

# Noninvasive Risk Score to Screen for Pulmonary Hypertension With Elevated Pulmonary Vascular Resistance in Diseases of Chronic Volume Overload



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**Volume overload promotes pulmonary hypertension (PH) through pulmonary venous hypertension. However, PH with elevated pulmonary vascular resistance (hereafter PH-PVR) may develop in patients with diseases of volume overload, such as heart failure or chronic kidney disease (CKD). In such cases, volume management alone may be insufficient to slow PH progression. An accurate, noninvasive method to screen for PH-PVR in these diseases would facilitate early targeted therapy. We integrated invasive hemodynamic and echocardiography data collected from a single-center clinical cohort and identified patients with CKD or heart failure at the time of assessment. We applied penalized regression to derive a risk score of clinical parameters and echocardiography data associated with PH-PVR and categorized patients into low- ( $\leq 5$  points), intermediate- (6-10 points), or high-risk ( $>10$  points) groups. Using an internal validation strategy, we evaluated the ability of this risk score to predict PH-PVR and determined the association of this risk classification with 3-year all-cause mortality. Of 2422 patients, 42.4% had PH-PVR. In adjusted analyses, tricuspid regurgitant velocity, right ventricular function, BMI, heart rate, and hemoglobin most strongly associated with PH-PVR. The risk score significantly associated with PH-PVR (age-adjusted odds ratio 11.69 for the highest-risk group, 95% confidence interval [CI] 6.54-20.92). The high-risk group also associated with a significantly higher risk of 3-year all-cause mortality in adjusted analyses (hazard ratio 1.85, 95% CI 1.50-2.27). In conclusion, a noninvasive risk score derived from echocardiography and clinical parameters significantly associated with PH-PVR and all-cause mortality in a cohort of patients with CKD and heart failure. Published by Elsevier Inc. (Am J Cardiol 2021;159:113–120)**

Pulmonary hypertension (PH) is categorized into hemodynamic subtypes based on pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP) as measured by right heart catheterization.<sup>1</sup> While diseases of volume overload, such as CKD and heart failure, can induce PH through elevated left-sided pressures, these diseases can also adversely affect vascular biology and increase PVR leading to poor outcomes.<sup>2,3</sup> This elevated PVR may promote PH alone or in concert with elevated PCWP. Patients with PH and elevated PVR (hereafter termed PH-PVR) may benefit from early application of pulmonary vasodilator therapy, even in select patients with volume overload.<sup>4-6</sup>

Echocardiography provides an effective screening tool for the diagnosis of PH in both CKD and HF cohorts;<sup>7,8</sup> in other populations, echocardiography can also estimate PVR.<sup>9,10</sup> A noninvasive method to screen for PH-PVR in diseases of volume overload would identify high-risk patients in whom definitive diagnostic procedures should proceed without delay to facilitate early targeted therapy, if indicated. We determined how select clinical parameters and echocardiography data associated with PH-PVR in patients with either CKD or heart failure referred for right heart catheterization; developed and internally validated a risk score comprised of parameters which are strongly associated with PH-PVR; and determined the association of this risk classification with all-cause mortality.

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## Methods

The study cohort included patients within Duke University Hospital referred for right heart catheterization between January 1, 2011 and December 31, 2014 with echocardiograms available  $\leq 6$  months before or after of catheterization. Patients with either CKD or heart failure were selected for this study. To identify patients with CKD, we calculated the estimated glomerular filtration rate (eGFR) from the median creatinine over the 6-month period prior to catheterization using the CKD-EPI equation. We defined CKD as an estimated glomerular filtration rate (eGFR) of  $<60$  ml/min/1.73 m<sup>2</sup>; proteinuria data were not available. Heart failure diagnosis was indicated by providers at the time of

catheterization and collected in the Duke Databank for Cardiovascular Disease (DDCD). Exclusion criteria included age <18 years; missing creatinine, catheterization, or echocardiogram data; kidney transplantation; and right heart catheterizations performed during hospitalizations for acute coronary syndrome or for evaluation for heart or lung transplantation. We included only the first study which met the inclusion/exclusion criteria. The Duke University Health Systems Institutional Review Board reviewed and approved this study.

We collected demographic information on age, sex, and self-reported race from the DDCD at the time of catheterization. We consolidated race into three categories: White, Black, and other. Diagnoses for diabetes mellitus, hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea, scleroderma, and systemic lupus erythematosus were obtained from the DDCD intake form and supplemented by diagnostic codes. We also collected the body mass index (BMI), systolic blood pressure, heart rate, and hemoglobin obtained closest to the time of the right heart catheterization. Patients with a heart rate  $\geq 200$  beats per minute were excluded.

