ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 04 | April - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATION OF INFLAMMATORY BIOMARKERS IN CHRONIC KIDNEY DISEASE ASSOCIATED WITH CARDIOVASCULAR DISEASE IN A TERTIARY CARE HOSPITAL OF WEST BENGAL

Medicine

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ABSTRACT

Introduction: Factors responsible for cardiovascular disease (CVD) become operational from the early course of CKD and are spread over the entire spectrum of it. The relative risks of cardiovascular events are inversely related to the estimated glomerular filtration rate (eGFR). A patient with CKD is more likely to die from CVD rather than CKD which denotes high burden of CVD in subpopulation and need for early intervention to reduce mortality. Generally in the population, early CKD, atherosclerotic disease is predominant cardiovascular disease but as the CKD progresses the burden of non-atherosclerotic disease increases. **Aims:** To evaluate relation of Inflammatory Biomarkers (IB) in CKD patients with and without ECG and Echocardiography evaluated LVH and IHD with hypokinetic or dyskinetic wall motion with specific ECG changes in KPCMCH. **Materials and method**: This study was conducted 18 months at KPC medical college and hospital jadavpur, kolkata-72. 100 patients were included in this study. **Result:** Our study showed that, majority number of patients were Abnormal [64 (87.7%)] in with Echo LVH compared to [16 (59.3%)] without Echo LVH it was statistically significant (p=0.0016) and we also found that, majority number of patients were Abnormal [64 (87.7%)] in with Echo LVH compared to [17 (63.0%)] it was statistically significant (p=0.0272). **Conclusion:** We concluded that the frequency and types of cardiovascular diseases associated with different stages of CKD, traditional risk factors in CVD associated with various stages of CKD.

KEYWORDS

Cardiovascular Disease, Estimated Glomerular Filtration Rate, CKD and Left Ventricular Hypertrophy.

INTRODUCTION

Factors responsible for cardiovascular disease (CVD) become operational from the early course of CKD and are spread over the entire spectrum of it. The relative risks of cardiovascular events are inversely related to the estimated glomerular filtration rate (eGFR). A patient with CKD is more likely to die from CVD rather than CKD which denotes high burden of CVD in subpopulation and need for early intervention to reduce mortality. Generally in the population, early CKD, atherosclerotic disease is predominant cardiovascular disease but as the CKD progresses the burden of non-atherosclerotic disease increases. Moreover with progression of CKD the risk of cardiovascular mortality also increases.

Besides the contribution of traditional cardiovascular risk factors in CKD, increased mortality in these patients may also be due to chronic inflammation and its consequences. Inflammation is part of the complex biologic response of vascular tissue to injury, infection, ischemia, and autoimmune diseases. Within physiologic limits, the inflammatory response enables removal of the inciting agent and initiates the healing process. Impaired excretory renal function prolongs plasma t1/2 of several proinflammatory cytokines such as IL-1 9 and IFNs which may result in enhanced inflammatory load. Unregulated chronic systemic inflammation is associated with increased morbidity and mortality. As a consequence of inflammation, a variety of cytokines and acute phase proteins are released in order to augment or attenuate the inflammatory response."

Cardiovascular abnormalities in CKD: The increasing risk of cardiovascular disease in those with CKD compared to age- and sex-matched general population ranges from 10- to 200- fold, depending on the stage of CKD. Most patients with CKD fall prey to cardiovascular disease before ever reaching stage 5 CKD 12.People with CKD are at increased risk for CVD, and the presence of CKD often complicates CVD treatment and prognosis.

Left ventricular hypertrophy (LVH) increases the risk of cardiovascular (CV) mortality and morbidity in the general population as well as in patients with chronic kidney disease (CKD). Abnormal cardiac geometry in patients with CKD has been attributed to a number of established risk factors as well as risk factors unique to CKD. Evidence from experimental studies indicates that cytokines regulate cardiac remodeling and contractile function. LVH occurs as a result of volume and pressure overload which occurs initially as compensatory response to maintain adequate stroke volume. This resulting cardiomyopathy of CKD leads to diastolic and systolic ventricular dysfunction.

MATERIAL AND METHODS

Place of study: KPC medical college and hospital jadavpur, kolkata-72
Period of study issues relevant to research work 18 months

Sample size / design Out of all the patients being admitted in KPCMCH with CKD, during the study period, first 100 consecutive patients fulfilling the study criteria was selected for the study.

