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Five-Year Outcomes of Patients Enrolled in the REVEAL Registry

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BACKGROUND: Pulmonary arterial hypertension (PAH) is a rare, severe disease characterized by worsening right-sided heart failure, decreasing functional status, and poor survival. The present study characterizes the 5-year survival in the United States of a new and previous diagnosis of PAH in patients stratified by baseline functional class (FC). The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) is a 55-center observational US registry of the demographics, disease course, and management of patients with World Health Organization (WHO) group 1 PAH.

METHODS: The REVEAL Registry enrolled newly and previously diagnosed patients aged ≥ 3 months with WHO group 1 PAH consecutively from March 2006 to December 2009. Demographics, disease characteristics, and hemodynamic data were collected at enrollment. Survival analysis was conducted by FC and other subgroups in patients aged ≥ 18 years.

RESULTS: Survival differences between previously diagnosed and newly diagnosed patients at 1 year (90.4% vs 86.3%) were maintained to 5 years; 5-year survival for previously diagnosed patients was 65.4% compared with 61.2% for newly diagnosed patients. Previously diagnosed patients in FC I, II, III, and IV had an estimated 5-year survival rate of 88.0%, 75.6%, 57.0%, and 27.2%, respectively, compared with 72.2%, 71.7%, 60.0%, and 43.8% for newly diagnosed patients in FC I, II, III, and IV, respectively.

CONCLUSIONS: Patient survival of advanced PAH remains poor at 5 years despite treatment advances. New York Heart Association FC remains one of the most important predictors of future survival. These observations reinforce the importance of continuous monitoring of FC in patients with PAH.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00370214; URL: www.clinicaltrials.gov

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ABBREVIATIONS: 6MWD = 6-min walk distance; APAH-CHD = pulmonary arterial hypertension associated with congenital heart disease including both repaired and unrepaired; FC = functional class; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; WHO = World Health Organization

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Pulmonary arterial hypertension (PAH) is a rare, severe disease characterized by worsening right-sided heart failure, decreasing functional status, and poor survival.[1] Outcome evaluation by functional class (FC) is a key variable in many predictive models of PAH. Because either improvement or decline of FC over time significantly predicts patient survival,[2] attainment of FC I or II is a critical treatment goal in practice and clinical trials.[2-4]

Although the association between FC and survival is well established, limited survival estimates exist in the literature for FC subgroups. Additionally, most available data have evaluated survival to 3 years and are based on site cohort studies.[2,5,6] Previous studies examining survival data based on FC have a small sample size and do not reflect current treatment strategies.[2,5-8] To date, there has been no multicenter, long-term analysis of survival by FC from a large cohort of patients with PAH.

The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) is an observational US disease registry providing current information about demographics, disease course, and management of patients with World Health Organization (WHO) group 1 PAH. Previous REVEAL Registry subset analyses demonstrate change in patient status, such as improvement from FC III to FC I/II or worsening from FC III to FC IV predicts significantly better or worse survival, respectively, than if the patient remained at FC III.[9] The present REVEAL Registry analysis characterizes 5-year survival of newly and previously diagnosed PAH in patients stratified by baseline FC and provides survival estimates for a range of commonly examined PAH subsets, emphasizing simple, descriptive data rather than advanced modeling. These data not only inform future clinical trial design but also increase awareness of the current burden at different stages of this illness.

Materials and Methods

The REVEAL Registry design has been described previously.[10] Briefly, the multicenter, observational, prospective registry enrolled patients aged ≥ 3 months with WHO group 1 PAH at 55 centers across the United States from March 2006 through December 2009.[10] The study was conducted in accordance with the amended Declaration of Helsinki, and the protocol was reviewed by the institutional review board of each participating center, with written informed consent obtained from all patients (e-Table 1).[10] PAH was confirmed by hemodynamic parameters using the Venice 2003 definition[11] and included mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest or mPAP ≥ 30 mm Hg with exercise contemporaneously with pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure < 18 mm Hg and pulmonary vascular resistance (PVR) ≥ 240 dyn/s/cm^5.

This analysis included patients aged ≥ 18 years, previously or newly diagnosed with WHO group 1 PAH (confirmed by right-sided heart catheterization > 90 days before enrollment or within 90 days, respectively), with mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg measured at rest (Fig 1). Patients with elevated PCWP (> 15 mm Hg) or who met entry criteria only during exercise and patients initially included in the 2003 definition of WHO group 1 PAH[11] who are now part of group 1′[12] were excluded. Patients were classified as having idiopathic PAH (IPAH), familial PAH (FPAH), PAH associated with congenital heart disease (APAH-CHD) (repaired or, if unrepaired, with or without Eisenmenger syndrome), and/or PAH associated with connective tissue disease (without significant interstitial lung disease as defined by moderate or severe fibrosis on chest imaging or total lung capacity of 60% predicted) based on the 2003 PAH classification scheme.[11]

Data were summarized by descriptive statistics. Kaplan-Meier survival estimates ± SE were calculated from the time of enrollment. Estimates were stratified by previously and newly diagnosed PAH in patients and additional variables of interest. Kaplan-Meier curve comparisons were made on the basis of the log-rank test.