We collected the following echocardiography data: tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitant velocity (TRV), left ventricular ejection fraction, left atrial anteroposterior diameter, right ventricular function (normal, mildly decreased, moderately decreased,

or severely decreased), mid right ventricular diameter, and left ventricular diastolic function (normal, grade 1 dysfunction, grade 2 dysfunction, or grades 3-4 dysfunction). We estimated right atrial pressure based on inferior vena cava size and respiratory variation and consolidated the estimated pressure into three values: 3 mmHg, 8 mmHg, or 15 mmHg. Echocardiograms which reported <50% of these measurements were excluded. Echocardiography measurements were reviewed for clear data outliers which resulted in the exclusion of one patient for a TAPSE >8 cm and another patient for a left atrial diameter of >11 cm.

We defined PH as a mean pulmonary artery pressure of >20 mmHg on right heart catheterization and categorized by hemodynamic subtype (Supplemental Materials).<sup>1</sup> We grouped patients into two phenotypes: PH-PVR versus normal PVR. The PH-PVR phenotype included cases of pre-capillary and combined pre- and post-capillary PH; all other patients were grouped into the normal PVR phenotype. We excluded outliers with either a negative PVR (2 patients) or PVR >100 Wood Units (2 patients). Vital status in the DDCD was determined using a combination of longitudinal follow-up data collected for all patients in the DDCD after left-heart catheterization and National Death Index query for the remaining patients.

We stratified the study cohort by PVR phenotype (Table 1) and PH hemodynamic subtypes (Supplementary

Table 1  
Clinical characteristics stratified by PVR phenotype

Characteristic	Total cohort (n = 2422)	PH-PVR (n = 1026)	Normal PVR (n = 1396)	p-value
Age (years)	65.2 $\pm$ 14.4	65.1 $\pm$ 14.1	65.3 $\pm$ 14.7	0.69
Women	1089 (45.0%)	541 (52.7%)	548 (39.3%)	<0.001
White	1684 (70.0)	639 (62.8)	1045 (75.3)	<0.001
Black	636 (26.4)	333 (32.7)	303 (21.8)	
Other	85 (3.5)	45 (4.4)	40 (2.9)	
eGFR (ml/min/1.73m <sup>2</sup> )	58.2 $\pm$ 24.9	57.2 $\pm$ 24.5	58.9 $\pm$ 25.1	0.10
BMI (kg/m <sup>2</sup> )	29.5 $\pm$ 7.2	29.2 $\pm$ 7.3	29.8 $\pm$ 7.1	0.05
Systolic Blood Pressure (mmHg)	132.5 $\pm$ 22.4	132.3 $\pm$ 22.5	132.7 $\pm$ 22.3	0.71
Heart Rate (bpm)	82.7 $\pm$ 23.4	84.6 $\pm$ 22.2	81.2 $\pm$ 24.1	<0.001
Hemoglobin (g/dl)	12.1 $\pm$ 2.1	12.2 $\pm$ 2.1	12.0 $\pm$ 2.2	<0.001
Hypertension	1545 (63.8%)	648 (63.2%)	897 (64.3%)	0.61
CKD	1393 (57.5%)	608 (59.3%)	785 (56.2%)	0.15
Heart failure	2123 (87.7%)	912 (88.9%)	1211 (86.8%)	0.13
Diabetes	721 (29.8%)	328 (32.0%)	393 (28.2%)	0.05
COPD	14 (0.6%)	3 (0.3%)	11 (0.8%)	0.19
OSA	222 (9.2%)	89 (8.7%)	133 (9.5%)	0.52
SLE	25 (1.0%)	14 (1.4%)	11 (0.8%)	0.24
Scleroderma	2 (0.9%)	14 (1.4%)	8 (0.6%)	0.07
TAPSE (cm)	1.7 $\pm$ 0.6	1.6 $\pm$ 0.5	1.8 $\pm$ 0.6	<0.001
TRV (m/s)	3.1 $\pm$ 0.7	3.3 $\pm$ 0.7	2.8 $\pm$ 0.5	<0.001
LVEF (IQR)	50.0 (30.0)	48.0 (31.0)	50.0 (29.0)	0.07
Right Atrial Pressure (mmHg)				<0.001
3	1142 (49.7%)	388 (39.5%)	754 (57.4%)	
8	528 (23.0%)	254 (25.8%)	274 (20.9%)	
15	627 (27.3%)	341 (34.7%)	286 (21.8%)	
Left atrial dimension (cm)	4.4 $\pm$ 0.9	4.4 $\pm$ 0.9	4.4 $\pm$ 0.8	0.32
Diastolic Dysfunction				<0.001
Normal	92 (6.9%)	28 (5.0%)	64 (8.2%)	
Grade 1	656 (49.1%)	246 (44.2%)	656 (49.1%)	
Grade 2	135 (10.1%)	47 (8.5%)	91 (11.3%)	
Grades 3-4	452 (33.9%)	235 (42.3%)	223 (27.7%)	
RV function				<0.001
Normal	1347 (55.8%)	401 (39.2%)	946 (68.0%)	
Mild decrease	522 (21.6%)	263 (25.7%)	259 (18.6%)	
Moderate decrease	392 (16.2%)	257 (25.1%)	135 (9.7%)	
Severe decrease	155 (6.4%)	103 (10.1%)	52 (3.7%)	
RV dimension, mid (cm)	3.2 $\pm$ 0.9	3.4 $\pm$ 0.9	3.0 $\pm$ 0.9	<0.001

