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Original Research Article

A Study to Find the Correlation amongst Clinical Cardiac Manifestations with 2D Echocardiographic Findings and Serum NT-Probnp Level in End Stage Renal Disease Patients on Maintenance Hemodialysis

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Abstract

Background: The incidence of cardiovascular morbidity and mortality in people with end stage renal disease (ESRD) on dialysis is higher than in the general population. The US Renal Data System estimates the prevalence of cardiovascular disease in ESRD patients on hemodialysis (HD) a 70.6% and that in peritoneal dialysis patients 57.8%. Furthermore, arrhythmia / cardiac arrest is the only cause of death in 40% of dialysis patients. There is little evidence to support the effectiveness of traditional risk factor modification approaches, drug use or lifestyle changes in this population. Furthermore, coronary artery revascularization in patients with documented coronary artery disease did not alter arrhythmia mortality rates. Therefore, optimal strategies for the diagnosis, prevention and management of cardiovascular disease need to be modified in patients with ESRD.

Method: Sixty one patients with end stage renal disease on maintenance hemodialysis attending OPD / IPD or dialysis centre were studied using random sampling method. We conveniently took 61 patients who are adequately dialysed (KT/V urea > 1.2 for last 4 weeks) out of total 165 patients. Their demographic profile, clinical (cardiac symptoms) and biochemical profile (NT-proBNP) was recorded. Assessment with 2D echocardiography was done to find cardiac structural or functional abnormality.

Results: All patients had significantly raised NT-proBNP level with mean NT-proBNP level of 15912.1 ± 13078.3 pg/ml. Prevalence of LV systolic dysfunction was 13.11%; out of them 3.28%, 4.9% and 4.9% patients had mild, moderate and severe systolic dysfunction respectively. Prevalence of LV hypertrophy (100%) and Diastolic dysfunction (98.36%) was very high. Significant correlation found between NT proBNP level and echocardiographic parameters. No significant correlation found between interdialytic weight gain (IDWG) and DD (P = 0.174), IDWG and dyspnea NYHA grade (P = 0.929) or IDWG and NT-proBNP level (P value = 0.39). Over 1 year of study period, 7 patients were hospitalized due to heart failure and 2 patients were died due to other causes with mean NT-proBNP level 25472.85 pg/ml and 30506 pg/ml respectively.

Conclusions: NT-proBNP is not a reliable marker for heart failure in end stage renal disease patients. However, if we increase it cut off to more than 11500 pg/ml that is 20 times more than present value, it may have diagnostic value. It can also have prognostic significance as high value is associated with increased risk of heart failure and mortality.

Keywords: End stage renal disease, Hemodialysis, 2D Echocardiography, NT-proBNP.

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Introduction

The incidence of cardiovascular morbidity and mortality in people with end stage renal disease (ESRD) is higher than in the general population.[5] The US Renal Data System estimates the prevalence of cardiovascular disease in ESRD patients on hemodialysis (HD) a 70.6% and that in peritoneal dialysis patients 57.8%.[6] As GFR decreases, the prevalence and severity of cardiovascular abnormalities increase and are accepted as a leading cause of morbidity and

mortality in people with chronic renal failure. The presence of congestive heart failure (CHF) in people with chronic renal failure carries a worse prognosis than either condition alone. Therefore, early detection and aggressive management of CHF are both highly desirable. A number of cardiac biomarkers (eg BNP and cardiac troponins) appear to have both increasing clinical importance and greater ease in detecting and stratifying CHF. However, when the e-GFR is less than 60 ml/min/1.73 m2, the accuracy of plasma BNP and NT-proBNP levels for detection and stratification of CHF becomes unreliable and the degree of responsiveness to treatment is not known.[7]

Given the high prevalence of cardiovascular death, there is growing interest in identifying structural changes in the heart that could be used to predict mortality risk in a given individual. Echocardiography is the most widely available, non-invasive, and inexpensive technology for assessing the structure and function of the myocardium in people with ESRD on dialysis at risk for cardiovascular disease.[8] In recent years, new echocardiography techniques, as well as the emergence of MRI scans have shown promise in identifying structural changes consistent with uremic cardiomyopathy. This study was carried out to evaluate the echocardiographic findings and its correlation with clinical cardiac manifestations and NT proBNP level in patients of ESRD on maintenance hemodialysis.