Primary survival analysis by FC was conducted for all patients with nonmissing FC data at enrollment (Fig 1). FC changes were assessed in patients with a first follow-up visit within 12 months after enrollment. The overall population was assessed based on time of enrollment. Secondary survival analysis was conducted by subgroup, including previously or newly diagnosed, age, sex, race, PAH etiology, comorbidities (COPD, diabetes, BMI > 30 kg/m^2), PAH clinical characteristics at baseline (6-min walk distance [6MWD], brain natriuretic peptide level, REVEAL Registry risk score,[13,14] hemodynamics [mPAP, mean right atrial pressure (mRAP), PVR, cardiac index], and echocardiographic findings [pericardial effusion and right ventricular dysfunction]). Patients with missing FC data at enrollment were included in secondary survival analyses of other subgroups. The final February 2013 REVEAL Registry data download was analyzed.

Results

Patient Demographics and Clinical Characteristics

The primary analysis cohort included 2,039 previously diagnosed and 710 newly diagnosed patients who were not missing FC data at enrollment (Fig 1). Demographics and clinical characteristics of each cohort according to FC are presented in Tables 1 and 2.[15] Median time from diagnosis to enrollment was 32.2 (interquartile range, 14.7-58.8) months for previously

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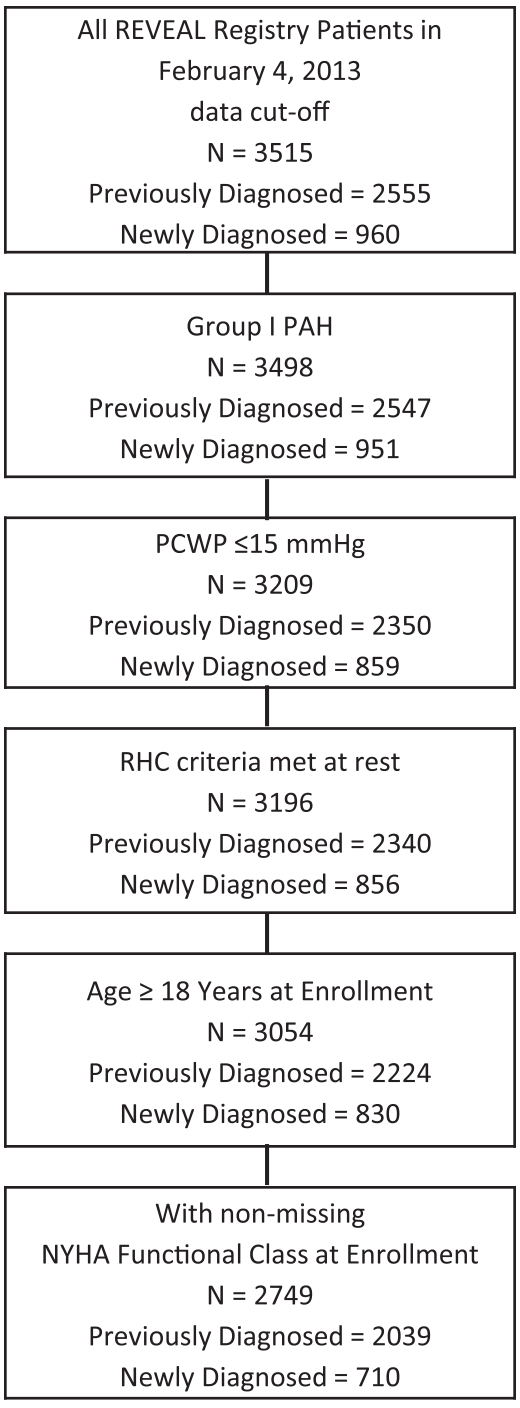


Figure 1 – *STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram of patient inclusion and exclusion criteria. NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right-sided heart catheterization.*

diagnosed and 0.5 (interquartile range, 0.0-1.6) months for newly diagnosed patients, respectively. In total, 1,085 previously diagnosed (53.2%) and 522 newly diagnosed (73.5%) patients were FC III or IV at enrollment. Although previously diagnosed patients in FC IV had a shorter 6MWD and higher mRAP at diagnosis than patients in other FCs, the mean cardiac index and mean PVR at diagnosis were similar across FC categories (Table 1).

Survival

Survival differences between previously diagnosed FC and newly diagnosed FC patients at 1 year (90.4% ± 0.7% vs 86.3% ± 1.3%) were maintained to 5 years; 5-year survival for previously diagnosed patients was 65.4% ± 1.1% compared with 61.2% ± 2.0% for newly diagnosed patients ($P = .003$ for the difference in survival times through 5 years) (Fig 2, e-Table 2).

Generally, compared with previously diagnosed patients, survival rates for newly diagnosed FC III and FC IV patients were numerically greater (Figs 3, 4, e-Table 2). However, FC I and II survival rates were numerically lower in the newly diagnosed cohort. In pooled patients in FC I and II, previously diagnosed PAH was associated with significantly better survival than newly diagnosed PAH (77.7% ± 1.4% vs 72.0% ± 3.5%, $P = .010$). FC was strongly associated with 5-year survival in specific etiologic groups. Previously diagnosed patients with IPAH or FPAH had estimated 5-year survival rates of 85.7% ± 3.8%, 79.7% ± 2.1%, 61.2% ± 2.3%, and 29.7% ± 7.8% for FC I, II, III, and IV, respectively (Table 3). Newly diagnosed patients with IPAH or FPAH had estimated 5-year survival rates of 100% ± 0.0%, 74.9% ± 5.5%, 68.0% ± 3.5%, and 52.9% ± 7.2% for FC I, II, III, and IV, respectively (Table 3). Estimated 5-year survival rates for previously diagnosed patients with APAH-CHD were 96.7% ± 3.0%, 71.1% ± 3.7%, 43.9% ± 3.2%, and 15.8% ± 6.4% for FC I, II, III, and IV, respectively (Table 3). Newly diagnosed patients with APAH-CHD had estimated 5-year survival rates of 57.1% ± 18.7%, 64.6% ± 7.1%, 44.5% ± 5.9%, and 19.8% ± 8.8% for FC I, II, III, and IV, respectively (Table 3).

