Predictive value of spot urine albumin-to-creatinine ratio for echocardiography-based left ventricular hypertrophy among newly diagnosed hypertensive patients

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Original Article

ABSTRACT

Objective: Studies have reported high prevalence of left ventricular hypertrophy (LVH) among patients with microalbuminuria. Both left ventricular hypertrophy and microalbuminuria (MA) are associated with increased risk of cardiovascular morbidity and mortality. The study aimed to determine the predictive value of spot urine albumin-to-creatinine ratio (ACR) for echocardiography-based LVH in newly diagnosed hypertensive patients.

Methods: LVH was defined as left ventricular mass index (LVMI) of >115g/m^2 in males and >95g/m^2 in females. Microalbuminuria was defined as ACR >30 mg/g and diagnostic value of MA for LVH assessed using X^2 2by2 table and the Receiver Operating Characteristics (ROC) curve plot.

Results: Sixty six (48.5%) males and 70(51.5%) females with a mean age of 44.8(10.5 %) years were studied. Left ventricular hypertrophy was observed in 36.8% while 42.7% had MA. The prevalence of MA in those with LVH was 66%. Microalbuminuria showed a sensitivity of 64% and specificity of 70% for echocardiography (echo) detected LVH, while the positive predictive value (PPV) and negative predictive value (NPV) were 55% and 77% respectively. Diagnostic accuracy of MA for echo LVH was 68% with an odd ratio of 4.1. ROC curve plot revealed an area under the curve of 0.73 at ACR of 36mg/g, improving the sensitivity and NPV to 85.7% and 83.8% respectively.

Conclusion: Microalbuminuria predicts LVH in treatment naïve Nigerian hypertensive patients. This can be used as a surrogate for LVH in outpatient settings, providing vital information for comprehensive management of patients.

Keywords: Hypertension, microalbuminuria, albumin-to-creatinine ratio, left ventricular hypertrophy

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Valeur prédictive de spot urine albumine-de-rapport créatinine pour échocardiographie basée hypertrophie ventriculaire gauche entre nouvellement diagnostiqués chez les patients hypertendus.

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Article Original

RÉSUMÉ

Objectifs: Des études ont signalé une forte prévalence de l'hypertrophie ventriculaire gauche (HVG) chez les patients ayant une microalbuminurie. Les deux hypertrophie ventriculaire gauche et une microalbuminurie (MA) sont associées à un risque accru de mortalité et la morbidité d'origine cardiovasculaire. Pour déterminer la valeur prédictive des spots urines albumine-de-rapport créatinine (ACR) pour échocardiographie-basée à HVG nouvellement diagnostiqués chez les patients hypertendus.

Méthodes: HVG était défini comme masse ventriculaire gauche indice (LVMI) de >115g/m chez les hommes et > 95 g/m chez les femmes. Microalbuminurie était définie comme ACR >30 mg/g et la valeur de diagnostic de la MA de HVG aévalué en utilisant *X*2 2by2 le tableau et le récepteur caractéristiques d'exploitation(courbe ROC) tracé.

Résultats: Soixante-six (48,5 %) hommes et 70 (51,5 %) étaient des filles avec une moyenne d'âge de 44,8 (10,5) ans ont été étudiés. Hypertrophie ventriculaire gauche a été observée à 36,8 % tandis que 42,7 % avaient MA. La prévalence de la MA dans ceux avec HVG était de 66 %. Microalbuminurie a montré une sensibilité de 64 % et la spécificité de 70% pour l'écho détecté HVG, tandis que la valeur predictive positive (VPP) et valeur prédictive négative (NPV) étaient de 55% et 77% respectivement. Précision du diagnostic de MA pour echo HVG était de 68 % avec une étrange ratio de 4,1. Courbe ROC tracé a révélé une aire sous la courbe de 0,73 à ACR de 36mg/g, l'amélioration de la sensibilité et la valeur predictive négative de 85,7 % et 83,8 % respectivement.

Conclusion: Microalbuminurie prédit HVG en traitement nigérian naïfs patients hypertendus. Ceci peut être utilisé comme un substitut des HVG dans les consultations ambulatoires, fournissant des informations vitales pour la gestion globale des patients.

