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The prognostic impact of a concentric left ventricular structure evaluated by transthoracic echocardiography in patients with acute decompensated heart failure: A retrospective study☆,☆☆

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ABSTRACT

Background: Left ventricular (LV) wall thickening relative to the LV radius, known as a concentric LV structure, is a mechanism that compensates for pressure overload and is related to the risk of cardiovascular events and heart failure. The prognostic value of a concentric LV structure, however, has not been examined in acute decompensated heart failure (ADHF).

Methods: This single-center, observational, retrospective, cohort study analyzed 385 consecutive patients hospitalized due to ADHF. On hospital admission, relative wall thickness (RWT) and the ratio of LV mass to LV end-diastolic volume (LVM/LVEDV) were measured by transthoracic echocardiography as markers of a concentric LV structure. The association of either RWT or LVM/LVEDV with all-cause death as the primary outcome was analyzed.

Results: During the follow-up period (median, 235 days), 95 (25%) patients died. The high-RWT group had a poorer prognosis than the low-RWT group (log-rank test, $P = 0.009$). High RWT was a significant risk (HR: 1.95, 95% CI: 1.28–2.97, $P = 0.002$) in the Cox proportional hazard model analysis adjusted by the Get With The Guideline score, which is an established risk score. In contrast, there was no significant difference in survival between the low and high-LVM/LVEDV groups ($P = 0.42$). In the non-severe valvular disease subgroup, patients with high RWT consistently showed worse survival than the low-RWT group ($P = 0.028$ by log-rank test, HR: 1.96, 95% CI: 1.24–3.11, $P = 0.004$). There was no significant difference in survival between the low and high-LVM/LVEDV groups ($P = 0.42$).

Conclusions: A concentric LV structure represented by a high RWT was associated with a poor prognosis in ADHF. The lack of association between LVM/LVEDV and mortality may result from methodological issues.

1. Introduction

The left ventricle adapts to stress to maintain the wall stress close to normal by altering its structure [1,2]. Pressure overload in particular results in a concentric left ventricular (LV) structure, which is a high ratio of LV wall thickness to the LV radius as a compensatory mechanism [1,2]. However, this structural alteration might be a maladaptation. A concentric LV structure involves systolic and diastolic dysfunction and is an independent predictor for cardiovascular events in patients with hypertension [3,4]. Furthermore, a concentric LV structure was a risk factor for heart failure in a large cohort study [5]. A concentric LV structure is thought to contribute to the development of heart failure under LV pressure overload.

Despite the knowledge of the risk of a concentric LV structure in developing chronic heart failure, evidence regarding the prognostic value of a concentric LV structure in acute decompensated heart failure (ADHF) is lacking. A concentric LV structure involves historical changes, including interstitial fibrous accumulation [6]. Our hypothesis is that such historical changes persist if the ADHF patient recovers from congestive symptoms, and a concentric LV structure is related to a worse prognosis.

Transthoracic echocardiography (TTE) can evaluate LV concentricity during hospital admission of patients with congestive symptoms. Either the relative wall thickness (RWT) or the ratio of LV mass to LV end-diastolic volume (LVM/LVEDV) is an index that represents the concentricity of the LV [7–9]. Those indices are computed using TTE

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☆☆ All of the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and discussed interpretation.

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measurements on two-dimensional imaging from a parasternal long-axis view [7] and can be measured during hospital admission from a technical viewpoint even if the ADHF patient is uncooperative with the examination due to congestive symptoms. The RWT is the ratio of the LV wall thickness to the radius on a two-dimensional image, and RWT = 2 × (PWth)/(LVDd), in which PWth = posterior wall thickness at end-diastole and LVDd = LV dimension at end-diastole [2]. LVM/LVEDV is the ratio of mass to volume. LV mass (LVM) and LV end-diastolic volume (LVEDV) are calculated by established equations on the basis of assumptions in which LV should be ellipsoid [2,7]. Both LVM and LVEDV requires the only linear measurements in a TTE parasternal long axis view [7] and calculated as follows; LVM = 0.8 × 1.04 [(IVSth + LVDd + PWth)^3 – LVDd^3] + 0.6 as Cube formula and LVEDV = {7/(2.4 + LVDd)} × LVDd^3 as Teichholz formula, in which IVSth = intraventricular septal thickness [7,10]. Given that advanced heart failure may change the LV structure from an elliptical to more-spherical chamber [11], LVM/LVEDV may be inadequate to estimate the concentricity.

The primary purpose of this study was to investigate the prognostic value of a concentric LV structure in AHDF, and the secondary purpose of this study was to compare the prognostic value of RWT and LVM/LVEDV in ADHF.

2. Methods

2.1. Participants

The present study was a single-center, retrospective, observational study conducted at a community hospital in Japan. A total of 426 consecutive patients admitted due to ADHF through our clinic or emergency room was recruited between June 2014 and April 2016 and were followed-up from June 2014 to October 2016. The diagnosis of ADHF was based on the Framingham criteria [12]. All participants had heart failure symptoms with New York Heart Association Class III or IV, and at least one of the following congestion signs; pulmonary edema, lower extremities pitting edema, distended jugular and or pleural effusion. A total of 41 patients were excluded for any of the following reasons: no TTE on admission (n = 35); and RWT or LVM/LVEDV not measured (n = 6). Finally, 385 patients were eligible for the analysis (Group A; Fig. A1). The patients were sub-grouped by excluding severe valvular diseases: severe aortic valve stenosis (AS) [13] (n = 21) in moderate and severe AS (n = 24); severe aortic valve regurgitation (AR) [14] (n = 8) in moderate and severe AR (n = 24); and severe mitral valve regurgitation (MR) [14] (n = 12) in moderate and severe MR (n = 59). Finally, 344 patients were enrolled in the non-severe valvular disease group (Group B; Fig. A1).

