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Original Article

Serum Brain Natriuretic Peptide Levels Correlate with the Severity of Hypertension in a Population of Nigerian Patients.

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Abstract

Background*:* Hypertension is a major global health concern requiring precise risk assessment. Brain Natriuretic Peptide (BNP) has emerged as a potential biomarker, but its relationship with hypertension severity requires exploration to evaluate its potential as a risk prediction tool. This study aimed to assess the relationship between serum BNP levels and the severity of hypertension in a population of Nigerian patients.

Methodology*:* This was an analytical cross-sectional case-controlled study involving 103 hypertensive patients and 98 controls. Participants were grouped based on World Health Organization (WHO) criteria for diagnosis of Hypertension and the severity of hypertension was categorized based on blood pressure readings. The mean BNP levels were assessed among different hypertension grades, while logistic regression was used to assess the odds of higher severity with elevated BNP.

Results*:* Serum BNP levels were significantly higher in hypertensive individuals (616.5 ± 66.3 pg/mL) compared to controls (501.1 ± 84.6 pg/mL) and varied significantly across different hypertension grades ($p = 0.000$). A positive correlation was observed between serum BNP and hypertension severity ($r = 0.736$, $p < 0.001$). Logistic regression analysis indicated increasing odds of higher severity with elevated BNP from Grade 1 to Grade 3 hypertension.

Conclusion*:* This study established a positive correlation between serum BNP levels and hypertension severity, indicating its potential as a predictive biomarker for risk stratification in hypertensive individuals.

Keywords: Brain Natriuretic Peptide (BNP); Correlate; Hypertension; Nigeria; Severity.

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Introduction:

Poorly controlled hypertension, even when asymptomatic, is associated with a high risk of various cardiovascular and other complications with serious and potentially life-threatening consequences.[1,2] Hypertension is often referred to as the "silent killer" because it may not cause noticeable symptoms until it reaches an advanced stage.[3] This underscores the importance of close monitoring for early diagnosis, evaluation of severity and prediction of future complications in affected individuals. Currently, this is done by assessment of blood pressure which although it has a strong correlation with severity, may not always possess a strong predictive value for future complications,[4–6]hence the need to explore other potential biomarkers.

Hypertension is a chronic medical condition characterized by elevated arterial blood pressure levels. It occurs when blood pressure values consistently exceed the normal range, typically defined as a blood pressure reading of ≥ 140 for systolic blood pressure (SBP) and/or ≥ 90 mmHg for diastolic blood pressure (DBP) in individuals who are not on antihypertensive medications.[7,8]This definition primarily serves the practical goal of simplifying the diagnosis and decision-making process for managing hypertension as there is a continuum in the relationship between blood pressure and complications of hypertension starting from levels as low as >115 mmHg (SBP) and >75 mmHg (DBP).[9] This may not be accounted for by severity assessments relying solely on blood pressure measurements.

Hypertension is the commonest non-communicable disease and the leading cause of cardiovascular disease in the world,[10,11]and its prevalence increases with age.[12,13]In Nigeria, an overall prevalence of 28.9% has been reported and it is projected that by 2030, there will be an increase in the incidence of the disease to about 39.1 million among people aged at least 20 years with a prevalence of 30.8%.[14]

Management of hypertension and its complications in Nigeria and the sub-Saharan African region has been suboptimal with emerging evidence suggesting that it accounts for about 22% of total mortality in the sub-region.[15] Opportunities for better outcomes are predicated on proper monitoring of disease severity and progression, and forecasting and prevention of complications. Current approaches for evaluation of the severity of hypertension are typically reliant on blood pressure measurements and evaluations of complications or organ damage both of which are fraught with limited accuracy due to factors relating to the patient, the device, the procedure or the observer to mention a few.[16] As such, other predictors have gained relevance with varying but unestablished predictive values. These are mostly involved in the pathophysiology of hypertension and may be of better predictive value since biochemical alterations usually precede clinical changes in disease states evidenced by rapid disease progression and the presence of complications in some patients with lower grades of hypertension.[9]

Brain Natriuretic Peptide (BNP), a hormone known to be progressively elevated with increasing severity of hypertension has emerged as a particularly promising option.[17] This forms the basis for the hypothesis that BNP may correlate with disease severity in the study population. It is a 32-amino acid ringed peptide[18,19]secreted predominantly in ventricular musculature in response to both ventricle volume expansion and pressure overload.[20]It has also been shown to increase with progressive hypertension and possess a high predictive index for adverse outcomes.[21,22] However, most studies assessing this relationship were carried out in Caucasian and other non-African populations while there is a paucity of such studies in the African sub-region. Therefore, this study aimed to assess the relationship between serum levels of BNP and the severity of hypertension in the study population.

