# Echocardiographic characteristics of patients with antisynthetase syndrome

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#### Abstract

Right ventricular (RV) dysfunction and pulmonary hypertension (PH) occurs in approximately one-third of patients with interstitial lung disease (ILD) and is associated with reduced 6-minute walk distance (6MWD), and increased hospitalizations and mortality. Although the impact of RV dysfunction and PH has been well described in several types of ILD, data is scarce on antisynthetase syndrome. Therefore, we sought to examine the presence of RV dysfunction and PH in patients with antisynthetase syndrome and the impact on clinical outcomes. We conducted a retrospective study of patients with antisynthetase syndrome. Seventy-five subjects were identified. Fifty-one (68%) subjects had echocardiographic data. Patients were grouped into those with normal fractional area change (FAC)  $\geq$  35% and reduced FAC < 35%. Clinical, echocardiographic, and right heart catheterization data were compared between the two groups. Subjects with FAC < 35% had lower diffusion capacity of the lung for carbon monoxide (29% vs. 47%, p = 0.004), fibrotic features on computed tomography of the chest (79% vs. 33%, p = 0.005), larger RV diameter (5.4 vs. 3.9 cm, p < 0.001), higher right atrial pressures (8 vs. 5 mmHg, p = 0.02), and required supplemental oxygen more frequently (100% vs. 44%, p < 0.001) compared to those with FAC  $\ge$  35%. We found no difference in 6MWD and hospitalizations between the two groups. The presence of RV dysfunction in antisynthetase syndrome may identify patients at risk of poor outcomes.

#### K E Y W O R D S

antisynthetase syndrome, echocardiography, pulmonary hypertension, right ventricular dysfunction

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# INTRODUCTION

Pulmonary hypertension (PH) due to chronic lung diseases (categorized as Group 3 PH) is the second most common cause of PH.<sup>1,2</sup> The presence of PH in interstitial lung disease (ILD) is associated with a reduction in exercise capacity, increased requirement for supplemental oxygen, and higher mortality.<sup>3-6</sup> In addition, patients with Group 3 PH have a worse prognosis than patients with Group 1 PH despite having a similar hemodynamic profile.<sup>7</sup> Until recently, patients with Group 3 PH had limited treatment options with immunomodulators, but no pulmonary vasodilator therapy. However, in a recent randomized controlled trial of patients with Group 3 PH secondary to ILD, treatment with inhaled prostacyclin resulted in a longer 6-minute walk distance (6MWD), stabilization of pulmonary function tests (PFTs) such as forced vital capacity, and reduction in hospitalizations compared to placebo.<sup>8</sup> Therefore, early identification, prognostication, and treatment of PH in ILD are imperative.

The most common method to identify subjects with PH in ILD is trans-thoracic echocardiography (TTE).<sup>9</sup> Besides a screening tool, TTE also serves as a useful prognostic tool in patients with PH-ILD.<sup>7,10</sup> Although prior studies have described echocardiographic features of patients with and without PH in ILD, there is limited data describing echocardiographic characteristics in patients with the antisynthetase syndrome.<sup>7,10</sup> In the study by Prins et al., which described echocardiographic features of subjects with Group 3 PH, 64 out of 147 patients had ILD.<sup>10</sup> However, the number of patients with the antisynthetase syndrome in this study is unknown. Another study examined PH and its impact on patients with the antisynthetase syndrome.<sup>4</sup> This study reported echocardiographic data in subjects with pre-capillary PH (n = 16) and was limited to only three variables, namely left ventricular ejection fraction, pulmonary artery systolic pressures, and the presence of right ventricular (RV) dilation. The remainder of the literature is limited to isolated care reports, and none of them provided any echocardiographic data with the exception of RV systolic pressures.<sup>11–13</sup> Due to the paucity of data, we sought to describe echocardiographic features in a larger group of subjects with the antisynthetase syndrome, and provide more in-depth details about the right ventricle in this cohort. In addition, given that RV systolic function on TTE serves as a prognostic tool in patients with PH-ILD,<sup>7,10</sup> we hypothesized that subjects with impaired RV function may have worse outcomes compared to those with normal RV function. Preliminary results from this analysis were presented at American Thoracic Society International Conference 2021 (AJRCCM 2021; 203:A3581).

#### **METHODS**

Our study was approved by our university's Institutional Review Board (202000868). The study data is available upon request.