Abbreviations: PVR = pulmonary vascular resistance; eGFR = estimated glomerular filtration rate; BMI = body mass index; bpm = beats per minute; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea; SLE = systemic lupus erythematosus; TAPSE = tricuspid annular systolic plane excursion; TRV = tricuspid regurgitant velocity; LVEF = left ventricular ejection fraction; RV = right ventricular.

Materials) and reported baseline demographic data, clinical parameters, and echocardiography measurements. Categorical data were presented as number and percentage of patients. Continuous variables were reported as mean  $\pm$  standard deviation (SD) if normally distributed or as median (interquartile range) if otherwise. To compare differences between continuous variables in the PH-PVR and normal PVR phenotypes, we used unpaired t-tests (when normally distributed) and Wilcoxon rank sum tests (when skewed). We used Pearson's Chi square tests to compare differences in categorical variables.

We first determined the association of each parameter with PH-PVR using univariate logistic regression. We then adjusted for age, race, sex, and diabetes in multivariable logistic regression models. To investigate whether eGFR or heart failure modified the association between any parameter and PH-PVR, we repeated regression analyses with the addition of interaction terms, first for eGFR and then for heart failure. Parameters with a significant interaction p-value for eGFR were further stratified by eGFR:  $<30$  ml/min/1.73 m<sup>2</sup>, 30-59 ml/min/1.73 m<sup>2</sup>, and  $\geq 60$  ml/min/1.73 m<sup>2</sup>. Parameters for which heart failure significantly modified the association with PH-PVR were stratified by the presence or absence of heart failure diagnosis.

To construct the risk score to screen for PH-PVR, we randomly divided the study cohort into training (70%) and validation (30%) cohorts. We excluded left ventricular diastolic function and mid right ventricular diameter due to data missingness, but retained them as auxiliary variables for multiple imputation (Supplemental Material). Using multiple imputations by chained equations (MICE) R package (version 3.11.0), we generated 10 imputed datasets. To facilitate inclusion in risk score calculations, we used the cutpoint R package (version 1.0.32) to select the optimal cutpoint for continuous variables which maximizes Youden's index (sensitivity + specificity - 1). We applied Least Absolute Shrinkage Selector Operator (LASSO) regression to select candidate variables within each of the 10 imputed training datasets. Based on prior analyses,<sup>11,12</sup> we included candidate variables selected in  $>50\%$  of the imputed training datasets in the final risk score. Each of these variables were included in a logistic regression model with PH-PVR as the outcome to generate odds ratios (OR); we assigned points to each variable by dividing each OR by the lowest OR. Since two variables included in the risk score were significantly modified by either eGFR (hemoglobin) or heart failure diagnosis (TRV), we also constructed a weighted risk score which modified the point total assigned to these variables based on the presence of CKD or heart failure diagnosis. We divided the scores into low risk ( $\leq 5$  points), intermediate risk (6-10 points), and high risk ( $>10$  points) categories.

