CLINICAL STUDY

Novel Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy in the Japanese General Population

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Summary

Although there are several diagnostic criteria for left ventricular hypertrophy (LVH), their sensitivity remains low. A recent study reported that the sum of the amplitude of the deepest S wave in any lead (SD) and the S wave in lead V4 (SV4) (SD + SV4) improved sensitivity compared with commonly used criteria. To test whether this new formula improves sensitivity in the Japanese general population, we analyzed 12-lead electrocardiograms for Japanese residents participating in the Iwaki Health Promotion Project (n = 866). Left ventricular mass was calculated by echocardiography, indicating that 156 (18%) of the study population had LVH. In receiver operating characteristic analyses, the sum of the R wave in limb lead I (RLI) and the S wave in V4 (SV4) (RLI + SV4) showed a higher area under the curve (AUC = 0.76) than the Sokolow-Lyon voltage criteria (0.61) and the SD + SV4 criteria (0.63), and almost the same AUC as the Cornell voltage criteria (0.74) and the Cornell product criteria (0.76). The validation study also showed similar results. The cutoff values of RLI + SV4 criteria were ≥1.6 mV in men and ≥1.4 mV in women with a sensitivity of 39% and a specificity of 89%, whereas the sensitivity and specificity calculated based on SD + SV4 criteria were 21% and 94%, respectively. Thus, the diagnostic criterion of RLI + SV4 seems to be more useful than the previous criteria for diagnosing LVH in the Japanese general population.

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Key words: Electrocardiography, Echocardiography, Cornell voltage, Sokolow-Lyon voltage

Left ventricular hypertrophy (LVH) is an important predictor of cardiovascular events,[1-4] and LVH diagnosed by electrocardiogram (ECG) has been reported to be related to cardiovascular events regardless of the presence or absence of high blood pressure.[1,5-8] These findings suggest that LVH should be diagnosed as early as possible to address the underlying disease, with further examination and treatment intervention as necessary. ECG provides a low-cost examination method; however, previous studies have shown that commonly used ECG diagnostic criteria have low sensitivity for detecting LVH. The sensitivity of the Cornell voltage criteria (men: RaVL + SV3 > 2.8 mV; women: RaVL + SV3 > 2.0 mV) is around 20%-40%, with a specificity of about 90%, and the sensitivity of the Sokolow-Lyon voltage criteria (SV1 + RV5 or RV6 ≥ 3.5 mV) is 20%, with a specificity of 100%.[9,10] Furthermore, the sensitivity of the Cornell product criteria [Cornell voltage (+0.6 mV in women) × QRS duration ≥ 244 mV × ms] is 25%-40%, with a specificity of around 90%.[11-13]

A recent American study reported that the sum of the amplitude of the deepest S wave in any lead (SD) and the S wave in lead V4 (SV4) (SD + SV4 ≥ 2.8 mV in men and ≥2.3 mV in women) provides a more sensitive measure for the ECG diagnosis of LVH (a sensitivity of 62% and a specificity of 90%) compared with the current criteria.[10] It is reported that the diagnostic criteria for LVH can differ between races.[14-17] The aim of the present study, therefore, was to test whether this new diagnostic criterion for LVH improved sensitivity in the Japanese general population.

Methods

This study was part of the Iwaki Health Promotion Project, an ongoing community-based health promotion study of Japanese people over 20 years of age with the aim of preventing lifestyle-related diseases and prolonging

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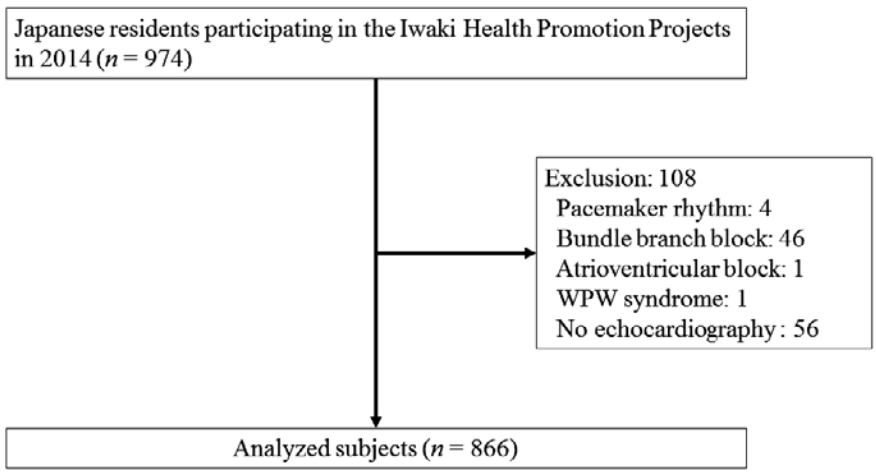

Figure 1. Study flowchart for the 2014 study group.

