International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Assessment of serum interleukin-17 level and interleukin-17A gene polymorphism in rheumatoid arthritis and systemic lupus erythematosus

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Abstract

RA and SLE are chronic autoimmune disorders that generate disability and low quality of life. The aim of the study was to evaluate the association between IL-17 serum level and IL-17A (rs2275913) gene polymorphism with the susceptibility of both diseases. The current study was conducted on 30 RA patients, 30 SLE patients and 30 healthy control subjects. IL-17 serum levels were assayed via ELISA. IL-17A gene polymorphism was performed using PCR based RFLP analysis. IL-17 serum level was significantly elevated in RA and SLE cases in comparison with to healthy control subjects ($p < 0.001$). ESR and CRP level was significantly elevated in both diseases and correlated with IL-17 high serum levels. There were no significant differences in the genotype and allele frequencies of IL-17A (rs2275913) between controls and patients with both diseases ($P > 0.05$). IL-17 serum level may play a role in pathogenesis of both diseases, and to be beneficial for predicting diseases inflammatory state. IL-17A (rs2275913) SNP isn't a risk factor for and may not be associated with the susceptibility to both diseases.

Keywords: IL-17A, Rheumatoid arthritis, Systemic lupus erythematous, SNP.

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1. Introduction

Interleukin 17A (IL-17A) is a proinflammatory protein that's synthesized mainly by T helper 17 (Th17) cells; a subset of T helper cells [1]. It plays a very important role in the developing and progression of inflammatory as well as autoimmune disorders [2]. It induces monocyte and neutrophil recruitment in addition to promoting the synthesis of chemokines and proinflammatory cytokines including TNF-α and IL-1β [3]. Among the complex network of inflammatory cells involved in the etiopathogenesis of autoimmune disorders including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), Th17 cells and IL-17A contribute to cartilage and bone destruction in these diseases by binding IL-17 specific receptors present on fibroblasts, endothelium, and epithelium. Moreover, it has been revealed that there is elevated expression of IL-17 mRNA in the joints of these patients [4]. Both diseases are characterized by severe inflammation of the synovial membranes of the joint capsule and tendons (synovitis) [5]. Clinically, symptoms range from chronic pain, lost joint functions, and deformities, to disability as well as systemic complications [6]. The precise etiopathogenesis is still unclear, yet evidence has revealed that it is affected by environmental, genetic, hormonal, and epigenetic factors; such factors function together in the immune system and lead to abnormalities [7]. Interleukin-17A is located on chromosome 6P12 [8]. The IL-17A 197 (rs2275913) polymorphism is present upstream of the IL-17A gene. It's present within a binding motif for the nuclear factor of activated T-cells (NFAT) which is an essential regulator of IL-17 expression leading to elevated release of IL-17, probably because of the elevated affinity of resulting sequence for NFAT. Accordingly, it may be involved in the pathogenesis of both SLE and RA [9].

Therefore, in this study, we aimed to evaluate the correlation between the serum levels of IL-17 and Th17A gene polymorphism and susceptibility to both RA and SLE.

2. Patients and Methods

2.1. Study subjects and design

This was a case control study carried out in Medical Microbiology and Immunology, Internal Medicine and Rheumatology departments of Faculty of Medicine, Beni-Suef University, Egypt from June 2020 to October 2021. The study included 30 clinically diagnosed RA patients (23 women and 7 men) with a mean age of 43.1 (±11.8) years, 30 clinically diagnosed SLE patients (26 women and 4 men) with a mean age of 40.1 (±12.1) years. In addition, 30 apparently healthy participants who were matched for age (mean age of 39(±9.7) years) and sex (25 females and 5 males) were included. Approval of the study was obtained from the local Ethics Committee of the Faculty of Medicine, Beni-Suef University, Egypt (approval No: FMBSUREC/08032020/ Abdel Fattah). All participants signed written informed consents.

2.2. Inclusion and exclusion criteria

All recruited cases fulfilled the criteria for RA and SLE diagnosis [12-13]. However, patients suffering from malignancies, chronic renal diseases, HTN, DM mellitus, infections, positive HCV antibodies, other rheumatological or CT diseases were excluded from the present study [12].

2.3. Clinical and laboratory assessment

A detailed history of any chronic inflammatory disease, history of corticosteroid treatment, cancer, and any other form of arthritis was collected. Laboratory evaluations, including complete blood count (CBC), ESR, and CRP, were performed or collected from the patients' clinical files.

2.4. Assessment of serum IL-17 levels

Blood samples were collected from patients and controls, the samples were centrifuged at 5000 rpm for 3 minutes to separate the serum which was stored at −20 °C until use. IL-17 serum level was measured via ELISA (IL-17 Human ELISA Kit, Cat. No. K0331194, Koma biotechnic, Korea) carried out according to the manufacturer's protocol.

