THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

# The Recruitment of Systemic-to-Pulmonary Arterial Collaterals in Chronic and Severe Precapillary Pulmonary Hypertension as an Adaptive or Misguided Mechanism

## ABSTRACT

**Background:** The clinical impact of systemic-to-pulmonary arterial collaterals (SPCs) across pulmonary hypertension (PH) groups remains unclear. The authors evaluated the prevalence, clinical correlates, and prognostic relevance of SPCs in a comprehensive PH cohort.

**Methods:** The authors retrospectively analyzed 434 adult PH patients diagnosed per European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines. Baseline risk was evaluated using multiparametric risk scores. All patients underwent diagnostic heart catheterization and angiography, with SPC recruitment semi-quantitatively graded from 0 (none) to 3 (severe, high grade: 2-3).

**Results:** Mean age was 51.9 ± 18.2 years (61.1% female; groups 1, 2, 3, and 4 comprised 51.6%, 3.4%, 10.1%, and 33.2%, respectively). High-grade SPCs were significantly more prevalent in group 4 (58.3%) compared to groups 1 (30.4%), 2 (20.0%), and 3 (6.8%) ($P$ <.001). Higher SPC grade significantly correlated with PH severity across clinical, echocardiographic, hemodynamic, and risk score measures ($P$ <.001). Although higher SPC grades were linked to clinical worsening requiring parenteral prostacyclins ($P$ = .027), they were not associated with overall 5-year survival, regardless of pulmonary vascular resistance severity or non-CTEPH etiology ($P$ = .920). Only the Registry to Evaluate Early and Long-Term PAH Disease Management 2.0 score independently predicted mortality (hazard ratio [HR] = 1.19, $P$ <.001, 95% CI: 1.13-1.26).

**Conclusion:** Systemic-to-pulmonary arterial collaterals are recruited across all PH etiology groups beyond group 4. While SPC recruitment serves as a marker of advanced pulmonary vascular involvement and elevated risk status, it does not act as an independent driver of long-term mortality.

**Keywords:** Bronchial collaterals, EUPHRATES, pulmonary hypertension

## INTRODUCTION

The normal lung contains 2 distinct circulations of strikingly different origins, proportions, and functions.[1] The first one is the pulmonary arterial (PA) circulation transmitting all of the venous cardiac return into the lungs for gas exchange, while the other is the diminutive systemic circulation, bronchial arterial (BA) circulation, which delivers 0.5%-2% of the oxygenated aortic blood to the lungs as nutrient flow to tissues, vessels, and nerves.[1-7] Scanning electron micrographic studies demonstrated the presence of a dense plexus of capillary network between the distal branches of BA (100 um in diameter) and PA circulation in continuity with the alveolar capillary blanket.[5-7] Three functions of BA circulation—nutrient, hemodynamic, and respiratory—have been previously well defined.[2-7] However, in cases of certain circumstances associated with systemic hypoxemia, such as bronchiectasis, chronic fibrosing pulmonary diseases, and various forms of curtailed PA blood flow, including pulmonary atresia, chronic thromboembolic PA obstructions, or other forms of pulmonary hypertension (PH), the hemodynamic and respiratory compensation functions of BA circulation may become more prominent with recruitment of systemic-to-pulmonary artery collateral arteries (SPCs), which

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**Received:** April 23, 2026
**Accepted:** October 6, 2026
**Available Online Date:** November 12, 2026

**Cite this article as:** Kaymaz C, Tokgöz HC, Kültürsay B, et al. The recruitment of systemic-to-pulmonary arterial collaterals in chronic and severe precapillary pulmonary hypertension as an adaptive or misguided mechanism. *Anatol J Cardiol.* 2026;XX(X):X-X.

DOI: 10.14744/AnatolJCardiol.2026.6587

can originate from BA or non-BA systemic arteries such as intercostal, subpleural, mammaria interna, or phrenic arteries, and rarely from coronary arteries.[8-15] It has also been hypothesized that SPCs and plexiform lesions with dilatation lesions and alveolar capillary network[9] observed in patients with Eisenmenger syndrome[15-16] or some other severe PH forms constitute the macrovascular and microvascular part of the anastomotic network continuum between PA and BA circulation, respectively.[17-21]

In this single-center study, the authors aimed to evaluate the frequency, clinical, laboratory, echocardiographic, and hemodynamic correlates of SPC recruitment as assessed by multislice computed tomography (MSCT) and/or selective angiography in different subgroups of severe PH.

## METHODS

### Study Population

This single-center study retrospectively evaluated 434 patients with PH enrolled in the Evaluation of Pulmonary Hypertension Risk Factors Associated with Survival (EUPHRATES) study. The diagnostic work-up including clinical, laboratory, echocardiographic, hemodynamic, MSCT, and pulmonary ventilation/perfusion scan assessments, and differential diagnosis for subgroups of PH has been based on the definitive criteria of the ESC/ERS 2015[22] and 2022 PH Guidelines,[23,24] depending on the time of the first hemodynamic confirmation.

Multiparametric risk scores (MRS) included a 3-strata risk prediction model from the 2022 ESC/ERS Guidelines for PAH,[24-25] adapted from the Swedish PAH Registry (SPAHR),[26] the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry,[27] and the French Pulmonary Hypertension Network (FPHN) registry low-risk model,[28] as well as the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), REVEAL 2.0 and its abridged 6-component REVEAL Lite 2.0 scores.[29] Exclusion criteria were as follows: segmental PH, type 4 truncus arteriosus, history of Fontan shunt operations or therapeutic embolization procedures to systemic-to-pulmonary shunts, and chronic renal failure.

### Imaging Protocol for Systemic-to-Pulmonary Arterial Collaterals

The recruitment of SPCs was initially assessed by MSCT in the first 91 patients and by selective angiography during coronary angiography performed as part of diagnostic heart catheterization in other patients.

All patients underwent retrospectively electrocardiogram (ECG)-gated CT using 256-MDCT scanners (iCT, Philips Medical Systems). Systemic-to-pulmonary arterial collaterals were detected by aortic late-phase imaging of pulmonary angiograms, and examination started from the tip of the arcus of aorta and ended at the bottom of the heart (around 25 cm and 4 Step and Shoot technique). The minimal slice thickness was 0.67 mm. Using the retrospective ECG gating technique, an isotropic spatial resolution of approximately 400 to 600 μm and a temporal resolution of approximately 83-175 ms were obtained. For radiation concern, the authors used the minimum reasonable dose for the patients (ALARA). The effective radiation dose estimated using the dose–length product method was 2.5-14 mSv depending on the acquisition and gating technique. Scanning was performed with both scanner types at 120 kV using 800-1000 mAs with a detector collimation of 0.625 mm and a gantry rotation speed of 0.27 seconds. Prospective gating was used for 12 patients (those who have less than 70 bpm) and retrospective gating for those who have more than 75 bpm and above. Retrospective gating takes the early diastolic phase of the R-R interval if the heart rate is around 75 bpm and above. Prospective gating is for the end diastolic phase (78% of R-R).

Selective visualization of SPCs was performed with left or right coronary Judkins diagnostic catheter when the catheter was pulled back to the descending aorta, and all possible SPC ostia were screened from upper to lower segments of thoracic aortas. Recruitment of SPCs was graded from none (0) to severe (3) semiquantitatively. Grades 0 and 1 were defined as the absence of any SPC and enlarged intercostal arteries, respectively. Grade 2 was described as the prominent bronchial and non-bronchial arteries, whereas grade 3 was defined as the extensive collateralization from bronchial, intercostal, left or right mammary interna, right coronary, phrenic, or subpleural arteries (Figure 1).

The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients.

### Statistical Analysis

Statistical analyses were conducted using a single-center, cross-sectional cohort design. The distribution of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of histograms. Data are presented as mean ± SD for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed variables. Categorical data are expressed as frequencies and percentages [n (%)].

For baseline comparisons across groups, one-way ANOVA with Tukey's post-hoc test was used for parametric data, while the Kruskal–Wallis test with Dunn–Holm correction was applied for non-parametric data. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate.

