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Original Research Article

Evaluation of Brain Natriuretic Peptide Hormone and Cardiac Troponin- T Levels among Patients with Chronic Kidney Disease and their Association with Cardiovascular Disease in Khartoum State, Sudan

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Abstract: ***Background:*** The danger of chronic kidney disease (CKD) is rising quickly worldwide and has become a main health crisis and most of these patients die from cardiovascular disease (CVD) prior to progression to end stage renal disease (ESRD), therefore, Poor cardiovascular outcomes in CKD patients have encouraged nephrologists to search for biomarkers that may improve risk stratification in this population. The aim of this study was to assess serum brain natriuretic peptide (BNP) hormone and cardiac troponin T (cTnT) levels in CKD patients and to determine their involvement with cardiovascular diseases. ***Methods:*** This analytical case control study was conducted at Ibn sina and Military hospitals in the period from February 2016 to March 2019, (n = 150) clinically diagnosed CKD patients (age range between 22 - 76 years, 105 males and 45 females), and (n = 150) healthy subjects were included as controls. Serum BNP hormone and cardiac troponin T (cTnT), were estimated by Cobas E-411® fully automated analyzer, serum creatinine by Cobas C-311® fully automated analyzer, hemoglobin by Sysmix, glomerular filtration rate (GFR) was calculated by Cocroft-Gault formula and blood pressure was measured by using mercuric sphygmomanometer. ***Results:*** Serum BNP, cTnT, creatinine, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI) were significantly higher in CKD patients than in controls, while hemoglobin and GFR were significantly lower. Moreover, serum BNP, cTnT, SBP and DBP were significantly higher in CKD patients with cardiovascular disease (CVD) than CKD patients without CVD. In addition, serum BNP, at cutoff level of 240 pg/ml, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 87%, 90%, 52% and 92%, respectively in relation to CVD, while serum cTnT, at cutoff level of 0.1 ng/ml, the sensitivity, specificity, PPV and NPV were 80%, 57%, 46% and 74%, respectively. Furthermore, there was an association between elevated BNP levels and CVD outcomes in patients with CKD, since it is a strong risk factor for CVD (OR: 1.48, *p.* value 0.031). ***Conclusions:*** BNP levels are significantly associated with cardiovascular events (left ventricular hypertrophy and systolic dysfunction) in patients who have CKD and are on maintenance hemodialysis (HD).

Keywords: Chronic kidney disease, cardiovascular disease, brain natriuretic peptide.

INTRODUCTION

Chronic kidney disease (CKD) is a diminish in kidney task with a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m^2 and/or kidney injure for 3 months or more (Lamb, 2013)**.** It is characterized by a broad variety of biochemical turbulence and many clinical symptoms and signs (Mathenge*et al.*, 2003).The change includes haematologic abnormalities, cardiovascular disorders, gastrointestinal disturbances, neurologic disorder, osteodystrophy, skin disorder and chnged sexual task (Moronkola *et al.*, 2006).

The elevated incidence of cardiovascular events in CKD merits a precise assessment of risk aimed at dipping the burden of disease and its complications (Luis *et al.*, 2015). The most common

sign of cardiovascular disease in CKD patients is left ventricular hypertrophy (LVH), predominantly as a result of hypertension and anaemia (Luis *et al.*, 2015). LVH is a influential independent predictor of cardiovascular disease (CVD) in CKD patients (Dobson *et al.*, 2005; Iwashima*et al.*, 2004; Anand*et al.*, 2006). Though, identifying which patients will undergo cardiovascular events is difficult and needs early recognition and treatment. The capability to notice significant cardiovascular dysfunction at an early stage could ease more aggressive and alert treatment of those at augmented risk (Dobson *et al.*, 2005; Iwashima*et al.*, 2004; Anand*et al.*, 2006).