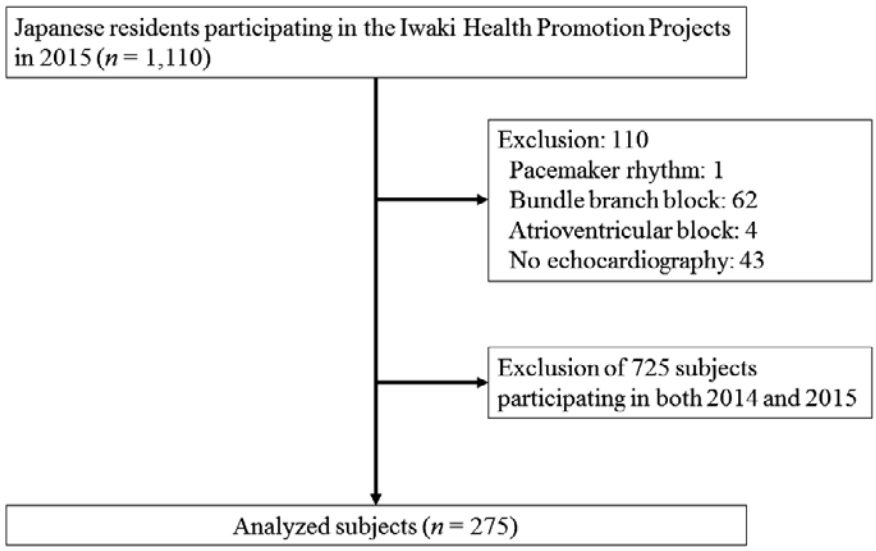

Figure 2. Study flowchart for the 2015 validation study group.

lifespans.[18-21] The study has been conducted annually since 2005 in the Iwaki area of the city of Hirosaki in Aomori Prefecture, northern Japan. All subjects volunteered to participate in response to a public announcement, and approximately 600 items of data from each participant, including body mass index, medical histories (hypertension, diabetes mellitus, and dyslipidemia), and blood pressure, were recorded. Most of the participants had undergone a standard 12-lead ECG and cardiac echocardiography. The subjects' past medical histories were obtained from a self-reporting system. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking treatment for hypertension. Dyslipidemia was defined as total cholesterol ≥ 220 mg/dL, triglyceride ≥ 150 mg/dL, or taking treatment for dyslipidemia.

This study was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine. Written informed consent was obtained from all the participants.

In the present study, we initially evaluated the 974 residents who participated in the Iwaki Health Promotion Project in 2014 and who underwent an ECG examination. Subjects with pacemaker rhythm, bundle branch block, atrioventricular block, or Wolff-Parkinson-White syndrome, or with no echocardiography data, were excluded. This resulted in the exclusion of 108 subjects, leaving 866 (mean age, 55.2 ± 14.7 years; 317 men) to be included in the 2014 analysis (Figure 1). As a validation study, we first obtained the data on 1,110 residents who participated in the project in 2015 and underwent an ECG examination. Of these, 110 were excluded by the exclusion criteria. Furthermore, 725 who participated in the project in both 2014 and 2015 were excluded. Finally, 275 subjects (mean age, 50.1 ± 16.5 years; 108 men) were included in the validation study (Figure 2).