Materials and Methods:

Ethical Considerations:

This study was conducted in compliance with the Declaration of Helsinki[23] and was approved by the Ethical Committee of the University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu with protocol number NHREC/05/012008B-FWA00002458-1RB00002323 on 24th May, 2017. Informed and written consent was obtained from all participants before data collection. To ensure confidentiality throughout the study, number codes were allotted to each recruited participant, and their clinical data and test results were locked out in secured spaces.

Study Design and Setting:

This study which was conducted between December 2018 and June 2019 (a period of 10 months) employed an analytical cross-sectional design to investigate the relationship between serum BNP levels and the severity of hypertension in a population of Nigerian hypertensive patients attending the medical out-patient clinic (MOPD) at UNTH Enugu, while apparently healthy age and sex-matched controls were recruited from routine medical outreaches in Amechi Awkunanaw a nearby community in Enugu-south Local Government Area.

The minimum sample size was calculated based on the prevalence of hypertension in the Nigerian population. Considering the anticipated 8.3% prevalence previously reported in the region, a significance level of 0.05, a power of 80%, and adjusted for a 10% non-response rate, the target minimum sample size was determined to be 130 participants.

The formula used for the sample size calculation was as follows:[24]

$n = [Z^2.P.(1 – p)] \div E^2$

where:

- n is the required sample size,
- Z is the Z-score corresponding to the desired level of confidence,
- P is the anticipated prevalence,
- E is the margin of error.

$n = [1.96^2 \times 8.3\% \times (1 – 8.3\%)] \div 10\% = 130$

Participants in this study were adult patients diagnosed with hypertension and apparently healthy age and sex-matched controls. Included in the study were consenting individuals aged 18 years or older, being managed for hypertension with an SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg at the point of recruitment and their matched controls. Patients that were less than 18 years, or pregnant, or with secondary hypertension or other major comorbid conditions were excluded to ensure the homogeneity of the study cohort.

Data Collection:

Patient biodata and medical history was obtained using a validated and structured research proforma. Variables of interest included demographics (age, gender), anthropometrical measurements (weight and height), clinical parameters (blood pressure measurements, duration of hypertension, medication use, etc.), and laboratory measurements (serum BNP levels).

Blood Pressure Measurement:

Blood pressure was measured after at least ten minutes of rest using a calibrated mercury sphygmomanometer (ACCOSON ENGLAND). The average of three consecutive readings taken at five-minute intervals was recorded and the procedure was repeated on a separate day for the control participants during the period of the study. The subject's left arm was used and Korotkoff sounds I and V served as respective markers for SBP and DBP. Hypertension severity was categorized into different grades based on the 2023 European Society of Hypertension (ESH) guidelines for the management of arterial hypertension.[25]

Serum BNP Measurement:

Five millilitres (5mLs) of venous blood samples were drawn from the median cubital vein into ethylenediaminetetraacetic acid (EDTA) vacutainer tubes while maintaining ascetic measures. The samples were centrifuged for 10 minutes at the speed of 2000 – 3000 rpm, after which the supernatant was collected and stored at -20^{o}C until analysis which was done in batches within one month. Serum BNP levels in picograms per millilitre (pg/mL) were assayed using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. The assay kits were provided by Bioassay Technology Laboratory 1008 Junjiang Inter. Bldg.228 Ninogguo Rd. Yangpu Dist. Shanghai. China.

Statistical Analysis:

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) computer software version 23.0 for windows (IBM, Inc, USA). Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize quantitative and qualitative variables. Univariate analysis was performed to compare the means of continuous independent variables like age, BMI and serum BNP levels in both groups of participants using the independent T-test, while the Chi square test was used for categorical independent variables like sex and educational status.

An analysis of variance (ANOVA) was performed to compare mean BNP levels across different severity categories of hypertension, and correlations between BNP levels and hypertension severity were assessed using Spearman's correlation coefficients for non-parametric distribution. The performance of serum BNP level as an indicator of hypertension severity was determined by logistic regression analysis while controlling for confounding factors like BMI and age. The Hosmer-Lemeshow goodness-of-fit test was used for the calibration of the model and values greater than 0.05 indicated a good fit. Statistical significance was at probability value of < 0.05.