The present study followed the tenets of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects proposed by the Ministry of Health and Welfare in Japan. The institutional ethics committee at Tomishiro Central Hospital approved the present study and waived informed consent because of the observational nature of the study.

2.2. Transthoracic echocardiography

Comprehensive TTE (GE Vivid 7 ultrasound system, GE Healthcare, UK) was performed during hospital admission by four medical technicians who had at least five years of experience in TTE. Their measurement followed established and standardized manner recommended by American Society of Echocardiography (ASE) and European Society of Cardiology [7]. At least two attending cardiologists certified by the Japanese Circulation Society and an experienced sonographer reviewed the echocardiography reports immediately after comprehensive TTE.

LV geometry including IVSth in diastole, PWth in diastole, and LVDd were measured in M-mode in a parasternal long axis view [7]. All measurements were performed from the leading edge to the leading edge according to the ASE Recommendation [7,15,16]. RWT was calculated as RWT = 2 × PWth/LVDd [7]. LVM was calculated by the Cube formula recommended by ASE and the European Association of Cardiovascular Imaging (EACVI) [7,15,16]. LVEDV was computed using the Teichholz formula as LVEDV = {7/(2.4 + LVDd)} × LVDd^3 [10]. LVM and LVEDV were indexed to body surface area as LVMI and LVEDVI. LV ejection fraction (LVEF) was measured by the biplane Simpson's method [7]. Peak transmitral early diastolic wave (E wave) velocity, atrial contraction wave (A wave) velocity, and deceleration time (DCT) were measured by the pulse wave Doppler signals of the mitral inflow in the apical four-chamber view [17]. AS, AR, and MR were graded as none, mild, moderate, and severe [18].

Prior to the allocation, the one-year mortality rate was estimated to be 10% in the lower risk group and 20% in the higher risk group [19]. With a power of 0.8 and alpha error of 0.05, each group required >155 patients. Considering the feasibility, the participants were divided by the median RWT and LVM/LVEDV. The patients with higher RWT than the median were allocated to the high-RWT group, and the others were allocated to the low-RWT group in the overall population (Fig. A1; Group A) and the non-severe valvular disease population (Fig. A1; Group B). The patients were also allocated into low and high-LVM/LVEDV groups according to the median LVM/LVEDV in the same manner (Fig. A1).

2.3. Data collection

Patients' medical charts were reviewed to collect their demographic characteristics and clinical data, including medications, laboratory tests, and hemodynamic data on admission. The primary outcome was all-cause death. Death was confirmed by the medical chart, telephone call with a patient's family, or obituary in local newspapers.

2.4. Statistical analysis

Continuous variables with normal and skewed distributions are expressed as means (SD) and medians [25%, 75%], respectively. The distribution of continuous variables was evaluated by a histogram. Categorical variables are expressed as numbers (%). Demographic characteristics, TTE parameters, and clinical characteristics on hospital admission were summarized. The data were compared between the low and high-RWT groups, and between the low and high-LVM/LVEDV groups in the overall population (Group A) and the non-severe valvular disease population (Group B). Student's *t*-test and the Mann-Whitney *U* test were used to compare normally distributed and non-normally distributed continuous variables, respectively, and Fisher's exact test was used for categorical variables.

2.5. Survival analysis

Survival analysis for all-cause death was performed. Time zero was the date of hospital admission, and observations were censored at all-cause death as the event or the last hospital visit without an event. Non-informative censoring was used, and no events at the end of follow-up had right-censoring at October 30, 2016. Kaplan-Meier curves of the low and high-RWT and low and high-LVM/LVEDVI groups were plotted. The log-rank test was used to compare survival curves.

2.6. Cox proportional hazard models

Univariate Cox proportional hazard models were used to compute hazard ratios (HRs) with 95% confidence intervals (CIs). Univariate linear regression models were built for the overall population (Group A). Each of the following 18 factors was entered into a model: clinical factors reported as prognostic factors in previous studies (sex [20], BMI [21], LVM [22], LVEDV [23], hemoglobin [24]); the Get With The Guideline score (GWGS) as an established scoring system for predicting short-term mortality in ADHF [25]; therapeutic drugs such as angiotensin-converting enzyme inhibitors (ACE-Is) [26] and/or angiotensin receptor blockers (ARBs) [26] and beta blockers [27]; possible confounders such as significant valvular diseases (AS [28], AR [29], MR [30]); comorbidities including hypertension, chronic obstructive pulmonary disease (COPD) [31] and old myocardial infarction (OMI) [32]; TTE parameters including a systolic function marker (LVEF) [28,33] and diastolic function markers [34] (E wave, A wave, and the ratio of the E wave to the A wave (E/A)); concentric LV structure indices (high RWT, high LVM/LVEDV), and log-transformed brain natriuretic peptide (LogBNP). LVEF and E/A were binarized by 50% and 2.0 [17,35]. LVH and LV dilation were defined as LVMI > 115 g/m^2, LVEDVI > 75 mL/m^2, respectively [7,36].

Cox proportional hazard models adjusted by GWGS were also built. The same 18 factors other than GWGS as above were entered in each model for the overall population (Group A). To avoid collinearity, Spearman's correlation coefficients between GWGS and each of the other continuous variables were calculated, and a scatter plot matrix including all of the continuous variables was drawn. There were no significant correlations between GWGS and each of the other factors.

In the same manner, univariate and adjusted Cox proportional hazard models were also built using 15 factors and 14 factors, respectively, other than valvular disease (AS, AR, and MR) in the non-severe valvular disease population (Group B).

As a sensitivity analysis, we performed multivariate Cox proportional hazard analysis including co-morbidities which previous study documented as prognostic clinical factors and are frequently co-existing in heart failure [31,32,37], and RWT or LVM/LVEDVI.

