

Autoimmune Features Are Risk Factors for Worse Transplant-Free Survival in Bronchiectasis-Associated Pulmonary Hypertension: A Retrospective Cohort Study

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Abstract

Background

Bronchiectasis-associated pulmonary hypertension (BE-PH) is a severe complication with poor prognosis. Are autoimmune features associated with worse transplant-free survival in BE-PH?

Methods

This single-center retrospective cohort study included 232 patients with BE-PH diagnosed by right heart catheterization at Shanghai pulmonary hospital between 2015 and 2025. Patients were stratified into three groups according to immune status: Ab(–) (autoantibody-negative, $n = 166$), Ab(+)/non-SARD (autoantibody-positive without definite SARD, $n = 56$), and SARD (definite systemic autoimmune rheumatic disease, $n = 10$). The primary endpoint was transplant-free survival (death or lung transplantation). Kaplan–Meier curves, Cox proportional hazards regression, and subgroup analyses were performed.

Results

During a median follow-up of 64 months, 130 patients (56%) reached the composite endpoint. The Ab(–) group had significantly better transplant-free survival than the Ab(+)/non-SARD and SARD groups, with a significant linear trend (5-year rates: 53.1% vs. 23.3% vs. 0%; P for trend < 0.001), although the pairwise comparison between SARD and Ab(+)/non-SARD was not significant after correction. In fully adjusted Cox models, both Ab(+)/non-SARD (HR 1.965, 95% CI 1.289–2.995) and SARD (HR 3.406, 95% CI 1.637–7.088) were independently associated with worse prognosis. Age, male sex, lower body mass index (BMI), and higher pulmonary vascular resistance (PVR) were also independent predictors. Subgroup analyses confirmed the detrimental effect of autoimmune features across most subgroups, with the exception of patients aged ≥ 70 years.

Conclusions

Autoimmune features, especially autoantibody positivity, with or without definite SARD, are associated with worse transplant-free survival in BE-PH. These findings support prospective validation of autoantibody screening for risk stratification.

Introduction

Bronchiectasis is a chronic respiratory disease characterized by irreversible airway dilation, recurrent infections, and progressive lung function decline. Its global prevalence is rising, with rates from 52.3 to > 1000 per 100,000 population [1, 2]. The burden is especially heavy in China, where it accounts for

substantial respiratory hospitalizations [3, 4]. Pulmonary hypertension (PH) complicates advanced bronchiectasis in 33%–48% of patients and markedly worsens outcomes, with 5-year survival rates of 53%–65% [5–10]. We previously identified pulmonary vascular resistance (PVR) as an independent prognostic factor in bronchiectasis-associated PH (BE-PH), with a cutoff of 4 Wood units effectively stratifying risk [10]. However, the mechanisms driving BE-PH progression remain poorly understood, and additional prognostic biomarkers are needed.

Autoimmune abnormalities are increasingly recognized as modifiers of both bronchiectasis and PH. In bronchiectasis, autoantibodies correlate with more severe disease and worse outcomes [11–13]. In pulmonary arterial hypertension (PAH), autoantibodies are common and may associate with worse hemodynamics [14–16]. Systemic autoimmune rheumatic diseases (SARD) such as systemic sclerosis and lupus are established causes of both conditions, and connective tissue disease-associated PAH carries a particularly poor prognosis (5-year survival as low as 31%) [17, 18]. Despite this, the prognostic significance of autoimmune features in BE-PH has not been systematically investigated. Specifically, it is unclear whether autoantibody positivity without definite SARD confers additional mortality risk beyond hemodynamic severity, and whether overt SARD is even worse.

Therefore, we aimed to: (1) evaluate the association between autoimmune features—from seropositivity without SARD to definite SARD—and transplant-free survival in BE-PH; (2) identify independent prognostic factors; and (3) test consistency across subgroups. We hypothesized that autoimmune features would be independently associated with a graded increase in mortality risk.

Methods

Study setting and patient population

This single-center retrospective cohort study included consecutive patients with bronchiectasis-associated pulmonary hypertension (BE-PH) who underwent right heart catheterization (RHC) at Shanghai Pulmonary Hospital between January 2015 and December 2025. Inclusion criteria were: (1) age ≥ 18 years; (2) bronchiectasis confirmed by high-resolution computed tomography; (3) precapillary PH confirmed by RHC, defined as mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and PVR > 2 Wood units; and (4) available baseline clinical, echocardiographic, hemodynamic, and autoantibody data. Exclusion criteria were: (1) combined postcapillary and precapillary pulmonary hypertension (CpcPH); (2) Group 3 PH due to lung diseases other than bronchiectasis; (3) concomitant pulmonary embolism; (4) other causes of precapillary pulmonary hypertension; (5) prior resectional lung surgery; (6) concomitant active malignancy; (7) incomplete baseline autoantibody data.

The study protocol was approved by the Institutional review board of Shanghai Pulmonary Hospital (approval number: 2026LY0855). Written informed consent was waived due to the retrospective nature of the study.

Data collection

Baseline data included age, sex, body mass index (BMI), World Health Organization functional class (WHO-FC), 6-minute walk distance (6MWD), serum N-terminal pro-brain natriuretic peptide (NT-proBNP), and bronchiectasis severity scores (Reiff, Bronchiectasis Severity Index (BSI), E-FACED). Pulmonary function tests were standardized. Echocardiography recorded tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (sPAP); TAPSE/sPAP ratio calculated. Right heart catheterization (RHC) measured mean PAP, pulmonary artery wedge pressure (PAWP), cardiac output (thermodilution), and mixed venous oxygen saturation (SvO₂). Derived parameters: cardiac index, stroke volume index (SVI), $PVR = (mPAP - PAWP)/CO$, and pulmonary arterial compliance (PAC) = stroke volume/(sPAP – diastolic PAP).

