Prognostic Values of N-Terminal-Pro Brain Naturetic Peptide and Myocardial Perfusion Single Photon Emission as diagnostic tools for Asymptomatic Cardiac Events in Chronic kidney Disease

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Abstract: Background: Patients with end stage renal failure (ESRF) have an increased risk of premature cardiovascular disease which is a leading cause of death. Circulating biomarkers play a major role in the early detection of cardiovascular disease in those patients. N-terminal-pro-BNP is a cardiac biomarker which is frequently elevated in patients with CKD. However, because NT-pro BNP clearance may depend on renal function, the significance of an elevated level in patients with chronic kidney disease (CKD) without cardiac symptoms is uncertain. The use of myocardial perfusion imaging (MPI) for patients with renal disease may be useful for diagnosing CAD and providing powerful information about the risk of future cardiac events. This study aimed to explore the prevalence of different cardiac events in CKD patients according to the grade of kidney damage , to explore the degree of elevation of N-terminal-pro-BNP in asymptomatic cardiac patients with varying degree of CKD; to clarify the relationship between the elevation of this biomarker and the occurrence of cardiac events in CKD patients and to study the usefulness of MPI by Single photon computed tomography (SPECT) as a diagnostic a diagnostic tool for cardiac events in patients with varying degree of CKD regardless hemodialysis. **Subjects and methods:** This case –control observational retrospective study was conducted on 40 CRF patients with varying degree of CKD, 13 –85 years old (mean age 47±17.3 years), recruited from the renal and dialysis unit, department of Internal Medicine, Assuit University Hospitals, Egypt from 2009-2010.In addition to 40 age and sex matched healthy persons as a control group .The patients were classified into two groups: 20 non-dialysis CRF patients on conservative treatment and 20 patients on hemodialysis. All are subjected to thorough history taking, full clinical examination, and anthropometric measurements. We measured serum levels of CRP and N-terminal-pro-BNP in all subjects. MPI by SPECT was done in some selected cases. **Results**: NT-pro BNP levels were elevated in all patients with significant higher levels in ESRD patients on HD. Whereas, the levels of NT-pro BNP were more significantly elevated with Hypertension, Anemia, Hypoalbuminemia, advanced LVH and LV dysfunction , their levels were not significantly elevated with gender ,advanced age and increased BMI. In CKD patients with varying degree, highly significant positive correlations between NT-pro BNP levels and LV mass and LV mass index were found; however, there was a highly significant negative correlation between their levels and systolic function tested by TTE. CRP levels were elevated in all studied patients with significant higher levels in ESRD patients on HD. perfusion defects have been seen in majority of CKD patients. Half of them showed a moderate degree hypoperfusion while one-fourth of cases had severer pattern. Multiple vessel affection was a characteristic feature. Significantly higher NT-pro BNP levels were seen in patients had moderate and severe degrees of hypoperfusion. A highly significant negative correlation between systolic function (EF) evaluated by MPI and NT-pro BNP levels. Majority of Patients with grade II-III CKD under SPECT had mild to moderate degrees of hypoperfusion with good systolic function and a characteristic two vessel affection. However, half of Patients with grade IV-V CKD under SPECT had a severe degree of hypoperfusion with an impaired systolic function .Two and multi-vessel affections are characteristic in Patients with grade IV-V CKD in equal percent. Nevertheless, there was a significant positive correlation between EF evaluated by MPI and TTE. **Conclusion:** In essence, MPI SPECT provides effective risk stratification across the entire spectrum of renal function in CKD patients. Moderate to severe degrees of hypoperfusion with multiple vessel affections were characteristic patterns especially in CKD patients on dialysis. N-terminal-pro-BNP level elevation in asymptomatic patients with CKD reflects underlying ischemic heart disease and hypertrophy independent of renal function in a population with anticipated high cardiac morbidity. Thus, N-terminal-pro-BNP can be a good parameter for predicting the severity of coronary vessels involvement and in evaluating cardiac risk in patients with ESRD especially those on HD besides other diagnostic tools. Severer degrees of hypoperfusion were associated with Higher NT-pro BNP levels. Moreover, there was a highly significant negative correlation between systolic function evaluated by MPI and NT-pro BNP levels.

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1. Introduction

Patients with chronic kidney diseases (CKD) represent a population not only at risk for progression to end stage renal disease (ESRD), but also at even greater risk for cardiovascular diseases (CVD) (**1**). The high prevalence and mortality of CVD in patients with ESRD are well known. The cardiovascular mortality rate in CKD patients is 15 to 30 times higher in than in the general population **(2.** The cardiovascular risk is increased very early on in the evolution of CKD (at a GFR of about 75 ml/min) and increases continuously with decrease in renal function. The CVD is independently associated with kidney function decline **(3).** Therefore, Patients with moderate to severe CKD are at a high risk of developing congestive heart failure (CHF) and that the majority of these patients have coronary heart disease or risk equivalents. Because these associations are observed early during the evolution of CKD, the presence of even subtle kidney dysfunction is a condition that should result in intensive prevention of cardiovascular risk (**4).** Recently, the importance of heart-kidney interaction has received widespread attention, and a new classification of the cardio-renal syndrome (CRS) with five subtypes has been proposed. In this classification, CRS type 4 is characterized by a condition of primary CKD contributing to decreased cardiac function, ventricular hypertrophy and/or increased risk of adverse cardiac events **(5).** The underlying pathological state is caused by a complex interplay of traditional and nontraditional risk factors that results in atherosclerosis, arteriosclerosis, and altered cardiac morphological characteristics. Sustained status of chronic inflammation and endothelial dysfunction are closely linked to several complications of CKD, such as vascular degeneration, myocardial fibrosis, and loss of appetite, insulin resistance, increased muscle catabolism and anemia. These consequences of a chronically activated immune system impact on the acceleration of atherosclerosis, vascular calcification and development of heart dysfunction**.** Albuminuria is a well-established predictor of increased cardiovascular risk. **(6).** Albuminuria is also associated with other cardiovascular risk factors, such as abnormalities in fibrinolysis, inflammation, and dyslipidemia; thus it may represent a glomerular reflection of a generalized increase in endothelial permeability **(7)**. Low thyroid hormone levels in CKD patients could act as an intermediate link between the inflammatory stress and impaired cardiovascular response. Low T3 levels specifically predicted cardiovascular mortality in CKD patients, and they were associated with left ventricular hypertrophy **(8).** Cardiovascular vascular ossification should currently be considered as a cardiovascular risk marker and not an etiological factor of CVD in CKD patients **(**9**).** Undoubtedly, Fat mass-adipokines imbalance act as protectors and as promoters of vascular disease in CKD **(10).** Oxidative stress appears to play a central role in the development and progression of CVD and its complications Increased levels of oxidative stress markers are present in the plasma of CKD patients, which indicates that uremia is a prooxidant state **(11).** Asymptomatic individuals with progressive CVD are a group of patients that deserve focused attention because early detection and intervention may provide the best opportunity for improved outcome. However, identifying CVD in asymptomatic patients with CKD or end-stage renal disease remains a significant hurdle in the management of these patients. **(12)**. The most common manifestation of cardiovascular disease in CKD patients is left ventricular hypertrophy (LVH), predominantly as a result of hypertension and anemia. LVH is a powerful independent predictor of cardiovascular disease in CKD patients. However, identifying which patients will suffer cardiovascular events is challenging and requires early identification and treatment. The ability to detect significant cardiovascular dysfunction at an early stage could facilitate more aggressive and focused treatment of those at increased risk **(13).** Recently, a number of cardiovascular biomarkers were identified as predictors of patient outcome in individuals with CVD. The critical role of these markers as promising prognostic indicators for patients with acute coronary syndrome is identified **.**Cardiovascular biomarkers may be used to guide the early diagnosis of and therapy for CVD in patients with CKD **(14).** N-terminal-pro-BNP is a polypeptide secreted by ventricles of the heart in response to excessive stretching of heart muscle cells. One of the major contributing factors for markedly elevated levels in this population is a very high prevalence of LV structural and functional abnormalities, where its levels are strongly associated with LV hypertrophy and systolic dysfunction in patients in all stages of CKD (**15).** Plasma BNP was a reliable marker of LV overload and had a powerful predictive potential for heart failure in non dialysis patients with CKD and also reflected the presence of myocardial ischemia in asymptomatic patients with CKD and ESRD **(16**). Lower GFR and hematocrite, and higher protein excretion may be associated with volume expansion in CKD patients and this suggest that these processes are associated with increased N terminal –pro-BNP level and may play a role in the development of heart failure **(17)** . So the levels of BNP and its partner have to be interoperated in light of the degree of renal

