

Original Research Article

Role of high sensitivity C- reactive protein as a marker of inflammation and its prognostic significance in chronic kidney disease patients

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ABSTRACT

Background: Chronic kidney disease (CKD) is a clinical syndrome due to irreversible renal dysfunction leading to excretory, metabolic and synthetic failure culminating into accumulation of non-protein nitrogenous substances and present with various clinical manifestations. Elevated circulating concentrations of CRP are a common phenomenon in ESRD patients. The prevalence and magnitude of inflammation increases as renal function declines.

Methods: The current cross-sectional observation study was conducted in Rajendra institute of medical sciences, Ranchi during study period October 2015 to September 2017 on admitted patients with chronic kidney disease. 90 patients of different age groups between 16-75 years were enrolled in the study. Samples were selected by using simple random sampling method. Informed consent was obtained from all the patients.

Results: 85.6% of the patients studied were males and 14.4% of the patients were females. Most cases of CKD were associated with hypertension (77.8%) out of which there were 62 males and 8 females, followed by DM (25.5%) where there were 20 males and 3 females. 44.4% cases had an elevated level of hs-CRP (more than 3 mg/L) while 55.6% patients had hs-CRP below 3 mg/L. Out of 40 high hs-CRP patients, 35 were male and 5 were female. Patients with elevated creatinine level had significant high hs-CRP level.

Conclusions: Chronic kidney diseases, Cardiovascular disease, HS-CRP, Inflammation

Keywords: Clinical, ETV, Hydrocephalus, Neuroendoscope

INTRODUCTION

Chronic kidney disease (CKD) is a clinical syndrome due to irreversible renal dysfunction leading to excretory, metabolic and synthetic failure culminating into accumulation of non-protein nitrogenous substances and present with various clinical manifestations. End stage renal disease is described as a terminal stage of chronic kidney disease that, without replacement therapy, would result in death. Despite various etiologies, CKD is the final common pathway of irreversible destruction of

nephrons ultimately resulting in alteration of 'Milieu interior' that affects every system in the body.¹

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures.² The prevalence of end-stage renal disease continues to rise world-wide. Even more alarming is the current number of patients with early chronic kidney disease- the pool from which future end-stage renal disease patients will emerge. It exceeds the present number with end-stage renal

disease by a factor of 30 to 60. The burden of chronic kidney disease (CKD) in India cannot be assessed accurately. The approximate prevalence of CKD is 800 per million population (pmp), and the incidence of end-stage renal disease (ESRD) is 150-200 pmp.³ “Screening and Early Evaluation of Kidney Disease” (SEEK), a community-based voluntary health screening program was started in India in 2006 and tests serum creatinine and urine analysis. SEEK reported a very high prevalence of 17.4% of CKD (unpublished and presented in the Annual Conference of the Indian Society of Nephrology) using an abbreviated modified diet in renal disease (MDRD) formula, a glomerular filtration (GFR) estimation formula. The Indian CKD Registry, a voluntary reporting body of CKD patients data, initiated in June 2005, has 199 contributing centers. The database has 63,538 patients enrolled, 70% of them are males and 73.6% of them have CKD stage 4 and 5. Diabetes is the cause of kidney disease in 30% of these patients. Only 20% of the ESRD registry patients are on some form of Renal Replacement Therapy.^{4,5}

METHODS

This study is a Cross-Sectional observation study by nature. Patients with chronic kidney disease admitted in Rajendra institute of medical sciences, Ranchi. The study period was 2 year from October 2015 to September 2017.

Sample size

Total 90 patients of different age groups between 16-75 years were enrolled in the study who are admitted in wards of Department of Medicine RIMS Ranchi. These samples were selected by using simple random sampling method. Informed consent was obtained from all the patients.

Inclusion criteria

CKD patients age group of 16 yr-75 yearr who were diagnosed as Chronic kidney disease patients attending Department of Medicine, RIMS Ranchi.

Criteria for chronic kidney disease

- Elevated blood urea, serum creatinine and decreased creatinine clearance.
- Ultra sound evidence of chronic kidney disease
- Bilateral contracted kidneys - size less than 8 cm in male and size less than 7 cm in female.
- Poor corticomedullary differentiation.
- Supportive laboratory evidence of CKD like anaemia, and serum electrolytes potassium and calcium etc.

