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Table 4: Association of IL-10 (1082 G/A) polymorphisms with clinical manifestations in SLE patients (n=75)

Clinical manifestations	Genotype GA/AA (n=59)	Genotype GG (n=16)	OR (95% CI)	p-value
Rash	34(57.6%)	5(31.3%)	2.99(0.93-9.70)	0.061
Oral ulcer	19(32.2%)	4(25.0%)	1.43(0.41-5.01)	0.579
Arthralgia	38(64.4%)	13(81.3%)	0.42(0.11-1.63)	0.2
Lupus nephritis	20(33.9%)	5(31.3%)	1.13(0.34-3.70)	0.842
Hematological disorder	1(1.7%)	1(6.3%)	0.26(0.02-4.38)	0.316

Note: *significant
P value reached from Chi-square test

Table 5: Association of IL-10 (-819 T/C) polymorphisms with clinical manifestations in SLE patients (n=75)

Clinical manifestations	Genotype TC/CC (n=61)	Genotype TT (n=14)	OR (95% CI)	p-value
Rash	33(54.1%)	6(42.9%)	1.57(0.49-5.07)	0.448
Oral ulcer	22(36.1%)	1(7.1%)	7.33(0.90-59.9)	0.034*
Arthralgia	39(63.9%)	12(85.7%)	0.30(0.06-1.44)	0.115
Lupus nephritis	22(36.1%)	3(21.4%)	2.07(0.52-8.22)	0.295
Hematological disorder	2(3.3%)	0(0.0%)	-	0.492

Note: *significant
P value reached from Chi-square test

Table 6: Association of IL-10 (-592 C/A) polymorphisms with clinical manifestations in SLE patients (n=75)

Clinical manifestations	Genotype CA/AA (n=57)	Genotype CC (n=18)	OR (95% CI)	p-value
Rash	32(56.10%)	7(38.9%)	2.01(0.68-5.94)	0.202
Oral ulcer	20(35.1%)	3(16.7%)	2.70(0.70-10.46)	0.14
Arthralgia	39(68.4%)	12(66.7%)	1.08(0.35-3.35)	0.889
Lupus nephritis	19(33.3%)	6(33.3%)	1.00(0.33-3.08)	1
Hematological disorder	2(3.5%)	0(0.0%)	-	0.421

Note: *significant
P value reached from Chi-square test

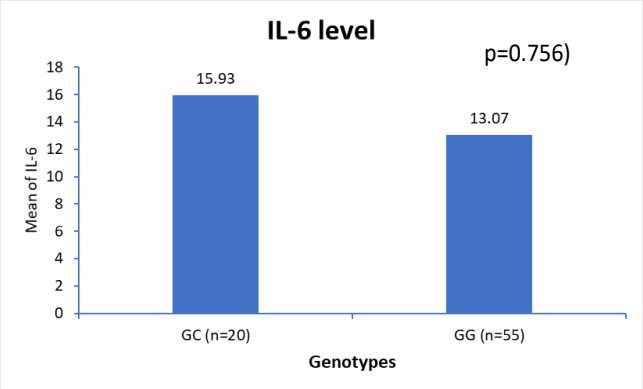

Figure 3: Bar diagram showing IL-6 level according to genotype distribution IL-6 174G/C

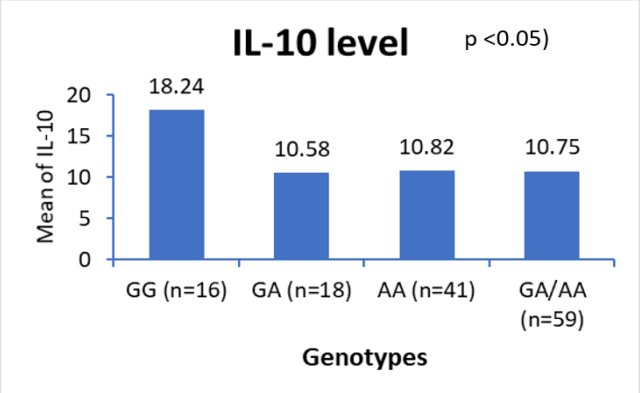

Figure 4a: Bar diagram showing IL-10 level according to Genotypes distribution IL-10 1082G/A

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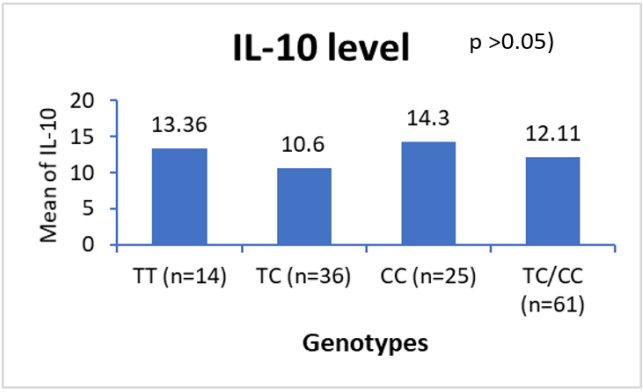

Figure 4b: Bar diagram showing IL-10 level according to Genotypes distribution IL-10 819T/C.

