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Comparison of the Performance of Three Commonly Used Electrocardiographic Indexes for the Diagnosis of Left Ventricular Hypertrophy in Black Hypertensive Patients with Reduced Kidney Function Managed at a Tertiary Healthcare Hospital: A Post-Hoc Analysis

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Abstract

Background: Reduced kidney function in blacks is associated with an increased frequency of left ventricular hypertrophy. Given the unavailability of echocardiography in most developing countries, the diagnostic performance of current ECG indexes needs to be evaluated. **Objective**: To compare the diagnostic performance of 3 commonly used ECG indexes (Sokolow-Lyon, Cornell voltage and Cornell product) in black hypertensive patients. **Methods**: Electrocardiography and echocardiography estimated left ventricular mass of 155 consecutive hypertensive patients who participated from January 2012 to January 2013 to an echocardiographic cross-sectional study of left ventricular structure was analyzed to compare Cornell voltage and Cornell product indexes with Sokolow-Lyon voltage index as a reference. Reduced kidney function was defined as eGFR < 60 ml/min/1.730.05 m^2. ROC curves in relation to LVH diagnosis were used to estimate the sensitivities and specificities of each index. $P < 0.05$ defined the level of the statistical significance. **Results**: The sensitivity and specificity were 43% and 85%, 23% and 77% and 26% and 77% for Sokolow-Lyon, Cornell voltage and Cornell product indexes, respectively. However, Sokolow-Lyon index (AUC; 95% CI: 0.64; 0.50 - 0.78)

showed better performance than Cornell voltage (0.42; 0.25 - 0.59) and Cornell product (0.43; 0.28 - 0.59). Sokolow-Lyon index cut-point ≥ 37 mm corresponded to the highest Youden index (39.4% of sensitivity and 92.3% of specificity). **Conclusion**: Although the overall performance of the 3 ECG indexes versus echocardiography was low, Sokolow-Lyon index performed better than the two other indexes in diagnosing LVH.

Keywords

Performance ECG Indexes, Reduced Kidney Function, Black Africans

1. Introduction

Hypertensive patients with reduced kidney function (RKF) are at the increased risk for cardiovascular disease [1] [2]. Thus, the knowledge and management of factors underlying this increased risk could be of great help in reducing CV risk in hypertensive patients especially those with RKF. Among identified factors, left ventricular hypertrophy (LVH) is thought to play a central role in the development and progression of CVD [3]. LVH has been reported to be associated with cardiac arrhythmias, ischemic heart disease, congestive heart failure, and sudden death [4]. Given the prognostic importance of LVH, accurate diagnosis and appropriate management of LVH have become a major component of the care of patients with hypertension [3]. However, there is little information on the diagnosis of LVH in black Africans [5].

LVH can be detected by chest X radiography, electrocardiography (ECG) and echocardiography, computerized tomography (CT) scan and magnetic resonance imaging (MRI) [5]. However, in daily clinical practice, ECG and echocardiography are the most widely used not only for reasons of availability, but mainly by the prognostic association that clearly predicts the increased CV risk when LVH is found [5]. Although echocardiography is the gold standard, the ECG is still the most widely used cost-effective tool and recommended for routine assessment of LVH [3] [6] [7]. Despite the low sensitivity of available ECG indexes ranging from 7% to 35% in mild hypertension and 10% to 50% in moderate to severe hypertension [8], ECG is still in use in many parts of the world including Sub-Saharan Africa where echocardiography is not often available [9]. The most commonly used ECG indexes for the diagnosis of LVH include Sokolow-Lyon voltage, Cornell voltage and Cornell product indexes [4] [7] [10]. Given the differences of sensitivity of these different indexes, it appears thus rational to assess and compare them with echocardiography to assess their suitability for routine use for the diagnosis of LVH in hypertensive patients especially those with RKF [4] [7].

In the Democratic Republic of the Congo, the prevalence of hypertension and chronic kidney disease is estimated to be of 30% and 12%, respectively [11] [12] [13] [14]; both conditions are associated with LVH [15] [16]. However, the ac-

curacy of commonly used ECG indexes relative to echocardiography as the gold standard for the diagnosis of LVH has not yet been evaluated. Therefore, the aim of the present post-hoc analysis was to compare the diagnostic performance of 3 commonly used ECG indexes namely Sokolow-Lyon voltage, Cornell voltage and Cornell product indexes in hypertensive black patients with RKF seen at tertiary level hospital in Kinshasa, the capital City.