Changes in FC and Treatment Initiation

In total, 1,866 patients in the previously diagnosed cohort had an FC assessment at enrollment and a follow-up assessment within 12 months. Of the 889 patients classified as FC III at enrollment, 173 (19%) improved to FC II within 12 months of enrollment; an additional 15 (2%) improved to FC I. Among patients in the newly diagnosed cohort with follow-up FC assessments within 12 months of enrollment, 169 (27.5%) improved, 387 (63.0%) had no change, and 58 (9.5%) worsened by FC (Table 4). When stratified by FC at

TABLE 1] Characteristics of Previously Diagnosed Patients[a] by FC at Enrollment (N = 2,039)

Characteristic	All FCs[b]	FC I	FC II	FC III	FC IV
Demographic characteristics at enrollment					
No. patients	2,039	162	792	991	94
Age, y	51.7 ± 14.5	47.0 ± 14.2	49.3 ± 14.4	54.1 ± 14.1	55.9 ± 14.9
Aged > 65 y	422 (20.7)	20 (12.3)	121 (15.3)	246 (24.8)	35 (37.2)
Female sex	1,619 (79.4)	120 (74.1)	610 (77.0)	813 (82.0)	76 (80.9)
Female:male ratio	3.9:1.0	2.9:1.0	3.4:1.0	4.6:1.0	4.2:1.0
Etiology of PAH at enrollment					
IPAH	950 (46.6)	83 (51.2)	367 (46.3)	462 (46.6)	38 (40.4)
FPAH	64 (3.1)	7 (4.3)	27 (3.4)	29 (2.9)	1 (1.1)
APAH-CTD	495 (24.3)	30 (18.5)	168 (21.2)	263 (26.5)	34 (36.2)
APAH-CHD	236 (11.6)	11 (6.8)	97 (12.2)	120 (12.1)	8 (8.5)
APAH-PoPH	110 (5.4)	13 (8.0)	45 (5.7)	48 (4.8)	4 (4.3)
APAH-HIV	39 (1.9)	7 (4.3)	18 (2.3)	10 (1.0)	4 (4.3)
APAH-drugs and toxins	121 (5.9)	9 (5.6)	58 (7.3)	51 (5.1)	3 (3.2)
Disease characteristics					
Most recent to enrollment[c]					
6MWD, m	376 ± 126	489 ± 107	424 ± 101	327 ± 114	214 ± 114
FEV_1, % predicted	76.6 ± 18.1	83.2 ± 17.1	79.0 ± 16.9	74.3 ± 18.5	70.1 ± 19.0
FVC, % predicted	80.8 ± 17.9	78.9 ± 16.7	83.2 ± 16.8	78.5 ± 18.2	73.6 ± 19.7
D_{LCO}, % predicted	61.0 ± 23.0	67.1 ± 19.8	65.8 ± 22.3	57.0 ± 22.7	51.0 ± 26.9
At diagnosis					
mPAP, mm Hg	51.4 ± 13.9	50.0 ± 14.3	52.6 ± 14.6	51.0 ± 13.4	49.1 ± 12.5
mRAP, mm Hg	9.2 ± 5.5	8.1 ± 4.8	8.6 ± 5.1	9.7 ± 5.7	11.6 ± 6.2
CO, L/min	4.3 ± 1.7	4.3 ± 1.5	4.3 ± 1.5	4.3 ± 1.9	4.2 ± 1.7
Cardiac index, L/min/m^2	2.3 ± 0.8	2.3 ± 0.8	2.4 ± 0.9	2.3 ± 0.8	2.3 ± 1.0
PVR, Wood units	11.5 ± 7.7	11.5 ± 10.0	11.8 ± 8.3	11.1 ± 6.8	11.8 ± 7.7
PCWP, mm Hg	9.1 ± 3.5	9.1 ± 3.2	8.9 ± 3.5	9.3 ± 3.5	9.6 ± 3.8

Data are presented as mean ± SD or No. (%). 6MWD = 6-min walk distance; APAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; APAH-CTD = pulmonary arterial hypertension associated with connective tissue disease including both repaired and unrepaired pulmonary arterial hypertension associated with congenital heart disease; APAH-drugs and toxins = pulmonary arterial hypertension associated with drugs and toxins; APAH-HIV = pulmonary arterial hypertension associated with HIV infection; APAH-PoPH = pulmonary arterial hypertension associated with portopulmonary hypertension; CO = cardiac output; D_{LCO} = diffusing capacity of lung for carbon monoxide; FC = functional class; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.

[a]Previously diagnosed subjects are those whose diagnostic right-sided heart catheterization fell > 90 d before enrollment.

[b]FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. FC II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea, fatigue, or both may even be present at rest. Discomfort is increased by any physical activity.

[c]Because no assessments were mandated by protocol, the measurement at enrollment reflects the most recent assessment up to or including enrollment. Percent predicted FEV_1 and FVC values are based on Hankinson et al.[15]

enrollment, 370 newly diagnosed patients were classified as FC III, 100 (27%) improved to FC II within 12 months of enrollment, and 12 (3%) improved to FC I. Among the 445 newly diagnosed patients in FC III or IV at baseline, 158 (35.5%) improved FC within 12 months of enrollment.

