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Research Article

Clinical significance of NT-proBNP levels in Chronic Kidney Disease Patients with or without Heart Failure: An Indian Perspective

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Abstract

Objective: N-terminal pro-brain natriuretic peptide (NT-proBNP) levels are extremely useful in detecting heart failure (HF). However, the effects of renal inadequacy on NT-proBNP levels in patients presenting with or without HF remains less clear. We sought to examine the correlation of NT-proBNP levels in all CKD patients and cut-off values of NT pro-BNP level for the diagnosis of HF in stable CKD patients as well as CKD patients who are on haemodialysis (HD).

Material and Methods: The study comprises 141 CKD patients of both sexes who presented with or without dyspnea to casualty of Lilavati Hospital, Mumbai, India, were prospectively enrolled, and blood samples collected to estimate NT-proBNP level.

Results: NT-proBNP cut-off level of 1850 pg/mL for stable CKD patients not on dialysis has a sensitivity of 95% and specificity of 80 %. NT-proBNP cut-off level of 8000pg/ml for CKD patients on HD has a sensitivity of 87 % and specificity of 79%. NT-proBNP cut-off level of 4200 pg/mL for all CKD patients has a sensitivity of 85% and specificity of 81%, for diagnosis of HF.

Conclusion: The clinical use of NT-proBNP is a valuable tool for the evaluation of dyspneic patients with suspected HF, irrespective of renal function. We recommend the above NT-proBNP cut-off levels for diagnosing HF patients in the presence of impaired renal function. Evaluation of the correlation between NT-proBNP levels in CKD is important to identify and to design treatment modalities in order to reduce CVD . Hence, NT-proBNP measurement can be a valuable tool for diagnosis and evaluation of dyspneic patients for early initiation of HF treatment.

Key words: natriuretic peptides; NT-proBNP; chronic kidney disease; heart failure; prognosis.

Introduction.

Chronic kidney disease (CKD) affects 10% - 20% of adults and is associated with adverse clinical outcomes, such as progression to end-stage renal disease (ESRD), increased risk of cardiovascular diseases (CVD) and death [1]. As per the latest data from Indian registry, the commonest cause of CKD in India is diabetic nephropathy (30.3%) followed by chronic glomerulonephritis (15.8%) and hypertension (HTN) (14.8%) [2]. Approximately 30% of patients with diabetes mellitus (DM) have diabetic nephropathy and with the growing number of DM patients and aging population, there can be a parallel increase in the incidence of CKD [3]. Several studies show that patients with CKD also have a higher prevalence of left ventricular (LV) hypertrophy, ischemic heart disease (IHD), cardiac arrhythmias and valvular calcification, leading to heart failure (HF) with a preserved LV ejection fraction (HFpEF), than in the general population [4-7]. This risk increases up to 10 to 100 fold when a patient begins dialysis [8].

Natriuretic peptides (NPs) includes B-type natriuretic peptide (BNP), and Amino-terminal prohormone of brain natriuretic peptide (NT-proBNP) are well established in the diagnosis of HF and in ruling out non-cardiac dyspnea [9-12]. In recent years, these peptide based tests have become a useful prognostic biomarkers to assess the response to therapeutic interventions in patients with HF. Of these two NPs, the most frequently used in clinical practice is NT-proBNP [13].

NT-proBNP is a 76 amino-acid long peptide, synthesized and secreted by the ventricular myocardium in response to elevated wall tension in the ventricles [14-16]. The upregulated NT-proBNP levels in the circulation can cause CVD [17], left ventricular dysfunction [18], volume overload [19], vasodilatation and renal output of sodium and water to counter the increased fluid volume resulting from decreased kidney function. Despite this risk, consensus on estimating future cardiovascular (CV) risk is poorly defined for patients with CKD due to heterogeneous relationships between increased levels of NT-proBNP and outcomes, at least in part due to its varying thresholds, and different outcomes across studies [20]. In non-CKD patients, the diagnostic power of NT-proBNP was quite

different among elderly vs. Non-elderly patients in acute dyspnoeic setting [21].

The elevated NT-proBNP concentration in patients with CKD acts as an independent predictor of all-cause death or major adverse cardiac events (MACEs) in CKD stages-1 to 5 [22, 23]. However, most studies evaluating the predictive power of NT-proBNP were conducted in patients with ESRD and on hemodialysis (HD) [22]. The cut-off values to exclude HF are not clearly defined. In addition, NT-proBNP levels need to be interpreted in light of the worsening degree of renal dysfunction. Thus, an optimal cut-off point, even in the presence of impaired renal function, would become a valuable prognostic marker for the diagnosis of dyspneic CKD patients. In the present study, we measured and compared the plasma concentrations of NT-proBNP in all CKD patients with or without HF, CKD patients on HD, and stable CKD patients not on HD with or without HF.

