DOI: 10.1002/pul2.12333

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases

Eva-Maria Didden[1] | **Di Lu**[2] | **Andrew Hsi**[3] | **Monika Brand**[1] | **Haley Hedlin**[2] | **Roham T. Zamanian**[3,4]

[1]Global Epidemiology, Rare Disease Epicenter, Actelion Pharmaceuticals Ltd, Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland

[2]Quantitative Sciences Unit, Stanford University, Stanford, California, USA

[3]Adult PH Program, Vera Moulton Wall Center University, Stanford, California, USA

[4]Division of Pulmonary, Allergy, and Critical Care Medicine, Stanford University, Stanford, California, USA

Correspondence
Eva-Maria Didden, Actelion Pharmaceuticals Ltd, Janssen Pharmaceutical Company of Johnson & Johnson, Gewerbestrasse 16, CH-4123 Allschwil, Switzerland.
Email: edidden@its.jnj.com

Funding information
Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson

Abstract

Pulmonary arterial hypertension (PAH) is a rare subgroup of pulmonary hypertension (PH). Claims and administrative databases can be particularly important for research in rare diseases; however, there is a lack of validated algorithms to identify PAH patients using administrative codes. We aimed to measure the accuracy of code-based PAH algorithms against the true clinical diagnosis by right heart catheterization (RHC). This study evaluated algorithms in patients who were recorded in two linkable data assets: the Stanford Healthcare administrative electronic health record database and the Stanford Vera Moulton Wall Center clinical PH database (which records each patient's RHC diagnosis). We assessed the sensitivity and specificity achieved by 16 algorithms (six published). In total, 720 PH patients with linked data available were included and 558 (78%) of these were PAH patients. Algorithms consisting solely of a P(A)H-specific diagnostic code classed all or almost all PH patients as PAH (sensitivity >97%, specificity <12%) while multicomponent algorithms with well-defined temporal sequences of procedure, diagnosis and treatment codes achieved a better balance of sensitivity and specificity. Specificity increased and sensitivity decreased with increasing algorithm complexity. The best-performing algorithms, in terms of fewest misclassified patients, included multiple components (e.g., PH diagnosis, PAH treatment, continuous enrollment for ≥6 months before and ≥12 months following index date) and achieved sensitivities and specificities of around 95% and 38%, respectively. Our findings help researchers tailor their choice and design of code-based PAH algorithms to their research question and demonstrate the importance of including well-defined temporal components in the algorithms.

KEYWORDS
administrative codes, clinical database, electronic health records, pulmonary arterial hypertension, pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is a progressive, life-threatening disease that is characterized by elevated mean pulmonary artery pressure and classified into five subgroups based on underlying etiology.[1] A diagnosis of Group 1 PH, pulmonary arterial hypertension (PAH), is made by excluding other possible causes of PH (e.g., pulmonary artery obstructions [Group 4 PH]) and should be confirmed using right heart catheterization (RHC), the gold standard diagnostic test.[1] PAH is an incurable, treatable, rare condition that is subgrouped further into idiopathic and hereditary cases, and cases associated with either another condition such as systemic scleroderma, or with the use of certain drugs and toxins.[1] The prevalence of PAH varies by country and was recently estimated to be 48–55 patients per million adults,[2] with idiopathic PAH accounting for around 30%–50% of all PAH cases.[3–5]

Research into rare diseases is challenging and data are often from disparate sources with low patient numbers. As such, administrative databases, including health insurance claims or Electronic Health Record (EHR) databases—which collect information from large, representative samples of the population—can support observational research in PAH.[6] Generating meaningful results from such observational healthcare databases relies on the accurate identification of patients based on administrative codes (e.g., for diagnoses, procedures or treatments). Correctly identifying patients of interest can be difficult as diagnostic codes are not always recorded and they do not necessarily correspond to a clinical diagnosis.[2] Rather, they are mainly a billing tool, entered for reimbursement purposes; they are not used to convey medical decision-making or the exact clinical scenario. For example, a PH diagnostic code may be entered to ensure reimbursement for a procedure to investigate the possible presence of PH. In addition, diagnostic codes for the five different subgroups of PH[1]—including PAH—were not available until October 2017[7] and there is often a delay between the introduction of a new code and its use by healthcare professionals.

Administrative codes are often combined into code-based algorithms (code sequences) to better identify patients. However, using combinations of codes does not resolve every issue: identifying PAH patients using drug codes can be imprecise since PAH-specific therapies may be used for off-label treatment of other PH Groups[1,8,9] and some PAH drugs are approved for other indications.[6] Additionally, although guidelines state a diagnosis of PAH must be confirmed by RHC[1] and it would therefore seem logical to identify PAH patients using procedure codes, not all PAH patients undergo invasive RHC.[10] For example, in under-resourced settings, PAH patients may be "diagnosed" using transthoracic echocardiography (which is only recommended to determine the probability of PH),[1] and some PAH patients may not be well enough to undergo RHC.[1] A previous study conducted a systematic literature search for PAH algorithms and assessed their performance in three US claims databases using PheValuator,[11] a diagnostic modeling tool. Specificity was high for all algorithms, but the positive predictive value (PPV) of the algorithms varied from 13% to 66%, depending on the complexity of the algorithm.[12] Studies to validate PAH algorithm performance, particularly against clinical data, are lacking and the relative performance of these algorithms remains unclear.

