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RESEARCH ARTICLE

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Association of risk assessment at diagnosis with healthcare resource utilization and health-related quality of life outcomes in pulmonary arterial hypertension

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Abstract

We aimed to describe the clinical characteristics, healthcare resource utilization (HCRU) and costs, health-related quality of life (HRQoL), and survival for patients with pulmonary arterial hypertension (PAH), stratified by 1-year mortality risk at diagnosis. Adults diagnosed with PAH at the Sheffield Pulmonary Vascular Disease Unit between 2012 and 2019 were included. Patients were categorized as low, intermediate, or high risk for 1-year mortality at diagnosis. Demographics, clinical characteristics, comorbidities, HCRU, costs, HRQoL, and survival were analyzed. Overall, 1717 patients were included: 72 (5%) at low risk, 941 (62%) at intermediate risk, and 496 (33%) at high risk. Low-risk patients had lower HCRU prediagnosis and 1-year postdiagnosis than intermediate- or high-risk patients. Postdiagnosis, there were significant changes in HCRU, particularly inpatient hospitalizations and accident and emergency (A&E) visits among high-risk patients. At 3 years postdiagnosis, HCRU for all measures was similar across risk groups. Low-risk patients had lower EmPHasis-10 scores (indicating better HRQoL) at diagnosis and at 1-year follow-up compared with intermediate- and high-risk patients; only the score in the high-risk group improved. Median overall survival decreased as risk category increased in analyzed subgroups. Low-risk status was associated with better 1-year survival and HRQoL compared with intermediate- and high-risk patients. HCRU decreased in high-risk patients postdiagnosis, with the most marked reduction in A&E admissions. The pattern of decreased per-patient inpatient hospitalizations and A&E visits at 3 years postdiagnosis suggests that a diagnosis of PAH helps to decrease HCRU in areas that are key drivers of costs.

KEYWORDS
healthcare resource utilization, health-related quality of life, pulmonary arterial hypertension, real-world evidence, risk assessment

Pulmonary hypertension (PH) is defined in the latest international guidelines by a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest.[1] Group 1, pulmonary arterial hypertension (PAH), is a severe, chronic, and progressive form of PH characterized by pulmonary arterial remodeling that, untreated, results in right heart failure and death.[2,3] It is divided into subgroups based on underlying etiology. Idiopathic PAH (IPAH) occurs without a clear cause; additional forms include heritable PAH (HPAH), drug- and toxin-induced PAH, and PAH associated with other medical conditions, including connective tissue disease (CTD), human immunodeficiency virus (HIV) infection, portal hypertension (PoPH), congenital heart disease (CHD), and schistosomiasis.[1] PAH is a rare disease with an annual incidence of 6 patients per million (ppm) and a prevalence of 48–55 ppm.[1]

Management is complex, requiring multidisciplinary care.[1] Earlier diagnosis and treatment improve outcomes; however, the initial symptoms of PAH are nonspecific, often leading to a diagnostic delay.[4] Treatment includes general measures such as physical activity and supervised rehabilitation, psychosocial support, and supportive drug therapy.[1] Current PAH-specific treatments target three pathways and include endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin analogs and receptor agonists.[1,5] Treatment with PAH-specific therapies has been shown to improve clinical outcomes, with combination therapy superior to monotherapy.[2] To guide management decisions, undertaking a multiparameter risk assessment is advocated.[6] The European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines classify patients at low, intermediate, or high risk of 1-year mortality (previously <5%, 5%–10%, and >10% risk of mortality within 1 year, respectively, but now <5%, 5%–20%, and >20%).[1,7]

Patients with PAH incur a heavy burden of healthcare resource utilization (HCRU) and associated costs in England[8]; however, there are currently no data available on how disease severity as assessed by risk score affects HCRU and costs or on its impact on patients' health-related quality of life (HRQoL). The aim of this study was to assess how risk status at diagnosis impacts HCRU, healthcare costs, and HRQoL.

METHODS

Data sources

Data were collected from the ASPIRE Registry from an electronic medical record database used at the Sheffield Pulmonary Vascular Disease Unit (Sheffield PVDU) based at Royal Hallamshire Hospital and were linked with data from the National Health Service (NHS) Hospital Episode Statistics (HES) database, as previously described.[9,10]

The Sheffield PVDU is a nationally designated PH referral center with a referral population of 15–20 million. Patients undergo systematic evaluation including blood testing, lung function, exercise testing, multimodality imaging, and right heart catheterization (RHC) according to nationally audited standards of care which are published annually.[11] A diagnosis of PAH was based on hemodynamic thresholds from contemporaneous guidelines requiring an mPAP ≥ 25 mmHg and a pulmonary vascular resistance ≥ 3 Wood Units and according to standard criteria, with the exception of patients with adult CHD where RHC was not mandatory. The ASPIRE Registry database contains clinical management and demographic data for all referred patients, including confirmed diagnoses, diagnostic procedures, clinical tests, treatment prescribed, and specialist consultations. The HES database contains details on patient comorbidities, hospital admissions, accident and emergency (A&E) visits, and outpatient consultations at all NHS hospitals in England.[12] HES data were linked by NHS Digital to Sheffield PVDU data before being deidentified and made accessible for analysis in this study. Death data in the Sheffield PVDU database were captured through linkage to NHS death records and were refreshed immediately before data extraction.

