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# Right ventricular diastolic dysfunction worsens clinical outcomes in Japanese patients with heart failure

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A R T I C L E I N F O

*Keywords:*
Heart failure
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A B S T R A C T

*Background:* Heart failure (HF) is a rapidly growing public health issue in super aging societies, such as Japan. Right HF is common in older patients. Therefore, the present study investigated the relationship between right ventricular diastolic function and poor clinical outcomes in patients with HF.

*Methods:* We retrospectively enrolled 387 Japanese HF patients. All data were obtained from our echocardiographic and jugular venous pulse (JVP) databases and medical records. A less-distensible right ventricle (RV) was identified by a deeper 'Y' descent than 'X' descent in the JVP waveform. We defined cardiac events of HF as follows: sudden death, death from HF, emergent infusion of loop diuretics, or hospitalization for deterioration of HF. Comparisons between patients with and without cardiac events and a multivariate analysis of cardiac events were performed.

*Results:* Eighty-five patients had cardiac events. Left ventricular ejection fraction (LVEF) was lower, average mitral E/e′ and the prevalence of a less-distensible RV were higher, and tricuspid annular plane systolic excursion was shorter in patients with than in those without cardiac events (median55vs65, $p < 0.001$; median15vs11, $p < 0.001$; 64 %vs27%, $p < 0.001$; median17vs20, $p < 0.001$, respectively). In a multivariate Cox proportional hazard model, LVEF and a less-distensible RV were independent risk factors for cardiac events (hazard ratio [HR]:0.983 per 1 % increase, $p = 0.048$; HR:3.150, $p < 0.001$, respectively). The event-free rate was the lowest for patients with LVEF $< 50$ % and a less-distensible RV (p for trend $< 0.001$).

*Conclusions:* When right ventricular diastolic function is impaired and irreversible, Japanese patients with HF may become intractable regardless of LVEF.

## 1. Introduction

Advances in our understanding of the physiological mechanisms underlying heart failure (HF) and the development of therapeutic strategies based on its pathophysiology have improved the management of HF [1,2]; however, the clinical outcomes of HF remain poor [3,4]. Since the incidence of HF increases with aging, this syndrome is a rapidly growing public health issue in Japan, a super aging society [5,6]. Therefore, research that focuses on cardiac dysfunctions associated with the severity of HF is important for overcoming this refractory syndrome.

The physiological importance of right ventricular (RV) function, which is regarded as an auxiliary pump for circulation, has been overlooked for decades [7]. However, signs or symptoms of RV HF, such as leg edema, are common in older patients with HF [8], indicating the negative impact of RV dysfunctions on HF. Previous studies reported that RV dysfunctions were also associated with the clinical outcomes of patients with HF, particularly HFpEF [9,10], and simultaneously identified several issues in RV examinations. Difficulties are associated with performing an echocardiographic assessment of right ventricle due to its complex anatomy [11]. Moreover, an echocardiographic method to evaluate RV diastolic function has not yet been established [12]. To overcome these issues, we used the jugular venous pulse (JVP) or right atrial waveform to infer RV diastolic function and demonstrated the pathophysiological meaning and clinical importance of a deeper Y descent than X descent in patients with HFpEF [13,14]. However, the clinical significance of a deep Y descent in HF with reduced left ventricular ejection fraction (LVEF) and mid-range LVEF has not yet been investigated. Further studies on the impact of RV diastolic function on HF will be useful for the development of therapeutic strategies for HF. Therefore, the present study attempted to clarify the relationship

