International Journal of Research in Medical Sciences
Renganathan SMS et al. Int J Res Med Sci. 2021 May;9(5):1434-1441
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20211882

Original Research Article

Brain natriuretic peptide in differentiating cardiogenic and non-cardiogenic dyspnoea in patients with renal dysfunction: a single centre study

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Received: 21 February 2021
Revised: 23 March 2021
Accepted: 25 March 2021

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ABSTRACT

Background: Both BNP (Brain Natriuretic Peptide) and renal function are prognostic indicators of survival in patients with congestive heart failure. However, relationship between BNP, renal function and heart failure as an emergency diagnosis are unknown. The usefulness of BNP as a diagnostic tool in patients with renal dysfunction is thus explored in this study.
Methods: The present study was prospectively designed diagnostic test evaluation study conducted in Banaras Hindu University, Varanasi. Out of 166 participants with renal dysfunction defined as creatinine >1.5mg/dl who presented with acute dyspnoea, clinical history, BNP, 2D Echo and baseline estimated glomerular filtration rate were assessed. Patients with severe anaemia, eGFR less than 15 ml/min/1.73 m^2 and those on dialysis therapy were excluded from the study. The final diagnosis was adjudicated by cardiologist who was blinded to BNP values.
Results: The final diagnosis of CHF was in 104 (62.7%). The correlation between BNP and eGFR values were r=-0.49 for those with CHF ($p<0.001$) and r=-0.279 ($p<0.028$) for those without CHF. Median BNP in patients with renal dysfunction with CHF was 1206 pg/ml and without CHF was 186 pg/ml. The area under the receiver operating characteristic curve and optimal cutpoints for EGFR categories 59-30 ml /min/1.73 m^2 and EGFR less than 30 ml/min/1.73m^2 were 0.992 and 491.5 pg/ml (sensitivity 97% and specificity 95%) and 1.000 and 512pg/ml (sensitivity 100% and specificity 95.5%) respectively.
Conclusions: Renal function weakly correlates with BNP in patients without CHF (congestive heart failure). BNP is an important bed side tool for distinguishing cardiogenic and non-cardiogenic dyspnoea in patients with renal dysfunction requiring higher diagnostic cut points. Thus, the present study emphasises BNP is the strong and independent predictor of CHF even after taking renal function into considerations.

Keywords: Brain natriuretic peptide, Renal dysfunction, Congestive heart failure

INTRODUCTION

Brain natriuretic peptide (BNP) is a neuro hormone secreted mainly in the cardiac ventricles in response to volume expansion and pressure overload.[1,2] Circulating levels of B-type natriuretic peptide (BNP) and N-terminal proB-type natriuretic peptide (NT-proBNP) have been reported to be closely associated with both the severity and prognosis of heart failure BNP assays are thus being used for the diagnosis of Congestive heart failure (CHF) in emergency cases.[3,4] But additional complexity arises in cases where the patients have chronic kidney disease (CKD), as the BNP levels or Natriuretic peptides (NP) in general, have been previously implicated as possible

mediators of the integrated response to functional renal mass loss, with a distinct contributory role depending both on the degree of renal failure and on the time elapsed from the beginning of renal function decline.

The disease state associated with the highest circulating levels of NP is said to be renal failure. In this case, increased NP circulating levels cannot linearly be interpreted as an expression of the activation of the NP system, as observed in the context of left ventricle (LV) wall stress associated with heart failure (HF) or volume overload.

Indeed, previous evidence from a number of studies have suggested that plasmatic levels of NP may be regulated both by the rate of synthesis/cardiac release of NP and by the rate of removal of the peptides from the circulation. As a consequence, NP circulating levels in patients with significant renal failure have to be interpreted in light of the severity of renal dysfunction and a higher cut point is expected as chronic kidney disease (CKD) stage advances.[5-12]

The diagnosis of CHF has been fundamentally unchanged and based on clinical history, physical examination, electrocardiogram (ECG), chest x-ray, and assessment of left ventricular function by echocardiography or nuclear ventriculography during the past several decades. Since patients with chronic kidney are at extremely high cardiovascular risk and frequently experience coronary events and heart failure, the increase of BNP and NT proBNP levels has been considered an unwanted confounder in the diagnosis of CHF.