Categories with <7 patients in tables have been masked in line with data protection requirements to ensure that patient confidentiality was maintained.[13] Where only a single count was masked as "<7" and therefore could be further identified, the category with the next lowest number was also suppressed to avoid calculation of the small value. However, no data were excluded from the analyses due to small number suppression.

Study design

Adult patients (≥18 years old at diagnosis) were included in this retrospective observational cohort study if they were diagnosed with PAH between January 1, 2012, and June 30, 2019, and had ≥90 days of potential follow-up in the Sheffield PVDU database. There was no required minimum follow-up or look-back time for the HES.

For all study participants, the study index date was defined as the date of PAH diagnosis within the study period based on Sheffield PVDU records (Figure 1).

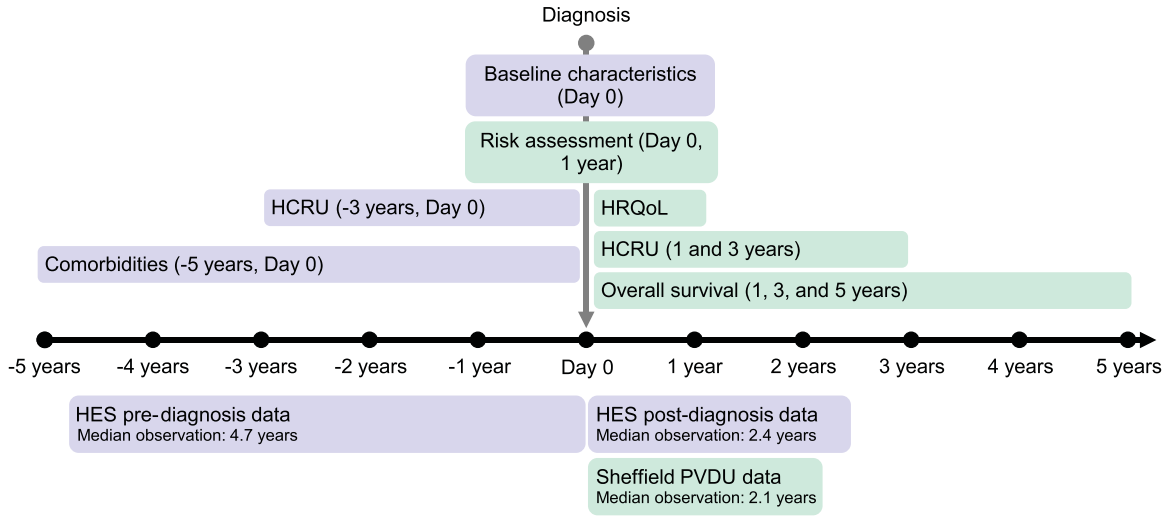

FIGURE 1 Overview of observation times and database coverage in the study. HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; HRQoL, health-related quality of life; Sheffield PVDU, Sheffield Pulmonary Vascular Disease Unit.

Patients were followed from diagnosis until the earliest of the following: date of death, date of last contact, or end of study observation (September 30, 2019).

Patients were categorized for the survival analyses by those with I/HPAH, which included IPAH and HPAH for the purposes of this analysis, and Other PAH, which included those with drug- and toxin-induced PAH and diagnoses associated with CHD, CTD, HIV infection, and PoPH. All other analyses were performed for the entire PAH cohort, overall, and stratified by risk category.

Risk categorization

The Kylhammar and colleagues risk assessment framework was adapted to categorize patients retrospectively as being at low, intermediate, or high risk of 1-year mortality at diagnosis and at 1-year postdiagnosis, using previously published thresholds for the incremental shuttle walk test (ISWT) instead of the 6-min walk distance (6MWD).[14–16] The composite risk score used measurements for five other clinical variables: World Health Organization functional class (WHO FC), right atrial pressure, cardiac index, mixed venous oxygen saturation (SvO_2), and right ventricular ejection fraction.[16] Each variable was graded from 1 to 3 (1 = low risk, 2 = intermediate risk, and 3 = high risk). A mean grade was calculated and rounded to the nearest integer to define the patient's risk category.[15] At a minimum, WHO FC and either ISWT or 6MWD were required to calculate a risk score. If either was unavailable, the score was classified as "missing/undetermined."

Study measures

Patient demographics and clinical characteristics; risk assessment; 1-, 3-, and 5-year survival; and changes in HRQoL were collected from the Sheffield ASPIRE PVDU database. HRQoL was evaluated using the EmPHasis-10, a PH-specific questionnaire[17,18]; scores range from 0 to 50, with higher scores indicative of worse HRQoL.[17]

Data collected from the HES included comorbidities identified in the 5 years before diagnosis; clinical management and HCRU 1, 2, and 3 years prediagnosis; HCRU 1, 3, and 5 years postdiagnosis; costs for patients who had 1 and 3 years of follow-up data; and 1-, 3-, and 5-year survival.

HCRU and costs included hospitalizations, outpatient visits, and A&E care. Inpatient hospitalizations were categorized as either longer than 1 day or "same-day spells," meaning the admission and discharge dates were the same. Outpatient visits were defined as any activity occurring in a hospital under an outpatient setting. Costs were calculated according to 2019 NHS tariff prices, which are based on the national average unit costs of providing each service and representative of the reimbursement received by hospitals in England.[19]

Statistical analysis

The statistical approach was descriptive, without predefined hypotheses. Categorical variables are reported as frequency (n) and percentage (%). Continuous variables are reported as median ($Q1$, $Q3$) and mean ($\pm$ standard

deviation). For the survival analyses, time-to-event was evaluated from the reference date with censoring at the date of last contact; survival probabilities (i.e., percentage of patients alive at specific time points) and respective 95% confidence intervals were based on the Kaplan–Meier estimates provided. Median survival duration was calculated for subgroups in which at least 50% of patients had died by the end of follow-up.

