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Developing Benchmarks in the Diagnosis and Treatment of Pulmonary Arterial Hypertension in a Tertiary, Academic Medical Center

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ABSTRACT

Benchmarks of clinical management are essential for improving the quality of care. However, the lack of established quality metrics for pulmonary arterial hypertension (PAH) contributes to practice heterogeneity. We assessed our center's diagnostic practices, therapeutic practices, and risk-adjusted survival patterns over time for the purpose of establishing quality benchmarks. We analyzed the demographics, clinical characteristics, and diagnostic evaluation of 702 PAH patients enrolled between 1999 and 2019. We examined outcomes in this cohort, including an analysis of risk stratification, therapeutic practice patterns, hospitalizations, organ transplant, and survival. Initial diagnostic workup of incident PAH cases demonstrated excellent completion of echocardiographic (99%) and pulmonary function testing (91%), with improved completion of VQ scanning over the study time period (90% between 2015 and 2019). Right heart catheterization (RHC) was performed in all patients; RHC performed at our center was more likely to include complete hemodynamic data than those performed at referring institutions (55.4% and 30.4% respectively). The average number of PAH-specific medications prescribed increased over time; however, there was no significant increase in the use of parenteral therapy over time, even when stratified by the REVEAL risk score. Survival rates in the cohort were 94% at 1 year, 75% at 5 years, and 60% at 10 years, comparable to those of other PAH cohorts. Analysis of our well-characterized cohort of PAH patients reveals the extent to which guideline-directed diagnostic and therapeutic care is delivered at our specialty center, and the associated outcomes; these data may serve as a benchmark for continued improvements in quality of PAH care.

Abbreviations: 6MWD, 6-min walk test distance; ACC, American College of Cardiology; AHA, American Heart Association; CCB, calcium channel blockers; CI, cardiac index; CMS, Centers for Medicare and Medicaid Services; CHD, congenital heart disease; CO, cardiac output; CT, computed tomography; CTD, connective tissue disease; DT-PAH, drug-and-toxin associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; ESC, European Society of Cardiology; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA FC, New York Heart Association Functional class; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE-5i, phosphodiesterase-5 inhibitor; PFT, pulmonary function test; PH, pulmonary hypertension; PSG, polysomnography; PVR, pulmonary vascular resistance; RHC, right heart catheterization; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SD, standard deviation; SAPHP, Stanford Adult Pulmonary Hypertension Program; VMWCDB, Vera Moulton Wall Center Database; VQ, ventilation/perfusion.

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1 | Introduction

Quality improvement is an ethically-mandated and multidimensional element of good clinical practice [1]. Publication of outcome measures as a component of the quality improvement process improves transparency and patient-centered approaches to clinical care. Furthermore, it is this process of quantifying quality that allows for the identification of practice patterns that can facilitate the improvement in quality of care at one and across multiple centers. To advance quality improvement at a national level, the Centers for Medicare and Medicaid Services (CMS) have partnered with multiple entities to form the Core Quality Measures Collaborative, whose primary aim is to identify a set of outcome measures to which providers and payers can communally adhere. The focus of these measures is on improving care quality in common and economically burdensome diseases with well-established, evidence-based interventions.

Conceivably, the same approach could improve care in rarer conditions, especially if implemented by expert specialized centers. Pulmonary arterial hypertension (PAH) is a chronic, progressive and fatal disease affecting the pulmonary vasculature resulting in a progressive rise in pulmonary vascular resistance (PVR) with consequent right ventricular failure [2]. Although PAH is a rare disease [2, 3], it imposes a significant economic burden on payers and patients [4]. Given the need for specialized management, it is recommended that PAH patients receive care at expert pulmonary hypertension centers [5].

Significant discrepancies remain between evidence-based recommendations and local practice patterns in the diagnostic evaluation and treatment of PAH, constituting a "care gap" in the management of these patients [6]. Efforts to improve adherence to evidence-based practice guidelines include the establishment of the PAH Quality Enhancement Research Initiative (PAH-Queri) [7] and an initiative by the Pulmonary Hypertension Association, a non-profit patient advocacy group, to accredit centers with expertise in the management of PAH. The American College of Cardiology (ACC) and the American Heart Association (AHA) have proposed a methodology for selecting performance measures to quantify the quality of care in cardiovascular diseases [1]. More recently, the European Society of Cardiology (ESC) has published quality indicators for care and outcomes in PAH [8]. Despite these initiatives and frameworks, a need remains for the clarification of quality benchmarks that are applicable across centers. Developing such metrics is dependent on understanding the current practice patterns and outcomes in usual care. There is limited data on current practice patterns, but studies have demonstrated suboptimal adherence to guidelines even among providers at specialty centers [9, 10]. To this end, we performed a single-center, descriptive analysis of a cohort of patients from a prospective, observational registry at the Stanford Adult Pulmonary Hypertension Program (SAPHP) that reflects our management practices. Our objectives were to (i) describe the demographics and risk factors of the cohort over time, (ii) characterize the diagnostic and therapeutic care provided at our center (iii) report longitudinal outcomes including hospitalization, transplantation, and overall survival rates, and (iv) assess changes in our practice patterns over time.

2 | Methods

2.1 | Study Population and Variables

The Vera Moulton Wall Center Database (VMWCDB) at Stanford University is an ongoing relational, observational registry of PH patients started in 1999. The VMWCDB captures demographic and clinical data of both incident and prevalent PAH patients diagnosed by right heart catheterization (RHC). Patients were diagnosed with PAH based on a mean pulmonary artery pressure (mPAP) of ≥ 25 mmHg on incident catheterization and expert clinical adjudication.

We performed a systematic database search for all World Health Organization (WHO) Group 1 PAH patients enrolled before December 2019. Patients with primarily WHO Groups 2, 3, 4 and 5 PH were excluded. To reflect changes in care patterns over time, patients were divided into four cohorts (pre-2005, 2005–2009, 2010–2014, 2015–2019) based on the date of inclusion into the VMWCDB. Patients were followed from the time of their initial enrollment until death or last clinic visit preceding database lock (December 2019).

Demographic and clinical variables collected in this study included age, gender, race, ethnicity, etiology of PAH, New York Heart Association functional class (NYHA FC), body mass index (BMI), 6 min walk distance (6MWD), and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. PAH-relevant medications at the time of enrollment and in subsequent visits were recorded, including pulmonary vasodilators, diuretics, and anticoagulants.