The current method of diagnostic testing for congestive heart failure, which is 2D-echocardiography with color Doppler has its own limitations in that it is not available in every acute care settings such as the emergency departments (EDs) and this results in a delay in the treatment of patients presenting with acute dyspnoea in the EDs. Compared to the 2D-echocardiography, BNP can be very cost-effective in analysing the causes of acute dyspnoea.

This study aimed to assess the levels of BNP due to cardiogenic and non-cardiogenic causes of dyspnoea in patients with renal dysfunction and thus sought to establish how kidney function affects BNP levels, focusing on the relationship between the circulating levels of the BNP during various stages of kidney function. The purpose of the present study is to determine if BNP levels could accurately differentiate dyspnoea due to CHF from dyspnoea of pulmonary etiologies in patients with kidney disease. It is extremely important for a rapid and accurate determination of the etiology of shortness of breath in CKD patients presenting with acute dyspnea. The usefulness of BNP as a diagnostic tool in patients with renal dysfunction is thus explored in this study.

Aims and objectives of the study was to evaluate role of brain natriuretic peptide in acute dyspnoea in patients with renal dysfunction. To evaluate the causes of acute dyspnoea in patients with renal dysfunction. To determine cut off level of BNP to differentiate between cardiogenic and non-cardiogenic causes of dyspnoea in patients with renal dysfunction. To determine the correlation between BNP and eGFR in patients presenting with acute dyspnoea.

METHODS

Inclusion criteria

Males and females>18 years of age with, creatinine>1.5 mg/dl presenting with acute dyspnea were included in the study.

Exclusion criteria

Age <18 years, Cases clearly not likely to be cardiogenic as traumatic pneumothorax/end stage renal disease with EGFR <15 ml/min/ 1.73 m^2, Patients on hemodialysis, Patients with severe anemia as defined as less than 7 g/dl, Patients with co morbidities (eg malignancy) that may affect 6 months of survival of the patients, Patients not willing to participate in the study.

Out of 166 participants with renal dysfunction defined as creatinine>1.5mg/dl who presented with acute dyspnoea, clinical history, BNP, and baseline creatinine and estimated glomerular filtration rate using the modification of diet in renal disease formula were assessed. calculated eGFR values were categorized as less than 30, 30 to 59 ml/min/ 1.73 m^2 based on the National Kidney Foundation (NKF)- Kidney Diseases Outcomes Quality Initiative (KDOQI) classification of kidney function, eGFR values less than 60ml/min/1.73m^2 were considered abnormal and indicative of moderately reduced kidney function.

Framingham risk criteria for diagnosis of Heart Failure (requiring two major or one major and two minor criteria for diagnosis of CHF) was scoped. All patients in the study population underwent 2D echocardiography (ECHO) with color doppler by a cardiologist who was blinded to the BNP values. Echocardiography was considered as gold standard in differentiating between cardiogenic versus non cardiogenic dyspnoea. The final diagnosis of cardiogenic and non-carcinogenic dyspnoea was adjudicated by expert panel taking all parameters into consideration. Measurement of BNP- 2ml EDTA anticoagulated venous blood was collected after informed consent from patient to measure BNP on Alera Triage-Cardio product insert by kit provided by Alera. It measures BNP in pg/ml through 3rd generation immunoassay method. Assay of creatinine serum creatinine was measured on the Dimension Max (Siemens Medical Solution Diagnostics, Tarrytown, NY) by using the Jaffe rate method with a calibrator traceable

to the international reference creatinine method (isotope dilution mass spectrometry). The CVs claimed by the manufacturer were 6.7% (0.67 mg/dL (59 µmol/L), 3.4% (0.85 mg/dL (75 µmol/L), 1.3% (2.09 mg/dL (185 µmol/L), and 1.3% (3.93 mg/dL) (347 µmol/L) for within-run imprecision and 7.9%, 5.8%, 1.9%, and 1.5%, respectively, for total imprecision.

