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ORIGINAL RESEARCH

# Identification of Distinct Subgroups in Moderately Severe Rheumatic Mitral Stenosis Using Data-Driven Phenotyping of Longitudinal Hemodynamic Progression

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**BACKGROUND:** Rheumatic mitral stenosis is a significant cause of valvular heart disease. Pulmonary arterial systolic pressure (PASP) reflects the hemodynamic consequences of mitral stenosis and is used to determine treatment strategies. However, PASP progression and expected outcomes based on PASP changes in patients with moderately severe mitral stenosis remain unclear.

**METHODS AND RESULTS:** A total of 436 patients with moderately severe rheumatic mitral stenosis (valve area 1.0–1.5 $cm^2$) were enrolled. Composite outcomes included all-cause mortality and hospitalization for heart failure. Data-driven phenotyping identified 2 distinct trajectory groups based on PASP progression: rapid (8.7%) and slow (91.3%). Patients in the rapid progression group were older and had more diabetes and atrial fibrillation than those in the slow progression group (all $P<0.05$). The initial mean diastolic pressure gradient and PASP were higher in the rapid progression group than in the slow progression group (6.2±2.4 mm Hg versus 5.1±2.0 mm Hg [$P=0.001$] and 42.3±13.3 mm Hg versus 33.0±9.2 mm Hg [$P<0.001$], respectively). The rapid progression group had a poorer event-free survival rate than the slow progression group (log-rank $P<0.001$). Rapid PASP progression was a significant risk factor for composite outcomes even after adjusting for comorbidities (hazard ratio, 3.08 [95% CI, 1.68–5.64]; $P<0.001$). Multivariate regression analysis revealed that PASP >40 mm Hg was independently associated with allocation to the rapid progression group (odds ratio, 4.95 [95% CI, 2.08–11.99]; $P<0.001$).

**CONCLUSIONS:** Rapid PASP progression was associated with a higher risk of the composite outcomes. The main independent predictor for rapid progression group allocation was initial PASP >40 mm Hg.

**Key Words:** composite outcomes ■ data-driven phenotyping ■ latent class trajectory modeling ■ pulmonary arterial systolic pressure ■ rheumatic mitral stenosis

Rheumatic heart disease is a significant global health issue, with 282 000 new cases occurring annually.[1] At least 15.6 million people are estimated to be living with rheumatic heart disease worldwide, and the prevalence of heart failure (HF) attributable to rheumatic heart disease increased by 88% from 1990 to 2015.[1,2] The mitral valve (MV) is the valve most frequently affected by rheumatic fever, and mitral stenosis (MS) develops as a result of repeated or persistent valvulitis.[3,4] Current guidelines define severe or significant MS as MV area (MVA) <1.5 cm.[5,6] However, previous studies investigating MS prognosis have commonly

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## CLINICAL PERSPECTIVE

### What Is New?

- This study leveraged a longitudinal value to evaluate the long-term trajectories of hemodynamic progression in patients with moderately severe rheumatic mitral stenosis.
- Two distinct trajectories were identified according to the progression of pulmonary arterial systolic pressure (PASP).
- The rapid progression of PASP was a significant prognostic factor for poorer clinical outcomes during a 10-year follow-up, and initial PASP >40 mm Hg was an independent determining factor for rapid progression group allocation.

### What Are the Clinical Implications?

- Careful clinical attention, including more frequent follow-up, is warranted for patients with rapid PASP progression.
- These results imply that patients with PASP >40 mm Hg, atrial fibrillation, and diabetes may require closer follow-up with increased surveillance with echocardiography because of the risk of a rapid increase in PASP.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **LCTM** | latent class trajectory modeling |
| **MV** | mitral valve |
| **MVA** | mitral valve area |
| **MVR** | mitral valve replacement |
| **PASP** | pulmonary arterial systolic pressure |
| **PBMC** | percutaneous balloon mitral commissurotomy |
| **TTE** | transthoracic echocardiography |

targeted patients with MVA ≤1.0 $cm^2$ based on prior guidelines.[7–8] Thus, there is a paucity of data on the natural course of patients with MS, especially those with moderately severe MS (1.0 $cm^2$<MVA≤1.5 $cm^2$), which was defined as moderate MS according to previous criteria.[9]

In addition to MVA, pulmonary arterial systolic pressure (PASP) is considered an essential parameter of the hemodynamic consequences of MS and is used as a reference value for guiding the decision to perform percutaneous balloon mitral commissurotomy (PBMC).[5] However, there is a lack of data on the serial changes in PASP and their impact on clinical outcomes in moderately severe MS. As such, the PASP cutoff to determine the timing of interventions and prognosis according to serial changes in PASP in patients with MS has not been established. Latent class trajectory modeling (LCTM) is a statistical method that identifies underlying subgroups characterized by longitudinal data obtained from repeated measurements.[10] Therefore, phenotyping using longitudinal hemodynamic data, such as PASP, may facilitate the identification of distinct progression patterns over time. Furthermore, by comparing the subgroups with the same underlying trajectory, we can determine which factors are associated with the changes in PASP.

This study aimed to delineate the progression of PASP and expected outcomes according to PASP changes in patients with moderately severe MS and to determine the clinical factors associated with PASP progression. To this end, we used a PASP trajectory-based method to identify different profiles of moderately severe MS.

## METHODS

The authors declare that all supporting data have been provided in the article and its online supplementary files. The data, methods used in the analysis, and materials used to conduct the research are available from the corresponding authors on reasonable request.

### Study Population

We analyzed a database of 2624 patients with MS in the prospectively updated MS registry that included MS diagnosed by transthoracic echocardiography (TTE) between January 2010 and December 2019 at Severance Hospital, Seoul, Korea. For the current analysis, we included patients with moderately severe rheumatic MS (1.0 $cm^2$<MVA≤1.5 $cm^2$). To ensure reliability of the trajectory analysis, at least 4 echocardiographic examinations were required. The echocardiographic data of patients were censored after they underwent MV replacement (MVR) or PBMC in the trajectory analysis. We reviewed the chart and confirmed that a primary physician conducted a chest computed tomography when idiopathic pulmonary fibrosis was suspected. A pulmonary function test was done to rule out chronic obstructive pulmonary disease when a coarse lung sound was heard on auscultation. Exclusion criteria were as follows: (1) underwent surgery before undergoing 3 echocardiographic examinations; (2) other causes of pulmonary hypertension attributed to primary lung problems, including idiopathic pulmonary fibrosis, chronic obstructive lung disease, and primary pulmonary hypertension; and (3) total echocardiographic follow-up period <3 months. A final total of 436 patients with moderately severe MS were included in the trajectory analyses (Figure 1).

