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Performance of the DETECT Algorithm for Pulmonary Hypertension Screening in a Systemic Sclerosis Cohort

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Abstract:

Objective: Pulmonary arterial hypertension (PAH) is one of the leading causes of mortality in systemic sclerosis (SSc). We assessed predictive accuracies of the DETECT algorithm and 2015 European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines in a SSc cohort that had a right heart catheterization (RHC) for pulmonary hypertension (PH) evaluation.

Methods: Subjects with SSc who had a diagnostic RHC, had no PH or had PAH, and had variables for application of DETECT and 2015 ESC/ERS guidelines were included for analysis. PH classification was based on hemodynamics using the 2018 revised criteria and extent of lung fibrosis on high resolution computed tomography. Sensitivity and predictive accuracies of the DETECT algorithm and 2015 ESC/ERS guidelines were performed including analysis of subjects with DLCO ≥ 60% predicted.

Results: Sixty-eight subjects with SSc had RHC; 58 subjects had no PH and 10 had PAH. The mean age of the cohort was 60.0 years and 58.8% had limited cutaneous SSc. The DETECT algorithm had a sensitivity of 1.00 (95% CI 0.69-1.00) and negative predictive value (NPV) of 1.00 (0.80-1.00) whereas 2015 ESC/ERS guidelines had a sensitivity of 0.80 (0.44-0.97) and NPV of 0.94 (0.81-0.99). In subjects with DLCO ≥ 60 % (N=27), the DETECT algorithm had a sensitivity of 1.00 (0.29-1.00) and NPV of 1.00 (0.59-1.00) whereas 2015 ESC/ERS guidelines had a sensitivity of 0.67 (0.09-0.99) and NPV of 0.94 (0.71-1.00).

Conclusion: The DETECT algorithm has a high sensitivity and NPV for diagnosis of PAH, including those with DLCO ≥ 60%.

Introduction

Systemic sclerosis (SSc) is a multi-organ system autoimmune disease characterized by fibrosis, inflammation, and vascular damage [1, 2]. Pulmonary arterial hypertension (PAH) is one of the leading causes of mortality in SSc, and in the past, SSc-associated PAH (SSc-PAH) had a significantly worse prognosis when compared to other forms of PAH. PAH may go unrecognized in SSc patients until the disease has reached advanced stages due to lack of or mild symptoms or attribution of symptoms to other comorbidities, such as interstitial lung disease (ILD) and/or myopathy.

PAH is present in 10 to 12% of patients with SSc and in 19% of those with a diffusion capacity for carbon monoxide (DLCO) < 60% predicted [1, 2]. Over the past decade, treatment for PAH has evolved dramatically due to the addition of new therapies and the transition from sequential to upfront combination therapy. Outcomes have recently improved in SSc-PAH and are now similar to those with idiopathic PAH [2, 3].

Previous observational studies have shown screening for PAH may lead to better outcomes. A French SSc-PAH registry showed that an active PAH screening program identified patients at a lower functional class with SSc-PAH and patients had better survival [4]. The PHAROS registry, a large North American registry of SSc subjects at-risk or with incident PAH that incorporated PAH screening, showed improved survival compared to historical cohorts [5].

Various screening algorithms and guidelines exist for the early detection of SSc-PAH. The European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines were published in 2009 on echocardiography and were revised in 2015 to improve sensitivity during screening for PAH [6]. These revisions included a combination of tricuspid regurgitation velocity (TRV), additional echocardiographic variables with assessment of the right ventricle (RV) size and pressure overload, the pattern of blood flow velocity out of the RV, the diameter of the pulmonary artery and an estimate of right atrial pressure. The DETECT algorithm is an evidence based screening algorithm created in 2013 as the result of a multicenter cross-sectional study that compared multiple clinical variables to the gold standard of right heart catheterization (RHC), which resulted in the development of a 2-step PAH detection algorithm; step 1 includes the combination of 6 clinical variables and step 2 includes echocardiographic

variables [7]. The DETECT algorithm has been recommended by a number of different societies, including the 2013 recommendations for screening and detection of connective tissue disease (CTD) associated PAH, 2015 ESC/ERS guidelines, and the 2018 6th World Symposium on Pulmonary Hypertension (WSPH) [6, 8, 9].

