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Association of IL-4 (– 590 C/T) and IL-6 (– 174 G/C) gene polymorphism in South Indian CKD patients

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Abstract

Aim The present study was undertaken to examine the role of IL-4 (– 590 C/T) (rs2243250) and IL-6 (– 174G/C) (rs1800795) polymorphism and the serum levels of IL-4 and IL-6 in chronic kidney disease (CKD).

Methods The IL-4 (– 590C/T) and IL-6 (– 174 G/C) polymorphisms were genotyped in 132 CKD patients and 161 controls using PCR–RFLP. Serum IL-4 and IL-6 quantifications were performed by ELISA.

Results Significant susceptible associations of CT genotype (OR = 4.56; $p < 1.84 \times 10^{-9}$) and T allele (OR = 1.56; $p < 0.010$) of IL-4 (– 590C/T) and CC genotype (OR = 2.63; $p < 0.032$) of IL-6 (– 174G/C) were observed for CKD. The CC genotype (OR = 0.27; $p < 9.314 \times 10^{-7}$) and C allele (OR = 0.63; $p < 0.010$) of IL-4 (– 590 C/T) revealed strong protective associations. Five-fold increased levels were observed for both IL-6 ($p < 0.0001$) and IL-4 ($p < 0.0043$) cytokines in CKD patients than the controls. The IL-4 serum levels (pg/ml) increased significantly in patients with CT and TT genotypes of IL-4 (– 590 C/T) than the controls (6.18 ± 1.80 vs. 3.33 ± 0.48 and 6.14 ± 1.96 vs. 3.21 ± 0.56 respectively). For IL-6 (– 174 G/C) polymorphism, the patients with CC genotype (6.50 ± 1.30 vs. 3.49 ± 1.39) revealed with higher IL-6 serum levels followed by GC genotype (5.00 ± 1.91 vs. 4.01 ± 1.74).

Conclusion The genotypes of IL-4 (590 C/T) and IL-6 (174 G/C) polymorphisms contribute differential susceptibility in south Indian CKD patients. A fivefold increased serum levels of IL-4 (anti-inflammatory) and IL-6 (pro- and anti-inflammatory) cytokines were documented in CKD patients. There observed an opposite trend in disease association for these two cytokines and associated SNPs with CKD in south India.

Keywords Cytokines, IL-4, IL-6, Chronic kidney disease, Inflammation, Cytokine dynamics, Polymorphism

Introduction

Chronic kidney disease (CKD) is a disease showing progressive loss of renal function, with decline in the estimated glomerular filtration rate (eGFR) (stages 1–5), that required either dialysis or kidney replacement therapy (KRT) [8, 39, 81]. The measurement of creatinine and urea helps to assess the renal function by reflecting the glomerular filtration rate (GFR). The calculation of the urea: creatinine ratio is help establishing a renal and/or non-renal cause. Cytokines are factors mainly influencing the atherosclerosis leading to CKD and subsequent ESRD [65]. The stability between anti-and/or pro-inflammatory cytokines determines the inflammatory response and mediates the progression of CKD [6]. These pro-inflammatory (IL-1, IL-6 and TNF-a) and anti-inflammatory (IL-4, IL-10 and IL-13) cytokines play essential roles in

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the development of CKD pathogenesis. Previous reports have documented a wide spectrum of impact of different cytokines on the glomerular basement membrane of kidneys in different populations [13, 15, 82]. Further, the polymorphism (SNPs) present within the coding and non-coding regions of cytokine genes may cause inter individual variation in their expression, leading to individual differences in immune responses leading to CKD [2, 43, 60, 66, 68]. The single nucleotide polymorphisms (SNPs) within the promoter region of these cytokine genes were reportedly influence the cytokine levels [73]. The cytokine gene promoter polymorphism vary among different ethnic groups and may contribute differently in disease processes and pathology [23, 36, 47, 78]. Further, the differences in graft survival rates among Black and other world populations have suggested the strong role of cytokines. However, other confounding issues such as socioeconomic factors, therapeutic compliance and immunological variables too contribute significantly.