Calculation of GFR

Measurement of serum creatinine was obtained from the first blood draw in the ED. eGFR (in millilitres per minute per 1.73 square meters) were calculated using the Modification of diet in renal disease formula 186.3* (serum creatinine_1.154)* (age-0.203)); calculated values were multiplied by 0.742 for women and 1.21 for African Americans. Calculated eGFR values were categorized as less than 30, 30 to 59, 60 to 89 and 90 or greater ml/min/ 1.73 m^2 based on the National Kidney Foundation (NKF)- Kidney Diseases Outcomes Quality Initiative (KDOQI) classification of Kidney function, eGFR values less than 60ml/min/1.73m^2 were considered abnormal and indicative of moderately reduced kidney

Statistical analysis

Statistical analysis was done using SPSS version 16.0. Etiological analysis of acute dyspnoea among patients with renal dysfunction in emergency department (ED) was evaluated. Receiver-operator curve (ROC) was generated to determine cut off level of BNP its sensitivity, specificity in diagnosing or excluding cardiogenic dyspnoea in patients with renal dysfunction. Univariate comparisons were made using chi square test. Spearman correlation coefficient was used to quantify the linear relationship between BNP and eGFR.

RESULTS

This cross-sectional study of 166 participants gives useful insight about role of point of care of BNP in patients with acute dyspnoea in patients with renal dysfunction. Most of the patients were elderly with median age of patients being 60 years. There was male predominance among patients in the study population (males n=107, females n=59).

Coronary artery disease with CHF was the most common etiological diagnosis of acute dyspnea in patients with renal dysfunction in our setting. Sepsis with ARDS was the most common etiological diagnosis of non-cardiogenic dyspnoea with renal dysfunction. Hypertension as risk factor was prevalent in 74.6% of patients in CKD stage 3 and 75.7% of patients in CKD stage 4. Type 2 diabetes mellitus was prevalent in 53.7% in CKD stage 3 group and 64.9% in CKD stage 4. Of the clinical examination variables, patients on average had blood pressures in range that centered over 140/80mm hg. Cardinal signs of CHF S3, hepatic congestion, alveolar edema were more frequent in the more severe CKD group. Rales, edema and cardiomegaly were prevalent in both CKD stage 3 and 4.

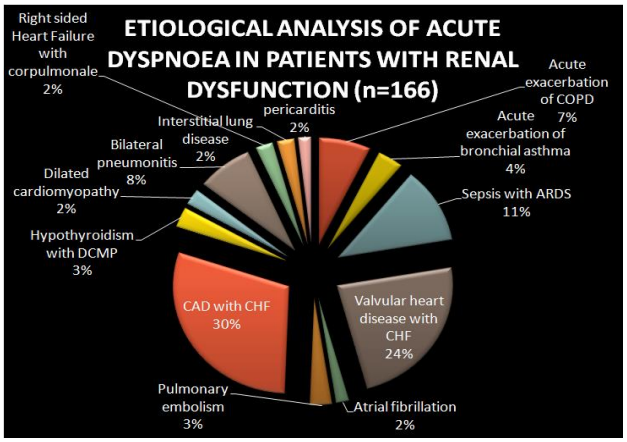

Figure 1: Etiological analysis of acute dyspnoea in patients with renal dysfunction (n=166).

Sixty-three percentage of patients had serum BNP level of more than 491 pg/ml. All of these patients had ejection fraction of <45% on 2D ECHO. The median BNP in patients with renal dysfunction with diagnosis CHF is 1206 pg/ml and without CHF is 186 pg/ml respectively.

Optimum cut off point for detection of cardiogenic dyspnea in patients with renal dysfunction was 491pg/ml at sensitivity and specificity were 98.1% and 93.5% respectively with p value of 0.001 at 95% confidence interval. The study found a statistically significant negative correlation between GFR and BNP level in patients with CHF than those without CHF.

