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RESEARCH ARTICLE

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Time to diagnosis of pulmonary hypertension and diagnostic burden: A retrospective analysis of nationwide US healthcare data

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Abstract

The main aim of this analysis was to investigate time from symptom onset (chronic unexplained dyspnoea [CUD]) to diagnosis of Group 1 pulmonary hypertension (PH)—pulmonary arterial hypertension (PAH)—and to characterize healthcare resource utilization leading up to diagnosis using a nationwide US claims and an electronic health record (EHR) database from Optum©. Eligible patients were ≥18 years old at first CUD diagnosis (index event) and had a PAH diagnosis on or after index date. Based on administrative codes, PAH was defined as right heart catheterization (RHC), ≥ 2 PAH diagnoses (1 within a year of RHC), and ≥1 post-RHC prescription for PAH treatment. All values are median (1st quartile–3rd quartile) unless otherwise stated. Of 854,722 patients with CUD in the claims database, 582 (0.1%) had PAH. Time from CUD to PAH diagnosis was 2.26 (0.73–4.22) years. PAH patients experienced 3 (2–4) transthoracic echocardiograms (TTEs), 6 (3–12) specialist visits, and 2 (1–4) hospitalizations during the diagnostic interval. Almost one-third of patients (29%) waited 10 months or more to have a TTE. Findings from the EHR database were broadly similar. Resource utilization during the diagnostic interval was also analyzed in an overall PH cohort: findings were generally similar to the PAH cohort (2 [1–3] TTEs, 4 [2–9] specialist visits and 2 [1–4] hospitalizations). These data indicate a delay in the diagnostic pathway for PAH, and illustrate the burden associated with PAH diagnosis.

KEYWORDS
chronic unexplained dyspnoea, pulmonary arterial hypertension, US electronic health records, US insurance claims

INTRODUCTION

Pulmonary hypertension (PH) is a life-threatening disease that is characterized by elevated pulmonary artery pressure and presents with nonspecific symptoms, such as dyspnoea.[1] PH is classified into five subgroups, according to underlying disease or etiology. Specific treatments are available for Group 1 PH (pulmonary arterial hypertension [PAH]), Group 4 PH (chronic thromboembolic PH [CTEPH]) and, more recently, for PH associated with interstitial lung disease, which is classified under Group 3 PH.[2,3] Without treatment, survival outcomes are very poor,[4,5] and delays in diagnosis have been shown to lead to higher mortality rates in PAH and CTEPH.[6,7] Despite efforts to improve early identification of PH, the mean delay in diagnosis of PAH has been reported to range from 2.5 to 3.9 years,[6,8] and does not appear to have improved since the National Institutes of Health (NIH) Primary PH registry in the 1980s.[9] Moreover, approximately three-quarters of PAH and CTEPH patients have severe disease (e.g., World Health Organization functional class [WHO FC] III/IV) at diagnosis,[10,11] further demonstrating the unmet need in early detection of PH.

PH is diagnosed by right heart catheterization (RHC), an invasive procedure that is associated with a small (<1%) risk of major complications.[3] While RHC may not be necessary in certain situations (e.g., most cases of established left heart disease or a high likelihood of left heart disease as the main cause of PH), RHC is needed to confirm the diagnosis of PH, particularly when considering PAH or CTEPH, and to support treatment decisions.[3] Physicians should first investigate for PH using non-invasive tests. Transthoracic echocardiography (TTE) is recommended for all patients with suspected PH and, as such, is considered the gold-standard screening test for PH.[12] The diagnosis of PH does not rely on these two tests alone; evidence of PH, its severity and/or underlying etiology can be gleaned from investigations such as electrocardiogram, chest radiography, and pulmonary function tests (PFT).[12] However, delays in diagnosis arise at every stage of the journey, starting with the time between patients noticing symptoms and seeing a doctor, with almost half (47%) of patients waiting over six months.[13] Referrals to specialists can also be delayed due to lack of awareness of PH by general practitioners (GP) and/or by the time taken to sequentially exclude other more common conditions such as anxiety or asthma.[13,14] In terms of investigative tests, TTE may not be performed or echocardiographic signs suggestive of PH can be missed,[15] due to a lack of awareness of early signals of PH. Understanding this journey in detail could help identify ways to expedite the detection of PH. Several registries have investigated the delay in diagnosis, but very few studies have characterized the patients' diagnostic journey.[6,8,16]

Large nationwide healthcare insurance claims and EHR databases are valuable and comprehensive sources of data collected during real-world clinical practice. Importantly, the use of this type of database allows a relatively large sample of patients with rare diseases such as PAH, compared with individual disease-specific assets.[17] This would be difficult to achieve with a disease-specific registry or clinical database.[17] Therefore, this study used the Optum© Deidentified claims and electronic health record (EHR) databases to generate up-to-date estimates of the time between the first diagnosis of chronic unexplained dyspnoea (CUD) and the diagnosis of PH or PAH for adults in the United States, and to evaluate healthcare resource utilization during this interval. Ultimately, this study aimed to further characterize the diagnostic pathway to help identify any barriers to timely diagnosis.

METHODS

Data sources

This analysis used data from two large US data assets provided by Optum©: an administrative claims database (Optum© Deidentified Clinformatics® Data Mart Database [OptumInsight]), and an EHR database (Optum© Deidentified EHR Data set). The claims database was used for the main analyses and the EHR database for sensitivity analyses and validation. At the time of these analyses, the latest data cut-offs available were March 2021 for the claims data and September 2020 for the EHR data. The databases contained over 71 million patients (claims) and almost 99 million patients (EHR), respectively. The claims database is an adjudicated US claims database for members of private health insurance who are fully insured in commercial plans or in administrative services only. Patient age is capped at 90 years old in this database and it includes outpatient pharmacy prescription dispensing claims (coded with National Drug Codes [NDC]), outpatient laboratory tests processed by large national laboratory vendors who participate in data exchange with Optum© (coded with LOINC codes), and claims processed from inpatient and outpatient settings for procedures (coded in CPT-4, HCPCs, ICD-9-CM, or ICD-10-PCS) and diagnoses (coded in International Classification of Diseases-9-Clinical Modification [ICD-9-CM] or ICD-10-CM). The EHR database is a US medical records database that includes clinical information, mainly from large integrated data networks,

such as medications prescribed and administered, laboratory results, vital signs, body measurements, diagnoses, procedures and information derived from clinical notes using Natural Language Processing (NLP).