In our analysis, we aimed to measure the accuracy of PAH algorithms against true clinical diagnoses by using a coded US EHR database with patient-level linkage to a clinical PH database, in which all patients had a recorded RHC. We also compared our approach and key findings with those using PheValuator.[12] The ultimate aim of the study was to develop guidance on the use of code-based algorithms for PAH patient identification.

METHODS

Study design

The cross-sectional observational cohort study evaluated code-based PAH algorithms using patient data recorded in two linkable data assets: the Stanford Healthcare administrative EHR database and the Stanford Vera Moulton Wall Center (VMWC) clinical PH database. Data for the VMWC PH database are collected on a regular basis from electronic medical records of patients attending the Stanford University Medical Center and, as such, represent the true diagnosis of patients. All patients are clinically reviewed by experts in PH and phenotyped as having PH. The Stanford EHR database uses: International Classification of Disease (ICD) 9/10 codes for diagnoses; Current Procedural Terminology (CPT), ICD9/10 and HCPCS codes for procedures; and written generic or brand names for medications.

Study population

Eligible patients were adults with a confirmed PH diagnosis (mean pulmonary artery pressure ≥25 mmHg, per the definition used by the 2015 European Society of Cardiology/European Respiratory Society guidelines, which were the current guidelines at the time of study),[13] based on ≥1 RHC performed at Stanford VMWC. Patients

must have had ≥6 months of observation (with ≥1 visit in that time) after their first RHC at Stanford VMWC, unless they died, in which case they must have had ≥1 visit between the first RHC and death. Patients were only eligible if their VMWC clinical records could be linked to the Stanford EHR database, that is, if they had records in both the clinical and the EHR database. This was done using a study identifier mapped to the patients' medical record numbers. Only records occurring after the EHR became fully operational in January 2010 were included; patients who underwent RHC before this time were excluded.

Code-based algorithms

This analysis tested six of the published code-based algorithms previously validated using PheValuator (Table 1).[12] The other algorithms tested using PheValuator[12] could not be validated because they either required users to be able to distinguish between in- and outpatient claims (and this level of detail was not available in the Stanford EHR database) or they contained administrative codes that were not used in the Stanford EHR database (e.g., 416.9 for *chronic pulmonary heart disease, unspecified*). Most of these algorithms lacked or did not define temporal components (e.g., maximum time between procedure and diagnosis), and only one included a procedure (which was not an additional requirement; it was included as an alternative way for a patient to qualify if they did not have a diagnostic code for PH) (Table 1). The present study planned to refine the best-performing of these six algorithms, and these modifications included the addition of temporal components as well as mandatory diagnostic and procedure codes. The performance of these proposed algorithms (also shown in Table 1) was also tested. The codes used in this analysis are listed in Supporting Information S1: Table S1. PAH treatments were defined as ambrisentan, bosentan, macitentan, epoprostenol, iloprost, selexipag, treprostinil, sildenafil, tadalafil, riociguat. ICD9 codes in published algorithms were translated to ICD10 equivalents for this analysis.

Study outcomes

The primary objective was to determine the number of correctly and incorrectly classified patients for each algorithm, and to calculate sensitivity, specificity, PPV, and negative predictive value (NPV) from these numbers. "True" PAH patients were those that had a PAH diagnosis in the clinical database. A secondary objective was to assess the performance of each algorithm for identification of patients with PAH when excluding those who also had a PH Group 2–5 diagnosis in the clinical database (Group 2 PH: PH due to left heart disease, Group 3 PH: PH due to lung disease and/or hypoxia, Group 4 PH: PH due to pulmonary artery obstructions, Group 5 PH: PH with unclear and/or multifactorial mechanisms).[1] This analysis allowed us to assess the performance of the algorithms in identifying PAH patients who had no other PH-associated conditions. We also compared our methodology and findings with those using PheValuator. The differences in methodology between these studies are summarized in Supporting Information S1: Table S2, with key differences being in the patient population (Sprecher et al. assessed the general population, while our validation work assessed the PH population), PAH prevalence in the databases (much lower in the database used by Sprecher et al. compared with ours), and the method used to identify "true" PAH patients (RHC-confirmed diagnosis in our study and PheValuator mathematical modeling in Sprecher et al.).[12]

Study analysis

We compared the algorithms' sensitivity, specificity, PPV and NPV, calculated as described in Supporting Information S1: Figure S1. The gold standard was the clinical result and judgment (i.e., RHC-confirmed diagnosis) documented in the VMWC database. We presented 95% confidence intervals (calculated using the Wald method) for all estimates of algorithm performance. The patient characteristics of true positives and true negatives identified by a group of selected algorithms (selected since they represent a range of sensitivities and specificities) were compared with the total cohort of PAH and non-PAH patients, respectively. All analyses were performed in SAS version 9.4 (SAS Institute) and R version 4.1.1 software (R Project for Statistical Computing).[20]

RESULTS

A total of 720 RHC-confirmed patients with PH had linked data available and were included in the analysis; of these, 558 (78%) were patients with PAH (Figure 1). Among these PAH patients, 141 (25%) were also diagnosed with another PH Group at some point in their medical history (Supporting Information S1: Table S3).

