

# Evaluation of Inflammatory markers in different stages of Chronic Renal Disease



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## ABSTRACT

**Background:** Chronic kidney disease (CKD) refers to a long-term loss of kidney function. The progression of CKD leads to the damage of other organs including cardiovascular disease which increased the risk of mortality. Early detection of kidney failure can slow down the end-stage renal disease. **Aims and Objectives:** To estimate the inflammatory marker Adenosine deaminase (ADA) activity in different stages of CKD. To correlate the level of ADA activity with Serum Creatinine with different stages of CKD on the basis of estimated glomerular filtration rate (eGFR). **Materials and Methods:** The participants having age more than 18 and <60 years having CKD have been enrolled as a study group. CKD was confirmed by calculating eGFR using Cockcroft-Gault equation, plasma creatinine estimation done in all the patients. This study was approved by the Ethical Committee of TMMC and RC. **Results:** It is observed that the incidence of CKD reaches its maximum strength during middle age. 28% of the young patients, i.e., 45 years of age or younger at the time of CKD, had increased level of ADA. Serum levels of ADA, Creatinine were higher among participants with lower level of eGFR. Inflammation was higher among those with lower eGFR. All biochemical parameter (ADA, CRP, ESR) shows the negative correlation with eGFR. eGFR shows a negative highly significant correlation with ESR with a correlation coefficient of  $r = -4.702$  ( $P < 0.001$ ). **Conclusion:** With the progression of Kidney disease (CKD stages 1–5) it comes to significantly increase of inflammatory markers as decrease in the eGFR with statistical significance. Inflammatory Biomarkers were inversely associated with the measure of kidney function. It is clear that a single indicator of renal function is not sufficient in evaluating the kidney disease stage.

**Key words:** Adenosine deaminase; Chronic kidney disease; Estimated glomerular filtration rate; C-reactive protein

## INTRODUCTION

Chronic kidney disease (CKD) generally causes reduction of the Glomerular Filtration Rate which indicates decreasing number of functioning nephrons.<sup>1</sup> Over the past 15 years, there has been an exponential growth of interest in inflammation in CKD and End-stage renal disease (ESRD).<sup>2,3</sup> CKD has become a public health problem. The definition of CKD was introduced by the National Kidney Foundation in 2002 and latter adopted by the International group Kidney Disease Improving Global Outcomes in

2004.<sup>4</sup> CKD is defined as abnormal kidney structure and functions persisting greater than 3 months. This can be determined either by evidence of kidney damage (presence of persistent albuminuria) or by decreased GFR.<sup>5,6</sup> Symptoms of kidney disease often developed only in advanced stages. The most commonly reported symptoms were weakness, decreased urine output, poor appetite, dyspnea, sleeping, bone or joint pain, breathlessness. Nearly 30% of CKD in our country are due to diabetic nephropathy and it is thus the single most common cause of Chronic renal failure.<sup>7</sup> It can be classified on the basis of estimated glomerular

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filtration rate (eGFR), low risk of progression to kidney failure start from stage 3. Data from the American National Health and Nutrition examination survey demonstrate that in the period 1999 to 2004 the prevalence of CKD stages 1–4 increased significantly when compared with the survey period 1988–1994 (13.1 vs. 10.0%) due to this high prevalence it is also associated with increases in diabetes mellitus and hypertension. Hypertension and diabetes are the crucial cause of CKD. ESRD is defined by an eGFR <15 ml/min/1.73 m<sup>2</sup>. Inflammation is an essential part of CKD. Inflammation is present in a wide spectrum of patients with CKD.<sup>8</sup> Chronic inflammation in the body can be measured by the increased level of inflammatory markers. Biomarkers of inflammation Adenosine deaminase (ADA) Activity, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR) could be increased as the kidney function decreases.<sup>9,10</sup>

ADA activity is expressed in the cytosol of all the cells. It's involved in the purines metabolism pathway, capable of catalyzing the deamination of adenosine, forming inosine in the result process. This enzyme act as a marker of inflammation being generally associated with processes of infectious origin.<sup>11</sup> Few studies have previously pointed out finding about the level of ADA enzyme in uremic patients, especially those suffering from kidney failure. According to the existing literature, it has been indicated that the development of hyperuricemia leads to the progression of existing renal disease and an increase in mortality.<sup>12</sup> The current study is done to investigate the inflammatory markers viz. Serum ADA activity in different stages of CKD. This study has specifically evaluated the biomarkers CRP, ESR, and Serum ADA activity as they are the markers of inflammation.