2.5. Genotyping of OPN and IL-17A polymorphisms via PCR-RFLP

Three milliliters of whole blood were collected on EDTA from all included patients and controls. Extraction of genomic DNA was carried out via the use of a commercial kit (Kit for the isolation of DNA from whole blood, Serum &Plasma. Cat. No. PR881612, Cinna Pure DNA, Tehran, IRAN) in accordance with the manufacturer's protocol. Storage of DNA was performed at −20 °C until use. For IL-17A (rs2275913) polymorphism, PCR amplification of IL-17A 197 (rs2275913) was performed via the following method:

- Forward primer: 5′-TCT CCA TCT CCA TCA CCT TTG-3′.
- Reverse primer: 5′-GTC CAA ATC AGC AAGAGC ATC-3′.

The PCR cycling conditions included a denaturation step at 94°C for five minutes, followed by thirty cycles of denaturation for one minute at the same temperature, annealing for one minute at 57 °C, and extension for one minute at 72 °C. Finally, the ultimate extension for five minutes at 72 °C was performed using a (Biometra TAdvanced S Gradient 96 Thermal Cycler). was digestion of PCR products via the restriction enzyme was carried out, XagI (New England Biolabs, Inc., MA USA) according to the manufacturer's instructions followed by analysis in 2% agarose gel stained with ethidium bromide and ultraviolet light for visualization.

2.6. Statistical Analysis

The data were coded for analysis using SPSS version 22. Qualitative variables were described as numbers, and percentages (%). Descriptive statistics were presented for quantitative variables as the mean, standard deviation (SD), range and median. Suitable statistical tests of significance were used Chi-square ($\chi 2$) tests for categorical data and independent sample t-test for numerical data. Spearman/Pearson correlation was conducted to assess the association between scale variables. ROC curve was used to determine the optimal cut-off for predicting the type of disease compared with the control. P-values ≤ 0.05 were considered to indicate statistical significance.

3. Results

3.1. Demographic and laboratory data of the study subjects

The demographic criteria of the participants who were statistically comparable for age and gender ranged between 43.1 (±11.8) years for patients with RA, 40.1 (±12.1) years for patients with SLE and 39(±9.7) years for control. The RA cases included 23 (76.7%) female and 7 (23.3%) males, while SLE cases included 26 (86.7%) female and 4 (13.3%) males. There was no significant difference between the three groups regarding their age and sex. There was statistically difference between the SLE and RA groups compared to control group regarding their level of CRP and ESR. CRP was significantly higher in SLE than RA (Table 1).

3.2. Assay of serum IL-17A levels

There were statistically significant differences between RA and SLE cases in comparison with the control subjects ($P < 0.001$) (Table 2). To detect the ability of plasma IL-17 to predict RA and SLE, at a cut-off of 9.3 with 80% sensitivity and 63.3% specificity suggested that IL-17 can identify RA (Figure 1 & Table 3). Furthermore, IL-17 marker could significantly predict the presence of SLE at cut-off 10 with 80% sensitivity and 73.3% specificity (Figure 2& Table 4). A significant strong linear positive correlation between IL-17 levels and CRP and ESR in both groups was detected.

3.3. Genotypic distribution and allelic frequency of IL-17A (rs2275913)

The size of the amplified PCR product was 815 bp. Restriction digestion for the homozygous GG genotype yielded 286, 259 and 270 bp fragments.

On the other hand, homozygous AA genotype yielded 286 and 529 bp fragments, while the heterozygous AG genotype produced a combination of both fragments (Figure 3). The genotypic distribution of interleukin-17A (rs2275913) polymorphisms was in Hardy-Weinberg equilibrium in RA, SLE patients as well as controls. The frequencies of the AA, AG, and GG genotypes were 20 percent, 43.3 percent, and 36.7 percent, in RA group, were 30

percent, 26.7 percent, and 43.3 percent respectively in SLE group and were 23.16 percent, 45.26 percent and 31.58 percent respectively in the controls. No significant differences in the genotype and allele frequency were observed.

