ORIGINAL ARTICLE

Development and Validation of a Electrocardiographic Diagnostic Score of Heart Failure Among Patients with Hypertension Attending a Tertiary Hospital in Ibadan, Nigeria: The RISK-HHF Case-Control Study

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Abstract

Objectives: **Hypertension is the leading cause of HF in sub-Saharan Africa. Electrocardiography (ECG) is a cheap and easily available stratification tool for the diagnosis and prognostication of individuals with hypertension. The aim of this study was to develop an ECG-based HF diagnostic score among patients with hypertension attending a specialist cardiology clinic.**

Methods: **One hundred and one (101) case-control age- and sex-matched pairs were recruited. The study population were adults with a clinical diagnosis of hypertensive HF failure (cases) and systemic hypertension without HF (controls). Participants underwent clinical assessment and ECG. Associations between ECG variables and HF risk were tested with chi square test. Logistic regression modelling (age- and sex adjusted) was trained on a random subset of participants and tested on the remaining participants to determine the ECG abnormalities that are diagnostic of HF and develop a HF diagnostic score. The HF diagnostic score was then validated in an independent dataset of the ECG-Hypertension Audit. Goodness of fit and c-statistics of the HF summed diagnostic score in the training, testing and validation datasets are presented. A two-sided p value of <0.05 was considered statistically significant.**

Results: **The independent ECG diagnostic markers of HF among hypertensive patients in this study in decreasing order of effect size were sinus tachycardia (aOR: 7.72, 95% CI: 2.31-25.85). arrhythmia (aOR: 7.14, 95% CI: 2.57-19.86), left ventricular hypertrophy (aOR: 4.47; 1.85-10.77) and conduction abnormality (aOR: 3.41, 95% CI: 1.21-9.65). The HF summed diagnostic score showed excellent calibration and discrimination in the training (Hosmer Lemeshow p=0.90; c-statistic 0.82; 95% CI 0.76−0.89) and test samples (Hosmer Lemeshow p=0.31; c-statistic 0.73 95% CI 0.60 to 0.87) of the derivation cohort and an independent validation audit cohort (Hosmer Lemeshow p=0.17; c-statistic 0.79 95% CI 0.74 to 0.84) respectively. The model showed high diagnostic accuracy in individuals with different intermediate pre-test probabilities of HF.**

Conclusions: **A ECG based HF score consisting of sinus tachycardia, arrhythmia, conduction abnormality and left ventricular hypertrophy is diagnostic of HF especially in those with intermediate pre-test probability of HF. This has clinical importance in the stratification of individuals with systemic hypertension.**

Keywords: Hypertensive HF, Sinus tachycardia, Arrhythmia, Conduction abnormalities, Left ventricular hypertrophy

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1. Introduction

Hypertension is the leading risk factor for cardiovascular diseases and cardiovascular related morbidity and mortality globally and is responsible for about 7.6 million deaths every year worldwide [1]. It is the leading cause of HF (HF) globally and especially in sub-Sahara Africa. Hypertension is the most frequent cause of HF in Nigeria accounting for up to 61% in a cohort in Abuja and 75.7% in another cohort of HF group in Ibadan, Nigeria [2,3]. Despite improvement in care of patients with systemic hypertension and development of potent anti-hypertensives, HF incidence continues to rise even in Nigeria [4]. Hypertensive HF predominantly affect younger age group in African populations thus leading to loss of economic productivity and poor quality of life [4,5].

Hypertensive HF continues to be a common presentation in clinical cardiology practice. The identification and appraisal of low cost, reliable and simple bedside tests to aid the identification, stratification and risk assessment of patients presenting with clinical features of HF especially in hypertensive heart disease has been an area of active investigation [6–8]. The management of such patients has usually been based on clinical signs, serum biochemistry, electrocardiography and echocardiography. While echocardiography has changed the landscape of clinical assessment of patients with suspected heart failure, electrocardiography remains an important assessment and stratification tool in the care of patients with heart diseases especially HF.

Electrocardiography is particularly useful in the early detection of arrhythmias, myocardial ischemia and chamber enlargement and hypertrophy which are poor prognostic factors in HF [9]. Electrocardiography is also sensitive in the detection of cardiovascular morbidities and has high negative predictive value in the assessment of patients with HF signs [7,10–12]. While HF diagnosis in specialist settings can be made with the help of echocardiography and novel markers like N-terminal Pro-BNP, this is not the case in low resource settings where electrocardiography may be very useful in characterizing such patients and in some cases, ascertaining the trigger and precipitant of HF. Abnormal electrocardiographic patterns are particularly common in patients with HF. Studies have shown that up to 93% of HF patients have abnormal electrocardiographic patterns [13]. Electrocardiographic left ventricular hypertrophy, arrhythmias and conduction abnormalities have been shown to be independent predictors of poor functional status and morbidity in HF patients.

Most studies on clinical electrocardiography in Nigeria have been descriptive studies in patients with hypertension and hypertensive heart disease [8,14,15]. Okeahialam et al. reported 10% arrhythmia among hypertensives with the common arrhythmias being ventricular ectopics, atrial ectopics and atrial fibrillation [16]. Electrocardiographic left ventricular hypertrophy has been reported in 18%–56% in different studies [16]. Few studies in Nigeria have assessed electrocardiographic predictors of HF in patients with HF especially hypertensive HF. Dzudie et al. [6] in the largest HF study in Africa till date, the THESUS-HF study found a prevalence of 97.7% of abnormal ECGs with increasing heart rate and atrial fibrillation on ECG tracings predicting worse clinical outcomes. However, this study contained a heterogeneous population of HF of different aetiologies. Only 43.2% of the study population were hypertensive HFs. Little is known till date about the unique ECG predictors of hypertensive HF in Africans and Nigerians in particular. Most of the studies done in this area in Nigeria and other sub-Saharan countries have been largely descriptive. Preventive and primary health approach to reducing the scourge of HF in patients with hypertension would

Abbreviations

ACEI/ARB	Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker
aOR	adjusted odds ratio
APC	Atrial premature complex
AUC	area under the curve
BMI	Body mass index
DBP	Diastolic blood pressure
ECG	Electrocardiography
HF	Heart failure
HHF	Hypertensive HF
IDI	Integrated discrimination index
IRB	Institutional review board
LAD	Left axis deviation
LAE	Left atrial enlargement
LVH	Left ventricular hypertrophy
NRI	Net reclassification index
NYHA	New York Heart Association class
SBP	Systolic blood pressure
STEPS	STEPwise approach to Surveillance
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
PVC	Premature ventricular contraction
ROC	receiver operating curve

benefit from early detection and identification of simple diagnostic predictors of HF in at risk populations using low-cost technologies like the ECG.