In the current analysis, we compared the predictive accuracies of the DETECT algorithm and the 2015 ESC/ERS guidelines in a SSc cohort that had RHC for pulmonary hypertension (PH) evaluation and applied the 2018 6th WSPH Task Force revised hemodynamic definition of Group I PH (PAH) [9].

Methods

Design and Subjects. This was a cross-sectional study of a cohort of SSc subjects at University of Michigan (U-M) who had a diagnostic RHC prior to March 14, 2019. All subjects were at least 18 years of age and met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc. This study was approved by the U-M Institutional Review Board and a waiver of consent was approved as this was a retrospective study. The study was carried out in compliance with the Helsinki Declaration.

The entire cohort included 261 subjects that had RHC from December 2004 through March 2019. Of those, 114 subjects did not have PH, 63 subjects had PAH, 30 subjects had Group II PH, 35 subjects had Group III PH, and 19 subjects had Group IV PH based on the 2018 hemodynamic classification [9]. We focused on the 68 subjects who had PAH or no PH and had variables available for application of the DETECT algorithm and the 2015 ESC/ERS guidelines. One hundred and nine subjects were excluded as they did not have availability of variables to calculate a DETECT score and/or did not have a transthoracic echocardiogram (TTE) available for review at U-M to apply the 2015 ESC/ERS guidelines. Demographics and additional clinical variables were obtained for each of the 68 subjects for analysis. Additional analyses were performed by applying the DETECT algorithm and the 2015 ESC/ERS guidelines to the 2009 hemodynamic definition of PAH [mean pulmonary arterial pressure (mPAP) ≥ 25mmHg

and pulmonary arterial wedge pressure (PAWP) ≤ 15mmHg] with no-to-minimal ILD as incorporated in the original DETECT publication [7, 10]. We also explored the performance of the DETECT algorithm for screening of Group II and III PH.

PAH Screening. All SSc subjects at U-M undergo PAH screening at SSc diagnosis and annually thereafter based on the 2013 CTD-PAH recommendations, which include clinical signs/symptoms, N-terminal pro b-type natriuretic peptide (NTproBNP), pulmonary function tests (PFTs), TTE variables, and the DETECT algorithm [8]. In clinical practice, we routinely apply the DETECT algorithm to subjects with SSc regardless of their DLCO. Subjects who had a diagnostic RHC with variables available for application of the DETECT algorithm and had TTE images at U-M prior to RHC were included for analysis. Every TTE was reanalyzed by a cardiologist (V Moles) using the TTE variables included in the 2015 ESC/ERS guidelines [6]. The data for this study was primarily derived after the 2013 publication of the DETECT algorithm and the 2013 CTD-PAH recommendations [7, 8].

PAH Classification. PAH classification was based on the 2018 WSPH Task Force revised hemodynamic definition of Group I PH (PAH) of mPAP > 20 mmHg, PAWP ≤ 15 mmHg, pulmonary vascular resistance (PVR) ≥ 3 Wood Units (WU) [9], and < 20% extent of ILD on high-resolution computed tomography (HRCT). Subjects classified as post-capillary PH or Group II PH had a mPAP > 20 mmHg, PAWP > 15 mmHg, and PVR < 3 WU. Subjects classified as Group III PH had pre-capillary PH due to chronic lung disease [HRCT showing > 20% total lung involvement due to ILD or if the total lung involvement due to ILD was 10-20% but the patient had concomitant moderate-to-severe emphysema; and if HRCT was not available, then forced vital capacity (FVC) < 70% predicted within a median of 2 months of the RHC].