The gene for IL-6 gene is located on human chromosome 7p15–p21 and the interleukin is primarily produced by T cells and macrophages [18]. The IL-6 is secreted by a number of cells including lymphocytes, adipocytes, macrophages, endothelial cells and fibroblasts. This cytokine has the ability to induce endothelial damage, stimulating the intracellular adhesion molecule-1 (ICAM-1) and enhancing the migration of leucocytes across the endothelial surfaces [56]. IL-6 cytokine has dual roles, and it exhibits both pro-anti-inflammatory effects [46]. The pro-inflammatory cytokines (IL-6) and tumour necrosis factor-α (TNF-α) were the key orchestrators of inflammatory response. Thus, these cytokines acted as key factors that accelerated atherogenesis, morbidity and mortality in kidney failure patients undergoing haemodialysis [3].

Recent studies have documented a clear correlation between expression of IL-6 and acute kidney injury (AKI). The cells such as mesangial, endothelial, podocytes and tubular epithelial (TECs) can secrete IL-6 under certain clinical conditions. The high glucose level induces IL-6 dependent secretion and stimulates IL-6 signal transduction in podocytes. This was inferred by blocking IL-6 and its downstream mediators such as IL-6R and gp130 attenuating the progression of diabetic nephropathy [33]. The reduced clearance of IL-6 as a consequence of impaired renal function also contributes to its accumulation. Further, the elevated IL-6 level could be attributed to oxidative stress, chronic inflammation and fluid overload. In ESRD patients, the therapeutic hemodialysis and peritoneal dialysis too stimulate IL-6 production and increased level of inflammatory response [4, 57, 71].

Previous studies have documented the association of polymorphisms in IL-6 promoter regions such as 572 G/C, 634 C/G, 174 G/C and 597 G/A with several diseases [60]. Among these, IL-6 (174 G/C) regulate a broad range of immune activities such as production of acute phase proteins and cell adhesion molecules that in turn orchestrated the release of other cytokines in response to inflammatory stimuli [34]. The 174G/C polymorphism in IL-6 gene revealed an independent risk factor for diabetic nephropathy in Greek and Turkish T2DM patients [31, 55]. The IL-6 (174-G/C) polymorphism has been reported to influence IL-6 expression, particularly the G allele being associated with accelerated expression [17, 26, 58, 72, 77]. Interestingly, IL-6 (174 G/C) polymorphism has reportedly been associated in a number of chronic diseases including arthritis, coronary heart disease and diabetes [16, 17, 83]. The higher level of IL-6 (−174 G/C) was associated with advanced carotid plaques [21]. However, no significant correlation of −174G/C polymorphism with ESKD was documented [15].

The IL-4 gene is 0.9 kb long and consists 4 exons located on chromosome 5 (5q31) along with other Th2-related cytokine genes (IL-3, -5, -9, -13 and -15) [38, 48]. IL-4 is an anti-inflammatory cytokine mainly involved in adaptive immunity and inhibits the secretion of IL-1, IL-6 and pro-inflammatory tumor necrosis factor (TNF) that in turn effectively down regulates macrophage function and stimulates the proliferation of activated T and B cells, regulates the differentiation of B cells, promotes type-2 T helper (Th2) cell activity and inhibits Th1 cell differentiation [50, 54, 62, 76]. The increased production of IL-4 is associated with reduced inflammation in CKD rats [69]. Further, in mouse model depicting inflammatory renal disease, the adoptive transfer of IL-4 induced M2 macrophages significantly reduces histological injury [80]. A number of previous studies too have implicated the IL-4 (590 C/T) (rs2243250) promoter region polymorphism with atopic dermatitis [40], multiple sclerosis, rheumatoid arthritis [59] and atopic asthma [41].

The present study was to investigate the association of SNPs in IL-4 (590 C/T) and IL-6 (174 G/C) polymorphisms and to correlate the serum levels of these cytokines with CKD pathogenesis in a south Indian CKD cohort.