Autoantibody testing and group definitions

All patients underwent comprehensive baseline autoantibody screening (ANA, RF, anti-CCP, anti-SSA/SSB, anti-dsDNA, ANCA, anti-U1-RNP, anti-chromatin, anti-Sm, anti-Jo-1, ACA, anti-Scl-70, anti-GBM). Assays used standard ELISA or chemiluminescence kits; positive results defined per manufacturer thresholds. To ensure data integrity, 23 patients with incomplete data were excluded. Patients were stratified into three groups: Ab(-) (all negative, no SARD), Ab(+)/non-SARD (at least one positive, not meeting SARD criteria), and SARD (fulfilling ACR/EULAR criteria for a specific SARD). SARD in this study was broadly defined to include systemic autoimmune rheumatic diseases and selected inflammatory arthritis.

Outcome definition

The primary endpoint was transplant-free survival (TFS), defined as time from RHC to death or lung transplantation, censored at last contact or June 30, 2026. Follow-up estimated by reverse Kaplan-Meier.

Statistical analysis

Continuous variables were compared using one-way ANOVA or Kruskal-Wallis test as appropriate, with Bonferroni correction for post-hoc pairwise comparisons. Categorical variables were compared using chi-square or Fisher's exact test. Kaplan-Meier curves with log-rank tests; survival probabilities with 95% CI via log-log transformation. Cox proportional hazards models identified independent predictors (variables with $P < 0.10$ in univariable analysis were entered into multivariable models). Model 1 adjusted for age, sex, BMI; Model 2 further adjusted for PVR, cardiac index, SvO₂, log-NT-proBNP, and BSI. Medication data (including PH-targeted therapies and immunosuppressants) were not included as time-fixed covariates, as treatment regimens evolved substantially during the long follow-up period and time-varying medication data were not comprehensively captured. This represents a limitation of the retrospective design. The proportional hazards assumption and multicollinearity were assessed. P for

trend was derived by entering the three groups as ordinal variable. To evaluate the incremental predictive value of autoimmune features, we constructed two nested Cox proportional hazards models. Model A included only clinical and hemodynamic variables (age, sex, BMI, and PVR). Model B additionally incorporated the autoimmune feature group. Harrell's C-index was calculated for both models. The improvement in model fit was assessed using the likelihood ratio test (LRT). A two-sided $P < 0.05$ was considered statistically significant. Subgroup analyses combined Ab(+)/non-SARD and SARD into an autoimmune feature-positive group [AF(+)], stratified by sex, age (< 70 vs ≥ 70 years), BMI (underweight vs non-underweight), and PVR (< 4 vs ≥ 4 WU). Within each stratum, Cox proportional hazards models were fitted separately to estimate the hazard ratio for AF(+) versus AF(-). The stratifying variable was not included in stratum-specific models because it is constant within each stratum and collinear with the baseline hazard. Stratum-specific models were adjusted for all Model 2 covariates except the stratifying variable. P values for interaction were obtained from overall Cox models including AF(+), the subgroup variable, and their interaction term, with adjustment for the remaining Model 2 covariates.

Results

Patient disposition and group assignment

Of the 294 patients with bronchiectasis who underwent RHC during the study period, 62 were excluded (Fig. 1): 10 with combined postcapillary and precapillary pulmonary hypertension (CpcPH), 4 with Group 3 PH due to lung diseases other than bronchiectasis, 6 with concomitant pulmonary embolism, 2 with other causes of precapillary pulmonary hypertension, 6 with prior resectional lung surgery, 3 with concomitant active malignancy, 23 with incomplete baseline autoantibody data, and 8 for other reasons. The remaining 232 patients constituted the final study population and were stratified by immune status: Ab(-) ($n = 166$, 71.6%), Ab(+)/non-SARD ($n = 56$, 24.1%), and SARD ($n = 10$, 4.3%). Among the 10 patients in the SARD group, 8 had rheumatoid arthritis (RA) and 2 had ankylosing spondylitis (AS). In the Ab(+)/non-SARD group, the most common autoantibodies were RF (62.5%), anti-CCP (26.8%), anti-RNP (21.4%), and ANA (17.9%). In the SARD group, RF (60.0%), anti-CCP (40.0%), and anti-RNP (30.0%) were also frequently observed. By definition, the Ab(-) group had no positive autoantibodies. No patients had systemic sclerosis or systemic lupus erythematosus in this cohort.

Baseline characteristics

As detailed in Table 1, the mean age was 60 years in Ab(-), 63 years in Ab(+)/non-SARD, and 63 years in SARD. Female proportion was 57.8%, 62.5%, and 70.0%, respectively. Median BMI was 19.4 kg/m² (IQR 16.8–22.9), 20.3 kg/m² (IQR 17.5–22.6), and 18.1 kg/m² (IQR 13.7–21.2). WHO-FC distribution, 6MWD (median 320, 322, and 306 m), NT-proBNP (median 646, 507, and 551 pg/mL), and all hemodynamic indices—including mean PAP (median 34, 34, and 31 mmHg), cardiac index (mean $\pm$ SD 3.34 ± 0.83 , 3.29 ± 0.74 , and 3.43 ± 0.64 L/min/m²), PVR (median 5.2, 5.3, and 4.9 WU), and SvO₂ (mean $\pm$ SD $64.9 \pm 7.9\%$, $63.1 \pm 7.4\%$, and $62.0 \pm 10.8\%$)—showed no meaningful differences across groups. Pulmonary function

parameters (FVC%pred, FEV1%pred, DLco%pred) and bronchiectasis severity scores (Reiff, BSI, E-FACED) were also similar among the three groups. All baseline characteristics were comparable among the three groups (all $P > 0.05$).