The RISK-HHF study is a case–control study designed as an initial step in the determination and characterization of the risk factors and diagnostic markers of hypertensive HF in Nigerian-Africans. We included 102 patients with hypertensive HF and similar number of age and sex-matched hypertensive controls without HF. The specific objectives were to characterize the ECG patterns in individuals with hypertensive HF compared to those with hypertension, and also to develop and evaluate the performance of a regression model of electrocardiographic patterns diagnostic of HF in individuals with hypertension.

2. Materials and methods

2.1. Participants

This study was approved by the joint University of Ibadan and University College Hospital Institutional Review Board (IRB) and complied with the principles outlined in the declaration of Helsinki [17]. The study also adhered to the STROBE guidelines on observational studies [18]. Written informed consent as approved by the IRB was obtained from all study participants.

2.2. RISK-HHF participants

Participants were recruited from the cardiology clinic and medical wards of the Department of Medicine, University College Hospital, Ibadan. Participants recruitment started in June, 2018 and the whole study lasted about 8 months. Patients aged 18 years old or above with clinical diagnosis of HF secondary to hypertension who were attending the hospital for the first time were recruited into the study as cases while age (5-year age range) and sex matched hypertension with no HF served as controls. Exclusion criteria for both cases and controls were HF diagnoses of other aetiologies, previous myocardial infarction or history of ischaemic heart disease, chronic obstructive pulmonary disease, being pregnant and consumption of $\geq$80 g of alcohol per day for the past 5 years.

Clinical diagnosis of HF was based on the modified Framingham criteria [19]. A patient was considered to have HF secondary to hypertension on the basis of self-reported history of hypertension and/or the use of blood pressure-lowering medication or documented blood pressure $\geq$ 140/90 mmHg [4].

Sample size (N) in each group was calculated using the formula for case control study [20].

$$N = [Z_{1-\alpha/2}\sqrt{2\pi(1-\pi)} + Z_{1-\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}]^2/(\pi_1-\pi_2)^2$$

$Z_{1-\alpha/2}$, standard normal deviate at α of 0.05 = 1.96

$Z_{1-\beta}$ at 95% power = 1.64

π_1, is the prevalence of electrocardiographic LVH (dominant marker) in hypertensives in HF in Agomuoh and Odia [8] = 49.3%

π_2, is the prevalence of electrocardiographic LVH in hypertensives without HF in Agomuoh and Odia [8] = 22%

$\pi = (\pi_1+\pi_2)/2$;

Thus, N = 78.5, adding a non-response rate of 25%, N becomes 98. One hundred and one (101) participants were recruited consecutively into each group from the study sites.

2.3. Procedures

A semi structured interviewer administered questionnaire was used for data collection. The questionnaire was developed and modified from a previous study and followed the STEPS format for epidemiologic surveys [21]. The questionnaire had three sections; sections A, B and C. Section A was divided into subsections on demographic data, medical history, lifestyle risk factors, symptoms and size, medications in use, examination and laboratory test results. Section B was the assessment of medication adherence using the Medication Adherence Questionnaire [22]. Section C contained the coding of electrocardiographic patterns according to the modified Minnesota coding system [23,24]. The questionnaire was pre-tested before the main study among 10 cases and 10 controls. The questionnaire was also translated into the Yoruba language which is the local language spoken by most patients attending the hospital.

Baseline clinical and demographic data was obtained from the subjects. Blood pressure measurements were obtained with a mercury sphygmomanometer according to standard guidelines [25]. Systolic and diastolic blood pressure were measured at Korotkoff sounds phase I and V, respectively. Two readings were taken at intervals of at least 2 min, and the average of the readings was used to represent the patient's blood pressure [26]. If there is > 5 mm Hg difference between the first and second readings, additional (1 or 2) readings was obtained, and then the average of these multiple readings was used [27,28].

Subjects were weighed without shoes and in light clothing on a standard beam balance. Height was measured to the nearest centimetre using anthropometrical plane with subjects not putting on shoes or headgear [29].

Body mass index (BMI) was calculated using the formula:

$$BMI = \text{Weight (Kg)}/\text{Height}^2\ (m^2)$$

Patients had full cardiovascular examination done. Patients with any of pedal oedema, abdominal distension, engorged neck veins, orthopnoea, paroxysmal nocturnal dyspnoea, basal lung crackles and rales were considered congested. Venous blood sample (20 mls) was taken for serum electrolytes, serum urea, serum creatinine and fasting serum lipids from each subject along with 5 mls of urine for dipstick urinalysis. Significant proteinuria was defined as more than trace proteinuria on dipstick [30]. Electrocardiography and echocardiography were also done for each study participant. The New York Heart Association (NYHA) functional class was assigned at recruitment in those with HF.

2.4. ECG-Hypertension Audit

We recruited 377 individuals with hypertension from the ECG-Hypertension Audit who were referred to our ECG laboratory for electrocardiography. These individuals underwent brief screening questions about lifestyle cardiovascular risk factors and indications for ECG referral. They also had focused cardiovascular examination including blood pressure measurement as earlier described [25,27,28]. This is the standard procedure in our ECG laboratory. The ECG-Hypertension Audit was used to validate the ECG regression model for the diagnosis of HF.