Materials and methods

Enrollment of samples

A total of 132 CKD patients and 161 healthy controls were enrolled during 2017–2019. The subjects were recruited from private hospitals in and around Madurai, Tamil Nadu. Enrolment of CKD patient was done under the supervision of the physician as per the guidelines of Kidney Disease Quality Outcome Initiative [51]. The present CKD study groups include dialysis, non-dialysis

and post-transplant subjects with and without complications in the age group >15 years. Pregnant women, AIDS and pediatric kidney failure cases were excluded. The healthy volunteers were selected randomly from the same geographical region without any major medical illness. A questionnaire was obtained from each patient and written informed consent was obtained from all the participants. The study was approved by the Institutional Ethical Committee (Ref. No: version 04 MMHRC-IEC).

IL-6 and IL-4 cytokines serum levels

Three ml blood was collected in vacutainer and centrifuged at 2000 rpm for 10 min for serum separation. The separated serum was stored at −80 °C in cryovials until further analysis. To measure the serum levels of IL-6 and IL-4, an enzyme-linked immunosorbent assay (ELISA) was performed for 50 CKD patients and 50 controls using cytokine detection kits (Bioassay Technology Laboratory, China).

Detection of IL-4 and IL-6 SNPs

To detect IL-4 (590C/T) and IL-6 (174 G/C) gene polymorphism, all DNA samples were tested by PCR–RFLP method as described previously with slight modifications [32]. The following primers were used for IL-4 (590 C/T): F: 5′-TAAACTTGGGAGAACATGGT, R: 5′-TGG GGAAAGATAGAGTAATA; and for IL-6 (174 G/C) F: 5′-TAGCCTCAATGACGACCTAAGCT-3′; R: 5′-GGG CTGATTGGAAACCTTATTAAG-3′. PCR reactions were performed in a volume of 12 µl containing 50 ng of genomic DNA, 0.24 mM dNTP, 0.04 U of Taq polymerase, 10X buffer, and 0.5 µm forward and reverse primers. The PCR conditions with initial denaturation at 95 °C for 5 min, followed by 30 cycles of 94 °C for 30 s, annealing at 55 °C for 30 s, and extension of 72 °C for 30 s with a final extension at 72 °C for 5 min were followed. The amplified PCR products was analyzed by 1.5% agarose gel electrophoresis. The amplified products of 252 bp product of IL-4 (590 C/T) were digested with AvaII (TT: 252 bp; GC: 252 + 192 + 60 bp; CC: 192 + 60 bp) and 532 bp product of IL-6 (174 G/C) was digested with BsmF1 (GG: 532 bp; GC: 532 + 474 + 58 bp; CC: 474 + 58 bp) enzyme and electrophorosed on 3% agarose gel at 100 V for 20 min. The digested products were detected in a Gel Documentation System (Vilbert Lourmat, France).

Statistical analysis

The cytokine levels were measured by Mann–Whitney test using Graphpad prism software. The Chi square test was used to test the deviation from Hardy–Weinberg Equilibrium (HWE) by comparing the observed and expected frequencies. The sample size of the study was calculated as described previously [5, 28]. The association between IL-4 (590C/T) and IL-6 (174 G/C) gene polymorphism with CKD was determined by using the Odds Ratio (OR) and 95% confidence intervals. The p value < 0.05 was considered statistically significant. Clinical characteristics are compared by using the Student unpaired t- test and the χ^2 test.

Results

Demographic characteristics

A total of 132 CKD patients (108 males; average age: 50.69 ± 15.29 years and 24 females; average age: 48.41 ± 15.53 years) and 161 healthy controls (96 males; average age: 43.34 ± 13.11 years; and 65 females; average age: 40.06 ± 13.15 years) were enrolled for the study. The study cohorts consisted more of males than females, attesting the fact of higher incidence of CKD in males [7, 22]. The clinical parameters such as urea (114.75 ± 35.97 mg/dl; range: 35–243 mg/dl), serum creatinine (7.99 ± 3.45 mg/dl; range: 1.8–40.1 mg/dl), and hemoglobin (8.92 ± 1.74 g/dl; range: 5.2–13.6 g/dl) were documented. The estimated glomerular filtration rate (eGFR) for the study cohort was 11.15 ± 11.93 ml/min/1.73 m^2). The most common documented comorbidities among the study subjects were diabetes, hypertension, cardiomyopathy and stroke. Ninety percent of (90.90%; n = 119) patients had undergone dialysis and the remaining 9.09% (n = 14) patients falls under non-dialysis group. Patients with Diabetic-CKD (39.9%; n = 60) and Non-diabetic-CKD (48.54%; n = 73) were analyzed separately.