Patients with CKD was identified and diagnosed according to KDIGO criteria 2012.

b. All patients of CKD were evaluated with proper history taking, clinical examination, lab investigations, and urine examination & imaging findings.
c. CKD patients were classified to an appropriate stage according to GFR which is calculated using CK.D-EP1 Creatinine 2009 Equation.
d. The structural and ischernic cardiac abnormalities of the patients were evaluated using echocardiography and 12 lead ECG.
e. C-reactive protein (CRP) was quantified in EIS IA plasma samples using specific laser-based immunonephelometric methods on the BNII.
f. Serum ferritin was measured with standard laboratory methods.
g. Data tabulation
h. Statistical analysis
i. Preparation for thesis writing.

Selection Criteria

Inclusion Criteria -

1. Patients diagnosed with CKD during hospital stay.
2. Known CKD patients admitted due to CKD related or CKD independent complications.
3. Patients on dialysis recently started or on a long course of dialysis giving informed consents.
4. Patients giving informed consent for the study

Exclusion Criteria-

1. Patients <14years & >85years
2. CKD due to vasculitis and other autoimmune diseases.
3. CKD due to storage disease or amyloidosis
4. AKI
5. Patients with Hepatorenal syndrome.

6. Congestive Cardiac Failure,
7. Monogenetic renal disease
8. Cirrhosis of liver
9. Any major infections or septicemia
10. Pregnant women
11. Recent blood transfusion
12. Patient having undergone recent renal transplant surgery
13. Patient on immunosuppressive therapy
14. Patients with malignancy

RESULT AND DISCUSSION

This study was conducted 18 months at KPC medical college and hospital jadavpur, kolkata-72. 100 patients were included in this study. In our study, out of 100 patients, most of the patients were 51-60 years of age [23 (23.0%)] and male population [56 (56.0%)] was higher than the female population [44 (44.0%)].

Faul C et al [1](2011) found that chronic kidney disease (CKD) is a public health epidemic that increases risk of death due to cardiovascular disease. Left ventricular hypertrophy (LVH) is an important mechanism of cardiovascular disease in individuals with CKD. Elevated levels of FGF23 have been linked to greater risks of LVH and mortality in patients with CKD, but whether these risks represent causal effects of FGF23 is unknown. Here, they report that elevated FGF23 levels are independently associated with LVH in a large, racially diverse CKD cohort.

Gupta J et al [2](2012) found that increased risk of mortality in patients with CKD has been attributed to inflammation. However, the association between kidney function, albuminuria, and biomarkers of inflammation has not been examined in a large cohort of CKD patients. This study measured the plasma levels of IL-1β, IL-1 receptor antagonist (IL-1RA), IL-6, TNF-α, TGF-β, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and serum albumin in 3939 participants enrolled in the Chronic Renal Insufficiency Cohort study between June 2003 and September 2008.

We found that, the mean CRP was higher [21.7961±16.0395] in 5 stage compared to [14.8536±23.3489] 4 stage, [12.0000±.0000] 5D stage, [7.0333±2.7142] 3A stage, [6.0000±.0000] 4D stage and [4.9692±2.3789] 3B stage which was statistically significant (p=0.0275). The mean Ferritin was higher [534.7255±278.9271] in 5 stage compared to [480.0000±.0000] 5D stage, [460.0000±.0000] 4D stage, [412.7857±165.2510] 4 stage, [359.0000±115.9416] 3B stage and [340.6667±132.1948] 3A stage which was statistically significant (p=0.0237).

It was found that, the mean CRP Echo was more [18.9795±17.5052] in with CRP Echo compared to without CRP Echo [9.8815±17.4270] which was statistically significant (p=0.0230). The mean Ferritin Echo was more [503.2055± 256.1932] in with Ferritin Echo compared to without Ferritin Echo [360.9630± 110.0448] which was statistically significant (p=0.0064).

Quiroga B et al [3](2012) found that interest in the association between inflammation and chronic kidney disease (CKD) is increasing. During the last 20 years, classical markers have shown an important association between inflammation and mortality in all stages of CKD. Newly discovered biomarkers can help to predict the course of CKD and identify patients at risk of cardiovascular disease and death. They may also come to play an important role in preventing CKD and it complications.

