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The Relationship between Neutrophil to Lymphocyte Ratio and Left Ventricular Function in Drug-naïve Asymptomatic Hypertensive Adults in Port Harcourt, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author NNU designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AMR and OOJ managed the analyses of the study. Authors NNU and AMR managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Systemic hypertension is the commonest cardiovascular disease, affecting over a billion people all over the world and causing deaths due to target organs damage. Left ventricular dysfunction could be the result of hypertension causing a mechanical alteration of cardiac performance. More importantly it can be the main cause of congestive heart failure. Lastly, left ventricular dysfunction can be either systolic or diastolic. Left ventricular dysfunction is thought to be related to endothelial dysfunction and several substrates have been identified as surrogate markers of this target organ damage including neutrophil to lymphocyte ratio (NLR).

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We aim to study the relationship of NLR to left ventricular function in treatment-naive African black hypertensive patients in Port Harcourt, Southern Nigeria.

Methods: A descriptive cross-sectional study of newly diagnosed, treatment-naive hypertensive patients, consecutively recruited over a six months' period. All underwent routine investigations for hypertension including a full blood count and a transthoracic echocardiography. The NLR was calculated using the total absolute neutrophil and lymphocyte count and correlated to the echocardiographically-determined left ventricular systolic and diastolic function.

Results: One hundred and forty-four patients and seventy-two controls were evaluated. The mean ages in subjects and controls were 51.4±12.9 years (Range 25–86 years) and 48.8±12.6 years (\Range 24 – 78 years) respectively. The mean body mass indices were 29.5±4.9 kg/m^2 and 27.2±5.0 kg/m^2 (P=0.001) in subjects and control respectively. Mean systolic blood pressure were 149.0±22.5 and 115.0±11.3 mmHg in subjects and controls respectively (P<0.001) while mean diastolic pressures were 93.0±13.6 mmHg and 70.6±9.1 mmHg respectively (P <0.001). Mean NLR in the subjects and controls were 1.35±0.8 and 1.23±0.6 respectively (P= 0.272). Mean NLR in subjects with normal left ventricular function was significantly lower compared with those with different grades of systolic dysfunction, (1.35 ±0.66 Vs 1.43. ±0.78 Vs 1.34± 0.56 Vs 2.43 ±1.11 (P = 0.009). The left ventricular ejection fraction and fractional wall shortening decreased with increasing NLR tertiles and the difference between tertiles was statistically significant (p=0.004 and 0.009).

Conclusion: NLR was highest in the subjects with LV systolic dysfunction and in those with severe LV systolic dysfunction. NLR is related to LV systolic dysfunction in patients with hypertension even in the absence of overt features of heart failure.

Keywords: Hypertension; left ventricular dysfunction; endothelial dysfunction; neutrophil to lymphocyte ratio.

1. INTRODUCTION

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease [1,2]. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years [1].

In Nigeria the only national survey for non-communicable diseases over two decades ago put the prevalence of hypertension at 11.1% for men and 11.2% for women [3]. Since then only minor surveys and hospital based studies have been carried out. These studies give very variable prevalence rates from different populations in various parts of the country by different researchers. The reported prevalence of hypertension in the general population ranged from 18.7% to 46.4% in the rural areas [4,5] and 12.4% to 44.6 % in the urban areas [6-8].

Hypertension can lead to severe end-organ damage and clinical manifestations, including coronary artery disease, congestive cardiac failure, chronic kidney disease and stroke, which constitute a leading cause of mortality in the general population. Vascular reactivity and endothelial dysfunction, which result in increased peripheral resistance, is one of the major hypotheses behind the pathogenesis of hypertension and the pathophysiology of its complications such as congestive cardiac failure [9]. Heart failure is a common clinical syndrome and its clinical presentations and etiology are numerous. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood. Even before the onset of overt features of heart failure some hypertensive patients might present with echocardiographically-determined indices of left ventricular dysfunction [10]. Left ventricular dysfunction is thought to be related to endothelial dysfunction that occurs as consequence of increased oxidative stress. In oxidative stress, the generation of reactive oxygen species is known to promote atherosclerosis, myocytes necrosis and apoptosis [11]. Several substrates including NLR have been identified as surrogate marker of this target organ damage [12,13]. NLR has been studied in various oncologic, hematologic, immunologic and infectious diseases and recently cardiac disorders as well. NLR has been evaluated in various cardiac disorders including heart failure and coronary artery disease in Caucasian populations. The studies revealed considerable prognostic value in addition to significant positive correlations with target organ damage in these cardiovascular

diseases [13]. This inexpensive haematological index could therefore be of immense value in the assessment of target organ damage in low resource setting such as Nigeria.