Potential effect modifiers of the prognostic value of RWT or LVM/LVEDV were presumed to be as follows: sex, old myocardial infarction, hypertension, LVEF, left ventricular hypertrophy (LVH), LV dilation, AS, AR, and MR. The interaction between potential effect modifiers and RWT or LVM/LVEDVI in the Cox model was assessed in the overall population (Group A).

2.7. Reliability of measurement of RWT and LVM/LVEDV

We examined the reliability of TTE measurements of RWT and LVM/LVEDVI in 25 patients whose TTE image quality was good and, all of those patients were performed TTE by the same one of four medical technicians. The medical technician and one another examiner re-measured IVSth, LVDd, and PWth using an off-line image analysis system (Nahri Aqua, Mehergen Group, Fukuoka, Japan), and RWT and LVM/LVEDV were computed. Bland-Altman plots were used for assessing the agreement between the measurement by the same examiner and different examiners [38].

2.8. Software

The statistical software used was R 3.4.3 (R Foundation for Statistical Computing, Vienna Austria). All reported *P* value are two-tailed, and a *P* value <0.05 was considered significant.

3. Results

3.1. Demographic data and echocardiographic parameters in the overall population (Table 1)

In the overall population (Group A), the age was 81 [70, 88] years, and there were 181/385 (47%) men. The GWGS was 38 ± 7. RWT and LVMI/LVEDV were 0.36 ± 0.12 and 1.41 ± 0.56, respectively.

In comparisons between the low and high-RWT groups, the high-RWT group had more elderly patients, women, and severe AS compared to the low-RWT group. There was no significant difference in the GWGS between groups. LVEF was greater in the high-RWT group than in the low-RWT group. LVEDV and LVEDVI were smaller in the high-RWT group than in the low-RWT group. There were no significant differences in LVM and LVMI between the groups. Systolic blood pressure was higher in the high-RWT group than in the low-RWT group.

In the comparison between the low and high-LVM/LVEDV groups, the high-LVM/LVEDV group had a higher body mass index (BMI) and more severe AS than the low-LVM/LVEDV group. There was no significant difference in the GWGS between the groups. LVEF was greater in the high-LVM/LVEDV group than in the low-LVM/LVEDV group. LVEDV and LVEDVI were smaller in the high-LVM/LVEDV group than

Table 1
Demographic data and echocardiographic parameters on admission for acute decompensated heart failure in the overall population.

	Overall	Relative wall thickness			LVM/LVEDV		
		Low	High	*P* value	Low	High	*P* value
	n = 385	n = 193	n = 192		n = 193	n = 192	
Demographic data							
Age, y	81 [70, 88]	80 [68, 87]	83 [73, 89]	0.021	81 [71, 88]	81 [70, 88]	0.82
Male, n (%)	181/385 (47)	104/193 (54)	77/192 (40)	0.008	90/193 (47)	91/192 (47)	0.92
Body weight, kg	60 ± 16	60 ± 15	60 ± 17	0.95	58 ± 15	61 ± 17	0.068
Height, cm	154 ± 10	156 ± 10	153 ± 10	0.002	154 ± 10	154 ± 10	0.79
Body surface area, m^2	1.51 ± 0.22	1.53 ± 0.22	1.49 ± 0.23	0.11	1.50 ± 0.22	1.53 ± 0.23	0.17
Body mass index, kg/m^2	22.8 ± 4.6	22.6 ± 4.5	23.0 ± 4.8	0.42	22.2 ± 4.5	23.5 ± 4.8	0.009
Past medical history, n (%)							
Hypertension	187/385 (49)	92/193 (48)	95/192 (49)	0.76	84/193 (44)	103/192 (54)	0.053
Chronic obstructive pulmonary disease	18/385 (4.7)	7/193 (3.6)	11/192 (5.7)	0.35	7/193 (3.6)	11/192 (5.7)	0.35
Diabetes mellitus	132/385 (34)	68/193 (35)	64/192 (33)	0.75	71/191 (37)	61/192 (32)	0.33
Old myocardial infarction	62/385 (16)	37/193 (19)	25/192 (13)	0.13	34/193 (18)	28/192 (15)	0.49
Get With The Guideline score	38 ± 7	38 ± 6	38 ± 8	0.99	39 ± 7	38 ± 8	0.19
Valvular disease, n (%)							
Moderate severe aortic valve stenosis	24/385 (6.2)	14/193 (7.3)	10/192 (5.2)	0.53	11/193 (5.7)	13/192 (6.8)	0.68
Severe aortic valve stenosis	21/385 (5.5)	3/193 (1.6)	18/192 (9.4)	0.001	5/193 (2.6)	16/192 (8.3)	0.014
Moderate severe aortic valve regurgitation	24/365 (6.2)	14/193 (7.3)	10/192 (5.2)	0.53	11/193 (5.7)	13/192 (6.8)	0.68
Severe aortic valve regurgitation	9/385 (2.3)	7/193 (3.6)	2/192 (1.0)	0.18	3/193 (1.6)	6/192 (3.1)	0.34
Moderate severe mitral valve regurgitation	59/385 (15)	39/193 (20)	20/192 (10)	0.01	40/193 (21)	19/192 (9.9)	0.004
Severe mitral valve regurgitation	14/385 (3.6)	9/193 (4.7)	5/192 (2.6)	0.42	9/193 (4.7)	5/192 (2.6)	0.42
Echocardiographic parameters							
Left ventricular ejection fraction, (%)	46 ± 17	41 ± 16	51 ± 16	<0.001	42 ± 17	50 ± 17	<0.001
LVEDV, mL	136 ± 58	166 ± 58	105 ± 40	<0.001	156 ± 59	115 ± 49	<0.001
LVEDVI, mL/m^2	90 ± 34	107 ± 33	72 ± 24	<0.001	104 ± 33	75 ± 28	<0.001
Left ventricular mass, g	168 [132, 211]	173 [135, 211]	164 [132, 208]	0.51	159 [127, 194]	181 [142, 228]	<0.001
Left ventricular mass index, g/m^2	113 [91, 138]	112 [91, 137]	116 [91, 139]	0.4	106 [85, 126]	121 [98, 146]	<0.001
LVDd, mm	52 ± 11	57 ± 9	47 ± 8	<0.001	56 ± 9	48 ± 9	<0.001
Intraventricular septum thickness, mm	9.4 ± 2.4	8.5 ± 2.0	10.4 ± 2.4	<0.001	7.8 ± 1.5	11.0 ± 2.0	<0.001
Posterior wall thickness, mm	9.1 ± 2.1	7.8 ± 1.3	10.3 ± 2.0	<0.001	7.9 ± 1.2	10.3 ± 2.1	<0.001
Relative all thickness	0.36 ± 0.12	0.28 ± 0.05	0.45 ± 0.12	<0.001	0.29 ± 0.06	0.44 ± 0.13	<0.001
LVM/LVEDV, g/mL	1.43 ± 0.56	1.10 ± 0.23	1.75 ± 0.61	<0.001	1.07 ± 0.18	1.79 ± 0.58	<0.001
E wave peak velocity, cm/s	97 ± 29	97 ± 30	97 ± 28	0.94	97 ± 29	97 ± 29	0.96
A wave peak velocity, cm/s	76 ± 32	70 ± 29	82 ± 34	0.011	74 ± 31	77 ± 33	0.59
E/A	1.21 [0.84, 1.83]	1.29 [0.89, 2.04]	1.15 [0.82, 1.68]	0.18	1.18 [0.84, 1.85]	1.27 [0.88, 1.75]	0.99
Deceleration time, msec	150 [123, 195]	150 [121, 196]	150 [128, 192]	0.49	150 [121, 184]	150 [129, 200]	0.16
Laboratory test							
Blood urea nitrogen, mg/dL	24 [17, 35]	24 [17, 34]	24 [17, 36]	0.77	24 [17, 35]	24 [16, 35]	0.83
Creatinine, mg/dL	1.14 [0.81, 1.52]	1.15 [0.83, 1.54]	1.09 [0.79, 1.51]	0.31	1.14 [0.80, 1.54]	1.13 [0.81, 1.51]	0.76
Na, mEq/L	139 ± 5	139 ± 5	138 ± 5	0.5	138 ± 6	139 ± 5	0.22
Brain natriuretic peptide, pg/mL	666 [427, 1266]	737 [449, 1376]	638 [403, 1154]	0.056	688 [446, 1374]	641 [406, 1154]	0.12
Hemoglobin, g/dL	12.0 ± 2.4	12.0 ± 2.4	11.9 ± 2.4	0.84	11.7 ± 2.4	12.1 ± 2.4	0.12
Medication, n (%)							
ACE-I or ARB	124/385 (32)	71/193 (37)	53/192 (28)	0.064	68/193 (35)	56/192 (29)	0.23
Beta blocker	153/385 (40)	78/193 (40)	75/192 (39)	0.84	78/193 (40)	75/192 (39)	0.84
Hemodynamics							
Systolic blood pressure, mmHg	132 ± 26	128 ± 24	135 ± 29	0.006	128 ± 23	135 ± 29	0.006
Heart rate, bpm	84 ± 21	83 ± 21	84 ± 21	0.81	82 ± 19	85 ± 22	0.26