2. Patients and Methods

To compare 3 ECG indexes (Sokolow-Lyon voltage, Cornell voltage and Cornell product) with echocardiography to assess their suitability for routine use in the diagnosis of LVH, we performed a post-hoc analysis of data from 155 consecutive adult black patients with established hypertension enrolled in an echocardiographic-based cross-sectional study of the relationship between renal function status and LV structure and function carried out at the outpatient cardiology clinic of the University of Kinshasa Hospital from January 2012 to January 2013. The details of the original study have been already described elsewhere [15]. In brief, according to American Society of Echocardiography (ASE) recommendations, LV end-diastolic internal diameter (LVIDd), interventricular septum thickness (IVSTd) and that of posterior wall of the LV (LVPWTd) were obtained during diastole, and the LV mass (LVM), in grams, was calculated according to the following formula: LVM = 0.8 × {1.04 [(IVSTd + LVIDd + LVPWTd)^3 − (LVIDd)^3]} + 0.6 g [17] and indexed to body surface area (g/m^2) in non-obese patients and height in obese ones (g/m$^{2.7}$) [18]. Overweight and obesity were defined as body mass index (BMI) ≥ 25 Kg/m^2 and ≥ 30 Kg/m^2, respectively [19]. MetS was defined according to harmonized definition [20], Hemoglobin levels < 12 g/dl for men and <11 g/dl for women defined anemia [21]. Echocardiographic diagnosis of LVH was made when LVM index (LVMI) was >125 g/m^2 in men and >110 g/m^2 in women or >51 g/m$^{2.7}$ for both sexes [22] [23]. From the relative wall thickness (RWT) calculated using the following formula: RWT = 2 × LVPWTd/LVIDd, two geometric patterns defined: concentric and eccentric patterns when RWT was ≥0.42 and <0.42, respectively [24]. For the purpose of the present post-hoc analysis, patient's ECG records were analyzed and evaluated for the presence of LVH using 3 ECG indexes: Sokolow-Lyon (SV1 + RV5 or V6 > 35 mm), Cornell voltage (SV3 + RaVL > 20 mm in women or >28 mm in men) and Cornell product (SV3 + RaVL × QRS > 2440 mm) [25] [26] [27]. RKF was defined as eGFR < 60 ml/min/1.73 m^2 using modification of diet in renal disease equation [28].

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (range) as appropriate. Categorical variables were expressed as percentages. Comparison of means or medians was done by student t test or Mann Whitney test, respectively. The sensitivity, specificity, positive and negative predictive values of each of the 3 indexes were estimated. Sensitivity and specificity were

calculated using 2 × 2 tables classifying ECG against echocardiographic LVH as gold standard. The specificity was calculated as true negatives divided by the sum of true negatives and false positives. Similarly, the sensitivity as true positives is divided by the sum of true positives and false negatives. Positive predictive value (PPV) was calculated as true positives divided by the sum of true positives and false positives, and negative predictive value (NPV) as true negatives divided by the sum of true negatives and false negatives. Analysis of the performance of LVM indexers and of sensitivities and specificities of the 3 ECG indexes was made using ROC curves [29]. The areas under the 3 ROC curves and their 95% confidence intervals (CI) were reported. The comparison of curves was made using the Chi-square statistic test. The reported optimal cut-point corresponded to the highest Youden index (sensitivity + specificity − 1). P value < 0.05 defined the level of statistical significance. The Ethical and Research Committee of the University of Kinshasa School of Medicine approved the study. The data were analyzed using the Statistical Package STATA/IC version 14.1 (StataCorp, Texas, USA).

3. Results

General characteristics of the study population as a whole and according to renal function status are summarized in **Table 1** and **Table 2**. RKF was observed in 74

Table 1. Clinical characteristics of the whole study population and according to kidney function status.