Aims and Objectives:

(1) To determine correlation amongst NT proBNP level, cardiac symptoms and 2D echocardiographic findings in ESRD patients.[9]

(2) To determine the reliability of NT-pro BNP for diagnosis of heart failure in patients with end stage renal disease on hemodialysis.[10,11]

Materials and Methods

Setting: This Study was carried out at a dialysis centre in a tertiary care hospital.

Inclusion Criteria:

1. All the patients above 18 years of age with End stage renal disease on maintenance hemodialysis with dialysis frequency of twice or thrice a week for at least 1 year.
2. Patients who have dialysis adequacy (as decided by KT/V urea ratio > 1.2) for last 4 weeks. (It is a routine protocol to have weekly KT/V urea of each patient in our dialysis unit)

Exclusion Criteria:

1. Patient who does not want to participate.
2. Patients who are on MHD for < 1 year.
3. Patients who are < 18 years of age
4. Patients with less dialysis adequacy (KT/V urea < 1.2 for last 4 weeks)

5) Patient who had pre-existing cardiac abnormality like ASD, Valvular heart disease and other known cardiac structural or functional abnormality before commencement of HD.

Methodology

This study was carried out between January 2021 and August 2022 after approval from institutional ethics committee. There are around 165 patients with ESRD on maintenance hemodialysis regularly coming to dialysis centre and also visiting OPD or admitted in ward as per need. It is a routine protocol to have weekly KT/V urea of each patient in our dialysis unit. We conveniently took sixty one patients who are adequately dialysed (KT/V urea > 1.2 for last 4 weeks). Data collection comprised of: (1) Demographic details, (2) Clinical history and laboratory parameter (NT-proBNP) and (3) Assessment of each patient with 2D echocardiography. Data collection was done through personal interview. Patients with previously known structural or functional cardiac abnormality were excluded. Data safety and confidentiality were given due consideration by not mentioning name of patients and keeping the file containing identity related details password protected. Data entry and analysis: The Data were entered in Microsoft Office Excel Worksheet 2007. Percentages were calculated for descriptive statistics. Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean. Analysis was done for variable like demography, symptoms, Laboratory parameters and echocardiographic findings. Association between variables was measured using Chi-squared test by using MedCalc Software.

Statistical Analysis: Descriptive Statistics [Mean (SD), Frequency (%)] is used to depict the baseline profile of the study participants. Chi square test is used to find association between different categorical variables. To compare continuous variables with categorical variables, Independent sample t test and ANOVA is used. A p value <0.05 is consider statistically significant. Statistical software STATA 14.2 is used for data analysis.

Results

Based on the results provided, the findings can be presented in the following tables with brief interpretations suitable for a dissertation or journal manuscript.

Table 1: Baseline Demographic and Dialysis Characteristics of Study Participants (N = 61)

Variable	Number (n)	Percentage (%)
Gender		
Male	44	72.1
Female	17	27.9
Mean age (years)	55.6 ± SD	-
Age group (years)		
<50	23	37.7
50–70	36	59.0
>70	2	3.3
Duration of Hemodialysis		
1–3 years	46	75.4
4–6 years	10	16.4
7–10 years	5	8.2
Frequency of Hemodialysis		
Twice weekly	23	37.7
Thrice weekly	38	62.3

The study included 61 ESRD patients undergoing maintenance hemodialysis, with a predominance of males (72.1%). Most participants belonged to the 50–70-year age group (59.0%), had been on dialysis for 1–3 years (75.4%), and received hemodialysis three times per week (62.3%).