Study population

Eligibility criteria for inclusion in the study cohorts are visualized in Supporting Information: Figure S1. All patients were required to have a CUD diagnosis (index event) in or after the study start date of January 2007 and a PH or PAH diagnosis on or after the index date. This study defines symptom onset as the first diagnosis of CUD as this is the most common symptom of PH and PAH.[18] Patients must have been at least 18 years old at the index date and have a minimum observation time of at least one year before index, to ensure that there was no earlier diagnosis of CUD, PH, or PAH. Patients must also have been diagnosed with CUD at least 3 years before the data-cut off and, in the claims database, have had continuous enrollment for at least 3 years. The minimum of 3 years of observation post-index was arrived at after sensitivity analyses (using a minimum of 1, 2, 2.5, 3, and 5 years) and ensured that patients were followed up for a sufficiently long time, thus minimizing the risk of overestimating the proportion of patients with a shorter time to diagnosis.

A combination of codes was used to define diagnosis of CUD, PH, and PAH, as specific codes are not available for CUD and were not available for most PH subgroups until the International Classification of Disease (ICD) version 10 update in October 2017. CUD was defined as at least two codes for unspecified dyspnoea or shortness of breath, at least 60 days apart. Sensitivity analyses demonstrated that requiring CUD diagnoses to be either 30, 60, or 90 days apart did not substantially affect the patient numbers and time-to-diagnosis calculations (Supporting Information: Table S1). The date of the first code of unspecified dyspnoea is the index date; therefore, changing of the interval between CUD diagnoses did not affect the time-to-diagnosis measurement.

PH patients were defined as those with a procedure code for a TTE or RHC on or after the index date (but not before) followed by at least two qualifying PH diagnoses, with at least one of those diagnoses being within 1 year after the procedure. Two diagnostic codes for PH are required as the codes can be used to ensure reimbursement for procedures in patients with suspected but not confirmed PH. The first code for PH diagnosis was used as the date of PH diagnosis. The development of this code-based definition of PH was based on the findings from a validation study that tested PH algorithms in four different US claims datasets (including the OPTUM claims database used in this study), using PheValuator, a diagnostic predictive modeling tool.[19,20] The most complex algorithm in this validation study (a PH diagnosis followed by RHC or TTE and another diagnosis) was used as a basis for the development of the PH algorithm in the present study (with some modifications), as it had the highest specificity and positive predictive value (PPV) of the algorithms tested. The sensitivity, specificity, PPV and negative predictive values (NPV) of our algorithm, as measured using PheValuator, were 49.9%, 99.9%, 79.4%, and 99.8%, respectively, in the OPTUM claims database (50.5%, 99.8%, 79.1%, and 99.3% in the OPTUM EHR database).

PAH patients are a subgroup of the overall PH cohort and were defined as those with (i) RHC on or after the index date, (ii) at least two qualifying PH diagnoses after RHC (one being within a year), and (iii) at least one prescription for PAH treatment (ambrisentan, bosentan, macitentan, epoprostenol, iloprost, treprostinil, selexipag, sildenafil, tadalafil, and riociguat) following RHC. Our code-based PAH definition was developed based on the findings from Sprecher et al. which tested published PAH algorithms in three claims databases using PheValuator.[21] Our algorithm combined the two approaches that outperformed others in terms of PPV and specificity, and was further refined such that it achieved a sensitivity, specificity, PPV and NPV of 10.8%, 96.9%, 100%, and 99.1%, respectively, in the OPTUM claims database (10.8%, 93.8%, 100%, and 99.8% in the OPTUM EHR database).

The code-based algorithms used to identify PH and PAH patients were chosen following sensitivity analyses, as they are very specific and selective, thus minimizing the number of wrongly identified patients. However, this does also mean that true cases may be missed. The diagnosis and procedure codes used to identify patients are shown in Supporting Information: Table S2.

Study outcomes

This study investigated the time from first CUD diagnosis to: PH diagnosis, PAH diagnosis (for PH patients with a PAH [PH Group 1] diagnosis), first TTE, first RHC (before or at date of PH or PAH diagnosis), first computed tomography (CT) scan, first pulmonary function test (PFT), first ventilation/perfusion (V/Q) scan, and first outpatient specialist visit (at any point between CUD diagnosis and PH/PAH diagnosis). The number of TTE, RHC, CT scan, PFT, and V/Q scan procedures, hospitalizations and specialist visits between

first CUD diagnosis and diagnosis of PH/PAH were also assessed. The procedure codes used for this analysis are shown in Supporting Information: Table S2 and Supporting Information: Table S3. A sensitivity analysis included time from first PH symptom to first PH or PAH diagnosis as recorded in the claims database, where symptom onset was defined as any early symptom of the following: shortness of breath, dyspnoea, fatigue, weakness, angina, chest pain, syncope, hemoptysis, and edema. Another analysis stratified time from CUD to PH/PAH diagnosis according to whether patients received their PH or PAH diagnosis before or after the 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines on PH were released.[12] Seven diagnoses, which can either confound diagnosis of PAH or be associated with PAH (asthma, chronic obstructive pulmonary disease [COPD], interstitial lung disease, left ventricular failure, pulmonary embolism, pulmonary fibrosis, and systemic sclerosis [SSc]) were also selected. PAH patients who had these diagnoses using the codes shown in Supporting Information: Table S4 were identified and grouped. The median time from CUD to PAH diagnosis was examined for each of the seven patient groups.

Statistical analysis

R version 4.0.4 was used for statistical analysis. All except one analysis in this study used descriptive statistics only. A supplementary analysis on differences between patients who received their diagnosis before or after the release of the 2015 ESC/ERS guidelines on PH were assessed using Pearson's χ^2 test (for categorical variables) and Wilcoxon rank sum test (for continuous variables).