Variables	All group n = 155	NKF n = 81	RKF n = 74	P
Gender, % M	49	51	47	0.681
F	51	49	53	
Age, years	58 ± 12	58 ± 12	59 ± 12	0.732
DHT, years	7 (2 - 13)	6 (1 - 13)	8 (4 - 12)	0.040
Smoking, %	20	22	18	0.470
Physical activity, %	60	66	54	<0.001
BMI, Kg/m^2	26 ± 5	25 ± 4	27 ± 5	0.047
Obesity, %	19	10	30	0.002
WC, cm	93 ± 14	90 ± 13	95 ± 14	0.031
Central obesity, %	47	39	55	0.048
SBP, mm Hg	158 ± 24	157 ± 24	159 ± 25	0.510
DBP, mm Hg	93 ± 17	94 ± 15	93 ± 18	0.890
PP, mm Hg	65 ± 20	63 ± 18	68 ± 22	0.180
HR, bpm	84 ± 14	83 ± 15	84 ± 14	0.600
AntiHT regimen, %				0.530
- Monotherapy	64	64	63	
- Bitherapy	28	28	27	
- ≥3 drugs	3	1	5	
Uncontrolled BP, %	69	62	77	0.040

Data are expressed as mean ± standard deviation, median (interquartile range) or relative frequency in percent. Abbreviations: RKF & NKF, reduced and relatively normal kidney function M, male F, female DHT, duration of hypertension BMI, body mass index WC, waist circumference SBP, systolic blood pressure DBP, diastolic blood pressure PP, pulse pressure HR, heart rate AntiHT, antihypertensive BP, blood pressure.

Table 2. Biological characteristics of the whole study population and according to kidney function status.

Variables	All group n = 155	NKF n = 81	RKF n = 74	P
Hb, g/dl	12 ± 2	13 ± 2	11 ± 2	<0.001
Ht, %	37 ± 7	40 ± 5	35 ± 7	<0.001
Anemia, %	39	24	54	<0.001
FPG, mg/dl	92 (82 - 109)	90 (79 - 97)	101 (86 - 128)	<0.001
Diabetes, %	21	6	38	<0.001
Uric acid, mg/dl	6.4 ± 2.6	5.5 ± 2.2	7.4 ± 2.8	<0.001
Hyperuricemia, %	39	21	54	<0.001
TC, mg/dl	188 (160 - 222)	192 (166 - 224)	185 (159 - 217)	0.358
LDL-c, mg/dl	111 (85 - 151)	116 (88 - 171)	100 (84 - 137)	0.660
HDL-c, mg/dl	44 (35 - 52)	44 (36 - 53)	40 (31 - 49)	0.160
TG, mg/dl	96 (76 - 125)	90 (76 - 110)	98 (77 - 128)	0.310
Dyslipidemia, %	79	80	77	0.630
MetS, %	46	31	62	<0.001
Creatinine, mg/dl	1.4 (1.0 - 2.6)	1.0 (0.9 - 1.2)	2.8 (1.8 - 4.0)	<0.001
MDRD-GFR, ml/min/1.73m^2	61 ± 37	89 ± 26	30 ± 15	<0.001
Dipstick-proteinuria, %	17	6	28	<0.001
RKF, stages, %				
3	-	-	46	
4	-	-	36	
5	-	-	18	

Data are expressed as mean ± standard deviation, median (interquartilerange) or relative frequency in percent. Abbreviations: RKF & NKF, reduced and relatively normal kidney function Hb, hemoglobin Ht, hematocrit FPG, fasting plasma glucose TC, total cholesterol LDL-c, low-density lipoprotein cholesterol HDL-c, high-density lipoprotein cholesterol TG, triglycerides MetS, metabolic syndrome MDRD, modification of diet in renal disease GFR, glomerular filtration rate.