## HIGHLIGHTS

- SPCs are common in all precapillary PH groups, notably peaking in Group 4 patients.
- High-grade SPCs strongly correlate with PH severity and multiparametric risk scores.
- Increased PVR is the most significant hemodynamic predictor for SPC recruitment.
- Advanced SPCs relate to clinical worsening but do not impact 5-year overall survival.
- SPCs may represent a macroscopic adaptive network across different PH phenotypes.

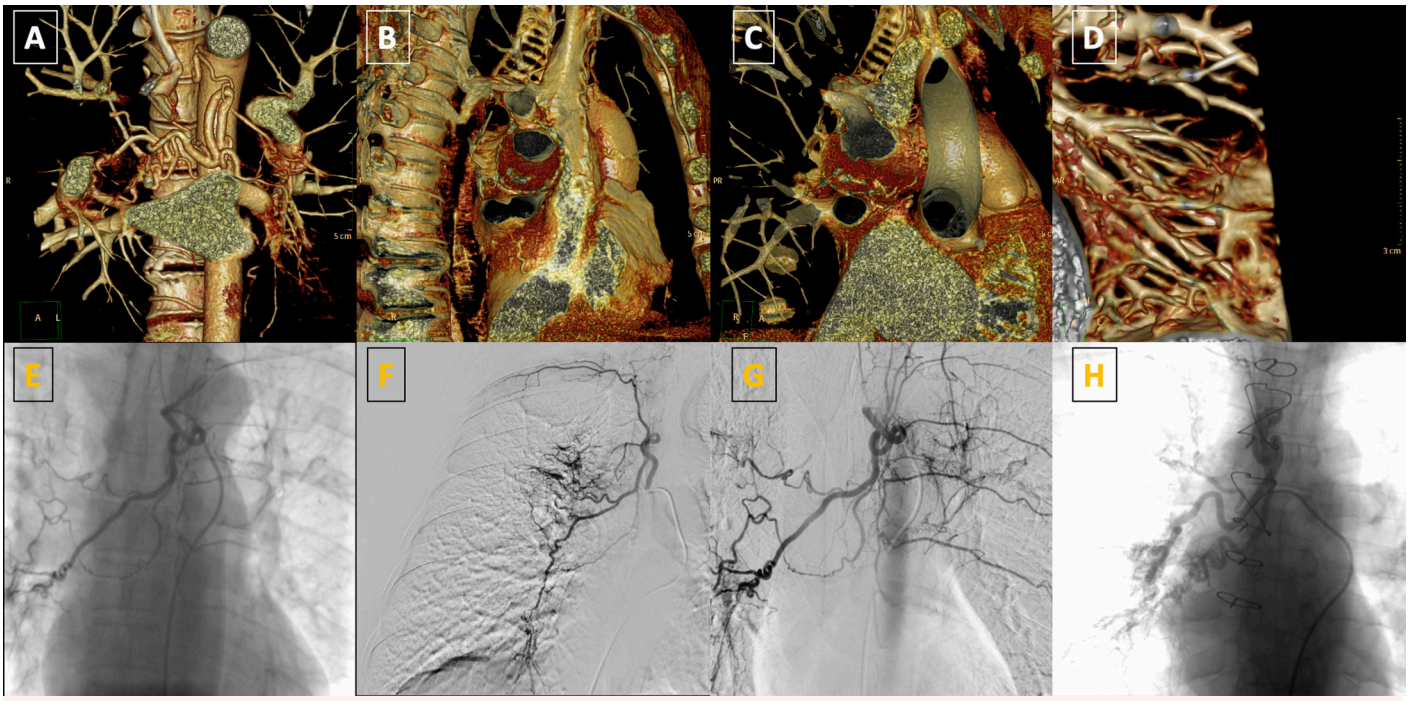



**Figure 1. Radiographic and angiographic visualization of systemic-to-pulmonary collateral (SPC) arteries. This composite figure demonstrates the diverse anatomical origins and the semi-quantitative grading of collateral circulation in patients with severe pulmonary hypertension. Upper panel (A-D): Multislice computed tomography (MSCT) Findings. MSCT images reveal extensive bronchial and non-bronchial SPCs in a patient with severe CTEPH. Specific origins include: (A) enlarged bronchial arteries, (B) left internal mammary artery, (C) phrenic artery, and (D) subpleural connections. In figures B and C, collateralization throughout the pulmonary artery wall and intraluminal thrombi are visible. Lower panel (E-H): Angiography and SPC grading. Selective bronchial artery angiography shows the typical appearance of collaterals across the grading spectrum used in the study, with the extent and complexity of the collateral network progressing from (E) to (H).**

The associations between SPC grades and clinical markers—including hemodynamic parameters, echocardiographic indices, and various MRSs (ESC/ERS 2022, SPAHR, COMPERA 3-strata, REVEAL, REVEAL 2.0, REVEAL Lite 2.0, and FPHN)—were evaluated using Spearman's rank correlation coefficients. Systemic-to-pulmonary arterial collateral grades were analyzed both as an ordinal variable (grades 0-3) and as a dichotomized variable (low grade: 0-1 vs. high grade: 2-3).

Survival analyses and time-to-event outcomes were performed using Kaplan–Meier curves and compared via the log-rank test. The impact of SPC grade on clinical outcomes was further assessed using Cox proportional hazards models, with proportionality assumptions verified through Schoenfeld residuals. Binary outcomes were evaluated using logistic regression models.

All statistical analyses were performed using R version 4.4.3. The following R packages were utilized for data processing and analysis: survival, survminer, rms, ggplot2. A 2-sided *P* value <.05 was considered statistically significant.

## RESULTS

Mean age was 51.9 ± 18.2, and female gender was noted in 61.1% of the overall study population.

Median and mean follow-up duration were 908 (IQR: 163-2133) and 1220 ± 1199 days, respectively.

Groups 1, 2, 3, and 4 were documented in 51.6%, 3.4%, 10.1%, and 33.2% of patients, respectively. Across PH groups, the overall frequency of SPC recruitment was 70.5% in group 1, 53.3% in group 2, 15.9% in group 3, and 74.3% in group 4, whereas the percentage of grade 2 or 3 SPCs in these groups was 30.4%, 20.0%, 6.8%, and 58.3%, respectively ($P < .001$) (Figure 2). In group 1 PH, grade 2 or 3 SPC recruitment was observed in 31.4% of patients with idiopathic PA hypertension (IPAH), 29.4% with PAH associated with connective tissue diseases, and 28.4% with PAH associated with congenital heart disease (IPAH $P = .200$, APAH-CTD $P = .530$, APAH-CHD $P = .072$).

Comparions of grade 0 or 1 versus grade 2 or 3 SPC recruitment in terms of demographic, clinical, echocardiographic and hemodynamic measures, MRSs, evolution of treatment patterns, and clinical course were given in Table 1 and Table 2, respectively. Correlations between SPC grade and clinical, echocardiographic, and hemodynamic measures and MRSs were given in Table 3. Grade of SPC was significantly related to WHO Functional class, pulse oxygen saturation, hemoglobin and uric acid levels, glomerular filtration rate, tricuspid regurgitation velocity, PA acceleration time, inferior vena cava and PA diameters, right atrial (RA) and PA systolic pressures (PASP) estimated by Doppler, and Tricuspid annular planar systolic excursion (TAPSE), and TAPSE to PASP ratio (TAPSE/PASP). Moreover, grade of SPC was also