Using the low-risk category as the referent, we used unadjusted and age-adjusted logistic regression to determine the OR for PH-PVR based on the risk score category in the validation cohort. In sensitivity analyses, we evaluated the risk score model performance after limiting the validation cohort to just patients with heart failure or CKD; we also assessed model performance in a validation cohort without imputation for data missingness by assigning zero

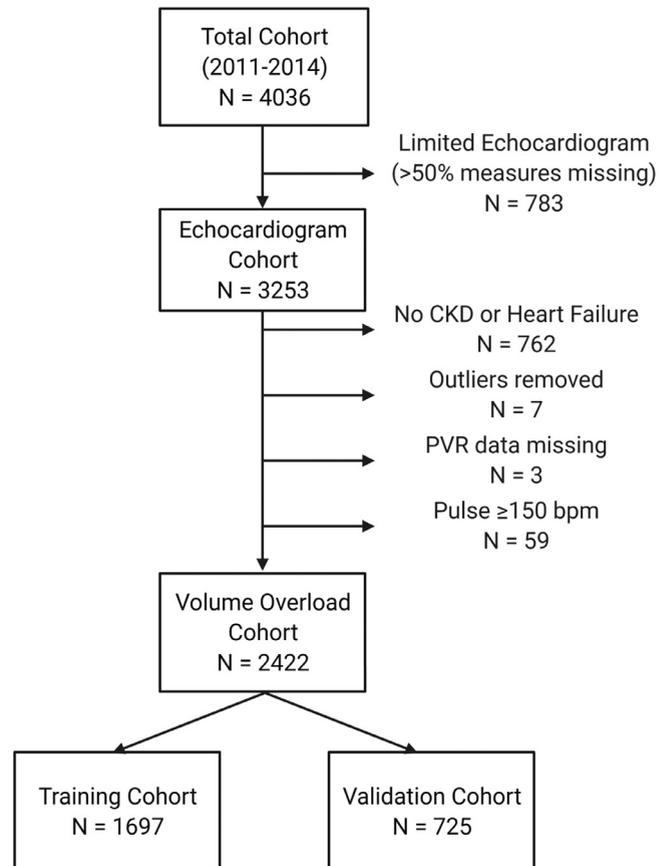


Figure 1. Study Consort Diagram.

Abbreviations: CKD = chronic kidney disease; PVR = pulmonary vascular resistance; bpm = beats per minute.

points for any missing value. All statistical analyses were conducted using R (version 3.6.3).

To evaluate the association of the risk score classification with mortality, we compared 3-year survival curves between risk classification groups using the log rank test in the un-imputed data cohort. We then evaluated the unadjusted, age-adjusted, and fully adjusted (age, sex, race, and diabetes diagnosis) associations with mortality. Since the survival curves violated the proportional hazards assumption, we included an interaction term for time.

## Results

The consort diagram for the study population is depicted in Figure 1. The clinical characteristics in the total study cohort stratified by PVR phenotype is presented in Table 1. The clinical characteristics stratified by each hemodynamic PH subtype is presented in the Supplemental Materials. The median number of days between echocardiogram and invasive hemodynamic assessment was -2.0 days (interquartile range -12.0 days, 0 days). Of the 2422 patients in the volume overload cohort, 1026 (42%) of patients had PH with an elevated PVR. PH-PVR was more common in women and persons of Black race. Among the differences in clinical parameters, heart rate at the time of right heart catheterization tended to be higher and BMI was lower in persons with PH-PVR. Hemoglobin was slightly but significantly

Table 2  
Association of clinical parameters and echocardiography measurements with PH-PVR phenotype

Characteristic	OR (95% CI)	p-value	aOR* (95% CI)	p-value
Age (per year)	1.00 (0.99-1.00)	0.69	N/A	N/A
Women	1.73 (1.47-2.03)	<0.001	N/A	N/A
Race				
White	1 (ref)	N/A	N/A	N/A
Black	1.80 (1.50-2.16)	<0.001	N/A	N/A
Other	1.84 (1.19-2.86)	0.006	N/A	N/A
BMI (per kg/m <sup>2</sup> )	0.99 (0.98-1.00)	0.04	0.98 (0.97-0.99)	0.001
Systolic Blood Pressure (per 10 mmHg)	0.99 (0.96-1.03)	0.71	0.96 (0.92-1.00)	0.07
Heart Rate (per 10 bpm)	1.06 (1.03-1.10)	0.001	1.06 (1.02-1.10)	0.002
Hemoglobin (per 1 g/L increase)	1.07 (1.03-1.11)	<0.001	1.12 (1.08-1.17)	<0.001
TAPSE (per 1 cm increase)	0.48 (0.40-0.57)	<0.001	0.43 (0.35-0.51)	<0.001
TRV (per 1 m/s increase)	5.53 (4.51-6.85)	<0.001	5.42 (4.39-6.74)	<0.001
LVEF (per 10% increase)	0.94 (0.90-0.99)	0.03	0.89 (0.84-0.94)	<0.001
Right Atrial Pressure (mmHg)				
3	1 (ref)	N/A	1 (ref)	N/A
8	1.80 (1.46-2.22)	<0.001	1.93 (1.56-2.40)	<0.001
15	2.32 (1.90-2.83)	<0.001	2.63 (2.14-3.25)	<0.001
Left atrial dimension (per 1 cm increase)	0.95 (0.86-1.04)	0.32	1.07 (0.96-1.19)	0.20
Diastolic Dysfunction				
Normal	1 (ref)	N/A	1 (ref)	N/A
Grade 1	1.37 (0.86-2.23)	0.19	1.36 (0.84-2.26)	0.22
Grade 2	1.22 (0.69-2.17)	0.49	1.32 (0.74-2.40)	0.35
Grades 3-4	2.68 (1.54-4.06)	<0.001	2.94 (1.80-4.91)	<0.001
RV function				
Normal	1 (ref)	N/A	1 (ref)	N/A
Mild decrease	2.40 (1.95-2.95)	N/A	2.92 (2.34-3.65)	<0.001
Moderate decrease	4.49 (3.54-5.71)	<0.001	5.60 (4.34-7.27)	<0.001
Severe decrease	4.67 (3.44-6.69)	<0.001	5.97 (4.13-8.71)	<0.001
RV dimension, mid (cm)	1.59 (1.40-1.81)	<0.001	1.73 (1.51-1.98)	<0.001