A wave, transmitral atrial contraction wave; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; E wave, transmitral early diastolic wave; LVDd, left ventricular dimension at end-diastole; LVEDV; left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVM, left ventricular mass.
Continuous variables with normal and with skewed distribution were expressed as mean ± SD and median [25%, 75%]. Categorical variables were expressed as the number (%).

in the low-LVM/LVEDV group. The high-LVM/LVEDV group had greater LVM and LVMI than the low-LVM/LVEDV group. Systolic blood pressure was higher in the high-LVM/LVEDV group than in the low-LVM/LVEDV group.

3.2. Demographic data and echocardiographic parameters in the non-severe valvular disease population (Table 2)

In the non-severe valvular disease population (Group B), the age was 81 [69, 88] years, and there were 166/344 (48%) men. The GWGS was 38 ± 7. RWT and LVMI/LVEDV were 0.36 ± 0.12 and 1.41 ± 0.56, respectively.

In the comparison between the low and high-RWT groups, the high-RWT group had more elderly patients and women than the low-RWT group. There was no significant difference in the GWGS between the groups. LVEF was greater in the high-RWT group than in the low-RWT group. LVEDV and LVEDVI were smaller in the high-RWT group than the in low-RWT group. There were no significant differences in LVM and LVMI between the groups. Systolic blood pressure was higher in the high-RWT group than in the low-RWT group.

In the comparison between the low and high-LVM/LVEDV groups, the high-LVM/LVEDV group had higher BMI and more hypertension than the low-LVM/LVEDV group. There was no significant difference in the GWGS between the groups. LVEF was higher in the high-LVM/LVEDV group than in the low-LVM/LVEDV group. LVEDV and LVEDVI were smaller in the high-LVM/LVEDV group than in the low-LVM/LVEDV group. The high-LVM/LVEDV group had greater LVM and LVMI than the low-LVM/LVEDV group. Systolic blood pressure was higher in the high-LVM/LVEDV group than in the low-LVM/LVEDV group.

Table 2
Demographic data and echocardiographic parameters on admission for acute decompensated heart failure in the non-severe valvular disease population.