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[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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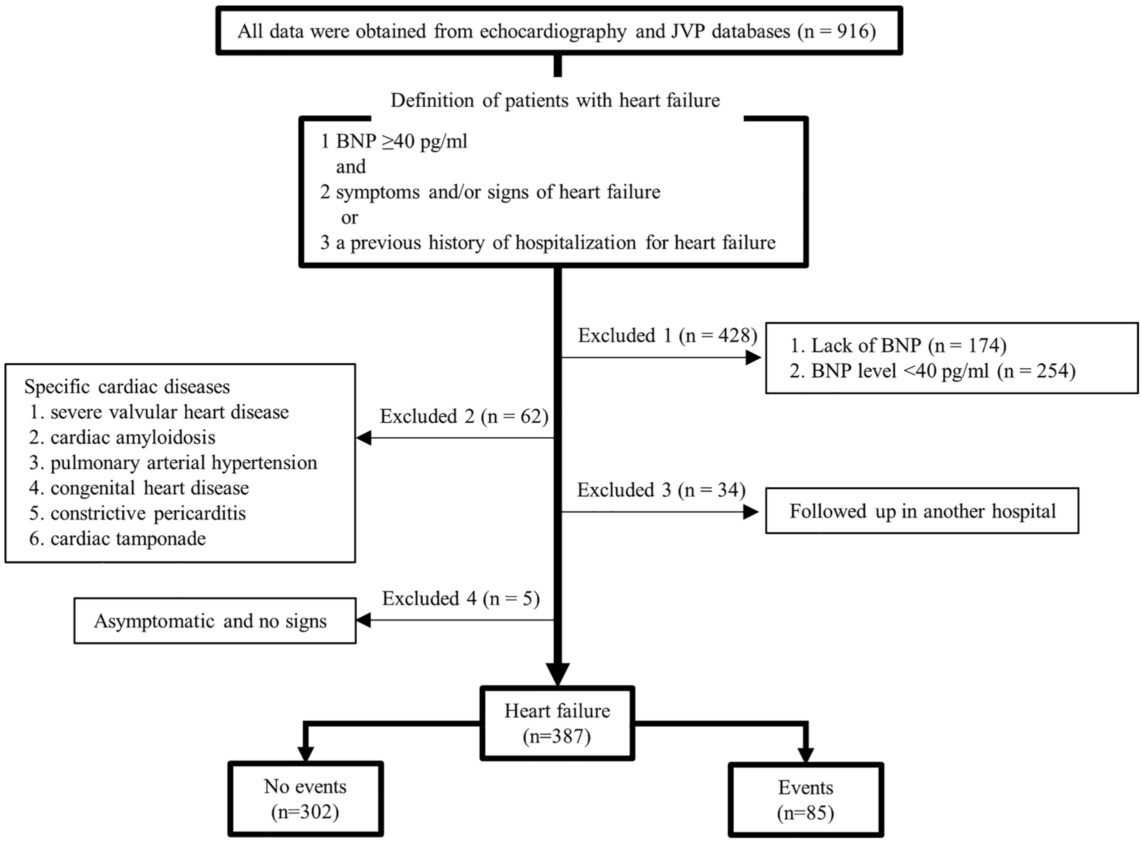



**Fig. 1.** Study flow chart. BNP, brain natriuretic peptide; JVP, jugular venous pulse.

between ventricular function, including RV diastolic function, and poor clinical outcomes in patients with HF.

## 2. Methods

### *2.1. Study design*

The institutional human subject review committee of our institute approved the present study (reference number is 023001). All data were retrospectively obtained from echocardiographic and JVP databases and medical records between April 2017 and March 2021. A study flow chart is shown in Fig. 1. All patients enrolled in the present study were Japanese. We defined patients with HF as those with a brain natriuretic peptide (BNP) level $\geq$ 40 pg/ml and symptoms and/or signs of HF or prior hospitalization for HF [1]. Patients were excluded if they lacked BNP or its level was $<$ 40 pg/ml. We excluded 62 patients with documented specific cardiac diseases, such as severe valvular heart disease, cardiac amyloidosis, pulmonary arterial hypertension, congenital heart