\* Adjusted for demographics (age, race, sex), diabetes.

Abbreviations: BMI = body mass index; TAPSE = tricuspid annular systolic plane excursion; TRV = tricuspid regurgitant velocity; LVEF = left ventricular ejection fraction; RV = right ventricular.

higher in the PH-PVR cohort. Key differences in echocardiography measurements included a higher prevalence of abnormal right atrial pressure and right ventricular function in persons with PH-PVR. Severe diastolic dysfunction was also more common in PH-PVR. TAPSE was significantly lower and TRV significantly higher in persons with PH-PVR.

The unadjusted and adjusted OR for PH-PVR for each candidate risk factor is presented in Table 2. In adjusted analyses, the echocardiography measurements most strongly associated with PH-PVR were TRV and right ventricular function. Clinical parameters associated with PH-PVR included BMI, heart rate, and hemoglobin. Figure 2 depicts the factors related to PH-PVR that were significantly modified by either eGFR (Figure 2A) or heart failure (Figure 2B) diagnosis. The most notable interactions included hemoglobin (OR increased with worsening CKD) and TRV (OR decreased with heart failure diagnosis). The risk factors selected by LASSO regression with assigned point values are listed in Table 3 for both the standard risk score and the weighted risk score which accounts for the significant interactions between TRV and heart failure and between hemoglobin and CKD.

Table 4 presents the unadjusted and age-adjusted OR for PH-PVR stratified by the standard and weighted risk scores

in the validation cohort. The age-adjusted OR was nominally higher for the weighted risk score. In sensitivity analyses, the risk score performed similarly in both the heart failure and CKD cohorts (Supplementary Materials). The association diminished when we assigned a score of zero for missing risk factors (Supplementary Materials).

The survival curve stratified by risk score for the study cohort without data imputation is presented in Figure 3. In both unadjusted and adjusted analyses, the intermediate- and high-risk scores associated with a significantly higher risk of 3-year mortality (Table 5).

## Discussion

In a cohort of 2422 patients with either CKD or heart failure, a risk score derived from clinical parameters and echocardiography measurements identified patients with PH-PVR with moderate accuracy and was associated with all-cause mortality. A weighted risk score accounting for select interactions between eGFR or heart failure and factors included in the risk score nominally increased the association with PH-PVR above the standard risk score. This study is the first to evaluate the performance of noninvasive risk factors as a method to screen for PH-PVR in a population restricted to CKD or heart failure. Due to the high

