Prevalence of Cardiac Diseases and its Association with Interleukin-6 Levels in Patients with Chronic Kidney Disease who were on Maintenance Hemodialysis

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ABSTRACT

Introduction: Interleukin-6 (IL-6) is a strong predictor of total and cardiovascular mortality than C-reactive protein, IL-1β, TNF and IL-18 in hemodialysis patients. Hence, the present study was undertaken to know the association between IL-6 and cardiac diseases in Chronic kidney disease (CKD) patients on maintenance hemodialysis.

Material and Methods: A total of 79 CKD Patients aged >18 years, who were on maintenance hemodialysis through arteriovenous (AV) Fistula, twice a week for at least three months were included in the study. The study group was divided into cardiovascular (CV) and non-cardiovascular (non-CV) disease groups. Data collection included blood pressure, hemoglobin, serum creatinine, calcium, phosphorus, alkaline phosphatase, albumin levels and serum IL-6.

Results: The prevalence of cardiac diseases in the present study was 83.5%. Left ventricular hypertrophy (73.4%) was observed as most common cardiac entity. Other cardiac diseases seen were systolic dysfunction (36.7%), ischemic heart disease (34.2%), congestive heart failure (24.1%), valvular heart disease (11.39%), pericarditis (5.06%), arrhythmias requiring treatment (7.6%), and pericardial effusion requiring intervention (1.27%). It was observed that age (p=0.002), Systolic Blood Pressure (p=0.016), Diastolic Blood Pressure (p<0.0001), body mass index (p=0.02), hemoglobin (p<0.0001), serum cholesterol (p=0.038), serum albumin (p<0.0001), serum phosphorous (p=0.003), serum IL-6 (p<0.0001) are statistically significant between CV and non-CV groups. IL-6 is significantly (p<0.05) elevated in patients of CV group when compared to non-CV group. Subgroup analysis revealed that IL-6 was very significant in ischemic heart disease, congestive heart failure, and systolic dysfunction patients.

Conclusions: IL-6 can be considered as an important risk factor for CVD in maintenance hemodialysis patients. Cardiac disease should be picked up and treated in early stages of kidney disease to decrease morbidity and mortality in patients on maintenance hemodialysis.

Keywords: Chronic Kidney Disease; Dialysis; Cardiac Diseases; Interleukin-6; Risk Factors.

INTRODUCTION

Chronic kidney disease (CKD) is a global threat to health in general and for developing countries in particular, because therapy is expensive and lifelong. In India 95% patients cannot afford the cost of dialysis or renal transplantation. Prevalence of CKD is estimated to be 8–16% worldwide and 10-12% in india.[1] According to Indian registry of CKD, the yearly incidence of end stage renal disease (ESRD) in India is approximately 150–200 per million population and diabetes mellitus (DM) is an important cause of CKD in approximately 30–40% of the patients.[2]

The annual mortality from cardiovascular disease (CVD) is significantly higher in CKD patients than in the general population. In dialysis patients, about fifty percent of the deaths are attributed to CVD. Hospitalizations of dialysis patients occur frequently and about a third result in death.[3] Cardiovascular disease (CVD) is the leading cause of death in ESRD patients.[4] The excess cardiovascular risk and mortality is demonstrable in early stages of renal disease and in patients with CKD, with the highest relative risk of mortality in the youngest patients.[5] The high risk for CVD results from the additive effect of multiple factors, including hemodynamic overload and several metabolic and endocrine abnormalities more or less specific to uremia.

Compared with the general population, dialysis patients have a 10 to 20 times greater incidence of cardiovascular death.[6] This excess cardiac mortality is, in part, caused by a high prevalence of cardiac disease before initiation of dialysis and is likely caused by the high prevalence of cardiovascular risk factors in patients with progressive kidney disease.[7] In addition, dialysis patients with cardiac disease have a higher case fatality rate than non-dialysis patients with cardiac disease.[8,9]

