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Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease

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Right Ventricular Myocardial Work Characterization in Patients With Pulmonary Hypertension and Relation to Invasive Hemodynamic Parameters and Outcomes

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ABSTRACT

Noninvasive evaluation of indexes of right ventricular (RV) myocardial work (RVMW) derived from RV pressure-strain loops may provide novel insights into RV function in precapillary pulmonary hypertension. This study was designed to evaluate the association between the indexes of RVMW and invasive parameters of right heart catheterization and all-cause mortality. Noninvasive analysis of RVMW was completed in 51 patients (mean age 58.1 ± 12.7 years, 31% men) with group I or group IV pulmonary hypertension. RV global work index (RVGWI), RV global constructive work (RVGCW), RV global wasted work (RVGWW), and RV global work efficiency (RVGWE) were compared with parameters derived invasively during right heart catheterization. Patients were followed-up for the occurrence of all-cause death. The median RVGWI, RVGCW, RVGWW, and RVGWE were 620 mmHg%, 830 mmHg%, 105 mmHg% and 87%, respectively. Compared with conventional echocardiographic parameters of RV systolic function, RVGCW and RVGWI correlated more closely with invasively derived RV stroke work index ($R = 0.63$, $p < 0.001$ and $R = 0.60$, $p < 0.001$, respectively). Invasively derived pulmonary vascular resistance correlated with RVGWW ($R = 0.63$, $p < 0.001$), RVGWE ($R = 0.48$, $p < 0.001$), and RV global longitudinal strain ($R = 0.58$, $p < 0.001$). RVGCW (hazard ratio 1.42 per 100 mmHg% < 900 mmHg%, 95% confidence interval 1.12 to 1.81, $p = 0.004$) and RVGWI (hazard ratio 1.46 per 100 mmHg% < 650 mmHg%, 95% confidence interval 1.09 to 1.94, $p = 0.010$) were significantly associated with all-cause mortality, whereas RV global longitudinal strain, RVGWE, and RVGWW were not. In conclusion, indexes of RVMW were more closely correlated with invasively derived RV stroke work index and peripheral vascular resistance than conventional echocardiographic parameters of RV systolic function. Decreased values of RVGCW and RVGWI were associated with all-cause mortality, whereas conventional echocardiographic parameters of RV function were not.

INTRODUCTION

A recently developed echocardiographic method of evaluating left ventricular (LV)¹ myocardial work to provide an estimate of right ventricular (RV) myocardial work,² using noninvasively derived pressure-strain loops, provides a quantitative estimate of ventricular deformation that accounts for afterload, dyssynchrony, and postsystolic shortening. The quantitative integration of these important components of RV function may provide the clinician a more comprehensive evaluation of the status of the right ventricle than standard echocardiographic evaluation of RV function. However, this novel method has not been investigated in patients with precapillary pulmonary hypertension. Therefore, this study was designed to (1) evaluate the association between the novel indexes of RV myocardial work and the invasively derived parameters and (2) to evaluate the association of RV myocardial work parameters with all-cause mortality in patients with precapillary pulmonary hypertension.

METHODS

Between January 2016 and March 2020, patients with pulmonary arterial hypertension (group I) or chronic thromboembolic pulmonary hypertension (group IV) who underwent right heart catheterization (RHC) at the AHEPA University General Hospital (Thessaloniki, Greece) were identified. Patients who underwent echocardiography within 6 weeks of the RHC were included for further evaluation. Diagnostic confirmation of group I or group IV pulmonary hypertension was performed according to the European Society of Cardiology guidelines on pulmonary hypertension, including RHC (pulmonary hypertension was defined by a mean pulmonary artery pressure [mPAP] ≥ 25 mmHg), nuclear ventilation/perfusion scan, pulmonary function tests, and the diffusing capacity of the lung for carbon monoxide.³ Patients with pulmonary hypertension because of left heart disease (group II, $n = 7$) or because of lung diseases and/or chronic hypoxia (group III, $n = 4$) and patients with an echocardiogram performed outside the specified time window ($n = 2$) or where RV myocardial work could not be analyzed ($n = 6$) were excluded. Because this study was designed to evaluate the effect of isolated elevated pulmonary pressure on RV work and invasive hemodynamics, patients with group II pulmonary hypertension were excluded. Additionally, patients with group III pulmonary hypertension were excluded because of the important association between hyperinflation, impaired LV filling, and reductions in stroke volume.⁴

Additionally, to create a control group with no structural cardiac disease to compare values of RV myocardial work with invasive hemodynamics, patients with systemic sclerosis referred for RHC at Leiden University Medical Center with normal diastolic function,⁵

normal systolic function (LV ejection fraction $\geq 50\%$), no significant ($\geq$ moderate) valvular heart disease, and with an mPAP < 25 mmHg on RHC were selected. Demographic and clinical data were prospectively collected. Due to the retrospective study design, the institutional review boards of AHEPA University General Hospital and Leiden University Medical Center waived the need for written informed consent.

All RHC procedures were performed by an experienced interventional cardiologist. A 7.5 French triple lumen Swan Ganz CCOMbo V thermodilution catheter (Edwards Lifesciences) was inserted by way of an 8 French introducer sheath through the right femoral or internal jugular vein under fluoroscopic guidance. Right atrial pressure, pulmonary artery wedge pressure, mPAP, systolic pulmonary artery pressure, and diastolic pulmonary artery pressure were obtained at end-expiration. Cardiac output was determined by thermodilution, according to guideline recommendations.³ Stroke volume was calculated by dividing cardiac output by heart rate, whereas cardiac index and stroke volume index were calculated by indexing cardiac output and stroke volume by body surface area. RV stroke work index was calculated using the following equation⁶: stroke volume index $\times$ (mPAP right atrial pressure) $\times 0.0136$. Peripheral vascular resistance (PVR) was calculated as⁷: (mPAP – pulmonary artery wedge pressure)/cardiac output. Transthoracic echocardiography was performed with a Vivid 7, E9 or E95 ultrasound system (General Electric Vingmed Ultrasound, Milwaukee, Wisconsin) equipped with a 3.5-MHz or M5S transducer, with patients at rest in the left lateral decubitus position. Electrocardiogram-triggered echocardiographic data were stored offline in a cine loop format for analysis with EchoPac software (EchoPac 204, General Electric Vingmed Ultrasound). LV ejection fraction, LV end-diastolic, and LV end-systolic volumes were calculated using the biplane Simpson method, with LV mass calculated using a linear 2-dimensional approach.⁸ Tricuspid annular plane systolic excursion (TAPSE) was derived from M-mode recordings of the lateral tricuspid annulus in an RV-focused apical view according to guideline recommendations.⁸ RV end-systolic and end-diastolic areas were measured in an RV-focused apical view, whereas RV fractional area change (FAC) was calculated with the following equation: $[(RV \text{ end-diastolic area} - RV \text{ end-systolic area}) / RV \text{ end-diastolic area}] \times 100$. Pulmonary artery systolic pressure (PASP) was estimated from the tricuspid regurgitation jet peak velocity using the modified Bernoulli equation ($PASP = 4 \times [\text{tricuspid regurgitation jet velocity}]^2 + \text{estimated right atrial pressure}$). Estimated right atrial pressure was calculated on the basis of the evaluation of the inferior vena cava diameter and its collapsibility.⁹ All other standard measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.⁸

