# Long-term Prognostic Significance of Admission Tricuspid Regurgitation Pressure Gradient in Hospitalized Patients With Heart Failure With Preserved Ejection Fraction: A Report From the Japanese Real-World Multicenter Registry

KAZUNORI OMOTE,[1] TOSHIYUKI NAGAI,[1] KIWAMU KAMIYA,[1] TADAO AIKAWA,[1] SHINGO TSUJINAGA,[1] YOSHIYA KATO,[1] HIROKAZU KOMORIYAMA,[1] HIROYUKI IWANO,[1] KAZUHIRO YAMAMOTO,[2] TSUTOMU YOSHIKAWA,[3] YOSHIHIKO SAITO,[4] AND TOSHIHISA ANZAI[1]

*Sapporo, Tottori, Tokyo, and Kashihara, Japan*

## ABSTRACT

**Background:** Doppler-estimated peak systolic tricuspid regurgitation pressure gradient (TRPG) is a representative noninvasive parameter for evaluating pulmonary artery systolic pressure, which can be a determinant of adverse outcomes in chronic heart failure with preserved ejection fraction (HFpEF). However, the prognostic implications of TRPG at admission for hospitalized patients with HFpEF are undetermined.

**Methods and Results:** We examined 469 consecutive hospitalized patients with decompensated HFpEF (left ventricular ejection fraction $\geq$ 50%) who underwent TRPG measurement at admission in our HFpEF multicenter registry. The primary outcome of interest was all-cause death. Admission TRPG was significantly correlated with estimated pulmonary capillary wedge pressure and left atrial dimension ($r = 0.24$, $P < 0.001$ and $r = 0.21$, $P < 0.001$, respectively). During a median follow-up period of 748 (IQR 540−820) days, 83 patients died. Higher TRPG was significantly associated with higher mortality compared to lower TRPG (log-rank; $P = 0.007$). Multivariable analysis revealed that elevated TRPG was an independent determinant of mortality (HR 1.02, 95% CI 1.01−1.04, $P = 0.008$) after adjustment for prespecified confounders and renal function.

**Conclusions:** Elevated TRPG at admission was an independent determinant of mortality in hospitalized patients with HFpEF, indicating that TRPG at admission could be a useful marker for risk stratification in these patients. (*J Cardiac Fail 2019;25:978−985*)

**Key Words:** Heart failure with preserved ejection fraction, prognosis, pulmonary hypertension, tricuspid regurgitation pressure gradient.

## Introduction

Heart failure (HF) remains one of the most important causes of death in patients with cardiovascular disease.[1] The number of patients with HF is increasing worldwide because of super-aged societies, in spite of advanced therapy and management for cardiovascular disease, resulting in a severe health care burden. Among them, it is noteworthy that the prevalence of HF with preserved ejection fraction (HFpEF) is increasing, and approximately half of hospitalized patients with HF are classified as having HFpEF.[2−5] There are no effective treatment strategies for HFpEF that achieve a reduction in morbidity and mortality.[6−8] Thus, accurate prognostication for patients with HFpEF could help to improve outcomes by identifying patients at high risk who might potentially benefit from intensive inpatient and outpatient monitoring and early referral for advanced HFpEF therapy.

Multiple comorbid conditions are commonly observed in patients with HFpEF, including pulmonary hypertension (PH), obesity, systemic hypertension, coronary artery disease, diabetes, and atrial fibrillation.[9,10] Among them, PH was reported to be a strong determinant in patients with HFpEF.[11,12] In fact, wireless pulmonary artery pressure-monitoring guided management reduced hospitalization for exacerbation of HF in patients with HFpEF.[13] Therefore, accurate and noninvasive estimation of PH is important for the management of HFpEF.

*From the [1]Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; [2]Department of Molecular Medicine and Therapeutics, Faculty of Medicine, Tottori University, Tottori, Japan; [3]Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan and [4]First Department of Internal Medicine, Nara Medical University, Kashihara, Japan.*

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Reprint requests: Toshiyuki Nagai MD, PhD, Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15 Nishi-7, kita-ku, Sapporo, Hokkaido, Japan. Tel: +81(11)7066974, Fax: +81(11)7067974. E-mail: tnagai@huhp.hokudai.ac.jp

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Doppler-estimated peak systolic tricuspid regurgitation pressure gradient (TRPG) could be a representative noninvasive echocardiographic parameter for the evaluation of pulmonary artery systolic pressure (PASP).[14,15] A previous report showed that high PASP estimated by TRPG could predict mortality in patients with chronic HFpEF.[12] Nevertheless, the prognostic implications of TRPG at admission in the acute decompensated phase of HF in relation to long-term outcomes in HFpEF patients are unclear. Accordingly, the aim of this study was to investigate whether TRPG at admission is associated with subsequent adverse events in patients with HFpEF.