The high risk of CVD in CKD most likely results from

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the additive effect of multiple risk factors, some of them considered traditional such as DM, hypertension, hyperlipidemia and others, more specific of renal disease, such as volume overload, anemia, and secondary hyperparathyroidism. However, even after adjusting for all these factors, an unexplained strong association between CKD and CVD remains. A new pathogenic construct of CVD has recently evolved in which the interplay of inflammation, oxidative stress and endothelial dysfunction plays a major role. CKD has been described as a ''micro-inflammatory state'', with a high prevalence of acute phase inflammation and oxidative stress, both of which are associated with a high rate of cardiovascular morbidity and mortality.[10] Interleukin-6 (IL-6) is a stronger predictor of total and cardiovascular mortality than C-reactive protein, IL-1β, TNF and IL-18 in hemodialysis patients.[11] Hence, the present study was undertaken to know the association between IL-6 and cardiac diseases in CKD patients on maintenance hemodialysis.

MATERIAL AND METHODS

This prospective observational study was conducted at department of Nephrology, Narayana Medical College & Hospital, Nellore over a period of two years between January-2012 and January-2014. A total of 79 CKD patients who were on maintenance hemodialysis and attended to the Nephrology ward & Dialysis unit were enrolled into the study. This study was approved by the institutional ethics committee of our institute and a written informed consent was obtained from all the study participants.

CKD Patients aged >18 years, who were on maintenance hemodialysis through arteriovenous (AV) Fistula, twice a week for at least three months were included in the study. Patients aged <18 years; acute kidney injury requiring dialysis; acute CKD requiring dialysis; CKD on MHD associated HIV, HBsAg, HCV positive ; CKD on MHD associated with conditions which cause raised IL-6 levels like inflammatory disorders (rheumatoid arthritis, osteoarthritis, asthma, interstitial lung disease, inflammatory bowel disease, systemic sclerosis, graves' disease, sepsis etc.) were excluded from the study.

The study group was divided into cardiovascular (CV) and non-cardiovascular (non-CV) disease group depending on clinical history, electrocardiogram (ECG) and 2D echo findings.

Study definitions

Ischemic heart disease (IHD): Present or previous history of angina, myocardial infarction (MI), coronary artery bypasses surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).[12]

Congestive heart failure (CHF): Dyspnea plus two of the following - raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension or interstitial edema on chest x-ray.[12]

Dysarrhythmia: Atrial or ventricular rhythm disorder requiring therapy.[12]

LV hypertrophy: Left ventricular mass index is >100 g/m^2 in females and >131 g/m^2 in males. These values are the upper limits of normality among healthy participants in the Framingham Heart Study.[12]

Systolic dysfunction: Fractional shortening of 25% on echocardiogram.[12]

Study procedure: At baseline and thereafter at yearly intervals, a clinical assessment was undertaken to detect the presence of CVD. At monthly intervals, the data collected included blood pressure, hemoglobin, serum creatinine, calcium, phosphorus, alkaline phosphatase and albumin levels. Blood pressure and blood tests were carried out immediately prior to dialysis in hemodialysis patients. Blood pressure was measured in the contralateral arm in patients with patent AV fistula or grafts. For each subject blood pressure and laboratory variables were reported as the mean of the monthly values while on dialysis therapy. Baseline and annual echocardiography were performed. Few patients with ischemic heart disease underwent coronary angiogram. At start of study we had 92 patients and subsequently at end of study period 79 patients were left for which the data is shown.

Serum IL-6 measurement: Serum IL-6 was measured in 79 patients at the end of study. Blood samples for IL-6 testing were collected and serum was collected immediately. Serum samples were stored at -20^0 C after processing for batched analysis. Biochemical analysis was done by DIACLONE HUMAN IL-6 ELISA kit (solid Sandwich). Serum IL-6 level was expressed as pg/ml.

STATISTICAL ANALYSIS

The data values were maintained in MS-Excel and Statistical analysis was performed by using SPSS v20.0 (IBM Corp, Somers, NY, USA) and Microsoft-Excel. For categorical variables, the values were expressed as Frequencies with Percentages and for continuous variables, the values were expressed as Mean ± Standard Deviation (SD) and analyzed with Independent samples t-test. P-value <0.05 was considered significant.

For risk factor identification in cardiovascular group logistic regression analysis was used. The interpretation of odds ratio for continuous type variable is not that much appropriate, for that we make use of another measure of accuracy known as Area Under Curve (AUC). The value of AUC between 0.5 and 1 was considered significant.