To assess each patient's risk profile, the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk score was calculated on initial enrollment and recalculated at each subsequent patient visit allowing for longitudinal restratification [11]. The REVEAL risk score is a simplified calculator derived and validated from data collected in a registry of WHO Group 1 PAH patients and estimates 1-year mortality. For each REVEAL risk score variable, the most recent value was used, a practice supported by previous studies on risk restratification in PAH [12]. Event rates were standardized to the year 2008 to allow comparisons which account for the changing patient demographics at the center.

Hemodynamic measurements from the initial RHC were collected. If the reported data were incomplete, we performed standard calculations to obtain absent values when possible. Specifically, mPAP was calculated as (systolic pulmonary artery pressure (sPAP) + 2*diastolic pulmonary artery pressure (dPAP))/3, or if only the sPAP was available, the mPAP was calculated as 0.6*sPAP. PVR was calculated as (mPAP − pulmonary artery wedge pressure (PAWP))/cardiac output (CO). Our database does not capture the frequency with which raw hemodynamic data was reviewed as opposed to reported values when performed at outside institutions.

Additionally, we collected data on the initial diagnostic testing that each patient underwent in the evaluation and classification of their PH, based on current guidelines; these data included results from chest computed tomography (CT), echocardiography,

pulmonary function testing (PFT), ventilation/perfusion (VQ) scanning, and polysomnography (PSG) [13].

2.2 | Outcomes

Measured outcomes included all-cause mortality (verified by the Social Security Death Index), double-lung or heart-lung transplantation, and hospitalizations. Event-free survival was defined by the combined absence of either death or transplantation. We captured and reported all-cause hospitalizations starting in 2007. All hospitalizations at Stanford Hospital were captured starting at this time and those at outside institutions were entered into the database when those records were available. Annual rates of these outcomes were calculated and reported as the number of events per 100 patient-years.

2.3 | Statistical Methods

For demographics, risk factors, diagnostic testing and therapeutic interventions, continuous variables were expressed as median (interquartile range [IQR]) or mean ± standard deviation (SD), and categorical variables were expressed as counts (percentages). Two sample *t*-tests were used to compare continuous variables, and chi-square or Fisher exact tests were used to compare categorical variables, as appropriate.

For evaluation of outcomes, standardized hospitalization and organ transplant event rates were calculated using the "epitools" R package, version 0.5-10 [14]. Kaplan–Meier estimates of survival and organ survival and log-rank *p*-values were calculated. Greenwood's formula was used to calculate the standard error to construct the 95% confidence intervals. When estimating survival, we right-censored any patient who did not die. When estimating organ survival, we right-censored any patient who did not die or undergo lung transplantation. The last visit before the database lock was used as the censoring time. We calculated standardized event rates to account for the changing patient makeup over time, using direct standardization with 2008 as the reference population. Exact 95% confidence intervals were calculated for the standardized event rates.[13]

All tests were two-sided and conducted at the 0.05 level of significance. As the goal of our study is to characterize a patient population rather than to formally test any hypotheses, we do not adjust our *p*-values for multiple comparisons. All analyses were performed in R version 3.5.1 [15]. Figures were created using the "ggplot2" package, version 3.1.0 [16].

3 | Results

3.1 | Baseline Cohort

Between January 1999 and December 2019, 702 patients with PAH were enrolled in the VMWCDB (Table 1). Overall, 535 of 702 (76%) were female and the overall mean age of the cohort was 49+/−16 years; mean age at enrollment increased across cohorts, from 42.2+/−15.2 in the pre-2005 cohort to 54.5+/−14.8 in the 2015–2019 cohort ($p < 0.01$). The majority of the patients in the cohort were Caucasian (54%, $n = 376$). Most of the patients enrolled had either connective tissue disease (CTD)-associated (29%, $n = 202$), drug and toxin-associated (28%, $n = 193$), or idiopathic (25%, $n = 175$) PAH (IPAH). While the fraction of patients presenting with drug and toxin-associated PAH (DT-PAH) increased by the most recent cohort (from 27% to 35%), that of congenital heart disease (CHD)-associated PAH decreased (from 18% to 8%). The majority of patients presented as NYHA FC III (53%, $n = 258$); there was no statistically significant change in the fraction of presenting cases of any one of the four NYHA-FCs over time. There was, however, a decrease in the baseline 6MWD (381.4 ± 134 to 328.0 ± 136 meters) and an increase in NT-proBNP (median value of 288 to 807 pg/dL) levels noted in the most recent cohort as compared to the pre-2005 cohort.

Upon enrollment, 438 of 702 (62%) of patients were treatment naïve, 188 of 702 (27%) of patients presented on pulmonary vasodilator monotherapy, 60 of 702 (9%) of patients presented on dual therapy, and 15 of 702 (2%) of patients presented on triple therapy; these fractions did not change significantly between cohorts (Table 2).

3.2 | Diagnostic Evaluation

The diagnostic testing performed in each cohort is outlined in Table 3. Of the 702 patients, 696 (99%) patients had echocardiography, 641 (91%) patients underwent PFT, 617 (88%) patients had a CT scan of the chest, and 655 (93%) patients had a 6-min walk test (6MWT). Overall, 574 (82%) patients underwent ventilation-perfusion scanning, which increased over the four time periods from 73% in the pre-2005 cohort to 90% in the 2015–2019 cohort. 135 (19%) patients underwent PSG. Excluding PSG, 67% of patients had complete diagnostic testing with an increase in the 2015–2019 cohort (72%) compared to pre-2005 cohort (58%). If PSG is considered a component of comprehensive evaluation 14% of patients underwent complete diagnostic testing.

All patients had undergone RHC either at their referring institution or at Stanford upon enrollment, as required for VMWCDB inclusion (Table 3). All initial outside and Stanford RHCs were analyzed for completeness of hemodynamic reporting. On the initial RHC of the 702 patients, 700 (99.7%) had mPAP values, 672 (95.7%) had mean right atrial pressure (mRAP) values, 573 (81.6%) patients had reported CO or cardiac index (CI) values, 664 (94.6%) patients had reported pulmonary artery wedge pressure values and 564 (80.3%) patients had reported PVR values. Catheterizations performed at Stanford had a higher percentage of patients with hemodynamic variables available: mRAP (98.7% vs. 84.2%), pulmonary PAWP (98.6% vs. 88.9%), CO/CI (98.9% vs. 79.9%) and PVR (98.0% *vs.* 74.2%); this remained the case when considering vasoreactivity testing (74.8% vs. 37.6%) (Figure 1). Some patients underwent a repeat RHC at Stanford for baseline measurements.

