Reduced Diffusing Capacity for Carbon Monoxide Predicts Borderline Pulmonary Arterial Pressure in Patients with Systemic Sclerosis

Abstract

Objective

Early intervention in pulmonary arterial hypertension associated with systemic sclerosis (SSc) may improve its prognosis. We aimed to establish an algorithm to detect mean pulmonary artery pressure (mPAP) > 20 mmHg using non-invasive examinations in SSc patients by modifying the DETECT algorithm.

Methods

This study included SSc patients who underwent right heart catheterization (RHC) in our hospital during 2010 to 2018. Following variables were assessed for performance to predict mPAP ≥ 25 mmHg or > 20 mmHg; anti-centromere or U1-RNP antibody, plasma BNP level, serum urate level, right axis deviation, forced vital capacity (FVC)/ diffusing capacity for carbon monoxide (DLCO) ratio, and tricuspid regurgitation velocity.

Results

Of 58 patients enrolled in this study, 24 had mPAP of ≥ 25 mmHg, and 9 had mPAP of 21-24 mmHg. Among variables tested, only FVC/DLCO elevated similarly in patients with mPAP of ≥ 25 mmHg (median 2.5) and those with mPAP of 21-24 mmHg (median 2.5) compared to those with mPAP of ≤ 20 mmHg (median 1.5).

Given the correlation between DLCO and mPAP of > 20 mmHg, we used weighted scoring to improve the screening ability of algorithm. We calculated the amount of weighted score of each parameter according to its odds ratio and assessed the adaptation of RHC. AUC of the total weighted score was 0.92.

Conclusions

Among conventional risk factors for PAH, decreased DLCO may predict mPAP > 20 mmHg with priority in SSc patients. Scoring algorithm weighting DLCO indicated good screening ability for early SSc-PAH patients.

Introduction

Pulmonary arterial hypertension (PAH) is an increased blood pressure in the pulmonary arteries and affects the right side of the heart, defined as a mean pulmonary artery pressure (mPAP) of ≥ 25 mmHg and a pulmonary artery wedge pressure of ≤ 15 mmHg. PAH occurs as an idiopathic disease of the pulmonary arterioles or as a complication of various diseases, with a particularly high prevalence in patients with systemic sclerosis (SSc). SSc-PAH is of great clinical significance because of its high mortality. Despite the recent development of pulmonary vasodilators, the median survival in SSc-PAH remains short at only 4 years (1). Poor outcome of SSc-PAH may be partially explained by disease-related comorbidities, but also by delay in diagnosis (2). Early detection of PAH is therefore critical to improve the outcome of those patients (3).

The gold standard of PAH diagnosis is right heart catheterization (RHC), but RHC is invasive examination and it is not appropriate for screening of PH because of its invasion. From the European group, an evidence-based algorithm to screen SSc-PAH was published according to one clinical trial, namely DETECT study (4). The DETECT algorithm includes a step-wise process in which non-echocardiographic variables are assessed first, with subsequent assessment of echocardiographic parameters. These variables were not invasive, and RHC is then recommended in high risk patients. Other cohorts have validated the high sensitivity and negative predictive value of the DETECT algorithm (5, 6).

Recent data have supported that mPAP of 21-24 mmHg, called borderline PAP, in SSc patients have

been considered as an early stage of SSc-PAH to be potentially treated (7). The diagnostic cut-off level of mPAP is suggested to decrease to > 20 mmHg from ≥ 25 mmHg in SSc-PAH to enable early intervention and improve the outcome (8). Therefore, a new strategy to screen SSc with mPAP of > 20 mmHg is required. This study aimed to predict mPAP of > 20 mmHg in SSc patients by non-invasive procedures modifying the DETECT algorithm.

