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PDF issue: 2026-11-16

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(Citation)
International Journal of Cardiovascular Imaging,36(7):1261-1269

(Issue Date)
2020-07

(Resource Type)
journal article

(Version)
Accepted Manuscript

(Rights)
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(URL)
https://hdl.handle.net/20.500.14094/90007675

Associations between functional tricuspid regurgitation and long-term outcomes for patients with pulmonary hypertension

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Abstract

Purpose: Functional tricuspid regurgitation (FTR) is associated with prognosis for various heart diseases, but its association with pulmonary hypertension (PH) remains unclear.

Methods: We studied 111 PH patients. Mid-term follow-up echocardiography was performed 7.1±4.1 months after PH-specific therapy. The severity of FTR was graded as none or trace, mild, moderate, or severe, while more than moderate TR was defined as significant. Moreover, mid-term improvement in FTR after therapy was defined as an improvement in severity of FTR by a grade of 1 or more. Long-term follow-up to determine the primary endpoint of death or hospitalization for heart failure lasted 39±14 months.

Results: Mid-term improvement in FTR after PH-specific treatment was observed in 25 patients (23%), and the primary end points occurred in 27 patients (24%) during the long-term follow-up. The Kaplan-Meier curve indicated that the non-FTR group showed more favorable long-term outcomes than the FTR group (log-rank P=0.008). It further indicated that patients with mid-term improvement in FTR also had more favorable long-term outcomes than those without such improvement (log-rank P=0.03). When divided into four sub-groups based on combined assessment of baseline FTR and mid-term improvement in FTR, long-term outcomes for patients without mid-term improvement in their baseline FTR were worse than for the other sub-groups (log-rank p = 0.02). Multiple regression analysis showed that a relative change in tricuspid annular diameter at the mid-term follow-up after PH-specific therapy was the only independent determinant parameters for mid-term improvement in FTR.

Conclusion: FTR appears to be a valuable factor for predicting long-term outcomes for PH patients, and combined assessment of baseline FTR and mid-term improvement in FTR after PH-specific therapy may have clinical implications for better management of such patients.

Key words; Echocardiography; Pulmonary hypertension; Functional tricuspid valve regurgitation

Introduction

Pulmonary hypertension (PH) is characterized by progressive increases in pulmonary vascular load, leading to marked increases in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR) and exercise intolerance, and is usually associated with a poor outcome [1, 2]. However, the prognosis of PH patients has been improving due to the development of PH-specific therapy. On the other hand, response to PH-specific therapy by PH patients cannot be expected to be homogeneous, although right ventricular (RV) systolic dysfunction has been shown to be strongly associated with outcomes [2-8]. While tricuspid regurgitation (TR) is a common echocardiographic finding, it has been found that mild or less TR does not affect the outcome [9-11]. In recent years, moderate or severe functional TR (FTR) has been reported to be associated with a worse prognosis in patients with various forms of heart disease, especially left-sided valvular disease or left ventricular (LV) dysfunction [11, 12]. In addition, moderate or severe FTR has reportedly been identified in 60% of patients with severe symptomatic PH, and its presence is associated with decreased exercise capacity and RV failure [13]. The development of FTR in PH patients has been associated with deteriorating PH and adverse RV remodeling, which is characterized by increased RV sphericity, tricuspid annular dilatation and tricuspid valve tethering [14-16]. In addition, the development of FTR in PH patients has been reported to be associated with outcomes [14, 16], although the association ~~of~~ between baseline FTR and mid-term changes in FTR after PH-specific therapy on the one hand and long-term outcomes for PH patients on the other remains uncertain.

The aim of our study was thus to investigate the association between the severity of FTR and long-term outcomes for PH patients. We also tested the hypothesis that mid-term improvement in FTR after PH-specific therapy is associated with favorable long-term outcomes for PH patients.

Materials and Methods

Study population

We prospectively recruited 111 PH patients who were admitted to the PH Clinic of Kobe University Hospital between January 2014 and December 2017. PH was defined as resting mean PAP (mPAP) >25mmHg measured by means of right-heart catheterization (RHC). Patients excluded from the study were those with: (1) pulmonary capillary wedge pressure ≥15mmHg as measured with RHC; (2) atrial fibrillation; (3) coronary artery disease, defined as a single coronary artery stenosis of >50% of the diameter of a major epicardial vessel or a previous history of myocardial infarction; (4) more than moderate mitral and aortic valvular heart disease; and (5) any pacemaker lead implantation in right ventricle. This study was approved by the ethics committee of our institution (No. 180190).

Echocardiographic examination

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). Digital routine grayscale 2-D cine loops and tissue Doppler cine loops were obtained from three consecutive beats with end-expiratory apnea and from standard apical and parasternal views. Sector width was optimized to allow for complete myocardial visualization while frame rate was maximized regardless of heart rate. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography[7]. Digital data were transferred to dedicated offline software (EchoPAC version BTO8; GE Vingmed Ultrasound AS) for subsequent offline speckle-tracking analysis. Mid-term follow-up echocardiography was performed 7.1±4.1 months after PH-specific therapy.

Determination of RV function by means of two-dimensional longitudinal speckle-tracking strain from the RV free-wall was previously described in detail [2, 5-8, 17-21]. RV free-wall longitudinal strain was calculated by averaging each of the three regional peak systolic strains along the entire RV free-wall, and was expressed as an absolute value.