Table 1
Baseline characteristics of patients with bronchiectasis-associated pulmonary hypertension (BE-PH), stratified by immune status

Parameters	Ab(-)	Ab(+)/non-SARD	SARD
Patients, n	166	56	10
Age, years	60 ± 12	63 ± 11	63 ± 8
Female, n (%)	96 (57.8)	35 (62.5)	7 (70)
BMI, kg/m ²	19.4 (16.8–22.9)	20.3 (17.5–22.6)	18.1 (13.7–21.2)
WHO-FC (II/III/IV)	17/126/23	3/36/17	1/8/1
6MWD, m	320 (235–396)	322 (230–375)	306(165–402)
NT-proBNP, pg/mL	646 (189–1949)	507 (200–2045)	551 (111–1370)
Reiff score	8 (6–13)	9 (8–15)	8 (5–12)
BSI score	13 (11–15)	13 (12–16)	14 (12–16)
E-FACED score	6 (6–7)	6 (6–7)	7 (6–7)
Pulmonary function test			
FVC/Pred, %	41.7 (34.4–53.2)	39.1 (33.9–52.5)	37.2 (33.4–40.8)
FEV1/Pred, %	29.2 (23.8–37.3)	29.2 (24.0–37.1)	27.2 (21.0–33.4)
FEV1/FVC, %	56.8 (48.8–68.9)	57.8 (50.5–74.2)	60.3 (51.1–77.5)
RV/TLC, %	71.5 (62.9–77.8)	71.6 (64.0–79.2)	74.4 (69.7–76.2)
DLco, %	53.4 (36.3–71.6)	50.5 (26.6–75.9)	49.2 (25.5–73.8)
Echocardiographic right ventricular parameters			
TAPSE, mm	19 (17–21)	19 (17–21)	19 (17–22)
sPAP, mmHg	60 (50–75)	59 (49–68)	48 (44–53)
TAPSE/sPAP, mm/mmHg	0.32 (0.24–0.38)	0.33 (0.26–0.41)	0.36 (0.34–0.46)

Patients were categorized into three groups: Ab(-), Ab(+)/non-SARD (autoantibody-positive without definite systemic autoimmune rheumatic disease), and SARD (definite systemic autoimmune rheumatic disease). Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Continuous variables were compared using one-way ANOVA or Kruskal-Wallis test as appropriate, with Bonferroni correction for post-hoc pairwise comparisons. Categorical variables were compared using chi-square or Fisher's exact test. No statistically significant differences were observed among the three groups (all $P > 0.05$). Abbreviations: BMI, body mass index; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; BSI, bronchiectasis severity index; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary arterial pressure; PAP, pulmonary arterial pressure; CO, cardiac output; SV, stroke volume; SVI, stroke volume index; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; SvO₂, mixed venous oxygen saturation.

Parameters	Ab(-)	Ab(+)/non-SARD	SARD
Hemodynamic parameters			
Mean PAP, mmHg	34 (28–42)	34 (28–41)	31 (27–35)
CO, L/min	5.1 (4.1–5.8)	4.8 (4.0–5.7)	5.2 (3.6–5.6)
Cardiac index, L/min/m ²	3.34 ± 0.83	3.29 ± 0.74	3.43 ± 0.64
SV, mL	56.1 (45.9–70.9)	54.9 (47.1–72.6)	60.6 (40.7–71.5)
SVI, mL/m ²	38.0 (31.5–46.0)	37.2 (31.7–44.2)	43.4 (30.0–47.9)
PVR, WU	5.2 (3.7–6.8)	5.3 (3.8–6.8)	4.9 (2.9–6.2)
PAC, mL/mmHg	1.47 (1.04–1.96)	1.39 (1.01–1.83)	1.56 (1.15–2.06)
SvO ₂ , %	64.9 ± 7.9	63.1 ± 7.4	62.0 ± 10.8
PH-targeted therapy, n (%)			
PDE5 inhibitor	62 (37.3)	20 (35.7)	4 (40)
Others	6 (3.6)	3 (5.4)	1 (10)
Patients were categorized into three groups: Ab(-), Ab(+)/non-SARD (autoantibody-positive without definite systemic autoimmune rheumatic disease), and SARD (definite systemic autoimmune rheumatic disease). Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Continuous variables were compared using one-way ANOVA or Kruskal-Wallis test as appropriate, with Bonferroni correction for post-hoc pairwise comparisons. Categorical variables were compared using chi-square or Fisher's exact test. No statistically significant differences were observed among the three groups (all <i>P</i> > 0.05). Abbreviations: BMI, body mass index; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; BSI, bronchiectasis severity index; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary arterial pressure; PAP, pulmonary arterial pressure; CO, cardiac output; SV, stroke volume; SVI, stroke volume index; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; SvO₂, mixed venous oxygen saturation.			

;

Transplant-free survival

The median follow-up was 64 months (IQR 35–99 months; estimated by reverse Kaplan-Meier). Overall, 130 patients (56%) reached the composite endpoint, of whom 125 died and 5 underwent lung transplantation; all 5 lung transplant recipients were from the Ab(-) group. The 1-, 3-, and 5-year transplant-free survival rates for the whole cohort were 86.3% (95% CI 81.1–90.2%), 59.3% (95% CI 52.1–65.8%), and 43.1% (95% CI 35.4–50.6%), respectively (Table 2). Stratified by group, the Ab(-) group had the best prognosis: 1-year 87.7% (95% CI 82.8–92.9%), 3-year 66.1% (95% CI 58.7–74.3%), 5-year 53.1% (95% CI 44.8–62.8%), median 65 months (95% CI 45–85%). The Ab(+)/non-SARD group showed intermediate outcomes: 1-year 85.5% (95% CI 76.6–95.3%), 3-year 46.2% (95% CI 33.9–63.0%), 5-year

23.3% (95% CI 12.9–42.1%), median 34 months (95% CI 22–46 months). The SARD group had the worst prognosis: 1-year 67.5% (95% CI 29.1–88.3%), 3-year 22.5% (95% CI 3.4–51.8%), 5-year 0% (not estimable; all events within 48 months), median 20 months (95% CI 6–34%). The Kaplan-Meier curves (Fig. 2) showed a clear stepwise separation (overall log-rank $\chi^2 = 25.552$, $P < 0.001$). Pairwise comparisons with Bonferroni correction ($\alpha = 0.0167$) were significant between Ab(–) and Ab(+)/non-SARD ($P < 0.001$) and between Ab(–) and SARD ($P < 0.001$); the difference between Ab(+)/non-SARD and SARD did not reach the corrected threshold ($P = 0.036$). A strong linear trend was observed across the ordered groups (P for trend < 0.001).

