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ORIGINAL RESEARCH

Association Between Highly-Sensitive C- Reactive Protein and Neutrophil to Lymphocyte Ratio as Markers of Inflammation Among Adult Nigerians with Essential Hypertension

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Abstract

Background: Hypertension is a medical condition with global public health importance that is associated with significant morbidity and mortality in both developed and developing countries. It is important to identify readily available parameters that may indicate the level of inflammation that is associated with hypertension.
Objective: To assess the relationship between highly-sensitive C-Reactive Protein (hs-CRP) and neutrophil-to-lymphocyte ratio (NLR) in hypertensive adults.
Methods: Three hundred and sixty adults comprising 240 hypertensive and 120 healthy normotensive subjects (control) were studied. The full blood count (FBC) and highly-sensitive C-Reactive Protein (hs-CRP) levels were determined using standard methods.
Results: The mean values of Total White Blood Cells count (WBC) ($p = 0.03$), absolute neutrophil count ($p = 0.03$), absolute lymphocyte count ($p = 0.01$), NLR ($p = 0.001$) and hs-CRP ($p < 0.001$) in the hypertensive subjects were significantly higher than in the normotensive subjects. The mean values also differed significantly with increasing severity of hypertension. There was a significant but weak positive correlation between NLR and hs-CRP ($r = 0.248$, $p < 0.001$). The Areas Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) of NLR and hs-CRP ($p = 0.01$) were 0.68 and 0.639 respectively.
Conclusion: NLR is closely associated with hs- CRP among hypertensive subjects. Therefore, NLR may be utilised routinely instead of hs-CRP as a screening test for inflammation in essential hypertension.

Key words: Essential Hypertension, Highly-Sensitive C-Reactive Protein, Inflammation, Lymphocyte, Neutrophil.

Introduction

Hypertension is a global health challenge affecting approximately 22% of the world population. [1] It is a major risk factor for cardiovascular mortality and morbidity. [2] Hypertension occurs as a result of multiple pathologies of the cardiovascular and renal systems. It is the most common risk factor for stroke, myocardial infarction, and other medical problems. [3, 4] Hypertension and inflammation are closely related. The pathological connection between the two entities has been the subject of several studies in both animals and humans. Inflammation is a rapid, non-specific defence response of the body that acts to maintain homeostasis by monitoring and clearing foreign bodies. [5] Inflammation is an important mechanism in the development and progression of cardiovascular diseases such as hypertension. [6] Inflammatory processes induce changes in cardiac function, peripheral vascular resistance, and renal control mechanisms of plasma electrolytes and volume. [7] Furthermore, renal and vascular inflammation is reported to increase oxidative stress and endothelial dysfunction leading to increased peripheral resistance and consequently, hypertension. [8] Systemic inflammation has been associated with increased arterial stiffness and renin–angiotensin–aldosterone system (RAAS) activity, atheroma formation, oxidative stress, and endothelial activation and dysfunction. [9]

Circulating inflammatory markers are elevated in hypertensive patients and their levels may predict the onset of the disease. [10] Plasma levels of these makers, include C-Reactive Protein (CRP), cytokines such as Tumour Necrosis Factor-alpha (TNFα) and interleukin – 6 (IL-6), chemokines such as monocyte chemoatractant protein – 1(MCP-1) and adhesion molecules such as P-selectin, serum intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are all elevated in the sera of subjects with essential hypertension. [11] Of these biomarkers, hs-CRP has been identified as one of the most important inflammatory markers in clinical and human studies. It is an acute-phase protein synthesized by the liver in response to inflammatory cytokines, in particular, interleukin-6. [12] Several properties of this molecule recommend it as a reliable marker of inflammation. It is neither related to fasting nor diurnal variation. It is stable with a half-life of 19 hours and has assay characteristics conducive to routine clinical use. Its serum levels are independent of age or ethnicity. [12] Although, CRP is a traditional marker of inflammation, it is expensive and requires a considerable material and personnel cost to perform routinely.