The quantification of parameters of RV myocardial work was performed using proprietary software (Echo-PAC version 204, GE Healthcare, Horten, Norway), which was originally developed for the assessment of LV myocardial work by 2-dimensional speck-

le-tracking echocardiography,¹ adapted for RV work analysis, as previously described.² Initially, an RV-focused apical 4-chamber view was used to derive RV global longitudinal strain (RVGLS) (including the regions of the RV free wall and interventricular septum) (Figure 1). Pulsed-wave Doppler was used to define the pulmonary valve opening and closure timings, whereas event timings of the tricuspid valve were derived from direct visualization of the valve leaflets on an RV-focused apical 4-chamber view. Subsequently, RVGLS and pulmonary arterial pressures were synchronized by valvular event timings, producing pressure-strain loops of the right ventricle. RV myocardial work was then calculated by integrating the product of the rate of segmental shortening and instantaneous RV pressure overtime to obtain myocardial work as a function of time during isovolumic contraction, ejection, and isovolumic relaxation. A total of 4 parameters of RV function were then derived from the analysis of the RV pressure-strain loops: (1) RV global work index (RVGWI), derived from the area within the global RV pressure-strain loop; (2) RV global constructive work (RVGCW), equal to the work contributing to myocardial shortening during systole and lengthening during isovolumic relaxation; (3) RV global wasted work (RVGWW), equal to the work contributing to myocardial lengthening during systole and shortening during isovolumic relaxation; and (4) RV global work efficiency (RVGWE), calculated by the following formula: $(RVGCW/[RVGCW + RVGWW]) \times 100\%$.

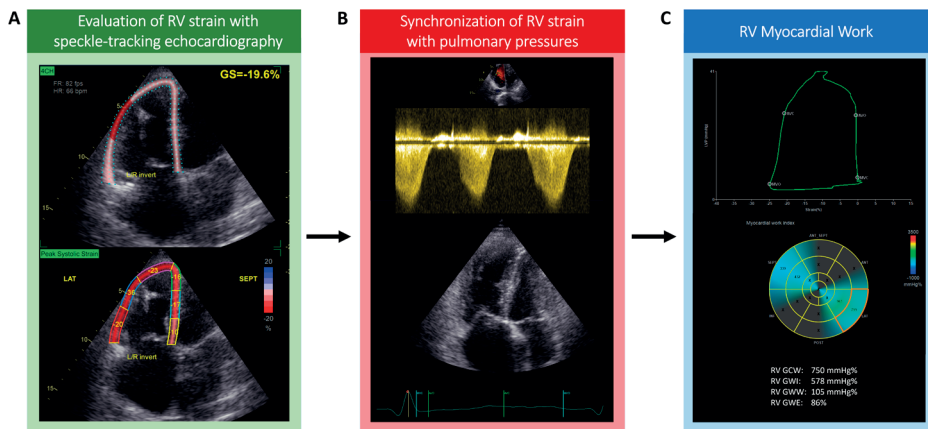


Figure 1: Method of acquisition of RV myocardial work parameters. RV myocardial work incorporates speckle-tracking echocardiography derived RV strain, pulmonary pressures, and cardiac valve opening and closure events to generate non-invasive pressure-strain loops of the right ventricle. Panel A depicts the acquisition of RV global longitudinal strain utilizing speckle-tracking echocardiography. The upper image in Panel B demonstrates an image used for the estimation of PASP from the TR jet peak velocity using the modified Bernoulli's equation. The lower image in Panel B demonstrates the synchronization of cardiac valvular event timings, performed through either direct visualization of the two-dimensional image presented, or using event timings established by pulsed-wave Doppler interrogation. Panel C demonstrates the non-invasive estimation of RV myocardial work indexes and a pressure-strain loop of the basal segment of the free wall of the right ventricle. TR = tricuspid regurgitation.

The primary end point of the study was all-cause mortality at follow-up. Mortality data were complete for all patients. Follow-up began from the date of echocardiography and data for all patients were included up to the last date of follow-up.

Statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Adherence to normality was verified through visual assessment of histograms of the sample data. Normally distributed continuous variables are presented as mean $\pm$ SD, whereas non-Gaussian variables are presented as median and interquartile range. Categorical variables are expressed as numbers and percentages. Spearman correlation was used to evaluate the association between prespecified invasive RHC (RV stroke work index, stroke volume index, and PVR) and echocardiographic variables (including indexes of RV myocardial work, standard parameters of RV systolic function, and PASP). Additionally, to evaluate the difference in the estimation of RV myocardial work indexes with invasively derived pulmonary pressures versus echocardiographically derived pulmonary pressures, intraclass correlation (ICC) coefficients were calculated. All analyses were performed only in patients in whom RV myocardial work analysis was feasible. For the evaluation of the end point of all-cause mortality, restricted cubic spline curve analysis was used to investigate the hazard ratio (HR) change for all-cause mortality across a range of values of RV myocardial work parameters. Likelihood ratio tests were used to determine the significance of nonlinearity. A threshold of RVGCW and RVGWI to dichotomize the population for Kaplan–Meier analysis was estimated using the fitted spline curves. Cumulative survival rates were calculated using the Kaplan–Meier method and the log-rank test was used to compare groups. The association of clinical, RHC, and echocardiographic variables with all-cause mortality was investigated by univariable Cox proportional hazards regression models. To optimize the balance between bias and variance while accounting for nonlinearity, RVGCW and RVGWI were refitted in the Cox proportional hazards regression models with linear spline terms, reducing variance and minimizing model overfitting.¹⁰ The proportional hazards assumption was verified through the assessment of scaled Schoenfeld residuals. The HR and 95% confidence intervals (CIs) were calculated and reported for each variable. To examine the reproducibility of indexes of RV myocardial work, 10 individuals were randomly selected for the evaluation of intra- and interobserver agreement using ICCs. The second observer was blinded to the measurements of the first observer for interobserver measurements. All tests were 2-sided and $p < 0.05$ were considered statistically significant.