Exclusion criteria

- Patient suffering from acute or chronic infection
- Previous Coronary artery disease

- Patient of acute kidney injury
- Recent surgery or Trauma
- Liver diseases
- Pregnancy
- Age less than 16 and more than 75 years.
- Patients of rheumatoid arthritis, infamatory bowel disease, ankylosing spondylitis and psoriasis.
- Patients who doesn't gave consent for the study.

Detailed clinical history and clinical examination was undertaken with preference to hs-CRP and renal diseases. The following investigations were performed.

- Complete blood count and peripheral blood smear for anemia.
- Urine routine and microscopic examination.
- Renal parameters like blood urea, serum creatinine.
- Serum electrolytes including sodium, potassium and calcium.
- Spot urine protein and serum protein.
- Serum hs-CRP level.
- USG abdomen for kidney size, echotexture.

Statistical analysis

Data was tabulated using MS Excel, Word and was analysed using SPSS ver20.0 software and MED CALC software. Mean and standard deviation of the measured values were calculated as appropriate. Data is represented as mean \pm standard deviation. Unpaired student's t-test (Independent sample t Test) and chi square test was used to calculate p value and assess statistical significance of differences between groups, p value <0.05 was considered as statistically significant. Chi-square test used and Pearsons correlation coefficient was used to assess the linear relationships between a pair of variables and p value of <0.05 is considered significant. Multivariate analysis was done using binary logistic regression procedure to study the influence of independent variables on dependent variable of interest

RESULTS

Total 85.6% of the patients studied were males and 14.4% of the patients were females. Most cases of CKD were associated with hypertension (77.8%) out of which there were 62 males and 8 females, followed by DM (25.5%) where there were 20 males and 3 females (Table 1).

Table 2 shows that 44.4% cases had an elevated level of hs-CRP (more than 3 mg/L) while 55.6% patients had hs-CRP below 3 mg/l. Out of 40 high hs-CRP patients, 35 were male and 5 were female (Table 2).

Elevated hs-CRP values were observed in 40 patients. Among these, 38 patients have low s. albumin levels (42.2%). whereas among 50 patients with normal hs-CRP level only 19 patients have low s. albumin, this outcome

signifies strong inverse relationship between hs-CRP and s. albumin ($p < 0.05$) (Table 3). Out of 40 patients with elevated hs-CRP, 32 patients had haemoglobin level < 8 g/dl. ($p < 0.05$) (Table 4).

Table 1: Co morbidities associated with CKD.

Diseases	Male (n=77)		Female (n=13)		Total (n=90)	
	No.	%	No.	%	No.	%
DM	20	22.2	3	3.3	23	25.6
HTN	62	68.9	8	8.9	70	77.8
GN	10	11.1	1	1.1	11	12.2
ON	4	4.4	0	0	4	4.4
SLE	0	0	3	3.3	3	3.3
MM	2	2.2	0	0	2	2.2
CPN	2	2.2	0	0	2	2.2
Recurrent UTI	8	8.8	2	2.2	10	11.1
Analgesic abuse	7	7.7	0	0	7	7.7

Where DM=diabetes mellitus, HTN=hypertension, GN=glomerulonephritis, ON=obstructive nephropathy, SLE=systemic lupus erythematosus, MM= multiple myeloma, CPN=chronic pyelonephritis, UTI=urinary tract infection.

Table 2: HS-CRP level in CKD patients.

HS-CRP	Male	Female	Total	Percent
< 3 mg/L	42	8	50	55.6
> 3 mg/L	35	5	40	44.4
Total	77	13	100	

Table 3: HS-CRP vs albumin.

HS-CRP	s.albumin > 3 g/dl	s.albumin < 3 g/dl	Pearson coefficient	P – value
< 3	31	19	31.09	0.000
> 3	2	38		
Total	33	57		

Table 4: hs-CRP with haemoglobin.

Hs-CRP	Hb > 8 g/dl	Hb < 8 g/dl	P- value
Hs-CRP < 3	26	24	0.04
Hs-CRP > 3	8	32	
Total	34	56	

Table 5: hs-CRP with mortality in CKD patients.

Hs-CRP	Hb > 8 g/dl	Hb < 8 g/dl	P- value
Hs-CRP < 3 mg/l	45	5	0.01
Hs-CRP > 3 mg/l	28	12	
Total	73 (m=65,f=8)	17 (m=12,f=5)	

Table 5 shows mortality of 17 out of 90 patients. Among these, elevated hs-CRP levels were observed in 12 patients. Also, the p-value is 0.01 (< 0.05) which means significant difference (Table 5).

