

Echocardiography in Low-Risk Hypertensive Patients

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Background—It is debated whether echocardiography should be part of the diagnostic workup in all hypertensive patients. We identified some factors potentially associated with left ventricular hypertrophy (LVH) at echocardiography in untreated hypertensive patients.

Methods and Results—We studied 2150 patients without LVH at ECG. All patients underwent standard 12-lead ECG and echocardiography. Mean age was 48.7 years, and mean office blood pressure was 154/97 mm Hg. Prevalence of echocardiographic LVH (LV mass >47.0 g/m^{2.7} in women and >50.0 g/m^{2.7} in men) was 37.1%. We developed a nomogram based on 7 items (age, smoking, body mass index, office systolic and diastolic blood pressure, Cornell voltage, and chronic kidney disease) on the basis of a multivariable logistic regression analysis. We internally validated the model by bootstrap recalibration and obtained a calibration curve to assess agreement in the validation data set. Probability of LVH at echocardiography ranged from $<10\%$ (score, ≤ 100 points) to $>90\%$ (score, ≥ 180 points). Proportion of patients with LVH progressively increased with the total score ($\chi^2=444.8$; $P<0.001$). Prevalence of LVH was $<2\%$ and 90% at the lower 5th and upper 95th percentile of its distribution, respectively.

Conclusions—We developed and validated a novel score to assess the probability of LVH at echocardiography in hypertensive patients without LVH at ECG. The score may guide the appropriateness of echocardiographic study in low-risk hypertensive patients. Echocardiography appears most appropriate for score values >136 in men and >124 in women. (*J Am Heart Assoc.* 2019;8:e013497. DOI: 10.1161/JAHA.119.013497.)

Key Words: blood pressure • body mass index • cardiovascular imaging • guideline • left ventricular hypertrophy

Indications to the use of echocardiography in the management of hypertensive patients remain vague.^{1,2} The committee of the scientific associations participating in the 2017 US guidelines explicitly indicates that the echocardiographic study is not recommended for evaluation and management of hypertensive adults. The European guidelines are more flexible and give a specific indication to echocardiography for detection of left ventricular hypertrophy (LVH), which might be extensively extended to LV geometry, to

influence treatment decisions. This is a reasonable recommendation, although it is unclear when clinical decisions can be really influenced by evidence of LVH. Presence of LVH in hypertensive patients strongly influences cardiovascular prognosis, and its regression/progression is associated with lower/higher incidence of cardiovascular events.^{3,4} Thus, its detection should force therapy to decrease blood pressure (BP) to <130 mm Hg,² but whether to refer patients to echocardiography laboratories to resolve this doubt remains largely arbitrary.

As a consequence of this ambiguity, one question remains unanswered: Should all patients with hypertension be screened with echocardiogram for LVH? At present, there is no clinical trial evidence addressing these questions, and the few expert opinions found in literature did not modify the present trend.⁵

One possibility to help decide whether to refer hypertensive patients for echocardiography in the clinical practice might be that of being guided by the pretest (“preechocardiography”) probability of LVH. This would be particularly appealing in those patients less likely to have LVH as a consequence of a normal ECG. These patients generally represent a relatively low-risk category, which, however, has been shown to present a significant prevalence of LVH on echocardiography.⁶ Accordingly, we designed the present

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Received August 22, 2019; accepted October 30, 2019.

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Clinical Perspective

What Is New?

- A simple score that includes 7 variables (age, smoking, body mass index, office systolic and diastolic blood pressure, ECG Cornell voltage, and chronic kidney disease) may accurately quantify the probability of left ventricular hypertrophy at echocardiography.
- Our findings are useful in daily practice to identify the hypertensive patients most likely to present left ventricular hypertrophy at echocardiography.

What Are the Clinical Implications?