4. Discussion

Systemic autoimmune disorders including SLE and RA are characterized by the presence of marked autoimmune responses, involving inherent as well as acquired immune systems. The etiology remains a mystery despite the pathogenesis appearing to be due to a complicated interaction between genetic and environmental factors [13]. Cytokines have a pivotal function in the pathogenesis of both diseases especially IL-17 that has a potent proinflammatory effect produced mainly by Th-17. The Th17/IL-17 axis enhances and promotes repetitive tissue destruction along with maladaptive repair, resulting in fibrosis, loss of architecture, and loss of organs functions [14]. The present study revealed significantly high levels of CRP and ESR among RA patients compared with the control group. Kim et al., (2013), Al-Saadany et al., (2016) and Wang et al., (2020) documented similar findings [15-17]. Nevertheless, Raza et al., (2005) reported non- significant differences between the RA group and controls regarding CRP and ESR levels [18]. Significant differences in the levels of CRP and ESR between SLE cases, and control subjects were obtained in the present investigation. Concurring results were demonstrated by Radwan et al., (2021) study who documented high levels of CRP and ESR between SLE patients [19]. In contrary with the previous results, Metoni et al., (2015) found non-significant correlation between CRP and ESR level and SLE patients when compared to controls [20]. These different laboratory investigations and results between different cohorts can be attributed to the ethnic and socioeconomic disparities. It may be also due to the lack of a central laboratory to ensure the accuracy of the laboratory results. Interestingly, IL-17 serum level was reported to have significant higher levels in RA cases than controls (P-value<0.001), which agreed with other studies of Kellner (2013), Sarkar et al., (2014) and Dhaouadi et al., (2018) who reported that IL-17 production among RA cases was elevated in comparison with that of controls ($P < 0.001$) [5,21-22]. It also agreed with other studies of Farag et al., (2020) and Ibrahim et al., (2023) who reported that circulating IL-17 level was consistently and significantly elevated in subjects diagnosed as having RA [23-24]. Regarding the diagnostic values of IL-17 by using ROC curve, the current study showed that the IL-17 marker can significantly predict the presence of RA at a cut-off of 9.3 pg/ml and the area under the ROC curve (AUC) was 0.792 with 80% sensitivity and 63.3% specificity. Dhaouadi et al., (2018); showed a cut-off value of 18.25 pg/ml with a 61.7% sensitivity; specificity was about 100% and AUC is 0.894 pg/ml [5]. Both results are quite similar to our results. These results were different from the findings in another study made by Marwa et al., (2017) in which for a cut-off value of 23 pg/ml of serum IL-17, the sensitivity was 55.56 percent and the specificity was one hundred percent with AUC of 0.91 pg/ml [25]. Meanwhile, in SLE patients, the present data suggested that IL-17 serum level is a risk factor for this autoimmune disease with significantly higher levels among SLE patients than controls (P-value<0.001). This concedes with the data obtained from previous studies of Vincent et al., (2013), Saber et al., (2017), Jin et al., (2018), Tang et al., (2019), Shen et al., (2020) and Mostafa et al., (2022); who demonstrated the presence of an association between higher serum IL-17 level and SLE susceptibility [26-31]. Nevertheless, a non-significant correlation was obtained between IL-17 serum level among the SLE cases and control group (7.24 pg/ml and 5.76 pg/ml, respectively) in the study of Hristova et al., (2021) [32]. ROC curve analysis for IL-17 among SLE cases, as a predictor of disease activity, revealed a cut-off level of 10 pg/ml, AUC of 0.793 pg/ml with 80% sensitivity and 73.3% specificity. This was lower than the cut-off value 19.7 pg/ml and AUC 0.95 pg/ml documented by Galil et al., (2015) [33]. By using ROC curve analysis, Tang et al., (2019); also documented a 33.95 pg/mL cut-off value with AUC= 0.616 pg/ml [29]. The limitations and variable results of these studies can be explained by the small numbers of patients in subgroups which reduces the statistical power. The present study denoted a significant association between serum level of IL-17 and ESR, and CRP levels; as indicators for inflammation in RA patients. The same results were previously reported in RA cases than in control subjects in a study of Rosu et al., (2012) and Al-Saadany et al., (2016) [16,34]. On the other side, Metawi et al., (2011) found that serum & synovial IL-17 level among RA cases had non-significant correlation with ESR [35]. In the same context, higher levels of ESR and CRP showed significant correlations with elevated serum IL-17 level among SLE cases. This agrees with the work of Radwan et al., (2012) who observed potential correlations between serum IL-17 levels and ESR in SLE cases [19]. On the contrary, the result of Galil et al., (2015) and Metoni et al., (2015) studies who found lack of correlation between CRP and ESR level and IL-17 serum level among SLE patients [20,33]. IL-17A (rs2275913) polymorphism was analyzed in the current work detecting a non-statistically significant association between IL-17A studied polymorphisms and RA susceptibility ($P>0.05$) with genotypic and allelic frequencies of 20%, 13%, and 11%, for AA, AG, GG genotypes respectively. The frequencies A and G alleles were 41.7%, and 58.3% respectively with codominance of G allele. In conjunction with the current data, earlier study by Montúfar-Robles et al., (2019) reported that IL-17A -197G/A SNP had the same genotypic and allelic frequency in cases with RA and among controls suggesting that it isn't a risk factor for RA with genotypic and allelic frequencies between RA cases and control subjects with a percentage of 2.4 %, 23.8%, and 73.8%, for AA, AG, GG genotypes respectively [4]. The frequency of A and G alleles were 14.3%, and 85.7% respectively with also G is the codominant allele.