Serum cytokine levels

Circulating serum levels of IL-4 and IL-6 cytokines in CKD patients and healthy controls were measured by ELISA method (pg/ml). We observed a significantly increased level of IL-4 and IL-6 cytokines in CKD patients than the controls (Fig. 1). Further, gender-based analyses have not revealed any significant variations (Table 1). The correlation analysis of serum IL-4 level and IL-4 (−590C/T) genotypes have revealed higher IL-4 cytokine levels in CKD patients with CT genotype ($p < 0.0001$) followed by TT (0.028) genotype (data not shown). The CKD patients with CC genotype revealed moderately elevated serum level of IL-4. Similarly, serum level of the IL-6 in relation to IL-6 (−174G/C) genotypes have revealed an higher IL-6 levels in CKD patients with CC genotype followed by the GG genotype as compared to serum levels in the controls (Fig. 2B; Table 2).

Genotype/allele frequencies of IL-4 (590 C/T) and IL-6 (174 G/C) polymorphism

The genotype and allele frequencies of IL-4 (590 C/T) and IL-6 (174 G/C) gene polymorphism for pooled (P),

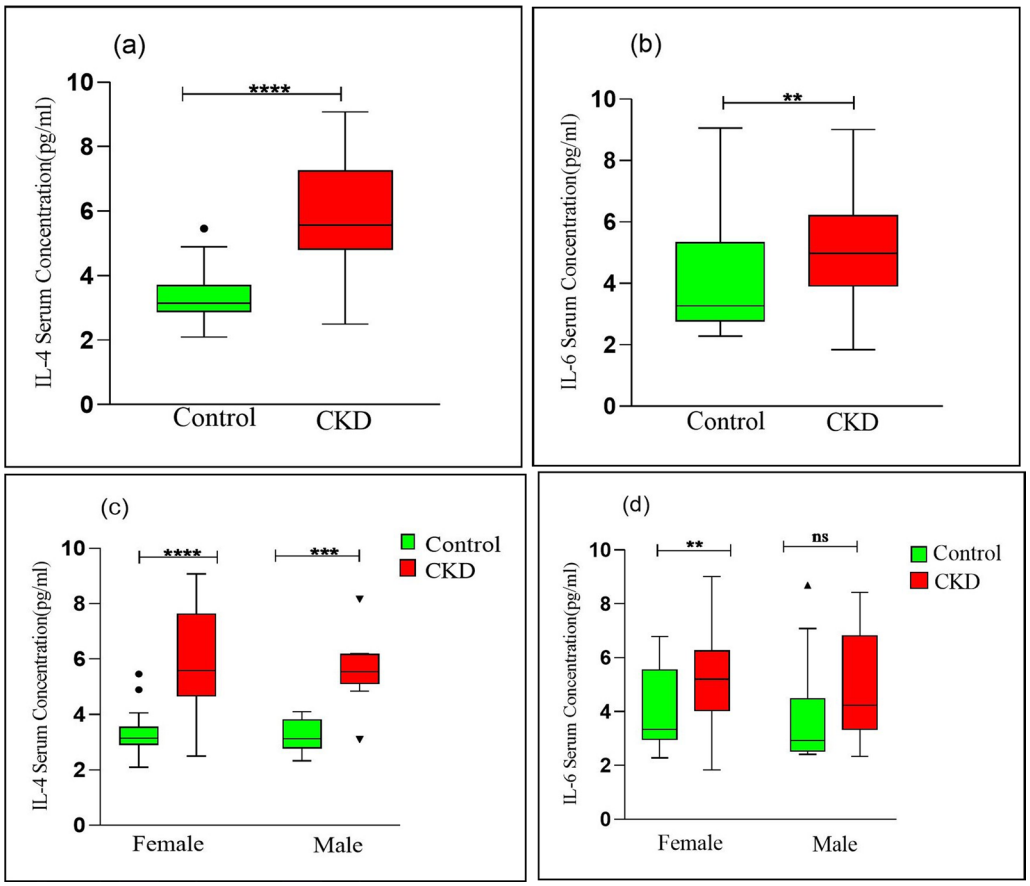

Fig. 1 **a** IL-4 serum concentration in CKD patients and controls, **b** IL-6 serum concentration in CKD patients and controls, **c** and **d** gender wise distribution of IL-4 and IL-6 serum concentration in CKD patients and control