Assessment of TR

Based on the guidelines of the American Heart Association/American College of Cardiology, TR was quantified in the RV-focused apical 4-chamber view by measuring the central jet area of TR[22]. Color flow Doppler settings were kept constant during the entire study. The severity of TR was graded as none or trace, mild ($<5.0cm^2$), moderate ($5.0\text{-}10.0cm^2$), or severe ($>10.0cm^2$). TR $\geq$ moderate was defined as significant. In addition, mid-term improvement of TR after PH-specific therapy was defined as a decrease in severity of TR by a grade of 1 or more. Assessment of TR grading was performed by at least two senior echocardiologists.

Hemodynamic measurements

All patients underwent RHC for hemodynamic measurements. mPAP, PVR, right atrial (RA) pressure and stroke volume were calculated by using the Fick principle for estimations. Pressure was measured by an investigator who was blinded to the echocardiographic data.

Definitions of long-term outcomes

Long-term unfavorable outcome events were pre-specified as primary end points of death or hospitalization for deteriorating right-sided heart failure. Mean long-term follow-up after administration of PH-specific drugs was 39±14 months.

Statistical analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally

distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of subgroups were compared by means of the Student *t* test or Mann-Whitney U test as appropriate, while proportional differences were evaluated by using Fisher's exact test or the χ^2 test as appropriate. Multiple regression analysis on the basis of enter selection was performed to identify independent determinants of mid-term improvement in FTR. Event-free survival curves were determined with the Kaplan-Meier method and comparisons of cumulative event rates with the log-rank test. The intraclass correlation coefficient was used to determine inter- and intra-observer reproducibilities for the central jet area of TR from 20 randomly selected patients using an identical cine-loop for each view. For all tests, a p value <0.05 was considered statistically significant. All the analyses were performed with commercially available software (MedCalc software version 18.1.1.; MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The baseline clinical and echocardiographic characteristics of the 111 PH patients are summarized in Table 1. Forty-four of the PH patients (40%) had pulmonary arterial hypertension, six (5%) had PH due to lung diseases, 58 (52%) had chronic thromboembolic pulmonary hypertension, and three (3%) unclear PH. The primary end point of pre-specified clinical events occurred in 27 of the 111 patients (24%): one (1%) death~~s~~ and 26 (23%) hospitalizations for deteriorating right-sided heart failure. No clinical events occurred between initial evaluation and mid-term echocardiographic follow-up. The intraclass correlation coefficient for inter-observer reproducibility of the central jet area of TR was 0.923 (95% confidence interval: 0.846–0.962), and the intraclass correlation coefficient for intra-observer reproducibility of the central jet area of TR was 0.959 (95% confidence interval: 0.916–0.978).

Comparison of patients in the FTR and non-FTR groups

The baseline clinical and echocardiographic characteristics of patients in the FTR and non-FTR group are summarized in Table 2. The FTR group consisted of 29 patients (26.1%) with FTR, which was defined as a more than moderate FTR, while the group with the remaining 82 patients (73.9%) was classified as the non-FTR group. The two groups showed similar baseline clinical and echocardiographic characteristics, except for the fact that PVR of the FTR group was significantly larger than that of the non-FTR group (1203.3±649.6 dyne sec cm^{-5} vs. 816.0±528.5 dyne sec cm^{-5}; P=0.02), as were plasma brain natriuretic peptide (272 (7-772) pg/mL vs. 87 (6-462) pg/mL; P<0.001), trans-tricuspid pressure gradient (60.1±20.5 mmHg vs. 43.6±16.4 mmHg; P<0.001), and right atrial area (25.7±8.0 cm^2 vs. 16.0±4.7 cm^2; P<0.0001). These differences suggest that patients in the FTR group were sicker.

This is confirmed by the Kaplan-Meier curve, which shows that the non-FTR group attained more favorable long-term outcomes than the FTR group (log-rank P=0.008) (Figure 1).

Comparison of patients with and without mid-term improvement FTR

Mid-term improvement in FTR defined as a decrease in severity in FTR by a grade of 1 or more was observed in 25 patients (22.5%), and the remaining 86 patients (77.5%) were classified as without mid-term improvement in FTR. The Kaplan-Meier curve indicated that patients with mid-term improvement in FTR showed favorable long-term outcomes than those without mid-term improvement in FTR (log-rank P=0.03, Figure 2).

Next, we divided into four sub-groups according to combined assessment of baseline FTR and mid-term improvement in FTR. There were 17 patients with baseline FTR without mid-term improvement in FTR. This pattern was associated with worse long-term outcome compared to other sub-groups (log-rank p = 0.02, Figure 3). In

addition, RV free-wall strain for each sub-group was as follows: non FTR group with mid-term improvement of FTR: 13.7±7.5%, non-FTR group without mid-term improvement of FTR: 17.8±6.9%, FTR group with mid-term improvement of FTR: 13.6±8.4%, FTR group without mid-term improvement of FTR: 14.2±9.1%.

Figure 4 shows representative cases patients with baseline FTR, but different response FTR after PH-specific therapy.

Association of mid-term improvement in FTR

Table 3 shows the results of the multiple regression analysis for the association of mid-term improvement in FTR with clinical and echocardiographic parameters. An important finding of the multiple regression analysis was that a relative change in tricuspid annular diameter at the mid-term follow-up after PH-specific therapy was the only independent determinant parameters for mid-term improvement in FTR.

Discussion

The findings of our study indicate that baseline FTR and mid-term improvement in FTR after PH-specific therapy were associated with long-term outcomes for PH patients. It was noteworthy that patients with baseline FTR without mid-term improvement in FTR after PH-specific therapy showed vastly worse long-term outcomes.