dysfunction (**18**). Majority of studies nearly suggest superiority of NT pro BNP over other biomarkers especially cTnT for prognostication and risk stratification of cardiovascular events and mortality including LV systolic function and LV mass index and CAD **(19)**. Less invasive methods such as stress ECG or cardiac scintigraphy have been used for the evaluation of coronary artery syndromes in CKD patients without any chest symptoms (**20**). However, is under dispute for the now recognized reduced sensitivity and specificity of non invasive testing in renal patients compared to that in general population, a finding that prompted many investigators to recommend direct diagnostic coronary angiography in high- risk patients, however it is found that the prevalence of significant CAD was less than 50% suggesting a need for better screening mechanisms that could identify high risk individuals **(21)**. Myocardial perfusion scan (MPS) provides effective risk stratification across the entire spectrum of renal function. Renal dysfunction is also an important independent predictor of cardiac death in patients undergoing MPS. Renal function and MPS have additive value in risk stratifying patients with suspected coronary artery disease. Patients with CKD appear to have a relatively less benign prognosis than those without CKD, even in the presence of a normal scan (**22)**. In this study we aimed to explore the level of elevation of N-terminal-pro-BNP in asymptomatic cardiac patients with varying degree of CKD; to clarify the relationship between the elevation of this biomarker and the occurrence of cardiac events in CKD patients such as left ventricular dysfunction, LV hypertrophy, coronary artery diseases (CAD) and sudden cardiac death, and to study the usefulness of stress myocardial perfusion abnormalities on single- photon emission CT (SPECT) in the risk stratification of patients of patients with varying degree of CKD on HD and non- dialysis patients.

2. Material and Methods:

This case –control observational retrospective study was conducted on forty CRF patients with varying degree of CKD, 13 –85 years old (mean age 47±17.3 years), recruited from the renal and dialysis unit, department of internal medicine, Assuit University Hospitals, Egypt from 2009-2010.In addition to forty apparently healthy persons, 17 –70 years old (mean age 42±13.25 years), recruited mainly from the medical staff and their families who underwent health examination at Assuit University Hospitals were enrolled in the study as a control group. The study was approved by the ethical committee of Faculty of Medicine, Assuit University and a written informed consent was obtained from each participant. All patients were classified into two groups. The first group included 20 non-dialysis CRF patients on conservative treatment (age range: 48-85 yr; 11 males, 9 females,). The second group included 20 hemodialysis (HD) patients (age range: 13-65yr; 10 males, 10 females). Patients were excluded if they had past or present history of cardiovascular events (heart failure or history of coronary artery disease (i.e., angina pectoris, previous myocardial infarction, and coronary artery intervention), congenital or organic valvular heart disease, Diabetes mellitus and Hypertension. GFR is estimated by modified MDRD equation, The mean duration of CKD is 1 ± 120 months with median 4.5 months. The HD patients were on regular HD (three session / week). The type of dialyzer membrane was polysulphone with bicarbonate dialysate with, the dialysate flow rate was 500 mL/ min, and blood flow ranged from 250 to 300 mL/min. The mean duration of HD is 1 ± 48 months with median 2 months. Dialysis adequacy was assessed by measuring urea kinetic modeling (mean urea kinetic modeling, 2.38 ±0.44). All patients are subjected to thorough history taking, full clinical examination, and anthropometric measurements including weight, height and BMI. Blood samples were drawn in the morning after an overnight fast of 12-16 hours. After centrifugation to yield platelet-poor plasma from samples on anticoagulant (3.8% sodium citrate) and serum from clotted blood samples, serum and plasma samples were stored in aliquots at _20 °C until assay. Peripheral hemogram was performed on whole blood samples on EDTA using Beckman Coulter Hmx, USA. Liver function tests, kidney function tests, serum electrolytes: Ca, K, Na and Mg. and lipogram were tested for both patients and controls and were measured by standard laboratory methods using Hitachi 911 autoanalyser. Urinary protein by dip stick method was performed. We measured serum levels of some cardiac biomarkers as CRP and N-terminal-pro-BNP in all patients. Blood samples for N-terminal-pro-BNP were collected from all patients before the commencement of a dialysis session, from the venous line. The samples were collected in chilled tubes containing (EDTA) and were immediately centrifuged at 4°C. Plasma was separated and stored at -20°C until assays were performed. NT-pro BNP was measured using a commercially available electro-chemoluminescence immunoassay that was performed on a Roche E2010 modular analytics system. Electrocardiogram (ECG) was performed to all participants for detection of Sokolow criteria of left ventricular hypertrophy, ischemic changes and abnormalities of electrolyte disturbances. Trans-thoracic Echocardiography (TTR) was done to all studied groups, on an inter-dialytic day in the evaluation phase. M-mode and two-dimensional images as well as spectral- and colour-flow Doppler

recordings were obtained (ATL). Left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), inter-ventricular septal thickness (IVST), left atrial diameter (LAD) and left ventricular posterior wall thickness (LVPWT) were measured. Left ventricular diastolic dysfunction obtained by transmitral flow velocity rely on E:A ratio. Left ventricular ejection fraction (LVEF) was calculated by standard techniques. Left ventricular mass (LVM) was calculated by the regression equation described by Devreux and Reichek. While myocardial perfusion imaging (MPI) by Single photon computed tomography (SPECT) was done in twelve selected cases.

Statistical analysis:

Data were analyzed with Statistical package for social sciences (SPSS) version 16 Chicago.USA. Data for continuous variables were expressed as means ±SD and median. Categorical variables were expressed as absolute numbers and percentages .comparison between two groups were analyzed by non –parametric test: Mann-Whitney test for continuous variables; and fisher exact test for discrete variables. The student unpaired *t*- test was used to determine significance for numeric variables. Spearman's rank univariate correlation study was done for correlation between two continuous variables. *P* value < 0.05 is considered statistically significant. Separate receiver operating characteristic curves (ROC) were generated for NT-pro-BNP and detection of systolic dysfunction, diastolic dysfunction; left ventricular hypertrophy (LVH) and segmental wall motion abnormality (SWMA). The best cut-off was defined on the basis of analysis of the ROC curves by identifying the value of the biomarker that gave the best combination of sensitivity and specificity, that is, the value that maximized the sum of the sensitivity and specificity. The ROC curve analysis was performed using the MedCalc software version 7.50 (Mariakerke, Belgium).

3. Results

In the present case –control observational retrospective study, the Demographic, laboratory characteristics and echocardiographic findings of the studied groups are presented in Table (1).Healthy volunteers and both groups of patients with CRF (on dialysis and on conservative treatment) did not differ significantly regarding age, sex and body mass index. Hemoglobin level and eGFR were significantly lower in all groups of CRF patients compared to controls. However, CRP and NT-pro BNP levels were significantly higher in all groups of CRF patients compared to controls. The left ventricular mass (LVM) and left ventricular mass index (LVMI) were higher than reference range in our patients when compared to controls .On the other hand , systolic cardiac function (EF) of the studied patients was statistically insignificantly lower than control group. According to measurement of glomerular filtration rate by modified MDRD equation (eGFR) half of CKD patients had grade V and underwent regular Hemodialysis, while non dialysis patients had grade I-IV represent the rest with statistically insignificant difference. Table (2) showed some cardiac risk factors in CRF patients where Hypertension, Hypocalcaemia and Hypoalbuminemia were highly statistically significantly elevated in HD patients when compared to non dialysis CRF patients, while Hyperlipedemia, Anemia and Albuminuria had no statistical difference in HD patients when compared to non dialysis CRF patients. The LVH on TTE was more prevalent in HD patients with high statistically significantly difference when compared to non dialysis CRF groups. Moreover, the mean values of LVM and LVMI were statistically significantly higher in HD patients compared to non-dialysis patients, the majority of patients had LV dysfunction (77.5%) with no statistically difference in HD patients compared to non-dialysis patients. Isolated diastolic dysfunction (60%) had equal prevalent in both groups of patients regardless HD, with no statistically difference. Systolic dysfunction was more prevalence in HD patients with no statistically difference when compared to non-dialysis patients , whereas 27.5% of patients had SWMA on TTE in the form of hypokinesia and akinesia, with more prevalence in HD patients with no statistically difference when compared to non-dialysis patients. Isolated SWMA (17.5%) had more prevalent in both groups of patients regardless HD than that changes associated with cardiomyopathy, with no statistically difference in HD patients when compared to non-dialysis patients. Uremic cardiomyopathy was observed only in HD patients (20%) but with no statistically difference when compared to non-dialysis patients, as shown in Table (3). Table (4) showed values of studied cardiac biomarkers: CRP and NT-pro BNP levels in studied patients according to CKD stages: the CRP and NT-pro BNP were elevated in all studied patients with statistically significant higher levels in ESRD patients on dialysis compared to those patients not undergo dialysis (with mean±SD of 77.70 ± 25.49 and 26.70 ±21.10 and 9048.0 ± 2316.39 and 4359.5 ±948.55, with $p<00001$ for each) respectively. Figure (1) showed a highly statistically significant positive correlation between NT-pro BNP levels and CRP (r= 0.751with p=0. 0001). Table (5a and b) showed that NT-pro BNP levels were not significantly elevated with advanced age , male gender and increased BMI ((mean±SD of 6737.50 ± 2670.51 , 7056.67± 3100.43 , 6746.47 ±2510.17 ,

