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Research Article

The Effects of -806 T/C and -857 T/C Single Nucleotide Polymorphisms in the TNF-α Gene on Rheumatoid Arthritis Severity and Inflammatory Markers

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Abstract

Background: Polymorphisms in the TNF-α gene affect the development and progression of rheumatoid arthritis. ***Objective***: To investigate the associations between (-806 T/C) and (-857 T/C) SNPs with rheumatoid arthritis severity and susceptibility in a sample of Iraqi patients. ***Methods***: A case-control study was conducted in Baghdad, Iraq. Twenty healthy controls and 63 patients confirmed to be newly diagnosed with rheumatoid arthritis were included. Those are divided into two groups (patients and controls), and the patients were further subdivided into severe and mild-moderate groups. Samples from those participants were analyzed for clinical and inflammatory parameter measurements. Genotyping by the Sanger method was performed to study the SNPs. ***Results***: No associations were demonstrated between rheumatoid arthritis and polymorphisms at positions -806 and -857. Additionally, there were no differences in the distribution of those SNP genotypes and alleles among the severe and mild-moderate groups. Also, the (-806 C/T) SNP was found to be correlated with DAS 28 in all patients and with hs-CRP in the mild-moderate group. Finally, the -857 C/T SNP was found to be correlated with TNF-α within the mild-moderate group. ***Conclusions***: Polymorphisms at positions -806 and -857 were not associated with rheumatoid arthritis susceptibility, and the CT genotype of -806 C/T SNP was associated with disease activity.

Keywords: Disease severity, Polymorphism, Rheumatoid arthritis, -806 C/T, -857 C/T.

تأثير تعدد أشكال النيوكلوتيدات المنفردة T/C 806- و T/C 857- في موروثة TNF-α على شدة التهاب المفاصل الرثوي ومعلمات الألتهاب

الخلاصة

الخلفية: يؤثر تعدد الأشكال في جين TNF-α على تطور التهاب المفاصل الروماتويدي. **الهدف**: التحقيق في الارتباطات بين تعدد أشكال النيوكيوتيدات المنفردة -806 T/C و -857 T/C SNPs مع شدة التهاب المفاصل الرثوي و في عينة من المرضى العراقيين. **الطرائق**: أجريت دراسة الحالات والشواهد في بغداد، العراق. تم تضمين عشرين ضابطا صحيا و 63 مريضا تم تشخيصهم حديثا بالتهاب المفاصل الرثوي. ينقسم هؤلاء إلى مجموعتين (المرضى والشواهد)، وتم تقسيم المرضى إلى مجموعات شديدة وخفيفة إلى معتدلة. تم تحليل عينات من هؤلاء المشاركين لقياس المعلمات السريرية والالتهابية. تم إجراء التنميط الجيني بطريقة سانجر لدراسة SNPs. **النتائج**: لم تظهر أي ارتباطات بين التهاب المفاصل الرثوي وتعدد الأشكال في المواضع -806 و -857. بالإضافة إلى ذلك، لم تسجل فروق في توزيع تلك الأنماط الجينية والأليلات SNP بين المجموعات الشديدة والمعتدلة الخفيفة. أيضا ، وجد أن SNP (-806 C / T) مرتبط ب DAS 28 في جميع المرضى ومع hs-CRP في المجموعة الخفيفة المتوسطة. أخيرا، تم العثور على C/T SNP 857- مرتبطا ب TNF-α داخل المجموعة الخفيفة والمتوسطة. **الاستنتاجات**: لم يرتبط تعدد الأشكال في المواضع -806 و -857 بحساسية الصابة بالتهاب المفاصل الرثوي، واقترن النمط الجيني CT ل C/T SNP 806- بنشاط المرض.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory chronic disease [1]. Females are more likely to get RA [2]. The disease mostly affects small joints in an asymmetrical order [3]. The disease incidence globally and among Iraqis is 1% [4,5]. The clinical features of the disease are different from one patient to another [6]. Defective treatment may lead to deformity, erosion of bones, and function retardation [3]. Early management, specifically using two disease-modifying anti-rheumatic drugs plus corticosteroids, can decrease the progression of the disease [6]. A big part of how RA works is that T