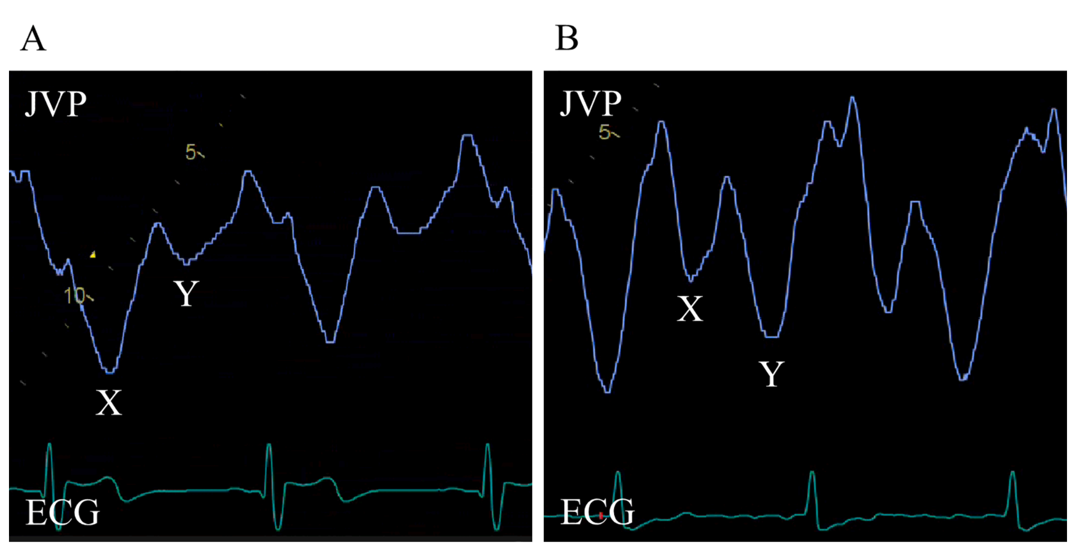



**Fig. 2.** Assessment of the jugular venous pulse. (A) A 78-year-old woman had a distensible right ventricle characterized by the deepest ‘X’ descent within a single cardiac cycle. (B) An 83-year-old female had a less-distensible right ventricle characterized by a deeper ‘Y’ descent than ‘X’ descent. ECG, electrocardiogram; JVP, jugular venous pulse.

disease, constrictive pericarditis, and cardiac tamponade, which are cardiac diseases with a poor prognosis, and/or treated by invasive procedures, such as surgery. Patients were also excluded if they were unable to be followed up in our hospital. Patients with no symptoms or signs of HF were also excluded. Therefore, we retrospectively enrolled 387 patients in the present study. Comparisons between patients with and without cardiac events were performed. A multivariate analysis was also conducted to clarify variables for cardiac events. Based on the arrangement of our hospital, all patients provided their informed consent. The present study complied with the Declaration of Helsinki.

### 2.2. Evaluation of cardiac function

Cardiac function was evaluated as described in our previous study [13]. An echocardiographic examination (Vivid 7, General Electric Healthcare, Wauwatosa, WI, USA) was performed with reference to the guidelines [15,16,17]. LV end-diastolic and end-systolic volumes were measured using a modification of Simpson's method. LVEF was calculated as the stroke volume divided by the end-diastolic volume. To evaluate diastolic properties, we measured early diastolic velocities (e′) using pulsed-wave tissue Doppler from the apical view. We measured septal and lateral E/e′, and averaged the values obtained for a more reliable assessment of LV diastolic function and filling pressure [15]. The left atrial volume index was obtained using the biplane method from both the apical 4- and 2-chamber views [16]. The LV mass was calculated using the Devereux formula and was divided by surface area [16]. Tricuspid annular plane systolic excursion (TAPSE) was measured from the apical four-chamber view. The tricuspid regurgitant jet was detected using the continuous Doppler technique to measure RV systolic pressure [17]. We regarded RV systolic pressure as systolic pulmonary arterial pressure (SPAP) because of the absence of a gradient across the pulmonic valve and RV outflow tract. The severity of valvular heart disease was examined according to the guidelines [18]. If patients had atrial fibrillation, we estimated velocity measurements from 10 cardiac cycles [15]. Using a pulse-wave transducer (TY-306, Fukuda Denshi, Tokyo, Japan), we measured JVP (Fig. 2). The methods employed to measure and judge JVP were the same as those in our previous study [8]. We previously reported that a deeper 'Y' descent than 'X' descent in JVP indicated a reduced RV preload reserve or less-distensible right ventricle, which are risk factors for cardiac events in patients with HFpEF [8,14]. LVEF, the mean mitral E/e′ ratio, SPAP, TAPSE, and the JVP waveform were used as indicators of LV systolic function, LV diastolic function, RV afterload, RV systolic function, and RV diastolic function, respectively, in the present study.

### 2.3. Documentation of endpoints

All 387 patients were followed up at our hospital. We defined cardiac events as follows: sudden death, death from HF, the emergent infusion of loop diuretics to treat lung congestion, or hospitalization for the deterioration of HF. These cardiac events were reported and adjudicated by cardiovascular specialists at our hospital.

### 2.4. Statistical analysis

Numerical data are expressed as the median (interquartile range). The Mann-Whitney *U* test and Fisher's exact test were used to compare numerical data and non-parametric data between the groups, respectively. In outcome analyses, we used Cox proportional hazard models to examine independent associations between features and cardiac events. In the Cox hazard models, we selected variables with a P value $< 0.2$ in the univariate analysis. The p-value did not meet the above criteria; however, sex, diabetes mellitus, ischemic heart disease, such as old myocardial infarction, and mitral regurgitation were also selected because these indices are associated with cardiac events [1]. We constructed the model using the Akaike information criterion because there are numerous explanatory variables relative to the sample size. Cardiac events of HF stratified by LVEF and RV diastolic function were estimated using the Kaplan-Meier method. Differences between the event-free curves were examined using the Log-rank chi-square test. Cox proportional hazard models were also used to compare the severity of HF among groups. Significance was established at $p < 0.05$. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19].