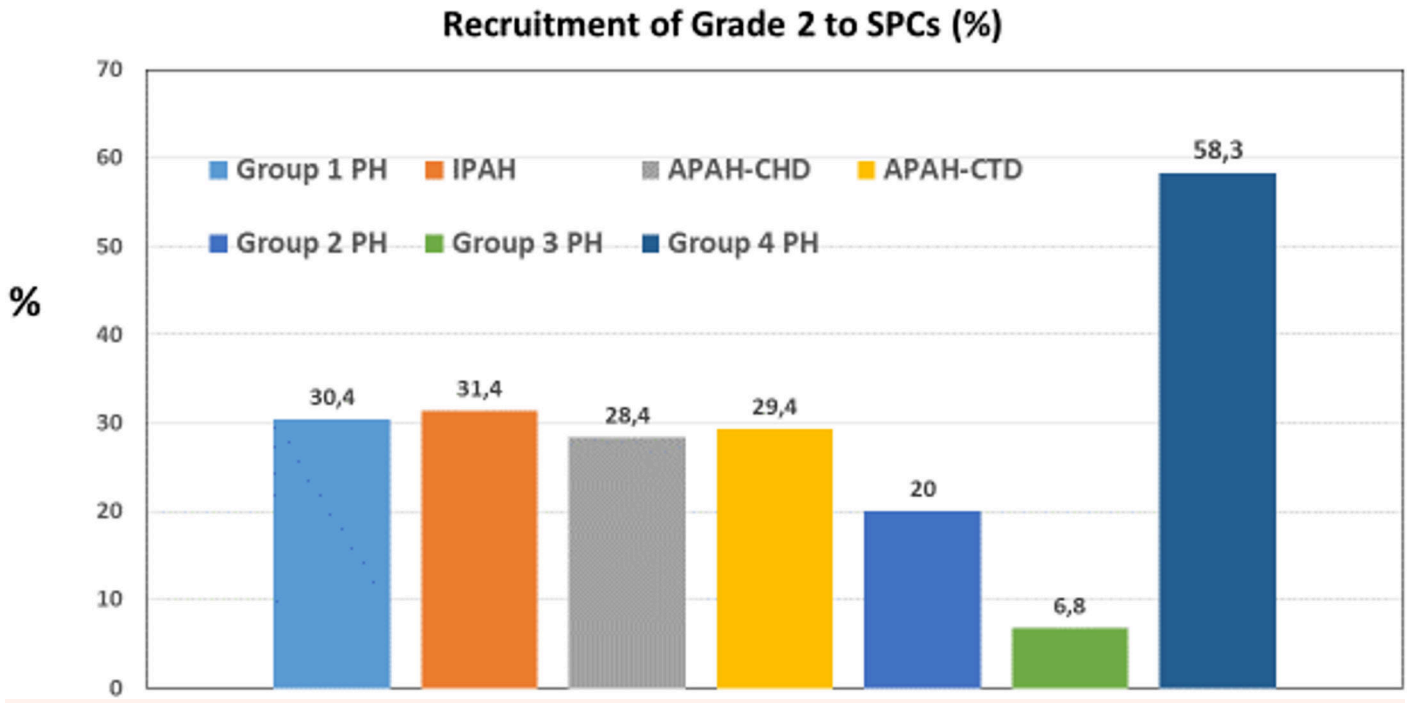



**Figure 2. Frequency of grades 2 and 3 SPCs across the groups and subgroups of PH.**

significantly correlated with invasively measured PA systolic, diastolic, and mean pressures, RA mean pressure, cardiac index, transpulmonary pulmonary gradient (TPG) and diastolic pulmonary gradient (DPG), pulmonary vascular resistance (PVR) and the ratio between pulmonary and systemic vascular resistances (PVR/SVR ratio), PA and aortic oxygen saturations, and MRSs including COMPERA, SPAHR, FPHN, REVEAL, REVEAL 2.0, and REVEAL Lite 2.0 risk status (Table 3) (Figure 3). Moreover, higher SPC grades related to clinical worsening episodes requiring parenteral prostacyclins ($P = .027$), but not with other measures of clinical worsening and overall survival ($P = .210$).

To identify clinical and hemodynamic indicators of collateral recruitment, a ROC analysis was performed on the 5 variables showing the strongest baseline correlations with SPC grade. Among these, PVR emerged as the most significant predictor of grade 2 or 3 SPC presence with an AUC = 0.634. At the optimal threshold (4.5 Wood Units), PVR demonstrated a sensitivity of 89.9% and a specificity of 36.5%. Other resistance and pressure-related indices showed slightly lower predictive capacities, including the PVR/SVR ratio (AUC = 0.631), PASP (AUC = 0.597), TPG (AUC = 0.595), and PAMP (AUC = 0.588) (Figure 4).

Logistic regression confirmed a dose-response relationship between pulmonary afterload and SPC recruitment; each 1 Wood Unit increase in PVR was associated with a 5.0% increase in the odds of grade 2 to 3 SPC presence ($P = .004$) and significantly predicted an ordinal increase to higher SPC grades (OR: 1.07, $P < .001$, 95% CI: 1.03-1.11) (Figure 5).

Grade of SPCs were not related to the 5-year overall survival difference in the PH population (Log rank $P = .920$) (Figure 6). The independent prognostic value of grade 2 to 3 SPCs was evaluated using multiple Cox proportional hazards models adjusted for the REVEAL 2.0 risk score. In the overall cohort, per point increase in REVEAL 2.0 score was independently associated with increased mortality (HR = 1.19, $P < .001$, 95% CI: 1.13-1.25), while neither the presence of grade 2 to 3 SPCs (HR = 0.87, $P = .359$, 95% CI: 0.64-1.17), nor the ordinal increase in SPC grade (HR = 0.94, $P = .321$, 95% CI: 0.82-1.07) was independently associated with mortality (Table 4). These findings remained consistent across major etiological subgroups. After adjusting for REVEAL 2.0 scores, SPC status did not independently predict survival in either the PAH subgroup (HR = 0.83, $P = .420$, 95% CI: 0.57-1.61) or the CTEPH subgroup (HR = 0.96, $P = .873$, 95% CI: 0.57-1.61). Furthermore, an interaction analysis confirmed that the prognostic impact of SPCs did not significantly differ between PAH and CTEPH patients (interaction $P = .704$) (Table 4).

To evaluate whether hemodynamic severity modifies outcomes, patients were stratified using a PVR threshold of 5 WU in the overall PH group and non-CTEPH patients. In multiple Cox models adjusted for REVEAL 2.0 scores, high-grade SPCs were not associated with mortality difference in either severe (PVR ≥ 5 WU; HR = 0.80, $P = .210$, 95% CI: 0.56-1.14) or mild-to-moderate disease (PVR < 5 WU; HR = 1.08, $P = .816$, 95% CI: 0.56-2.01), with no significant interaction ($P$ for interaction = .487). Furthermore, incremental PVR per 1 WU increase carried no mortality risk in either low-grade ($P = .517$) or high-grade SPC strata ($P = .912$). According to the PVR severity and SPC grades, survival comparisons were given in Figures 7A, B, C, and D). The presence or absence of high-grade SPCs were not associated with any survival difference regardless of the PVR severity in the overall PH population or non-CTEPH etiology.

**Table 1. Comparison of the Grade 0-1 vs. 2-3 SPC Groups in Terms of Demographic, Clinical, and Echocardiographic Measures**

