Independent evaluation of a simple clinical prediction rule to identify right ventricular dysfunction in patients with shortness of breath[★],[★★]

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Abstract

Background—Many patients have unexplained persistent dyspnea after negative computed tomographic pulmonary angiography (CTPA). We hypothesized that many of these patients have isolated right ventricular (RV) dysfunction from treatable causes. We previously derived a clinical decision rule (CDR) for predicting RV dysfunction consisting of persistent dyspnea and normal CTPA, finding that 53% of CDR-positive patients had isolated RV dysfunction. Our goal is to validate this previously derived CDR by measuring the prevalence of RV dysfunction and outcomes in dyspneic emergency department patients.

Methods—A secondary analysis of a prospective observational multicenter study that enrolled patients presenting with suspected PE was performed. We included patients with persistent dyspnea, a nonsignificant CTPA, and formal echo performed. Right ventricular dysfunction was defined as RV hypokinesis and/or dilation with or without moderate to severe tricuspid regurgitation.

Results—A total of 7940 patients were enrolled. Two thousand six hundred sixteen patients were analyzed after excluding patients without persistent dyspnea and those with a significant finding on CTPA. One hundred ninety eight patients had echocardiography performed as standard care. Of those, 19% (95% confidence interval [CI], 14%–25%) and 33% (95% CI, 25%–42%) exhibited RV dysfunction and isolated RV dysfunction, respectively. Patients with isolated RV dysfunction or overload were more likely than those without RV dysfunction to have a return visit to the emergency department within 45 days for the same complaint (39% vs 18%; 95% CI of the difference, 4%–38%).

Conclusion—This simple clinical prediction rule predicted a 33% prevalence of isolated RV dysfunction or overload. Patients with isolated RV dysfunction had higher recidivism rates and a trend toward worse outcomes.

1. Introduction

Dyspnea is a common complaint encountered in the emergency department (ED), accounting for more than 3 million ED visits annually in the United States [1]. Management remains difficult because dyspnea has many etiologies requiring varied treatment, and clinicians fail to identify the cause in nearly one-half of ED patients [2]. Imaging with computed tomographic pulmonary angiography (CTPA) is commonly used in the ED to evaluate for pulmonary embolism (PE) [3,4], and also provides additional alternative diagnostic information [5].

Assessment of persistently symptomatic patients after a negative CTPA continues to pose a challenge for clinicians. Kline et al [6] found that 40% of patients who receive one CTPA to evaluate for possible PE underwent a second CTPA, which seldom demonstrated an actionable diagnosis. Because patients who have persistent dyspnea are more likely to return for repeat evaluation and undergo repeated nondiagnostic CTPA in the near term,

determining the cause of dyspnea may help guide the disposition of ED patients after a negative CTPA.

Many patients with dyspnea have evidence of coincident right ventricular (RV) dysfunction or overload. Right ventricular dysfunction may originate from intrinsic muscle damage caused by ischemia or cardiomyopathies. More commonly, however, RV dysfunction occurs from increases in RV after load, caused by treatable etiologies such as chronic obstructive pulmonary disease, obstructive sleep apnea, pulmonary arterial hypertension, or pulmonary hypertension secondary to left heart disease or chronic thromboemboli [7–13]. Detection of RV dysfunction from pulmonary hypertension is frequently under diagnosed. Once recognized, it is usually associated with a delay in evaluation and treatment [7,8,14,15]. Patients with underlying RV dysfunction, including RV dilation with or without RV hypokinesis, have increased morbidity and mortality [7,12]. In ED patients with dyspnea, RV dilation is an independent predictor of 1-year mortality [16].

In our derivation article [17], we derived a simple clinical decision rule (CDR) to identify patients with a high probability for isolated RV dysfunction or overload. This rule was derived from both inpatients and ED patients who were all adults older than 17 years and who underwent CTPA for suspected PE. The final rule consisted of persistent dyspnea plus a normal CTPA scan. With a positive rule, 22 (53%) of 41 (95% confidence interval [CI], 37%–69%) patients with transthoracic echocardiography performed had isolated RV dysfunction or overload. In the derivation cohort, when broadening normal CTPA, which excluded patients with underlying chronic diseases such as emphysema or cardiomegaly, to "CTPA without acute process", the CDR predicted 64 (36%) of 179 (95% CI, 29%–43%) patients to have isolated RV dysfunction or overload. These results were similar to the 30% prevalence of RV dysfunction in dyspneic patients reported by Chen et al [16] in the PRIDE study, which examined ED patients with shortness of breath, but was not restricted to those who had CTPA.

