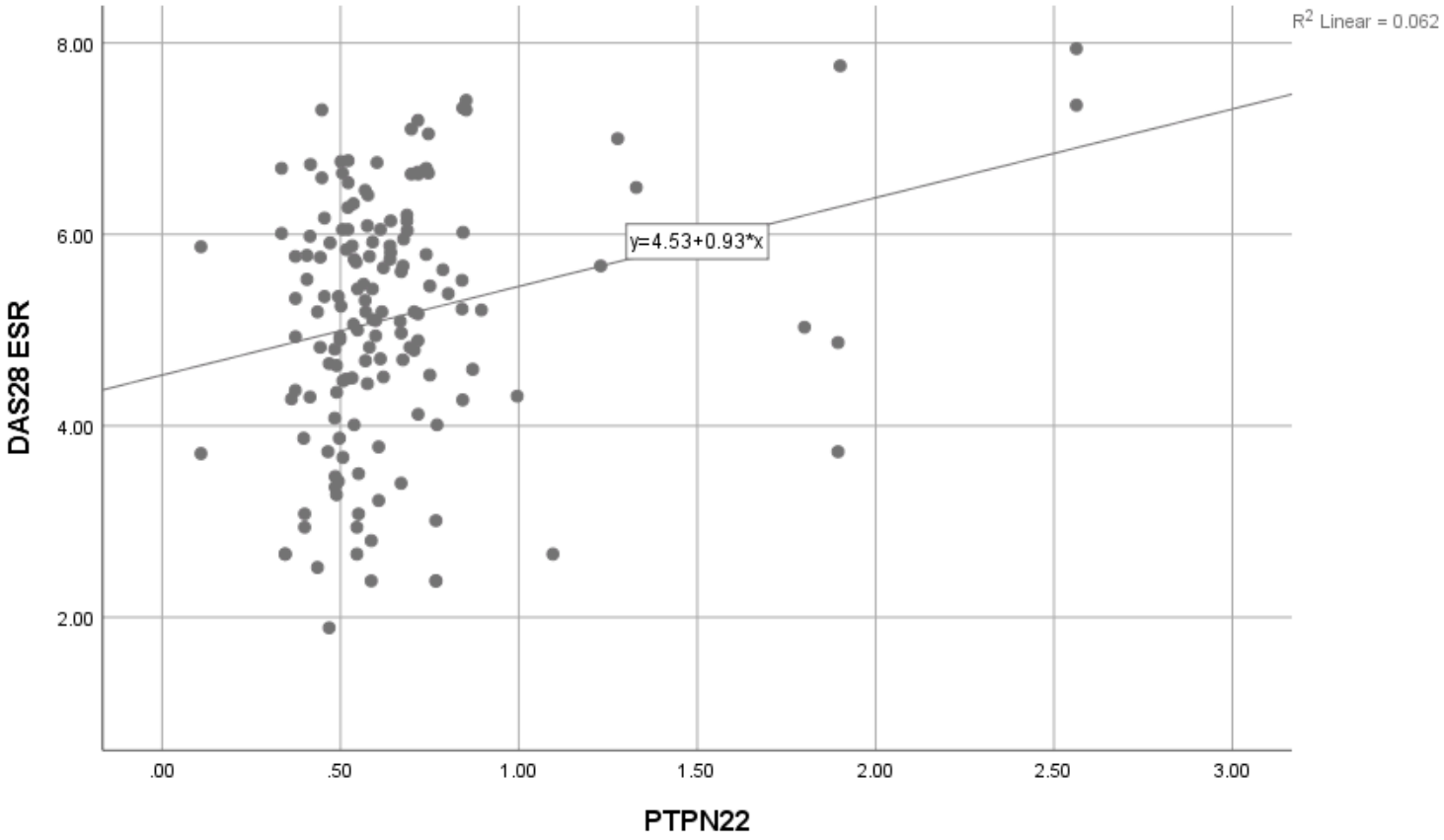


Figure 7

Correlations between PTPN22 and DAS28 ESR