Overall 409 of the total 702-subject (58.2%) cohort underwent vasoreactivity testing. Of the 366 subjects with idiopathic, heritable or DT-PAH 150 underwent an index catheterization at an

TABLE 1 | Baseline patient demographics and clinical characteristics.

Patient characteristics	Total cohort (n = 702)	Pre-2005 ($n = 175$)	2005-2009 ($n = 160$)	2010-2014 ($n = 223$)	2015-2019 ($n = 144$)	p-value
Demographics						
Age – years ± SD	48.99 ± 16.1	42.25 ± 15.1	44.35 ± 14.8	54.09 ± 15.5	54.46 ± 14.8	< 0.01[a]
Gender – n (% female)	535 (76)	141 (80)	117 (73)	170 (76)	107 (74)	< 0.01[c]
Race – n (%)						0.03[b]
Caucasian	376 (54)	103 (59)	78 (49)	123 (55)	72 (50)	
Asian	75 (11)	18 (10)	16 (10)	24 (11)	17 (12)	
African American	35 (5)	4 (2)	7 (4)	15 (7)	9 (6)	
Native American	8 (1)	2 (1)	2 (1)	2 (1)	2 (1)	
Hawaiian/Pacific Islander	9 (1)	2 (1)	1 (1)	3 (1)	3 (2)	
Other	135 (19)	21 (12)	36 (22)	46 (21)	32 (22)	
Unknown	64 (9)	25 (14)	20 (12)	10 (4)	9 (6)	
Ethnicity – n (%)						0.13[c]
Hispanic or Latino	117 (17)	20 (11)	34 (21)	36 (16)	27 (19)	
Not Hispanic or Latino	488 (70)	108 (62)	96 (60)	176 (79)	108 (75)	
Unknown	97 (14)	47 (27)	30 (19)	11 (5)	9 (6)	
Clinical Characteristics						
Etiology – n (%)						
Idiopathic PAH	175 (25)	45 (26)	38 (24)	55 (25)	37 (26)	0.97[c]
Familial PAH	7 (1)	1 (1)	2 (1)	3 (1)	1 (1)	0.88[b]
CTD-APAH	202 (29)	40 (23)	40 (25)	78 (35)	44 (31)	0.04[c]
CHD-APAH	98 (14)	31 (18)	35 (22)	21 (9)	11 (8)	< 0.01[c]
Drugs & Toxins-APAH	193 (28)	47 (27)	46 (29)	50 (22)	50 (35)	0.08[c]
PoPHTN	79 (11)	24 (14)	9 (6)	33 (15)	13 (9)	0.02[c]
HIV-APAH	12 (2)	3 (2)	4 (3)	4 (2)	1 (1)	0.72[b]
PVOD	5 (1)	0 (0)	2 (1)	1 (0)	2 (1)	0.38[b]
NYHA – n (%)	$n = 632$	$n = 157$	$n = 144$	$n = 198$	$n = 133$	0.56[c]
I	26 (4)	7 (4)	4 (3)	9 (5)	6 (5)	
II	135 (21)	35 (22)	34 (24)	42 (21)	24 (18)	
III	338 (53)	76 (48)	71 (49)	112 (57)	79 (59)	
IV	133 (21)	39 (25)	35 (24)	35 (18)	24 (18)	

(Continues)

TABLE 1 | (Continued)

Patient characteristics	Total cohort (n = 702)	Pre-2005 ($n = 175$)	2005-2009 ($n = 160$)	2010-2014 ($n = 223$)	2015-2019 ($n = 144$)	*p*-value
BMI – kg/m^2	29.30 ± 8.2 ($n = 505$)	28.91 ± 8.1 ($n = 152$)	28.49 ± 7.9 ($n = 123$)	29.01 ± 7.1 ($n = 120$)	31.07 ± 9.6 ($n = 110$)	0.08[a]
6MWD – m	354.03 ± 140.2 ($n = 632$)	381.43 ± 134.4 ($n = 154$)	384.09 ± 129.4 ($n = 153$)	329.15 ± 147.6 ($n = 209$)	328.00 ± 135.7 ($n = 139$)	< 0.01[a]
NT-proBNP – pg/dL – median (IQR)	623.5 (1791.8) ($n = 628$)	288 (1268.8) ($n = 106$)	605.5 (1693.8) ($n = 156$)	740.5 (2076.6) ($n = 222$)	807 (1753.8) ($n = 144$)	< 0.01[d]

Note: Data are shown as mean ± standard deviation, except where noted.

Abbreviations: Etiology: APAH = associated PAH, CHD = congenital heart disease, CTD = connective tissue disease, NYHA = New York Heart Association symptom classification, 6MWD = Distance walked in 6 minutes, min, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAH = pulmonary arterial hypertension, PoPHTN = portopulmonary hypertension, PVOD = Pulmonary veno-occlusive disease.

[a] ANOVA

[b] Fisher's exact test

[c] Chi-square test

[d] Kruskal–Wallis test.

outside institution with 61 (41%) undergoing vasoreactivity testing at that time. Of these 366 subjects, 361 underwent one or more catheterizations at Stanford with vasoreactivity testing performed in 264 (73.1%) of those initial catheterizations and 339 (93.9%) having vasoreactivity testing performed at least once over the course of their catheterizations at Stanford. A total of 42 of the 409 subjects (10.3%) were found to be vasoreactive (Table 3). Among these 42 vasoreactive subjects 26 (61.9%) had IPAH, DT-PAH or heritable PAH (HPAH) as their underlying etiology. Vasoreactivity testing performance improved after the pre-2005 cohort.

3.3 | Risk Stratification

The REVEAL risk score of all patients was obtained at baseline and updated at each subsequent encounter. The distribution of REVEAL risk scores every year is displayed in Figure 2. Both incident and prevalent patients are included to allow for an assessment of the cumulative risk of our entire cohort. The majority of patients were low-risk (REVEAL score ≤ 7). Each year, the proportion of patients with a high-risk score (REVEAL score ≥ 10) was low, peaking at 15.2% in 2003. (Figure 2).