RESULTS

Overview

Overall, 1717 patients diagnosed with PAH at the Sheffield PVDU between 2012 and 2019 were included in the analyses. The median period from the first record in HES to diagnosis at Sheffield PVDU was 4.7 years (Figure 1). The median follow-up time from diagnosis to the end of observation was 2.1 years in Sheffield PVDU and 2.4 years in HES. A total of 663 (39%) patients died during the study period.

Demographics and risk assessment

Patient demographics and clinical characteristics at diagnosis, stratified by risk group, are shown in Table 1. The median (*Q*1, *Q*3) age at diagnosis was 61 (44, 72) years. A total of 503 (29%) patients had I/HPAH and 1214 (71%) had other types of PAH. Among 1509 patients with available risk assessment at diagnosis, 72 (5%) were at low risk, 941 (62%) were at intermediate risk, and 496 (33%) were at high risk of 1-year mortality.

Comorbidities identified before diagnosis of PAH

Figure 2 summarizes comorbidities identified in the 5 years before PAH diagnosis, stratified by risk category at diagnosis. Among respiratory comorbidities, chronic obstructive pulmonary disease, other obstructive lung disease, and asthma were the most common. The most common cardiovascular comorbidity was hypertension, followed by heart failure, valvular heart disease, and ischemic heart disease. The proportions of all respiratory and cardiovascular comorbidities were higher among high-risk patients versus intermediate-risk patients, particularly for renal failure and heart failure. Among low-risk patients, only hypertension was recorded in the 5 years prediagnosis (in ≥7 patients).

HCRU and costs

Inpatient hospitalizations in the intermediate- and high-risk groups were similar pre- and post-diagnosis and remained low among low-risk patients postdiagnosis. Median (*Q*1, *Q*3) duration of inpatient hospitalization per patient in the first year after diagnosis was 4.0 (2.0, 8.3) days overall, 2.8 (2.0, 6.2) days in the low-risk group, 3.3 (2.0, 7.0) days in the intermediate-risk group, and 6.0 (2.5, 10.5) days in the high-risk group. Median per-patient numbers of same-day spells and outpatient consultations for any cause pre- and post-diagnosis were similar between risk groups at each time period (Figure 3; for mean values, see Supporting Information S1: Table 1). A&E visits for high-risk patients markedly decreased from a median (*Q*1, *Q*3) of 3 (0.0, 8.0) prediagnosis to 0 (0.0, 1.0) in the first year postdiagnosis.

Costs were driven by same-day spells, followed by outpatient consultations; these costs were broadly similar across all risk groups (Figure 4, Supporting Information S1: Figure 3). In the first year following diagnosis, high-risk patients had the highest median per-patient costs due to inpatient hospitalizations when compared with other risk groups (Figure 4, Supporting Information S1: Figure 3).

HRQoL

In patients with assessments at both diagnosis and at 1-year follow-up ($N = 411$), low-risk patients ($n = 17$) had lower EmPHasis-10 scores at both time points compared with intermediate- ($n = 244$) and high-risk patients ($n = 131$) (Figure 5), corresponding to a better quality of life. The median (*Q*1, *Q*3) change from diagnosis to 1-year postdiagnosis was −2 (−9, 2) in the low-risk group, 0 (−6, 4) in the intermediate-risk group, and −6 (−12, 0) in the high-risk group.

Overall survival

Median overall survival decreased as the baseline risk category increased in both the I/HPAH and Other PAH cohorts. In the I/HPAH cohort, median overall survival (*Q*1, *Q*3) was 5.3 years (2.1, n.a.; $n = 255$) for intermediate-risk patients and 2.7 years (1.2, 5.3; $n = 202$) for high-risk patients (Supporting Information S1: Figure 1). Median overall survival was not reached among low-risk I/HPAH patients; 1-year survival probability was 100% ($n = 13$), and there were not enough patients to calculate the probability at 3 and 5 years. Survival probabilities at 1, 3, and 5 years were 91%, 68%,

TABLE 1 Demographics and clinical characteristics at diagnosis in patients with PAH.