with $p<0.9$ for each) respectively whereas, their levels were more significantly elevated with Hypertension, Anemia and Hypoalbuminemia (with mean±SD of 7440.65 ± 2915.84, 7083.13 ±3066.90 and 7790.74 ±2941.42, with $p<00001$for each) respectively in all studied patients when compared to controls. Table (6) showed the significant higher levels of NT-pro BNP levels were found in patients with advanced LVH, diastolic and systolic dysfunction and segmental wall motion abnormality in studied patients when compared to those patients had no LVH, LV dysfunction and SWMA in their TTE (mean ±SD 7873.57± 2719.31, 7524.52±2824.74, 10371.43 ± 2771.71, and 8709.09 ± 3512.39 with $p<00001$) respectively. A highly significant positive correlations between NT-pro BNP levels and LV mass and LV mass index (r= 0.772 and r= 0.715with $p=0.0001$ for each) were found as shown in figures (2 a and b) however, there is a highly significant negative correlation between NT-pro BNP levels and systolic function (EF %) tested by TTE (r= -0.483, $p=0.0001$) as shown in figure (2 c). Receiver operating curve (ROC) shows high sensitivity and specificity of NT-pro BNP values with LVH, diastolic dysfunction , systolic dysfunction and SWMA in CKD in varying degrees (sensitivity = 92.9% , specificity=83.3%, sensitivity = 96.8% , specificity=93.9%, sensitivity = 85.7%, specificity=81.8%, and sensitivity = 54.5%, specificity=93.1% with optimum cut off of > 4700 , 3990, 8700, and 9500 respectively and AUC of 0.936, 0.984, 0.887, 0.478 respectively as shown in figures (3 a, b, c) . For patients with echocardiograms, NT-pro BNP level predicted prior CAD events independent of LVH. Their levels are strongly associated with LV hypertrophy and systolic dysfunction in patients in all stages of CKD. Table (7) showed that defects in MPI by Single photon computed tomography (SPECT) have been seen in majority of CKD patients (n=11; 91.7%). 50% of them show mild to moderate and moderate degree hypoperfusion while severe degree hypoperfusion have been shown only in 25% of cases. One patient had normal perfused myocardium with negative correlation to the grade of CKD. Multiple vessel affection was a characteristic feature. The Majority of patients (n=6; 50%) had two vessel affection while Multi-vessel affection was found in only 3 cases (25%). Half of the patients (n=6; 50%) had an impaired systolic function. (EF < 50%). 83.3% of Patients with grade II-III CKD under SPECT MPI had mild, moderate and mild to moderate degrees of hypoperfusion with only one patient of them(16.7%) had an impaired systolic function (EF < 50%) and half of patients (50%) had two vessel affection. Severe degree of hypoperfusion and multi-vessel affections had not been detected in this group of patients .However, 50% of Patients with grade IV-V CKD under SPECT MPI had a severe degree of hypoperfusion with mild to moderate degrees of hypoperfusion in 33.3% of cases. The majority of patients (83.3%) had impaired systolic function (EF < 50%) and whole patients had two and multi-vessel affections in equal percent 50% for each as shown in table (8). High NT-pro BNP levels were significantly recorded in patients have moderate and severe degrees of hypoperfusion (means ±SD of 8550.0 ± 3809.86 and 4600.0 ±463.68, with $p<0.035$, respectively) as shown in Table (9). Figure (4) showed that there was a highly significant negative correlation between systolic function (EF) evaluated by MPI and NT-pro BNP levels (r= -0.804; $p=0.0001$). Nevertheless, Figure (5) showed that there was a significant positive correlation between systolic function (EF) evaluated by MPI and by TTE (r = 0.607; $p=0.036$).

Table (1): Demographic and laboratory characteristics of the studied groups

Studied groups / Characters	Cases (n= 40) No. %	Control (n= 40) No. %	*P*-value
Age:			
< 40 years	12(30.0)	18(45.0)	NS
≥ 40 years	28(70.0)	22(55.0)	
Mean ± SD	47.63 ± 17.93	42.00 ± 13.25	NS
Range	13-85 years	17-70 years	
Sex:			
Male	21(52.5)	25(62.5)	NS
Female	19(47.5)	15(37.5)	
BMI:			
Mean ± SD	24.86 ± 6.28	23.10 ± 2.65	NS
Range	17 – 40	18 – 30	
HB level (Mean ± SD)	8.40±2.14	12.49±1.02	0.000*
e GFR (Mean ± SD)	24.3±23.75	105.18 ± 10.20	0.000*
CRP level (Mean SD)	52.20±34.65	6.00±0.00	0.000*
NT pro BNP(Mean SD)	6703.75±2947.68	124.83±140.40	0.000*
LVM (Mean ± SD)	253.95±104.53	123.23 ± 13.17	0.000*
LVMI (Mean ± SD)	71.87 ± 26.23	33.43 ± 5.50	0.000*
EF by echocardiography	61.65 ± 10.17	66.85 ± 6.15	NS

LVM=left ventricular mass. LVMI=left ventricular mass index. CRP=C - reactive protein
HB= hemoglobin NS =non significant Highly significant= **P<0.000

Table (2): Cardiac risk factors in the studied patients

Risk factors	Total (n= 40)		Non hemodialysis patients (n= 20)		Hemodialysis patients (n= 20)		*P*-value
	No.	%	No.	%	No.	%	
Hypertension	31	77.5	11	55.0	20	100.0	0.001*
Hyperlipidemia	18	45.0	7	35.0	11	55.0	NS
Anemia	32	80.0	15	75.0	17	85.0	NS
Hypocalcaemia	32	80.0	13	65.0	19	95.0	0.044*
Hypoalbumenaemia	27	67.5	8	40.0	19	95.0	0.000**
Albuminurea	30	75.0	15	75.0	15	75.0	NS

NS =non significant **P*<0.05 = is significant ***P*<0.000 = is highly significant

Table (3): Echocardiographic findings in the studied patients

Echocardiographic findings	Total cases (n= 40)		Non Hemodialysis Patients n= (20)		Hemodialysis patients (n= 20)		*P*-value	
	No.	%	No.	%	No.	%		
LVH								
Total cases of LVH	28	70.0	9	45.0	19	95.0	0.001*	
LVMI (Mean ± SD)	71.87±26.23		54.72±17.29		89.02±22.22		0.000*	
LVM (Mean ± SD)	253.95±104.53		178.75±63.64		329.15±80.44		0.000*	
LV dysfunction								
Isolated diastolic dysfunction	24	60.0	12	60.0	12		60.0	NS
Total	31	77.5	13	65.0	18		90.0	NS
None	9	22.5	7	35.0	2		10.0	NS
SWMA								
Total	11	27.5	4	20.0	7	35.0		NS
Isolated SWMA	7	17.5	4	20.0	3	15.0		NS
Associated with cardiomyopathy	4	10.0	0	0.0	4	20.0		NS

Non significant = *P*>0.05. **P*<0.0001 = highly significant

Table (4): Degree of elevation of cardiac biomarkers (CRP and N-terminal –pro BNP) in the studied patients according to CKD stage

Biomarker	Total (n= 40)	Non dialysis Patients (n= 20)	Dialysis Patients (n= 20)	*P*-value
	Mean ± SD	Mean ± SD	Mean ± SD	
CRP	52.20±34.65	26.70±21.10	77.70±25.49	0.000*
NT- pro- BNP	6703.75±2947.68	4359.50±948.55	9048.00±2316.39	0.000*

***P*<0.0001 =A highly significant**

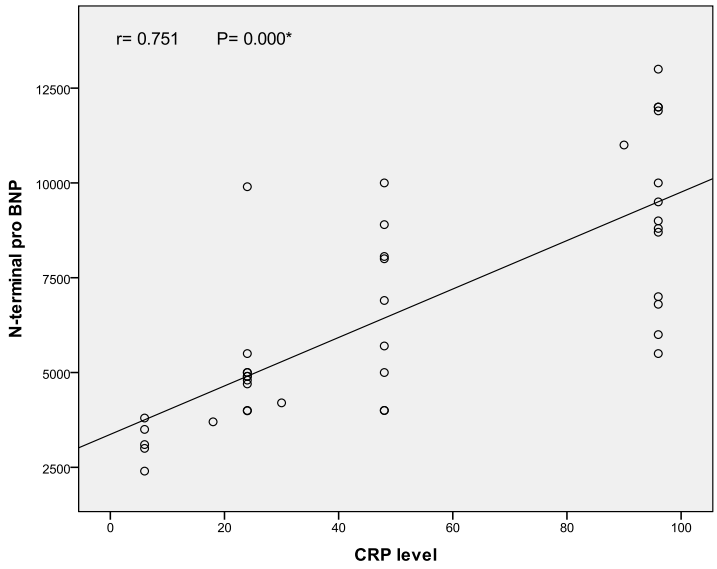


Figure (1): Correlation between CRP and N-terminal-pro BNP levels in the studied patients

Table (5): Factors affecting the level of NT pro-BNP (5a) in studied patients compared to controls.