The results are also in accordance with a previous report in the Tunisian population made by Dhaouadi et al., (2018) who documented genotypic and allelic frequencies of 15.6%, 74.8%, and 73.8%, for AA, AG, GG genotypes respectively, 53.1%, and 46.9 % A and G alleles respectively among RA patients [5]. Another meta-analysis obtained from 10 studies made by Mohammadi et al., (2019); didn't confirm the significant associations of IL17A gene rs2275913 polymorphism and RA susceptibility. Contrastingly, the meta-analysis performed by Shao et al., (2021); postulated that rs2275913 G allele elevated the possibility of RA [37].

Table 1: Comparison between the studied groups as regards the serum concentration of CRP and ESR.

Items	Disease	Control (no=30)	P-value
	RA **(no=30)**		
CRP (mg/dl)	20.9±8	9.6±2	<0.001*
ESR (mm/hr)	47.9±20.6	25.8±18.2	<0.001*
	SLE **(no=30)**		
CRP (mg/dl)	59.3±15	9.6±2	<0.001*
ESR (mm/hr)	60.6±38.1	25.8±18.2	<0.001*

*P-value is significant

Table 2: Comparison between the two groups as regards the serum concentration of Interleukin 17.

Items	Control (no=30)	Disease
		RA (no=30)
IL-17 (pg/ml)	7±4.6	11.8±3.6
P-value		<0.001*
		SLE (no=30)
IL-17 (pg/ml)	7±4.6	13±6.36
P-value		<0.001*

*P-value is significant

Table 3: Area under the ROC curve for prediction of RA from IL-17 serum level.

AUC (95% CI)	P-value	Cut off (pg/ml)	sensitivity	Specificity
0.792 (0.677-0.907)	<0.001*	9.3	80%	63.3%