Characteristic	All patients	Low risk[a]	Intermediate risk[a]	High risk[a]
Cohort size, *n* (%)	1717 (100)	72 (4)	941 (55)	496 (29)
Median age (range), years	61 (18–89)	51 (18–82)	60 (18–89)	65 (18–87)
Gender; female, *n* (%)	1174 (68)	57 (79)	636 (68)	341 (69)
Etiology, *n* (%)				
I/HPAH	503 (29)	13 (3)	255 (51)	202 (40)
Other PAH	1214 (71)	59 (5)	686 (57)	294 (24)
Ethnicity, *n* (%)				
White	1271 (74)	59 (82)	706 (75)	390 (79)
Indian/ Pakistani/ Bangladeshi	91 (5)	<7[b]	55 (6)	26 (5)
Black	27 (2)	0	13 (1)	suppressed[b]
Other Asian	22 (1)	<7[b]	12 (1)	8 (2)
Mixed	7 (0.4)	0	<7[b]	0
Other	<7[b]	0	<7[b]	0
Missing/ unknown	294 (17)	<7[b]	145 (15)	suppressed[b]
WHO functional class, *n* (%)				
I	suppressed[b]	<7[b]	<7[b]	<7[b]
II	128 (7)	43 (60)	70 (7)	<7[b]
III	1410 (82)	25 (35)	830 (88)	387 (78)
IV	165 (10)	<7[b]	35 (4)	107 (22)
Exercise capacity, median (*Q*1, *Q*3) [*n*]				
ISWT, m	130 (50, 250) [1283]	425 (360, 500) [66]	180 (80, 270) [773]	60 (20, 120) [444]
Hemodynamics, median (*Q*1, *Q*3) [*n*]				
Heart rate, bpm	80 (71, 90) [1074]	78 (70, 90) [50]	80 (71, 89) [652]	81 (71, 90) [300]
MAP, mmHg	100 (89, 111) [1063]	106.5 (93, 113) [50]	101.6 (90, 114) [647]	95 (86, 106) [295]
RHC at diagnosis, *n* (%)[c]	1156 (67)	52 (72)	685 (73)	337 (68)
mRAP, mmHg	9 (6, 14) [870]	5 (4, 7) [39]	8 (5, 10) [536]	16 (12, 19) [238]
mPAP, mmHg	46 (36, 54) [1117]	30 (27, 41) [51]	44 (33, 53) [672]	52 (46, 59) [316]
PAWP, mmHg	11 (8, 13) [1094]	10 (8, 11) [50]	10 (8, 13) [665]	12 (9, 15) [304]
Cardiac index, L/min/m^2	2.35 (1.84, 2.95) [1067]	3.16 (2.85, 3.56) [50]	2.60 (2.12, 3.12) [651]	1.77 (1.47, 2.08) [297]
PVR, Wood units	8.9 (5.7, 12.8) [990]	4.1 (3.6, 7.0) [36]	7.5 (4.9, 10.5) [596]	12.8 (9.2, 16.7) [290]
SvO_2, %	63.9 (56.9, 69.8) [985]	73.9 (69.4, 75.5) [40]	66.9 (62.4, 71.6) [601]	54.1 (48.8, 58.2) [277]

(Continues)

TABLE 1 (Continued)

Characteristic	All patients	Low risk[a]	Intermediate risk[a]	High risk[a]
Lung function, median (*Q*1, *Q*3) [*n*]				
FEV1/FVC, %	72 (66, 79) [1007]	74 (67, 77) [42]	73 (66, 80) [577]	71 (64, 79) [324]
DLCO, % predicted	37.1 (25.6, 52.9) [888]	56.0 (44.4, 70.8) [40]	39.5 (27.8, 54.9) [531]	31.4 (22.2, 44.2) [264]

Abbreviations: bpm, beats per minute; CHD, congenital heart disease; DLCO, carbon monoxide transfer factor; FEV1/FVC, forced expiratory volume/forced vital capacity; I/HPAH, idiopathic or heritable PAH; ISWT, incremental shuttle walk test; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RVEF, right ventricular ejection fraction; SvO_2, mixed venous oxygen saturation; WHO, World Health Organization.

[a]A mean grade was calculated and rounded off to the nearest integer to define the patient's risk group. At minimum, two variables (WHO functional class and ISWT) were required to calculate a risk score. For 208 patients (33 patients in the I/HPAH cohort; 175 in the Other PAH cohort), one or both values were not available, and the score was recorded as "missing/undetermined" (i.e., 1509 patients had available risk assessment at diagnosis).

[b]Small numbers were suppressed in line with data protection requirements. A result of "<7" substitutes any patient count that is below 7 unique patients and therefore masked for data privacy reasons. "Suppressed" substitutes the next lowest number in a row or column that can be used to reverse calculate a masked value of "<7." This means that a number that has been "Suppressed" could substitute a number >7. Values of zero or missing do not require suppression.

[c]RHC was performed in patients with PAH with the exception of patients with adult CHD. United Kingdom national standards of care do not mandate repeat RHC before commencing PAH therapy in patients with adult CHD if investigations that may include previous RHC are consistent with a diagnosis of PAH. For patients in Sheffield undergoing treatment with PH therapies with the exclusion of patients with CHD, the percentage of patients undergoing RHC before treatment ranged annually between 94% and 98% from 2016 to 2019 where data are available.[20]

and 51% for those at intermediate risk and 81%, 42%, and 27% for those at high risk.

Median overall survival was not reached within the study period among low-risk Other PAH patients (*Q*1, 5.9; *Q*3, n.a.; $n = 59$); it was 6.0 years (2.9, n.a.; $n = 686$) for intermediate-risk patients and 3.3 years (0.93, n.a.; $n = 294$) for high-risk patients (Supporting Information S1: Figure 2). The survival probabilities at 1, 3, and 5 years were 100%, 89%, and 82% for low-risk patients; 92%, 74%, and 58% for intermediate-risk patients; and 74%, 51%, and 42% for those at high risk.

DISCUSSION

This retrospective study has generated pre- and post-diagnosis real-world observations for patients diagnosed with PAH at a large European PH referral center and analyzed outcomes by low-, medium-, and high-risk stratification at diagnosis. In addition to reporting on survival and HRQoL, we have analyzed HCRU by risk category and found that following diagnosis, there were notable changes among high-risk patients for inpatient hospitalizations and A&E measures, which decreased to a median of zero.

