Heart Failure Risk In Chronic Kidney Disease Patients

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Abstract

The high prevalence of chronic kidney disease (CKD) and its predisposing of a serious condition called cardiorenal syndrome (CRS) is a major concern. In this study, B-type natriuretic peptide (BNP) was used to study the heart failure risk among patients with different CKD stage. Twenty-six patients with different CKD stages based on their estimated glomerular filtration rate (eGFR) were included. The BNP levels of the CKD patients were compared with twenty apparently healthy control subjects. Plasma creatinine, urea and BNP levels increases when CKD intensifies. Significant positive relationship was found between BNP with age, creatinine and urea level. Significant negative relationship was found between BNP and eGFR. ROC analysis of patient group against control group showed an area under curve (AUC) of 0.81; while CKD stage III versus controls was 0.77 and CKD stage IV + V versus controls was 0.94. It is concluded that BNP has high diagnostic accuracy in detecting heart failure in patients with chronic kidney disease.

Key words: cardiorenal syndrome, heart failure

Introduction

Diabetes, hypertension and obesity are major contributing factors of CKD[1,2]. Acute or chronic dysfunction in either heart or kidney may lead to the presence of acute or chronic dysfunction in the other[3,4,5]. This bidirectional injury is called cardiorenal syndrome (CRS). CKD patients with increased BNP levels are important warning signs of developing CRS. CKD is a slow and gradually advancing disease[6-10]. The accumulation of visceral adiposity will cause kidney compression and increased hydrostatic pressure of the renal interstitial fluid[9]. Increased serum sodium concentration is also an independent risk factor for developing CKD[11]. A serious complication of CKD is the development of CRS.

Estimated glomerular filtration rate (eGFR) is usually used to classify people into five different stages according to their severity and showed as Table.1[12-15].

CRS can be defined as a complex syndrome that dysfunctional kidney or heart is capable of initiating insults and perpetuating disease in the other organ, in which acute and chronic kidney problems can actually cause acute and chronic cardiac problems and *vice versa*[3,16-18]. It is now agreed that there are five types of CRS[19-25] (Table. 2).

BNP is first synthesized as preproBNP, preproBNP is then cleaved into BNP as an active hormone and an inactive NT-proBNP. The half-life of BNP is approximately 20 minutes compare to NT-proBNP of 2 hours; thus NT-proBNP level is more stable but BNP can quickly reflect hemodynamic changes[28,31].

Table. 1. CKD staging classification

CKD stages	Description
Stage I	A normal eGFR (above 90ml/min), but other tests have detected signs of kidney damage.
Stage II	A slightly reduced eGFR (60-89ml/min), with other signs of kidney damage.
Stage III	An eGFR of 30-59ml/min, regardless of whether evidence of kidney disease has been detected.
Stage IV	An eGFR of 15-29ml/min, regardless of whether evidence of kidney disease has been detected.
Stage V	An eGFR below 15ml/min, meaning the kidneys have lost almost all of their function.

Table. 2. CRS classification[24]

Cardiorenal Syndrome (CRS) General Definition: A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ
CRS Type I (Acute Cardiorenal Syndrome) Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acutely decompensated congestive heart failure) leading to acute kidney injury
CRS Type II (Chronic Cardiorenal Syndrome) Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and potentially permanent chronic kidney disease
CRS Type III (Acute Renocardiac Syndrome) Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS Type IV (Chronic Renocardiac Syndrome) Chronic kidney disease (e.g. chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS Type V (Secondary Cardiorenal Syndrome) Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

Both BNP and NT-proBNP are useful diagnostic markers of acute congestive and symptomatic heart failure in emergency units and as a superior risk factor to predict mortality, morbidity of heart failure[28-33]. Studies showed that NT-proBNP was a superior predictor of mortality across all stages of CKD[33] and is a better predictor of heart failure in all CKD stages[29]. Conversely, BNP could act as a predictor of mortality related to patients with acute kidney injury receiving continuous renal replacement therapy[34] and sudden death in chronic heart failure patients[35].

This study investigated the heart failure risk among CKD patients by serum BNP level. The diagnostic accuracy of BNP as a heart failure marker was also determined by receiver operator characteristics curve.

Materials and Methods

Archived EDTA serum samples were collected from twenty six CKD patients and twenty healthy subjects based on their serum creatinine levels. Modification of Diet in Renal Disease formula [GFR (mL/min/1.73 m^2) = 175 x (serum creatinine level)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African or American)][36] was used to calculate eGFR and to classify subjects into different CKD stages. BNP assay is a chemiluminescent microparticle immunoassay[37].