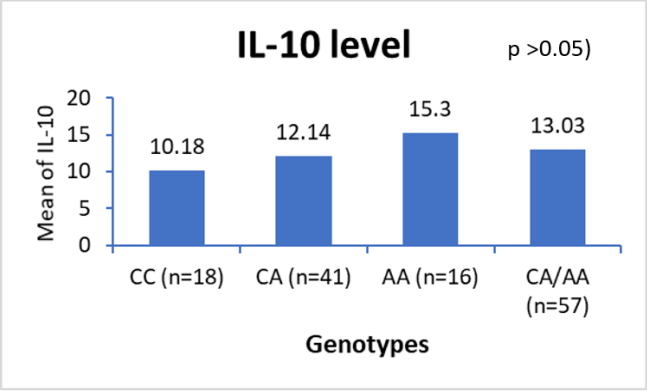

Figure 4c: Bar diagram showing IL-10 level according to Genotypes distribution IL-10 592C/A

Note:

p-value reached from Mann-Whitney U test.

P <0.05 considered as statically significant.

Discussion

SLE is a chronic systemic disease with variable clinical presentation. The exact pathological mechanisms of SLE remains elusive, and the etiology of SLE is known to be multifactorial, involving genes, sex hormones, and environmental factors including sunlight, drugs, and infections. Cytokines have been suggested to be involved in the pathogenesis of SLE, as they are fundamental components in the regulation of immune response, intervening in both cellular and humoral responses. Several immunogenetic studies demonstrated that polymorphisms at several loci, including the major histocompatibility complex, complement proteins, immunoglobulin receptors, cytokine genes and are associated with SLE, implying that the gene products of these loci are involved in the pathogenesis of SLE [24].

The high prevalence of female in this study agreed with a study conducted in Iraq [25], where female represented 98% of total patients involved in that study. The female predominance was reported 88% among 1,103 patients by a largest American study [26]. This finding indicates that female sex is considered as one of the predisposing factors of the disease and the hormones (oestrogen) contribute to increase the prevalence of SLE among women. The gene known to contribute to the pathogenesis of SLE is CD40 which is located on chromosome X [27].

Several genome-wide association studies (GWAS) have confirmed non-HLA genes are linked with SLE. IL-6 is involved in various inflammatory and proliferative diseases, as well as being proposed as a strong candidate for novel targeted biological therapeutics. It has been reported that IL-6 gene polymorphism is associated with susceptibility and outcome of a variety of acute and chronic inflammatory diseases including rheumatoid arthritis, diabetes mellitus, atherosclerosis, Alzheimer disease and juvenile chronic polyarthritis [9]. The earlier studies have identified the polymorphisms in the IL-6 gene locus, which are known to be associated with SLE susceptibility and disease progression [28]. The increased level of IL-6 in SLE patients may derive from constitutively increased cellular production. Peripheral blood mononuclear cell (PBMC) from SLE patients produce significantly more IL-6 upon in vitro stimulation than PBMC from normal control [29]. In the study the homozygous GG genotype of IL-6 (-174G/C) was significantly found in SLE patients compared to healthy controls. The heterozygous GC genotype was found more in healthy controls than SLE patients (26.7%). G allele was found to be significantly higher in cases than control group. Similarly, a study conducted in Malaysia, confirmed the association of GG genotype and G allele of IL-6 (-174G/C) with SLE. In this study it is also suggested that the C allele has a masking effect over the G allele in the heterozygous G/C genotype, which may be due to a complex interaction of both alleles when present co-dominently [30]. In contrast, a study in German Caucasians SLE patients, the IL-6 (-174G/C) polymorphism does not contribute to SLE susceptibility [18]. In this study, any phenotypic association of SLE with the IL-6 (174G/C) polymorphism was not observed. On the other hand, Scotte et al (2001) found that the G allele of IL-6 (-174G/C) is responsible for the presentation of discoid skin leisons in Caucasian German SLE patients [29].