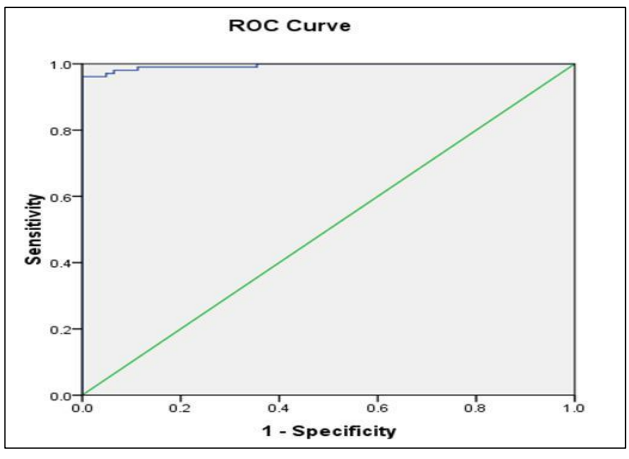

Figure 2: Receiver operating curve for determination of cardiogenic and non-cardiogenic dyspnoea in patients with renal dysfunction.

Table 1: Basic characteristics and clinical variables of participants (n=166).

Variables	Number of participants (n=166)		
Age	60 (49.5-66 years)		
Gender (male)	104 (64.5 %)		
Female	59 (35.5%)		
Baseline characteristics Variables	Non cardiogenic dyspnoea	Cardiogenic dyspnoea	P value
Age	57.39±13.110	57.16±13.694	0.918
Creatinine	2.265±0.4760	2.141±0.6251	0.183
eGFR	30.761±7.0375	33.484±10.386	0.069
Vital signs at initial presentation	Non cardiogenic dyspnoea (n=62)	Cardiogenic dyspnoea (n=104)	P value
Heart rate	98.94±8.394	104.10±11.738	0.003
Systolic blood pressure	139±15.393	145.81±19.889	0.025
Diastolic blood pressure	79.5±6.419	84.29±12.945	0.001
Rales			
Yes	15 (24.2%)	100 (96.2%)	<0.001
No	47 (75.8%)	4 (3.8%)	
Edema			
Yes	14 (22.6%)	95 (91.3%)	<0.001
No	48 (77.4%)	9 (8.7%)	
Cardiomegaly			
Yes	0	86 (82.7%)	<0.001
No	62 (100%)	18 (17.3%)	
S3			
Yes	0	20 (19.2%)	<0.001
No	62 (100%)	84 (80.4%)	
Hepatic congestion			
Yes	0	41 (39.4%)	<0.001
No	62(100%)	63 (60.6%)	
Alveolar edema			
Yes	0	14 (13.5%)	<0.007
No	62(100%)	89 (85.6%)	
LVEF	59.97±6.739	44.61±6.068	<0.001
BNP (pg/ml)	186 (48.07 – 343.0)	1206 (889.25-1915.0)	

Note that the data was expressed as Mean ±Standard Deviation or n (%) or Median and Interquartile Range (IQR).

ROC curve for BNP in patients with renal dysfunction who presented with cardiogenic and non-cardiogenic dyspnoea at confidence interval 95% with p value of <0.05, the area under the curve is 0.994. Optimum cut-off for determination of cardiogenic and non-cardiogenic dyspnoea in patients with renal dysfunction was 491 pg/ml (sensitivity 98.1%, specificity 93.5%).

ROC curve for BNP in Patients with eGFR of 60-30 ml/min/1.73m2 who presented with cardiogenic and non-cardiogenic dyspnoea at confidence interval 95% with p value of <0.05, the area under the curve is 0.992. Optimum cut-off for determination of CHF and without CHF in patients with eGFR of 60-30 ml/min/1.73 m2 is 491.5 pg/ml (sensitivity 97%, specificity 95%).

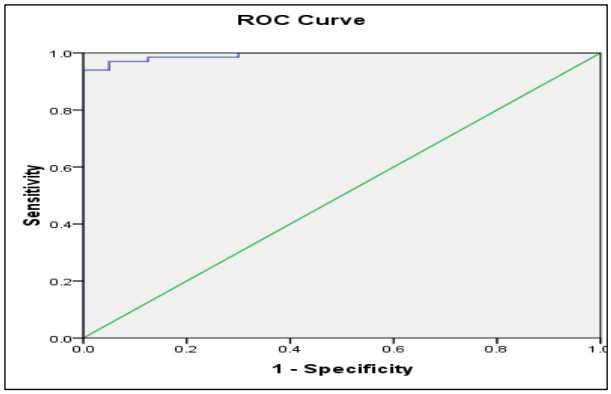

Figure 3: Receiver operating curve for determination of cardiogenic and non-cardiogenic dyspnoea in patients with eGFR 60-30 ml/min/1.73 m^2 as estimated by MDRD formula.