Neutrophil-to-Lymphocyte Ratio (NLR) on the other hand, is simpler and easier to obtain. It is derived from the full blood count values as the ratio of absolute neutrophil count to absolute lymphocyte count. This parameter is increasingly being utilized as an index of systemic inflammation in a plethora of clinical conditions such as sickle cell disease, [13] pre-eclampsia, [14] Diabetes mellitus, [15] cancers, [16] and in anaemia [17] among pregnant women. Clinical research confirmed the sensitivity of NLR in the diagnosis and stratification of systemic infections, sepsis, and bacteraemia as well as its robust predictive and prognostic values. [18] Several authors have suggested that the leukocyte ratios may predict how subjects respond to inflammatory injury, since neutrophils increase as a result of stress while lymphocyte population decrease by apoptosis. [13] Therefore, the NLR may be used to identify those subjects who do not have the physiological reserve to resist inflammatory events. [13] Since the leukocyte ratios have been associated with inflammation in several other disease conditions, [13 - 16] leukocyte ratios may be correlated with traditional markers of inflammation among hypertensive subjects. This is important to enable healthcare providers to identify routinely assayed blood cell parameters that may be used as surrogate

markers of inflammation in resource-limited settings like Nigeria. This study was conducted to determine the association between hs-CRP and NLR among subjects with essential hypertension.

Methods

This study was conducted at Immanuel General Hospital, Eket, Nigeria. It was a case-controlled, cross-sectional study where blood samples were drawn for laboratory investigations and blood pressure measurements and other anthropometric data were taken from participants. The participants included individuals diagnosed with essential hypertension attending the Immanuel General Hospital, Eket. The necessary blood samples were drawn from these participants in Eket but laboratory analysis was performed at the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria. Age-matched, normotensive individuals were recruited from health care workers, blood donors, and students as control subjects.

A total of 240 hypertensive subjects of both sexes were recruited as the cases while 120 age-matched normotensive individuals were enrolled as control subjects. Hypertension was classified as mild if the systolic blood pressure ranged between 140-159 mmHg and diastolic 90 - 99 mmHg, moderate if the systolic blood pressure ranged from 160 – 179 mmHg and diastolic 100-109 mmHg, and severe, if the systolic blood pressure was ≥ 180 mm Hg and diastolic blood pressure greater than 110 mm Hg. [19]

Inclusion and Exclusion Criteria

Adults of both sexes with a systolic blood pressure of 140mm/Hg and above and diastolic blood pressure of 90mm/Hg and above and who were clinically diagnosed as hypertensive were recruited as cases. Age-matched individuals with systolic and diastolic blood pressure less than 140mm/Hg and 90mm/Hg respectively were included as control subjects.

Individuals who are known smokers, diabetics, and pregnant, as well as those with chronic infections such as hepatitis, nephritis, tuberculosis, HIV/AIDS, sexually transmitted diseases, and cancers were excluded from the study.

Blood sample Collection

Exactly 5mL of venous blood was aseptically drawn from each subject without stasis. Two millilitres of blood were dispensed into a labelled sample bottle containing 0.02mL of 10% Ethylene diamine-tetra-acetic acid (EDTA) while the remaining 3mL was dispensed into a plain sample bottle and allowed to clot at room temperature. The latter was centrifuged at 3000rpm for 10mins and the serum separated into another clean labelled tube. The serum was kept frozen at -20^{o}C until analyses were done while anticoagulated samples were stored at 2-6^{o}C till tests were performed within 6-8 hours.

Laboratory analysis

Full blood count was performed using the automated SYSMEX haematological auto analyser KX 2, Kobe, Japan. Highly-Sensitive C-Reactive Protein (hr-CRP) was measured by sandwich ELISA technique using kits obtained from CALBIOTECH, California, USA. The neutrophil–to–lymphocyte ratio was derived by dividing the absolute neutrophil count by the absolute lymphocyte count, obtained from full blood counts.

Statistical analysis

The data were analysed using a statistical software package (SPSS version 21, IBM, IL, USA). Variables were summarized as mean with standard deviation. One-way analysis of variance (ANOVA) was used to compare multiple mean values (between mild, moderate, and severe hypertension) while Student's t-test was used to compare two mean values between hypertensive subjects and normotensive subjects. Correlation analysis was also performed using the Pearson correlation coefficient and receiver operating

characteristics (ROC) to test the relationship between NLR and measured inflammatory markers. *P* values less than 0.05 defined statistical significance.

Ethical consideration

Ethical approval for this study was obtained from the Health Research Ethics Committee of Akwa Ibom State Ministry of Health via letter with ref. MH/PRS/99/V.IV/19 dated 30th July, 2017. All participants gave informed consent before blood samples were drawn from them. Confidentiality of data was also maintained.

Results

Table I shows the anthropometric characteristics of the study population. The mean BMI (p = 0.03) systolic blood pressure (p = 0.001) and diastolic blood pressure (p = 0.001) of hypertensive subjects were significantly higher than those of the normotensive subjects.