Demographic and clinical data, including medical histories of hypertension, diabetes, chronic kidney disease (CKD), or atrial fibrillation (AF), were obtained from the electronic medical records. Hypertension and diabetes were defined based on diagnosis and medication prescription. CKD was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$. AF was defined as documented on 12-lead ECGs. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[11] The Institutional Review Board of Yonsei University approved this study (approval number: 2021-0979-001) and waived the requirement for informed consent because of the retrospective nature of the research.

## Transthoracic Echocardiography

Comprehensive 2-dimensional TTE and standard measurements were performed according to the recommendations of the American Society of Echocardiography.[12] Chamber size, left ventricular ejection fraction, and wall thickness were obtained using an M-mode study. Left atrial volume was acquired from apical 4-chamber and 2-chamber views using biplane Simpson's method and then indexed to body surface area. Rheumatic MS was defined as features of commissural fusion of either the medial or lateral annulus, fibrothickened valve, and diastolic doming of an anterior mitral leaflet. MVA was measured at the narrowest area between leaflet tips by direct planimetry with maximal MV opening in the parasternal short axis view early in the diastole using 2-dimensional- or 3-dimensional-guided biplane imaging.[13–15] To estimate the mean diastolic pressure gradient, sample volume was placed at the coaptation point of the MV in the apical 4-chamber view. Valvular regurgitations were graded using semiquantitative methods for the vena contracta width, color Doppler regurgitation area, and proximal isovelocity surface area.[16] Right atrial pressure was estimated based on inferior vena cava size and its change in diameter according to respiration based on the method of Rudski et al.[17] The degree of PASP was calculated from the maximum tricuspid regurgitant velocity using the simplified Bernoulli equation (PASP=4×(velocity)$^2$+right atrial pressure). Parameters were averaged over 3 consecutive cardiac cycles in sinus rhythm and 5 cardiac cycles in AF. All echocardiographic examinations were reviewed by 2 attending cardiologists blinded to the patients' clinical information.

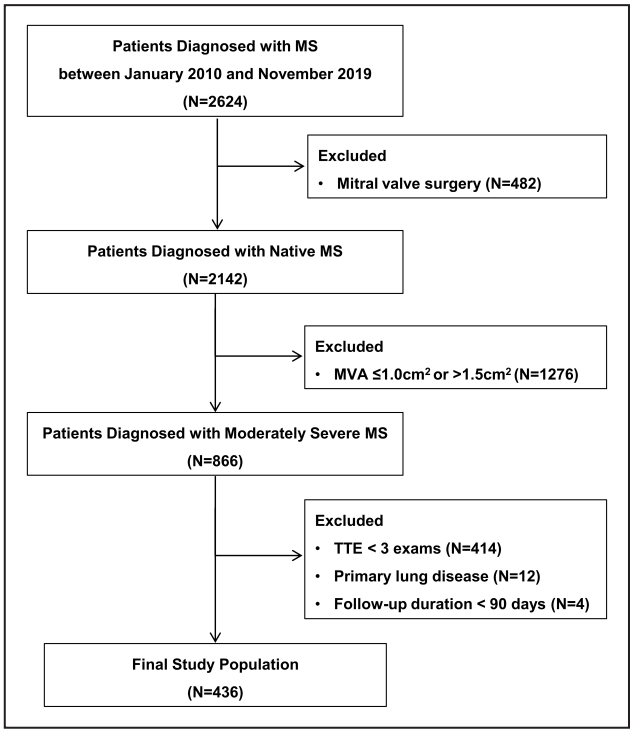


**Figure 1. Flowchart of patient selection for the final analysis.**
MS indicates mitral stenosis; MVA, mitral valve area; and TTE, transthoracic echocardiography.

## Outcomes

The composite end point was defined as all-cause mortality and hospitalization attributed to HF. Mortality outside the hospital was ascertained based on the national mortality data of the Korean Ministry of the Interior and Safety. The survival and death information of all legal citizens of South Korea is retained in the Korean Ministry of the Interior and Safety registry on a real-time basis. The vital status of all patients was virtually verified using this registry. Hospitalization attributed to HF was defined as admission because of dyspnea and for treatment with intravenous diuretics. Furthermore, we analyzed whether patients received any form of MV intervention, including MVR or PBMC during the follow-up period.

## Derivation of Moderately Severe MS Trajectories

Distinct trajectories of PASP progression in patients with moderately severe MS were classified using LCTM.[18] We performed 4 steps of trajectory modeling for analyzing the PASP progression (Data S1, Table S1). The following criteria were considered to define the best-fitting model: (1) the Bayesian information criterion, (2) average posterior probability assignment, (3) relative entropy, and (4) proportions by class.[19–21] We constructed 7 different imputations of trajectory membership to account for the uncertainty in PASP trajectory group assignment. After selecting the appropriate number of classes using the Bayesian information criterion, patients were allocated to the group with the highest posterior probability of belonging to that

trajectory. For model adequacy, relative entropy value and proportions for each class were calculated. For statistically meaningful analysis, a frequency of >5% for the trajectory groups was required (see details regarding the model in Table S2 and Figure S1).

## Statistical Analysis

Baseline characteristics, comorbidities, and echocardiographic parameters were evaluated using descriptive statistics. Continuous variables were expressed as mean±SD and compared using a Student *t* test or Mann–Whitney *U* test as appropriate. Categorical variables were reported as frequencies with percentages and compared using a $\chi^2$ test or Fisher exact test as appropriate. We used a time-dependent Cox proportional hazards regression model to estimate the hazard ratio (HR) and corresponding 95% CI for the composite outcome that included all-cause death and HF hospitalization.[22] Time-dependent Cox regression analysis with covariates for PBMC and MVR was conducted to assess the impact of PBMC and MVR during the follow-up period. To control for confounding factors, we adjusted for age and comorbidities, including hypertension, diabetes, CKD, and AF. Kaplan–Meier curves were used to report overall event-free survival rates according to the identified trajectories with a log-rank test for between-group comparisons. Univariate and multivariate logistic regression analyses were conducted to determine the risk of rapid progression group allocation. Receiver operating characteristic curve analysis was conducted to identify the predictive value of PASP for group classification. We constructed a cubic spline curve to examine the association between the composite outcomes and continuous values of PASP. The reference value that exhibited the best sensitivity and specificity in the receiver operating characteristic curve was set according to the PASP.