2.5. Electrocardiography

The standard resting 12 lead ECG was performed on all subjects at a paper speed of 25 mm/s, standardized at 0.1mv/mm and analysed. Electrocardiogram measurements were done with a ruler on the resting ECG tracings and was expressed as the average of three determinations on consecutive QRS complexes [31]. R-wave amplitude in aVL and S-wave depth in V3 were measured as the distance (mm) from the isoelectric line of their zenith and nadir, respectively [31,32]. QRS duration was measured from the beginning to the end of the QRS complex. QRS duration $\geq$0.12s was defined as prolonged. QT interval was calculated as the interval from the beginning of the QRS to the end of the T wave in seconds while QT_c interval was calculated using the Bazzett's formula. QTc prolongation was defined as a QTc >450 ms in men and 460 ms in women [31].

Sinus rhythm was defined as a rhythm in which each QRS complex is preceded by an upright P wave in Lead II with heart rate 60–100/minute [33]. Sinus Tachycardia is a sinus rhythm with heart rate greater than 100/minute while sinus bradycardia is sinus rhythm with heart rate less than 60/minute. Atrial fibrillation was defined as absence of discernible P waves in lead II with fibrillary waves in V1 and irregular RR intervals [33]. Arrhythmia was defined as the presence of any of atrial premature complexes, premature ventricular complexes or atrial fibrillation.

Left axis deviation was defined as QRS axis of −30 to −90º [33]. Left atrial enlargement (LAE) was diagnosed when P wave duration is $\geq$ 0.12s and/or negative component of P wave in lead V1 greater than 1 mm in depth and/or notched P wave with interpeak duration > 0.04s (P mitrale) or area of negative P terminal force in lead V1 > 0.04 s mm [34,35]. Left ventricular hypertrophy (LVH) was diagnosed using the Sokolow-Lyon criteria, Cornell criteria and/or Framingham criteria [31,32,36]. Left bundle branch block was defined as broad QRS complexes with slurred R waves in lateral leads, secondary ST depression with T wave inversion in left lateral leads, deep S waves in right precordial leads and/or loss of septal Q waves [32,37]. Right bundle branch block was defined as broad QRS complexes, delayed intrinsicoid deflection >0.05 in right precordial leads, rSR′or M pattern in right precordial leads, secondary ST depression and T wave inversion in right precordial leads and deep S waves in left lateral leads [32,37]. Left anterior hemiblock was defined as significant left axis deviation with an initial small q wave and positive QRS complex in lead I, negative QRS complex in lead II and aVR, and small r wave in lead III and no other cause for the left axis deviation [37]. Left posterior hemiblock was defined as significant right axis deviation, a small q wave in lead III and small r wave in lead I, prominent S waves in lead I and R waves in leads II and III with no other cause for the right axis deviation [37]. Conduction abnormality was defined as presence of any bundle branch block or atrioventricular block. Prolonged QTc interval was defined as QTc interval $\geq$450 ms in men and $\geq$460 ms in women. A diagnosis of ischaemic heart disease was made based on the American Heart Association criteria [31].

2.6. Statistical analysis

Data were analysed using STATA version 12(StataCorp LLC, Lakeway Drive, College Station, Texas,

USA). Normality of data were determined using Shapiro–Wilk test. Proportions were used to summarize categorical variables while continuous clinical variables were summarized as means (standard deviations).

Hypertension group and hypertensive heart failure group were compared in exploratory analyses using classical non-regression analyses. Association between categorical variables and heart failure risk were determined using chi square test while association between continuous variables and heart failure risk were determined using independent sample t-test.

The RISK-HHF dataset was then randomly divided into training and test datasets in ratio (75:25) respectively. For the training dataset, univariable logistic regression model was used to explore the relationship between various electrocardiographic patterns and HF risk. Multivariable logistic regression analysis was then used to develop models of the relationship between ECG variables and HF risk. Iterative model building was done and confirmed with forward stepwise selection method. Only ECG variables which accounted for at least 5% of the variance in HF and which were significant in univariable logistic regression at 5% significance level using the Wald test were retained in the multivariable model.

Model discrimination was defined using receiver operating characteristic curves (ROC) while goodness of fit of the model was assessed using the Hosmer–Lemeshow statistic. Incremental value of addition of other ECG variables to the model was tested with net reclassification index (NRI) and integrated discrimination improvement (IDI) programs in stata. A bootstrap analysis of 1000 random samples of the training dataset was then used to assess the internal validity of the multivariable model using the 'roctab' command in stata. This was used to obtain the 95% confidence intervals of the ROC. A HF summed diagnostic score was then created with the variables in the multivariable model based on the strength of association by β coefficients, as previously described [38]. Using this summed diagnostic rule score on a continuous scale, we then evaluated its diagnostic performance by the area under the receiver-operating characteristic curve (AUC), or c statistic. We compared the performance of the multivariable model with the summed diagnostic rule score using the 'roccomp' command in stata to test the difference between the two AUCs. The accuracy of the HF summed diagnostic rule score at different probabilities of HF was also determined.

The performance of the summed diagnostic rule score was then evaluated in the test dataset. The c-statistics was calculated and the ROC of the summed diagnostic rule score in the training dataset was plotted while the goodness of fit was also determined. Bootstrap analyses of 1000 random samples of the test dataset were also done as earlier described. The performance of the HF summed diagnostic rule score was then confirmed in the whole dataset of the RISK-HHF study using k-fold cross validation analyses. The HF summed diagnostic rule score was then validated by applying it to the independent ECG-Hypertension Audit dataset. Model discrimination and calibration were also tested as earlier outlined. The performance and accuracy of the model was also explored across different ranges of predicted probabilities of HF in the ECG-Hypertension Audit as earlier described. Forest plot of the adjusted odds ratio of the ECG variables was plotted using the 'ipdmetan' package in stata. A p value < 0.05 was considered statistically significant in all analyses.

3. Results

A total of one hundred and one (101) age and sex matched case control pairs were recruited into the RISK-HHF study. Table 1 shows the sociodemographic, clinical and electrocardiographic data of the subjects. The mean age of the subjects was 62.4 years (cases) and 60.7 years (controls) with similar proportion of males and females.