Our aim was to evaluate the association, if any between NLR and left ventricular systolic and diastolic function among treatment-naive hypertensive patients seen in the cardiac clinic of a tertiary hospital in southern Nigeria.

The study protocol was approved by the Clinical Ethics committee of the University of Port Harcourt Teaching Hospital and informed written consent was obtained from the committee and from each patient.

2. PATIENTS AND METHODS

2.1 Study Design and Population

This was a descriptive cross-sectional study carried out in the cardiac clinics of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria from January 2016 to June 2016.

2.2 Study Population

A total of 144 consecutive treatment naive hypertensive subjects referred to the cardiac clinic of the University of Port Harcourt Teaching Hospital for evaluation were recruited. Hypertension was defined as diastolic blood pressure (DBP) of ≥90 mmHg, and/or systolic blood pressure (SBP) of ≥140 mmHg as defined by JNC7 [14]. The purpose of utilizing these blood pressure cut-off values was to make a diagnosis of hypertension and not necessarily in determining a treatment BP target. These subjects had no history or clinical evidence of congestive heart failure, myocardial infarction, arrhythmias, cardiac valve disease, coronary bypass surgery or angioplasty, diabetes mellitus and renal insufficiency, and absent clinical evidence of secondary hypertension. Seventy-two non-hypertensive, apparently healthy age- and sex- matched individuals were selected from the hospital staff and patients' relatives using a simple random technique which participants assigned numbers using a random number table. This group of participants were classified as controls. The sample size was calculated based on a prevalence of hypertension of 15.2% as determined by Onwubere et al. [5] from a hospital-based study since a national prevalence rate for hypertension is unavailable.

After informed written consent had been obtained, all patients and controls had full clinical evaluation and fasting blood samples collected for lipid profile, renal indices assessment, full blood count and urinalysis. A standard 12-lead ECG was done and the patients underwent a standard transthoracic echocardiography. Fasting cholesterol and triglyceride (TG) levels were measured using the enzymatic method with a reagent from Atlas Medical Laboratories (Atlas Development Corporation, Calabasas, CA, USA). Fasting high-density lipoprotein (HDL) was measured with the precipitation method. Low-density lipoprotein (LDL) cholesterol values were calculated using the Friedewald equation when the TG level was <4.0 mmol/L [15].

NLR was calculated by absolute neutrophil count divided by absolute lymphocyte count, both obtained from the same blood sample [16]. There is no consensus on the cut-off points to define the levels of the NLR [17]; therefore the subjects were stratified into tertiles based on NLR values. The low, medium and high tertiles were defined as NLR≤1.81, 1.81<NLR≤3.2 and NLR>3.2 respectively [18]. Previous studies that have investigated the effect of NLR on clinical outcomes have generally used three methods for categorization of NLR. The first is to treat NLR as a continuous variable and correlate with desired outcome. The second is using an NLR <5 or ≥5 as cut-off values [19,20]. The third is by categorizing patients into equal tertiles on the basis of their NLR value [18]. In this study, we used the third methods of analysis.

Blood pressure measurements (BP) was measured with a standard Accoson mercury sphygmomanometer (AC Cossons and Son [Surgical] Ltd, Essex, UK) with an appropriate cuff size and observing standard protocol for measurement. The presence and severity of hypertension was defined based on the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7) guidelines [14].

Echocardiographic evaluation was carried out with an Aloka Prosound SSD 4000 echocardiography machine (Fair Medical Company Ltd, Matsudo, Japan) equipped with a 2.5 Hz transducer. Measurements were care carried out in line with the guidelines of the ACC [21]. LV mass (in grams) was automatically calculated with the internal software of the machine. LV mass was indexed to the body surface area using cut-off values of 115 g/m^2 and

95g/m^2 for men and women, respectively [22]. Relative wall thickness (RWT) was calculated as 2× posterior wall thickness in end diastole/LV end diastolic diameter. A partition value of 0.42 for RWT was used for both men and women [22]. Patients with increased LV mass index (LVMI) and increased RWT were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased or normal RWT were considered to have concentric remodelling or normal geometry, respectively. Left ventricular systolic function was assessed by the Teicholz method, using the ejection fraction and fractional shortening [22] while the diastolic function was assessed using the peak mitral inflow velocity measurements (E/A ratio) and the deceleration time (DT). The severity of left ventricular systolic dysfunction was graded as mild, moderate or severe [23].

