Prognostic Significance of the Mitral L-Wave in Patients With Hypertrophic Cardiomyopathy

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A mitral L-wave indicates advanced diastolic dysfunction with elevated left ventricular filling pressure. Previous studies have reported that the presence of a mitral L-wave is associated with a poor prognosis in patients with heart failure. However, whether the L-wave can predict adverse events in patients with hypertrophic cardiomyopathy (HC) is still unclear. Therefore, we aimed to investigate the prevalence of a mitral L-wave in patients with HC, and the prognosis of patients with or without an L-wave. We analyzed 445 patients with HC. The end points of this study were HC-related death, such as sudden death or potentially lethal arrhythmic events, heart failure-related death, and stroke-related death. A mitral L-wave was defined as a distinct mid-diastolic flow velocity after the E wave with a peak velocity >20 cm/s. The prevalence of an L-wave was 32.4% in patients with HC. Patients with an L-wave were significantly younger, more likely to be women, had higher New York Heart Association functional class, and had a higher prevalence of atrial fibrillation than did patients without an L-wave. Patients with an L-wave had a significantly higher incidence of HC-related death compared with those without an L-wave (log-rank, $p < 0.001$). The L-wave was an independent determinant of HC-related death in multivariate analysis adjusted for imbalanced baseline variables (adjusted hazard ratio 2.38; 95% confidence interval 1.42 to 4.01; $p = 0.001$). In conclusion, the presence of a mitral L-wave may be associated with adverse outcome in patients with HC. **(Am J Cardiol 2020;130:130−136)**

In patients with Hypertrophic cardiomyopathy (HC), one of the main pathophysiological features is diastolic dysfunction.[1−5] However, atrial fibrillation (AF) makes accurate evaluation of diastolic function difficult.[6] A mitral L-wave, as detected by pulsed Doppler echocardiography of mitral inflow, indicates advanced diastolic dysfunction with elevated left ventricular (LV) filling pressure, even in patients with AF.[7,8] Previous studies have reported that the presence of a mitral L-wave is associated with a poor prognosis in patients with heart failure with or without AF.[8−10] However, whether the mitral L-wave can predict adverse events in patients with HC is still unclear. Therefore, this study aimed to evaluate the prevalence of a mitral L-wave in patients with HC, and the prognosis of patients with HC with or without an L-wave.

Methods

This retrospective study consecutively included 446 patients with clinically diagnosed HC at Tokyo Women's Medical University Hospital, Tokyo, Japan, from January 2003 to December 2015. The initial evaluation was the first clinical assessment in which patients were diagnosed with HC by echocardiogram at our hospital. The most recent evaluation was performed in the outpatient clinic up to June 2018. HC was diagnosed by identification using an echocardiogram of a hypertrophied, nondilated LV in the absence of any other cardiac or systemic disease capable of producing a similar degree of hypertrophy.[1]

The disposition of the study population is shown in Figure 1. Of the 446 patients, 445 (99.9%) were included in our final analysis, excluding one who could not be evaluated by pulsed Doppler of mitral inflow because of mitral annular calcification. Ambulatory electrocardiograms covering at least a 24-hour period were reviewed to detect nonsustained ventricular tachycardia and AF. Nonsustained ventricular tachycardia was defined as a minimum of 3 consecutive ventricular extra beats at a rate of ≥120 beats/min and lasting for <30 seconds. The presence of AF was documented by 12-lead at rest electrocardiography or ambulatory electrocardiography.[1] This study was conducted according to the principles of the Declaration of Helsinki. The review board of Tokyo Women's Medical University Hospital approved the protocol.

A comprehensive transthoracic echocardiography (TTE) study, which included 2-dimensional, M-mode, Doppler echocardiography, and tissue Doppler imaging, was performed according to recommendations of the American Society of Echocardiography.[11] TTE examinations were performed using a Vivid 7 ultrasound (GE Healthcare, Horten, Norway) or an iE33 and Sonos 5500 ultrasound (Philips Healthcare, Bothell, WA, USA). Doppler data were obtained as the mean of three cardiac cycles in patients in sinus rhythm and five cardiac cycles in those with AF. Using pulsed Doppler of mitral inflow from the