Material and Methods.

(a).Study subjects.

This is a prospective observational study, carried out in Lilavati Hospital and Research Centre, a tertiary care hospital in Mumbai, India from September 2016 to September 2017.The study enrolled 141 CKD patients including males and females who presented with or without dyspnea. Patient's demographic information including age, gender, history of DM and HTN were collected through interviewing. Detailed history regarding symptoms at presentation, duration of kidney disease, past history of co-morbid illnesses, personal history like smoking, drugs and alcohol consumption, and family details have also been collected.

(b).Methods.

Two-dimensional echocardiography (2D-ECHO) was performed in all patients using Vivid E9 machine in the cardiology department of Lilavati Hospital by single operator and reported in accordance to the standards outlined by the American Society of Echocardiography [24]. Patients with acute kidney injury, renal transplant recipients, recently admitted for HF within last 30 days and other causes of dyspnea like sepsis, pulmonary embolism, pneumonia, Chronic obstructive pulmonary disease (COPD) and severe anemia were excluded.

The initial diagnosis of suspected HF was done on basis of history, physical examination supplemented with ECG and chest X-ray using the modified Framingham criteria [25]. All the HF patients received cardiology consultation during their hospitalization to further confirm the diagnosis of HF.

Assay of NT-proBNP

At admission, venous blood (~5 cc) from patients was collected into Ethylene-Diamine-Tetra-Acetic acid (EDTA) coated Vacutainer (Becton Dickinson, NJ, USA). Plasma was separated by centrifugation at 1,000 × g for 10 minutes at 4°C to remove blood clots. Further centrifugation of the plasma was done at 14,000 × g for 10 minutes at 4°C to remove cell debris. The upper plasma was collected, aliquots (~ 200 µl) were prepared, and stored at -80°C or processed immediately for the quantification of NT-proBNP levels using automated electro chemiluminescence immunoassay "ECLIA" protocol (Cobas e411 analyzers, Roche Diagnostics) as suggested by the manufacturers.

In addition to the estimation of complete blood count (CBC) and hemoglobin (Hb) levels, the levels of Na, K, Cl, HCO3, Ca, PO4, uric acid, protein, albumin, globulin, creatinine and blood urea nitrogen (BUN) levels were determined using standard methods routinely followed in our hospital.

Evaluation of renal function

We used serum creatinine to estimate the glomerular filtration rate (GFR) according to the 4-variable Modification of Diet in Renal Disease (MDRD) equation reported earlier [26, 27]. Estimated GFR (eGFR) values represented as units of ml/min/1.73 m2. We chose a threshold of eGFR <60 ml/min/1.73 m2 for >3 months to indicate CKD.

Statistical analysis

Results were analyzed using IBM-SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 6.0 software packages. Continuous distributed data are expressed as mean ± standard deviation (SD). Log-transformation was used for NT- proBNP levels to achieve normality in distribution. Spearman's correlation coefficient was used to correlate echocardiographic parameters with NT-proBNP levels. Comparison of means was carried out by Student's unpaired't' test for numerical data. Relationship between renal function expressed as GFR and NT-proBNP was evaluated by Pearson Correlation Coefficient (r). Sensitivity (true positive value i.e reflecting a test's ability to correctly identify subjects who have a condition) and specificity (true negative i.e reflecting a test's ability to correctly identify subjects who do not have a condition) was determined and expressed as percentages [28]. Receiver operating characteristic (ROC) curve analyses was performed for stable CKD and CKD on HD to assess optimal NT-proBNP cut-off values in patients with HF and without HF. 'P' value of <0.01 level was considered statistically significant. (S: Significant; NS=Non-significant; t=Student's't' test; F=Fisher exact probability test value).

Results.

(1).Characteristics of the study population

(a).Etiology of study subjects

Characteristics of study participant are shown in Table 1. The most common cause of CKD in study subjects (n=141) was diabetic kidney disease (n=85) followed by chronic glomerular nephritis (n=16). Other causes included were: hypertensive nephrosclerosis (n=3), autosomal dominant polycystic kidney disease (n=3), cancer treatment induced diarrhea (CTID) (n=7), CKD post-acute kidney injury (AKI) (n=3), cardio-renal syndrome (n=5), light chain deposition disease (LCDD) (n=1), medullary sponge kidney (n=1), analgesic nephropathy (n=4), congenital single kidney (n=5), UTI (n=2) and unknown etiology (n=6).