## Methods

### Study Design

Data from the JASPER (Japanese Heart Failure Syndrome with Preserved Ejection Fraction) registry, obtained between November 2012 and March 2015, were retrospectively analyzed. Details of the JASPER registry have been described previously.[16] Briefly, the study is a multicenter, observational, prospective cohort that includes consecutive patients aged $\geq$ 20 years and requiring hospitalization because of diagnoses of acute decompensated HF according to the Framingham criteria.[17] At least 2 experienced cardiologists diagnosed the patients as having preserved left ventricular (LV) systolic function, defined as LV ejection fraction (LVEF) $\geq$ 50% by the modified Simpson method or LV fractional shortening (LVFS) $\geq$ 25% by echocardiography. Patients with acute coronary syndrome who were receiving hemodialysis or had histories of heart transplantation or severe valvular heart disease were excluded. The primary outcome of interest was all-cause death. This study was approved by the Institutional Review Board of each site and registered under the Japanese University Hospital Medical Information Network (UMIN) Clinical Trials Registration (UMIN000010601).

### Study Population

Of 535 patients enrolled in the JASPER registry, those without accessible TRPG data at admission were excluded. Ultimately, 469 patients were examined.

### Echocardiography

Echocardiographic examination was usually performed within 6 hours of admission, and the results were digitally recorded. TRPG was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole; the modified Bernoulli equation ($\Delta P = 4\ v^2$) was used to calculate gradients from the velocities.[14] LVEF was calculated from apical 4- and 2-chamber views using the biplane method of disks.[18] LV end-diastolic dimension (LVDD), LV end-systolic dimension and left atrial dimension (LAD) were measured. LV interventricular septum diameter (LVIVSD) and LV posterior wall diameter were measured at end diastole. LV inflow (E), deceleration time of early-diastolic flow (DcT) and atrial-systolic peak velocity (A) were measured using pulsed-wave Doppler. Using the apical 4-chamber view, e´ was measured at the septal and lateral sides of the annulus. The ratio of LV inflow E to e´ measured at the septum was used to estimate pulmonary capillary wedge pressure (PCWP) (PCWP = 11.96 + 0.596*E/e´ septal), as reported in a comparative simultaneous Doppler-catheterization study.[19]

### Statistical Analysis

Continuous variables are presented as mean ± SD when normally distributed and as median and interquartile range (IQR) when non-normally distributed. Comparisons of differences between groups were made by analysis of variance (ANOVA) with the Bonferroni post hoc testing for continuous variables, and by the $\chi^2$ test or the Fisher exact test for dichotomous variables, when appropriate. The Pearson correlation coefficient was used to evaluate the correlations among TRPG and estimated PCWP, E/e´ (average) and LAD. The changes in TRPG during hospitalization were evaluated by the Wilcoxon signed rank test.

For the total population, Kaplan-Meier survival plots were constructed by dividing TRPG at baseline into quartiles to study the influence of TRPG on all-cause mortality. To evaluate the influence of TRPG on all-cause death, we constructed 4 Cox proportional hazard models: Model 1, unadjusted; Model 2, age- and sex-adjusted; Model 3, prespecified covariates derived from our previous study[16] and renal function; and Model 4, clinically relevant prognostic variables for decompensated HF, including age, sex, systolic blood pressure, serum sodium, log brain natriuretic peptide (BNP), and important HFpEF parameters as measured by echocardiography, such as left atrial volume index (LAVI) and PCWP as estimated by E/e´, which were used as covariates in a previous study.[12] The discriminative ability of the multivariable models was evaluated by Harrell C-statistics. All tests were 2-tailed, and a value of $P < 0.05$ was considered statistically significant. All analyses were performed using Stata MP64 version 15 (StataCorp, College Station, Texas, USA).

## Results

### Baseline Characteristics

The baseline characteristics of the total 469 studied patients are shown in Table 1. Patients with higher TRPG quartiles had lower hemoglobin and higher systolic blood pressure, prevalence of prior HF hospitalization, prevalence of chronic kidney disease, serum blood urea nitrogen, creatinine, and plasma BNP levels, and prevalence of use of loop diuretics and vasodilators compared to those with lower TRPG quartiles. There were no significant differences across the quartiles in terms of age, sex, body mass index, New York Heart Association functional class, heart rate, prevalence of prior myocardial infarction or atrial