2.3 Statistical Analysis

All data were analysed using the commercially available Statistical Package for the Social Sciences (SPSS) version 17.0 analytic software (IBM Corporation, Armonk, NY, USA). Data were expressed as mean ± standard deviations, and frequencies as a percentage. Continuous variables were compared with the Students t-test, or one-way analysis of variance, as considered appropriate. Proportions or categorical parameters were compared with the chi-square test. Relationships between continuous variables were assessed using Pearson's correlation coefficient, multiple linear regression analysis, and binary regression analysis. The study population was divided into tertiles according to their continuous NLR. All tests were considered to be statistically significant at the P-value <0.05.

3. RESULTS

3.1 Demographic Data

There were 144 hypertensive subjects with a female-to-male ratio of 1.2:1. The age range of the hypertensive subjects was 25–86 years, with a mean age of 51.4±12.9 years. The age range of the control subject was 24–78 years with a mean age of 48.8±12.6 years. There was no statistically significant difference in the mean ages of the subjects and controls (P=0.159). The mean body mass index of the subjects was 29.5±4.9 kg/m^2, which was significantly higher than that of the controls 27.2±5.0 kg/m^2; (P=0.001). The mean systolic blood pressure in the subjects and controls were 149.0± 22.5 mmHg and 115.0 ±11.3 mmHg respectively (P < 0.001) while the mean diastolic blood pressure was 93.0± 13.6 mmHg and 70.6± 9.1 mmHg respectively (P < 0.001).

The mean left ventricular mass index in the subjects and controls were 166.3± 65.57 gm/m^2 and 100.5± 32.53 gm/m^2 respectively (P < 0.001) while the mean ejection fractions were 61.2±15.7% and 63.4 ±10.9% respectively (P=0.340). The inter-ventricular septal diameter and left ventricular posterior wall diameter in diastole were significantly higher in the subjects than the controls (1.37±0.35 cm versus 0.98±0.26 cm; p<0.001) and (1.43±0.40 cm versus 1.04±0.29 cm; p<0.001) respectively. Left ventricular hypertrophy LVH was present in 72.5% of the entire study population. Eighty-nine percent of the hypertensive subjects had LVH while 40.7% of the normotensive subjects had LVH (X^2=45.810, P<0.0001). In the subjects with left ventricular hypertrophy, the most common geometric pattern among the hypertensives was concentric hypertrophy, while the majority of the controls had normal LV geometry.

The baseline clinical and laboratory characteristics of the total study population are shown in Table 1. The echocardiographic parameters in the total study group are shown in Table 2.

When echocardiographic parameters were evaluated with respect to tertiles category of NLR, there were significant differences with respect to interventricular septal diameter in diastole (IVSDd), left ventricular posterior wall diameter in diastole (LVPWd) and left ventricular mass index (p=0.004; 0.023 and 0.014) (See Table 4). When Post-Hoc analysis was performed for these parameters using the Tuskey HSD, we found that for the IVSDd there was a statistically significant difference between low and medium tertiles of the NLR (P=0.004). We also found that for LVPWd there was a significant differences between the low and high tertiles (P=0.04). There was however no significant difference across the tertiles for LVMI.

The left ventricular ejection fraction (Fig. 2) and fractional wall shortening (Fig. 3) decreased with increasing NLR tertiles and the difference between tertiles was statistically significant (p=0.004 and 0.009) (Table 3). Post-Hoc analysis using the Tuskey HSD revealed that

there was a significant difference between the low and high tertiles for the EF (P=0.008). Further analysis using the Tuskey HSD, also showed that there was a statistically significant difference between the low and high tertiles for the FS (P=0.028).

