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Research Article

Serum High Sensitivity C-Reactive Protein and Uric Acid as Biomarkers of Left Ventricular Hypertrophy in Hypertensive Patients in Makurdi, Nigeria

Mba I.N.[1], Basil B.[2], Myke-Mbata B.[2], Olayanju O.A.[3], Okpara I.C.[4], Adebisi S.A.[2]

[1]*Department of Chemical Pathology, Nile University of Nigeria, Abuja, Nigeria,*
[2]*Department of Chemical Pathology, Benue State University, Markurdi, Nigeria,*
[3]*Department of Chemical Pathology Babcock University Teaching Hospital, Ilisan, Nigeria,*
[4]*Department of Internal Medicine, Benue State University Teaching Hospital, Markudi, Nigeria.*

ABSTRACT

Hypertension is a major cause of mortality worldwide and a major global health challenge. Hypertensive heart diseases including left ventricular hypertrophy are chronic complications of hypertension and are associated with worsening prognosis and progression to poor outcomes in affected patients. It is imperative that left ventricular hypertrophy is detected early to forestall these untoward outcomes. Current diagnostic tools available often detect structural and functional defects, however markers like hsCRP and uric acid are expressed much earlier before structural defects begin and may help to delay and possibly prevent hypertensive heart diseases when detected early. A total of 211 hypertensive patients with and those without left ventricular hypertrophy were recruited, hsCRP and uric acid were measured and compared between the two groups. Both markers were significantly elevated in hypertensive patients with left ventricular hypertrophy compared to those without left ventricular hypertrophy. hsCRP and uric acid also showed high sensitivity (76.1% vs 77.9%) and diagnostic efficiency (70.1% vs 71.1%) when used individually and when both are combined (77.6% and 74.4%), in detecting left ventricular hypertrophy in hypertensive patients. Thus, these markers may be employed in monitoring hypertensive patients to improve their quality of life and treatment outcomes.

Keywords: *Uric acid, hsCRP, Left ventricular hypertrophy, hypertension*

**Author for correspondence: Email: simeonadebisi2003@yahoo.com; Tel: +234- 8033563489*

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INTRODUCTION

Hypertension contributes approximately 13% to the total mortality worldwide; it is a major risk factor for hypertensive heart diseases (HHD) and premature death and is of tremendous burden for both patients and the health-care system. (WHO global status report on noncommunicable diseases 2014. Geneva Switzerland. World health Organization, Aje *et al*., 2009) Left ventricular hypertrophy (LVH) is one of the prominent manifestations of HHD and can lead to death if not detected early and treated appropriately. (Drazner M H, 2011) However, detection rate, treatment success and control of HHD are very poor in Nigeria despite the prevalence of HHD ranging from 18 to 46% in the population, making it the most common long term sequalae of hypertension in the country. (Aje *et al*., 2009, Ogah *et al*., 2012)

Of all the HHD, LVH is arguably the most potent predictor of poor cardiovascular outcome in the hypertensive patients and an independent risk factor of the commonly reported cardiovascular diseases.(Gradman and Alfayoumi, 2006) The gravity of the morbidity rate associated with LVH is worsened by its high prevalence amongst hypertensive patients, thus, early identification is critical.(Rayner and Becker, 2006, Vidt and Prisant, 2005) Currently, physical examination of the cardiovascular system, the use of radiological tests like x-rays and electrocardiography forms the basis for diagnosing HHD. Other ancillary test methods include magnetic resonance imaging, thallium imaging, coronary angiography, and ultra-fast computed tomography scanner. (Aje *et al*., 2009) These diagnostic approaches are based on changes in organ's structure and functional impairments which occur following a much earlier expression of biochemical markers in disease settings. (Silbergeld and Davis, 1994, Zhong *et al*., 2013) Thus, assessment of biochemical markers with known associations with LVH, may provide very informative guide to detecting its onset long before overt structural and functional changes appear amongst

hypertensive patients. This is expected to provide opportunities to delay the onset of and possibly prevent the development of HHD in hypertensive patients.