	Overall	Relative wall thickness			LVM/LVEDV		
		Low	High	*P* value	Low	High	*P* value
	n = 344	n = 172	n = 172		n = 172	n = 172	
Demographic data							
Age, y	81 [69, 88]	79 [68, 86]	82 [71, 88]	0.043	80 [72, 87]	81 [67, 88]	0.68
Male, n (%)	166/344 (48)	94/172 (55)	72/172 (42)	0.023	83/172 (48)	83/172 (48)	1
Body weight, kg	61 ± 16	61 ± 15	61 ± 17	0.81	59 ± 15	63 ± 17	0.058
Height, cm	155 ± 10	156 ± 10	153 ± 10	0.009	155 ± 10	154 ± 10	0.87
Body surface area, m^2	1.52 ± 0.22	1.54 ± 0.22	1.51 ± 0.23	0.16	1.51 ± 0.22	1.54 ± 0.23	0.16
Body mass index, kg/m^2	23.1 ± 4.6	22.9 (4.4)	23.2 (4.8)	0.5	22.4 ± 4.3	23.7 ± 4.8	0.008
Past medical history, n (%)							
Hypertension	168/344 (49)	84/172 (49)	84/172 (49)	1	74/172 (43)	94/172 (55)	0.04
Chronic obstructive pulmonary disease	16/344 (4.7)	6/172 (3.5)	10/172 (5.8)	0.44	5/172 (2.9)	11/172 (6.4)	0.2
Diabetes mellitus	123/344 (36)	64/172 (37)	59/172 (34)	0.65	65/172 (38)	58/172 (34)	0.5
Old myocardial infarction	58/344 (17)	34/172 (20)	24/172 (14)	0.2	31/172 (18)	27/172 (16)	0.67
Get With The Guideline score	38 ± 7	38 ± 6	37 ± 8	0.41	38 ± 6	37 ± 8	0.21
Valvular disease, n (%)							
Moderate aortic valve stenosis	14/344 (4.1)	7/172 (4.1)	7/172 (4.1)	1	8/172 (4.7)	6/172 (3.5)	0.79
Moderate aortic valve regurgitation	14/344 (4.1)	7/172 (4.1)	7/172 (4.1)	1	8/172 (4.7)	6/172 (3.5)	0.79
Moderate mitral regurgitation	41/344 (12)	29/172 (17)	12/172 (7)	0.007	28/172 (16)	13/172 (7.6)	0.019
Echocardiographic parameters							
Left ventricular ejection fraction, (%)	46 ± 17	41 ± 16	52 ± 16	<0.001	42 ± 17	50 ± 17	<0.001
LVEDV, mL	136 ± 58	166 ± 58	106 ± 40	<0.001	158 ± 60	114 ± 47	<0.001
LVEDVI, mL/m^2	89 ± 33	107 ± 33	71 ± 23	<0.001	104 ± 34	74 ± 26	<0.001
Left ventricular mass, g	168 [132, 208]	170 [134, 211]	164 [132, 207]	0.57	157 [126, 191]	181 [142, 226]	<0.001
Left ventricular mass index, g/m^2	111 [90, 137]	110 [90, 136]	112 [91, 137]	0.46	104 [85, 125]	118 [96, 141]	<0.001
LVDd, mm	52.1 ± 9.7	57.2 ± 8.7	46.9 ± 7.9	<0.001	55.8 ± 9.2	48.3 ± 8.8	<0.001
Intraventricular septum thickness, mm	9.3 ± 2.4	8.4 ± 2.0	10.3 ± 2.4	<0.001	7.8 ± 1.5	10.9 ± 2.0	<0.001
Posterior wall thickness, mm	9.0 ± 2.1	7.8 ± 1.2	10.2 ± 2.0	<0.001	7.8 ± 1.1	10.2 ± 2.1	<0.001
Relative all thickness	0.36 ± 0.12	0.28 ± 0.05	0.45 ± 0.12	<0.001	0.29 ± 0.06	0.44 ± 0.13	<0.001
LVM/LVEDV, g/mL	1.41 ± 0.56	1.09 ± 0.22	1.73 ± 0.61	<0.001	1.05 ± 0.17	1.77 ± 0.58	<0.001
E wave peak velocity, cm/s	96 ± 28	98 ± 31	94 ± 25	0.32	97 ± 29	95 ± 27	0.5
A wave peak velocity, cm/s	76 ± 31	70 ± 28	82 ± 33	0.014	75 ± 30	77 ± 33	0.62
E/A	1.20 [0.84, 1.82]	1.27 [0.89, 2.04]	1.12 [0.80, 1.62]	0.084	1.18 [0.81, 1.85]	1.21 [0.86, 1.69]	0.81
Deceleration time, msec	150 [125, 200]	150 [123, 200]	152 [125, 196]	0.61	150 [122, 192]	152 [129, 201]	0.14
Laboratory test							
Blood urea nitrogen, mg/dL	24 [17, 35]	24 [17, 34]	24 [17, 35]	0.83	24 [17, 35]	24 [16, 35]	0.96
Creatinine, mg/dL	1.14 [0.82, 1.52]	1.16 [0.85, 1.53]	1.09 [0.79, 1.51]	0.24	1.13 [0.80, 1.54]	1.15 [0.86, 1.51]	0.96
Na, mEq/L	139 ± 5	139 ± 5	139 ± 5	0.78	138 ± 6	139 ± 5	0.12
Brain natriuretic peptide, pg/mL	627 [403, 1187]	682 [427, 1348]	572 [384, 981]	0.025	669 [427, 1276]	598 [380, 981]	0.077
Hemoglobin, g/dL	12.0 ± 2.5	12.1 ± 2.4	11.9 ± 2.5	0.615	11.8 ± 2.4	12.2 ± 2.5	0.11
Medication, n (%)							
ACE-I or ARB	112/344 (33)	63/172 (37)	49/172 (28)	0.14	58/172 (34)	54/172 (31)	0.73
Beta blocker	140/344 (41)	70/172 (41)	70/172 (41)	1	71/172 (41)	69/172 (40)	0.91
Hemodynamics							
Systolic blood pressure, mmHg	132 ± 27	128 ± 24	136 ± 29	0.003	128 ± 24	136 ± 29	0.007
Heart rate, bpm	84 ± 21	84 ± 20	84 ± 21	0.94	82 ± 18	86 ± 23	0.089

A wave, transmitral atrial contraction wave; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; E wave, transmitral early diastolic wave; LVDd, left ventricular dimension at end-diastole; LVEDV; left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVM, left ventricular mass.
Continuous variables with normal and with skewed distribution were expressed as mean ± SD and median [25%, 75%]. Categorical variables were expressed as the number (%).