Table 1 Cytokine IL-4 and IL-6 concentration in CKD patients and controls

Cytokines	Description	Patients (n = 50)	Controls (n = 40)	*P* value
IL-4	Pooled	5.86 ± 1.76	3.27 ± 0.67	0.0001
	Male	5.90 ± 1.85	3.27 ± 0.72	0.0001
	Female	5.65 ± 1.34	3.25 ± 0.58	0.0002
IL-6	Pooled	5.08 ± 1.78	3.92 ± 1.57	0.0043
	Male	5.13 ± 1.72	3.96 ± 1.38	0.0058
	Female	4.94 ± 2.05	3.84 ± 1.96	0.1858

$P < 0.05$ significant

male (M) and female (F) CKD patients were presented (Table 3). We observed a significantly increased frequencies of heterozygous CT genotype (P: OR = 4.56; $p < 1.84 \times 10^{-9}$; M: OR = 4.17; $p < 2.97 \times 10^{-6}$; F: OR = 6.33; $p < 5.72 \times 10^{-4}$) and T allele (P: OR = 1.56; $p < 0.010$) of IL-4 (590 C/T) gene polymorphism in CKD pooled patients. Further, decreased frequencies of CC genotype (P: OR = 0.27; $p < 9.314 \times 10^{-7}$; M: OR = 0.30; $p < 1.98 \times 10^{-4}$; F: OR = 0.18; $p < 0.004$) and C allele (P: OR = 0.637; $p < 0.010$) revealed significant association. We observed a weak protective association for TT genotype (OR = 0.439; $p < 0.059$) in CKD patients, however, without a statistical significance. Similarly, an increased frequency of CC genotype (OR = 2.63; $p < 0.032$) and a decreased frequency of GC genotype (OR = 0.54; $p < 0.021$) of IL-6 (174 G/C) among CKD patients were documented. No significant gender-based differences were observed for IL-6 (− 174 G/C) genotypes.

Genetic model analysis

The disease association analyses based on genetic models for IL-6 (174 G/C) and IL-4 (590 C/T) genotypes with CKD susceptibility were presented (Table 3). For IL-6 (174 G/C) genotypes, a significantly increased risk of CKD susceptibility was observed for Recessive (OR = 2.638; $p < 0.993$) and Additive (OR = 1.892; $p < 0.239$) models, however, without a statistical significance. Nonetheless, a significant protective association

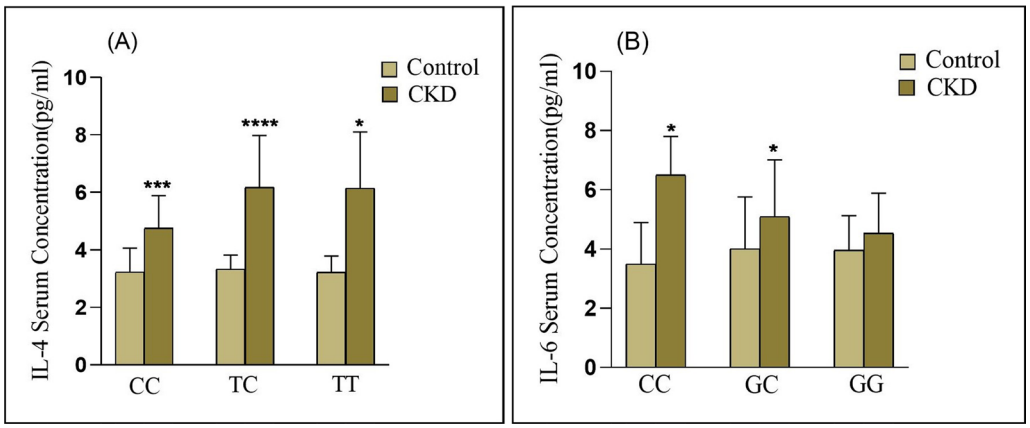

Fig. 2 **A** Correlation between IL-4 concentration and IL-4(590G/C) polymorphism. **B** Correlation between IL-6 concentration and IL-6 (174 G/C) polymorphism