- We developed a new scoring system, composed of 7 variables, to predict the probability of left ventricular hypertrophy at echocardiography, helping clinicians in risk profiling and decision making in untreated patients with essential hypertension.

study to identify a method to optimize the selection of patients who are most likely to benefit from an echocardiographic study specifically aimed to detect LVH.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study to attention of Dr Paolo Verdecchia (verdecchiapaolo@gmail.com).

The PIUMA study is a prospective observational registry of morbidity and mortality in initially untreated hypertensive patients, which was initiated in June 1986. The registry was approved by the Local Ethics Committee of the Italian National Health Service. All subjects provided their informed consent to participate. Details of the study have been previously published.^{7,8} Entry criteria include an office BP ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic, measured by a physician, according to reported methods, on at least 3 visits; and no previous treatment for hypertension (70%) or history consistent with occasional treatment of hypertension in the past, but in all cases withdrawn over the 4 weeks before the study (30%). The more frequent causes of discontinuation were poor adherence to treatment, excessive hypotension, and supposed adverse effects of drugs. Additional entry criteria include the absence of secondary causes of hypertension, previous cardiovascular disease, or life-threatening conditions. The study population included patients who were 100% white, with no history of coronary

artery disease or significant valvular defects. Shift workers were excluded.

For the present analysis, we included participants without ECG LVH at the initial visit, being echocardiographic LVH expected in most patients with ECG LVH.⁹ None of the patients had an established indication to the echocardiographic study different from identification of LVH for refining risk stratification.⁸ Figure 1 shows the selection of participants forming the population study. The Strengthening the Reporting of Observational Studies in Epidemiology checklist has been used in conjunction with this article (freely available at <http://www.epidem.com/>). Chronic kidney disease has been defined as estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 , and proteinuria has been defined as frank proteinuria (> 300 mg/24 h or > 300 mg/g).^{5,6}

Echocardiography

The M-mode echocardiographic study of the LV mass was performed under 2-dimensional guide, according to recommendations issued by the American Society of Echocardiography.¹⁰ Only frames with optimal visualization of interfaces and showing simultaneous visualization of septum, LV internal diameter, and posterior wall were used for reading. Details about reading procedures and reproducibility in our laboratory have been reported previously.⁸ We calculated LV mass using a standard formula and corrected by height in meters at the power of 2.7.^{11,12} We defined LVH by a LV mass $> 47.0 \text{ g/m}^{2.7}$ in women and $> 50.0 \text{ g/m}^{2.7}$ in men.²

Statistical Analysis

Statistical analysis was performed using SAS, release 9.4 (SAS Institute, Cary, NC), and R, release 3.5 (R Foundation, Vienna, Austria). Continuous data were expressed as mean \pm SD, and categorical variables were expressed as proportions. Unpaired *t* test was used to compare continuous variables across groups, and χ^2 test was used for categorical variables. The normal distribution assumption was tested using Shapiro-Wilks test.

On the basis of current recommendations for the routine workup of hypertensive patients,² we estimated the probability of echocardiographic LVH using multivariable logistic regression with backward stepwise selection method to identify a model with a parsimonious set of explanatory covariables.¹³ Our final model included age, body mass index, smoking, office systolic and diastolic BP, Cornell voltage, and the presence of chronic kidney disease.

We assessed the model using 2 metrics, calibration and discrimination. Model calibration, the degree of agreement between observed and predicted probabilities, was assessed graphically.¹⁴ To evaluate the model ability to discriminate patients with and without LVH, we used the c-index and a histogram of predicted probabilities.¹⁵ The model was internally

validated using 1000 bootstrap samples (resampling with replacement), as this method has been shown to perform more reliably than other methods of internal validation.^{13,16,17} We then developed a nomogram using the results of the validated multivariable model.¹⁸ A nomogram maps the predicted probabilities into points on a scale from 0 to 100 in a user-friendly graphical interface. The total points accumulated by the various covariables correspond to the predicted probability of LVH for a patient.^{13,19}

Results

Among the PIUMA study participants without ECG LVH, 37% showed echocardiographic LVH. Table 1 shows the general characteristics of the study population, according to presence or absence of LVH at echocardiography. Participants with LVH were older, were less likely to be women, were heavier, had a higher prevalence of diabetes mellitus, had a higher BP, and had a higher prevalence of concentric LV geometry (all $P < 0.01$).