**Table 1**
Patient characteristics according to the development of cardiac events.

| | Total (n = 387) | No event (n = 302) | Event (n = 85) | p-value |
|---|---|---|---|---|
| Age, years | 77 (70–83) | 76 (69–81) | 83 (75–87) | <0.001 |
| Male, % | 208 (54) | 161 (53) | 47 (55) | 0.806 |
| Body mass index, kg/m$^2$ | 23 (21–26) | 23 (21–26) | 22 (20–25) | 0.019 |
| Heart rate, bpm | 65 (58–77) | 65 (57–76) | 66 (60–82) | 0.082 |
| Systolic blood pressure, mmHg | 132 (118–143) | 132 (118–142) | 133 (113–145) | 0.755 |
| Diastolic blood pressure, mmHg | 70 (59–79) | 70 (60–79) | 68 (54–78) | 0.043 |
| Mean blood pressure, mmHg | 90 (80–100) | 90 (81–100) | 89 (74–99) | 0.227 |
| Prior hospitalization for heart failure, % | 159 (41) | 106 (35) | 53 (62) | <0.001 |
| Symptoms and signs of heart failure at diagnosis | | | | |
| Dyspnea (on exertion or orthopnea), % | 367 (95) | 288 (95) | 79 (93) | 0.405 |
| Leg edema, % | 197 (51) | 130 (43) | 67 (79) | <0.001 |
| Lung congestion on chest X-ray, % | 140 (36) | 91 (30) | 49 (58) | <0.001 |
| Pleural effusion, % | 125 (32) | 74 (25) | 51 (60) | <0.001 |
| Underlying disorders | | | | |
| Hypertension, % | 312 (81) | 248 (82) | 64 (75) | 0.165 |
| Diabetes mellitus, % | 93 (24) | 76 (25) | 17 (20) | 0.389 |
| Atrial fibrillation, % | 114 (29) | 80 (26) | 34 (40) | 0.022 |
| Old myocardial infarction, % | 64 (17) | 51 (17) | 13 (15) | 0.130 |
| Prior open-heart surgery, % | 34 (9) | 26 (9) | 8 (10) | 0.828 |
| Medications | | | | |
| ACEI/ARB, % | 283 (73) | 219 (73) | 64 (75) | 0.679 |
| Mineral corticoid receptor antagonist, % | 123 (32) | 81 (27) | 42 (49) | <0.001 |
| ARNI, % | 9 (2) | 7 (2) | 2 (2) | 1 |
| Beta-blockers, % | 260 (67) | 201 (67) | 59 (69) | 0.695 |
| Calcium channel blockers, % | 153 (40) | 123 (41) | 30 (35) | 0.382 |
| Loop diuretics, % | 180 (47) | 111 (37) | 69 (81) | <0.001 |
| SGLT-2 inhibitors, % | 38 (10) | 31 (10) | 7 (8) | 0.683 |
| eGFR, ml/min/1.73 m$^2$ | 60 (47–74) n = 379 | 62 (50–75) n = 295 | 52 (34–69) n = 84 | <0.001 |
| Hemoglobin, g/dl | 13 (11–14) n = 380 | 13 (12–14) n = 295 | 12 (10–14) n = 85 | <0.001 |
| Brain natriuretic peptide, pg/ml | 151 (76–328) | 123 (69–240) | 409 (216–599) | <0.001 |

Data are shown as the number of patients (%) or a median (interquartile range). ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; SGLT-2, sodium glucose co-transporter 2.

## 3. Results

### 3.1. Patient characteristics

Patient characteristics and the results of blood tests obtained from medical records are shown in Table 1. Age, the rate of prior hospitalization for HF and volume overload (leg edema, lung congestion, and pleural effusion), and the prevalence of atrial fibrillation were significantly higher, while body mass index and diastolic blood pressure were significantly lower in patients with than in those without cardiac events.