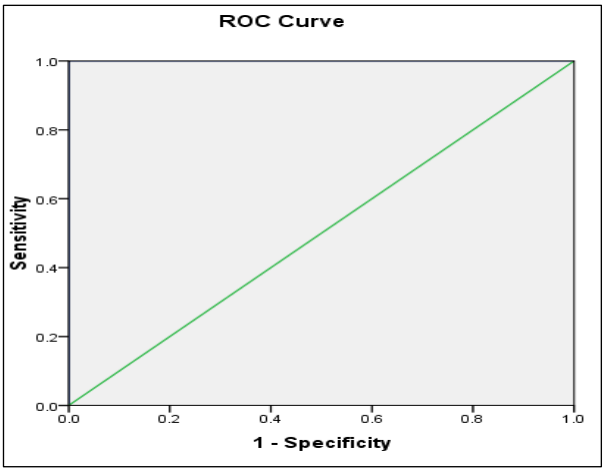

Figure 4: Receiver operating curve for determination of cardiogenic and non-cardiogenic dyspnoea in patients with eGFR <30 ml/ min/1.73 m2 as estimated by MDRD formula.

ROC curve for BNP in Patients with eGFR less than 30 ml/min/1.73 m^2 who presented with cardiogenic and non-cardiogenic dyspnoea at confidence interval 95% with p value of <0.05, the area under the curve is 1.000. Optimum cut-off for determination of CHF and without CHF in patients with eGFR of less than 30 ml/min/1.73 m^2 is 512 pg/ml (sensitivity 100%, specificity 95.5%.

Correlation between GFR and BNP level

Spearman Correlation coefficient was used to quantify the linear relationship between BNP and eGFR. There is a statistically significant negative correlation between GFR and BNP level in patients with CHF r = -0.49 with a p value of <0.001. But for those without CHF there was no statistically significant correlation between eGFR and BNP with r = -0.279 with p value of <0.028.

DISCUSSION

One of the most common reason for in hospital admissions especially to emergency department and acute care units is acute dyspnoea. This study gives us useful insight in the importance of BNP in acute care settings in diagnosing etiology and accordingly management of acute dyspnoea in patients with renal dysfunction.[18-22]

According to previous studies, prevalence of common diseases which cause dyspnoea in general population is 2%, 5 to 10% and 5% for congestive heart failure, chronic obstructive pulmonary disease and asthma respectively.[23,24] Depending on the hospital setting, Acute Heart Failure Syndromes (AHFS) accounts for 30% to 70% of acute dyspnoea in the emergency department (Wang et al, 2005).[25,26]

In the present study which evaluated the etiology of acute dyspnoea in patients with renal insufficiency. Coronary artery disease (29.5%) with CHF was found to be the most common cause of dyspnoea. Followed by valvular heart disease (23.5%). The other etiologies of patients who presented with acute dyspnoea in emergency with renal dysfunction were sepsis with ARDS (11.4%), Bilateral Pneumonitis (7.8%), acute exacerbation of COPD (7.2%).

Biomarkers, measurable biological markers of a pathological process, have established a growing role in modern medical practice over the last fifty years. Although BNP is a very sensitive marker for cardiogenic dyspnoea but application of this analysis in clinical setting is often limited by the absence of universally accepted cut off level. Very few studies has been done to determine cut off level of BNP to distinguish between cardiogenic and non-cardiogenic dyspnea in patients with renal dysfunction and none of them had sensitivity of more than 80%. Cut-off values that provided a reasonably high sensitivity had a very low specificity and vice versa. The screening test must be simple and quick and based on routine procedure.[27-30]

In contrast to previous studies on brain natriuretic peptide, this study was successful in deciding exact cut off level of BNP in differentiating between cardiogenic vs non cardiogenic dyspnoea in patients with renal dysfunction. This study gives optimum cut off point for detection of cardiogenic dyspnoea at 491 pg/ml with sensitivity and specificity of 98.1% and 93.5% respectively.