Also, as shown in Table 1, individuals with HF were more likely to have lower education attainment, more likely to have history of kidney disease and also more likely to have ever consumed alcohol. Conversely, diabetes, obesity and smoking were not significantly associated with HF. Subjects with hypertensive HF had higher pulse rate, but lower systolic (SBP) and diastolic (DBP) blood pressure than hypertensive individuals without heart failure. Furthermore, HF was significantly associated with sinus tachycardia, arrhythmias (including atrial fibrillation, atrial premature complexes and premature ventricular complexes), conduction abnormalities, left atrial enlargement (LAE) and left ventricular hypertrophy (LVH) on ECG. Other details are as shown in Table 1.

3.1. Univariable diagnostic predictors of HF

The univariable logistic regression of various electrocardiographic patterns investigated as potential diagnostic predictors of heart failure in the training dataset is shown in Table 2. Among the

Table 1. Baseline characteristics of participants in the RISK-HHF study (data are summarized as % for categorical variables and mean ± SD for continuous variables).

Variables	Cases: HHF (101)	Controls Hypertension without HF (102)	P value
Socio-demographic and lifestyle variables			
Age	62.4 ± 14.3	60.7 ± 13.0	0.36
Male	50 (49.5)	50 (49.5)	1.00
Low education (below tertiary education)	74 (73.3)	59 (58.4)	0.03*
Diabetes	12 (11.9)	16 (15.8)	0.41
Kidney disease	11 (10.9)	2 (3⟍2.0)	0.02*
Obesity	16 (15.8)	22 (21.8)	0.28
Exercise	42 (41.6)	47 (46.5)	0.48
Ever smoked	15 (14.8)	10 (9.9)	0.28
Ever consumed alcohol	47 (46.5)	24 (23.8)	0.001**
Clinical profile			
BMI (kg/m^2)	27.6 ± 9.4	27.8 ± 6.7	0.83
Pulse (/min)	87.9 ± 15.4	89.3 ± 6.4	0.84*
SBP (mmHg)	126.8 ± 23.6	145.7 ± 20.1	<0.001**
DBP (mmHg)	79.4 ± 18.3	86.0 ± 19.0	0.01*
ECG abnormalities			
Sinus tachycardia	28 (27.7)	7 (6.9)	<0.001**
Atrial fibrillation	19 (18.8)	2 (2.0)	<0.001**
APCs	18 (17.8)	6 (5.9)	<0.01*
PVCs	24 (23.8)	3 (3.0)	<0.001**
Any arrythmia	45 (44.5)	11 (10.9)	<0.001**
Conduction abnormality	35 (34.6)	9 (8.9)	<0.001**
LAD	53 (52.5)	35 (34.6)	0.01*
LAE	53 (52.5)	39 (38.6)	0.05*
LVH	76 (75.2)	55 (54.5)	<0.01*
QRS duration (ms)	110.4 ± 25.2	98.8 ± 20.9	<0.001**
QTc interval (ms)	464.7 ± 66.2	447.5 ± 53.0	0.04*

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; APCs: atrial premature complexes; PVCs: premature ventricular complexes; LAD: left axis deviation; LAE: left atrial enlargement; LVH: left ventricular hypertrophy.
Any arrhythmia: defined as any of PACs, PVCs or atrial fibrillation. Conduction abnormality: defined as any of atrioventricular block, bundle branch blocks or hemiblocks.
*$p \leq 0.05$; **$p \leq 0.001$.

ECG variables, sinus tachycardia was associated with a 7-fold increased risk of Hypertensive HF, atrial fibrillation was associated with 6.5-folid increased risk of HHF, premature ventricular complexes (PVCs) was associated with about 12-fold increased risk of HHF the presence of any arrythmia was associated with about 7-fold increased risk of HF. Conduction abnormality was associated with about 5-fold increased likelihood of HHF while left atrial enlargement and left ventricular hypertrophy (LVH) were associated with 2-fold and 3.5-fold increased risk of HHF respectively. Arrhythmia on ECG (especially PVCs) and sinus tachycardia accounted for much of the variance in HHF risk as shown by the R^2 in univariable regression.

3.2. Development of the HF summed diagnostic score

The multivariable logistic regression model of electrocardiographic diagnostic predictors of HHF is shown in the forest plot in Fig. 1 below. In the age- and sex adjusted multivariable model, only sinus tachycardia, arrhythmia, conduction abnormality and LVH remained significant diagnostic predictors of HF in hypertension. While the effect sizes of sinus tachycardia and arrhythmia remained largely the same, the effect size of conduction abnormality was attenuated to aOR of 3.4 while that of LVH was magnified to aOR of 4.5. This model exhibited excellent calibration (Hosmer Lemeshow goodness of fit $p = 0.90$) and discrimination of HF from

Table 2. Univariable logistic regression of electrocardiographic patterns in training dataset.

variables	OR (95% CI)	P value	R^2 (%)
Sinus tachycardia	7.32 (2.39–22.41)	<0.001	7.8
Atrial fibrillation	6.54 (1.41–30.34)	0.02	3.8
APCs	4.17 (1.31–13.21)	0.01	3.3
PVCs	11.59 (2.59–51.81)	0.001	8.1
Any arrythmia	6.71 (2.84–15.85)	<0.001	11.0
Conduction abnormality	4.62 (1.94–11.00)	0.001	6.6
Left axis deviation	2.17 (1.13–4.18)	0.02	2.6
Left atrial enlargement	2.95 (1.53–5.72)	0.001	5.1
Left ventricular hypertrophy	3.46 (1.74–6.90)	<0.001	6.2
QRS duration (per ms increase)	1.02 (1.01–1.04)	<0.01	5.2
QTc duration (per ms increase)	1.01 (1.00–1.01)	0.05	2.0