With CHF	Without CHF	%
DM	3	2.1
CGN (Chronic glomerular nephritis)	16	11.3
AKI (Acute kidney injury)	3	2.1
CRS (Cardio renal syndrome)	5	3.5
CTID (Chronic tubulointerstitial nephritis)	7	5.0
DKD (Diabetic kidney disease)	85	60.3
HTN (Hypertension)	3	2.1
LCDD (Light chain deposit disease)	1	0.7
MSK (Medullary sponge kidney)	1	0.7
NSAIDS (Analgesic nephropathy)	4	2.8
Single Kidney	5	3.5
UTI (Urinary tract infection)	2	1.4
Unknown	6	4.4
Total	141	100

Table 1: Etiology of CKD in study population

(b).Comparison of age, gender and CKD duration among patients with or without HF

Of the total 141patients, 92 (65.2%) were males and 49 (34.8%) were females. Among 82 HF patients, 55 (67.1%) were males and 27 (32.9%) were females [Figure 1a). The mean age of patients varies from 27 to 91

years, with a mean age of 64.10 yrs (range 50-80 yrs). The average age of patients with HF (n=82) was 67.38 ± 11.71 yrs and without HF (n=59) was 59.75 ± 11.81 yrs.. Among the 59 patients without HF, 37 (62.70%) were males and 22 (37.30%) were females, this difference in gender was found to be non-significant. Non-significant difference was also observed in the mean duration of CKD in patients with HF (4.07 ± 2.85 yrs) and without HF (4.42 ± 3.37 yrs).

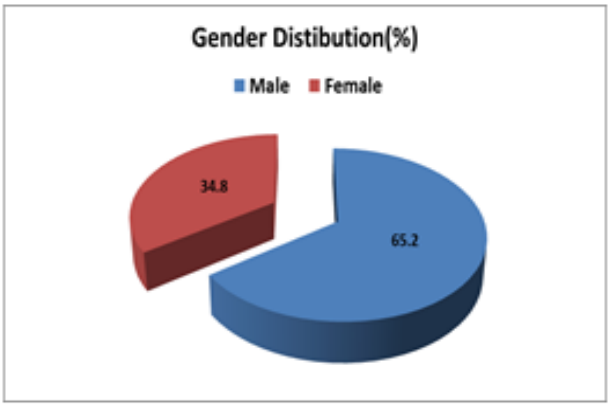

Figure 1a: Distribution of gender in study population.

(c). CKD stage distribution of study population

CKD stage distribution was performed with an aim to evaluate the association of NT- proBNP levels in CKD patients with and without cardiac dysfunction, and to determine the cut-off values for NT-proBNP levels in stable CKD patients not on HD, and CKD patients on HD versus those presenting with acute breathlessness. Based on CKD stage, 67 (47.50%) stable CKD patients on HD were in stage 5D and 74 (52.40%) stable CKD patients were not on HD. Among these 74 CKD patients, 31(22.0%) were in CKD stage-3 (GFR 30-60), 32 (22.70%) were in CKD stage-4 (GFR 15-30) and 11 (7.80%) were in CKD stage-5 ND (GFR<15) [Figure1b].

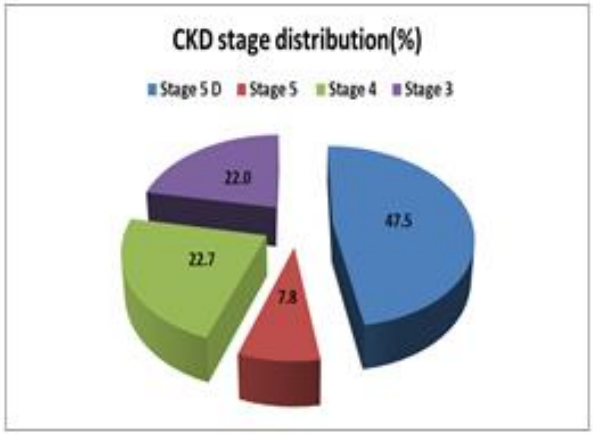

Figure 1b: CKD stage distribution in study population.

2. Comparison of risk factors of CVD in CKD patients with or without HF

(A).Comparison of past history (DM, HTN, HF, AF & MI) among patients with or without HF.