**Table 2**
Cardiac morphology and function according to the development of cardiac events.

| | Total (n = 387) | No event (n = 302) | Event (n = 85) | p-value |
|---|---|---|---|---|
| Left heart | | | | |
| LAVI, ml/m$^2$ | 45 (34–62) | 42 (33–59) | 54 (42–77) | <0.001 |
| LVMI, g/m$^2$ | 116 (97–142) | 114 (96–140) | 128 (108–149) | 0.002 |
| LVEF, % | 64 (54–71) | 65 (57–72) | 55 (41–69) | <0.001 |
| LVEDD, mm | 47 (43–52) | 47 (43–51) | 48 (44–52) | 0.244 |
| DT of mitral inflow, ms | 206 (170–247) n = 374 | 211 (174–250) n = 291 | 180 (155–228) n = 83 | <0.001 |
| Average mitral e′, cm/s | 6 (4.8–7.8) n = 386 | 6.2 (4.9–8.1) n = 301 | 5.5 (3.8–7.2) n = 85 | 0.008 |
| Average mitral E/e′ ratio | 12 (10–16) n = 386 | 11 (9–15) n = 301 | 15 (12–20) n = 85 | <0.001 |
| Moderate MR, % | 57 (15) | 44 (15) | 13 (15) | 0.863 |
| Right heart | | | | |
| RVOT, mm | 29 (26–32) n = 386 | 29 (26–31) n = 301 | 30 (27–33) n = 85 | 0.040 |
| TAPSE, mm | 19 (17–22) n = 384 | 20 (17–23) n = 300 | 17 (15–20) n = 84 | <0.001 |
| SPAP, mmHg | 27 (22–34) n = 369 | 24 (21–28) n = 285 | 29 (24–39) n = 84 | <0.001 |
| Less-distensible right ventricle, % | 131 (36) n = 369 | 77 (27) n = 285 | 54 (64) n = 84 | <0.001 |
| Moderate TR, % | 40 (10) | 18 (6) | 22 (26) | <0.001 |
| Inferior vena cava, mm | 13 (10–17) n = 379 | 13 (10–16) n = 296 | 15 (11–19) n = 83 | <0.001 |

Data are shown as the number of patients (%) or a median (interquartile range). DT, deceleration time; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral regurgitation; RVOT, right ventricular outflow tract; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

The rate of administration of mineral corticoid receptor antagonists and loop diuretics was significantly higher in patients with than in those without cardiac events. Patients with cardiac events had a lower estimated glomerular filtration rate and hemoglobin level and higher BNP level than those without cardiac events. Patient characteristics according to LVEF are shown in supplementary Table 1.

### 3.2. *Cardiac function and morphology assessed by echocardiographic and JVP examinations*

Cardiac function and morphology assessed by echocardiographic and JVP examinations are shown in Table 2. Regarding the function and morphology of the left heart, the left atrial volume index was larger, the LV mass index was heavier, LVEF was lower, the deceleration time of mitral inflow was shorter, average mitral e′ was slower, and the average mitral E/e′ ratio was higher in patients with than in those without cardiac events. Regarding the function and morphology of the right heart, the RV outflow tract and inferior vena cava were larger, SPAP and the prevalence of a less-distensible right ventricle and moderate tricuspid regurgitation were higher, and TAPSE was shorter in patients with than in those without cardiac events.

### 3.3. *Univariate and multivariate analyses of cardiac events*

Univariate and multivariate analyses of cardiac events are shown in Table 3. Multivariate Cox proportional hazard models demonstrated that LVEF (hazard ratio [HR], 0.983 per 1 %, 95 % confidence interval [CI], 0.966–1.000, $p = 0.048$) and a less-distensible right ventricle (HR, 3.150, 95 %CI, 1.860–5.335, $p < 0.001$) were independent risk factors for cardiac events, whereas average mitral E/e′ and TAPSE were not.

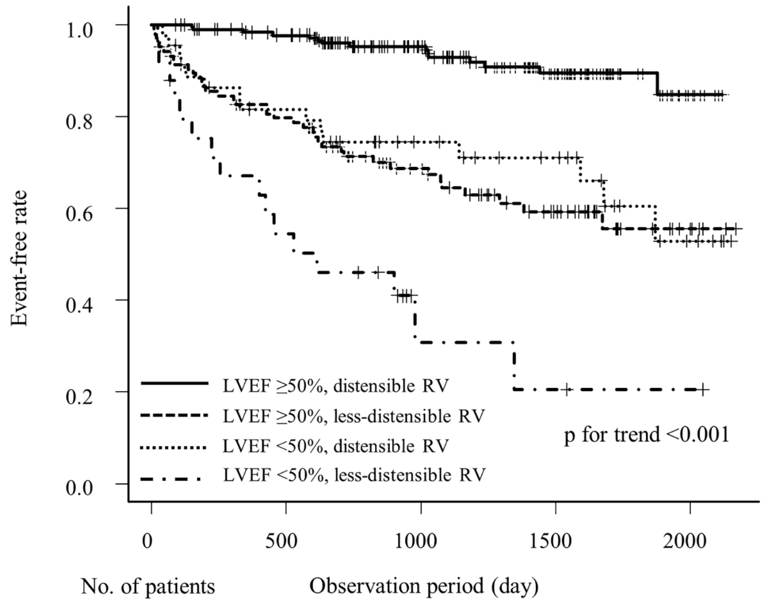
**Table 3**
Cox proportional hazard model.

