CJC Open ■ (2023) 1–10

Systematic Review/Meta-analysis

Diagnostic Accuracy of ECG to Detect Left Ventricular Hypertrophy in Patients with Left Bundle Branch Block: A Systematic Review and Meta-analysis

Isabela A.F. de Souza, MD,[a] Eduardo M.H. Padrao, MD,[b] Isabela R. Marques, MD,[c] Isabele A. Miyawaki,[d] José Eduardo Riceto Loyola Júnior, MD,[e] Vittoria Caporal S. Moreira,[f] Cintia Gomes, MD,[g] Caroliny H.A. Silva,[h] Carson Oprysko, DO,[i] Augusto Barreto do Amaral Neto, MD,[j] Rhanderson Cardoso, MD,[k] Nelson Samesiana, MD, PhD,[l] Carlos Alberto Pastore, MD, PhD,[l] and Caio A.M. Tavares, MD, PhD[l,m]

[a] *Faculdade de Medicina de Petrópolis, Petrópolis, Rio de Janeiro, Brazil;* [b] *Department of Pulmonary and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA;* [c] *Universitat Internacional de Catalunya, Barcelona, Catalunya, Spain;* [d] *Universidade Federal do Paraná, Curitiba, Paraná, Brazil;* [e] *Hospital Alemão Oswaldo Cruz, São Paulo, SP, Brazil;* [f] *Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, SP, Brazil;* [g] *Universidade Federal de Santa Maria, Santa Maria, Rio Grande do Sul, Brazil;* [h] *Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil;* [i] *Department of Internal Medicine, University of Connecticut, Farmington, Connecticut, USA;* [j] *Central Montana Medical Center, Lewistown, Montana, USA;* [k] *Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA;* [l] *Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, São Paulo, SP, Brazil;* [m] *Academic Research Organization (ARO), Hospital Israelita Albert Einstein, São Paulo, SP, Brazil*

ABSTRACT

Background: Electrocardiographic (ECG) criteria to detect left ventricular hypertrophy (LVH) in patients with left bundle branch block (LBBB) remain under debate. We conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of different ECG criteria for diagnosing LVH in patients with LBBB.

Methods: We searched PubMed, Embase, Cochrane, and LILACS for articles evaluating the diagnostic accuracy of ECG criteria for LVH in patients with LBBB published between 1984 and 2023. Echocardiogram, magnetic resonance imaging, or autopsy were used as the reference standard for diagnosis of LVH. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. The co-primary outcomes were sensitivity, specificity, the diagnostic odds ratio, and likelihood ratios, estimated using a bivariate generalized linear mixed model for each ECG criterion. The prespecified protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO).

RÉSUMÉ

Contexte : Les critères électrocardiographiques (ECG) visant à détecter une hypertrophie ventriculaire gauche (HVG) chez les patients présentant un bloc de branche gauche (BBG) font encore l'objet de discussions. Nous avons réalisé une synthèse des publications et une méta-analyse afin d'évaluer l'exactitude diagnostique de différents critères ECG pour le diagnostic de l'HVG chez les patients présentant un BBG.

Méthodologie : Nous avons effectué une recherche dans les bases de données PubMed, Embase, Cochrane et LILACS afin de recenser les articles publiés entre 1984 et 2023 portant sur l'évaluation de l'exactitude de critères ECG pour le diagnostic d'une HVG chez les patients présentant un BBG. L'échocardiographie, l'imagerie par résonance magnétique et l'autopsie ont servi de normes de référence pour le diagnostic de l'HVG. Le risque de biais a été évalué au moyen de l'outil QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies). Les principaux critères d'évaluation étaient la sensibilité, la spécificité, le risque relatif approché

Left ventricular hypertrophy (LVH) is an important prognostic marker in pressure-overloaded states.[1] In patients with hypertension, the presence of LVH is associated with increased mortality and risk for cardiovascular events.[2-4] Additionally, in individuals with aortic stenosis, LVH is associated with a higher risk of mortality and hospitalization.[5,6] Early identification of LVH is necessary for the appropriate clinical management of hypertension and other concomitant conditions.[7,8]

Cardiac imaging modalities, including magnetic resonance imaging (MRI), computed tomography, and echocardiography, provide a more comprehensive assessment of left ventricular mass, cardiac structure, and function, compared with the electrocardiogram (ECG), and they are more accurate in identifying LVH.[7,9,10] However, given its low cost, widespread availability,

Received for publication May 22, 2023. Accepted August 24, 2023.

Corresponding author: Dr Isabela A.F. de Souza, Faculdade de Medicina de Petrópolis - Av. Barão do Rio Branco, 1003, Petrópolis, Rio de Janeiro 25680-120, Brazil. Tel.: +1-231-393-5500.

E-mail: isabelaazevedofe@gmail.com (I. A.F. de Souza)

See page 8 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.08.010

Results: We included 12 studies with a total of 1023 patients. We analyzed 10 criteria for LVH on ECG, including the Sokolow-Lyon criterion, the Cornell criterion, the RaVL (R wave in aVL) criterion, the Gubner-Ungerleider criterion, and the Dálfo criterion, among others. The Dalfó criterion was used for 487 patients and had the highest pooled sensitivity of 86% (95% confidence interval [CI] 57%-97%). All the other criteria had poor sensitivities. The Gubner-Ungerleider criterion and the RV5 or RV6 $>$ 25 mm criterion had the highest specificities, with the former being used for 805 patients, obtaining a specificity of 99% (95% CI 80%-100%) and the latter being used for 355 patients, obtaining a specificity of 99% (95% CI 94%-100%).

Conclusions: In patients with LBBB, the use of ECG criteria had poor performance for ruling out LVH, mostly due to low sensitivities. None of the criteria analyzed demonstrated a balanced tradeoff between sensitivity and specificity, suggesting that ECG should not be used routinely to screen for LVH.