Several biomarkers have been identified for detecting individuals at high risk for cardiovascular diseases; high sensitivity C-reactive protein (hsCRP) and uric acid are among some of the most promising. (Tsounis *et al*., 2014, Wang *et al*., 2007, Seo *et al*., 2013) hsCRP has continually been used as a routine component of cardiovascular risk assessment to prevent clinical events and has been approved by the Center for Disease Control (CDC) and Prevention and the American Heart Association (AHA).(Xanthakis *et al*., 2013) In a study done in Nigeria, plasma concentration of hsCRP was found to be significantly higher in hypertensive subjects compared to those of the normotensive subjects, though LVH was not factored into the analysis.(Idemudia and Idogun, 2012) Another study which found similar trend also reported that higher levels of hsCRP portends increased severity of heart failure and are independently associated with undesirable outcomes. (Anand *et al*., 2005)

Similarly, hyperuricaemia which is one of the most reproducible markers for predicting hypertension, was reported to be associated with a two-fold increased risk for developing HHD. (Kanbay *et al*., 2013, Ekundayo *et al*., 2010) In a prospective study done in Japan, hypertensive patients with higher baseline values of Uric acid had a significantly higher frequency of cerebrovascular disease and mortality over a mean follow-up period of seven years.(Kawai *et al*., 2012) A similar study done on hypertensive patients in Nigeria reported that HHD was present more in patients with hyperuricaemia compared to those whose Uric acid levels were within reference interval.(Adewuya *et al*., 2020) However, these biomarkers have not been interrogated with respect to LVH in hypertensive patients, thus, this study was designed to determine the individual and collective utility of serum hsCRP and uric acid as biomarkers for left ventricular hypertrophy in hypertensive patients.

MATERIALS AND METHODS

Participants: This was a hospital based cross-sectional study on hypertensive patients attending cardiology clinics at the Benue State University Teaching Hospital, Makurdi and Federal Medical Centre Makurdi, Benue State, Nigeria. A structured research proforma was used to obtain biodemographic information from the patients after a written informed consent. Age specification for recruitment was 20 to 70 years and there was no gender restriction. Patients with diabetes mellitus, renal dysfunction, malignancies, and arthritis were exempted from the study. Other exclusion criteria included alcoholism, gout, pregnancy, obesity, steroid use and major surgery in the last six months. Ethical clearance for the study was obtained from the ethical committee of Benue State University Teaching Hospital Makurdi, Benue State.

LVH Diagnosis: Standard M-mode and 2-dimensional echocardiography (Siemens-SC2000; Munich, Germany) which was equipped with a 3.5-MHz transducer was conducted on all patients. The Left ventricular measurements were done according to the provisions of the American Society of Echocardiography.(Devereux and Reichek, 1977) Left Ventricular Mass (LVM) was calculated according to the formula of Devereux and Reichek.(Devereux and Reichek, 1977) LVM was indexed to the body surface area and presented as LVM Index (LVMI). The criteria for LVH diagnosis was defined as LVMI > 115 g/m^2 in men and LVMI > 95 g/m^2 in women. (Devereux, 1987) Following this, the patients were categorized into two; those with and those without LVH.

Sample processing and laboratory analysis: Venous blood sample, through a single venipuncture, was collected using a plain vacutainer from every patient after an overnight fast. Samples were left for about one hour to clot before being centrifuged at 3000rpm for 10 minutes within 60 minutes of the blood draw, the serum obtained was stored frozen at -85^{o}C until assayed. Serum hsCRP was measured using a quantitative sandwich enzyme-linked immunoassay (ELISA) technique, kit was acquired from the hsCRP AccuBind® ELISA test system supplied by Monobind Inc (Batch no: EIA-31K1D9; April 2019). Manufacturer's supplied analytical sensitivity was 0.014ug/ml. Serum uric acid was determined using the uricase method as described by Fossati *et al*. (Fossati *et al*., 1980) Reagents used were procured from the Agappe Diagnostic Limited (Kit Batch no: 37120157; Year of manufacture of kit: November 2018).

Statistical Analysis:
Numerical data were reported as number (%) and mean ± standard deviation. Comparisons of variables between patients with LVH and patients without were done using student independent t-test. Diagnostic performance for identifying LVH by hsCRP alone, uric acid alone and combination of hsCRP and uric acid was determined by computing sensitivity, specificity, positive predictive value, negative predictive value, diagnostic efficiency and the receivers operating characteristic curve. P-values <0.05 were considered statistically significant. Data analysis was done with the Statistical Package for Social Sciences (SPSS) version 20 (IBM Corporation, Armonk, NY, USA)..