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Hazard ratio (95 % confidence interval) | p-value | Hazard ratio (95 % confidence interval) | p-value |
| Age, per 1 year | 1.090 (1.061–1.120) | <0.001 | 1.039 (1.004–1.074) | 0.026 |
| Male | 1.079 (0.703–1.655) | 0.729 | | |
| Body mass index, per 1 kg/m$^2$ | 0.927 (0.870–0.988) | 0.020 | | |
| Heart rate, per 1 bpm | 1.011 (1.000–1.023) | 0.054 | | |
| Mean blood pressure, per 1 mmHg | 0.986 (0.971–1.002) | 0.088 | | |
| Prior hospitalization for heart failure | 2.768 (1.784–4.295) | <0.001 | 2.089 (1.287–3.391) | 0.003 |
| Hypertension | 0.649 (0.396–1.062) | 0.085 | | |
| Diabetes mellitus | 0.727 (0.427–1.237) | 0.240 | | |
| Atrial fibrillation | 1.605 (1.039–2.479) | 0.033 | | |
| Old myocardial infarction | 0.947 (0.524–1.709) | 0.856 | | |
| ACEI/ARB | 1.122 (0.685–1.837) | 0.648 | | |
| Mineral corticoid receptor antagonist | 2.416 (1.578–3.699) | <0.001 | | |
| Beta-blockers | 1.033 (0.651–1.640) | 0.889 | | |
| Loop diuretics | 6.847 (3.967–11.82) | <0.001 | 3.608 (1.973–6.596) | <0.001 |
| eGFR, per 1 ml/min/1.73 m$^2$ | 0.977 (0.966–0.988) | <0.001 | | |
| Hemoglobin, per 1 g/dl | 0.776 (0.707–0.850) | <0.001 | 0.8902 (0.793–1.000) | 0.049 |
| Brain natriuretic peptide, per 1 pg/ml | 1.001 (1.001–1.001) | <0.001 | 1.001 (1.000–1.001) | <0.001 |
| LAVI, per 1 ml/m$^2$ | 1.016 (1.009–1.022) | <0.001 | | |
| LVMI, per 1 g/m$^2$ | 1.007 (1.003–1.012) | 0.002 | | |
| LVEF, per 1 % | 0.967 (0.954–0.980) | <0.001 | 0.983 (0.966–1.000) | 0.048 |
| Average mitral E/e ′ ratio, per 1 | 1.056 (1.034–1.079) | <0.001 | | |
| Moderate MR | 1.131 (0.623–2.043) | 0.682 | | |
| TAPSE, per 1 mm | 0.903 (0.857–0.951) | <0.001 | | |
| SPAP, per 1 mmHg | 1.073 (1.053–1.094) | <0.001 | 1.028 (1.004–1.052) | 0.020 |
| Less-distensible right ventricle | 4.044 (2.586–6.323) | <0.001 | 3.150 (1.860–5.335) | <0.001 |
| Moderate TR | 3.598 (2.213–5.849) | <0.001 | | |

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; eGFR, estimated glomerular filtration rate. LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral regurgitation; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

### 3.4. *Event-free rate of HF according to LVEF and RV diastolic function*

We divided patients into four groups according to LVEF and RV diastolic function in association with cardiac events. The results of the Kaplan-Meier analysis are shown in Fig. 3. The event-free rate was the lowest for patients with LVEF < 50 % and a less-distensible right ventricle (p for trend < 0.001). The results of the Cox proportional




| No. of patients | | | | | |
|---|---|---|---|---|---|
| LVEF ≥50%, distensible RV | 193 | 175 | 118 | 63 | 7 |
| LVEF ≥ 50%, less-distensible RV | 106 | 80 | 50 | 28 | 7 |
| LVEF <50%, distensible RV | 45 | 34 | 23 | 17 | 5 |
| LVEF <50%, less-distensible RV | 25 | 13 | 3 | 2 | 1 |

**Fig. 3.** Kaplan-Meier curves for event-free rates according to LVEF and right ventricular diastolic function. Patients with LVEF < 50 % and a less-distensible right ventricle had the lowest event-free rate among the four groups. LVEF, left ventricular ejection fraction; RV, right ventricle.

hazard analysis are shown in Table 4. A less-distensible right ventricle increased the risk of cardiac events regardless of LVEF. The risk of cardiac events was higher in patients with LVEF $<$ 50 % and a less-distensible right ventricle than in those with LVEF $\geq$ 50 % and a distensible right ventricle (HR, 14.36; 95 %CI, 6.810–30.26, $p < 0.001$ in the age-adjusted model).