FTR in PH patients

TR is a common finding that is often considered benign unless associated with significant PH or RV or LV dysfunction [9, 10]. The etiology of TR is generally classified into organic, because of its intrinsic association with tricuspid valve disease, and functional, in the absence of structural abnormalities of the tricuspid leaflets. Organic TR results from structural abnormalities of the tricuspid valve (TV) apparatus, may be congenital or acquired and accounts for only 8-10% of all severe TR [11, 23].

FTR is a consequence of deformation of the TV apparatus, such as dilatation and geometric deformation of the tricuspid annulus. FTR is frequently caused by increased RV afterload and it is associated with advanced stages of left-sided valve, LV myocardial or pulmonary diseases. Nath et al confirmed that mild or less TR did not affect the outcome, but moderate or greater TR was associated with a worse prognosis, even in the absence of LV dysfunction or PH in 5223 patients[11].

For PH patients, FTR progression was associated with worsening PH and adverse RV remodeling, characterized by an increase in RV sphericity, tricuspid annular dilatation, and tricuspid valve tethering[14-16]. Once FTR has become significant, progressive RV remodeling and dysfunction due to chronic volume overload result in further papillary muscle displacement and leaflet tethering, which worsen FTR and lead to further RV dilatation. Moderate or severe FTR has been reported in 60% of patients with severe symptomatic idiopathic PH, and its presence is associated with reduced exercise capacity and RV failure [13]. Moreover, Medvedofsky et al. showed a reduction in PAP was found to be associated with RV reverse remodeling and reversal of tricuspid annular dilatation and tricuspid valve tenting, leading to lessening of FTR and a more favorable clinical outcome in PH patients [14]. They also showed FTR progression was associated with worsening PH and adverse RV remodeling including tricuspid annular dilatation. Our group also reported that PAH patients with mid-term RV reverse remodeling after PH-specific treatment showed more favorable long-term outcomes than those without, and the multivariate Cox proportional hazards analysis showed that mid-term RV reverse remodeling after PH-specific treatment was an independent predictors of long-term outcomes as well as of RV free-wall strain [24]. In accordance with a previous study by Medvedofsky et al. [14], we showed that RV reverse remodeling such as a relative change in tricuspid annular diameter at the mid-term follow-up after PH-specific therapy was highly associated with mid-term

improvement in FTR. Thus, RV remodeling plays an important role for prognosis in PH patients.

Clinical implications

Response to PH-specific therapy by PH patients cannot be expected to be homogeneous, and, while there are many prognostic predictors for PH patients [25], not all of them can be used for individual patients. The development of one of these predictors, hemodynamic measurements including mean PAP, PVR, and RA pressure, RV systolic function, has been associated with adverse outcomes regardless of the underlying clinical entity [2-8]. According to our findings, baseline FTR and mid-term improvement in FTR play an important role in disease progression and prognosis for PH patients. In addition, it appears that baseline FTR without mid-term improvement in FTR is associated with vastly worse long-term outcome. Thus, identification of established baseline risk parameters and also the assessment of FTR including its mid-term improvement could be of prognostic value for the stratification of long-term risk, regardless of whether it is associated with an improvement in symptoms.

Study limitations

This study covered a small number of patients in a single-center retrospective study, so that studies involving larger numbers of patients will be required to verify our findings. In addition, the quantification of TR is somewhat challenging. The severity of TR was quantified by measuring the central jet area of TR in this study[22], however other quantification of TR[26] such as regurgitant volume, effective regurgitant orifice area, or vena contracta width was not part of this study. Thus, future studies with other quantification of will be needed to validate our findings. Finally, the enrollment in this study covered patients with various etiologies of PH such as Group I, III, IV, and V. Especially in Group 4, 31 patients underwent balloon pulmonary angioplasty, 5

underwent pulmonary endarterectomy, 3 underwent both, and remaining 9 underwent received medical therapy only. No patients received lung transplantation among whole patients. Since patients in this study were treated by a number of methods, associations between FMR and long-term outcomes for PH patients may consider each group.

Conclusion

FTR appears to be a valuable factor for predicting long-term outcomes for PH patients, and combined assessment of baseline FTR and mid-term improvement in FTR after PH-specific therapy may have clinical implications for better management of such patients.

Compliance with Ethical Standards

Conflict of interest:

Jun Mukai declares that he has no conflict of interest. Hidekazu Tanaka declares that he has no conflict of interest. Hiroyuki Sano declares that he has no conflict of interest. Shun Yokota declares that he has no conflict of interest. Makiko Suto declares that she has no conflict of interest. Hiroki Takada declares that he has no conflict of interest. Fumitaka Soga declares that he has no conflict of interest. Yutaka Hatani declares that he has no conflict of interest. Hiroki Matsuzoe declares that he has no conflict of interest. Keiko Hatazawa declares that she has no conflict of interest. Kensuke Matsumoto declares that he has no conflict of interest. Kazuhiko Nakayama declares that he has no conflict of interest. Noriaki Emoto declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

FIGURE LEGENDS

Figure 1: The Kaplan-Meier curve indicates that the baseline non-functional tricuspid regurgitation (FTR) group showed more favorable long-term outcomes than the baseline FTR group.

Figure 2: The Kaplan-Meier curve indicates that patients with mid-term improvement in functional tricuspid regurgitation (FTR) after pulmonary hypertension-specific therapy showed more favorable long-term outcomes than did those without such improvement.