3.3. Survival analysis (Fig. 1)

During follow-up (235 [92, 425] days), 95/385 (25%) patients died in the overall population (Group A), and 80/344 (23%) patients died in the non-severe valvular disease population (Group B).

Kaplan-Meier curves for all-cause death comparing the high and low-RWT groups and comparing the high and low-LVM/LVEDV groups in the overall population and in the non-severe valvular disease population are shown in Fig. 1.

In the overall population, the high-RWT group had a higher incidence of death than the low-RWT group (31% vs. 19%, $P = 0.009$). The high-RWT group had worse survival than the low-RWT group (Log-rank, $P = 0.009$; Fig. 1A). In contrast, there were no significant differences in the mortality rate (27% vs. 22%, $P = 0.33$) and survival (log-rank, $P = 0.42$; Fig. 1B) between the low and high-LVM/LVEDV groups.

In the non-severe valvular disease population, the high-RWT group had a higher incidence of death than the low-RWT group (29% vs. 18%, $P = 0.03$). The high-RWT group had worse survival than the low-RWT group ($P = 0.028$; Fig. 1C). In contrast, there were no significant differences in the mortality rate (26% vs. 21%, $P = 0.37$) and survival (log-rank, $P = 0.42$; Fig. 1D) between the low and high-LVM/LVEDV groups.

3.4. Univariate and adjusted cox proportional hazard models (Table 3)

In the overall population, univariate Cox proportional hazard models demonstrated that GWGS, sex, BMI, LVCOPD, RWT, severe AS, hemoglobin, A wave, and LogBNP were the significant factors related to the risk of all-cause death in ADHF patients. Cox proportional hazard models adjusted by the GWGS demonstrated that BMI, LV dilation, RWT, severe AS, and A wave were the significant factors related to the risk of all-cause death in ADHF patients.

In the non-severe valvular disease population, univariate Cox proportional hazard models demonstrated that GWGS, sex, BMI, COPD, LV dilation, RWT, hemoglobin, E wave, A wave, and LogBNP were the significant factors related to the risk of all-cause death in ADHF patients. Cox proportional hazard models adjusted by the GWGS demonstrated that BMI, LV dilation, RWT, hemoglobin, and A wave were the significant factors related to the risk of all-cause death in ADHF patients.

3.5. Interaction between clinical factors and RWT or LVM/LVEDVI

There were no interactions between high RWT and clinical factors (sex, OMI, hypertension, LVEF, LVH, LV dilation, severe AS, severe AR, and severe MR; Fig. A2) and between high LVM/LVEDV and clinical factors (Fig. A2).

3.6. Reliability of measurement of RWT and LVM/LVEDV

In intra-observer reliability, Bland-Altman plots showed no systematic error in both of RWT and LVM/LVEDVI (Fig. A3A, A3B). In inter-observer reliability, Bland-Altman plots showed no systematic error in both of RWT and LVM/LVEDVI neither (Fig. A3C, A3D).

3.7. Sensitivity analysis

Cox-proportional hazard models demonstrated that high RWT was a significant factor associated with mortality in overall and non-severe valvular disease populations (Table 3). In contrast, high LVM/LVEDV was not a significant factor.

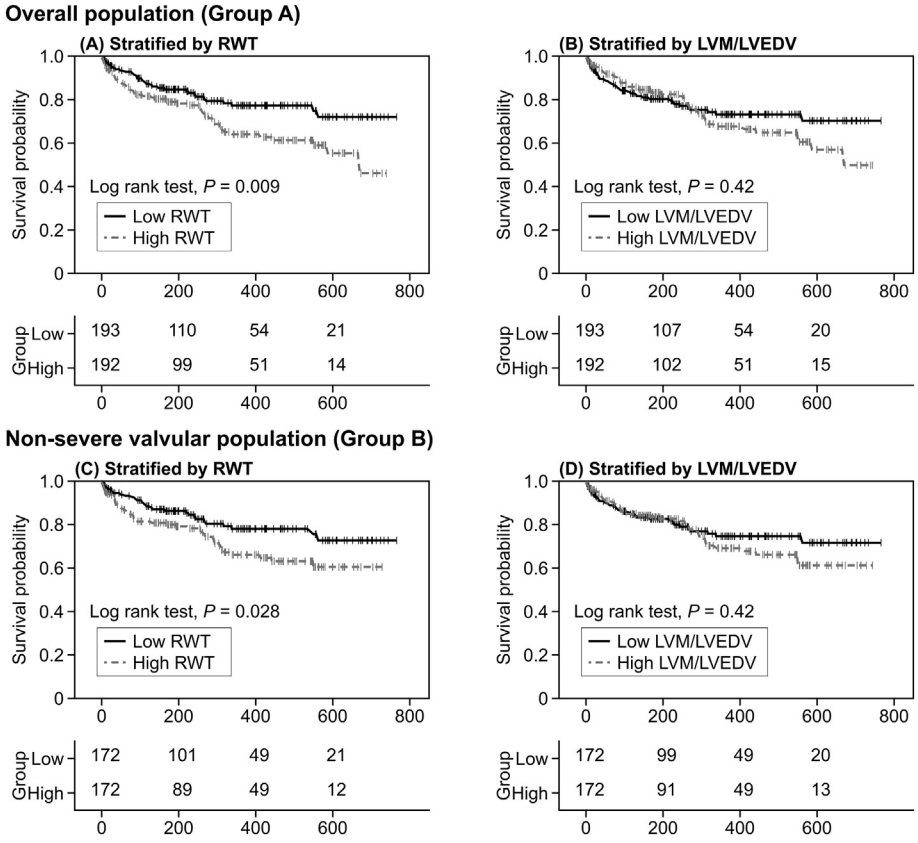

Fig. 1. Kaplan-Meier curves for all-cause death stratified by left ventricular concentricity in patients with acute decompensated heart failure. LVM/LVEDV, ratio of left ventricular mass to left ventricular end-diastolic volume; RWT, relative wall thickness. Patients were allocated to two groups according to the median RWT or LVDVI. The cut-off was based on the median RWT or LVM/LVEDV. (A) Kaplan-Meier curves stratified by RWT in the overall population. (B) Kaplan-Meier curves stratified by LVM/LVEDV in the overall population. (C) Kaplan-Meier curves stratified by RWT in the non-severe valvular disease population. (D) Kaplan-Meier curves stratified by LVM/LVEDV in the non-severe valvular disease population.