Statistical Analysis. Descriptive statistics for subjects without PH and with PAH were calculated for demographic and clinical characteristics using means and standard deviations for continuous variables and percentage for categorical variables. For continuous variables, the differences between the subject groups without PH and with PAH were compared using Student's t-test if the variable followed normal distribution, or Wilcoxon Rank Sum test if the variable did not follow normal distribution. For categorical

variables, Fisher's exact test was conducted due to small, expected counts. Predictive accuracies were calculated, and 95% confidence intervals (CI) were obtained via binomial method for comparison between non-PH and Group I, II, and III PH. A significance level of 0.05 was used for all statistical tests. Missing data, if any, was not imputed. Analyses were conducted in SAS 9.4 (SAS Institute Inc.).

Results

Baseline Demographics of Cohort

Of the 261 subjects in this cohort who had a RHC, 63 subjects had PAH and 114 subjects had no PH (a total of 177 subjects). Of these 177 subjects, 68 subjects were included who had variables to calculate a DETECT score and availability of TTE to apply the 2015 ESC/ERS guidelines. When comparing the 68 subjects to those 109 subjects who had missing data, we found that subjects with missing data were more likely to have limited cutaneous SSc (lcSSc) (70.6% vs 58.8%), higher TRV (3.2 vs 2.8 m/sec), mPAP (31.7 vs 23.5 mmHg), and PVR (4.4 vs 2.3 WU) (p value < 0.05 for all comparisons; data not shown).

Of the 68 subjects, 58 subjects did not have PH and 10 subjects had PAH. The mean age (SD) for the overall cohort was 60.0 (11.7) years, average age at initial non-Raynaud's phenomenon sign/symptom was 50.5 (12.8) years, and average disease duration was 9.5 (7.6) years. The cohort was mainly composed of subjects who were female (85.3%), Caucasian (85.3%), and had lcSSc (58.8%) (Table 1).

Cardiopulmonary Characteristics of Cohort

In those with PAH, 42.9% of subjects were anti-centromere antibody positive, prevalence of ILD was lower than those without PH (42.9% vs. 76.9%, p value 0.08), and subjects had lower mean DLCO% predicted (47.8 vs. 54.6, p value 0.29) and higher FVC%/DLCO% predicted (2.0 vs. 1.6, p value 0.03; Table 1).

TTE variables for those with PAH compared those without PH indicated higher mean TRV at 3.3 m/sec vs 2.7 m/sec (p value <.0001) and estimated right ventricular systolic

pressure (RVSP) at 52.0 vs 34.4 mmHg (p value 0.0006), respectively. On RHC, the mPAP in the PAH group was 34.2 mmHg, cardiac output was 5.1L/min and PVR was 4.8 WU (Table 1).

Predictive Accuracies of the DETECT Algorithm and 2015 ESC/ERS Guidelines for SSc-PAH

Using the 2018 revised hemodynamic definition of Group I PH (PAH), the DETECT algorithm performed better as a PAH screening tool compared to the 2015 ESC/ERS guidelines. The DETECT algorithm sensitivity was 1.00 (95% CI 0.69-1.00) and negative predictive value (NPV) was 1.00 (95% CI 0.80 -1.00), whereas the 2015 ESC/ERS guidelines had two false negative subjects resulting in a sensitivity of 0.80 (95% CI 0.44-0.97) and NPV of 0.94 (95% CI 0.81-0.99; Table 2). As expected for a screening tool, specificity and positive predictive value (PPV) of the DETECT algorithm were low at 0.29 (95% CI 0.18-0.43) and 0.20 (95% CI 0.10-0.33), respectively, and specificity and PPV for 2015 ESC/ERS guidelines were 0.57 (95% CI 0.43-0.70) and 0.24 (95% CI 0.11-0.42), respectively (Table 2). The 2009 hemodynamic definition of PAH (mPAP ≥ 25mmHg and PCWP ≤ 15mmHg with no-to-minimal ILD), as incorporated in the original DETECT publication, was also evaluated for 70 subjects in this cohort who had no PH or PAH and had variables available to apply the DETECT algorithm and 2015 ESC/ERS guidelines, with the DETECT algorithm showing higher sensitivity and NPV compared to the 2015 ESC/ERS guidelines (Table 3).