Figure 3: Patients were divided into four sub-groups based on combined assessment of baseline functional tricuspid regurgitation (FTR) and mid-term improvement of FTR. There were 17 patients with baseline FTR without mid-term improvement. This pattern was associated with worse long-term outcome than that for the other sub-groups.

Figure 4: Representative cases involving patients with baseline FTR, but with different responses of FTR after PH-specific therapy.

REFERENCES

[1] Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M (2010) Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 35:1079-1087

[2] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37:67-119

[3] Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM (2006) Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 174:1034-1041

[4] Ghio S, Klersy C, Magrini G, D'Armini AM, Scelsi L, Raineri C, Pasotti M, Serio A, Campana C, Vigano M (2010) Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. Int J Cardiol 140:272-278

[5] Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, Kane GC (2013) Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging 6:711-721

[6] Haeck ML, Scherptong RW, Marsan NA, Holman ER, Schalij MJ, Bax JJ, Vliegen HW, Delgado V (2012) Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging 5:628-636

[7] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the

American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28:1-39 e14

[8] Motoji Y, Tanaka H, Fukuda Y, Ryo K, Emoto N, Kawai H, Hirata K (2013) Efficacy of right ventricular free-wall longitudinal speckle-tracking strain for predicting long-term outcome in patients with pulmonary hypertension. Circ J 77:756-763

[9] Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF (2002) Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J 144:524-529

[10] Hung J, Koelling T, Semigran MJ, Dec GW, Levine RA, Di Salvo TG (1998) Usefulness of echocardiographic determined tricuspid regurgitation in predicting event-free survival in severe heart failure secondary to idiopathic-dilated cardiomyopathy or to ischemic cardiomyopathy. Am J Cardiol 82:1301-1303, A1310

[11] Nath J, Foster E, Heidenreich PA (2004) Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 43:405-409

[12] Tornos Mas P, Rodriguez-Palomares JF, Antunes MJ (2015) Secondary tricuspid valve regurgitation: a forgotten entity. Heart 101:1840-1848

[13] Hinderliter AL, Willis PWt, Long WA, Clarke WR, Ralph D, Caldwell EJ, Williams W, Ettinger NA, Hill NS, Summer WR, de Boisblanc B, Koch G, Li S,

Clayton LM, Jobsis MM, Crow JW, Group PPHS (2003) Frequency and severity of tricuspid regurgitation determined by Doppler echocardiography in primary pulmonary hypertension. Am J Cardiol 91:1033-1037, A1039

[14] Medvedofsky D, Aronson D, Gomberg-Maitland M, Thomeas V, Rich S, Spencer K, Mor-Avi V, Addetia K, Lang RM, Shiran A (2017) Tricuspid regurgitation progression and regression in pulmonary arterial hypertension: implications for right ventricular and tricuspid valve apparatus geometry and patients outcome. Eur Heart J Cardiovasc Imaging 18:86-94

[15] Mutlak D, Aronson D, Lessick J, Reisner SA, Dabbah S, Agmon Y (2009) Functional tricuspid regurgitation in patients with pulmonary hypertension: is pulmonary artery pressure the only determinant of regurgitation severity? Chest 135:115-121

[16] Chen L, Larsen CM, Le RJ, Connolly HM, Pislaru SV, Murphy JG, McGoon MD, Frantz RP, Kane GC (2018) The prognostic significance of tricuspid valve regurgitation in pulmonary arterial hypertension. Clin Respir J 12:1572-1580

[17] Fukuda Y, Tanaka H, Sugiyama D, Ryo K, Onishi T, Fukuya H, Nogami M, Ohno Y, Emoto N, Kawai H, Hirata K (2011) Utility of right ventricular free wall speckle-tracking strain for evaluation of right ventricular performance in patients with

pulmonary hypertension. J Am Soc Echocardiogr 24:1101-1108

[18] Motoji Y, Tanaka H, Fukuda Y, Sano H, Ryo K, Sawa T, Miyoshi T, Imanishi J, Mochizuki Y, Tatsumi K, Matsumoto K, Emoto N, Hirata K (2016) Association of Apical Longitudinal Rotation with Right Ventricular Performance in Patients with Pulmonary Hypertension: Insights into Overestimation of Tricuspid Annular Plane Systolic Excursion. Echocardiography 33:207-215

[19] Fukuda Y, Tanaka H, Motoji Y, Ryo K, Sawa T, Imanishi J, Miyoshi T, Mochizuki Y, Tatsumi K, Matsumoto K, Shinke T, Emoto N, Hirata K (2014) Utility of combining assessment of right ventricular function and right atrial remodeling as a prognostic factor for patients with pulmonary hypertension. Int J Cardiovasc Imaging 30:1269-1277

[20] Fukuda Y, Tanaka H, Ryo-Koriyama K, Motoji Y, Sano H, Shimoura H, Ooka J, Toki H, Sawa T, Mochizuki Y, Matsumoto K, Emoto N, Hirata K (2016) Comprehensive Functional Assessment of Right-Sided Heart Using Speckle Tracking Strain for Patients with Pulmonary Hypertension. Echocardiography 33:1001-1008

[21] Motoji Y, Tanaka H, Fukuda Y, Sano H, Ryo K, Imanishi J, Miyoshi T, Sawa T, Mochizuki Y, Matsumoto K, Emoto N, Hirata K (2015) Interdependence of right ventricular systolic function and left ventricular filling and its association with outcome

for patients with pulmonary hypertension. Int J Cardiovasc Imaging 31:691-698

[22] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD, Members AATF (2014) 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129:e521-643