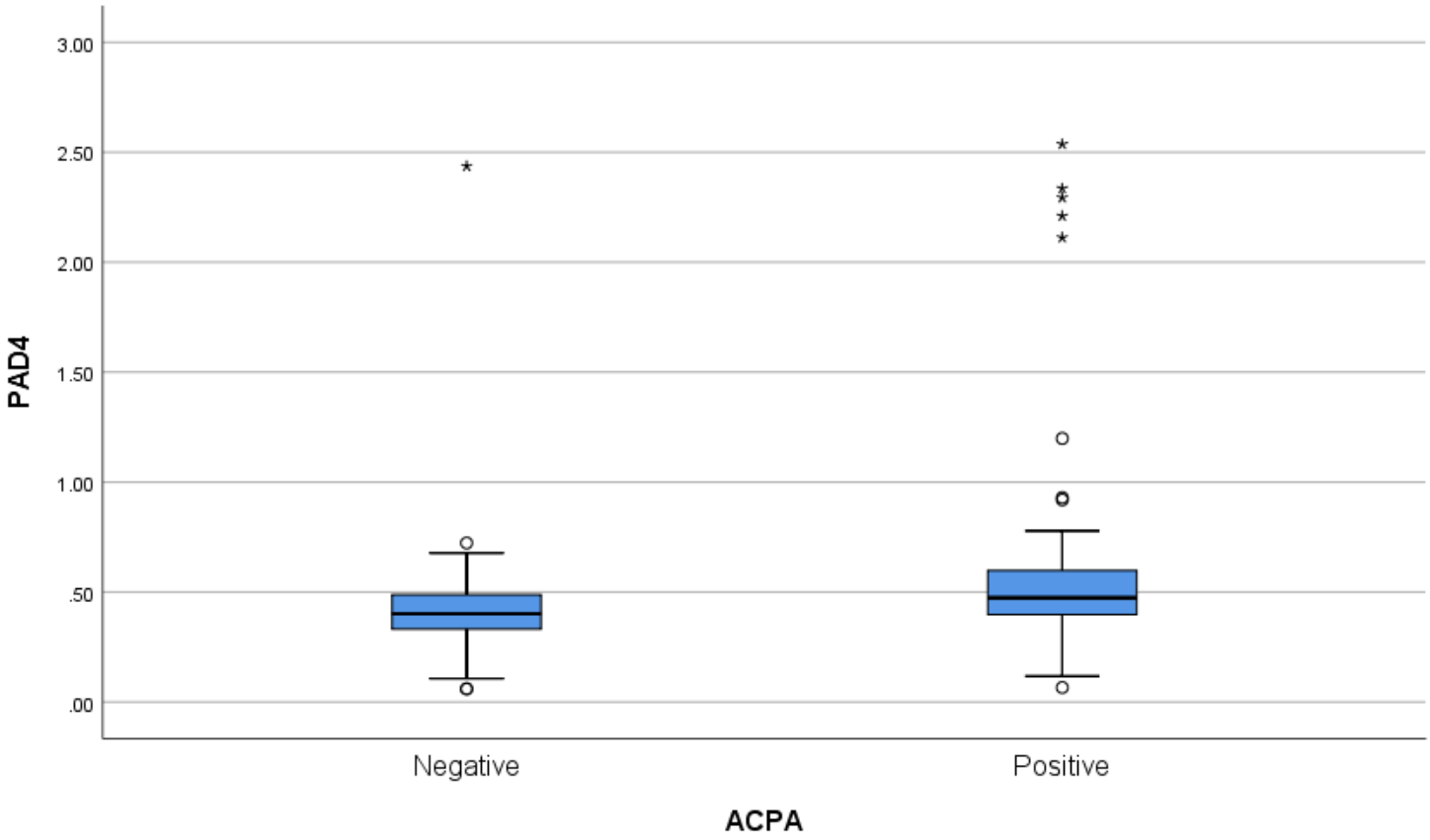


Figure 8

Correlations between PAD4 and ACPA

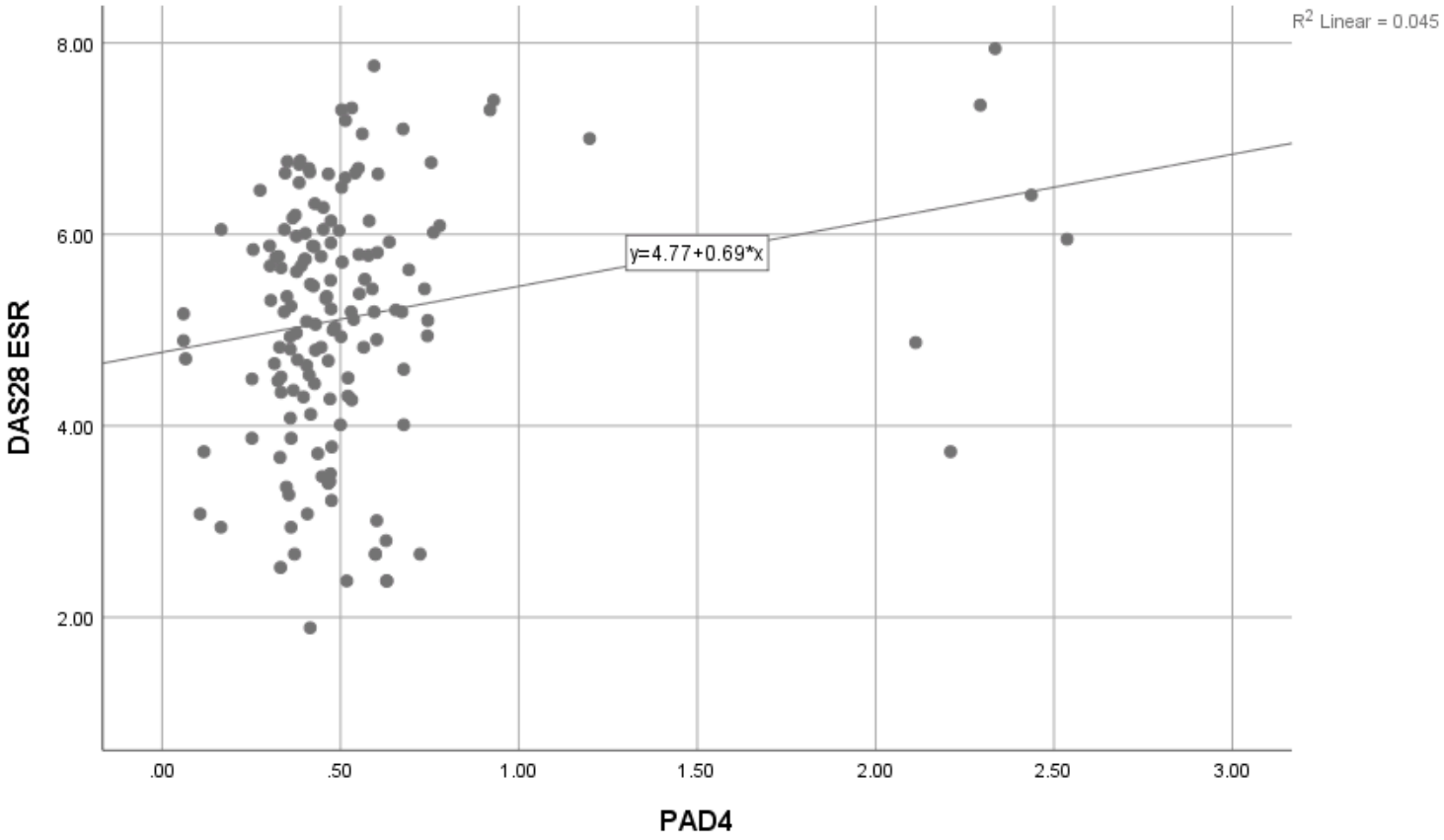