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.05.040

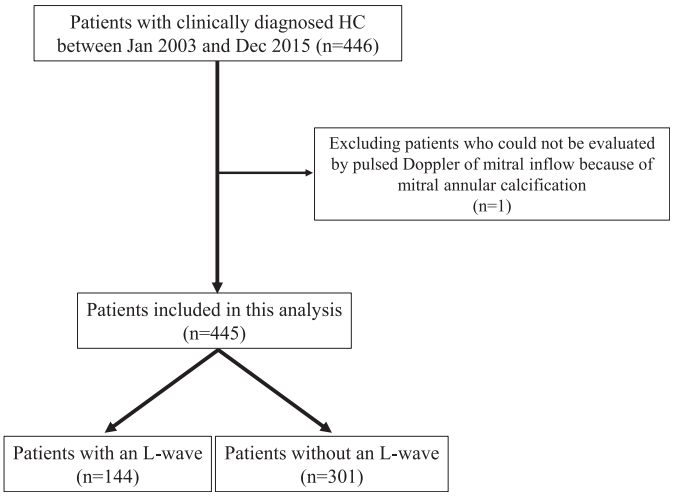

Figure 1. Flow chart of the study patients. Of 446 patients with clinically diagnosed HC, 445 were included in our final analysis. One patient was excluded who could not be evaluated by pulsed Doppler of mitral inflow because of mitral annular calcification. HC= hypertrophic cardiomyopathy.

four-chamber view, a mitral L-wave was defined as a distinct mid-diastolic flow velocity after the E wave with a peak velocity >20 cm/s.[7,12,13] Maximum LV wall thickness was defined as the greatest thickness in any single segment. Color Doppler imaging and pulsed Doppler imaging were used to localize the site of obstruction. LV outflow tract obstruction caused by systolic anterior motion of the anterior mitral valve leaflet, was considered to be present when the estimated peak instantaneous gradient was ≥30 mm Hg. Left mid-ventricular obstruction, apical hypertrophy, and apical aneurysm were defined as indicated in previous studies.[1,14] End-stage HC was defined as a hypokinetic and dilated LV with an LVEF <50% and LV end-diastolic dimension exceeding the reference upper 95% confidence limit for body surface area and age.[15,16]

For the purpose of survival analysis, 3 modes of HC-related death were defined as follows: 1) a combined end point of sudden death or potentially lethal arrhythmic events, in which unexpected death occurred in the absence of or <1 hour from symptom onset in patients who had previously experienced a stable or uneventful course, including successful resuscitation after cardiac arrest (i.e., ventricular fibrillation or ventricular tachycardia with pulseless collapse) and appropriate implantable cardioverter-defibrillator interventions; 2) heart failure-related death in the context of progressive cardiac decompensation ≥1 year before death, including patients with advanced refractory heart failure who received heart transplants; and 3) stroke-related death, which occurred in patients who died as a result of ischemic stroke.[1,14]

Results are presented as mean with standard deviation, median with interquartile range, or frequency. The Student's *t* test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used for ordinal variables between groups. The chi-square or Fisher's exact test (when an expected value was <5) was used to compare nominally scaled variables. The probability of end points was estimated by the Kaplan-Meier method, after which the log-rank test was used to compare survival curves. Univariate and multivariate Cox proportional hazards models were used to evaluate the effect of the L-wave on end points. Because of the small number of end points in this study, we avoided including all potential confounders in one multivariable model. Therefore, multivariable analysis was performed using the following two separate models. Model 1 was adjusted for conventional markers of sudden death, such as a family history of sudden death, unexplained syncope, non-sustained ventricular tachycardia, and maximal LV wall thickness ≥30 mm[1,2]. Model 2 was adjusted for imbalanced baseline variables, such as age, gender, New York Heart Association functional class, and AF. In all analyses, two-tailed p values <0.05 were considered statistically significant. All analyses were performed with statistical software (SAS system v9.4; SAS Institute, Cary, NC, USA) at an independent biostatistics and data center (STATZ Institute, Inc., Tokyo, Japan).

Results

Of 445 patients with clinically diagnosed HC, 144 (32.4%) showed a mitral L-wave (Figure1). The baseline demographic and clinical characteristics of patients with and those without an L-wave at initial evaluation are shown in Table 1. Echocardiographic parameters of patients with and without an L-wave are shown in Table 2. Box and whisker plots of left atrial dimension and tricuspid regurgitation velocity in patients without and with an L-wave are shown in Figure2. Representative cases of patients with and without an L-wave are shown in Figure 3.