### Aims and objectives

To estimate level of ADA activity in patients of Chronic Kidney Disease. To correlate the level of CRP, ESR & ADA activity with different stages of Chronic Kidney Disease on the basis of eGFR.

## MATERIALS AND METHODS

The materials used for the analysis of the parameters of the present study are as follows: 60 patients (within age 18 and 60 between) along with 60 controls from Jan 1, 2018, to Dec 31, 2018, at Teerthanker Mahaveer Hospital were enrolled.

Patient history required for the estimation of eGFR i.e. age, sex and body size (height and weight) were recorded. History of CKD was confirmed later on by calculating eGFR using Cockcroft-Gault (CG) equation.

$eGFR \text{ (ml/min)} = (140 - \text{age [year]}) \times \text{weight (kilogram)} / 72 \times \text{Serum creatinine (mg\%)} (\times 0.85 \text{ if female})$ , plasma creatinine estimation done in all the patients. Total of 2 ml of blood was collected from each subject. Blood samples were collected from the antecubital vein in a plain vial and were subjected to centrifugation with the speed of 3000 rounds/min for 10 min. To obtain serum for the estimation of ADA activity, Serum Creatinine. Informed consent was signed from each patient before collecting the blood sample. This study was approved by the Ethical Committee of TMMC and RC. In all 60 patients, inflammatory markers were quantified: Serum ADA activity (U/L) was measured by Giustiani Galanti enzymatic method<sup>13</sup> Serum Creatinine (mg/dl) was measured by modified Jaffe's method (18). Serum CRP (mg/dl) and ESR (mm/hour) were measured by Latex agglutination and Wintrobe's<sup>14</sup> method respectively.

### Statistical analysis

Result of various biochemical parameters were calculated by using Statistical Package for Social Science Version 16. Mean  $\pm$  SD were calculated for all the parameters analysed were compared by Student's t-test and correlated by calculating Pearson's correlation coefficient P-value considered significant were as follows. P < 0.001 – highly significant, P < 0.05 – significant.

## RESULTS

- 1) Estimation of inflammatory markers in CKD patients.
- 2) Role of ADA in CKD.
- 3) Correlation of ADA & eGFR biochemical markers.

## DISCUSSION

Patients who develop kidney problems usually have no symptoms early on, although the condition puts them at risk of developing more serious kidney disease. It is important to take steps to protect kidneys before the problem advances. The present study examined inflammatory markers in blood sample and correlate their levels with estimated eGFR for the assessment of early renal damage in CKD patients and compare it with that of controls. It was carried out in Teerthanker Mahaveer Medical College and Research Centre, Moradabad.

Of 80, 60 patients were taken in which 44 were male and rest 16 were female. All the 60 patients were between the age groups of 18–60 years. The maximum number of cases 30 were observed in the age group of 51–60 years followed by 17 cases in the age of 41–50 years, seven cases in the age group of 18–30 years and 6 cases in the age group of 31–40 group (Table 1 and Figure 1).

It is observed that the incidence of CKD reaches its maximum strength during middle age. 28% of the young patients, i.e., 45 years of age or younger at the time of CKD, had increased level of CRP.

Out of 60 controls, 30 were male and 30 were female. About 40% were found in the age group 18–30 years, 18.3% were found in 31–40 years of age group, 18.3% were found 41–50 years age group and 23.4 % found in 51–60 years age groups (Table 2 and Figure 1).

### Estimation of inflammatory markers in CKD patients

In the previous study, we have found that level of CRP and ESR were increased in CKD patients as compare to the control.<sup>15</sup> In this study, the levels of inflammatory marker studied viz. ADA activity in CKD patients as this is also an inflammatory marker so it should be elevated in the CKD patients. Table 3 shows that ADA levels increased in all patients (n=60) with CKD (with the mean value 18.98±8.973 U/L). This result was highly significant (P<0.001) in CKD patients when compared with that of control group (7.420±2.246 U/l) (Figure 2 and 3).