Table 2: Association of NT-proBNP with Demographic and Dialysis Variables

Variable	P-value	Statistical Significance
Age (<50 vs. 50–75 years)	0.423	Not Significant
Duration of dialysis	0.900	Not Significant
Frequency of dialysis	0.986	Not Significant
Age >75 years	Not applicable	Insufficient sample

Serum NT-proBNP levels showed no statistically significant association with age, duration of maintenance hemodialysis, or dialysis frequency. These findings suggest that elevated NT-proBNP levels are independent of dialysis duration and treatment frequency.

Table 3: Echocardiographic Findings and Their Association with NT-proBNP

Echocardiographic Parameter	Findings	P-value
LV Systolic Function		
Normal	53 (86.9%)	
Mild dysfunction	2 (3.3%)	
Moderate dysfunction	3 (4.9%)	
Severe dysfunction	3 (4.9%)	**0.015**
Diastolic Dysfunction		
Normal	1 (1.6%)	
Grade I	13 (21.3%)	
Grade II	16 (26.2%)	
Grade III	31 (50.8%)	**0.0006**
Left ventricular hypertrophy	61 (100%)	
LV Mass Index vs NT-proBNP	Significant association	**0.0186**

Most patients had preserved left ventricular systolic function, although NT-proBNP levels increased significantly with worsening systolic dysfunction. Nearly all patients had diastolic dysfunction, with Grade III dysfunction being the most common. NT-proBNP levels also demonstrated a strong positive association with worsening diastolic dysfunction and increased LV mass index.

Table 4: Cardiac Symptoms and Their Association with Echocardiographic Parameters and NT-proBNP

Variable	Number (%)	P-value
NYHA Grade I	35 (57.4)	
NYHA Grade II	18 (29.5)	
NYHA Grade III	2 (3.3)	
NYHA Grade IV	6 (9.8)	
Orthopnea	7 (11.5)	
Paroxysmal Nocturnal Dyspnea	5 (8.2)	
Dyspnea vs LVEF		**0.015**
Orthopnea vs LVEF		**0.029**
PND vs LVEF		**0.041**
Dyspnea vs LV Mass Index		0.091
Dyspnea vs Diastolic Dysfunction		0.323
Orthopnea vs Diastolic Dysfunction		0.327
PND vs Diastolic Dysfunction		0.590
Dyspnea vs NT-proBNP		**0.0177**
Orthopnea vs NT-proBNP		0.2823
PND vs NT-proBNP		0.3691

Dyspnea was the most common cardiac symptom, with the majority of patients presenting with NYHA Grade I or II symptoms. Worsening dyspnea correlated significantly with impaired left ventricular systolic function and elevated NT-proBNP levels. Orthopnea and PND were significantly associated with reduced LVEF but not with diastolic dysfunction or NT-proBNP levels.

Table 5: Interdialytic Weight Gain, Comorbidities, and Clinical Outcomes

Variable	Findings	P-value
IDWG vs Diastolic Dysfunction	No association	0.174
IDWG vs NYHA Grade	No association	0.929
IDWG vs NT-proBNP	No association	0.390
Patients with anemia	51 (83.6%)	-
Patients with hypertension	35 (57.4%)	-
Hospitalization for heart failure	7 (11.5%)	-
Death during follow-up	2 (3.3%)	-
Mean NT-proBNP (overall)	16,549.47 pg/mL	-
Mean NT-proBNP (heart failure admissions)	25,472.85 pg/mL	-
Mean NT-proBNP (deaths)	30,506 pg/mL	-

Interdialytic weight gain was not significantly associated with diastolic dysfunction, dyspnea severity, or NT-proBNP levels. Anemia and hypertension were highly prevalent among patients with left ventricular hypertrophy, indicating their contributory role in cardiac remodeling. Patients requiring hospitalization for heart failure and those who died had substantially higher mean NT-proBNP levels than the overall study population, suggesting that markedly elevated NT-proBNP is associated with adverse cardiovascular outcomes and increased mortality.