Result:

A total of 201 participants comprising of 103 known hypertensive patients and 98 apparently well controls were included in this study. Table 1 shows the clinical and demographic characteristics of both categories of participants. Statistically significant differences were seen in the hypertensive versus non-hypertensive participants with regards to BMI (28.1 ± 7.0 kg/m^2 versus 25.2 ± 4.1 kg/m^2; $p = 0.001$), blood pressure ($p=0.000$) and different occupational groups ($p=0.003$). However, no significant differences in age, sex and educational status were noted.

Table 1: Clinical and demographic characteristics of participants.

Participant Characteristics	Total (N=201) Mean±SD or n (%)	Non-Hypertensive (N=98) Mean±SD or n (%)	Hypertensive (N=103) Mean±SD or n (%)	p-Value
Age (years)	51.4 ± 12.6	50.8 ± 14.4	51.9 ± 10.3	0.516
Sex:				
Male	96 (47.8)	53 (54.1)	43 (41.7)	0.081
Female	105 (52.2)	45 (45.9)	60 (58.3)	
Occupation:				
Civil Servants	90 (44.8)	43 (43.9)	47 (45.6)	
Retired Civil Servants	10 (5.0)	8 (8.2)	2 (1.9)	
Traders	74 (36.8)	30 (30.6)	44 (42.7)	0.003*
Farmers	15 (7.5)	7 (7.1)	8 (7.8)	
Students	10 (5.0)	10 (10.2)	-	
Teachers	2 (1.0)	-	2 (1.9)	
Educational status:				
Primary	32 (15.9)	12 (12.2)	20 (19.4)	0.237
Secondary	63 (31.3)	29 (29.6)	34 (33.0)	
Tertiary	106 (52.7)	57 (58.2)	49 (47.6)	
BMI (kg/m^2)	26.7 ± 5.9	25.2 ± 4.1	28.1 ± 7.0	0.001*
Blood pressure:				
SBP (mmHg)	140.9 ± 26.9	119.2 ± 8.8	161.5 ± 21.6	0.000*
DBP (mmHg)	88.4 ±12.3	78.4 ± 5.8	98.0 ± 8.8	
BNP (pg/mL)	560.2 ± 95.1	501.1 ± 84.6	616.5 ± 66.3	0.000*

*N = Number of participants in main group; n = Number of participants in sub-group; SD = Standard Deviation; *p-value significant at <0.05.*

The mean serum BNP level of the participants was 560.2 ± 95.1 pg/mL. Participants with hypertension had significantly higher mean BNP value (616.5 ± 66.3 pg/mL) compared to non-hypertensive participants with a mean value of 501.1 ± 84.6 pg/mL ($p < 0.001$). Its levels across hypertension severity categories are presented in Table 2. Mean BNP levels showed statistically significant variations among participants with different degrees of blood pressure reading, ranging from 462.2 ± 89.2 pg/mL in participants with optimal BP readings of SBP < 120 mmHg and DBP < 75 mmHg to 672.5 ± 59.8 pg/mL in participants with Grade 3 hypertension (SBP >180 mmHg and DBP >110 mmHg) ($p = 0.000$). When adjusted for BMI and occupation, serum BNP and severity of hypertension had significant positive and strong correlation ($r = 0.736$, p-value < 0.001).

Table 2: Serum BNP levels across different severity categories of hypertension.

Categories of Hypertension Severity (mmHg)	Total (N=201) n (%)	Serum BNP Mean ± SD (pg/mL)	p-Value
Optimal BP *(SBP < 120; DBP < 75)*	16 (8.0)	462.2 ± 89.2	
Normal BP *(SBP 120 – 129; DBP 75 – 84)*	46 (22.9)	499.4 ± 74.7	
High-Normal BP *(SBP 130 – 139; DBP 85 – 89)*	36 (17.9)	520.5 ± 90.5	0.000*
Grade 1 HTN *(SBP 140 – 159; DBP 90 – 99)*	41 (20.4)	578.0 ± 53.9	
Grade 2 HTN *(SBP 160 – 179; 100 – 109)*	37 (18.4)	621.2 ± 54.1	
Grade 3 HTN *(SBP > 180; DBP > 110)*	25 (12.4)	672.5 ± 59.8	