Résultats : Nous avons recensé 12 études, comptant au total 1 023 patients. Nous avons analysé 10 critères pour le diagnostic d'HVG à l'ECG, notamment l'indice de Sokolow-Lyon, l'indice de Cornell, l'onde R en aVL, l'indice de Gubner-Ungerleider et l'indice de Dálfo. Ce dernier a été utilisé pour 487 patients et avait la sensibilité regroupée la plus élevée, soit 86 % (intervalle de confiance [IC] à 95 % : 57-97 %). La sensibilité de tous les autres critères était faible. L'indice de Gubner-Ungerleider et le critère de l'onde R en V5 ou V6 $>$ 25 mm étaient associés aux spécificités les plus élevées. Le premier a été utilisé pour 805 patients et présentait une spécificité de 99 % (IC à 95 % : 80-100 %). Le second a été utilisé pour 355 patients et présentait une spécificité de 99 % (IC à 95 % : 94-100 %).

Conclusions : Chez les patients présentant un BBG, l'utilisation de critères ECG a été associée à un rendement médiocre pour exclure un diagnostic d'HVG, principalement en raison de la faible sensibilité de ces critères. Aucun des critères analysés n'offrait un compromis équilibré entre la sensibilité et la spécificité, ce qui porte à croire que l'ECG ne devrait pas être utilisée systématiquement pour dépister une HVG.

and diagnostic and prognostic value, the ECG remains relevant.[2] Furthermore, ECG findings of LVH are associated with a higher risk of subsequent cardiovascular morbidity and mortality independent of anatomic LVH assessed by imaging methods.[11] Current guidelines recommend obtaining an ECG as part of routine assessments for patients with hypertension.[7,12]

ECG criteria for detecting LVH are typically based on measurements of QRS voltage, duration, or a combination of both. However, the presence of a left bundle-branch block (LBBB) can pose challenges to establishing an accurate diagnosis, as it alters the electrical activation pattern of the left ventricle, resulting in changes to QRS morphology and duration.[13]

The prevalence of LBBB and cardiovascular diseases increases with aging.[14,15] Coupled with the ongoing global trend of populational aging,[16] this increase will result in a significant proportion of individuals worldwide who will be at risk for LVH in the coming decades. In this context, the ECG, with its distinctive features, could emerge as a valuable tool for identifying LVH within this expanding population. However, most criteria to diagnose LVH were developed and validated in patients without conduction disorders.[17]

The diagnostic accuracy of ECG criteria in individuals with LBBB has been explored in a limited number of studies, leading to conflicting evidence. As a result, the applicability of these criteria remains a topic of debate.[18-29] Moreover, new ECG criteria to define LBBB have been proposed recently.[30]

Therefore, we performed a systematic review and meta-analysis to evaluate the diagnostic test accuracy and clinical utility of ECG criteria for detecting LVH in patients with concomitant LBBB, facilitating the development of more precise and cost-effective diagnostic strategies.

Material and Methods

A predefined protocol was established and prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42022361459.[31] The study is in accordance with the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[32] and the Preferred Reporting Items for Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement.[33]

Data sources and search strategy

We searched Embase, PubMed (MEDLINE), Cochrane Database of Systematic Reviews, Clinicaltrials.gov, and LILACS (Latin American and Caribbean Health Sciences Literature). We used the following keywords—"ventricular hypertrophy," "left ventricular hypertrophy," "LBBB," and "left bundle branchblock"—for our search strategy, which is available in Supplemental Appendix S1. We also searched for references within the articles included in our analysis.

Study selection and eligibility criteria

We included studies assessing the sensitivity and specificity of ECG criteria for LVH in adult patients with concomitant LBBB. Table 1 provides a comprehensive overview of different ECG criteria along with corresponding cutoff values used for diagnosing LVH. Echocardiography or MRI or autopsy were considered as the reference standard. We included all types of studies except case reports and case series. The authors were contacted by e-mail if the study did not provide the necessary information. Studies that did not provide sufficient information on diagnostic test accuracy for our meta-analysis were excluded. Additionally, abstracts that did not result in a publication or did not provide sufficient information for data collection were excluded, as shown in Figure 1. No language restrictions were applied. Studies with overlapping patient populations were excluded, and only the largest cohort was examined.

Data collection

Two review authors (I.A.F.S. and C.G.) independently performed study selection and data extraction. In cases of disagreement between the 2 reviewers, a third review author

Table 1. Electrocardiogram (ECG) criteria and cutoffs for left ventricular hypertrophy in patients with left bundle branch block

Criteria	Formula	Threshold
Sokolow-Lyon	SV1 + tallest R wave (V5 or V6)	≥ 3.5 mV
Cornell voltage	RaVL + SV3	≥ 2.8 mV, male ≥ 2.0 mV, female
RaVL	RaVL	≥ 1.1 mV or > 1.1 mV
Lewis index	(RI + SIII) − (RIII+ SI)	> 1.7 mv
Dalfó	RaVL + SV3	> 1.6 mV, male > 1.4 mV, female
RV6/RV5 ratio	RV6/RV5	> 1
RV5 or RV6 > 25 mm	RV5 or RV6	> 25 mm
Gubner-Ungerleider	RI + SIII	> 25 mm
QRS > 160 ms	QRS duration	> 160 ms
Left atrial enlargement	Baranowski[18]: P wave duration in II > 100 ms and/or P terminal force in V1 ≥ 0.04 mV/s Burgos[19]: P wave alteration at D2 with slurring in the apex or Morris signal in V1; terminal component with duration and amplitude ≥ 0.04 mm/s	P wave duration II > 100 ms; P terminal force V1 ≥ 0.04 mV/s P wave D2 with slurring in the apex; Morris signal in V2; terminal component duration and amplitude ≥ 0,04 mm/s

RaVL, R wave in aVL.

(E.M.H.P.) was involved in resolving the discrepancies. Two reviewers (I.A.F.S. and C.G.) extracted the following information: (i) the ECG criteria for LVH used in the study; (ii) the method used for the diagnostic reference standard; (iii) the description of LBBB criteria used; (iv) the values for sensitivity, specificity, true positives, true negatives, false positives, and false negatives for each ECG criteria; (v) the total number of patients with LBBB; (vi) the number of patients positive for the target disease (LVH) according to the reference standard diagnostic test; (vii) demographic data; and (viii) the time between the reference standard and the ECG. Because some studies did not test the same ECG criteria, we selected ECG criteria that were available in at least 3 studies.