**Table 1.** Baseline Patient Characteristics at Admission and During In-hospital Treatment

| Variables | All patients | TRPG | | | | *P* value |
|---|---|---|---|---|---|---|
| | | First quartile ≤ 26 mmHg | Second quartile 27−34 mmHg | Third quartile 35−43 mmHg | Fourth quartile ≥ 44 mmHg | |
| Number | 469 | 106 | 120 | 121 | 122 | |
| Age, years | 78.3 ± 10.0 | 76.3 ± 11.3 | 78.0 ± 9.6 | 79.1 ± 9.3 | 79.5 ± 9.9 | 0.076 |
| Female | 232 (49.5) | 45 (42.5) | 67 (55.8) | 56 (46.3) | 64 (52.5) | 0.175 |
| BMI, kg/m$^2$ | 23.6 ± 5.0 | 23.5 ± 5.4 | 24.3 ± 5.1 | 23.7 ± 4.7 | 23.0 ± 4.9 | 0.22 |
| NYHA functional class, n (%) | | | | | | |
| I | 3 (0.7) | 0 (0) | 2 (1.7) | 0 (0) | 1 (0.9) | 0.75 |
| II | 105 (23.3) | 27 (27.0) | 27 (22.9) | 28 (24.6) | 23 (19.5) | |
| III | 191 (42.4) | 43 (43.0) | 51 (43.2) | 45 (39.5) | 52 (44.1) | |
| IV | 151 (33.6) | 30 (30.0) | 38 (32.2) | 41 (36.0) | 42 (35.6) | |
| Vital signs | | | | | | |
| Heart rate, beats/min | 78 (65−100) | 80 (70−104) | 81 (66−107) | 75 (64−93) | 77 (62−99) | 0.073 |
| Systolic BP, mmHg | 149.2 ± 36.0 | 143.3 ± 39.6 | 145.9 ± 35.8 | 158.3 ± 35.7 | 148.5 ± 31.6 | 0.009 |
| Diastolic BP, mmHg | 78.7 ± 22.9 | 78.3 ± 21.4 | 78.6 ± 24.2 | 82.0 ± 24.4 | 75.9 ± 21.2 | 0.23 |
| Past history, n (%) | | | | | | |
| Smoking | 41 (10.5) | 12 (13.3) | 6 (6.5) | 14 (13.5) | 9 (8.8) | 0.30 |
| Prior HF admission | 177 (39.1) | 34 (33.0) | 42 (35.9) | 42 (36.2) | 59 (50.4) | 0.032 |
| Prior myocardial infraction | 59 (12.7) | 15 (14.4) | 14 (11.8) | 17 (14.2) | 13 (10.7) | 0.79 |
| Coronary artery disease | 94 (20.3) | 19 (18.3) | 22 (18.5) | 26 (21.7) | 27 (22.5) | 0.80 |
| Atrial fibrillation | 302 (65.1) | 64 (61.0) | 81 (68.4) | 76 (63.9) | 81 (66.4) | 0.66 |
| Diabetes mellitus | 173 (37.0) | 32 (30.5) | 45 (37.5) | 47 (39.2) | 49 (40.2) | 0.44 |
| Dyslipidemia | 186 (39.9) | 43 (40.6) | 52 (43.3) | 46 (39.0) | 45 (36.9) | 0.77 |
| Cerebrovascular disease | 109 (23.6) | 20 (19.1) | 29 (24.6) | 32 (26.7) | 28 (23.5) | 0.59 |
| Chronic kidney disease | 245 (52.5) | 43 (41.0) | 61 (50.8) | 73 (60.8) | 68 (55.7) | 0.022 |
| COPD/asthma | 52 (11.3) | 7 (6.7) | 18 (15.1) | 12 (10.4) | 15 (12.4) | 0.24 |
| Clinical signs, n (%) | | | | | | |
| Breathlessness | 412 (90.4) | 93 (90.3) | 103 (89.6) | 110 (92.4) | 106 (89.1) | 0.82 |
| Elevated JVD | 211 (51.1) | 41 (43.2) | 54 (51.9) | 54 (52.4) | 62 (55.9) | 0.32 |
| Lower extremity edema | 345 (74.0) | 71 (67.6) | 90 (75.6) | 95 (78.5) | 89 (73.6) | 0.30 |
| Laboratory data at admission | | | | | | |
| Sodium, mEq/L | 139.9 ± 4.2 | 139.4 ± 4.5 | 139.8 ± 4.7 | 140.2 ± 3.7 | 140.1 ± 3.9 | 0.51 |
| BUN, mg/dL | 22 (16−32) | 19 (16−27) | 22 (15−30) | 23 (17−35) | 25 (17−36) | 0.005 |
| Creatinine, mg/dL | 1.1 (0.8−1.5) | 1.0 (0.8−1.3) | 1.0 (0.7−1.4) | 1.1 (0.8−1.8) | 1.1 (0.8−1.8) | 0.038 |
| Hemoglobin, g/dL | 11.2 ± 2.2 | 11.7 ± 2.2 | 11.3 ± 2.3 | 10.9 ± 2.2 | 10.7 ± 1.9 | 0.002 |
| BNP, pg/mL | 423 (233−691) | 338 (188−595) | 395 (224−629) | 438 (274−726) | 488 (265−834) | 0.006 |
| C-reactive protein, mg/dL | 0.4 (0.1−1.4) | 0.4 (0.2−1.1) | 0.3 (0.1−1.4) | 0.5 (0.1−2.1) | 0.4 (0.1−1.5) | 0.43 |
| Albumin, g/dL | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.7 ± 0.4 | 0.73 |
| Total cholesterol, mg/dL | 156.2 ± 38.4 | 156.1 ± 38.1 | 161.9 ± 42.9 | 156.4±32.0 | 150.9 ± 39.0 | 0.23 |
| Total bilirubin, mg/dL | 0.8 (0.6−1.1) | 0.8 (0.6−1.1) | 0.7 (0.6−1.1) | 0.8 (0.5−1.0) | 0.8 (0.6−1.1) | 0.57 |
| Medications before admission, n (%) | | | | | | |
| ACEIs/ARBs | 274 (58.4) | 52 (49.1) | 73 (60.8) | 76 (62.8)) | 73 (59.8) | 0.160 |
| $\beta$-blockers | 207 (44.1) | 41 (38.7) | 50 (41.7) | 58 (47.9) | 58 (47.5) | 0.41 |
| Loop diuretics | 252 (53.7) | 48 (45.3) | 63 (52.5) | 62 (51.2) | 79 (64.8) | 0.025 |
| MRAs | 100 (21.3) | 23 (21.7) | 27 (22.5) | 24 (19.8) | 26 (21.3) | 0.97 |
| Digitalis | 54 (11.5) | 6 (5.7) | 16 (13.3) | 17 (14.1) | 15 (12.3) | 0.188 |
| Anticoagulants | 224 (47.8) | 43 (40.6) | 61 (50.8) | 59 (48.8) | 61 (50.0) | 0.40 |
| Initial treatment, n (%) | | | | | | |
| Intravenous diuretics | 380 (81.0) | 80 (75.5) | 99 (82.5) | 100 (82.6) | 101 (82.8) | 0.43 |
| Vasodilators | 275 (58.6) | 49 (46.2) | 63 (52.5) | 85 (70.3) | 78 (63.9) | < 0.001 |
| Length of hospital stay, days | 16 (11−23) | 16 (11−22) | 15 (11−21) | 16 (11−23) | 18 (12−24) | 0.27 |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, plasma brain-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; HF, heart failure; JVD, jugular venous distention; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; TRPG, tricuspid regurgitation pressure gradient.