Figure 9

Correlations between PAD4 and DAS28 ESR

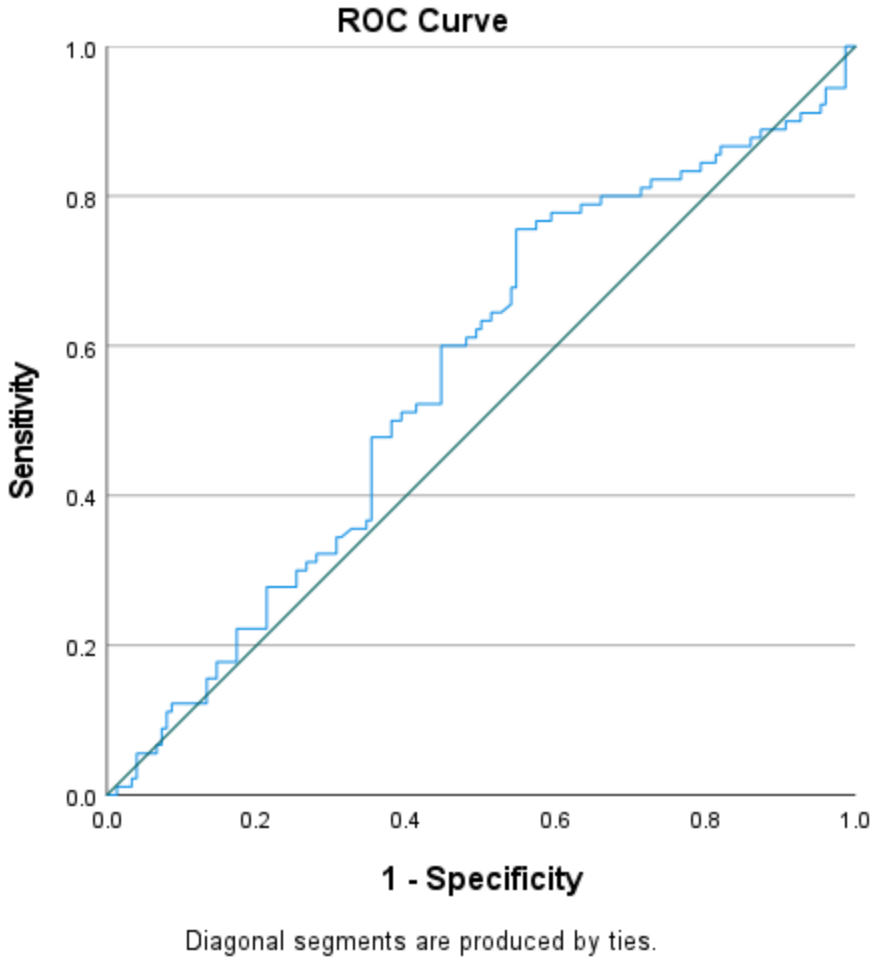