RESULTS

A total of 57 patients (mean age 58 ± 13 years, 31% men) fulfilled the study inclusion criteria, with RV myocardial work analysis feasible in 51 patients. The median time between echocardiogram and RHC was 1 (0 to 10) day. A total of 21 patients with systemic sclerosis and without structural cardiac disease were included to facilitate comparison with the precapillary pulmonary hypertension group. A summary of clinical and RHC characteristics of both groups are presented in Table 1.

Table 1: Clinical and right heart catheterization characteristics

Variable	Overall (N = 72)	Pre-Capillary Pulmonary Hypertension (N = 51)	No Structural Cardiac Disease (N = 21)	P-value
Age (years)	56 (± 13)	58 (± 13)	49 (± 10)	0.003
Men	27 (38%)	16 (31%)	11 (52%)	0.094
Systolic blood pressure (mmHg)	124 (20)	126 (21)	116 (16)	0.044
PDE-5 inhibitor	18 (25%)	18 (35%)	0 (0%)	0.002
Endothelin receptor antagonist	17 (24%)	17 (33%)	0 (0%)	0.002
Guanylate cyclase stimulator	7 (9.9%)	7 (14%)	0 (0%)	0.18
Prostacyclin	3 (4.2%)	3 (5.9%)	0 (0%)	0.55
Right atrial pressure (mmHg)	7 (4 to 9)	7 (5 to 10)	6 (4 to 7)	0.033
sPAP (mmHg)	56 (± 25)	67 (± 20)	28 (± 5)	<0.001
dPAP (mmHg)	20 (13 to 27)	23 (18 to 30)	11 (9 to 13)	<0.001
mPAP (mmHg)	34 (20 to 45)	41 (34 to 48)	16 (14 to 19)	<0.001
Stroke volume index (ml/m ²)	38 (± 11)	38 (± 12)	40 (± 7)	0.34
Cardiac index (L/min/m ²)	2.95 (± 0.90)	2.92 (± 1.00)	3.02 (± 0.63)	0.62
RV stroke work index (ml.mmHg/m ²)	12 (7 to 17)	16 (12 to 20)	6 (5 to 7)	<0.001
PVR (WU)	4.1 (2.0 to 6.8)	5.4 (4.0 to 8.2)	1.5 (1.0 to 1.8)	<0.001
PAWP (mmHg)	10 (8 to 12)	10 (8 to 12)	9 (6 to 11)	0.089

Values are presented as mean $\pm$ SD, median (IQR) or n (%).

dPAP = Diastolic pulmonary artery pressure, mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure, PDE5 = phosphodiesterase type 5 inhibitor; PVR = peripheral vascular resistance; sPAP = Systolic pulmonary artery pressure; WU = Wood units

Table 2 provides a summary of the echocardiographic characteristics of the study population. Conventional parameters of RV systolic function were decreased, with a mean RVFAC of $30 \pm 11\%$ and mean RVGLS of $-15.5 \pm 5.5\%$. Median RVGWI, RVGCW, and RVGWW were 620 (446 to 848) mmHg%, 830 (660 to 1,201) mmHg%, and 105 (56 to 166) mmHg%, respectively; whereas median RVGWE was 87 (82 to 93)%. The ICCs for intraobserver variability were 0.96 for RVGWI, 0.92 for RVGCW, and 0.90 for RVGWE demonstrating excellent reliability (Supplementary Table S1). The ICC for intraobserver

variability for RVGWW was 0.78, signifying good reliability. Similarly, the ICCs for interobserver variability were 0.97 for RVGWI and 0.97 for RVGCW, indicating excellent agreement, whereas the interobserver variability was 0.87 for RVGWE and 0.76 for RVGWW, indicating good reliability (Supplementary Table S1).

Table 2: Echocardiographic characteristics

Variable	Overall (N = 72)	Pre-Capillary Pulmonary Hypertension (N = 51)	No Structural Cardiac Disease (N = 21)	P-value
RV basal diameter (mm)	44 (±10)	46 (±10)	39 (±7)	<0.001
RV mid-diameter (mm)	36 (±11)	39 (±10)	27 (±7)	<0.001
Tricuspid annulus diameter (mm)	32.7 (±6.3)	32.3 (±6.6)	33.7 (±5.6)	0.39
Moderate or severe tricuspid regurgitation	7 (9.7%)	7 (14%)	0 (0%)	0.10
Right atrial volume index (ml/m²)	32 (21 to 44)	37 (26 to 49)	23 (18 to 33)	0.001
RV end-diastolic area (cm²)	26 (20 to 31)	30 (22 to 36)	21 (15 to 24)	<0.001
RV FAC (%)	36 (±14)	30 (±11)	51 (±7)	<0.001
TAPSE (mm)	20.3 (±4.4)	19.2 (±4.4)	22.8 (±3.1)	<0.001
RV GLS (%)	-17.0 (±5.4)	-15.5 (±5.5)	-20.7 (±2.8)	<0.001
RV FWLS (%)	-20 (±7)	-18 (±7)	-24 (±4)	<0.001
PASP (mmHg)	48 (39 to 74)	65 (47 to 81)	29 (25 to 39)	<0.001
Right ventricular global work index (RV GWI) (mmHg%)	564 (442 to 691)	620 (446 to 848)	544 (403 to 591)	0.047
Right ventricular global constructive work (RV GCW) (mmHg%)	708 (592 to 998)	830 (660 to 1,201)	588 (489 to 651)	<0.001
Right ventricular global wasted work (RV GWW) (mmHg%)	68 (38 to 134)	105 (56 to 166)	38 (21 to 51)	<0.001
Right ventricular global work efficiency (RV GWE) (%)	90 (85 to 94)	87 (82 to 93)	93 (91 to 96)	0.001
LV mass index (g/m²)	77 (±22)	77 (±23)	77 (±18)	0.88
LV end-diastolic volume (ml)	99 (±33)	96 (±34)	104 (±30)	0.34
LV end-systolic volume (ml)	38 (27 to 50)	39 (28 to 55)	34 (26 to 47)	0.45
LV ejection fraction (%)	63 (55 to 68)	60 (53 to 65)	66 (62 to 70)	0.006
Left atrial volume index (ml/m²)	32 (21 to 38)	29 (21 to 38)	35 (25 to 38)	0.57

Values are presented as mean±SD, median (IQR) or n (%).