The natriuretic peptides are a family of hormones that have a key role in sodium and body volume homeostasis; especially they control natriuresis, vasodilatation, and diuresis (Fasset*et al.*, 2011). Three main natriuretic peptides have been recognized: atrial natriuretic peptide (ANP), Brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), they all share a common 17-amino-acid ring structure and have actions that are targeted at defensive the cardiovascular system from the effect of volume overload (Iwanga and Miyazaki, 2010).

BNP and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) are co-secreted in equimolar amounts from the heart in response to left ventricular overload. Diagnostically they are used as rule-out tests to keep out heart failure in patients presenting with shortness of breath. The natriuretic peptides have been shown to predict survival in patients with congestive heart failure (Dobson *et al.*, 2005; Iwashima*et al.*, 2004; Anand*et al.*, 2006).

Troponins T, I, and C are components of the contractile machinery of muscle (Dobson *et al.*, 2005). Specific forms of troponin T and I are exist in the heart muscle, namely cardiac troponin T (cTnT) and troponin I (cTnI), and are released into the circulation with myocardial injury (Dobson *et al.*, 2005). Thus, measuring circulating cTnT and cTnI level using high-sensitivity assays has become the gold standard approach in diagnosing acute myocardial necrosis (Dobson *et al.*, 2005).

A current survey in nondialysis patients with end stage of renal disease (ESRD) reported that serum cTnT was increased above the 99th percentile in 43% of all patients with ESRD, compared with 18% for cTnI. In addition, the prevalence of amplified serum cTnT and cTnI increased with increasing severity of CKD (Alpert *et al.*, 2000).

The current study aims to evaluate the development of cardiovascular disease through the estimation of BNP hormone and cTnT among the CKD patients on dialysis.

MATERIALS AND METHODS

The study comprised a total of 300 individuals of which 150 individuals with evidence of CKD were included on the basis of clinical features and laboratory diagnosis of CKD. Other 150 healthy persons were served as a control group, whose age and sex matched healthy. Part of the CKD patients they suffering from CVD in which they are diagnosed with CVD based on family histories of the patients, risk factors, physical examination, using an array of laboratory tests and imaging studies. Individuals who are diagnosed with CKD and they have other disease such as liver cirrhosis, sepsis and hyperthyroidism were excluded from this study.

Informedconsentwastakenfromthepatientsandsubjectswhoparticipatedinthepresentstudy, and after agree ment of general managers of Ibn sina hospital and Military hospitals. Ethical committee approval has also been obtained from Omdurman Islamic University and ministry of health.

In both groups serum BNP hormone and cTnT levels were measured by Cobas E-411® fully automated analyzer, serum creatinine were measured by Cobas C-311® fully automated analyzer, hemoglobin was measured by Sysmix fully automated analyzer, GFR was calculated using Cocroft-Gault formula and blood pressure was measured by using mercuric sphygmomanometer.

All obtained were expressed as mean ± SD. Statistical analysis was performed using SPSS version 20 (Statistical Package for the Social Sciences). Difference in mean values between groups was evaluated by t-test and chi-squared. The person correlation test was used to find the correlation between two variables. A *P*-value ≤0.05 was considered significant differences.

RESULTS

Three hundred individuals were recruited in this study (150 CKD patients, 150 controls). Table (1) shows the demographic and descriptive statistics of the patients with CKD. The most common cause of CKD among study subjects is HTN 55(36.7%), followed by DM 46(30.7%) then chronic glomerulonephritis 18(12%) and finally polycystic kidney disease 16(10.7%). 22(14.7%) of the CKD patients they have both DM and HTN.29(19.3%) of the CKD patients have CVD as comorbid disease. 103(69%) of the CKD patients their ages (< 50 year) while 47(31%) their ages is (≥ 50 year), 68(45.3%) of the CKD patients their BMI was normal, 71(47.3%) were overweight and 11(7.4%) were obese (>30 kg/m^2), 56(37.3%) of the study populations had CKD for (≤5 year) whereas 94(62.7%) had the CKD for (>5 years), 78(52%) of the CKD patients had low level of Hb (<11 g/dl) whereas 72(48%) had Hb level (≥11 g/dl), 30(20%) of the study populations were smokers.