Patient status at enrollment affected treatment history and interventions. As expected, patients with more

TABLE 2] Characteristics of Newly Diagnosed Patients[a] by FC at Enrollment (N = 710)

Characteristic	All FCs[b]	FC I	FC II	FC III	FC IV
Demographic characteristics at enrollment					
No. patients	710	27	161	426	96
Age, y	53.1 ± 15.4	51.5 ± 16.5	51.2 ± 15.5	53.4 ± 15.2	55.6 ± 15.6
Aged > 65 y	170 (23.9)	6 (22.2)	34 (21.1)	100 (23.5)	30 (31.3)
Female sex	552 (77.7)	19 (70.4)	127 (78.9)	331 (77.7)	75 (78.1)
Female:male ratio	3.5:1.0	2.4:1.0	3.7:1.0	3.5:1.0	3.6:1.0
Etiology of PAH at enrollment					
IPAH	340 (47.9)	9 (33.3)	65 (40.4)	207 (48.6)	59 (61.5)
FPAH	14 (2.0)	0 (0.0)	3 (1.9)	8 (1.9)	3 (3.1)
APAH-CTD	218 (30.7)	9 (33.3)	58 (36.0)	129 (30.3)	22 (22.9)
APAH-CHD	39 (5.5)	3 (11.1)	12 (7.5)	20 (4.7)	4 (4.2)
APAH-PoPH	44 (6.2)	3 (11.1)	9 (5.6)	27 (6.3)	5 (5.2)
APAH-HIV	12 (1.7)	1 (3.7)	2 (1.2)	8 (1.9)	1 (1.0)
APAH-drugs and toxins	37 (5.2)	2 (7.4)	9 (5.6)	24 (5.6)	2 (2.1)
Disease characteristics					
Most recent to enrollment[c]					
6MWD, m	310 ± 126	367 ± 134	394 ± 105	291 ± 113	221 ± 130
FEV_1, % predicted	73.7 ± 19.5	81.1 ± 12.1	79.3 ± 19.2	71.8 ± 20.1	71.7 ± 16.8
FVC, % predicted	78.0 ± 20.3	86.9 ± 12.3	84.4 ± 18.9	75.0 ± 20.5	79.2 ± 19.9
D_{LCO}, % predicted	50.9 ± 21.5	51.8 ± 23.1	56.3 ± 24.0	49.5 ± 20.3	48.5 ± 21.7
At diagnosis					
mPAP, mm Hg	50.1 ± 12.9	44.3 ± 10.8	46.8 ± 12.0	50.6 ± 13.1	55.4 ± 11.6
mRAP, mm Hg	10.0 ± 6.0	6.3 ± 4.6	9.1 ± 5.8	9.9 ± 5.7	12.8 ± 7.3
CO, L/min	4.2 ± 1.4	4.6 ± 1.5	4.4 ± 1.5	4.2 ± 1.4	3.6 ± 1.1
Cardiac index, L/min/m^2	2.2 ± 0.7	2.5 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	1.9 ± 0.6
PVR, Wood units	11.2 ± 6.0	9.1 ± 6.0	9.9 ± 5.3	11.3 ± 6.1	14.1 ± 5.6
PCWP, mm Hg	9.3 ± 3.6	8.2 ± 4.0	9.0 ± 3.7	9.4 ± 3.5	10.2 ± 3.5

Data are presented as mean ± SD or No. (%). See Table 1 legend for expansion of abbreviations.

[a]Newly diagnosed subjects are those whose diagnostic right-sided heart catheterization fell within 90 d before enrollment.

[b]FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. FC II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea, fatigue, or both may even be present at rest. Discomfort is increased by any physical activity.

[c]Because no assessments were mandated by protocol, the measurement at enrollment reflects the most recent assessment up to or including enrollment. Percent predicted FEV_1 and FVC values are based on Hankinson et al.[15]

recent PAH diagnoses were more likely to initiate therapy than previously diagnosed patients. Only 82 (4.0%) and 31 (1.5%) previously diagnosed patients received a first PAH-specific therapy (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin, or prostacyclin analogs) within 90 days before enrollment and 90 days after enrollment, respectively (Table 4). In contrast, 251 (35.4%) newly diagnosed patients received a first PAH-specific therapy within 90 days before enrollment and 210 (29.6%) 90 days after enrollment (Table 4).

Survival Subgroup Analyses

Patient status and risk is commonly categorized by FC. However, because risk in PAH is multifactorial,[16] other potential variables were considered. These secondary analyses included patients with missing FC categorization. The analysis set included 2,224 previously diagnosed