Baseline characteristics for PAH and other PH patients are presented in Table 2. Compared with other

TABLE 1 Published PAH algorithms for assessment.

Algorithm ID	Algorithm	Example publication, PMID
Published PAH algorithms		
1	≥1 primary PH ICD code	27851838[14]
2	≥1 primary PH or other secondary PH/pulmonary heart disease ICD code	28678692[15]
3	≥1 primary PH, secondary PH/pulmonary heart disease or chronic pulmonary heart disease ICD code	28762848[16]
	OR ≥ 1 RHC	
	AND ≥ 1 PAH treatment	
4	≥1 primary PH, secondary PH/pulmonary heart disease or chronic pulmonary heart disease ICD code	29485908[17]
	AND ≥ 1 ICD code for PAH-associated diseases	
	AND ≥ 1 PAH treatment	
	AND no ICD codes for Group 2–5 PH-associated diseases	
	AND first diagnosis claim must be before first pharmacy claim	
5	≥1 primary PH, secondary PH/pulmonary heart disease or chronic pulmonary heart disease ICD code	30566510[18a]
	AND ≥ 1 calcium channel blocker ***OR*** ≥ 1 PAH treatment	
	AND no ICD codes for Group 2–5 PH-associated diseases	
6	≥1 primary PH, secondary PH/pulmonary heart disease or chronic pulmonary heart disease ICD code in 6 months before index date	30421652[19]
	AND ≥ 1 PAH treatment (first = index date)	
	AND continuous enrollment for ≥6 months before and ≥12 months following index date	
Proposed (unpublished) PAH algorithms		
7	≥1 primary PH ICD code	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND ≥ 1 diagnostic code must be within 180 days following RHC/TTE	
7b	≥1 primary PH ICD code	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND no ICD codes for Group 2–5 PH-associated disease	
	AND ≥ 1 diagnostic code must be within 180 days following RHC/TTE	
8	≥1 primary PH ICD code	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND ≥ 1 diagnostic code must be within 365 days following RHC/TTE	
9	≥2 primary PH or other secondary PH/pulmonary heart disease ICD codes	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND ≥ 1 of the primary/secondary PH diagnosis ICD codes within 180 days after RHC/TTE	
9b	≥2 primary PH or other secondary PH/pulmonary heart disease ICD codes	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND no patients with Group 2–5 PH-associated disease ICD codes	
	AND ≥ 1 of the primary/secondary PH ICD codes within 180 days after RHC/TTE	

TABLE 1 (Continued)

Algorithm ID	Algorithm	Example publication, PMID
10	≥2 primary PH or other secondary PH/pulmonary heart disease ICD codes	N/A
	AND ≥ 1 RHC	
	AND ≥ 1 PAH treatment	
	AND ≥ 1 of the primary/secondary PH ICD codes within 180 days after RHC	
11	≥1 primary PH ICD code	N/A
	AND ≥ 1 RHC	
	AND ≥ 1 PAH treatment	
	AND ≥ 1 diagnostic code must be within 180 days following RHC	
12	≥1 primary PH or other secondary PH/pulmonary heart disease ICD code	N/A
	AND ≥ 1 RHC ***OR*** ≥ 1 TTE	
	AND ≥ 1 PAH treatment	
	AND PAH treatment must be after RHC/TTE	
13	≥1 primary PH, secondary PH/pulmonary heart disease or chronic pulmonary heart disease ICD code	N/A
	AND ≥ 1 RHC	
	AND ≥ 1 PAH treatment	
	AND RHC must be followed by treatment record and pharmacy claim must be within 60 days of RHC	
13b	≥1 primary PH or other secondary PH/pulmonary heart disease ICD code	N/A
	AND ≥ 1 RHC	
	AND ≥ 1 PAH treatment	
	AND RHC must be followed by treatment record and pharmacy claim must be within 60 days of RHC	

Note: Color coding—blue, diagnosis code; green, procedure code; yellow, pharmacy claim; orange, exclusionary code; grey, temporal component. ICD9 codes in published algorithms were translated to ICD10 equivalents.

Abbreviations: ICD, International Classification of Diseases; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PMID, PubMed identification; RHC, right heart catheterization; TTE, transthoracic echocardiography.

[a]Song et al. also exclude patients with comorbidities associated with secondary PAH (e.g., PAH associated with connective tissue diseases); however, as we are not aiming to identify idiopathic PAH, we did not use this part of the algorithm in our analysis.

PH patients, PAH patients were younger on average (mean age at RHC: 49.8 vs. 63.7 years) and a higher percentage were female (75.3% vs. 54.9%).

Performance of published algorithms

Table 3 shows the performance of the six published PAH algorithms in distinguishing all PAH patients (i.e., all those with a PAH diagnosis, regardless of whether they also had another PH Group diagnosis) from other PH patients, and Table 4 shows the equivalent data when excluding PAH patients who also had another PH Group diagnosis in the database. The findings were very similar regardless of the exact specification of the PAH cohort, that is, all PAH or PAH-only. Hereafter, we describe performance in the all-PAH group, unless otherwise stated.