Table 2. Transplant-free survival rates stratified by immune status groups

Group	N	1-year TFS (%)	3-year TFS (%)	5-year TFS (%)	Median TFS (months, 95% CI)
Total	232	86.3 (81.1-90.2)	59.3 (52.1-65.8)	43.1 (35.4-50.6)	53 (43-63)
Ab(–)	166	87.7 (82.8-92.9)	66.1 (58.7-74.3)	53.1 (44.8-62.8)	65 (45-85)
Ab+/non-SARD	56	85.5 (76.6-95.3)	46.2 (33.9-63.0)	23.3 (12.9-42.1)	34 (22-46)
SARD	10	67.5 (29.1-88.3)	22.5 (3.4-51.8)	0 (not estimable)*	20 (6-34)

Data are presented as survival probability (95% confidence interval), estimated by the Kaplan–Meier method. TFS, transplant-free survival; CI, confidence interval; Ab(–), autoantibody-negative group; Ab(+)/non-SARD, autoantibody-positive without definite systemic autoimmune rheumatic disease; SARD, definite systemic autoimmune rheumatic disease. CI for survival probabilities was calculated using the log-log transformation method. *In the SARD group, all patients had reached the composite endpoint within 48 months; therefore, the 5-year survival rate is 0% and the corresponding CI is not applicable.

Prognostic factors for transplant-free survival

Univariate and multivariable Cox regression analyses (Table 3) identified group, age, sex, BMI, PVR, cardiac index, SvO₂, log-NT-proBNP, and BSI as significant univariate predictors (all $P < 0.05$). In Model 1 (adjusted for age, sex, BMI), both Ab(+)/non-SARD (HR 2.169, 95% CI 1.433–3.283; $P < 0.001$) and SARD (HR 2.966, 95% CI 1.455–6.045; $P = 0.003$) remained independently associated with worse survival. In fully adjusted Model 2 (further adjusted for PVR, cardiac index, SvO₂, log-NT-proBNP, and BSI), the associations persisted: Ab(+)/non-SARD (HR 1.965, 95% CI 1.289–2.995; $P = 0.002$) and SARD (HR 3.406, 95% CI 1.637–7.088; $P = 0.001$). Additional independent predictors in Model 2 were age (per 1-year increase: HR 1.036, 95% CI 1.015–1.058; $P = 0.001$), male sex (HR 1.660, 95% CI 1.143–2.411; $P = 0.008$), BMI (per 1-kg/m² increase: HR 0.900, 95% CI 0.853–0.950; $P < 0.001$), and PVR (per 1-WU increase: HR 1.138, 95% CI 1.048–1.236; $P = 0.002$). Cardiac index, SvO₂, log-NT-proBNP, and BSI were

not independently significant in the final model (all $P > 0.05$). The P for trend across the three ordered groups in Model 2 remained < 0.001 .

Table 3

Univariate and Multivariable Cox proportional hazards Regression Analysis for Transplant-Free Survival

Variables	Univariate Analysis	Model 1 (Adjusted for Age/Sex/BMI)	Model 2 (Fully Adjusted)
Group (Ref: Ab(-))			
<i>Ab(+)/non-SARD</i>	2.062 (1.377–3.087) ^{***}	2.169 (1.433–3.283) ^{***}	1.965 (1.289–2.995) ^{**}
<i>SARD</i>	4.124 (2.036–8.351) ^{***}	2.966 (1.455–6.045) ^{**}	3.406 (1.637–7.088) ^{**}
Age (per 1-year increase)	1.023 (1.008–1.039) ^{**}	1.031 (1.013–1.049) ^{**}	1.036 (1.015–1.058) ^{**}
Sex (male vs. female)	1.477 (1.043–2.093) [*]	1.539 (1.075–2.203) [*]	1.660 (1.143–2.411) ^{**}
BMI (per 1-kg/m ² increase)	0.918 (0.879–0.960) ^{***}	0.890 (0.848–0.933) ^{***}	0.900 (0.853–0.950) ^{***}
BSI score (per 1-point increase)	1.095 (1.023–1.172) ^{**}	---	0.960 (0.883–1.043)
WHO-FC (III/IV vs. I/II)	1.736(0.847–3.577)	---	---
log-NT-proBNP (per log-increase)	1.683 (1.251–2.263) [*]	---	1.171 (0.840–1.631)
TAPSE (per 1-mm increase)	0.766 (0.451–1.301)	---	---
TAPSE/sPAP (per 1-mm/mmHg increase)	0.429 (0.112–1.644)	---	---
Mean PAP (per 1-mmHg increase)	1.008 (0.983–1.041)	---	---
PVR (per 1-WU increase)	1.160 (1.092–1.233) ^{***}	---	1.138 (1.048–1.236) ^{**}
Cardiac Index (per 1-L/min/m ² increase)	0.748 (0.594–0.942) [*]	---	0.959 (0.735–1.251)
SvO ₂ (per 1-percent increase)	0.953 (0.932–0.974) ^{***}	---	0.981 (0.955–1.007)

• Data are presented as hazard ratio (HR) with 95% confidence interval (CI). Abbreviations: BMI, body mass index; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; WU, Wood units; WHO-FC, World Health Organization functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; BSI, bronchiectasis severity index; SARD, definite systemic autoimmune rheumatic disease.