RESULTS

The mean age of the study patients was 45.66±13.43 (range 21-74 years). The total number of males were 51 (64.56%) and females 28 (35.44%). Out of 79 patients, 29 (36.71%) patients were diabetics. The mean duration of dialysis in months was 22.80±14.92. Table-1 shows the demographic variables and other clinical characteristics of our study population.

The study group was divided into cardiovascular (CV) and non-cardiovascular (non-CV) groups depending on clinical

history, ECG and 2-D echo findings. Out of 79 patients, 66 (83.54%) patients were in CV group and 13 (16.16%) patients were in non-CV group.

Prevalence of cardiac diseases in the study

The prevalence of cardiac diseases in the present study was 83.5%. Patients in the study group had one or more cardiac disease and there was substantial overlap between various cardiac diseases. Left ventricular hypertrophy (LVH) (73.4%) was observed as most common cardiac entity. Other cardiac diseases seen were systolic dysfunction (36.7%), ischemic heart disease (IHD) (34.2%), congestive heart failure (CHF) (24.1%), valvular heart disease (11.39%), pericarditis (5.06%), arrhythmias requiring treatment (7.6%), and pericardial effusion requiring intervention (1.27%). Findings on prevalence of cardiac diseases is shown in figure-1.

IHD & Coronary angiogram (CAG) in the study

Out of 27 IHD patients, 15 (55%) patients underwent coronary angiogram (CAG) which revealed single vessel disease in 3 (20%) patients, double vessel disease in 6 (40%) patients, triple vessel disease in 4 (27%) patients and normal in 2 (13%) patients (figure-2).

Risk factors identified:

The CV group and non-CV groups were compared using tools like Independent samples t-test and logistic regression analysis to identify the risk factors for CVD on maintenance hemodialysis patients. Table-2 shows comparison between CV group and non-CV group.

On performing Independent sample t-test, it was observed that Age ($p=0.002$), Systolic Blood Pressure (SBP) ($p=0.016$), Diastolic Blood Pressure (DBP) ($p<0.0001$), BMI ($p=0.02$), hemoglobin (Hb) ($p<0.0001$), serum cholesterol ($p=0.038$), serum albumin ($p<0.0001$), serum phosphorous ($p=0.003$), serum IL-6 ($p<0.0001$) are statistically significant, which means that while comparing these variables between CV and non-CV groups, the subjects vary significantly and the subjects belonging to these groups show the mean difference. In particular this test is carried out to study only the significant variation between CVS and Non-CVS groups.

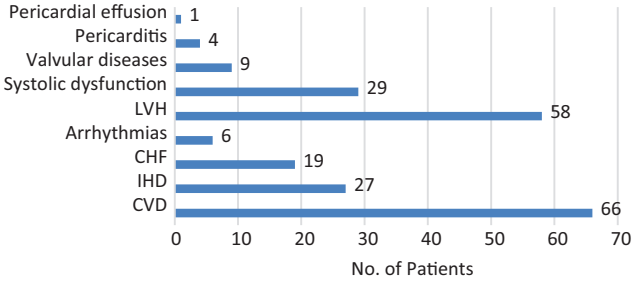
Risk factors

The risk factors found in the present study for cardiac diseases are presence of diabetes mellitus, hypertension, high serum interleukin-6 levels and high phosphorous

Parameters	Mean ± SD / n (%) (n=79)
Age (in years)	45.66 ± 13.43
Male/female	51 / 28
Diabetics	29 (36.71%)
Systolic blood pressure (mm Hg)	149.29 ± 6.73
Diastolic blood pressure (mm Hg)	94.25 ± 5.77
Duration of hemodialysis (in months)	22.80 ± 14.92
BMI (kg/m^2)	20.20 ± 1.79
Hb (g/dL)	8.85 ± 0.93
Sr. Creatinine (mg/dL)	8.18 ± 1.51
Sr. Cholesterol (mg/dL)	142.48 ± 17.98
Sr. Triglycerides (mg/dL)	124.72 ± 33.08
Sr. Albumin (g/dL)	3.39 ± 0.38
Sr. Calcium (mg/dL)	8.12 ± 0.64
Sr. Phosphorous (mg/dL)	4.78 ± 1.62
Sr. CaXP (mg^2/dL^2)	38.85 ± 13.48
Sr. IL-6 (pg/mL)	63.72 ± 23.09
Kt/V	1.22± 0.04