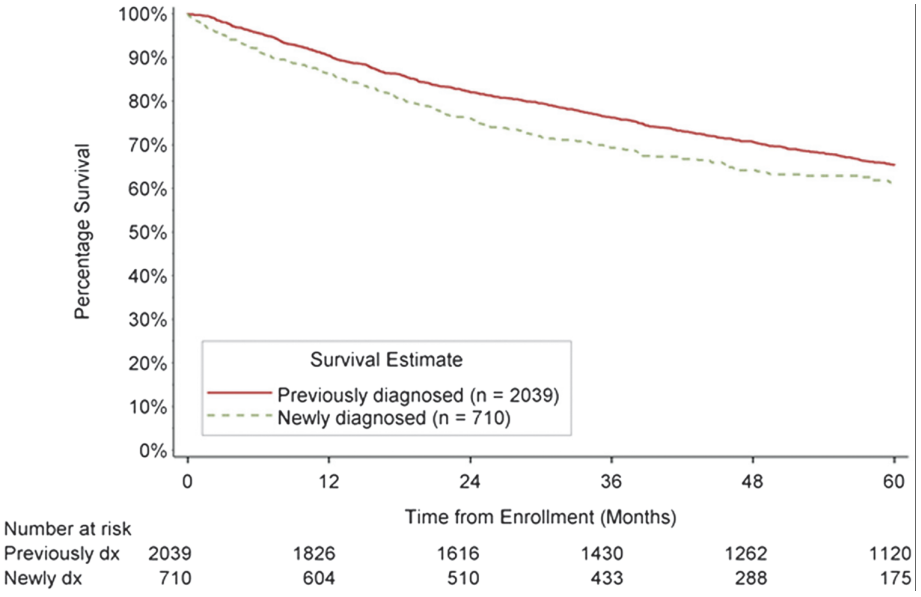


Figure 2 – *Kaplan-Meier estimates of 5-y survival for previously diagnosed and newly diagnosed patients. dx = diagnosis.*

patients and 830 newly diagnosed patients (Table 3). As expected, known risk factors, including baseline 6MWD, mRAP, and brain natriuretic peptide, were associated with survival (Table 3). Compared with other races or ethnicities, white patients, previously or newly diagnosed, have relatively poor 5-year survival rates (63.5% ± 1.2% and 57.4% ± 2.3%, respectively). PVR ≤ 5 Wood units was associated with greater survival. Among previously diagnosed patients, 405 had a PVR ≤ 5 Wood units and a 5-year survival of 73.9% ± 2.3%; 797 had a PVR of 5 to 10 Wood units and a 5-year survival of 66.0% ± 1.8%. Among newly diagnosed patients, 108 had a PVR ≤ 5 Wood units and a 5-year survival of 70.1% ± 4.9%; 292 had a PVR of 5 to 10 Wood units and a 5-year survival of 57.3% ± 3.2%. Finally, in a potential instance of the obesity paradox,[17] higher

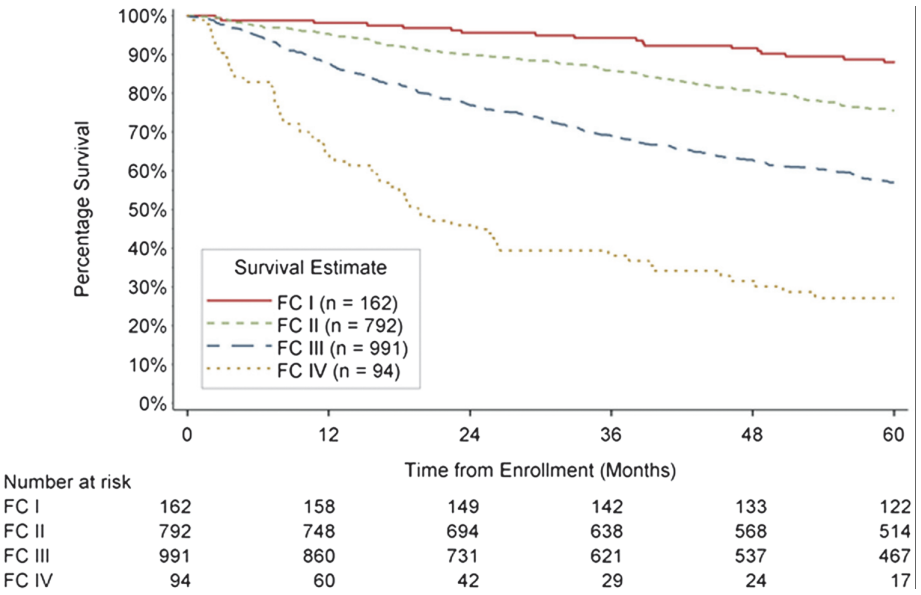
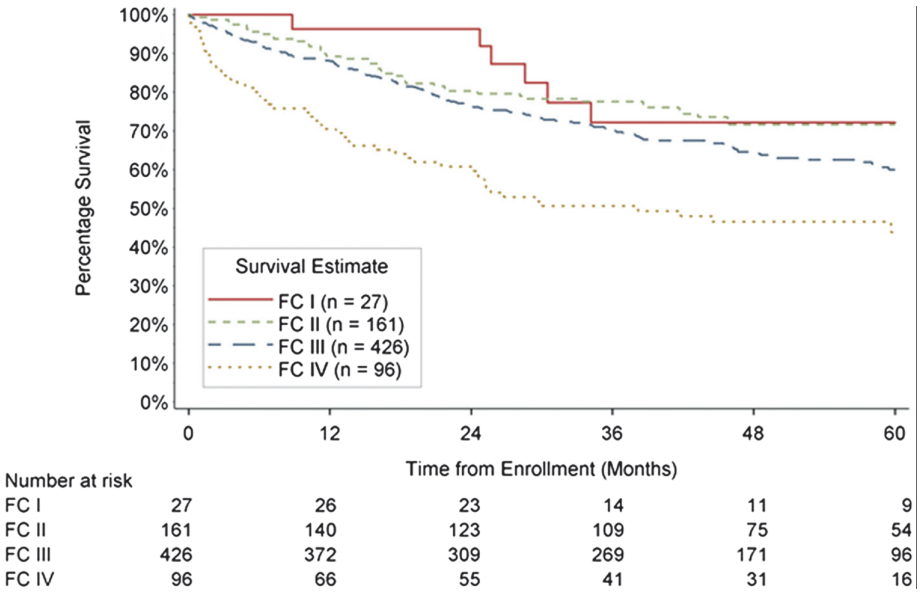