RESULTS

Patients

Among 854,722 patients in the claims database with a first diagnosis of CUD in or after 2007, 44,809 (5.2%) patients met the study definition of a PH patient, and 582 (0.1%) patients were classified as PAH patients (Figure 1). The majority of patients were female (61% with PH, 66% with PAH) and White (70% PH, 64% PAH) and the median age at diagnosis was 77 years for PH and 69 years for PAH (Table 1).

Considering any early PH symptom, there were 1,940,467 patients with PH symptoms, of whom 68,746 (3.5%) had PH and 716 (0.04%) had PAH. There was a large degree of overlap between the CUD and the all-symptom groups of patients, as unexplained dyspnoea was the first reported symptom for 38%–45% of PH/PAH patients and almost all patients reported at least one diagnosis of dyspnoea or shortness of breath.

In the EHR database (the sensitivity analysis), there were 1,275,854 patients with CUD, of whom 63,065 (4.9%) were PH patients and 1229 (0.1%) were PAH patients (Figure 1). Compared with their counterparts in the claims database, PH and PAH patients in the EHR database were slightly younger at diagnosis and a lower proportion of patients were Hispanic (Table 1).

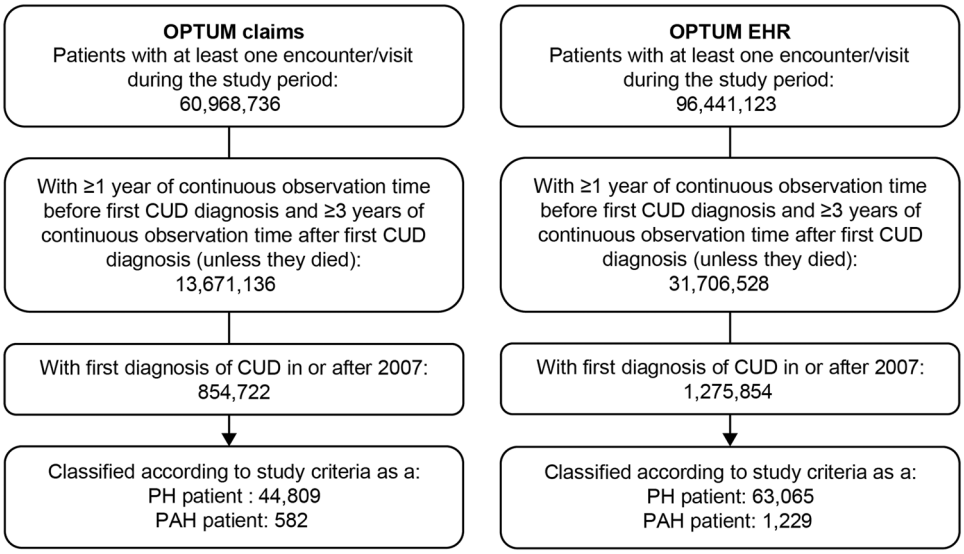


FIGURE 1 Patient flowchart. CUD, chronic unexplained dyspnoea; EHR, electronic health record; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

TABLE 1 Patient characteristics at diagnosis in the insurance claims database and EHR database

	Claims database		EHR database	
	PH ($N = 44,809$)	PAH ($N = 582$)	PH ($N = 63,065$)	PAH ($N = 1229$)
Female, *n* (%)	27113 (60.5)	386 (66.3)	37,845 (60.0)	816 (66.4)
Race, *n* (%)				
White	31384 (70.0)	375 (64.4)	53,406 (84.7)	927 (75.4)
Black/African American	4780 (10.7)	93 (16.0)	7115 (11.3)	241 (19.6)
Hispanic	4434 (9.9)	57 (9.8)	713 (1.1)	17 (1.4)
Asian	923 (2.1)	9 (1.5)	536 (0.8)	15 (1.2)
Unknown	3288 (7.3)	48 (8.2)	1295 (2.1)	29 (2.4)
Median (Q1, Q3) age at CUD diagnosis, years	74 (68, 80)	67 (55, 73)	71 (61, 78)	61 (52, 71)
Median (Q1, Q3) age at PH/PAH diagnosis, years	77 (71, 83)	69 (58, 76)	74 (63, 81)	63 (54, 73)

Abbreviations: CUD, chronic unexplained dyspnoea; EHR, electronic health record; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; Q, quartile.

A small percentage of patients received medications approved for the treatment of PAH (mostly phosphodiesterase-5 inhibitors) before CUD diagnosis, and the mean time between prescription and CUD diagnosis suggests that treatment was unrelated to their CUD and/or PH diagnosis (Supporting Information: Table S5).