### Role of ADA in CKD

ADA activity is expressed in the cytosol of all the cells. It is involved in the purine metabolism pathway, capable

of catalyzing the deamination of adenosine, forming inosine in the result process.<sup>16</sup> ADAs include 2 isoforms with different biochemical properties. ADA1 can exist as a small monomer with 30–40 KDa molecular weight. ADA2 can exist as a large dimer with 280 KDa molecular weight. The ADA1 is found in all the cells of mammalian tissue, with the highest activity in lymphocytes and monocyte, whereas ADA2 is predominant isoform in the serum of normal subjects. Major source of ADA2 is monocyte – macrophage system. It is produced in response to pathogen factors and encoded by CECRI gene. ADA2 is strongly increased in inflammatory diseases such as CKD, rheumatoid arthritis, and tuberculosis. ADA, an enzyme essential for the proliferation and differentiation of lymphocyte and monocyte-macrophage system. It is used for monitoring several immune system diseases. This enzyme was considered as a suitable marker of cell mediate immunity. The activity of ADA is more in lymphocyte as compared to erythrocyte. Assay of ADA activity in the serum is very important for the diagnosis of many pathological conditions. Hemodialysis (HD) effect chiefly ADA activity. It has been seen that decrease in ADA

Age (Years)	Number of cases		Total	%
	Male	Female		
18–30	5 (8.3%)	2 (3.3%)	7	11.6
31–40	5 (8.3%)	1 (1.7%)	6	10
41–50	13 (21.7%)	4 (6.7%)	17	28.4
51–60	21 (35%)	9 (15%)	30	50
Total	44	16	60	100

Age (Years)	Number of cases		Total	%
	Male	Female		
18–30	10 (16.7%)	14 (23.3%)	24	40
31–40	3 (5%)	8 (13.3%)	11	18.3
41–50	7 (11.6%)	4 (6.7%)	11	18.3
51–60	10 (16.7%)	4 (6.7%)	14	23.4
Total	30	30	60	100

S. No.	Biochemical Parameters	Controls Mean±SD	Cases Mean±SD	P-value
1.	ADA (U/L)	7.420±2.246	18.98±8.973	0.000
2.	CREATININE (mg/dl)	0.9063±0.308	5.377±4.277	0.000

ADA: Adenosine Deaminase (N-<40 U/L), Creatinine (N 0.9–1.3mg/dl for male : 0.6–1.1 mg/dl for female, SD: Standard Deviation

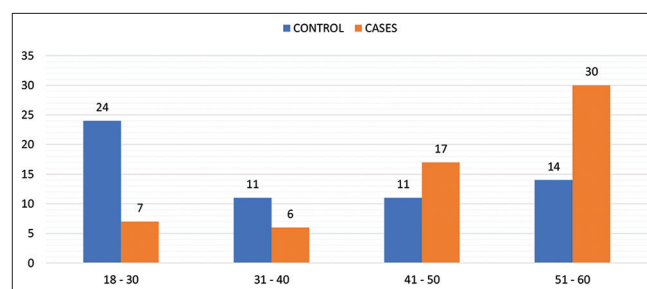


Figure 1: Distribution of cases and controls according to age

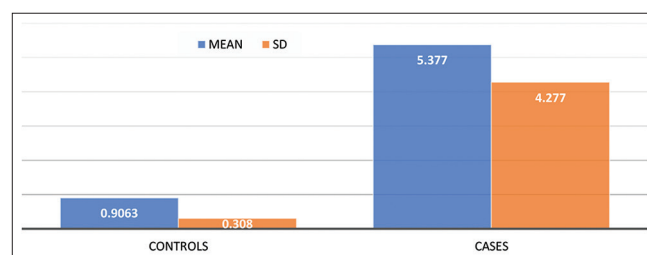


Figure 2: Comparison of creatinine between cases and controls

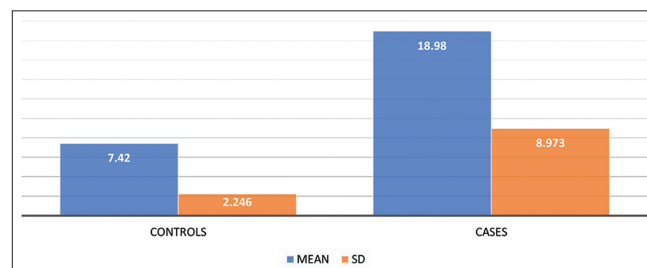


Figure 3: Comparison of ADA between cases and controls. ADA: Adenosine deaminase

activity causes mild to moderate or moderate to complete lack of immune function. Hence, the most patients with renal failure suffer from weakening in the immune system, especially those on dialysis process.<sup>17</sup>

### Role of ESR and CRP in CKD

It is possible to assess inflammation and infection indirectly in a number of ways including using the ESR and C-RP level. ESR test is a simple test. It is still widely used in medical practice for the detection of the inflammatory process. Aggregation of erythrocytes stimulates falling and increases the ESR, however, RBCs are negatively charged and tend to repel one another. Thus, the presence of positively charged (acute phase protein such as fibrinogen and immunoglobulin) increases the ESR.<sup>18</sup> ESR and CRP are widely used laboratory markers of systemic inflammation.