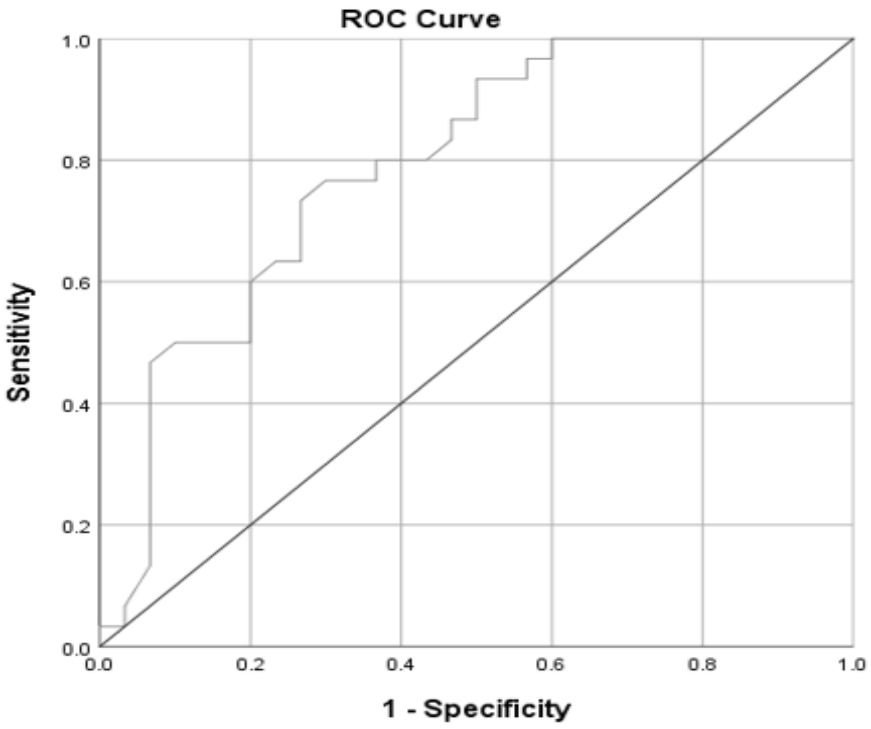

Figure 1: ROC curve for prediction of RA from IL-17 serum level

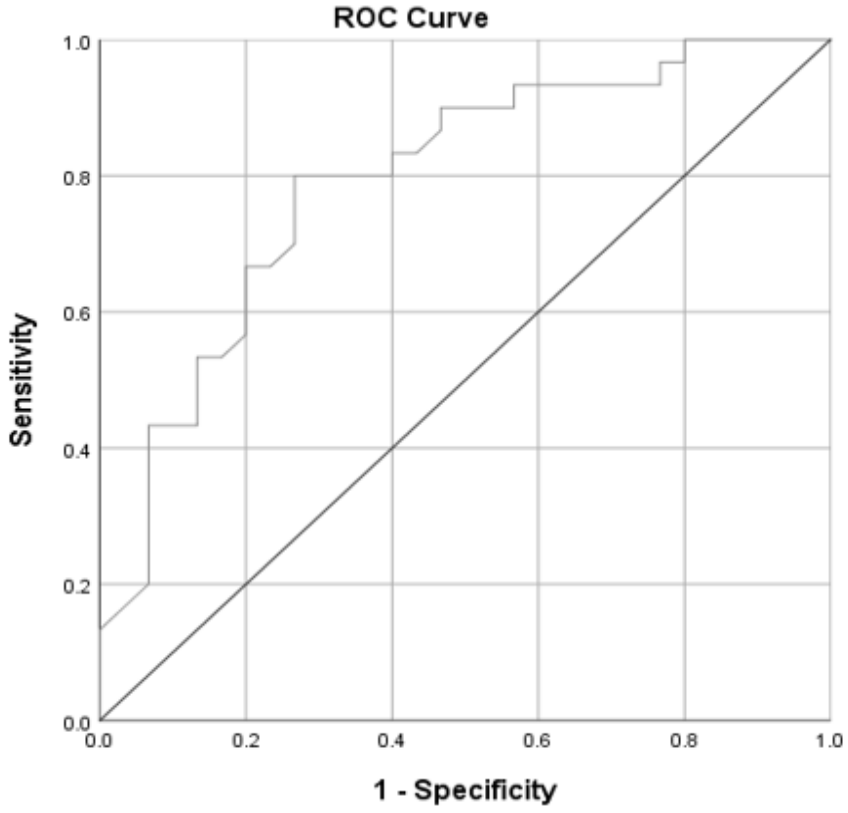

Figure 2: ROC curve for prediction of SLE from IL-17 serum level.

Table 4: Area under the ROC curve for predicting SLE from IL-17 serum level.

Area under curve (95% CI)	P-value	Cut off (pg/ml)	Sensitivity	Specificity
0.793 (0.678-0.907)	<0.001*	10	80%	73.3%

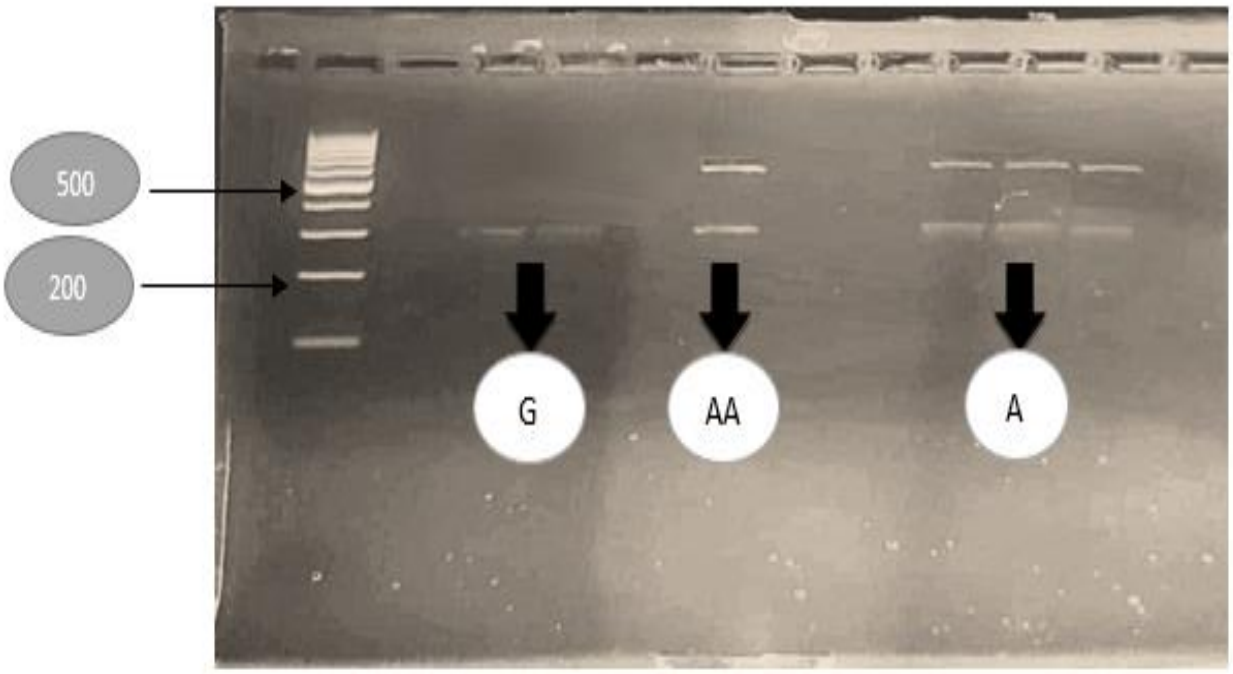

Figure 3: The three genotypes of IL-17 gene polymorphism.