Table (2) shows the clinical and laboratory parameters of CKD patients and controls. The ratio of patients to controls was 1:1. The BMI of patients were greater than that of the controls (25.5 ± 3.5 kg/m^2 versus 23.3 ± 3.0 kg/m^2), *p* .value = 0.000. The mean BNP hormone level was significantly higher in patients (178.8 ± 68.3 pg/ml) than that of the controls (58.8 ± 12.9 pg/ml), *p* .value = 0.000, and the mean cTnT level was significantly higher in patients (0.07 ± 0.02 ng/ml) than that of the controls (0.01 ± 0.01 ng/ml), *p* .value = 0.000. The mean of creatinine level was significantly higher in patients (8.40 ± 2.80 mg/dl) when compared with controls (0.80 ± 0.20 mg/dl), *p* .value = 0.000, while the mean GFR and hemoglobin were significantly lower in patients (14.2 ± 10.1 ml/min/1.73 m^2 and 10.5 ± 2.00 g/dl) when compared with controls (115 ± 30.1 ml/min/1.73 m^2 and 13.5 ± 1.60 g/dl), *p* .value = 0.000 and 0.005 respectively. Both the systolic (154 ± 21.0 mmHg) and diastolic (85.0 ± 12.0 mmHg) blood pressure were significantly higher in CKD patients when compared to that of the controls (117 ± 8.00 mmHg and 77.0 ± 6.00 mmHg), *p* .value = 0.003 and 0.006 *respectively*.

Table (3) The results shows that there is significant increase in the means of BNP, cTnT, SBP and DBP in CKD patients with CVD when compared with CKD patients without CVD in case group, while there is insignificant increase in the mean of BMI and creatinine and insignificant decrease in the mean of GFR and hemoglobin in CKD patients with CVD when compared with CKD patients without CVD in case group.

Table (4) shows that there is an association between elevated cardiovascular biomarker (BNP) levels and CVD outcomes in patients with CKD, it is a strong risk factor for CVD.

Table (5) shows that there is insignificant increase in the means of BMI, SBP, DBP, creatinine and hemoglobin in male when compared with female in CKD patients, while there is insignificant decrease in the mean of BNP, cTnTand GFR in male when compared with female in CKD patients.

Table (6) regarding serum BNP, at cutoff level of 240 pg/ml, the sensitivity, specificity, PPV and NPV were 87%, 90%, 52% and 92%, respectively in relation to CVD. With regard to serum cTnT, at cutoff level of 0.1 ng/ml, the sensitivity, specificity, PPV and NPV were 80%, 57%, 46% and 74%, respectively in relation to CVD.

Figure (1)express thatin the patient with CKD, when BNP level was 240 pg/ml and the area under the curve (AUC) was 0.963 (95% CI), a diagnosis of CVD was made with sensitivity of 87% and specificity of 90%.

Figure (2)express thatin the patient with CKD, when cTnT level was 0.1 ng/ml and the AUC was 0.593 (95% CI), a diagnosis of CVD was made with sensitivity of 80% and specificity of 57%.

Figure (3) shows thatin the patient with CKD, when BNP was used against cTnT at 0.1 ng/ml and the AUC was 0.471 (95% CI), a diagnosis of CVD was made with sensitivity of 55% and specificity of 60%.

Figure (4) shows thatin the patient with CKD, when cTnT was used against BNP at 240 pg/ml and the AUC was 0.391 (95% CI), a diagnosis of CVD was made with sensitivity of 38% and specificity of 75%.