Table 2 IL-6 and IL-4 level in CKD patients and control with specific gene polymorphism

	Control	CKD	*P* value
IL-6 (174 G/C)			
CC	3.49 ± 1.39	6.50 ± 1.30	0.031*
GC	4.01 ± 1.74	5.09 ± 1.91	0.025*
GG	3.39 ± 1.16	4.53 ± 1.34	0.499
IL-4 (590 C/T)			
CC	3.23 ± 0.82	4.75 ± 1.12	0.0003*
CT	3.33 ± 0.48	6.18 ± 1.80	0.0001*
TT	3.21 ± 0.56	6.14 ± 1.96	0.028*

*Significant *p* value

was observed for Co-dominant model (OR = 0.543; $p < 0.017$). Whereas for IL-4 (590 C/T) genotypes, there observed an increased risk of association for Dominant (OR = 3.763; $p < 0.000$) and Co-dominant (OR = 4.560; $p < 0.000$) models. Interestingly, a significant protective association was observed for Recessive model (OR = 0.272; $p < 0.000$) (Table 4). Thus, there observed to be an opposite trend in disease associations for these two cytokine markers with CKD in south India.

Discussion

Inflammation is one of the common factors to increase with the severity of the CKD disease. The cytokine SNPs and their genotypes have been associated with unfavorable outcomes in patients undergoing organ transplantation. Expression level of cytokines can be influenced by polymorphisms (SNPs) in the genes encoding these cytokines, as demonstrated for IL-1 [63], IL-10 [10, 75], IL-6 [67] and IL-4 [20]. Certain polymorphisms such as HLA alleles (MHC) [64], allograft inflammatory factor-1 (AIF-1) [79], RANTES/CCL5 [35], CTLA4 and TLR4 gene products [19] have all been implicated in acute graft dysfunction (GD), acute rejection (AR) and graft dysfunction (GD).

IL-4 is a multifunctional cytokine and negatively regulates proinflammatory cytokine production in renal inflammation. The study results have revealed a significant disease association of CT genotype and T allele of IL-4 (590 C/T) polymorphism in CKD patients. The genetic model analyses have revealed susceptible association for 'dominant' and 'co-dominant' models in IL-4 (590 C/T). However, we observed a susceptible association of 'recessive' and 'additive' models for IL-6 without statistical significance. Thus, genetic model analyses have presented a diverse trend for these cytokines in CKD. Present observations are in concordance with earlier reports in north Indian population that documented the increased frequency of T allele and TT genotype of IL-4 (− 590 C/T) in diabetic CKD cases than the controls. However, no significant differences in allele frequencies were observed in CKD patients without T2DM. Thus, the presence of T allele of IL-4 (− 590 C/T) gene polymorphism is associated with increased risk of diabetic CKD [52].

The T allele of IL-4 (590 C/T) polymorphism influenced the prognosis and the clinical course of the disease in INS patients from North India [25]. It has been documented earlier IL-4 (590 C/T) polymorphism was reportedly associated with the susceptibility to ESRD patients from north India [49]. A significant association was documented in IL-4 (590 C/T) in T2DM patients with diabetic nephropathy (DN) from Rafsanjan population from southeast Iran [30]. In another study from a Japanese population, IL-4 polymorphism was shown to be associated with the progression in immunoglobulin mediated nephropathy [44]. However, no significant

Table 3 Genotype and allele frequencies of IL-4 (590 C/T) and IL-6 (174 G/C) polymorphism in CKD patients and controls