Quality assessment

The revised Quality Assessment of Diagnostic Accuracy Studies[34] tool was used by 2 independent reviewers (I.A.F.S. and C.G.) to assess the quality and potential bias of all studies, as recommended per Cochrane.[32] Conflicts were resolved via discussion with and involvement of a third author (E.M.H.P.).

Statistical analysis

The Cochrane Handbook for Systematic Reviews[32] was used to guide the data synthesis. A bivariate generalized linear mixed model of sensitivity and specificity, as proposed by Chu and Cole,[35] was fitted to estimate pooled sensitivity and specificity, likelihood ratios(LRs), and diagnostic odds ratios (DORs), along with their 95% confidence intervals (CIs) for each ECG criterion. The hierarchical summary receiver operator characteristics (HSROC) parameters were estimated using the bivariate model parameters and the equivalence equations.[36] Analysis was performed using the program MetaDTA, as recommended per Cochrane.[32] The MetaDTA program uses the R language in an interactive approach through the {glmer} package.[37]

Diagnosis of heterogeneity was carried out through the asymmetry of the summary receiver operator characteristics (SROC) curve and the degree of dispersion of the included studies as recommended per the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[32] Additionally, we took into consideration the correlation coefficient between sensitivity and specificity. To explore potential heterogeneity, we conducted 2 sensitivity analyses for certain ECG criteria, specifically focusing on risk of bias and the setting (inpatient or outpatient) in a post hoc analysis. Furthermore, we conducted a post hoc sensitivity analysis for the RaVL (R wave in aVL) criterion, owing to the use of 2 different cutoff values across studies. Analysis of the risk of publication bias was conducted when the number of studies was sufficient. We used the Deeks test to check for funnel plot asymmetry when appropriate, as recommended.[38] We used the {metafor} package in R software (version 3.6.2, R Foundation, Vienna, Austria)[39] to perform the Deeks test.

We utilized decision curve analysis to assess the clinical utility of ECG criteria by assessing the balance between the benefits (true positive results) and harms (false positive results) at different threshold probabilities, with the net benefit (NB) used as the measure to evaluate this tradeoff.[40] Threshold probability refers to the minimum probability of disease above which any intervention or treatment would be considered.[41,42] In our study, we examined the performance of ECG criteria across a wide range of threshold probabilities (0%-50%) and compared it to 2 hypothetical strategies—one in which cardiac imaging was performed for all patients ("treat-all"), and another in which cardiac imaging was not performed for any patient ("treat-none"). To construct decision curves, we used a simulated dataset of 1000 individuals, with a 58% prevalence of LVH, which is the observed pooled prevalence of LVH in the meta-analysis. Two sensitivity analyses also were conducted using the lowest and highest observed prevalence from the studies included in our analysis.

Results

Study characteristics

We obtained a total of 2009 abstracts or manuscripts. A complete flow diagram is presented in Figure 1. After removing duplicate records and those studies that met the exclusion criteria based on title and abstract review, 33 studies remained, and these were fully reviewed for inclusion and exclusion criteria. Of those, 21 had one or more exclusion

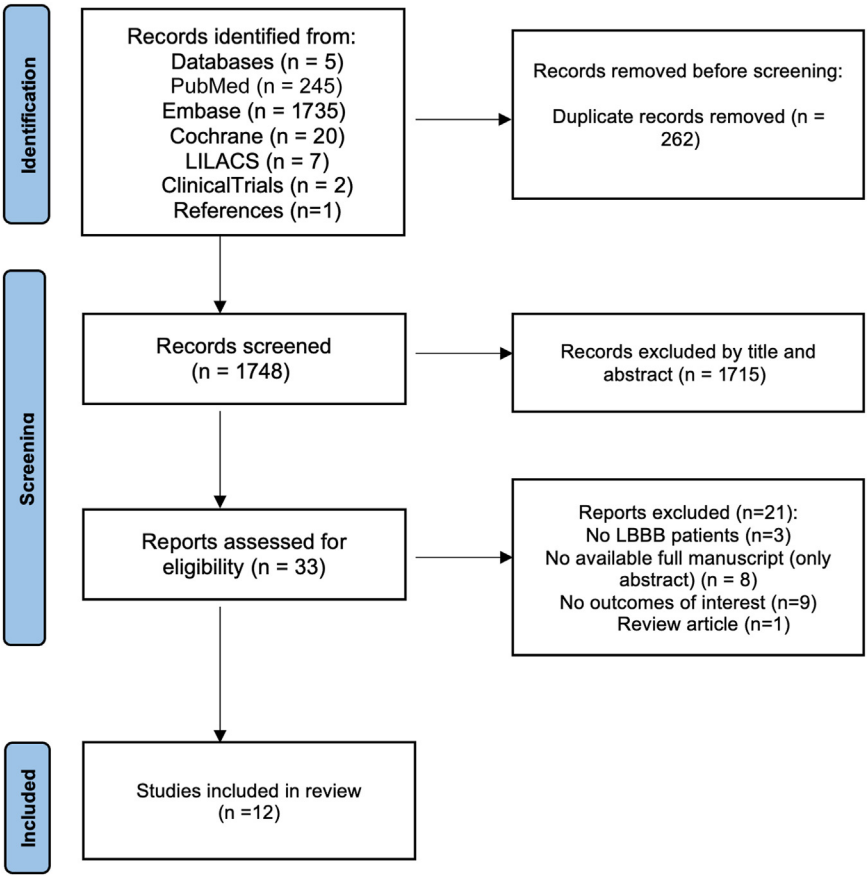

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram: Flow diagram of study selection. LBBB, left bundle branch block; LILACS, Latin American and Caribbean Health Sciences Literature.

criteria, as explained in Figure 1. Twelve manuscripts met all inclusion criteria.[18-29]

Evaluation of bias

The risk of bias was considered high for 7 studies, per the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Supplemental Table S1), due to patient selection and reference standard domains. Regarding patient selection, 2 studies were considered high risk due to a lack of consecutive analysis of patients with LBBB[18,19] and inappropriate exclusions.[19] For the reference standard domain, 4 studies were deemed high risk due to researchers potentially having knowledge of index test results before the reference standard test was performed.[21,24,26,28] One study was considered high risk on the reference standard domain because of incorrect classification of the target condition.[23] All of the included studies in this review had low applicability concerns, which included patient selection, index test, and reference standard.[18-29]