We found that LV systolic dysfunction was found in 25.47% of the total study population. Twenty-seven percent of the hypertensive subjects had LV systolic dysfunction while 22.0% of the apparently healthy control subjects had LV systolic dysfunction (X^2=0.578, P=0.447). This study also revealed that severe LV systolic dysfunction was found in 1.7% of subjects within the low tertiles, 5.3% of subjects within the medium tertiles, and 33.3% of those within the high tertiles (X^2=18.682, P=0.005). The NLR was highest in the patients with severe LV systolic dysfunction (p=0.009) (Fig. 1). Further analysis using the Tuskey HSD statistical tool showed that the NLR was able to delineate statistically significant differences between severe left systolic dysfunction, moderate LV systolic dysfunction (P=0.017), mild LV systolic dysfunction (P=0.023), and normal LV systolic

Table 1. Baseline clinical and laboratory characteristics of the entire study population

Variables	Hypertension group (n=144)	Control group (n=72)	Student t-test P value
Age (years)	51.4±12.9	48.8±12.8	0.159
BMI (Kg/m^2)	29.5±4.9	27.2±5.0	0.001*
SBP (mmHg)	149.0±22.5	115.0±11.3	<0.001*
DBP (mmHg)	93.0±13.6	70.6±9.1	<0.001*
TC (mmol/l)	5.09±1.2	4.61±0.7	0.002*
TG (mmol/l)	1.18±0.5	0.92±0.4	<0.001*
HDL-c (mmol/l)	0.89±0.2	1.07±0.5	0.004*
LDL-c (mmol/l)	3.50±1.1	3.30±0.7	0.004*
FBG (mmol/l)	5.27±1.2	4.82±0.7	0.010*
WCC (X10^9/L)	5.99±1.6	5.47±1.4	0.029*
N (%)	51.06±11.9	50.41±11.5	0.715
L (%)	44.32±21.0	45.91±11.9	0.388
NLR	1.35±0.8	1.23±0.6	0.272
ESR (mm/h)	28.06±20.5	7.73±8.4	<0.001*
PCV (%)	38.96±5.3	40.81±5.1	0.021*

*BMI= Body mass index; WC= Waist circumference; WHR= Waist-hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; TC= Total cholesterol; TG= Triglycerides; HDL-c= High density lipoprotein cholesterol; LDL-c= Low density lipoprotein cholesterol; FBG= Fasting blood glucose; WCC= White cell count; N= Neutrophil count; L= Lymphocyte count; NLR= Neutrophil-lymphocyte ratio; ESR= Erythrocytes sedimentation rate; PCV= Packed cell volume. *Significant P-value*

Table 2. Baseline echocardiographic characteristics of the study entire population

Variables	Hypertension group (n=144)	Control group (n=72)	Student t-test P value
Mean IVSD (cm)	1.37±0.35	0.98±0.26	<0.001*
Mean LVPWD (cm)	1.43±0.40	1.04±0.29	<0.001*
Mean LVIDs (cm)	4.70±0.94	4.57±0.59	0.346
Mean LVIDd (cm)	6.15±5.30	3.02±0.70	0.340
Mean LVMI (g/m^2)	166.3±65.57	100.5±32.53	<0.001*
Mean EF (%)	61.2±15.7	63.4±10.9	0.340
Mean FS (%)	33.7±11.3	34.9±8.5	0.452
Mean RWT	0.62±0.2	0.44±0.1	<0.001*
LVH (%)	72.5	27.5	<0.001*
Mean E/A Ratio	1.24 ±0.83	1.43 ±0.42	0.091
Mean DT	188.6± 57.7	171.6 ±49.2	0.058

*IVSD= Interventricular septal thickness in diastole; LVIDd= Left ventricular internal diameter in diastole; LVIDs= Left ventricular internal diameter in systole; LVPWd= Left ventricular posterior wall thickness in diastole; EF= Ejection fraction; FS= fractional shortening; LVMI= Left ventricular mass indexed to body surface area; RWT= Relative wall thickness; DT = Deceleration time, *Significant P-value*

Table 3. Baseline laboratory and echocardiographic characteristics with respect to NLR tertiles of the entire study population