lymphocytes get activated, which makes rheumatoid factor (RF), antibodies to citrullinated protein/peptide antigens (ACPAs), and other antibodies (AB). Some patients may be seropositive; those with a high level of ACPAs and/or RF and others with no AB are considered seronegative. Cytokine deregulation has a central role in the pathogenesis of RA. Tumor necrosis factor-alpha (TNF-α) is a cornerstone in the inflammatory process; it activates bone erosion and cartilage destruction [7]. Both genetic and environmental predisposing factors interact and affect RA susceptibility. Genetics plays a prime role in RA development. The major contributing genes that are responsible for 60% of the genetics of RA are located within the major histocompatibility complex (MHC) locus. Protein tyrosine phosphatase, non-receptor type 22 (PTPN22) and peptidyl arginine deiminase type IV are two other genes that play a role [5]. Cytokine gene polymorphism, primarily TNF-α gene polymorphism, also affects the development and progression of the RA. Many of these genetic variations occur in the promoter region of TNF-α genes, and it was found that sixty percent of TNF production is of genetic origin [8]. To date, a lot of research has tried to find the exact association between RA susceptibility, association, severity, and single nucleotide polymorphisms SNPs. However, conflicting findings are achieved in those studies [8–11]. According to my knowledge, previous studies didn't investigate the effect of the rs4248158 (-806 C/T) SNP on RA severity and susceptibility. Additionally, the rs1799724 (-857 C/T) association with severity and disease activity was not studied previously in Iraqi patients who were newly diagnosed with RA. The goal of this study was to look into the link between disease activity and severity and genetic polymorphisms at positions (-806) and (-857) in the TNF promoter region. It was also meant to look into how these SNPs affect the release of inflammatory markers in a group of new Iraqi RA patients.

METHODS

Study design

This case-control study, which is a part of PhD thesis, was conducted during the period from January 2021 to August 2021 in Baghdad City. Twenty randomly selected healthy adults and sixty-three newly diagnosed RA patients participated in the current study. Additionally, the patients were divided into severe and mild-moderate groups based on the Disease Activity Score in 28 Joints (DAS28) [12]. Those patients who enrolled in this research were confirmed to be newly diagnosed with RA by a specialist physician based on the diagnostic criteria set by the European League Against Rheumatism and the American College of Rheumatology [13]. From each participant, informed consent was obtained.

Ethical consideration

This study was ethically approved by the Scientific and Ethical Committee in the College of Pharmacy at the University of Baghdad and the Rheumatology Medical Department at Baghdad Teaching Hospital (RECAUBCP-2692020) on September 29, 2020.

Demographic data and sample collection

The demographic data including sex, age, and smoking were obtained and recorded in the previously designed patient information chart and venous blood was withdrawn from each participant.

DAS28 estimation

Patient stratification into severe and mild-moderate groups depending on their DAS28 is calculated as shown below [14]:

$$DAS28 = (0.56*\sqrt{[TJC]}) + (0.28*\sqrt{[SJC]}) + (0.7*\ln[ESR]) + (0.014*VAS)$$

The interpretation of the results is that >5.1 is considered a highly active disease, >3.2 and ≤ 5.1 mean moderate disease activity, ≥2.6 and ≤3.2 indicate low disease activity, and <2.6 represents remission. Patients with a DAS score >5.1 are classified into the severe RA group, and patients with a DAS score range of 2.6–5 are classified into the mild–moderate RA group.

Determination of the inflammatory markers

The modified Westergren method was used to determine the erythrocyte sedimentation rate (ESR) [15]. The agglutination method was used to assess RF with the Spinreact kit [16]. TNF-α and hs-CRP levels in blood can be measured using the sandwich ELISA method [17] and a commercial kit from Cusabio, South Korea.