Transthoracic echocardiography was used to estimate the left ventricular mass using the Devereux formula: left

ventricular mass (g) = 0.80 × {1.04 × [(septal thickness + internal diameter + posterior wall thickness)^3 − (internal diameter)^3]} + 0.6. The left ventricular mass was indexed according to body surface area. LVH was defined as a left ventricular mass index greater than 115 g/m^2 in men and greater than 95 g/m^2 in women, according to the ASE/EACVI 2015 guidelines.[22]

Each participant's ECG was analyzed as follows. The amplitudes of the R and S waves were measured in all the 12 leads using the PR segment as baseline (Figure 3A and B). The sex-specific Cornell voltage criteria for LVH were used as the main comparison. These were computed as the amplitude of R in the aVL lead plus the amplitude of S or the QS complex in V3 (i.e., RaVL + SV3), with a cutoff of > 2.8 mV in men and > 2.0 mV in women.[23] Calculation of the Cornell product criteria was performed as the Cornell voltage (+0.6 mV in women) × QRS duration, with a cutoff of ≥ 244 mV × ms.[12,13,24] The Sokolow-Lyon voltage criteria for LVH were also used, obtained by adding the amplitude of S in V1 and the amplitude of R in V5 or V6 (i.e., SV1 + RV5 or RV6), with a cutoff of ≥ 3.5 mV.[25]

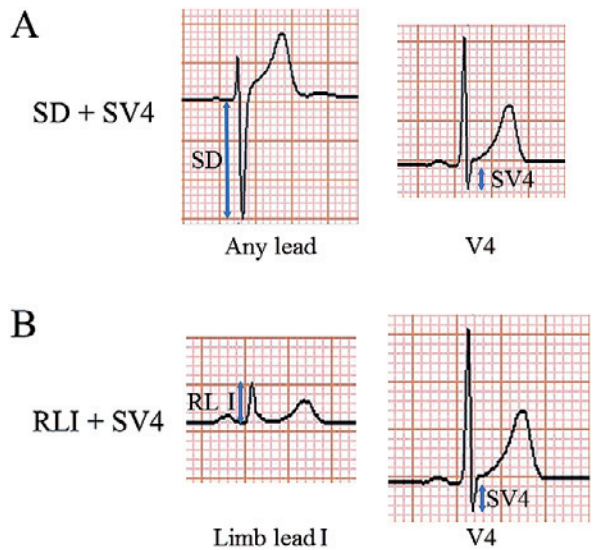

Figure 3. **A:** Example of electrocardiogram showing the deepest S wave in any lead (SD) and the S wave in lead V4 (SV4), used in the SD + SV4 diagnostic criteria for left ventricular hypertrophy. **B:** Example of electrocardiogram showing the R wave in limb lead I (RLI) and the S wave in V4 (SV4), used in the RLI + SV4 diagnostic criteria for left ventricular hypertrophy.

The normality of distributions was assessed using the Shapiro-Wilk test. The differences between two categories were compared using *t*-tests or Wilcoxon tests. Categorical variables were compared using the chi-square test or Fisher's exact test. A *P*-value < 0.05 was considered to be statistically significant. We used receiver operating characteristic analysis to assess the sensitivity and specificity for diagnosing LVH for each lead and for the sums of pairs of leads, as well as for the Cornell voltage, the Cornell product, and the Sokolow-Lyon voltage criteria, comparing the respective areas under the curve (AUCs). Data were analyzed using the statistical software JMP (version 12.0) and were expressed as mean ± standard deviation, or *n* (%).

Results

On the basis of the echocardiography results, LVH was observed in 156 (18%) of the 866 subjects in the 2014 study group. The baseline characteristics of this study population are shown in Table I. Compared with the subjects without LVH, those with LVH had significantly higher age, blood pressure, and prevalence of hypertension and diabetes. However, there were no significant differences in the prevalence of atrial fibrillation, heart rate, and dyslipidemia. The distribution of age in the 2014 study group is shown in Figure 4, where the 60s account for approximately 30% and the 20s account for only 5%.

The ECG analysis for the 2014 study group showed that the R waves in LI and aVL were good predictors for LVH, with the R wave in aVL being the most accurate for the diagnosis of LVH (AUC: 0.73; $P < 0.01$) (Table II). We selected pairs of leads with AUC > 0.65 and $P < 0.05$ and compared the AUCs for the summed amplitudes (Table III). The highest AUC was shown by the sum of the R wave in limb lead I and the S wave in V4 (RLI + SV4); this proved to have the highest AUC out of all the criteria