Variables	Low (NLR≤1.81) N=146	Medium (1.81<NLR≤3.2) N=45	High (NLR>3.2) N=25	ANOVA P value
WC (cm)	93.34±16.36	91.27±12.95	89.50±10.62	0.715
TC (mmol/l)	5.05±1.0	4.71±1.1	4.42±1.5	0.140
TG (mmol/l)	1.11±0.48	1.04±0.39	0.90±0.22	0.456
HDL-c (mmol/l)	1.22±0.42	1.01±0.44	1.04±0.37	0.501
LDL-c (mmol/l)	3.53±0.92	3.19±1.00	2.76±1.53	0.055
FBG (mmol/l)	4.95±0.83	5.20±0.78	4.68±0.83	0.361
WCC ($x10^9$/l)	5.73±1.49	6.04±1.87	7.13±1.62	0.077
PCV (%)	39.8±5.2	40.2±5.5	34.5±7.0	0.049*
ESR (mm/h)	19.1±20.3	17.5±14.3	14.0±11.1	0.866
PLT ($x10^9$/l)	230.6±77.0	255.9±41.7	294.4±108.3	0.139
N (%)	47.7±9.9	64.8±4.3	69.3±15.0	<0.001*
L (%)	48.1±10.2	32.4±3.8	18.2±3.6	<0.001*
EF (%)	62.9±12.4	57.0±14.2	45.9±23.5	0.004*
FS (%)	34.5±9.1	30.2±8.9	24.3±13.8	0.009*
LVIDd (cm)	4.66±0.69	4.39±1.33	5.22±1.12	0.084
RWT	0.52±0.15	0.65±0.22	0.51±0.13	0.003*
E/A ratio	1.32±0.67	1.22±0.81	1.33±0.17	0.810
DT (ms)	180.4±45.0	191.6±96.4	195.7±23.7	0.581

*WC= Waist circumference; TC= Total cholesterol; TG= Triglycerides; HDL-c= High density lipoprotein cholesterol; LDL-c= Low density lipoprotein cholesterol; FBG= Fasting blood glucose; WCC= White cell count; N= Neutrophil count; L= Lymphocyte count; PLT= Platelet count; PCV= Packed cell volume; ESR=Erythrocyte sedimentation rate; EF= Ejection fraction; FS= Fractional shortening; LVMI= Left ventricular mass indexed to body surface area; RWT= Relative wall thickness. *Significant P-value*

Table 4. Baseline echocardiographic characteristics with respect to NLR tertiles of the total study population

Variables	Low (NLR≤1.81) N=146	Medium (1.81<NLR≤3.2) N=45	High (NLR>3.2) N=25	ANOVA P value
LVIDd (cm)	4.66±0.69	4.39±1.33	5.22±1.12	0.084
LVIDs (cm)	3.14±0.88	3.43±1.24	3.64±2.32	0.001*
IVSDd (cm)	1.16±0.34	1.42±0.42	1.33±0.30	0.004*
LVPWd (cm)	1.21±0.35	1.35±0.24	1.59±1.03	0.023*
LVMI (g/m^2)	129.7±51.9	158.7±76.3	181.9±83.2	0.014*
RWT	0.52±0.15	0.65±0.22	0.51±0.13	0.003*
EF (%)	62.9±12.4	57.0±14.2	45.9±23.5	0.004*
FS (%)	34.5±9.1	30.2±8.9	24.3±13.8	0.009*
E/A ratio	1.32±0.67	1.22±0.81	1.33±0.17	0.810
DT (ms)	180.4±45.0	191.6±96.4	195.7±23.7	0.581

*IVSD=Interventricular septal thickness in diastole; LVIDd= Left ventricular internal diameter in diastole; LVIDs= Left ventricular internal diameter in systole; LVPWd= Left ventricular posterior wall thickness in diastole; EF= Ejection fraction; FS= Fractional shortening; LVMI= Left ventricular mass indexed to body surface area; RWT= Relative wall thickness; DT= Deceleration time. *Significant P-value*

function (P=0.004) respectively. Correlation analysis showed that NLR was negatively associated with left ventricular ejection fraction [LVEF, (r= -0.190; p=0.025)] and is depicted in Fig. 2.

In simple regression analysis, NLR was found to be associated with LV systolic dysfunction (r= 0.190; p=0.025). However, when SBP, FBG and BMI were included in the multiple linear regression model, NLR failed to contribute to (β=-0.090, P=0.314) the variance observed in LVEF (F= 2.638; P=0.037) Most of the variance observed in LVEF was contributed by SBP (P=0.029) and FBG (P=0.021).

When the subjects were assessed for LV diastolic dysfunction, it was found that LV diastolic dysfunction was present in 45.3% of the total study population. Fifty-eight percent of the hypertensive subjects had LV diastolic dysfunction while 22.0% of the non-hypertensive subjects had LV diastolic dysfunction (X^2=19.730, P<0.0001). There was however no significant difference in mean E/A ratio and deceleration time values when compared with respect to NLR tertiles (See Table 3). Likewise, when correlation analysis was done, there was no association between diastolic function and NLR.