Mots clés: hypertension artérielle, une microalbuminurie, albumine-rapport créatinine, hypertrophie ventriculaire gauche.

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INTRODUCTION

Hypertension remains a leading cause of cardiovascular morbidity and mortality through its impact on the heart, kidney, vasculature and the brain (1). Indicators of hypertension-related end-organ damage include left ventricular hypertrophy (LVH), increased intima-media thickness and increased urinary albumin excretion (2). Microalbuminuria (MA) is an early clinical expression of hypertensive nephropathy and an important prognosticator of cardiovascular and renal diseases (3).

Studies have reported a high prevalence of LVH using echocardiography (echo) amongst hypertensive individuals with MA, indicating that the two develop in parallel (3). Both LVH and MA are associated with increased risk of all-cause mortality, cardiovascular disease (CVD) morbidity and mortality, and deterioration of renal function in patients with diabetes and hypertension (4). In line with the concept of total cardiovascular risk assessment in individuals with hypertension, guidelines on evaluation and management of hypertension recommend routine screening for MA in all subjects with hypertension, the metabolic syndrome, and those with high normal blood pressure (5, 6).

We sought to determine the predictive value of MA, defined using spot urine albumin-creatinine-ratio (ACR) for echo-based LVH among newly diagnosed hypertensive patients.

MATERIALS AND METHODS

This was a cross-sectional study in which one hundred and thirty six newly diagnosed hypertensive patients aged 23 to 65 years were consecutively recruited from the cardiology clinic of the University of Maiduguri Teaching Hospital from June 2007 through February 2008. Excluded from the study are those with overt proteinuria (using conventional dipstick urinalysis), haematuria, glycosuria, presence of nitrite on dipstick urinalysis, diabetes mellitus, impaired renal function (defined as a eGFR<90ml/min), valvular heart disease, cardiac failure, pregnancy, athletic/sporting background, use of antihypertensive medication, suboptimal image quality on Echo and refusal of consent .

Relevant clinical history was obtained using a pre-validated questionnaire. Weight was measured with the subjects light-clothed and height without shoes or head gear. Body mass index (BMI) in Kg/m^2 was calculated from weight in kilograms divided by square of the height (in m^2) and body surface area (BSA) was determined using the formula, $BSA = (W^{0.425} x H^{0.725}) \times 0.007184$ (7). Blood pressure was measured using a mercury sphygmomanometer after a five minute rest in the sitting position with the arm and back supported. The cuff was inflated above the systolic blood pressure (SBP) as determined by palpation of the brachial pulse and gradually deflated at the rate of 2mmHg/sec. Systolic blood pressure was recorded as the cuff pressure corresponding with the appearance of the first Korotkoff sound (phase 1), while diastolic blood pressure (DBP) was taken as the cuff pressure corresponding with disappearance of the Korotkoff sound (phase 5). Measurements were repeated twice at five minutes interval and the average recorded as the patients' blood pressure. Hypertension was defined as an average blood pressure of $\geq$140mmHg systolic and/or $\geq$90mmHg diastolic taken on two separate occasions (5, 6).

Transthoracic echocardiography was performed on all subjects by the lead author using Scanner 250 (PIE Medical, Japan). Echocardiographic measurements were carried out using the leading-edge-to-leading edge convention (8). Left ventricular mass (LVM) was determined as $LVM = 0.8 \times \{1.04[(LVID_d + PWT_d + SWT_d)^3 - (LVID_d)^3]\} + 0.6g$ where $LVID_d$ and PWT_d is left ventricular internal dimension and posterior wall thickness in diastole, while SWT_d is septal wall thickness in diastole. Left ventricular mass index (LVMI) was determined as LVM divided by BSA and LVH defined as LVMI >115g/m^2 in males and

$>95 g/m^2$ in females (8).