*Note:* Continuous variables are presented as mean ± SD if normally distributed and as median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).

fibrillation, or levels of serum sodium and albumin. Patients with higher TRPG quartiles had higher LAD, LAVI, LVMI, E/e′ (septum), E/e′ (average), and PCWP, whereas there were no significant differences across the quartiles regarding LVEF, LVDD, LVPWD, LVIVSD, A wave, DcT, or inferior vena cava diameter (IVCD) (Table 2). We assessed the relationship between mitral regurgitation (MR) grade and TRPG. Patients with higher grades of MR had significantly higher levels of TRPG (Fig. 1).

### Correlations Between TRPG and PCWP, E/e′, and LAD

TRPG was positively correlated with PCWP in patients with both low PCWP and high PCWP, which was divided

**Table 2.** Echocardiographic Parameters at Admission

| Variable | All patients | TRPG | | | | *P* value |
|---|---|---|---|---|---|---|
| | | First quartile (≤ 26 mmHg) | Second quartile (27−34 mmHg) | Third quartile (35−43 mmHg) | Fourth quartile (≥ 44 mmHg) | |
| Number | 469 | 106 | 120 | 121 | 122 | |
| LVEF, % | 60 ± 8 | 58 ± 8 | 60 ± 8 | 61 ± 8 | 60 ± 9 | 0.058 |
| LAD, mm | 46 ± 9 | 43 ± 10 | 45 ± 7 | 46 ± 10 | 48 ± 9 | 0.002 |
| LAVI, mL/m$^2$ | 60 (43−80) | 48 (37−74) | 54 (40−73) | 60 (44−81) | 73 (53-93) | 0.015 |
| LVDD, mm | 46 ± 7 | 46 ± 6 | 47 ± 7 | 47 ± 7 | 47 ± 7 | 0.24 |
| LVPWD, mm | 11 ± 2 | 11 ± 2 | 10 ± 2 | 11 ± 2 | 11 ± 2 | 0.20 |
| LVIVSD, mm | 11 ± 3 | 11 ± 3 | 11 ± 2 | 11 ± 3 | 11 ± 3 | 0.55 |
| LVMI, g/m$^2$ | 118 ± 35 | 110 ± 37 | 115 ± 31 | 123 ± 37 | 123 ± 32 | 0.012 |
| E wave, cm/s | 102 ± 34 | 86 ± 29 | 99 ± 28 | 104 ± 33 | 118 ± 40 | <0.001 |
| A wave, cm/s | 78 ± 32 | 73 ± 29 | 78 ± 33 | 82 ± 27 | 79 ± 40 | 0.51 |
| E/A | 1.3 (0.8−1.7) | 1.0 (0.7−1.6) | 1.1 (0.8−1.7) | 1.1 (0.9−1.5) | 1.4 (0.8−2.0) | 0.24 |
| DcT, ms | 193 ± 67 | 193 ± 74 | 191 ± 57 | 193 ± 59 | 196 ± 77 | 0.95 |
| E/e′ (septum), cm/s | 17 (13−22) | 15 (12−20) | 16 (13−22) | 18 (13−23) | 19 (16−26) | 0.001 |
| E/e′ (lateral), cm/s | 12 (9−16) | 10 (8−15) | 12 (9−18) | 11 (9−15) | 15 (10−18) | 0.077 |
| E/e′ (average), cm/s | 14 (11−18) | 12 (10−16) | 14 (10−19) | 13 (11−17) | 16 (12−21) | 0.047 |
| PCWP, mmHg | 23 ± 6 | 22 ± 5 | 23 ± 5 | 24 ± 6 | 25 ± 7 | 0.002 |
| TRPG, mmHg | 37 ± 13 | 21 ± 5 | 31 ± 2 | 39 ± 3 | 53 ± 8 | <0.001 |
| IVCD, mm | 20 ± 6 | 19 ± 6 | 19 ± 6 | 20 ± 6 | 20 ± 6 | 0.82 |