Time between symptom onset and detection of PH

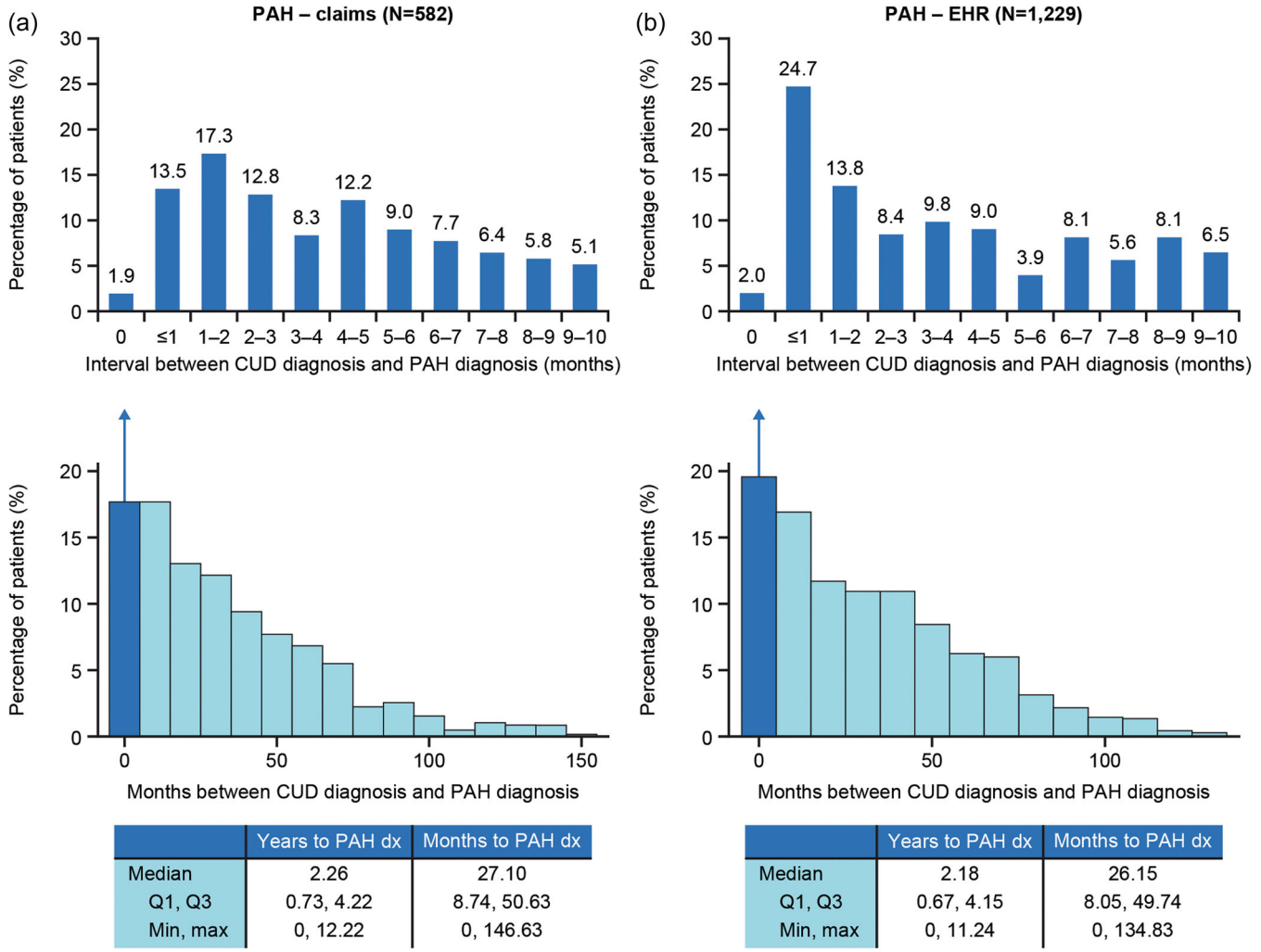
The median time from CUD to PAH diagnosis was over 2 years (Figure 2). This was also true of PH patients (Supporting Information: Figure S2), however, it is important to note that PH develops secondary to an underlying condition in PH Groups 2, 3, and 4 and the point at which these underlying conditions were diagnosed is not captured in this analysis. As expected—given the large overlap in patient population—findings were similar when considering any PH symptom (not only CUD): the median (Q1, Q3) time between onset of any PH symptom and diagnosis was 2.7 (0.8, 5.0) years for PH patients and 2.5 (0.9, 4.6) years for PAH patients in the claims database.

The numbers of PAH patients who had other diagnoses that PAH is often mistaken for (e.g., asthma) or associated with (e.g., PAH secondary to SSc) are shown in Table 2, together with the median time to PAH diagnosis in each of these groups of patients. This analysis did not capture the point at which these (non-PAH) conditions developed. Among these patients, time from CUD to PAH diagnosis was highest in patients with asthma ($n = 87$, 2.5 years), pulmonary fibrosis ($n = 67$, 2.6 years), and SSc ($n = 34$, 2.1 years), according to the claims data. EHR data were broadly similar (Table 2).

Supporting Information: Tables S6 and S7 show the time from CUD to PH/PAH diagnosis according to whether diagnoses were made before or after the 2015 ESC/ERS guidelines were published. The diagnostic interval was significantly longer for patients who were diagnosed on or after 2015 across all patient cohorts. However, statistically significant differences in patient characteristics at diagnosis were also observed. For example, claims data showed that, compared with patients diagnosed in or after 2015, patients diagnosed before 2015 were younger at diagnosis ($p < 0.001$) and a larger percentage of patients were White ($p < 0.01$). Among patients with PAH diagnosed before 2015, the percentage of females was also significantly higher than for those diagnosed in or after 2015 ($p < 0.05$) (Supporting Information: Table S6).

Characterization of the diagnostic interval

On average, patients had approximately 2–3 TTEs between first CUD diagnosis and diagnosis of PH or PAH (Table 3). This analysis did not capture the results of these tests, or any other detailed clinical information, as they were not available in the source data. According to the claims database, PH and PAH patients waited a median of 1.6 and 1.5 months, respectively, from their first CUD diagnosis until a first TTE. However, while



	Years to PAH dx	Months to PAH dx
Median	2.26	27.10
Q1, Q3	0.73, 4.22	8.74, 50.63
Min, max	0, 12.22	0, 146.63

	Years to PAH dx	Months to PAH dx
Median	2.18	26.15
Q1, Q3	0.67, 4.15	8.05, 49.74
Min, max	0, 11.24	0, 134.83

FIGURE 2 Time from diagnosis of CUD to diagnosis of PAH based on insurance claims (a) and EHR (b) database. CUD, chronic unexplained dyspnoea; dx, diagnosis; EHR, electronic health record; PH, pulmonary hypertension; Q, quartile; SD, standard deviation.

approximately 45% of patients (PH and PAH) had a first TTE within 1 month of CUD diagnosis, 34.9% of PH patients and 28.5% of PAH patients waited at least 10 months (Figure 3a,b). Median wait-time until TTE was longer for PH and PAH patients identified in the EHR database (7.7 and 4.4 months, respectively; Figure 3d,e).