Over a median follow-up of 8.8 (5.1 to 12.3) years, 65 (14.6%) patients experienced HC-related death, including 17 with sudden cardiac death, 25 with appropriate implantable cardioverter-defibrillator shocks, 11 with successfully resuscitated cardiac arrest (with documented ventricular fibrillation [n = 7] and with documented ventricular tachycardia with pulseless collapse [n = 4]), 8 with heart failure-related death including 2 with heart transplantation, and 4 with stroke-related death. In patients with an L-wave, 37 (25.7%) patients experienced HC-related death, including 9 with sudden cardiac death, 11 with appropriate implantable cardioverter-defibrillator shocks, 8 with successfully resuscitated cardiac arrest (with documented ventricular

Table 1
Baseline demographic and clinical characteristics

Variable	L-wave YES (n = 144)	L-wave NO (n = 301)	p value
Men	80 (56%)	209 (69%)	0.006
Age at diagnosis (years)	49 ± 18	52 ±15	0.027
Family history of sudden death	26 (18%)	36 (12%)	0.112
Left ventricular outflow tract obstruction	28 (19%)	72 (24%)	0.061
Left mid-ventricular obstruction	18 (13%)	33 (11%)	0.751
Apical hypertrophy	54 (38%)	98 (38%)	0.357
Apical aneurysm	11 (8%)	15 (5%)	0.367
End-stage HC	18 (13%)	30 (10%)	0.520
NYHA functional class			0.036
I	63 (44%)	162 (54%)	
II	71 (49%)	127 (42%)	
≥III	10 (7%)	12 (4%)	
Unexplained syncope	20 (14%)	59 (20%)	0.179
Non-sustained ventricular tachycardia	50 (35%)	110 (37%)	0.788
Atrial fibrillation	54 (38%)	80 (27%)	0.025

Values are mean ± standard deviation or number (%).
HC, hypertrophic cardiomyopathy; NYHA, New York Heart Association.

fibrillation [n = 7] and with documented ventricular tachycardia with pulseless collapse [n = 1]), 6 with heart failure-related death including 1 with heart transplantation, and 3 with stroke-related death, over a median follow-up of 8.5 (4.9 to11.7) years. In patients without an L-wave, 28 (9.3%) patients experienced HC-related death, including 8 with sudden cardiac death, 14 with appropriate implantable cardioverter-defibrillator shocks, 3 with successfully resuscitated cardiac arrest (with documented ventricular tachycardia with pulseless collapse [n = 3]), 2 with heart failure-related death including 1 with heart transplantation, and 1 with stroke-related death, over a median follow-up of 8.9 (5.8 to 12.6) years. Kaplan-Meier estimates of HC-related death are shown in Figure 4. Patients with an L-wave had a significantly higher incidence of HC-related death compared with those without an L-wave (Figure 4A, log-rank test, $p < 0.001$). Patients with an L-wave had a significantly higher incidence of sudden death or potentially lethal arrhythmic events compared with those without an L-wave (Figure 4B, log-rank test, $p = 0.001$). Furthermore, patients with an L-wave had a significantly higher incidence of HC-related death compared with those without an L-wave, regardless of the presence or absence of LV intracavitary obstruction (Figure 5). In the Cox proportional hazards model, an L-wave was associated with a higher rate of HC-related death in univariate analysis. Additionally, the L-wave was an independent determinant of HC-related death in multivariable analysis, which was adjusted for conventional markers of sudden death (i.e., family history of sudden death, unexplained syncope, nonsustained ventricular tachycardia, and maximal LV wall thickness ≥30 mm) (Table 3, Model 1). Furthermore, the L-wave was independently associated with an increased incidence of HC-related death in multivariable analysis, which was adjusted for imbalanced baseline variables, including age, gender, New York Heart Association functional class, and AF (Table 3, Model 2).

Table 2
Echocardiographic parameters

Variable	L-wave YES (n = 144)	L-wave NO (n = 301)	p value
Left ventricular end-diastolic dimension (mm)	46 ± 6	46 ± 7	0.954
Left ventricular end-systolic dimension (mm)	29 ± 7	30 ± 7	0.885
Left ventricular ejection fraction (%)	53 ± 10	55 ± 11	0.086
Maximal left ventricular wall thickness (mm)	20 ± 5	19 ± 5	0.056
Maximal left ventricular wall thickness ≥30 mm	8 (6%)	17 (6%)	>0.999
Left atrial dimension (mm)	41 ± 9	39 ± 8	0.012
Left atrial volume index (cm^3/m^2)	61 ± 54	47 ± 37	0.004
E/e' (septal)	16 ± 8	15 ± 7	0.202
Tricuspid regurgitation velocity (m/sec)	2.5 ± 0.4	2.3 ± 0.4	<0.001
PASP (mmHg)	36 ± 10	32 ± 8	<0.001

Values are mean ± standard deviation or number (%).
PASP, pulmonary arterial systolic pressure.