• Univariate analysis was performed by entering each covariate separately. Model 1 additionally adjusted for age, sex and BMI. Model 2 adjusted for age, sex, BMI, PVR, cardiac index, SvO₂, log-NT-

Variables	Univariate Analysis	Model 1 (Adjusted for Age/Sex/BMI)	Model 2 (Fully Adjusted)
proBNP, and BSI score. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. • P for trend across the three groups (Ab(-), Ab(+)/non-SARD, and SARD) in Model 2 was < 0.001, calculated by entering the three groups as an ordinal variable. • The incremental predictive value of adding autoimmune features to the base model (age, sex, BMI, and PVR) was assessed by the likelihood ratio test ($\chi^2 = 17.065$, $df = 2$, $P < 0.001$), with the C-index improving from 0.68 to 0.73.			

To assess the incremental predictive value of autoimmune features, we calculated Harrell's C-index for two Cox models. The model containing only clinical and hemodynamic variables (age, sex, BMI, and PVR) yielded a C-index of 0.68 (95% CI 0.64–0.72). Adding autoimmune features significantly improved the C-index to 0.73 (95% CI 0.69–0.77). The likelihood ratio test confirmed that the addition of autoimmune features significantly improved the model fit ($\chi^2 = 17.065$, $P < 0.001$). This indicates improved risk discrimination beyond traditional hemodynamic assessment.

Subgroup analyses

To assess consistency across clinically relevant strata, we combined Ab(+)/non-SARD and SARD into an AF(+) group (n = 66) versus AF(-) (n = 166) as reference (Fig. 3). The stratifying variable was not included in stratum-specific Cox models, which were adjusted for the remaining Model 2 covariates. In males, the HR for death or transplantation was 3.094 (95% CI 1.628–5.880; $P = 0.001$), whereas in females it was 1.740 (95% CI 1.005–3.024; $P = 0.045$), with a significant sex interaction ($P = 0.036$). For age < 70 years, HR 2.496 (95% CI 1.562–3.989; $P < 0.001$); for age ≥ 70 years, HR 1.328 (95% CI 0.477–3.702; $P = 0.587$; interaction $P = 0.940$). In underweight patients (BMI < 18.5 kg/m²), HR 2.224 (95% CI 1.086–4.556; $P = 0.029$); in non-underweight patients, HR 2.357 (95% CI 1.377–4.094; $P = 0.002$; interaction $P = 0.066$). By PVR, < 4 WU: HR 4.475 (95% CI 1.761–11.372; $P = 0.002$); ≥ 4 WU: HR 1.796 (95% CI 1.124–2.869; $P = 0.014$; interaction $P = 0.244$). Thus, the autoimmune-associated risk was significantly stronger in males, while broadly consistent across BMI and PVR strata. Although the association was not statistically significant in patients aged ≥ 70 years, the interaction was not significant, and the small number of events in this subgroup limits interpretation. P values for interaction were obtained from overall Cox models including AF(+), the subgroup variable, and their interaction term.

Discussion

In this BE-PH cohort, autoimmune features—from autoantibody positivity without SARD to overt SARD—were independently associated with worse transplant-free survival, with a significant linear trend across groups (P for trend < 0.001). The Ab(-) group had the best prognosis (5-year 53.1%), followed by Ab(+)/non-SARD (23.3%) and SARD (0% at 5 years). However, the pairwise difference between Ab(+)/non-SARD and SARD did not reach the Bonferroni-corrected significance threshold ($P = 0.036$ vs α

= 0.0167), and the SARD subgroup was very small ($n = 10$); therefore, the apparent gradient should be interpreted with caution. This association persisted after adjusting for hemodynamic and clinical factors, indicating added prognostic value beyond traditional risk assessment. Age, male sex, lower BMI, and higher PVR were also independent predictors. The detrimental effect was significantly more pronounced in males (interaction $P = 0.036$).

The present results not only confirm the independent prognostic value of PVR but also demonstrate that autoimmune features provide additional prognostic information beyond hemodynamic parameters [10]. This suggests that BE-PH prognosis is determined not only by mechanical hemodynamic burden but also by systemic immune status.

The graded nature of the association should be interpreted cautiously. The significant linear trend across the three groups—seronegative, seropositive without SARD, and overt SARD—is consistent with a possible continuum of immune dysregulation rather than a simple threshold effect. However, because the SARD subgroup was very small ($n = 10$) and the pairwise comparison between Ab(+)/non-SARD and SARD did not reach the Bonferroni-corrected significance threshold, this gradient should be regarded as hypothesis-generating. Larger studies are needed to confirm whether the risk truly increases stepwise from seronegativity to seropositivity to overt SARD in BE-PH.

The poor outcomes observed in the SARD group must be interpreted with caution because this subgroup included only 10 patients. Among them, 8 had RA and 2 had ankylosing spondylitis. Data from the French Pulmonary Hypertension Registry showed that the prevalence of RA among patients with pulmonary hypertension (0.35%) is similar to that in the general population [19], suggesting that the co-occurrence of RA and PH in our BE-PH cohort may not simply represent SARD-associated PAH with incidental bronchiectasis. It is possible that in patients with underlying bronchiectasis and RA, PH develops through bronchiectasis-related pathways—such as chronic hypoxia, airway inflammation, and vascular remodeling—with RA acting as a disease modifier rather than the primary driver of PH. However, this is only a hypothesis. Given the very small SARD subgroup, we cannot draw conclusions about mechanisms or treatment implications, and these observations require validation in larger cohorts.

Several mechanisms may explain the observed association between autoimmune features and worse transplant-free survival in BE-PH. First, systemic autoimmune inflammation may exacerbate both bronchiectasis (through repeated airway injury and impaired host defense) and PH (through endothelial dysfunction and smooth muscle proliferation) [16, 20–22]. Second, the presence of autoantibodies may reflect a more inflammatory endotype of bronchiectasis, which has been associated with more frequent exacerbations, worse lung function, and poorer outcomes [23, 24].