DcT, deceleration time of early-diastolic flow; IVCD, inferior vena cava diameter; LA, left atrial; LAD, left atrial dimension; LAVI, left atrial volume index; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVIVSD, left ventricular interventricular septum diameter; LVMI, left ventricular mass index; LVPWD, left ventricular posterior wall diameter; PCWP, post capillary wedge pressure; TRPG, tricuspid regurgitation pressure gradient.

*Note:* Continuous variables are presented as mean ± SD if normally distributed.

by the median value (PCWP = 22.3 mmHg) (Fig. 2, A−C), and with E/e′ (average) (r = 0.28, P < 0.001), a similar finding to that of PCWP. Furthermore, TRPG was significantly correlated with LAD, regardless of the history of atrial fibrillation (Fig. 2, D−F).

### Influence of Change in TRPG During Hospitalization on Postdischarge Mortality

TRPG significantly improved following inhospital treatment from 36 (IQR 28−46) to 28 (IQR 22−34) mmHg. Furthermore, we constructed a multivariable Cox proportional hazard model adjusted for prespecified covariates derived from our previous study and renal function so as to evaluate the influence of change in TRPG during hospitalization on all-cause death. As a consequence, the change in TRPG did not reach significance as a determinant (HR 1.003, 95% CI 0.98−1.03) of subsequent risk of postdischarge mortality.

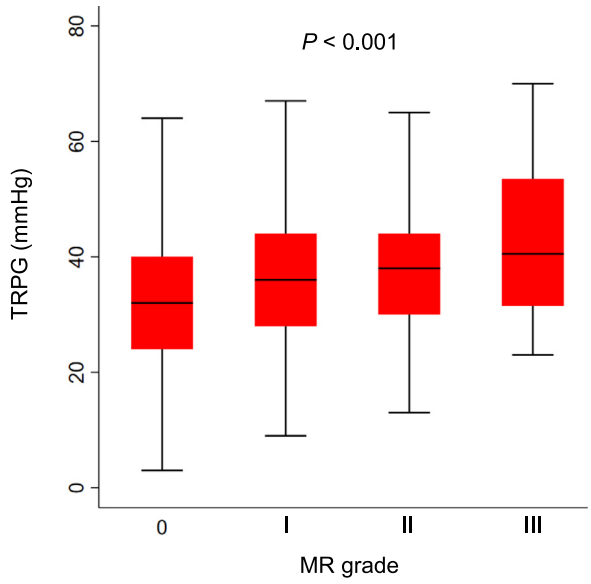


**Fig. 1.** Levels of TRPG at admission according to MR grade. MR, mitral regurgitation; TRPG, tricuspid regurgitation pressure gradient.

### TRPG at Admission and Long-Term Mortality

During a median follow-up period of 748 (IQR 540−820) days, 83 patients died. Kaplan-Meier analysis demonstrated that all-cause death more commonly occurred in patients with higher TRPG than in those with lower TRPG (Fig. 3). Multivariable Cox regression analysis also revealed that elevated TRPG at admission was an independent determinant of mortality, even after adjustment for prespecified confounders, blood urea nitrogen levels and important HFpEF parameters as measured by echocardiography (Table 3).