Discussion

Sixty one patients with end stage renal disease on maintenance hemodialysis were studied. (males 44, females 17; mean age 55.6 years). 59% patients were in age group 50 to 70 years while less people were in younger age group. Rajapurkar M et al.[12] studied 38,193 CKD patients with mean age of 47.9 ± 16.8 years. Most of the patients were male (72.1%) and only 27.9% of the patients were female in our sudty. Rajapurkar M et al.[98] study also showed male predominance (69.6%). In the present study, we found higher NT pro-BNP levels (16449.47 ± 13192.9) in all 61 (100%) patients with impaired renal function. Nitta and colleagues [13] also reported that the mean serum NT pro-BNP level was higher (688.5 ± 154.5 pg/ml) in ESRD patients on haemodialysis than in normal healthy subjects.

In the present study, 86.9% patients had normal LV systolic function while systolic dysfunction was observed in 13.11% with mild, moderate and severe dysfunction in 3.3%, 4.9% and 4.9% respectively. In Abeera Mansur et al.[14], 36.3% CKD patients had severe and 13.6% had mild LVSD.

In the present study, diastolic dysfunction was observed in 60 (98.36%) patients with only 1 (1.64%) patient had no diastolic dysfunction. Among these, 21.3% patients had grade 1, 26.2% had grade 2 and 50.8% had grade 3 diastolic dysfunctions. This shows very high prevalence of diastolic dysfunction in CKD patients and almost

half of the patients had grade 3 DD. In Rajat Tagore et al.[15] 52% had no DD while 32% and 15% patients had grade 1 and grade 2 DD respectively. In our study, we found that all 61 (100%) patients had left ventricular hypertrophy with high LV mass and LV mass index. Out of these, 60 (98.36%) patients had concentric LVH while only 1 (1.64%) patient had concentric remodelling. Nardi E. et al.[16] also found that prevalence of LVH is very high (62.8% of 293) in hypertensive patients with CKD compared to 51.9% (of 289) in hypertensive patients without renal dysfunction (P < 0.0001). We also observed that with increase in LV mass, diastolic function gets worsen and level of NT proBNP increases. Nitta and colleagues [13] also found significant positive correlation between plasma BNP levels and LV mass index (P < 0.05).

In our study, there is statistically significant (P value = 0.015) inverse correlation seen between LV systolic dysfunction and NT proBNP level. Among different groups with various degree of LV dysfunction, more significant inverse correlation with NT-proBNP was seen between patients with normal LV function and severe LV dysfunction (P = 0.028). David S et al.[17] also found significant inverse correlation between LVEF and NT proBNP levels (r = -0.77, P value < 0.0001).

We also observed that more severe the diastolic dysfunction, higher the value of NT-proBNP we will get. In our study 13 patients with grade 1 DD had mean NT-proBNP value of 9297.3077 ± 9672.0369; 16 patients with grade 2 DD had 9183.9188 ± 9531.2382 and 31 patients with grade 3 DD had 21542.848 ± 13085.461, which is statistically significant (P = 0.0006). Memon L et. al.[18] also demonstrate higher NT-proBNP in patients with diastolic dysfunction compared to patients without DD in CKD (P < 0.017) and stated that NT-proBNP represents a biochemical marker providing positive evidence of the presence of diastolic dysfunction in CKD.

In our study, we assessed each patient with 2D echocardiography. We found significant inverse correlation between orthopnea & LV systolic dysfunction (P = 0.029); PND and LV systolic dysfunction (P = 0.041) and between dyspnea and LV dysfunction (P = 0.015). Similarly, significant positive correlation was seen between dyspnea and LV mass index. Mean LVMI was increasing with worsening of dyspnea (P value = 0.091). But no significant correlation found between symptoms and diastolic dysfunction (P value for orthopnea and DD = 0.327; for PND and DD = 0.59 and for dyspnea and DD = 0.323). David S et al.[17] demonstrated that an NT-proBNP cut-off value of >7200 ng/L could be used for the diagnosis of LVD regardless of the patient's fluid status, with a sensitivity of about 80% and a specificity of 90%.