| Measures | 0-1, (n = 275) | 2-3, (n = 159) | *P* |
|---|---|---|---|
| Sex, male (%) | 95 (35) | 70 (44) | .050 |
| Age (years) | 55 (35, 67) | 56 (40, 68) | .32 |
| Status (%) | | | .069 |
| Incident (%) | 243 (88) | 149 (94) | |
| Prevalent (%) | 32 (12) | 10 (6.3) | |
| Median follow-up (days) | 1,030 (190, 2,084) | 655 (73, 1,851) | .019 |
| PH group (%) | | | <.001 |
| 1 | 156 (57) | 68 (43) | |
| 2 | 12 (4.4) | 3 (1.9) | |
| 3 | 41 (15) | 3 (1.9) | |
| 4 | 60 (22) | 84 (53) | |
| 5 | 4 (1.5) | 0 (0) | |
| Group 1 PH | 156 (57) | 68 (43) | .005 |
| IPAH (%) | 76 (28) | 35 (22) | .20 |
| APAH-CTD (%) | 12 (4.4) | 5 (3.1) | .53 |
| Overall APAH-CHD (%) | 65 (24) | 26 (16) | .072 |
| APAH-Eisenmenger (%) | 35 (13) | 13 (8.2) | .15 |
| APAH-SP shunt (%) | 10 (3.6) | 1 (0.6) | .062 |
| APAH-small shunt (%) | 4 (1.5) | 1 (0.6) | .66 |
| APAH-repaired shunt (%) | 18 (6.5) | 12 (7.5) | .69 |
| APAH-ASD (%) | 30 (11) | 9 (5.7) | .063 |
| APAH-VSD (%) | 26 (9.6) | 7 (4.4) | .052 |
| APAH-PDA (%) | 11 (4.0) | 2 (1.3) | .15 |
| Group 2 PH (%) | 12 (4.4) | 3 (1.9) | .17 |
| Group 3 PH (%) | 41 (15) | 3 (1.9) | <.001 |
| Group 4 PH (%) | 60 (22) | 84 (53) | <.001 |
| WHO FC (%) | | | .25 |
| 1 (%) | 4 (1.5) | 0 (0) | |
| 2 (%) | 27 (9.8) | 11 (7.0) | |
| 3 (%) | 158 (57) | 88 (56) | |
| 4 (%) | 86 (31) | 59 (37) | |
| 6MWD (m) | 274 (118, 360) | 232 (100, 330) | .075 |
| Pulse oximetric oxygen saturation (%) | 93 (89, 96) | 91 (86, 95) | .030 |
| Heart rate (%) | 87 (77, 98) | 92 (80, 100) | .019 |
| Systolic blood pressure (mm Hg) | 116 (106, 130) | 119 (105, 131) | .42 |
| Diastolic blood pressure (mm Hg) | 70 (64, 80) | 75 (68, 87) | .031 |
| BNP/NT-proBNP status | | | .25 |
| High (%) | 75 (41) | 60 (51) | |
| Intermediate (%) | 64 (35) | 35 (30) | |
| Low (%) | 42 (23) | 22 (19) | |
| Creatinine (mg/dL) | 0.74 (0.62, 0.93) | 0.80 (0.65, 0.92) | .16 |
| Glomerular filtration rate (mL/min/1.73 $m^2$) | 103 (73, 121) | 94 (75, 113) | .26 |
| Albumin (g/dL) | 40.0 (36.0, 43.0) | 39.0 (35.0, 43.0) | .40 |
| White blood cells (count/mL) | 8.19 (6.56, 9.78) | 8.33 (6.60, 9.85) | .79 |
| Hemoglobin (g/dL) | 13.30 (11.80, 15.00) | 13.90 (11.90, 15.50) | .11 |
| Platelet (count/mL) | 236 (180, 287) | 239 (188, 290) | .67 |
| Echocardiographic measures | | | |
| Pericardial effusion (%) | 33 (12) | 18 (11) | .82 |
| RAP (mm Hg) | 8.0 (5.0, 10.0) | 10.0 (5.0, 10.0) | .023 |

(*Continued*)

**Table 1. Comparison of the Grade 0-1 vs. 2-3 SPC Groups in Terms of Demographic, Clinical, and Echocardiographic Measures (*Continued*)**

| Measures | 0-1, (n = 275) | 2-3, (n = 159) | *P* |
|---|---|---|---|
| PASP (mm Hg) | 70 (54, 90) | 78 (60, 92) | .012 |
| PAMP (mm Hg) | 46 (40, 60) | 50 (41, 60) | .17 |
| RA area ($cm^2$) | 22 (18, 28) | 21 (17, 27) | .53 |
| PAMP-PR (mm Hg) | 45 (36, 60) | 40 (35, 55) | .66 |
| PA ACT (msec) | 70 (59, 81) | 63 (53, 74) | .007 |
| TAPSE (cm) | 2.00 (1.60, 2.26) | 1.80 (1.50, 2.20) | .10 |
| TAPSE /PASP Ratio | 0.272 (0.189-0.380) | 0.236 (0.178, 0.329) | .038 |
| St (cm/sec) | 12.0 (10.0, 14.0) | 11.4 (9.8, 14.0) | .18 |

6MWD, 6-minute walk distance; ACT, acceleration time; APAH, associated pulmonary arterial hypertension; APAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; ASD, atrial septal defect; BNP, B-type natriuretic peptide; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; PAMP, mean pulmonary artery pressure; PASP, systolic pulmonary artery pressure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PR, pulmonary regurgitation; RAP, right atrial pressure; RV, right ventricle; SP shunt, systemic-to-pulmonary shunt; S′, tricuspid annular systolic tissue velocity; TAPSE, tricuspid annular plane systolic excursion; VSD, ventricular septal defect.

**Table 2. Comparison of the Grade 0-1 vs. 2-3 SPC Groups in Terms of Hemodynamic, Multiparametric Risk Scores, Evolution of Treatment Patterns and Clinical Course**

| Measures | 0-1, (n = 275) | 2-3, (n = 159) | *P* |
|---|---|---|---|
| Hemodynamic measures | | | |
| Aortic-systolic pressure (mm Hg) | 131 (115, 150) | 132 (118, 150) | .93 |
| Aortic-diastolic pressure (mm Hg) | 70 (63, 78) | 72 (65, 83) | .049 |
| Aortic-mean pressure (mm Hg) | 92 (84, 103) | 95 (86, 105) | .11 |
| LVEDP (mm Hg) | 11.5 (9.0, 14.0) | 12.0 (10.0, 13.0) | .45 |
| PCWP (mm Hg) | 11.0 (9.0, 14.0) | 11.0 (9.0, 13.0) | .42 |
| PASP (mm Hg) | 68 (53, 93) | 78 (64, 94) | <.001 |
| PADP (mm Hg) | 24 (18, 33) | 28 (21, 35) | .005 |
| PAMP (mm Hg) | 40 (32, 52) | 45 (39, 55) | <.001 |
| RAP (mm Hg) | 7.0 (5.0, 10.0) | 8.0 (5.0, 12.0) | .040 |
| CO (L/min) | 4.40 (3.60, 5.10) | 4.10 (3.50, 5.00) | .35 |
| CI ($L/min/m^2$) | 2.50 (2.10, 2.90) | 2.30 (1.92, 2.70) | .014 |
| TPG (mm Hg) | 27 (20, 41) | 33 (26, 44) | <.001 |
| TSG (mm Hg) | 85 (76, 96) | 86 (77, 96) | .47 |
| DPG (mm Hg) | 12 (7, 22) | 16 (10, 24) | .012 |
| Aortic mean pressure—PCWP difference (mm Hg) | 81 (73, 92) | 84 (74, 93) | .12 |
| PVR (Wood Units) | 5.5 (4.0, 9.2) | 7.0 (5.5, 11.0) | <.001 |
| SVR (Wood Units) | 20 (16, 25) | 21 (17, 26) | .43 |
| PVR/SVR ratio | 0.30 (0.20, 0.44) | 0.40 (0.29, 0.50) | <.001 |
| Qp/Qs ratio | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) | <.001 |
| Mixed venous $O_2$ Saturation (%) | 63 (58, 68) | 62 (56, 68) | .20 |
| DLCO (mL/min/mm Hg) | 66 (37, 91) | 68 (26, 78) | .45 |
| Multiparametric risk scores | | | |
| REVEAL | 9.00 (7.50, 10.00) | 9.00 (8.00, 11.00) | .016 |
| REVEAL 2.0 | 9.0 (7.0, 11.0) | 9.0 (7.0, 12.0) | .003 |
| REVEAL LİTE 2.0 | 8.00 (6.00, 10.00) | 9.00 (7.00, 11.00) | .070 |
| COMPERA | 1.67 (1.33, 2.17) | 1.80 (1.40, 2.33) | .056 |
| SWEDISH (SPAHR) | 1.50 (1.29, 2.00) | 1.67 (1.33, 2.17) | .073 |
| FPHN Low-risk status (%) | | | .11 |
| 0 | 125 (45) | 88 (56) | |
| 1 | 120 (44) | 61 (39) | |

(*Continued*)