Table I. Baseline Characteristics of the 2014 Study Population

	Total (n = 866)	LVH (n = 156)	Non-LVH (n = 710)	*P*-value
Male, *n* (%)	317 (37)	46 (29)	271 (38)	< 0.05
Age (years)	55 ± 15	66 ± 9	53 ± 15	< 0.01
BMI (kg/m^2)	22.8 ± 3	24.1 ± 3	22.5 ± 3	< 0.01
Body surface area (m^2)	1.60 ± 0.18	1.57 ± 0.16	1.60 ± 0.18	< 0.05
Atrial fibrillation, *n* (%)	7 (1)	3 (2)	4 (1)	0.11
Systolic blood pressure (mmHg)	130 ± 19	144 ± 21	127 ± 18	< 0.01
Diastolic blood pressure (mmHg)	78 ± 11	82 ± 12	77 ± 11	< 0.01
Heart rate (bpm)	63 ± 12	64 ± 10	66 ± 10	0.18
Hypertension, *n* (%)	399 (46)	128 (82)	271 (38)	< 0.01
Diabetes mellitus, *n* (%)	82 (9)	29 (19)	53 (7)	< 0.01
Dyslipidemia, *n* (%)	396 (46)	81 (52)	315 (44)	0.09

Values are mean ± standard deviation or *n* (%). LVH indicates left ventricular hypertrophy; and BMI, body mass index.

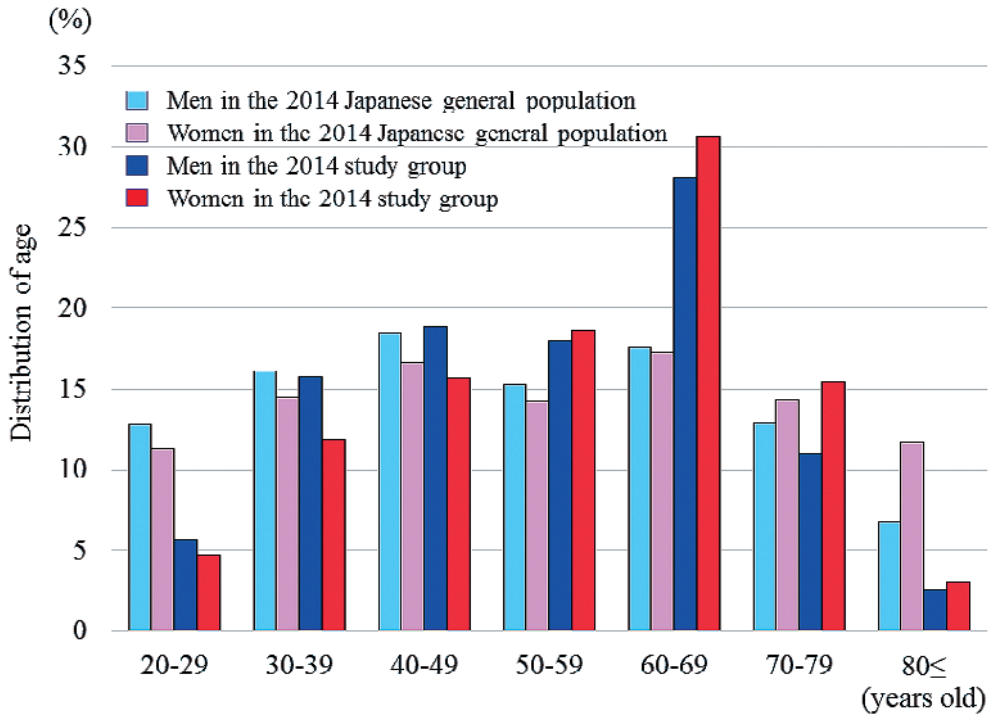

Figure 4. Distribution of age in the 2014 study group and in the 2014 Japanese general population.