LV = Left ventricular; LVEF = Left ventricular ejection fraction; PASP = Pulmonary artery systolic pressure; RV = right ventricular; RV FAC = right ventricular fractional area change; RV FWLS = Right ventricular free wall longitudinal strain; RV GLS = Right ventricular global longitudinal strain; TAPSE = Tricuspid annular plane systolic excursion

Compared with PASP and conventional echocardiographic parameters of RV systolic function (including RVGLS, TAPSE, and RVFAC), RVGCW and RVGWI correlated more closely with invasively derived RV stroke work index ($R = 0.63$, $p < 0.001$ and $R = 0.60$, $p < 0.001$, respectively) (Figure 2, Figure S1). In contrast, RVGLS ($R = 0.57$, $p < 0.001$) cor-

related more closely with invasively derived stroke volume index than RVGCW, RVGWI and RVGWE ($R = 0.34$, $p = 0.016$, $R = 0.48$, $p < 0.001$ and $R = 0.47$, $p < 0.001$, respectively) (Figure 3). Invasively derived PVR correlated with RVGWW ($R = 0.63$, $p < 0.001$), RVGWE ($R = 0.48$, $p < 0.001$), RVGLS ($R = 0.58$, $p < 0.001$), and PASP ($R = 0.66$, $p < 0.001$) (Figure 4). Moreover, similar correlations were observed in the patient cohort without structural cardiac disease: RVGCW and RVGWI demonstrated an association with RV stroke work index ($R = 0.62$, $p = 0.003$ and $R = 0.48$, $p = 0.028$, respectively), RVGLS showed an association with invasively derived stroke volume index ($R = 0.49$, $p = 0.023$), and RVGWW was correlated with invasively derived PVR ($R = 0.51$, $p = 0.017$).

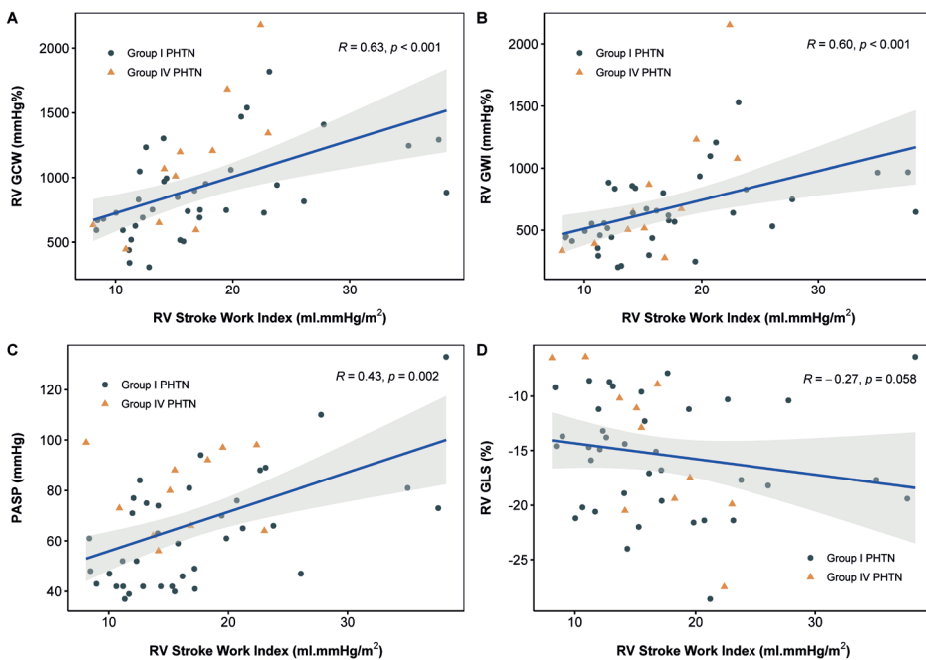


Figure 2: Correlation between invasively derived right ventricular stroke work index and echocardiographic parameters. RV stroke work index assessed with right heart catheterization demonstrated a significant association with RVGCW (A), RVGWI (B) and PASP (C). The association between RVGLS and RV stroke work index was not significant (D). PHTN = pulmonary hypertension.

Over a median follow-up of 35 (interquartile range 25 to 45) months, a total of 17 patients (33%) died. Spline curve analyses showed significant increases in the hazard for all-cause mortality with progressively lower values of RVGCW (Figure 5) and RVGWI (Figure 5), although not for RVGWE, RVGWW, or RVGLS (Supplementary Figure 2). Likelihood ratio tests demonstrated that there was significant nonlinearity for RVGCW ($p = 0.031$) and RVGWI ($p = 0.043$), with an increasing hazard for mortality, evident from values of <900 mmHg% for RVGCW and for values of <700 mmHg% for RVGWI. To dichotomize

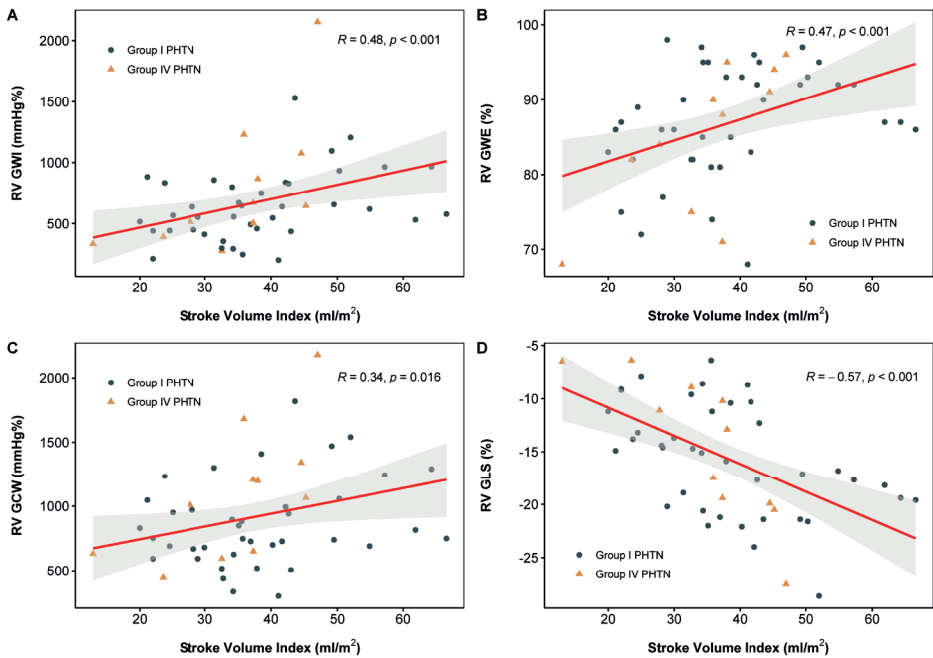


Figure 3: Correlation between invasively derived stroke volume index and echocardiographic parameters. Stroke volume index assessed with right heart catheterization demonstrated a significant association with RVGWI (A), RVGWE (B), RVGCW (C) and RVGLS (D). PHTN=pulmonary hypertension.