Discussion

Previous studies have reported that the prevalence of an L-wave was 0.5% to 35%, according to varying clinical conditions of patients. The prevalence of an L-wave was reported to be approximately 0.5% in patients with a normal LV ejection fraction (LVEF) and sinus rhythm,[17] whereas it increased up to approximately 35% in patients with AF and impaired diastolic function.[8,18] Additionally, in patients with sinus rhythm, an L-wave was observed in 36.2% of patients with heart failure with a preserved LVEF and in 28.0% of patients with heart failure with a reduced LVEF.[9] The high prevalence of an L-wave in this study can be explained by diastolic dysfunction and prolonged LV relaxation in patients with HC. Despite, our study was based on a selective cohort of patients from a single tertiary referral center in Japan, our results may have generalizability and provide additional epidemiological information about the L-wave in patients with HC.

The appearance of an L-wave is closely related to advanced diastolic dysfunction complicated by increased LV filling pressure.[7] In echocardiographic parameters, the ratio of the velocity of the E wave using pulsed Doppler of mitral inflow and e' using tissue Doppler velocity (E/e') and the Doppler restrictive filling pattern can estimate LV filling pressure in patients with HC.[19,20] Furthermore, E/e' is related to exercise capacity and a worse outcome.[20–22] The Doppler restrictive pattern is also associated with an increased risk of HC-related death.[19] Therefore, the presence of an L-wave might be associated with advanced diastolic dysfunction and increased LV filling pressure, and is associated with an increase in HC-related death in patients with HC.

Assessment of LV diastolic function in HC can be limited. Additionally, conventional Doppler parameters are unreliable for estimating LV filling pressure in HC, especially in patients with AF. In contrast, the L-wave can be detected not only in patients with sinus rhythm, but also in patients with AF.[8,9,18] Furthermore, detection of an L-wave

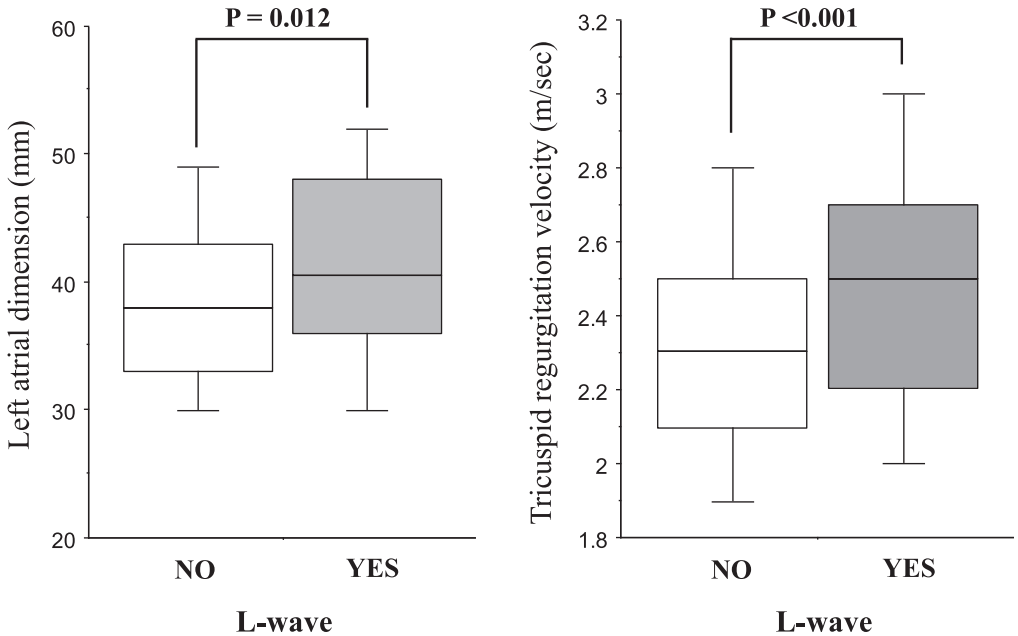

Figure 2. Box and whisker plots of left atrial dimension and tricuspid regurgitation velocity in patients without and with an L-wave. The line across each box represents the median left atrial dimension and tricuspid regurgitation velocity; the box represents the interquartile range (25-75th percentile); and the I bars represent the 95% confidence intervals.