Given the importance of RV function on outcomes in a variety of disease states, we believe that early identification and initiation of therapy targeted at the cause of isolated RV dysfunction or overload, if possible, may improve outcome.

The aim of this study was to test the external validity of the previously derived CDR by measuring the prevalence of isolated RV dysfunction or overload and outcomes in ED patients with persistent shortness of breath and CTPA without acute process.

2. Methods

2.1. Study design and setting

This study was a secondary analysis of the Pulmonary Embolism Rule Out Criteria (PERC) database, a prospective observational study involving 12 EDs, that collected data on patients presenting to the ED with suspected PE. Institutional review boards approval was obtained at all participating hospitals. The methods from this study have been published previously [18].

2.2. Selection of participants

Patients were enrolled from July 1, 2003, until November 30, 2006. For our main analysis, we included ED patients with persistent shortness of breath, CTPA without acute process, and formal echocardiography performed. Persistent dyspnea was defined as patient's ongoing subjective feeling of shortness of breath at rest while breathing room air, during the index ED visit or hospital stay. "CTPA without acute process" was defined as a CTPA without evidence of PE, pulmonary infiltrate, thoracic malignancy, pneumothorax, aortic dissection, aortic aneurysm, or congestive heart failure. Exclusion criteria were patients without a history or complaint of shortness of breath or persistent shortness of breath, patients with a CTPA positive for PE or other acutely significant CT findings, patients with an admission and/or discharge diagnosis of PE, and patients without an echocardiography performed.

2.3. Study protocol

Patients were deemed eligible for enrollment if a diagnostic test for PE was ordered by or under the supervision of a board-certified emergency physician. The decision to order this test followed standard care and was based on history and physical examination findings. Diagnostic tests for PE included CTPA scan, pulmonary angiography, and ventilation-perfusion lung scanning. Patients were excluded if they had a known diagnosis of PE found on pulmonary vascular imaging performed in the previous 7 days or if they were at risk for loss to follow-up (eg, homeless, international travelers, and prisoners). Study enrollment varied by site and consisted of consecutive enrollment or random selection in 8-hour blocks of time with subsequent medical record review of eligible but unenrolled patients.

2.3.1. Clinical data—Treating clinicians collected and recorded data concurrently with routine patient care and prior to the clinician knowing the results of diagnostic tests. Data were collected on a standardized, Web-based form, with more than 65 data points.

2.3.2. Computed tomographic pulmonary angiography interpretation—The radiology department at each individual institution regulated scanning protocols. All data collected were from final interpretations by a board-certified radiologist. A diagnosis of PE was made if a pulmonary arterial filling defect was detected by the interpreting radiologist and identified as an acute PE.

2.3.3. Transthoracic echocardiography—All echocardiograms were performed at the discretion of the clinical care team. All institutions had facilities with Intersocietal Commission for the Accreditation of Echocardiography Laboratories accreditation, and board-certified cardiologists with echocardiography fellowship training provided final written interpretations of echocardiograms. Accordingly, all reports included estimate of left ventricular (LV) ejection fraction; an estimate of tricuspid regurgitation (TR) graded as none, mild, moderate, or severe; a Doppler measurement of tricuspid jet velocity (if obtainable); and a qualitative assessment of RV size (normal or enlarged) and function (normal or hypokinetic). Transthoracic echocardiography was categorized into 5 categories including the following: (1) normal LV and RV size and function, (2) LV ejection fraction

(LVEF) less than 45%, (3) isolated moderate to severe TR, (4) isolated RV hypokinesis and dilation, or (5) RV hypokinesis and dilation with moderate to severe TR.

2.3.4. Follow-up—Patients were followed up at 45 days postenrollment for outcome. All data, including explicit terms of LV and RV function, were abstracted by trained coordinators and transferred into a Web-based data collection instrument [19]. Direct patient contact was via telephone or mail, supplemented as needed by the medical record and/or a death registry review [18].