Statistical analyses were conducted using R version 4.0.1 (R Foundation for Statistical Computing) and MedCalc version 20.011 (MedCalc Software, Ostend, Belgium). A $P<0.05$ was considered statistically significant, and all tests were 2-tailed.

# RESULTS

## Baseline Characteristics of the Cohort With Moderately Severe MS

The study cohort comprised 436 patients with moderately severe MS. The baseline characteristics of the patients are presented in Table 1. Mean age was 58.7±11.8 years, and 340 patients (78.0%) were women. In total, 111 patients (25.5%) had a history of hypertension, and 68 patients (15.6%) had diabetes; 14 (3.2%) had CKD and 267 (61.2%) had AF, respectively. Initial mean diastolic pressure gradient was 5.24±2.03 mm Hg, and mean MVA by planimetry was 1.32±0.14 $cm^2$. An enlarged left atrial (77.82±28.33 $mL/m^2$) was noted, and PASP was as high as 33.84±9.94 mm Hg in all enrolled patients. Concomitant severe mitral regurgitation was observed in 11 patients (2.5%).

**Table 1. Baseline Characteristics of the Study Population (N=436)**

| | |
|---|---|
| Clinical characteristics | |
| Age, y | 58.68±11.75 |
| Female sex | 340 (78.0) |
| BMI, $kg/m^2$ | 23.04±2.85 |
| SBP, mm Hg | 118.8±16.11 |
| DBP, mm Hg | 74.33±12.15 |
| Comorbidities | |
| Hypertension | 111 (25.5) |
| Diabetes | 68 (15.6) |
| Chronic kidney disease | 14 (3.2) |
| Atrial fibrillation | 267 (61.2) |
| Echocardiographic data | |
| Initial MDPG, mm Hg | 5.24±2.03 |
| Initial MVA by planimetry, $cm^2$ | 1.32±0.14 |
| LV end diastolic dimension, mm | 49.00±4.94 |
| LV end systolic dimension, mm | 33.21±5.18 |
| LV ejection fraction, % | 63.22±9.02 |
| LV mass index, $g/m^2$ | 94.16±24.57 |
| LAVI, $mL/m^2$ | 72.82±28.33 |
| Initial PASP, mm Hg | 33.84±9.94 |
| Severe AR | 11 (2.5) |
| Severe MR | 11 (2.5) |
| Severe TR | 27 (6.2) |
| MVR | 123 (28.2) |
| PBMC | 178 (40.8) |

Data are presented as number (percentage) for categorical variables and mean±SD for continuous variables. AR indicates aortic regurgitation; BMI, body mass index; DBP, diastolic blood pressure; LAVI, left atrial volume index; LV, left ventricular; MDPG, mean diastolic pressure gradient; MR, mitral regurgitation; MVA, mitral valve area; MVR, mitral valve replacement; PASP, pulmonary arterial systolic pressure; PBMC, percutaneous balloon mitral commissurotomy; SBP, systolic blood pressure; and TR, tricuspid regurgitation.

## Identification and Characteristics of PASP Trajectories

We identified 2 distinct trajectories that were the best-fitting model with regard to PASP progression. In the fittest model, we named the 2 trajectories based on the pattern of changes in PASP over time as the (1) rapid progression group (n=38, 8.7%) and (2) slow progression group (n=398, 91.3%) (Figure 2).

The baseline characteristics and echocardiographic data of the trajectory groups are presented in Table 2. Patients in the rapid progression group were significantly older (64.8±10.4 versus 58.1±11.7 years; $P<0.001$) than those in the slow progression group. No significant difference

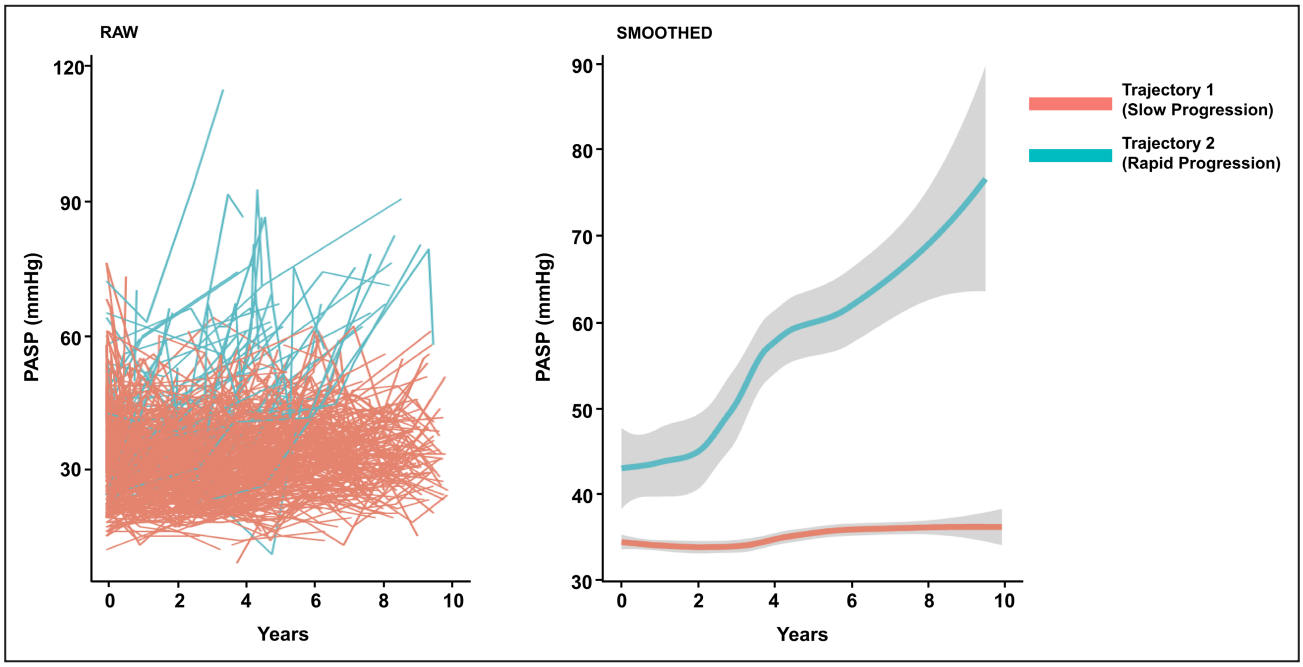


**Figure 2. Trajectory profiles of PASP progression.**
Based on predefined criteria, we identified the following 2 distinct trajectory subgroups: slow progression and rapid progression. PASP indicates pulmonary arterial systolic pressure.

was observed in the proportion of women or prevalence of CKD between the 2 groups. All comorbidities were higher in the rapid progression group, whereas significant differences in the number of patients with diabetes and AF were seen between the slow and rapid progression groups ($P$=0.001 and $P$=0.002, respectively). No significant differences were observed in severe valvular regurgitations for all valves between the 2 groups.

