Plasma B-type Natriuretic Peptide Concentration for Diagnosis of Acute Heart Failure with Renal Insufficiency.

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Abstract:

Background : Plasma B-type natriuretic peptide (BNP) is the diagnostic tool for acute heart failure (AHF).This natriuretic peptide level depends on renal function, through renal metabolism and excretion. Therefore we examined the effect of renal impairment on plasma BNP level during diagnosis of AHF. **Objective:** The objective of the study was to assess the effect of renal dysfunction on plasma BNP level and to determine appropriate cutoff value of plasma BNP to diagnose the patients of AHF with renal insufficiency. **Methods:** This cross sectional analytical study was conducted in the Department of Biochemistry Bangabandhu Sheikh Mujib Medical University (BSMMU). The study was done among 90 AHF patients selected from cardiology emergency department during the period of July 2012 to June 2013. After enrollment plasma BNP concentration was measured and eGFR was estimated from serum creatinine by the four parameter Modification of Diet and Renal Disease (MDRD) equation and then grouped into two groups on the basis of empirical cut off value of eGFR 60 ml/min/1.73 m^2. **Results:** In this study a significant negative correlation was found between plasma BNP level and eGFR ($P<0.001$), with higher BNP levels observed as eGFR declined. The optimal BNP cutoff value for diagnosis of AHF patients with renal insufficiency was 824 pg/ml. At this cutoff level AHF with renal insufficiency could be diagnosed with sensitivity and specificity of 84% and 71%, respectively. **Conclusions:** By adjusting the cutoff value, plasma BNP can be used to diagnose AHF with renal insufficiency with an acceptable sensitivity and specificity.

Keywords: Acute Heart failure, B-Type natriuretic peptide, Estimated glomerular filtration rate, Renal insufficiency.

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Introduction:

Heart failure is a complex clinical syndrome that can results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.[1] Heart failure is a major public health issue with a current prevalence of over 23 million worldwide and over 5.8 million in the USA.[2] In developed countries around 1% to 2% of the adult population suffers from heart failure, but in those over the age of 65, this increases to 6–10%.[3]

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Heart Failure (HF) is a significant and growing health problem in the aged population because of rapid rise of aging populations and the prolongation of the lives of cardiac patients by modern therapy.[4] Despite improvements in therapy, mortality and morbidity of HF remain high in our country and it has become an increasingly frequent cause of admission and carries a poor prognosis.[5]

Over recent years, the field of medicine has been challenged by the twin epidemic of heart failure and renal insufficiency. Concomitant renal insufficiency is being recognized as one of the most common and most confounding co-morbidity in acute decompensated heart failure. The coexistence of the two problems in the same patient, referred to as 'cardiorenal syndrome' (CRS) and has an extremely poor prognosis.[6] Studies have shown

that more than 30% of the overall AHF patients develop renal dysfunction.[7]

A reduced cardiac output in AHF patients resulting in decreased renal perfusion could be an easy explanation for the development of renal insufficiency.[8] This decline in renal function, despite a presumed preservation of blood flow to the kidneys, has led to the search for mechanisms including the role of the renin-angiotensin-aldosterone system (RAAS), various chemicals (nitric oxide, prostaglandins, natriuretic peptides, endothelins, etc), oxidative stress and sympathetic overactivity.[9]

For the diagnosis of AHF a variety of diagnostic tests are available including assessment of clinical signs and symptoms of HF, laboratory blood tests, radiological examinations, electrocardiography and echocardiography.[10] Echocardiogram is mostly concerned to characterize the specific structural and functional abnormalities associated with the syndrome but do not determine the diagnosis of heart failure.[11] In 1988 a new cardiac natriuretic peptide, B-type natriuretic Peptide (BNP) was discovered which is useful as an objective marker for the diagnosis of congestive heart failure (CHF) caused by systolic and diastolic dysfunction.[12]

B-natriuretic peptide (BNP) is a peptide secreted from the cardiac ventricles in response to ventricular wall stress, ventricular dilatation and pressure overload. Circulating BNP acts as an antagonist of the renin-angiotensin-aldosterone system, and protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nervous system.[13]

BNP is eliminated by receptors located in the liver, lung, kidney, and vascular endothelium and through the kidney. Renal dysfunction affects this peptide. Thus, to contribute clinical value, BNP measurements need to be explored within the context of renal function when developing patient treatment strategies .[14]

Methods:

This cross sectional analytical study was conducted in the Department of Biochemistry Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of July 2012 to June 2013. A total of 90 diagnosed AHF subjects (70 male and 20 female) selected from cardiology emergency department of BSMMU, NICVD and DMCH were included in the study. Diagnostic criteria for heart failure were based on history, radiological and echocardiographic findings, which included clinical symptoms fulfilling Framingham's criteria (requiring two major or one major and two minor criteria) for congestive heart failure.[15] Patients with renal failure, liver diseases, thyroid disorders and malignancy were excluded from the study. Ethical clearance for the study was taken from the central ethical committee of BSMMU and written informed consent was obtained from all participants. Preformed questionnaires were used to collect data. For measurement of plasma BNP blood sample was collected aseptically into ethylene diamine tetraacetic acid (EDTA) containing tube and centrifuged. Plasma BNP was measured by microparticle enzyme immunoassay (MEIA) principle (AxSym system, Abbott USA).Serum creatinine was measured on Dimension Max (Siemens Medical Solution Diagnostics, Tarrytown, NY) by using the Jaffe reaction method. Estimated glomerular filtration rate (GFR) was calculated based on the creatinine level using four parameters Modified Diet in Renal Disease (MDRD) formula[16]. Study participants were divided into two groups on the basis of empirical cut off value of eGFR 60 ml/min/1.73 m^2. Group I includes 31 (34.4%) subjects with eGFR more than 60 ml/min/1.73 m^2 and group II includes 59 (65.6%) subjects with eGFR less than 60 ml/min/1.73m^2.

Analysis of data was done with the help of software-SPSS (Statistical Package for Social Sciences) for windows version 20.Group comparisons of BNP values were made by using Mann-Whitney test. Receiver operating characteristic curve was generated for BNP and the final diagnosis of AHF with impaired renal function. Correlation analyses between plasma BNP and eGFR were performed using Spearman's correlation test. A p-value of less than 0.05 was considered indicative of statistical significance.

Results:

The study was done among 90 AHF patients diagnosed according to Framingham Criteria for Congestive Heart Failure. Plasma BNP was measured and eGFR was

estimated from serum creatinine by the four parameter MDRD equation of all study subjects on enrollment and then grouped into two groups on the basis of empirical cut off value of eGFR 60 ml/min/1.73 m².

Table-I

Distribution of plasma BNP among study subjects

Plasma BNP (pg/ml)	Group I (n=31)	Group II (n=59)	p-value
Median	601	1774	0.000
IQR	264-904	1083-3054	

p-value obtained from Mann-Whitney test
IQR= Interquartile range
Group I= eGFR > 60 ml/min/1.73m²
Group II= eGFR < 60 ml/min/1.73m²

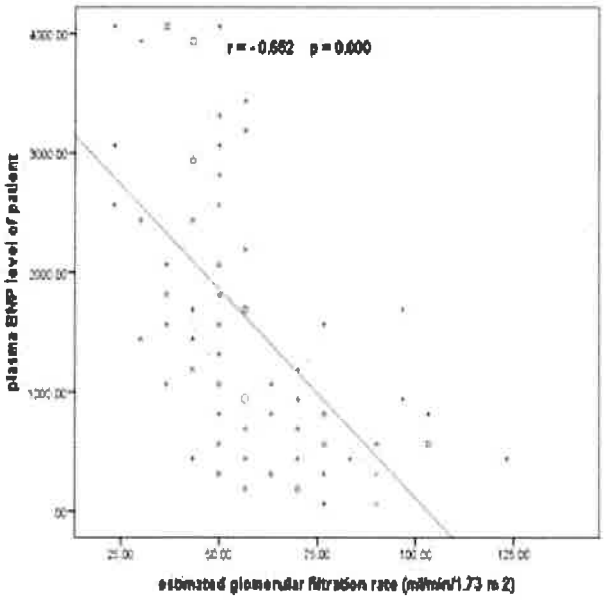

Fig-1: Correlation curve for plasma BNP and eGFR (r = -0.652, p = 0.000) among total study subjects.

The scatter diagram shows a linear negative correlation between plasma BNP and eGFR. The values of Spearman correlation coefficient was - 0.652 which was statistically significant (p = 0.000).

Table-II

Performance of plasma BNP for the diagnosis of AHF patients with renal insufficiency (eGFR < 60 ml/min/1.73m²) considering Framingham Criteria for Congestive Heart Failure as a gold standard.