At our institution, we apply the DETECT algorithm to all subjects with SSc including those with DLCO ≥ 60% predicted. Within this cohort, there were 27 subjects with DLCO ≥ 60% predicted who had no PH or PAH according to the 2018 revised hemodynamic definition of PAH and had both DETECT scores and a TTE to review for the 2015 ESC/ERS guidelines. The DETECT algorithm had a sensitivity of 1.00 (95% CI 0.29-1.00) and NPV of 1.00 (95% CI 0.59-1.00), whereas the 2015 ESC/ERS guidelines had a sensitivity of 0.67 (95% CI 0.09-0.99) and NPV of 0.94 (95% CI 0.71-1.00) (Table 2). The results were similar in subjects with DLCO ≥ 60% predicted who had no PH or PAH when using the 2009 hemodynamic definition of PAH used in the original DETECT publication (Table 3).

Application of the DETECT Algorithm and 2015 ESC/ERS Guidelines for Group II and III PH Screening

Additionally, we evaluated the application of the DETECT algorithm and the 2015 ESC/ERS guidelines in subjects with Group II PH (N=12) and Group III PH (N=12) using the 2018 revised hemodynamic definitions. The performance of the DETECT algorithm was overall similar to the 2015 ESC/ERS guidelines in subjects with Group II PH with NPV of 0.94 (95% CI 0.71-1.00) compared to NPV of 0.92 (95% CI 0.76-0.98), respectively, and in subjects with Group III PH with NPV of 0.94 (95% CI 0.71-1.00) compared to NPV of 0.97 (95% CI 0.85-1.00) (data not shown in a tabular form).

Discussion

We compared predictive accuracies of the DETECT algorithm and the 2015 ESC/ERS guidelines in an SSc cohort who had RHC for PH evaluation using the 2018 WSPH Task Force revised hemodynamic definition of Group I PH (PAH). Our results demonstrate that the DETECT algorithm works well as a screening tool for PAH with 100% NPV and 100% sensitivity and it was effective in those with DLCO ≥ 60% predicted. We also evaluated the DETECT algorithm using the 2009 PAH definition that was used in the original DETECT study and showed high sensitivity and NPV.

Our performance of the DETECT algorithm using both the 2009 and 2018 revised hemodynamic definitions of PAH was similar to previously published studies in the literature, which have utilized the 2009 hemodynamic definition of PAH. In the original DETECT derivation study by Coghlan et al., the DETECT algorithm had a sensitivity of 96%, NPV of 98%, specificity of 48%, and PPV of 35% [7]. In a study by Castillo et al. with 63 subjects who had PAH or no PH, the sensitivity of the DETECT algorithm was 100%, NPV was 100%, specificity was 42.9%, and PPV was 68.6% [11]. Hao et al. analyzed a prospective cohort of 61 subjects with PAH or no PH, which resulted in the DETECT algorithm having a sensitivity and NPV of 100%, specificity of 35.3% and PPV of 55.1% [12]. In a prospective cohort by Vandecasteele et al., DETECT was applied in an SSc population and resulted in a 6% PPV (95% CI 2–17%); they did not report sensitivity or NPV in that study [13].

The World Health Organization defines a screening test as the presumptive identification of an unrecognized disease in a patient who is asymptomatic (https://apps.who.int/iris/bitstream/handle/10665/330829/9789289054782-eng.pdf). TTE has been advocated by different societies and is included as part of screening and diagnostic algorithms. In the original DETECT study, TTE (according to the 2009 ESC/ERS guidelines) missed 29% of patients who were eventually found to have PAH on RHC [7]. Most of the published literature regarding the detection of PAH through routine screening of SSc patients based on TTE uses the 2009 ESC/ERS guidelines, which are based on symptoms and TRV [14]. In the previously published studies by Castillo et al., Hao et. al, and Coghlan et. al, the 2009 ESC/ERS guidelines had lower sensitivity ranging from 71.0%-96.3%, and NPV ranging from 88.9% to 90.9% [7, 11-12]. One manuscript discussed the application of the 2015 ESC/ERS guidelines for asymptomatic detection of SSc-PAH but the authors did not provide sensitivity or NPV [13].