3.4 | Therapeutics

The number of prescribed PAH-specific therapies changed for the cohort over the study period (Figure 3). The number of patients on > 1 PAH medication increased over the time period in low, intermediate, and high-risk patients. (Supporting Information S1: Figure A, B) The percentage of patients treated with parenteral prostacyclins each year ranged from 4.3% to 14.7%; there did not appear to be any meaningful change in the proportion of low, intermediate, or high-risk patients on prostacyclin therapy over time (Supporting Information S1: Figures C, D). By the subsequent encounter following incident catheterization, 19–42 (45.2%) vasoreactive patients were prescribed calcium channel blockers. Calcium channel blocker use in four vasoreactive patients was unknown.

3.5 | Outcomes

Between 2008 and 2019 there were a total of 1900 all-cause hospitalizations among 486 patients resulting in 158.3 hospitalizations per year (range: 91–220/year). The REVEAL risk score-adjusted hospitalization rate ranged between 14.8 (95% CI 11.2–19.3) and 22.33 (95% CI 18.3–27.0) hospitalizations per 100 person-years annually (Figure 4). The rate was increasing until the 2019 calendar year when the risk-adjusted hospitalization rate decreased. The REVEAL risk score-adjusted organ survival rate ranged from 0 (95% CI 0.0–4.88) to 6.0 (95% CI 3.9–8.9) events per 100 person-years annually (Figure 5); these did not change meaningfully over time.

There were 249 deaths during the study period; 46 (7%) patients underwent lung or heart-lung transplantation. Survival rates in the study population were 94% (95% CI: 93%–96%) at 1 year,

TABLE 2 | Baseline therapeutic regimen.

Patient characteristics	Total cohort ($n = 702$)	Pre-2005 ($n = 175$)	2005–2009 ($n = 160$)	2010–2014 ($n = 223$)	2015–2019 ($n = 144$)	*p*-value
Baseline medications						
PDE-5i	183 (26)	14 (8)	60 (38)	70 (31)	39 (27)	< 0.01[c]
ERA	96 (14)	19 (11)	28 (17)	37 (17)	12 (8)	0.04[c]
Prostanoid	74 (11)	31 (18)	16 (10)	23 (10)	4 (3)	< 0.01[c]
CCB	161 (27)	68 (41)	38 (26)	26 (19)	29 (21)	< 0.01[c]
IPAH patients on anticoagulation[a]	77 (51) ($n = 150$)	26 (62) ($n = 42$)	17 (47) ($n = 36$)	21 (58) ($n = 36$)	13 (36) ($n = 36$)	0.11[c]
Diuretics	326 (55) ($n = 594$)	101 (60) ($n = 169$)	92 (62) ($n = 148$)	71 (51) ($n = 140$)	62 (45) ($n = 137$)	0.01[c]
Number of medications – n (%)						< 0.01[b]
None	438 (62)	120 (69)	84 (52)	134 (60)	101 (70)	
Monotherapy	188 (27)	47 (27)	52 (32)	57 (26)	32 (22)	
Dual Therapy	60 (9)	7 (4)	20 (12)	23 (10)	10 (7)	
Triple Therapy	15 (2)	1 (1)	4 (3)	9 (4)	1 (1)	

Note: Data are shown as number and percentage relative to the corresponding cohort.
Abbreviations: CCB = calcium channel blocker, ERA = endothelin receptor antagonist, hypertension, IPAH = idiopathic pulmonary arterial, PDE-5i = phosphodiesterase-5 inhibitor.
[a]Anticoagulation defined as warfarin or aspirin.
[b]Fisher's exact test
[c]Chi-square test.

83% (95% CI: 81%–86%) at 3 years, 75% (95% CI: 72%–79%) at 5 years, and 60% (95% CI: 56%–65%) at 10 years (Figure 6). Similarly, organ survival rates were 94% (95% CI: 93%–96%) at 1 year, 83% (95% CI: 80%–86%) at 3 years, 74% (95% CI: 70%–77%) at 5 years and 56% (95% CI: 52%–61%) at 10 years. No statistically significant difference was observed when comparing organ survival by time cohort (Supporting Information S1: Figure E).

4 | Discussion

Important aspects of care at a PAH specialty center include appropriate initial evaluation of newly referred patients and timely treatment initiation based on risk stratification. However, despite a wealth of extant data in well-characterized cohorts that suggest worse outcomes with delays in therapy and the suggestion of improved outcomes with initiation of combination therapy, published data that can inform quality improvement in usual care settings is lacking [17, 18]. In this study, we present the real-world experience of our center in the evaluation and treatment of PAH patients, with the goal of informing metrics about quality of care for other PAH programs. Our chosen quality metrics, informed by our own historic quality measures and dependent on the data collected in the VMWCDB, largely align with the ACC/AHA guidelines and the ESC position paper [1, 8]. Specifically, we analyzed a well-phenotyped cohort of PAH patients over a designated period of time and identified the most clinically pertinent dimensions of care. The ESC proposes five domains of care [1]: structural framework [2], diagnosis and risk stratification [3], initial treatment [4] follow-up and [5] outcomes—each with their own proposed specific quality indicators. Our proposed quality metrics of [1] diagnostic evaluations [2], therapeutic practice patterns and [3] risk-adjusted outcomes of hospitalization and death are thematically aligned with four of those domains. To facilitate an analysis of practice patterns over time we arbitrarily divided our cohort into four time periods.

All patients enrolled in our database had RHC-confirmed PAH. Patients who underwent RHC at our specialty center were more likely to have complete reporting of hemodynamic values, although some cases from referring hospitals could have missing data calculated from values noted in the original reports. Additionally, vasoreactivity testing was performed more often at our center as compared to referring institutions. While guidelines recommend vasoreactivity testing in incident patients with IPAH, DT-PAH, and HPAH our practice has been to perform testing in all WHO Group 1 PAH patients at both initial and subsequent catheterizations unless deferred. Our database does not capture reasons for deferring vasoreactivity testing but explanations include lower mPAP values and elevated PAWP values at the time of catheterization. Our data suggest that when possible, initial catheterization should be performed at a PAH specialty center, as is recommended in diagnostic guidelines for PAH [19].

The mean age at enrollment increased significantly across cohorts, possibly reflecting a change in screening practices and general echocardiography usage over that period of time. There was a notable decrease in the baseline 6MWD and an increase in NT-proBNP levels noted in the most recent cohort. These

TABLE 3 | Diagnostic testing.