*N = Number of participants in main group; n = Number of participants in sub-group; SD = Standard Deviation; *p-value significant at <0.05.*

The performance of serum BNP levels as an indicator of various categories of hypertension severity was assessed by logistic regression analysis (Table 3). It showed that an increase in serum BNP in participants with Grade 1 hypertension was significantly associated with a 0.3% increase in the odds of higher hypertension severity (OR=1.003, 95% CI: 0.999 – 1.007, p=0.044) and progressively increases to 3.1% increase in Grade 3 (OR=1.031, 95% CI: 1.019 – 1.043, p <0.001). The Hosmer-Lemeshow goodness-of-fit tests ranged from 0.357 to 0.952 indicating that the model was a good fit for the observed data.

Table 3: Performance of BNP as an indicator of Hypertension Severity.

Categories of hypertension severity	B	SE	OR	95% CI for OR	p-value
Optimal BP	-0.010	0.003	0.990	0.985 – 0.995	< 0.001*
Normal BP	-0.009	0.002	0.991	0.987 – 0.995	< 0.001*
High Normal BP	-0.005	0.002	0.995	0.991 – 0.999	0.008*
Grade 1 hypertension	0.003	0.002	1.003	0.999 – 1.007	0.044*
Grade 2 hypertension	0.011	0.003	1.011	1.006 – 1.017	< 0.001*
Grade 3 hypertension	0.031	0.006	1.031	1.019 – 1.043	< 0.001*

**p-value significant at <0.05; B = Regression coefficient; SE = standard error; OR = Odds Ratio; CI = Confidence Interval*

Discussion:

The identification of BMI as a significant factor associated with hypertension in this study corroborates with established epidemiological patterns.[26] This association with BMI emphasizes the role of obesity in hypertension development, likely through mechanisms involving insulin resistance and sympathetic nervous system activation.[27-29] The diversity in occupational patterns contributing to hypertension further underscores the multifactorial nature of this condition.

The observed elevation in serum BNP levels in hypertensive individuals in the index study is consistent with the known pathophysiology of hypertension. B-type natriuretic peptide (BNP), primarily secreted by the ventricles in response to increased cardiac wall stress, serves as a compensatory mechanism in hypertensive states.[20,30] The progressive elevation of BNP with increasing severity of hypertension in this study corresponds with its role as a marker of cardiac strain and ventricular dysfunction in the setting of sustained elevated blood pressure.[31] Hence, this increase does not only indicate increasing severity but also increased risk of pathological organ changes. Previous studies suggest that BNP levels correlate with the degree of myocardial involvement in hypertensive heart disease, providing insights into the continuum of hypertensive cardiac damage.[32] This aligns with our observation of a positive correlation and statistically significant variations in BNP levels across different degrees of blood pressure readings emphasizing the potential role of BNP as a dynamic biomarker indicative of the severity of hypertension. This becomes particularly relevant when considering the close association between hypertension severity and the risk of complications.[33]

In addition to its correlation with severity of hypertension, the significant associations between increasing BNP and higher odds of hypertension severity demonstrated via logistic regression analysis is an indication of its predictive ability. Our findings are consistent with previous studies which demonstrated the prognostic value of BNP in predicting cardiovascular events in hypertensive patients,[34,35] as well as its ability to identify events like heart failure, a condition often intricately linked with hypertension, as reported in a prospective study.[36] Therefore, understanding the link between BNP and hypertension severity not only informs risk assessment but also opens avenues for more targeted interventions, with the goal of mitigating the risk of complications.

The potential of serum BNP to predict severity and stratify risk could improve risk assessment and treatment strategies. Future longitudinal studies should explore BNP-guided therapeutic interventions and its integration into risk prediction models. However, the cross-sectional nature of the index study limits the establishment of causation while its specific population focus may impact generalizability. Also, the absence of detailed information on the use and impact of anti-hypertensive medications among hypertensive participants introduces a potential confounding factor. Prospective, multicenter studies with diverse cohorts are warranted to validate and extend our findings while future studies in the population should adjust for the impact of therapeutic interventions.

Conclusion:

This study establishes a strong positive correlation between serum BNP levels and the severity of hypertension in the study population. Its potential predictive capacity emphasizes its relevance in the comprehensive management of hypertensive individuals, with implications for the future of precision medicine in hypertension.

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