Table 3
Cox proportional hazard models for all-cause death.

	Overall population									Non-severe valvular disease								
	Univariate					Adjusted by GWGS				Univariate					Adjusted by GWGS			
Factor	HR	95% CI			*P* value	HR	95% CI		*P* value	HR	95% CI			*P* value	HR	95% CI		*P* value
GWGS	1.1	1.07	–	1.13	<0.001	(Adjustment factor)				1.09	1.06	–	1.12	<0.001	(Adjustment factor)			
Male	0.57	0.37	–	0.86	0.008	0.71	0.46	– 1.09	0.11	0.62	0.39	–	0.97	0.036	0.75	0.47	– 1.2	0.23
BMI, kg/m^2	0.87	0.82	–	0.92	<0.001	0.89	0.84	– 0.95	<0.001	0.87	0.82	–	0.93	<0.001	0.9	0.84	– 0.95	<0.001
Hypertension	1.03	0.69	–	1.54	0.88	1.06	0.71	– 1.6	0.77	1.03	0.69	–	1.54	0.88	0.93	0.59	– 1.45	0.73
COPD	2.17	1.09	–	4.32	0.027	1.4	0.69	– 2.84	0.35	2.41	1.16	–	5.01	0.018	1.54	0.72	– 3.29	0.26
OMI	0.63	0.34	–	1.15	0.13	0.7	0.38	– 1.29	0.26	0.67	0.35	–	1.26	0.21	0.72	0.38	– 1.37	0.32
LVEF <50%	0.82	0.55	–	1.24	0.35	0.76	0.5	– 1.15	0.2	0.82	0.55	–	1.24	0.35	0.76	0.5	– 1.15	0.2
LVH	0.57	0.31	–	1.05	0.073	0.66	0.35	– 1.25	0.21	0.57	0.31	–	1.05	0.073	0.66	0.35	– 1.25	0.21
LV dilation	1.98	1.3	–	3.02	0.002	1.82	1.18	– 2.79	0.006	1.98	1.3	–	3.02	0.002	1.82	1.18	– 2.79	0.006
RWT, high	1.72	1.14	–	2.61	0.01	1.95	1.28	– 2.97	0.002	1.65	1.05	–	2.58	0.03	1.96	1.24	– 3.11	0.004
LVM/LVEDV, high	1.18	0.79	–	1.77	0.42	1.35	0.9	– 2.04	0.15	1.2	0.77	–	1.86	0.42	1.35	0.86	– 2.12	0.19
Severe AS	2.76	1.43	–	5.32	0.002	2.25	1.15	– 4.39	0.018									
Severe AR	0.75	0.18	–	3.03	0.68	0.56	0.14	– 2.28	0.42									
Severe MR	0.9	0.28	–	2.83	0.85	0.83	0.26	– 2.63	0.75									
Hemoglobin, g/dL	0.89	0.81	–	0.98	0.013	0.91	0.82	– 1	0.051	0.88	0.8	–	0.97	0.013	0.9	0.81	– 1	0.048
E wave, cm/s	0.99	0.99	–	1	0.22	0.99	0.99	– 1	0.19	0.99	0.98	–	1	0.04	0.99	0.98	– 1	0.056
A wave, cm/s	1.01	1.01	–	1.02	0.002	1.01	1.01	– 1.02	<0.001	1.01	1	–	1.02	0.006	1.02	1.01	– 1.03	0.003
E/A > 2	0.47	0.22	–	1.01	0.054	0.58	0.27	– 1.25	0.16	0.47	0.22	–	1.01	0.054	0.58	0.27	– 1.25	0.16
ACE-I or ARB	0.92	0.59	–	1.41	0.69	0.95	0.61	– 1.48	0.81	0.93	0.59	–	1.49	0.78	0.97	0.6	– 1.58	0.91
Beta blocker	0.77	0.51	–	1.18	0.23	0.74	0.49	– 1.13	0.16	0.82	0.52	–	1.28	0.38	0.77	0.49	– 1.21	0.26
LogBNP, log(pg/mL)	1.61	1.21	–	2.13	<0.001	1.32	0.99	– 1.75	0.06	1.48	1.10	–	2.01	0.011	1.23	0.91	– 1.68	0.18

A wave, peak transmitral atrial contraction wave; ACE-I, angiotensin converting enzyme inhibitor; AR, aortic valve regurgitation; ARB, angiotensin receptor blocker; AS, aortic valve stenosis; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E wave, peak transmitral early diastolic wave; E/A, ratio of peak transmitral early diastolic wave to peak transmitral atrial contraction wave; GWGS, Get With The Guideline Score; HR, hazard ratio; LogBNP, log-transformed brain natriuretic peptide; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVM/LVEDV, ratio of left ventricular mass to left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; MR, mitral valve regurgitation; OMI, old myocardial infarction; RWT, relative wall thickness.
LVH and LV dilation were defined as LVMI >115 g/m^2, LVEDVI >75 mL/m^2.