Kolmogorov Smirnov test was used to test data normality. Kruskal-Wallis test was performed to study the statistical difference among target group and control group, also between different CKD stages. Mann-Whitney U test was performed when data were statistically different by Kruskal-Wallis test. CKD stage IV and V are combined because of their small sample size.

Scatter diagrams were used to study the relationship between BNP level and other laboratory results including age, eGFR, serum creatinine and urea level. Receiver operator characteristic plots were performed between patient and control groups, CKD stage III versus control group and CKD stage IV + V versus control group. Area under curve (AUC) was calculated to estimate the diagnostic accuracy of BNP assay as a heart failure biochemical marker.

Results

Patient characteristic and laboratory results were shown in Table. 3.

Table. 3. Baseline characteristics and laboratory data of the study population according to different CKD stage.

Apply mean ± SD for continuous variables below	Patient group (total)	CKD stage III	CKD stage IV	CKD stage V	Control group
Number of subject	26	19 (73.08%)	5 (19.23%)	2 (7.69%)	20
Male Gender	18 (69.23%)	14 (73.68%)	2 (40%)	2 (100%)	6 (30%)
Age (years)	60.04 ± 13.45	58.84 ± 15.08	62.8 ± 8.14	64.5 ± 7.78	49.45 ± 12.74
Creatinine (mg/dL)	2.02 ± 1.15	1.57 ± 0.19	2.26 ± 0.23	5.72 ± 0.82	0.76 ± 0.08
Urea (mg/dL)	73.34 ± 26.64	62.41 ± 19.89	90.48 ± 6.99	128.85 ± 18.03	29.96 ± 6.78
BNP (pg/mL)	63.09 ± 73.6	45.38 ± 60.47	64.98 ± 40.25	226.6 ± 60.67	20.31 ± 19.63
eGFR (mL/min/1.73 m^2)	37.28 ± 13.12	N/A	N/A	N/A	90.48 ± 11.40

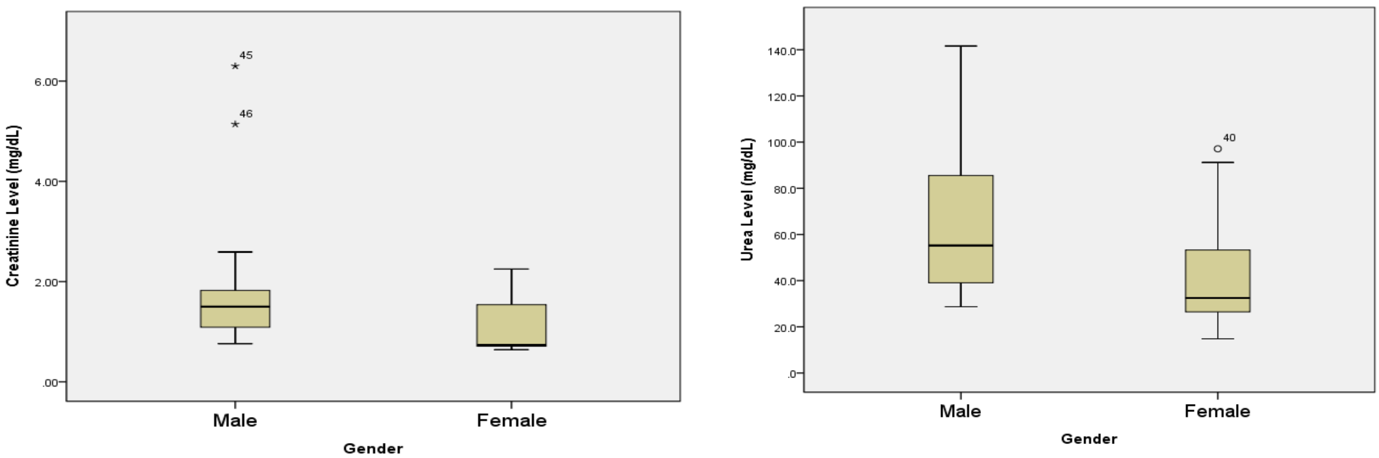

Figure. 1. Distribution of serum creatinine and urea level for all 46 subjects classified by gender