Figure 10

Serum PTPN22 ROC curve

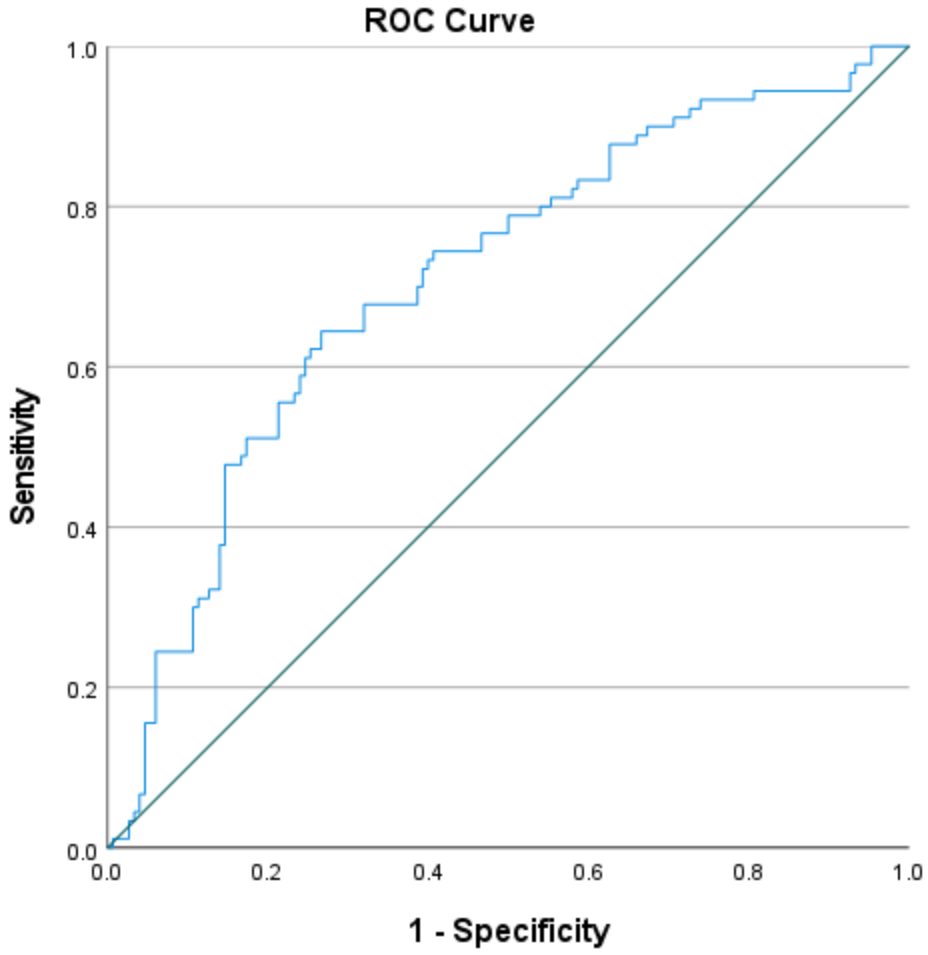


Figure 11

Serum PAD4 ROC curve