Genotyping

Genomic DNA extraction from the blood sample was performed using the Promega ReliaPrep® Blood gDNA Miniprep System [18]. The 1008 base pair TNF region that contains (-806) and (-857) was amplified by a thermal cycler polymerase chain reaction (PCR) analyzer using 5`-TGTAAAACGACGGCCAGTGCTTCAGGGATATGT GATGG-3` forward and 5`-CAGGAAACAGCTATGACCCTTCTGTCTCGGTTTC TTCTC-3 reverse primers that were produced by Macrogen Company and designed using Primer Premier 3 software.

Primer optimization

The desired annealing temperature which is 60 ºC was determined by DNA template amplification at different temperatures, and then the confirmation of the amplification by agarose gel electrophoresis was done (Figure 1).

Sequencing

The sequencing of the PCR product was performed by a DNA analyzer (ABI3730XL) (Macrogen Corporation, Korea) using the Sanger method. The data were generated

by Geneious Prime software (V 2021.1.1) (www.geneious.com; Biomatters Ltd., New Zealand).

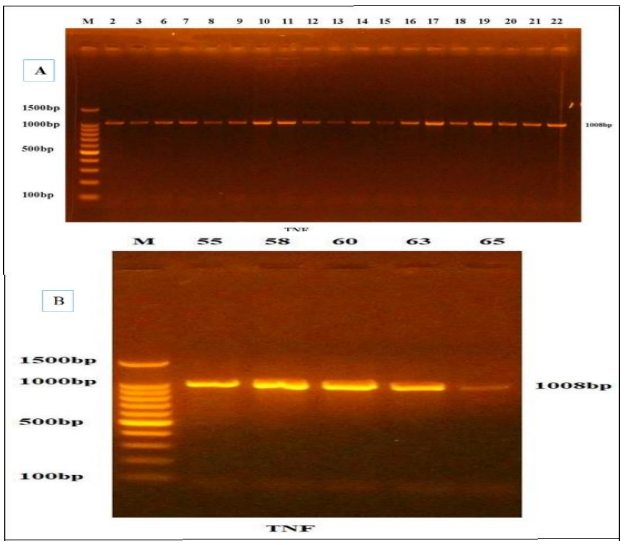

Figure 1: Optimization of TNF primers (A); Gel electrophoresis of the amplified DNA (B).

Statistical analysis

GraphPad Prism (USA) and SPSS for Windows 26.0 software (USA) were used for data analysis. Numbers and frequencies were used for categorical data presentation. The mean and standard deviation were used for continuous parameter presentation. An independent sample T-test calculated the mean differences of two independent samples for data with a normally distributed distribution. The difference between the two groups of categorical values was analyzed by Fisher's exact or Chi-square tests. The phi coefficient test was used to test the association between two categorical values. The correlations between continuous and categorical variables were analyzed by univariate logistic regression analysis. A probability that equals or is less than 0.05 was considered significant.

RESULTS

Non-significant differences were observed in the demographic data (age, gender, body weight, and smoking) between the patients and the controls (Table 1).

Table 1: Demographic data and inflammatory parameters for the patients and controls

Category		Patients	Controls	*p*-value
Age (year)		34.2±7.0	32.1±5.6	0.1
Gender	Female	55(87.3)	17(85)	0.97
	Male	8(12.7)	3(15)	1.0
Smoking		5(7.9)	2(8.7)	0.67
Positivity to ACPA		25(39.7)	0(0)	0.0004
RF Positivity		41(65.1)	0(0)	<0.0001
hs-CRP (µg/ml)		7.9±3.4.4	3.18±1.3	<0.0001
TNF-α (pg/ml)		247±124	60±25	<0.0001
Total number		63	20	

Values are presented as mean±SD, frequency, and percentage. ACPA: anti-citrullinated protein/peptide antibody, RF: rheumatoid factor, hs-CRP: highly sensitive C-reactive protein, TNF-α: tumor necrosis factor-alpha.