hypertensive patients (53% females, mean age 59 ± 12 years) with 46%, 36% and 18% being at RKF stage 3, 4 and 5, respectively. Compared to patients with normal renal function, those with RKF had in average a longer duration of hypertension [8 (4 - 12) vs. 6 (1 - 13) years; p = 0.040), higher BMI (27 ± 5 vs. 25 ± 4 Kg/m^2; p = 0.047) and WC (95 ± 14 vs. 90 ± 13cm; p = 0.031). Sixty-three percent, 27% and 5% of patients with RKF were receiving one, two and more than two antihypertensive drugs, respectively. Patients with RKF had also a significantly higher proportion (77% vs. 62%; p = 0.040) of subjects with uncontrolled hypertension compared to those with normal renal function. They had in addition significantly higher levels of FPG [101 (86 - 128) vs. 90 (79 - 97) mg/dl; p < 0.001], uric acid (7.4 ± 2.8 vs. 5.5 ± 2.2 mg/dl; p < 0.001) and lower hemoglobin levels (11 ± 2 vs. 13 ± 2 g/dl; p < 0.001).

Cardiovascular risk factors in the study population as a whole and according to renal function status are also depicted in Table 1 and Table 2. Patients with RKF had a higher proportion of subjects with global obesity (30 vs. 10%; p = 0.002), central obesity (55% vs. 39%; p = 0.048), diabetes (38% vs. 6%; p < 0.001), hyperuricemia (54% vs. 21%; p < 0.001), dipstick-proteinuria (28% vs. 6%; p <

0.001), MetS (62% vs. 31%; $p < 0.001$) and anemia (54% vs. 24%; $p < 0.001$).

The median echocardiographic-LVMI in non-obese and obese patients with RKF was 276 (198 - 348) g/m^2 and 72 (47 - 88) g/m$^{2.7}$, respectively (Figure 1 and Figure 2); these values were significantly higher than those observed in patients with normal renal function ($p < 0.01$, respectively). Echocardiographic-LVH was observed in 92% of patients with RKF with concentric and eccentric patterns in 50% and 42% of them, respectively. However, the differences observed in comparison with patients with normal renal function were not statistically significant.

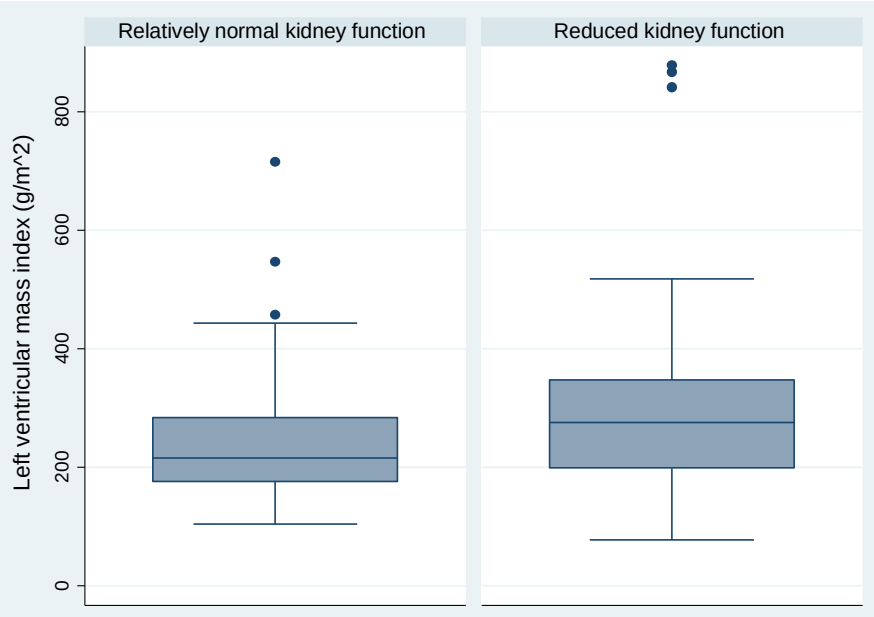

Figure 1. Echocardiographic left ventricular mass index in non-obese patients according to kidney function status.