[23] Mutlak D, Lessick J, Reisner SA, Aronson D, Dabbah S, Agmon Y (2007) Echocardiography-based spectrum of severe tricuspid regurgitation: the frequency of apparently idiopathic tricuspid regurgitation. J Am Soc Echocardiogr 20:405-408

[24] Sano H, Tanaka H, Motoji Y, Fukuda Y, Sawa T, Mochizuki Y, Ryo K, Matsumoto K, Emoto N, Hirata K (2015) Right ventricular function and right-heart echocardiographic response to therapy predict long-term outcome in patients with pulmonary hypertension. Can J Cardiol 31:529-536

[25] Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, Guidelines ESCCfP (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of

Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30:2493-2537

[26] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ (2017) Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 30:303-371

Table 1
Baseline characteristics of patients

	PH Patients (n=111)
Age, years	64.3±15.9
Gender (Female), n (%)	83 (75)
Systolic blood pressure, mmHg	122.7±22.5
Diastolic blood pressure, mmHg	69.1±14.0
Heart rate, bpm	70.1±13.1
Brain natriuretic peptide, pg/mL	138.1 [4.4-1054]
6-minute walk distance, m	255.3±165.1
Etiology of PH, n (%)	
Group I, n (%)	44
Group III, n (%)	6
Group IV, n (%)	58
Group V, n (%)	3
PH specific medication, n (%)	
Prostacycline	18 (16)
Endothelin receptor antagonistss	40 (36)
Phosphodiesterase 5 inhibitors	39 (35)
Soluble guanylate cyclase	23 (21)
Child-Pugh classification, n (%)	18 (16)
A	109 (98)
B	2 (2)
C	0 (0)
Hemodynamic parameters	
mPAP, mmHg	32.0±11.5
PVR, dyne· s^{-1}· cm^{-5}	931.5±594.0
Cardiac output, L/min	3.97±1.39
Cardiac index, L/min/m^2	2.48±0.76
Mean RA pressure, mmHg	5.43±3.55

Echocardiographic parameters	
LV end-diastolic volume, mL	63.8±27.8
LV end-systolic volume, mL	21.6±12.7
LVEF, %	67.8±9.4
LA volume index, mL/m^2	33.2±14.5
TR-PG, mmHg	47.8±19.0
RV area (end-diastole), cm^2	20.7±7.4
RA area (end-systole), cm^2	18.0±6.8
Tricuspid annulus diameter, mm	33.6±5.9
TAPSE, cm	18.5±5.2
RVFAC, %	32.6±12.4
RV free-wall strain, %	16.2±7.7

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

WHO, World Health Organization; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RA, right atrial; LVEF, left ventricular ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; RVFAC, right ventricular fractional area change

Table 2
Baseline characteristics of FTR and non-FTR group

	FTR Group (n=29)	Non-FTR Group (n=82)	P value
Age, years	70.8±10.9	61.9±16.7	<0.01
Gender (Female), n (%)	21 (72)	62 (76)	0.736
Systolic blood pressure, mmHg	122.6±20.4	122.8±23.2	0.979
Diastolic blood pressure, mmHg	70.2±14.6	68.6±13.7	0.628
Heart rate, bpm	69.9±13.6	70.5±11.7	0.827
Brain natriuretic peptide, pg/mL	272 [7-772]	87 [6-462]	<0.0001
6-minute walk distance, m	243.8±148.3	260.2±171.5	0.700
Etiology of PH, n (%)			
Group I, n (%)	10 (34.5)	34 (41.4)	0.659
Group III, n (%)	2 (6.9)	4 (4.9)	0.650
Group IV, n (%)	15 (51.7)	43 (52.4)	0.971
Group V, n (%)	2 (3.4)	1 (1.2)	0.167
PH specific medication, n (%)			
Prostacycline	6 (21)	12 (15)	0.558
Endothelin receptor antagonistss	10 (34)	30 (37)	1.000
Phosphodiesterase 5 inhibitors	9 (31)	31 (38)	0.654
Soluble guanylate cyclase	6 (21)	17 (21)	1.000
Child-Pugh classification, n (%)			
A	27 (93)	82 (100)	0.665
B	2 (6.9)	0 (0)	0.665
C	0 (0)	0 (0)	1.0
Hemodynamic parameters			
mPAP, mmHg	35.3±12.6	30.6±10.8	0.131
PVR, dyne· s^{-1}· cm^{-5}	1203.3±649.6	816.0±528.5	0.024
Cardiac output, L/min	3.67±1.36	4.09±1.38	0.255
Cardiac index, L/min/m^2	2.18±0.56	2.60±0.79	0.036
Mean RA pressure, mmHg	6.11±3.56	5.18±3.52	0.351

Echocardiographic parameters			
LV end-diastolic volume, mL	55.6±22.7	66.5±28.9	0.086
LV end-systolic volume, mL	20.6±12.9	21.9±12.6	0.651
LVEF, %	66.3±10.6	68.3±8.2	0.319
LA volume index, mL/m^2	37.1±21.6	31.8±10.3	0.142
TR-PG, mmHg	60.1±20.5	43.6±16.4	<0.0001
RV area (end-diastole), cm^2	22.2±7.7	20.3±7.3	0.298
RA area (end-systole), cm^2	25.7±8.0	16.0±4.7	<0.0001
Tricuspid annulus diameter, mm	37.1±7.2	34.7±7.3	0.139
TAPSE, cm	16.4±3.8	19.2±5.5	0.018
RVFAC, %	30.2±12.2	33.0±12.4	0.350
RV free-wall strain, %	14.0±8.9	16.8±7.3	0.139

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

FTR, functional tricuspid regurgitation

Other abbreviations as in Table 1.