Among potential biological promoters of LVH and the routinely proposed workup tests, age (years), current smoking (no or yes), body mass index, office systolic and diastolic BP (mm Hg), Cornell voltage (R in aVL + S in V3), and presence of chronic kidney disease (estimated GFR < 60 mL/min per 1.73 m² or proteinuria) (no or yes) were included in the final model (Table 2). The model c-statistic (0.784; 95% CI, 0.764–0.804) showed good discrimination, and the internal

validation of the model using 1000 bootstrap samples did not materially change the optimism-corrected value of the c-statistic (0.781; bootstrap 95% CI, 0.753–0.798). The bootstrap bias-corrected calibration curve is shown in Figure 2. The closeness of the calibration curve to the 45° line demonstrates excellent model validation on an absolute probability scale for the occurrence of LVH.

A nomogram was, thus, generated on the basis of the multivariable logistic regression analysis. As depicted in Figure 3, each indicator is measured, and the corresponding points are assigned using the first row (“Points”). The sum is reported on the row “Total Points,” and the corresponding probability of LVH is identified in the last row.

We evaluated the prevalence of observed LVH also in relation to deciles of the total points score by nomogram (Figure 4). Prevalence of LVH increased progressively across deciles of total point score, ranging from 3% in the lower decile (median points, 96) up to $\approx 80\%$ in the highest decile (median points, 167) (Figure 4).

Figure 5 shows the nomogram total points in relation to observed values of LV mass.

Discussion

The novel finding of the present study was the development of a nomogram to estimate the probability of LVH at

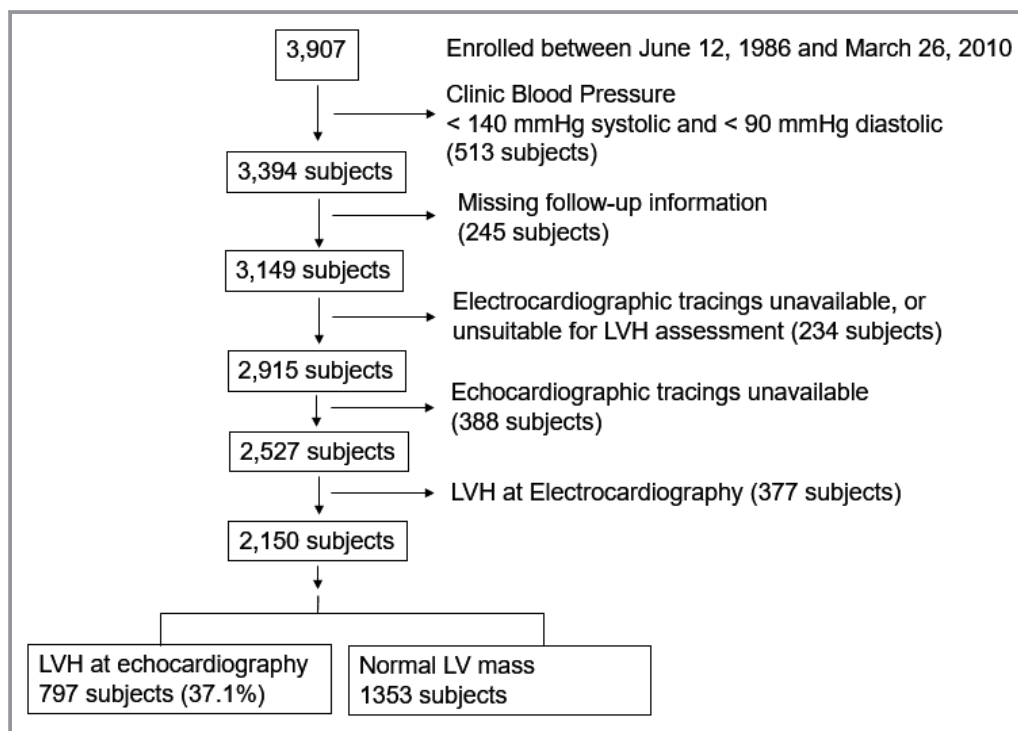


Figure 1. Selection of PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study participants without electrocardiographic left ventricular hypertrophy (LVH).