Table II. AUC for LVH in Single Lead

Lead	AUC	*P*-value	Lead	AUC	*P*-value
RLI	0.71	< 0.01	RV1	0.54	0.06
SLI	0.57	< 0.01	SV1	0.49	0.98
RLII	0.61	< 0.01	RV2	0.59	< 0.01
SLII	0.54	< 0.05	SV2	0.54	0.08
RLIII	0.69	< 0.01	RV3	0.58	< 0.01
SLIII	0.67	0.7	SV3	0.67	< 0.01
RaVR	0.5	0.62	RV4	0.57	< 0.01
SaVR	0.55	0.13	SV4	0.68	< 0.01
RaVL	0.73	< 0.01	RV5	0.64	< 0.01
SaVL	0.65	< 0.01	SV5	0.66	< 0.01
RaVF	0.67	< 0.01	RV6	0.61	< 0.01
SaVF	0.59	0.5	SV6	0.57	< 0.01
			SD	0.55	0.02

AUC indicates area under the curve.

tested (AUC: 0.76; $P < 0.01$). Relatively high AUCs were also shown by the R wave in the aVL + S wave in V3 (RaVL + SV3), the R wave in the aVL + S wave in V4 (RaVL + SV4), and the R wave in the aVL + S wave in V5 (RaVL + SV5).

Table IV shows the sensitivity, specificity, and AUC of each criterion. RLI + SV4 criteria and the Cornell product criteria showed the highest AUC (0.76). The cutoff values of RLI + SV4 criteria were ≥ 1.6 mV in men and ≥ 1.4 mV in women, and the sensitivity for diagnosing LVH was 39% and the specificity was 89% (Table IV and Figure 5). The sensitivity of the Cornell product criteria was 21% and the specificity was 97%.

In comparison with the 2014 study group, the 2015 validation study group had a lower prevalence of LVH on echocardiography (14%), probably due to younger mean age. The ECG analyses for the validation study group showed results similar to those of the 2014 study group (Table V). Again, RLI + SV4 criteria and the Cornell product criteria showed high AUCs (0.73 and 0.75, respectively). The sensitivity and specificity of RLI + SV4 criteria were 41% and 90%, respectively, whereas those of the Cornell product criteria were 20% and 95%, respectively (Table V and Figure 6).

To compare the criteria impartially, the cutoff values of each diagnostic criterion were adjusted on the 2014 study group, so that the best balance of sensitivity and specificity was obtained (Table VI). SD + SV4 criteria showed the same cutoff values as shown in Table IV even after the adjustment. Notably, the sensitivity and specificity calculated based on the formula of the Cornell voltage (RaVL + SV3) were 42% and 89%, respectively, and those based on the formula of the Cornell product [RLI + SV4 (+0.6 mV in women) × QRS duration] were 39% and 90%, respectively. These values were higher than or equal to those obtained from RLI + SV4 criteria.

Discussion

LVH is an important manifestation of preclinical cardiovascular disease that strongly predicts cardiovascular events in hypertensive patients as well as in the general population.[26] It has been reported that diagnostic criteria based on the ECG were better for predicting cardiovascular events than a diagnosis of LVH using MRI.[27] In addition, it has been shown that the risk of a cardiovascular event increases with increasing LVH and decreases with the regression of LVH in response to antihypertensive

Table III. AUC for LVH in Summation of Two Leads

Leads	AUC	*P*-value	Leads	AUC	*P*-value	Leads	AUC	*P*-value
RLI + RLII	0.56	< 0.05	RLII + RLIII	0.66	< 0.01	RLIII + RaVL	0.52	0.53
RLI + RLIII	0.51	0.76	RLII + RaVL	0.58	< 0.01	RLIII + SaVL	0.68	< 0.01
RLI + RaVL	0.73	< 0.01	RLII + SaVL	0.64	< 0.01	RLIII + RaVF	0.68	< 0.01
RLI + SaVL	0.64	< 0.01	RLII + RaVF	0.64	< 0.01	RLIII + SV3	0.55	< 0.05
RLI + RaVF	0.51	0.67	RLII + SV3	0.60	< 0.01	RLIII + SV4	0.53	< 0.05
RLI + SV3	0.74	< 0.01	RLII + SV4	0.61	< 0.01	RLIII + RV5	0.53	< 0.05
RLI + SV4	0.76	< 0.01	RLII + RV5	0.56	< 0.01	RLIII + SV5	0.54	0.13
RLI + RV5	0.70	< 0.01	RLII + SV5	0.54	0.20	RLIII + RV6	0.51	0.87
RLI + SV5	0.75	< 0.01	RLII + RV6	0.52	0.19	SD + SV4	0.63	< 0.01
RLI + RV6	0.68	< 0.01						
RaVL + SaVL	0.65	< 0.01	SaVL + RaVF	0.69	< 0.01	RaVF + SV3	0.56	< 0.01
RaVL + RaVF	0.52	0.44	SaVL + SV3	0.61	< 0.01	RaVF + SV4	0.54	< 0.05
RaVL + SV3	0.74	< 0.01	SaVL + SV4	0.62	< 0.01	RaVF + RV5	0.53	< 0.05
RaVL + SV4	0.75	< 0.01	SaVL + RV5	0.60	< 0.01	RaVF + SV5	0.54	0.13
RaVL + RV5	0.72	< 0.01	SaVL + SV5	0.56	< 0.01	RaVF + RV6	0.52	0.94
RaVL + SV5	0.74	< 0.01	SaVL + RV6	0.56	< 0.01	SV3 + SV4	0.68	< 0.01
RaVL + RV6	0.71	< 0.01	SV4 + RV5	0.71	< 0.01	SV3 + RV5	0.70	< 0.01
RV5 + SV5	0.70	< 0.01	SV4 + SV5	0.68	< 0.01	SV3 + SV5	0.68	< 0.01
RV5 + RV6	0.63	< 0.01	SV4 + RV6	0.70	< 0.01	SV3 + RV6	0.69	< 0.01
SV5 + RV6	0.68	< 0.01						

