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**Right ventricular dimension index by cardiac magnetic resonance for prognostication in
connective tissue diseases and pulmonary hypertension**

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ABSTRACT

Objectives: Pulmonary hypertension in patients with connective tissue disease (PH-CTD) is a heterogeneous condition affected by left heart disease, chronic lung disease and thromboembolism as well as pulmonary vascular disease. Recent studies using cardiac magnetic resonance (CMR) have shown that right ventricular (RV) dysfunction is predictive for mortality in patients with PH, but limited to pulmonary arterial hypertension (PAH). This study aimed to analyse prognostic factors in PH-CTD.

Methods: This retrospective analysis comprised 84 CTD patients, including systemic sclerosis, who underwent both CMR and right heart catheterization from 2008 to 2018. Demographics, laboratory findings, and hemodynamic and morphological parameters were extracted. The prognostic value of each parameter was evaluated by multivariate analysis using covariables derived from propensity score to control confounding factors.

Results: Of 84 patients, 65 had RHC-confirmed PH (54 PAH, 11 non-PAH). Nine out of these PH patients died during a median follow-up period of 25 months. In 65 patients with PH, RV end-diastolic dimension index (RVEDDI) evaluated by CMR was independently associated with mortality (Hazard ratio 1.24, 95% confidence interval 1.08-1.46, $p = 0.003$). At ROC analysis, RVEDDI highly predicted mortality with area under the curve of 0.87. The 0.5-2 year-follow-up data revealed that RVEDDI in both survivors and non-survivors did not significantly change in the clinical course, leading to the speculation that RVEDDI would be determined early to predict prognosis.

Conclusion: RVEDDI simply evaluated by CMR would serve as a significant predictor of mortality in PH-CTD. Further validation cohort study is needed to confirm its usability.

KEYWORDS: Magnetic resonance imaging, Propensity score, Pulmonary hypertension, Right ventricular dimension

KEY MESSAGES

- Right ventricular end-diastolic dimension index would predict prognosis in pulmonary hypertension with connective tissue diseases.
- Further prospective validation cohort study is required to confirm its utility as a prognostic factor.

INTRODUCTION

Pulmonary hypertension (PH) is defined as an increased mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, being progressively life-threatening, unless treated [1]. Based on World Health Organization (WHO) classification, PH is clinically classified into following five groups: group 1, pulmonary arterial hypertension (PAH); group 2, PH due to left heart diseases (LHD-PH); group 3, PH due to chronic lung disease (CLD-PH); group 4, chronic thromboembolic pulmonary hypertension (CTEPH); and group 5, PH due to unclear multifactorial mechanisms [1].

Connective tissue diseases (CTDs) including systemic sclerosis (SSc), and systemic lupus erythematosus (SLE) are one of the backgrounds of PAH. However, the pathophysiology of PH in patients with CTD (PH-CTD) comprises not only PAH but also other cardiopulmonary comorbidities including LHD-PH, CLD-PH and CTEPH. CTD is also known as a definite factor of poor prognosis in patients with newly-diagnosed PH [2-4]. Therefore, prompt and appropriate

management based on the pathogenesis in each patient is necessary for PH-CTD. However, the prognostic factors in PH-CTD remain incompletely understood.

In patients with PAH, several measurements have been used to evaluate disease severity and to estimate prognosis, such as WHO functional class [2], right ventricular (RV) functional impairment [5, 6], exercise capacity on 6-minute-walk test [5, 6]. However, these measurements have some problems of reproducibility, subjective evaluations and the invasive property. Cardiac magnetic resonance imaging (CMR) provides cardiac morphological and functional parameters with high accuracy and reproducibility [7, 8]. Its measurements such as RV end-diastolic volume (RVEDV) and RV ejection fraction (RVEF), and RV-pulmonary artery (PA) coupling metrics, have the prognostic value [9, 10].

A recent large cohort study based on ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry revealed that hemodynamic and cardiac morphologic parameters evaluated by CMR and right heart catheterization (RHC), including right ventricular structure and pulmonary arterial stiffness, are independent prognostic factors through analysing in a total of 576 patients with PAH [11, 12]. Although this study included 147 CTD patients, the aetiology of PH was restricted to PAH. In addition, longitudinal follow up data of cardiac morphological and functional parameters evaluated by CMR were not provided. The other cohort study based on Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) reported long-term outcomes in patients with SSc and PH, but also limited to PAH [13]. In fact, definite discrimination between PAH and other forms of PH is difficult in patients with CTD at real-world clinical setting, especially those with SSc. Therefore,

an analysis of prognostic factors in patients with PH-CTD including various forms of CTD as well as various forms of PH, remains a matter of research.

The present pilot derivation study aimed to detect prognostic factors in PH-CTD by adding longitudinal follow-up data of RV function precisely evaluate by combining CMR and RHC on real-world clinical setting.

METHODS

Patients and data extraction

We retrospectively identified 84 consecutive patients who were diagnosed with CTD including SSc, SLE, mixed connective tissue disease (MCTD) and Sjögren's syndrome (SS), and underwent CMR from January 2008 to March 2018 at Hokkaido University Hospital. In 65 of these 84 patients, PH was confirmed by RHC, and classified into WHO PH category based on following definitions; the diagnosis of group 1, PAH requires mPAP ≥ 25 mmHg and a concomitant elevated pulmonary vascular resistance (PVR) > 240 dyne $\cdot$ sec $\cdot$ cm $^{-5}\cdot$ m 2 [1, 14] and to exclude the remaining categories of PH; patients with group 2, LHD-PH need to agree with pulmonary artery wedge pressure (PAWP) ≥ 15 mmHg and a normal or reduced cardiac output; the diagnosis of group 3, CLD-PH is made with the evidence of CTD associated moderate to severe interstitial lung disease (ILD) with pulmonary dysfunction and/or radiographic changes affecting > 20 percent of the lung; group 4, CTEPH is diagnosed by thromboembolic occlusion of the pulmonary vasculature using ventilation-perfusion lung scanning and pulmonary angiography. The baseline and one-year follow-up data of the selective patients were extracted including demographics, blood test findings, and parameters of transthoracic echocardiography (TTE), RHC, CMR and pulmonary function test (PFT). The follow-up period was defined as the interval from evaluation with initial CMR until

death due to PH or until the end of this study. By comparing the parameters described above between survivors and non-survivors, we analysed and determined prognostic factors. Overall, one-year, and three-year mortality rates were individually analysed. The diagnostic criteria of CTDs are detailed in Supplementary material. Ethical approval for conducting this study was granted by Institutional Review Board of Hokkaido University hospital (reference number: 017-0327). The present study complied with the Declaration of Helsinki. We obtained the patient informed consents for this study and publication from all the patients including in this study.