Among the 82 HF patients, 62 (75.6%) had prior history of DM, and of 59 patients without HF 37 (62.7%) had prior history of DM. Among the 82 HF patients, 70 (85.4%) had prior history of HTN, and among 59 patients without HF, 50 (84.7%) had prior history of HTN. These past history were found to be not significant among patients with or without HF. Among the 82 HF patients, 57 (69.5%) had past history of HF and among 59 patients without HF, 6 (10.2%) had past history of HF. Among the 82 HF patients, 28 (34.1%) had past history of atrial fibrillation (AF) and among 59 patients without HF, 1(1.7%) had past history of AF. Among the 82 HF patients, 49 (59.8%) had past history of MI, and among 59 patients without HF 5 (8.5%) patients had past history of AF. These three past histories (HF, AF & MI) were found to be significant (P<0.001) in patients with HF as compared to patients without HF [Table-2].

Past history	With CHF (n=82)	Without CHF (n=59)	'P' Value
DM	62 (75.6%)	37 (62.7%)	NS
HTN	70 (85.4%)	50 (84.7%)	NS
CHF	57 (69.5%)	6 (10.2%)	(P<0.001)
AF	28 (34.1%)	1(1.7%)	(P<0.001)
MI	49 (59.8%)	5 (8.5%)	(P<0.001)

Table 2: Comparison of past history among patients with or without CHF.

(b).Comparison of NT pro-BNP levels in stable CKD patients with or without HF

A significant difference in the mean levels of NT-proBNP in stable CKD patients (n=43) presented with HF (15505.2 ± 15293.40 pg/mL) and those without HF (n=31) (1609.70 ± 3013.40 pg/mL) was recorded. The log mean values of NT-proBNP in stable CKD patients with HF (3.99 ± 0.45) or without HF (2.79 ± 0.60) were found to be significant between them. The log mean values of NT-proBNP levels in CKD patients on HD with HF (4.46 ± 0.55) and without HF (3.56 ± 0.52) were found to be significant [Table-3].

CKD Patients	**NT**-pro-BNP levels	Log NT pro-BNP levels	Level of significance ('P" Value)
Stable CKD patients with CHF	15505.2 ± 15293.40	3.99 ±0.45	(P<0.001)
Stable CKD patients without CHF	1609.70± 3013.40	2.79± 0.60	(P<0.001)
CKD patients on HD with CHF	47751.20 ±42924.7	4.46± 0.55	(P<0.001)
CKD patients on HD without CHF	8142.30 ±13813.3	3.56± 0.52	(P<0.001)

Table 3: Comparison of NT-pro-BNP concentrations (pg/mL) in stable CKD patients with or without CHF.

(c).Comparison of NT pro-BNP levels in CKD patients on HD with or without HF.

A significant difference in the mean levels of NT-proBNP in stable CKD patients on HD presented with HF (n=39) measured to be 47751.20 ± 42924.7 pg/mL. Mean levels of NT-proBNP in CKD patients on HD without HF (n=28) were estimated to be 8142.30±13813.3 pg/mL.

Based on the mean NT-proBNP levels, stable CKD patients with and without cardiac dysfunction were further subdivided into four groups. The mean value of NT-proBNP levels in stable CKD patients (not on HD) with GFR <30ml/min was 23581.30 pg/mL, and for patients not on HF and HD with GFR <30ml/min was 4510.60 pg/mL. The mean value of NT-proBNP levels in stable CKD patients (not on HD) with GFR >30 mL/min was 14923.10 pg/mL, and for patients not on HF and HD with GFR >30ml/min was 1257.20 pg/mL. These results were statistically significant (P<0.001) across all groups [Figure 2].

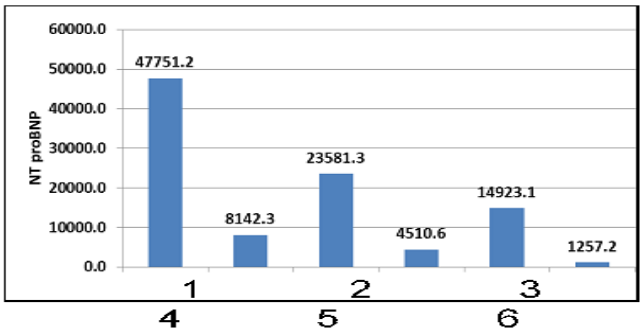

Figure 2: NT-proBNP levels in stable CKD patients on HD. (1: HD-HF, 2: HD no HF, 3: No HD-HF (GFR <30), 4: No-HD, No-HF (GFR <30), 5: No HD-HF (GFR >30 6: No-HD, No-HF (GFR >30)

(d).Comparison of serum biochemical parameters and 2D-ECHO results in: (a) stable CKD patients with or without HF and (b) CKD patients on HD with or without HF.