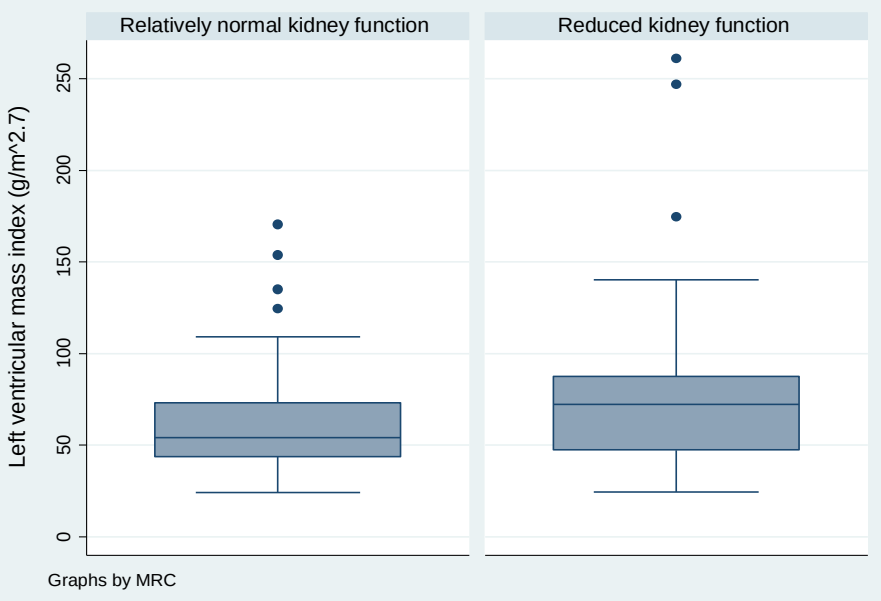

Figure 2. Echocardiographic left ventricular mass index in obese patients according to kidney function status.

Mean ECG-LVM in patients with RKF was 36 ± 11 mm, 21 ± 8 mm and 2087 ± 714 mm·sec for Sokolow-Lyon, Cornell voltage and Cornell product, respectively (Table 3). The prevalence of ECG-LVH in patients with RKF by voltage criteria was 45%, 22% and 23% for Sokolow-Lyon, Cornell voltage and Cornell product, respectively. However, the differences in prevalence of LVH between patients with and without RKF were not statistically significant.

The performance of the 3 ECG indexes for the diagnosis of LVH was similar in patients with than without RKF. Sensitivity and specificity were 43% and 85%, 23% and 77% and 26% and 77% for Sokolow-Lyon, Cornell voltage and Cornell product, respectively. However, the PPV of the 3 indexes were relatively high (>90%) (Table 4).

ROC curves of the 3 ECG indexes are presented in Figure 3. The performance of Sokolow-Lyon index for the diagnosis of LVH was low [area under the curve (AUC); 95% CI: 0.64; 0.50 - 0.78] while Cornell voltage (AUC: 0.42; 0.25 - 0.59) and Cornell product (AUC: 0.43; 0.28 - 0.59) showed no diagnostic interest. The optimal cut-point value of Sokolow-Lyon index corresponding to the highest Youden index was ≥37 mm (39.4% of sensitivity and 92.3% of specificity).

4. Discussion

The main findings of the present post-hoc analysis are as follows. First, the test performance of all the 3 ECG indexes was low. Second, Sokolow-Lyon index performed better than the two other indexes for the diagnosis of LVH.

The poor performance of ECG indexes in detecting LVH has been already reported in African Black hypertensives with and without RKF [4] [6] [30] [31] [32] [33] [34] as well as in the general population [7]. A similar finding has been also found in hypertensive patients out of Africa [35] [36] [37] [38] [39]. The reasons for the different performances of electrocardiographic criteria are not

Table 3. Electrocardiographic left ventricular mass and hypertrophy of the whole study population and according to kidney function status.

ECG index	All group n = 155	NKF n = 81	RKF n = 74	P
LVM				
Sokolow-Lyon, mm	34 ± 11	32 ± 11	36 ± 11	0.045
Cornell Voltage, mm	21 ± 8	21 ± 8	21 ± 8	0.600
Cornell Product, mm·sec	2069 ± 722	2052 ± 734	2087 ± 714	0.761
LVH				
Sokolow-Lyon, %	41	37	45	0.339
Cornell-Voltage, %	23	25	22	0.651
Cornell product, %	26	28	23	0.441
3 indexes combined, %	58	56	61	0.508

Data are expressed as mean ± standard deviation or relative frequency in percent. Abbreviations: RKF & NKF, reduced and relatively normal kidney function disease ECG, electrocardiogram LVM, left ventricular mass LVH, left ventricular hypertrophy.