	Total cohort ($n = 702$)	Pre-2005 ($n = 175$)	2005–2009 ($n = 160$)	2010–2014 ($n = 223$)	2015–2019 ($n = 144$)	p-value
Initial right heart catheterization – n (%)	702 (100)	175 (100)	160 (100)	223 (100)	144 (100)	
Hemodynamics – median (IQR)						
mRAP – mmHg	8.0 (8.0) ($n = 672$)	9.0 (9.0) ($n = 155$)	8.0 (8.0) ($n = 155$)	8.0 (7.0) ($n = 218$)	9.0 (7.0) ($n = 144$)	0.02[d]
mPAP – mmHg	50 (20.0) ($n = 700$)	52 (21.0) ($n = 173$)	52 (17.5) ($n = 160$)	45 (20) ($n = 223$)	48.5 (19.2) ($n = 144$)	< 0.01[d]
CO – L/min	3.63 (1.62) ($n = 573$)	3.67 (1.58) ($n = 113$)	3.39 (1.46) ($n = 124$)	3.8 (1.62) ($n = 198$)	3.59 (1.68) ($n = 138$)	0.10[d]
PAWP – mmHg	10.0 (6.0) ($n = 664$)	11.0 (6.0) ($n = 153$)	10.0 (7.0) ($n = 153$)	10.0 (6.0) ($n = 217$)	12.0 (5.0) ($n = 141$)	0.02[d]
PVR – WU	10.1 (9.9) ($n = 564$)	10.7 (8.5) ($n = 106$)	12.2 (8.5) ($n = 126$)	8.7 (9.0) ($n = 196$)	10.0 (9.3) ($n = 136$)	< 0.01[d]
Vasoreactivity testing performed – n (%)	409 (58)	83 (48)	97 (61)	138 (62)	91 (63)	0.01[c]
Echocardiography	696 (99)	173 (99)	159 (99)	223 (100)	141 (98)	0.09[c]
Pulmonary function testing	641 (91)	160 (92)	142 (89)	210 (94)	129 (90)	0.22[c]
Ventilation-perfusion scintigraphy	574 (82)	127 (73)	118 (74)	199 (89)	130 (90)	< 0.01[c]
Chest CT imaging	617 (88)	146 (84)	144 (90)	202 (91)	125 (87)	0.17[c]
Polysomnography	135 (19)	56 (32)	35 (22)	28 (13)	16 (11)	< 0.01[c]
6 min walk test	655 (93)	154 (89)	153 (96)	209 (94)	139 (97)	0.02[c]
Complete diagnostic testing*	468 (67)	102 (58)	95 (59)	167 (75)	104 (72)	< 0.01[c]
Complete diagnostic testing w/ polysomnography	100 (14)	42 (24)	26 (16)	21 (9)	11 (8)	< 0.01[c]

Note: Combined Stanford and outside hospital data are shown as number and percentage relative to the corresponding cohort.
Abbreviations: CO = cardiac output, mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary artery wedge pressure, PVR (WU) = pulmonary vascular resistance (Wood units). Complete diagnostic testing includes right heart catheterization, pulmonary function testing, echocardiography, ventilation-perfusion scintigraphy, and chest CT imaging.

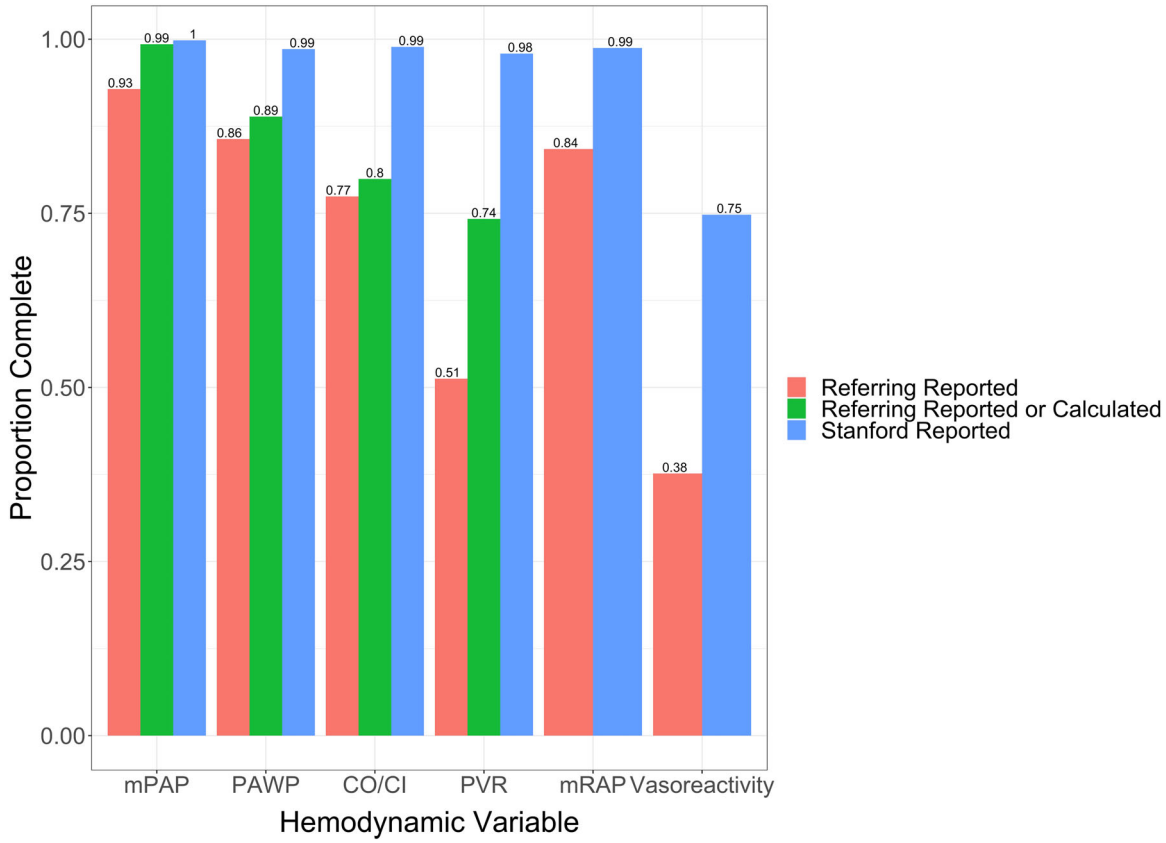

FIGURE 1 | Proportion of right heart catheterizations that report specific hemodynamic measures from outside facilities versus Stanford. Referring Reported: data obtained from documentation from the referring facility. Referring Reported/Calculated: both data obtained from documentation and data calculated from the available data using standard hemodynamic relationships. Stanford: data obtained from documentation from Stanford. CO = cardiac output, CI = cardiac index, mRAP = mean right atrial pressure, mPAP = mean pulmonary artery pressure, PAWP = pulmonary artery wedge pressure, PVR = pulmonary vascular resistance.

findings may be attributable to an overall older cohort and possibly reflective of a greater fraction of subjects with higher-risk CTD-associated PAH.