RESULTS

A total of 211 patients were recruited for this study, while 107 of them had LVH following echocardiography, the remaining 104 did not have LVH at the time of evaluation. The mean age of patients with LVH was 54 ± 11.5 years which was significantly higher than the mean age of patients without LVH which was 46 ± 13.8; p value was 0.036. There was no difference in the gender distribution of the two groups; there were 56 (52.3%) males in the group with LVH and 56 (53.9%) males also in the group without LVH; p value was 0.539.

Table 1 shows the comparison of the biomarkers hsCRP and uric acid between patients with LVH and those without LVH. Both biomarkers are significantly higher in patients with LVH. It also shows there was no difference in the values of the biomarkers across gender distribution.

Table 1:
Comparison of hsCRP and uric acid between hypertensive patients with and without left ventricular hypertrophy and across gender distribution

	Left Ventricular Hypertrophy			Gender		
	LVH absent	LVH present	p-value	Male	Female	p-value
Mean hsCRP (µg/ml)	3.51 ± 1.01	6.62 ± 2.38	0.029*	4.27 ± 1.04	5.98 ± 1.38	0.097
Mean uric acid (mmol/l)	0.39 ± 0.14	0.54 ± 0.26	0.004*	0.46 ± 0.18	0.47 ± 0.17	0.134

*NB: Values are reported in mean ± standard deviation, *p values below 0.05 are statistically significant*

Table 2:
Diagnostic performances of hsCRP, Uric acid individually and in combination for LVH

	hsCRP	Uric acid	HsCRP and Uric acid
Specificity	65.9%	66.4%	71.2%
Sensitivity	76.1%	77.9%	77.6
Negative predictive value	79.5%	81.4%	75.5%
Positive predictive value	61.5%	61.4%	73.5%
Diagnostic efficiency	70.1%	71.1%	74.4%
Area under ROC curve;	0.631;	0.712;	0.760;
p-value	0.031*	<0.001*	0.002*

ROC- receiver operating characteristics,
**p value below 0.005 are statistically significant*

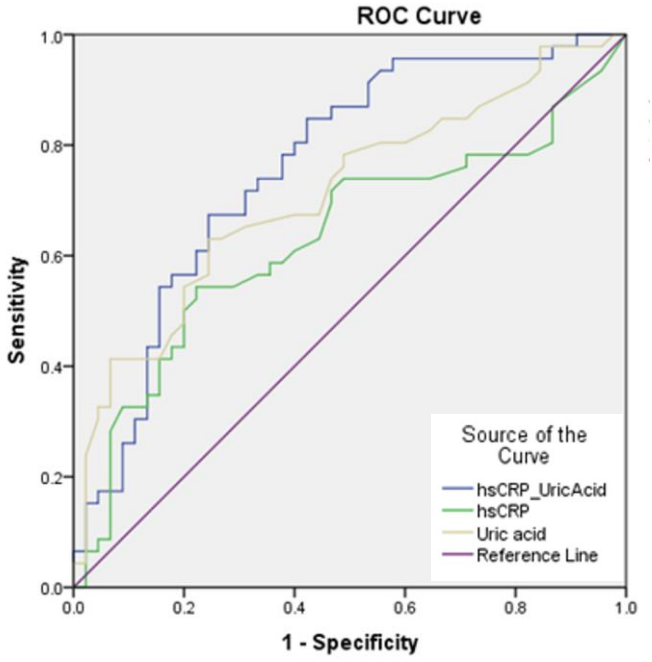

Figure 1:
Receiver operating characteristics curve of hsCRP alone, Uric acid alone and combination of both

The diagnostic performance analysis showed hsCRP having a sensitivity of 76.1% and a specificity of 65.9%, while uric acid had a sensitivity of 77.9% and a specificity of 66.4%. Combination of both hsCRP and uric acid had a sensitivity of 77.6% and a specificity of 71.2%. Other performance characteristics are shown in Table 2 and Figure 1.

DISCUSSION

Current modalities of diagnosing hypertensive heart diseases detect structural and functional abnormalities, some of them at advanced stages where accompanying morbidity may have already interfered with quality of life.(Ha *et al*., 2014, Trevisol *et al*., 2011) This study evaluated biochemical markers hsCRP and uric acid, which are expressed much earlier before structural and functional damages, in hypertensive patients. This study essentially showed that hypertensive patients with LVH are significantly older than those without LVH; patients with LVH had significantly higher levels of hsCRP and uric acid compared to patients without LVH; and that although diagnostic performance of each of the biomarkers are impressive, a combination of both biomarkers produced a higher performance than when either of them is used alone.