Table-1: Demographic and descriptive statistics of the patients with chronic kidney disease:

Characteristics	Frequency (%)
Age	
<50 years old	103 (69%)
≥50 years old	47 (31%)
BMI (kg/m^2)	
Normal	68 (45.3%)
Overweight	71 (47.3%)
Obese	11 (7.4%)
Duration of CKD	
≤ 5 years	56 (37.3%)
> 5 years	94 (62.7%)
cTnT	
< 0.1 ng/ml	124 (82.7%)
≥ 0.1 ng/ml	26 (17.3%)
BNP	
< 240 pg/ml	120 (80.0%)
≥ 240 pg/ml	30 (20.0%)
Hb	
< 11 g/dl	78 (52%)
≥ 11 g/dl	72 (48%)

SBP	
< 130 mmHg	108 (72%)
≥ 130 mmHg	42 (28%)
DBP	
< 90 mmHg	110 (73.3%)
≥ 90 mmHg	40 (26.7%)
Smoking	
Yes	30 (20%)
No	120 (80%)
CVD	
Yes	29 (19.3%)
No	121 (80.7)
Primary kidney diseases (%)	
DM	
Yes	46 (30.7%)
No	104 (69.3%)
HTN	
Yes	55 (36.7%)
No	95 (63.3%)
Both DM and HTN	
Yes	22 (14.7%)
No	128 (85.3%)
Chronic glomerulonephritis	
Yes	18 (12%)
No	132 (88%)
Polycystic kidney disease	
Yes	16 (10.7%)
No	134 (89.3%)

Table-2: Clinical and laboratory parameters of the CKD patients and controls.

Characteristics	CKD (N= 150)	Control (N= 150)	*P*. value
BNP (pg/ml)	178.8 ± 68.3	58.8 ± 12.9	0.000**
cTnT (ng/ml)	0.07 ± 0.02	0.01 ± 0.01	0.000**
Creatinine (mg/dl)	8.40 ± 2.80	0.80 ± 0.20	0.000**
GFR (ml/min/1.73 m^2)	14.2 ± 10.1	115 ± 30.1	0.000**
Hemoglobin (g/dl)	10.5 ± 2.00	13.5 ± 1.60	0.005*
BMI (kg/m^2)	25.5 ± 3.50	23.3 ± 3.00	0.000**
SBP mmHg	154 ± 21.0	117 ± 8.00	0.003*
DBP mmHg	85.0 ± 12.0	77.0 ± 6.00	0.006*

** Highly significant different at 0.01
* Significant different at < 0.05

Table-3: Clinical and laboratory parameters of the CKD patients with CDV and CKD without CVD.

Characteristics	CKD with CVD (N= 29)	CKD without CVD (N= 121)	*P*. value
BNP (pg/ml)	265 ± 29.2	158 ± 58.1	0.000**
cTnT (ng/ml)	0.17 ± 0.02	0.06 ± 0.10	0.041*
BMI (kg/m^2)	26.1 ± 3.50	25.4 ± 3.4	0.315 ^{NS}
SBP mmHg	157 ±16.0	134 ± 18.0	0.032*
DBP mmHg	94.0 ± 10.0	85.0 ± 12.0	0.022*
Creatinine (mg/dl)	9.04 ± 3.10	8.30 ± 2.70	0.252 ^{NS}
GFR (ml/min/1.73 m^2)	13.5 ± 9.40	14.4 ± 10.3	0.668 ^{NS}
Hemoglobin (g/dl)	10.0 ± 2.20	10.6 ± 2.00	0.136 ^{NS}

**Highly significant different at 0.01, *Significant different at < 0.05, $^{NS:}$No significant different

Table-4: Risk estimation among CKD patients with cardiovascular disease

Characteristics	Positive (%) n	Negative (%) n	OR	CI 95%	*p.* value
Smoking	30 (20.0%)	120 (80.0%)	1.05	(0.38- 2.87)	0.853
Hypertension	55 (36.7%)	95 (63.3%)	0.78	(0.30- 1.99)	0.650
Diabetes mellitus	46 (30.7%)	104 (69.3%)	0.66	(0.26- 1.69)	0.382
BNP (pg/ml)	30 (20.0%)	120 (80.0%)	1.48	(1.28 –1.71)	0.031
cTnT (ng/ml)	26 (17.3%)	124 (82.7%)	1.38	(0.43 – 4.39)	0.575

n: number; OR: odd ratio; CI: confident interval, *p.* value less than 0.05 was statistically considered significant.