We observed high (≥11.04 ±1.85g/dL), low (<10.21 ±1.35 g/dL) levels of hemoglobin (Hb), and reduced kidney function (GFR < units mL/ min/ 1.73 m2) were strong predictors of CKD patients. Hb levels were significantly decreased in stable CKD patients with or without HF. However, no such difference was seen between CKD patients on HD with or without HF. Also, no change in CBC count, Na, K, Cl, HCO3, Ca, PO4, uric acid, protein and albumin levels were observed. There was a significant variation among the 2D-ECHO parameters like regional wall motion abnormality (RWMA), global hypokinesia (GH) and diastolic dysfunction (DD) in both stable CKD patients and CKD patients on HD with or without HF [Table-4].

Parameter	Stable CKD patients		CKD-HD patients	
-	With CHF	Without CHF	With CHF	Without CH
HB	10.21 ± 1.35	11.04 ±1.85	10.06 ±2.05	10.81 ±1.84
Cr	2.48 ± 0.93	3.15 ±2.30	6.09 ±2.24	6.37 ±1.66
BUN	31.43 ± 13.56	35.80 ±29.65	47.86 ±23.05	53.57 ±15.51
Na	135.35 ± 4.54	137.23± 4.51	134.26 ±5.03	135.68± 3.47
K	4.51 ± 0.62	4.68 ±0.58	4.44 ±0.89	4.90 ±0.76
CL	97.44 ± 5.41	99.32 ±6.45	92.46 ±13.78	96.82 ±4.97
$HCO3^-$	18.38 ± 4.56	19.69 ± 2.91	18.38 ±4.56	19.69 ± 2.91
Ca	8.75 ± 0.56	8.76 ±0.80	8.50 ±0.76	8.61 ±0.61
PO4	4.67 ± 1.06	4.47 ±1.32	4.81 ±1.99	5.45 ±1.25
Uric acid	6.50± 1.80	6.34 ± 1.49	5.98 ±2.06	6.38 ±1.22
Protein	7.00± 0.81	7.26 ± 0.65	7.26 ±0.86	7.21 ± 0.57
Albumin	3.41 ± 0.40	3.62 ±0.41	3.26 ±0.49	3.39 ±0.46
Globulin	3.59 ± 0.73	3.65 ±0.52	3.97 ±0.74	3.82 ±0.66
RWMA	19 (44.20 %)	2(6.5%)	8(20.5%)	0(0.0%)
GH	14 (32.6%)	3(9.7%)	24(61.5%)	6(21.4%)
DD	14 (32.6 %)	4 (12.9 %)	15(38.5%)	1(3.6%)
LVH	9 (20.9%)	6 (19.4%)	12(30.8%)	6(21.4%)

Table 4: Comparison of serum biochemical and 2D- ECHO parameters of stable CKD patients with (n=43) or without CHF (n=31), and CKD patients on HD with (n=43) or without CHF (n=31). Values are the mean ± SD.

(e).Association between renal function and NT-proBNP levels in stable CKD patients with or without HF.

Next, the association between renal function (expressed as GFR) and NT-proBNP levels in stable CKD patients with or without HF was evaluated using Pearson Correlation Co-efficient (r) analysis. The mean levels of NT-proBNP across the groups showed rising pattern suggesting a rise in mean levels of NT-proBNP with a fall in GFR, albeit this inverse relation was not highly significant (P=0.06) [Figure 3].