Figure 3 – *Kaplan-Meier estimates of 5-y survival for the subgroup of previously diagnosed patients, by FC at enrollment. FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. FC II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea, fatigue, or both may even be present at rest. Discomfort is increased by any physical activity. FC = functional class.*



Number at risk						
FC I	27	26	23	14	11	9
FC II	161	140	123	109	75	54
FC III	426	372	309	269	171	96
FC IV	96	66	55	41	31	16

Figure 4 – *Kaplan-Meier estimates of 5-y survival for the subgroup of newly diagnosed patients, by FC at enrollment. FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. FC II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. FC IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea, fatigue, or both may even be present at rest. Discomfort is increased by any physical activity. See Figure 3 legend for expansion of abbreviation.*

BMI was associated with improved survival; 1,453 previously diagnosed patients with BMI $\leq$ 30 kg/m^2 and 477 newly diagnosed patients had estimated survival rates of 64.6% $\pm$ 1.3% and 58.3% $\pm$ 2.5%, respectively; 658 previously diagnosed patients with BMI $>$ 30 kg/m^2 and 289 newly diagnosed patients had estimated survival rates of 69.6% $\pm$ 1.9% and 69.6% $\pm$ 2.9%, respectively (Table 3).

Discussion

This REVEAL Registry analysis demonstrates that 5-year survival remains poor despite progress in PAH-specific therapy options and improved patient support strategies. Survival rates in previously diagnosed patients with PAH at 1, 3, and 5 years were 90.4%, 76.2%, and 65.4%, respectively; in newly diagnosed patients, survival rates were 86.3%, 69.3%, and 61.2%, respectively (e-Table 2). Prior to the development of PAH-specific therapies, median survival after diagnosis of IPAH (formerly primary pulmonary hypertension) was 2.8 years, with survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively.[7] Furthermore, the present analysis shows that the prognosis for patients with advanced disease remains poor.

The poorest outcome was observed among patients in FC III or IV in both previously and newly diagnosed cohorts, with 5-year survival rates of 57.0% and 27.2%, and 60.0% and 43.8%, respectively. In addition to baseline FC status, FC change with treatment impacts patient outcome. A large number of newly diagnosed FC III and IV patients improved one FC within 12 months of enrollment. A previous REVEAL Registry analysis demonstrated that improvement from FC III to FC I/II is associated with significantly better survival than had the patient remained in FC III or worsened to FC IV.[9] Previously diagnosed patients classified as FC IV at enrollment have prior PAH-specific therapy exposure and fewer therapeutic options and may, thus, represent a cohort of patients nonresponsive or less responsive to therapy. In contrast, newly diagnosed patients classified as FC IV at enrollment represent a treatment-naive population with a greater opportunity to improve with PAH-specific therapy.[18] This analysis demonstrates single point-in-time measurement of FC remains among the most important predictors of future survival in patients with PAH, despite its limitations. The current study includes a large cohort size, allowing various subgroup analyses and more detailed data on FC and FC changes during the enrollment period.

In addition to FC and disease duration before enrollment, survival in patients with PAH was influenced by other clinical factors. Compared with the previously

TABLE 3] K-M Estimates of 5-Year Survival by Previously vs Newly Diagnosed Patients[a]

Characteristic	Previously Diagnosed		Newly Diagnosed	
	No.	5-y K-M ± SE, %	No.	5-y K-M ± SE, %
Age at enrollment, y				
18-34	305	78.8 ± 2.5	110	78.5 ± 4.0
35-54	951	71.5 ± 1.5	312	70.7 ± 2.8
55-64	503	60.7 ± 2.3	199	52.4 ± 4.0
≥ 65	465	49.2 ± 2.4	209	42.8 ± 4.2
Sex				
Male	456	57.4 ± 2.4	188	53.0 ± 4.0
Female	1,768	67.5 ± 1.2	642	62.9 ± 2.1
Race/ethnicity				
White	1,618	63.5 ± 1.2	588	57.4 ± 2.3
Black	274	67.7 ± 3.0	120	66.0 ± 4.6
Hispanic	201	73.2 ± 3.3	65	67.6 ± 6.0
Other	131	71.4 ± 4.2	57	74.7 ± 5.9
Etiology of PAH at enrollment[b]				
IPAH	1,027	69.4 ± 1.5	399	68.0 ± 2.5
FPAH	64	65.8 ± 6.1	19	73.7 ± 10.1
APAH-CTD	556	55.8 ± 2.2	254	47.6 ± 3.8
SSc	339	46.2 ± 2.8	165	39.6 ± 4.7
Non-SSc	217	71.3 ± 3.2	89	63.3 ± 5.8
APAH-CHD	262	70.0 ± 2.9	40	73.9 ± 7.1
APAH-PoPH	122	49.6 ± 4.7	55	34.3 ± 6.8
APAH-HIV	40	73.8 ± 7.1	14	73.0 ± 14.0
APAH-drugs and toxins	124	76.9 ± 3.9	40	74.9 ± 7.6
Etiology of PAH by FC, both at enrollment				
IPAH/FPAH				
FC I	90	85.7 ± 3.8	9	100 ± 0.0
FC II	394	79.7 ± 2.1	68	74.9 ± 5.5
FC III	491	61.2 ± 2.3	215	68.0 ± 3.5
FC IV	39	29.7 ± 7.8	62	52.9 ± 7.2
APAH-CHD				
FC I	11	96.7 ± 3.0	3	57.1 ± 18.7
FC II	97	71.1 ± 3.7	12	64.6 ± 7.1
FC III	120	43.9 ± 3.2	20	44.5 ± 5.9
FC IV	8	15.8 ± 6.4	4	19.8 ± 8.8
Comorbidities at enrollment				
Diabetes				
Yes	249	53.5 ± 3.3	112	46.0 ± 5.0
No	1,932	67.0 ± 1.1	690	63.5 ± 2.0
COPD				
Yes	190	49.9 ± 3.8	114	46.8 ± 5.0
No	1,991	66.9 ± 1.1	688	63.4 ± 2.0
BMI > 30 kg/m^2				