Genotype/allele	Patients (P = 132) (M = 108) (F = 24)	Controls (P = 161) (M = 91) (F = 70)	OR	95% CI	χ^2	*P* value
IL-4 (590 C/T)						
CC	21.21 (28)	49.68 (80)	0.273	0.162–0.458	24.065	9.314×10^{-7}
	22.22 (24)	48.35 (44)	0.305	0.165–0.563	13.851	1.98×10^{-4}
	16.66 (04)	51.42 (36)	0.189	0.059–0.609	7.470	0.004
CT	71.96 (95)	36.02 (58)	4.560	2.772–7.501	36.133	1.84×10^{-9}
	70.37 (76)	36.26 (33)	4.174	2.304–7.563	21.835	2.97×10^{-6}
	79.16 (19)	35.71 (25)	6.330	2.06–24.06	11.864	5.72×10^{-4}
TT	6.81 (09)	14.28 (23)	0.439	0.196–0.985	3.425	0.059
	7.40 (08)	15.38 (14)	0.440	0.176–1.102	2.436	0.111
	4.16 (01)	12.85 (09)	0.295	0.035–2.457	0.653	0.443
C	57.19 (151)	67.70 (218)	0.637	0.455–0.894	6.422	0.010
	57.40 (124)	66.48 (121)	0.679	0.451–1.023	3.066	0.079
	56.25 (27)	69.28 (97)	0.570	0.291–1.118	2.156	0.114
T	42.80 (113)	32.29 (104)	1.569	1.119–2.199	6.422	0.010
	42.59 (92)	33.51 (61)	1.472	0.977–2.216	3.066	0.079
	43.75 (21)	30.71 (43)	1.755	0.894–3.442	2.156	0.114
HWE P	0.570	0.680				
IL-6 (174 G/C)						
CC	12.12 (16)	4.9 (08)	2.638	1.092–6.375	4.029	0.032
	12.03 (13)	6.59 (06)	1.939	0.706–5.326	1.123	0.231
	12.5 (03)	2.85 (02)	4.857	0.760–31.042	1.663	0.103
GC	59.84 (79)	73.29 (118)	0.543	0.332–0.889	5.356	0.017
	59.25 (64)	71.42 (65)	0.582	0.321–1.055	2.696	0.076
	62.5 (15)	75.71 (53)	0.535	0.199–1.440	0.969	0.290
GG	28.03 (37)	21.73 (35)	1.402	0.822–2.390	1.228	0.223
	28.70 (31)	32.96 (30)	1.429	0.748–2.732	0.846	0.329
	25.0 (06)	21.42 (15)	1.222	0.413–3.621	0.006	0.779
C	42.04 (111)	41.61 (134)	1.018	0.732–1.416	0.000	0.933
	41.66 (90)	42.30 (77)	0.974	0.653–1.452	0.001	0.919
	43.75 (21)	40.71 (57)	1.133	0.584–2.197	0.039	0.737
G	57.95 (153)	58.38 (188)	0.982	0.706–1.366	0.000	0.933
	58.33 (126)	68.68 (125)	0.638	0.422–0.966	4.107	0.037
	56.25 (27)	59.28 (83)	0.883	0.455–1.713	0.039	0.737
HWE P	0.420	0.420				

CKD: Chronic kidney disease; $p < 0.05$-significant; P: Pooled; M: Male; F: Female; HWE: hardy Weinberg equilibrium

differences were documented between IL-4 (590 C/T) allele distribution in Caucasians (UK) and Kuwait idiopathic nephritic syndrome (INS) patients [1, 53]. The frequency of T allele was significantly lower in Japanese Children with INS [32]. Further, it has been reported that T allele of the IL-4 (590 C/T) polymorphism was strongly associated with increased IL-4 gene promoter activity [27, 29]. We observed a striking male:female difference in cytokine levels with reference to this SNP, substantiating the predominance of CKD in males. The gender-based disease associations were exceedingly pronounced for CC (OR = 0.305) genotype towards protective and for CT (OR = 4.174) genotype towards susceptible associations.