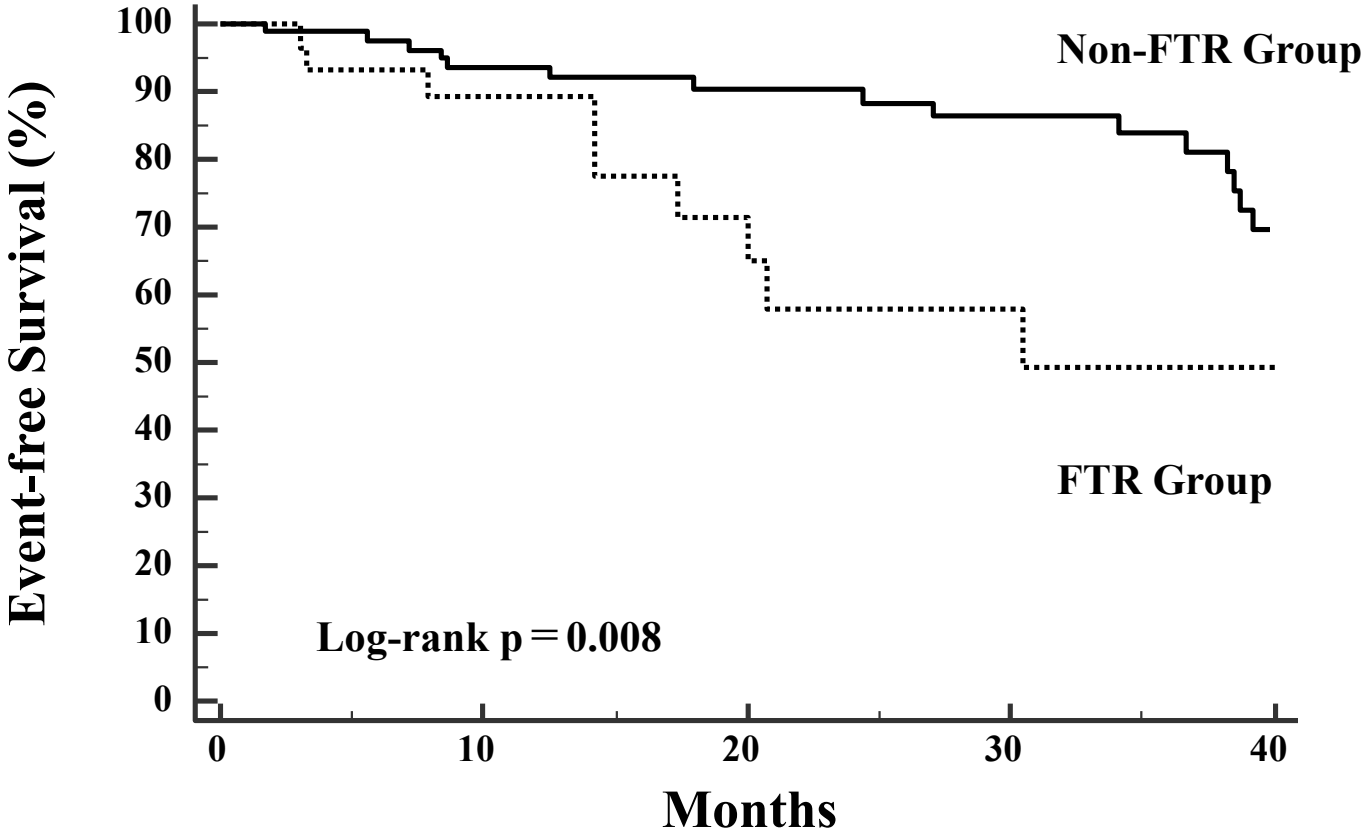
Table 3

Multiple regression analysis for the association of mid-term improvement in FTR

Independent variables	Coefficient	Standard error	t value	p value
Age	0.005	0.003	1.586	0.125
Gender	-0.129	0.133	-0.967	0.343
RV free-wall strain	-0.003	0.009	-0.356	0.725
ΔTricuspid annular diameter	1.013	0.350	2.898	0.008
ΔPVR	-0.010	0.036	-0.290	0.774
ΔmPAP	0.561	0.275	2.039	0.052