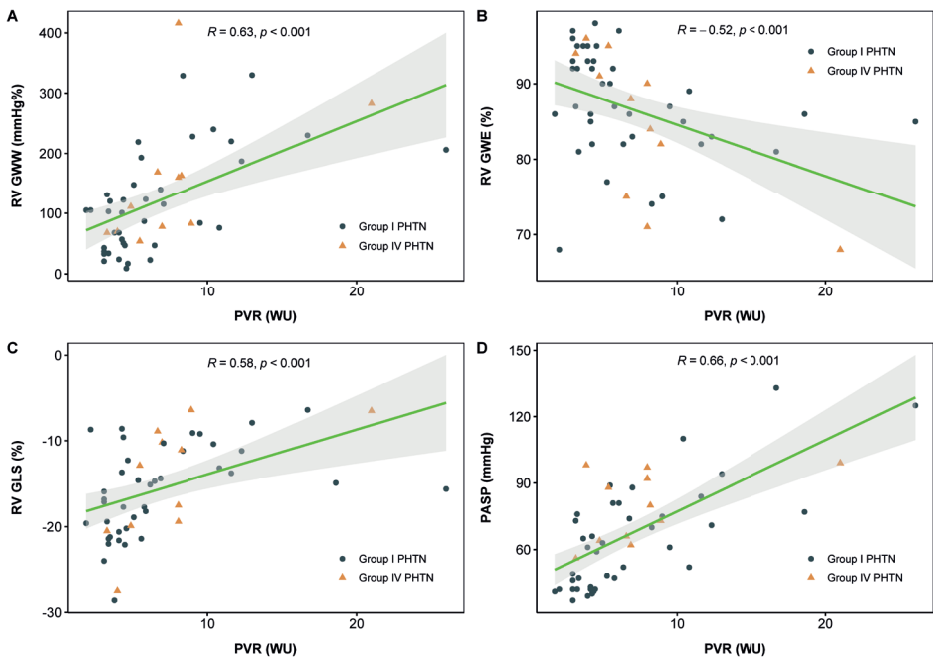


Figure 4: Correlation between invasively derived PVR and echocardiographic parameters. PVR assessed with right heart catheterization demonstrated a significant association with RVGWW (A), RVGWE (B), RVGLS (C) and PASP (D). PHTN = pulmonary hypertension.

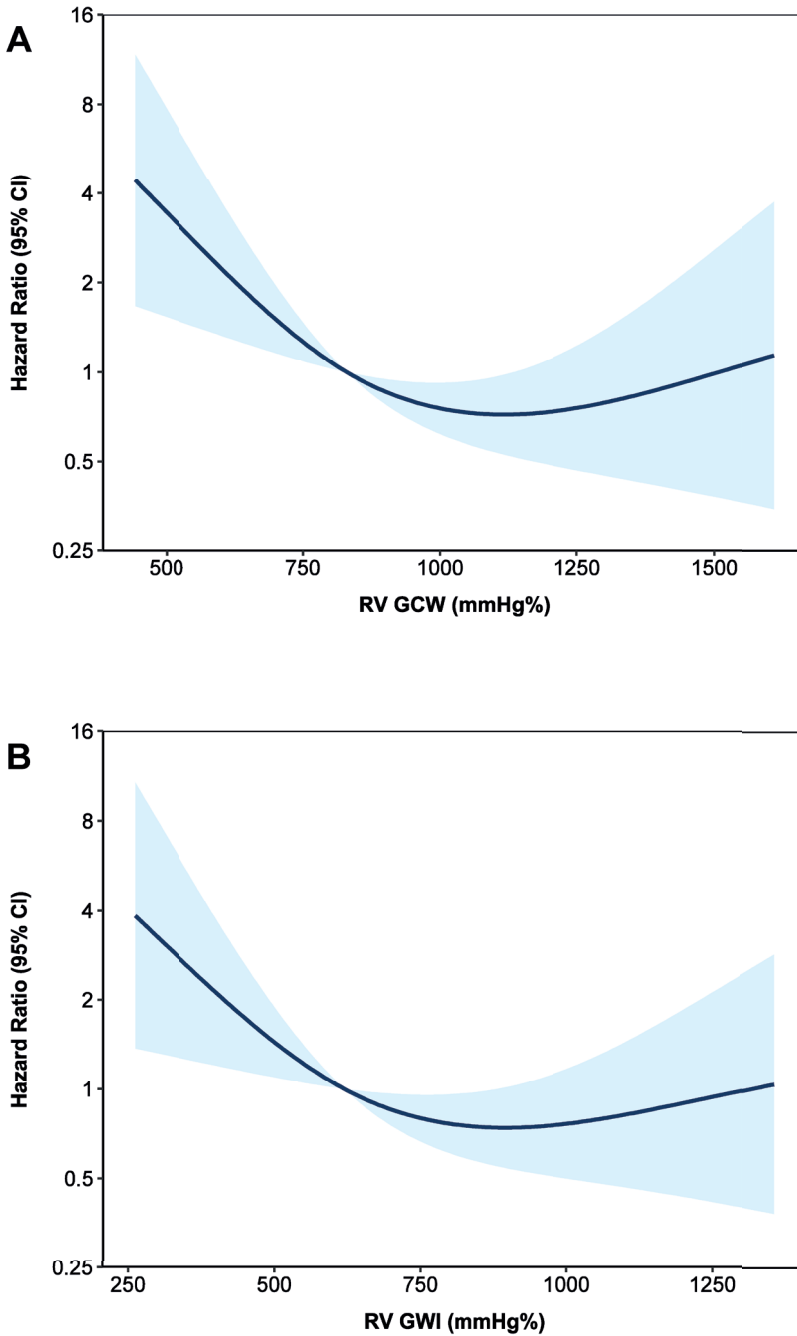


Figure 5: Spline curves demonstrating the hazard ratio for all-cause mortality according to RVGCW (A) and RVGWI (B). The curves in (A) and (B) demonstrate the hazard ratio change for all-cause mortality with 95% confidence intervals (blue shaded areas) in patients with precapillary pulmonary hypertension, across a range of values of RVGCW (A) and RVGWI (B) at the time of echocardiography.