Spot urine sample was collected from each patient on the day of echocardiography and urine creatinine concentration (µmol/L) determined using the routine Jaffe reaction (9).Urine albumin concentration was determined using mALB antibody reagent and assay buffer by RANDOX (MA-2426, RANDOX laboratories Ltd. United Kingdom). Spot urine albumin-to-creatinine ratio (ACR) in mg/g was obtained by dividing urine albumin concentration in mg/dl by the urine creatinine concentration in g/dl. Microalbuminuria was defined as ACR of 30 to 300 mg/g (10).

Statistical analyses were performed using SPSS (version 14.0 software, Chicago, IL, USA). The ACR was log transformed for the parametric analyses. A Chi-square 2 by 2 contingency table was used in determining sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratios, likelihood ratios and diagnostic accuracy of spot urine ACR for echo-determined LVH. Multiple regression analysis was used in determining the predictors of LVH. A p-value of ≤ 0.05 was considered significant.

Approval for this study was granted by the Research and Ethics Committee of the University of Maiduguri Teaching Hospital (UMTH). All subjects granted an informed consent before enrolment into the study.

RESULTS

The subjects were made of 66 (48.5%) males and 70 (51.5%) females with a mean age of 44.8 (SD 10.5) years. Mean systolic and diastolic blood pressures were 161.4 (SD 18.8) mmHg and 98.1 (10.00) mmHg respectively. The mean LVM was 181.01 (SD 66.09)g, whilst the mean LVMI was 100.47 (SD 33.78) g/m^2. The prevalence of LVH was 36.8%. The overall prevalence of MA was 42.7%, increasing to 66% amongst those with LVH. A strong positive correlation was observed between ACR and both LVM (p=0.001, r=0.773) and LVMI (p=0.001, r=0.414). Multiple regression analysis revealed SBP, pulse rate and ACR to be significant independent predictors of LVH.

Microalbuminuria showed a sensitivity of 64% (95% CI: 0.60 – 0.80) and specificity of 70% (95% CI: 0.66 – 0.88) for echo-detected LVH, while the PPV and NPV were 55% (95% CI: 0.42 – 0.68) and 77% (95% CI: 0.66 – 0.87) respectively. The diagnostic accuracy of MA for echo-detected LVH was 68% (95% CI: 0.61 – 0.76) with an odds ratio of 4.1 (95% CI: 1.07 – 7.13), (Table 1). The discriminating value of ACR for echo detected LVH using the receiver operating characteristic (ROC) curve plot revealed an area under the curve of 0.73 at ACR of 36mg/g, improving the sensitivity and NPV to 85.7% and 83.8% respectively (Fig. 1).

DISCUSSION

We have demonstrated in this study that spot urine ACR predicts echo-based LVH in treatment naïve Nigerian hypertensive subjects. To our knowledge, this is the first study evaluating the diagnostic usefulness of single void, spot urine ACR for echo detected LVH in newly diagnosed Nigerian hypertensive patients.

The prevalence of 36.8% for LVH in our study compares to what was reported in other parts of Nigeria (11, 12, 13). However, higher prevalence was recorded for MA compared to other workers (14). Odili and Okeahialam reported a prevalence of 36% in 200 newly diagnosed hypertensive patients using micral strips, while Salako *e.t al.* found a prevalence of 37% using 24-hour urine collection (13, 15). These differences could be due to variation in methods of detecting MA.

The predictive values of ACR for LVH compares to findings among hypertensive patients reported by other workers. Post *et al* reported a NPV and PPV of 77% and 58% respectively, among young hypertensive African-American men (16). Similarly, the MAGIC study showed a NPV and PPV of 76% and 69% (17). However, comparison with the latter is not feasible,

given the fact they used a cut-off point of 11.5mg/g for defining MA. In addition, studies have indicated that blacks have a higher propensity to have albuminuria compared to whites, the population studied in the MAGIC study (17, 18, 19). This assertion is corroborated by our study since decreasing the diagnostic cut-off value to 11.5mg/g as used in the MAGIC study would translate into higher prevalence of MA.