The most inclusive algorithm, Algorithm 2, which required at least one ICD code related to primary or secondary PH, had the highest sensitivity and lowest specificity. With increasing algorithm complexity, sensitivity decreased and specificity increased. The two algorithms that excluded patients with codes for disease associated with Group 2–5 PH (Algorithms 4 and 5) performed best in terms of specificity (0 false positives,

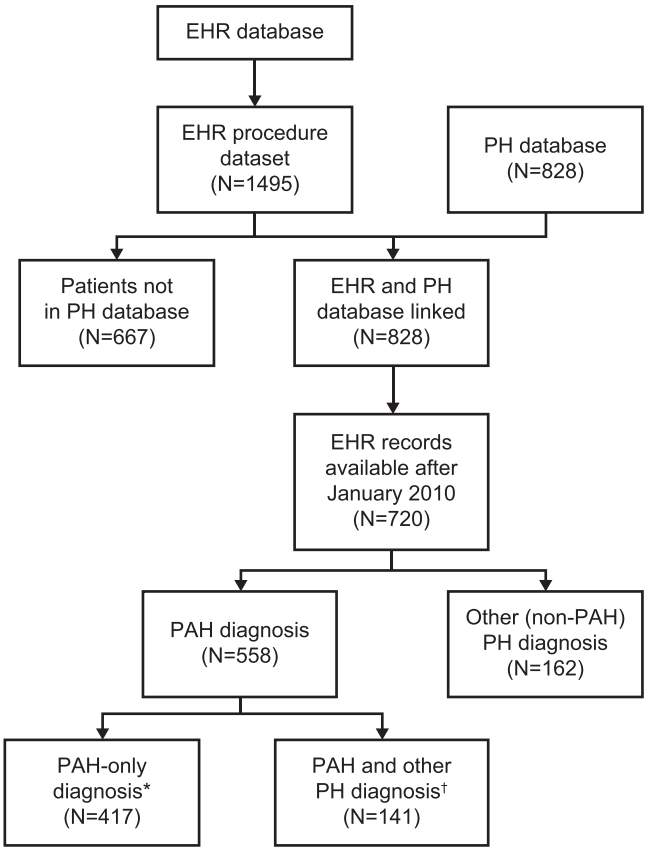

FIGURE 1 Study cohort derivation flow diagram. *Patients with a PAH diagnosis and no PH WHO Group II–V diagnosis at any point in their medical history. †Patients with a PAH diagnosis and a PH WHO Group II–V diagnosis at any point in their medical history. EHR, electronic health record; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO, World Health Organization.

specificity: 100%) but missed over 90% of true PAH patients (sensitivity 4%–7%) (Table 3, and Supporting Information S1: Table S4). Algorithms 3 and 6, which included multiple components, performed better in terms of achieving reasonable sensitivity (95%) as well as specificity (38%) (Supporting Information S1: Table S3). However, they still falsely classified 126 of 720 (17.5%) patients as PAH or other PAH (Supporting Information S1: Table S4).

The corresponding PPVs ranged from 78% (Algorithm 2, most inclusive) to 100% (Algorithms 4 and 5), and NPVs ranged from 0% (Algorithm 2) to 70.4% (Algorithms 3 and 6) (Table 3). It should be noted that PPVs are directly proportional to disease prevalence (and NPVs inversely proportional); as such, PPVs are uniformly high in this database of 78% PAH patients.

TABLE 2 Patient demographics and characteristics at the time of PH/PAH diagnosis, unless otherwise stated.

Demographic/ characteristic	Total PH cohort ($N = 720$) PAH ($n = 558$)	Other PH ($n = 162$)
Mean (SD) age at RHC, years	49.82 (15.90)	63.65 (13.12)
Female, *n* (%)	420 (75.3)	89 (54.9)
Race, *n* (%)		
White	291 (52.2)	87 (53.7)
Asian	65 (11.6)	15 (9.3)
Black	29 (5.2)	18 (11.1)
Hawaiian or Pacific Islander	9 (1.6)	1 (0.6)
Native American	7 (1.3)	1 (0.6)
Other	124 (22.2)	31 (19.1)
Unknown	33 (5.9)	9 (5.6)
Ethnicity, *n* (%)		
Hispanic or Latino	109 (19.5)	22 (13.6)
Not Hispanic or Latino	406 (72.8)	133 (82.1)
Unknown	43 (7.7)	7 (4.3)
PH subgroup diagnosis,[a] *n* (%)		
Group 1 PH	558 (100.0)	0 (0)
Group 2 PH	62 (11.1)	85 (52.5)
Group 3 PH	111 (19.9)	82 (50.6)
Group 4 PH	12 (2.2)	41 (25.3)
Group 5 PH	16 (2.9)	26 (16.0)
Mean (SD) BMI, kg/m^2	28.96 (7.73)	31.57 (8.62)
NYHA FC, *n* (%)		
I/II	137 (24.6)	32 (19.8)
III/IV	336 (60.2)	105 (64.8)
Missing	85 (15.2)	25 (15.4)
Mean (SD) 6MWD, m	360.72 (144.92)	313.31 (137.62)
Mean (SD) RAP, mmHg	9.26 (5.27)	10.78 (4.93)
Mean (SD) PAP, mmHg	49.90 (14.77)	40.96 (11.71)
Mean (SD) PAWP, mmHg	11.28 (4.77)	15.72 (6.53)
Mean (SD) CO, L/min[b]	3.84 (1.42)	4.30 (1.50)