Table 6: hs-CRP with need of dialysis in CKD patients.

Hs-CRP	Dialysis need (times per week)					p-value
	1/wk	2/wk	3/wk	4/wk	5/wk	
< 3 mg/L	19	7	18	6	0	.000
> 3 mg/L	3	2	10	16	9	

Table 7: hs-CRP with CKD stage.

Hs-CRP	Stage 3	Stage 4	Stage 5	P – value
< 3 mg/L	5	15	30	0.000
> 3 mg/L	0	3	37	
Total	5	18	67	

Table 8: hs-CRP with diabetes mellitus and hypertension.

Parameters	Hs-CRP < 3	Hs-CRP > 3	Total	P – value
Dm	14	9	23	0.55
Htn	34	36	70	0.01

Table 9: hs-CRP with dyslipidemia.

Parameters	Hs-CRP < 3	Hs-CRP > 3	P – value
Dyslipidemia	10 (11.11%)	14 (15.55%)	0.11
Normal lipid	40 (44.44%)	26 (28.88%)	
	50	40	

CKD patients with elevated hs-CRP levels need frequent and early need of hemodialysis. ($p < 0.00$) (Table 6). The above table shows p value of 0.000 which means significant difference, that is 40 out of 90 patients have elevated hs-CRP, out of which 37 belong to stage 5 CKD (ESRD) (Table 7).

Out of 23 diabetic patients, 9 have elevated levels of hs-CRP, while in 70 hypertensive patients, 36 have elevated levels of hs-CRP. P value for diabetic patients is 0.55 which means no significant difference was observed, so relationship between diabetes and hs-crp cannot be established. P value for hypertensive patients is 0.01 which means significant difference. So, majority of hypertensive patients (36 out of 70) have elevated level of hs-CRP (Table 8).

Dyslipidemia was present in 24 patients (26.66%) out of which 14 (15.55%) patients had hs-CRP > 3 mg/L. p-value for this study is 0.11, so relationship between lipid profile and hs-CRP cannot be established in this study (Table 9).

Out of 44 patients with elevated hs-CRP, 33 had abnormal 2d-echo, among which 28 were male and 5 were female and p value was 0.000 which means significant difference (Table 10).

Table 10: hs-CRP with 2d echo abnormality.

Parameters	hs-crp<3	Hs-crp>3	Total	p-value
Normal 2d echo	42	15	57(m=49f=8)	0.000
Abnormal echo	4	29	33(m=28f=5)	
Total	46	44		

Table 11: hs-CRP with creatinine.

S. creatinine	Hs-CRP <3	Hs-CRP >3	p-value
1.3- 3 mg/dl	14 (15.6%)	0 (0%)	0.000
3.1- 6	18 (20%)	9 (10%)	
6.1- 9	9 (10%)	10 (11.1%)	
9.1- 12	6 (6.7%)	9 (10%)	
12.1- 15	2 (2.2%)	3 (3.3%)	
>15	1 (1.1%)	9 (10%)	

Up-to 9 mg/dl of creatinine level, 41 patients belongs to <3 and 19 patients in >3 Hs CRP level group. But above 9 mg/dl of level, significant higher no of patients was present in >3 Hs CRP level group (Table 11).

DISCUSSION

Despite improvement in dialysis technology over the past decade, mortality and morbidity in ESRD remains high.¹ Recent evidence points to chronic inflammation as a major contributor to this mortality and morbidity.² Traditional risk factors alone cannot explain the unacceptable high prevalence and incidence of cardiovascular disease in this population. Inflammation and other non-traditional risk factors are likely to contribute.⁶ Several factors have been implicated as potential causes of inflammation. These include impaired renal clearance of cytokines, accumulation of advanced glycation end-products (AGEs), atherosclerosis per se, other inflammatory diseases and unrecognised persistent infections. In addition, the uremic syndrome and the dialysis procedure per se has been linked to an increased risk of inflammation. The uremic syndrome and the disease state associated with advanced renal impairment involve more than renal excretory failure. A host of metabolic and endocrine functions normally performed by the kidneys is also impaired or suppressed, and this results in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, FGF23, insulin, glucagon, steroid hormones including vitamin D and sex hormones, and prolactin, change with CKD as a result of reduced excretion, decreased degradation, or