## 4. Discussion

In the present study, we non-invasively assessed cardiac function in patients with HF using echocardiography and JVP. We also examined ventricular functions that are independent risk factors for cardiac events in patients with HF. The main results obtained were as follows. Ventricular systolic and diastolic functions were impaired in patients with HF who developed cardiac events. In the multivariate Cox proportional hazard model, indices of LV systolic and RV diastolic functions were associated with cardiac events in patients with HF, whereas those of LV diastolic function and RV systolic function were not. A less-distensible right ventricle increased the risk of cardiac events regardless of LVEF and the combination of LVEF $<$ 50 % and a less-distensible right ventricle had the greatest effect on cardiac events.

Ventricular systolic and diastolic functions were worse in patients with than in those without cardiac events in the present study. These dysfunctions deteriorate hemodynamics, but exert different effects on the clinical outcomes of HF. Differences in the impact of these indices on the development of cardiac events need to be considered.

### *4.1. Hemodynamic features of left ventricle and treatment for LV dysfunction*

A high pressure is needed to supply blood to the systemic circulation, except to the lungs; therefore, left ventricle is characterized by high contractility. Higher contractility is associated with the weaker effect of the afterload on stroke volume [20]; however, once LV systolic function is impaired, an increase in the afterload markedly affects hemodynamics, leading to an increased LV filling pressure. LV stroke volume may also be decreased when the LV preload reserve reaches its limit. Positive inotropic medicines may be selected to increase LV contractility; however, their long-term usage was previously shown to adversely affect the clinical outcomes of patients with HF and reduced LVEF [21]. Direct interventions for LV contractility are challenging. As an alternative to positive inotropic medicines, antihypertensive and negative chronotropic medicines, which reduce the LV workload, may improve LVEF [22,23]. Clinical outcomes were improved in cases in which reverse remodeling occurred [24]. These findings suggest that a decrease in LVEF is associated with cardiac events in patients with HF. LV relaxation abnormalities due to aging and LV hypertrophy are common [15], and tachycardia or high blood pressure leads to incomplete LV relaxation, which increases LV filling pressure [2]. LV diastolic failure due to a LV relaxation abnormality may be addressed to some extent with current treatments. Negative chronotropic medicine prevents tachycardia, anti-hypertensive medicine reduces blood pressure, diuretics are used to treat excessive volume overload, and specific cardiac diseases, such as ischemic heart disease, which deteriorates LV diastolic function, are treated by non-pharmacological therapy. Compensatory mechanisms for chronic increases in left atrial pressure have also been reported in patients with HF [25]. Therefore, the average mitral $E/e'$ ratio may not be an independent risk factor for cardiac events.

### *4.2. Hemodynamic features of right ventricle and treatment for RV dysfunction*

RV ejection is more dependent on the Frank-Starling mechanism than on contractility [20]; therefore, it functions as a volume pump, not as a pressure pump, as is the case for left ventricle. RV systolic function may not affect hemodynamics as markedly as RV diastolic function. A previous study showed that TAPSE alone was not a prognosticator for HF [26]. An increase in the RV afterload affects hemodynamics because of low natural RV contractility; however, the high compliance of right ventricle alleviates the effects of an increased RV afterload. Once the limitation of the RV preload reserve due to RV diastolic dysfunction

**Table 4**
Relationships among four groups with cardiac events in a Cox proportional hazard analysis.

| | LVEF ≥ 50 % & DRV | LVEF ≥ 50 % & LRV | LVEF < 50 % & DRV | LVEF < 50 % & LRV |
|---|---|---|---|---|
| Unadjusted HR (95 % CI) | | | | |
| Cardiac events | 1.0 | 5.452 (2.998–9.914)[‡] | 4.497 (2.191–9.230)[‡] | 16.08 (7.780–33.22)[‡] |
| Age-adjusted model HR (95 % CI) | | | | |
| Cardiac events | 1.0 | 5.527 (3.021–10.11)[‡] | 5.413 (2.632–11.13)[‡] | 14.36 (6.810–30.26)[‡] |
| Unadjusted HR (95 % CI) | | | | |
| Cardiac events | – | 1.0 | 0.853 (0.468–1.553) | 2.503 (1.385–4.522)[†] |
| Age-adjusted model HR (95 % CI) | | | | |
| Cardiac events | – | 1.0 | 1.000 (0.545–1.837) | 2.170 (1.199–3.927)[*] |
| Unadjusted HR (95 % CI) | | | | |
| Cardiac events | – | – | 1.0 | 3.032 (1.464–6.282)[†] |
| Age-adjusted model HR (95 % CI) | | | | |
| Cardiac events | – | – | 1.0 | 2.549 (1.198–5.423)[*] |