The median time to RHC was at least 1.7 years for PAH patients in either database (Figure 3c,f). In the claims database, a total of 6374 PH patients (14.2%) underwent RHC after a median (Q1, Q3) of 2.2 (0.4, 4.5) years following CUD. In the EHR database, 10,581 (16.8%) PH patients underwent RHC with a median (Q1, Q3) time to RHC of 2.2 (0.5, 4.2) years.

In terms of other investigative procedures, PAH patients waited a median (Q1, Q3) of 5.4 (0.2, 22.0) months for CT scan, 4.8 (0.8, 21.1) months for PFT, and 5.2 (0.8, 21.8) months for V/Q scan, according to claims data. The equivalent values from the EHR database were 9.5 (0.7, 32.3), 6.0 (0.6, 25.9), and 6.2 (0.7, 25.6) months, respectively. In the claims database, median (Q1, Q3) wait-times for PH patients were 6.6 (0.1, 29.3) months for a CT scan, 4.6 (0.4, 22.8) months for a PFT, and 4.6 (0.4, 22.7) months for a V/Q scan. EHR data were consistent, with wait-times of 9.5 (0.4, 32.3), 6.0 (0.4, 26.9) and 5.8 (0.4, 26.2) months, respectively. The number of CT scans, PFTs and V/Q scans patients had between CUD diagnosis and PH/PAH diagnosis is shown in Supporting Information: Table S8.

Data on hospitalizations and specialist outpatient visits from the claims and EHR databases are shown in Table 3; there are slight differences between the two databases. In the claims database, PH and PAH patients waited a median of around 2 and 1 months, respectively, from first CUD diagnosis for an outpatient specialist visit (to either a cardiologist or pulmonologist) (Table 3). The interval was longer when only considering first visits to a pulmonologist (approximately 7 months). It is important to note here that specialty was not specified for all

TABLE 2 Time from CUD to PAH diagnosis in patients who were also diagnosed with a condition that could confound PAH diagnosis and/or be associated with PAH

Diagnosis[a]	Number of patients	Median time from CUD diagnosis to given diagnosis, years	Median time from CUD diagnosis to PAH diagnosis, years
Analysis of claims data ($N = 361$)			
Asthma	87	0.15	2.46
COPD	54	0.61	1.54
Coronary artery disease	54	1.24	1.12
Interstitial lung disease	2	0.07	0.56
Left ventricular failure	3	0.03	1.91
Pulmonary embolism	60	0.11	1.36
Pulmonary fibrosis	67	0.11	2.60
Systemic sclerosis	34	0.04	2.13
Analysis of EHR data ($N = 752$)			
Asthma	201	0.08	2.93
COPD	136	0.29	1.86
Coronary artery disease	131	0.83	1.48
Interstitial lung disease	5	0.34	0.38
Left ventricular failure	3	1.92	1.08
Pulmonary embolism	78	0.07	1.68
Pulmonary fibrosis	131	0.08	2.11
Systemic sclerosis	67	0.02	1.81

Abbreviations: COPD, chronic obstructive pulmonary disease; CUD, chronic unexplained dyspnoea; EHR, electronic health record; PAH, pulmonary arterial hypertension.

[a]Patients were required to have two or more diagnoses at least 7 days apart, and time was calculated from the first such diagnosis.

healthcare providers in the database; therefore, some specialist visits may have been missed in this analysis. This limitation could be overcome by applying multiple imputation approaches, but such approaches may also introduce bias, especially if provider information is not missing at random. Between diagnosis of CUD and final PH/PAH diagnosis, patients had a median of four (PH) and six (PAH) outpatient specialist visits, although 25% of patients with PH and 10% of those with PAH had no record of a visit (inpatient or outpatient) to a specialist between CUD and PH diagnosis. During the same interval between CUD and diagnosis, PH/PAH patients experienced a median of two hospitalizations (Table 3).

DISCUSSION

This analysis of two types of US nationwide healthcare databases provides current estimates of the interval between symptom onset and investigations for PH and eventual diagnosis of PH or PAH in the United States. Across PH and PAH, patients in both the claims and EHR databases, approximately 40%–50% underwent TTE within 2 months of first diagnosis of CUD, however, ≥29% waited more than 10 months. Median time between symptom onset and PAH diagnosis was over 2 years and during this interval, claims data showed that half of patients underwent TTE at least three times and were hospitalized at least twice. These results help highlight parts of the diagnostic pathways on which to focus efforts to decrease the diagnostic gap between start of symptoms and diagnosis.

The median diagnostic interval of over 2 years for PAH is consistent with data from registries, including the NIH registry from the 1980s.[4] Registry data from Australia, France, New Zealand and the USA between 2002 and 2017 have shown the average time from symptom onset to PAH diagnosis to be 2.3–3.9 years.[6,8,11,22] A 2019 analysis of a Polish registry found a slightly shorter median interval of 1.5 years, suggestive of improvement; however, 92% of