Patients and Methods

Patients

This cross-sectional study involved a cohort of consecutive SSc patients who underwent RHC with suspicion of PAH from July 2010 to July 2018 in Our Hospital. We performed RHC when the patient had the symptoms of respiratory discomfort. The results of examination were not considered for decision of performing RHC. SSc was diagnosed based on the 2013 American College of Rheumatology criteria. Patients were excluded if they had interstitial lung disease with a forced vital capacity (FVC) < 60% of predicted, renal insufficiency, pulmonary embolism, left heart disease such as left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular disease, obstruction and congenital cardiomyopathies, congenital /acquired pulmonary veins stenosis, and pulmonary artery wedge pressure of > 15 mmHg.. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval was obtained from the Local Ethics Committee. Patients' privacy data were strictly protected. Informed consent was obtained from all individual participants included in the study. Admission number of ethical committee is 17-0327.

Methods

All data were extracted from the medical records. We adopted the following risk factors of having PAH in SSc patients with reference to the DETECT study (4); anti-centromere or U1-RNP antibody, plasma BNP level,

serum urate level, right axis deviation, FVC/diffusing capacity for carbon monoxide (DLCO) ratio and tricuspid regurgitation velocity (TRV).

Cut-off levels of these factors were defined to maximize Youden Index with sensitivity of more than 70% using ROC curve. Screening performance of each factor was expressed as area under ROC curve (AUC), sensitivity, specificity and odds ratio.

Statistical analysis

Continuous variables were expressed as median [min-max or quartile] and compared using Wilcoxon's test. Categorical variables were expressed as number (percentage) and compared using the chi-square test. Statistical significance was defined as the probability value less than 0.05. All analyses were performed using the JMP Pro software (ver. 14.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

In total, 58 patients including 51 females and 7 males were enrolled in this study; 24 patients (41%) had mPAP of ≥ 25 mmHg, 9 (16%) had mPAP of 21-24 mmHg, and 25 (43%) had mPAP of ≤ 20 mmHg. Patient characteristics were summarized in Table 1 and Supplementary Table 1. Plasma BNP level was significantly higher in patients with mPAP of ≥ 25 mmHg (median 120 pg/mL, $p = 0.03$) than those with mPAP of ≤ 20 mmHg (median 61 pg/mL), but did not differ statistically in those with mPAP of 21-24 mmHg (median 35 pg/mL). Serum urate level was not different among the groups. Right axis deviation in ECG was found in 63% of patients with mPAP of ≥ 25 mmHg, whereas it was less frequent in patients with mPAP of 21-24 mmHg (11%) or ≤ 20 mmHg (4%). Interestingly, FVC/DLCO elevated similarly in patients with mPAP of ≥ 25 mmHg (median 2.5) and those with mPAP of 21-24 mmHg (median 2.5) compared to those with mPAP of ≤ 20 mmHg (median 1.5).

Predictive value of each factor for mPAP ≥ 25 mmHg or > 20 mmHg

AUC, cut-off value, sensitivity, specificity and odds ratio of each risk factor to predict mPAP ≥ 25 mmHg or > 20 mmHg were summarized in Table 2. AUC was calculated in the quantitative values including plasma BNP level, serum urate level and FVC/DLCO. AUC of plasma BNP level (0.70 to 0.61) and that of serum

urate level (0.67 to 0.63) both decreased if the cut-off level of mPAP was sifted from ≥ 25 mmHg to > 20 mmHg; conversely, AUC of FVC/DLCO did not decrease (0.71 to 0.80). Among the qualitative values including autoantibodies and right axis deviation, the latter had a high specificity (0.94 and 0.96, respectively) and a high odds ratio (26.7 and 22.2, respectively) for both mPAP ≥ 25 mmHg and > 20 mmHg. These results indicate FVC/DLCO and right axis deviation as important factors with priority to predict mPAP > 20 mmHg.

A pilot algorithm to detect early pulmonary hypertension (mPAP > 20 mmHg) in SSc patients

Finally, we made a pilot algorithm to detect mPAP > 20 mmHg in SSc patients. Prior to the development of algorithm, we weighted each non-echocardiographic factor based on its odds ratio (Table 2). The weighted score was approximately half value of the odds ratio. Compared to the number of positive risk factors, the total weighted score showed a higher predictive value for mPAP > 20 mmHg (AUC 0.84 vs 0.88) (Figure 1A and B). If the cut-off value was set as five, the sensitivity and the specificity of the total weighted score were 97% and 52%, respectively. By adding TRV (cut-off 2.8 m/s, weighted score 4) to the non-echocardiographic factors, AUC of the total weighted score further increased to 0.92 (Figure 1C) when the cut off value was set as 11. The sensitivity and the specificity were 87.5% and 92%. The detail of our final algorithm is described in Supplementary Figure 1.