**Table 2. Comparison of the Grade 0-1 vs. 2-3 SPC Groups in Terms of Hemodynamic, Multiparametric Risk Scores, Evolution of Treatment Patterns and Clinical Course (*Continued*)**

| Measures | 0-1, (n = 275) | 2-3, (n = 159) | *P* |
|---|---|---|---|
| 2 | 19 (6.9) | 7 (4.4) | |
| 3 | 11 (4.0) | 2 (1.3) | |
| Baseline PAH treatment (%) | | | .93 |
| Overall (%) | 16 (5.9) | 10 (6.3) | |
| Monotherapy (%) | 9 (3.3) | 6 (3.8) | |
| Double PAH combination (%) | 4 (1.5) | 3 (1.9) | |
| Triple PAH combination (%) | 3 (1.1) | 1 (0.6) | |
| Final PAH Treatment (%) | | | <.001 |
| Overall (%) | 194 (71) | 128 (81) | |
| Monotherapy (%) | 66 (24) | 74 (47) | |
| Double PAH combination (%) | 68 (25) | 26 (16) | |
| Triple PAH combination (%) | 60 (22) | 28 (18) | |
| CWE ≥15 % decrease in 6MWD (%) | 22 (10.0) | 13 (10) | .91 |
| CWE - ≥ 1 increase in WHO FC (%) | 80 (36) | 57 (45) | .10 |
| CWE requiring iv diuretic (%) | 60 (27) | 31 (24) | .58 |
| CWE requiring iv prostacyclin (%) | 114 (52) | 81 (64) | .027 |
| CWE requiring add-on PAH treatment (%) | 38 (17) | 24 (19) | .69 |
| CWE requiring PAH-related hospitalization (%) | | | .084 |
| No | 94 (43) | 52 (41) | |
| 1 CWE | 104 (47) | 66 (52) | |
| 2 CWE | 10 (4.5) | 5 (3.9) | |
| 3 CWE | 8 (3.6) | 0 (0) | |
| 4 CWE | 4 (1.8) | 1 (0.8) | |
| 5 CWE | 0 (0) | 2 (1.6) | |
| 8 CWE | 1 (0.5) | 0 (0) | |
| 10 CWE | 0 (0) | 1 (0.8) | |
| Death rate (%) | 109 (40) | 53 (34) | .21 |

CI, cardiac index; CO, cardiac output; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CWE, clinical worsening episode; DLCO, diffusing capacity of the lung for carbon monoxide; DPG, diastolic pressure gradient; ESC, European Society of Cardiology; ERS, European Respiratory Society; FPHN, French Pulmonary Hypertension Network; LVEDP, left ventricular end-diastolic pressure; $O_2$, oxygen; PA, pulmonary artery; PAMP, mean pulmonary artery pressure; PASP, systolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary-to-systemic blood flow ratio; RAP, mean right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management score; REVEAL 2.0, updated REVEAL score; REVEAL LITE 2.0, six-component abridged version of the REVEAL 2.0 score; SVR, systemic vascular resistance; SWEDISH, Swedish Pulmonary Arterial Hypertension Registry (SPAHR); TPG, transpulmonary pressure gradient; TSG, transsystemic pressure gradient.

## DISCUSSION

The study revealed the frequency of SPC recruitment across different PH groups and PAH subgroups, beyond group 4 PH. Across the PH groups, the percentage of grade 2 or 3 SPC recruitment was highest in group 4 compared with those in other clinical PH groups, whereas rates of SPC recruitment were comparable among subgroups of group 1 PH. The grade of SPC recruitment appear to be associated with severity of PH as assessed by clinical, echocardiographic and hemodynamic measures, MRSs, and clinical worsening requiring parenteral prostacyclins, but not with overall 5-year survival regardless of the PVR severity or non-CTEPH etiology.

Since it was first documented by F. Ruysch in 1731, the BA circulation remained a neglected part of the systemic circulation, through the arteries supplying the bronchial walls, lung vessels, nerves, and alveolar tissues.[1-5] Moreover, under special circumstances, BA circulation may transform from a supplier into a circulation unit that provides hemodynamic and respiratory compensations.[3-9] Histopathologically, PH is characterized by lesions including medial hypertrophy/hyperplasia, intimal and adventitial fibrosis, and in situ thrombosis and plexiform lesions mainly occurring in distal muscular-type arteries, ranging in diameter from 500 μm down to 70 μm, resulting in stiffening of elastic main, lobar, and segmental Pas.[20,21] Pre-capillary arterioles ranging in diameter from 70 μm down to 20 μm show loss and obliteration, abnormal muscularization, perivascular inflammation, and involvements of capillary and post-capillary pulmonary compartments with varying grades of severity are also reported in all groups of human and experimental PH.[20,21] Whether plexiform lesions represent morphologic sequelae

**Table 3. Correlations Between SPC Grade and Clinical, Echocardiographic, and Hemodynamic Measures**

| Variables | Spearman *R* value | *P* |
|---|---|---|
| Clinical | | |
| WHO FC | 0.104 | .030 |
| Hemoglobin | 0.121 | .012 |
| Uric acid | 0.136 | .045 |
| Glomerular filtration rate | −0.223 | .006 |
| Echocardiographic measures | | |
| TR Vmax | 0.181 | .001 |
| IVC diameter | 0.184 | .001 |
| RAP | 0.155 | .003 |
| PASP | 0.219 | .000 |
| Main PA diameter | 0.125 | .033 |
| PA ACT | −0.246 | .001 |
| TAPSE/PASP ratio | −0.181 | .001 |
| Invasive hemodynamic measures | | |
| PASP | 0.296 | <.0001 |
| PADP | 0.229 | <.0001 |
| PAMP | 0.267 | <.0001 |
| Transpulmonary gradient | 0.275 | <.0001 |
| Diastolic pulmonary gradient | 0.217 | .000 |
| RV EDP | 0.126 | .010 |
| RAP | 0.134 | .006 |
| PVR | 0.289 | <.0001 |
| PVR / SVR ratio | 0.298 | <.0001 |
| Qp / Qs ratio | −0.144 | .003 |
| PA $SPO_2$ | −0.136 | .008 |
| LV $SPO_2$ | −0.148 | .002 |
| Aortic $SPO_2$ | −0.132 | .007 |
| Multiparametric risk scores | | |
| COMPERA | 0.119 | .013 |
| SWEDISH | 0.107 | .025 |
| FPHN | −0.165 | .001 |
| REVEAL | 0.111 | .020 |
| REVEAL 2.0 | 0.148 | .002 |
| REVEAL Lite 2.0 | 0.105 | .029 |

ACT, acceleration time; CI, cardiac index; CO, cardiac output; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DPG, diastolic pressure gradient; EDP, end-diastolic pressure; FPHN, French Pulmonary Hypertension Network; IVC, inferior vena cava; LV, left ventricle; PADP, diastolic pulmonary artery pressure; PA, pulmonary artery; PAMP, mean pulmonary artery pressure; PASP, systolic pulmonary artery pressure; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary-to-systemic blood flow ratio; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management score; REVEAL 2.0, updated REVEAL score; REVEAL LITE 2.0, six-component abridged version of the REVEAL 2.0 score; RV, right ventricle; $SPO_2$, peripheral oxygen saturation; SVR, systemic vascular resistance; SWEDISH, Swedish Pulmonary Arterial Hypertension Registry (SPAHR); TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary pressure gradient; TR, tricuspid regurgitation; TSG, transsystemic pressure gradient; Vmax, maximum velocity; WHO FC, World Health Organization functional class.

of the raised intravascular pressure or actively contribute to the course of the disease is still debated.[4,9,16,17,19] These lesions seem to work as a "misguided" adaptive mechanism in response to fibrotic thickening of the distal PA vasculature in some precapillary severe PH forms.[7,21,22] Plexiform lesions are reported to occur in side twigs arising from a parent PA branch 200-400 μm in diameter, whereas fibrous or cellular intimal thickening usually develops in dichotomous branches at the periphery of PA.[9,16,17] The distal part of the plexiform lesions communicates with the vein-like dilatation lesions.[9,21] Some of these extend towards alveolar capillaries, while others communicate with terminal bronchial arteries running along a bronchiole or with those forming the vasa vasorum of a PA branch.[9,20,21] The SPCs and plexiform lesions with dilatation lesions and alveolar capillary network seem to constitute the macrovascular and microvascular part of the anastomotic network continuum between PA and BA circulations, respectively.[9,20,21] Moreover, large fibrous vascular structures named "SiMFis" (singular millimetric fibrovascular lesions) seem to connect the systemic circulation to PAs and pulmonary veins in severe PH.[21] However, whether these connecting structures would allow short-circuiting in cases of PA obstruction remains to be clarified.[9,21] Interestingly, a relation between the development of SPCs in the lungs and nail fold neovascularization in digital clubbing has also been noted 4 decades ago.[3,4]