This study had a cohort of 166 patients presenting with acute dyspnoea with elevated creatinine of >1.5 mg/dl. Point of care BNP level was estimated in all these patients and all these patients were subjected to 2D echocardiography as gold standard and the most important part was that the cardiologist doing echocardiography was blinded of BNP result.

The study also focused on clinical diagnosis vs BNP and ECHO correlation in patients with renal dysfunction. Serum BNP level of more than 491pg/ml had 95.1 percent ECHO correlation with cardiogenic causes. 8 patients having non cardiogenic clinical diagnosis had BNP more than the cutpoint of 491pg/ml. Among the 8 patients, one had the final diagnosis of Sepsis with ARDS, 2 had final diagnosis of pulmonary embolism, 4 patients had final diagnosis of right heart failure with corpulmonale. One had the final diagnosis of Interstitial Lung Disease.

At BNP level of less than 491pg/ ml two patients had cardiogenic dyspnoea with final diagnosis of coronary artery disease with CHF. Thus, bedside measurement of serum BNP had diagnostic sensitivity and specificity almost equivalent to that of 2D ECHO which is itself gold standard.

The above findings also emphasis that BNP values should not interpreted in isolation and should be integrated with

other findings in diagnostic evaluation. Importantly, CKD appears to influence the optimum cut points for BNP in the diagnosis of CHF.

Median age of patients in our study population is 60 years with interquartile range 49.5 to 66 years. Most of the patients were elderly between 51-60 years of age (31.9%) followed by 61-70 years of age (28.7%). 16.3% of the population were between 30-40 years and 12.7% of the population were more than 70 years of age. The study by Redfield et al and according to the Heart Disease and stroke statistics, BNP levels increase with the age in the normal population free of ventricular function.[35,36]

There was male predominance among study population (107 males and 59 females). In our setting male: female disparity is commonly seen for most disease conditions suggesting a gender bias in health care seeking behavior of population. The relationship of BNP levels with gender is less well defined, demonstrating variabilities between studies. One trial by Maisel et al, has shown that females have higher value of BNP than males, and female gender is an independent predictor of BNP levels in older adult even without cardiac dysfunction.[37,38] Other studies by Knudsen et al did not find any significant interaction between age and BNP levels in the older adult even without cardiac dysfunction. The discrepancy among the findings in these studies is likely explained in part by the differences in the study designs and study populations. When compared to previous studies which showed that BNP level is higher in females, this study concluded that there is no significant correlation between sex and BNP levels.

The 'Breathing Not Properly' study was a multi-national, international study recruited 1586 patients. BNP had a diagnostic accuracy of 83.4% at a cut-off of 100pg/ml and a cut-off of 50 pg/ml had a negative predictive value of 96%. In patients with eGFR<30 ml/min/1.73 m^2 BNP had a diagnostic accuracy of 86% at a cut off of 225 pg/ml (65 fmol/ml) and In patients with eGFR 59-30 ml/min / 1.73 m^2 BNP had a diagnostic accuracy of 81% at a cut off of 201.2 pg/ml (58.1 fmol /ml).[39,40]

In contrast to it, current study concluded with high cut off level of BNP but at the same time diagnostic accuracy was also higher. In the present study patients with eGFR <30 ml/min/1.73 m^2 BNP had a diagnostic accuracy of 100% at cut point of 512 pg/ml and in patients with eGFR 59-30 ml/min/1.73 m^2 BNP had a diagnostic accuracy of 97% at the cut point of 491.5 pg /ml.

This study also showed that even in patients with acute exacerbation of COPD, rise in BNP is significant among only those with cor pulmonale that too not in cardiogenic range. There were 12 cases of acute exacerbation of COPD, but none of them had BNP above 491pg/ml. Four cases with right sided heart failure (RSHF) and normal left ventricular function had significantly elevated BNP. With cut off value of 491 pg/ml it was difficult to differentiate patients with left sided heart failure from those with corpulmonale.

In contrast to other studies which have shown that while evaluating acutely dyspneic patients, it is important to keep in mind other non-cardiogenic etiologies of acute dyspnea when an elevated BNP level is noted especially when BNP levels fall in the "gray" zone (100-500 pg/ml for BNP), this study clearly determines that chances of cardiogenic dyspnea is <5% at BNP level of <491 pg/ml in patients with renal dysfunction.