Cardiac resonance imaging acquisition and analysis

We performed CMR using a 1.5-Tesla Philips Achieva magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) with a cardiac five-channel coil equipped with Master gradients (maximum gradient amplitude, 33 mT/m; maximum slew rate, 100 mT/m/m), and performed imaging with breath-holding in inspiration for up to ten seconds. Electrocardiogram-gated cine imaging was performed using a balanced steady-state free precession pulse sequence, during repeated breath-holds. Cine image acquisition parameters were as follows: FOV, 380 9380 mm; repeat time/echo time, 2.8/1.38 ms; acquisition matrix, 192×192 pixels; reconstruction matrix, 256×256 pixels; slice thickness, 10 mm; flip angle, 60 deg; and SENSE factor, 2. A total of scan time was about 40 minutes.

Gadolinium-enhanced CMR was performed with intravenous administration of 0.1mmol/kg Gadolinium-DTPA (diethylenetriamine penta-acetic acid) (Magnevist, Bayer, Whippany, NJ). After ten minutes from the injection, a delayed enhancement image with fat saturation of spectral presaturation with inversion recovery was obtained using a breath-holding, inversion recovery-prepared, three-dimensional turbo field echo pulse sequence with electrocardiogram gating.

Images analysis was performed on Extended MR Work Space ver. 2.6.3 (Philips Medical Systems,

Amsterdam, The Netherlands). Left ventricle (LV) volumes were obtained from LV short axis images configured from coronal and sagittal scout images, and LV endocardial borders of short axis images at end-diastole and end-systole were manually traced to calculate LV ejection fraction (EF) and stroke volume (SV). RV volumes, EF and SV were measured in trans axial orientation, according to the previous studies [15, 16]. Manual contouring of endocardial and epicardial ventricular surfaces were performed for quantification of the volume of LV and RV wall. The interventricular septum was considered as a part of the LV. RV end-diastolic dimension (RVEDD) and RV end-systolic dimension (RVESD) were assessed by measuring the RV end-diastolic and end-systolic basal diameters in trans axial orientation (Figure 1A and B). Aside from ventricular EF, these measurements were indexed for body surface area. Relative area change (RAC) of PA was defined as the following equation: $RAC\ of\ PA = (maximum\ PA\ area - minimum\ PA\ area) / minimum\ PA\ area$ (Figure 1C and D) [17]. The quantitative analysis was performed by NOM. The qualitative analysis for image quality and presence of late gadolinium enhancement was performed by NOM and colleagues. The MRI-readers were blinded to the clinical information and findings from right heart catheterization.

Right heart catheterization and clinical evaluation

RHC was performed using a balloon-tipped 7.0F thermodilution catheter (Becton-Dickinson, Franklin Lakes, NJ), and was usually performed via the internal jugular vein or the femoral vein. To define PAH, the values of mPAP and PAWP were obtained. PVR was determined as follows: $PVR = (mPAP - PAWP) / cardiac\ output\ (CO)$. CO was measured by thermodilution technique. PVR and CO were indexed for body surface area. Equations of other parameters are detailed in Supplementary Table 1.

PA and RV stiffness metrics, and PA-RV coupling measurements

PA stiffness including PA capacitance, distensibility, compliance, elastic modulus and stiffness index β , as well as RV stiffness were calculated from RHC and CMR data [11, 18].

RV elastance (Ees) was calculated as follows: $Ees = mPAP / RVESV$ index (RVESVI). Pulmonary arterial elastance (Ea) was estimated as following equation: $Ea = mPAP - PAWP / SV$ index (SVI). Therefore, the PA-RV coupling metric, Ees/Ea, evaluated by a combined CMR and RHC was defined as follows: $Ees / Ea = (mPAP / RVESVI) / [(mPAP - PAWP) / SVI]$. CMR estimated Ees/Ea (CMR Eea/Ea) was defined as $SV / RVESV$ for simplicity to ignore the effect of downstream pressure in pulmonary circulation [19-21].

The PA stiffness metrics and PA-RV coupling measurements are summarized in Supplementary Table 1.

Echocardiography and pulmonary function test

TTE was performed with commercially available ultrasound systems (Vivid q system, GE Healthcare, Milwaukee, WI, US; Aplio XG SSA-790A or Aplio Artida SSH 880CV, Toshiba Medical Systems, Tochigi, Japan), and images were analysed after the procedure. TTE and PFT methods are detailed in Supplementary material.

Statistical analysis

We used Mann-Whitney U test or Kruskal-Wallis test, and Fisher's exact tests to compare the values of continuous variables with two or more groups, and proportions of categorical variables between the groups, respectively. For multiple comparisons, Steel-Dwass procedure was applied.

We used Wilcoxon rank sum test for paired comparisons of continuous variables assessed at baseline and at follow-up.

Factors related to mortality were assessed using univariate and multivariate Cox proportional logistic regression analysis. For multivariate analysis, a forward stepwise approach was adopted for risk factors significant to mortality at univariate analysis ($p < 0.2$). Because of the relatively few fatal cases due to PH for multivariable modelling, we used propensity score adjustment for each of the above risk factors. Propensity score was created separately for each candidate risk factor, subsequently used as a covariate in the model assessing the adjusted effect of each factor. The details of propensity score calculation is in Supplementary material.

In Receiver operating characteristic (ROC) analysis was performed to evaluate prognostic significance of candidate predictors of mortality with area under the curve (AUC). Kaplan-Meier survival curves were produced to illustrate the prognostic value of CMR measurements using median threshold values. Groups were compared using the log-rank test.

We used JMP® Pro 13 (SAS Institute Inc., Cary, NC, USA) for all analyses. We performed Bonferroni correction on the univariate prognostic candidates ($n = 19$). The variables were considered as statistically significant with p-value less than 0.0026. When the p-value was below 0.05, the results showed statistical significance for all the other analysis. All statistical tests were two-sided.

RESULTS

Patients characteristics

A total of 84 CTD patients who underwent CMR were identified and 65 patients had PH. The median follow-up period of the PH patients was 42 [13-86] months. Of these patients, 54 were classified into PAH and 11 into other forms of PH. Table 1 summarizes the baseline characteristics of all the patients included in the present study and compares patients with PAH, those with PH without PAH, and those without PH. In CMR analysis, the patients with PAH showed significantly higher RVEDVI, RVESVI, and ratio of RV to LV in EDV and ESV, and lower RVEF than those without PH ($p < 0.001$, respectively). The patients in the PAH-group had stiffer PA on the indices of distensibility, compliance and elastic modulus than those in non-PH group ($p < 0.001$, respectively). The PA-RV coupling metric, Ees/Ea ratio, was significantly low in the PAH-patients compared with the non-PH patients ($p < 0.001$).