Table 4. Performance of 3 ECG criteria of LVH versus echocardiography among the study population and according to kidney function status.

ECG criteria	All group n = 155	NKF n = 81	RKF n = 74	P
Sokolow-Lyon index				
Se, %	43	41	46	0.513
Sp, %	85	100	67	-
PPV, %	97	100	94	-
NPV, %	12	14	10	0.424
Cornell voltage				
Se, %	23	24	22	0.785
Sp, %	77	71	83	0.111
PPV, %	92	90	94	0.298
NPV, %	8	8	9	0.645
Cornell product				
Se, %	26	28	24	0.566
Sp, %	77	71	83	0.111
PPV, %	92	91	94	0.433
NPV, %	9	9	9	0.859
3 indexes combined				
Se, %	59	57	62	0.496
Sp, %	54	57	50	0.397
PPV, %	93	93	93	0.875
NPV, %	11	11	10	0.952

Abbreviations: RKF & NKF, reduced and normal kidney function disease ECG, electrocardiogram Se, sensitivity Sp, specificity PPV, positive predictive value NPV, negative predictive value.

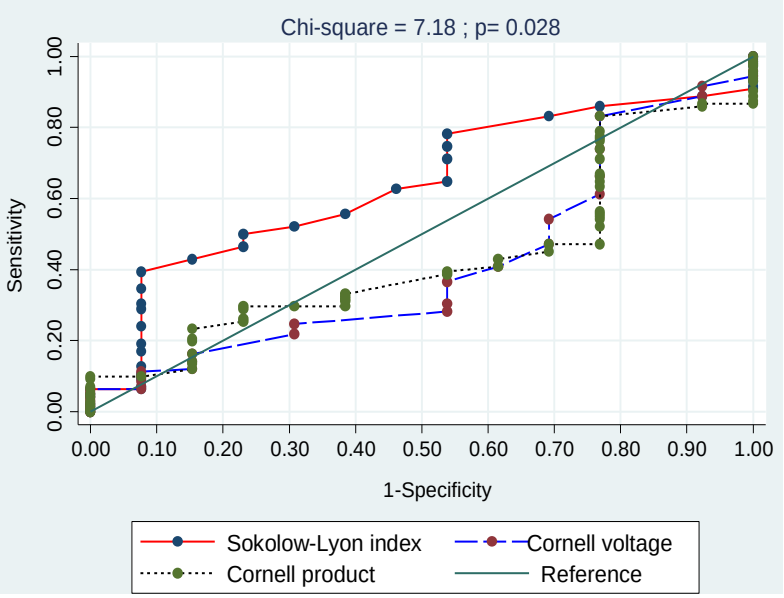

Figure 3. ROC curve of Sokolow-Lyon index, Cornell voltage and Cornell product for diagnosis of left ventricular hypertrophy.

clear and understanding reasons for the discrepancies in detection of LVH by ECG versus imaging could help improve the diagnostic ability of ECG [40] [41]. These discrepancies are thought to rely upon a number of extracardiac factors such as age, gender, body habitus and cardiac factors such as LVH severity and geometry [7] [42]. With reference to cardiac factors, Bacharov *et al.* [40] [41] reported that differences in the prevalence estimates between ECG-based and imaging-based LVH could probably be explained by the complex structural and functional remodeling of the myocardium that occur as a result of hypertrophy. In addition to changes in the size of left ventricle, structural changes at the tissue level including changes of cardiomyocytes, interstitial fibrosis, diminished coronary reserve and myocardial dysfunction [40] [41] are common occurrences. These multi-dimension complex changes are not easily captured by a modality that depends on recording electric activity such as ECG. As a result of the complex structural and functional remodeling of myocardium occurring as a result of hypertrophy, the conduction velocity is slowed, and consequently the sequence of ventricular activation is altered [40] [41]. Using computer simulations, it has been shown that the mass and shape of the left ventricle in LVH are not the only determinant of QRS voltage, the key feature upon which almost all ECG-LVH criteria relies on [40] [41]. Diffuse or regional slowing in conduction velocity changes the sequence of ventricular activation in a way that is consistent with ECG-LVH patterns even in situations when the anatomy of left ventricle is not changed. These findings provide further support that the ECG criteria for LVH do not necessarily mirror changes in LV mass all the time, which explains the too many criteria, none of which provide a high level of diagnostic accuracy. Clearly, the usefulness of ECG-LVH as a tool for prediction of outcomes seems to surpass its value as a tool to diagnose anatomical LVH. Therefore, it may be the time to modify the current or create new ECG-LVH criteria with the main focus being prediction of outcomes rather than the anatomical correlates [40] [41].