The inflammatory parameters, including positivity to RA, ACPA, hs-CRP, and TNF-α, were found to be significantly higher in the patients compared to the controls. The present study demonstrated a significant increase in the serum levels of hs-CRP and TNF-α in the severe RA patient compared to the mild-moderate group. Also, the positivity for ACPA was significantly higher in the group of severe diseases. However, the RF positivity was not significantly different between the two groups (Table 2).

Table 2: Inflammatory parameters differences between the patient groups

Parameter	Mild-moderate	Severe	*p*-value
RF Positivity	25(78.1)	16(51.6)	0.24
ACPA Positivity	5(21.8)	20(64.5)	0.03
hs-CRP (µg/ml)	6.9±1.4	8.9±4.4	0.02
TNF-α (pg/ml)	191±55	247±124	0.024

Values are presented as mean±SD numbers and percentages. ACPA: anti-citrullinated protein/peptide antibody, RF: rheumatoid factor, hs-CRP: highly sensitive C-reactive protein, TNF-α: tumor necrosis factor-alpha.

Table 3 demonstrates a non-significant increased prevalence of the CC genotype of -806 C/T and -857 C/T SNPs in both the patient and control groups. Also, the present study indicates a non-significant difference in the distribution of the CT genotypes of both SNPs between the patients and controls. Additionally, the C allele of 806 C/T and 857 C/T SNPs was found to be predominantly present in all study participants.

Table 3: Alleles and genotype distribution for patients and controls

Variants	Patients	Controls	*p*-value
- 806 C/T			
CC	56(88.9)	20(100)	0.19
CT	7(11.1)	0(0)	0.19
Allele			
C	119(94.4)	40(100)	0.19
T	7(5.6)	0(0)	0.19
- 857 C/T			
CC	48(76.2)	18(90)	0.22
CT	15(23.8)	2(10)	0.22
Allele			
C	111(88.09)	38(95)	0.36
T	15(11.9)	2(5)	0.36

Values were expressed as numbers and percentages. Fisher's exact test used for data analysis.

However, the T allele of 806 C/T was distributed in a small number of patients and was not distributed in any healthy control. A non-significant difference in the incidence of the T allele of -856 C/T between participants was observed. Furthermore, the current study indicates that the CC genotype of both -806 C/T and -857 C/T SNPs was more prevalent in patients with mild-moderate RA than in severe RA patients; however, the difference was non-significant. The scenario was inverted for the CT genotype, which is found to be more prevalent in the mild-moderate group. Again, the difference was non-significant. In addition to the above results, the C alleles of both SNPs were found in all the severe and mild-moderate members. Whereas the T allele was non-

significantly distributed in the severe and mild-moderate RA patients (Table 4).

Table 4: Distribution of alleles and genotype within the patients group

Variants	Severe	Mild-moderate	*p*-value
- 806 C/T			
CC	30(96.77)	26(81.25)	0.1[a]
CT	1(3.23)	6(18.75)	0.1 [a]
Allele			
C	61(98.3)	58(90.6)	0.11[a]
T	1(1.7)	6(9.4)	0.11[a]
- 857 C/T			
CC	24(77.41)	24(75)	0.82[b]
CT	7(22.59)	8(25)	0.82[b]
Allele			
C	55(88.7)	56(87.5)	0.83[b]
T	7(11.3)	8(12.5)	0.83[b]

Values were expressed as numbers and percentages. [a] Fisher's exact test, [b] Chi square.

Table 5 demonstrates a significant association between (-806) C/T and DAS 28 among all patient groups. Also, it states a non-significant difference between the inflammatory markers (hs-CRP, TNF-α, RF, and polymorphism at position (-806).