### **Study population**

We conducted a retrospective study of patients aged  $\geq$ 18 years diagnosed with antisynthetase syndrome at our university's Interstitial Lung Disease Clinic between 2010 and 2020. To identify these patients, we queried our institution's data repository for all patients who had the following antibodies tested: anti-Jo1, anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-Zo, anti-SC, anti-JS, anti-HA, and anti-YRS. A total of 9036 patients were obtained. From this initial list, we screened for patients with the diagnosis of the antisynthetase syndrome (Figure 1).

#### Definition of antisynthetase syndrome

Antisynthetase syndrome was diagnosed by two clinicians with expertize in ILD (D.G. and D.P.) using the classification proposed by Connors et al.<sup>14</sup> and Solomon et al.<sup>15</sup> Connor's requires the presence of an antiaminoacyl transfer RNA (tRNA) synthetase autoantibody and one or more of the following criteria: Raynaud's syndrome, arthritis, ILD, fever (not attributable to another cause), and mechanics' hands. Solomon's requires the presence of an auto-antibody plus two major criteria (ILD not attributable to another cause and myositis), or one major and two minor criteria (arthritis, Raynaud's phenomenon, and mechanics' hands). Patients were excluded from the study if there was any discrepancy between the reviewers. Given that neither Connor's nor Solomon's criteria have been shown to correlate with long-term outcomes, we included both.

#### Data collection

Variables such as comorbidities, serologies, computed tomography (CT) of chest findings,<sup>16,17</sup> PFTs,<sup>18</sup> 6MWD,<sup>19</sup> echocardiography,<sup>20–22</sup> right heart catheterization (RHC)<sup>23</sup> data and clinical outcomes such as hospitalizations, death, and/or lung transplant were collected. Details of the methodology for the variables collected are described in detail in the Supporting Information (Section 1). The median time from diagnosis of antisynthetase syndrome to PFTs,



\* Antibodies of interest: Jo1, PL7, PL12, OJ, EJ, KS, ZO, SC, JS, HA, YRS

\*\* Other diagnoses: Hypersensitivity Pneumonitis (N=1), Cryptogenic Organizing Pneumonia (N=1), Interstitial Pneumonia with Auto-immune Features (N=1), Sjogren's ILD (N=1), Overlap Syndrome (N=6), Rheumatoid ILD (N=1)

**FIGURE 1** Flow diagram of patient selection.

echocardiography, and RHC was 3 (0.6-10), 1.9 (0.7-12.2), and 6.4 (1.1-26.3) months, respectively.

# Echocardiography

Comprehensive echocardiographic examinations were performed using commercially available equipment (Philips IE33; Phillips Ultrasound) at our university's Echocardiography Laboratory. All measurements were performed according to the American Society of Echocardiography (ASE) chamber quantification and right heart assessment guidelines on an offline workstation by a board-certified cardiologist with Core Cardiology Training Symposium level 3 competence in echocardiography (R.M.).<sup>20–22</sup> The details of each measurement are described in the Supporting Information (Section 2). We also compared subjects with and without echocardiography to understand if any differences in clinical characteristics could have contributed to the decision to obtain a TTE (Supporting Information: Table 1).

# RHC

Patients underwent RHC as part of a transplant evaluation or if echocardiography suggested a high probability of PH.<sup>9</sup> The details of each measurement are described in the Supporting Information (Section 3).

# Comparison of subjects with normal RV systolic function defined as fractional area change (FAC) ≥ 35% versus subjects with reduced RV systolic function defined as FAC < 35%

We compared clinical, PFTs, echocardiographic, and RHC data between subjects with normal and reduced FAC%. We specifically chose FAC% as the grouping variable as it has been shown to correlate with RV ejection fraction most closely on cardiac magnetic resonance imaging (MRI) and is associated with outcomes in ILD.<sup>10,24</sup> Hospitalizations were included only if they were due to a respiratory event such as pneumonia, decompensated RV failure and/or ILD exacerbation per the treating clinician.

# Comparison of subjects with and without PH

PH was defined according to the 2018 World Symposium on Pulmonary Hypertension associated with chronic lung diseases.<sup>25</sup> Accordingly, PH was defined as mean pulmonary artery pressure (MPAP) 21–24 mmHg with pulmonary vascular resistance (PVR)  $\geq$  3 Wood units (WU), or MPAP 25–34 mmHg obtained by RHC. Severe PH was defined as MPAP  $\geq$  35 mmHg, or MPAP  $\geq$  25 mmHg

# Pulmonary Circulation

**TABLE 1**Comparison of patients with normal (FAC  $\geq$  35%)and reduced (FAC < 35%) right ventricular systolic function</td>