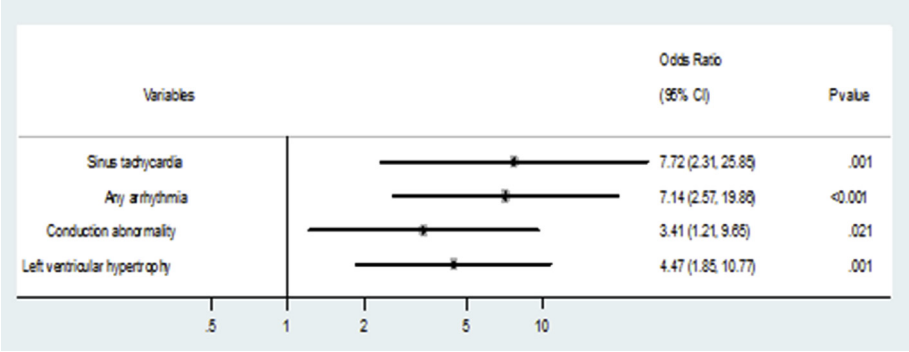

Fig. 1. Multivariable logistic regression model of electrocardiographic patterns in the training dataset (Odds ratios are age- and sex adjusted). In the reference population with no sinus tachcyardia, arrhythmia, conduction abnormality or LVH, the odds ratio of HF (i.e the intercept) was 0.09 (95%CI 0.01, 0.81).

controls (c-statistic 0.83; 95% CI 0.76 to 0.89) as shown in Fig. 2 below. Addition of either of left atrial enlargement or QTc interval to the model did not add to the performance of the model in net reclassification index and integrated discrimination improvement analysis.

We generated a summed score based on this multivariable model by assigning points to each variable in the model based on the strength of association in logistic regression as measured by the β coefficients (shown in Table 3). We assigned 2 points to each of sinus tachycardia and arrhythmia while 1 point each was assigned to each of conduction abnormality and LVH, thus making a total score of 6. The odds of having HF increased by a factor of 3 (OR 2.96; 95% CI 2.09–4.20) for every unit increase in the score. The HF summed diagnostic score provided strong discrimination of HF from controls (c-statistic 0.82; 95% CI, 0.76–0.89) and showed excellent calibration (Hosmer Lemeshow p value = 0.95). Bootstrap analysis showed similar c-statistics. The test for equality of the AUC of the multivariable model and the HF summed diagnostic score showed no difference, thus confirming reliability of the summed diagnostic score (p = 0.54), see Fig. 2 below.

The performance of the HF summed diagnostic score at different predicted probabilities of HF in the training dataset is shown in Table 4 below. The HF summed diagnostic score had high accuracy at the probabilities ranging from 40 to 80% with the best performance at predicted probabilities of 40%–60% where the sensitivity, specificity, positive predictive value and negative predictive value were 70.5%, 81.1%, 79.7% and 72.3% respectively with accuracy of 75.7%. The HF summed diagnostic score demonstrated excellent calibration (Hosmer Lemeshow goodness of fit p = 0.31) and similar discrimination (c-statistic 0.73; 95%CI 0.60 to 0.87) when applied to the testing dataset and bootstrap analysis showed similar c-statistics as shown in Fig. 3 below. We then tested the model again in the whole original dataset of 202 participants using k-fold cross validation bootstrap analysis as shown in Fig. 4. Here again, the model exhibited satisfactory discrimination with cvAUC of 0.80 (bootstrapped bias corrected 95%CI 0.70 to 0.84). The relationship of the HF summed diagnostic score with predicted probabilities of HF presence in the whole of RISK-HHF study is shown in Fig. 5 below. The graph shows increasing probability of HF with increase in the summed diagnostic score with a score of 6 predicting HF correctly 100%.

3.3. Performance of the HF summed diagnostic score in the ECG-Hypertension validation cohort

Finally, we examined the performance of the model in the validation dataset of the ECG-Hypertension Audit. The clinical characteristic of the subjects in the ECG-Hypertension audit is shown in Table 5 below. The mean age of the participants was 69.7 years with 42% males. The prevalence of HHF was 33.7%.

In this validation cohort, the electrocardiographic model also showed excellent discrimination (c-statistic 0.79; 95%CI 0.74 to 0.84) as shown in Fig. 6. K-fold cross validation analysis confirmed the internal validity of the model in this validation cohort (cvAUC of 0.79; bootstrapped bias corrected 95%CI 0.68 to 0.80, Hosmer–Lemeshow statistic for goodness of fit; p = 0.17), see Fig. 7.

The performance of the model was again tested across range of different predicted probability of HF as displayed in Table 6 below. The model

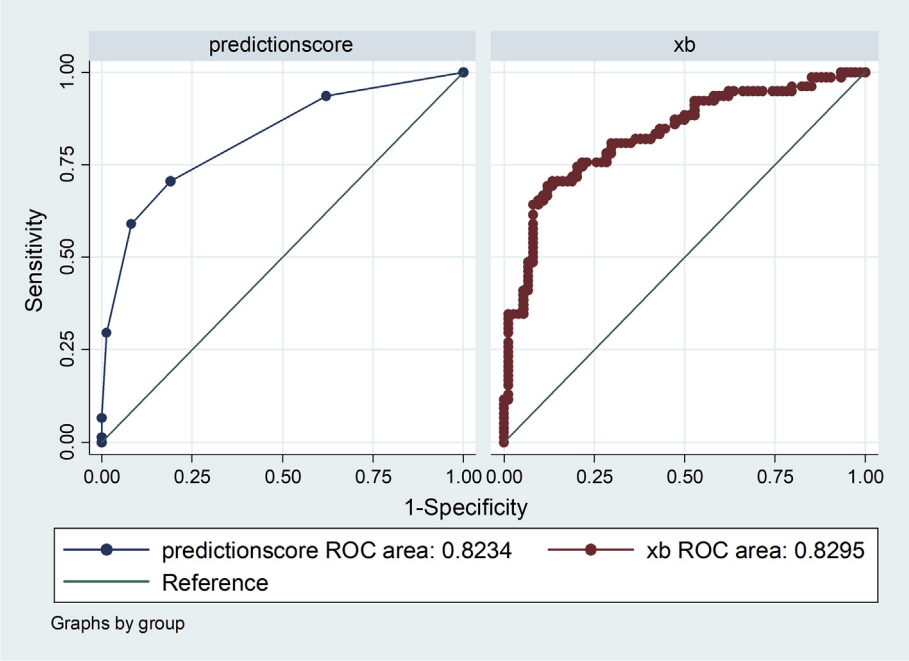

Fig. 2. ROCs curve of the regression model (xb) and the derived HF summed diagnostic rule score with c-statistics of training dataset of random sample of 152 participants; p value for equality of ROCs = 0.54 (Hosmer–Lemeshow statistic for goodness of fit of model p = 0.90 for regression model; Hosmer–Lemeshow statistic for goodness of fit of the HF prediction score p = 0.95 for regression model).