Table IV. Sensitivity, Specificity, and AUC for LVH in Various Criteria in the 2014 Study Group

	Cutoff value	Sensitivity (%)	Specificity (%)	AUC
RLI + SV4 criteria		39	89	0.76
Men	≥ 1.6 mV			
Women	≥ 1.4 mV			
Cornell voltage criteria		12	99	0.74
Men	> 2.8 mV			
Women	> 2.0 mV			
SD + SV4 criteria		21	94	0.63
Men	≥ 2.8 mV			
Women	≥ 2.3 mV			
Sokolow-Lyon criteria	≥ 3.5 mV	15	94	0.61
Cornell product criteria	≥ 240 mV × ms	21	97	0.76

treatment. Thus, the detection, prevention, and reversal of LVH are important goals in the management of hypertension.[28]

Although several diagnostic simple voltage criteria have been currently used for LVH, their sensitivity is low. In the present study, RLI + SV4 with appropriate cutoff values showed better diagnostic performance than the other criteria examined, suggesting that this criterion may be more useful than the previous criteria for diagnosing LVH in the Japanese general population. Although the Cornell product criteria also showed good performance to diagnose LVH, they are more complicated than simple voltage criteria.

The prevalence of LVH in the general population and in hypertensive outpatients is reported to be 6%-20% and 20%-40%, respectively.[11,27,29] Several studies have shown that both obesity and diabetes are independent predictors for increased left ventricular mass, and having both conditions may increase the odds of LVH.[30-32] In the present study, the prevalence of LVH in the 2014 study population was 18%, which is consistent with previous studies. Furthermore, subjects with LVH in this population had a higher BMI and a greater prevalence of hypertension and diabetes than those without LVH. All these findings support a significant association of LVH with hypertension, obesity, and diabetes, as seen in previous studies.

Previous studies have shown that the amplitudes of the R wave in aVL and the R wave in lead I are a good single lead predictor for LVH.[10,23] The findings of the present study are consistent with this: the highest AUC for a single lead was shown by the R wave in aVL (0.73) and the R wave in lead I (0.71). Both the leads are therefore considered to be effective on the basis of the previous and present results. As shown in Table IV, the sensitivity and specificity of the Cornell voltage criteria, SD + SV4 criteria, Sokolow-Lyon voltage criteria, and Cornell product criteria were 12%-21% and 94%-99%, respectively. These findings suggest that the validity of these diagnostic criteria may be low in the Japanese general population. On the contrary, the RLI + SV4 criteria had a sensitivity of 39%