abnormal regulation. Finally, CKD is associated with worsening systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, whereas levels of so-called negative acute-phase reactants, such as albumin and fetuin, decline with progressive reduction in GFR. Thus, the inflammation associated with CKD is important in the malnutrition-inflammation-atherosclerosis/calcification syndrome, which contributes in turn to the acceleration of vascular disease and comorbidity associated with advanced kidney disease.¹ Raised levels of hsCRP and other cytokines have been linked to anaemia leading to poor outcome in these patients. The process of inflammation evidenced by elevated hs-CRP levels also causes loss of muscle mass and changes in plasma composition leading to poor nutritional outcomes in ESRD population. The haemopoietic response to inflammation includes anaemia secondary to reduced erythropoiesis. This has been attributed to the inhibition of erythropoietin secretion by pro-inflammatory cytokines. Inflammation can also induce a functional iron deficiency, as cytokines can inhibit the delivery of iron from the reticuloendothelial cells to haemopoietic cells.² The higher incidence of CVD in these patients signify a strong correlation between cardiovascular disease and inflammation in ESRD. There are several ways in which inflammation can promote vascular injury, i.e., through alterations in lipoprotein structure and function, changes in the composition of plasma proteins, alterations in the vascular endothelium, and changes in the expression of specific ligands on the surfaces of platelets, neutrophils, and mononuclear cells.^{7,8}

hs-CRP levels correlated inversely with serum albumin. Albumin, like other nutritional markers, such as pre-albumin and transferrin, is a negative acute phase protein. The synthesis of these proteins decreases during inflammation, as does their serum concentrations, changes that are entirely independent of nutritional status. These results indicate that elevated serum markers of inflammation are associated with a poor nutritional outcome in ESRD patients resulting in increased morbidity and mortality. Further, hs-CRP levels were predictive of poor clinical outcome and early need for haemodialysis. Though there have been quite a few studies in India which have demonstrated an association between hs-crp and chronic kidney disease. The Key findings included:

Demographic profile- Overall incidence in male (85.6%) is higher than in female (14.4%). This means that frequency of CKD increases on increasing age. In a similar type of study done by Keith et al and Foley et al, they found that as age increases, incidence of CKD increases.^{9,10} It was also shown by Chen et al, and Levey et al.^{11,12} In present study, mean age was 48.79 with standard deviation of 13.92, which is similar to the study of Singh et al with (mean±SD) 45.2±15.2 done on 5588 urban patients. On region wise study, out of total 90 patients, 50 patients belong to rural area and 40 belong to

urban area. Majority of patients come under stage 5 CKD (67 patients, 74.4%) followed by stage 4 (18 patients, 20%).

In present study we found that among total (n=90) patients, 70 (75.6%) were associated with hypertension, among which males were 62 (68.9%) and females 8 (8.9%). 23 (25.6%) patients were associated with diabetes mellitus in which 20 (22.2%) were male and 3 (3.3%) female. 11 (12.2%) young patients were associated with glomerulonephritis. It showed that in our study, CKD was most commonly associated with Hypertension which is almost similar to the study carried out by Chhetri et.al.¹³ Mean levels of eGFR (mean± SD) was 11.14 ± 7.85 while the lower and upper limit of eGFR was 2 ml/min/1.73m² and 36 ml/min/1.73m² respectively. Patients with low eGFR had high hs-CRP value.

In this study we were trying to establish relationship between various biochemical parameters like haemoglobin, s. albumin serum urea, creatinine, urinary protein, lipid profile and eGFR with hs-CRP. Comorbidities like diabetes mellitus, hypertension, cardiovascular events, mortality and need of hemodialysis were also compared with patients hs-CRP levels. In present study out of 90 patients, 40 patients (44%) had elevated levels of hs-CRP while 50 patients (55.6%) had hs-CRP value below 3 mg/L.

In due course, we found that in cases (n=90) serum hs-CRP (Mean± SD) was 3.62 ± 2.18 , by taking in account of confidence interval of 95%, while the lower and upper limit of serum hs-crp was 1 and 10 respectively. Mean hs-CRP was 2.06 ± 1.82 in a similar study done by Nand et al. Mean levels of s. albumin (n=90) (mean±SD) is 3.21 ± 0.64 , while the lower and upper limits of s. albumin were 2 g/dl and 6 gm/dl respectively which is similar to Nand N et al, which was 3.26 ± 0.96 . P-value for hs-crp and s.albumin <0.05 and correlation coefficient r value is -0.621, which means hs-crp levels correlated inversely with s. albumin. out of 90 CKD patients, elevated hs-CRP values were observed in 40 patients, among which 38 patients have low s. albumin level (42.2%).¹⁴