Some studies have addressed high ESR in patients with ESRD. Bathon et al.,<sup>19</sup> studied this issue in 48 patients before and after HD. They concluded that ESR is high in pre and post HD patients and found no difference between pre and post-HD readings.<sup>18</sup> In one more study from Brouillard et al., evaluated that the ESR in 45 HD patients. They also concluded that the ESR was mildly elevated in HD patients.<sup>20</sup>

CRP is a acute phase protein that is a member of the pentraxin. It is a pattern recognition protein that are an integral part of the innate immune system. It is synthesized in the liver in response to inflammatory cytokines and assists in complement binding and phagocytosis by macrophages.<sup>21</sup>

In the present study, serum ADA, CRP and ESR were increased in CKD patients. With the progression of CKD stages 1–5 it comes to significantly increased of inflammatory markers ADA, CRP and ESR with statistical significance. It has been proven in numerous study that different inflammatory markers are significantly increased in CKD which followed connection between albuminuria, kidney function, and inflammatory biomarkers, found a higher level of CRP among patients with lower eGFR. Studies have shown that epithelial cells of renal epithelium can also produced CRP under certain circumstances. Synthesis of CRP in the liver is triggered by pro-inflammatory cytokines released from monocytes and macrophages. The pro-inflammatory response leads to the secretion of IL-1 $\beta$  and Tumour necrosis factor  $\alpha$  which further results in the release of IL-6, a messenger cytokine that stimulates the liver to secrete CRP. In chronic inflammatory conditions, CRP can rise as much as 50–100 mg/l within 4–6 h. CRP levels double every

8 h and peak 36–50 h after the onset of inflammation or injury. Mild increases in CRP b/w 2 mg/l and 10 mg/l are considered to be metabolic inflammation. Levels of CRP fall quickly because of its short half life (4–7 h) once inflammation subsides. The exact cause of increase in ADA levels is not known, the activity may be increased due to its release from damaged cells and increased cellular proliferation in CKD patients. ESR, CRP and ADA are generally risk in tandem with inflammation in CKD patients.

Fox et al., found that serum CRP level was high in patients with CKD in 2010. A study done by Fox et al., in 2007 on African American patients of CKD also shows increased levels of CRP in CKD patients.<sup>21</sup>

Table 4 shows the comparison of ADA, CRP, ESR between different stages of CKD.

The levels of serum ADA mean in stage 3 is  $16.85 \pm 4.016$  compare to the stage 4 is  $19.35 \pm 6.054$  whereas in stage 5  $20.75 \pm 13.74$ . Which shows the significant increased levels of serum ADA between stages 3, 4, and 5.

The mean levels of serum CRP in stage 3 are  $29.95 \pm 6.896$  compare to the stage 4 is  $32.40 \pm 12.97$  whereas in stage 5  $44.28 \pm 23.83$ . This finding shows the significant increased levels of serum CRP between stages 3, 4, and 5.

The mean levels serum ESR in stage 3 is  $27.1 \pm 3.79$  compare to the stage 4 is  $34.95 \pm 8.87$  whereas in stage 5 is  $53 \pm 14.42$ . Overall finding shows the significant increased levels of serum ESR between stage 3, 4, and 5.

All the markers tested shows an upregulation from stage 3 to 5 (Figures 4-6).

### Correlation of ADA and eGFR biochemical markers

Table 5 shows the correlation of ADA with AGE, Weight, Creatinine, ESR.