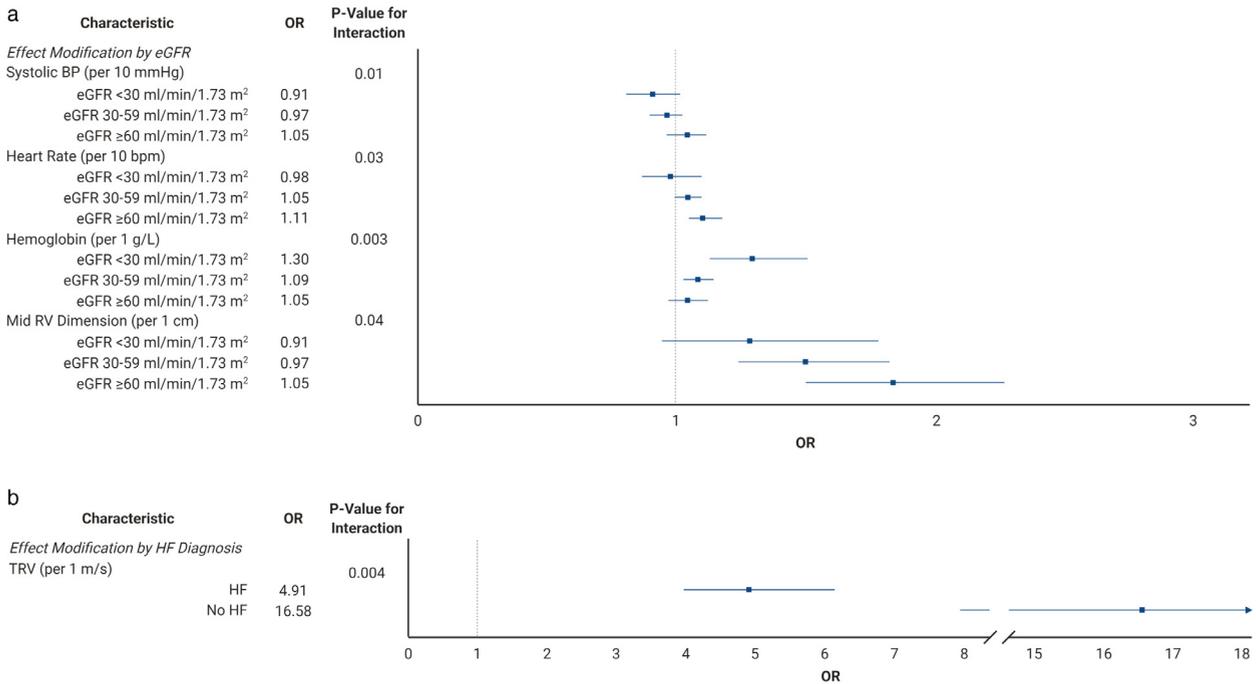


Figure 2. Effect modification by (A) estimated glomerular filtration rate and (B) heart failure diagnosis. Abbreviations: eGFR = estimated glomerular filtration rate; bpm = beats per minute; RV = right ventricular; HF = heart failure; TRV = tricuspid regurgitant velocity; OR = odds ratio.

Table 3  
Standard and weighted risk scores

Risk Factor	Standard Score		Weighted Score	
	Strata	Points	Strata	Points
Sex	Female	2	Female	2
	Male	0	Male	0
Race	Black Race	1.5	Black Race	1.5
	Non-Black, Non-White Race	1	Non-Black, Non-White Race	1
	White Race	0	White Race	0
TRV	≥3.2 m/s	4	≥3.2 m/s + no HF history	8
	<3.2 m/s	0	≥3.2 m/s + HF history	4
TAPSE	≤1.65 cm	1.5	<3.2 m/s	0
	>1.65 cm	0	≤1.65 cm	1.5
RV Function	Moderate-Severely Reduced	2.5	>1.65 cm	0
	Mildly Reduced	1.5	Moderate-Severely Reduced	2.5
Right Atrial Pressure	Normal	0	Mildly Reduced	1.5
	15 mmHg	1.5	Normal	0
	8 mmHg	1	15 mmHg	1.5
LVEF	3 mmHg	0	8 mmHg	1
	>55%	1	3 mmHg	0
	≤55%	0	>55%	1
Heart Rate	≥60 bpm	1.5	≤55%	0
	<60 bpm	0	≥60 bpm	1.5
BMI	<30 kg/m <sup>2</sup>	1	<60 bpm	0
	≥30 kg/m <sup>2</sup>	0	<30 kg/m <sup>2</sup>	1
Hemoglobin	≥11.2 g/L	1.5	≥30 kg/m <sup>2</sup>	0
	<11.2 g/L	0	≥11.2 g/L + CKD	2
			≥11.2 g/L + no CKD	1.5
<b>Maximum Score</b>		<b>18</b>	<11.2 g/L	0

Low Risk ≤5 points, Intermediate Risk 6-10 points, High Risk >10 points

Abbreviations: BMI = body mass index; TAPSE = tricuspid annular systolic plane excursion; TRV = tricuspid regurgitant velocity; LVEF = left ventricular ejection fraction; RV = right ventricular.