Table I: Mean anthropometric parameters of the study participants

Variables	*Hypertensive Mean ± SD (n = 240)*	*Normotensive Mean ± SD (n = 120)*	*p-value*
Age (Years)	51.05±11.9	49.0±13.7	0.22
Weight (kg)	67.6±15.4	66.03±11.9	0.38
Height (m)	1.57±0.12	1.56±0.14	0.87
BMI (kg/m^2)	27.8±0.0	25.56±4.4	0.03
SBP (mmHg)	166.4±26.3	119.17±5.8	0.001
DBP (mmHg)	102.4±13.3	78.0±8.3	0.001

BMI - Body Mass Index; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure.

Table II shows that the hypertensive subjects had significantly higher mean TWBC count (p = 0.03), absolute lymphocyte count (p = 0.02), absolute neutrophil count (p =0.03), absolute lymphocyte count (p = 0.02), hs-CRP (P = 0.01) and NLR (P=0.01) than normotensive subjects.

Table II: Comparison of the mean values of haematological parameters of hypertensive and normotensive subjects

Variables	*Hypertensive Mean ± SD (n = 240)*	*Normotensive Mean ± SD (n = 120)*	*p-value*
Hb (g/dL)	14.6 ±1.2	13.9 ±1.1	0.06
PCV (l/L)	44 ± 2.4	42.0 ± 1.8	0.07
TWBC (10^9/L)	8.46 ± 1.6	6.13 ±1.4	0.03
Neutrophil (10^9/L)	7.97 ± 1,3	4.03 ± 1.5	0.03
Platelets (10^9/l)	235.5 ± 24.4	130.6 ± 28.3	0.02
Lymphocytes (10^9/L)	3.40 ±1.4	2.58 ±1.0	0.02
Monocytes (10^9/L)	1.94 ± 0.5	0.92 ± 0.3	0.04
NLR	2.34 ± 0.3	1.76 ± 0.2	0.01
Hs CRP (mg/dL)	6.84±2.0	5.39 ±1.8	0.01

CRP - C - Reactive Protein, Hb - Haemoglobin concentration, NLR – Neutrophil-to-Lymphocyte Ratio, PCV - Packed Cell Volume, TWBC - Total White Blood Cell count.

In Table III, the hypertensive subjects had progressively significantly higher mean values of CRP (p = 0.01) across levels of severity of hypertension: mild, moderate, and severe hypertension. Similarly, the mean levels of NLR (p = 0.01) progressively increased with statistical significance across mild, moderate, and severe hypertension among hypertensive subjects. Figure 1 shows a significant but positive correlation between hs–CRP and NLR (r = 0.248, p <0.001). Figure 2 shows that the ability of NLR and CRP to define inflammation in hypertensive subjects was 0.64 and 0.64 respectively.

Table III: Comparison of levels of inflammatory markers in subjects with mild, moderate and severe hypertension

Parameters	*Mild Hypertension Mean±SD n = 93*	*Moderate Hypertension Mean±SD n = 87*	*Severe Hypertension Mean±SD n = 60*	*F-Value*	*p-value*
Hs-CRP (mg/dL)	6.65±2.8	6.98±2.78	8.52±3.09	3.8	0.01
NLR	2.25±0.05	2.30±0.6	2.89±0.4	3.2	0.01

Hs-CRP - Highly-Sensitive C - Reactive Protein; NLR - Neutrophil to Lymphocyte Ratio.

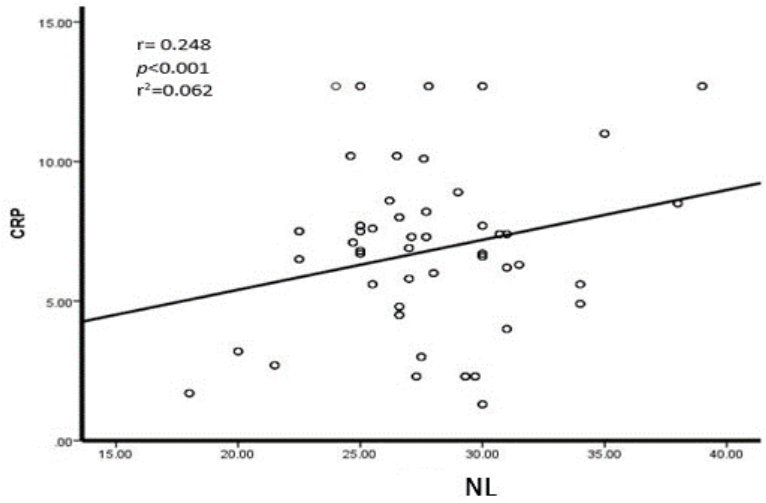

Figure 1:Correlation Graph Showing the relationship between hs-CRP and NLR among hypertensive subjects.