TABLE 2 (Continued)

Demographic/ characteristic	Total PH cohort ($N = 720$) PAH ($n = 558$)	Other PH ($n = 162$)
Mean (SD) CI, L/min/m^2[b]	2.12 (0.70)	2.20 (0.65)
Mean (SD) PVR, WU[b]	11.44 (6.48)	6.94 (4.44)

Note: Group 1 PH, PAH; Group 2 PH, PH due to left heart disease; Group 3 PH, PH due to lung disease and/or hypoxia; Group 4 PH, chronic thromboembolic PH; Group 5 PH, PH due to unclear multifactorial mechanisms.

Abbreviations: 6MWD, 6-min walk distance; BMI, body mass index; CI, cardiac index; CO, cardiac output; PAP, pulmonary arterial pressure; NYHA FC, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance measured; RAP, right atrial pressure; RHC, right heart catheterization; SD, standard deviation; WU, wood units.

[a]Patients could have more than one PH group diagnosis in their records (e.g., Group 1 PAH and Group 3 PH), hence the percentages may sum to over 100%.

[b]Measured by Fick method.

Performance of additional proposed (unpublished) algorithms

The performance of the proposed additional (unpublished) PAH algorithms is shown in Table 3. As observed with the published algorithms, simpler algorithms (Algorithms 7, 8, and 9) were more sensitive and less specific than more complex algorithms and vice versa, with algorithms involving exclusionary codes being the most specific and least sensitive ones (Algorithms 9b and 7b). Algorithms performed similarly regardless of whether they were distinguishing PAH-only (Table 4) or all PAH (Table 3) from other PH.

Several algorithms demonstrated a balance between sensitivity and specificity, as displayed in the sensitivity-specificity plot (Figure 2a). Algorithms 3 (PAH treatment and either PH diagnosis or RHC procedure code) and 6 (PH diagnosis, PAH treatment and continuous enrollment for a specified length of time) performed best in terms of fewest misclassified patients (Supporting Information S1: Table S4). The sensitivity-specificity plot helps illustrate the "redundant" algorithms that have worse sensitivity and specificity than similar algorithms. For example, while Algorithms 11 and 12 both have a balance of sensitivity and specificity, Algorithm 11 outperforms Algorithm 12 in both measures.

Algorithms 1, 3, 5, 8, 11, and 13b were selected for further assessment as they provide a range across the sensitivity-specificity plot. Alluvial plots showing change in performance for the selected algorithms are shown in Figure 2b. Algorithm 8, as the most sensitive and least specific of those selected, identified the highest percentage of true positives (77%), but also the highest percentage of false positives (22%). Algorithm 5, at the opposite end of the spectrum, identified the fewest true positives (5%) and the most negatives—both true (23%) and false (72%) negatives. Algorithms 3 and 11 perform better in terms of balancing the need for reasonable sensitivity and specificity. Figure 2c,d illustrates the effect of excluding codes for disease associated with PH Groups 2–5. Algorithms 7 and 9 identify almost all patients as PAH with a consequently high percentage of false positives; Algorithms 7b and 9b identify the vast majority of patients as other PH with a high percentage of false negatives due to the addition of exclusionary codes.

Characteristics of true positives and true negatives identified by selected algorithms

Supporting Information S1: Table S5 shows the patient characteristics of true positives identified by the selected algorithms (1, 3, 5, 8, 11, and 13b) compared with the total cohort of true PAH patients. The various cohorts of true positives were broadly consistent with the total cohort of PAH patients, except for the smallest cohort identified by Algorithm 5 ($n = 38$), with patients slightly younger, who had a higher 6-min walk distance and lower NT-proBNP levels on average, and a lower percentage were white. The characteristics of true negatives versus the total other PH (non-PAH) cohort are shown in Supporting Information S1: Table S6. Characteristics were again broadly similar, with the exception of the smallest cohorts of true negatives identified by Algorithms 8 ($n = 3$) and 1 ($n = 19$). None of these patients identified by Algorithms 1 and 8 were in New York Heart Association functional class (NYHA FC) I or II, whereas 25% of the full PAH cohort were in NYHA FC I/II.

DISCUSSION

Summary of findings

Researchers have designed and used a wide range of code-based algorithms for identification of PAH patients in administrative databases; however, data on the accuracy of the proposed algorithms are largely lacking. This study evaluated the performance of 16 PAH algorithms in a coded US EHR database linked with a clinical PH database, in which all patients had

TABLE 3 Performance of code-based algorithms for identification of all PAH patients in database (including those with a PH Group 2–5 diagnosis), as measured by RHC, ranked by sensitivity.