## Association Between Trajectories and Predictors of Adverse Composite Outcomes

During a mean follow-up of 7.0±3.0 years, 19 patients died and 38 were admitted because of HF. The incidence rate of composite outcomes was higher in the rapid progression group (42.1%) than in the slow progression group (10.3%) ($P$<0.001). Kaplan–Meier analysis revealed that patients with rapid PASP progression had a higher risk of all-cause mortality and HF hospitalization compared with patients with slow PASP progression (log-rank $P$<0.001) (Figure 3).

The factors associated with the composite outcomes in univariate and multivariate time-dependent Cox proportional regression analysis are presented in Table 3. Univariate analysis indicated that rapid PASP progression, advanced age, and comorbidities, including hypertension, diabetes, and CKD, were significantly associated with poor composite outcomes (all $P$<0.001). Mean diastolic pressure gradient and MVA were not significantly associated with the outcomes. After adjusting for confounding variables, rapid PASP progression was an independent predictor of outcomes (HR, 3.08 [95% CI, 1.68–5.64]; $P$<0.001). Other potential risk factors for composite outcomes were advanced age (HR, 1.07 [95% CI, 1.04–1.10]; $P$<0.001) and diabetes (HR, 1.78 [95% CI, 1.01–3.13]; $P$=0.045).

## Optimal Initial PASP Value for Predicting PASP Progression

The receiver operating characteristic curve in Figure S2 presents the prediction of PASP progression using initial PASP values. The cutoff PASP value of 40 mm Hg had a sensitivity of 57.9% and specificity of 85.1% for predicting PASP progression (area under the receiver operating characteristic curve, 0.709; $P$<0.001). Restricted spline curve analysis based on a knot vector of PASP=40 mm Hg demonstrated the association between the risk of rapid progression group allocation and PASP on a continuous scale, with an increasing risk from the cutoff value of PASP=40 mm Hg (Figure 4). In multivariate logistic regression analysis, patients with an initial PASP >40 mm Hg (odds ratio [OR], 4.95 [95% CI, 2.08–11.99]; $P$<0.001), diabetes (OR, 2.44 [95% CI, 1.15–5.22]; $P$=0.02), and AF (OR, 5.14 [95% CI, 1.43–33.06]; $P$=0.032) were more likely to be allocated to the rapid progression group (Table S3).

# DISCUSSION

In this long-term follow-up registry study, we investigated heterogenous trajectories of PASP in patients with moderately severe rheumatic MS. A total of 2

**Table 2. Baseline Characteristics of the Trajectory Groups**

| | Trajectory 1 (slow progression; n=398) | Trajectory 2 (rapid progression; n=38) | *P* value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, y | 58.10±11.72 | 64.79±10.35 | <0.001 |
| Female sex | 309 (77.6) | 31 (81.6) | 0.313 |
| BMI, kg/m$^2$ | 22.95±2.79 | 23.94±3.29 | 0.042 |
| SBP, mm Hg | 118.31±16.17 | 124.13±14.75 | 0.033 |
| DBP, mm Hg | 74.48±12.20 | 72.66±11.59 | 0.376 |
| Comorbidities | | | |
| Hypertension | 99 (24.9) | 12 (31.6) | 0.365 |
| Diabetes | 55 (13.8) | 13 (34.2) | 0.001 |
| Chronic kidney disease | 12 (3.0) | 2 (5.3) | 0.349 |
| Atrial fibrillation | 235 (59.0) | 32 (84.2) | 0.002 |
| Echocardiographic data | | | |
| Initial MDPG, mm Hg | 5.14±1.97 | 6.23±2.35 | 0.001 |
| Initial MVA by planimetry, cm$^2$ | 1.32±0.14 | 1.29±0.16 | 0.168 |
| LV end diastolic dimension, mm | 48.92±4.89 | 49.76±5.47 | 0.318 |
| LV end systolic dimension, mm | 33.15±5.07 | 33.82±6.21 | 0.448 |
| LV ejection fraction, % | 63.22±8.95 | 63.24±9.89 | 0.991 |
| LV mass index, g/m$^2$ | 92.67±23.52 | 109.65±29.85 | <0.001 |
| LAVI, mL/m$^2$ | 71.02±26.02 | 91.66±42.04 | <0.001 |
| Initial PASP, mm Hg | 33.03±9.18 | 42.26±13.33 | <0.001 |
| Severe AR | 11 (2.8) | 0 (0.0) | 0.610 |
| Severe MR | 9 (2.3) | 2 (5.3) | 0.260 |
| Severe TR | 23 (5.8) | 4 (10.5) | 0.246 |
| MVR | 103 (25.9) | 20 (52.6) | <0.001 |
| PBMC | 167 (42.0) | 11 (28.9) | 0.119 |

Data are presented as number (percentage) for categorical variables and mean±SD for continuous variables. AR indicates aortic regurgitation; BMI, body mass index; DBP, diastolic blood pressure; LAVI, left atrial volume index; LV, left ventricle; MDPG, mean diastolic pressure gradient; MR, mitral regurgitation; MVA, mitral valve area; MVR, mitral valve replacement; PASP, pulmonary arterial systolic pressure; PBMC, percutaneous balloon mitral commissurotomy; SBP, systolic blood pressure; and TR, tricuspid regurgitation.

distinct trajectories were identified based on PASP progression using LCTM, namely, rapid and slow progression groups. Patients in the rapid progression group had a higher risk of all-cause mortality and HF hospitalization compared with patients in the slow progression group. Compared with lower initial PASP (≤40 mm Hg), higher initial PASP (>40 mm Hg) was associated with a 5-fold higher risk of rapid progression.