## Discussion

In the present study, higher admission TRPG was a significant independent determinant of long-term mortality in patients with decompensated HFpEF. It is noteworthy that patients categorized in the highest quartile of TRPG (≥ 44 mmHg) had markedly higher subsequent mortality, indicating that special attention should be paid to these patients. Increased PASP estimated by Doppler-estimated peak systolic TRPG has been shown to predict mortality in patients with acute myocardial infarction,[20] coronary artery disease,[21] aortic valve stenosis,[22]

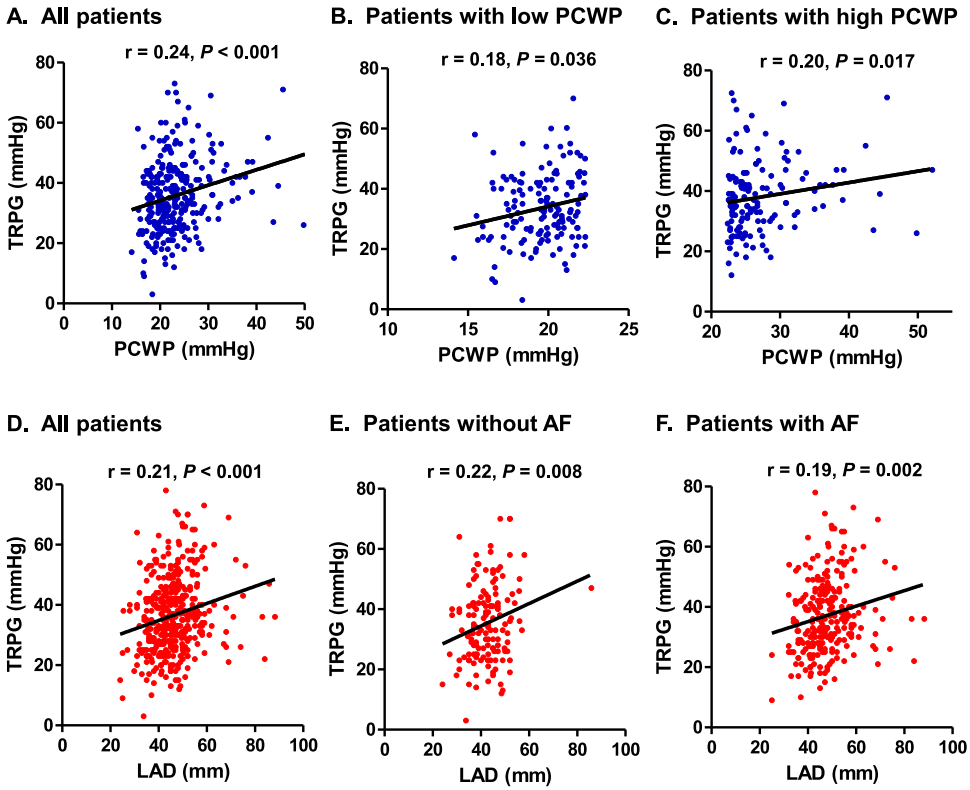


**Fig. 2.** A, Relationship between TRPG and PCWP. B, PCWP in patients with low PCWP. C, PCWP in patients with high PCWP. D, Relationship between TRPG and LAD. E, LAD in patients without AF. F, LAD in patients with AF. AF, atrial fibrillation; LAD, left atrial diameter; PCWP, pulmonary wedge pressure; TRPG, tricuspid regurgitation pressure gradient.

acute pulmonary embolism,[23] and primary pulmonary hypertension.[24] In addition to these findings, a previous study demonstrated that PASP strongly predicted mortality in patients with chronic HFpEF.[12] Our present findings are consistent with these previous studies and provide additional information regarding the long-term prognostic significance of admission TRPG in the acute decompensated phase of HFpEF. In fact, the previous study reported that elevated PASP was an independent determinant of mortality, with adjustment for only HFpEF echocardiographic parameters in patients with chronic HF. We further showed that elevated TRPG at admission remained an independent determinant of mortality, even after adjustment not only for HFpEF echocardiographic parameters but also for well-known strong prognostic factors for acute

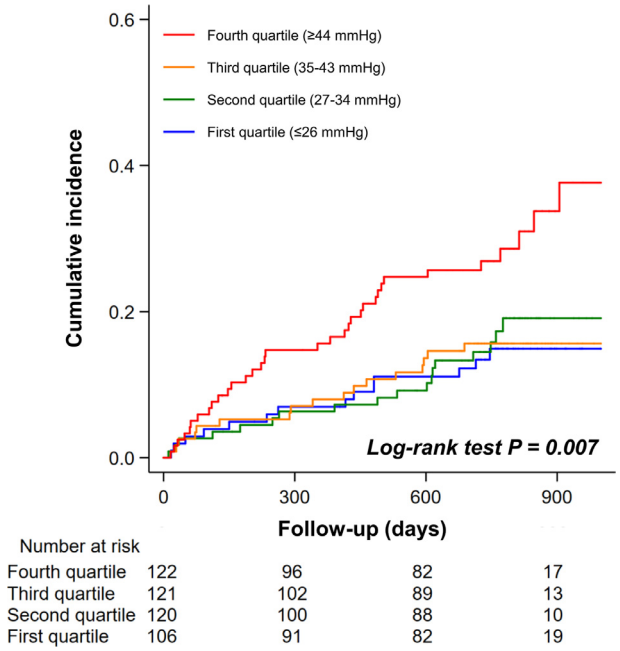


**Fig. 3.** Kaplan-Meier analysis of all-cause death categorized by TRPG. TRPG, tricuspid regurgitation pressure gradient.