In the present post-hoc analysis, Sokolow-Lyon index performed better than the two other comparator indexes. This finding contrasts with the generally accepted better performance of Cornell indexes vs. Sokolow-Lyon index reported by several studies [7] [35] [36] [43]. Noble *et al.* [44] tried to explain the better performance of Cornell-based criteria through vector cardiographic changes induced by LVH. Indeed, the LVM orients the electric forces horizontally corresponding to the RaVL and posteriorily corresponding to the SV3. Furthermore, the V3 lead is closer to the LV and is probably less influenced by variations in the distance between the myocardium and the leads. However, our finding is consistent with the report of a few studies [4] [32] [37] of a better performance of Sokolow-Lyon index vs. Cornell indexes. The exact mechanism underlying the better performance of Sokolow-Lyon index is not clear and could be related to age and BMI of the studied patients as well as the modality of LVM indexation. QRS voltage amplitude depends to both cardiac (electric properties of both the conduction system and the myocardium) and extra-cardiac factors such as age,

gender, BMI [40]. In this regard, Tsiachris *et al.* [45] reported that in elderly patients the Sokolow-Lyon index was associated with LVH detection when LVM was indexed for height whereas Cornell-based indexes were associated with echocardiographic detection of LVH indexed to BSA. In contrast to the above finding, Cornell voltage in middle-aged subjects was the only ECG index that was associated with LVH detection irrespective of indexation [46]. Another plausible explanation could be the fact that the evidence indicates that the sensitivity of several ECG criteria decreases from normal-weight to overweight and obesity [47]. In this regard, a recent study from Italy found that BMI-corrected Sokolow-Lyon voltage and Cornell voltage criteria provided better results for detection of echocardiographic LVH compared with unadjusted parameters [47]. LVH-induced conduction system abnormalities could also contribute to the observed better performance of Sokolow-Lyon index in the present post-hoc analysis. Indeed, Burgos *et al.* [48] reported in hypertensive patients that among ECG criteria with the best performance for LVH and complete Left bundle branch block (CLBBB), Sokolow-Lyon index stood out with a better sensitivity and specificity. They concluded that despite the significant decrease in performance with regards to sensitivity and specificity in patients with LVH and CLBBB, Sokolow-Lyon index presented the best performance.

The interpretation of the findings of the present analysis should consider some limitations. First, it was a post-hoc analysis with a small sample size; second, only a single observer made the diagnosis of echocardiographic LVH; it is well-known that echocardiographic measurements are observer dependent and no agreement test was carried out in the present analysis; third, the original study was a tertiary clinic-based cross-sectional study with selection bias; fourth, echocardiography was used for comparison instead of more accurate tools like computerized tomography or magnetic resonance imaging; unfortunately, these techniques were not available. However, echocardiography has been reported to have a strong correlation with autopsy findings [17]. Notwithstanding these limitations, the present study is the first one comparing the performance of ECG criteria in relation with echocardiography in our setting with limited resources.

5. Conclusion

Although the overall performance of ECG criteria studied was low, Sokolow-Lyon index had a better performance than that of the two others criteria in diagnosing LVH.

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Author's Contribution

L. F. B. wrote the protocol, participated in data analysis and wrote the manu-

script.

M. C. M. B. collected data, participated in data analysis and revised the manuscript.

M. F. I. N. conducted data analysis and revised the manuscript.

M. J. R. participated in data analysis and revised the manuscript.

K. P. K. participated in data analysis and revised manuscript.

K. F. M. revised the manuscript.

K. E. V. revised the manuscript.

M. K. J. R. revised the manuscript.

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