Rheumatic MS is an acquired progressive form of valvular heart disease that is characterized by diffuse leaflet thickening, fusion of the commissures, and chordae tendineae.[23,24] Previous studies characterizing the natural history of rheumatic MS included a small number of patients (<100 patients) or a relatively short follow-up duration (<5 years).[25–29] Moreover, most of these studies focused predominantly on changes in a few specific values, such as MVA or mean diastolic pressure gradient.[25–27] Although several studies have reported the association between PASP and postoperative prognosis in patients with MS, the literature on PASP in MS is scarce.[8,30] Furthermore, there is a paucity of studies evaluating serial changes in PASP and their effects on MS progression and outcomes.

LCTM classifies trajectories using serial measurements based on the assumption that distinct underlying subpopulations can be identified. In data-driven phenotyping, we do not distinguish the patient groups based on the assumption but, rather, the algorithm differentiates the distinctive groups of patients. This method does not require the same number of measures per patient or the same time points of measurement.[18,31] Several attempts have been made to identify trajectories in other cardiovascular fields such as HF and coronary artery disease.[32,33] Accordingly, LCTM may be a particularly useful method to examine the hemodynamic progression of PASP in patients with moderately severe MS using longitudinal data-driven trajectory analysis. To the best of our knowledge, no study has, to date, examined serial changes in PASP in patients with moderately severe MS using LCTM. Latent class modeling, which was employed herein, enables the

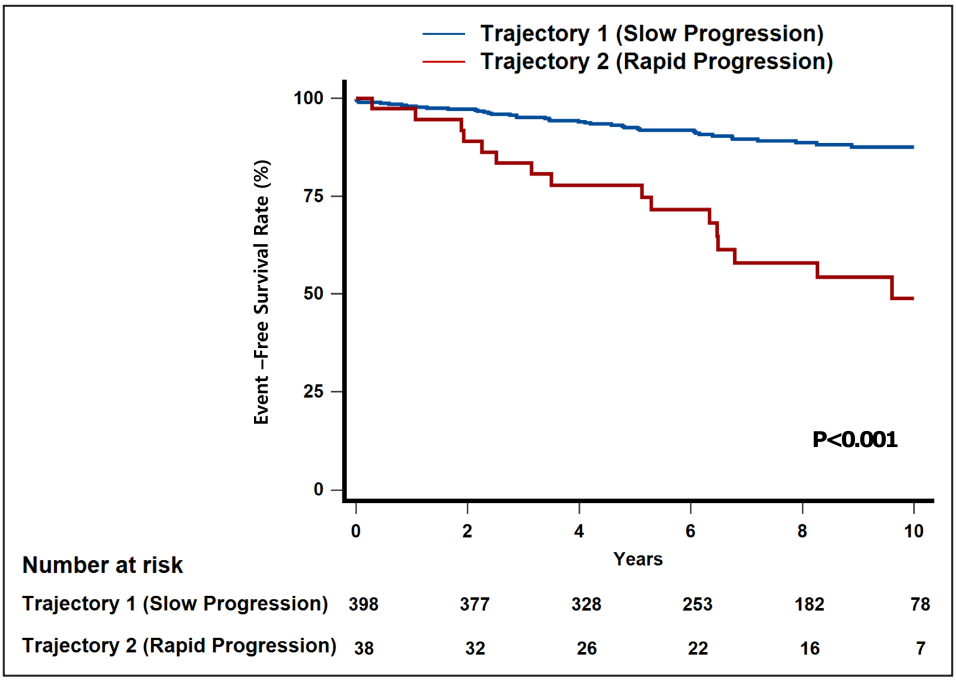


**Figure 3. Kaplan–Meier analysis for composite outcomes.**
The Kaplan–Meier graph shows event-free survival rates for the composite outcomes (all-cause mortality and heart failure hospitalization). Rapid pulmonary arterial systolic pressure progression was associated with higher adverse outcome rates, including all-cause death and hospitalization attributed to heart failure (log-rank *P*<0.001).

identification of different patterns of PASP changes as separate trajectory groups. In this study, classification of patients into 2 distinct trajectory groups according to rapid or slow progression of PASP permitted an investigation of subgroup heterogeneity based on changes in PASP over 10 years.

Composite outcomes were poorer for the rapid PASP progression group than for the slow PASP progression group. Indeed, the rapid progression group exhibited a 3-fold higher risk of composite outcomes even after adjusting for other clinical factors. Previous studies using PASP values measured at a single time point have reported that elevated PASP was associated with a poor prognosis in patients with MS undergoing PBMC or MVR. Patients with PASP >70 mm Hg and severe pulmonary artery stiffness showed no improvements while showing continued deterioration in right ventricular function despite an increase in MVA after PBMC. Furthermore, an elevated PASP value was associated with an increase in mortality in patients undergoing MVR, and the 5-year mortality rate reached 20% in patients with PASP >60 mm Hg.[34] Our study is distinct in that it used longitudinal data rather than single-point data, but our findings are additive to

**Table 3. Predictors of Long-Term Composite Outcomes**

| Variables | Univariate analysis, HR (95% CI) | *P* value | Multivariate analysis HR, (95% CI) | *P* value |
|---|---|---|---|---|
| Rapid PASP progression | 4.95 (2.72–9.00) | <0.001 | 3.08 (1.68–5.64) | <0.001 |
| Age | 1.09 (1.06–1.11) | <0.001 | 1.07 (1.04–1.10) | <0.001 |
| Hypertension | 3.16 (1.62–6.14) | <0.001 | 1.80 (0.91–3.58) | 0.093 |
| Diabetes | 2.87 (1.67–4.93) | <0.001 | 1.78 (1.01–3.13) | 0.045 |
| Chronic kidney disease | 2.93 (1.63–5.26) | <0.001 | 1.34 (0.73–2.47) | 0.348 |
| Atrial fibrillation | 1.86 (0.88–3.91) | 0.102 | | |
| MDPG per 1 mm Hg increase | 0.98 (0.87–1.11) | 0.754 | | |
| MVA per 0.1 $cm^2$ decrease | 1.00 (0.83–1.20) | 0.993 | | |

All variables were subjected to time-dependent Cox regression analysis using percutaneous balloon mitral commissurotomy and mitral valve replacement as time-dependent covariates. HR indicates hazard ratio; MDPG, mean diastolic pressure gradient; MVA, mitral valve area; and PASP, pulmonary arterial systolic pressure.