CI, confidence interval; DRV, distensible right ventricle; LRV, less-distensible right ventricle; LVEF, left ventricular ejection fraction; HR, hazard ratio.
[*] $p < 0.05$;
[†] $p < 0.01$;
[‡] $p < 0.001$.

occurs, RV stroke volume markedly decreases and systemic congestion is easily induced in response to an increase in the RV afterload. The relaxation ability of right ventricle is lower than that of left ventricle because of low elastic recoil based on RV contractility. The volume of right ventricle is larger than that of left ventricle. Therefore, RV diastolic function is characterized by high distensibility. Although ventricular relaxation abnormalities and impairments in ventricular distensibility are both ventricular diastolic dysfunctions, different therapeutic strategies are employed. In contrast to LV relaxation abnormalities, RV diastolic dysfunctions based on impaired RV distensibility, namely, a less-distensible right ventricle, cannot be addressed with current treatments and, thus, symptomatic therapy for the restrictive RV physiology may be adopted. Heart rate reductions to prevent incomplete relaxation are useful for HF and LV relaxation abnormalities; however, these reductions may exert negative effects on the restrictive RV physiology because of the dependence of cardiac output on heart rate [14]. The excessive use of diuretics may reduce RV filling pressure, resulting in a decreased stroke volume. A less-distensible right ventricle worsens the pathophysiology of HF and, thus, is associated with cardiac events in patients with HF.

### *4.3. Clinical importance of RV diastolic function in patients with HF*

The event-free rate was similar in patients with a less-distensible right ventricle and those with LVEF < 50 %. This result suggests that a less-distensible right ventricle is of approximately equal importance to reduced LVEF in terms of cardiac events. It was the lowest in patients with LVEF < 50 % and a less-distensible right ventricle, indicating that a less-distensible right ventricle exacerbates the pathophysiology of HF. Although RV diastolic dysfunction needs to be considered, RV diastolic function is not evaluated because of the difficulties associated with its assessment. RV diastolic function was not regarded as an explanatory variable for cardiac events in previous studies [7,9,10,26] and has not been documented in the Japanese guidelines [1]. To the best of our knowledge, this is the first study in which RV diastolic dysfunction, a less-distensible right ventricle, assessed by JVP was associated with cardiac events in Japanese patients with HF. The results obtained herein are of importance. We previously reported the impact of a less-distensible right ventricle on the effectiveness of negative chronotropic medicine in patients with HF and preserved LVEF [27]; however, it remains unclear whether these results are applicable to patients with HF, LVEF < 50 %, and a less-distensible right ventricle. We also revealed that the rate of a less-distensible right ventricle increased with aging [28]. The percentage of patients with HF due to RV diastolic failure may increase worldwide in the future, similar to Japan, which is a super aging society. Therefore, the development of therapeutic strategies for RV diastolic failure may become a matter of urgency.

### *4.4. Study limitations*

The present study has several limitations. This was a retrospective study conducted at a single center. BNP levels were used to select patients with HF, but were not investigated in approximately 19 % of patients who underwent echocardiography and JVP examinations, which may have caused a selection bias. Furthermore, there were more missing values on RV function than on LV function because of the difficulties associated with the echocardiographic assessment of right ventricle [11]. The small number of cardiac events may have limited the number of explanatory variables to create Cox proportional hazard models in the present study. In addition, angiotensin receptor-neprilysin and sodium glucose co-transporter 2 inhibitors, which improve the clinical outcomes of patients with HF, were rarely prescribed for patients with HF in our cohort [29] because they were only approved for the treatment of HF in Japan from August 2020 and November 2020, respectively. Since the effects of these medicines on the present results remain unclear, further clinical studies are warranted to elucidate the effectiveness of these medicines for patients with HF and a less-distensible right ventricle.

When RV diastolic function is impaired and irreversible, Japanese patients with HF may become intractable regardless of LVEF.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101291.

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