Table 5. Evaluation of echocardiographic parameters with respect to grades of systolic dysfunction

Variables	Mild (45%-54%)	Moderate (30%-44%)	Severe (<30%)	ANOVA P value
LVIDd (cm)	4.57±0.84	5.43±0.84	5.78±1.03	<0.001*
LVIDs (cm)	3.52±0.49	4.44±0.73	5.71±0.40	0.993
IVSDd (cm)	1.17±0.24	1.31±0.41	1.46±0.11	0.272
LVPWd (cm)	1.43±0.57	1.09±0.32	1.59±0.42	0.035*
LVMI (g/m^2)	133.6±51.3	182.5±99.4	258.9±60.1	<0.001*
RWT	0.57±0.18	0.47±0.15	0.47±0.10	0.227
EF (%)	50.7	41.5	19.6	<0.001*
FS (%)	25.7	20.6	9.1	<0.001*
E/A ratio	1.14±0.47	1.87±1.60	2.16±1.75	0.002*
DT (ms)	207.1±58.2	210.1±98.1	176.4±52.6	0.015*

*IVSD=Interventricular septal thickness in diastole; LVIDd= Left ventricular internal diameter in diastole; LVIDs= Left ventricular internal diameter in systole; LVPWd= Left ventricular posterior wall thickness in diastole; EF= Ejection fraction; FS= Fractional shortening; LVMI= Left ventricular mass indexed to body surface area; RWT= Relative wall thickness; *Significant P-value*

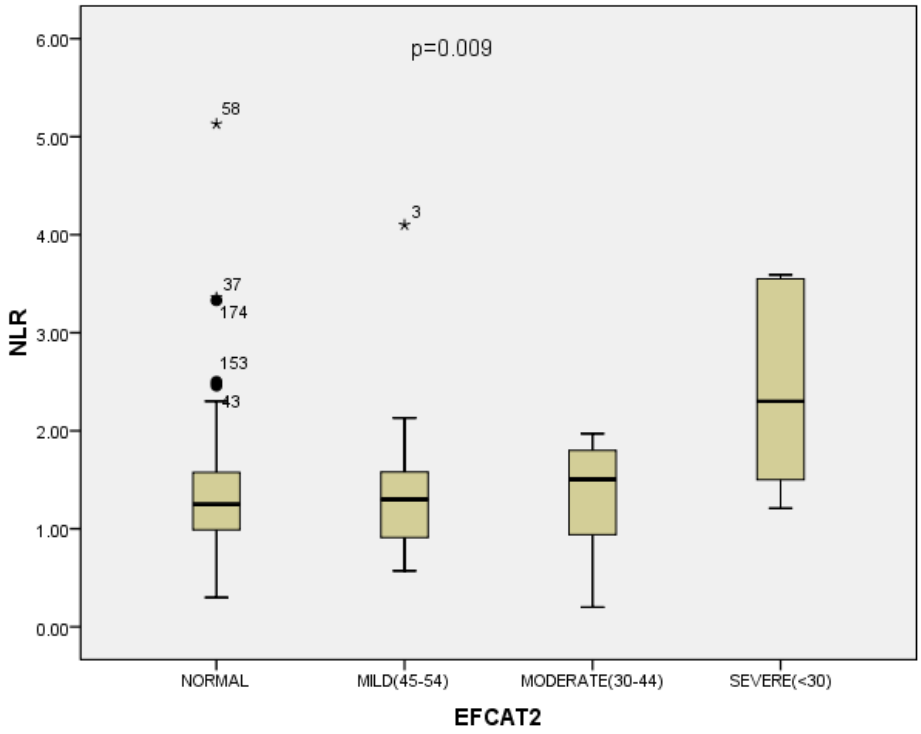

Fig. 1. Comparison between mean NLR and severity of LV systolic dysfunction of the total study population using ANOVA