Discussion

The pathogenesis of hypertension is complex and multifactorial and there are many risk factors associated with the condition. Activated inflammatory response is one of the major pathologic mechanisms underlying the initiation and sustenance of hypertension in both animals and humans. [18] However, the causal link between the two conditions remains unclear. Nevertheless, chronic inflammation is known to activate the immune system leading to the release of various compounds such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17) produced by activated T lymphocytes. These changes contribute to hypertension by inducing oxidative stress due to nitric oxide depletion, endothelial injury and dysfunction. [15] This leads to the narrowing of the blood vessels and an increase in vascular peripheral resistance and hypertension. [20]

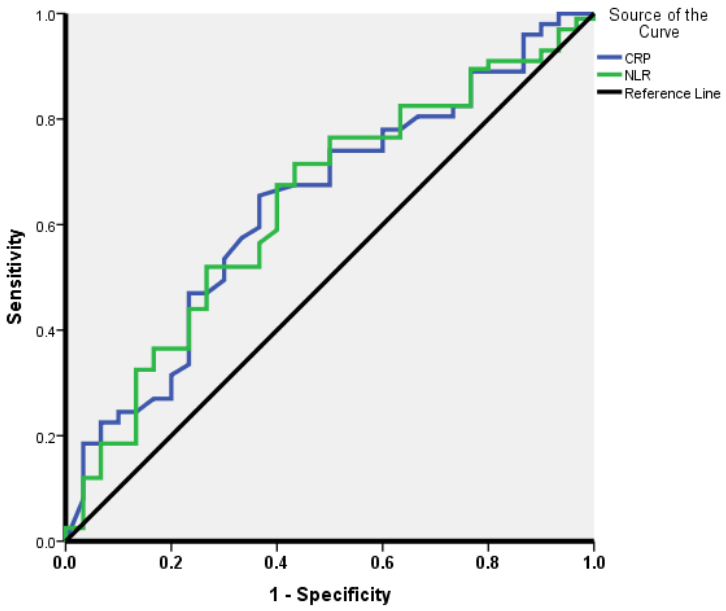

Figure 2: The Receiver Operating Characteristic curve showing the relationship between hs-CRP and NLR among the hypertensive subjects (AUC = 0.640; AUC = 0.639).

Chronic inflammation also causes vascular damage, increased vascular stiffness, and loss of vascular elasticity. This results in increased vascular resistance and the elaboration of inflammatory molecules including the acute phase reactant, C-Reactive Protein, p- p-selectin, and cell adhesion molecules in the sera of hypertensive subjects. [7, 21] Highly-Sensitive C-Reactive Protein (hs-CRP) remains one of the most studied inflammatory markers in many aspects of cardiovascular diseases. It was earlier reported to be increased in the sera of patients suffering from a spectrum of inflammatory stimuli. [22] hs-CRP is one of the most widely known biomarkers of inflammation in cardiovascular diseases. [23] Elevated hs-CRP has been associated with many non-communicable diseases such as coronary heart disease (CHD), ischaemic stroke, insulin resistance, hypertension, metabolic syndrome, and peripheral artery disease. [12]

Neutrophil-to-Lymphocyte Ratio (NLR) has also emerged as another cost-effective and reliable inflammatory marker in several diseases. NLR reflects the dynamic relationship between innate (neutrophils) and adaptive cellular immune response (lymphocytes) during illnesses and various pathological states. [24] It is widely used across almost all medical disciplines as a reliable and easily available marker of immune response to various infectious and non-infectious stimuli. [18] Moreover, NLR was recently considered as part of the decision-making processes concerning the admission/recovery of patients with COVID-19 pneumonia, [25] and as a marker of COVID-19 in Saudi Arabia. [26] The normal range of NLR is between 1 and 3. Values higher than 3.0 and below 0.7 in adults are generally considered pathologic and may serve as an early warning of pathological states such as cancer, atherosclerosis, infection, inflammation, psychiatric disorders, and stress. [27]