NT pro-BNP / variables	CKD patients n=40	Controls n=40
	Mean ± SD	Mean ± SD
Age:		
< 40 years	6625.00 ± 3645.70	260.83 ± 134.97
≥ 40 years	6737.50 ± 2670.51	268.09 ± 146.13
P-value	NS	NS
Sex:		
Male	7056.67 ± 3100.43	257.40 ± 152.97
Female	6313.68 ± 2799.84	218.53 ± 117.42
P-value	NS	NS
BMI:		
Normal	6646.09 ± 3288.76	234.48 ± 144.15
Overweight/ obese	6746.47 ± 2510.17	271.56 ± 130.28
P-value	NS	NS

Non significant = *P*>0.05.

(5 b) Factors affecting the level of NT pro-BNP only in the studied patients.

Variable \ NT pro-BNP	Present Mean ± SD	Absent Mean ± SD	*P*-value
Hypertension	7440.65 ±2915.84	4165.56 ± 1059.68	0.002*
Anemia	7083.13 ± 3066.90	4186.25 ± 1861.36	0.04*
Hypoalbumenamia	7790.74 ± 2941.42	4446.15 ± 1145.73	0.000*
Albuminurea	6805.00 ± 3101.13	6400.00 ± 2554.73	NS

*** A highly significant = *P*<0.0001 Non significant = *P*>0.05.**

Table (6): The relation of N-terminal pro BNP levels to the LVH, LV diastolic dysfunction, systolic dysfunction and segmental wall motion abnormality (SWMA) detected by Transthoracic Echocardiography.

Parameter	N-terminal pro BNP Mean ± SD		*P* value
	Present	Absent	
LVH	**7873.57± 2719.31**	**1103.90 ± 1661.38**	**0.000***
LV diastolic dysfunction	**7524.52 ± 2824.74**	**910.27 ± 1475.19**	**0.000***
LV Systolic dysfunction	**10371.43± 2771.71**	**2811.82 ± 3256.14**	**0.000***
SWMA	**8709.09± 3512.39**	**2638.59 ± 3211.91**	**0.000***
A highly significant = *P*<0.0001			

Figure (2a): Correlation between N terminal pro BNP and LVM

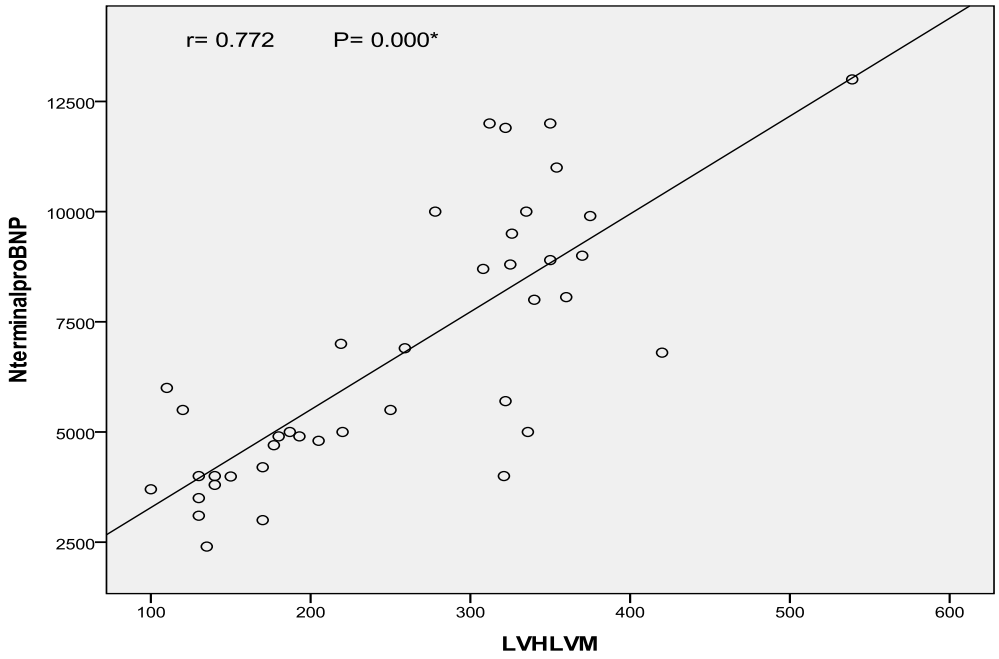


Figure (2b): Correlation between N terminal pro BNP and LVMI

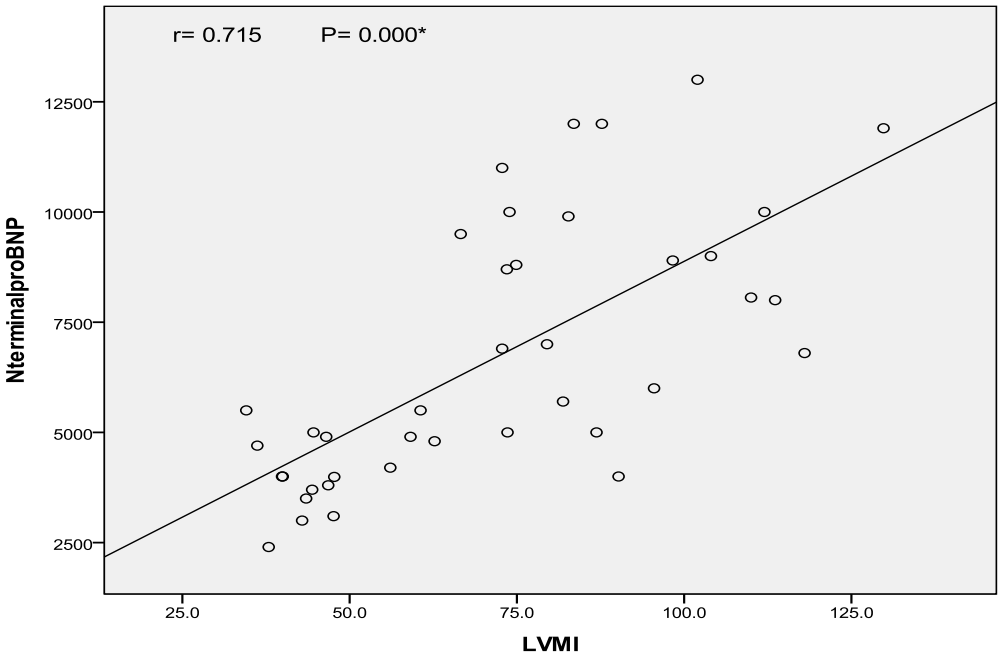


Figure (2c) Correlation between N-terminal and EF (systolic function) by echocardiography