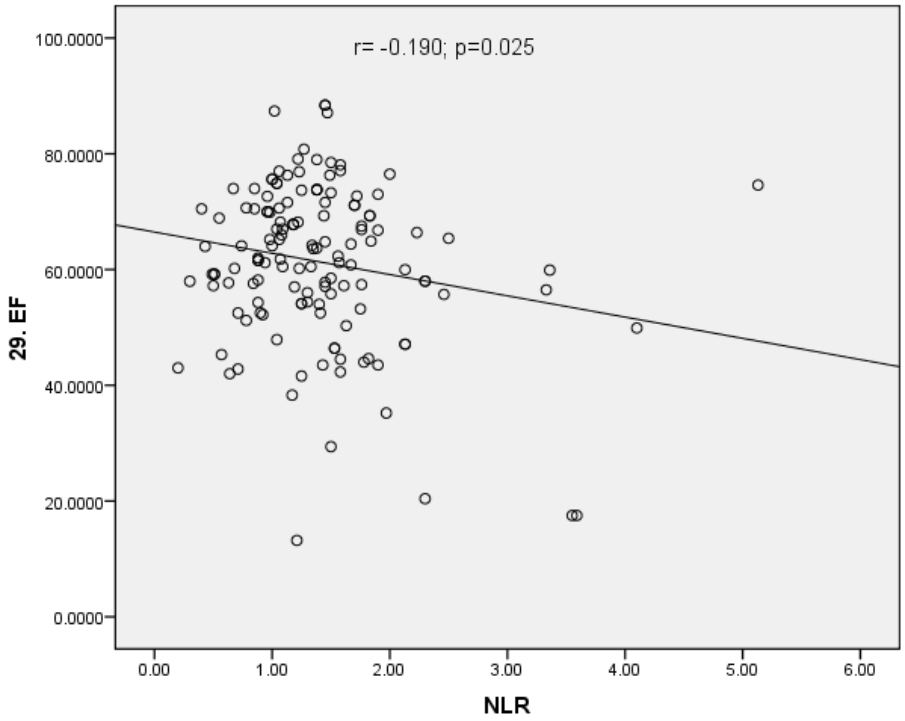

Fig. 2. Correlation analysis of NLR with LV ejection fraction of the total study population

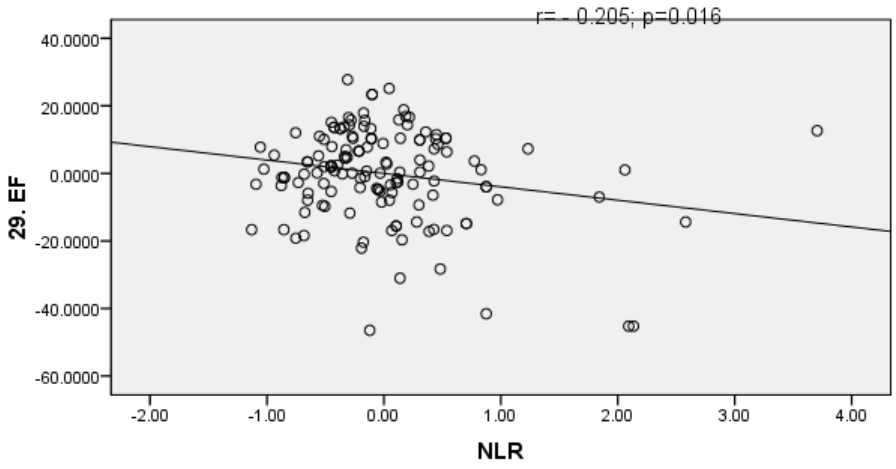

Fig. 3. Regression plot between NLR and LV ejection fraction of the total study population

4. DISCUSSION

This study of treatment naive hypertensive patients found a high incidence of cardiac complications with 72.5% of hypertensive subjects having evidence of left ventricular hypertrophy on echocardiography. This figure is much higher than that obtained by studies from Ibadan**,** Enugu and Port Harcourt in Nigeria [24-26]. The higher prevalence of LVH may be related to the fact that these studies used the electrocardiogram to identify LVH while our study is echocardiography-based which usually has a better sensitivity in term of identifying LVH. Echocardiographically-determined left ventricular systolic dysfunction was present in 27.5% of the hypertensive subjects without any symptoms, this was severe in 4.9% (EF <30%), moderately severe (EF 30-44%) in 8.82% and mild (EF 45-54%) in 13.73% of subjects. Thus significant

asymptomatic cardiac complications had set in amongst these treatment-naive hypertensive subjects. Studies from various parts of Nigeria have also documented significant left ventricular systolic dysfunction in untreated hypertensive subjects using either peak systolic myocardial velocity or ejection fraction with values ranging from 10.8% to 18.1% [27-29].