Table 5: Correlations between (-806) C/T SNP and RA severity and inflammatory markers

Patients	Φ coefficient	Odds Ratio	95% CI	*p*
DAS 28	-0.89	0.41	0.18-0.95	0.038
hs-CRP (µg/ml)	-0.02	0.98	0.76-1.25	0.85
TNF-α (pg/ml)	-0.001	0.99	0.99-1.01	0.84
Phi-coefficient	***Value***		***p***	
RF Positivity	0.06		0.64	
ACPA Positivity	0.0		1.0	
Mild-moderate group	***Φ coefficient***	***Odds Ratio***	***95% CI***	***p***
DAS28	-0.77	0.46	0.10-2.05	0.31
hs-CRP (µg/ml)	-0.72	0.48	0.25-0.93	0.03
TNF-α (pg/ml)	-0.01	0.99	0.97-1.01	0.39
Phi-coefficient	***Value***		***p***	
RF Positivity	0.13		0.45	
ACPA Positivity	-0.14		0.55	
Severe group	***Φ coefficient***	***Odds Ratio***	***95% CI***	***p***
DAS28	-0.49	0.61	0.002-137.9	0.86
hs-CRP (µg/ml)	0.4852	1.6245	0.72-3.67	0.24
TNF-α (pg/ml)	0.01	1.01	0.99-1.03	0.19
Phi-coefficient	***Value***		***p***	
RF Positivity	0.19		0.3	
ACPA Positivity	-0.14		0.55	

Analysis were made by univariate regression and Phi-coefficient. DAS 28: disease activity score in 28-joint, ACPA: anti-citrullinated protein/peptide antibody, RF: rheumatoid factor, hs-CRP: highly sensitive C-reactive protein, TNF-α: tumor necrosis factor-alpha.

Table 5 also showed that hs-CRP has a significant correlation with polymorphism at position (-806). However, associations are not established when compared with other parameters and DAS 28. In addition, the study failed to find any association between the (-806) C/T SNP and the study parameter among the patients with severe RA. Regarding (-857) C/T SNP, the present study found no association with DAS 28 and other mediators, both within the all-patient group and the severe groups. Additionally, the present study showed a significant association between (-857) C/T and TNF-α in patients with mild-moderate RA. However, no associations were found regarding the rest of the inflammatory mediators (Table 6).

Table 6: correlations between (-857) C/T SNP and RA severity and inflammatory markers

Patients	Φ coefficient	Odds Ratio	95% CI	*p*
DAS28	-0.04	0.096	0.57-1.62	0.88
hs-CRP (µg/ml)	0.05	0.95	0.78-1.16	0.62
TNF-α (pg/ml)	-0.001	0.99	0.99-1.01	0.79
Phi-coefficient	***Value***		***p***	
RF Positivity	-0.097		0.44	
ACPA Positivity	0.11		0.39	
Mild-moderate group	***Φ coefficient***	***Odds Ratio***	***95% CI***	***p***
DAS 28	0.84	2.33	0.57-9.47	0.24
hs-CRP (µg/ml)	0.74	2.09	0.94-4.68	0.07
TNF-α (pg/ml)	0.019	1.03	1.001-1.04	0.04
Phi-coefficient	***Value***		***p***	
RF Positivity	0.005		0.98	
ACPA Positivity	-0.005		0.98	
Severe group	***Φ coefficient***	***Odds Ratio***	***95% CI***	***p***
DAS28	0.39	1.48	0.16-13.84	0.73
hs-CRP (µg/ml)	0.19	0.82	0.55-1.24	0.36
TNF-α (pg/ml)	-0.006	0.99	0.98-1.01	0.29
Phi-coefficient	***Value***		***p***	
RF Positivity	-0.15		0.41	
ACPA Positivity	0.15		0.41	

Analysis was performed using univariate regression and Phi-coefficient. DAS28: disease activity score in 28-joint, ACPA: anti-citrullinated protein/peptide antibody, RF: rheumatoid factor, hs-CRP: highly sensitive C-reactive protein, TNF-α: tumor necrosis factor-alpha.