Additionally, the strong association between lower BMI and worse prognosis in our study (HR 0.900 per 1-kg/m² increase) highlights the importance of nutritional status in BE-PH. BMI is a marker of disease severity in bronchiectasis and has been incorporated into the BSI [25]. In PH, low BMI has been associated with worse outcomes, reflecting the catabolic state of right heart failure [26]. The

independent prognostic value of BMI in our fully adjusted model suggests that malnutrition is a key modifiable risk factor in BE-PH.

In exploratory subgroup analyses, the detrimental association of autoimmune features with transplant-free survival appeared more pronounced in males than in females, with a significant sex interaction ($P = 0.036$). This sex-specific difference may reflect differences in immune responses or hormonal modulation of vascular remodeling, but it should be regarded as hypothesis-generating and warrants further mechanistic investigation. Because the stratifying variable was not included in stratum-specific models and interaction terms were tested in overall models, these subgroup findings should be interpreted as exploratory.

Our findings have several clinical implications. First, routine autoantibody screening should be considered in all BE-PH patients, as the presence of autoantibodies—even in the absence of a definite SARD—identifies a higher-risk subset of patients who warrant closer monitoring and more aggressive treatment. Second, the immune-prognostic gradient we observed suggests that patients with autoantibody positivity may benefit from early referral to rheumatology for comprehensive evaluation and potential immunomodulatory therapy, although the role of immunosuppression in BE-PH requires further investigation. Importantly, the observed prognostic association of autoimmune features remained significant after adjusting for hemodynamic and clinical parameters, suggesting that it is not merely a reflection of differential treatment intensity, although we cannot completely exclude the possibility of unmeasured treatment-related confounding. Third, the independent prognostic value of PVR, BMI, and age reinforces the importance of multidisciplinary management addressing hemodynamic optimization, nutritional support, and age-appropriate care in this complex patient population.

Several limitations should be acknowledged. First, this was a single-center retrospective study, subject to selection bias and unmeasured confounding, and the small SARD subgroup ($n = 10$) limited subgroup analyses. Second, treatment data (PH-targeted therapies and immunosuppressants) were not included as covariates, as medication regimens varied substantially over the long follow-up and could not be reliably modeled as time-fixed variables. Future multicenter prospective studies with larger samples and mechanistic investigations are needed to validate our findings and explore immunomodulatory interventions.

Conclusions

Autoimmune features are independently associated with worse transplant-free survival in BE-PH, with a significant linear trend across groups, although the pairwise difference between Ab(+)/non-SARD and SARD was not significant after correction and the SARD subgroup was small. Routine autoantibody screening may improve risk stratification and guide management. Early recognition and multidisciplinary care are essential for this high-risk population.

Abbreviations

6MWD, 6-minute walk distance; Ab(-), autoantibody-negative; Ab(+)/non-SARD, autoantibody-positive without systemic autoimmune rheumatic disease; ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology; AF(+), autoimmune feature-positive; BE-PH, bronchiectasis-associated pulmonary hypertension; BMI, body mass index; BSI, bronchiectasis severity index; C-index, Harrell's concordance index; CO, cardiac output; DLco, diffusing capacity of the lung for carbon monoxide; E-FACED, E-FACED score (Exacerbations, FEV1, Age, Chronic colonization, Extension, Dyspnea); ELISA, enzyme-linked immunosorbent assay; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; LRT, likelihood ratio test; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAC, pulmonary arterial compliance; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; Reiff, Reiff score; RHC, right heart catheterization; RV/TLC, residual volume/total lung capacity; SARD, systemic autoimmune rheumatic disease; sPAP, systolic pulmonary arterial pressure; SV, stroke volume; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TFS, transplant-free survival; VIF, variance inflation factor; WHO-FC, World Health Organization functional class; WU, Wood units.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Shanghai Pulmonary Hospital (approval number: 2026LY0855). Written informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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Author Contribution

JW and SG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JW, SG, and QZ contributed substantially to the acquisition, analysis, and interpretation of the data. JW and SG drafted the original manuscript. QZ contributed to data acquisition and validation. JX and LW supervised the study, acquired funding, contributed to the methodology, administered the project, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work

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Availability of data and materials