The management of PAH imposes a heavy clinical burden, but there is limited real-world evidence of HCRU and costs based in European healthcare systems. Our HCRU results are largely in line with a retrospective comparison of the burden of PAH in England between 2013 and 2017 based on data from HES[8] (see Supporting Information S1: Table 1). In that study, the mean annual number of outpatient visits ranged from 9.4 to 10.3, and the mean number of A&E visits from 0.8 to 0.9.[8] Mean annual inpatient hospital visits ranged from 2.9 to 3.2, which is similar to this study if inpatient and same-day spells are considered together. In patients with PAH, an increase in hospitalizations can indicate clinical worsening and is associated with increased mortality.[5,21] In our study, the pattern of decreased per-patient inpatient hospitalizations and A&E visits at 1 and 3 years postdiagnosis suggests that a diagnosis of PAH helps to decrease HCRU in areas that are key drivers of costs.

A retrospective analysis of hospitalization data from 2012 to 2016 using the French national hospital discharge database evaluated the number of inpatient and outpatient visits in a cohort of 2173 patients diagnosed with PAH.[22] In this study, inpatient visits represented 52% of total hospital events, with a mean of between 2.2 and 2.3 inpatient visits per year per patient. After the first inpatient hospitalization, 55% of patients had a second inpatient hospitalization during the diagnosis year, and the proportion of patients with at least a third inpatient hospitalization during the diagnosis year increased from 35% in 2013 to 43% in 2016. Outpatient visits showed a similar trend; the average number per patient per year increased from 1.4 to 2.5 (2012 to 2016). This increased HCRU postdiagnosis differs from our study, in which most HCRU decreased or remained similar to prediagnosis. This may reflect differences in healthcare systems, with more patients in the United Kingdom treated in 1 day (same-day spells) or via outpatient consultations rather than overnight hospitalization.

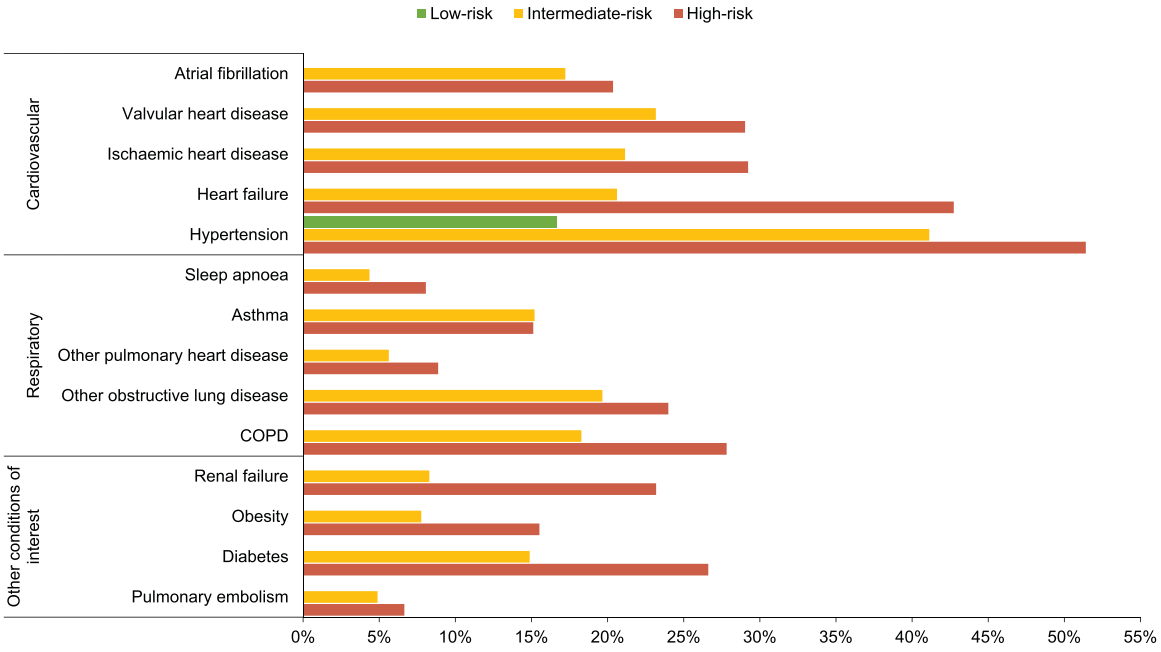

FIGURE 2 Comorbidities recorded as present in the 5 years before pulmonary arterial hypertension diagnosis overall and by risk group. Data were collected from the Hospital Episode Statistics database. In almost all categories for low-risk patients, there were <7 patients, which meant data suppression applied. Renal failure comprised International Classification of Diseases, 10th Revision, codes I12.0, I13.1, I13.2, K76.7, N17, N18.4, N18.5, N19, N99.0, O08.4, O90.4, T86.1, Y84.1, and Z99.2. COPD, chronic obstructive pulmonary disease.