Algorithm ID	Algorithm includes					Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	Dx	RHC/ TTE	Rx	Excl	🕒				
Published algorithms									
2						1.000 (0.993, 1.000)	0.000 (0.000, 0.000)	0.775 (0.742, 0.805)	0.000 (0.000, 0.000)
1						0.978 (0.962, 0.988)	0.117 (0.072, 0.177)	0.792 (0.760, 0.822)	0.613 (0.421, 0.781)
6						0.953 (0.932, 0.969)	0.383 (0.307, 0.462)	0.841 (0.810, 0.869)	0.704 (0.597, 0.797)
3						0.953 (0.932, 0.969)	0.383 (0.307, 0.462)	0.841 (0.810, 0.869)	0.704 (0.597, 0.797)
5						0.068 (0.048, 0.092)	1.000 (0.977, 1.000)	1.000 (0.907, 1.000)	0.237 (0.206, 0.271)
4						0.041 (0.026, 0.061)	1.000 (0.977, 1.000)	1.000 (0.851, 1.000)	0.232 (0.201, 0.265)
Proposed (unpublished) algorithms									
9						0.998 (0.990, 1.000)	0.000 (0.000, 0.000)	0.775 (0.742, 0.804)	0.000 (0.000, 0.000)
7						0.996 (0.987, 0.999)	0.018 (0.003, 0.053)	0.777 (0.745, 0.807)	0.600 (0.146, 0.947)
8						0.996 (0.987, 0.999)	0.018 (0.003, 0.053)	0.777 (0.745, 0.807)	0.600 (0.146, 0.947)
10						0.944 (0.922, 0.961)	0.383 (0.307, 0.462)	0.840 (0.809, 0.868)	0.666 (0.561, 0.761)
11						0.845 (0.813, 0.874)	0.562 (0.481, 0.639)	0.869 (0.837, 0.896)	0.514 (0.438, 0.589)
12						0.774 (0.737, 0.808)	0.488 (0.408, 0.567)	0.838 (0.804, 0.869)	0.385 (0.318, 0.455)
13						0.509 (0.466, 0.551)	0.617 (0.537, 0.692)	0.821 (0.776, 0.859)	0.267 (0.223, 0.315)
13b						0.509 (0.466, 0.551)	0.617 (0.537, 0.692)	0.821 (0.776, 0.859)	0.267 (0.223, 0.315)
7b						0.069 (0.050, 0.094)	1.000 (0.977, 1.000)	1.000 (0.909, 1.000)	0.237 (0.206, 0.271)
9b						0.068 (0.048, 0.092)	1.000 (0.977, 1.000)	1.000 (0.907, 1.000)	0.237 (0.206, 0.271)

Note: These results are based on a PH population with a PAH prevalence of 78%. Clock symbolizes temporal component. Red borders are to highlight high sensitivities and specificities.

Abbreviations: CI, confidence interval; Dx, diagnostic code; Excl, exclusionary codes; NPV, negative predictive value; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPV, positive predictive value; RHC, right heart catheterization; Rx, pharmacy claim; TTE, transthoracic echocardiography.

undergone RHC and, as such, is the first study of its kind. The accuracy of algorithms varied widely and several of the PAH algorithms had either very low specificity (<0.20) and high sensitivity (>0.95) or very low sensitivity (<0.10) and high specificity (1.00) in this PH database (with 78% PAH patients). Some of the algorithms in the literature perform better than others, regardless of the measure used. Specifically, Algorithm 11 clearly outperforms Algorithm 12 in terms of both sensitivity and specificity, as illustrated in Figure 2a. Figure 2a also shows that Algorithm 5 is a slightly better choice than Algorithm 4, and that Algorithms 3 and 6 perform slightly better than Algorithm 10. There were a number of algorithms that showed a reasonable balance for sensitivity and specificity, and most of these consisted of well-defined temporal sequences of procedure, diagnosis, and treatment codes (Algorithms 3, 6, 11, 12, 13, and 13b). This finding is in line with expert recommendations for PAH algorithm development.[21] Notably, only two of these six balanced algorithms (Algorithms 3 and 6) were published at the time of the study. Therefore, this suggests that the algorithms currently described in the literature may require additional fine-tuning.

TABLE 4 Performance of code-based algorithms for PAH identification, when excluding those PAH patients who also have a PH Group 2–5 diagnosis, as measured by RHC, ranked by sensitivity.