	FAC < 35% N = 14	$FAC \ge 35\%$ $N = 36$	p Value	
Age in years	55 (48–59)	51 (41-61)	0.51	
Body mass index (kg/m <sup>2</sup> )	27 (24–32)	30 (25-35)	0.34	
Gender: male/ female ( <i>n</i> )	8/6	5/31	0.004	
History of cigarette smoking, <i>n</i> (%)	6 (43)	13 (36)	0.66	
Oxygen use, $n$ (%)	14 (100)	16 (44)	< 0.001	
Oxygen (LPM)	3 (2-3)	3 (3-3.3)	0.94	
Six-minute walk distance (m)*	303 (183–387)	339 (220–385)	0.90	
Borg dyspnea scores at rest*	1 (0-3)	0.5 (0-1.3)	0.53	
Borg dyspnea scores at exercise*	3 (0.5-4)	3 (2-5)	0.51	
Hospitalizations	1 (0.5-4)	1 (0-3)	0.27	
Pulmonary artery size (cm)	3.1 (2.6–3.3)	2.7 (2.5–3)	0.06	
Clinical findings, n (%)				
Raynaud's	4 (29)	10 (28)	1	
Mechanic's hands	1 (3)	7 (19)	0.41	
Arthritis	3 (21)	17 (47)	0.118	
None	6 (43)	10 (28)		
Myositis, $n (\%)^{**}$				
Elevated CK or aldolase	13 (93)	23 (64)	0.076	
Pathologic evidence	1 (7)	7 (19)		
Abnormal EMG	0	2 (6)		
None	1 (7)	0		
Serology, n (%)				
Jo1	7 (50)	26 (72)	0.10	
PL12	4 (28)	7 (19)	0.48	
EJ	2 (14)	1 (3)	0.19	
PL7	1 (8)	1 (3)	0.49	
Radiographic gindings, <i>n</i> (%)				
Honeycoming	4 (29)	3 (8)	0.08	
Traction bronchiectasis	11 (79)	12 (33)	0.005	

#### **TABLE 1** (Continued)

	FAC < 35% N = 14	FAC≥35% N=36	p Value
Groud glass opacities	13 (93)	26 (72)	0.148
Current status, n (%)			
Alive	8 (57)	27 (75)	0.04
Dead or lung transplant	6 (43)	8 (22)	
Unknown	0	1 (3)	
Pulmonary function tests			
FEV1 (%)	59 (50-69)	58 (48-75)	0.82
FVC (%)	55 (44-61)	59 (48-71)	0.27
DLCO Hg (%)	29 (21-42)	47 (40-67)	0.004
TLC (%)	53 (44-60)	54 (47-72)	0.44
FVC/DLCO	1.8 (1.0-3.2)	1.2 (1-1.5)	0.045
Right heart catheterization			
Total number of patients*** n (%)	12 (86)	7 (19)	
SVO <sub>2</sub> (%)	72 (62–75)	69 (62-74)	0.90
RAP (mmHg)	8 (5-12)	5 (1.3-6.5)	0.02
RV systolic (mmHg)	45 (32–78)	35 (31–37)	0.062
RV diastolic (mmHg)	7 (5–8)	5 (1.3-6.5)	0.075
MPAP (mmHg)	30 (18-50)	22 (18-24)	0.09
PAOP (mmHg)	9 (8–15)	8.5 (4-13)	0.31
CO (L/min)	4.6 (2.7-5.9)	6 (4.4-6.5)	0.13
CI (L/min/m <sup>2</sup> )	2.3 (1.6-2.9)	2.9 (2.3-3.2)	0.18
PVR (WU)	3.1 (1.9–10)	2.2 (1.3-3.08)	0.09
Stroke volume (ml)	50 (36-90)	72.3 (56-88)	0.27
RAP/PAWP	0.8 (0.6–1.3)	0.5 (0.4–0.6)	0.012
PAPI	3.9 (2.4-5.6)	3.6 (2.4–20.5)	0.72
PA elastance (mmHg/ml)	1.0 (0.4–1.8)	0.5 (0.4–0.5)	0.15
PA compliance (ml/mmHg)	1.2 (0.9–4.1)	3.7 (3.1-4.7)	0.13
Echocardiography $(n = 50)$			
LVEF (%)	60 (55-65)	63 (60-65)	0.12
RVSP (mmHg)	55 (45-75)	30 (30-40)	< 0.001