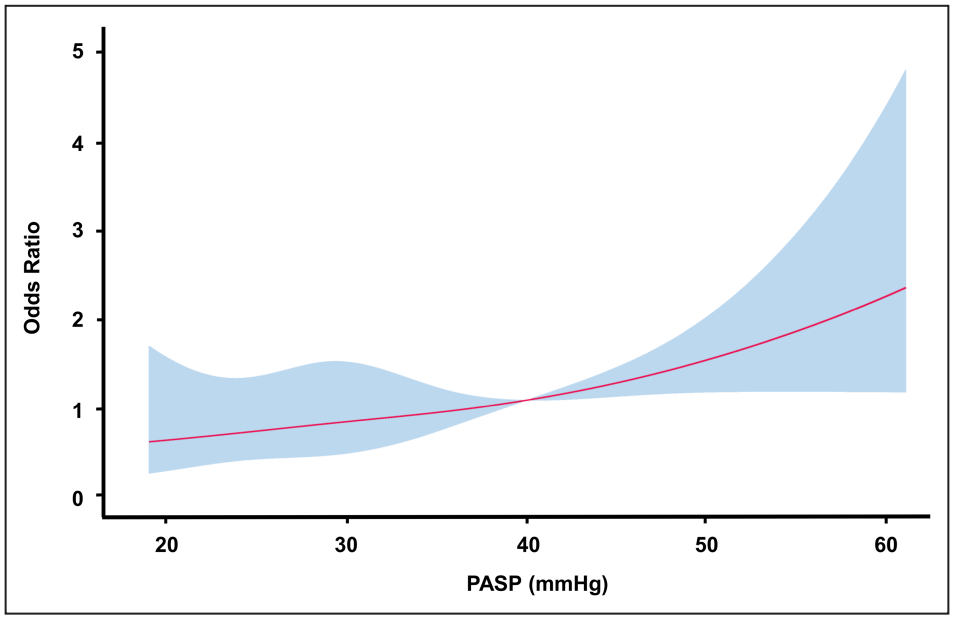


**Figure 4. Restricted cubic spline curve for the risk of rapid progression group allocation.** Based on the significant PASP value of 40 mm Hg in the receiver operating characteristic curve, the relationship between PASP progression and changes in PASP was calculated as a spline curve. PASP indicates pulmonary arterial systolic pressure.

previous reports, suggesting that patients in the rapid progression group are more likely to reach high PASP levels faster than patients in the slow progression group.[8,30]

Restricted cubic spline analysis suggested that the risk of rapid PASP progression increased gradually based on an initial PASP of 40 mm Hg. Moreover, an initial PASP >40 mm Hg was the main independent factor significantly associated with rapid progression. A notable finding in our study was that the slow progression group demonstrated minimal changes in PASP, whereas the rapid progression group exhibited a gradual increase in PASP, which increased more rapidly after 2 years. Thus, follow-up TTE tests may be necessary at shorter intervals, and the possibility of rapid progression should be explained to patients with an initial PASP >40 mm Hg. Current guidelines recommend PASP as the main hemodynamic parameter when selecting the most appropriate treatment strategy for patients with MS, and the cutoff value of PASP has recently been changed from 30 mm Hg to 50 mm Hg.[5,35] In this study, we investigated the impact of hemodynamic progression of PASP on clinical outcomes in patients with moderately severe MS, and the findings of this study may provide supporting evidence for clinical guidelines.

AF and diabetes were factors associated with rapid PASP progression in univariate analysis. Although they did not show statistical significance in multivariate analysis, these diseases may contribute to an increased PASP, both mechanistically and pathophysiologically. For instance, MV obstruction results in an increase in left atrial pressure and consequent left atrial remodeling. These changes increase the risk of AF occurrence, which promotes atrial remodeling.[36,37] Results from animal studies have demonstrated that diabetes affects pulmonary vasculature via direct effects of hyperglycemia and pulmonary hypertension.[38,39] This phenomenon may explain the observation that patients with chronic respiratory disease and diabetes have more severe pulmonary hypertension compared with patients with respiratory disease alone.[40] In consideration of these pathophysiologic changes, careful attention is warranted for patients with these comorbidities.

## Limitations

This study has several limitations. First, this study was conducted in a single tertiary center. As such, there may have been referral bias, and the results may not be generalizable. Second, a relatively small number of patients were included in the trajectory analysis. Nevertheless, considering the prevalence of MS and the inclusion criterion of patients with moderate MS patients undergoing TTE at least 3 times, our study analyzed a relatively large number of patients compared with previous studies. Third, we used TTE, but not cardiac catheterization, for measuring PASP. Because TTE is noninvasive, it may be more suitable for repeated measurements to identify hemodynamic changes in patients with MS.

## CONCLUSIONS

A total of 2 distinct trajectories were identified based on PASP progression in data-driven phenotyping of trajectories among patients with moderately severe rheumatic MS. We observed that the rapid progression of PASP was strongly associated with poorer outcomes, including all-cause mortality and HF hospitalization. In addition, PASP >40 mm Hg was independently associated with rapid PASP progression. Further prospective studies with a larger study population are warranted to confirm our findings.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

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## Supplemental Material

## Supplemental Methods

### PASP Trajectory Modeling

We performed modeling in a stepwise manner according to guidelines and studies on LCTM.[19-21,31] The comparison of model fit for the number of groups was conducted using the Bayesian information criterion (BIC), with lower values indicating better fit. After selecting the appropriate number of classes using BIC, patient assignment was performed based on the APPA, which defined the likelihood that an individual trajectory would occur in each class. A high probability of APPA (close to 1.0) indicates high confidence or quality of the classification, and the value should exceed 0.7 in all groups. Relative entropy is a summarized value for the quality of the classification; the closer the value is to 1, the higher the classification accuracy. Although Jung and Wickrama regarded 1% of the total count as an acceptable proportion of classes, we set a minimum of 5% for all classes due to the relatively small sample size of enrolled patients.[41]

Longitudinal hemodynamic data in patients with moderately severe rheumatic MS were fitted as two to four discrete trajectories using LCTM. Model 3 satisfied the APPA value of >0.70 in each class but had the highest BIC value and lowest relative entropy among the models. Model 2 had the highest entropy value but comprised a subgroup with less than 5% of the proportion of classes, and the BIC values were higher than those of Model 1. Model 1 had the second-highest relative entropy and

lowest BIC value, and none of the APPA values assigned to each class was less than 70%. Accordingly, model 1 was selected as the most suitable model because the ratio allocated to each class also exceeded 5%.