Additionally, Garcia De La Pena et al., (2017); stated that the IL-17A rs2275913 polymorphism is accompanied susceptibility [38]. In a similar context, non-significant differences were determined for IL-17 rs2275913 SNP in genotypic distribution or allele frequency ($p>0.05$) between SLE cases and controls, with genotypic percentages of 30, 26.7, and 43.3 % for AA, AG, GG genotypes respectively, and allelic percentages of 43.3, and 56.7 % for A and G alleles respectively with codominance of G allele among SLE patients. Earlier previous studies conducted by Hammad et al., (2016) on Egyptian children concluded that the lack of significant difference in genotype as well as allele frequency of IL-17A gene polymorphisms among SLE cases and controls [39]. The frequencies were 4.3, 38.3, 57.4 % for AA, AG, GG genotypes respectively, and 23.5, and 76.5 % for A and G alleles respectively with codominance of G allele concurring with the present results. Research by Montúfar-Robles et al., (2019) also reported that IL-17A -197G/A SNP had the same genotypic distribution and allelic frequency between SLE cases and controls suggesting that it isn't a risk factor for SLE; the frequencies were 4.1, 22.9, and 73%, for AA, AG, GG genotypes respectively. A and G alleles frequencies were 15.5, and 84.5 % respectively with codominance of G allel [4]. In contrast, the study done by Elkoumi et al., (2020); concluded that the IL-17 rs2275913 A allele and A/A genotype might participate in the vulnerability to SLE in Egyptian children as well as adolescents [40]. The frequencies were 27, 34, 39, 46, and 54% for AA, AG, GG genotypes, A and G alleles respectively. The IL-17 rs2275913 A/A genotype along with the A allele were accompanied by significant elevation of serum IL-17 level among studied cases (mean = 85.6 ± 23.7 pg/mL for the A/A genotype and 74.8 ± 25.9 pg/mL for the A allele; $p<0.01$) in comparison with other IL-17 genotypes & G allele. The current study revealed that IL-17 A gene polymorphism has non- significant differences as regard genotypes and allele frequencies between control subjects and RA patients or SLE patients, suggesting that they may not be related to the vulnerability to both diseases among Egyptian population. Interestingly, all the earlier studies haven't suggested their conclusions. It's reasonable to contemplate that the principal cause for such contradictory results might be because of the differences in allelic distribution between various ethnic populations. It may be also related to the sample size, different age, and sex groups.

5. Conclusions

This study indicated that the level of IL-17 is increased in serum of patient with RA and SLE compared to healthy controls, so it can be used as a biomarker to detect disease susceptibility. Furthermore, the elevated levels of IL-17 appear to correlate with the inflammatory markers CRP and ESR, which seems to be beneficial for predicting diseases inflammatory state. In contrast, no association between IL-17A polymorphism, rs2275913 (G/A) gene polymorphism, and the risk of both RA and SLE was found. The IL-17 rs2275913 did not seem to influence RA and SLE susceptibility. Further studies that evaluate other interleukin 17A and IL 17F polymorphisms and their association with diseases activity and severity would be interesting to help with understanding their role in the pathogenesis of RA and SLE. The current study had some limitations that may lead to false results such as small sized sample that might not sufficient for the detection of an association of the gene with RA and SLE.

Conflict of interest

None.

Funding

No funding sources.

Acknowledgements

The authors offer great thanks to all participants who helped all through the process of the research.

References

[1] D. A. B. Rex, S. Dagamajalu, M. M. Gouda, G. P. Suchitha, J. Chanderasekaran, R. Raju, Y. P. Bhandary. (2023). A comprehensive network map of IL-17A signaling pathway. Journal of Cell Communication and Signaling. 17 (1): 209-215.

[2] A. M. Shah, R. Zamora, Y. Vodovotz. (2023). Interleukin-17 as a spatiotemporal bridge from acute to chronic inflammation: Novel insights from computational modeling. WIREs Mechanisms of Disease. 15 (3): e1599.

[3] C. Chizzolini, A. M. Dufour, N. C. Brembilla. (2018). Is there a role for IL-17 in the pathogenesis of systemic sclerosis? Immunology Letters. 195: 61-67.

[4] I. Montúfar-Robles, R. E. Barbosa-Cobos, I. Alemán-Ávila, J. Ramírez-Bello. (2019). IL-17A haplotype confers susceptibility to systemic lupus erythematosus but not to rheumatoid arthritis in Mexican patients. International Journal of Rheumatic Diseases. 22 (3): 473-479.

[5] T. Dhaouadi, M. Chahbi, Y. Haouami, I. Sfar, L. Abdelmoula, T. Ben Abdallah, Y. Gorgi. (2018). IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. PloS one. 13 (3): e0194883.

[6] B. Razi, S. E. Reykandeh, S. Alizadeh, A. Amirzargar, A. Saghazadeh, N. Rezaei. (2019). TIM family gene polymorphism and susceptibility to rheumatoid arthritis: Systematic review and meta-analysis. PLoS One. 14 (2): e0211146.

[7] M. P. Mireles-Canales, S. A. González-Chávez, C. M. Quiñonez-Flores, E. A. León-López, C. Pacheco-Tena. (2018). DNA damage and deficiencies in the mechanisms of its repair: implications in the pathogenesis of systemic lupus erythematosus. Journal of Immunology Research, 2018.