**Table 3.** Cox Proportional Hazard Models for All-Cause Death

| | TRPG (per 1 mmHg increase) | | |
|---|---|---|---|
| | HR | 95% CI | *P* value |
| Model 1 | 1.02 | 1.01–1.04 | 0.004 |
| Model 2 | 1.02 | 1.01–1.04 | 0.009 |
| Model 3 | 1.02 | 1.01–1.04 | 0.008 |
| Model 4 | 1.04 | 1.001–1.07 | 0.043 |

Model 1 was unadjusted. Model 2 was adjusted by age and gender. Model 3 was adjusted by age, gender, systolic blood pressure, serum sodium, log brain natriuretic peptide, serum albumin, and blood urea nitrogen. Model 4 was adjusted by age, gender, systolic blood pressure, serum sodium, log brain natriuretic peptide, pulmonary capillary wedge pressure, and left atrial volume index. Harrell C-indexes of Models 3 and 4 are 0.77 and 0.72, respectively. CI, confidence interval; HR, hazard ratio.

decompensated HF, such as age, systolic blood pressure, serum sodium, albumin, plasma BNP levels, and renal function. Identifying at admission patients at high risk who need early intervention, careful monitoring and referral for advanced care is important for early inpatient care for those with acute decompensated HF.

PH develops commonly in patients with HF, and it has been reported to be observed in approximately 40%−80% of patients with HFpEF.[25−28] Current consensus classifies PH with left-side heart disease as isolated postcapillary PH (Ipc PH) and combined post- and precapillary PH (Cpc PH).[29] In our real-world registry, we observed significant correlations between TRPG and estimated PCWP and/or LAD, regardless of history of atrial fibrillation, indicating that the postcapillary contribution of pulmonary venous congestion was associated with higher severity of PH. The mechanism is that increased LV filling pressure leads to left atrial hypertension, resulting in left atrial dilation and stiffening.[30] This, consequently, leads to pulmonary venous congestion and PH.[31] Furthermore, chronic pulmonary congestion in left-side HF leads to functional and morphologic alterations of pulmonary vessels, including muscularization of pulmonary venules, hemangiomatosis-like endothelial cell proliferation in pulmonary capillaries and pulmonary arterial remodeling with intimal hypertrophy, resulting in chronically increased afterload of the right side of the heart.[11,32] In patients with HFpEF and Ipc PH, TRPG could be strongly correlated with PCWP. On the other hand, in patients with Cpc PH, TRPG could not necessarily have a good relationship with PCWP because some patients experience pulmonary artery remodeling. Unfortunately, it would be hard to distinguish these 2 types of PH in our cohort because of limited data. However, the present study revealed that elevated TRPG was independently associated with increasing likelihood of subsequent mortality, even after adjustment for estimated left-sided filling pressures, suggesting that precapillary PH may be an important pathogenesis factor for risk stratification in hospitalized patients with HFpEF; this is consistent with the previous study.[33]

We also demonstrated that patients with higher grades of MR had significantly higher TRPG. MR induces compensatory LV and LA dilation in the initial phase, but over time, it causes LV systolic and diastolic dysfunction, reduced LA compliance and elevated LA pressure in the decompensated phase.[34] For this reason, TRPG could be associated with the grade of MR. Interestingly, our study showed that there was no difference in LVDD among the groups, but there was increasing LAVI as TRPG worsened. These findings might indicate the possibility of atrial functional MR[35] resulting from annular dilation in the pathogenesis of pulmonary artery pressure elevation in decompensated HFpEF. Unlike heart failure with reduced ejection fraction, MR worsening LV and LA dilation may not apply to HFpEF due to the stiffer chambers. Thus, MR could tend to contribute to v-wave elevation and pulsatile loading of the pulmonary circulation out of proportion to the elevation in PCWP, as reported previously.[36]

Importantly, greater severity of PH could be 1 of the causes of right ventricular dysfunction, and a recent study demonstrated that right ventricular dysfunction was associated with a nearly 2-fold increased risk of death in patients with HFpEF.[37] Therefore, evaluation of the presence of PH and its severity should carry important clinical implications for the diagnosis and treatment of patients with HFpEF.