Mean levels of haemoglobin (mean±SD) were 7.86 ± 2.58 while the lower and upper limit of haemoglobin was 3 gm/dl and 16 gm/dl respectively, which is almost similar to the studies done by Nand N et al, in which the values were 7.11 ± 1.07 . In present study, p value for hs-CRP and haemoglobin is 0.04, Out of 40 patients with elevated hs-crp, 32 patients have haemoglobin level < 8 g/dl, which means patients with high hs-CRP have low haemoglobin levels.¹⁴

Dyslipidemia was found in 24 patients out of 90, and among these 24 patients, only 14 had elevated hs-crp levels and p value was 0.11 which means no significant difference. So relationship between lipid profile and hs-CRP cannot be established in this study. This was also found by Diana Jalal et al.¹⁵

Diabetes mellitus is present in 23 patients out of 90. Among these diabetic patients, only 9 had elevated levels of hs-crp and also the p value is 0.5, which means there is no relationship between diabetic nephropathy and hs-crp, which is similar to study done by Friedman AN et al.¹⁶

2D echo abnormality was detected in 33 patients, among which most common echo finding was left ventricular hypertrophy, followed by dilated cardiomyopathy. Among these, 29 patients had elevated hs-CRP levels. Thus, higher incidence of cardiovascular disease in CKD patients signify a strong correlation between cardiovascular events and inflammation in End Stage renal disease, resulting in increased morbidity and mortality.

Mortality in CKD patients was 17 (12 male and 5 female) out of 90 patients. Out of these 17 patients, elevated hs-CRP levels were observed in 12 patients. Also, the p-value was 0.01 (<0.05) which means significant difference. 2D echo abnormality (left ventricular hypertrophy, followed by dilated cardiomyopathy) was also present in these 12 patients. Early and frequent haemodialysis was required in patients who had elevated hs-CRP levels. Thus hs-CRP levels were predictive of poor clinical outcome and early need of haemodialysis.

Few cases were also found of connective tissue diseases like SLE, chronic analgesic abuse, obstructive nephropathy, multiple myeloma, polycystic kidney disease and chronic pyelonephritis.

Total 44.4% of cases had an elevated level of hs-CRP (mean 2.06 ± 1.82 mg/dl) and the incidence of cardiovascular events was increased in patients with high values of hs-CRP. Haemoglobin, serum albumin and BMI (body mass index) were significantly higher in patients having low hs-CRP (p <0.001, p <0.05). Very few patients with low hs-CRP required dialysis, whereas 88.75% of patients in high hs-CRP group required haemodialysis (p < 0.001). In this study they found 44.4% of cases had an elevated level of hs-CRP and result were consistent with this study.

A 10-year prospective cross-sectional study carried out at the University of Ilorin Teaching Hospital, Ilorin. Patients were recruited who met diagnostic criteria for stages 4 and 5 CKD were included. All had their standard 12-lead electrocardiogram (ECG) recorded. Results were overall, 86% of the patients had at least one form of ECG abnormality, with hypertension (HTN) and anemia being the main contributory factors. These include left ventricular hypertrophy (LVH) (27.6%), left atrial enlargement (LAE) (21.6%), combination of LVH and LAE (17.2%), and ventricular premature contractions (6%). In present study out of 90 patients 33 patients had echo abnormality with 29 (32.2%) patients had high hs-crp level. Most common echo finding was LVH (22%) followed by dilated cardiomyopathy (8.8%) and IHD

(4.4%). In present study Cardiovascular mortality is major cause of death among CKD patients.

CONCLUSION

Elevated circulating concentrations of CRP are a common phenomenon in ESRD patients. The prevalence and magnitude of inflammation increases as renal function declines. A substantial number of patients with Chronic kidney disease had elevated levels of hs-CRP. Mean hs-CRP levels correlated inversely with serum albumin. These results indicate that elevated serum markers of inflammation are associated with a poor nutritional status, greatly increased risk of cardiovascular disease in ESRD patients resulting in increased morbidity and mortality. There was a linear relationship between hs-CRP and clinical events leading to haemodialysis in this study, suggesting that inflammation influences the clinical outcome in these patients. Further, hs-CRP levels were predictive of poor clinical outcome and early need for haemodialysis. These results suggest that high CRP provides prognostic information in patients with CKD.

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