Table-5: Clinical and laboratory parameters of the CKD patients according to gender.

Characteristics	Male	Female	*P.* value
BNP (pg/ml)	177± 71.9	181 ± 59.9	0.764^{NS}
cTnT (ng/ml)	0.06 ± 0.04	0.09 ± 0.14	0.115^{NS}
BMI (kg/m²)	25.7 ± 3.05	25.0 ± 4.37	0.237^{NS}
SBP mmHg	138 ± 14.5	136 ± 15.0	0.332^{NS}
DBP mmHg	89.3 ± 10.0	88.0 ± 12.0	0.512^{NS}
Creatinine (mg/dl)	8.67 ± 2.71	8.13 ± 2.96	0.285^{NS}
GFR (ml/min/1.73 m^2)	13.8 ± 10.1	15.1 ± 10.2	0.481^{NS}
Hemoglobin (g/dl)	10.5 ± 2.11	10.3 ± 1.97	0.577^{NS}

^{NS}: No significant different

Table-6: Sensitivity, specificity, PPV and NPV of the study parameters.

Parameters	Sensitivity	Specificity	Positive predictive value	negative predictive value
BNP (pg/ml)	87%	90%	52%	92%
cTnT(ng/ml)	80%	57%	46%	74%

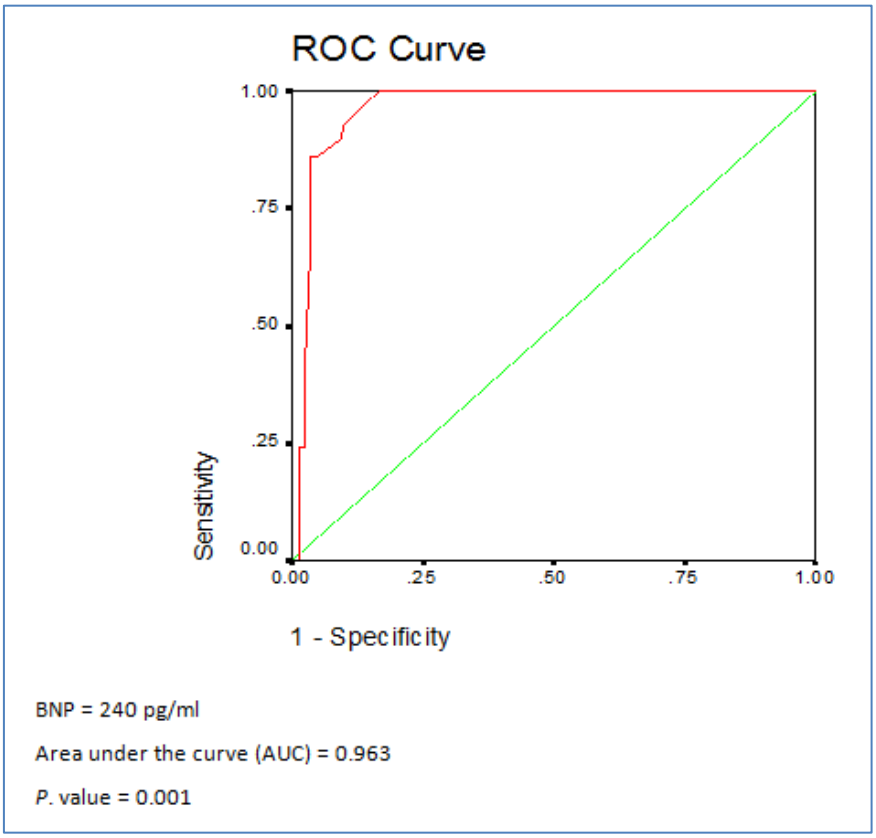

Fig-1: Receiver operating characteristic (ROC) curve for serum BNP accuracy and reference value for diagnosis CVD in patients with CKD.