Recently, it has been reported that hemodynamic-guided management using the CardioMEMS heart sensor, which can monitor real-time PASP, markedly reduced HF rehospitalization compared with standard HF management, based on subanalyses of the CHAMPION trial in 119 patients with HFpEF.[13] In that study, medication for HF was more likely to be changed in the device-implanted group in response to pulmonary artery pressure information than in the control group. However, the device has not yet been approved in many countries, including Japan, and is more expensive than other noninvasive modalities such as echocardiography. In addition, it is hard to use the device during the initial treatment of acute HF. Alternatively, for these patients, direct measurement of PASP by right-heart catheterization allows accurate risk stratification at admission; however, the routine use of this invasive modality shows little evidence of favorable outcomes because of its higher complications and medical costs.[38,39] Thus, the assessment of TRPG can overcome these issues. Notably, TRPG has several advantages in that it is a noninvasive, simple, repeatable, common measurement, with low health care cost compared to invasive hemodynamic monitoring. A previous study demonstrated a very strong correlation between Doppler-estimated TRPG and PASP measured by right-heart catheterization ($r = 0.97$, standard error of the estimate = 4.9 mmHg).[14] This study also demonstrated that estimating right atrial pressure and adding it to the Doppler-determined right-ventricular−to-right-atrial pressure gradient simultaneously was not necessary to provide clinically relevant data for stratifying the subsequent risk of adverse events. In fact, the guidelines for echocardiographic assessment of the right heart in adults show that IVCD and respiratory variation offer only semiquantitative assessment of right atrial pressure and may lead to erroneous inference, especially in patients with intermediate values (5−10 mmHg).[40] In the present study, we did not consider right atrial pressure estimated by IVCD and respiratory change because these data were not always accessible in the acute decompensated phase of HF. Accordingly, we believe that admission TRPG could be a useful noninvasive indicator for developing novel treatment strategies to improve outcomes in hospitalized patients with HFpEF.

### Limitations

There are several potential limitations in the present study that should be acknowledged. First, the sample size of this study was relatively small, thereby limiting the ability to generalize the findings and the statistical power for

detecting differences in negative data. Therefore, a larger-scale study is warranted to confirm the relationship between increased TRPG and worse clinical outcomes in hospitalized patients with HFpEF. Second, we did not consider the use of medications, including vasodilators, which reduce TRPG during echocardiography measurement. In this situation, the actual admission TRPG might have been underestimated. Third, although we demonstrated that patients with higher grades of MR had significantly higher TRPG, patients with grade IV MR were excluded, as described in the eligibility criteria of JASPER. Fourth, only 81% of the study patients received intravenous diuretic therapy. We speculate that the reasons may be as follows. The phenotype of HFpEF in our study population was varied, with some patients having isolated elevation of PCWP and diffuse pulmonary edema along with high systolic blood pressure. These patients were classified as clinical scenario 1 (CS 1),[41] in whom noninvasive positive pressure ventilation and/or vasodilators were recommended; however, diuretics were rarely indicated unless associated with volume overload according to the previous Japanese Circulation Society guidelines for the treatment of AHF, which were applied during the enrollment period in the JASPER study.[42] In fact, 254 (54%) patients met the criteria for CS 1 in this study. Among these, 220 (87%) patients had histories of hypertension. Fifth, there were no data concerning right ventricular function, such as tricuspid annular plane systolic excursion orright ventricular s′. Sixth, important international differences exist in HF management and health care policy between Western countries and Japan. Notably, Japanese patients hospitalized for HF have longer lengths of hospital stays than Westerners.[43] In fact, patients hospitalized for HF in Japan are reported to have longer lengths of hospital stays than those in Europe and the United States (Japan: 15−21 days; Europe: 7−9 days; US: 4 days) because of the specific health care system of each country.[43]

Japanese patients hospitalized due to HF not only receive treatment for acute decompensation but also undergo diagnostic tests to screen for comorbidities (eg, coronary artery disease, cardiac amyloidosis, hypertrophic cardiomyopathy) during the indexed hospitalization. For this reason, lengths of hospital stays are often longer in Japan and include days without diuretic therapy. Furthermore, important international differences also exist in HFpEF phenotypes across regions. Importantly, Japanese patients with HFpEF have substantially lower body mass indexes and a higher prevalence of atrial fibrillation than Westerners.[16,44] Thus, our findings may be applicable only to specific phenotypes (eg, nonobese and atrial fibrillation) in Western patients with HFpEF. Finally, we demonstrated that the change in TRPG during hospitalization did not reach significance as a determinant of subsequent risk of postdischarge mortality, but the limited sample size and events might have influenced the results. Accordingly, a further study that can confirm the relationship between tracked changes in TRPG from admission to discharge and long-term clinical outcomes in patients with HFpEF is warranted.

## Conclusions

High TRPG at admission was an independent determinant of worse clinical outcomes in hospitalized patients with HFpEF, suggesting that TRPG at admission is useful for risk stratification of patients with decompensated HFpEF.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.010.

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