[8] J. M. Reynolds, P. Angkasekwinai, C. Dong. (2010). IL-17 family member cytokines: regulation and function in innate immunity. Cytokine & growth factor reviews. 21 (6): 413-423.

[9] H. F. Pasha, E. A. Tantawy, M. A. Youssef. (2019). Osteopontin and interleukin-17A genes polymorphisms in Egyptian systemic lupus erythematosus patients: a relation to disease activity and severity. Gene. 702: 107-113.

[10] J. H. Humphreys, S. M. Verstappen, C. A. Scire, T. Uhlig, B. Fautrel, T. Sokka, D. P. Symmons. (2014). How Do We Classify Rheumatoid Arthritis in Established Disease—Can We Apply the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria? The Journal of Rheumatology. 41 (12): 2347-2351.

[11] M. Aringer, K. Costenbader, D. Daikh, R. Brinks, M. Mosca, R. Ramsey-Goldman, S. R. Johnson. (2019). 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis & rheumatology. 71 (9): 1400-1412.

[12] S. Ghalamkari, M. Nasiri, S. Ariannia, R. Farrokhseresht. (2017). G-protein coupled-receptor 65 5´ UTR gene polymorphism in the pathogenesis of systemic lupus erythematosus. Rheumatology Research. 2 (4): 139-143.

[13] L. Ortíz-Fernández, J. Martín, M. E. Alarcón-Riquelme. (2023). A summary on the genetics of systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and Sjögren's syndrome. Clinical Reviews in Allergy & Immunology. 64 (3): 392-411.

[14] F. C. Paquissi, H. Abensur. (2021). The Th17/IL-17 axis and kidney diseases, with focus on lupus nephritis. Frontiers in Medicine. 8: 654912.

[15] J. Kim, S. Kang, J. Kim, G. Kwon, S. Koo. (2013). Elevated levels of T helper 17 cells are associated with disease activity in patients with rheumatoid arthritis. Annals of laboratory medicine. 33 (1): 52.

[16] H. M. Al-Saadany, M. S. Hussein, R. A. Gaber, H. A. Zaytoun. (2016). Th-17 cells and serum IL-17 in rheumatoid arthritis patients: Correlation with disease activity and severity. The Egyptian Rheumatologist. 38 (1): 1-7.

[17] J. Wang, H. Xi, K. Zhang, Z. Li, L. Li, J. Chen, Z. Lou. (2020). Circulating C-Reactive Protein to Prealbumin Ratio and Prealbumin to Fibrinogen Ratio are Two Promising Inflammatory Markers Associated with Disease Activity in Rheumatoid Arthritis. Clinical Laboratory. 86 (5).

[18] K. Raza, F. Falciani, S. J. Curnow, E. J. Ross, C. Y. Lee, A. N. Akbar, M. Salmon. (2005). Early

rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. Arthritis research & therapy. 7: 1-12.

[19] N. Radwan, M. T. Hamza, I. M. El Ghareeb, M. H. Ezzat. (2021). Serum interleukin-17 expression in a group of Egyptian patients with juvenile systemic lupus erythematosus. Egyptian Journal of Pediatric Allergy and Immunology. 19 (2): 97-103.

[20] A. Metoni, P. Balanescu, A. Dima, E. Balanescu, C. Badea, R. Ionescu, D. Matei. (2015). Interleukin-17-association to silent lupus nephritis and disease activity. Journal of Translational Medicine and Research. 20 (2): 71-75.

[21] H. Kellner. (2013). Targeting interleukin-17 in patients with active rheumatoid arthritis: rationale and clinical potential. Therapeutic advances in musculoskeletal disease. 5 (3): 141-152.

[22] S. Sarkar, S. Justa, M. Brucks, J. Endres, D. A. Fox, X. Zhou, S. R. Bommireddy. (2014). Interleukin (IL)-17A, F and AF in inflammation: a study in collagen-induced arthritis and rheumatoid arthritis. Clinical & Experimental Immunology. 177 (3): 652-661.

[23] M. A. Farag, F. E. El Debaky, S. M. Abd El-Rahman, S. M. Abd el-khalek, R. M. Fawzy. (2020). Serum and synovial fluid interleukin-17 concentrations in rheumatoid arthritis patients: Relation to disease activity, radiographic severity and power Doppler ultrasound. The Egyptian Rheumatologist. 42 (3): 171-175.

[24] M. E. Ibrahim, S. A. Fattah, M. Abdelfattah, E. Mehanna. (2023). AB0003 interleukin 17a rs2275913 gene polymorphism is related to severity and disease activity of rheumatoid arthritis and increased serum il17a levels in egyptian patients.

[25] O. S. Marwa, T. Kalthoum, K. Wajih, H. Kamel. (2017). Association of IL17A and IL17F genes with rheumatoid arthritis disease and the impact of genetic polymorphisms on response to treatment. Immunology letters. 183: 24-36.