Studies and population characteristics

Twelve studies were included in the meta-analysis, yielding a total of 1023 patients. The characteristics of included studies are summarized in Table 2. Echocardiogram was the most common reference standard for diagnosis and was used in 10 studies.[19-21,23-29] Autopsy[22] and cardiac MRI[15] were each used in one study, respectively. Among the studies that used echocardiogram as the reference standard, 6 used left ventricle m-mode mass index,[19,20,23,25,27,29] and 5 used left ventricle m-mode mass.[20,21,24,26,28]

The included studies differed in the LBBB definition criteria used. Only one study [29] used a strict definition for LBBB (Strauss criteria) as the diagnostic criterion for true LBBB. Although some minor differences were noticed in LBBB criteria, most studies used the following: (i) QRS interval $\geq$ 120 ms; (ii) absence of q waves in leads I, V5, V6, and aVL; (iii) notched or slurred R wave in leads I, aVL, V5, and V6; (iv) broad slurred S waves in V1 and V2. Supplemental Table S2 summarizes the LBBB criteria used in each study. Among the LVH criteria, the Sokolow-Lyon criterion was used most commonly, in 11 studies. The Gubner-Ungerleider and the RaVL criteria were used in 8 studies, RV5 or RV6 $>$ 25 mm criterion were used in 6 studies, and the left atrial enlargement criterion were used in 6 studies. Other ECG LVH criteria were found in 5 or fewer studies, as shown in Table 3. The prevalence of LVH in the studies ranged from 45.9% to 89.3%, with the greatest prevalence being in Noble et al.[26] and the lowest prevalence being in Haskell et al.[21] The mean age of the participants ranged from 39 to 78 years, and the prevalence of female participants ranged from 0% to 71.4%. The time between the ECG and the reference standard that was performed ranged from simultaneous completion to 6 months.

Table 2. Baseline characteristics of included studies

Study (year)	Study design	Population and exam setting	Reference standard	LVH criteria (reference standard)	Time between ECG and reference standard	Number of patients (%)		Age, y	Female sex	Dilated cardiomyopathy	Coronary artery disease	Hypertrophic cardiomyopathy	Valvular disease	Hypertension
						LBBB only	LBBB + LVH							
Baranowski et al.[18] (2012)	R	Patients with CMRI with LBBB on ECG. Setting not available.	CMRI	Exceeding reference values for sex and age in the normal population according to A. M. Maceira et al.[51]	NA	36 (100)	17 (47.2)	57 ± 12	15 (41.6)	15 (41.6)	Ischemic cardiomyopathy: 9 (25)	4 (11.1)	NA	NA
Burgos et al. [19] (2017)	P	Hypertensive patients. Outpatient setting.	Echo	LV mass index ≥ 96 g/m^2 for women and ≥ 116 g/m^2 for men.	Same day	186 (8.3)	126 (5.62)	63.4 ± 8.5	112 (60.2)	0	NA	NA	NA	186 (100)
Fragola et al.[20] (1990)	P	23–92 years old with CLBBB on ECG. Outpatient and inpatient setting.	Echo	LV mass > 241 g or > 120 g/m^2.	15 d	100 (100)	66 (66)	39 ± 14	42 (42)	19 (19)	22 (22)	4 (4)	10 (10)	27 (27)
Haskell et al.[21] (1987)	P	Complete LBBB, available for echo. Setting not available.	Echo	LV mass > 281 g	Same day	37 (100)	20 (54)	60.7 ± 12.0	23 (62)	51%	16%	NA	24%	Hypertensive heart disease: 5%
Havelda et al. [22] (1982)	R	Autopsied male patients. Inpatient setting.	Autopsy	LV mass > 180 g	NA	70 (100)	48 (68.57)	LBBB + LAXD 67.1 ± 7.8 and LBBB nl axis 64.6 ± 11.6	0	NA	1-vessel: 21.4% 2-vessel: 17.1% 3-vessel: 7.14%	NA	NA	NA
Kafka et al.[23] (1985)	P	LBBB adult patients selected from ECG files. Setting not available.	Echo	LV mass index ≥ 115 g/m^2	NA	125 (100)	LV mass ≥ 215 g: 56% LVM ≥ 115g/m^2: 7%	66	40.8%	NA	44.8%	NA	8%	12.8%
Klein et al.[24] (1984)	R	LBBB adult patients selected from ECG files. Setting not available.	Echo	LV mass > 260 g based on M-mode or LV posterior wall thickness > 1.1 cm	Up to 6 mo	44 (100)	21 (47.7)	NA	NA	NA	29.4%	4.54%	29.4%	29.4%
Lépori et al.[25] (2015)	R	CLBBB adult patients who had a TTE performed. Outpatient and inpatient setting.	Echo	LV mass index > 116 g/m^2 (men) or > 96 g/m^2 (women)	Up to 6 mo	101 (100)	60 (59.4)	68 ± 12	42.5%	NA	42%	NA	12%	85%
Noble et al.[26] (1984)	P	LBBB adult patients selected from ECG files. Setting not available.	Echo	Echo LV mass > 215 g	NA	30 (100)	25 (83.3)	68	0%	NA	30%	NA	6.6%	20%
Rodríguez-Padial et al.[27] (2012)	R	LBBB adult patients selected from ECG files with simultaneous TTE. Outpatient setting.	Echo	LV mass index > than 134 g/m^2 (men) or > 110 g/m^2 (women).	Same day	233 (12.45)	140 (7.46)	67.1 +- 12.6	46.8%	NA	NA	NA	NA	62.3%
Rohatgi et al.[28] (1993)	P	LBBB adult patients selected from ECG files. Setting not available.	Echo	LV mass of 215 g or more	NA	20 (100)	10 (50)	Between 34 and 52	NA	NA	0	NA	NA	55%
Tavares et al. [29] (2021)	R	LBBB adult patients with echocardiogram selected from ECG files. Outpatient and inpatient setting.	Echo	LV Mass Index > 95 g/m^2 in females and > 115 g/m^2 male subjects	Up to 6 mo	68 (100)	46 (67.6)	78.4 (IQR 73.3–83.4)	55.9%	NA	47.1%	NA	NA	73.5%

Values are n (%) or mean ± standard deviation, unless otherwise indicated.