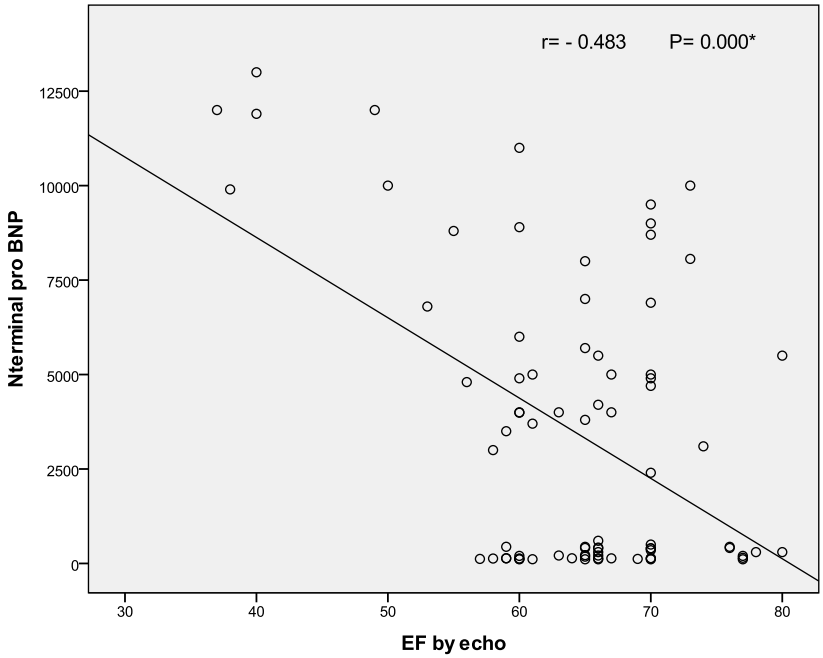
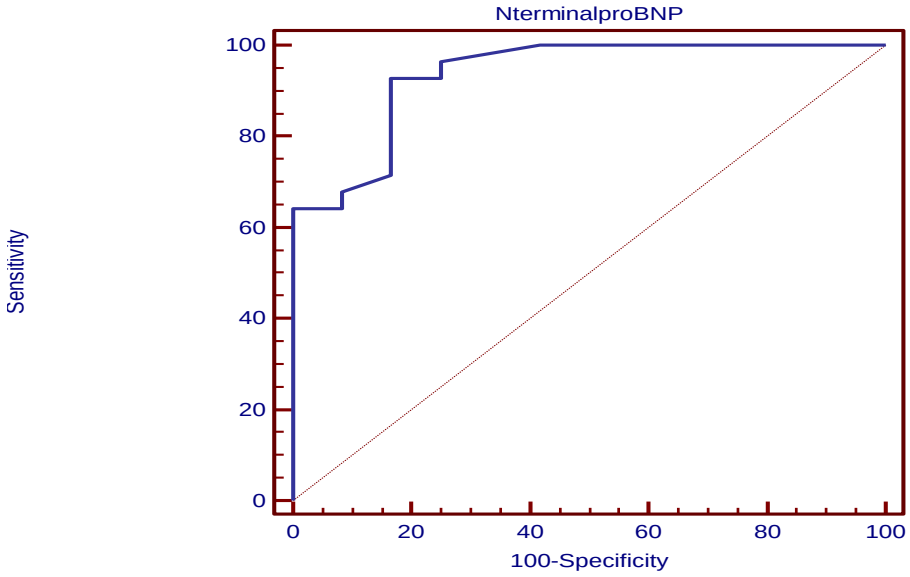
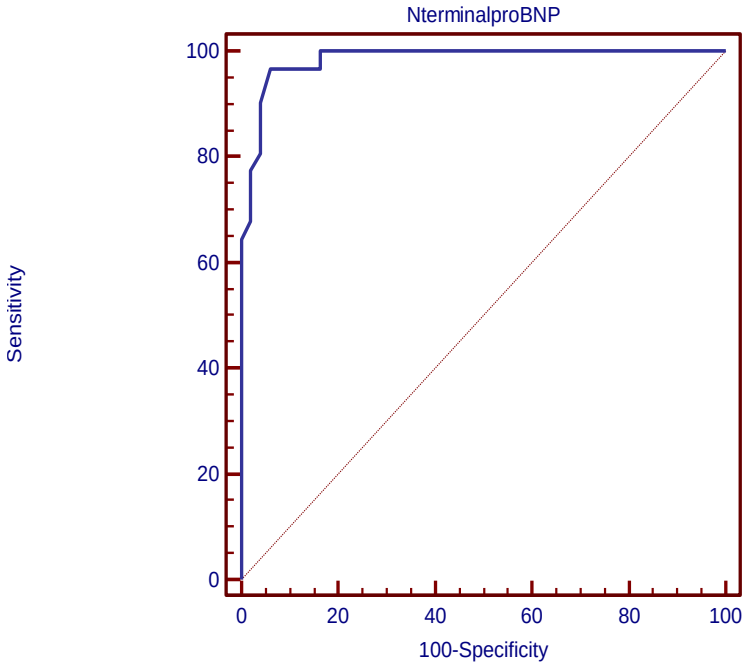


Figure (3a) Receiver operating characteristic curve (ROC) for N terminal pro BNP to detect LVH in CKD patients



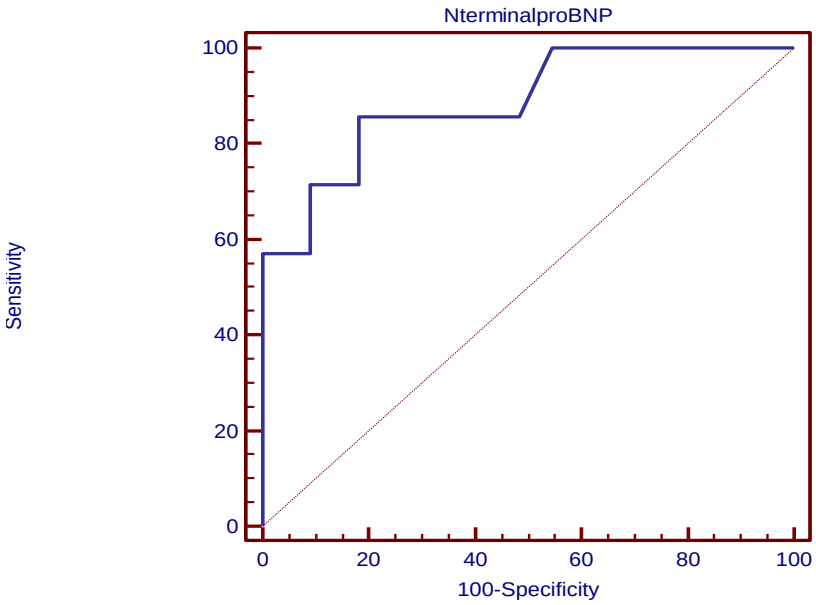
Sensitivity=9
2. Criterion>4700 Specificity= 83.3%
AUC= 0.936

Figure (3 b) Receiver operating characteristic curve (ROC) for NT- pro- BNP to detect diastolic dysfunction in CKD patients



Sensitivity= 96.8% Criterion > 3990
Specificity= 93.9% AUC= 0.984

Figure (3c) Receiver operating characteristic curve (ROC) for N terminal pro BNP to detect systolic dysfunction in CKD patients



Sensitivity= 85.7% Criterion > 8700
Specificity= 81.8% AUC= 0.887

Table (7): Myocardial Perfusion Imaging by Single photon Computed Tomography (SPECT) in the studied Twelve patients.

MPI variables	No. of patients (n= 12)	%
Perfusion defects:		
Present	**11**	**91.7**
Absent	**1**	**8.3**
Severity of hypo perfusion:		
Normal perfusion	**1**	**8.3**
Mild	**2**	**16.7**
Moderate	**3**	**25.0**
Mild to moderate	**3**	**25.0**
Severe	**3**	**25.0**
EF by MPI:		
< 50%	**6**	**50.0**
≥ 50%	**6**	**50.0**
Number of affected vessel:		
None	**1**	**8.3**
One vessel	**2**	**16.7**
Two vessel	**6**	**50.0**
Multi-vessel	**3**	**25.0**

Table (8): Effect of CKD grades on parameters of MPI by SPECT in Twelve studied patients.