DISCUSSION

The present study focused on the effect of two SNPs on the severity of inflammation in patients with RA. Additionally, it showed the association of these SNPs with RA susceptibility. The increased levels of TNF-α, hs-CRP, ESR, and the positivity to both RF and ACPA in rheumatoid patients compared to controls and in patients with severe disease compared to mild disease were intensively studied earlier, and the results of these studies agreed with our results [11,19–22]. Rheumatoid arthritis is a multifactorial and polygenic disease [23]. And multiple gene loci affect the disease's susceptibility and severity [24,25]. It's known that TNF-α plays a central role in the RA inflammatory process, and its production is largely affected by SNPs in the TNF-α gene [26,27]. In the current study, there is no association between SNP at position -806 in the promoter region of the TNF gene and susceptibility to RA. The CC genotype was distributed among all controls and 88.9% of patients. Whereas the CT genotype was present in 11.1% of RA patients and none of the controls. The C allele was present in all the patients and controls, while the T allele was present in only 5.6% of patients. One very recent study was done in Iraq that looked at the link between SNPs in the -806 C/T response to biological therapy. The results showed that the CC and CT genotypes were spread out in a way that was similar to the current study [28]. However, these SNPs were studied in another disease. Katkam *et al.* found that 80% of patients with systemic lupus erythematosus and 75% of

controls had the CC genotype, and 18% and 17% had the CT genotype in the patients and controls, respectively [29]. A study on the Chinese population didn't find an association between atrial fibrillation and the -806 C/T SNP [30]. Multiple studies have investigated the association of RA with other SNPs. In the study by Hakamata *et al*., 97% of the GG genotypes of -238 and -308 SNPs were found in both healthy people and people with RA. No link between the genotypes and RA was found [31]. A study in Al-Najaf, Iraq, found a significant association between polymorphisms at -238 and -308 and the susceptibility to the disease [32]. However, our findings need further studies in Iraq and also in different countries with different ethnicities to confirm the results. This study also found that the CC genotype of the (-806 C/T) SNP was more common in people with severe disease (97%) compared to those with mild to moderate disease (82%), while the CT genotype was more common in the mild to moderate disease group (18%). Additionally, the C allele was distributed in both patient groups, while the T allele increased in the mild-moderate group (9.4%). However, these results were statistically non-significant and indicated a weak effect of the (-806 C/T) SNP on the severity of the disease. According to my knowledge, this is the first study to investigate the distribution of the (-806 C/T) SNP among severe and mild-moderate RA patients. One previous Iraqi study investigated the distribution of SNPs among RA patients with different severities; nevertheless, it dealt with different SNPs than the current study SNPs. The results show that there is a big difference between the groups in the number of people with the GG, GA, and AA genotypes in TNF-308 and -283 SNPs [32]. Karray *et al.* (2011) found that sixty-three percent of the non-remission group and only twenty-one percent of the patients with remission RA had the TT genotype. While the CT genotype was more prevalent in the group of remission. Again, these findings don't investigate (-806 C/T) SNP but instead focus on (-1031 C/T) SNP [33]. Our study observed an association between RA disease activity and the (-806 C/T) SNP in all the patients. However, no associations were present between the severe and mild-moderate groups. This controversy might be attributed to the small size of our groups, which may affect the statistical data. This controversy was also observed in studying other genes. Fabris *et al.* determine a correlation with severity when investigating the -238 G/A SNP [34]. In a study that involved seven SNPs in new RA patients, no association between these SNPs and DAS 28 was observed [35]. Our results fail to find any association between the -806 C/T SNP and hs-CRP, TNF-α, RF positivity, or ACPA Positivity. When analyzing the patient group, the same was obtained concerning the severe RA group. However, the association was observed only with hs-CRP within the patient with the mild-moderate disease. These results indicate no effect of the -806 C/T SNP on the severity of RA. A study in Egypt also didn't find an association between hs-CRP, TNF-α, and RF and SNP at position -1031 [36]. El-Hakeim *et al*. found that the levels of hs-CRP, TNF-α, RF, and ACPA were significantly different between the AA, CC, and CA genotypes of the