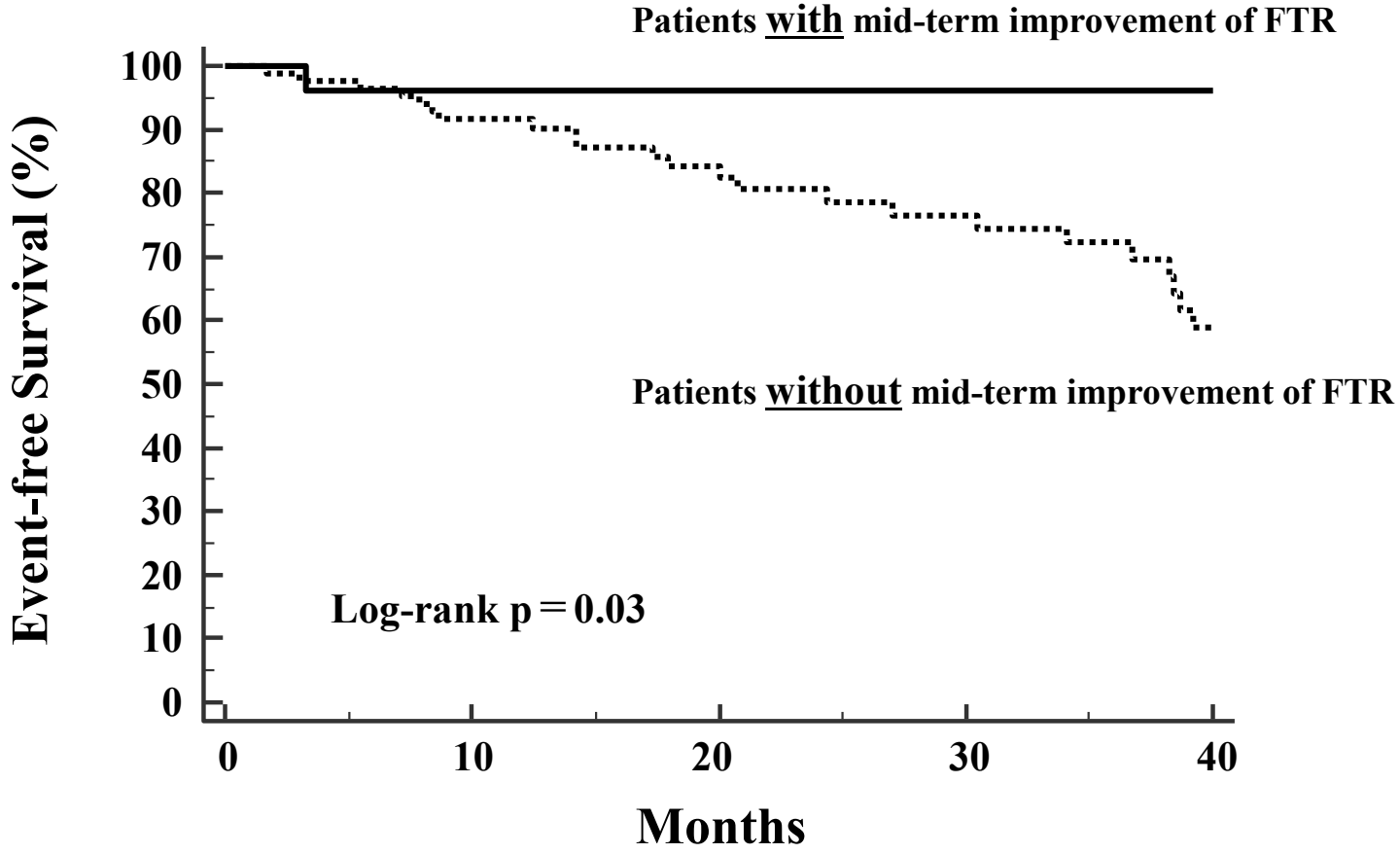
ΔTricuspid annular dimension, a relative change in tricuspid annular diameter at the mid-term follow-up after PH-specific therapy; ΔPVR, a relative change in PVR at the mid-term follow-up after PH-specific therapy; ΔmPAP, a relative change in mPAP at the mid-term follow-up after PH-specific therapy

Other abbreviations as in Table 1 and 2.