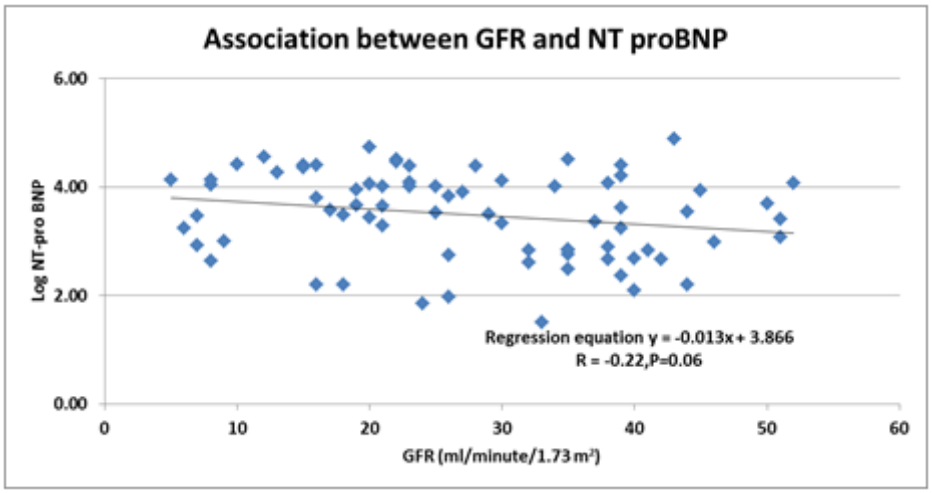

Figure 3: Correlation between GFR and plasma NT-proBNP concentrations was evaluated in CKD patients with or without HF. It was found that with fall in GFR there was a rise in NT pro-BNP concentration, albeit this inverse association was non-significant.

(3). Receiver operating characteristic (ROC) analyses

(a). CKD patients with or without HF

Next, we used receiver operating characteristic (ROC) analyses to determine optimal NT-proBNP cut-off values for (a) stable CKD patients with or without HF, (b) CKD patients on HD with or without HF and (c) stable CKD patients on HD with or without HF.

To accurate diagnosis of HF, sensitivity (true positive rate) and specificity (true negative rate) were determined. The results revealed that NT-proBNP levels were sensitive as well as specific, reflected in the AUC of 0.94 in CKD patients [Figure 4a]. The cut-off value that yielded 97% sensitivity and 74.0% specificity was 1200 pg/mL. Increasing the cut point that yielded 95% specificity and 80.0% specificity was 1850 pg/mL. The cut-off value that yielded 86% sensitivity and 90.0% specificity was 3100 pg/mL.

(b). CKD patients on HD with or without HF

The CKD patients on HD with or without HF, the levels of NT-proBNP were 4000 pg/mL, and is associated with a sensitivity and specificity of 92% and 75% respectively. Increasing the cut-off values of NT pro-BNP level to 8000 pg/mL the sensitivity was reduced to 87%, however specificity increased to 79%. These results indicated that NT-proBNP levels were both sensitive and specific, reflected in the AUC of 0.89 [Figure 4b].

(c). Stable CKD patients on HD with or without HF

In stable CKD patients, the levels of NT-proBNP were 3100 pg/mL, and is associated with the sensitivity of 91% and specificity of 74%. Increasing the cut-off NT pro-BNP levels to 4200 pg/mL reduces the sensitivity to 85%, but increases specificity to 81%. At NT-proBNP levels of 6500 pg/mL, the sensitivity reduced to 79% and specificity to 86 %. These results indicated that NT-proBNP levels were both sensitive and specific, reflected in the AUC of 0.89 [Figure 4c].

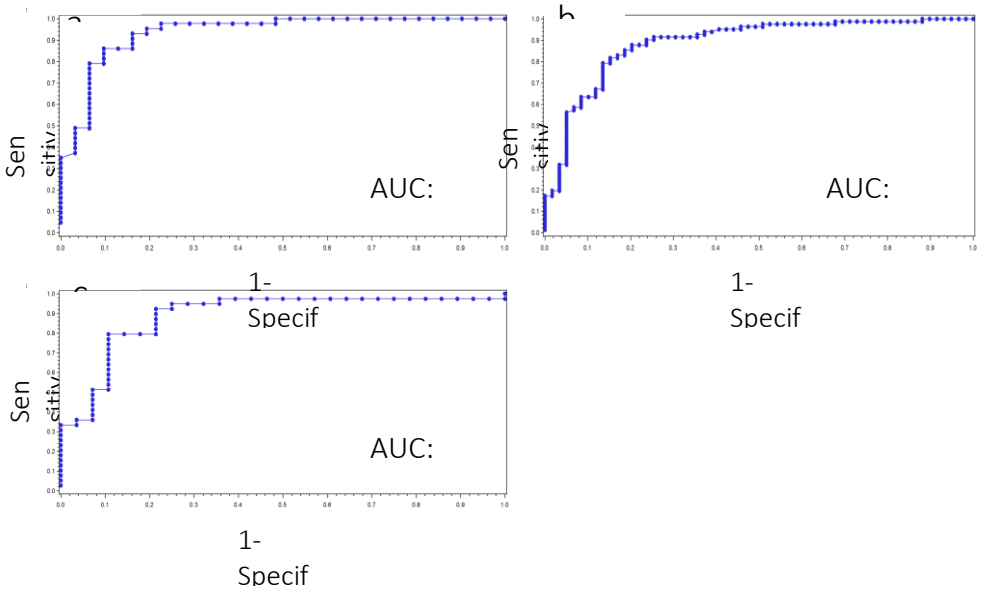

Figure 4a: ROC curves to compare the performance of NT-proBNP for the diagnosis of HF in all CKD patients (a), CKD patients on HD (b) and stable CKD patients not on HD (c).