It was demonstrated that the BA system developed before the PAs during early fetal development and the vascular plexus of the lung buds is connected to segmental arteries arising from the dorsal aorta.[13,14,19] When normal PA blood flow is reduced or obstructed in specific circumstances including the complex CHD, CTEPH, or severe PAH, SPCs from BAs or other origins including intercostal arteries, internal mammary arteries, branches of subclavian arteries, phrenic arteries, or occasionally coronary arteries can develop.[10-13,21] Recruitment of SPCs can increase blood flow by a factor of 10 and contribute up to 25% of pulmonary oxygenation.[3-7] The SPCs can supply either desaturated venous PA blood flow or highly oxygenated systemic arterial blood flow to the alveolar precapillary level via this extensive capillary by-pass plexus.[3-7,9,11-14] Because the blood flow continuity through SPCs is driven by the pressure gradient between proximal (PA or aortic mean pressure) and distal (PA wedge pressure) ends of the circulatory unit, theoretically PA-to-alveolar precapillary or BA-to-alveolar precapillary bypass blood flow can be maintained until thrombotic or inflammatory blockade of either pathway, which may be sufficient to raise the peripheral resistance beyond a certain critical point.[11-14] The development of SPCs was previously reported to be related to the hemodynamic severity of precapillary PH..[30] The present study also confirmed that SPC recruitment appear to be associated with severity of PH as assessed by clinical, echocardiographic and hemodynamic measures, MRSs, and clinical worsening requiring parenteral prostacyclins. Increased PVR and PVR/SVR ratio are the 2 strongest hemodynamic indicators for the development of SPCs in PH. However, only the REVEAL 2.0 score, but not the grade of SPCs, was independently associated with increased mortality during

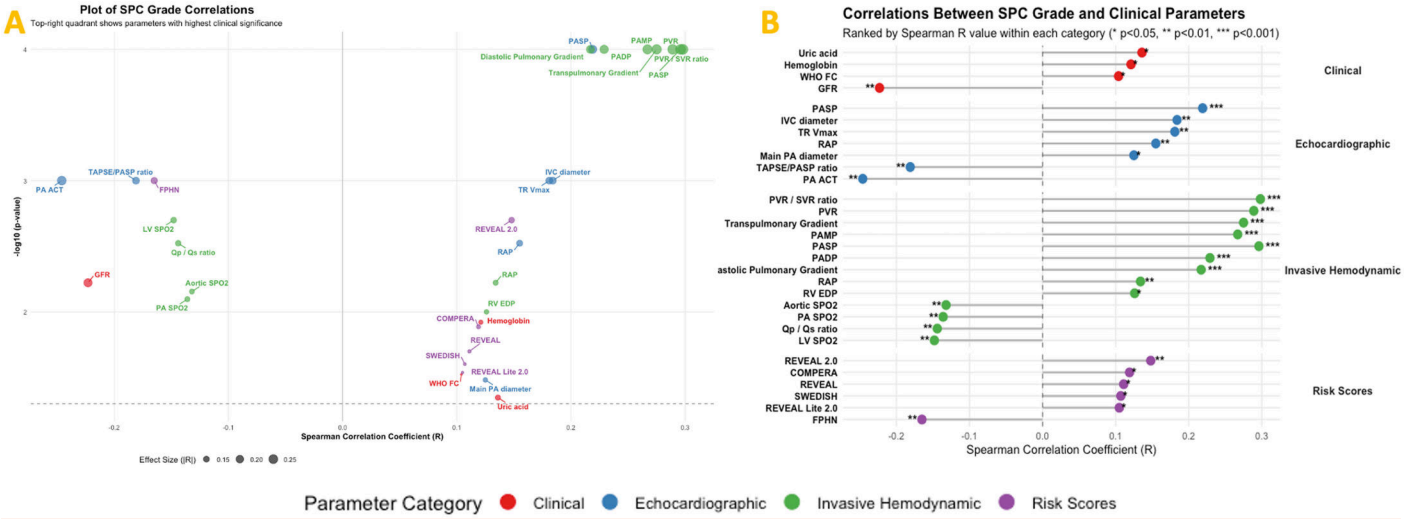



**Figure 3. Identifying key hemodynamic and clinical drivers of SPC formation. (A) Distribution of factors associated with SPC presence. This panel visualizes the statistical significance and strength of association for clinical parameters. Variables in the upper right quadrant, particularly invasive hemodynamic markers like PVR and PASP, represent the most significant drivers associated with the presence of collaterals. (B) Correlation-based ranking of markers for SPC severity. This panel ranks key PH markers based on their Spearman correlation coefficients with SPC grade. Invasive hemodynamic indices exhibit the strongest correlations, outperforming clinical risk scores and non-invasive measures in predicting the quantitative progression and complexity of the collateral network.**

a 5-year follow-up regardless of the PVR severity or non-CTEPH etiology. However, it is apparent that recruitment of high-grade SPCs showed no survival disadvantage even among patients with a PVR of 5 WU or higher, a subset where advanced vascular disease typically carries a poorer prognosis. Systemic blood supply directed to distal ischemic lung

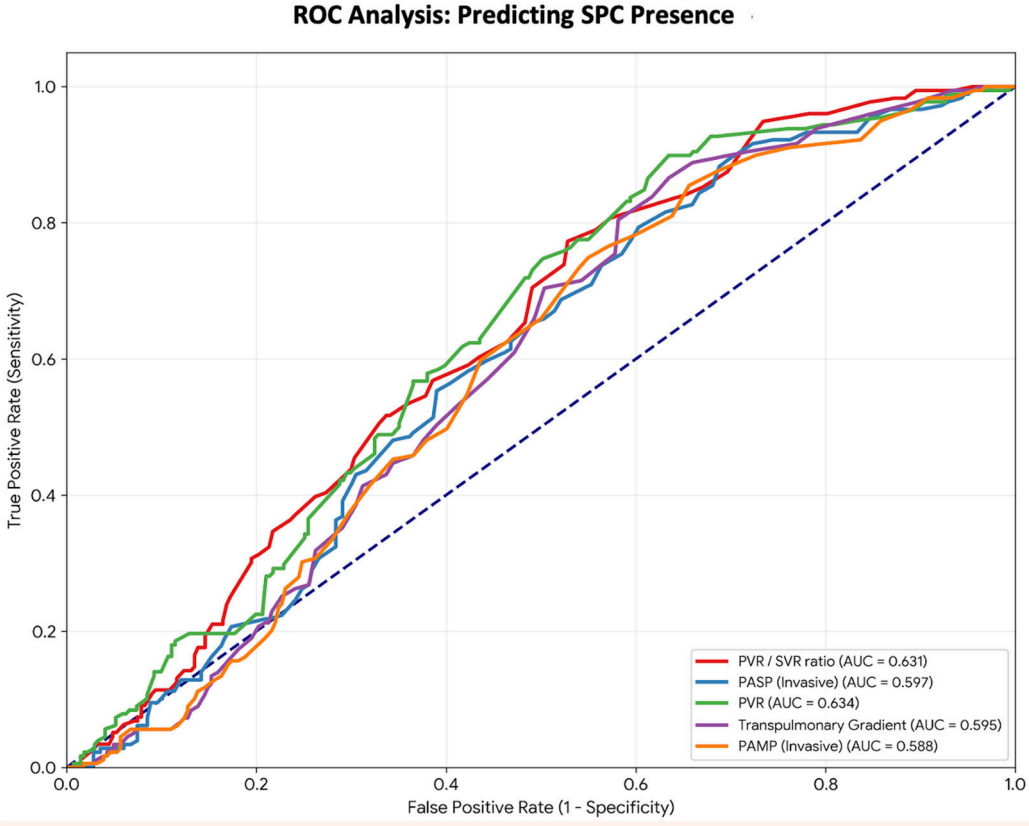



**Figure 4. ROC analysis of hemodynamic predictors for grade 2 to 3 SPC presence. This figure evaluates the diagnostic accuracy of the 5 hemodynamic variables showing the strongest baseline correlations with collateral recruitment.**