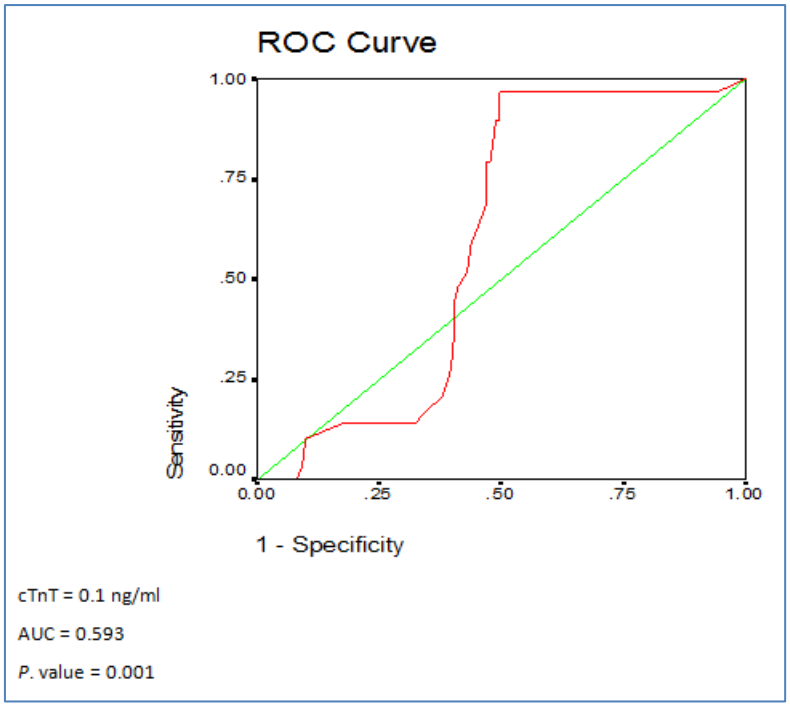

Fig-2: ROC curvefor serum cTnT accuracy and reference value for diagnosis CVD in patients with CKD.

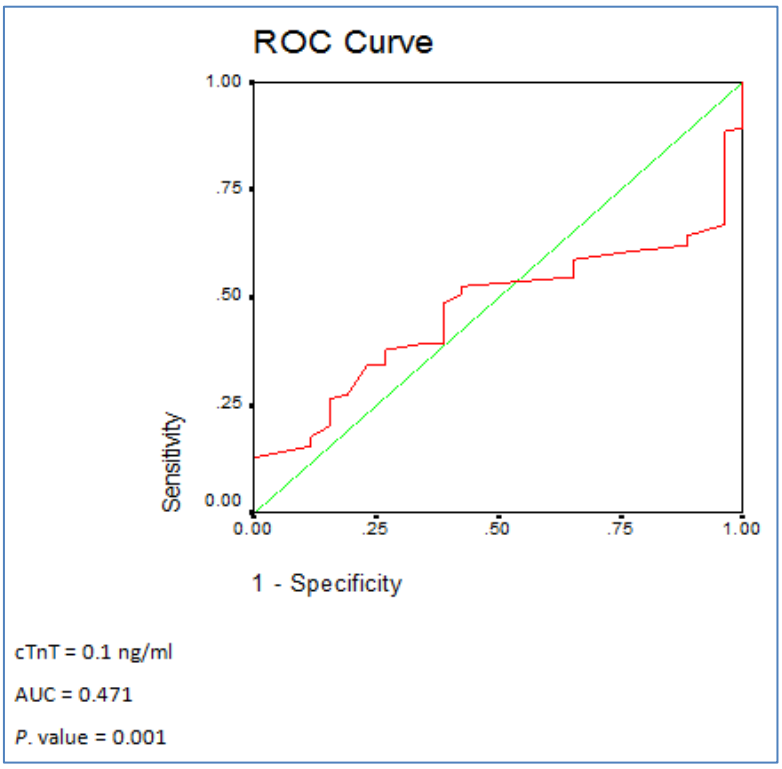

Fig-3: ROC curve for BNP against cTnT accuracy and reference value for diagnosis CVD in patients with CKD