4. Discussion

To the best of our knowledge, the present study is the first to show that a concentric LV structure evaluated by RWT is associated with mortality in ADHF patients. From the present study, two major findings emerged. First, high RWT was the risk factor for all-cause death in both the overall and the non-severe valvular disease populations (Fig. 1A, C; Table 3). Second, LVM/LVEDV was not associated with prognosis in ADHF (Fig. 1B, D; Table 3). In previous studies, RWT was found to be an echocardiographic marker associated with poor cardiovascular outcomes in patients with hypertension [4]. The present study suggested that RWT may also predict prognosis in patients with ADHF.

This epidemiological study cannot address the pathophysiological mechanism that the concentric LV structure had worse prognosis. Possible explanations are as follows. A previous magnetic resonance imaging (MRI) study suggested that concentric LV structure had myocardial fibrous from the MRI findings, resulting in poor LV diastolic function or stroke volume in hypertensive patients [39]. Given that echocardiography finding in the present high-RWT patients showed a greater A wave (Tables 1, 2), impaired LV relaxation accompanied with a concentric LV structure may persist and progress the stage of heart failure after discharge. Considering Frank-starling law, less physiological reserve of LV function should be expected in patients with concentric LV structure.

4.1. The difference in the prognostic values of RWT and LVM/LVEDV

Univariate and adjusted Cox proportional hazard models also showed that LV dilation, high RWT were the significant factors. LV dilation has been reported as a LV geometry which is associated with mortality in ADHF. Our study revealed that LV concentric structure evaluated by RWT was also the risk for mortality.

RWT was directly measured on a two-dimensional image [2,7]. In contrast, both LVM and LVEDV were calculated by equations based on the assumption that the LV should be ellipsoid [10]. Suzuki et al. demonstrated that ADHF model dogs induced by right heart rapid pacing have spherical LV dilation [40]. LV shape would have shifted from an elliptical to a more-spherical chamber in the present study population. Thus, the equations for LVM and LVEDV might be inadequate, and LVM/LVEDV may not accurately represent the concentricity of the LV.

The high-LVM/LVEDV group had greater LVM than the low-LVM/LVEDV group. This finding was not observed in the comparison between the high and low-RWT groups. In light of this finding, LVM/LVEDV might reflect increased LVM, not LV concentricity (Tables 1, 2). Concentricity was more precise in evaluating the severity of LV stress in developing heart failure than LVM.

In sensitivity analysis, multivariate Cox proportional hazard models including RWT or LVM/LVEDV as a continuous variable demonstrated that both RWT and LVM/LVEDV were the significant factors. This result regarding with RWT was consistent.

4.2. Sub-group analysis

The present study population included both valvular and non-valvular diseases. The effects of hemodynamic alternations on LV structure may differ with or without valvular diseases. Less prognostic impact of RWT is expected in chronic AR that imposes volume overload resulting in LV dilatation [41]. In contrast, AS imposes pressure overload. Previous studies implied that the prognostic impact of RWT might be more prominent under co-existing AS [42]. Lack of an interaction between AR or AS and the risk of death in the high-RWT group suggest that there is consistency in terms of the prognostic value of RWT between the presence and absence of AR or AS. However, combinations of valvular diseases may distort the prognostic value of RWT. Several co-existing valvular diseases occur frequently in ADHF patients. One should be cautious when using RWT for risk assessment in ADHF patients with valvular diseases. The present study included a few valvular diseases. Further

studies including sufficient numbers of patients with each valvular disease to confirm the prognostic value of RWT are warranted.

4.3. Clinical significance

The position during TTE on hospital admission in ADHF patients may be restricted to Fowler's position or the sitting position because of the patients' congestive symptoms [43]. The strong point of this study is that the RWT that was obtained by simple measurement in the parasternal long axis view has prognostic value. Physicians other than cardiologists may see ADHF patients and treat them in primary care settings because ADHF is common [44]. Handy portable echocardiography that can measure IVSth and PWth is developing and spreading [45]. The measurement of IVSth and PWth in the parasternal long axis view is not very difficult. Thus, RWT is a clinically acceptable and feasible tool for risk stratification in patients with ADHF, regardless of the examiner's expertise or the device. RWT, as well as established prognostic markers, should be included in patient evaluation. ADHF treatment and management are still challenging because of the progressive nature of the disease even if congestive symptoms are treated and disappeared. Early recognition of the risk in ADHF would be beneficial.

5. Study limitations

The present study had several limitations. Diastolic dysfunction could not be diagnosed according to the guideline recommended by the ASE and EACI [17], because almost all patients did not undergo tissue Doppler echocardiography or have measurements of tricuspid regurgitation velocity or left atrial volume on hospital admission. The relatively new parameters, such as global longitudinal strain, were not measured. Furthermore, detailed studies to investigate the relationships between LV concentric structure and such functional parameters in ADHF patients are warranted. Cardiac magnetic resonance imaging, considered the gold standard for the measurement of LV structure, was not used to validate RWT measured by TTE. LVEDV by the biplane Simpson method could not be obtained from the echocardiography reports. Further, the possibility of cardiomyopathy and sarcoidosis was not excluded by biopsy, contrast magnetic resonance, or positive emission tomography. The number of participants had been planned for two-group comparison according the sample size estimation considering the mortality rate in patients with ADHF [19]. However, to confirm the trend, it needs more number of study population for three or more group comparison. The design of this study was retrospective and conducted at a single center. Single center design might be a merit regarding with transthoracic echocardiography (TTE) measurement as a pilot study. In fact, the reliability of RWT and LVM/LVEDV were confirmed in 25 patients (Fig. A3). From this observation, less technical variety sonographers at our institution was confirmed. To validate robustness of the present study, well-designed a large number of prospective multicenter study in which standardization of measurement technique should be assured is warranted.

6. Conclusions

LV concentric structure represented by the RWT in a parasternal long axis view on TTE during hospital admission had a significant prognostic impact in patients with ADHF.

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