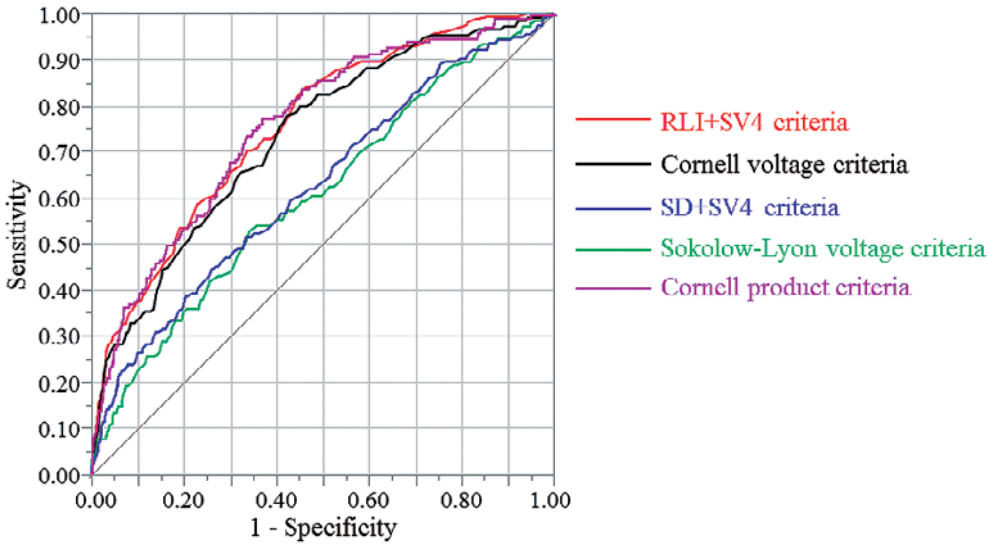

Figure 5. Receiver operating characteristic curves comparing five diagnostic criteria for left ventricular hypertrophy using the data from the 2014 study group. The criteria are as follows: sum of the R wave in limb lead I and the S wave in V4 (RLI + SV4), Cornell voltage criteria, sum of the amplitude of the deepest S wave in any lead and the S wave in lead V4 (SD + SV4), Sokolow-Lyon voltage criteria, and Cornell product criteria.

Table V. Sensitivity, Specificity, and AUC for LVH in Various Criteria in the 2015 Validation Study Group

	Cutoff value	Sensitivity (%)	Specificity (%)	AUC
RLI + SV4 criteria		41	90	0.73
Men	≥ 1.6 mV			
Women	≥ 1.4 mV			
Cornell voltage criteria		8	98	0.68
Men	> 2.8 mV			
Women	> 2.0 mV			
SD + SV4 criteria		21	88	0.59
Men	≥ 2.8 mV			
Women	≥ 2.3 mV			
Sokolow-Lyon criteria	≥ 3.5 mV	15	90	0.58
Cornell product criteria	≥ 240 mV × ms	20	95	0.75

and a specificity of 89%, with cutoff values ≥ 1.6 mV in men and ≥ 1.4 mV in women. This suggests that the RLI + SV4 criteria seem to be more effective for diagnosing LVH in the Japanese general population than the previous diagnostic criteria. It should be noted that by adjusting the cutoff values, the formulas of the Cornell voltage and the Cornell product criteria showed similar or higher sensitivity and specificity than the RLI + SV4 criteria (Table VI). These findings indicate that both Cornell formulas may have the potential to become good predictors for LVH in the Japanese general population after adjusting the cutoff values. Further studies are needed to confirm this possibility.

Several studies have reported differences in the ECGs between races. The reasons for this are unclear, but it may be related to the low prevalence of obesity and the low body mass index among Asian people.[17,33,34] Previous studies have shown that obesity may be associated with QRS left axis excursion; the cause of this axis shift is uncertain, but it may be related to a leftward and more horizontal orientation of the heart attributed to the diaphragmatic pressure from visceral obesity.[35] Furthermore, left ventricular mass was reported to be smaller in Asian-American than in White-American and African-American people.[36] These factors may be related to the low sensitivity of the diagnostic simple voltage criteria. As described earlier, a recent study showed that SD + SV4 improved the sensitivity for diagnosing LVH compared with commonly used criteria,[10] but this criterion was not so effective in the present study of a Japanese population. A major difference between the two studies is that SD is not a good indicator in the present study. Approximately 70% of the SD was the S wave in V2 in this study, and the V2 lead is thought to be affected by various factors other than the right chamber in front. Thus, SD and SD + SV4 did not seem to be good predictors of LVH in the present study population. However, this discrepancy may also be dependent on the difference in the pattern and/or persis-