#### **TABLE 1** (Continued)

	FAC < 35% N = 14	$FAC \ge 35\%$ $N = 36$	p Value
TAPSE (mm)	14 (10-23)	23 (20-24)	0.006
TAPSE/PASP	0.2 (0.1–0.5)	0.67 (0.56–0.86)	<0.001
RV/LV ratio	1.1 (0.6–1.4)	0.6 (0.5–0.7)	0.009
TRV $(m s^{-1})$	3.1 (2.8-3.8)	2.5 (2.3-2.6)	< 0.001
RA volume (ml)	65 (49-88)	35 (28-45)	< 0.001
RA area (cm <sup>2</sup> )	22 (17-26)	14.5 (12.3–18)	< 0.001
RIMP	0.6 (0.4-0.9)	0.2 (0.1-0.3)	< 0.001
FAC (%)	24.3 (18.7–27.3)	43.2 (40.5-51.3)	<0.001
RV basal diameter (mm)	53 (47-59)	39 (34-43)	<0.001
RV length (mm)	81 (69-91)	73 (68–78)	0.036
RV thickness (cm)	0.9 (0.7–1.1)	0.5 (0.45-0.7)	0.005
RAP (mmHg)	8 (8-15)	8 (3-8)	0.001

*Note*: Continuous variables are specified using median with interquartile ranges. Categorical variables are specified as percentages. Continuous variables are compared using Mann–Whitney U test. Categorical variables are compared using Fisher's Exact test.

Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; CI, cardiac index; CK, creatinine kinase; CO, cardiac output; DLCO Hg, diffusion capacity of lung for carbon monoxide corrected for hemoglobin; FAC, fractional area change; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HIV, human immunodeficiency virus; LPM, liters per minute; LV, left ventricle; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAOP, pulmonary arterial occlusion pressure; PAPI, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RHC, right heart catheterization; RIMP, right ventricular index of myocardial performance; RV, right ventricle; RVOT VTI, right ventricular outflow tract velocity time integral; RVSP, right ventricular systolic pressure; SVO2, mixed venous oxygenation %; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; TRV, tricuspid regurgitant velocity.

\*Ten patients with FAC < 35% and 24 patients with FAC  $\geq$  35% had 6MWT data.

\*\*Statistical analysis was performed for only CK or aldolase as all included patients had these levels measured.

\*\*\*Twenty patients had RHC data of which one patient did not have echocardiography.

with low cardiac index  $(CI) < 2.0 \text{ Lmin}^{-1} \text{ m}^{-2}$ . All patients who met this definition of PH had forced vital capacity <70%. We compared hemodynamic, echocardiographic, and clinical characteristics of subjects with and without PH.

### **Statistics**

We summarized continuous variables as medians with interquartile ranges and categorical variables as percentages. For comparison of subjects with normal and reduced FAC% and those with and without PH by RHC, categorical variables were compared using Fisher's Exact test and continuous variables were compared using Mann–Whitney test. All statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.

#### RESULTS

A total of 9036 patients were obtained using the search criteria (Figure 1). One hundred and sixteen (1.3%) of patients had the antibodies of interest. Seventy-five patients were diagnosed with the antisynthetase syndrome. Other diagnoses are reported in Figure 1. Fiftytwo (69%) patients met Solomon's criteria and 75 (100%) patients met Connor's criteria for the antisynthetase syndrome.<sup>14,15</sup> Fifty-one (68%) patients had echocardiographic data and 20 (27%) patients had RHC data. The baseline characteristics of these patients are summarized (Supporting Information: Table 2). The median age was 53 (42-61) years. Fifty-nine (79%) of the subjects were female. Non-Hispanic Blacks and non-Hispanic Whites constituted the majority of the patients-34 (45%) and 31 (41%), respectively. Subjects with echocardiographic data had higher Borg dyspnea scores at rest (0.5 vs. 0, p = 0.04) and at exercise (3 vs. 0.75, p = 0.02), respectively and subjects in the echocardiography group also had more hospitalizations (1 vs. 0, p < 0.001) compared to the non-echocardiography group. There was no difference in body mass index, smoking history, oxygen use, sixminute walk distance, PA size, or PFTs between groups (Supporting Information: Table 1).

# Comparison of subjects with reduced (FAC < 35%) versus normal (FAC ≥ 35%) RV systolic function

A total of 50 (66%) subjects had measurable FAC%. Males were more common amongst those with FAC% < 35% (p = 0.004) (Table 1). There was no difference in serology and clinical findings. However, subjects with reduced FAC% were more likely to have fibrotic features on the CT chest at presentation such as traction bronchiectasis (79% vs. 33%, p = 0.005), and there was a trend toward increased honeycombing (29% vs. 8%, p = 0.08). Subjects

# Pulmonary Circulati<u>on</u>

with lower FAC% had higher mortality and/or transplant rates (43% vs. 22%, p = 0.04).