Discussion

In this study, we demonstrated increased FVC/DLCO and right axis deviation as important factors to predict mPAP > 20 mmHg in SSc patients. Considering the relatively low sensitivity of right axis deviation (48%), FVC/DLCO may be more feasible to predict mPAP > 20 mmHg in clinical settings.

Substantial numbers of SSc patients with borderline PAP is thought to be preceding stage and to easily progress to SSc-PAH (7). In the PHAROS cohort study comprising SSc patients with borderline or normal PAP, 2 year-follow-up showed that 55% of patients with borderline PAP developed PAH (9). Another cohort study also showed that SSc patients with borderline PAP were more likely to develop PAH in the follow-up period than those with normal PAP (7). Pulmonary arteriopathy of SSc progresses gradually and silently, although it worsens rapidly and critically once PAH developed. Previous studies have suggested that early intervention in the disease course may give us potential benefit. Patients with SSc-PAH identified in an active screening program had better prognosis than those identified in the routine practice (10). Therefore, in general, an early detection of PAH results in the better outcome in SSc patients.

Multiple screening algorithms to refer for RHC using non-invasive markers have been proposed; the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines (11), the Australian Scleroderma Interest Group (ASIG) algorithm (12), recommendations from American College of Rheumatology (13) and the DETECT algorithm (4). Among these algorithms, DETECT has been well

accepted, because of the high sensitivity, and less missed patients with SSc-PAH (14). Therefore, we evaluated risk factors and established an algorithm to predict borderline PAP referring to the DETECT algorithm. We assessed anti-U1-RNP antibody in addition to anti-centromere antibody, since anti-U1-RNP antibody is another risk of SSc-PAH in Asian population (15). We also included patients with DLCO of ≥ 60% to evaluate early change of DLCO in early phase of SSc-PAH, whereas the DETECT study excluded those patients.

The novel finding of this study is the elevation of FVC/DLCO in pre- and early stage of SSc-PAH. FVC/DLCO may be sensitive to detect early change of pulmonary blood flow due to vascular bed impairment, whereas other markers, such as plasma BNP and NT-proBNP levels, reflect cardiac compensation for progressed obstruction of pulmonary vasculatures which occurs after the progression of PAH.

This study had several potential limitations. First, it was conducted at a single center, had a small sample size, and used a retrospective cross-sectional design. Moreover, our study included only Japanese population. Second, this study lacks external validation cohorts. Therefore, further investigations would confirm and polish our pilot algorithm.

We proposed an algorithm to predict mPAP > 20 mmHg in SSc patients. Our data showed that weighting FVC/DLCO and right axis deviation may improve its predictability.

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Figure Legend

Figure 1. Predictive value of three different algorithms for mPAP > 20mmHg in SSc patients. **(A)** The number of positive non-echocardiographic risk factors including anti-centromere and/or U1-RNP antibody, plasma BNP > 24.8 pg/mL, serum urate > 4.5 mg/dL, right axis deviation and FVC/DLCO > 1.78. **(B)** The total weighted score. Weighted score of each non-echocardiographic risk factor is described in Table 2. **(C)** Addition of TRV (cut-off 2.8 m/s, weighted score 4) to **B**.

Supplementary Figure 1. In this algorithm, we assessed six parameters; autoantibodies, plasma BNP level, serum urate level, FVC/DLCO, and TRV. Then, We calculated the amount of weighted score of each parameter according to its odds ratio. The weighted score was approximately half value of the odds ratio. If the total score is over 11, the patient is recommended to undergo right heart catheterization.