Karl Pearson correlation coefficient (r-value) was calculated. It shows a positive and significant correlation

**Table 4: Comparison of ADA, CRP, and ESR between different stages of CKD**

S. No.	Biochemical parameters	Stage 3	Stage 4	Stage 5
1.	ADA	$16.85 \pm 4.016$	$19.35 \pm 6.054$	$20.75 \pm 13.74$
2.	CRP	$29.75 \pm 6.896$	$32.40 \pm 12.97$	$44.28 \pm 23.83$
3.	ESR	$27.1 \pm 3.79$	$34.95 \pm 8.87$	$53 \pm 14.42$

ADA: Adenosine deaminase (mg/dl), CRP: C-reactive protein (mg/dl), ESR: Erythrocyte sedimentation rate (mm/hour) (N- 0-22 mm/h for men and 0-29 mm/h for women)

between the serum ADA activity and UREA level. With a correlation coefficient of  $r=0.696$  ( $P<0.001$ ) and ADA showed the negative correlation with age and weight with the correlation coefficient of  $r=-0.075$ ,  $-0.46$ , respectively. ADA also shows the positive correlation with creatinine, uric acid, and ESR with the correlation coefficient of  $r=0.235$ ,  $0.322$ ,  $0.343$ , respectively.

Table 6 shows the correlation of eGFR with ADA, CRP, and ESR. All biochemical parameter (ADA, CRP, ESR) shows a negative correlation with eGFR. eGFR shows a negative highly significant correlation with ESR with a correlation coefficient of  $r=-4.702$  ( $P<0.001$ ).

**Table 5: Pearson correlation coefficient (r-value) of ADA with various biochemical parameters (age, weight, creatinine, ESR)**

S. No.	Parameter	P-value	r-value
1.	AGE (year)	0.568	-0.075
2.	WEIGHT (kg)	0.725	-0.46
3.	CREATININE (mg/dl)	0.071	0.235
4.	ESR (mm/hour)	0.007	0.343

ADA: Adenosine deaminase, ESR: Erythrocyte sedimentation rate

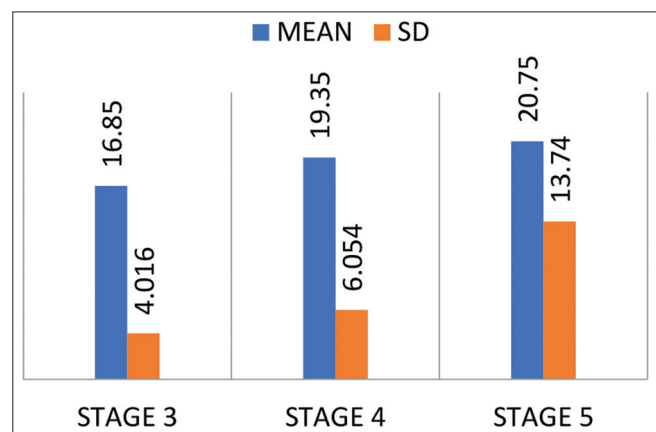


Figure 4: Comparison of ADA between different stages of CKD

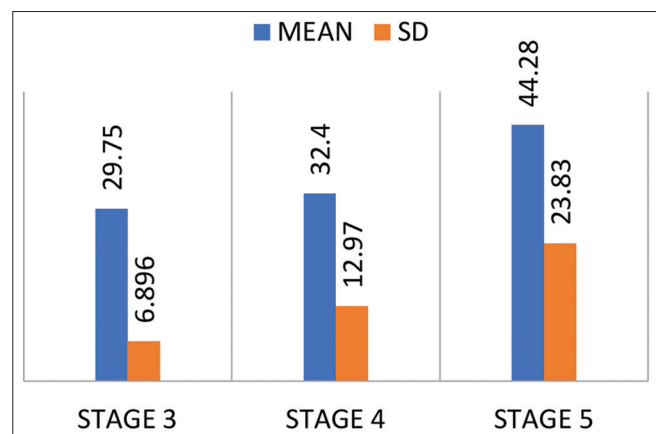


Figure 5: Comparison of CRP between different stages of CKD

Examining the interaction of inflammatory biomarkers with eGFR revealed that the negative association between inflammation and progression of CKD were stronger in high baseline eGFR.

This study shows that the increased levels of inflammatory biomarkers are associated with faster decline in eGFR (Figures 7-9).