**Table S1. Steps for Establishing a Latent Class Trajectory Model**

| Step | Step description | Criteria for selection |
|---|---|---|
| 1 | Generate several trajectory models based on pulmonary arterial systolic pressure (PASP) progression ($\mathrm{K}$=1–7) | Bayesian information criterion (BIC) value |
| 2 | Render models to confirm the optimal number of classes ($\mathrm{K}$=2–4) | Univariate linear model<br>Univariate quadratic model<br>Multivariate linear model<br>Multivariate quadratic model |
| 3 | Evaluate model adequacy | Average posterior probability assignment (APPA)<br>Relative entropy<br>Proportions per class |
| 4 | Examine graphical presentation of models | Express individual classes over time as spaghetti plots |

Bayesian information criterion (BIC) is defined as:

$$\mathrm{BIC} = -2 * \mathrm{LL} + \log(\mathrm{N}) * \mathrm{K}$$

where $LL$ is the log-likelihood of the model, $N$ is the number of examinations in the sample, and $K$ is the number of parameters in the model.

The average posterior probability assignment (APPA), $\hat{p}_k$, assesses whether individuals are assigned with high probability and the overall average probability of assignment to each class.

Entropy is a global measure of classification uncertainty. The entropy of a model is calculated using the following equation and derives values from [0, ∞].

$$E = -\sum_{i=1}^{N}\sum_{k=1}^{K} \hat{p}_{ik} \log \hat{p}_{ik}$$

Relative entropy is a standardized version of entropy in the interval [0,1], defined as

$$E_K = 1 - \frac{E}{N \log K'}$$

**Table S2. Adequacy Assessments of Latent Class Trajectory Models**

| Model | BIC | APPA (%) | Relative entropy | Proportions by class (%) |
|---|---|---|---|---|
| Model 1 | 14752.66 | 0.97 : 0.88 | 0.84 | 91.28 : 8.72 |
| Model 2 | 14767.08 | 0.97 : 1.00 : 0.85 | 0.89 | 90.37 : 0.23 : 9.40 |
| Model 3 | 14774.49 | 0.78 : 0.79 : 0.87 : 0.76 | 0.64 | 55.96 : 1.15 : 8.72 : 34.17 |

APPA, average posterior probability assignment; BIC, Bayesian information criterion; LCTM, latent class trajectory modeling.

**Table S3. Probability of Rapid Progression Group Allocation in Univariate and Multivariate Logistic Regression Analysis**

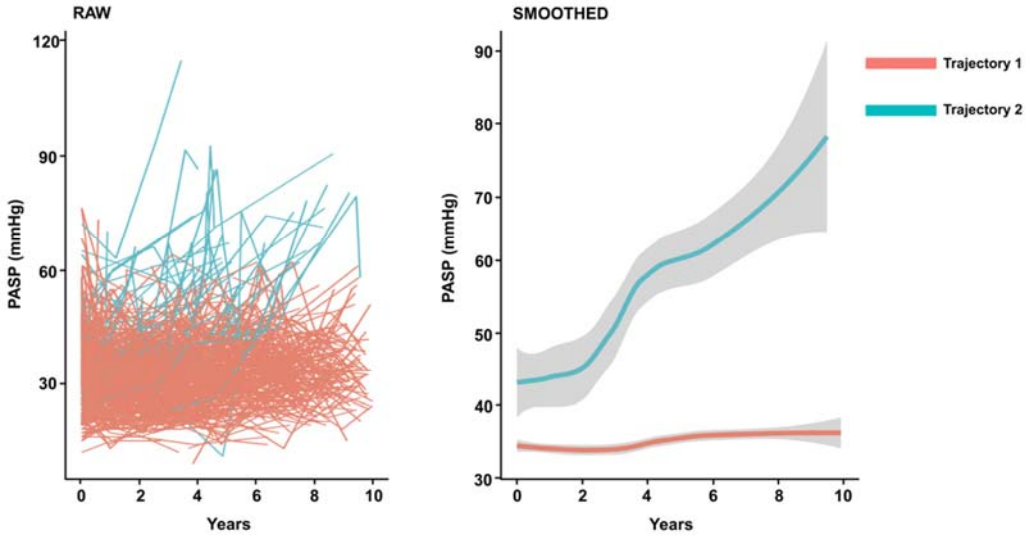
| Variables | Univariate analysis OR (95% CI) | *P*-value | Multivariate analysis OR (95% CI) | *P*-value |
|---|---|---|---|---|
| PASP >40 mmHg | 7.83 (3.91 – 16.02) | <0.001 | 4.94 (2.13 – 11.60) | <0.001 |
| Age | 1.05 (1.02-1.09) | <0.001 | 1.03 (0.99 – 1.07) | 0.109 |
| Hypertension | 1.39 (0.66 – 2.81) | 0.366 | | |
| Diabetes | 3.24 (1.53 – 6.63) | 0.002 | 2.01 (0.87 – 4.47) | 0.092 |
| Chronic kidney disease | 1.77 (0.73 – 3.92) | 0.459 | | |
| Atrial fibrillation | 3.70 (1.62 - 10.00) | 0.004 | 2.49 (0.99 – 7.24) | 0.068 |
| MDPG per 1 mmHg | 1.24 (1.08 – 1.42) | 0.002 | 1.13 (0.93 – 1.38) | 0.206 |
| MVA per 0.1cm$^2$ decrease | 1.17 (0.93 – 1.47) | 0.169 | | |

CI, confidence interval; OD, odds ratio; MDPG; mean diastolic pressure gradient; MVA, mitral valve area; PASP, pulmonary arterial systolic pressure.