The independent predictive value of ACR for LVH is in keeping with reports of other workers, depicting the parallel development of MA and LVH in hypertensive subjects. Jensen *et al* reported the first prospective study on the predictive roles of MA in the development of cardiovascular events in a 10-year follow-up of 204 untreated hypertensive subjects (20). The LIFE study reported a higher frequency and degree of MA in hypertensive patients with greater LVM independent of SBP, age, race or co-existing diabetes (21). In the MAGIC study, higher prevalence of electrocardiographic LVH was reported in patients with elevated urinary albumin excretion rate (17). Similarly, Tsioufis *et al* found that hypertensive subjects with MA exhibited higher incidence of unfavorable LV geometric patterns compared to those without (22). Our findings of SBP and pulse rate as independent predictors of LVH contrasted with that of Salako *et al* where only SBP was significantly related to LVH (13).

The mechanisms leading to increased cardiovascular morbidity and mortality in patients with microalbuminuria are not fully understood. Albuminuria has been linked to risk factors for atherosclerosis including hypertension, aging and diabetes mellitus (23). This could be a reflection of microvascular injury in the glomeruli and vasculature, with increased lipid insudation and atherogenesis. This provides the substrate for thrombosis in the cerebral and coronary vessels leading to increased cardiovascular morbidity and mortality (24). Left ventricular hypertrophy sets the stage for diastolic dysfunction, myocardial ischaemia and arrhythmogenesis, resulting in increased CV morbidity and mortality (25).

Urinary ACR and LVH are adjudged to be predictors of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction (26).Given the greatest risk associated with hypertensive TOD, and the potential benefit of early intervention, guidelines recommends screening for LVH and MA in patients with hypertension (5,6). Assessment of MA using the spot urine ACR can be easily carried out during out-patient consultation to serve as a surrogate for LVH where echo is not readily available.

The limitations of this study include the relatively small sample size and the use of single void urine sample rather than multiple urine specimens, given the fact that albumin excretion is variable. Excluding urinary tract infection on the basis of dipstick nitrite alone, might not be conclusive since not all organisms causing urinary tract infection produce nitrite.

Conflict of interest: None declared.

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Table 1: Diagnostic value of microalbuminuria for left ventricular hypertrophy

	ACR>30mg/g	95% CI
Sensitivity	0.64	0.53 – 0.79
Specificity	0.70	0.60 – 0.80
PPV	0.55	0.43 – 0.69
NPV	0.77	0.67 – 0.89
LR+	2.13	1.50 – 3.19
LR-	0.52	0.35 – 0.77
OR	4.10	1.07 – 7.13

ACR=albumin-to-creatinine ratio; CI=Confidence interval; PPV=Positive predictive value; NPV=Negative predictive value; LR+=Positive likelihood ratio; LR=Negative likelihood ratio; OR=odd ratio

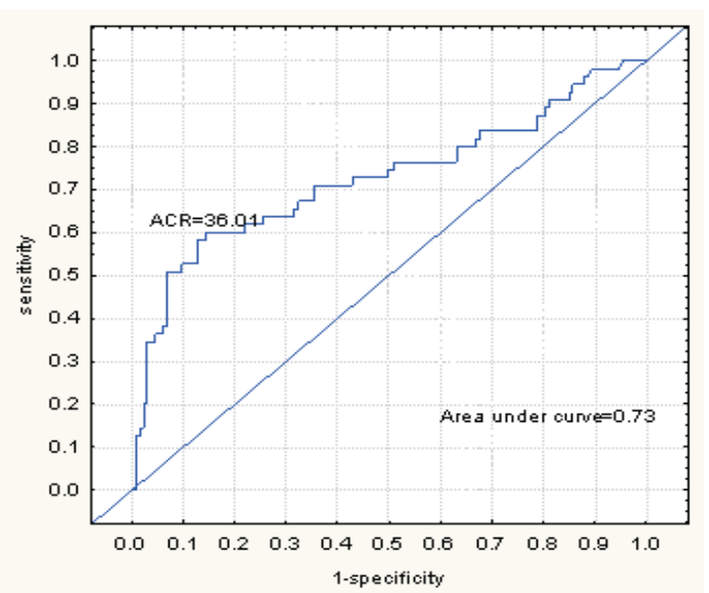

Fig 1: Receiver Operating Characteristics curve for diagnostic value of Albumin - to - Creatinine Ratio (ACR) for left ventricular hypertrophy.