Table 1. Main Features of the Population

Variable	All Patients (N=2150)	LV Mass (N=1353)	LV Hypertrophy (N=797)	P Value
Age, y	48.7 (11)	47.2 (11)	51.2 (11)	<0.001
Body mass index, kg/m ²	26.6 (4)	25.7 (4)	28.2 (4)	<0.001
Known duration of hypertension, y	3.6 (5)	3.1 (5)	4.4 (6)	<0.001
Women, %	45	47	42	0.011
Diabetes mellitus, %	6.1	5.1	7.8	0.006
Current smokers, %	25	24	27	0.068
Total cholesterol, mmol/L	5.56 (1.1)	5.57 (1.1)	5.54 (1.1)	0.521
HDL cholesterol, mmol/L	1.29 (0.3)	1.32 (0.3)	1.25 (0.3)	<0.001
LDL cholesterol, mmol/L	3.57 (0.9)	3.58 (0.9)	3.56 (0.9)	0.687
Creatinine, mmol/L	85.3 (20)	85.0 (16)	85.8 (24)	0.408
eGFR <60 mL/min per 1.73 m ² , %	6.4	5.3	8.2	<0.01
Proteinuria, %	5.3	4.3	7.0	0.02
Glucose, mmol/L	5.46 (1.1)	5.37 (0.9)	5.62 (1.2)	<0.001
Uric acid, mmol/L	279 (82)	273 (82)	289 (81)	<0.001
Office blood pressure				
Systolic, mm Hg	154 (17)	150 (15)	160 (19)	<0.001
Diastolic, mm Hg	97 (9)	96 (8)	99 (10)	<0.001
Interventricular septum thickness, cm	1.09 (0.20)	1.00 (0.15)	1.23 (0.19)	<0.001
LV internal diameter, cm	4.92 (0.49)	4.81 (0.46)	5.10 (0.47)	<0.001
Posterior LV wall thickness, cm	0.99 (0.17)	0.92 (0.13)	1.10 (0.16)	<0.001
Relative LV wall thickness	0.41 (0.08)	0.39 (0.07)	0.44 (0.08)	<0.001
LV mass, g/m ^{2.7}	46.5 (11)	39.5 (6)	58.2 (9)	<0.001
Cornell voltage, mm	14.2 (4.6)	13.2 (4.5)	15.7 (4.4)	<0.01

Data are given as mean (SD), unless otherwise indicated. *P* values refer to unpaired *t* test for continuous variables and χ^2 test for categorical variables. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular.

echocardiography, based on routine workup clinical variables, in hypertensive patients without LVH at ECG. This model allowed identification of consistent groups of hypertensive

patients with high or very high or, conversely, low or very low probability of LVH. The nomogram may help in optimizing the selection of patients most likely to benefit from the echocardiographic study for diagnosis of LVH. By providing a continuous score (ie, the nomogram total point), this method has the potential of guiding the decision of whether a patient needs to be referred for echocardiography.