2.4. Data analysis

We compared means and bivariate frequencies measured in patients with and without echocardiography and in patients with and without isolated RV dysfunction or overload. Means were compared with an unpaired t test, and bivariate frequencies were compared with a χ^2 test. Our main analysis was the point estimate of the prevalence of isolated RV dysfunction or overload observed in persistently short of breath patients with a CTPA negative for PE or other significant finding and formal transthoracic echocardiography performed. Right ventricular dysfunction or overload was defined as RV hypokinesis and/or dilation with or without moderate to severe TR. Isolated RV dysfunction or overload was defined as RV dysfunction in the absence of LV systolic dysfunction.

We calculated percentages of RV dysfunction and isolated RV dysfunction or overload in those patients with a positive decision rule and echocardiography, with 95% CIs from the exact binomial formula (Stats Direct, v 2.7.9, Cheshire, England, UK). Statistical significance was accepted for $P < .05$.

3. Results

A total of 7940 patients were enrolled from the PERC database. Of these, 4784 patients were excluded because they did not meet the criteria for persistent dyspnea or did not have a CTPA scan performed. Five hundred forty patients were then excluded because their CTPA was positive for a PE or other acute process. Of the remaining 2616 patients included for analysis, 198 had formal transthoracic echocardiography performed. Figure shows a flow diagram of patients meeting the inclusion criteria. Table 1 shows patient characteristics comparing all enrolled patients with and without echocardiography. Overall, patients with echocardiography were older, were admitted to a higher level of care, and had more cardiovascular disease.

Analysis of the 198 patients with echocardiography (Table 2) yielded 38 (19%; 95% CI, 14%–25%) patients with evidence of RV dysfunction or overload, including RV dilation and/or hypokinesis with or without moderate to severe TR. One hundred sixty (81%; 95% CI, 74%–85%) patients had no evidence of RV dysfunction or overload; 53% were female. Compared with patients without RV dysfunction, patients with evidence of RV dysfunction or overload on echocardiography were more likely to be sicker, with 18% vs 7% (95% CI, of the difference, 0.4%–26%) being admitted to the intensive care unit (ICU), and tended to have a greater history of wheezing and tobacco use.

Of the 198 patients with an echocardiogram, 115 had normal LVEF, defined as ejection fraction greater than 45%. Thirty-five (30%; 95% CI, 23%–39%) of the patients with normal LVEF had moderate to severe TR without RV dilation. Thirty-eight (33%; 95% CI, 25%–42%) of the 115 patients with normal LVEF had isolated RV dysfunction or overload, 14 with RV dilation and moderate to severe TR and 24 with RV dilation without significant TR.

Table 3 compares outcomes of patients with and without isolated RV dysfunction or overload on echocardiography. Patients with RV dysfunction or overload were more likely to have a return visit to the ED within 45 days for the same complaint (39% vs 18%; 95% CI of the difference, 4%–38%) and tended to have more repeat CTPA scans within 45 days (10% vs 5%; 95% CI of the difference, −4% to 19%) and a higher mortality rate (16% vs 5%; 95% CI of the difference, −0.5% to 25%). Also, patients with isolated RV dysfunction or overload were more often discharged with a primary diagnosis of pulmonary hypertension ($P < .05$) than those patients without evidence of RV dysfunction or overload (Table 3).

4. Discussion

Unexplained RV dysfunction or overload was found to have a prevalence of 19% (95% CI, 14%–25%) in persistently dyspneic ED patients with a nonsignificant CTPA. The prevalence of RV dysfunction or overload increased to 33% (95% CI, 25%–42%) when excluding patients with abnormal LVEF.

Prior research has looked to define the prevalence of RV dysfunction in ED patients presenting with dyspnea. The PRIDE study looked to determine the use of N-terminal pro-brain natriuretic peptide (NT-proBNP) compared with echocardiographic parameters in ED patients with shortness of breath. In the PRIDE study, 134 (23%) of 599 dyspneic patients had an echocardiogram. Similar to our study, patients who received an echocardiography in the PRIDE study had more severe symptoms and were more likely to have a history of heart disease. Interestingly, 30% of these patients had changes in RV fractional area or RV dilation, 20% had RV hypokinesis, and 30% had moderate or severe TR [16].

Our derivation article found that patients with a positive CDR (consisting of persistent dyspnea and normal CTPA) and echocardiography performed as routine management exhibited a prevalence of isolated RV dysfunction or overload of 53% (95% CI, 37%–69%). This number decreased to a prevalence of 36% (95% CI, 29%–43%) when broadening the definition of normal CTPA (which excluded patients with underlying chronic diseases such as emphysema) to CTPA without acute process. This latter definition more accurately reflects the definition of negative CTPA used in this article.