The preponderance of LVH in older age group, as found in this study may not be unconnected with the progressive remodeling of the myocardium in hypertensive patients as reported in previous studies.(González *et al*., 2018, Lakatta and Levy, 2003) sectional increases and altered physical properties of the myocardial collagen is contributory to the sharp increases in LVH seen with increasing age.(Lakatta and Levy, 2003) Thus, aging is accompanied by several changes in the cardiovascular system including conduction disorders, cardiac arrhythmias, left ventricular hypertrophy, and other forms of hypertensive heart disease.(Chow *et al*., 2012) Oxidative stress and inflammation are two major mechanisms which have been shown to play central roles in age-related LVH.(Wu *et al*., 2014) A dysfunctional regulatory feedback network in response to oxidative stress may initiate an exaggerated proliferations of mitochondrial reactive oxygen species (ROS) thus leading to aging and aging-related heart remodeling.(Wang *et al*., 2013)

The concentration of hsCRP was significantly higher in hypertensive patients with LVH than in those without LVH. This finding essentially re-emphasises role of inflammation in the development of LVH, although the underlying mechanism behind this is not clear. It has been shown that hsCRP could produce myocardial effects that eventually cause intimal hypertrophy of the left ventricle.(Wang *et al*., 2003) Furthermore, systemic inflammation may contribute to LVH development in hypertensive patients by altering the architecture of the cardiac vascular smooth muscle cells leading to increased loss of vascular elasticity.(Mahmud and

Feely, 2005) The significance of elevated hsCRP, as reported in studies done in Turkey and Sweden, is in the augmentation of other inflammatory proteins which may worsen hypertension and its complications. (Seyfeli *et al*., 2016, Masiha *et al*., 2013) Local studies have highlighted similar finding making hsCRP a cardinal marker in the management of hypertensive heart diseases. (Idemudia and Idogun, 2012, Akinlade *et al*., 2020)

Hypertensive patients with LVH also had higher values of uric acid than those without LVH in this study. Uric acid has been reported to be involved in mediating cardiac remodeling through the induction of hyperplasia and hypertrophy of cardiac myocytes and vascular smooth muscle cells via angiotensin II and the up-regulation of collagen synthesis in the heart. (Yokoyama *et al*., 1997) Also, by activating the renin–angiotensin–aldosterone system, both at the local and systemic levels, promotes interstitial fibrosis and cardiomyocyte hyperplasia, which are the pathologic hallmarks of LVH.(Watanabe *et al*., 2002) Consequently, repetitive measurement of uric acid has been recommended in all hypertensive patients by a study that found a similar trend as this study. (Adewuya *et al*., 2020)

Both hsCRP and uric acid demonstrated impressive diagnostic performance for LVH in hypertensive patients in this study. At a sensitivity level of 76.1% and 77.9% respectively, both may be deployed as viable tools for monitoring hypertensive patients, especially for early detection of LVH thus necessitating appropriate action to forestall disease progression. Negative predictive value of at least 80% for either biomarker may also be a strong indication for use as screening tool for hypertensive patients. Combining both markers showed a significantly higher area under the curve than either of the biomarkers when used alone, thus providing a stronger diagnostic performance for LVH. These findings are corroborated by similar studies done in Japan and Italy with even stronger diagnosic performance for uric acid (Mitsuhashi H. *et al*., 2009, Cuspidi C. *et al*., 2017), they suggested that treatment of hyperuricaemia can prevent the development of LVH or improve the outcomes in hypertensive patients.

In conclusion, this study showed that hypertensive patients with LVH had higher levels of hsCRP and uric acid than those with absence of LVH, furthermore, combination of both biomarkers may serve as a better modality for screening for LVH in hypertensive patients. It is recommended that more studies regarding the utility of hsCRP and uric acid be done in hypertensive patients with LVH and other HHD be done on a larger population, this is expected to improve early detection especially in locations where there are no facilities for echocardiography. More so, these biomarkers are more readily available and cheaper than the routine echocardiography

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