(Continued)

TABLE 3] *(continued)*

Characteristic	Previously Diagnosed		Newly Diagnosed	
	No.	5-y K-M ± SE, %	No.	5-y K-M ± SE, %
Yes	658	69.6 ± 1.9	289	69.6 ± 2.9
No	1,453	64.6 ± 1.3	477	58.3 ± 2.5
Disease characteristics at enrollment[b]				
6MWD, m				
< 165	121	28.7 ± 4.4	83	35.7 ± 5.9
165 to < 440	1,184	63.8 ± 1.5	361	65.4 ± 2.8
≥ 440	547	81.9 ± 1.7	81	83.8 ± 4.8
BNP, pg/mL				
> 180	414	41.3 ± 2.5	193	46.8 ± 4.0
50-180	342	67.1 ± 2.7	94	74.1 ± 4.7
< 50	334	85.5 ± 2.0	53	92.3 ± 3.7
REVEAL Registry risk score at enrollment				
1-7	1,211	80.9 ± 1.2	284	80.9 ± 2.6
8	363	62.9 ± 2.7	153	69.2 ± 4.0
9	273	51.1 ± 3.3	150	58.9 ± 4.4
10-11	302	29.6 ± 2.8	176	34.3 ± 4.5
≥ 12	75	12.3 ± 4.0	67	29.8 ± 5.8
Hemodynamics at enrollment[b]				
mPAP, mm Hg (at rest)				
< 50	1,146	66.8 ± 1.5	427	60.5 ± 2.7
≥ 50	1,010	63.9 ± 1.6	363	60.9 ± 2.7
Cardiac index, L/min/m^2				
≥ 2	1,289	69.1 ± 1.3	386	62.1 ± 2.8
< 2	478	59.6 ± 2.3	265	58.6 ± 3.3
mRAP, mm Hg				
< 10	1,278	70.6 ± 1.3	394	64.1 ± 2.7
10-14	458	62.8 ± 2.3	192	55.2 ± 3.9
≥ 15	280	47.4 ± 3.1	134	54.3 ± 4.6
PVR, Wood units				
≤ 5	405	73.9 ± 2.3	108	70.1 ± 4.9
5-10	797	66.0 ± 1.8	292	57.3 ± 3.2
< 10	1,202	68.7 ± 1.4	400	60.7 ± 2.7
10-16	586	60.3 ± 2.1	262	63.2 ± 3.2
≥ 17	225	59.8 ± 3.4	119	56.9 ± 4.9
Echocardiographic findings at enrollment[b]				
Pericardial effusion[c]				
Yes	437	50.8 ± 2.5	179	58.4 ± 4.0
No	1,312	69.9 ± 1.3	389	59.9 ± 2.7
Right ventricular dysfunction[d]				
Yes	814	57.2 ± 1.8	363	59.2 ± 2.9
No	927	72.9 ± 1.5	214	60.4 ± 3.6

(Continued)

TABLE 3] *(continued)*

Characteristic	Previously Diagnosed		Newly Diagnosed	
	No.	5-y K-M ± SE, %	No.	5-y K-M ± SE, %
Lung function at enrollment				
FEV_1,[e] % predicted				
< 80%	813	60.0 ± 1.8	289	51.5 ± 3.4
≥ 80%	615	71.2 ± 1.9	171	66.8 ± 4.0
FVC,[e] % predicted				
< 80%	684	57.9 ± 1.9	250	52.4 ± 3.5
≥ 80%	749	71.0 ± 1.7	215	63.4 ± 3.7
DLCO, % predicted				
< 80%	1,065	63.2 ± 1.5	389	53.8 ± 2.8
≥ 80%	269	74.8 ± 2.8	55	84.6 ± 5.5

BNP = brain natriuretic peptide; K-M = Kaplan-Meier; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; SSc = systemic sclerosis. See Table 1 legend for expansion of other abbreviations.

[a]Newly diagnosed subjects are those whose diagnostic right-sided heart catheterization fell within 90 d before enrollment. Previously diagnosed subjects are those whose diagnostic right-sided heart catheterization fell > 90 d before enrollment.

[b]Because no assessments were mandated by protocol, the measurement at enrollment reflects the most recent assessment up to or including enrollment.

[c]Mild, moderate, moderate-severe, and severe are categorized as yes; none is categorized as no.

[d]Moderate, moderate-severe, and severe are categorized as yes; mild and none are categorized as no.

[e]Percent predicted values are based on Hankinson et al.[15]

diagnosed patients, Kaplan-Meier survival estimates of newly diagnosed patients demonstrated early decreases in survival. The present newly diagnosed patient cohort includes substantially more patients in FC III and IV (74% vs 53%). The highest mortality risk in patients with PAH may present at the time of diagnosis and before treatment initiation.[5,8] The data support a difference in risk profiles for previously vs newly diagnosed patients and a high, immediate risk in newly diagnosed patients.