CLBBB, complete left bundle branch block; CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; Echo, echocardiogram; IQR, interquartile range; LAXD, left axis deviation; LBBB, left bundle branch block; LV, left ventricle; LVH, LV hypertrophy; NA, not available; P, prospective; R, retrospective; TTE, transthoracic echocardiography.

Table 3. Pooled results

Criteria	Number of studies (number of patients)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Diagnostic odds ratio (95% CI)	Positive likelihood ratio	Negative likelihood ratio
Sokolow-Lyon	11 (922)	0.34 (0.24−0.46)	0.88 (0.80−0.93)	3.70 (2.44−5.62)	2.78 (1.98−3.97)	0.75 (0.66−0.86)
Cornell	5 (688)	0.64 (0.40−0.82)	0.47 (0.17−0.79)	1.53 (0.84−2.78)	1.19 (0.84−1.70)	0.78 (0.60−1.02)
RaVL	8 (805)	0.15 (0.09−0.24)	0.95 (0.83−0.98)	3.12 (1.04−9.32)	2.80 (0.98−7.96)	0.90 (0.83−0.97)
Left atrial enlargement	6 (494)	0.47 (0.29−0.66)	0.88 (0.77−0.94)	6.22 (1.70−22.74)	3.78 (1.52−9.4)	0.61 (0.40−0.92)
Lewis index	4 (423)	0.26 (0.17−0.37)	0.94 (0.78−0.98)	5.12 (1.20−21.81)	4.06 (1.06−15.54)	0.79 (0.68−0.92)
QRS > 160 ms	5 (374)	0.46 (0.27−0.66)	0.74 (0.50−0.89)	2.44 (1.39−4.29)	1.78 (1.12−2.85)	0.73 (0.59−0.90)
Gubner-Ungerleider	8 (805)	0.16 (0.05−0.44)	0.99 (0.80−1.00)	18.39 (2.21−152.72)	15.59 (1.68−144.36)	0.85 (0.70−1.03)
RV5 or RV6 > 25 mm	6 (355)	0.08 (0.03−0.19)	0.99 (0.94−1.00)	11.28 (1.25−101.53)	10.43 (1.20−90.32)	0.92 (0.86−1.00)
RV6/RV5 ratio	4 (619)	0.61 (0.36−0.81)	0.30 (0.08−0.69)	0.68 (0.32−1.43)	0.88 (0.74−1.04)	1.29 (0.72−2.32)
Dalfó	3 (487)	0.86 (0.57−0.97)	0.20 (0.02−0.78)	1.56 (0.42−5.79)	1.08 (0.77−1.51)	0.69 (0.26−1.84)

CI, confidence interval.

Pooled sensitivities

The Dalfó criterion had the highest pooled sensitivity at 86% (95% CI 57%-97%), being used in 3 studies and for 487 patients. The second-highest pooled sensitivity was obtained with the Cornell criterion, reaching 64% (95% CI 40%-82%), which were used in 5 studies and for 688 patients. The RV6/RV5 ratio obtained a similar pooled sensitivity of 61% (95% CI 36%-81%), being used in 4 studies and for 619 patients. All other criteria had poor sensitivity, ranging from 8% to 47%, as shown in Table 3.

Pooled specificities

The Gubner-Ungerleider and the RV5 or RV6 > 25 mm criteria had the highest specificities. The Gubner-Ungerleider criterion was used in 8 studies and for 805 patients, yielding a specificity of 99% (95% CI 80%-100%), and the RV5 or RV6 > 25 mm criterion was used in 6 studies and for 355 patients, yielding a specificity of 99% (95% CI 94%-100%). The Lewis index and the RaVL criterion also had high specificities, > 90%. The Lewis index had a specificity of 94% (95% CI 83%-98%), and was used in 4 studies and for 423 patients. The RaVL criterion had a specificity of 95% (95% CI 83%-98%), and was used in 8 studies and for 805 patients. Other criteria pooled specificities are shown in Table 3.

DOR, positive LR, and negative LR

The highest DOR obtained was 18.39 (95% CI 2.21-152.72) with the Gubner-Ungerleider criterion, which also had the highest positive LR, 15.59 (95% CI 1.68-144.36). Additionally, the RV5 or RV6 > 25 mm criterion had a high DOR of 11.28 (95% 1.25-101.53), with a high positive LR of 10.43 (95% CI 1.20-90.32). All 3 criteria had large CIs. The RV6/RV5 ratio had the lowest DOR, 0.68 (95% CI 0.32-1.43). Table 3 presents all results obtained for DOR, and positive and negative LRs.

SROC

We present an ROC graph with the pooled number of patients, sensitivity, and specificity for each criterion (Fig. 2). We present the SROC for each LVH criterion (Supplemental Figs. S1-S10). We also performed sensitivity analysis as planned when data were available. For the Sokolow-Lyon, Gubner-Ungerleider, left atrial enlargement, and RaVL criteria, we were able to perform sensitivity analysis for high and low risk of bias studies and according to the reference standard (Supplemental Table S3; Supplemental Figs. S11-S14). We performed a post hoc sensitivity analysis of the studies using the criterion of RaVL > 11 mm and those using the criterion of RaVL ≥ 11 mm (Supplemental Table S3; Supplemental Fig. S15), as the studies used these 2 different thresholds for RaVL. Post hoc sensitivity analysis according to the setting (inpatient, outpatient, or mixed) is shown in Supplemental Table S3 and Supplemental Figures S16-S18. We also present a SROC with all criteria and studies (Supplemental Figure S19).

Clinical utility and decision curve analysis

Across the threshold probability range of 0%-50%, the "treat-all" hypothetical strategy was found to have a higher net benefit than all ECG criteria, indicating little to no clinical utility of all the ECG criteria (Fig. 3). This finding was consistent across the sensitivity analysis using the lowest (46%) and highest (89%) prevalence of LVH (Supplemental Figs. S20 and S21).