JX had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figures

Study Flow Diagram

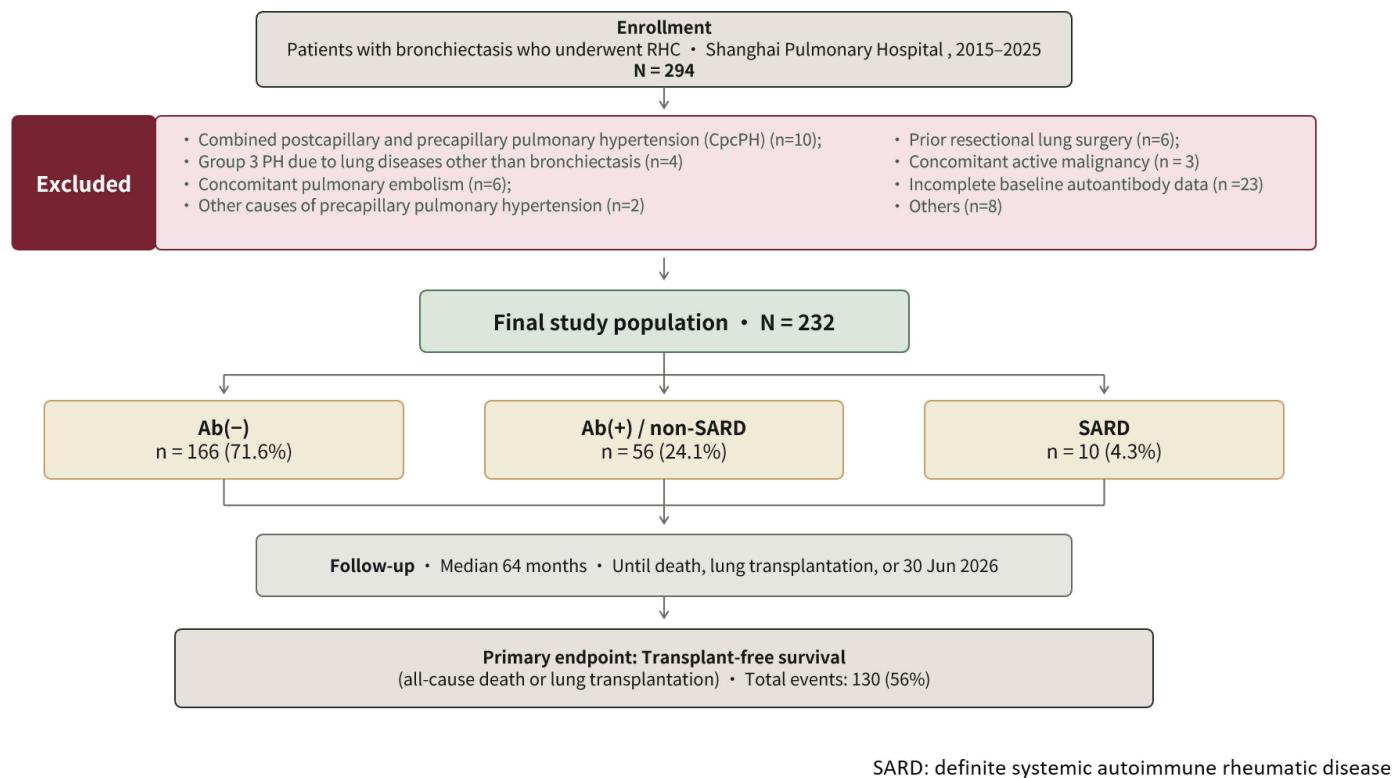


Figure 1

Study flow diagram. Of 294 patients with bronchiectasis undergoing RHC, 62 were excluded, leaving 232 patients: Ab(–) (n=166), Ab(+)/non-SARD (n=56), and SARD (n=10). Median follow-up was 64 months. The primary endpoint was transplant-free survival (death or lung transplantation), reached by 130 patients (56%). RHC, right heart catheterization; SARD, systemic autoimmune rheumatic disease.