Algorithm ID	Algorithm includes					Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	Dx	RHC/ TTE	Rx	Excl	🕒				
Published algorithms									
2	■					1.000 (0.991, 1.000)	0.000 (0.000, 0.000)	0.720 (0.681, 0.756)	0.000 (0.000, 0.000)
1	■					0.973 (0.953, 0.986)	0.117 (0.072, 0.177)	0.739 (0.700, 0.775)	0.633 (0.438, 0.800)
6	■		■		■	0.966 (0.944, 0.981)	0.383 (0.307, 0.462)	0.801 (0.763, 0.835)	0.815 (0.710, 0.895)
3	■	■	■			0.966 (0.944, 0.981)	0.383 (0.307, 0.462)	0.801 (0.763, 0.835)	0.815 (0.710, 0.895)
5	■		■	■		0.083 (0.059, 0.114)	1.000 (0.977, 1.000)	1.000 (0.900, 1.000)	0.297 (0.259, 0.338)
4	■		■	■	■	0.050 (0.031, 0.076)	1.000 (0.977, 1.000)	1.000 (0.838, 1.000)	0.290 (0.253, 0.329)
Proposed (unpublished) algorithms									
9	■	■			■	0.997 (0.986, 0.999)	0.000 (0.000, 0.000)	0.720 (0.681, 0.756)	0.000 (0.000, 0.000)
7	■	■			■	0.995 (0.982, 0.999)	0.018 (0.003, 0.053)	0.723 (0.684, 0.759)	0.600 (0.146, 0.947)
8	■	■			■	0.995 (0.982, 0.999)	0.018 (0.003, 0.053)	0.723 (0.684, 0.759)	0.600 (0.146, 0.947)
10	■	■	■		■	0.954 (0.929, 0.972)	0.383 (0.307, 0.462)	0.799 (0.761, 0.833)	0.765 (0.658, 0.852)
11	■	■	■		■	0.853 (0.816, 0.886)	0.562 (0.481, 0.639)	0.833 (0.795, 0.867)	0.599 (0.516, 0.677)
12	■	■	■		■	0.777 (0.733, 0.816)	0.488 (0.408, 0.567)	0.796 (0.753, 0.834)	0.459 (0.383, 0.536)
13	■	■	■		■	0.494 (0.445, 0.543)	0.617 (0.537, 0.692)	0.768 (0.713, 0.817)	0.321 (0.269, 0.376)
13b	■	■	■		■	0.494 (0.445, 0.543)	0.617 (0.537, 0.692)	0.768 (0.713, 0.817)	0.321 (0.269, 0.376)
7b	■	■		■	■	0.086 (0.061, 0.117)	1.000 (0.977, 1.000)	1.000 (0.902, 1.000)	0.298 (0.260, 0.338)
9b	■	■		■	■	0.083 (0.059, 0.114)	1.000 (0.977, 1.000)	1.000 (0.900, 1.000)	0.297 (0.259, 0.338)

Note: These results are based on a PH population with a PAH prevalence of 72%. Clock symbolizes temporal component.

Abbreviations: CI, confidence interval; Dx, diagnostic code; Excl, exclusionary codes; NPV, negative predictive value; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPV, positive predictive value; RHC, right heart catheterization; Rx, pharmacy claim; TTE, transthoracic echocardiography.

Findings in context of other literature

Our findings complement previous validation work which used PheValuator—a diagnostic predictive modeling tool—as the ground truth.[12] As the study by Sprecher et al. was conducted in a general population, in which PAH is rare (in contrast to our study of a PH database with a disproportionately high percentage of PAH patients) (Supporting Information S1: Table S2), the actual performance metrics are not directly comparable. However, although the sensitivity-specificity trade-off was less pronounced in the PheValuator study than reported here (wherein some algorithms had a sensitivity of 0.000 and a specificity of exactly 1.000), both studies demonstrated that sensitivity decreases and specificity increases with increasing algorithm complexity. As such, the most inclusive algorithm (Algorithm 2; ≥1 diagnostic code for primary PH or other secondary PH/pulmonary heart disease) was the most sensitive algorithm in both studies,[12] and the least specific algorithm in our study as it identified all PH patients as PAH patients. Therefore, this algorithm is unlikely to be useful as a PAH algorithm in most research. This is in line with other previous validation work.[6,22,23] Of the multicomponent algorithms assessed by Sprecher et al.,