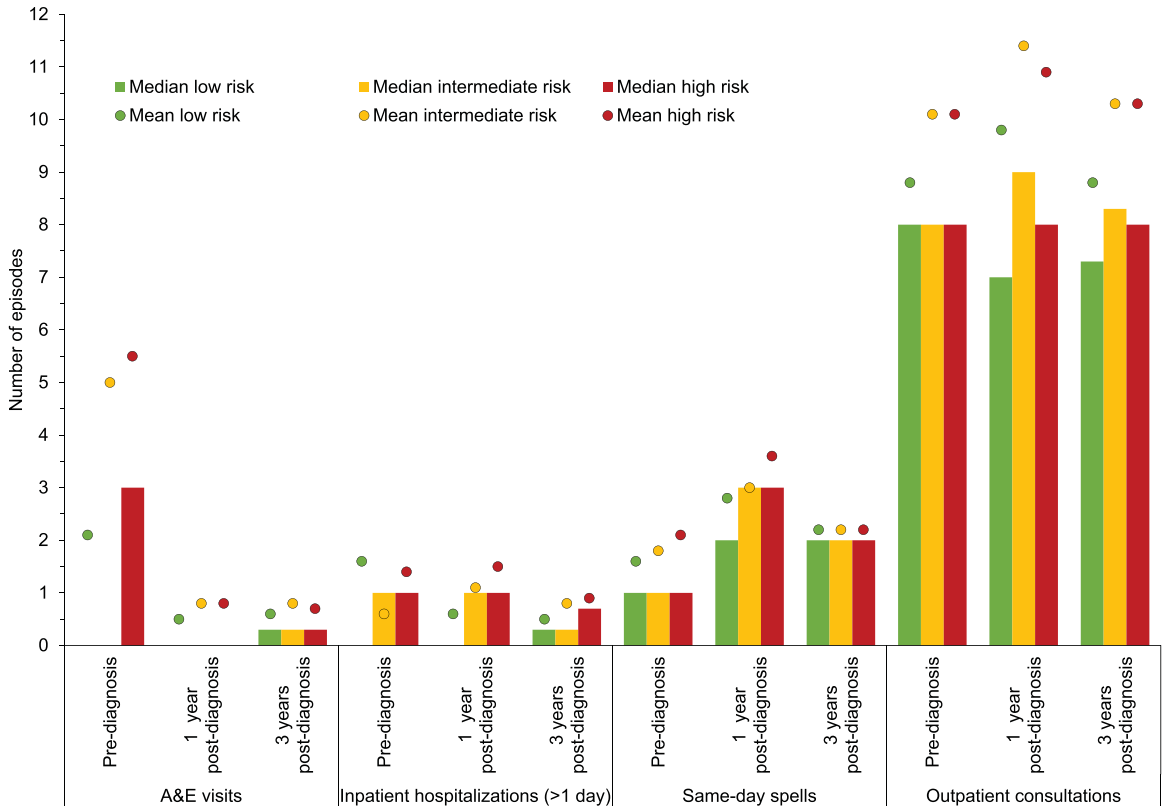

FIGURE 3 Median and mean all-cause healthcare resource utilization (HCRU) episodes per patient per year, 1 year before and 1 and 3 years* after pulmonary arterial hypertension diagnosis, by risk group. *HCRU at 3 years postdiagnosis represents median and mean values per year of follow-up over 3 years for patients with available follow-up data, not the median and mean during the third year only.