Briasoulis A et al [4](2013) found that chronic kidney disease (CKD) is associated with accelerated cardiovascular disease (CVD) risk and a higher CVD event rate. Substantial data from prospective cohort studies support the concept that dialysis patients as well as those with advanced stage (stages 3–5) CKD are associated with an increased risk for all-cause and cardiovascular mortality. The risk for coronary artery disease (CAD) increases exponentially with declining kidney function, i.e., stage 3 or higher CKD. Indeed, CVD accounts for more than 50 % of deaths in patients with CKD.

Sharain K et al [5](2013) found that chronic kidney disease (CKD) has reached epidemic levels. It is a multisystem disease associated with elevated systemic inflammatory and hypercoagulable states.

Our study showed that, majority number of patients were Abnormal [64 (87.7%)] in with Echo LVH compared to [16 (59.3%)] without Echo LVH it was statistically significant (p=0.0016) and we also found that, majority number of patients were Abnormal [64 (87.7%)] in with Echo LVH compared to [17 (63.0%)] it was statistically significant (p=0.0272).

Tucker P et al [6](2015) found that approximately 10% of Australians show signs of chronic kidney disease (CKD), an irreversible condition characterized by declining kidney function and reduced life expectancy. The majority of CKD-related complications stem from cellular and molecular damage associated with poor blood pressure regulation, exaggerated levels of oxidative stress and inflammation, and reductions in genomic stability.

Xu TY et al [7](2014) found that a positive association between inflammation and chronic kidney disease (CKD) has been reported but the impact of hypertension on this relation remains unclear. The aim of this study is to investigate the association of various inflammation markers with risk of CKD in hypertensive patients. 387 hypertensive patients (mean age 55.5 years) were recruited. Serum matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1(TIMP-1), high-sensitivity C-reactive protein (hsCRP) and osteopontin (OPN) were measured by ELISA.

D'Marco L et al [8](2015) found that the high incidence of cardiovascular events in chronic kidney disease (CKD) warrants an accurate evaluation of risk aimed at reducing the burden of disease and its consequences. The use of biomarkers to identify patients at high risk has been in use in the general population for several decades and has received mixed reactions in the medical community. Some practitioners have become staunch supporters and users while others doubt the utility of biomarkers and rarely measure them. In CKD patients numerous markers similar to those used in the general population and others more specific to the uremic population have emerged; however their utility for routine clinical application remains to be fully elucidated.

We showed that, majority number of patients were Abnormal [31 (88.6%)] in Elevated compared to Depressed [26 (81.3%)] it was statistically significant (p=0.0475). Majority number of patients were Abnormal [32 (91.4%)] in Elevated compared to Depressed [27 (84.4%)] this was statistically significant (p=0.0020).

Niizuma S et al [9](2017) found that mortality among the patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) remains high because of the very high incidence of cardiovascular disease (CVD) such as coronary artery disease, cardiac hypertrophy, and heart failure. Identifying CVD in patients with CKD/ESRD remains a significant hurdle and the early diagnosis and therapy for CVD is crucial in these patients. Therefore, it is necessary for the better management to identify and utilize cardiovascular (CV) biomarkers in profiling CVD risk and enabling stratification of early mortality.

Schwab S et al [10](2018) found that chronic kidney disease (CKD) is associated with high morbidity and mortality. In the past, residual kidney function in CKD patients was assessed by serum creatinine-based equations. However, due to low accuracy of those calculations there is a need for alternative biomarkers. As cardiovascular disease is a major cause of increased mortality in patients with CKD novel biomarkers to estimate risk of cardiovascular death are vital.

Mihai S et al [11](2018) found that despite being a “silent epidemic” disease, chronic kidney disease (CKD) is considered one of the major causes of mortality, together with its main complication, the cardiovascular disease, which contributes to the poor prognosis of these patients. Inflammation has been recognized as an essential part of CKD and is closely linked to cardiovascular complications.

Savoj J et al [12](2019) found that cardiovascular disease is prevalent in patients with chronic kidney disease (CKD) and responsible for approximately half of all CKD-related deaths. Unfortunately, the presence of CKD can lead to a challenging interpretation of cardiac biomarkers essential in accurate diagnosis and prompt management of heart failure and acute coronary syndrome. There is growing interest in novel cardiac biomarkers that may improve diagnostic accuracy reflecting myocardial injury, inflammation, and remodeling. Interpretation of these biomarkers in CKD can be complicated, since

elevated levels may not reflect myocardial injury or wall tension but rather decreased urinary clearance with retention of solutes and/or overall CKD-associated chronic inflammation.