Practice guidelines for the diagnosis and management of PAH outline the diagnostic testing necessary for the appropriate classification of PH. The overwhelming majority of our cohort underwent echocardiography, PFTs, CT chest imaging, and 6MWT, consistent with current guidelines. The overall percentage undergoing PSG was considerably lower at 135/702 (19%); this value notably excludes overnight oximetry testing which is not captured in our database. It is possible that the low percentage undergoing PSG is secondary to a combination of patient inconvenience, cost to patient and clinician discretion in deferring testing in a patient with a low pre-test probability for sleep-disordered breathing. The fraction of patients who had undergone V/Q scanning increased significantly over the four time periods and reached 90% for patients in the final time cohort with a corresponding increase in complete diagnostic testing (67%) with PSG excluded and 14% with PSG included.

Reflecting the availability of new therapies and clinical trial results, guideline recommendations regarding therapy have changed over the time the VMWCDB has operated. The current recommendation is upfront dual therapy for most low and moderate-risk patients, while parenteral prostacyclins are recommended for high-risk patients [20]. In our cohort, there were notable increases in the number of medications prescribed to patients within the cohort, corresponding to the introduction of newly-approved therapies. After 2007, the majority of patients in our cohort were on >1 PAH-specific drug. Surprisingly, there was no significant difference between high, intermediate, and low-risk patients in terms of number of therapies or proportion of parenteral prostacyclins. This could be explained by many factors, including improvement in REVEAL risk score after initiation of these therapies or provider/patient decisions to forego specific therapies despite high-risk features. Studying therapeutic approaches presents greater challenges than diagnostic practices or outcomes with respect to creating benchmarks. Along with an increasing number of approved agents is the paucity of trials comparing various regimens across a range of different risk profiles. A comprehensive longitudinal analysis of therapeutic practice patterns over time in different risk profiles among incident and prevalent patients could be the basis of a future study.

Survival in our cohort was comparable to other large cohorts of PAH patients [21–23]. Notably, survival remained relatively constant over the time periods studied, despite improvements in rates of diagnostic testing, more favorable

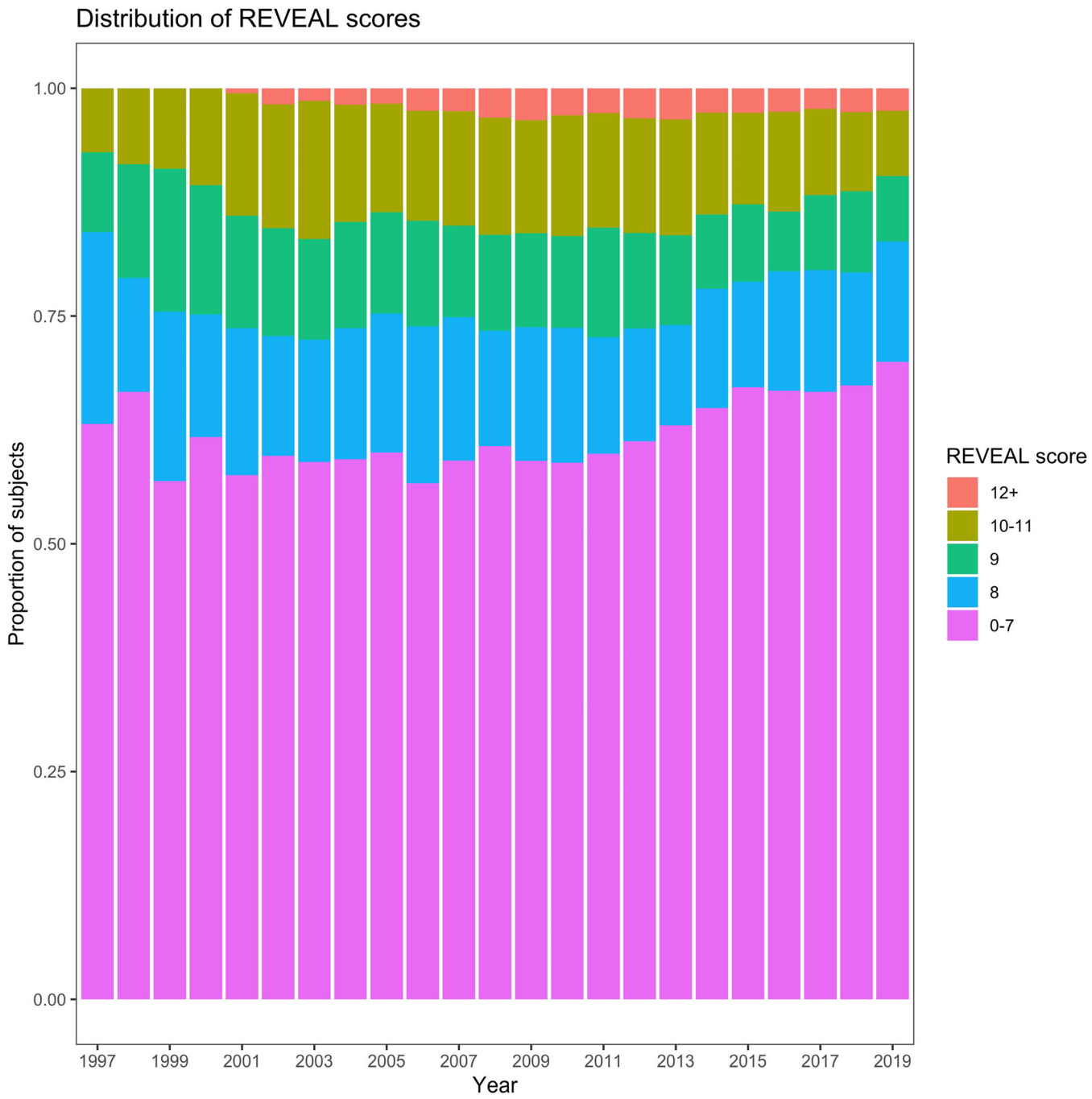

FIGURE 2 | Distribution of REVEAL risk scores by year.

baseline hemodynamics at presentation, and an increase in the number of approved therapeutic options. It is possible that because our incident patients over time were older and more frequently male, fixed variables associated with poorer outcomes in other studied cohorts, our outcomes did not improve over time [24]. Additionally, these outcomes may been influenced by co-morbid conditions which were not analyzed in this data set.