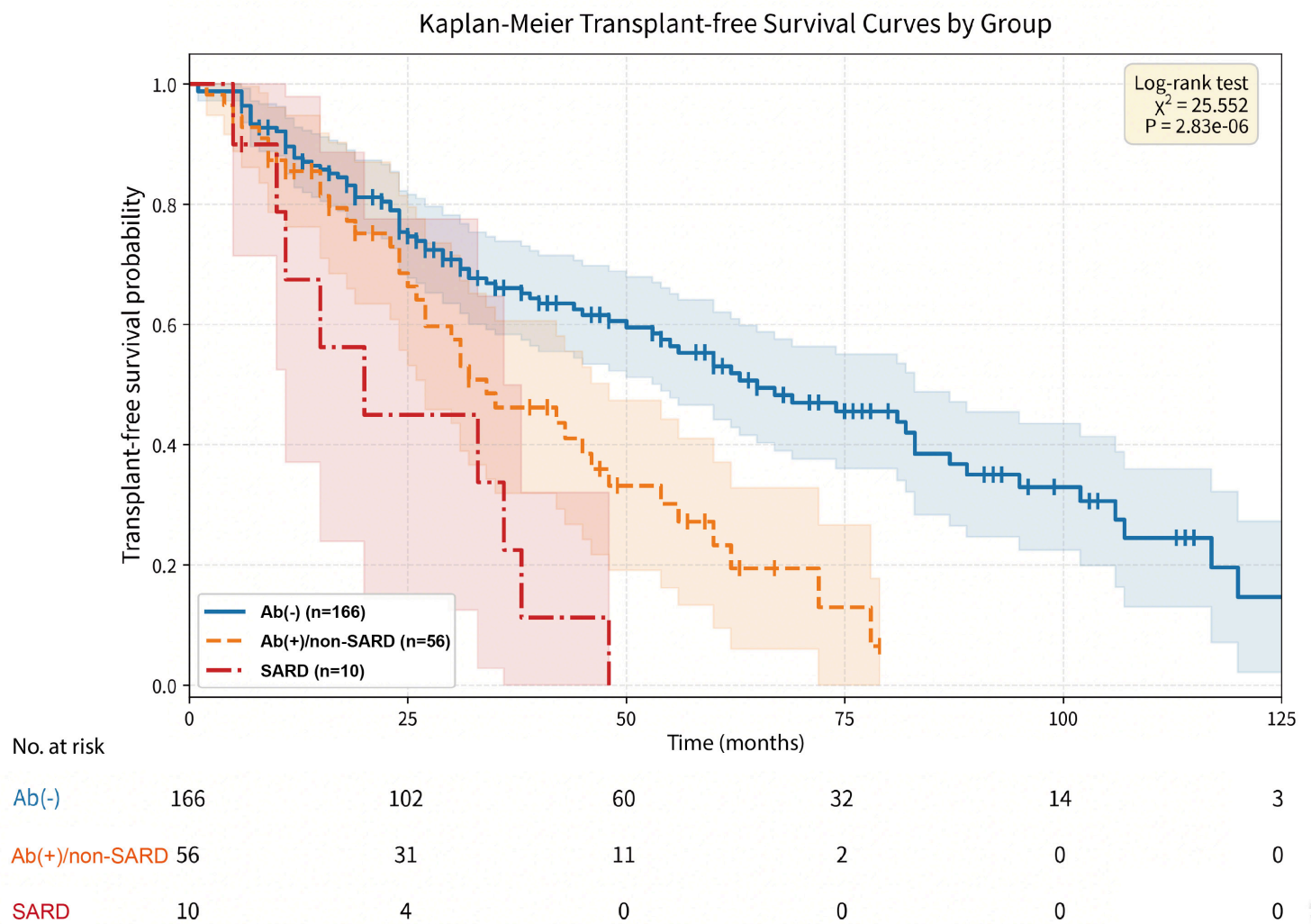


Figure 2

Kaplan–Meier curves for transplant-free survival stratified by immune status. The SARD group had the worst prognosis, followed by Ab(+)/non-SARD, while Ab(–) group had the best survival (log-rank $\chi^2 = 25.552$, $P < 0.001$). Pairwise comparisons (Bonferroni-corrected): Ab(–) vs. Ab(+)/non-SARD, $P < 0.001$; Ab(–) vs. SARD, $P < 0.001$. The pairwise comparison between Ab(+)/non-SARD and SARD did not reach the Bonferroni-corrected significance threshold ($P = 0.036$ vs $\alpha = 0.0167$). P for trend across the three ordered groups was < 0.001 . Ab(–), autoantibody-negative; Ab(+)/non-SARD, autoantibody-positive without definite SARD; SARD, definite systemic autoimmune rheumatic disease; TFS, transplant-free survival.

Subgroup Analysis of Prognostic Factors

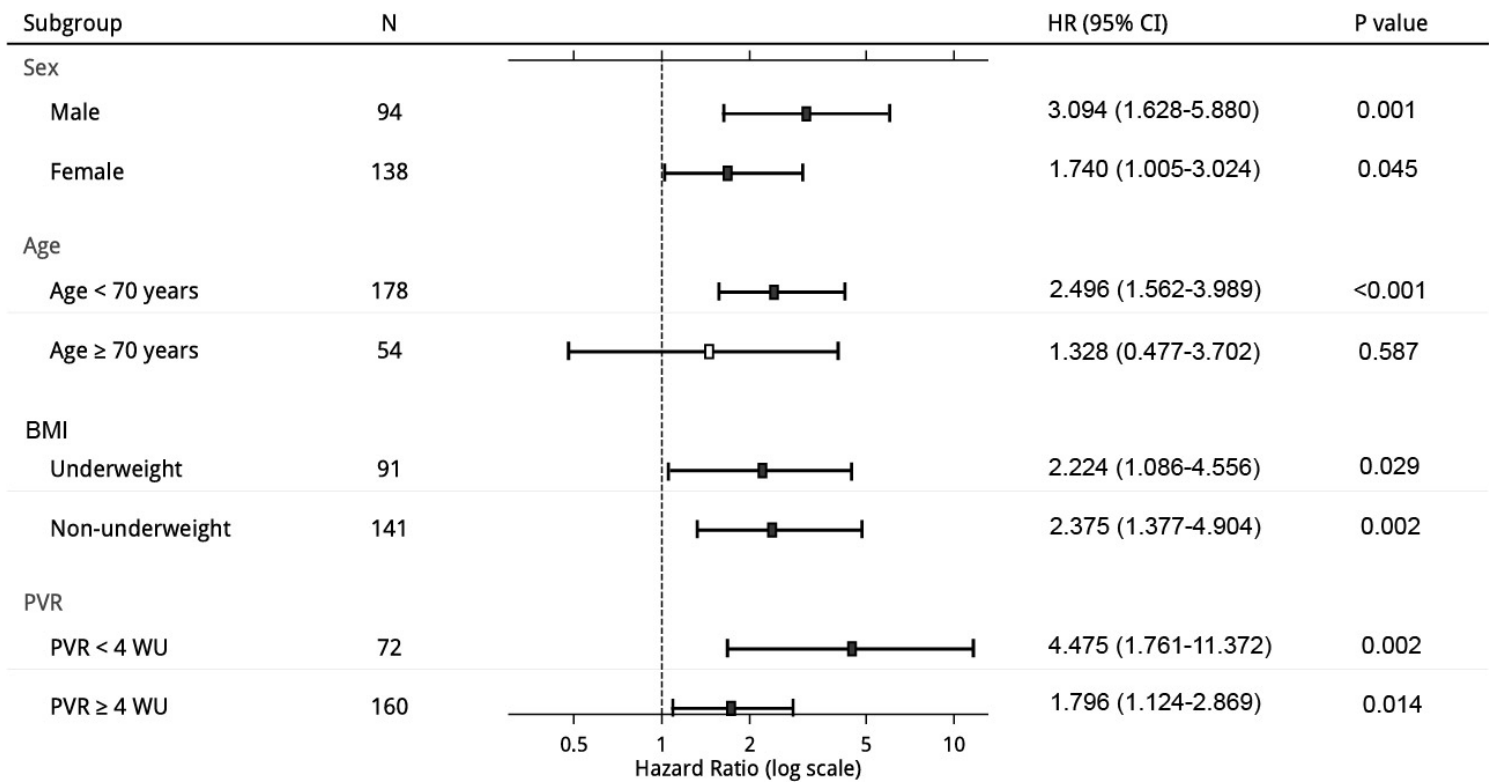


Figure 3

Subgroup analysis for transplant-free survival comparing autoimmune feature-positive [AF(+), combining Ab(+)/non-SARD and SARD, n = 66] versus AF(–) (n = 166). The forest plot shows subgroup-specific HRs for the comparison of AF(+) versus AF(–), stratified by sex, age, BMI, and PVR. The stratifying variable was not included in stratum-specific Cox models, which were adjusted for all Model 2 covariates except the stratifying variable. *P* values for interaction were derived from overall Cox models including an AF(+) × subgroup interaction term.. The AF(+) association was significantly stronger in males (interaction *P* = 0.036) and broadly consistent across other subgroups (interaction *P* values: age 0.940, BMI 0.066, PVR 0.244). AF, autoimmune feature; BMI, body mass index; PVR, pulmonary vascular resistance; WU, Wood units; HR, hazard ratio; CI, confidence interval.