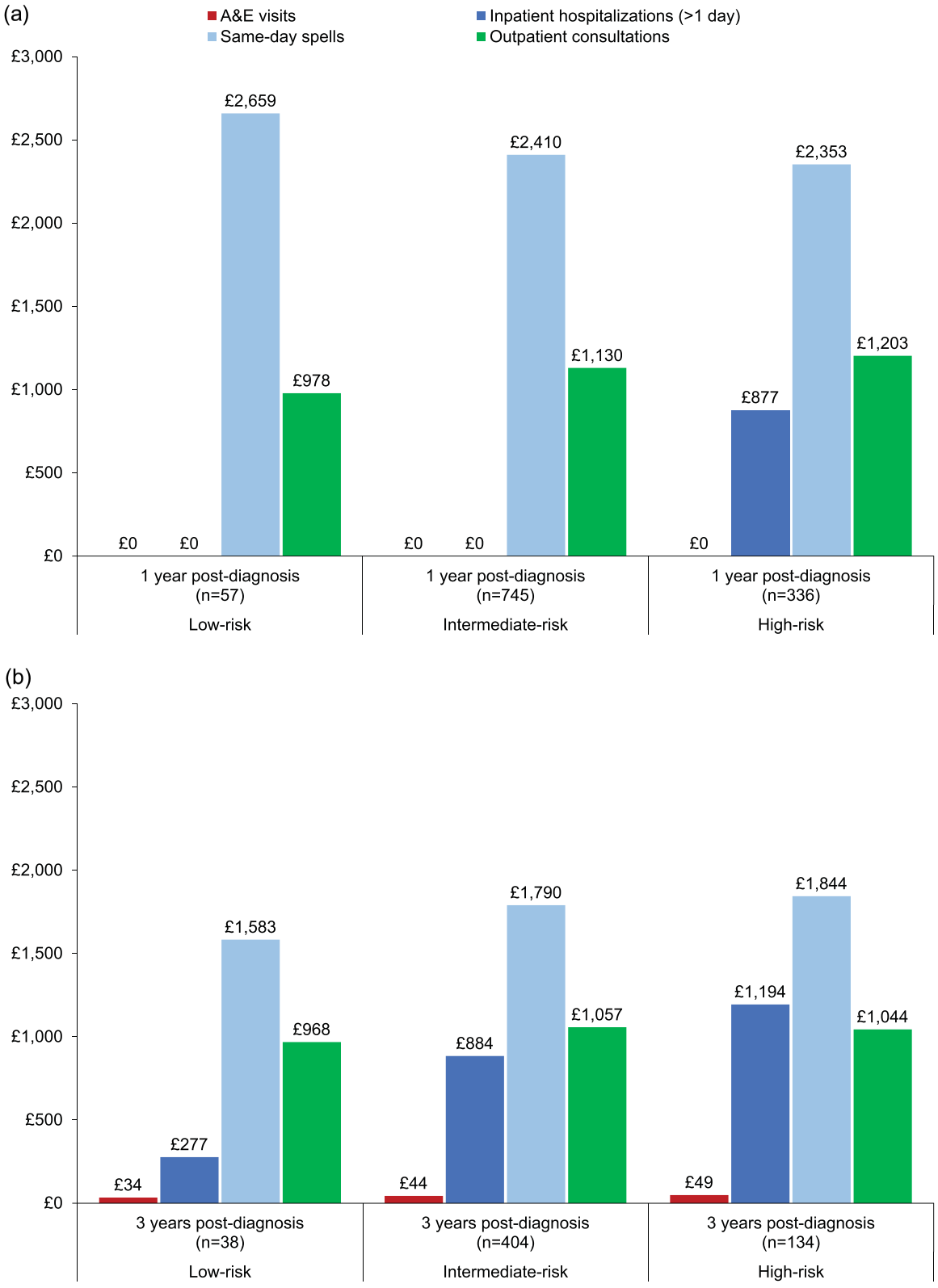

FIGURE 4 Median cost per patient per year of follow-up, (a) 1 year and (b) 3 years postdiagnosis by risk group. A&E, accident and emergency.

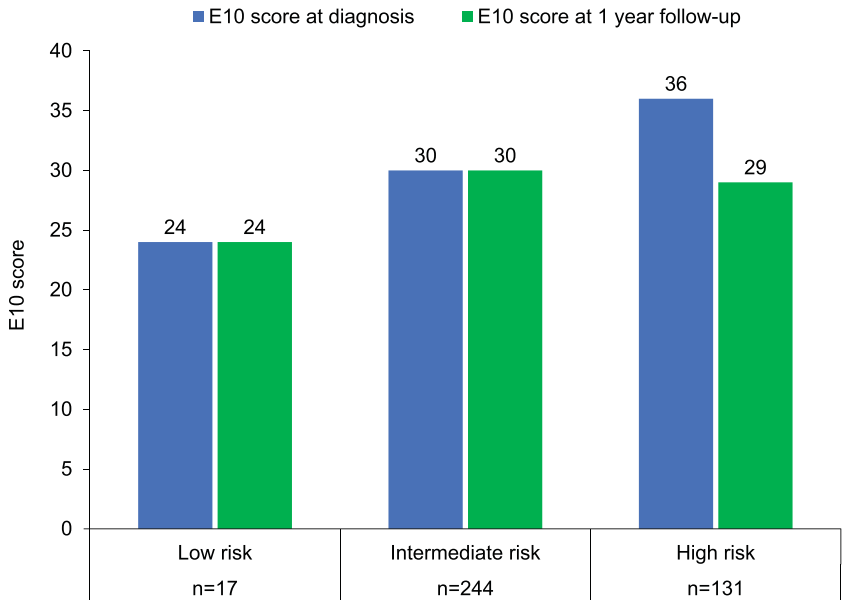

FIGURE 5 Median EmPHasis-10 (E10) scores at diagnosis and 1-year postdiagnosis, overall and by risk group at diagnosis. Only patients with assessments at both time periods are included in the figure. The E10 is an instrument developed and validated specifically for assessment of health-related quality of life (HRQoL) in patients with pulmonary hypertension.[17,18] Higher scores are indicative of worse HRQoL.[17]

Risk assessment plays a key role in the management of patients with PAH by providing a prediction of 1-year mortality risk. Based on this risk, clinicians can determine a patient's prognosis and optimize their treatment approach. This study applied a modified risk framework proposed by Kylhammar et al.,[15] which is itself adopted from the three-stratum risk assessment from the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH,[7] to retrospectively categorize patients by risk. In 2022, the ESC/ERS risk assessment tool was updated, including the estimates of 1-year mortality: <5% for low risk, 5%–20% for intermediate risk, and >20% for high risk. Our 1-year survival estimates align with this update. Longer-term survival (at 3 and 5 years) was poor among intermediate- and high-risk patients in the I/HPAH and Other PAH cohorts. Attaining a low-risk profile is a desirable treatment goal.[23]

Comparison of our results with data from 131 patients with incident PAH (mean age 64 years) and a high level of comorbidities (66.4%) treated between 2016 and 2018 at four German PH centers show some differences in risk stratification at baseline and subsequent survival rates.[24] In the German study, most patients (76%) were classified at intermediate risk, 13.8% at high risk, and 9.9% at low risk. In our study, most patients were also classified as intermediate risk, but there was a much higher proportion of patients at high risk (33%). In our study, for instance, a high proportion of patients in the intermediate- and high-risk groups had respiratory and cardiovascular comorbidities, while only hypertension was recorded in low-risk patients. In the German study, survival at 1 year was 96% in the intermediate-risk group and 89% in the high-risk group compared with 91% and 81% in our I/HPAH cohort. Comparable with our study, all patients classed as low-risk in the German study were alive at 1 year.[24]