A total of 15 patients (15/65, 23.1%) died. Of these patients, nine (9/65, 13.8%) died of right heart failure due to PH. Other causes of death included infection (2/65, 3.1%), liver cirrhosis (1/65, 1.5%), respiratory failure due to interstitial lung disease (2/65, 1.5%), and unknown aetiology (1/65, 1.5%). One-year and three-year-cumulative mortality rate due to PH were 4.6% (3/65) and 11% (7/65), respectively.

The Baseline of the patient's characteristics between survivors and non-survivors including demographics, parameters of RHC, those of CMR, and RV-PA coupling metrics are described in Table 2. The duration from PH onset to study entry of initial CMR and the follow-up period from study entry were similar between survivors and non-survivors (35 [9-76] vs 19 [4-40], months, $p = 0.090$). Also, there were no significant differences regarding age at study entry, sex, underlying CTDs, PH classification, mild ILD concomitance and medication. In laboratory findings, the survivors demonstrated significantly lower level of B-type natriuretic peptide (BNP) (52.8

[29.1–260] vs. 624 [134–845], pg/mL, $p = 0.013$) and higher frequency of anti-DNA antibody (20 [36%] vs. 0, $p = 0.049$) compared with the non-survivors. Notably, no parameters of RHC including mPAP and PA stiffness parameters had significant difference between these groups. In the hemodynamic indices evaluated by CMR, the survivors showed lower RVEDDI (25.3 [22.1–28.6] vs. 36.6 [28.3–47.6], mm/m², $p < 0.001$), lower RVESVI (20.1 [18.4–26.7] vs. 30.2 [18.3–36.3], mm/m², $p = 0.008$), lower RVEDV/LVEDV ratio (1.44 [1.21–1.93] vs. 2.38 [1.41–2.81], $p = 0.029$) and lower RVESV/LVESV ratio (2.17 [1.58–3.76] vs. 3.74 [2.60–5.49], $p = 0.029$) than the non-survivors while ventricular end-phase volume index had no significant difference. The survivors demonstrated higher CMR Ees/Ea ratio than the non-survivors (0.80 [0.58–1.07] vs. 0.39 [0.28–0.87], $p = 0.022$). Further classified non-survivors into short (within one year) and long (within three years) term fatalities (Table 2). In the parameters described above, these short-term-fatalities demonstrated higher level of BNP, high RVEDDI, high RVESVI, high RVESV/LVESV ratio and low CMR-derived Ees/Ea.

Analysis of prognostic significance

We next performed univariate Cox proportional hazards regression analysis to confirm the prognostic significance of the factors extracted in the previous analysis (Table 2). Because no event was observed in those with SLE, LHD-PH, CLD-PH and anti-DNA antibody, these items were excluded in univariate and following multivariate analysis. BNP level (Hazard ratio [HR] 1.003, 95% confidence interval [CI] 1.001–1.004, $p = 0.001$) and RVEDDI (HR 1.237, 95%CI 1.131–1.396, $p < 0.001$) significantly predicted mortality at univariate Cox regression analysis after Bonferroni correction. In multivariable logistic regression analyses using propensity score, RVEDDI remained associated with mortality due to PH-CTD (Table 3). Age, SSc and ILD presence, diuretics medication, and the other CMR-derived hemodynamic and RV-PA coupling parameters were not associated with mortality in PH-CTD. At ROC analysis, RVEDDI was highly

predictive of mortality (area under the curve of 0.87) (Figure 2A). Optimal thresholds at ROC analysis were identified for RVEDDI: 32 mm/m² with sensitivity of 67%, specificity of 96%, positive predictive value of 75% and negative predictive value of 95%. Kaplan-Meier survival curves using this optimal threshold of RVEDDI were showed in Figure 2B.

Follow-up of data in the laboratory and hemodynamic parameters

We extracted the follow-up data of laboratory and hemodynamic parameters at half a year to two years after initial CMR conducted (median 7, interquartile range 4-12, months). Although there were a few non-survivors who completed follow-up data collection (n = 4), non-survivors still showed significantly high BNP levels (p = 0.007), RVEDDI (p = 0.003), RVESDI (p = 0.015), RVEDV/LVEDV ratio (p = 0.047) and RVESV/LVESV ratio (p = 0.041) compared with survivors at the follow-up. While non-survivors demonstrated no significant difference of these parameters in the clinical course, BNP levels (p = 0.032), RVEDV/LVEDV ratio (p = 0.047), RVESV/LVESV ratio (p = 0.038) and CMR Ees/Ea ratio (p = 0.010) significantly ameliorated in survivors. The values of RVEDDI in both survivors and non-survivors were not significantly changed in the clinical course (Figure 3).

Subgroup analysis of SSc-associated PAH

Nine non-survivors included six patients (67%) with SSc-associated PAH (SSc-PAH) (p = 0.066). At initial CMR analysis, SSc-PAH patients demonstrated higher RVEDDI (28.5 [25.1–32.2] vs. 23.9 [21.1–27.6], mm/m², p = 0.003), lower Ees (0.59 [0.49–0.72] vs. 0.80 [0.62–1.00], mmHg/mL/mm², p = 0.013), higher FVC/DLco (forced vital capacity / diffusing capacity of carbon-monoxide, 2.57 [1.19–3.40] vs. 1.69 [1.41–2.27], min/mmHg, p = 0.031) than other non-survivors.

DISCUSSION

This study investigated predictive factors of mortality in PH-CTD. The results in multivariate analysis using propensity score demonstrated that RVEDDI evaluated by CMR had the higher predictive value for mortality. On the contrary, other laboratory and hemodynamic parameters including BNP, CMR derived volumetrics and PA-RV couplings had no significant association with mortality.

Previous studies have demonstrated the effectiveness of hemodynamic, morphological and coupling metrics of RV and PA evaluated by CMR and RHC for prognostication in patients with PAH. RV adaptation to the increased pressure overload is closely associated with the survival in patients with PAH. A recent large cohort study based on ASPIRE PH registry showed RVEDVI and proximal PA stiffness had prognostic accuracy in the evaluation of PAH patients [11]. The prognostic value of the measurements including RVEDV, RVEF and Ees/Ea was clarified in retrospective studies [9, 10]. As expected, our study also demonstrated that RV morphological metrics, including RV/LV end-diastolic/systolic volume ratio, and RV functional indices such as Ees/Ea, were significantly predictive for mortality at univariate analyses although PA stiffness indices including PA RAC and PA distensibility had no significant association with prognosis. Notably, our multivariate analysis using propensity score showed that RVEDDI remained as an independently and highly predictive factor for mortality. Furthermore, RVEDDI did not significantly change during 0.5–2 year-follow-up period in both survivors and non-survivors despite treatment with selective PA vasodilators. Our study suggested that RVEDDI, a diameter of the RV basal portion in diastolic phase, would become determined on early phase and be an early predictor of prognosis in patients with PH-CTD.