The rate of hospitalizations in our patient population appears to be low when considering the morbidity and mortality of PAH and is comparable to the frequency of hospitalization among patients with similar survival rates, such as end-stage left heart failure [25]. It is possible that the decrease in risk-adjusted hospitalization rate noted in 2019 is at least partially attributable to the implementation of a post-hospitalization clinic. Given the financial and psychosocial burden of hospitalizations, this overall metric is an important benchmark for the care of PAH patients. We believe that these risk-adjusted metrics of hospitalization and death can function as benchmarks for other programs interested in studying their quality outcomes.

Our study represents, to the best of our knowledge, the only published markers of risk-adjusted hospitalization, event-free survival, and all-cause mortality rates for a well-described

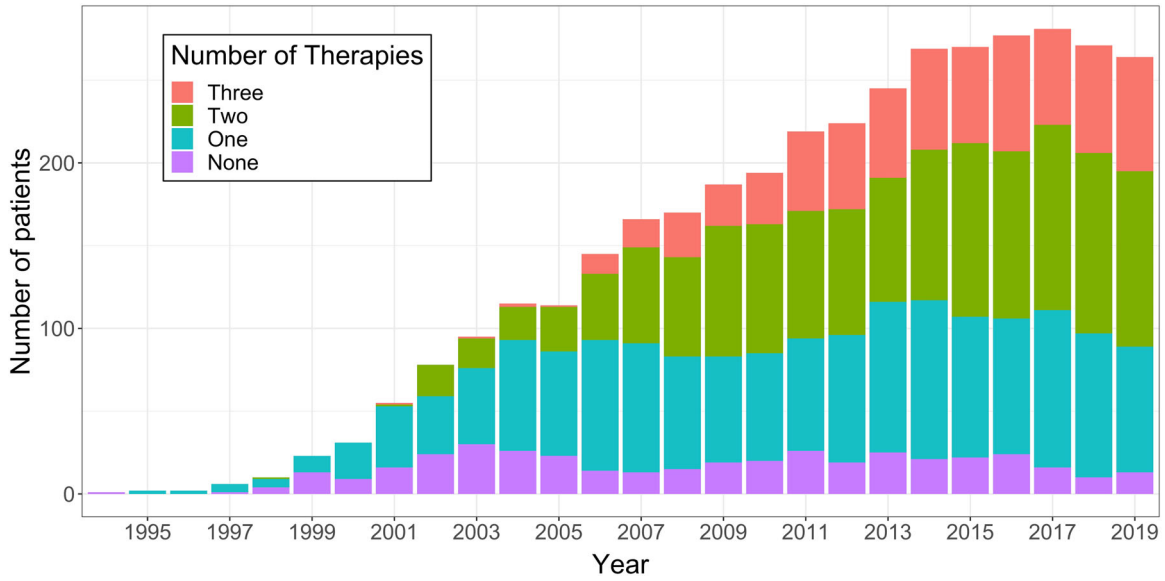

FIGURE 3 | Number of pulmonary vasodilator therapies prescribed by year in the overall cohort.

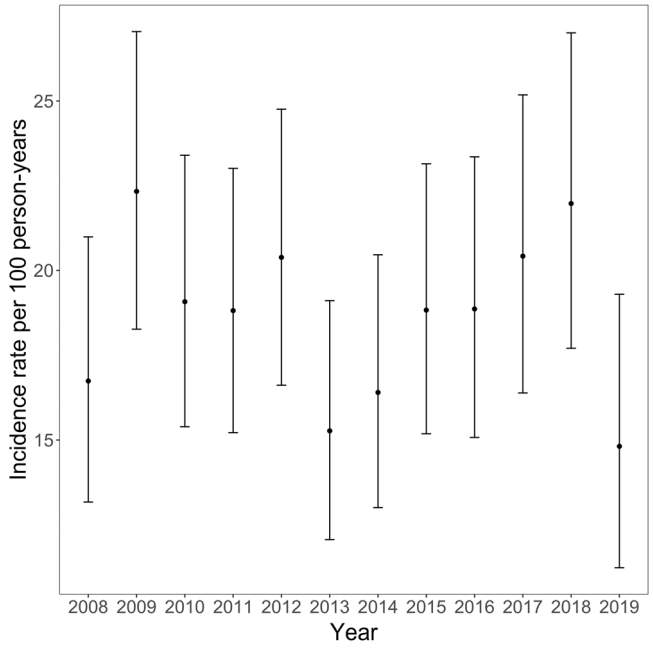

FIGURE 4 | Risk-adjusted hospitalization rates by year expressed in events per 100 patient-years at risk.

cohort of PAH patients which we believe is a vital quality metric. Hendriks et al. performed a two-center analysis of survival and treatment strategies with similarly timed cohorts of patients but without risk adjustment or an analysis of diagnostic patterns or hospitalization rates [26]. They did not note an improvement in all-cause mortality rate over time as well.

Our centre is a PHA-accredited Comprehensive Center of Care with the attendant support of all the services required for such a designation. Inpatients with PAH are admitted to a primary service attended by a PAH specialist and intensive care services are conducted in a coronary care unit. Outpatient services are supported by experienced advanced practice nurse practitioners, registered nurses, physician assistants and a dedicated social worker. The number of providers facilitates prompt appointments for both referrals and post-hospitalization encounters. These elements constitute the vital portions of the 'structural framework' domain noted in the ESC position paper.

Our study has notable limitations. While the cohort is robust this is nonetheless a single-center study. Despite being prospective, the VMWDB is still prone to missing data. For incidents in which practice deviated from the standard of care, the VMWDB lacks justifying documentation. For example, the less-than-expected rate of CCB use in patients with positive vasoreactivity testing could be partially explained by a subset of patients who developed vasoreactivity during the course of their PAH treatment who were not prescribed CCB in addition to their extant regimen. Our study did not specifically evaluate initial treatment practice patterns, the one unaddressed ESC domain. Our study intentionally evaluated incident and prevalent cases together during a given time period for the purposes of establishing the overall risk of the cohort when evaluating risk-adjusted outcomes. Indeed, the VMWDB stretches over a long period of time, during which practice patterns and guideline recommendations for diagnostics and therapeutics have changed. With respect to outcomes our hospitalization rates reflect completely those at our institution but it is possible that hospitalizations at outside institutions are not fully captured if we were not made aware of them.