Table 3. The HF summed diagnostic rule score.

ECG Variable	β coefficient (95% CI)	Points
Sinus Tachycardia	2.04 (0.83, 3.25)	2
Arrhythmia	1.97 (0.94, 2.99)	2
Conduction abnormality	1.23 (0.19, 2.27)	1
Left ventricular hypertrophy	1.50 (0.62, 2.38)	1
Summed total diagnostic score	6	

demonstrated good sensitivity and specificity within the range of probability of HF of 30–60%.

4. Discussion

The mean age of the cases and controls in this study is 62.5 ± 14.3 years and 60.7 ± 13.0 respectively. This is in tandem with the findings by Akintunde [15]and Mene-Afejuku et al. [12] who have reported a higher mean age of 62.1 ± 14.2 years and 64.56 ± 11.85 years respectively among patients with hypertensive heart failure. The age of the hypertension group here is higher than that reported by most investigators in Nigeria [39,40]. However, this is because they were matched with the cases who had a higher age.

The electrocardiographic patterns seen in those with HF in our study is in tandem with reports by other investigators. The commonest ECG patterns in both groups were LVH, LAD, LAE, arrhythmia, conduction abnormalities and sinus tachycardia. Olubodun et al. reported that the commonest ECG abnormalities in patients with hypertensive HF was LVH and left atrial enlargement which were seen in 76.7% of the subjects [41]. Karaye et al. [42] in Kano reported that LVH was the commonest finding in

Table 4. HF summed diagnostic rule score performance according to predicted probability of HF in the RISK-HF training dataset.

Predicted probability of HF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Proportion correctly identified (%)
20%	93.6	37.8	61.3	84.8	66.4
30%	93.6	37.8	61.3	84.8	66.4
40%	70.5	81.1	79.7	72.3	75.7
50%	70.5	81.1	79.7	72.3	75.7
60%	70.5	81.1	79.7	72.3	75.7
70%	59.0	91.9	88.5	68.0	75.0
80%	59.0	91.9	88.5	68.0	75.0
90%	29.5	98.6	95.8	57.0	63.2

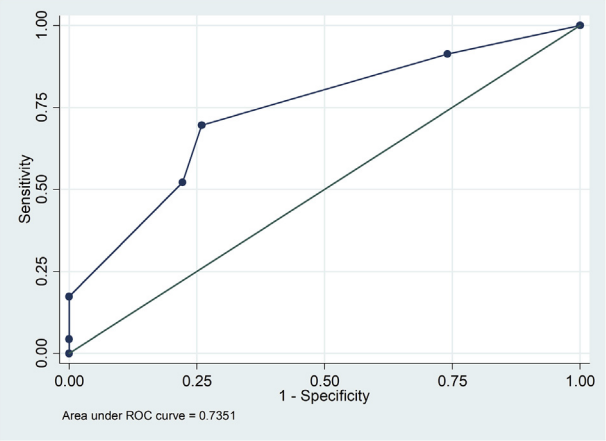

Fig. 3. HF summed diagnostic rule score performance in the test dataset of 50 participants (Hosmer–Lemeshow statistic for goodness of fit of model p = 0.31; c statistic 0.73, 95%CI of c-statistic 0.60, 0.87).

both HFrEF and HFpEF occurring in 77.5% and 50% respectively. In a study of HF patients in Ghana, Owusu et al. [43] reported presence of abnormal ECG patterns in 93% of 394 subjects studied which is similar to the 98% found in our study. In Owusu et al., the commonest abnormalities were LVH (43.7%), LAD (39.6%), left bundle branch block (19.2%), LAE (25.6%), premature ventricular ectopics (11.2%) and atrial fibrillation (8.9%) [43]. Agumuoh et al. observed that sinus tachycardia, atrial fibrillation and left axis deviation were commoner in patients with hypertensive HF compared with those with hypertension [8].

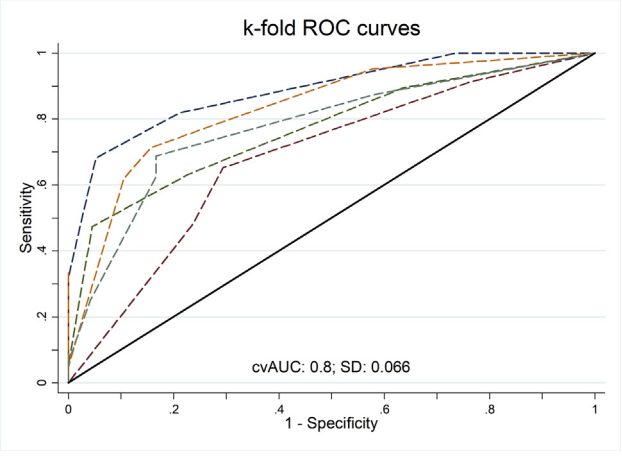

Fig. 4. HF summed diagnostic rule score performance using k-fold cross validation in the whole RISK-HHF dataset of 202 participants (Bootstrapped bias corrected 95%CI of c-statistic 0.70, 0.84) Hosmer–Lemeshow statistic for goodness of fit of model p = 0.85.