Compared to subjects with normal FAC%, those with reduced FAC% had lower DLCO (29% vs. 47%, p = 0.004), higher FVC/DLCO (1.8 vs. 1.2, p = 0.04), higher RAP (8 vs. 5 mmHg, p = 0.02) and increased signs of RV remodeling such as larger RV diameter (53 vs. 39 mm, p < 0.001) and RV thickness (0.9 vs. 0.5 cm, p = 0.001). There was trend toward higher PVR in subjects with lower FAC% (3.1 vs. 2.2 WU, p = 0.09). Oxygen use was more common in subjects with FAC < 35% compared to subjects with normal FAC% (100% vs. 44%, p < 0.001) (Table 1). We found no differences in 6MWD and hospitalizations between the two groups (Table 1).

# Comparison of subjects with and without PH

Clinical characteristics of patients with PH are described in Table 2. There was no difference in clinical, serologic and radiographic findings between the two groups. TLC% was lower in subjects with PH compared to subjects without PH (44% vs. 55%, p = 0.002) (Table 2). We found no difference in FVC/DLCO ratio (1.64 vs. 1.81, p = 0.90) between the two groups. Other significant findings included lower TAPSE (10.5 vs. 23.5 mm, p = 0.01) and higher RIMP (0.91 vs. 0.15, p = 0.02) in the PH group. In addition, right sided remodeling features such as RV enlargement (53.5 vs. 43 mm, p = 0.002), RA area enlargement (25.5 vs. 14.2 cm<sup>2</sup>, p = 0.01), and septal flattening (75% vs. 18%, p = 0.02) were more prominent in subjects with PH. There was a trend towards lower FAC% in the PH group (24% vs. 37%, p = 0.07).

# DISCUSSION

Antisynthetase syndrome is a rare rheumatologic disorder with antibodies directed against aminoacyl-tRNA synthetase along with clinical manifestations such as ILD, Raynaud's phenomena, myositis, and mechanics hands.<sup>14,15</sup> PH has been described in approximately 8% of patients with the antisynthetase syndrome.<sup>4</sup> Our study examined echocardiographic characteristics in this cohort and the impact of impaired RV function. The main findings of our study are (1) amongst those with echocardiographic data and measurable FAC, FAC < 35% was presented in 14/ 50 (28%) subjects, (2) subjects with FAC < 35% more often had fibrotic changes and larger pulmonary arterial diameter on CT chest, reductions in DLCO, and RV remodeling, and (3) mortality and/or lung transplant rates were higher in subjects with FAC < 35%.

RV dysfunction in PH-ILD is estimated to occur in 37%–49% of patients.<sup>10,26</sup> The variable prevalence in reported studies is likely due to the definition used, the type of ILD and the severity of ILD at the time of the study.<sup>27</sup> In our study, 28% of patients had impaired RV function. In a study of 167 patients (89 of whom had FAC % measured) with Group 3 PH by Prins et al., impaired RV function defined as FAC < 28% was present in 58% of subjects.<sup>10</sup> In another study of subjects with interstitial pneumonia with autoimmune features, 15/39 (38%) of subjects had FAC < 35%.<sup>28</sup> The lower percentage of subjects with impaired FAC% in our study compared to the study by Prins et al. could be due to variation in the study population.<sup>10</sup> Their study consisted of a mixed group of Group 3 PH such as chronic obstructive pulmonary disease, combined pulmonary fibrosis and emphysema, obesity related lung disease and ILD, whereas our study was limited to antisynthetase syndrome alone. It is also possible that the study by Prins et al. had a sicker cohort of patients as seen by lower FAC % in their cohort compared to our population,  $29 \pm 10$ versus  $39 \pm 13$ , respectively.<sup>10</sup>

We compared our cohort of patients based on FAC% as it has been shown to correlate with long term survival in Group 3 PH patients.<sup>10</sup> Furthermore, FAC% is a twodimensional parameter that incorporates the longitudinal, transverse shortening, and septal displacement into one measure and also has a strong correlation with cardiac MRI derived RV ejection fraction, which has emerged as a goal standard to evaluate RV function.<sup>24,29</sup> In our study, subjects with FAC < 35% had lower DLCO, higher FVC/DLCO, and were more likely to have fibrotic lung disease features. There was no difference in serology between the two groups. Similar findings were noted by Hervier et al. who found higher prevalence of ILD, lower DLCO and higher FVC/DLCO in those with PH and no difference in serology between those with and without PH.<sup>4</sup> Subjects with FAC < 35% also had higher rates of RV remodeling, a finding noted in other studies examining ILD patients with and without PH.<sup>10,28</sup> Another significant finding was higher mortality rates or lung transplant requirements in those with FAC < 35%compared to those with FAC  $\geq$  35%. Similar findings were reported by Prins et al. who not only found higher mortality in those with impaired FAC% but also a direct association between reduced FAC% and mortality or hospitalization. We did not examine whether there was an association between FAC% and mortality given the small sample size.