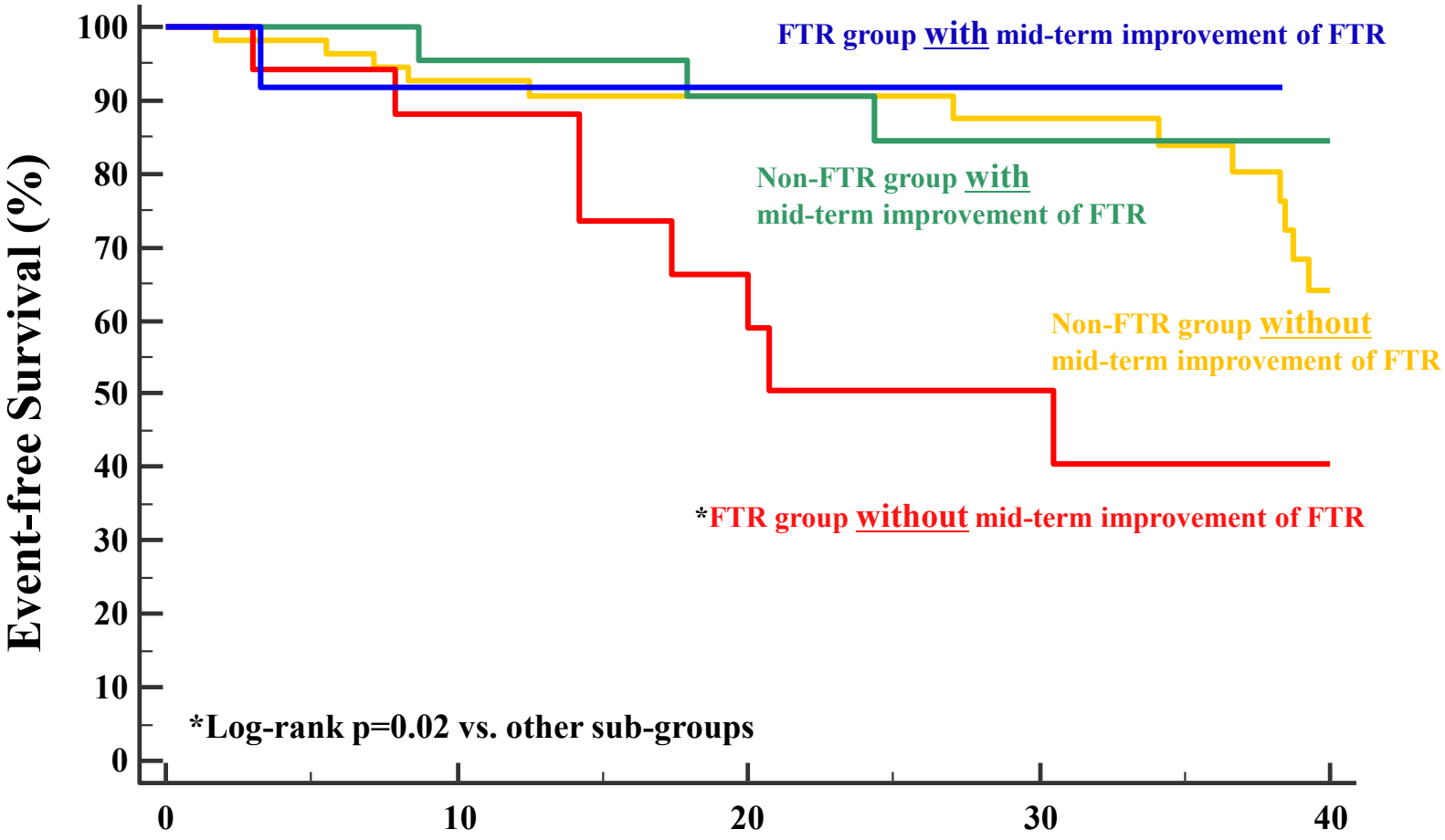
Number at risk

Non-FTR Group	**82**	**68**	**49**	**39**	**23**
FTR Group	**29**	**21**	**11**	**7**	**4**



Number at risk

Patients with mid-term improvement of FTR	**25**	**19**	**12**	**10**	**6**
Patients without mid-term improvement of FTR	**86**	**70**	**48**	**36**	**21**



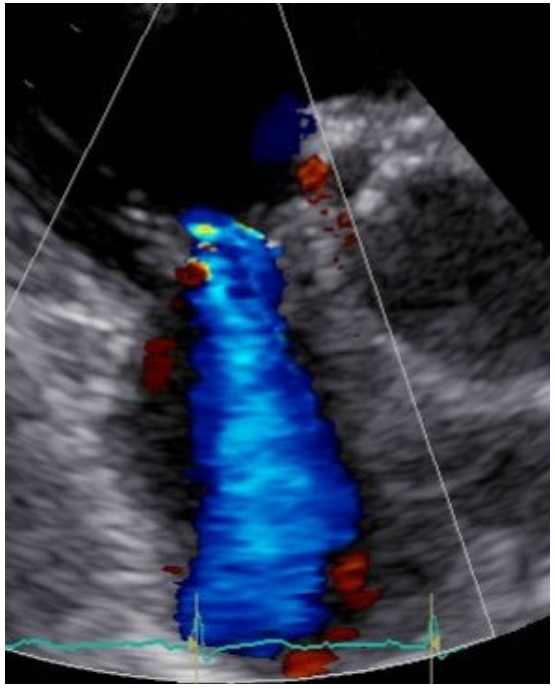
Number at risk

FTR group with mid-term improvement of FTR	12	8	2	2	0
Non-FFR group with mid-term improvement of FTR	24	21	16	13	7
Non-FTR group without mid-term improvement of FTR	58	47	33	26	16
FTR group without mid-term improvement of FTR	17	13	9	5	4

FTR group without mid-term improvement of FTR (83 year-old-female)

Baseline		6 months after PH-specific therapy	
mPAP	38mmHg	mPAP	26 mmHg
PVR	1246 dyne·s^{-1}·cm^{-5}	PVR	1107 dyne·s^{-1}·cm^{-5}

Severe FTR



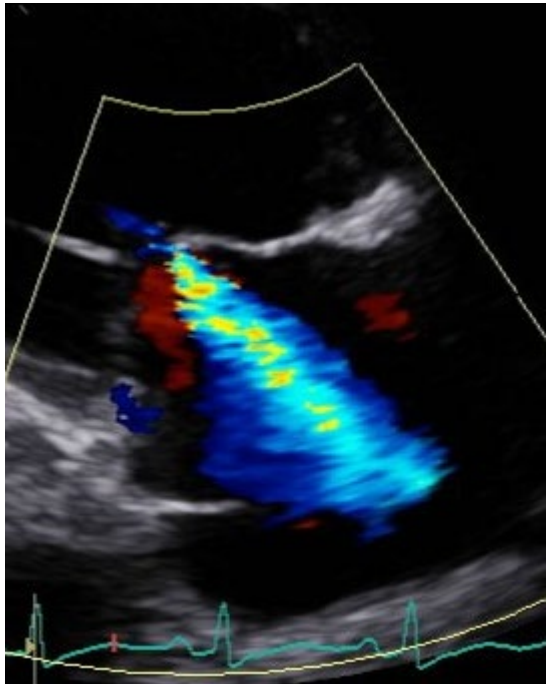
Severe FTR



FTR group with mid-term improvement of FTR (73 year-old-male)

Baseline		6 months after PH-specific therapy	
mPAP	34 mmHg	mPAP	23 mmHg
PVR	805 dyne·s^{-1}·cm^{-5}	PVR	636 dyne·s^{-1}·cm^{-5}

Severe FTR



Mild FTR