To date, volumetric markers have been demonstrated superior to diametric markers for the prognosis prediction in PAH. The dimension may not match the full extent of ventricular enlargement, and ventricular size may be underestimated in the diametric assessment compared with volumetric assessment [22, 23]. However, our report showed the superiority of diametrics over volumetrics despite accurate assessment of ventricular diameters and volumes using CMR. The regional heterogeneity of RV remodelling may be associated with diametrical change over volumetric change [24]. In PAH patients, regional heterogeneity of RV dysfunction derived from hypertrophy in the RV outflow tract was reported [25]. While patients with severe RV dysfunction showed a generalized RV hypertrophy, patients with less severe RV dysfunction had the changes in regional structure and function of RV, particularly in the outflow tract, which proceeded overt hemodynamic RV decompensation. A previous study on RV contraction and relaxation demonstrated that the extent of fibre shortening was lesser in infundibulum (the outflow tract) than in sinus, leading to the asymmetrical hypertrophic response of the RV outflow tract to wall pressure stress [26]. A functional analysis of regional variations in curvature in PAH patients using three-dimensional echocardiography revealed that patients with PAH had higher (rounder) curvature in the outflow tract with a more flattened apical wall throughout cardiac cycles than healthy controls [27]. These results were consistent with regional hypertrophic response to increased pressure stress, especially in the outflow tract, in PH patients. RVEDD would reflect the enlargement of RV basal portion affected by the regional wall pressure stress compared with RVEDV. Therefore, it is thus biologically plausible that the increase of RVEDDI correlates with RV dysfunction and the mortality in patients with early phase of PH.

Risk stratification approach using clinical, functional and haemodynamic variables was reported

in patients with PAH [2, 6, 28-30]. However, CMR parameters have even limited evidences for prediction of prognosis in PAH. Several reports demonstrated that RVEF, evaluated by CMR, had a prognostic value and low RVEF was associated with poor survival rate independent from PVR [31, 32]. Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society Guidelines 2015 proposed risk stratification method using right atrial area and the presence of pericardial effusion assessed by TTE or CMR [33]. Therefore, prompt measurement of RVEDDI in patients with PH would be one of the efficient risk stratification strategy, leading to sufficient treatment and improvement of prognosis.

In our subgroup analysis, the patients with SSc-PAH showed higher RVEDDI, lower Ees in comparison with Ea, and higher FVC/DLco than other PH patients. PAH is an independent risk factor for poor prognosis in patients with SSc, and the mortality rate is unacceptably high even in modern era with PAH-specific vasodilator treatment [34, 35]. A meta-analysis including a total of 2244 SSc-PAH patients revealed three-year survival rate of 52 percent [35]. The prognosis of SSc-PAH patients is worse than that of idiopathic PAH patients [36]. Regarding RV function in patients with SSc-PAH, a previous report demonstrated depressed RV contractility without enhanced pulmonary vascular resistive [37]. In addition, RVESVI was identified as a significant predictor of mortality in CTD-PAH [11]. We previously reported that RVEDV/LVEDV ratio evaluated by CMR was significantly higher in SSc-PAH patients than other CTD-PAH patients [38]. Regarding RV dysfunction, our current study demonstrating lower Ees in SSc-PAH patients with poor prognosis is consistent with previous studies. A basic study revealed that myocytes of SSc-PAH had lower calcium-activated force compared with those of idiopathic PAH, leading depressed contractile reserve [39]. Furthermore, myocyte passive stiffness from length-tension relations was increased in SSc-PAH. Therefore, both systolic and diastolic RV pronounced dysfunction would correlate

with unfavourable outcome in SSc-PAH patients.

This is a single centre retrospective study. Although there were a small number of fatal cases, we used propensity score to avoid the decrease of statistical power in multivariate analysis. MRI has limitations such as contraindications in patients with pacemaker, foreign metallic bodies and claustrophobia which may be considered in approximately five percent of PH cases [40]. The cost of MRI is high, and its availability is limited compared with conventional modalities, such as WHO functional class and 6-minute-walk-test. However, considering the high objectivity of CMR, CMR could be useful in the assessment of PH patients. Previously, load independent metrics including Ees and Ea were reported to be superior to load dependent volumetric parameters [41], opposed to our results. Although the number of patients in our analysis was small, validation cohort study is warranted. Prognosis is dependent on the severity of disease at the time of assessment and on response to therapy. Our results indicated that RVEDDI would be determined in early phase of PH-CTD onset from follow-up data, although the number used in this analysis was small. Further evaluation of the value of follow-up CMR in a large cohort study is needed.

In conclusion, we demonstrated that RVEDDI would serve as a simplified but significant predictor of mortality evaluated by CMR in PH-CTD even in the era of volumetrics and coupling metrics. Further validation cohort study using the data from our current study is needed to confirm prognostic factors for patients in PH-CTD.

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TABLE

Table1. Baseline characteristics of the patients

	All patients (n = 84)	PAH (n = 54)	PH without PAH (n = 11)	Control (n = 19)	p value
Demographics					
Age at initial CMR, year	58 [46–68]	56 [45–65]*	61 [49–65]	58 [46–68]	0.030
Sex Female	74 (88%)	51 (94%)	6 (55%)	17 (89%)	0.003
WHO functional class					
I	8 (10%)	4 (7%)	0	4 (21%)	
II	29 (35%)	12 (22%)	5 (45%)	12 (63%)	
III	38 (45%)	31 (57%)	4 (36%)	3 (16%)	
IV	9 (11%)	7 (13%)	2 (18%)	0	
6MWD, meter	315 [211–392]	290 [180–394]	342 [124–446]	348 [224–380]	0.85
CTD					
SSc, diffuse/limited	41 (49%), 16/25	24 (44%), 10/14	4 (36%), 3/1	13 (68%), 3/10	
SLE	15 (18%)	13 (24%)	0	2 (11%)	
SS	24 (29%)	15 (28%)	4 (36%)	5 (26%)	
MCTD	15 (18%)	12 (22%)	0	3 (16%)	
Concomitant mild ILD	46 (56%)	27 (50%)	7 (63%)	12 (63%)	0.55
Medication					
Immunosuppressant	59 (70%)	39 (72%)	12 (73%)	10 (53%)	0.78
ETRA	36 (43%)	31 (57%)	3 (27%)	2 (11%)	0.080
PDE5 Inhibitor	39 (46%)	37 (69%)	2 (18%)	0	<0.001
Prostanoid	31 (37%)	23 (43%)	1 (9%)	7 (37%)	0.074