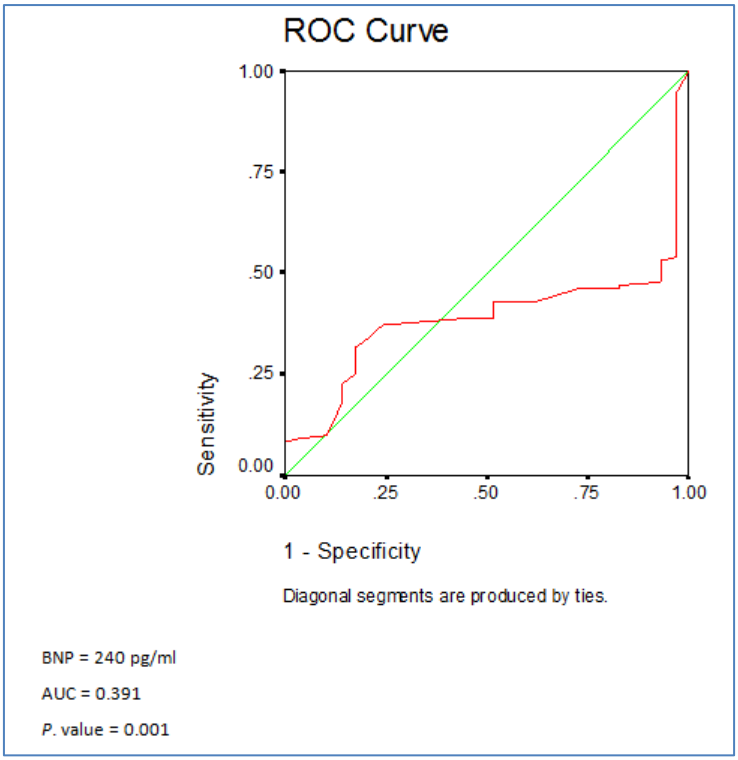

Fig-4: ROC curvefor cTnT against BNP accuracy and reference value for diagnosis CVD in patients with CKD

DISCUSSION

The present study indicated that, the percentages of HTN, DM, chronic glomerulonephritis and polycystic kidney disease among CKD patients were, 55(36.7%), 46(30.7%), 18(12%) and 16(10.7%) respectively. Meanwhile the CKD is common in elderly than young adult who account 2.2 fold, this finding in accord with other study conducted by Alebiosu and their colleagues; they stated that, the third and fourth decades of life account for the high incidence of CKD. Other studies in developed countries found that, the prevalence of CKD increases with advancing age and the peak incidence is found in 7th and 8th decades (Alebiosu*et al*., 2006; Aisola*et al*., 2004). In contrast, the early onset of CKD in undeveloped countries attributed to the socioeconomic status, risk factors and miss-diagnosis which lead to late intervention and thus CKD (Chijioke and Adeniyi, 2003). Moreover, the current study revealed that, the CKD is most frequent among overweight patients followed by normal weight and obese, these findings have been shown previously by Morales and their colleagues, they stated that, the frequency of overweight and obese were higher in CKD patients, therefore considered as risk factor (Morales *et al.*, 2003).