Table 2. Predictors of Echocardiographic LVH in the Final Multivariable Regression Model

Covariate	Units	Odds Ratio	95% CI	P Value
Age	1 y	1.027	1.015 to 1.038	<0.001
Smoking	No	Reference
	Yes	1.683	1.319 to 2.149	<0.001
BMI	1 kg/m ²	1.216	1.180 to 1.253	<0.001
Office SBP	1 mm Hg	1.027	1.020 to 1.035	<0.001
Office DBP	1 mm Hg	1.016	1.003 to 1.030	0.014
Cornell voltage	0.1 mV	1.119	1.092 to 1.146	<0.001
CKD	No	Reference
	Yes	1.409	1.007 to 1.972	0.046

BMI indicates body mass index; CKD, chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m² and/or proteinuria); DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Use of the nomogram would help abiding by the indications of several guidelines on arterial hypertension, from the Italian guidelines in 2008 to the most recent European Society of Cardiology/European Society of Hypertension 2018 guidelines, to refer for echocardiography when results are supposed to address decision making in the management and in primary prevention.^{2,20} Adoption of a probability score might be a reasonable balance between the position of the European Society of Cardiology/European Society of Hypertension 2018 guidelines, which reported a class 2b recommendation to the echocardiographic study, and the lack of clear indications from other recent guidelines.^{1,2,1,22} A class 2b recommendation to the echocardiographic study reflects the current uncertainty in the scientific community about the

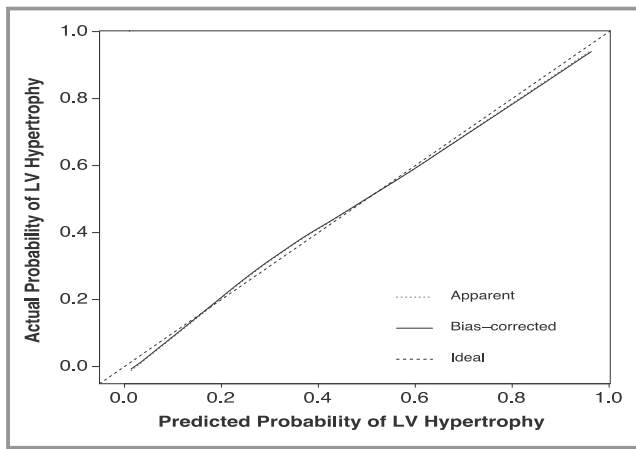


Figure 2. Observed vs predicted rates of echocardiographic left ventricular hypertrophy (LVH). This figure depicts observed (*y*-axis) vs predicted (*x*-axis) probability of echocardiographic LVH in patients with hypertension. The bias-corrected line represents the adjusted calibration curve accounting for optimism, as assessed by bootstrap validation.

practical relevance of this diagnostic procedure when recommended in all hypertensive patients.

In addition to BP, our nomogram total score was generated on the basis of other well-known biological promoters of LVH, including age, body mass index, smoking habit, and chronic kidney disease. Age is a potent correlate of increased LV mass.^{23,24} Obesity is as important as a BP-independent stimulus for development and maintenance of LVH in different clinical settings and population ethnicities.^{25–27} Obesity is also a barrier for regression of LVH during antihypertensive treatment.^{26,28} Smoking habit has been shown to amplify effects of stimuli for development of LVH also in young individuals who have had limited exposure to smoking.²⁹

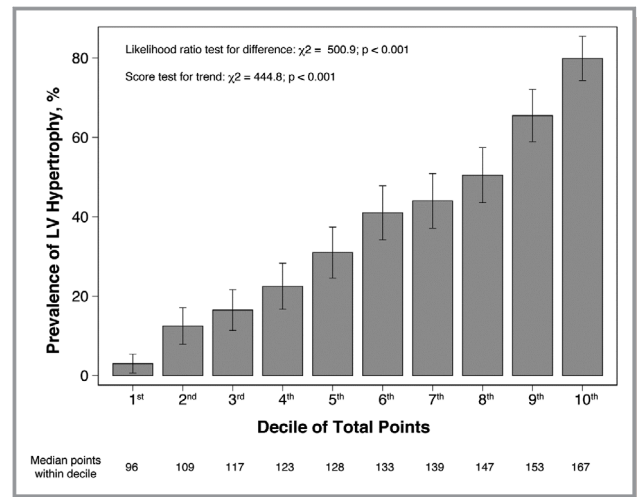


Figure 4. Prevalence of echocardiographic left ventricular (LV) hypertrophy, according to deciles of the nomogram total points, as displayed in Figure 3.