Discussion

CKD can cause HF and vice-versa [29], which indicates that the heart and renal functions are closely interlinked. Cardio-renal syndrome (CRS) is often used to describe this condition and represents an important model for exploring the functional status of heart and kidney. HF can occur due to deranged renal function (patients with CKD are more likely to have HF) [30].

In clinical practice, serum levels of NT-proBNP are used for the diagnosis and prognosis of HF, but its diagnostic value is limited. HF is a complex clinical syndrome that can result from any structural or functional disorder in the heart that impairs the ability of the ventricles to fill or eject blood leading to raised intracardiac pressures [31]. NT-proBNP levels are increasingly used in the diagnostic evaluation of dyspnoeic patients [32, 9]. NT-proBNP is rapidly released by the ventricles of the heart in response to myocardial stretch. It affects body fluid volume (natriuresis and diuresis) and vascular tone. In the present study, we determined the cut-off values of NT-proBNP in CKD patients present with or without breathlessness for the diagnosis of HF in Indian population. There is no such study on Indian patients, and there is a generalization that NT-proBNP is elevated in CKD patients without knowing the cut-off values. In this study, we tried to find out cut point values of NT-pro-BNP in CKD patients presenting with or without dyspnea for an accurate diagnosis of HF.

Significant decrease of Hb levels in stable CKD patients with or without HF was observed, which suggests increased adverse events in HF. In contrast, no difference was seen between CKD patients on HD with or without HF. The effect of CKD on NT-proBNP based HF diagnosis revealed serum biochemical profiles, co-morbid conditions and past history were significantly associated with HF. This can be explained as due to high prevalence of DM (70.2%) and HTN (85.1%) in our study population as the most common cause of CKD was diabetic kidney disease, and the study included patients with moderate to severe kidney disease as well as those who were on hemodialysis (HD).

The plasma NT-proBNP concentrations were positively related to the age. Gender subgroup analysis revealed that NT-proBNP levels in the female group were higher than that of male group, albeit the difference was not statistically significant (Data not shown). The comparison of past history for AF and MI was statistically significant in patients with or without HF (P<0.001). Further, our data show that there was no significant difference among sex in patients with HF and without HF. These results are in agreement with the data reported by Anwaruddin et al (2006) [33], wherein these authors demonstrated the effects of renal insufficiency on NT-proBNP based HF diagnosis and prognosis.

Takami et al (2004) [34] reported that in 103 non-dialysis dependent patients with renal impairment, without HF had a higher level of serum NT-proBNP than patients with HTN and normal renal function. In a prospective study of 1586 patients with acute dyspnea based on NT-proBNP levels revealed that age and past MI were strong independent predictors of HF [32]. Koch et al (2006) [35] reported that NT-proBNP levels decreased with increasing age. In a classical review by Menon et al (2005) [36] described that cardiovascular risk factors in CKD patients associated with traditional (e.g. older age, DM, HTN, smoking, valvular heart disease, dyslipidemia) as well as non-traditional risk factors. The upper limit of normal values is another important consideration of the usefulness of NT-proBNP in the diagnostic evaluation of patients with acute dyspnea [32, 9]. The prognosis based on the NT-proBNP levels has not been widely studied in CKD patients, and there is no standard cut points for NT-proBNP to predict adverse events. In asymptomatic CKD patients who did not yet require HD, more than half of the patients had elevated NT-proBNP levels [37].

ROC analysis for all stable CKD patients, CKD patients on HD and stable CKD not on HD with or without HF was carried out to determine the sensitivity and specificity of NT-proBNP for the diagnosis of HF [38]. GFR is generally accepted as the best overall index of kidney function. A meta-analysis published in 2015 summarized the value of NT-proBNP <300 pg/ml, in the acute setting, showed a very high negative predictive value (NPV) when using low cut-off levels (NT-proBNP <300 pg/ml). These cut-off values, recommended by the European Society of Cardiology (ESC) guidelines are good in excluding diagnosis of HF. They also help to distinguish HF from non-cardiac causes of dyspnoea [39]. ROC curve analysis for discrimination of a GFR of <30 mL/min indentified area under the curve (AUC). For our study, we refer to a GFR <60 ml/min/1.73 m2 as decreased GFR and a GFR <15 ml/min/1.73 m2 as kidney failure.