Table 1. Patient characteristics

	Total (n = 58)	mPAP ≥ 25 mmHg (n = 24)	25 mmHg > mPAP > 20 mmHg (n = 9)	20mmHg ≥ mPAP (n = 25)	p value*
Age, years [min-max]	62 [49-70]	58 [49-70]	60 [57-67]	65 [47-73]	0.76
Female, n (%)	51 (88%)	21 (88%)	9 (100%)	21 (84%)	0.27
Anti-centromere antibody, n (%)	17 (29%)	6 (25%)	4 (44%)	7 (28%)	0.56
Anti-U1-RNP antibody, n (%)	23 (40%)	10 (42%)	4 (44%)	9 (36%)	0.88
Plasma BNP (pg/mL), median [quartile]	73 [25-169]	120 [54-222]	35 [22-79]	61 [14-176]	**0.03**
Serum urate (mg/dL), median [quartile]	5.2 [4.4-6.5]	5.3 [4.9-7.1]	4.5 [4.2-5.6]	4.5 [4.0-6.0]	0.10
Right axis deviation, n (%)	17 (29%)	15 (63%)	1 (11%)	1 (4%)	**< 0.01**
FVC/DLCO, median [quartile]	1.9 [1.5-2.7]	2.5 [1.7-3.6]	2.5 [2.4-2.9]	1.5 [1.3-2.0]	**< 0.01**
TRV (m/s), median [quartile]	3.1 [2.7-3.7]	3.7 [3.3-4.3]	3.1 [2.4-3.3]	2.7 [2.4-3.0]	**< 0.01**

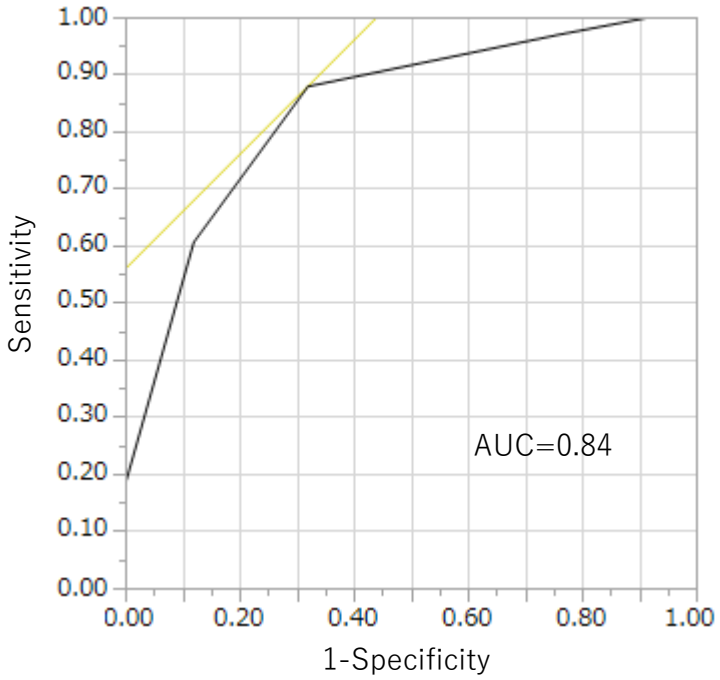
*Continuous variables were compared using Wilcoxon's test, and categorical variables using the chi-square tests. FVC/DLCO, forced vital capacity/diffusing capacity for carbon monoxide; mPAP, mean pulmonary artery pressure; TRV, tricuspid regurgitation velocity.

Table 2. Predictive value of each factor for mPAP ≥ 25 mmHg or > 20 mmHg

	mPAP ≥ 25 mmHg					mPAP > 20 mmHg					
	AUC	**Cut-off**	Sensitivity	Specificity	Odds ratio	**AUC**	**Cut-off**	Sensitivity	Specificity	Odds ratio	**Weighted score**
Autoantibodies*	**-**	**positive**	0.67	0.29	0.8	**-**	**positive**	0.72	0.36	1.4	**1**
Plasma BNP (pg/mL)	**0.70**	**79.3**	0.71	0.66	4.8	**0.61**	**24.8**	0.85	0.35	3.1	**2**
Serum urate (mg/dL)	**0.67**	**4.9**	0.83	0.53	5.5	**0.63**	**4.5**	0.82	0.44	3.6	**2**
Right axis deviation	**-**	**positive**	0.63	0.94	26.7	**-**	**positive**	0.48	0.96	22.2	**11**
FVC/DLCO	**0.71**	**1.47**	1.00	0.32	-	**0.80**	**1.78**	0.78	0.72	9.1	**5**