The present study provides evidence that, serum BNP hormone and cTnT levels were significantly increased in CKD patients than control group. These findings indicate that, CKD has a direct impact on skeletal and/or cardiac muscle, since could lead to elevated BNP levels. Indeed, several studies have reported high levels of cardiac markers (such as CK-MB, troponin T, BNP and NT-pro-BNP) in CKD patients, a situation that cannot be explained solely by reduced clearance in CKD (Sharma *et al.*, 2006). In addition, circulating BNP and cTnT levels are strongly associated with LV hypertrophy and systolic dysfunction in patients who have ESRD and are on maintenance HD or PD (Madsen *et al.*, 2007; Mallamaci*etal.*, 2002).

On the other hand, Fahie-Wilson and their colleagues found that, circulating free intact cTnT form was detected in both patients with kidney failure and acute coronary syndrome, which consider as predictor and diagnostic marker of cardiac diseases (Fahie-Wilson *et al.*, 2006).

Concurrent with previous finding, both systolic and diastolic blood pressure were significantly increased in CKD patients in comparison with control group, this finding in agreement with previous study conducted by Eric and colleague, they stated that, sustained elevations in blood pressure worsen the progression of kidney disease, in contrast, the declines in kidney function could lead to rises in blood pressure (Eric and David, 2015). In fact that, hypertension is the second leading cause of CKD (Bosan*et al.*, 2006).

The results of creatinine and GFR level expressed that, most CKD patients are in advanced stages of the disease, this finding in agreement with other study conducted by Khmer, he stated that, the prognosis of advanced CKD in most Sub-Saharan Africa is still very poor due to late presentation/referral and inability to pay for treatment (Khmer, 2002).

The current study also revealed that, there is insignificant decrease in the mean of BNP, cTnT, total cholesterol and HDL-C in male group when compared with female in CKD patients, this finding in agreement with previous studies conducted by Liying, Pornpen and their colleagues (Liying*et al*,. 2014, Pornpen*et al.*, 2010). Meanwhile, the mean of TG, LDL-C, SBP and DBP levels were insignificantly increased, this finding disagree with previous study conducted in China by Liying and their colleagues, this may be due to ethnicity and social habits (Liying*et al*,. 2014).

Concurrent with previous finding, there is significant increase in the means of BNP and cTnT in CKD patients with CVD when compared with CKD patients without CVD, this finding in agreement with previous study conducted by Ishii and Taniguchi and their colleagues, they reported that, the combination of cTnT and BNP measurements might be complementary and highly effective for risk stratification in CKD patients with CVD (Ishii *et al*., 2003; Taniguchi *et al*., 2004). Moreover the present study showed that, there is insignificant decrease in the mean of GFRin CKD patients with CVD when compared with CKD patients without CVD, this finding in accord with other study conducted by Tarek and their colleagues, they stated that, the reduction of GFR lead to worsen of the CVD outcomes in CKD patients (Tarek*et al*., 2017).

Furthermore, both SBP and DBP were significantly increased in CKD patients with CVD when compared to that without CVD, this finding in agreement with other study conducted by Lancet, who stated that, in adults, each 20-mm Hg increase in SBP or 10-mm Hg increase in DBP doubles the death rates from CVD in patients who have CKD (Lancet, 2002).

The current study revealed the association of elevated BNP with CVD outcomes in patients with CKD, since it is a strong risk factor for CVD, this finding in agreement with other study conducted by Cheng and their colleagues, they found that, an increased BNP levels was associated with increased cardiovascular morbidity and mortality (Cheng *et al*., 2013).

In the present study, regarding serum BNP ROC curve when it was used against cTnT cutoff, it revealed high specificity and sensitivity, meanwhile serum cTnT ROC curve when it was used against BNP cutoff, it revealed low specificity and sensitivity, thus, the overall, BNP has higher specificity and sensitivity than cTnT, this finding in accord with other studies conducted by (Khan *et al.*, 2006; Goto *et al.*, 2002).

CONCLUSION

The present study concluded that CKD patients with CVD had higher BNP more than CKD without CVD, so that serial measurement of BNP may help in identification of potential complication in CKD patients.

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