4.1. ECG as a diagnostic tool for HF in hypertension

Heart failure remains an enigmatic diagnosis in low resource settings in sub-Saharan Africa where access to cardiology specialist services is limited to tertiary hospitals. The development of a simple clinical HF diagnostic score using a test as simple as the ECG for stratification of those at high risk of heart failure has the potential to facilitate early treatment and secondary preventive health services. The electrocardiogram is a cheap and widely available test which is easily interpreted by technicians and other ancillary health workers.

In this study, we have shown the increased frequency of various electrocardiographic abnormalities in individuals with HHF. Furthermore, our HF summed diagnostic score consisting of sinus tachycardia, rhythm abnormalities, conduction abnormalities and LVH showed excellent discrimination for the diagnosis of HF and has good internal and external validity in cohorts of patients with hypertension. In low risk individuals of both the derivation and validation cohorts, the sensitivity of our diagnostic score was 100% and is similar to the Framingham criteria for HF diagnosis in this regard. However, in these low risk individuals, the specificity of the model was very low and up to half to one-third of patients with predicted probability of HF of 20% would be misclassified. As expected, in high-risk individuals with high pre-test probability of HF of 90%, the specificity was 98.6% in the training subset of the derivation cohort and 99.5% in the validation cohort. In individuals with intermediate pre-test probability of HF, our electrocardiographic HF score showed high diagnostic accuracy and good sensitivity and specificity. This has significant clinical implication in general outpatient clinics and low resource settings where there is

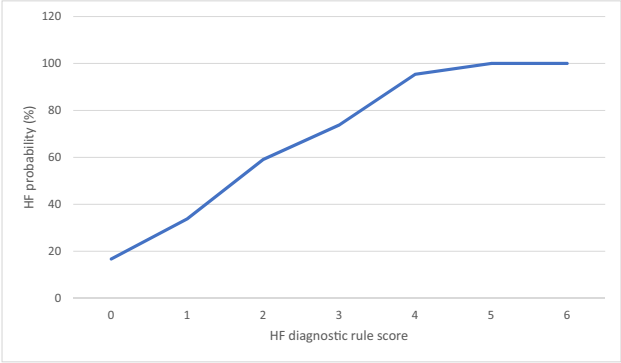

Fig. 5. Relationship of HF summed diagnostic rule score with probability of presence of heart failure in the whole RISK-HHF dataset.

Table 5. Clinical characteristics of participants in the ECG-Hypertension Audit (data are summarized as % for categorical variables and mean ± SD for continuous variables).

Variables	N = 377
Age	67.9 ± 35.8
Male	158 (42)
Low education (below tertiary education)	255 (70.2)
Diabetes	54 (16.9)
Kidney disease	13 (3.4)
Ever smoked	42 (11.2)
Ever consumed alcohol	110 (29.4)
Heart failure diagnosis	127 (33.7)
BMI (kg/m^2)	28.3 ± 6.5
Pulse (/min)	84.3 ± 15.7
SBP (mmHg)	138.1 ± 26.7
DBP (mmHg)	81.3 ± 13.0
Sinus tachycardia	54 (15.8)
Atrial fibrillation	20 (5.9)
APCs	41 (12.1)
PVCs	30 (8.8)
Any arrythmia	62 (18.5)
Conduction abnormality	92 (27.0)
LAD	129 (37.8)
LAE	112 (33.5)
LVH	152 (45.2)
QRS duration (ms)	93 ± 57.5
QTc interval (ms)	435.7 ± 71.6

diagnostic uncertainty. In this instance, an electrocardiogram has value in the stratification of patients for specialist referral and commencement of appropriate therapy. The wide range of abnormal ECG findings seen in the group with HF lends credence to the view that the ECG is a cheap and reliable diagnostic and prognostic tool in the evaluation of patients at high risk of HF. This is especially true of bundle branch blocks, PVCs, PACs, atrial fibrillation, which often herald incipient failure. Indeed, this has been shown in earlier studies like the Framingham study. Electrocardiographic LVH has been shown in the Framingham study to be an independent predictor of HF and HF mortality and corroborated in later studies [44,45]. Gencer et al. [46] also reported that major ECG abnormalities like LVH and atrial fibrillation were predictive of HF incidence. In the MESA study, LBBB (a type of conduction abnormality) was associated with 4-fold increased risk of incident HF while LAD and LVH were each associated with 1.6- and 1.9-fold increased risk of incident HF [45]. Our study has also corroborated the increased risk associated with conduction abnormalities. Whether electrocardiographic abnormalities are a result of progressive myocardial dysfunction, causation of dissociation in electromechanical activation and conduction in heart failure or both is difficult to determine [7]. However, mechanistic studies suggest that electrocardiographic abnormalities develop early in the progression of HF and abnormalities of electrical coupling are harbingers of dangerous ventricular rhythms and ventricular dis-synchrony which have been associated with worse prognosis in patients with HF [47]. LVH is the harbinger of electrical and mechanical remodelling that occurs in HF. Sustained tachycardia provides a substrate for rhythms like atrial fibrillation and ventricular tachycardias which have been implicated in the electrical remodelling and "tachycardia induced cardiomyopathy that occurs in the transition to HF and they infact cause HF on their own in patients who already have structural heart disease especially left ventricular hypertrophy [47]. Findings from the Framingham and MESA studies support this pathway [44,45]. Thus, early detection of these rhythm and

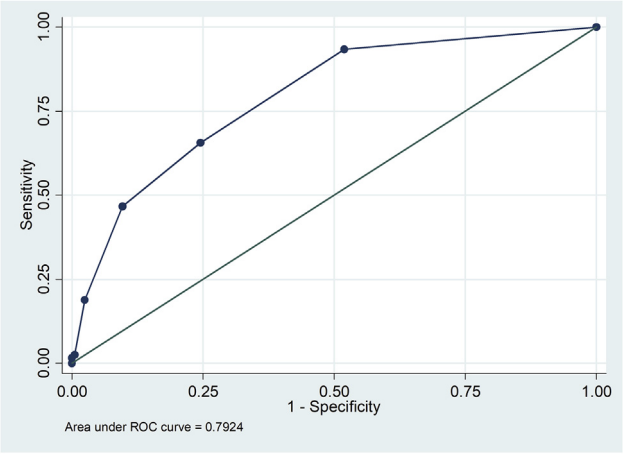

Fig. 6. HF summed diagnostic rule score performance in the ECG-Hypertension Audit dataset (95%CI of c-statistic 0.74, 0.84).