Collecting HRQoL data in patients with PH has been routine in the United Kingdom since 2014.[25] One of the commonly used tools, the EmPHasis-10, has been shown to correlate reliably with clinical parameters, such as breathlessness and psychological morbidity. However, HRQoL is not incorporated in current risk assessment tools. Median EmPHasis-10 scores at diagnosis in the low- and intermediate-risk groups in our study (24 and 30) are comparable to median EmPHasis-10 scores reported for patients with PAH from a large UK multicenter study of 1745 patients, which included patients from our center, and a multicenter study from the United States of 498 patients included in the Pulmonary Hypertension Association Registry.[25,26] In the United Kingdom study, 751 patients with CTD-PAH had a median EmPHasis-10 score of 30 at baseline, and those with IPAH had a median score of 28 ($n = 994$).[25] In the United States study, the median score overall was 26.[26] High-risk patients in our study had high EmPHasis-10 scores at diagnosis (median: 36), indicative of poor HRQoL. Sarzyńska et al. have shown that treatment of patients with PAH improves HRQoL.[27] Results in the high-risk group of our study appear to support this finding based on the decrease (i.e., improvement) in 1-year scores. However, there was no change in scores among low- or intermediate-risk patients. More research is needed in this area to determine how treatment improves HRQoL in patients with PAH.

This study had some limitations. The cohort of patients with PAH described in this cohort is heterogeneous and included patients with both respiratory and cardiac comorbidities; for example, patients with IPAH

and the lung phenotype, and also patients with CTD with varying degrees of interstitial lung disease. However, it is representative of patients who receive PAH therapies. Hospitalization data may have been underreported because HES data are collected only in England, and thus some hospitalizations for HES-registered patients residing or traveling outside of the country could have occurred outside of England, although this activity should be minimal. In addition, some information items are not fully captured in HES depending on care setting; e.g., there are lower rates of data capture on diagnosis for outpatient appointments and emergency department care because there is no requirement for hospitals to record these data for reimbursements in those care settings. Also, as it is not possible to assess the quality of local coding, a potential underestimation of the costs and HCRU specifically associated with outpatient and emergency care may have resulted. Additionally, patients might seek private healthcare or incur out-of-pocket expenses, which are not covered in HES.

CONCLUSIONS

This study has linked two databases to provide a real-world evidence profile of patients treated for PAH stratified by risk of 1-year mortality. Some analyses should be interpreted with caution due to small patient numbers within subgroups by risk category; however, this did not prevent the interpretation of planned measures. Overall, these data add to the literature for PAH, corroborating that intermediate- and high-risk patients with PAH have poor survival outcomes and poor HRQoL, and demonstrating a pattern of decreased per-patient HCRU postdiagnosis, particularly for inpatient hospitalizations and A&E visits. Thus, a diagnosis of PAH, regardless of risk category, appears to reduce costly HCRU, an important consideration for healthcare systems.

AUTHOR CONTRIBUTIONS

Study conception: David G. Kiely, Allan Lawrie, Ruvimbo Muzwidzwa, Amélie Beaudet, and Audrey Muller. *Study design*: David G. Kiely, Fernando Exposto, Ruvimbo Muzwidzwa, Amélie Beaudet, Audrey Muller, and Rafael Sauter. *Data acquisition*: Allan Lawrie, Neil Hamilton, Steven Wood, and Louise Raiteri. *Data analysis*: Allan Lawrie, Neil Hamilton, Steven Wood, Fernando Exposto, and Louise Raiteri. *Data interpretation*: Allan Lawrie, David G. Kiely, Neil Hamilton, Fernando Exposto, Ruvimbo Muzwidzwa, Louise Raiteri, Amélie Beaudet, Audrey Muller, Rafael Sauter, and Nadia Pillai. All authors contributed to drafting the work and revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors confirm that GPP3 guidelines were followed throughout the development of the article.

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CONFLICTS OF INTEREST STATEMENT

Allan Lawrie is supported by a British Heart Foundation Senior Basic Science Research Fellowship (FS/18/52/33808) and has received honoraria and funding from Janssen Pharmaceuticals to attend scientific meetings. Amélie Beaudet, Audrey Muller, Rafael Sauter, and Nadia Pillai are employees of Actelion Pharmaceuticals Ltd. Amélie Beaudet and Audrey Muller own stock in Johnson & Johnson. Neil Hamilton has received honoraria payments from Janssen Pharmaceuticals, Vifor Pharmaceuticals, and MSD. David G. Kiely has received grants from Janssen Pharmaceuticals and Ferrer; consulting fees from Janssen Pharmaceuticals, MSD, Ferrer, Altavant, and United Therapeutics; honoraria from Janssen Pharmaceuticals, MSD, Ferrer, and United Therapeutics; funding from Janssen Pharmaceuticals, MSD, and Ferrer to attend scientific meetings; has participated in a Data Safety Monitoring Board or Advisory Board for Janssen Pharmaceuticals and MSD; serves on the Specialist Respiratory Clinical Reference Group (unpaid) and as the UK National Audit Chair. Steven Wood has received grants from Janssen Pharmaceuticals in support of the current study. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The reported study was noninterventional, and the analysis was based on secondary data. No identifying data were prospectively collected in any of the planned approaches. Ethics approval was obtained from the Research Ethics

Committee (REC) of the NHS Health Research Authority and from the Confidentiality Advisory Group (CAG) to secure s251 approval for the linkage of patient identifiable data. Following approval from the REC and CAG, an application was submitted through the NHS Digital Data Access Request Service to access the required HES data. This application was reviewed and endorsed by the Independent Group Advising on the Release of Data. NHS Digital and the involved entities signed a Data Sharing Agreement to secure access to the HES data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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