Publication bias analysis

Due to the paucity of studies for most LVH criteria, we were able to perform only the Deek's test for the evaluation of publication bias for the Sokolow-Lyon criterion (Supplemental Fig. S22). Studies were distributed evenly on both sides of the regression line with a *P*-value of 0.68, suggesting no publication bias.

Discussion

This meta-analysis and systematic review of the diagnostic accuracy of ECG criteria for LVH found that most ECG criteria for LVH in patients with LBBB have poor sensitivity but high specificity. Driven by the low sensitivity, the overall negative LR obtained was poor. The positive LR obtained yielded important values for only the Gubner-Ungerleider and the RV5 or RV6 > 25 mm criteria.

The only criterion with sensitivity above 70% was the Dalfó, with a pooled sensitivity of 86% (95% CI 57%-97%). However, the amount of data was limited, which likely led to wide CIs. The data also did not show a balanced tradeoff between sensitivity and specificity, expressed in poor positive LR value, negative LR, and DOR, resulting in low clinical utility.

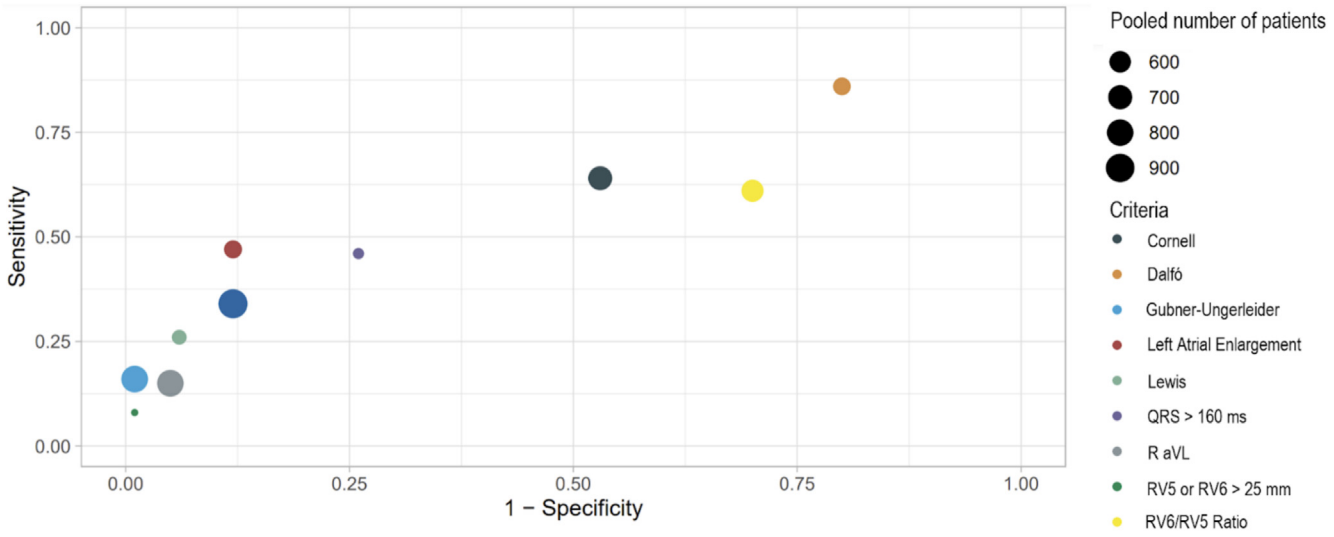

Figure 2. Summary receiver operator curve with pooled sensitivity and specificity for each study: Each criterion for left ventricular hypertrophy, with its pooled sensitivity and specificity, is plotted on the graph according to the size of the pooled population.

Given that the prevalence of LBBB and associated cardiovascular diseases increases with age,[15] robust evidence is needed to guide the clinical utility of ECG in this growing population.[43] ECG is a low-risk, quick, reproducible, and economically feasible test that could be used routinely to detect LVH and provide follow-up information after treatment modification, such as regression of LVH on the ECG—which also confers prognostic information.[44,45] Our study found that most ECG criteria have high specificity but lack clinical utility to support their routine use for detection of LVH in patients with LBBB.

The majority of ECG criteria for LVH demonstrated reasonably high specificity, with the Sokolow-Lyon criterion, the RaVL criterion, the left atrial enlargement criterion, the Lewis index, the Gubner-Ungerleider criterion, and the RV5 or RV6 > 25 mm criterion having specificities ranging from 88% to 99%. However, because the ability of diagnostics tests to make determinations in a certain condition depends on both sensitivity and specificity, none of the tested ECG criteria would have enough power to determine LVH properly. The high specificities observed are mostly eroded by the low sensitivities.[46] Exceptions include the Gubner-Ungerleider criterion and the RV5 or RV6 > 25 mm criterion, for which the positive LR was higher than 10. However, an important point to acknowledge is that the 95% CIs for both these criteria exhibit a considerable degree of imprecision, thereby limiting their clinical utility and interpretation. Furthermore, none of the ECG criteria had a good negative LR. A high negative LR would be useful for safely ruling out LVH and avoiding further testing, such as an echocardiogram.