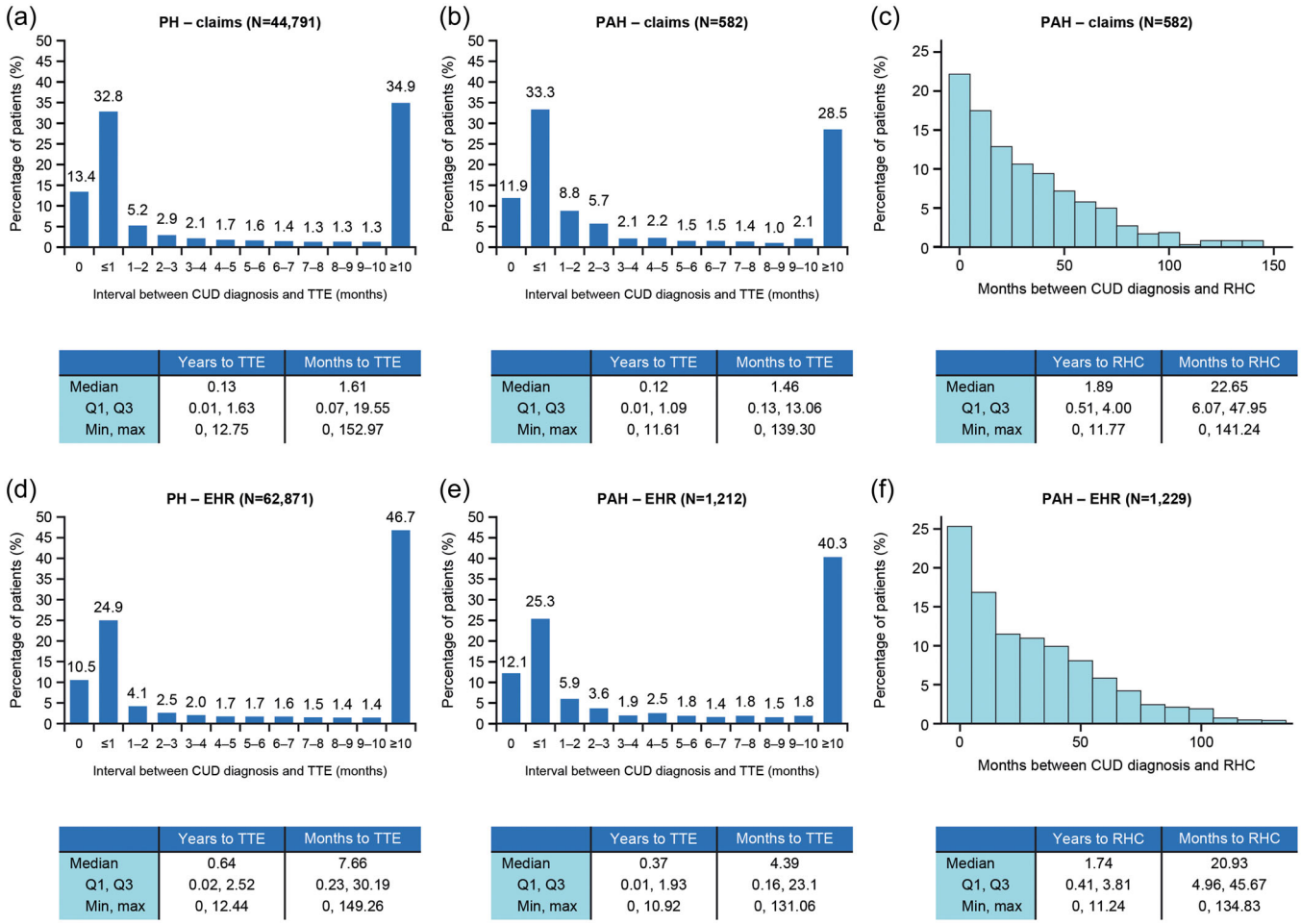
TABLE 3 Healthcare resource utilization during the diagnostic interval for PH and PAH patients in the insurance claims and EHR databases

	Claims database		EHR database	
	PH ($N = 44,809$)	PAH ($N = 582$)	PH ($N = 63,065$)	PAH ($N = 1229$)
No. of TTEs between CUD and PH/PAH dx[a]				
Patients with available data, *n*	44,395	570	62,159	1136
Median (Q1, Q3)	2 (1, 3)	3 (2, 4)	1 (1, 2)	2 (1, 4)
Hospitalizations between CUD diagnosis and PH/PAH diagnosis				
Hospitalizations				
Patients with data available, *n*	42,329	561	58,417	1173
Patients who were hospitalized, *n*	33,652	469	47,098	987
No. of hospitalizations				
Median (Q1, Q3)	2 (1, 4)	2 (1, 4)	2 (1, 5)	3 (1, 5)
Length of stay, days				
Median (Q1, Q3)	5.0 (3.3, 7.0)	5.5 (3.7, 9.0)	1.0 (1.0, 1.5)	1.0 (1.0, 1.2)
Specialist visits—outpatient only				
Patients who visited a specialist, *n*	28,997	475	47,703	1152
No. of visits between CUD and PH/PAH dx				
Median (Q1, Q3)	4 (2, 9)	6 (3, 12)	6 (2, 15)	10 (4, 23)
Months to first specialist visit				
Median (Q1, Q3)	1.5 (0.1, 14.7)	1.2 (0.2, 8.4)	1.0 (0.0, 9.9)	1.0 (0.0, 8.3)
Months to first cardiologist visit				
Median (Q1, Q3)	2.0 (0.2, 17.6)	1.8 (0.3, 14.2)	1.6 (0.1, 14.9)	3.4 (0.3, 17.6)
Months to first pulmonologist visit				
Median (Q1, Q3)	6.9 (0.9, 28.0)	7.1 (1.2, 23.2)	4.5 (0.5, 23.4)	3.9 (0.4, 20.7)

Abbreviations: CUD, chronic unexplained dyspnoea; dx, diagnosis; EHR, electronic health record; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; Q, quartile; TTE, trans-thoracic echocardiogram.

[a]TTEs must be at least 7 days apart.

patients were in WHO FC III/IV at diagnosis.[16] The REVEAL registry also found 72% of PAH patients were in WHO FC III/IV at diagnosis.[17] It is important to acknowledge the limitation that our data are based on administrative codes rather than clinical data. Therefore, we do not know if the entirety of this diagnostic interval represents a delay, or whether PAH developed partway through this period of time for example, secondary to an underlying condition. We examined the time to diagnosis in PAH patients who were also diagnosed with conditions that can be associated with PAH or confound diagnosis of PAH. Of the eight selected diagnoses (asthma, COPD, coronary artery disease, interstitial lung disease, left ventricular failure, pulmonary embolism, pulmonary fibrosis, and SSc), the median time between CUD and PAH diagnosis was less than 2 years for all but three cohorts (SSc, 2.1 years [$n = 34$]; asthma, 2.5 years [$n = 87$]; pulmonary fibrosis, 2.6 years [$n = 67$]) according to claims data. Based on these data, there was no evidence that associated PAH (i.e., PAH developing subsequent to an underlying condition) was skewing the estimation of the diagnostic interval higher. However, we can still not conclude that a diagnostic interval of over 2 years necessarily represents a diagnostic delay of over 2 years without additional data (e.g., clinical test results during the lead up to diagnosis or clinical data on disease severity —neither of which are possible for this analysis). Nevertheless, the long time to PAH diagnosis for patients with asthma (2.5 and 2.9 years in claims and EHR databases, respectively) is consistent with the finding that PAH is often misdiagnosed as asthma.[23] The time-to-TTE data also supports the conclusion that the PAH diagnostic interval represents a delay: although up to around half of patients had a TTE within 2 months of CUD,