the population for Kaplan–Meier analyses, cut-offs of 550 mmHg% for RVGCW and 500 mmHg% for RVGWI were estimated from the respective spline curves. Kaplan–Meier analysis demonstrated significantly worse survival for patients with RVGCW <550 mmHg% than patients with an RVGCW ≥550 mmHg% (96% and 64% vs 71% and 14%, at 1 and 5 years of follow-up, respectively, $p = 0.0007$; Figure 6). Additionally, patients with an RVGWI <500 mmHg% had significantly worse estimated survival than those with

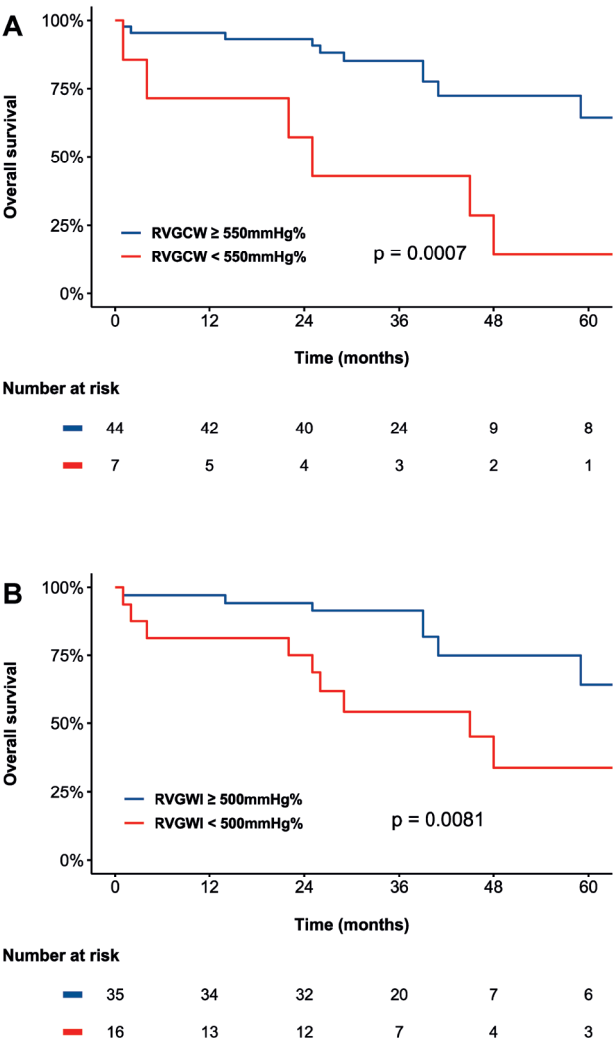


Figure 6: Kaplan–Meier curves for all-cause mortality for RV myocardial work parameters for patients with precapillary pulmonary hypertension. Panel A demonstrates the Kaplan–Meier curve for RVGCW of 550 mm Hg%, while Panel B shows the Kaplan–Meier curve for RVGWI at a cut-off of 500 mmHg%.

an RVGWI ≥ 500 mmHg% (97% and 64% vs 81% and 34%, at 1 and 5 years of follow-up, respectively, $p = 0.008$; Figure 6). Univariable Cox regression analysis demonstrated an association between all-cause mortality and RVGCW (HR 1.42 per 100 mmHg% < 900 mmHg%, 95% 1.12 to 1.81, $p = 0.004$) and all-cause mortality and RVGWI (HR 1.46 per 100 mmHg% < 650 mmHg%, 95% CI 1.09 to 1.94, $p = 0.010$). Additionally, an association was observed between age, RV stroke work index, and all-cause mortality. However, no association was observed between RVGLS, RVFAC, TAPSE, PASP, PVR, RVGWE, or RVGWW and all-cause mortality (Table 3).

Table 3: Univariable Cox Regression for Association with All-Cause Mortality

Variable	HR (95% CI)	P-value
Age (per year)	1.05 (1.00 to 1.10)	0.045
PDE-5 inhibitor	0.73 (0.25 to 2.10)	0.55
Endothelin receptor antagonist	0.83 (0.30 to 2.30)	0.72
Guanylate cyclase stimulator	0.61 (0.14 to 2.72)	0.52
Right atrial pressure (per mmHg)	0.88 (0.74 to 1.06)	0.18
sPAP (per mmHg)	0.98 (0.95 to 1.01)	0.11
mPAP (per mmHg)	0.95 (0.90 to 1.00)	0.064
Stroke volume index (per ml/m ²)	0.97 (0.92 to 1.02)	0.19
RV stroke work index (per ml.mmHg/m ²)	0.89 (0.80 to 0.99)	0.038
PVR (per WU)	0.93 (0.83 to 1.05)	0.26
PAWP (per mmHg)	0.90 (0.74 to 1.10)	0.30
$\geq$ Moderate tricuspid regurgitation	0.26 (0.03 to 2.14)	0.21
Right atrial volume index (per ml/m ²)	0.99 (0.98 to 1.01)	0.59
RV end-diastolic area (per cm ²)	1.03 (0.98 to 1.09)	0.19
RV FAC (per %)	0.98 (0.94 to 1.03)	0.45
TAPSE (per mm)	1.03 (0.92 to 1.16)	0.56
RV GLS (per %)	1.07 (0.98 to 1.17)	0.13
PASP (per mmHg)	0.99 (0.97 to 1.01)	0.21
LV ejection fraction (per %)	0.99 (0.95 to 1.04)	0.78
Left atrial volume index (per ml/m ²)	1.01 (0.97 to 1.05)	0.77
Right ventricular global work index (RV GWI) (per 100mmHg% below 650mmHg%)	1.46 (1.09 to 1.94)	0.010
Right ventricular global constructive work (RV GCW) (per 100mmHg% below 900mmHg%)	1.42 (1.12 to 1.81)	0.004
Right ventricular global wasted work (RV GWW) (per mmHg%)	1.00 (0.99 to 1.00)	0.18
Right ventricular global work efficiency (RV GWE) (per %)	1.00 (0.95 to 1.07)	0.88