Diuretics	41 (49%)	30 (54%)	5 (45%)	6 (32%)	0.21
Laboratory data					
BNP, pg/mL	57.7 [28.6–251]	60.4 [28.9–302]	63.4 [44.9–277]	36.8 [15–93.9]	0.119
ANA	81 (96%)	53 (98%)	9 (82%)	19 (100%)	0.074
nucleolar pattern	16 (20%)	8 (15%)	1 (9%)	7 (37%)	0.140
anti-Scl-70	12 (16%)	5 (10%)	2 (18%)	5 (26%)	0.21
ACA	20 (27%)	13 (24%)	0	7 (37%)	0.088
anti-DNA	22 (27%)	18 (33%)	2 (18%)	2 (11%)	0.127
anti-Ro/SSA	27 (34%)	21 (39%)	1 (9%)	5 (26%)	0.131
anti-U1-RNP	34 (41%)	28 (52%)	1 (9%)	5 (26%)	0.013
Echocardiography					
Stroke volume, mL	56.5 [45.4–71.4]	51.2 [43.1–66]	75.5 [42–92.5]	66.5 [53.7–71.9]	0.091
TAPSE, cm	17.0 [15.0–22.2]	16.0 [15.0–21.7]	17.0 [15.5–24.5]	22.5 [13.5–26.8]	0.38
Right heart catheterization					
mPAP, mmHg	29 [21–40]	34 [27–42]*†	26 [21–29]	15 [13–18]	<0.001
PAWP, mmHg	8 [6–10]	8 [6–10]	8 [6–10]	7 [4–8]	0.23
CI, L/min/m ²	2.84 [2.35–3.31]	2.84 [2.37–3.29]	3.24 [2.29–3.85]	2.69 [2.21–3.06]	0.35
PVRI, dyne·sec·cm ⁻⁵ ·m ²	540 [318–924]	674 [492–1022]*	395 [272–728]	275 [183–308]	<0.001
PA capacitance, mL/mmHg	2.30 [1.35–3.16]	1.73 [1.22–2.51]*†	2.93 [1.86–4.91]	3.22 [2.43–4.33]	<0.001
RVED compliance, mL/mmHg	11.7 [8.11–16.7]	11.1 [7.27–15.0]	12.4 [10.1–17.5]	14.7 [10.5–26.8]	0.052
Cardiac magnetic resonance					
Hemodynamic indices					
RVEDVI, mL/m ²	80.6 [63.9–99.0]	91.8 [62.7–104.2]*	92.2 [62.7–134.3]*	58.3 [50.2–66.3]	<0.001
RVESVI, mL/m ²	42.2 [31.5–60.1]	51.6 [37.9–66.0]*	45.1 [36.0–92.4]*	24.0 [18.4–34.8]	<0.001
RVEDDI, mm/m ²	25.5 [23.1–29.1]	25.9 [22.6–29.8]	26.2 [23.8–29.2]	25.9 [23.7–27.2]	0.84
RVESDI, mm/m ²	20.1 [17.0–24.8]	20.4 [18.1–25.9]	22.0 [14.9–22.6]	18.4 [15.5–21.5]	0.086

RVEF, %	46.3 [38.2–52.7]	43.5 [35.8–50.3]*	47.2 [39.5–49.5]*	58.9 [51.1–65.1]	<0.001
LVEDVI, mL/m ²	57.7 [49.4–67.2]	56.4 [46.5–66.5]	57.7 [50.3–72.0]	59.4 [55.6–67.2]	0.31
LVESVI, mL/m ²	20.4 [15.5–29.9]	19.7 [15.3–29.2]	30.5 [17.2–38.7]	18.7 [13.3–27.8]	0.109
LVEF, %	62.9 [58.1–70.8]	63.1 [58.3–71.0]	60.4 [48.2–65.0]	63.0 [56.4–73.8]	0.35
RVEDV/LVEDV	1.35 [1.10–1.86]	1.57 [1.23–2.22]*	1.33 [1.07–2.21]*	1.03 [0.81–1.19]	<0.001
RVESV/LVESV	1.94 [1.36–3.51]	2.54 [1.69–4.13]*	1.83 [1.34–3.72]	1.21 [0.93–1.69]	<0.001
PA stiffness metrics					
PA relative area change	0.34 [0.23–0.47]	0.26 [0.15–0.40]*	0.38 [0.32–0.48]*	0.47 [0.28–0.69]	<0.001
PA distensibility, %/mmHg	1.18 [0.70–2.20]	0.83 [0.43–1.27]*†	1.50 [0.98–2.28]	2.59 [1.85–4.51]	<0.001
PA compliance, mm ² /mmHg	6.62 [3.91–10.4]	5.07 [3.09–8.15]*†	9.65 [5.00–10.5]	10.6 [6.48–16.9]	<0.001
PA elastic modulus, mmHg	84.9 [45.3–143]	121 [78.8–238]*†	66.5 [43.9–101]	38.6 [22.2–54.1]	<0.001
PA stiffness index β	2.83 [2.01–4.57]	3.31 [2.22–7.30]	2.34 [1.75–2.84]	2.60 [1.58–3.49]	0.042
RV–PA coupling metrics					
Ea, mmHg/mL/mm ²	0.51 [0.29–0.93]	0.65 [0.43–1.06]*	0.36 [0.24–0.63]	0.20 [0.16–0.29]	<0.001
Ees, mmHg/mL/mm ²	0.66 [0.48–0.87]	0.67 [0.50–0.89]	0.56 [0.38–0.72]	0.65 [0.44–0.93]	0.28
Ees/Ea ratio	1.40 [0.76–2.13]	1.12 [0.61–1.54]*	1.57 [0.97–2.42]*	3.20 [2.16–4.18]	<0.001
CMR Ees/Ea ratio	0.88 [0.59–1.21]	0.74 [0.50–1.00]*	0.93 [0.51–1.25]*	1.63 [1.05–1.99]	<0.001
Late gadolinium enhancement	52 (68%, n = 76)	36 (75%, n = 48)	8 (80%, n = 10)	8 (44%, n = 18)	0.058
Pulmonary function test					
FVC/DLco	1.78 [1.43–2.61]	2.02 [1.50–2.66]	1.81 [1.57–3.02]	1.45 [1.24–1.94]	0.051

Values are presented as n (%) or median [IQR]

Kruskal-Wallis test was used for comparison of continuous variables. Fisher's exact test compared categorical variables.