During the development of the DETECT algorithm, the key inclusion criteria included a disease duration of greater than three years and a DLCO < 60% predicted, largely to account for those at higher risk of PAH. However, this should not be interpreted as SSc patients with DLCO ≥ 60 % predicted are not at risk for developing PAH. Previously published data from Royal Free Hospital showed that approximately 10% with PH had DLCO ≥ 60% [15], and in the study by Hao et al., 6.5% of patients (N=4) with PAH had DLCO > 60% [12]. If a strict DLCO < 60% predicted was enforced to apply the DETECT algorithm, 3 subjects with PAH would have been missed in our current analysis using the 2018 revised hemodynamic definition and 5 subjects with PAH would have been missed using the 2009 PAH hemodynamic definition. Our data using DLCO ≥ 60% predictive is supportive of the 2018 WSPH recommendations that proposed the DETECT algorithm, along with the 2015 ESC/ERS guidelines or FVC/DLCO ratio >1.6 (assuming none-to-mild ILD) and >2-fold upper limit of normal of NTproBNP in those with uncorrected DLCO < 80% predicted.

The DETECT algorithm is being increasingly incorporated into clinical practice and was developed to discriminate between PAH and non-PH. In our cohort, the performance of the DETECT algorithm was similar in those with Group II and Group III PH versus the

2015 ESC/ERS guidelines, and we do not advocate to incorporate DETECT into clinical practice to distinguish between Group II or III PH and non-PH. We should also remember that the DETECT algorithm is a screening tool with high sensitivity and NPV that provides guidance on if a patient should get a RHC. High sensitivity is preferred in a screening tool but the tradeoffs include increased number of RHCs to exclude PAH, as seen in the original DETECT cohort [7]. Since PAH is the leading cause of mortality and recent meta-analysis suggests better outcomes with utilization of screening algorithms and upfront combination therapy [2], we believe it is justified to have higher rate of RHC to rule out PAH. In a patient who does not meet the criteria for a RHC at a single time point according to the DETECT algorithm (i.e., the DETECT score does not advocate for referral for RHC), we continue to incorporate the DETECT algorithm on an annual basis during clinic visits with spirometry with DLCO to assess FVC/DLCO ratio, serum uric acid, and NTproBNP. If TTE is recommended, it is performed as part of the screening algorithm. In subjects who are recommended for a RHC based on the DETECT score, but do not have PH on RHC (53% of subjects in our cohort), DETECT is no longer a valid tool in screening for PH. In this scenario, we follow the 6th WSPH recommendations with annual screening with TTE, incorporate 2015 ESC/ERS guidelines, assess for worsening of DLCO and FVC/DLCO ratio >1.6 (assuming none-to-mild ILD) and >2-fold upper limit of normal value of NTproBNP. In addition, new signs/symptoms suggestive of PH should lead to a clinical evaluation for PH.

We uniformly screen SSc patients with published recommendations for CTD-PAH [8]. Although we had 261 subjects in this cohort who had a RHC and 114 subjects did not have PH and 63 subjects had PAH, our analysis focused on 68 subjects where a screening algorithm was largely applied prospectively and TTE was available for reassessment using 2015 ESC/ERS guidelines highlighting the inherent limitation of a cohort study. The more severe hemodynamic findings in the missing data cohort may reflect a lack of uniform screening in the patient population prior to 2014, which was when DETECT and the 2013 CTD-PAH recommendations were published [7, 8]. This is a single center study with small numbers of patients that needs to be validated in a prospective study in the future. In addition, we did not exclude patients with moderate-

to-severe ILD in the non-PH group, which may impact the diagnostic accuracy of our analysis.