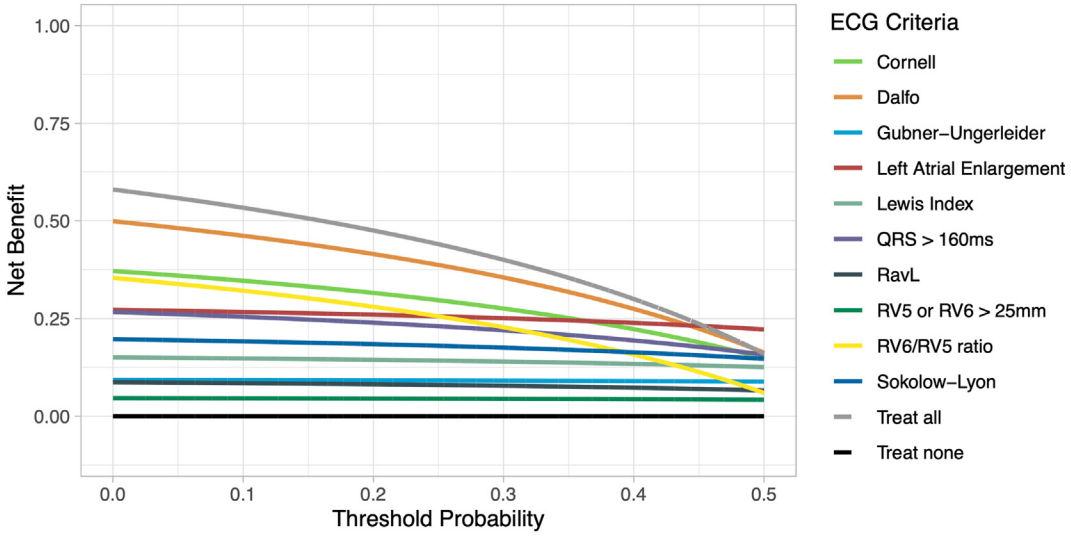

Figure 3. Decision curve analysis: Across the threshold probability range of 0%-50%, the "treat-all" hypothetical strategy was found to have a higher net benefit than all electrocardiogram (ECG) criteria, indicating little to no clinical utility of all ECG criteria. This finding was consistent across the sensitivity analysis using the lowest (46%) and highest (89%) prevalence of left ventricular hypertrophy (Supplemental Figs. S21 and S22).

The ECG criteria utilized for detecting LVH in patients without conduction disease typically exhibit low sensitivities.[46] These criteria are employed primarily to confirm the presence of LVH. In a recent meta-analysis,[47] the diagnostic performance of the Sokolow-Lyon and the Cornell voltage criteria yielded higher positive LRs than those observed in our study (8.0 vs 2.78 and 5.14 vs 2.19, respectively). This finding further suggests that in patients with LBBB, the ECG has limited utility in both ruling in and ruling out LVH.

According to current guidelines, all diagnosed cases of LBBB should be investigated with an imaging modality for cardiac morphologic assessment.[48] This standard approach is appropriate for a population with an intermediate-high pretest probability of disease, as demonstrated by our study, in which the prevalence of LVH ranged between 46% and 89%. As the detection of LVH in clinical practice is important and can impact clinical management and outcomes,[7,12] the use of any of the tested ECG criteria without further testing would lead to an unacceptably high number of false negatives. This conclusion is further supported by the results of the decision curve analysis performed in our study (Fig. 3). The objective of applying a decision curve analysis was to assess the effectiveness of using ECG criteria as a guide for determining the need for additional cardiac imaging, such as an echocardiogram. The decision curve considers the physician's willingness to tolerate a certain number of false-positive cases (ordering echocardiograms without LVH) in order to avoid missing a false-negative case (a patient who shows an LVH on echocardiogram but does not meet the LVH criteria on ECG). In our study population, considering the observed pooled prevalence of LVH, ordering echocardiograms for all patients was determined to have resulted in a higher net benefit across all threshold probabilities, as compared to an approach based on ECG criteria. Our findings were consistent with similar conclusions from other studies,[20] even when more-strict criteria for LBBB were used.[29,30]

Therefore, due to the lack of sensitivity of most criteria, our study supports the current American Heart Association guidelines, which recommend obtaining an echocardiogram for all patients with LBBB.[48] For places with limited resources, where an echocardiogram is not feasible for all patients, we were unable to conclude that the use of ECG criteria had adequate diagnostic performance for the detection of LVH. Our results do not support the routine use of any ECG criteria to guide a specific approach, to order further imaging, or to inform treatment decisions.

Limitations

Our study has several limitations. First, the studies had different populations, LVH prevalence, settings in which the exams were performed (inpatient vs outpatient), and reference standards. This resulted in wide CIs in most tests. Among the studies that used echocardiogram as a reference standard, many did not use the mass index or the appropriate reference range recommended.[49] However, sensitivity analysis for low risk of bias studies resulted in results similar to those for analysis including all studies. Second, only one study used more-stringent criteria for LBBB.[30] Use of less-strict criteria for LBBB may include those patients who have left ventricle myocardial disease and not necessarily purely conduction system disease. This approach may falsely inflate the sensitivity of the ECG criteria, which in most pooled results are already low. Nevertheless, our results are similar to those of the single study that included only patients with strict LBBB criteria.[29] Third, the LVH criteria used by different studies were slightly different, which can undermine the accuracy of the sensitivity and specificity. However, sensitivity analyses comparing the different cutoffs for those criteria showed similar results. Fourth, an important point to note is that our findings may be limited by the high prevalence of LVH in the studied population, which could artificially alter specificities and sensitivities, owing to the spectrum effect.[50] Finally, we were not able to assess the potential impact of differences in the characteristics of the populations included in the studies.

Conclusion

In patients with LBBB, ECG criteria had poor performance in diagnosing LVH, mostly due to having low sensitivity. Although the tests have high specificity, none of the criteria had a balanced tradeoff between sensitivity and specificity, nor did they demonstrate clinical utility. This finding suggests that ECG alone should not be used routinely to detect LVH or inform treatment decisions in this population. Further research in patients with LBBB, using stricter definitions, is needed.

Acknowledgements

The authors thank Dr. Douglas D'Andrea.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines. All data are publicly available in the relevant primary and secondary papers.

Patient Consent

The authors confirm that patient consent is not applicable to this article. Meta-analysis is conducted using data extracted from previously published research, and all the data and study materials are available in the public domain. The authors of this meta-analysis do not have access to patient-level data of the individual studies.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 2000;102:470-9.

2. Sundström J, Lind L, Arnlöv J, et al. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. Circulation 2001;103:2346-51.

3. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol 1998;32:1454-9.

4. Okin PM, Wachtell K, Devereux RB, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA 2006;296:1242-8.

5. Gonzales H, Douglas PS, Pibarot P, et al. Left ventricular hypertrophy and clinical outcomes over 5 years after TAVR: an analysis of the PARTNER trials and registries. JACC Cardiovasc Interv 2020;13:1329-39.