CI = Confidence Interval; HR = Hazard Ratio; LV = Left ventricular; LVEF = Left ventricular ejection fraction; mPAP = Mean pulmonary artery pressure; PASP = Pulmonary artery systolic pressure; PAWP = Pulmonary artery wedge pressure; PDE5 = phosphodiesterase type 5 inhibitor; PVR = peripheral vascular resistance; RV = right ventricular; RV FAC = right ventricular fractional area change; RV GLS = Right ventricular global longitudinal strain; sPAP = Systolic pulmonary artery pressure; TAPSE = Tricuspid annular plane systolic excursion; WU = Wood units

DISCUSSION

RV performance is a major determinant of prognosis in patients with precapillary pulmonary hypertension and may be evaluated with invasive techniques, including RHC or non-invasive methods, such as echocardiography or cardiac magnetic resonance.¹¹ Current guidelines state that RHC is the gold standard for the evaluation and diagnosis of group I and group IV pulmonary hypertension.^{3,12} PVR and mPAP provide an evaluation of RV afterload and stroke volume index provides an indirect estimate of RV contractility, whereas RV stroke work index estimates RV workload through the incorporation of both RV function and hemodynamics.¹³ However, because of cost, training requirements, and associated risks, there is a driving interest in the development of non-invasive alternatives for the serial monitoring and assessment of RV performance in pulmonary hypertension.¹⁴ Although conventional echocardiographic parameters of RV function have been demonstrated to be prognostically important in precapillary pulmonary hypertension¹⁵ they reflect the interaction between pulmonary vascular load and the contractility of the right ventricle, providing a significantly afterload dependent evaluation of RV performance.¹⁶ Indeed, because right heart failure is often a direct consequence of increased afterload and not only the consequence of primary myocardial disease, a full physiologic analysis of the cardiopulmonary unit is necessary to correctly interpret clinical and imaging data.¹⁶ For instance, parameters such as RV ejection fraction and TAPSE are typically decreased in patients with group I pulmonary hypertension, despite evidence of increased contractility when RV end-systolic elastance is evaluated.¹⁷ Contrarily, RV myocardial work derived noninvasively from pressure-strain loops provides an estimate of RV performance that accounts for afterload and mechanical efficiency. Unlike RVGLS, TAPSE, and RVFAC, these novel indexes do not only reflect system function¹⁶ but also provide an evaluation of RV performance that accounts for afterload and myocardial work efficiency.

In the future, the non-invasive evaluation of RV myocardial work may have the potential to enhance echocardiographic monitoring of patients with precapillary pulmonary hypertension. Hemodynamic parameters derived from RHC during follow-up after treatment (such as PVR and stroke volume index) have been shown to be independently associated with adverse prognosis.^{18,19} Monitoring with serial RHC may improve the risk stratification and management of patients with group I pulmonary hypertension.^{3,20} However, with a rate of serious complications of approximately 1%, cheaper, non-invasive alternatives to serial RHC are needed.²¹ Changes in conventional echocardiographic parameters of RV performance, such as RVGLS, have been independently associated with clinical deterioration and all-cause mortality in patients with group I pulmonary hypertension, implying a possible role for the monitoring of these patients with speckle-tracking echocardiography.²² However, simultaneous evaluation

of indexes of RV myocardial work may contextualize any changes in RVGLS by providing an estimate of RV performance that also accounts for afterload and mechanical work efficiency.

Several studies have demonstrated that pressure-strain loops of the left ventricle derived from speckle-tracking echocardiography strongly correlate with myocardial glucose metabolism by 18F-fluorodeoxyglucose positron emission tomography.^{1,23} RV myocardial work may also provide a non-invasive estimate of regional myocardial energetics and could be useful for the evaluation of the right ventricle, considering that the extent of RV glucose uptake on 18F-fluorodeoxyglucose positron emission tomography in patients with precapillary pulmonary hypertension has been associated with pressure overload, RV dysfunction, and poor prognosis.^{24,25} The present study showed that RVGCW and RVGWI were associated with all-cause mortality, and that this relation was significantly nonlinear. Conversely, RVGLS, TAPSE, RVFAC, and PASP, conventional parameters of RV function, were not associated with all-cause mortality.

This study is limited by its retrospective, observational design and limited sample size. Additional large prospective studies are required to confirm the prognostic value of RV myocardial work parameters in patients with precapillary pulmonary hypertension. Additionally, RHC was not performed simultaneously with echocardiography and hemodynamics may change substantially over relatively short time periods in patients with precapillary pulmonary hypertension. Importantly, the software used for the analysis of RV myocardial work was originally designed for the evaluation of LV pressure-strain loops rather than for those of the right ventricle. However, in patients with severe group I and group IV pulmonary hypertension, pressure volume loops of the right ventricle change with increasing pulmonary arterial pressure, closely resembling those of the left ventricle.^{26,27}

CONCLUSION

In conclusion, in a patient cohort with group I and group IV pulmonary hypertension, indexes of RV myocardial work were more closely correlated with invasively derived RV stroke work index and PVR than conventional echocardiographic parameters of RV systolic function. Decreased values of RVGCW and RVGWI were associated with all-cause mortality, whereas conventional echocardiographic parameters of RV function were not.

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SUPPLEMENTARY MATERIAL

Table S1: Intraclass correlation coefficients for intra-observer measurements, inter-observer measurements and RV myocardial work indices derived from invasive versus non-invasive systolic pulmonary artery pressure

Variable	Intraclass correlation coefficient (95% CI)	P
RV myocardial work derived from invasive vs non-invasive pulmonary pressures		
RV GWI (mmHg%)	0.942 (0.901 to 0.966)	<0.001
RV GCW (mmHg%)	0.916 (0.857 to 0.951)	<0.001
RV GWW (mmHg%)	0.947 (0.909 to 0.969)	<0.001
RV GWE (%)	1 (1 to 1)	<0.001
Intra-observer variability		
RV GWI (mmHg%)	0.956 (0.832 to 0.989)	<0.001
RV GCW (mmHg%)	0.919 (0.707 to 0.979)	<0.001
RV GWW (mmHg%)	0.781 (0.345 to 0.940)	0.001
RV GWE (%)	0.898 (0.645 to 0.974)	<0.001
Inter-observer variability		
RV GWI (mmHg%)	0.969 (0.889 to 0.992)	<0.001
RV GCW (mmHg%)	0.971 (0.893 to 0.992)	<0.001
RV GWW (mmHg%)	0.759 (0.271 to 0.935)	0.005
RV GWE (%)	0.871 (0.565 to 0.966)	<0.001