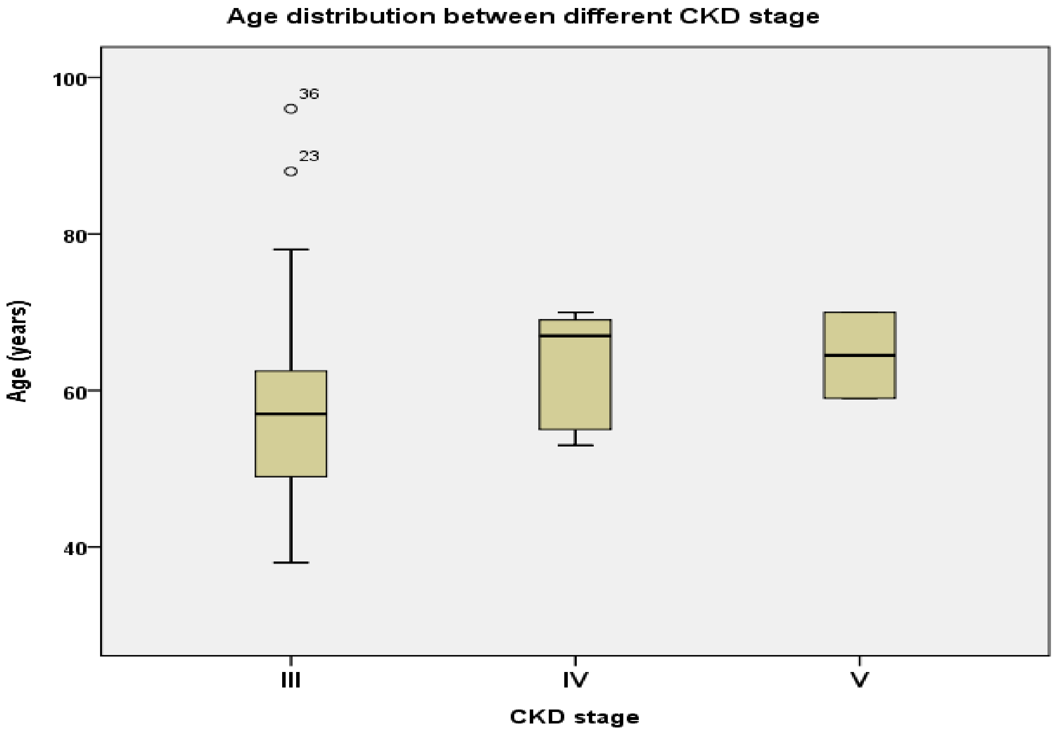

Figure. 2. Age distribution between different CKD stages

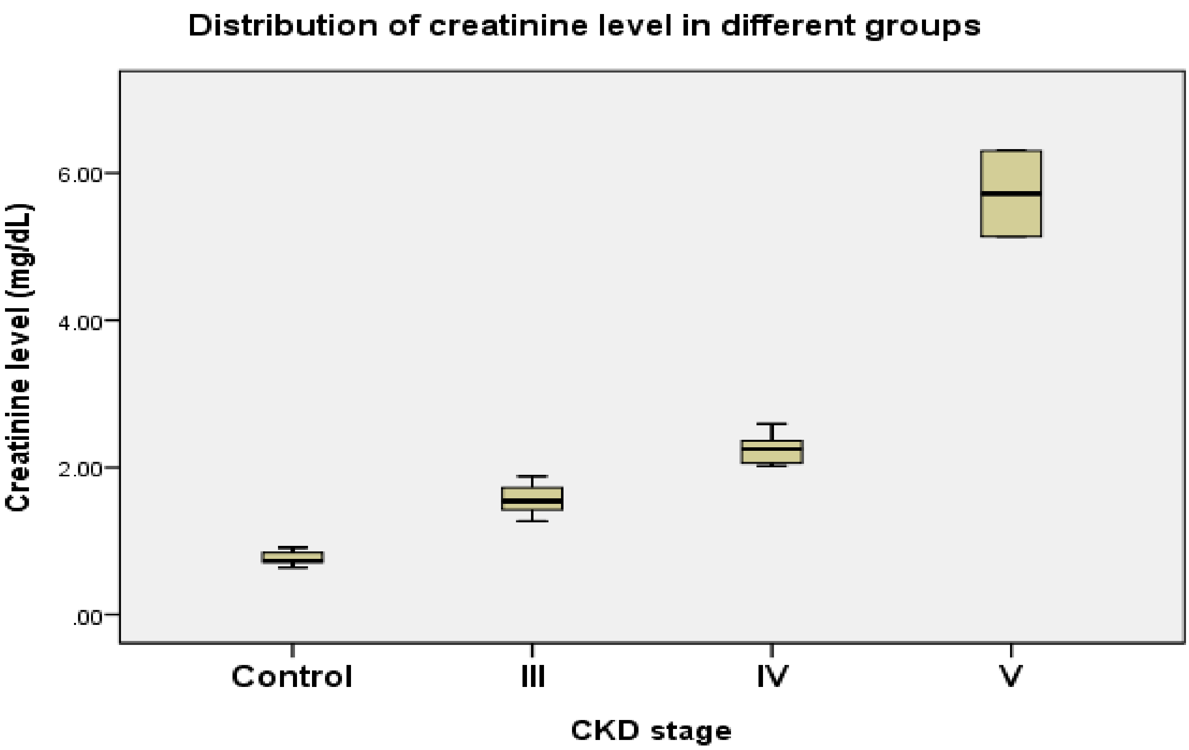

Figure. 3a. Distribution of creatinine levels in control and CKD patients

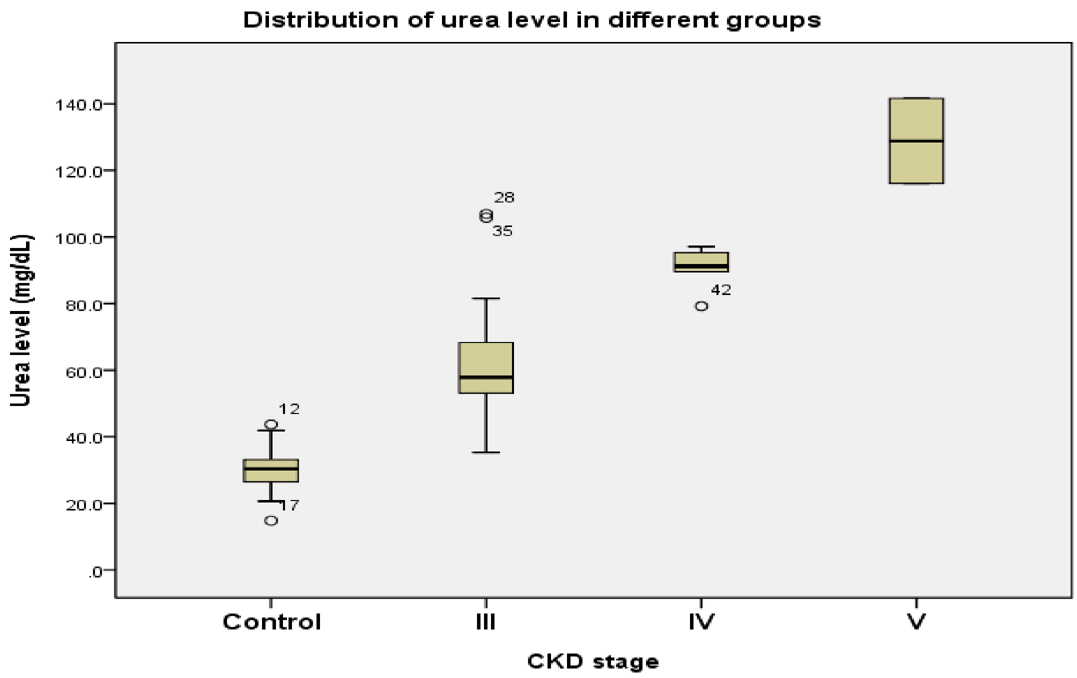

Figure. 3b. Distribution of urea levels in control and CKD patients

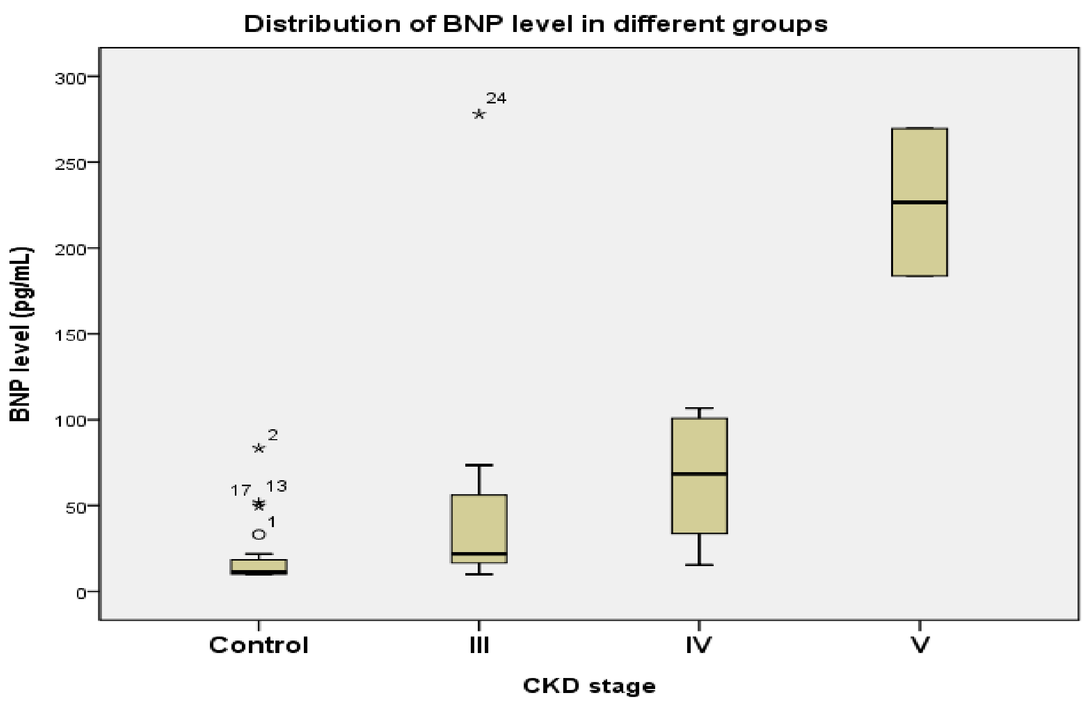

Figure. 3c. Distribution of BNP levels in control and CKD patients

Upward trend was observed in serum urea, creatinine and BNP when CKD become more serious (Figure. 3a, 3b and 3c).

BNP correlated positively with age, creatinine and urea levels; while BNP correlates negatively with eGFR (Figure. 4a – 4d).

ROC plot result in all subjects (target group and control group) showed an area under the curve for BNP of 0.81 (95% CI 0.68 – 0.94, P-value < 0.001; Figure.5). BNP assay had a good diagnostic accuracy as a heart failure marker in CKD patients. The suggested BNP cut-off value of 15.2 pg/mL has a sensitivity of 84.6% and a specificity of 75%.

The ROC plot analysis of CKD stage III and control; CKD stage IV + V and control were shown in Figure.6. The AUC of CKD stage III was 0.77 (95% CI 0.61 - 0.92, P-value = 0.005), CKD stage IV + V was 0.94 (95% CI 0.84 – 1.00, P-value = 0.001)