Our study showed statistically significant correlation between echocardiographic parameters and mean NT proBNP level (P value < 0.015 in correlation of LV systolic dysfunction and mean NT proBNP; P value < 0.0006 in correlation of LV diastolic dysfunction and mean NT proBNP; P value 0.0186 in correlation of LV mass index and NT proBNP). Similarly, significant correlation was seen between echocardiographic parameters and cardiac symptoms. In patients with more severe dyspnea (with increase in NYHA grading), the mean LV mass index value is found to be on higher side compared to patients with less severe dyspnea and it is statistically significant (P value = 0.0191). Similarly, there was significant correlation between dyspnea severity and mean NT-proBNP level (P value 0.0177). Few patients were symptomatic even at lower NT-proBNP level while many were completely asymptomatic with very higher level of NT proBNP. So, we can conclude that, there is significant correlation found between echocardiographic parameters and NT-proBNP level; echocardiographic parameters and cardiac symptoms but no significant correlation seen between NT proBNP level and cardiac symptoms in ESRD patients. This is correlated with the result of J. racek et al. [19] study which reported that diagnostic ability of NT proBNP is questionable under circumstance of renal dysfunction. In a prospective study, Rajat Tagore et al[15] reported that in 74 patients (Out of 142 patients) without diastolic dysfunction, the NT-proBNP level was significantly higher but not BNP level in the setting of renal dysfunction. Unlike NT-proBNP, plasma BNP level is relatively independent of GFR. BNP may therefore be the more appropriate biomarker to screen for cardiac dysfunction in CKD.

In our study, we did not find significant correlation between IDWG and NT-proBNP level (P value = 0.39). But Goto J et al.[20] found that NT-proBNP level was higher in patients with higher IDWG (rho = 0.54, p < 0.001) compared to patients with lower IDWG and a limitation in IDWG to < 2.5% and longer ultra-filtration duration may reduce cardiac strain during HD. Similarly, we did not find any association between grade of diastolic dysfunction and IDWG (P value: 0.174). Charalampos el al.[21] in their study found that diastolic dysfunction gets worsened between two dialysis sessions but whether these intradialytic and interdialytic alterations translate into long-term consequences in cardiac function or not need to be evaluated by further study.

Our study shows very high prevalence of anemia (83.6%) among patients with LVH. A study demonstrates that anemia in CKD has been associated with increased risk of left ventricular hypertrophy.[22] This suggests that anemia is an additive factor for development of left ventricular

hypertrophy in patients with CKD. Similarly, prevalence of hypertension was also high among patients with LVH (57.4%). Taddei S et al.[23] also stated that hypertension increases pressure overload to myocardium and contributes to development of LVH. In our study, 7 patients were hospitalized for heart failure in 1 year with mean NT-proBNP 25472.85 pg/ml and 2 patients died at 1 year follow up with mean NT-proBNP level 30506 pg/ml. These values are very high compared to mean NT-proBNP of all study participants (16549.47 pg/ml). It indicates high morbidity and mortality in patients with high NT-proBNP level.

Conclusion:

In our study, we found very high NT-proBNP level. Many patients with elevated NT proBNP level were even free of cardiac symptoms but tissue Doppler echocardiography of all (100%) patients showed left ventricular hypertrophy and diastolic dysfunction of various grade. Few patients were also found to have systolic dysfunction. NT-proBNP level has diagnostic utility for heart failure in ESRD patients only if its cut off is kept > 11500 pg/ml. However, it has good prognostic value as high level is associated with significant morbidity and mortality. Patients with higher NT proBNP level should be subjected to further testing like Echocardiography or Coronary angiography for better evaluation of cardiac function.

Suggestion:

We suggest higher NT-proBNP value (11500 pg/ml) as a cut off to diagnose HF in ESRD patients. We propose NT-proBNP has prognostic implication also as it was significantly high in patients who required hospitalization for heart failure and died due to any cause.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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