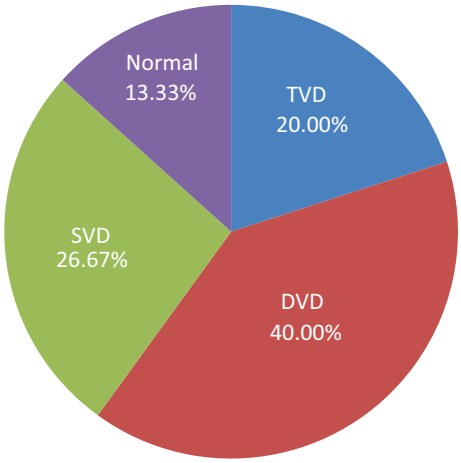
BMI: body mass index; Hb: hemoglobin; CaXP: calcium-P product; IL-6: interleukin-6; SD: standard deviation.

Table-1: Baseline demographic and clinical variables.



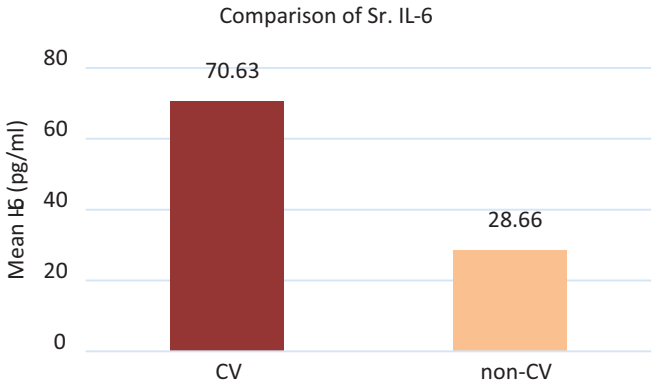
CKD: chronic kidney disease; LVH: left ventricular hypertrophy; CHF: congestive heart failure; IHD: ischemic heart disease; CVD: cardiovascular disease.

Figure-1: Prevalence of Cardiac diseases in CKD patients.



SVD: single vessel disease; DVD: double vessel disease; TVD: triple vessel disease.

Figure-2: Distribution of coronary artery disease.



CV: cardiovascular disease group; non-CV: non-Cardiovascular disease group; Sr.: serum; IL-6: interleukin-6.

Figure-3: Comparison of Serum IL-6 in CV and non-CV groups.

Parameters	CV Group (n=66)	non-CV Group (n=13)	p-value
Age (in years)	47.71 ± 12.94	35.23 ± 11.14	0.002*
Male/female	44/22	7/6	------
Diabetics	28 (42.4%)	1 (7.7%)	------
Systolic blood pressure (mmHg)	150.09 ± 6.52	145.23 ± 6.56	0.016*
Diastolic blood pressure (mmHg)	95.58 ± 5.19	87.54 ± 3.48	< 0.0001*
Duration of hemodialysis (in months)	22.83 ± 15.44	22.62 ± 12.46	0.962
BMI (kg/m²)	19.99 ± 1.73	21.24 ± 1.81	0.02*
Hb (g/dL)	8.67 ± 0.92	9.73 ± 0.26	<0.0001*
Sr. Creatinine (mg/dL)	8.11 ± 1.60	8.52 ± 0.91	0.218
Sr. Cholesterol (mg/dL)	140.62 ± 17.32	151.92 ± 19.03	0.038*
Sr. Triglycerides (mg/dL)	121.82 ± 32.24	139.46 ± 34.64	0.079
Sr. Albumin (g/dL)	3.27 ± 0.28	4.02 ± 0.19	<0.0001*
Sr. Calcium (mg/dL)	8.12 ± 0.66	8.11 ± 0.64	0.964
Sr. Phosphorous (mg/dL)	4.94 ± 1.70	3.97 ± 0.79	0.003*
Sr. CaXP (mg²/dL²)	40.14 ± 14.08	32.33 ± 7.21	0.056
Sr. Interleukin-6 (pg/mL)	70.62 ± 18.26	28.66 ± 8.17	<0.0001*
Kt/V	1.21 ± 0.05	1.23 ± 0.03	0.132

CV: cardiovascular; BMI: body mass index; Hb: hemoglobin; CaXP: calcium-P product.
*Indicates significant p-value.