can be recorded in the general outpatient clinic without tissue Doppler imaging, and does not require a clinic specialized for HC. Moreover, determining the presence or absence of an L-wave is relatively easy compared with E/e' for which the threshold has not been fully established for patients with HC.[3,21,22] Our results suggest that the L-wave may be useful as an indicator of advanced diastolic dysfunction and prognostic prediction in patients with HC. However, there are still many unanswered questions about the relations among mitral L-waves, diastolic dysfunction, elevated LV filling pressure, and adverse outcomes in patients with HC. In this study, for example, there was no differences in the E/e' between patients with and without an L-wave, although the E/e' is a marker of increased LV filling pressure similar to the L-wave. Several reports have shown that LV diastolic dysfunction as assessed by E/e' in

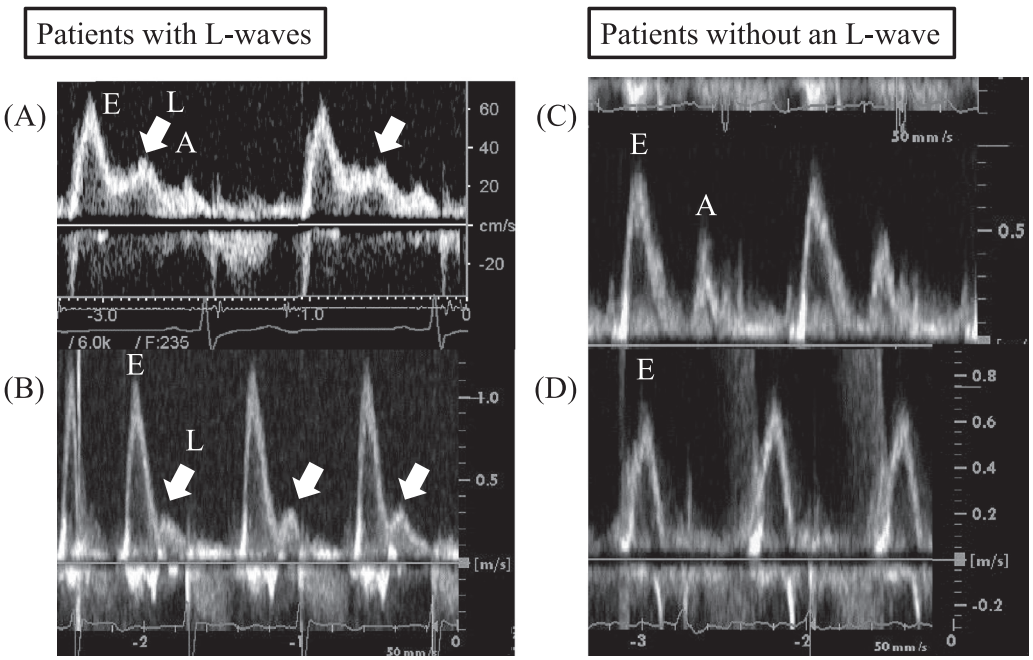

Figure 3. Representative echocardiographic images of pulsed Doppler imaging of mitral inflow in patients with HC with an L-wave and without an L-wave. (*A, B*) Mitral L-waves in a patient with sinus rhythm (A) and in a patient with atrial fibrillation (*B*). (*C, D*) A patient without a mitral L-wave and with sinus rhythm (*C*) and a patient without a mitral L-wave with atrial fibrillation (*D*). White arrows indicate an L-wave. HC, hypertrophic cardiomyopathy.