In the future, comprehensive assessments of practice patterns across centers can provide the means to establish meaningful benchmarks.

Delivering quality care to patients with PAH requires subspecialty experience, and the publication of benchmarks in diagnostic and therapeutic testing from specialized PH centers is an important aspect of quality improvement in the field. In total, we present our center's experience with initial evaluation

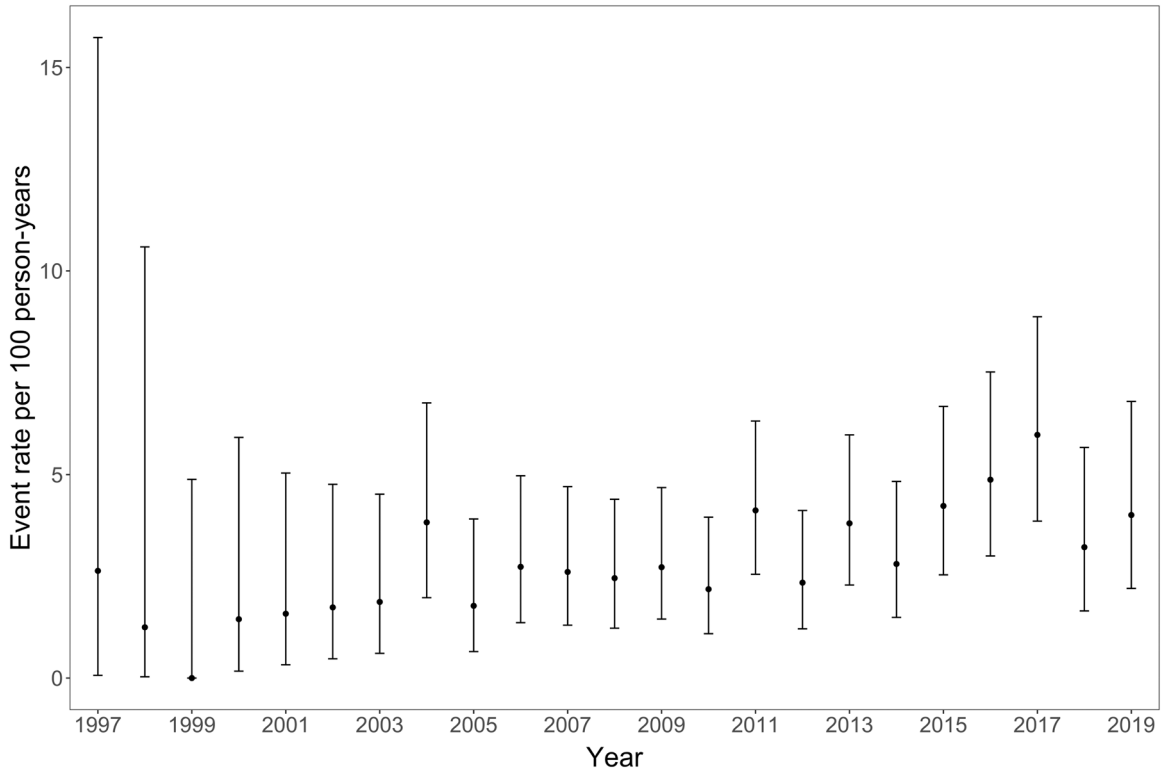

FIGURE 5 | Risk-adjusted death and transplant rates by year expressed in events per 100 patient-years at risk.

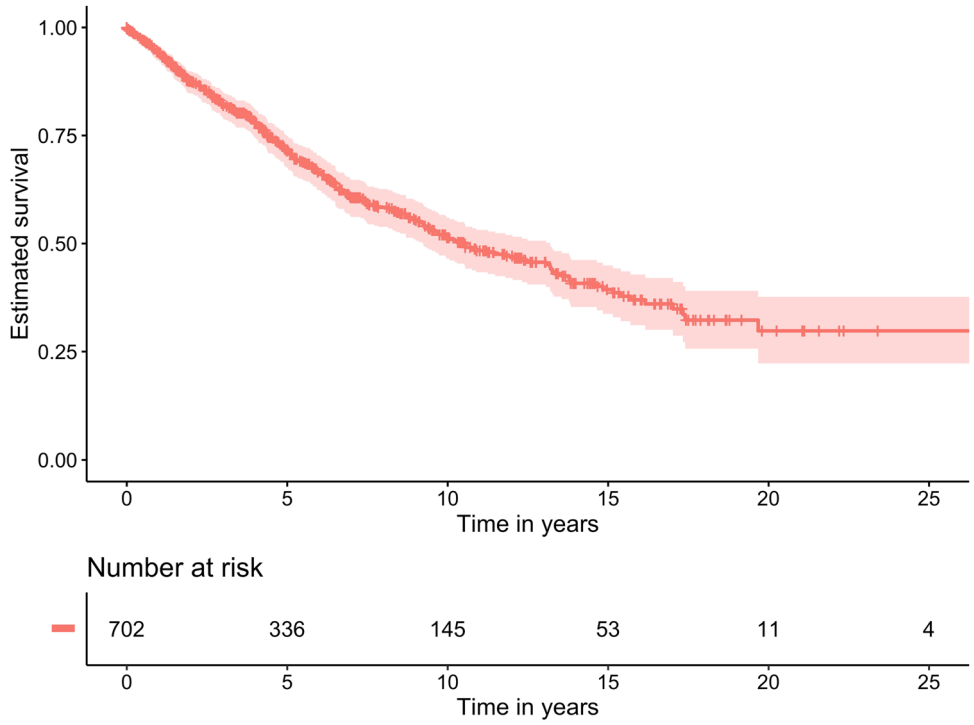

FIGURE 6 | Kaplan–Meier survival estimates for overall cohort.

in PAH, as well as treatment characteristics and outcome rates over the longitudinal course of care. We believe our data can assist in the creation of benchmarks and offer our single-center data as a starting point for the PAH community to develop these metrics.

Author Contributions

C.A.K. takes responsibility for the content of the manuscript including the data and its analysis. A.H. is responsible for data collection and

database management. J.H.L., J.R., H.H. are responsible for data analysis and figure creation. C.A.K., K.E.S., R.T.Z., Y.K.S. all contributed substantially to the study design, data analysis, and drafting of the manuscript. J.L., K.T.K., A.J.S., E.F.S., R.L.L., A.M.A. and V.J.P. contributed to the critical review of the manuscript.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.