In CKD patients, increase in NT-proBNP levels implicated in the compensatory increase in GFR. In these patients, GFR ranged from 15 ml/min/1.73 m2 to 24 ml/min/1.73 m2. NT-proBNP cut point of 1850 pg/ml for stable CKD patients with GFR <60 ml/min/1.73 m2 has a sensitivity of 95% and specificity of 80% for the diagnosis of HF (AUC, 0.94; 95% CI, 0.89-0.96, P =0.001) in stable CKD patients with or without HF.NT-proBNP cut point of 8000 pg/ml for CKD patients on HD with GFR <60 ml/min/1.73 m2 and its corresponding sensitivity and specificity were 87% and 79% , respectively for the diagnosis of HF (AUC, 0.89; 95% CI, 0.882-0.906, P=0.001). NT-proBNP cut-off level of 4200 pg/ml across all CKD patients with GFR <60 ml/min/1.73 m2 has a sensitivity of 85% and specificity of 81% (AUC, 0.89; 95% CI, 0.896-0.910, P=0.001).

CKD patient who have acute breathlessness, but NT-proBNP values are below the above mentioned cut-off values, should prompt the evaluation for other causes of acute dyspnea [9]. Anwaruddin et al (2006) [33] undertook the analysis of participants from ProBNP investigation of dyspnea in the emergency department (PRIDE) study. They reported the value of NT-proBNP for the diagnostic evaluation of patients with dyspnea and suspected HF. NT-proBNP values of 450 pg/ml for patients ages <50 years and 900 pg/ml for patients >50 years had a sensitivity of 85% and a specificity of 88% for diagnosing acute HF among subjects with GFR >60 ml/min/1.73 m2.Using a cut point of 1,200 pg/ml for subjects with GFR <60 ml/min/1.73 m2, they found 89% sensitivity and 72% specificity. Fu et al (2013) [40] reported that NT-proBNP predicted all causes of death with cut-off values of 369.50 pg/ml and 2584.10 pg/ml in non-CKD and CKD patients respectively.

Summary and Conclusion

The present study is summarized as follows: (1) the most common cause of CKD in Indian population was diabetic kidney disease followed by chronic glomerulonephritis (n=16), (2) the mean age of patients with HF was higher compared to patients without HF, (3) there was an overall higher prevalence of traditional risk factors in CKD patients, (4) presence of past history of AF and MI was found to be associated with an increased risk of HF, (5) anemia was also found to have increased risk for HF in stable CKD patients, (6) the rise in the NT-proBNP levels in CKD patients with worsening of renal function suggests inverse relationship between NT-proBNP and GFR, (7) NT-proBNP values are elevated in all CKD stages from 3 to 5-HD, hence mere elevation of NT-proBNP in CKD patients presenting with acute dyspnea should not prompt the diagnosis of HF, (8) NT-proBNP should be measured in all CKD patients presenting with symptoms such as dyspnoea and/or fatigue, as their use facilitates the early diagnosis and help in HF risk stratification, (9). NT-pro BNP has high diagnostic accuracy in discriminating HF from other causes of dyspnoea; the higher the NT-proBNP, the higher the likelihood that dyspnoea is caused by HF, (10). It was found that NT-proBNP cut-off levels for the diagnosis of acute HF in patients presenting with acute dyspnoea are higher compared to those used in the diagnosis of chronic HF in patients with dyspnoea on exertion. Taken together, it may be conclude that, NT-proBNP levels can be used not only in the acute setting but also in the

diagnosis of chronic HF and even possibly in identification of patients at risk of developing HF.

Limitations of the study

The present study is not without limitations, which need to be addressed when interpreting results. We understand that this is a single centre study limited by a small number of study population. Larger studies are needed to confirm present findings. In our study population, several factors can affect plasma NT-proBNP levels and patient outcomes, although the results were adjusted for multiple covariates that may be associated with circulating NT-proBNP levels and outcomes, there is a possibility of residual confounding factors. In view of cost involved, present study did not include serial evaluation of NT-proBNP levels, which may be useful in detection of failure/timely modification of treatment.

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Conflict of interest

The authors declare that they have no competing interests.

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