Besides mortality, impaired RV systolic function in PH-ILD is also associated with other clinical outcomes such as oxygen requirement, hospitalizations, and 6MWD.<sup>6,10,26</sup> In our study, patients with reduced FAC%

**TABLE 2**Comparison of patientswith and without pulmonaryhypertension diagnosed by right heartcatheterization

# Pulmonary Circulation

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	PH ( <i>n</i> = 9)	No PH ( <i>n</i> = 11)	p Value
Age in years	53 (40-71)	57 (44–70)	0.07
Body mass index (kg/m <sup>2</sup> )	29.9 (22.8–37)	30.3 (21.3-39.3)	0.47
Gender: male/female (n)	5/4	4/7	0.65
Borg dyspnea score with rest	2 (0-2)	2 (0.5–3)	0.74
Borg dyspnea score with exertion	2 (0.5–2)	5 (1.75-5.5)	0.536
Six-minute walk distances (m)	213.36 (150–213.36)	330 (213.42-419.06)	0.27
Hospitalizations	4 (1-4)	0 (0-3.5)	0.238
Clinical findings			
Raynaud's	3 (33)	2 (18)	0.62
Mechanic's hands	0	1 (9)	1
Arthritis	3 (33)	6 (55)	0.37
None	5 (56)	3 (27)	
Myositis, n (%)			
Elevated CK or aldolase	7 (78)	6 (67)	0.37
Serology, n (%)			
Jo1	5 (56)	7 (64)	1
PL12	2 (22)	3 (27)	1
EJ	0	0	0.57
PL7	2 (22)	1 (9)	
Radiographic gindings, n (%)			
Honeycoming	1 (11)	2 (18)	1
Traction bronchiectasis	6 (67)	7 (64)	1
Groud glass opacities	9 (100)	9 (100)	1
Current status, n (%)			
Alive	3 (33)	6 (55)	0.41
Dead or transplant	6 (67)	5 (45)	
Pulmonary function tests			
FEV1 (%)	42 (37–50.5)	58 (54–76)	0.003
FVC (%)	43 (40-46)	57 (49-65.5)	0.001
FEV1/FVC	82 (79-85.75)	88 (82-89)	0.351
TLC (%)	44 (38.5–49.25)	55 (49.5–59.5)	0.002
DLCO (%)	26.5 (15-41.5)	37 (23-44.5)	0.351
FVC/DLCO	1.64 (1.03–3.67)	1.81 (1.18–2.42)	0.904
Right heart catheterization			
RAP (mmHg)	10 (8-13.5)	5 (4.25-6.25)	0.025
MPAP (mmHg)	39 (27.75-61.25)	20 (17.75–23.25)	< 0.001
PAOP (mmHg)	9.5 (8.25–14.25)	8.5 (4.75–14.25)	0.552
CO (L/min)	3.85 (2.68-5.35)	6.1 (4.67–6.57)	0.01
CI (L/min/m <sup>2</sup> )	1.95 (1.53-2.75)	2.95 (2.48-3.2)	0.02

TABLE 2 (Continued)