Both the PRIDE and derivation studies show a similar prevalence of isolated RV dysfunction or overload, comparable to the current work, but comprise a different heterogeneous population and subset of data. Our study differs from the PRIDE study, however, in that we further risk stratified patients using CTPA to rule out PE or other significant findings. Furthermore, because LV failure is a leading cause of RV dysfunction [20], we examined the prevalence of isolated RV dysfunction or overload by excluding patients with an abnormal LVEF. In the derivation study, we defined isolated RV dysfunction or overload by excluding

patients with both systolic and/or diastolic LV dysfunction. However, in the present work, we were unable to exclude patients with LV diastolic dysfunction because this secondary analysis lacked echocardiographic information on LV diastolic function. Nonetheless, the prevalence of isolated RV dysfunction or overload is similar in the derivation and validation samples (36% vs 33%, respectively).

Prior literature has shown that patients with RV dysfunction or overload have worse outcomes. In patients with left heart failure or COPD, RV dysfunction or overload is associated with increased acute exacerbations and increased hospital readmissions compared with patients with normal RV function [7,21,22]. Patients with pulmonary hypertension complicated by RV dysfunction generally have a significantly poorer prognosis and decreased longevity [12,13,15].

This study corroborates findings in the derivation study showing a trend toward higher rates of return visits with repeat CTPA scanning among patientswith isolated RV dysfunction or overload. In the present study, patients with isolated RV dysfunction or overload had statistically significant higher rates of ICU admissions and return visits within 45 days for the same complaint. They also exhibited higher mortality rates and higher rates of repeat chest imaging within 45 days, but these outcomes did not reach statistical significance. Patients with RV dysfunction or overload were more likely to be diagnosed at hospital discharge with pulmonary hypertension than those patients without evidence of RV dysfunction on echocardiography. These results support the need for a clinical pathway to refer rule-positive patients for screening with echocardiography followed by evaluation in a multidisciplinary dyspnea clinic.

4.1. Limitations

This study analyzed a subset of patients from a previously collected sample where ordering an echocardiogram was not standardized but was ordered at the discretion of the treating physician. The patients may have had characteristics or severity of symptoms not easily identified by a secondary analysis, which persuaded clinicians to order the echocardiogram. Also, this was a multi-institution study with a lot of intrinsic variation, especially with availability of echocardiography among these institutions. Therefore, there was some selection bias in the patients who had an echocardiogram performed, as these patients were older and sicker.

Findings on echocardiography were divided into 5 categories as listed in the Methods section. It is possible that some patients included in the moderate to severe TR subgroup may have also had evidence of RV dysfunction and not recorded as such. As previous literature has shown, moderate to severe TR has a high correlation with RV dysfunction and/or dilation [23]. Thus, the prevalence of RV dysfunction may be underestimated and may actually be larger than 19%. We also defined isolated RV dysfunction or overload on echocardiography as evidence of RV dysfunction without concurrent LV systolic dysfunction. Because this was a secondary analysis of previously collected data, we lacked echocardiographic information on LV diastolic function, as this was not recorded in the original data set. In light of this, the prevalence of isolated RV dysfunction may actually be less than 33%. Lastly, there were no sample size calculations because this was a secondary

analysis. We had a small sample size of 198 patients, which is the result of a subset analyses from a much larger data set and therefore have larger CIs. A prospective study of echocardiogram findings in all cases of persistent dyspnea and negative CTPA might find a different prevalence of isolated RV dysfunction or overload with smaller CIs.

5. Conclusions

In an independent sample, RV dysfunction or overload has a prevalence of 19% in patients with persistent shortness of breath with a non-significant CTPA. In the subset of patients with preserved LVEF, the prevalence of isolated RV dysfunction or overload increases to 33%. Among patients selected for echocardiography based on standard clinical judgment, this CDR predicts significant risk for isolated RV dysfunction or overload, higher recidivism, and worsened outcomes. These data suggest a need for wider use of echocardiography to screen this subset of patients for RV dysfunction or overload and a need for specialist referral to identify treatable causes of RV dysfunction or overload. Future goals will be to prospectively validate this rule in the ED setting, with a next step of using bedside ultrasound to further risk stratify these patients.