Conclusion

Early detection of PAH in SSc is necessary to implement early treatment, which can improve outcomes for SSc-PAH [2]. To our knowledge, this is the first cohort study that assesses the performance of the DETECT algorithm and 2015 ESC/ERS guidelines using the 2018 revised hemodynamic definition of PAH. The DETECT algorithm is a better screening tool for SSc-PAH than TTE. Although the original derivation study for DETECT excluded subjects with higher DLCO values, our analysis suggests that subjects with DLCO ≥ 60% predicted can have PAH and the DETECT algorithm performs well in this group.

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Table 1. COHORT CHARACTERISTICS

	Total Cohort (N=68)	No PH (N=58)	PAH (N=10)	P Value
Age (years) at RHC, mean (SD), N=68	60.0 (11.7)	59.4 (12.0)	63.2 (9.6)	0.39 ǂ
Age at Initial Non-RP Sign/Symptom (years), mean (SD), N=68	50.5 (12.8)	49.8 (13.1)	54.4 (10.7)	0.34 ǂ
Female Sex, N (%), N=68	58 (85.3%)	49 (84.5%)	9 (90.0%)	1.00 ¶
Race, N (%), N=68				
Caucasian	58 (85.3%)	49 (84.5%)	9 (90.0%)	1.00 ¶
African American	5 (7.4%)	4 (6.9%)	1 (10.0)	
Asian	2 (2.9%)	2 (3.5%)	0 (0.0%)	
Other	3 (4.4%)	3 (5.2%)	0 (0.0%)	
SSc Subtypes, N (%), N=68				

Limited Cutaneous SSc	40 (58.8%)	33 (56.9%)	7 (70.0%)	
Diffuse cutaneous SSc	27 (39.7%)	24 (41.4%)	3 (30.0%)	0.77 ¶
Sine Scleroderma	1 (1.5%)	1 (1.7%)	0 (0.0%)	
Disease Duration (years), mean (SD), N=68	9.5 (7.6)	9.6 (7.8)	8.8 (6.8)	0.87 ǂ
Autoantibodies, N (%)				
ANA Positivity, N=64	59 (92.2%)	50 (90.9%)	9 (100.0%)	1.0000 ¶
ANA Pattern, N=59				
Nucleolar	13 (22.0%)	10 (20.0%)	3 (33.3%)	
Centromere	12 (20.3%)	8 (16.0%)	4 (44.4%)	0.0355 ¶
Other	34 (57.6%)	32 (64.0%)	2 (22.2%)	
Ant-Scl-70 antibody, N=60	11 (18.3%)	11 (21.2%)	0 (0.0%)	0.33 ¶
Anti-RNA Polymerase III antibody, N=31	6 (19.4%)	6 (21.4%)	0 (0.0%)	1.00 ¶
Anti- Centromere antibody, N=54	10 (18.5%)	7 (14.9%)	3 (42.9%)	0.11 ¶
HRCT with ILD (near RHC) N (%), N=59	43 (72.9%)	40 (76.9%)	3 (42.9%)	0.078 ¶
PFTs (near RHC)				
Time from PFT to RHC (months), mean (SD), N=68	4.5 (7.3)	4.0 (5.4)	7.4 (14.1)	0.82 ǂ
FVC %, mean (SD), N=68	79.8 (19.5)	78.6 (19.4)	86.5 (19.5)	0.26 ǂ
DLCO %, mean (SD), N=67	53.6 (18.8)	54.6 (18.6)	47.8 (20.2)	0.29 §
FVC %/DLCO %, mean (SD), N=67	1.6 (0.6)	1.6 (0.6)	2.0 (0.7)	0.03 ǂ
TTE (near RHC)				
Time from TTE to RHC (months), mean (SD), N=68	4.0 (7.8)	3.6 (6.9)	6.1 (12.0)	0.76 ǂ
RA Area cm^2, mean (SD), N=68	15.7 (4.3)	15.3 (4.2)	17.7 (4.5)	0.10 §
TRV m/sec, mean (SD), N=54	2.8 (0.5)	2.7 (0.4)	3.3 (0.4)	<.0001 §
RVSP mmHg, mean (SD), N=54	37.3 (11.8)	34.4 (9.0)	52.0 (13.7)	0.0006 ǂ
RHC				
mPAP mmHg, mean (SD), N= 68	23.5 (7.0)	21.6 (5.4)	34.2 (6.1)	<.0001 §
mPAWP mmHg, mean (SD), N=68	10.9 (3.0)	10.8 (3.2)	11.2 (2.1)	0.81 ǂ
CO (TD) L/min, mean (SD), N =68	5.7 (1.5)	5.8 (1.5)	5.1 (1.3)	0.0999 ǂ
PVR WU, mean (SD), N=68	2.3 (1.4)	1.9 (0.6)	4.8 (2.0)	<.0001 ǂ