It has been suggested that certain SNPs in the promoter region of IL-10 could be associated with the elevated expression of its cytokine and increased susceptibility to various inflammatory and autoimmune disorders such as asthma, rheumatoid arthritis and SLE [31]. Increased production of IL-10 by peripheral blood mononuclear cells has been associated with-592A allele [32]. In this study the genotypic distribution for the IL-10 (592C/A) gene polymorphism was significantly different between patients

and healthy controls. The homozygous AA genotype was found in higher frequency (21.3%) in SLE patients than (9.3%) healthy control group. The combined genotype CA/AA was significantly found in patients compared to healthy controls. The A allelic frequency was higher (48.7%) in SLE patients compared to control (30.0%). These finding indicates that AA genotype, AA/CA genotype and A allele are associate with the risk of SLE. The finding of this study is similar with another study in India where the-592A allele frequency was significantly higher (46.8%) in SLE patients compared with controls (35.1%) (P=0.0002), and the frequency of CA/AA was also found to be significantly higher (74.5%) in SLE patients than controls (56.2%) (P=0.0001) [33]. Further in a meta-analysis [20] Liu et al. (2013) reported -592C allele to be associated with decreased risk of SLE in an Asian population but not in European population. Similar with this finding, in the present study, IL-10 (-592CC) genotype was increased significantly in controls compared to SLE patients (P=0.001). In the present study there was no significant association of IL-10 (-592C/A) genotype distribution with clinical manifestations. In contrast, The IL-10 (-592 A) allele has been reported to be associated with the development of lupus nephritis among Chinese SLE [21].

This study compared IL-10 (-819T/C) gene polymorphisms with SLE patients and healthy control group. The C allelic frequency was higher (57.3%) in case group than (43.3%) in control group (P=0.015). Moreover, the TT genotype was found in higher frequency in healthy control than patient group(P=0.041). A significant distribution of the -819T/C polymorphism and the C allele are present in Asian SLE patients [22]. Presence of complete linkage disequilibrium between the -819 and -592 alleles have been reported [34]. The function of the -819 C allele in regards to IL-10 production is not completely validated. Increase of the -819 C allele frequency in patients with SLE may not entirely reflect the association of -819 C allele and SLE susceptibility but could be the result of complete linkage disequilibrium between -819 and -592 alleles. In the present study, the frequency of TC/CC (36.1%) was found to be significantly higher in patients with oral ulcer as compared with patients having TT (7.1%) genotype (P=0.034). In the present study, no significant difference in IL-10 (-1082G/A) genotype and allele frequencies was found between control and SLE patients in Bangladeshi population. The association of -1082 G allele with susceptibility to SLE was reported in Caucasians [35]. There was no significant association of IL-10 (-1082G/A) genotype distribution with clinical manifestations in this study. However, Discoid rash in a Spanish [36], Neurological disorders in a Dutch [37] and Renal disorder in a Chinese popuations [21] were found in several studies. And these controversial results about clinical features could be due to the genetic heterogenesity of SLE in different ethnicities.

In this study it was found that patients having IL-10 (-1082 GG) genotype had significantly higher level of serum IL-10 than those with IL-10 (-1082 G/A). No other genotype of IL-6 and IL-10 gene showed such significant association with serum level of cytokines in patient group. The -1082G allele is proven to be the most important positive regulatory factor for the constitutive and inducible expression of IL-10 but the significance of -1082 GG to SLE susceptibility may be diminished by the rarity of -1082G in Asians [38]. In a study, it was found that GG genotype of IL-10 (-1082G/A) associated with higher level of IL-10 but it was not significant due to rarity of G allele [23]. A study in Mexico conducted by Palafox-Sanchez et al (2015) found that patients having CC genotype showed higher IL-10 level than AA genotype of IL-10 (-592C/A) [39]. In contrast, a study in Egypt found no such association with the level of cytokine and genotype distribution of IL-6 and IL-10 gene [2]. These conflicting results may be due to cytokine secretion not only depends on the constitutive production but also inducible factors such as level of other cytokine, ethnicity and age of patients, stimulating agents and cell types etc are associated with plasma level of cytokines. Multi-centered study should be conducted on other SNPs of IL-6 and IL-10 along with other cytokine gene polymorphisms with SLE susceptibility and clinical features of SLE in Bangladeshi population.

Conclusion

The study indicates that GG genotype and G allele of IL-6 (-174G/C) may be associated with susceptibility to SLE while GC genotype of IL-6 (-174G/C) has been associated with decreased susceptibility to SLE in Bangladeshi population. AA genotype, CA/AA genotype and A allele of IL-10 (-592C/A) gene may be associated with the susceptibility to SLE. Moreover, TC/CC genotype and T allelic frequency of IL-10 (-819T/C) gene may also play role in SLE susceptibility. On the contrary, CC genotype of IL-10 (-592C/A) gene and TT genotype of IL-10 (-819T/C) gene are associated with the decreased susceptibility of SLE in Bangladeshi population. The TC/CC genotype of IL-10 (-819 T/C) is associated with oral ulcer of SLE. GG genotype of IL-10 (-1082G/A) gene might influence increased production of IL-10 in SLE patients.

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Authors' contributions

Conception: NN and SA.

Methodology: NN, SA, SKS, RRK and REB.

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Sample collection and laboratory analysis: NN.

Statistical analysis: NN and SA.

Writing—first draft: NN.

Writing—revision and editing: NN and REB.

Supervision: SA, SKS and RRK.

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Declarations Competing interests:

The authors declare that they have no competing interests.

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