CKD appears to influence the optimum cut points for BNP in the diagnosis of CHF. The Breathing not multinational trial concluded that in general, as CKD stage advances, a higher cut point of BNP is implied, with a cut point of approximately 200 pg/ml (57.8 fmol/ml) being reasonable for those with eGFR less than 60 ml/min /1.73 m^2. The present study provides cut point of approximately 491pg/ml for patients with eGFR less than 60 ml/min/1.73m^2. Using this approach, BNP would maintain a high level of diagnostic utility with AUC greater than 0.80 across all CKD groups.

Hypertension was prevalent in 74.6% of patients in CKD stage 3 and 75.7% of patients in CKD stage 4. In the study by Mccullough et al, hypertension was prevalent in 59.5% in CKD stage 3 and 81.1% in CKD stage 4 respectively.[40] Type 2 Diabetes Mellitus was prevalent in 53.7% in CKD stage 3 group and 64.9% in CKD Stage 4. In the study by McCullough et al, type 2 diabetes mellitus was prevalent in 25.4% of patients in CKD stage 3 and 44.6% in CKD stage 4 group.

Of the clinical examination variables, patients on average had blood pressures in range that centered over 140/80mm hg. This finding was similar to the Breathing not multinational Trial. Cardinal signs of CHF S3, hepatic congestion, alveolar edema was more frequent in the more severe CKD group. However, Rale, edema and cardiomegaly were prevalent in both CKD stage 3 and 4.

There is a statistically significant negative correlation between GFR and BNP level in patients with CHF r=-0.49 with a p value of <0.001. But for those without CHF there was no statistically significant correlation between eGFR and BNP with r=-0.279 with p value of <0.028. This clearly suggest that BNP is the strong and independent predictor of CHF even after taking renal function into consideration. The study by Mc cullough also shows significant negative correlation between BNP and eGFR in patients with CHF (r=-0.19 with p value of <0.001).[40] In the present study the median BNP and inter quartile range in patients with renal dysfunction in patients with CHF is 1206 pg/ml and 889.25-1915 .0 and without CHF is 186 pg/ml and 48.07 -343.0 respectively.

Our study has multiple limitations related to any study that attempts to create a gold standard for a clinical syndrome. We acknowledge that misclassification bias is

possible and difficult to quantify, especially with respect to falsely decreased eGFR caused by poor renal perfusion, use of diuretics, or relative intravascular volume contraction. Some elevations of serum creatinine levels may have been caused by acute renal failure, which is not captured in data reporting process. It is also possible that measurement of BNP could have been confounded by other factors, including subclinical acute ischemia which can result in elevations of serum creatinine levels, and hence falsely lowered eGFR.

Although 2D echocardiography is gold standard to rule out cardiogenic dyspnea but it requires cardiologist for interpretation. Thus, this study is especially important for common hospital setting in our country where cardiologist is not available for 24x7 hours. Measurement of BNP is an easy and quick bed side method which does not require any specialised skill. Thus, this study gives us a reliable cut off level of 491 pg/ml of BNP which clearly distinguishes between cardiogenic vs non cardiogenic dyspnea in patients with renal dysfunction. This differentiation is very crucial because it decides management in these patients.

CONCLUSION

We believe an important finding of this study is the observation that CHF as a diagnosis is much more common in patients with CKD presenting to ED with dyspnoea. It appears that BNP level correlates weakly but significantly with eGFR even in patients without CHF, suggesting chronic increased blood volume and increased left ventricular wall tension. However, eGFR does not appear to confound the interpretation of BNP levels, especially in patients with BNP level greater than 491pg/ml, in whom nearly 90 % will have CHF as the proven diagnosis of dyspnoea. Thus the present study emphasizes BNP is the strong and independent predictor of CHF even after taking renal dysfunction into consideration.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Renganathan SMS, Rai M, Tiwari JP, Singh TB. Brain natriuretic peptide in differentiating cardiogenic and non-cardiogenic dyspnoea in patients with renal dysfunction: a single centre study. Int J Res Med Sci 2021;9:1434-41.