Table 4  
Association of standard and weighted risk scores with PH-PVR phenotype

Risk score	% Patients with Score	Unadjusted OR (95% CI)	P Value	Age-adjusted OR (95% CI)	p Value
<b>Standard Risk Score</b>					
≤5 (Low)	164 (23%)	1 (ref)	N/A	1 (ref)	N/A
6-10 (Intermediate)	353 (49%)	3.89 (2.28-6.64)	<0.001	3.94 (2.31-6.72)	<0.001
>10 (High)	208 (29%)	11.52 (6.43-20.63)	<0.001	11.69 (6.54-20.92)	<0.001
<b>Weighted Risk Score</b>					
≤5 (Low)	142 (20%)	1 (ref)	N/A	1 (ref)	N/A
6-10 (Intermediate)	364 (50%)	4.68 (2.49-8.78)	<0.001	4.71 (2.51-8.85)	<0.001
>10 (High)	219 (30%)	13.68 (6.87-27.23)	<0.001	13.80 (6.92-27.48)	<0.001

Abbreviations: OR = odds ratio; CI = confidence interval.

prevalence of PH due to volume overload in this population and the potential for alternative therapeutic approaches for patients with elevated PVR, such a noninvasive screening tool would allow clinicians to identify patients who may not improve with volume management alone to facilitate earlier definitive diagnosis by right heart catheterization and application of targeted therapies.

Echocardiography has been used to screen for elevated PVR in other populations, including measurements not available in our study such as right ventricular outflow tract velocity time integral or indices of pulmonary pressure reflection.<sup>9,10,13,14</sup> In this study, TRV, right ventricular function, and TAPSE strongly associated with PH-PVR. These markers of right ventricular systolic function each variably associate with outcomes in PH.<sup>10,15-19</sup> In contrast,

an abnormal left ventricular ejection fraction associated with lower odds of PH-PVR; this finding likely reflects the substantial prevalence of isolated post-capillary PH in patients with heart failure with a reduced ejection fraction.<sup>20</sup> This combination of left- and right-sided echocardiography measurements improved the accuracy of screening for PH-PVR.

Select clinical parameters significantly associated with PH-PVR in this study. Consistent with prior studies,<sup>21</sup> we report an increased odds of PH-PVR for women. While idiopathic PAH predominantly affects persons of White race, persons of Black race are more likely to present with PAH associated with other diseases.<sup>22</sup> This important distinction likely underlies why Black race and other non-White races associated with an increased odds of PH-PVR in our study