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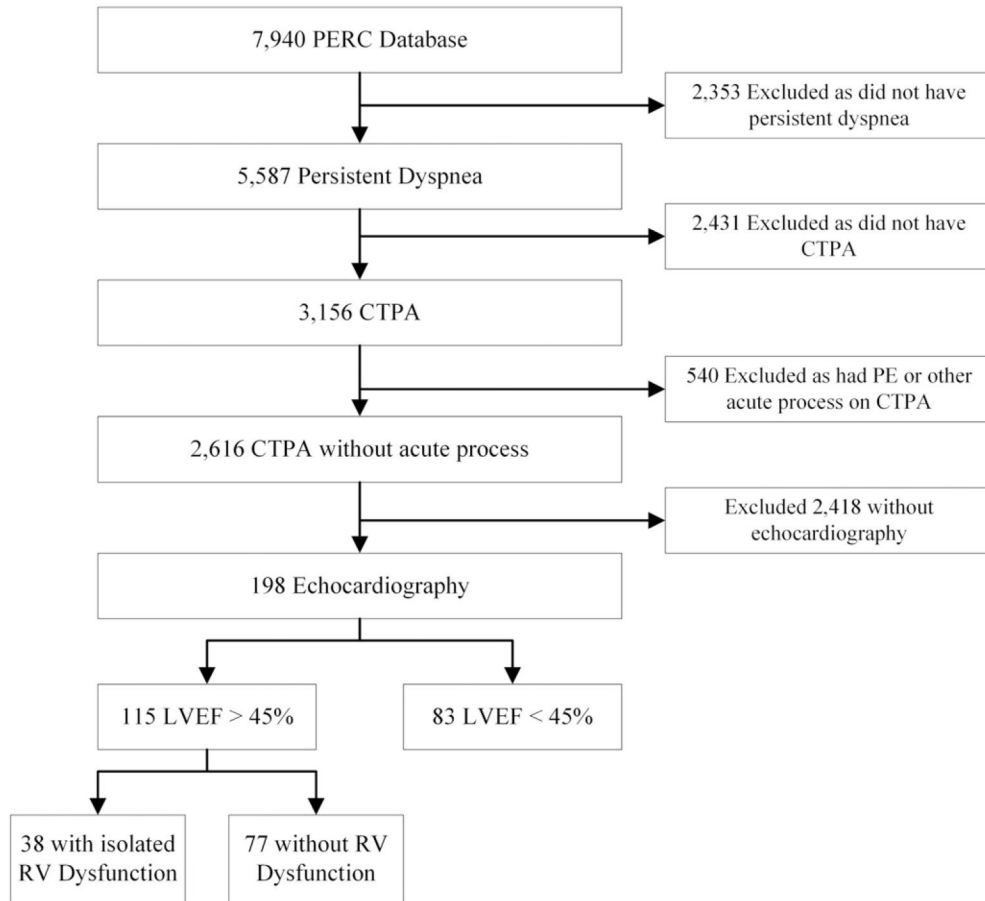
Figure.
Flow diagram of patients meeting inclusion criteria.

Table 1

Patient characteristics

	Echo (n = 198)	No echo (n =2418)	P^a
Demographics			
Age (y)	60 ± 17	51 ± 18	**<.05**
Male	83 (42)	716 (30)	**<.05**
BMI (kg/m^2)	30 ± 9	30 ± 9	.439
Ethnicity			
White	117 (59)	1362 (57)	.45
Black	68 (34)	853 (35)	.791
Other	13 (7)	203 (8)	.368
Vital signs			
Highest heart rate (beats/min)	103 ± 26	94 ± 22	**<.05**
Systolic blood pressure (mm Hg)	128 ± 28	132 ± 25	.058
Respiratory rate (breaths/min)	23 ± 6	22 ± 5	**<.05**
Oxygen saturation (%)	94 ± 6	96 ± 4	**<.05**
Temperature (°F)	98 ± 1	98 ± 1	.379
Associated symptoms			
Wheezing	36 (18)	345 (14)	.795
Chest pain at rest	49 (25)	1134 (47)	**<.05**
Prior visit for same symptoms	64 (32)	563 (23)	.268
Comorbidities			
Chronic lung disease	60 (30)	637 (26)	.867
Tobacco use	84 (42)	899 (37)	.142
Hematologic disease	2 (1)	54 (2)	
CHF	16 (8)	53 (2)	**<.05**
Hypertension	117 (59)	940 (39)	**<.05**
CAD	46 (23)	267 (11)	**<.05**
Connective tissue disease	7 (4)	107 (4)	.555
PE or DVT	27 (14)	331 (14)	.285
CKD on HD	7 (4)	28 (1)	**<.05**
Diabetes	55 (28)	330 (14)	**<.05**
CVA	19 (10)	96 (4)	**<.05**
Anxiety	17 (9)	274 (11)	.237
Malignancy	35 (18)	378 (16)	.448
Disposition			
ICU	19 (10)	48 (2)	**<.05**
Telemetry bed	121 (62)	633 (26)	**<.05**
Unmonitored bed	35 (18)	325 (13)	.096
Observation	8 (4)	270 (11)	**.002**
Discharge	12 (6)	1142 (48)	**<.05**