We observed that, most of the patients were Abnormal [32 (91.4%)] in with Dyskinesia group compared to [27 (84.4%)] without Dyskinesia which was statistically significant (p=0.0452). Most of the patients were Abnormal [59 (88.1%)] in with Wall Motion compared to without Wall Motion [19 (56.3%)] though it was statistically significant (p=0.0015).

CONCLUSION

- In our study, out of 100 patients, most of the patients were 51-60 years of age and male population was higher than the female population and male: female ratio was 1.27:1.
- We found that, the mean CRP was higher in 5 stage compared to 4 stage, 5D stage, 3A stage, 4D stage and 3B stage which were statistically significant. The mean Ferritin was higher in 5 stage compared to 5D stage, 4D stage, 4 stage, 3B stage and 3A stage which was statistically significant.
- It was found that, the mean CRP Echo was more in with CRP Echo compared to without CRP Echo which was statistically significant. The mean Ferritin Echo was more in with Ferritin Echo compared to without Ferritin Echo which was statistically significant.
- Our study showed that, majority number of patients were Abnormal in with Echo LVH compared to without Echo LVH it was statistically significant and we also found that, majority number of patients were Abnormal in with Echo LVH compared to it was statistically significant.
- We showed that, majority number of patients were Abnormal in Elevated compared to Depressed it was statistically significant. Majority number of patients were Abnormal in Elevated compared to Depressed this was statistically significant.
- We observed that, most of the patients were Abnormal in with Dyskinesia group compared to without Dyskinesia which was statistically significant. Most of the patients were Abnormal in with Wall Motion compared to without Wall Motion though it was statistically significant.
- We concluded that the frequency and types of cardiovascular diseases associated with different stages of CKD, traditional risk factors in CVD associated with various stages of CKD.

Table: Association between CRP Group: Echo LVH

	ECHO -LVH					
		No	Yes	TOTAL	Chi-square value	p-value
CRP Group	Abnormal Row % Col %	16 20.0 59.3	64 80.0 87.7	80 100.0 80.0	9.9442	0.0016
	Normal Row % Col %	11 55.0 40.7	9 45.0 12.3	20 100.0 20.0		
	TOTAL Row % Col %	27 27.0 100.0	73 73.0 100.0	100 100.0 100.0		
Ferritin group	Abnormal Row % Col %	17 21.8 63.0	61 78.2 83.6	78 100.0 78.0	0.0272	0.0272
	Normal Row % Col %	10 45.5 37.0	12 54.5 16.4	22 100.0 22.0		
	TOTAL Row % Col %	27 27.0 100.0	73 73.0 100.0	100 100.0 100.0		

Table: Distribution of mean CRP ECHO, Ferritin Echo: LVH

		Number	Mean	SD	Minimum	Maximum	Median	p-value
CRP Echo	No	27	9.8815	17.4270	3.0000	96.0000	6.0000	0.0230
	Yes	73	18.9795	17.5052	3.0000	96.0000	12.0000	
Ferritin Echo	No	27	360.9630	110.0448	139.0000	570.0000	355.0000	0.0064
	Yes	73	503.2055	256.1932	53.5000	1170.0000	460.0000	

Table: Distribution of mean Ferritin Echo: LVH

Table: Distribution of mean CRP: CKD STAGE

		Number	Mean	SD	Minimum	Maximum	Median	p-value
CRP	3A	6	7.0333	2.7142	4.2000	12.0000	6.0000	0.0275
	3B	13	4.9692	2.3789	3.0000	12.0000	4.2000	
	4	28	14.8536	23.3489	4.0000	96.0000	7.0000	
	4D	1	6.0000	.0000	6.0000	6.0000	6.0000	
	5	51	21.7961	16.0395	3.0000	49.0000	12.0000	
	5D	1	12.0000	.0000	12.0000	12.0000	12.0000	

Table: Distribution of mean CRP ON DIALYSIS: NOT

		Number	Mean	SD	Minimum	Maximum	Median	p-value
CRP On Dialysis	CD	43	22.8326	19.3239	4.0000	96.0000	12.0000	0.0012
	ED	23	18.5348	21.8204	3.1000	96.0000	12.0000	
	ND	33	7.2727	4.5138	3.0000	24.0000	6.0000	
	NO	1	4.2000	.0000	4.2000	4.2000	4.2000	

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