6. Stein EJ, Fearon WF, Elmariah S, et al. Left ventricular hypertrophy and biomarkers of cardiac damage and stress in aortic stenosis. J Am Heart Assoc 2022;11:e023466.

7. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104 [Erratum in Corrigendum to: 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2019;40:475].

8. Cuspidi C, Facchetti R, Bombelli M, et al. High normal blood pressure and left ventricular hypertrophy echocardiographic findings from the PAMELA population. Hypertension 2019;73:612-9.

9. Oseni AO, Qureshi WT, Almahmoud MF, et al. Left ventricular hypertrophy by ECG versus cardiac MRI as a predictor for heart failure. Heart 2017;103:49-54.

10. Kühl JT, Nielsen JB, Stisen ZR, et al. Left ventricular hypertrophy identified by cardiac computed tomography and ECG in hypertensive individuals: a population-based study. J Hypertens 2019;37:739-46.

11. Aro AL, Chugh SS. Clinical diagnosis of electrical versus anatomic left ventricular hypertrophy: prognostic and therapeutic implications. Circ Arrhythm Electrophysiol 2016;9:e003629.

12. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13-115 [Erratum in Correction to: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e140-4].

13. Tan NY, Witt CM, Oh JK, Cha YM. Left bundle branch block: current and future perspectives. Circ Arrhythm Electrophysiol 2020;13:e008239.

14. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. Circulation 1998;98:2494-500.

15. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res 2012;110:1097-108.

16. The Lancet Healthy Longevity. Care for ageing populations globally.". Lancet Healthy Longev 2021;2:e180.

17. Hancock EW, Deal BJ, Mirvis DM, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:992-1002.

18. Baranowski R, Małek L, Prokopowicz D, Spiewak M, Miśko J. Electrocardiographic diagnosis of the left ventricular hypertrophy in patients with left bundle branch block: Is it necessary to verify old criteria? Cardiol J 2012;19:591-6.

19. Burgos PF, Luna Filho B, Costa FA, et al. Electrocardiogram performance in the diagnosis of left ventricular hypertrophy in hypertensive patients with left bundle branch block. Arq Bras Cardiol 2017;108:47-52.

20. Fragola PV, Autore C, Ruscitti G, Picelli A, Cannata D. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block: a wasted effort. Int J Cardiol 1990;28:215-21.

21. Haskell RJ, Ginzton LE, Laks MM. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block. J Electrocardiol 1987;20:227-32.

22. Havelda CJ, Sohi GS, Flowers NC, Horan LG. The pathologic correlates of the electrocardiogram: complete left bundle branch block. Circulation 1982;65:445-51.

23. Kafka H, Burggraf GW, Milliken JA. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block: an echocardiographic study. Am J Cardiol 1985;55:103-6.

24. Klein RC, Vera Z, DeMaria AN, Mason DT. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block. Am Heart J 1984;108:502-6.

25. Lépori AJ, Mishima RS, Rodriguez G, et al. Relationship between electrocardiographic characteristics of left bundle branch block and echocardiographic findings. Cardiol J 2015;22:397-403.

26. Noble LM, Humphrey SB, Monaghan GB. Left ventricular hypertrophy in left bundle branch block. J Electrocardiol 1984;17:157-60.

27. Rodríguez-Padial L, Rodríguez-Picón B, Jerez-Valero M, et al. Diagnostic accuracy of computer-assisted electrocardiography in the diagnosis of left ventricular hypertrophy in left bundle branch block. Rev Esp Cardiol (Engl Ed) 2012;65:38-46.

28. Rohatgi R, Mittal S, Bhardwaj B, Gupta M. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block: an echocardiographic correlation. Int J Cardiol 1993;39:147-50.

29. Tavares CAM, Samesima N, Lazar Neto F, et al. Usefulness of ECG criteria to rule out left ventricular hypertrophy in older individuals with true left bundle branch block: an observational study. BMC Cardiovasc Disord 2021;21:547.

30. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011;107:927-34.

31. de Souza IAF, Gomes CP, Padrao EMH, et al. The role of ECG for detecting left ventricular hypertrophy in patients with left bundle branch block: a systematic review and meta-analysis of diagnostic test accuracy. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=361459. Accessed October 27, 2023.

32. Leeflang MMG, Deeks JJ, Takwoingi Y, Macaskill P. Cochrane diagnostic test accuracy reviews. Available at: https://doi.org/10.1186/2046-4053-2-82. Accessed October 27, 2023.

33. Salameh JP, Bossuyt PM, McGrath TA, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ 2020;370:m2632.

34. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.

35. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol 2006;59:1331-2.

36. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. Biostatistics 2007;8:239-51 [Erratum in Biostatistics 2008; 9:779].

37. Patel A, Cooper NJ, Freeman SC, Sutton AJ. Graphical enhancements to summary receiver operating characteristic plots to facilitate the analysis and reporting of meta-analysis of diagnostic test accuracy data. Res Synth Methods 2021;12:34-44.

38. Van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. BMC Med Res Methodol 2014;14:70.

39. R Core Team. The R project for statistical computing. Available at: https://www.R-project.org/. Accessed October 27, 2023.

40. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565-74.

41. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. Diagn Progn Res 2019;3:18.

42. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA 2015;313:409-10.

43. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374:1196-208.

44. Ascher SB, de Lemos JA, Lee M, et al. Intensive blood pressure lowering in patients with malignant left ventricular hypertrophy. J Am Coll Cardiol 2022;80:1516-25.

45. Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA 2004;292:2343-9.

46. Pewsner D, Battaglia M, Minder C, et al. Ruling a diagnosis in or out with "SpPIn" and "SnNOut": a note of caution. BMJ 2004;329:209-13.

47. Yu Z, Song J, Cheng L, et al. Peguero-Lo Presti criteria for the diagnosis of left ventricular hypertrophy: a systematic review and meta-analysis. PLoS One 2021;16:e0246305.

48. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:932-87.

49. Marwick TH, Gillebert TC, Aurigemma G, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr 2015;28:727-54.

50. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. BMJ 2016;353:i3139.

51. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2006;8:417-26.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.08.010.