Data presented as number (percent) and mean ± SD. Bold numbers are values reaching statistical significance (P < .05).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Chronic lung disease, chronic obstructive pulmonary disease, asthma, and interstitial lung disease; CKD, chronic kidney disease; CVA, cerebrovascular disease; DVT, deep venous thrombosis; HD, hemodialysis.

[a]P values from unpaired t test or χ^2 test.

Table 2

Comparison of patients with and without RV dysfunction on echocardiography

	RVD (n = 38)	No RVD (n = 160)	P^a
Demographics			
Age (y)	63 ± 18	59 ± 17	.193
Male	18 (47)	65 (41)	.449
BMI (kg/m^2)	29 ± 7	30 ± 9	.286
Ethnicity			
White	25 (66)	92 (58)	.35
Black	10 (26)	58 (36)	.246
Other	3 (8)	10 (6)	.713
Associated symptoms			
Wheezing	10 (26)	26 (16)	.148
Chest pain at rest	8 (21)	41 (26)	.557
Prior visit for same symptoms	12 (32)	52 (33)	.913
Comorbidities			
Chronic lung disease	13 (34)	47 (29)	.809
Tobacco use	20 (53)	64 (40)	.156
CHF	12 (32)	37 (23)	.165
Hypertension	23 (61)	94 (59)	.841
CAD	13 (34)	33 (21)	.074
PE or DVT	7 (18)	20 (13)	.339
CKD on HD	2 (5)	5 (3)	.521
Diabetes	10 (26)	45 (28)	.822
Anxiety	3 (8)	14 (9)	.865
Malignancy	7 (18)	28 (18)	.893
Disposition			
ICU	7 (18)	12 (8)	**.039**
Telemetry bed	23 (60)	101 (63)	.765
Unmonitored bed	4 (11)	31 (19)	.198
Observation	1 (3)	7 (4)	.623
Discharge	3 (8)	9 (6)	.598

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Chronic lung disease, chronic obstructive pulmonary disease, asthma, and interstitial lung disease; CKD, chronic kidney disease; DVT, deep venous thrombosis; HD, hemodialysis; RVD, RV dysfunction.

^{a}P values from unpaired t test or χ^2 test. Data presented as number (percent) and mean± SD.

Table 3

Patient outcomes with normal LVEF

	RVD (n = 38)	No RVD (n = 77)	p^a
Mortality	6 (16)	4 (5)	.117
Return visits	15 (39)	14 (18)	**.013**
Repeat CTPA	4 (10)	4 (5)	.290
Final diagnosis			
COPD	8 (21)	8 (10)	.120
Asthma	1 (3)	3 (4)	.727
ILD	2 (5)	2 (3)	.463
Pneumonia	5 (13)	8 (10)	.659
CHF	7 (18)	12 (16)	.730
MI	1 (3)	1 (1)	.607
Sepsis	1 (3)	0 (0)	.152
Chest pain	3 (8)	14 (18)	.143
Pulmonary HTN	9 (24)	0 (0)	**<.05**
Other	10 (26)	37 (48)	**.025**

Data presented as number (percent). Other included dyspnea, valvular heart disease, syncope, acute bronchitis, pleural effusion, cancer, atrial dysrhythmias, anemia, hypertensive emergency, scleroderma, sleep apnea, renal failure, and pericarditis. Abbreviations: CHF= congestive heart failure; COPD, chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; HTN, hypertension; ILD, interstitial lung disease; MI, myocardial infarction; RVD, RV dysfunction.

[a]P values from unpaired t test or χ^2 test.