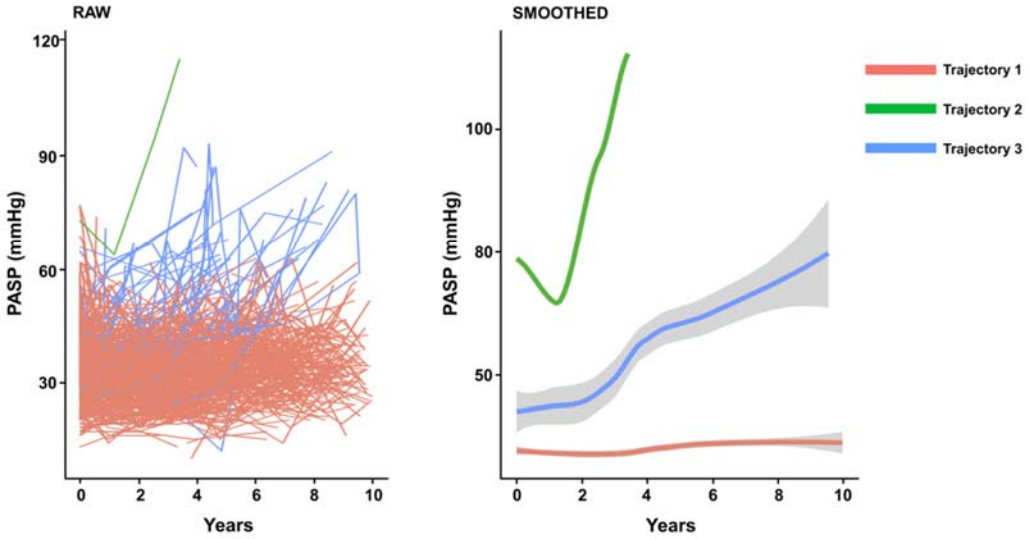
Univariate logistic regression analysis was performed using the standard value of PASP 40mmHg obtained from ROC curve analysis to estimate the probability of rapid PASP progression group allocation. Univariate analysis of age and other comorbidities

was also conducted. PASP >40 mmHg remained a sole significant factor even after performing multivariate analyses (OR: 4.94, 95% CI: 2.13-11.60, *P*<0.001).

**A** **Model 1**




**B** **Model 2**



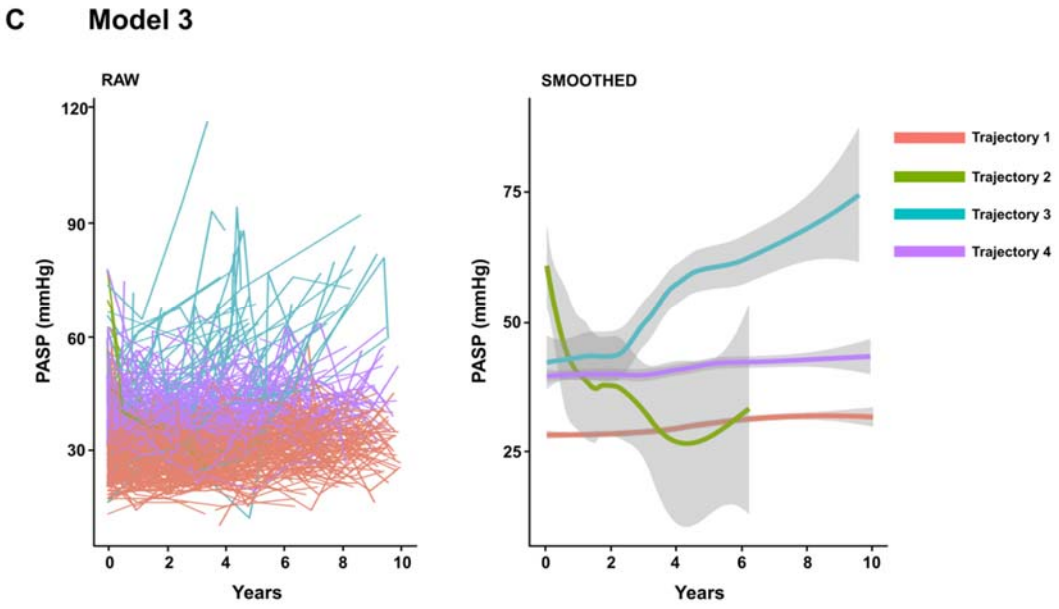



**Figure S1. Trajectory models of moderately severe mitral stenosis.** The trajectory models were refined to the optimal number of classes (K =2–4). To facilitate interpretation, we plotted PASP trajectories for each group and included smoothing lines. PASP, pulmonary arterial systolic pressure.

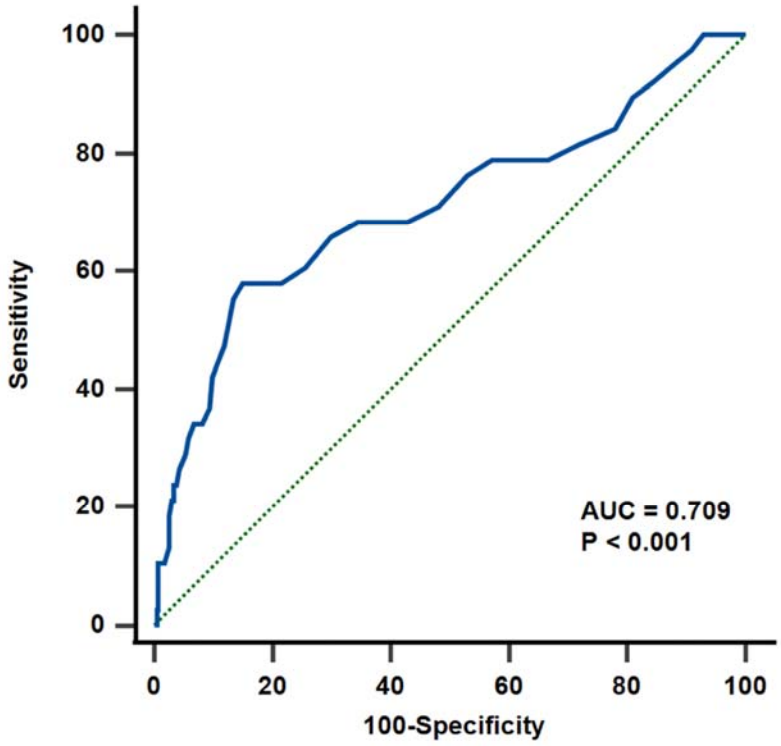



**Figure S2. Receiver operating characteristics curve for predicting the progression of pulmonary arterial systolic pressure in the overall cohort**. A PASP of 40 mmHg was a predictive factor for the degree of PASP progression (AUC: 0.709, sensitivity: 57.9%, specificity: 85.1%, *P*<0.001). AUC, area under the curve; PASP, pulmonary arterial systolic pressure.