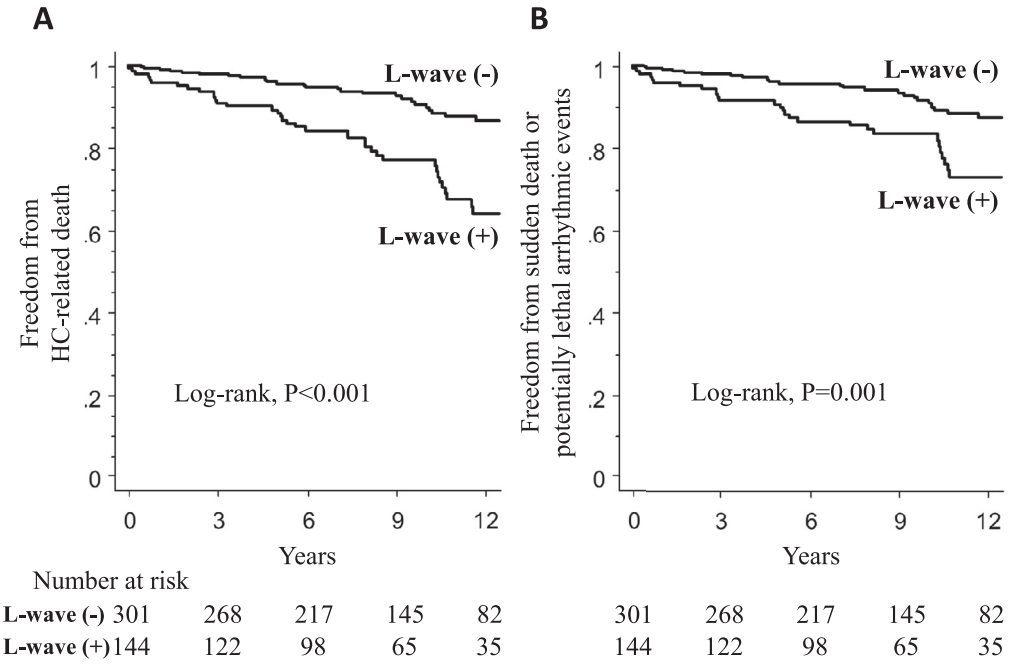

Figure 4. Kaplan-Meier estimate of (*A*) HC-related death and (*B*) sudden death or potentially lethal arrhythmic events in patients with clinically diagnosed HC with or without an L-wave. HC, hypertrophic cardiomyopathy.

patients with HC is not precisely predictive of outcomes in patients with intracavitary obstruction, and is unrelated to sudden death.[3,23] Contrary, in this study, patients with an L-wave had a significantly higher incidence of sudden death or potentially lethal arrhythmic events, and had a significantly higher incidence of HC-related adverse events regardless of the presence or absence of LV intracavitary obstruction, compared with those without an L-wave. In addition, although there was no significant difference, patients with an L-wave tended to have fewer outflow tract obstruction than patients without an L-wave. In this respect, mainly because of the heterogeneity of the patient