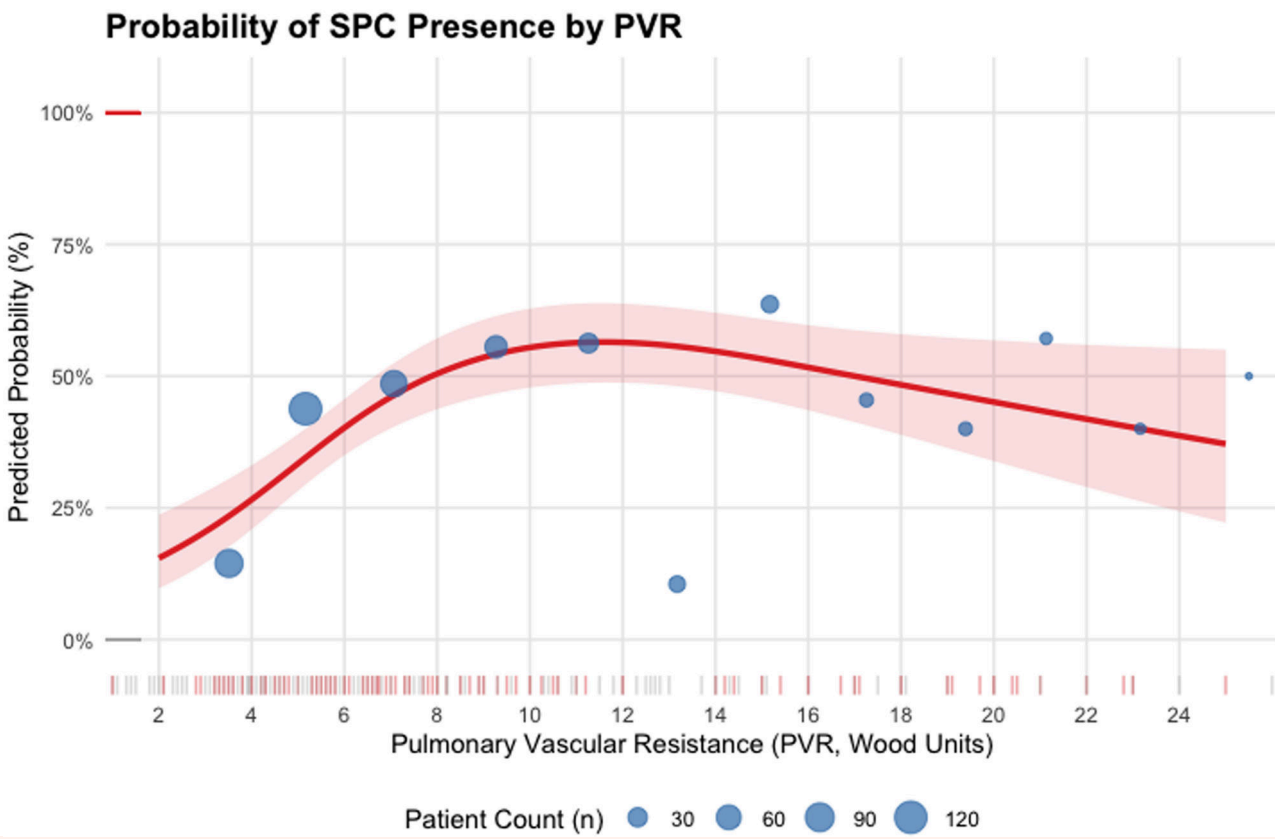



**Figure 5. Association between pulmonary vascular resistance and predicted probability of high-grade SPC presence. The red curve displays the non-linear relationship between pulmonary vascular resistance (PVR, in Wood Units) and the predicted probability of high-grade systemic-to-pulmonary arterial collaterals (SPCs), with the shaded area indicating the 95% CI. Blue circles represent observed proportions, with circle size proportional to patient count (n = 30 to 120). The rug plot on the x-axis shows individual patient data (red ticks: SPC presence; grey ticks: SPC absence). Collateral probability increases sharply with PVR up to approximately 11-12 Wood Units before reaching a plateau.**

tissue might provide a compensatory effect that balances out the excess mortality risk expected from high PVR. These findings suggest that while collateral formation marks more severe hemodynamic load, it does not directly drive long-term mortality difference.

Moreover, if antegrade pulmonary flow is compromised in complex cardiac abnormalities such as pulmonary atresia, Fallot tetralogies with severe pulmonary flow obstruction, type 4 truncus arteriosus, tricuspid atresia, complex transposition, unbalanced atrioventricular canal defects, single left ventricle, or double-outlet right ventricle, SPCs named as major aortopulmonary collateral arteries (MAPCAs) can supply the majority or all of the PA blood flow.[19-21] The prevalence of intraoperatively identified MAPCAs among patients with pulmonary atresia is 53%-77%.[10-14,19-21] These MAPCAs show variations in the number, origin, course, branching patterns, and anastomoses with PAs, and may be classified according to the 3 main characteristics: vessel of origin, communication with PAs, and impact of stenosis, respectively.[10-14,19-21] Regardless of the MAPCAs in complex CHDs, or SPCs secondary to acquired pulmonary vascular obstructions, these collaterals involve both beneficial and deleterious effects.[3-7,10-15,21]

Although the mechanisms of this adaptive or misguided neovascularization are not completely understood, the expansion of systemic arterial circulation into the PA territory through these SPCs may provide further microvascular targets for novel PH treatments.[30] Selective injection of prostaglandin (PG) E1, PG F2, PGD2 into the BAs, direct infusion of PGI2 into the PA, and inhaled PG F2 have been documented to induce significant vasodilation in BA circulation.[5-7] Moreover, a dose-dependent decrease in BA vascular resistance following the selective injection of PGE1 was reported in an animal model.[5-7]

In addition to well-established treatments targeted to endothelin, nitric oxide, and prostacyclin pathways,[31-35] promising results of the PA denervation studies, novel treatments targeted to rebalancing the anti-proliferative and pro-proliferative signaling,[36,37] or inhibiting the platelet-derived growth factor receptor, colony-stimulating factor 1 receptor, and mast or stem cell growth factor receptors[38] should be considered as different aspects of a paradigm shift in the understanding of the pathogenetic mechanisms and the future treatments of PH. Accordingly, the following questions may arise: Despite the well-defined target pathways responsible for the pathogenesis of precapillary PH,