With the calibration of probability offered by the nomogram total score, in each context and in all health systems, no matter if private or public, decisions of whether to perform echocardiogram in hypertensive patients might be taken more appropriately. A policy oriented to maximization of sensitivity of echocardiography for detection of LVH would assume indication to the study in all patients above the fifth percentile of the nomogram total point distribution (N=1862/1998), which would lead to exclusion of only 136 subjects with low probability of LVH (ie, 4.7%). In this group, avoiding echocardiography might be a reasonable cost-effectiveness choice. Conversely, a policy oriented to maximization of specificity would reserve the echocardiographic study to the subset with nomogram total score >170 points (ie, >95th percentile of the distribution) and the highest probability of LVH (≈90%).

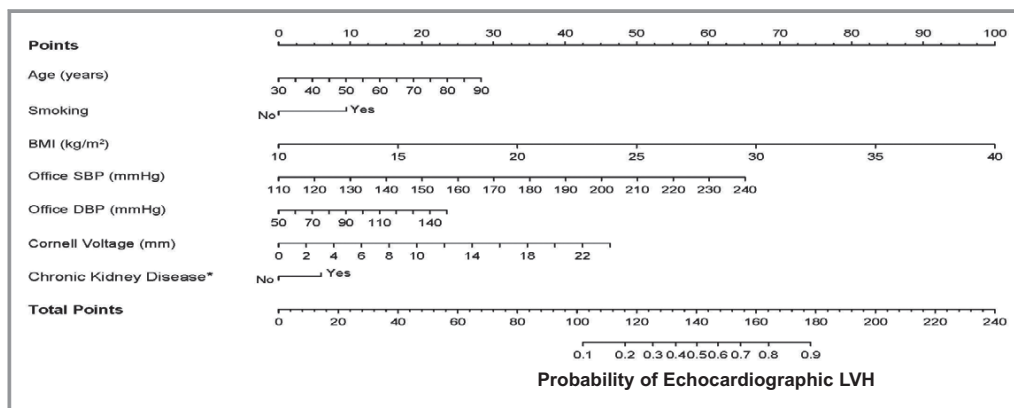


Figure 3. Nomogram for prediction of probability of echocardiographic left ventricular hypertrophy (LVH), based on 7 indicator variables. Each indicator is measured, and the corresponding points are assigned using the first row (“Points”). The sum is reported on the row “Total Points,” and the corresponding probability of LVH is identified in the last row. BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Estimated glomerular filtration rate <60 mL/min per 1.73 m² and/or proteinuria.