CI = confidence interval; RV = right ventricular; RV GCW = right ventricular global constructive work, RV GWW = right ventricular global wasted work, RV GWE = Right ventricular global work efficiency, RV GWI = Right ventricular global work index

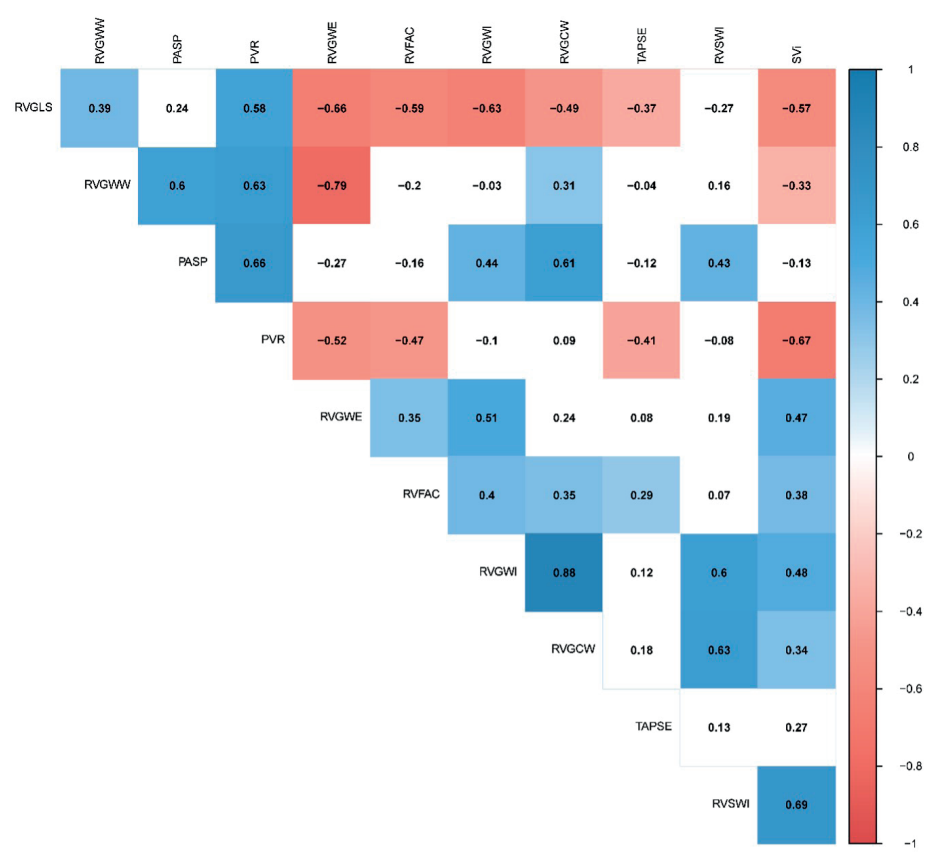


Figure S1: Correlation matrix of echocardiographic and RHC parameters of interest. White colored squares in the correlation matrix indicate a p-value ≥ 0.05 , while red or blue colored squares indicate correlation coefficients with a p-value < 0.05 . PASP = pulmonary artery systolic pressure, PVR = pulmonary vascular resistance, RHC = right heart catheterization, RVFAC = right ventricular fractional area change, RVGCW = right ventricular global constructive work, RVGLS = right ventricular global longitudinal strain, RVGWE = right ventricular global work efficiency, RVGWI = right ventricular global work index, RVGWW = RV global wasted work, RVSWI = right ventricular stroke work index, TAPSE = tricuspid annular plane systolic excursion, SVi = stroke volume index

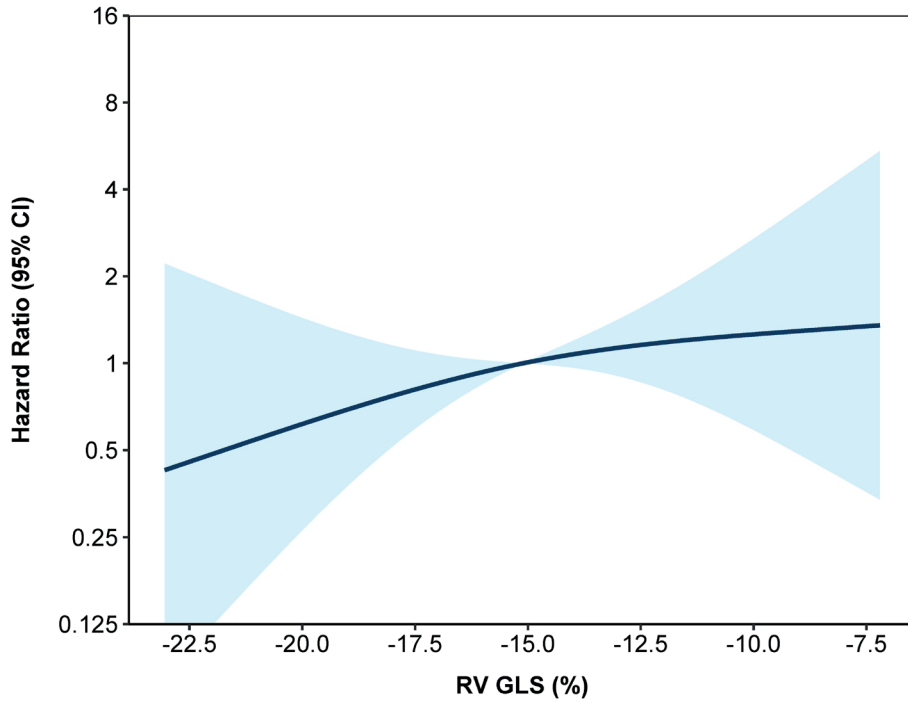


Figure S2: Spline curve demonstrating the hazard ratio for all-cause mortality according to RV GLS. The curve demonstrates the hazard ratio change for all-cause mortality with 95% confidence intervals (blue shaded areas) in patients with pre-capillary pulmonary hypertension, across a range of values of RV GLS at the time of echocardiography.