The data presented here documented a significant association for CC genotype of IL-6 (174 G/C) polymorphism. We observed a higher risk of association in 'recessive' and 'additive' models, however, without statistical significance. The protective association of 'co-dominant'

Table 4 Genetic model analysis of IL-4 (590 C/T) and IL-6 (174 G/C) in CKD patients and controls

Genetic model	OR	95% CI	*P*-value*
IL-4 (590 C/T)			
(CT + CC) versus TT[a]	3.763	1.749–8.097	0.000*
CC versus TT[b]	0.894	0.370–2.162	0.822
CC versus (TT + CT)[c]	0.273	0.162–0.458	0.000*
CT versus (TT + CC)[d]	4.560	2.772–7.501	0.000*
IL-6 (174 G/C)			
(GC + CC) versus GG[a]	0.713	0.418–1.216	0.223
CC versus (GC + GG)[b]	2.638	1.092–6.375	0.993
CC versus GG[c]	1.892	0.720–4.973	0.239
GC versus (GG + CC)[d]	0.543	0.332–0.889	0.017*

*Significant *p* value

[a] Dominant effect

[b] Additive effect

[c] Recessive effect

[d] Co-dominat effect

model for IL-6 (174 G/C) polymorphism reiterated the significance of its pro-inflammatory role in disease process. Several previous reports have documented IL-6 (174 G/C) polymorphism as a predictive marker for the progression of complications, especially in kidney patients with T2DM disease [12, 37] and tuberculosis [14]. A significant association was observed for IL-6 (174 G/C) polymorphism in diabetic CKD patients from North India [52]. However, few studies revealed no association of this polymorphism with diabetic nephropathy [24]. Our results were consistent with previously published data from southern Italian CKD patients with CC genotype showing higher circulating levels of IL-6 than those with GC or GG genotypes [70]. Thus, there existed population level differences of cytokine levels as influenced by IL-6 (174 G/C) polymorphism that in turn influence the disease pathogenesis.

In the present study, the CC genotype conferred higher risk of developing CKD than GG genotype. Similarly, the C allele of IL-6 (174 G/C) was reportedly associated with increased production of IL-6 in Indian ESRD cases with malnutrition-inflammation-complex syndrome [74]. Some previous studies involving patients with other inflammatory clinical entities have reported CC genotype as protective, as it maintains lower circulating levels of IL-6 [17, 42]. An association of GG and GC genotypes with increased IL-6 levels than the CC genotype in Caucasian and African American ESRD patients undergoing long-term dialysis was reported [2]. Further, it is interesting to note that the individuals with higher IL-6 production were shown to be at increased risk for acute organ rejection episodes [9, 45]. The development of oxidative stress, accumulation of uremic toxins, fluid overload with other CKD related manifestations may contribute to this rise in plasma IL-6 levels and hence the observed higher degree of inflammation. The dialysis procedure also contributes to the inflammatory response, thereby increasing IL-6 production. It has been reported that the hemodialysis (HD) may increase the production of cytokines of pro-inflammatory immune response [61]. Further, chronic HD patients were shown to exhibit increased inflammation as pro-inflammatory mediators were released in uremic milieu [11].

Conclusions

Our findings suggest that polymorphisms at the anti-inflammatory IL-4 and pro-inflammatory IL-6 cytokines could be a useful predictor for CKD diagnosis and prognosis. The limitation of our study is the relatively small number of patients examined for these circulating inflammatory markers. Hence, future investigation with larger cohort is necessary to confirm these findings and to translate these observations into deliverables in clinical management of CKD. A clear understanding of cytokine dynamics will facilitate better clinical management of highly debilitating diseases such as chronic kidney disease in a transplantation setting.

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Author contributions

BK and RC conceptualized the idea, supervised the data collection and analysis, revised the manuscript critically for important intellectual content. VS and SP collected the data, analysed it. SK and DT supervised in the data collection. All authors agree to be accountable for all aspects of the work.

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Not applicable.

Availability of data and materials

We do have all the research data required for the manuscript and we will provide all the data and material for the publication.

Declarations

Ethics approval and consent to participate

The well-defined detailed questionnaire was obtained from each patient. Written informed consent was collected from all the participants and the study was approved by the Institutional Ethical Committee (Ref. No: version 04 MMHRC-IEC).

Consent for publication

Consent for the data publication was obtained.

Competing interests

The authors declare that they have no conflicts of interest.

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