CKD grades / Variable	Mild to moderate renal impairment(stage GII,GIII) No =6		Severe renal impairment(stage GIV,V) No =6	
Perfusion defects:				
Present	5	83.3%	6	100%
Absent	1	16.7%	0	0
Severity of hypoperfusion:				
None	1	16.7%	0	0
Mild	2	33.3%	0	0
Moderate	2	33.3%	1	16.7%
Mild to moderate	1	16.7%	2	33.3%
Severe	0	0	3	50%
EF by MPI:				
< 50%	1	16.7%	5	83.3%
≥ 50%	5	83.3%	1	16.7%
Number of affected vessel:				
None	1	16.7%	0	0
One- vessel	2	33.3%	0	0
Two vessel	3	50%	3	50%
Multi-vessel	0	0	3	50%

Table (9) Relation of N terminal pro BNP serum levels and The severity of hypoperfusion on MPI by SPECT in the studied twelve patients

Biomarker	Mild/ mild to moderate hypoperfusion Mean ± SD	Moderate/ severe hypoperfusion Mean ± SD	*P*-value
N-terminal pro BNP	4600.00 ± 463.68	8550.00 ± 3809.86	0.035*

***P* <0.05 = significant**

Figure (4) Correlation between N-terminal pro BNP and EF detected under MPI by SPECT in the studied twelve patients

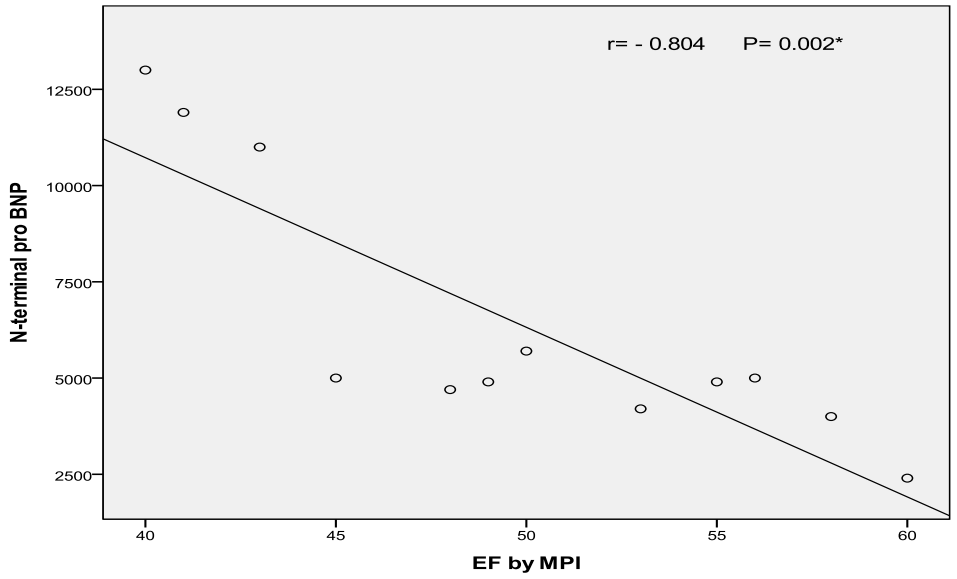
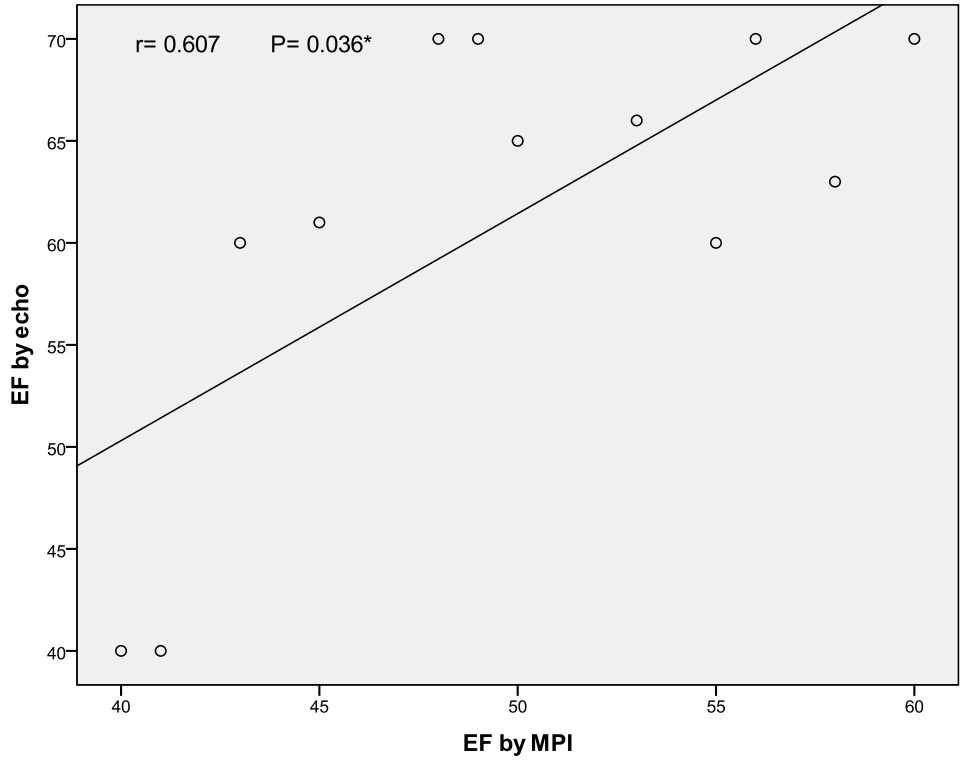


Figure (5) Correlation between systolic function (EF) detected by TTE and systolic function (EF) on MPI by SPECT in Studied twelve patients.



4. Discussion:

Chronic kidney disease (CKD) is a growing health burden all over the world. Although many CKD patients will develop renal failure, most will die of cardiovascular disease (CVD) before dialysis and patients with CKD are at higher risk for CVD than patients in the general population. There is accumulating evidence that the increase in CVD burden is present in patients prior to dialysis, due to both conventional risk factors as well as those specific to kidney disease. **Levin (23)** stated that even in patients with mild kidney disease, the risk of cardiovascular events and death is increased relative to patients without evidence of kidney disease**.** Hypertension and dyslipidemia are traditional cardiovascular risk factors. In addition to these traditional risk factors, patients with CKD may have other risk factors for increase cardiovascular risk such as inflammation, oxidative stress, anemia, metabolic disorders, calcium-phosphorous disorders, hypervolemia, and structural and functional abnormalities of heart, which may help to explain the high cardiovascular morbidity and mortality in such patients **(24).** Four main structural abnormalities of the heart have been described in patients with CKD: LV hypertrophy, expansion of the nonvascular cardiac interstitium leading to intermyocardiocytic fibrosis, changes in vascular architecture, and myocardial calcification **(25)**. All these abnormalities promote systolic as well as diastolic LV dysfunction which predisposes to symptomatic heart failure, and is considered as a risk factor for premature death. Various diagnostic modalities, both invasive and noninvasive such as electrocardiography, echocardiography and radionuclide scans are utilized for diagnosing left ventricular hypertrophy and dysfunction. Cardiac assessment by echocardiography is non-invasive, inexpensive to perform and generates detailed information about gross cardiac anatomy, objective quantification of LVM and the geometry of left ventricle hypertrophy (LVH), along with measures of function during systole and diastole **(25).** However, echocardiography services are very often stretched in hospitals and not routinely performed .Therefore circulating biomarkers that identify patients with subclinical heart diseases or diseased myocardium may have a potentially important clinical value in allowing early detection, interventions and possibly ongoing surveillance of high –risk patients. In recent years, the naturetic peptides have emerged as promising cardiac biomarkers in this aspect **(26, 27)**. The diagnostic and prognostic roles of NT-pro-BNP have been well established in a variety of cardiac diseases. Most investigators have excluded CKD patients from their studies because of potentially elevated levels of the peptide. However, an easily measurable biomarker for cardiac disease is sorely needed in CKD patients, because symptoms mimicking congestive heart failure occur very often among them **(27)**. Renal hypertension is considered a major traditional cardiac risk factor; where it plays a major role in determining

cardiac damage at all stages of CKD, including the dialytic phase.

In the present study, hypertension was found in the majority of CKD patients; mainly those on HD with a statistically significant difference when compared to non dialysis patients. These finding nearly came in agreement with **Ifeoma *et al.* (29), Parikh_ *et al.* (30)**, **Patrick *et al.* (31), Rigas *et al.* (32), Shirley *et al.* (33) and Wendy *et al.* (34), who** stated that higher prevalence of hypertension was present in CKD patients with varying degrees due to high prevalence of hypertensive nephropathy and/ or diabetes etiological factors. Our study showed the more prevalence of hypertension in HD patients. This was in agreement with **Saha *et al.* (35).** On the contrarily to our findings, **Imed *et al.* (36)** was founded that less prevalence of hypertension in HD patients and contributed this finding to an efficient dialysis and good compliance of patients to medications than our patients. In current study, we found that Hyperlipedemia was present in most of our patients regardless HD. This finding is in concordance with **Patrick *et al.* (31)** and **Wendy *et al.* (34)** who reported that most CKD patients with varying grades had hyperlipedemia, however, **Masafumi *et al.* (37)** stated that few patients with CKD patients had Hyperlipedemia depending only on measurement of total cholesterol level which decreased in CKD patients. Thus, Hyperlipedemia can be considered as a second traditional risk factor for cardiac events. Anemia has been shown to be significantly associated with left ventricular hypertrophy (LVH) in both dialysis patients and patients with early CKD, suggesting that anemia is primarily implicated in the development of LVH in CKD. Anemia is a potentially modifiable risk factor; its treatment seems to have a more beneficial effect on LVH regression if it is corrected as early as possible during the course of CKD and before patients have reached ESRD **(38).** In our study, the majority of patients regardless HD had experienced anemia even in the earlier stages of kidney disease with high prevalence in those patients with advanced renal disease and longer duration of dialysis. Therefore anemia can be considered as an important novel cardiac risk factor in CKD patients. Our findings came in agreement with **Saha *et al.* (35), Afshar *et al.* (39) and Chinwuba *et al.* (40)** who stated that high prevalence of anemia in CKD patients with varying grades especially those with advanced CKD grades (grade IV and V). On the other hand, **McClellan *et al.* (41)** in a large-scale, cross-sectional, US multicenter survey study documented a lower prevalence of anemia which might be explained in part by other causes peculiar to the environment, including helminthic and other infestations and malnutrition.