Table-2: Comparison of risk factors between CV and non-CV Group.

Parameters	Odds ratio	AUC
Diabetic mellitus	0.113	
Systolic blood pressure (mmHg)	2.334	0.722
Diastolic blood pressure (mmHg)	0.221	0.917
Sr. Phosphorous (mg/dL)	1.103	0.689
Sr. IL-6 (pg/ml)	0.364	0.999

AUC: area under the curve; Sr.: serum; IL-6: interleukin-6.

Table-3: Odds ratio and AUC for risk factors in cardiovascular group.

Parameters	Status of parameter	Sr. IL-6 (pg/ml) Mean ± SD	t-value	p-value
LVH	P (N=58)	68.39 ± 17.59	-3.152	0.011
	N (N=8)	86.85 ± 15.22		
CAD	P (N=27)	88.46 ± 12.07	11.42	< 0.0001
	N (N=39)	58.29 ± 9.38		
CHF	P (N=19)	85.39 ± 13.05	4.847	< 0.0001
	N (N=47)	64.66 ± 16.66		
Systolic dysfunction	P (N=29)	86.06 ± 13.24	9.193	< 0.0001
	N (N=37)	58.53 ± 11.08		

LVH: left ventricular hypertrophy; CAD: coronary artery disease; CHF: congestive heart failure; Sr: serum; IL-6: interleukin-6; SD: standard deviation; P: positive; N: negative.

Table-4: Comparison of IL-6 in various cardiovascular diseases.

levels. The measures of performances, such as odds ratio and Area under the curve (AUC) are reported in table-3.

Interleukin-6 in study population

Interleukin-6, an inflammatory marker, was measured in study population. On performing Independent sample t-test, it was observed that IL-6 is significantly ($p<0.05$) elevated in patients of CV group when compared to non-CV group (figure-3). Subgroup analysis (table-4) revealed that IL-6 was very significant in IHD, CHF, and systolic dysfunction patients.

DISCUSSION

The results of the present study revealed that the prevalence of cardiac disease is high, about 83.5% on maintenance hemodialysis patients. LVH (73.4%) is most common cardiac abnormality followed by systolic dysfunction (36.7%), IHD (34.2%), CHF (24.1%), valvular heart disease (11.39%), arrhythmias requiring treatment (7.6%), pericarditis (5.06%), pericardial effusion requiring intervention (1.27%). In comparison hemo study showed at baseline, 80% of patients had cardiac diseases, including IHD (39%), CHF (40%) and arrhythmias (31%).[13]

IHD, CHF and LVH are interrelated. It is likely that all share risk factors and that each condition can lead to the other. These diseases are associated with poor outcomes in hemodialysis patients. Data from various studies suggest that a lowering of LV dimensions is associated with improved cardiovascular outcomes in dialysis patients, suggesting that for many patients, LVH shares the dual nature of risk factor and disease state.[14]

Study done by Foley et al[15] revealed the prevalence of LV alterations, including LVH, is high among CKD and ESRD patients in all age groups. The prevalence of LVH is already increased in early renal disease and progresses with a decrease in renal function. On starting dialysis, 75% of adults have LVH, LVH with concentric hypertrophy was seen in 42% of patients and eccentric hypertrophy in 44% of patients. In a prospective, multicentric study Levin et al[16] has identified a decrease in hemoglobin level and an increase in systolic blood pressure as the principal predictors of LVH and its progression. Our study revealed that LVH is the most common abnormality and is present in 73.4% of maintenance hemodialysis patients and risk factors associated with LVH are diabetes and hypertension and low hemoglobin levels.

National registries had reported the prevalence of IHD on starting dialysis, which was 42.9% in the USA, 36% in Australia and New Zealand, and 28% in Canada. In USA the prevalence of heart failure on starting dialysis was 40%.[4] In Canadian multicenter longitudinal study, the prevalence of angina pectoris was 21%, myocardial infarction 18% and heart failure 35%.[17] In our study we observed the prevalence of IHD is about 34.2%. We have done coronary angiogram in 55% of IHD patients which revealed single vessel disease in 20% of IHD patients, double vessel disease in 40%, triple vessel disease in 27% and normal in 13% of IHD patients.