	Years to TTE	Months to TTE
Median	0.13	1.61
Q1, Q3	0.01, 1.63	0.07, 19.55
Min, max	0, 12.75	0, 152.97

	Years to TTE	Months to TTE
Median	0.12	1.46
Q1, Q3	0.01, 1.09	0.13, 13.06
Min, max	0, 11.61	0, 139.30

	Years to RHC	Months to RHC
Median	1.89	22.65
Q1, Q3	0.51, 4.00	6.07, 47.95
Min, max	0, 11.77	0, 141.24

	Years to TTE	Months to TTE
Median	0.64	7.66
Q1, Q3	0.02, 2.52	0.23, 30.19
Min, max	0, 12.44	0, 149.26

	Years to TTE	Months to TTE
Median	0.37	4.39
Q1, Q3	0.01, 1.93	0.16, 23.1
Min, max	0, 10.92	0, 131.06

	Years to RHC	Months to RHC
Median	1.74	20.93
Q1, Q3	0.41, 3.81	4.96, 45.67
Min, max	0, 11.24	0, 134.83

FIGURE 3 Time from diagnosis of CUD to first TTE for PH and PAH patients in the insurance claims (a, b) and EHR database (d, e) and time from diagnosis of CUD to first RHC for PAH patients in the claims (c) and EHR database (f). CUD, chronic unexplained dyspnoea; EHR, electronic health record; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; Q, quartile; RHC, right heart catheterization; SD, standard deviation; TTE, trans-thoracic echocardiogram.

approximately 30% waited at least 10 months, despite TTE being recommended for all patients with CUD.[3] In contrast, we cannot draw any conclusions on whether the diagnostic interval in the overall PH cohort (also over 2 years) represents any delay, as this cohort includes many patients in whom PH has developed secondary to another condition (e.g., left heart or lung disease). However, the time-to-TTE data show that there is a delay in the investigation of symptoms in the PH cohort as over a third of patients waited at least 10 months for a TTE. Altogether, these data—which do not capture the additional delay in patients reporting symptoms to their doctor[13,16]—demonstrate that timely diagnosis of PAH remains a major unmet need.

Our data suggest that there is room for improvement in how early PH is considered a possibility by physicians. Efforts to increase awareness of PH among GPs are ongoing and have not yet markedly reduced the diagnostic interval. Development of better tools and strategies for detecting PH, such as the recent InShape II algorithm for detecting CTEPH following pulmonary embolism,[24] the DETECT algorithm for PAH detection in SSc,[25] or enhancement of readily accessible investigative tests with artificial intelligence,[26–28] are key to tackle the delay caused by sequential exclusion of more common causes of dyspnoea.[29]

Only 14% of the PH patients had a procedure code for RHC. The other 86% of patients may include some Group 2 PH patients for whom RHC is not recommended. Even accounting for this, these data do suggest an under-utilization of RHC in PH, and this is consistent with other studies' findings.[30–33]

There were mixed findings in terms of time until a specialist visit. Median wait-time until first cardiologist *or* pulmonologist visit was 1.2 months for PAH patients in the claims database but considerably longer when considering only pulmonologist visits (7.1 months) versus cardiologist visits (1.8 months). It is not

mandatory for patients with suspected or confirmed PH to be referred to a pulmonologist, but respiratory medicine specialists often lead expert PH referral centers in the United States[34,35] and collaborative management of PH by cardiologists and pulmonologists is thought to be ideal.[34,36] The slight differences in findings from the claims database compared with the EHR database (e.g., shorter time-to-first pulmonologist visit) likely reflects differences between the EHR and claims patient populations. The EHR database includes uninsured patients and patients with Medicaid support (i.e., not insured through their employer or Medicare) and there may be gaps in the patients' diagnostic journey. In addition, specialty was not specified for all healthcare providers in the database. Equivalent data on wait-time until specialist visits (and TTE) are not available in the literature; thus, these findings are an important quantification of the time taken to complete these first investigative steps.

An analysis stratifying time to PH/PAH diagnosis according to whether patients received their diagnosis before or after the 2015 ESC/ERS guidelines on PH were released[12] showed that the diagnostic interval was significantly longer post-2015 for all cohorts. However, there were also significant differences in patient characteristics, including race, male:female ratio and age and these are likely partly because there are changes in the data that OPTUM acquire over time. For example, the proportion of Medicare patients (≥65 years old) in the OPTUM claims database has increased since 2015, therefore increasing the median age of the population. This is likely the reason for the relatively high overall age reported herein, compared with other PH cohorts.[22,37] The reasons for the longer interval in the post-2015 group versus the pre-2015 are unknown, and it is not possible to draw conclusions, given the differences between the two patient subpopulations.

In terms of healthcare resource utilization during the diagnostic interval, 54% of patients had multiple TTEs and the median numbers of hospitalizations and specialist visits were 2–3 and 4–10, respectively. The reasons for multiple TTEs are unknown and could simply be due to routine follow-up. However, it is worth noting that there is evidence in the literature that TTEs in patients with suspected PH often do not have PH mentioned in the notes[15] and often do not include relevant parameters of interest for PH,[38] hence, it is possible that TTEs were repeated because the initial TTE did not provide adequate information. In either case, automating TTE interpretation would likely improve the diagnostic pathway.[28] The number of specialist visits in this study is in line with previous data[13,16] including the DELAY study, which reported 3.0 (SD: 2.1) specialist reviews before patients were seen at an expert PH center,[8] and a study of 40 patients with CTEPH, in which patients were found to visit a median of 4 (IQR 4–5) different physicians (GPs and specialists) for a median of 13 (IQR 10–18) consultations before receiving a final PH/PAH diagnosis.[39] However, it is not clear from our data if the visits were with different specialists. Our hospitalization data are approximately in line with the UK study in which the average patient with idiopathic PAH experienced 25 hospital events in the 3 years before diagnosis.[40] Altogether, these findings illustrate the significant burden in the time leading up to diagnosis. Importantly, hospitalizations and specialist visits are opportunities for PH to be detected (if present), therefore, the claims and EHR data could reflect chances being missed across multiple healthcare settings (inpatient, outpatient, primary, and specialist), although clinical data would be needed to investigate this hypothesis.