Of note, survival analysis in PAH cohorts are prone to survivor bias[19] when patients with different disease durations are pooled. Under these conditions, survival estimates for the overall cohort are more favorable than if the survival estimate is derived using newly diagnosed patients only, since prevalent patients have a better prognosis than incident or newly diagnosed patients.[5,13] Previously and newly diagnosed patients have different risk profiles because many higher-risk patients do not survive for a sufficient duration to be enrolled as previously diagnosed patients. Thus, the previously diagnosed cohort will always contain a smaller percentage of patients in FC IV compared with the newly diagnosed cohort. The persistence of survivor bias after adjustment for risk profile differences has not been established.

Here, the survival disadvantage of newly diagnosed patients is most pronounced among patients in FC I and II, suggesting a relatively favorable risk profile at diagnosis reflects an earlier diagnosis but does not necessarily guarantee a good outcome. Conversely, any survival advantage associated with a previous diagnosis is absent for patients in FC III and IV. Previously diagnosed patients who remain short of treatment goals (eg, FC III) likely have less potential for future improvement, but a negative outcome is not inevitable. Improvement in a high percentage of patients in newly diagnosed FC III is likely related to administration of initial PAH-specific therapy within 90 days before or 90 days after enrollment, thus providing an opportunity to respond to treatment. In contrast, few previously diagnosed patients initiated first PAH-specific therapy at enrollment, and a smaller percentage in the previously diagnosed FC III group at enrollment improved to FC II, suggesting an already maximized response. Although treatment decisions were left to the contributing providers and were not mandated by REVEAL Registry, it is clear that patients experience greatest risk in the initial months after diagnosis.[20-23] Thus, treatment should be initiated as early as possible as newly diagnosed patients are at greatest risk and have the greatest opportunity to show functional improvements. FC assessment is remarkably predictive of survival in PAH; its use as a tool in clinical practice and trials should continue.

This analysis was hypothesis generating and, therefore, explored many variables. Trends of interest must be

TABLE 4] Timing of Diagnosis, First Medication Use, and Change in FC by Previously vs Newly Diagnosed Patients[a]

Variable	Previously Diagnosed (n = 2,039)	Newly Diagnosed (n = 710)
Time from diagnosis to enrollment, mo		
Median (interquartile range)	32.2 (14.7-58.8)	0.5 (0.0-1.6)
Mean ± SD	44.4 ± 44.5	0.8 ± 1.3
Timing of first PAH-specific medication[b]		
>90 d before enrollment	1,834 (89.9)	102 (14.4)
1-90 d before enrollment	82 (4.0)	251 (35.4)
Day of enrollment	11 (0.5)	62 (8.7)
1-90 d after enrollment	31 (1.5)	210 (29.6)
>90 d after enrollment	34 (1.7)	48 (6.8)
Never initiated[c]	47 (2.3)	37 (5.2)
FC change between diagnosis and enrollment,[d] all patients		
Improved between diagnosis and enrollment	534 (35.0)	73 (11.1)
No change between diagnosis and enrollment	845 (55.4)	557 (84.7)
Worsened between diagnosis and enrollment	146 (9.6)	28 (4.3)
FC change between enrollment[d] and 12-mo update, all patients		
Improved by 12-mo update	267 (14.3)	169 (27.5)
No change by 12-mo update	1,378 (73.9)	387 (63.0)
Worsened by 12-mo update	221 (11.8)	58 (9.5)
FC I or II at enrollment		
Improved by 12-mo update	43 (4.7)	11 (6.5)
No change by 12-mo update	690 (76.0)	113 (66.9)
Worsened by 12-mo update	175 (19.3)	45 (26.6)
FC III or IV at enrollment		
Improved by 12-mo update	224 (23.4)	158 (35.5)
No change by 12-mo update	688 (71.8)	274 (61.6)
Worsened by 12-mo update	46 (4.8)	13 (2.9)

Data are presented as No. (%) unless otherwise indicated. See Table 1 legend for expansion of abbreviations.
[a]Newly diagnosed subjects are those whose diagnostic right-sided heart catheterization fell within 90 d before enrollment. Previously diagnosed subjects are those whose diagnostic right-sided heart catheterization fell >90 d before enrollment.
[b]First initiation of an endothelin receptor antagonist, phosphodiesterase-5 inhibitor, prostacyclin, or prostacyclin analog.
[c]Thirty-nine of 84 patients initiated calcium channel blockers for PAH.
[d]Because no assessments were mandated by protocol, the measurement at enrollment reflects the most recent assessment up to or including enrollment.

externally validated. Comparisons were not risk adjusted and stratified only by diagnosis (previously vs newly); many differences may be explained by confounding factors. Although developments in treatment may explain differences in the disease trajectory for previously and newly diagnosed patients, other factors also affect disease management. Upon new diagnosis, changes in patient care, access to health care, and lifestyle changes all affect treatment efficacy. However, registries are not ideally designed to specifically address many of these issues. Moreover, because REVEAL Registry is a US-based cohort, generalization of these observations to other countries is unknown.

Conclusions

Although overall survival for patients with WHO group 1 PAH has greatly improved in the current treatment era, this analysis of the REVEAL Registry shows that patient prognosis remains poor. Relative to corresponding previously diagnosed patients, newly diagnosed patients have a survival disadvantage. FC, whether with newly or previously diagnosed disease, is predictive of survival. These data reinforce the importance of continuous monitoring of FC in patients with PAH.

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