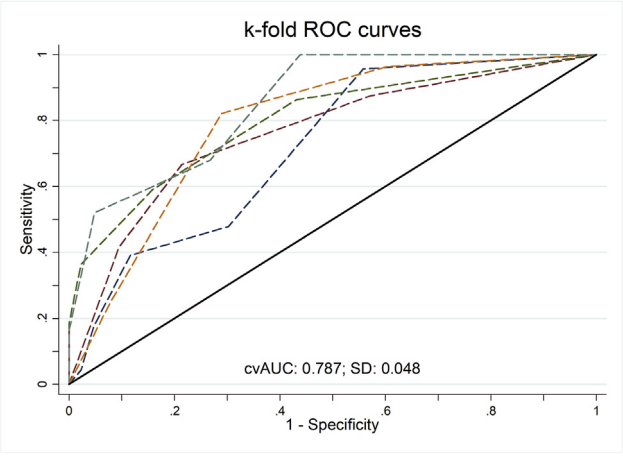

Fig. 7. HF summed diagnostic rule score performance using K fold cross validation in the ECG-Hypertension Audit dataset (Bootstrapped bias corrected 95%CI interval of c-statistic 0.68, 0.80) Hosmer–Lemeshow statistic for goodness of fit of model p = 0.17.

Table 6. HF summed diagnostic rule score according to predicted probability of HF in ECG-Hypertension Audit dataset.

Predicted probability of HF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)	Correctly classified (%)
20%	93.4	48.1	51.3	92.6	64.8
30%	65.6	75.5	61.1	78.9	71.8
40%	65.6	75.5	61.1	78.9	71.8
50%	46.7	90.4	74.0	74.3	74.2
60%	46.7	90.4	74.0	74.3	74.2
70%	18.8	97.6	82.1	67.2	68.5
80%	18.8	97.6	82.1	67.2	68.5
90%	2.5	99.5	75.0	63.5	63.6

conduction abnormalities can help identify patients who are increased risk before they develop heart failure. ECGs are attractive cheap and easily readable tests that may be used in stratification of patients who may need specialised care.

The strength of this study includes the matching of cases with control in the derivation RISK-HHF cohort which reduces the confounding effects of age and sex in heart failure risk. In addition, by using easily measured electrocardiographic profiling to generate a HF diagnostic score in characterising the patients, this can be readily deployed in the day-to-day clinical assessment of patients and their stratification. Furthermore, the good internal validity of the HF summed score and its confirmation in an independent validation cohort makes the likelihood of selection bias very low. More so, the diagnosis of HF was made via comprehensive clinical and imaging assessment based on current guidelines. The individuals in the validation cohort represent day-to-day clinical practice. Testing the HF summed score at different levels of predicted HF probability also allowed diagnostic accuracy of the model to be determined.

This study is not without limitations. First, the derivation RISK-HHF cohort is a highly selected group of patients, though efforts have been made to reduce confounding. Thus, the finding is only generalisable to patients with hypertension who are at risk of HF. Also, the model requires further validation in larger cohorts especially in the community. This model is not intended to supplant comprehensive clinical assessment in specialist setting and we have not explored the additive roles of other markers e.g NT-Pro-BNP assay and serum creatinine. We do not know yet the value of this model in individuals of other racial identities. As mentioned earlier, it is difficult to conclude whether the electrocardiographic risk factors are actual risk factors or markers of an already established state. A cohort study is better to investigate these relationships. Coronary angiography was not done to completely rule out co-existing ischaemic heart disease, however, the definitions used to exclude ischaemic heart disease have been used in other studies in this population and the probability of misclassification of patients is low. Moreover, the prevalence of ischaemic heart disease in Nigeria is still low and hypertension still accounts for most of the HF in our population.

5. Conclusion

In conclusion, we have shown in this study that a simple ECG based score derived from a logistic regression model consisting of sinus tachycardia, arrhythmia, conduction abnormalities and LVH is diagnostic of HF in individuals with hypertension. This is independent of age and sex. Regular routine electrocardiography should be done in patients on treatment for hypertension to identify early, these markers of HF. This will aid early detection and secondary prevention. A comprehensive HF registry should be established in all tertiary health institutions. This will help in further large-scale studies and validation of these results. Finally, a larger case–control study or even a cohort study is needed to confirm the findings of this research.

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Author contributions

Conception and design of study: Ayodipupo S. Oguntade, IkeOluwapo O. Ajayi. Analysis and interpretation of data: Ayodipupo S. Oguntade, IkeOluwapo O. Ajayi, Akinyemi Aje. Supervision of the research: IkeOluwapo O. Ajayi, Akinyemi Aje, Adewole A. Adebiyi, Okechukwu S. Ogah, Abiodun M. Adeoye. Funding for the research: Ayodipupo S. Oguntade. Research investigation and analysis: Ayodipupo S. Oguntade, Akinyemi Aje, Adewole A. Adebiyi, Okechukwu S. Ogah, Abiodun M. Adeoye. Data collection: Ayodipupo S. Oguntade, Akinyemi Aje, Adewole A. Adebiyi, Okechukwu S. Ogah, Abiodun M. Adeoye. Literature review: Ayodipupo S. Oguntade, IkeOluwapo O. Ajayi. Drafting of

manuscript: Ayodipupo S. Oguntade, IkeOluwapo O. Ajayi, Akinyemi Aje, Adewole A. Adebiyi, Okechukwu S. Ogah, Abiodun M. Adeoye. Critical review: Ayodipupo S. Oguntade, IkeOluwapo O. Ajayi.

Conflict of interest

We declare no conflict of interest.

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