A key strength of this work is that it uses two of the largest nationwide collections of patients' healthcare data from the United States to generate current and novel estimates of the diagnostic interval and diagnostic burden in PH. A total of 854,722 (claims) and 1,275,854 (EHR) patients with CUD were identified from these databases. The Optum© claims database is a closed data set that collates all insurance claim information on a patient, including diagnoses and procedures, ensuring availability of high-quality information for analysis of diagnostic patient pathways. The claims database records the information of patients over a period of time, including when they switch from Commercial coverage to Medicare coverage, which typically happens at 65 years old (around the average age at PH diagnosis).[41]

A limitation of the claims database is that patients may have switched between insurance plans during the observation period, resulting in a delay in the recording of claims. Other limitations include the lack of historical information available before enrollment in an insurance plan captured in the database, and that these patients cannot be considered truly representative of the United States population as, for example, no Medicaid-covered or uninsured patients were included in the claims database.

Limitations specific to the EHR database include the fact that participating companies change over time, so data availability can vary, and that there are potential gaps in patients' disease journeys (as we cannot be sure if the absence of records reflects that the patient is healthy, or has moved to another country or died, for example). In contrast, in the claims database, the enrollment periods are clearly defined, and all reimbursement-relevant information is usually accurately captured during these enrollment periods. There are some slight differences

between claims and EHR data that may be due to EHR data gaps. For example, the slightly longer time-to-TTE with the EHR cohort versus the claims cohort may result from some procedures being performed outside the EHR network. Overall, there were no major differences between claims and EHR data, suggesting that these results are robust.

An important limitation of the whole analysis is that exact clinical data, test results and detailed physician notes were not available, therefore, we cannot be certain that the whole period in between first CUD diagnosis and first PH or PAH diagnosis represents a delay, as PH may have developed during this interval. This is particularly pertinent for the overall PH cohort, as this cohort includes many patients in which PH has developed secondary to an underlying condition. While we cannot draw any conclusions on whether the diagnosis of PH is delayed, we have reported the length of the diagnostic interval in PH, so it can be used as a benchmark for future studies to compare any change against. We also cannot be certain that we have identified all PH/PAH patients correctly. To minimize the risk of patients being misclassified as PH or PAH patients, we used algorithms that required a composition of procedure, diagnosis, and—for PAH—treatment codes and have been validated using the PheValuator diagnostic predictive modeling tool.[19–21] Such complex algorithms have previously been shown to perform best in terms of specificity and PPV,[20,21] minimizing the inclusion of "false positives," but potentially resulting in conservative estimates of the numbers of PH and PAH patients. Fine-tuning of the algorithm (e.g., in terms of the definition of time windows) was based on the results of extensive sensitivity analyses and on authors' expertize, which included epidemiology, data science and the clinical input of the authors with medical expertize.

The algorithm to identify PH patients did not require a code for RHC; the "qualifying" procedure could be TTE or RHC, whereas RHC was required for all PAH patients. This decision was taken because RHC is not always performed to confirm PH diagnosis; indeed, it is not usually recommended in patients with established, or a high likelihood of left heart disease.[3] The PH algorithm identified 38,435 (85.8%) patients whose PH diagnosis had not been confirmed by RHC, according to the claims data. Some of these patients may have been misclassified, however, we have taken the above-mentioned measures to avoid misidentifying patients.

Other limitations of the analyses include that the data cut-offs for this analysis overlap with the beginning of the COVID-19 pandemic, and elective procedures may have been delayed during this time. Future analyses could examine the diagnostic journey before and during the pandemic to examine its impact.

It is not clear from our data whether—and to what extent—the signs of PH are being missed or misdiagnosed but, nevertheless, development of better tools to detect PH is sure to expedite diagnosis.[29] Future work will examine the drivers of delayed diagnosis and determine which patient profiles tend to be diagnosed early versus late in their disease progression. The impact of delayed diagnosis on resource utilization and outcomes must also be investigated, including a more detailed look at the reasons for hospitalization. Last but not least, these findings should be verified in non-US databases, to get insights into whether and to which extent they might be generalizable across countries and healthcare systems.

CONCLUSIONS

Around one-third of PAH and PH patients waited 10 months following CUD to undergo TTE. In the interval between CUD and PAH diagnosis (over 2 years), PAH patients underwent TTE a median of three times, were hospitalized twice and had six specialist visits, according to claims data. Therefore, our data suggest there is a substantial delay in considering PAH as a possible cause of CUD and investigating accordingly, which results in substantial healthcare resource utilization and adds to the burden for patients in the time leading up to diagnosis.

This study highlights the need to address delays in PAH diagnosis through improvement in screening processes and tools and their use. This would ensure patients receive the treatment and support they require in a timely manner and ultimately improve patient outcomes.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception or design of the analysis, interpretation of the data, and review and approval of the manuscript. Eva-Maria Didden and Eileen Lee performed the analyses. Eva-Maria Didden also contributed to the writing of the manuscript.

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CONFLICTS OF INTEREST

E. M. D., and D. Q. are employees of Janssen Pharmaceutical Companies of Johnson & Johnson and have shares in the company. E. L., J.W., and L.P. were also employees of Janssen Pharmaceutical Companies of Johnson & Johnson at the time of analysis. E. M. D. is the named guarantor of this analysis.

ETHICS STATEMENT

This study did not require informed consent or institutional/ethical review board approval as this study is a noninterventional study based on secondary data use. All aggregated patient data used were compliant with the Health Insurance Portability and Accountability Act of 1996.

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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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