Statistically significant by Steel-Dwass test (p value < 0.05), *versus control, or †versus non-PAH

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; CMR, cardiac magnetic resonance; WHO, World Health Organization; 6MWD, 6-minute walk distance; CTD, connective tissue disease; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; ILD, interstitial lung disease; ETRA, endothelin receptor antagonist; PDE5, phosphodiesterase-5; BNP, B-type natriuretic peptide; ANA, antinuclear antibody; ACA, anti-centromere antibody; RNP, ribonucleoprotein; TAPSE, tricuspid annular plane systolic excursion; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVRI, pulmonary vascular resistance index; PA, pulmonary artery; RVED, right ventricular end-diastole; R(L)VEDV(S)I, right(left) ventricular end-diastolic(systolic) volume index; R(L)VED(S)DI, right(left) ventricular end-diastolic(systolic) dimension index; R(L)VEF, right(left) ventricular ejection fraction; Ea, pulmonary arterial elastance; Ees, right ventricular elastance; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide.

Table 2. Demographics and comparison of survivors versus non-survivors with PH-CTD

	All PH-CTD (n = 65)			All non-survivors (n = 9)	
	Survivors (n = 56)	Non-survivors (n = 9)	p value	1-year-fatalities (n = 4)	3-year-fatalities (n = 7)
Demographics					
Age at initial CMR, year	56 [45–65]	60 [56–69]	0.25	59 [49–68]	66 [57–74]
Sex Female	50 (89%)	7 (78%)	0.30	3 (75%)	5 (71%)
Duration from PH onset to study entry, year	0 [0–2]	0 [0–4]	0.87	1 [0–6]	0 [1–7]
Follow-up period from study entry, month	35 [9–76]	19 [4–40]	0.090	4 [1–6]	6 [2–23]
CTD					
SSc	22 (39%)	6 (66%)	0.158	2 (50%)	4 (57%)
SLE	13 (23%)	0	0.185	0	0
SS	18 (33%)	2 (22%)	0.71	0	2 (29%)
MCTD	9 (16%)	2 (22%)	0.64	1 (25%)	1 (14%)
PH classification					
PAH	46 (82%)	8 (89%)	1.0	3 (75%)	6 (86%)
LHD	3 (5%)	0	1.0	0	0
CLD	5 (21%)	0	0.67	0	0
CTEPH	2 (4%)	1 (14%)	0.37	1 (25%)	1 (14%)
Concomitant mild ILD	29 (83%)	6 (67%)	0.49	2 (50%)	4 (57%)
Medication					
Immunosuppressant	43 (77%)	5 (56%)	0.23	3 (75%)	3 (43%)
ETRA	29 (52%)	5 (56%)	1.0	2 (50%)	4 (57%)
PDE5 Inhibitor	33 (59%)	6 (67%)	1.0	2 (50%)	4 (57%)
Prostanoid	19 (34%)	6 (67%)	0.140	2 (50%)	3 (43%)

Diuretics	32 (57%)	3 (33%)	0.28	2 (50%)	3 (43%)
Laboratory data					
BNP, pg/mL	52.8 [29.1-260]	624 [134-845]	0.013	739 [237-862]	669 [175-880]
anti-DNA	20 (36%)	0	0.049	0	0
anti-U1-RNP	24 (44%)	4 (44%)	1.0	1 (25%)	2 (29%)
Right heart catheterization					
mPAP, mmHg	32 [26-42]	37 [29-44]	0.27	35 [25-42]	43 [32-45]
PAWP, mmHg	8 [6-10]	8 [6-11]	0.88	11 [7-15]	9 [8-13]
CI, L/min/m ²	2.93 [2.37-3.37]	2.63 [2.31-2.88]	0.189	2.45 [2.30-2.62]	2.58 [2.29-2.69]
PVRI, dyne·sec·cm ⁻⁵ ·m ²	609 [454-980]	930 [637-1204]	0.140	1000 [390-1273]	1068 [931-1452]
PA capacitance, mL/mmHg	2.01 [1.26-2.81]	1.42 [0.91-20.4]	0.145	1.28 [0.90-2.84]	0.93 [0.89-1.62]
RVED compliance, mL/mmHg	11.5 [8.86-15.6]	7.88 [4.94-20.8]	0.348	5.59 [4.73-8.12]	5.31 [4.58-7.76]
Cardiac magnetic resonance					
Hemodynamic indices					
RVEDVI, mL/m ²	91.7 [76.2-100.7]	131 [72.7-163]	0.197	132 [79.1-272]	131 [64-133]
RVESVI, mL/m ²	25.3 [22.0-30.2]	82.8 [37.5-118]	0.177	90.3 [44.5-202]	82.8 [32.3-93.5]
RVEDDI, mm/m ²	25.3 [22.1-28.6]	36.6 [28.3-47.6]	<0.001	47.6 [29.9-54.0]	38.6 [24.6-49.4]
RVESDI, mm/m ²	20.1 [18.4-26.7]	30.2 [18.3-36.3]	0.008	30.6 [20.7-43.6]	30.2 [22.8-32.0]
RVEF, %	43.5 [36.9-49.8]	45.7 [34.3-50.8]	0.79	42.6 [34.3-50.8]	45.7 [35.6-50.5]
RVEDV/LVEDV	1.44 [1.21-1.93]	2.38 [1.41-2.81]	0.029	2.40 [1.75-4.75]	2.38 [1.46-2.68]
RVESV/LVESV	2.17 [1.58-3.76]	3.74 [2.60-5.49]	0.028	4.27 [3.35-5.83]	3.74 [2.83-4.81]
PA stiffness metrics					
PA relative area change	0.30 [0.23-0.42]	0.23 [0.10-0.41]	0.35	0.33 [0.13-1.12]	0.23 [0.11-0.42]
PA distensibility, %/mmHg	1.07 [0.67-1.52]	0.49 [0.18-1.25]	0.172	0.95 [0.33-6.27]	0.68 [0.19-1.14]
PA compliance, mm ² /mmHg	6.27 [3.47-8.88]	3.80 [1.50-9.30]	0.36	7.60 [2.39-31.8]	3.8 [1.60-10.5]
PA elastic modulus, mmHg	93.6 [65.9-149]	205 [80.6-543]	0.172	110 [31.3-423]	146 [87.5-520]