**Multiple comparisons of ADA, CRP and ESR between different stages of CKD**

Table 7 shows the multiple comparisons of ADA between different stages, the value of mean difference between stage three and stage four is  $-2.5$ . The value of mean difference

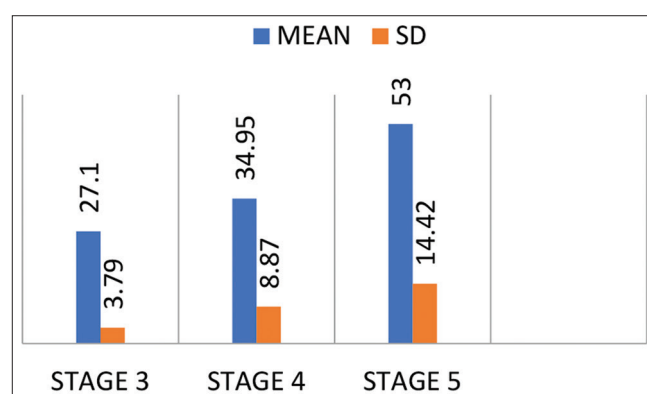


Figure 6: Comparison of ESR between different stages of CKD

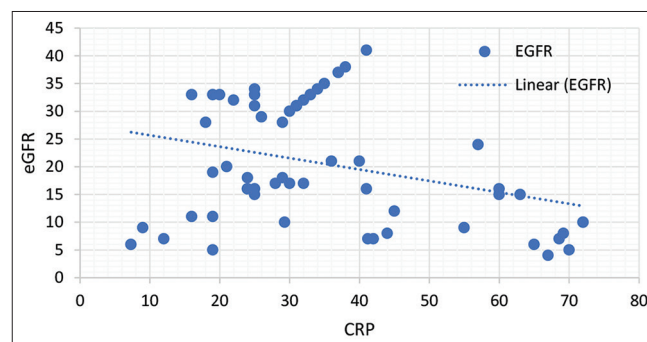


Figure 7: Correlation of eGFR with CRP. eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein

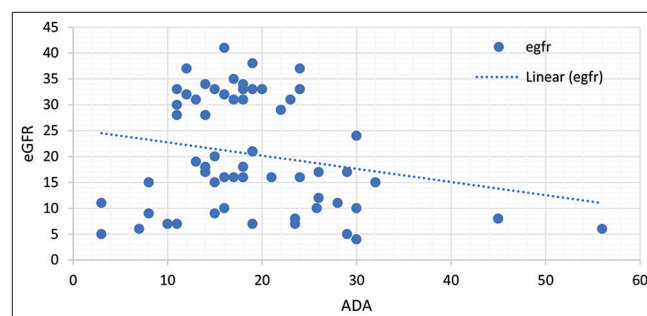


Figure 8: Correlation of ADA with eGFR. ADA: Adenosine deaminase, eGFR: Estimated glomerular filtration rate

**Table 6: Pearson correlation coefficient (r-value) of eGFR with various common parameters (ADA, CRP, ESR)**

S. No.	Biochemical parameters	P-value	r-value
1	ADA	0.114	-0.206
2	CRP	0.012	-0.321
3	ESR	0.000	-0.702

eGFR: Estimated glomerular filtration rate, ADA: Adenosine deaminase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

**Table 7: Multiple comparisons of ADA between different stages of CKD**

Stage	Stages	Mean difference	P-value	
ADA	3	4	-2.5-3.9	0.286
		5		0.455
	4	3	2.5-1.40	0.286
		5		0.909
	5	3	3.9	0.455
		4	1.4	3.35

ADA: Adenosine deaminase, CKD: Chronic kidney disease

**Table 8: Multiple comparison of CRP between different stages of CKD**

Stage	Stages	Mean Difference	P-value	
CRP	3	4	-2.65-14.4	0.702
		5		0.041
	4	3	2.65-11.8	0.702
		5		0.143
	5	3	14.4	0.041
		4	11.8	0.143

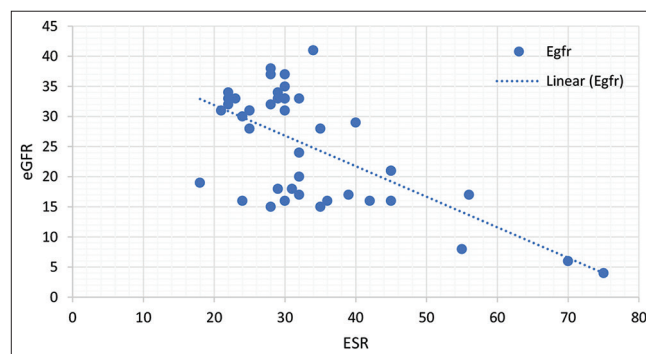
CRP: C-reactive protein, CKD: Chronic kidney disease