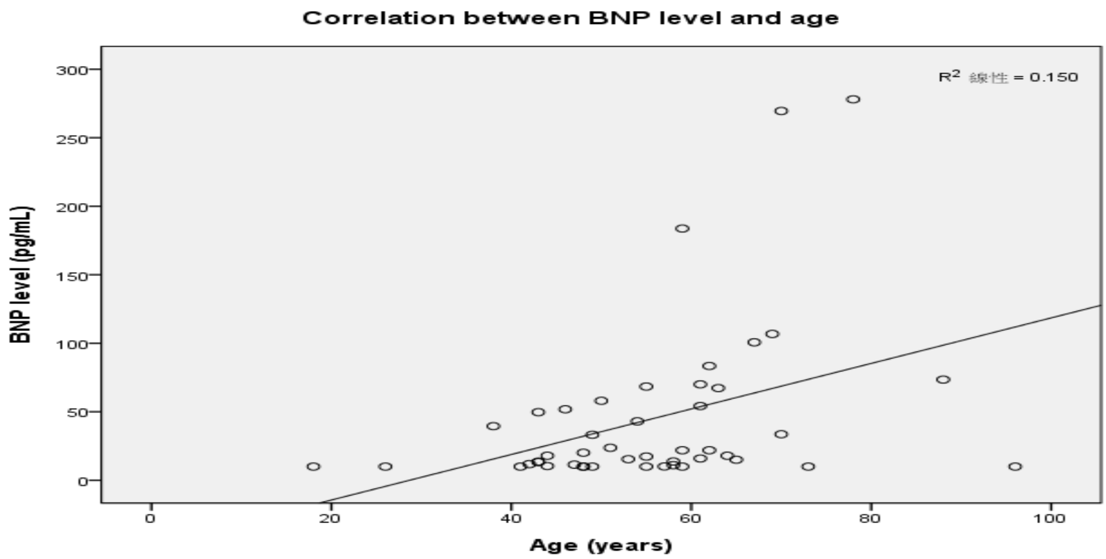

Figure. 4a

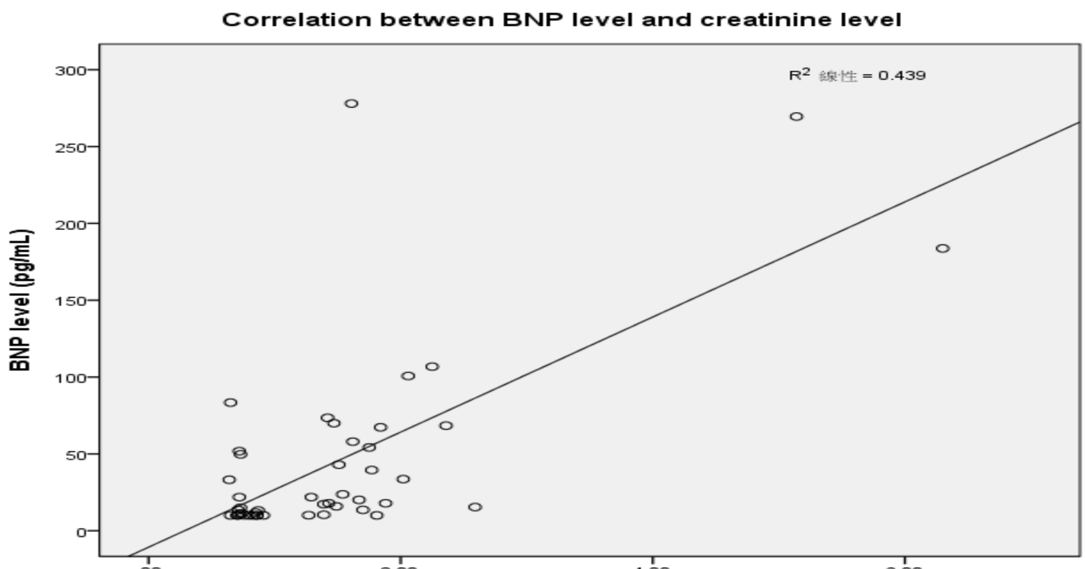

Figure. 4b

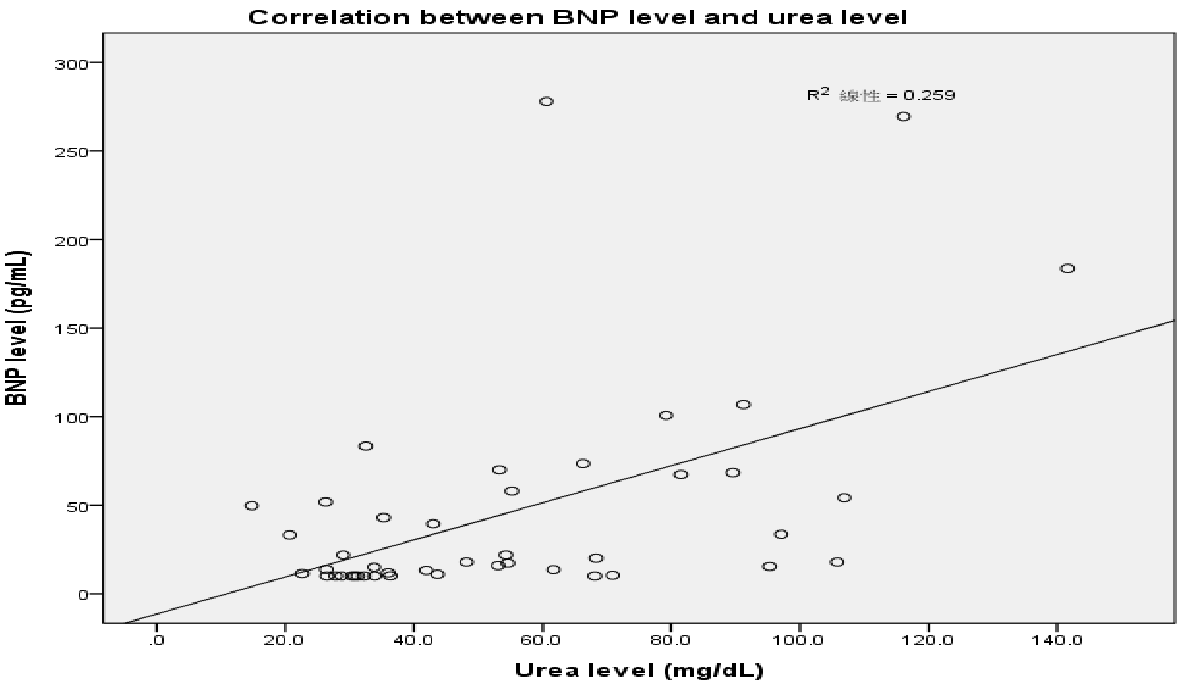