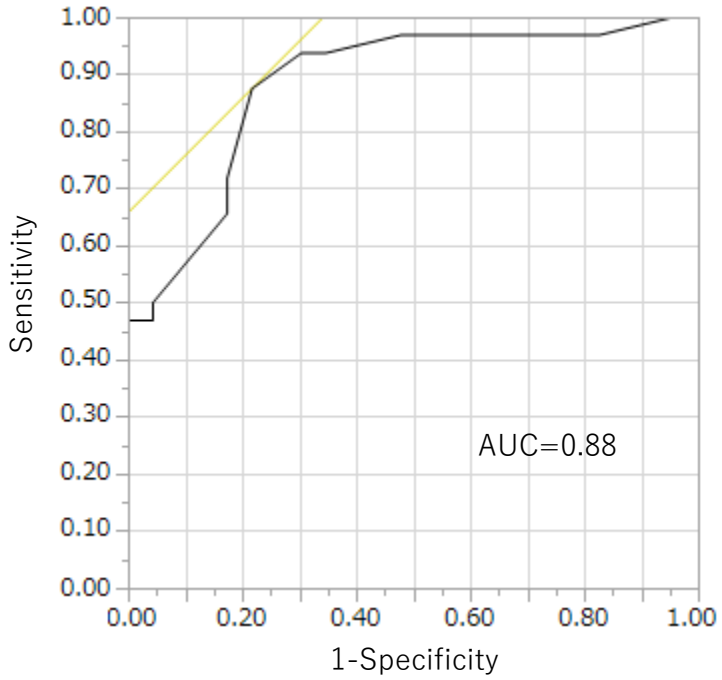
*Anti-centromere antibody and/or anti-U1-RNP antibody. The weighted score is approximately half value of odds ratio.

A



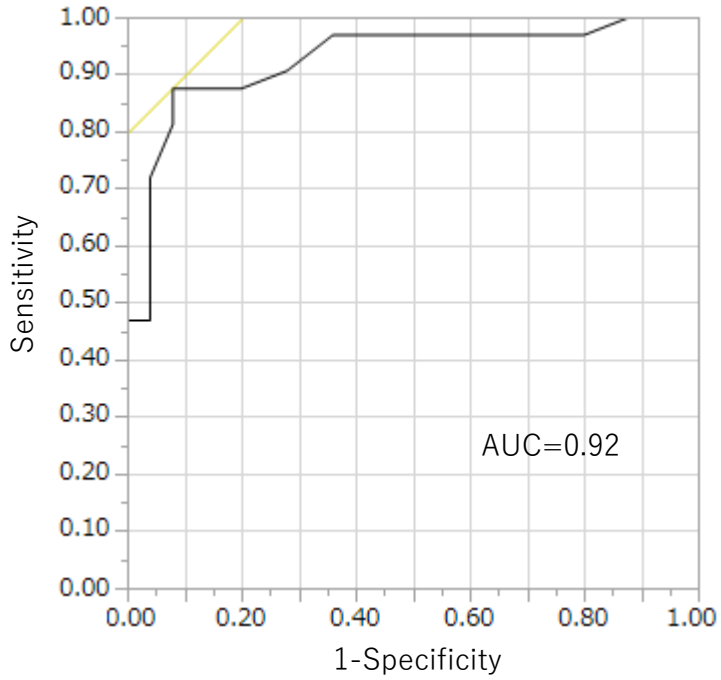
Variables	Score
Autoantibodies	1
Plasma BNP level	1
Serum urate level	1
Right axis deviation	1
FVC/DLco	1

B



Variables	Weighted score
Autoantibodies	1
Plasma BNP level	2
Serum urate level	2
Right axis deviation	11
FVC/DLco	5

C



Variables	Weighted score
Autoantibodies	1
Plasma BNP level	2
Serum urate level	2
Right axis deviation	11
FVC/DLco	5
TRV	4