NLR is a marker of inflammation in anaemia in pregnancy, [13] diabetes mellitus, [15] sickle cell disease, [16] cancers, [28] inflammatory bowel disease, [29] and following highly active antiretroviral therapy (HAART) in HIV. [30] The NLR is reported to be a more specific marker of inflammation in hypertension than absolute neutrophil or absolute lymphocyte counts. [31]

In this study, significantly higher levels of hs-CRP and NLR were recorded among hypertensive subjects compared with the control subjects. The mean values of hs-CRP correlated with NLR among hypertensive subjects. These observations are consistent with findings in a previous study. [20] The authors in that study reported that elevated levels of NLR was associated with worse clinical outcomes in various cardiovascular diseases such as hypertension. Generally, a positive correlation between increasing concentrations of C-Reactive Protein and the risk of developing hypertension was reported. The relative risk (RR) of developing hypertension increased with increasing concentrations of C-Reactive Protein in excess of 3.5 mg/L and RR of 2.50 (95% CI, 2.27-2.75). The finding of the association between hs-CRP and NLR levels with hypertensive disease severity also aligned with findings in some previous studies. [32, 33]

The mean hs-CRP level in normotensive subjects in this study was higher than the normal value according to the American Heart Association and the US Centres for Disease Control and Prevention risk group definition. [34] We propose three possible explanations for this finding. Firstly, this might suggest the presence of underlying factors such as environmental stressors, and mild bacterial or viral infections that may lead to vascular abnormalities and hence, raised hs-CRP levels in these subjects. Secondly, it could indicate that the subjects are at higher risk of developing hypertension in the near future. This is because hs-CRP level had earlier been shown to be an independent predictor of hypertension in normotensive subjects. [32, 35] Thirdly it might also indicate that their parents may have been hypertensive since serum hs-CRP levels were reportedly higher in normotensive offspring of parents with hypertension compared with offspring of parents without parental hypertension. [36]

In the present study, we noted an increase in both the mean levels of hs-CRP and NLR with increasing severity of hypertension. This pattern may be attributed to the likelihood of increasing severity of hypertension being associated with increasing shear stress and vascular damage. These changes are known to lead to increased elaboration of inflammatory cytokines resulting in an elevated level of hs–CRP. On the relationship between hs-CRP and NLR, it was noted that hs-CRP correlated positively with NLR among hypertensive subjects. This finding also aligned with previous studies among patients with cardiovascular diseases. [37] This result is significant because systolic blood pressure is known to have a greater influence on hypertension-related vascular endothelial damage than diastolic blood pressure. [38]

In a study that evaluated the role of NLR in the prediction of heart failure, it was reported that NLR correlated positively with heart failure and was also an independent predictor of mortality from heart failure. [39] Heart failure is intimately connected with diastolic blood pressure than systolic blood pressure. Consequently, the finding of increased NLR levels among hypertensive subjects in the present study might indicate that these subjects could be at risk of hypertensive heart failure.

The abilities of the AUC of hs-CRP and NLR to define hypertension were 0.64 and 0.637 respectively using the ROC curve. A value of 0.5 suggests no discrimination while the range of 0.7 to 0.89 is considered excellent and more than 0.9 is considered outstanding. [40] In the present study, we noted the close association between NLR and hs-CRP both by correlation analysis and by the areas under the curve of the ROC. This suggests that NLR may be used in place of hs-CRP in the evaluation of inflammation in hypertension. Although hs-CRP is a traditional marker of inflammation, it is expensive and requires the relevant expertise. Therefore, it is not readily available in most health facilities in resource-limited

settings. On the other hand, NLR is readily available and easily derived from the components of a full blood count and at no extra cost to the patient.

Limitation

A major limitation of this study is its hospital-based scope and cross-sectional design, rather than a population-based longitudinal study which might further examine the utility of NLR as a surrogate marker to hs-CRP in the evaluation of inflammation in hypertension in Nigeria.

Conclusion

This study indicates that hs-CRP is closely associated with NLR in all classes of hypertension among hypertensive subjects. Both parameters also increased with disease severity in all the studied classes of hypertension. NLR can, therefore, be employed as a surrogate marker to hs-CRP in the assessment of inflammation in hypertension in resource-limited settings where hs-CRP estimation may not be feasible.

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Authors' Contributions: USS and EMA conceptualized and designed the study and did literature review. All the authors performed data analysis and interpretation. USS, EJE and IAE drafted the manuscript. USS and EMA revised the draft manuscript for sound intellectual content. All authors have read and approved the final version of the manuscript.

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