Figure. 4c

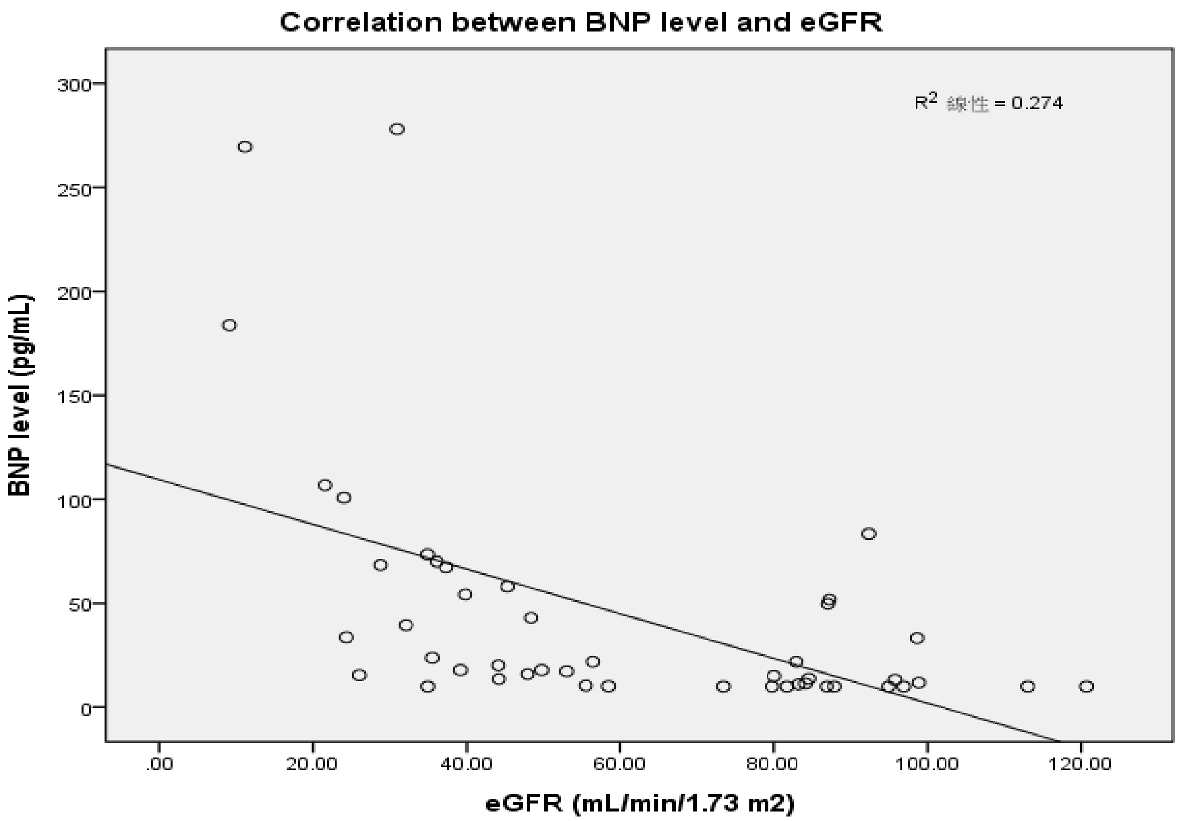

Figure. 4d

Figure. 4. Scatter plot showing correlations of BNP level with age, creatinine, urea and eGFR.