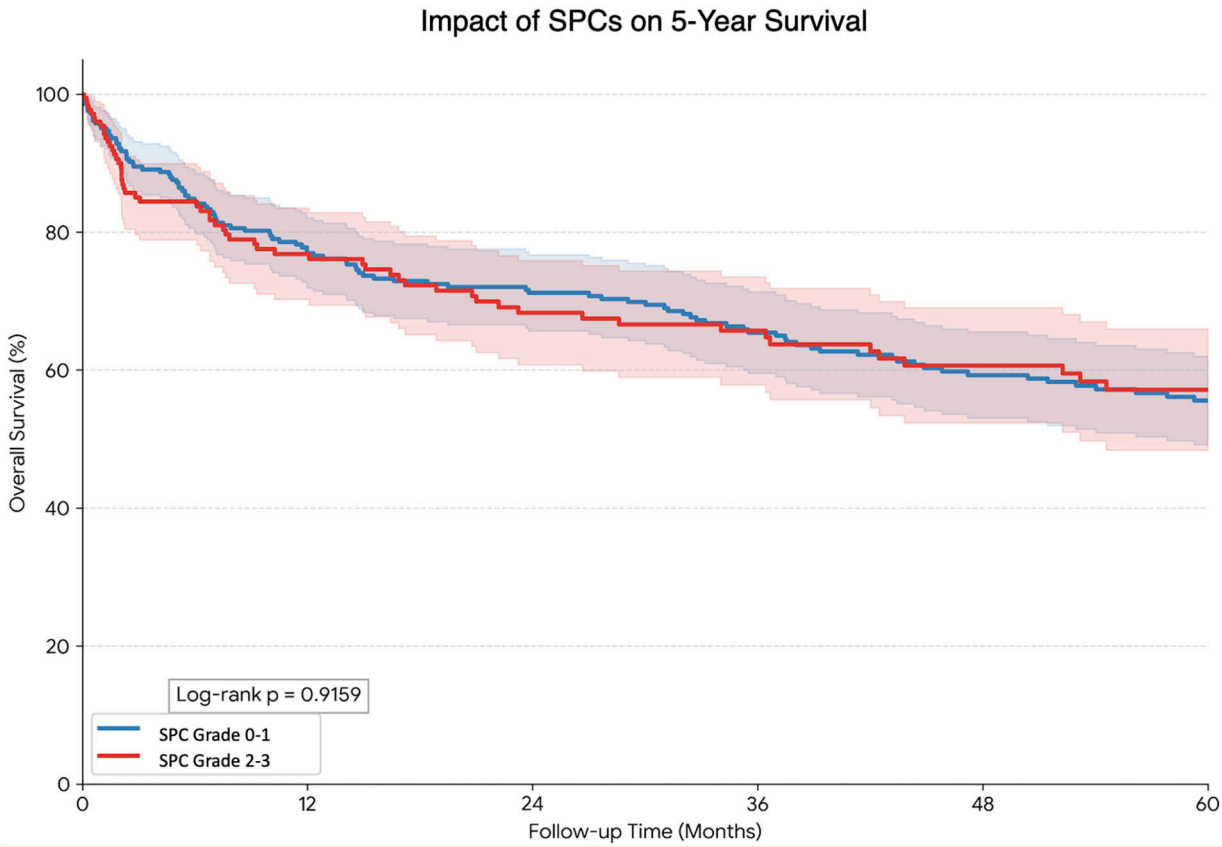



**Figure 6. Kaplan–Meier Survival Analysis by SPC Grade. This figure illustrates the long-term survival trajectories of the study population, categorized by the extent of collateral recruitment.**

and several therapies providing promising results in terms of morbidity and/or mortality benefits, is something wrong in the scenario to define the modes of action in the presence of nearly occluded distal PA vascular bed? Could targeted agents realistically modulate the systemic endothelium invading the distal lung circulation through these SPCs? Does the absence of the recruitment of SPCs in the post-capillary PH characterized by elevated PA wedge pressure play a role in the failure of currently available targeted PAH treatments in patients with PH due to left heart diseases.[21-23,31] Moreover, phenotyping of idiopathic PAH seems to provide new insights into the differential outcome across this spectrum.[39,40]

**Table 4. Multiple Cox Proportional Hazards Regression Analysis for Mortality**

| Analysis | Predictor Variable | Hazard Ratio (95% CI) | *P* |
|---|---|---|---|
| Overall cohort | REVEAL 2.0 Score (per point increase) | 1.19 (1.13-1.26) | <.001 |
| | SPCs (Binary: grade 0-1 vs. grade 2-3) | 0.87 (0.64-1.17) | .359 |
| | SPCs (Ordinal: per grade increase) | 0.94 (0.82-1.07) | .321 |
| Subgroup analysis | | | |
| Group 1: PAH | SPCs (Binary: grade 0-1 vs. grade 2-3) | 0.83 (0.54-1.30) | .420 |
| Group 4: CTEPH | SPCs (Binary: grade 0-1 vs. grade 2-3) | 0.96 (0.57-1.60) | .873 |
| Interaction analysis | SPCs × PH group (PAH vs. CTEPH) | — | .704 |

CI, Confidence interval, CTEPH, Chronic thromboembolic pulmonary hypertension, HR, Hazard ratio, PAH, Pulmonary arterial hypertension, PH, Pulmonary hypertension, REVEAL 2.0, Registry to Evaluate Early and Long-Term PAH Disease Management 2.0 score, SPCs, Systemic-to-pulmonary arterial collaterals.

## Study Limitations

The first limitation is the lack of longitudinal data to test the impact of serial changes of SPCs in relation to clinical outcomes in patients treated by targeted agents and in patients who underwent pulmonary endarterectomy. Secondly, the absence of interobserver and intraobserver agreement evaluation in the grading of SPCs might be considered a methodological limitation. The absence of in vivo volumetric measures of SPCs is another important limitation. However, only a few studies on BA blood flow in humans have been published, and Fick's principle has been reported in the majority of these studies while indicator dilution, phase contrast MRI, or Doppler Flowire techniques have been used in others.[10,13,14] The newly developed cardiac MR techniques for volumetric flow measurement can be useful regarding the risk stratifications, tailored management strategies of SPCs, and evolution of SPCs after PAH treatments or after endarterectomy.[10,13,14] The lack of histopathological data, which may provide adaptive or

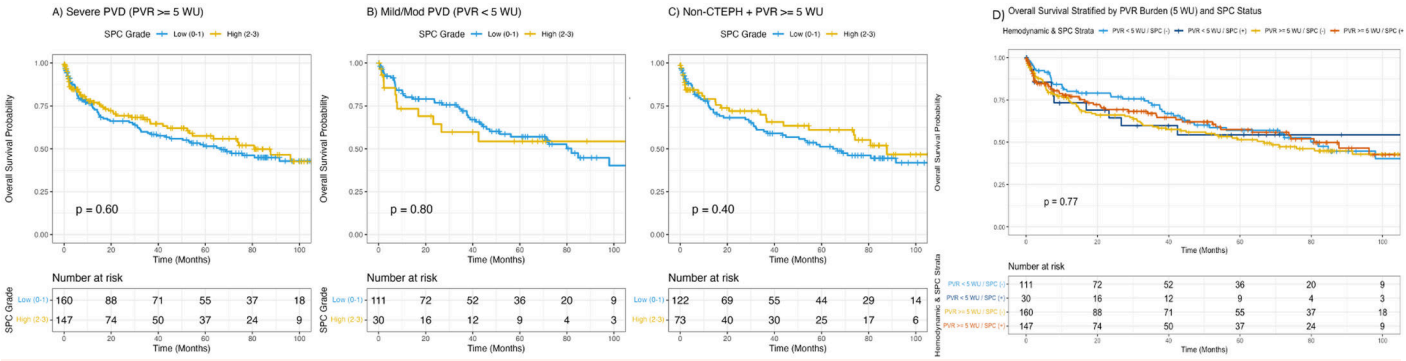



**Figure 7. Kaplan–Meier survival curves stratified by pulmonary vascular resistance and SPC status. Overall survival trajectories across hemodynamically defined patient subgroups: (A) Severe pulmonary vascular disease (PVR ≥ 5 Wood Units [WU]), (B) Mild-to-moderate disease (PVR < 5 WU), (C) Non-CTEPH cohort with severe PVD (PVR ≥ 5 WU), and (D) Combined 4-strata comparison across PVR burden and SPC presence. Across all subgroups and etiologies, high-grade SPC presence showed no statistically significant impact on long-term survival.**

"misguided" maladaptive microvascular changes beyond the limits of currently available imaging technologies, is another limitation of this study. The histopathological evaluation of lung explants may provide further insights for pulmonary microvascular remodeling in patients with PH.

## CONCLUSION

Across the PH groups, grade 2 or 3 SPCs were more frequent in group 4 compared with those in other clinical groups, whereas the rate of SPCs was not different across Group 1 PH patients. The grade of SPCs was correlated with the severity of PH as assessed by clinical, echocardiographic and hemodynamic measures, MRSs, and clinical worsening requiring parenteral prostacyclins, but not with overall survival, irrespective of the severity of PVR or non-CTEPH etiology. Comparable survival with high-grade SPCs, even in the presence of PVR of 5 Wood Units or higher, a subset expected to carry a poor prognosis, should be taken into consideration. These SPCs may serve as an adaptive or misguided mechanism to maintain continuity of PA-to-alveolar or systemic arterial-to-alveolar capillary blood flow in specific circumstances. However, the clinical significance of SPCs in the era of novel targeted therapies and interventional procedures remains to be determined.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Kartal Koşuyolu Heart and Research Hospital (Approval No: 2013.3/4, Date: 12.07.2013).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – C.K., B.K., N.O.; Design – C.K., B.K., N.O.; Supervision – C.K., N.O.; Resources – C.K., N.O., A.K.; Materials – C.K., H.C.T., S.T., C.B.; Data Collection and/or Processing – H.C.T., B.K., S.T., C.B., C.E.C., M.I.D., M.K., B.Ke., A.H., D.S., T.G., Z.B.; Analysis and/or Interpretation – C.K., B.K., H.C.T., I.H.T., N.O.; Literature Search – B.K., H.C.T., S.T., C.B., C.E.C., M.I.D., M.K., B.Ke., A.H., D.S., T.G., Z.B.; Writing – B.K., C.K.; Critical Review – C.K., A.K., I.H.T., N.O.

**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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