PA stiffness index β	2.84 [2.07–4.57]	4.59 [2.57–11.6]	0.185	3.11 [1.06–9.60]	3.57 [2.29–11.6]
RV–PA coupling metrics					
Ea, mmHg/mL	0.56 [0.41–1.02]	0.94 [0.53–1.05]	0.39	0.94 [0.40–1.00]	1.03 [0.94–1.17]
Ees, mmHg/mL	0.67 [0.49–0.85]	0.52 [0.27–0.99]	0.33	0.38 [0.16–1.04]	0.52 [0.25–1.22]
Ees/Ea ratio	1.24 [0.72–1.62]	0.91 [0.43–1.42]	0.186	0.80 [0.23–1.25]	0.81 [0.44–1.19]
CMR Ees/Ea ratio	0.80 [0.58–1.07]	0.39 [0.28–0.87]	0.022	0.31 [0.09–0.73]	0.39 [0.28–0.86]

Values are presented as n (%) or median [IQR]

Mann-Whitney U test was used for comparison of continuous variables. Fisher's exact test compared categorical variables.

Abbreviations: CTD, connective tissue disease; PH, pulmonary hypertension; CMR, cardiac magnetic resonance; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; LHD, left heart disease; CLD, chronic lung disease; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; ETRA, endothelin receptor antagonist; PDE5, phosphodiesterase-5; BNP, B-type natriuretic peptide; RNP, ribonucleoprotein; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVRI, pulmonary vascular resistance index; PA, pulmonary artery; RVED, right ventricular end-diastole; R(L)VEDV(S)I, right(left) ventricular end-diastolic(systolic) volume index; R(L)VED(S)DI, right(left) ventricular end-diastolic(systolic) dimension index; R(L)VEF, right(left) ventricular ejection fraction; Ea, pulmonary arterial elastance; Ees, right ventricular elastance

Table 3. Univariate and multivariate Cox proportional hazards regression analysis demonstrating prognostic significance

	Unadjusted hazard ratio	p value	Adjusted hazard ratio	p value
Demographics				
Age at initial CMR, year	1.050 [0.999–1.107]	0.059	1.006 [0.943–1.075]	0.86
Sex Female	0.482 [0.116–3.235]	0.40		
CTD				
SSc	3.857 [1.009–18.39]	0.049	0.488 [0.055–3.545]	0.48
SS	0.617 [0.092–2.560]	0.53		
MCTD	1.367 [0.204–5.670]	0.70		
PH classification				
PAH	1.601 [0.292–29.77]	0.64		
CTEPH	1.956 [0.105–10.72]	0.56		
Concomitant ILD	2.449 [0.639–11.69]	0.194	1.669 [0.350–10.06]	0.53
Medication				
Immunosuppressant	0.463 [0.122–1.874]	0.26		
Selective pulmonary vasodilator	1.663 [0.301–30.99]	0.61		
Diuretics	0.308 [0.065–1.176]	0.085	0.465 [0.087–2.062]	0.32
Laboratory data				
BNP, pg/mL	1.003 [1.001–1.004]	0.001*	1.001 [0.999–1.004]	0.171
Cardiac magnetic resonance				
Hemodynamic indices				
RVEDDI, mm/m ²	1.237 [1.131–1.396]	< 0.001*	1.235 [1.081–1.456]	0.003
RVESDI, mm/m ²	1.139 [1.048–1.234]	0.003	0.917 [0.737–1.161]	0.46
RVEDV/LVEDV	2.271 [1.238–3.826]	0.011	1.329 [0.334–4.166]	0.64
RVESV/LVESV	1.484 [1.043–2.080]	0.030	1.143 [0.613–1.904]	0.64

RV-PA coupling metrics

CMR Ees/Ea ratio

0.082 [0.007–0.697]

0.018

0.578 [0.017–2.749]

0.66

Data in parentheses are 95% confidence intervals. Hazard ratios of continuous variables are per 1-unit increase.

Hazard ratio was derived from multivariable Cox proportional logistic regression analysis. Propensity score was used as an adjustment covariate for each factor separately derived as a function of the other candidate risk factors.

*Significant after Bonferonni correction at univariate analysis.

Abbreviations: CMR, cardiac magnetic resonance; CTD, connective tissue disease; SSc, systemic sclerosis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; BNP, B-type natriuretic peptide; RVED(S)DI, right ventricular end-diastolic(systolic) dimension index; R(L)VEDV(S)I, right(left) ventricular end-diastolic(systolic) volume index; Ea, pulmonary arterial elastance; Ees, right ventricular elastance

FIGURE LEGENDS

Figure 1. Images detailing ventricular dimension and pulmonary artery (PA) relative area change analysis.

Images showing biventricular end-systolic (A) and end-diastolic dimension (B), and PA maximal (C) / minimal (D) size for relative area change of PA. Cine image acquisition parameters: FOV, 380 9380 mm; repeat time/echo time, 2.8/1.38 ms; acquisition matrix, 192×192 pixels; reconstruction matrix, 256×256 pixels; slice thickness, 10 mm; flip angle, 60 deg; and SENSE factor, 2.

Abbreviations: MR, magnetic resonance; RVED(S)D, right ventricular end-diastolic(systolic) dimension

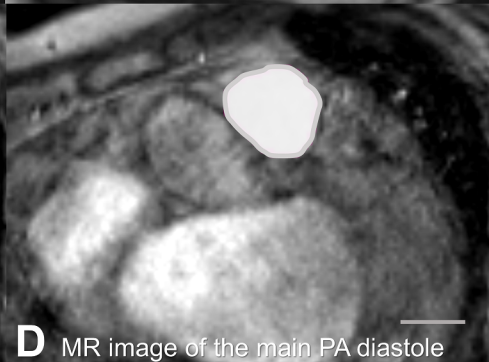
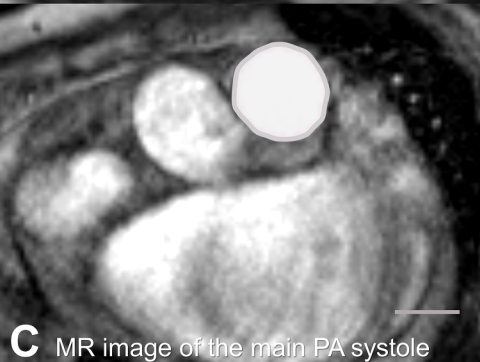
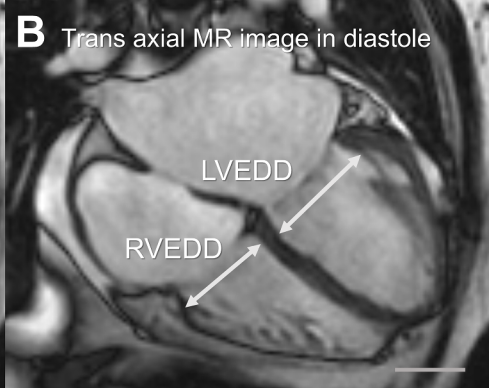
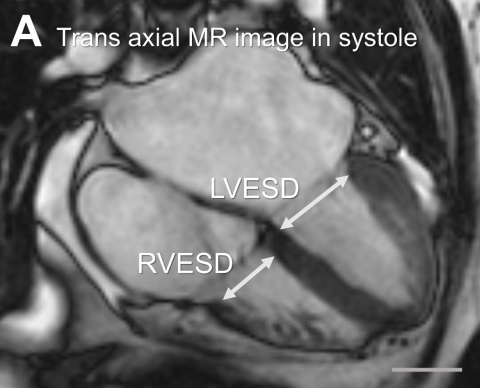
Figure 2. Receiver operating characteristics (ROC) and Kaplan-Meier survival analysis with right ventricular end-diastolic dimension index (RVEDDI)