[26] F. B. Vincent, M. Northcott, A. Hoi, F. Mackay, E.F. Morand. (2013). Clinical associations of serum interleukin-17 in systemic lupus erythematosus. Arthritis research & therapy. 15: 1-9.

[27] N. Z. Saber, S. H. Maroof, D. A. Soliman, M. S. Fathi. (2017). Expression of T helper 17 cells and interleukin 17 in lupus nephritis patients. The Egyptian Rheumatologist. 39 (3): 151-157.

[28] L. Jin, R. Bai, J. Zhou, W. Shi, L. Xu, J. Sheng, H. Yuan. (2018). Association of serum T cell immunoglobulin domain and mucin-3 and interleukin-17 with systemic lupus erythematosus. Medical science monitor basic research. 24: 168.

[29] Y. Tang, H. Tao, Y. Gong, F. Chen, C. Li, X. Yang. (2019). Changes of serum IL-6, IL-17, and complements in systemic lupus erythematosus patients. Journal of Interferon & Cytokine Research. 39 (7): 410-415.

[30] H. H. Shen, Y. Fan, Y. N. Wang, C. N. Zhao, Z. K. Zhang, H. F. Pan, G. C. Wu. (2020). Elevated circulating interleukin-17 levels in patients with systemic lupus erythematosus: a meta-analysis. Immunological Investigations. 49 (6): 662-675.

[31] A. T. Mostafa, A. A. Abd Allah, S. A. A. Abd Alwahed, R. Hafez, S. Hussien, R.M. Bakry. (2022). Interleukin 17 role as a biomarker in Systemic Lupus Erythematosus patients. Sohag Medical Journal. 26 (1): 42-50.

[32] M. Hristova, Z. Kamenarska, G. Dzhebir, S. Nikolova, R. Hristova, K. Mihova, L. Dourmishev. (2021). The role of IL-17 rs2275913, IL-17RC rs708567 and TGFB1 rs1800469 SNPs and IL-17A serum levels in patients with lupus nephritis. Rheumatology international. 41 (12): 2205-2213.

[33] S. M. A. Galil, N. Ezzeldin, M. E. El-Boshy. (2015). The role of serum IL-17 and IL-6 as biomarkers of disease activity and predictors of remission in patients with lupus nephritis. Cytokine. 76 (2): 280-287.

[34] A. Rosu, C. L. Margaritescu, A. Stepan, A. Musetescu, M. Ene. (2012). IL-17 patterns in synovium, serum and synovial fluid from treatment-naive, early rheumatoid arthritis patients. Romanian Journal of Morphology and Embryology. 53 (1): 73-80.

[35] S. A. Metawi, D. Abbas, M. M. Kamal, M. K. Ibrahim. (2011). Serum and synovial fluid levels of interleukin-17 in correlation with disease activity in patients with RA. Clinical rheumatology. 30: 1201-1207.

[36] F. S. Mohammadi, S. Aslani, S. Mostafaei, A. Jamshidi, P. Riahi, M. Mahmoudi. (2019). Are genetic variations in IL-21–IL-23R–IL-17A cytokine axis involved in a pathogenic pathway of rheumatoid arthritis? Bayesian hierarchical meta-analysis. Journal of cellular physiology. 234 (10): 17159-17171.

[37] M. Shao, W. Xu, H. Yang, Y. Chen, X. Gao, S. Xu, F. Pan. (2021). Interleukin-17 Gene Polymorphism (Rs2275913 G/A, Rs763780 C/T) in Rheumatoid arthritis : Meta-analysis Based on Ethnicity. Immunological Investigations. 50 (6): 685-699.

[38] M. Garcia De La Pena, N. E. Herrera-González, E. Garrido Guerrero, A. Galicia Lopez, G. Pozo Molina, R. Méndez Cruz. (2017). Polymorphism rs2275913 of Interleukin-17A is related to more intensive therapy with disease-modifying anti rheumatic drugs in Rheumatoid Arthritis Mexican patients. Acta reumatologica portuguesa. (2).

[39] A. Hammad, Y. M. Mosaad, E. M. Hammad, S. Elhanbly, S. R. El-Bassiony, M. F. Al-Harrass, I. M. Fawzy. (2016). Interleukin-17A rs2275913, Interleukin-17F rs763780 and rs2397084 gene polymorphisms as possible risk factors in Juvenile lupus and lupus related nephritis. Autoimmunity. 49 (1): 31-40.

[40] M. A. Elkoumi, M. A. Allah, F. Y. Mohamed, N. F. Boraey, S. H. Abdellatif, M. M. Shehab, M. A. Farghaly. (2020). Association of interleukin-17A gene polymorphisms and susceptibility to systemic lupus erythematosus in Egyptian children and adolescents: a multi-centre study. Lupus. 29 (7): 767-775.