Performance tool	Plasma BNP level (at a cut off value 824 pg/ml)
Sensitivity	84%
Specificity	71%
PPV	84%
NPV	71%
Accuracy	80%
LR+	3
LR-	0.21

PPV- Positive predictive value
NPV- Negative predictive value
LR+ - Positive likelihood ratio
LR- - Negative likelihood ratio

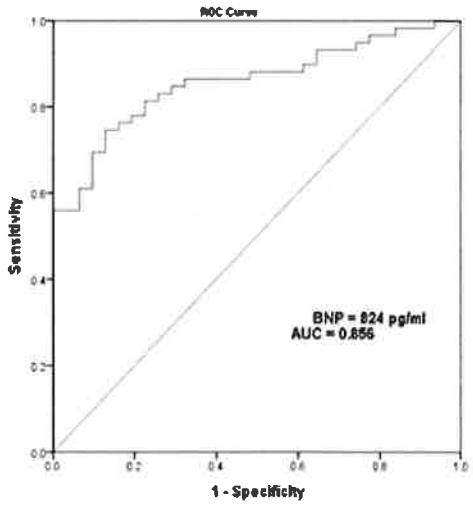

Fig-2: Receiver Operating Characteristic (ROC) Curve of plasma BNP level for the diagnosis of AHF patients with renal insufficiency (eGFR <60 ml/min/1.73 m²).

The ROC analyses suggested that the use of a single cut point of 824 pg/ml for patients with eGFR <60 ml/min/1.73 m² was optimal, with sensitivity of 84% and specificity to 71%. Plasma BNP level shows highest predictive value with AUC (area under curve) 0.856 (95% CI 0.780-0.932).

Discussion:

The effects of renal function on plasma BNP level in AHF patients are controversial. In our study a strong and significant negative correlation was found between plasma BNP and eGFR (P<0.001), with higher BNP levels observed as eGFR declined. Vickery et al. (2005) were among the first investigators to demonstrate that as renal function declined, BNP levels increased.[17]

To confirm the accuracy of measurement of plasma BNP level in diagnosis of AHF in patients with renal insufficiency, receiver operating characteristic (ROC) curve analysis was performed. The cutoff value was defined as the value with the highest sensitivity and specificity on the ROC curve. There is still a great deal of controversy regarding the cutoff value of BNP level in the diagnosis of heart failure in patients with renal impairment. In general, heart failure is unlikely at BNP values <100 pg/ml and is very likely at BNP values >500 pg/ml.

In current study cutoff value of plasma BNP for detecting acute heart failure has been adjusted in patients with renal impairment especially those with an eGFR <60 ml/min/1.73 m2.The ROC analyses suggested that the use of a single cut point of 824 pg/ml for patients with eGFR <60 ml/min/1.73 m² was optimum with sensitivity of 84% and specificity to 71%. In current study positive predictive value, negative predictive value, accuracy, positive likelihood ratio and negative likelihood e found to be 84%, 71%, 80%, 3 and 0.21 respectively.

McCullough et al.[18] reported for the first time that the optimal cutoff for BNP to diagnose CHF should be increased for patients with an eGFR <60 ml/min/1.73 m2. In a study done by Yang et al.[19] it was found that heart failure could be diagnosed in patients with kidney dysfunction using BNP cutoff value 858.5 pg/ml with 77% sensitivity and 72% specificity. Similar cutoff value was observed by Wang et al.[20] who noted that a diagnosis of cardiac failure could be made with sensitivity and specificity of 66% and 70% respectively, using a BNP cutoff value of higher than 829 pg/ml in patients with renal impairment. Kim et al.[21] demonstrated that a diagnosis of cardiac failure could be made with sensitivity and specificity of 77% and 71% respectively, using a BNP cutoff value of higher than 600 pg/ml in patients with impaired kidney function. Forfia and colleagues[22] reported that despite similar hemodynamic overload, patients with an eGFR ≤ 60 mL/min had 4 fold higher plasma BNP levels than those with an eGFR >60 mL/min.

The area under the curve (AUC) of a receiver operating characteristic (ROC) curve is a way to reduce ROC performance to a single value representing expected performance. In present study among patients with an eGFR ≤60 ml/min/1.73m² the area under ROC curve was 0.85, indicating extremely high sensitivity and specificity of the assay for detection of AHF. Among patients with similar renal function in the Breathing Not Properly Study, ROC analyses for BNP demonstrated an area under the curve range of 0.81 to 0.86, depending on severity of renal function impairment.[19] Yang et al.[20] in his study found that the area under the curve (AUC) was 0.823 and diagnosis of heart failure was made with sensitivity of 77% and specificity of 72%.

The data presented underlines that eGFR is a significant confounder of BNP measurement in AHF patients especially when renal status is compromised. Decreased clearance from the kidney contributes to the elevated BNP in AHF patients with renal dysfunction, especially in patients with an eGFR <60 ml/min.

Conclusion:

Heart failure is a significant and growing health problem in the aged population. Renal insufficiency is being recognized as one of the most common and most confounding co-morbidity in acute decompensated heart failure. So we therefore conclude that by adjusting the cutoff value plasma BNP may be used as a potential cardiorenal marker in Acute Heart Failure patients with renal insufficiency.

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