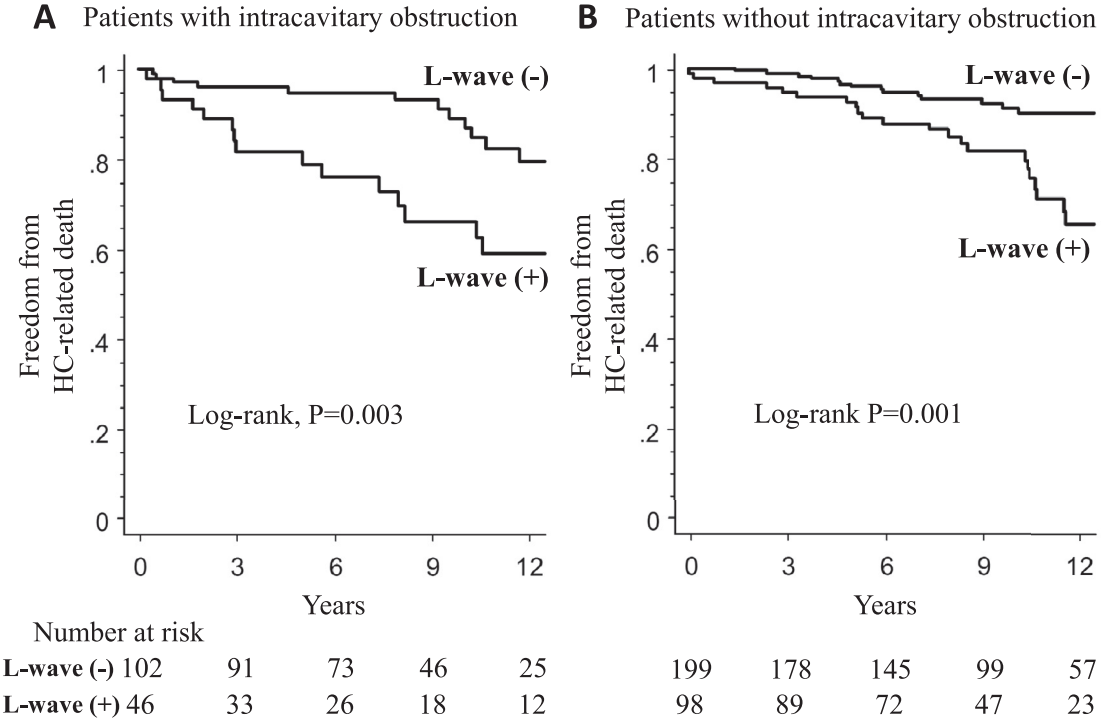

Figure 5. Kaplan-Meier estimate of HC-related death in patients with clinically diagnosed HC with or without an L-wave, stratified by the presence (*A*) or absence (*B*) of left ventricular intracavitary obstruction. HC, hypertrophic cardiomyopathy.

Table 3
Crude and adjusted hazard ratios for HC-related death associated with the presence of an L-wave in patients with HC

Independent variable	Model type	Hazard ratio*	95% confidence interval	p value
Patients without an L-wave	Reference	1		
Patients with an L-wave	Univariable	2.86	1.75-4.67	<0.001
	Multivariable Model 1[a]	2.90	1.76-4.77	<0.001
	Multivariable Model 2[b]	2.38	1.42-4.01	0.001

* Hazard ratios were obtained by univariate and multivariate Cox proportional hazards models.
[a] Model 1 was adjusted for conventional markers of sudden death, such as a family history of sudden death, unexplained syncope, non-sustained ventricular tachycardia, and maximal left ventricular wall thickness ≥30 mm. [b]Model 2 was adjusted for imbalanced baseline variables, including age, gender, New York Heart Association functional class, and atrial fibrillation. HC, hypertrophic cardiomyopathy.

population and our incomplete understanding of the pathophysiology, the meanings of an L-wave and E/e' may be slightly different, and further study is awaited for its elucidation.

The single-center, retrospective, observational design of our study makes establishing causal relations difficult. Further, our HC cohort was derived from a single tertiary referral center in Japan and was thus subject to selection bias by including a highly selected population of patients with HC. In this study, genetic tests were not performed, and there was a potential chance for contamination of study population with other cardiac conditions mimicking HC. Despite adjustments by multivariable analysis, we cannot exclude the effects of residual measured and/or unmeasured confounders on our results. On the basis of previous studies, a mitral L-wave was defined as a distinct forward flow velocity after E wave with a peak velocity >20 cm/s in the present study.[7,12,13] Arbitrary cut-off values of the L-wave and the beat-to-beat variability in AF affect the appearance and degree of the mitral L-wave.[7] Recently, Ghosh et al reported that the L-wave was a manifestation of intraventricular recirculating vortex flow, rather than transmitral flow during diastolic phase and elevated filling pressure.[24] However, we did not evaluate the vortex flow in this study, and further study will be needed in this field. Finally, the L-wave is a dynamic measurement and may have significant fluctuations over time.[7] However, in this study, the L-wave was evaluated at only one time point (initial evaluation), and was not measured during follow-up. Therefore, the prognostic effect of serial measurements of mitral L-waves in patients with HC is unclear.

In conclusion, our data suggest that the presence of a mitral L-wave is associated with an adverse outcome in patients with HC. Further studies on the pathophysiology and prognostic significance of the L-wave are required in patients with HC.

Credit Author Statement

Chihiro Saito: Conceptualization, Investigation, Writing-Original Draft, Visualization. **Yuichiro Minami:** Conceptualization, Methodology, Writing-Review and Editing, Supervision. **Kotaro Arai:** Validation, Resources. **Shintaro Haruki:** Formal analysis, Data curation. **Shota Shirotani:** Data Curation, Visualization. **Satoshi Higuchi:** Formal analysis, Resources. **Kyomi Ashihara:** Methodology, Supervision. **Nobuhisa Hagiwara:** Supervision, Project administration.

Acknowledgments

We thank Yuki Iijima and Katsunori Shimada, PhD (Statistical Analysis and Data Center, STATZ Institute Inc., Tokyo, Japan) for their excellent support and assistance. We also thank Ellen Knapp, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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