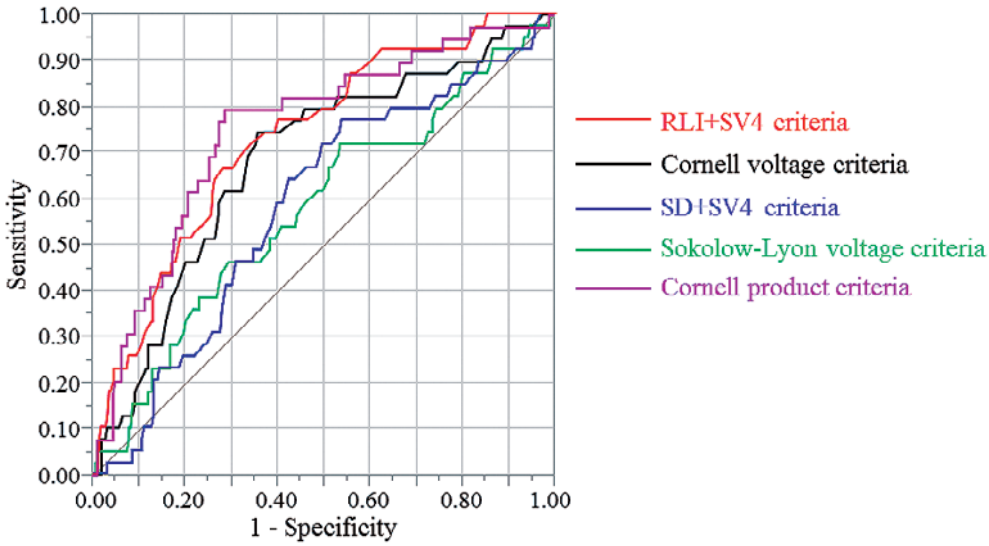

Figure 6. Receiver operating characteristic curves comparing five diagnostic criteria for left ventricular hypertrophy using the data in the 2015 validation study group. The criteria are described in Figure 5.

Table VI. Sensitivity and Specificity for LVH with Various Formulas, Calculated Using Cutoff Values Obtained from Our Data in the 2014 Study Group

	Cutoff value	Sensitivity (%)	Specificity (%)
RLI + SV4 criteria		39	89
Men	≥ 1.6 mV		
Women	≥ 1.4 mV		
RaVL + SV3 criteria*		42	89
Men	> 1.9 mV		
Women	> 1.5 mV		
SD + SV4 criteria		21	94
Men	≥ 2.8 mV		
Women	≥ 2.3 mV		
SV1 + RV5 or V6 criteria†	≥ 3.2 mV	24	89
RLI + SV4 (+ 0.6 mV in women) × QRS duration§	≥ 210 mV × ms	39	90

*RaVL + SV3 criteria is the same formula of the Cornell voltage criteria. †SV1 + RV5 or V6 criteria is the same formula of the Sokolow-Lyon voltage criteria. §RLI + SV4 (+ 0.6 mV in women) × QRS duration is the same formula of the Cornell product criteria.

tence of obesity, and in the heart axis, the overall mechanism still remains unclear.

This study has some limitations. First, the subjects were limited to residents of the Iwaki area in northern Japan. The distribution of age in the subjects of the present study is almost similar to the Japanese general population,[37] but slightly different as shown in Figure 4. There are more subjects in the 50s and 60s, and fewer in the 20s, 30s, and over 80s in the 2014 study group than in the 2014 Japanese general population. However, the subjects in this study are mostly healthy residents; therefore, RLI + SV4 criteria may be useful for an early diagnosis of LVH in a health examination. Further studies in other areas are clearly needed even if RLI + SV4 criteria are useful for the diagnosis of LVH. Second, although the validation study showed similar results, the number of subjects (n = 275) in the 2015 validation study group was not enough to confirm our results. Third, subjects' past medical histories were obtained from a self-reporting system; hence, information on underlying diseases may have been inaccurate. Finally, although many diagnostic criteria are currently available, the Cornell voltage criteria, Cornell product criteria, and Sokolow-Lyon voltage criteria were only examined in the present study. Further studies including more diagnostic criteria are needed.

Conclusions

Diagnostic criteria based on RLI + SV4 seem to be more effective for the diagnosis of LVH in the Japanese general population than the previous diagnostic criteria for LVH. Our study provides important clinical implications for hypertensive patients in order to prevent cardiovascular events.

Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

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