In our study, the majority of patients had Albuminurea and hypoalbumenamia especially those treated by heamodialysis. Hypoalbuminamia may be due to albuminurea and/or nutritional deficiency which may leads to MIA syndrome (malnutrition, infection, and atherosclerosis) and predispose to cardiovascular events in CKD. Albuminurea in CKD may represent diffuse endothelial damage and hence considered as novel cardiac risk factor and therefore it can be considered as cardiac biomarker in CKD patients.

In current study, we founded that the total prevalence of LVH (LVM and LVMI) in all CKD patients with varying grades was much higher than the reference range and controls. This was in agreements with **Rathod *et al.* (25), Ifeoma *et al.* (29), Paoletti *et al.* (42), Peterson *et al.* (43)** who stated that the high prevalence of LVH in CKD patients with varying degrees in developing countries. However, **Stack and Saran (44) and Nardi *et al.* (45) and Shih *et al.* (46)** reported the low prevalence of LVH in CKD patients with varying degree in disagreement with our findings .The higher prevalence of LVH in our study might be due to high prevalence of both hypertension and anemia in our patients which were the strongest contributing factors in LVH development as well as presence of hypocalcaemia with secondary hyperparathyroidism and its powerful intimate relation to LVH and myocardial fibrosis. The marked decline in GFR by modified MDRD formula may play a role in high prevalence of LVH in our patients. **Nardi *et al.* (45)** and many studies recorded that the inverse relation between GFR and LVH prevalence. In the present study, LVH (LVM and LVMI) was significantly more prevalent in heamodialyzed patients than those not on dialysis and this may be due to the higher prevalence of all cardiac risk factors hypertension, anemia, hyperlipidemia, hypoalbuminemia and hypocalcaemia in the our HD patients. This finding was in agreement with **Angela *et al.* (26, 27)**, **Rajiv *et al.* (47)** and **Mayara *et al.* (48)** who founded the high prevalence of echocardiographic LVH among chronic hemodialysis patients than those not on dialysis. Moreover, **Rathod *et al.* (25)**, Paoletti ***et al.*** **(42), Shih *et al.* (46), Jeffrey *et al.* (49) and Rachel *et al.* (50)** reported that the significantly more prevalence of LVH in severe stages of CKD with lower prevalence of LVH in mild /moderate CKD stages under conservative treatment and not starting RRT yet. In the present study, we founded the high incidence of LV dysfunction (systolic and diastolic) in the majority of our studied CKD patients in agreement with **Rathod etal (25).** Furthermore, we

founded that LV dysfunction was more prevalent in CKD patients under hemodialysis than non dialysis patients due to a more prolonged duration of CKD, a more severe stage of CKD resulting in more severe anemia, hypertension and fluid overload, or to specific dialysis-associated factors that further impair left ventricular function in those patients. Moreover, isolated diastolic dysfunction was the frequent form of LV dysfunction in CKD which may be exceeding the prevalence of LVH and this denoting that diastolic dysfunction may precede LVH occurrence as many studies documented. Our results matched with **Rathod *et al.* (25)** who reported that the more prevalence of LV dysfunction in CKD patients with higher incidence of isolated diastolic dysfunction than systolic dysfunction. **Shih *et al.* (46)** who stated that LV diastolic dysfunction were more prevalent in severe CKD than mild⁄ moderate CKD stages by his usage of pulse tissue Doppler in assessment of diastolic dysfunction which is considered more accurate than E/A ratio which may under estimate diastolic dysfunction. Moreover, in the present study, apparently equal and an insignificant prevalence of isolated diastolic dysfunction had been detected in HD and non dialysis patients. This finding may be due to a small sample size and the prevalence of hypertension and anemia as cardiac risk factors in early stages of CKD. This finding was not in concordance with **Arodiwe *et al.* (51,52)** stated that the diastolic dysfunction had more prevalence in HD patients and this might be due to a more prolonged duration of CKD, a more severe stage of CKD resulting in more severe anemia and fluid overload, or to specific dialysis-associated factors that further impair left ventricular function in those patients. On the other hand , **Mark *et al.* (53)** who reported the low prevalence of diastolic dysfunction in HD patients which could be explained by they had obtained the echocardiograms immediately post-dialytic and therefore filling pressures might not substantially elevated at the time of echocardiography, while our echocardiograms were obtained in inter dialytic day. In the current study, we founded that systolic dysfunction was insignificantly more prevalent in HD than non dialysis patients. The prevalence of systolic dysfunction in severe CKD group may be due to patient's factors as anemia and hypertension and non efficient dialysis. Our results came in agreement with **Rathod *et al.* (25**) and **Shirley *et al.* (33)** who reported an insignificant difference between systolic and the diastolic dysfunction which were more prevalent in those with severe CKD than those with mild to moderate CKD. The prevalence in severe CKD group may be due to patient's factors as anemia and hypertension and non efficient dialysis. While **Yan *et al.* (54)** who reported the low prevalence of systolic dysfunction in CKD with varying grades and we could explained this result by that he used EF less than 40% for definition of systolic dysfunction but we define systolic dysfunction as EF less than 50%. Moreover**, Szu *et al.* (55**) reported the same feature inspite of his use of EF less than 55% for definition of systolic dysfunction, only one third of CKD patients enrolled in his study had grade V while half of our patients had grade V and systolic dysfunction was more prevalent in this grade than earlier ones.

Coronary artery disease (CAD) is frequent co morbidity in patients with CKD and Presence or absence of chest pain does not correlate well with CAD in CKD patients; Regional wall motion abnormalities and myocardial thinning with systole all correlate well with critical narrowing of the coronary lumen. In the present study, we founded the resting wall motion abnormality by conventional echocardiography in our CKD patients with insignificantly higher prevalence in HD patients than those not starting RRT. Resting wall motion abnormality may be regional (segmental) i.e. in anatomic distribution of certain coronary artery and this was founded in 17.5% of total patients with insignificantly higher prevalence in predialysis patients and this may be explained by high frequency of uremic cardiomyopathy in HD patients which associated with global hypokinesia of LV wall segments . This insignificant difference between both groups may be due to small comparative sample size. Global hypokinesia of LV wall segments with low EF in our patients may be due to multi-vessel coronary affection including intramyocardial vessels and/or myocardial fibrosis and hibernation and / or volume overload and hypertension at the time of echocardiography performance. This finding was in agreement with **Young *et al.* (56), Charles *et al.* (57) and Solmaz *et al.* (58)** who stated that the more prevalence of segmental wall motion abnormality (SWMA) in dialysis patients than predialysis patients with significant difference. This may be due to large sample size of studied patients and assessment of SWMA was done in intradialytic which favor dialysis induced ischemia and it is considered a well known phenomenon and mostly reversible. In contrast to our findings, **Jwa *et al.* (59)** reported the lower prevalence of SWMA in newly HD patients and this may be explained by the enrolled patients in his study underwent coronary intervention and this may improve their cardiac status as well as good medical treatment and type of dialysis may be different with the high prevalence of cardiac risk factors as hypertension in our patients.

NT-pro-BNP is released from myocytes in response to ventricular wall stretch and wall tension.