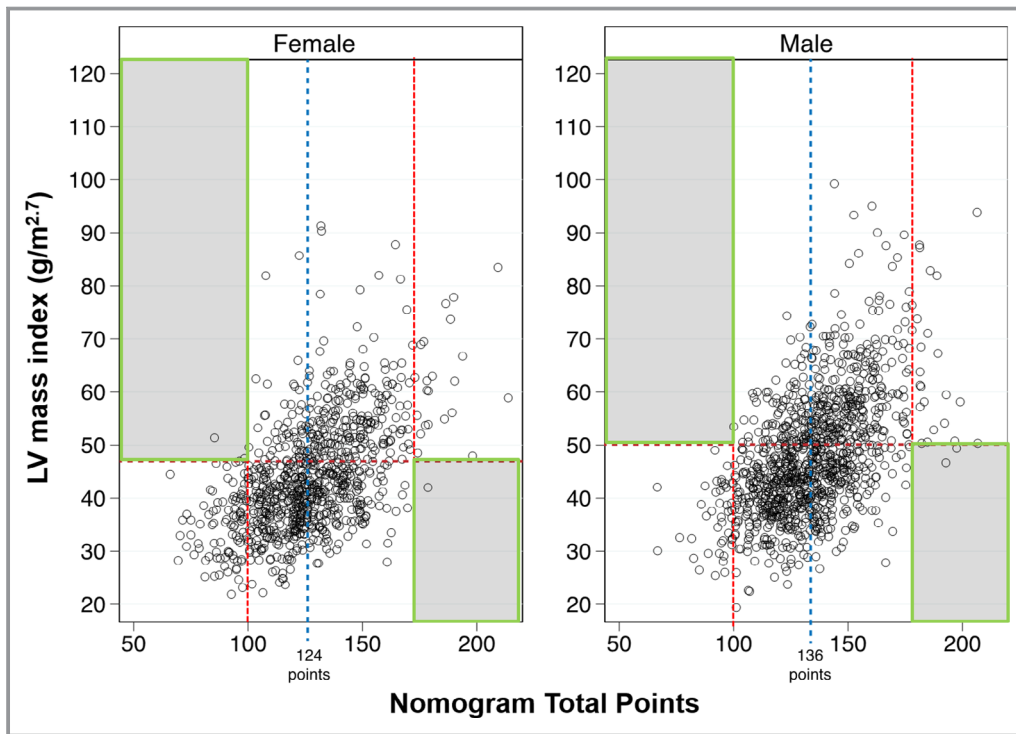


Figure 5. Nomogram total points (NTPs) in relation to observed values of left ventricular (LV) mass index. The red lines represent 5th and 95th sex-specific percentiles of the NTP distribution, corresponding to maximization of sensitivity or specificity (see text). The gray areas are the false negative and false positive. The blue line is the NTP sex-specific median, corresponding to the proposed balanced scenario.

A balanced position could be that of considering echocardiography above the sex-specific median of nomogram total score (>136 in men and >124 in women). Using this policy, we would reserve the echocardiographic study to the patients with probability of LVH $>50\%$ (570/1027 subjects, or 56%). Approximately 2 echocardiographic examinations would be needed in these patients to diagnose one patient with LVH.

Adoption of policies mostly oriented to sensitivity or specificity depends also on conditions and settings not primarily medical in nature, but involving types of health system (whether private or government based), hospital or outpatient points-of-care organization, capital investment, and, eventually, priorities defined on the basis of resource allocation. Although nobody denies the potential utility of echocardiographic information in the management of hypertensive patients, doubts remain about its efficacy on decision making, conditioned on a convenient cost/benefit ratio. As said, the few analyses available suggest that identification of echocardiographic LVH might make the increased cost of screening convenient,^{21,22} but we still lack structured analyses on long-term effects on morbidity, mortality, quality of life, and subsequent treatment costs.³⁰ In a prior analysis conducted in selected hypertensive patients at low cardiovascular risk, we found that LVH defined by echocardiography effectively changed the risk status defined by the occurrence

of subsequent major cardiovascular events.⁶ The proposed nomogram point score can help in making a decision and further improving the cost/benefit ratio. Systolic and diastolic function in PIUMA study low-risk participants has been previously reported.³¹

Our study has some limitations. It has been conducted using a longitudinal registry of initially untreated white patients with office hypertension. Therefore, extrapolation of results to different ethnic groups, or treated patients at the time of initial echocardiographic study, requires caution. Furthermore, although we internally validated the model through 1000 bootstrap samples, our results merit to be externally tested in an independent validation sample.

In conclusion, we derived a novel score to evaluate the probability of echocardiographic LVH. The proposed score uses simple variables, readily obtainable, associated with prevalent LVH. The score can identify hypertensive patients most likely to benefit from echocardiographic study for recognition of LVH in terms of risk profiling and decision making.

Sources of Funding

This work was supported in part by the no-profit foundation “Fondazione Umbra Cuore e Ipertensione-ONLUS,” Perugia, Italy.

Disclosures

None.

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