**Table 9: Multiple comparison of ESR between different stages of CKD**

Stage	Stages	Mean difference	P-value	
ESR	3	4	-7.85	0.003
		5	-25.9	0.000
	4	3	7.85	0.003
		5	-18.1	0.000
	5	3	25.9	0.000
		4	18.1	0.000

ESR: Erythrocyte sedimentation rate, CKD: Chronic kidney disease

between stage 3 and stage 5 is -3.9. The value of mean difference between stage 4 and stage 3 is 2.5 whereas the stage 4 and stage 5 is -1.40. The value of mean difference between stage 5 and stage 3 is 3.9 compare to the stage 5 and stage 4 is 1.4. Table 8 shows the multiple comparisons of CRP between different stages The value of mean difference between stage 3 and stage 4 is -2.65 compare to the stage 3 and stage 5 is -14.4.



**Figure 9:** Correlation of ESR with eGFR. ESR: Erythrocyte sedimentation rate, eGFR: Estimated glomerular filtration rate

The value mean difference between stage 4 and stage 3 is 2.65 whereas the value of stage 4 and stage 5 is -19.8. The value of mean difference between stage 5 and stage 3 is 14.4. the value of mean difference between stage 5 and stage 4 is 11.8. Table 9 shows the multiple comparisons of ESR between different stages the value of mean difference between stage 3 and stage 4 is -7.85 compare to the stage 3 and stage 5 is -25.9. The value of mean difference between stage 4 and stage 3 is 7.85, whereas stage 4 7 stage 5 is -18.1. The value of mean difference between stage 5 and stage 3 is 25.9 compare to the stage 5 and stage 4 is 18.1 All the markers are progressively increased with increase in the stages of CKD i.e. the markers are increased in proportionality with the increase in the severity of CKD.

**Limitations of the study**

Pregnant and Lactating women were excluded in this study. Diagnosed cases of following Disease i.e. Hepatitis, Rheumatoid arthritis, Tuberculosis, Chronic peptic ulcer, Asthma, Ulcerative colitis and Sinusitis was the limitation criteria of this study.

**CONCLUSION**

Currently, ADA, CRP and ESR are the markers used to evaluate kidney disease stages, however, each of these has its own limitation. With the progression of Kidney disease (CKD stages 1-5) it comes to significantly increase of inflammatory markers as decrease in the eGFR with statistical significance.

CKD is characterized by decreased glomerular filtration rate and increased inflammation. In order to device a means to protect kidneys at an early stage, the present study examined ADA, CRP and ESR in serum along with eGFR by CG formula as a prediction of early renal damage. The Mean ± SD of ADA and Creatinine

between CKD patients ( $18.98 \pm 8.973$ ,  $5.377 \pm 4.277$ ) and controls ( $7.420 \pm 2.46$ ,  $0.9063 \pm 0.308$ ), respectively, there was a significant increase of inflammatory marker ADA in CKD patients.

The mean  $\pm$  SD of ADA, CRP and ESR between different stages of CKD, stage 3 ( $16.85 \pm 4.016$  U/L,  $23.75 \pm 6.896$  mg/L,  $27.1 \pm 3.79$  mm/h), stage 4 ( $19.35 \pm 6.054$  U/L,  $32.40 \pm 12.97$  mg/L,  $34.95 \pm 8.87$  mm/h), stage 5 ( $20.75 \pm 13.74$  U/L,  $44.28 \pm 23.83$  mg/L,  $53 \pm 14.42$  mm/h) was seen. All the biomarkers tested demonstrated an upregulation in mean conc. from stage 3 to stage 5 indicating a progressive increase in the level of inflammatory markers with the increase in severity of renal dysfunction. CRP, ADA and ESR correlated with the eGFR and found to be significant at r-value ( $-0.321$ ,  $-0.206$ ,  $-0.702$  respectively). eGFR shows the negative correlation with ADA, CRP and ESR which shows that there is an increase in inflammatory markers level with decrease eGFR revealing that a positive association between inflammation and progression of CKD.

## ETHICAL COMMITTEE

This study was approved by the Ethical Committee of Teerthanker Mahaveer Medical College and Research Centre.

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**FK-** Concept and design of the study, prepared manuscript, statistical analysis and Interpretation of the results; **SK-** Interpreted the results, reviewed the literature and manuscript preparation

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