Pulmonary Circulation

	PH ( <i>n</i> = 9)	No PH ( <i>n</i> = 11)	p Value
PVR (WU)	7.5 (3.58–18.5)	1.75 (1.43–2.28)	< 0.001
SV (ml)	46.57 (29.25–79.54)	76.69 (66.65–90.66)	0.034
SVO <sub>2</sub> (%)	63 (56.75-74.25)	72 (66–74)	0.238
PAPI	3.85 (2.38-6.63)	4 (2.6–10)	0.970
PA elastance (mmHg/ml)	1.59 (0.53–2.74)	0.46 (0.36-0.50)	0.012
PA compliance (ml/mmHg)	1.08 (0.62-3.92)	3.96 (2.98-4.63)	0.051
Echocardiography			
LVEF (%)	60 (60-68.75)	65 (60-66.25)	0.663
TAPSE (mm)	10.5 (9.25–20.25)	23.5 (19.75-26.5)	0.021
RIMP	0.913 (0.24–0.96)	0.153 (0.115-0.355)	0.047
FAC%	24.14 (14.19–34.23)	37.5 (24.32-43.12)	0.069
RV basal diameter (mm)	53.5 (49-61.75)	43 (34.25-45)	0.002
RVSP (mmHg)	60 (35-60)	45 (35–53.5)	0.038
TRV (m s <sup>- 1</sup> )	3.63 (2.81-4.80)	2.95 (2.73-3.14)	0.129
RAP (mmHg)	11.5 (8–15)	8 (3-8)	0.364
RA area (cm <sup>2</sup> )	25.5 (21.5–34)	14.18 (12.75–19.13)	0.01
RA volume (ml)	73 (51–73)	29 (27.5-45.5)	0.009
RV/LV ratio	1.07 (1.05–1.07)	0.58 (0.5-0.64)	< 0.001
Interventricular septal flattening, <i>n</i> (%)	6 (75)	2 (18.2)	0.024

*Note*: Continuous variables are specified using median with interquartile ranges. Continuous variables were compared using Mann–Whitney U test.

Abbreviations: CI, cardiac index; CO, cardiac output; DLCO Hg, diffusion capacity of lung for carbon monoxide corrected for hemoglobin; FAC, fractional area change; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HIV, human immunodeficiency virus; LPM, liters per minute; LV, left ventricle; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAOP, pulmonary arterial occlusion pressure; PAPI, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RIMP, right ventricular index of myocardial performance; RV, right ventricle; RVOT VTI, right ventricular outflow tract velocity time integral; RVSP, right ventricular systolic pressure; SVO<sub>2</sub>, mixed venous oxygenation %; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; TRV, tricuspid regurgitant velocity.

required supplemental oxygen more frequently than those without any echocardiographic abnormalities. In addition, patients with RV dysfunction reported higher dyspnea scores, a finding observed in other studies of subjects with PH and ILD.<sup>30,31</sup> We found no differences in 6MWD, and hospitalizations when stratified by the echocardiographic function (normal vs. reduced FAC %). We suspect that the discrepancy in our study is likely due to the small sample size as only 34 out of 50 subjects with echocardiographic data had 6MWD performed. In addition, the time between the echocardiography and the 6MWD test was variable between patients, which could have contributed to a

discrepancy between echocardiographic findings and 6MWD performance.

We suspect that the main classification of PH in our cohort is Group 3 PH. In our study, all subjects with PH confirmed by RHC had FVC < 70% suggesting a Group 3 process (Table 3). All PH subjects had some manifestation of ILD (namely ground-glass opacities and traction bronchiectasis), a finding noted by Hervier et al., who also reported nonspecific interstitial pneumonia patterns among subjects with PH in 81% of subjects.<sup>4</sup> However, direct vascular involvement is also possible as seen in three subjects (#2, #3, and #6) who had PVR ranging from 10 WU to 21 WU, suggesting an out of proportion

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PH (Table 3). Direct vascular injury was noted in an invitro study of lung endothelial cells in subjects with anti-Jo1 antibodies.<sup>32</sup> In the study, sera from patients with anti-Jo1 induced expression of intracellular adhesion molecule in endothelial cells, a process thought to contribute to Group 1 PH.<sup>32,33</sup> Our study differs from the study by Hervier et al. in that they reported a high prevalence of arthritis and an elevated FVC/DLCO in the PH group compared to the non-PH group.<sup>4</sup> This could be due to a small sample size in our group. However, a notable difference is that they compared PH subjects identified by RHC to patients with