In this study, we found that although the mean NLR was greater in the hypertensive subjects compared with controls, it was not statistically significant. This was similar to the finding by Wasilewski et al. [30] but in contrast to the finding by Liu et al. [31]. The disparity in results may be explained by difference in methodology. Liu et al. carried out a longitudinal study involving 1,824 individuals, who were followed up for a period of 6years to see if the development of hypertension in these individuals was predicted by NLR. They also utilized higher values of NLR in quintiles before any statistical difference could be reported. Furthermore, compared with our study (See Table 3), participants in the in top 4 NLR quintiles of their study tended to be older and had higher waist circumference, triglycerides than those in the lowest quintiles in a statistically significant manner. The elevated levels of NLR in their subjects who developed hypertension when compared to those who did not might therefore be explained by the additive pro-inflammatory effects of the other components of the metabolic syndrome.

We found also found in this study that the subjects with medium and high tertiles of NLR were most likely to have to have thicker interventricular septum and LV posterior walls than those with low tertiles of NLR despite the finding that the tertiles of NLR were unable to discriminate LVMI. Therefore, we hypothesize that low-grade systemic inflammation (which NLR measures) may affect the myocardium in a selective manner. This association might be related to impaired epicardial and microvascular perfusion due to rheological changes related to absolute and relative neutrophilia [32], which might be linked to pro-inflammatory cytokine release and lack of cytoskeletal flexibility [33]. This physiological derangement may ultimately culminate in LV contractile abnormality.

The main finding of this study was that high tertiles of NLR was associated with left ventricular systolic dysfunction in patients with hypertension even when the comparative baseline LVEF and fractional shortening between the hypertensive patients and controls were not statistically significant (See Table 2). The NLR increase is associated with increasing left ventricular systolic dysfunction (i.e. decreasing ejection fraction) and negatively correlated with left ventricular ejection fraction and thus there was an association between left ventricular systolic dysfunction and NLR in these untreated hypertensive Nigerian subjects. Kasapraka et al. also reported an association between higher NLR and reduced LVEF [34]. The statistical difference in indices of LV systolic dysfunction in our study was solely distinct between the low and high tertiles of NLR. The higher NLR may therefore be adjuncts to risk stratify LV systolic dysfunction. When the grades of systolic dysfunction were evaluated in relation to NLR, the patients with severe LV systolic dysfunction had the highest values of NLR while the patients with mild LV systolic dysfunction had the lowest NLR, supporting an association between systolic dysfunction and NLR (Fig. 1; $p=0.009$). There was also a negative correlation between NLR and LVEF in the study population ($r= -0.190$; $p=0.025$) (Fig. 2). Studies in Caucasian populations have also shown higher NLR in hypertensive and heart failure subjects with negative correlation with left ventricular ejection fraction as well as an independent predictor of mortality in heart failure patients [35-36]. Although simple linear regression showed an association between NLR and LV systolic dysfunction, a multivariate regression however showed that this effect may occur via a blood pressure-dependent mechanism. NLR as markers of inflammation may therefore play a pivotal role in the prognostication of LV systolic function even in asymptomatic hypertensive subjects [37,38]. This inflammatory mediator could merely be a marker of the underlying process causing left ventricular modelling and HF. This is because endothelial leukocyte activation and cytokine production is known to cause endothelial dysfunction by provoking and sustaining the generation of reactive oxygen species and inflammation. Furthermore, in the presence of sustained inflammatory stimulus, leukocytes release many inflammatory cytokines, such as tumor necrotic factor-alpha (TNF-α), interleukin-6 (IL-6), and complement reactive protein (CRP), as well as proteolytic enzymes which have destructive effects on the myocardium leading to myocardial remodelling, decreased LV function and ultimately heart failure [39,40]. Moreover, it has been shown that oxidative stress can cause contractile dysfunction [41].

5. CONCLUSION

In conclusion, the NLR is related to LV systolic dysfunction in patients with hypertension even in the absence of overt symptoms of heart failure. Total and differential WCC are readily available and relatively inexpensive laboratory methods that could be used for evaluating patients with hypertension for complications in resource-poor settings. The practice of using an NLR count may be useful for identifying patients at high-risk or who have already developed asymptomatic left ventricular systolic dysfunction.

6. STUDY LIMITATIONS

The small sample size and the nature of cross sectional study may make it difficult for absolute causality to be inferred. Therefore, a larger prospective study should be performed to emphasize the clinical application and importance of NLR in asymptomatic hypertensive individuals in order to ascertain the number of patients that eventually develop overt features of hypertensive LV systolic dysfunction.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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