USRDS 2013 reported the prevalence of CHF as 42.9% in CKD population. Studies showed that the prevalence of CHF on the initiation of ESRD was high (31%). The patients without heart failure at baseline subsequently developed heart failure, at a rate of 7% per year. Risk factors for CHF include older age, pre-existing cardiac diseases (systolic dysfunction, LVH and IHD), and potentially reversible abnormalities related to chronic uremia including anemia, hypertension and hypoalbuminemia.[18,19] In our study we found CHF in 24.1% of maintenance hemodialysis patients. CHF was associated with systolic failure, LVH and IHD and risk factors found were older age, pre-existing cardiac diseases, hypertension and anemia which were comparable to the study done by Harnett et al.[19]

Logistic regression analysis showed that the presence of diabetes mellitus, high diastolic blood pressure, high systolic blood pressure and high serum phosphorous levels and high serum interleukin-6 levels are the risk factors for the cardiac diseases in CV group.

In the Canadian study, mean serum albumin levels were 3.9±0.4 g/dL in hemodialysis patients. Among hemodialysis patients, each 1 g/dL decrease in mean serum albumin was independently associated with the development of de novo and recurrent cardiac failure, de novo and recurrent IHD, cardiac mortality and overall mortality. Hypoalbuminemia is a cardiac risk factor for cardiac failure and IHD because it may be a marker for malnutrition, inadequate dialysis, an associated prothrombotic state, dyslipidaemia, chronic inflammation or vitamin deficiency, all of which could potentially pathogenetic to heart.[20] In our study mean serum albumin in CV group was 3.27 ± 0.28 g/dL and in non-CV group 4.02 ± 0.19 g/dL which was statistically significant.

It was reported that 6% increase in mortality per one mg/dl increase in serum phosphorus concentration.[21] Klassen et al.[22] found that phosphorus concentration was directly associated with pulse pressure and that 1-year mortality was 8% higher per 1 mg/dl increase in phosphorus concentration. Preliminary analysis of data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) shows a 5% increase in the adjusted risk of mortality per 1 mg/dl increase in phosphorus concentration. Thus, numerous data sources confirm that as phosphorus concentration rises above normal limits, mortality is increased. In this study, we also found increased phosphorus levels associated with increased CVD which indicates the need of control of phosphorus levels on maintenance hemodialysis patients.

Inteleukin-6 is a proinflammatory cytokine which is markedly elevated in ESRD patients, which may be due to impaired removal of cytokines, and increased synthesis due to various infectious processes, co-morbid conditions such as coronary heart disease, chronic heart failure.[23] IL-6 is a strong predictor of total and cardiovascular mortality than C-reactive protein in hemodialysis patients.[23] A direct link between IL-6 and cardiovascular mortality was reported in hemodialysis patients.[23-27]

In our study we found IL-6 as a risk factor (AUC=0.999) for development of CVD in patients on maintenance hemodialysis. IL-6 levels were significantly ($p<0.0001$) elevated in patients with IHD, CHF and systolic dysfunction. This finding highlights the importance of inflammation as an unfavorable cardiovascular prognostic factor in hemodialysis patients. In future multicenter and randomized control trials are needed to confirm the role of IL-6 as a risk factor in dialysis patients with cardiovascular diseases. Research has to be done to know whether the treatment with humanized anti–IL-6 receptor (IL-6R) antibody (tocilizumab) can reduce cardiovascular morbidity and mortality in patients with high levels of IL-6.

CONCLUSION

Interleukin-6 can be considered as an important risk factor for CVD in maintenance hemodialysis patients. Keeping cardiovascular risk factor analysis into consideration, patients risk factor profile needs to be improved in terms of, management of diabetic status, control of hypertension, by applying preventive strategy and treatment of inflammation and lastly by advocating measures to prevent hyperphosphatemia. Cardiac disease should be picked up and treated in early stages of kidney disease to decrease morbidity and mortality in patients on maintenance hemodialysis.

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