IL-12B gene (rs3212227 A/C) SNPs [37]. Concerning the 857 C/T SNP, the CC genotype was found to be prevalent in 90 % of healthy participants and 76% of the patients, whereas the incidence of the CT genotype was 24% and 10% within the patients and controls, respectively. Furthermore, the C allele was present in all the participants, while the T allele was distributed only in 11.9% of the patients and 5% of the controls. To date, only a single study has investigated the -857 C/T SNPs in Iraqi RA patients. This study was published in March 2022 and investigated the effect of this SNP on etanercept responsiveness. It was found that 78.75% of patients have the CC genotype, and only 21.25% have the CT genotype [38]. However, plenty of research that investigated the association of RA with this SNP worldwide showed a large controversy. Similar findings were shown in the Caucasian population. In this study, 85% of controls and 86% of RA patients contained the CC genotype, and 14% of patients and 13% of controls had the CT genotype [11]. A non-significant association was also reported in a Japanese study. However, the distribution of the CC and CT genotypes was different in comparison to our study [39]. A Chinese case-control study in 452 RA and 373 control participants demonstrated contradictory findings: the CC genotype is distributed in about 45% of patients and 56% of patients, while the CT genotype has an incidence of 48% in patients and 34% in controls, and the TT genotype prevalence was 7 % and 10% in patients and controls, respectively [10]. The ethnic differences between various countries account for the variation. This ethnic diversity was very clear in Hakamat *et al.*, a study that found different distributions of CC and CT genotypes between Chinese, Japanese, and Caucasians [31]. The current study didn't find any differences between the severe and mild-moderate patient groups in the distribution of the CC and CT genotypes or the C and T alleles of the -857 C/T SNP. To my knowledge, no previous authors investigated the prevalence of the 857 C/T SNP among patients with different DAS 28. Samer *et al*. failed to find an association between the CC and CT genotypes and differences in DAS 28 over 6 months [38]. Barton *et al.* don't find differences in the distribution of C and T alleles among patients with erosive and non-erosive diseases [40]. In another report, the incidence of the above genotypes significantly differed between responders and non-responders [41]. According to a previous report, the -857 C/T SNP may affect TNF-α production [42]. This effect is due to the inhibition of TNF-α transcription in the carrier of the T allele [43]. This may exert an effect on the severity of the disease. Our observation doesn't find any relation between SNP at position -857 and DAS 28 in the patients, severe, and mild-moderate groups. Also, no associations were found with hs-CRP, TNF-α, RF positivity, or ACPA positivity in all the study groups except for an association with TNF-α in patients with severe RA. It's complicated to find the effect of SNPs on RA severity because different elements interact and affect the disease severity [5]. To date, no previous studies have investigated these criteria and these

relationships. However, the authors examined different severity markers. In agreement with our findings, there is no association between RA severity and RF in Caucasian patients [44]. One report found an association between the TT genotype of -857 C/T SNP and ACPA levels [45]. Emonts *et al.* also fail to find an association between RA severity and the 857 C/T SNP. However, they classify severity depending on anti-TNF-α therapy [11]. Additionally, an association was also absent between inflammatory polyarthritis severity measured by erosion and no-erosion status and the -857 C/T SNP [36]. Two different polymorphisms (rs3811047 and rs911263) were reported to be associated with RA severity [46,47]. Despite those previous reports, the effect of polymorphisms at position -857 is still in debate. This is partly due to the previously mentioned multiple factors that affect the severity [5]. Another factor could be related to the diversity of RA-severity detentions. Furthermore, the different criteria and study designs were measured in the previous reports.

Study limitations

The small number of participants and the single-center setting might affect the accuracy of the statistical analysis.

Conclusion

We found no associations between the -806 C/T SNP and RA susceptibility. However, an association was found with DAS28 in all patients. Additionally, in patients with mild-moderate disease, a correlation with hs-CRP was demonstrated. We also concluded that the -857 C/T SNP does not affect RA disease activity, susceptibility, or severity.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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