The present study showed that there were elevated levels of cardiac biomarker NT-pro-BNP in the studied patients with significant an inverse correlation to CKD grades where their levels were significantly more elevated in HD patients. This may be owing to increased risk of cardiac events as the kidney problem worsened. Our results were in agreement with **Wendy *et al.* (34), Katharina *et al.* (60) and Srisawasdi *et al.* (61)** who stated that the level of NT-pro-BNP was significantly increased with more deterioration in kidney function and the degree of change is also dependent on the LVEF which may reflect an increased volume overload of the heart as a consequence of volume expansion due to restricted GFR. **Astor *et al.* (62)** stated that NT-pro-BNP levels are elevated in individuals with reduced kidney function, although it remains unknown whether this is due to solely to increased LVM and prevalence of heart failure or whether reduced clearance of NT-pro-BNP, volume overload, or other factors related to uremia may play a role. In the present study, we clearly stated that NT-pro-BNP plays a spurious role for the diagnosis of **LVH**. Significant highest levels of NT-pro-BNP were seen in uremic patients had left ventricular hypertrophy with strong significant positive correlations with both LVM and LVMI with high sensitivity and specificity and the cut off value provided by use of ROC analysis curve of NT-pro-BNP and hence, it may be considered to have a prognostic value in evaluation of cardiac -uremic patient. This finding was in agreement with **Astor *et al.* (62)** who stated that circulating level of NT-pro-BNP serves as a sensitive marker of both LVH and volume expansion and increased levels of NT-pro-BNP strongly predict mortality among patients with heart failure and acute coronary syndromes. However, this biomarker could be elevated in uremic patients who had not have any LVH changes in their TTE, and this could explained by the early ventricular wall stretch prior to LVH occurrence with high prevalence of diastolic dysfunction .This was in agreement with **Imed *et al.* (36) , Bargnoux *et al.* (63)** and **Rajat *et al.* (64)** who reported that NT-pro-BNP significantly positively correlated with LVMI and recommend more trials for determination of specific value for diagnosis. **Khan *et al.* (65)** revealed that this biomarker considered a significant predictor for indicating LVH as provided by use of ROC curve analysis. Limited data suggest that the higher levels of this biomarker predict progression of kidney disease. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has become increasingly important in diagnosing left ventricular dysfunction (LVD).In our study , we founded a highly significant increase in NT-pro-BNP level in our patients who experienced LV systolic dysfunction than those who hadn't and there was a negative correlation between patients 'ejection fraction by TTE and the level of this biomarker and ROC analysis curve shows that at cutoff value of 8700 pg/ml we can discriminate CKD patients with systolic dysfunction than those who hadn't (AUC 0.887;85.7%senstivity and 81.8% specificity). This finding was in concordance with **David *et al.* (66)** who stated that level of this biomarker was highly significantly higher in those with LV systolic dysfunction than those without with a highly significant inverse correlation between LV ejection fraction and NT-pro-BNP levels and also documented that at a higher NT-pro-BNP cut-off value, the higher sensitivity and specificity for the presence of LVD. Moreover, **Jung *et al.* (28)** stated that optimum cut points should be stratified according to renal function, however, in our study due to usage of small sample size we cannot discriminate optimum cutoff value for each CKD grade. Therefore, we hypothesized that a serum NT-pro-BNP cut-off value adjusted for patients with CKD could serve as a biochemical marker to detect LVD in those patients regardless of chronic fluid overload. On the other hand, LV diastolic dysfunction which was the commonest cardiac abnormality in our patients with a significant direct association between NT-pro-BNP level and diastolic dysfunction. In our study, we founded a highly significant elevation of NT-pro-BNP in those who had diastolic dysfunction than those hadn't regardless HD with high sensitivity and specificity by using ROC analysis curve in diagnosis of LV diastolic dysfunction. This finding was in concordance with **John *et al.* (67)** who stated a positive correlation between the level of this biomarker and diastolic dysfunction assessed by Tran- thoracic echo or nuclear medicine scintigraphy depending on factors that associated with volume overload in CKD patients on HD. Moreover, **Wendy *et al.* (34)** who stated a highly positive correlation between the level of NT-pro-BNP and diastolic in CKD patient not receiving HD who had much higher level of this biomarker. According to these findings, NT-pro-BNP could be identified as the strongest predictor of LV dysfunction in CKD patients. This finding was in concordance with **Shahabi *et al.* (14)** who stated that in all patients with LV ejection fraction less than 40%, plasma NT-pro-BNP level was higher than 100 pg ⁄ml; therefore NT-pro-BNP can be a good parameter for predicting the severity of cardiac events. In contrast, **Astor *et al.* (62)** stated that NT-pro-BNP levels may be less relevant for the diagnosis of prevalent left ventricular dysfunction and heart failure in individuals with CKD, owing to the confounding associations with kidney function, hemoglobin, serum albumin and medication use suggesting that NT-pro-BNP levels can strongly

predict CVD events and mortality in persons with CKD independent of kidney function and medication use. In the current study, by using ROC curve analysis, NT-pro-BNP had the highest diagnostic value for severe LV hypertrophy and systolic dysfunction compared to CRP, irrespective of residual renal function. This finding was in agreement with **Wang *et al.* (16)** who reported that at a higher cutoff value of NT-pro-BNP, the higher sensitivity and specificity in the diagnosis of severe LVH were considered has been postulated. However most authors recommend measurement of NT-pro-BNP for this purpose. In our study, the level of NT –pro-BNP was significantly affected by hypertension, anemia and hypoalbumenamia; all these factors can lead to development of LVH in those patients. This finding was in agreement with **Rajat *et al.* (64)** stated that NT –pro-BNP levels were significantly affected by hypertension, hemoglobin level. In current study, the advanced age, gender and BMI had no significant effect on the NT –pro-BNP levels. This finding was in agreement with **Imed *et al.* (36)** who reported no correlation between NT –pro-BNP levels and gender while **Rajat *et al.* (64)** reported that the NT –pro-BNP levels had significantly affected with increased age which could be explained by his large sample size of patients and also older age of studied patients compared to our patients. Asymptomatic coronary artery diseases (CAD) were considered a common cardiac event in CKD patients, the echocardiographic findings revealed that NT-pro-BNP was highly significantly more elevated in our asymptomatic patients who had SWMA than those hadn't, and this could be explained by high prevalence of LVH and diastolic dysfunction and reflecting underlying ischemic heart disease. Our ROC analysis curve showed the high sensitivity and specificity at cutoff value of 9500 pg/ml. These findings were in agreement with **Jung *et al.* (28), Khan *et al.* (65)** and **Christopher *et al.* (68)** who reported that the elevation of NT-pro-BNP levels in asymptomatic patients with CKD reflects underlying ischemic heart disease and hypertrophy independent of renal function in a population with anticipated high cardiac morbidity**.** With advances in technology, many options are available for screening, diagnosis and follow up of coronary artery disease in renal patients. Noninvasive imaging has been reported to be effective in risk assessment before renal transplantation. In the present study, selected twelve patients with varying degree of CKD (according to TTE findings and Levels of N-terminal –pro –BNP) had undergone SPECT myocardial perfusion scan using dipyridamole 99mTc-Sestamibi MPI. Perfusion defects were discovered in the majority of those patients and most of them had moderate to severe degree of hypoperfusion in the course of two or multi-vessel affection. Moreover, we observed that patients who had severe renal impairment (grade IV, V) had the highest percentage of perfusion defects; the severer degree of hypoperfusion; the lowest ejection fraction; and the two and multi-vessel affections than those who had mild to moderate renal impairment (grade II, III). These findings were in agreement with **Jwa *et al.* (59) and Sunita *et al.* (69)** who stated that perfusion defects on SPECT were founded in most of the studied CKD patients with severe degree and were recorded at high risk according to number of segment affected with lowest EF. **Tsuguru *et al.* (70)** also revealed that myocardial SPECT has an incremental value for predicting cardiac events and survival in CKD patients with much lower eGFR. In the current study, a positive correlation between EF estimated by resting TTE and by stress MPI was present. The NT-pro-BNP levels were statistically significantly higher in patients who had a moderate /severe degree of hypoperfusion than those had a milder degree. However, there was a highly significant negative correlation between the level of this biomarker and estimated EF by stress MPI. These results were in concordance with **Mikko *et al.* (71)**, who stated that in CKD patients undergone stress SPECT, the myocardial perfusion defects were associated with increased level of BNP;NT-pro-BNP which increased more in the high ischemia group compared to the low ischemia group. These studies with our results assure that the intimate relation between the rise in the level of this hormone and CAD which was proved by coronary angiography in CKD patients and patients with normal kidney function. **Okwuosa *et al.* (2)** stated that the annual cardiac death rate was significantly higher among patients with an abnormal SPECT MPI and CKD compared to patients with an abnormal SPECT MPI with no CKD .The presence of perfusion abnormalities was strongly predictive of cardiac death, myocardial infarction, and non-fatal myocardial infarction across all levels of renal dysfunction compared to normal scans. This trend was stronger among patients with more severe renal dysfunction. Therefore, it has been suggested that SPECT MPI is diagnostically accurate and can be used to risk stratify patients with CKD—even asymptomatic patients—and should be considered for the detection of CAD among patients with renal dysfunction. In our study, SPECT MPI provided effective risk stratification in patients with CKD. However, the subjects were predominantly male with a high prevalence of CKD and CAD risk factors, including diabetes and hypertension.

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