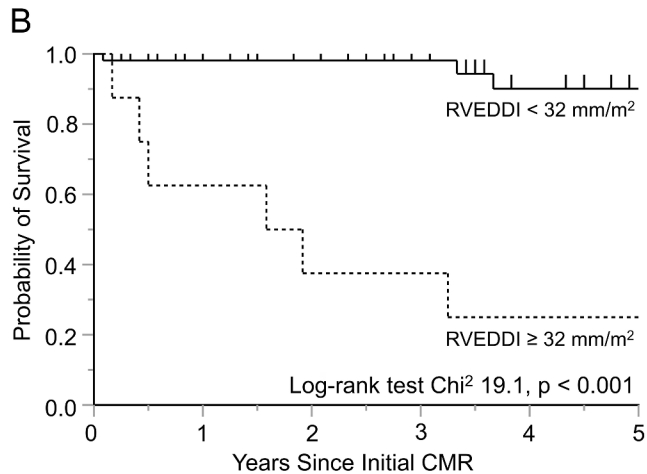
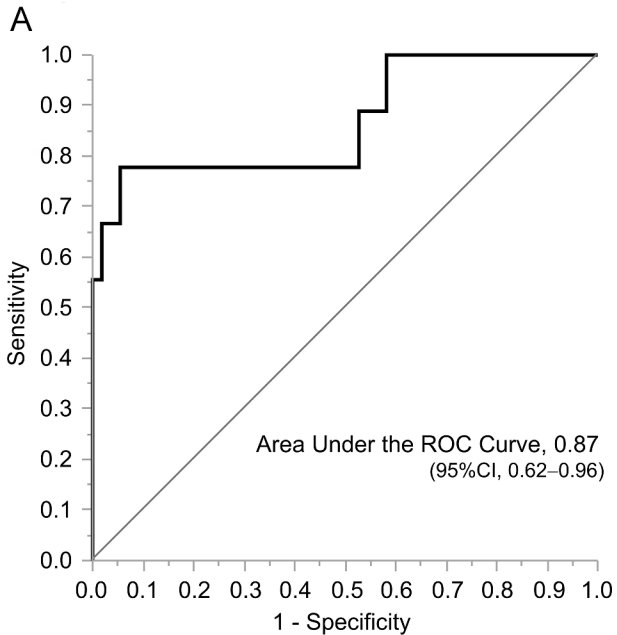
(A) ROC curves of RVEDDI demonstrating predictiveness of mortality in the patients with connective tissue diseases and pulmonary hypertension. (B) Kaplan-Meier survival curves demonstrating the outcome of RVEDDI.

Figure 3. Data at initial cardiac magnetic resonance (CMR) performed and at 0.5-2 years after initial CMR.

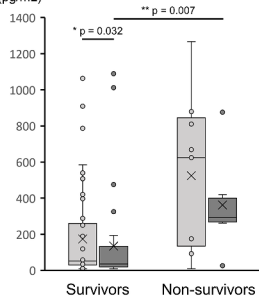
Data of B-type natriuretic peptide (BNP) (A), right ventricular end-diastolic/systolic dimension index (RVEDDI and RVESDI) (B, C), right ventricular end-diastolic/systolic volume (RVEDV and RVESV) / left ventricular end-diastolic/systolic volume (LVEDV and LVESV) ratio (D, E) and CMR derived Ees/Ea (right ventricular elastance/ pulmonary arterial elastance) (F) in survivors and non-survivors are described. Data are median with interquartile range. * $p < 0.05$,

****p < 0.01**, Mann-Whitney U test for unpaired comparisons, Wilcoxon rank sum test for paired comparisons.

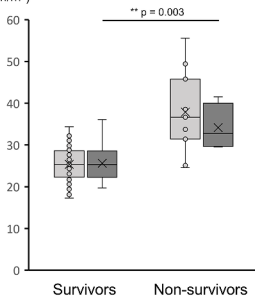




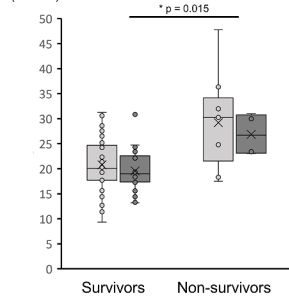
A BNP
(pg/mL)



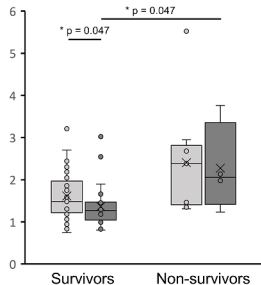
B RVEDDI
(mm/m²)



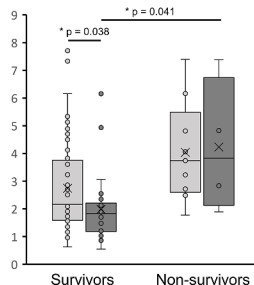
C RVESDI
(mm/m²)



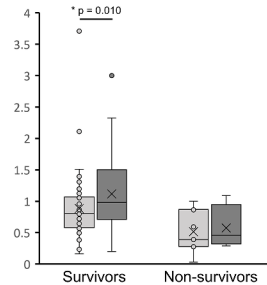
D RVEDV/LVEDV ratio



E RVESV/LVESV ratio



F CMR Ees/Ea ratio



■ Data at initial CMR

■ Data at 0.5-2 years after initial CMR