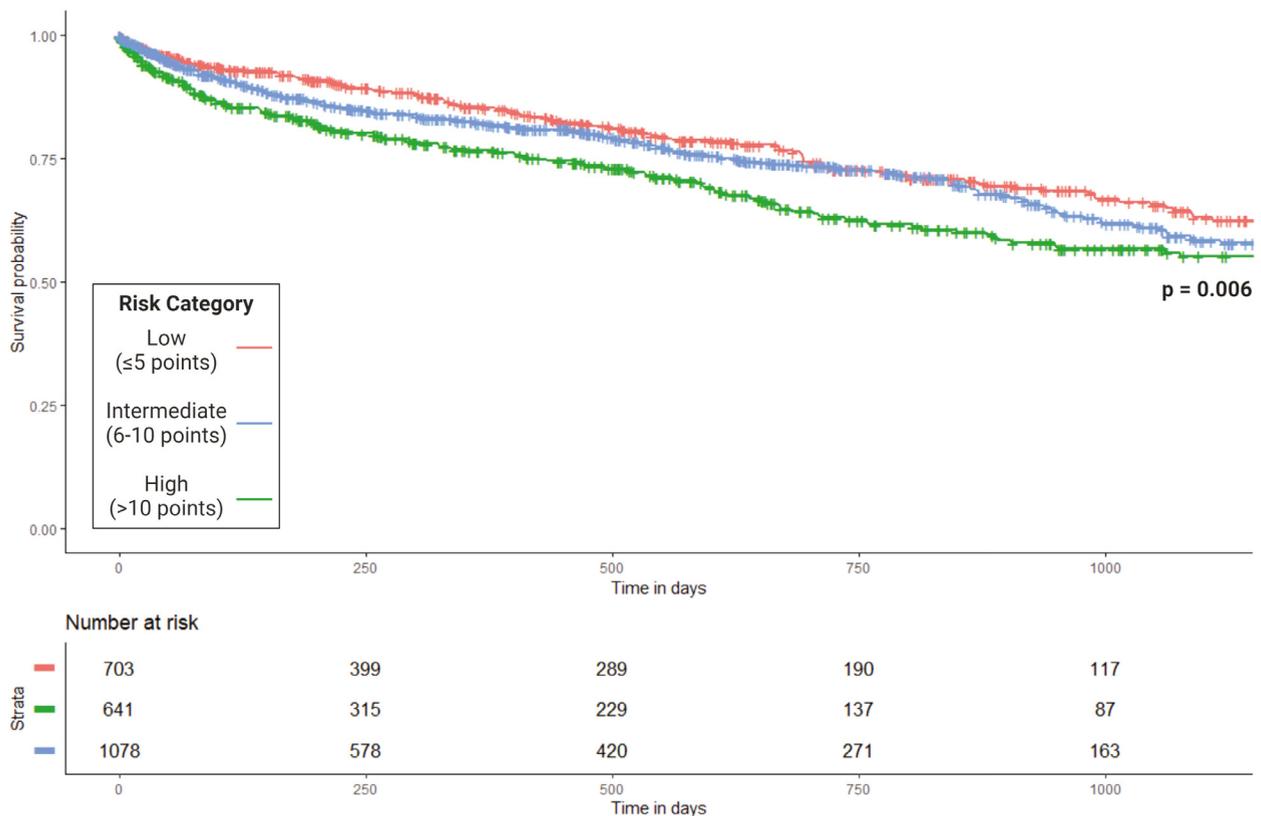


Figure 3. Kaplan-Meier survival curve stratified by standard risk score classification.

Table 5  
Association of the standard risk score with 3-year all-cause mortality without data imputation

Risk Category	Unadjusted OR (95% CI)	p Value	Age-Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
≤5 (Low)	1 (ref)	N/A	1 (ref)	N/A	1 (ref)	N/A
6-10 (Intermediate)	1.31 (1.09-1.58)	0.004	1.37 (1.13-1.65)	0.001	1.39 (1.15-1.67)	0.001
>10 (High)	1.68 (1.37-2.06)	<0.001	1.79 (1.46-2.20)	<0.001	1.85 (1.50-2.27)	<0.001

Abbreviations: HR = hazard ratio; CI = confidence interval. Adjusted for age, sex, race, and diabetes mellitus diagnosis.

cohort. Heart rate less than 60 beats-per-minute associated with a lower risk of PH-PVR in this study. While not previously applied to discern hemodynamic PH subtypes, a lower resting heart rate associates with a reduced risk of a composite of death or lung transplant in persons with PAH.<sup>23,24</sup> While BMI exhibits a complicated and at times paradoxical relationship with PH,<sup>23-25</sup> we report an increased risk of PH-PVR at BMI <30 kg/m<sup>2</sup>. While anemia serves as a risk factor for mortality in persons with PH,<sup>26,27</sup> the strong link with heart failure may explain the inverse association between lower hemoglobin less than 11.2 g/L and PH-PVR uncovered in our study.<sup>28</sup> Compared to other populations, these clinical parameters may play a larger role in discerning PVR elevation in persons at risk for volume overload.

We acknowledge several limitations to the study design. First, all data were all collected within the context of clinical care. This limitation enriches both the overall prevalence of PH and the proportion of patients with elevated PVR in the study population. Additionally, we cannot assess interobserver variability for study measurements. Echocardiogram and right heart catheterization may be separated by a meaningful intervention which influences the relationship between these two diagnostic modalities. The echocardiograms in this study did not report measurements known to associate with PVR, including right ventricular outflow tract acceleration velocity-time integral or the presence of notching in the pulmonary artery outflow signal associates with pre-capillary PH.<sup>10,29</sup> While we eliminated limited echocardiograms, select measurements were still absent from a proportion of echocardiograms. The absence of these measurements does not imply the absence of pathology.<sup>30</sup> Another limitation introduced by the use of clinical data is the definition of CKD based on a median of 6 months of creatinine data; rapid progression of CKD or acute kidney injury prior to right heart catheterization may lead to misclassification. Lastly, despite our robust sample size, external validation better ensures generalizability. The ideal cohort for such validation is an asymptomatic population with prospective data collection; however, the invasive nature of right heart catheterization limits the feasibility of large studies in such a cohort.

This study also has strengths. The large population with granular data collection of clinical parameters, echocardiography, and right heart catheterization data provides a robust study cohort. To our knowledge, this study is the first to noninvasively screen for elevated PVR in a population with CKD. A risk score to screen for elevated PVR has numerous clinical and research applications, including earlier suspicion for PH-PVR which facilitates timely diagnosis and application of targeted therapies; improved pre-transplant assessment of kidney transplant candidates; and selection

of enriched populations for clinical studies of PH in CKD and/or heart failure. In summary, we derived a risk score from clinical parameters and echocardiography measurements to identify patients at high risk for PH due to a PVR phenotype with moderate accuracy in a population with a high prevalence of volume overload.

### Disclosures

The authors report no relevant financial disclosures or conflicts of interest related to this study.

### Declaration of interests

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

### Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2021.08.016>.

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