Patient #	1	2	3	4	5	6	7	8	9
Age at time of diagnosis (years)	66	55	57	38	53	50	37	36	55
BMI (kg/m <sup>2</sup> )									
Gender	Female	Male	Male	Male	Male	Female	Male	Female	Female
Serology	PL12	JO-1	PL7	JO-1	JO-1	JO-1	PL12	JO-1	PL7
Physical exam signs	Raynaud's, arthritis	None	None	None	Raynauds	None	Arthritis	None	Raynaud's, arthritis
Muscle enzyme elevation (CK or aldolase)	Present	Absent	Present	Present	Present	Absent	Present	Present	Present
Right heart catherization									
RAP (mmHg)	8	8	15	3	15	15	8	3	
MPAP (mmHg)	42	65	65	30	50	36	21	27	31
PAOP (mmHg)	15	8	10	12	15	9	2	9	8
CO (L/min)	3.67	2.67	2.5	5.89	4.6	2.7	4.04	5.6	5.3
PVR (WU)	7.4	21.3	21.8	3.1	7.6	10	4.7	3.2	4.34
PA compliance (ml/mmHg)	0.93	0.44	0.51	5.17	0.93	1.23	1.58	4.69	
PA elastance (mmHg/ml)	1.64	4.12	3.06	0.46	1.55	1.78	0.74	0.44	
Echocardiography									
LVEF (%)	60	60	70	50	60	65	70	60	
RVSP (mmHg)	60	110	110		50	75	35		
FAC (%)	23.08	9.09	17.14	25.20	13.21	25.81	43.75	37.04	
TAPSE (mm)	8	10	11	9	10	12	30	23	
Pulmonary function tests									
FVC (%)	59		43	40	40	47	29	43	43
DLCO Hg (%)	15		24	55	44	34	4	29	15
FVC/DLCO	3.9		1.8	0.72	0.9	1.4	7.25	1.5	2.9
CT chest findings	Diffuse GGO, TB	Lower lobes GGO, TB	Lower lobes GGO, TB, honey- combing	Lower lobes GGO, TB	Lower lobes GGO, TB	Lower lobes GGO	Lower lobe GGO	Upper lobes GGO	Diffuse GGO, TB

Abbreviations: BMI, body mass index; CK, creatinine kinase; CO, cardiac output; DLCO Hg, diffusion capacity of the lung for carbon monoxide; FAC, fractional area change; FVC, forced vital capacity; GGO, ground glass opacities; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TB, traction bronchiectasis. echocardiographic data only suggesting that PH patients could have a more severe disease manifestation such as arthritis. Nevertheless, FVC/DLCO may be a useful finding to identify patients with both impaired RV function and those with PH.<sup>34</sup>

The strengths of our study are as follows. First, we had a decent sample size of 75 patients with antisynthetase syndrome of whom 51 had echocardiographic data. We included subjects with antibodies directed against anti-aminoacyl tRNA synthetase only, unlike the study by Hervier et al. who included patients with other antibodies (SSA, SSB, RBP, ds-DNA, centromere).<sup>4</sup> In addition, all patients' diagnosis was reviewed by two Pulmonologists with expertize in ILD, and echocardiographic parameters were obtained by a Cardiologist with Core Cardiology Training Symposium level 3 competence. Second, to the best of our knowledge, our study is novel in that we are the first to comprehensively describe RV echocardiographic characteristics and examine the impact of RV dysfunction on clinical outcomes in this patient population. Third, we add to the growing body of literature that PH is a complication of the antisynthetase syndrome and it may not be a rare event. RV dysfunction was present in almost a third of patients and amongst those with RHC data, PH occurred in 9 subjects. Hervier et al. reported PH in 16 of 172 subjects (all subjects did not have RHC).4

Our study has several limitations. First, our study is a single-center retrospective cohort study. Second, our study was conducted at a tertiary center where patients tend to be sicker at presentation, and thus our data may not be generalizable to the community. For example, it is possible that echocardiography was only obtained in patients who might have reported higher dyspnea scores or those who were hospitalized (Supporting Information: Table 1). As such, the selection bias could have led to an overestimation of RV dysfunction (e.g., FAC%) in this cohort, particularly if the echocardiogram was obtained while admitted for respiratory decompensation. However, patients with reduced FAC% also had other features of RV remodeling such as RV wall hypertrophy and RV enlargement suggesting a chronic process. Third, we could not examine whether there is a direct association between reduced FAC% and mortality due to the small sample size.

In summary, RV dysfunction is not a rare complication in patients with antisynthetase syndrome and is associated with with higher rates of mortality and/or lung transplantation. Clinicians should be aware of this complication and could consider using echocardiography to identify those at risk of poor outcomes.

#### AUTHOR CONTRIBUTIONS

Akram Khan and Jeffrey Robinson: Investigation, Project administration, Writing – reviewing and editing. Veronica Keteyeva, Abheek Raviprasad, Omkar Betageri, and Eduardo Milla: data curation, writing original draft. Divya Patel: Data curation, Investigation, Project administration, Writing – reviewing and editing. Jaimie L. Bryan, Ralph Matar, Diana G. Manjarrez, Saminder S. Kalra, Raju Reddy – Data curation, Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – reviewing, and editing.

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#### **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

#### ETHICS STATEMENT

The study was approved by The University of Florida's Institutional Review Board (202000868).

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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