ǂ Wilcoxon rank sum test; ¶ Fisher exact test; § T test

PH=Pulmonary Hypertension; PAH=Pulmonary arterial hypertension; SSc=systemic sclerosis; RP= Raynaud's Phenomenon; ANA=Antinuclear antibody; HRCT=High resolution computed tomography; ILD=Interstitial lung disease; PFT=Pulmonary function test; FVC=Forced vital capacity; DLCO= Diffusing capacity for carbon monoxide; TTE=Transthoracic echocardiogram; RHC=Right heart catheterization; RA= Right atrial ; TRV=Tricuspid regurgitation velocity ; RVSP=Right ventricular systolic

pressure; mPAP=Mean pulmonary arterial pressure ; mPAWP=Mean pulmonary arterial wedge pressure; CO (TD)= Cardiac Output (thermodilution); PVR= Pulmonary vascular resistance; WU=Wood units.

Table 2. Predictive Accuracies of the DETECT Algorithm and 2015 ESC/ERS Guidelines

	2018 Revised Hemodynamic PAH Definition and All DLCO Values (N=68)				2018 Revised Hemodynamic PAH Definition and DLCO ≥ 60% predicted (N=27)			
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
DETECT	1.00	0.29	0.20	1.00	1.00	0.29	0.15	1.00
(95% CI)	(0.69-1.00)	(0.18-0.43)	(0.10-0.33	(0.80-1.00)	(0.29-1.00)	(0.13-0.51)	(0.03-0.38)	(0.59-1.00)
2015 ESC/ERS Guidelines	0.80	0.57	0.24	0.94	0.67	0.67	0.2	0.94
(95% CI)	(0.44-0.97)	(0.43-0.70)	(0.11-0.42)	(0.81-0.99)	(0.09-0.99)	(0.45-0.84)	(0.03-0.56)	(0.71-1.00)

PAH=Pulmonary arterial hypertension; DLCO= Diffusing capacity for carbon monoxide; PPV=Positive predicted value; NPV=Negative predictive value; ESC/ERS=European Society of Cardiology/European Respiratory Society; 95% CI= 95% confidence interval.

Table 3. Predictive Accuracies of the DETECT Algorithm and 2015 ESC/ERS Guidelines

	2009 PAH Hemodynamic Definition From Original DETECT Study and All DLCO Values (N=70)				2009 PAH Hemodynamic Definition From Original DETECT Study and DLCO ≥ 60% predicted (N=28)			
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
DETECT	1.00	0.33	0.36	1.00	1.00	0.30	0.24	1.00
(95% CI)	(0.82-1.00)	(0.21-0.48)	(0.23-0.50)	(0.80- 1.00)	(0.48-1.00)	(0.13-0.53)	(0.08-0.47)	(0.59-1.00)
2015 ESC/ERS Guidelines (95% CI)	0.74 (0.49-0.91)	0.61 (0.46-0.74)	0.41 (0.25-0.59)	0.86 (0.71-0.95)	0.60 (0.15-0.95)	0.70 (0.47-0.87)	0.30 (0.07-0.65)	0.89 (0.65-0.99)

PAH=Pulmonary arterial hypertension; DLCO= Diffusing capacity for carbon monoxide; PPV=Positive predicted value; NPV=Negative predictive value; ESC/ERS=European Society of Cardiology/European Respiratory Society; 95% CI= 95% confidence interval.