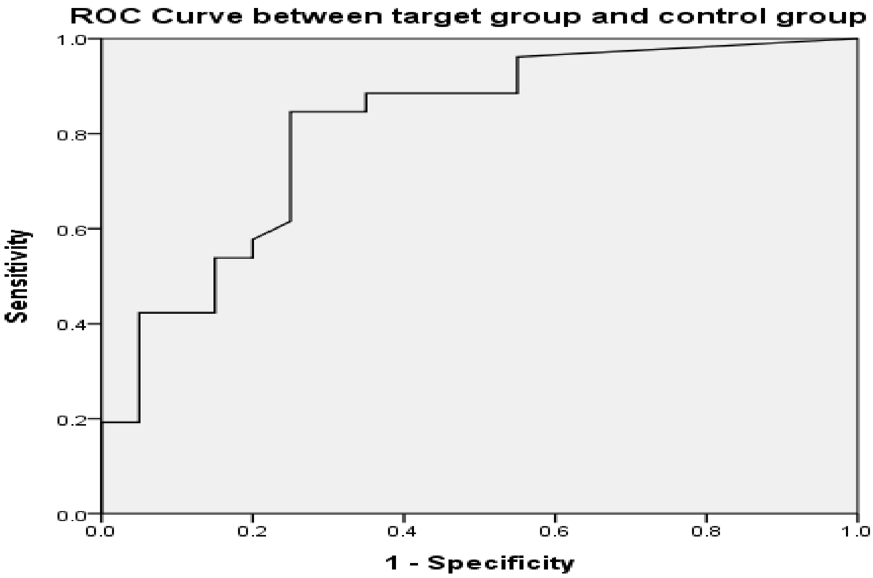

Figure 5. ROC plot analysis of BNP in all subjects. The AUC of all subjects (target group and control group) was 0.81 (95% CI 0.68 – 0.94, P-value < 0.001).

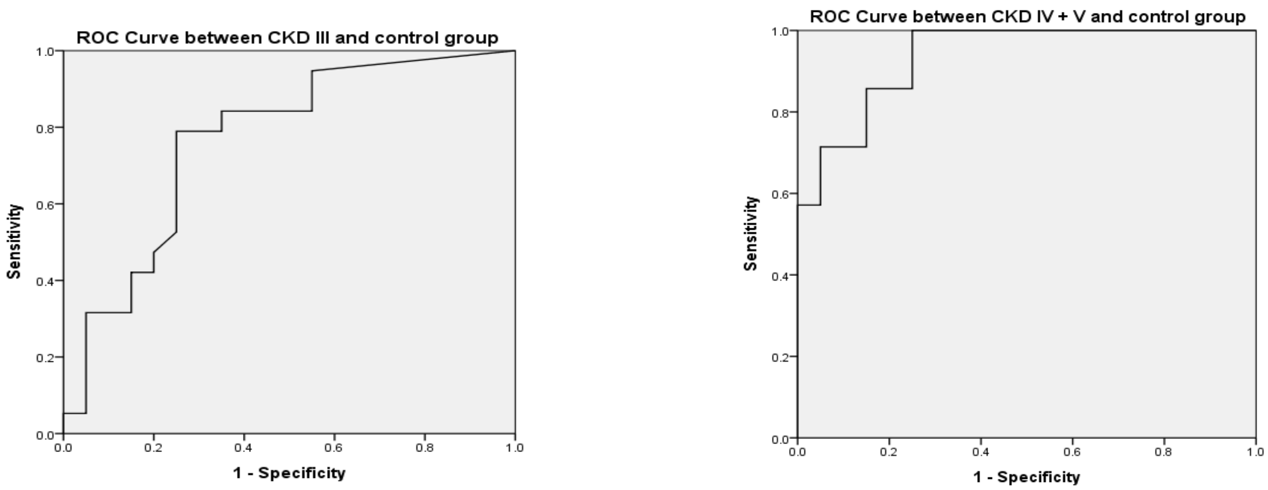

Figure 6. ROC plot analysis of BNP in CKD stage III and in CKD stage IV + V. The AUC of CKD stage III was 0.77 (95% CI 0.61 - 0.92, P-value = 0.005), CKD stage IV + V was 0.94 (95% CI 0.84 – 1.00, P-value = 0.001).

Conclusion

This study showed that BNP levels was increased when kidney function (eGFR) declined; with the highest BNP level in stage V CKD patients. Hence CKD increases heart failure risk and the development of CRS in CKD patients. It is also shown that BNP has a good diagnostic accuracy of heart failure in CKD patients. The major limitation of this study is the small sample size in both the CKD group and in the control group; affecting accuracy of the statistical tools used. This study showed that BNP is a powerful marker for the identification of heart failure risk in CKD patients; elevated BNP level is a clear warning sign. It is also suggested that further studies should include more new markers to study the complex pathophysiology of CRS.

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