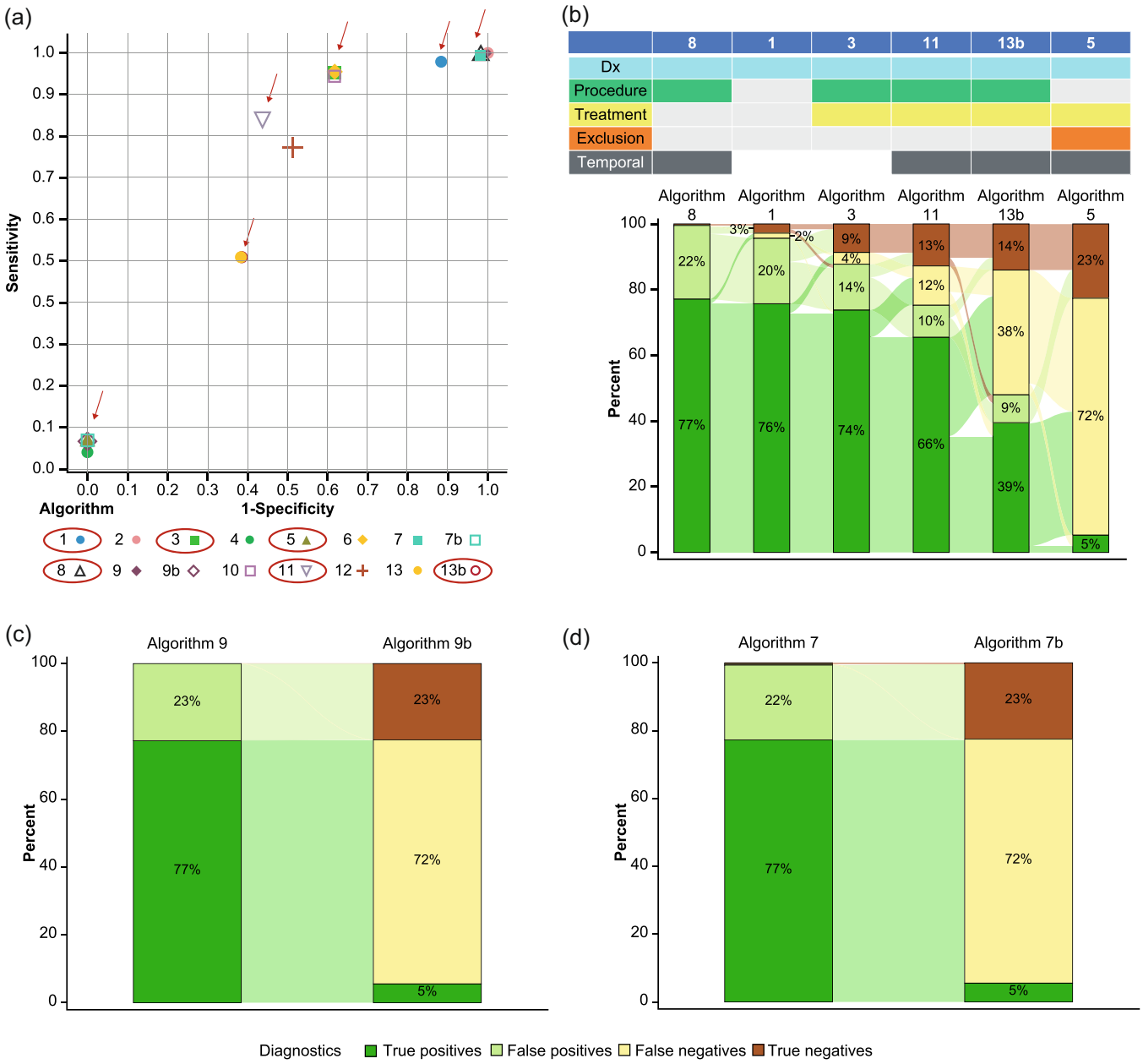

FIGURE 2 Further investigation of selected algorithms. (a) Sensitivity-specificity plot of all algorithms, with an arrow indicating algorithms selected for further investigation, (b) Alluvial plot for selected algorithms (selected to represent a range across the sensitivity-specificity plot) showing the change in performance associated with different algorithms and their components, (c, d) the impact of adding exclusionary codes to the performance of Algorithms 9 (c) and 7 (d).

Algorithms 3 and 6 demonstrated mid-range sensitivity and PPVs.[12] This is also in line with our observation that—in terms of balanced performance—these algorithms were the best of the six published algorithms that we assessed. Both studies also identified the algorithms that used exclusionary codes (Algorithms 4 and 5) as the least sensitive algorithms.

Other validation works by Papani et al.[23] and Gillmeyer et al.[6] also support the finding that multi-component algorithms performed best across all performance parameters. Papani et al. developed a set of algorithms using the EHRs from the University of Texas Medical Branch (PAH prevalence, 28%), and validated them in the University of Virginia Health System (15.8% prevalence). They found that algorithms including ICD codes, EHR encounter diagnosis (initial diagnosis/suspicion at first clinic visit), procedure codes for RHC and transthoracic echocardiography, and PAH-specific medications performed best (in terms of sensitivity and PPV) compared with ICD codes alone, ICD plus PAH medication, and ICD plus EHR encounter diagnosis plus PAH

medication.[23] Gillmeyer et al. developed and validated a set of increasingly complex algorithms in all Veterans Health Administration hospitals and the Boston Medical Center. Each algorithm was validated using clinical data from a random sample of 50 patients from the corresponding database. Gillmeyer et al.[6] found that ICD codes alone performed poorly, the addition of RHC code led to slight improvements in PPV, and the best performing algorithm in both settings included PAH medications and RHC.

While some algorithms are unquestioningly less suitable than other algorithms in most research, it is not possible to identify or recommend a "universal" PAH algorithm for all research, from our or any other validation study, as the choice of algorithm should always be aligned with the research question being investigated. However, these study findings can help researchers determine the algorithm that is most fit-for-purpose. For example, for studies that require the PAH cohort to contain as few non-PAH patients as possible (e.g., to compare time-to-diagnosis between PAH patients and patients with other types of pulmonary heart diseases), researchers should consider a complex algorithm with high specificity. However, researchers should be aware that exclusionary codes will remove many PAH patients with comorbidities, thus sacrificing sensitivity for specificity and including a selection bias that limits generalizability of results. Therefore, algorithms that combine multiple components, such as diagnostic, procedure, and treatment codes plus a temporal component (e.g., Algorithms 11 and 13) may be assessed against those that use exclusionary codes (e.g., Algorithm 9b). In contrast, a simpler algorithm with high sensitivity may be appropriate in other studies where a large, diverse pool of PAH patients is required as a "baseline" cohort, from which sub-types will be identified and compared. For example, studies looking at PAH treatment patterns may examine a large baseline cohort, and then apply further eligibility criteria to compare PAH treatment patterns among different subgroups of the initial pool. For these types of studies, more inclusive algorithms that allow a broader range of diagnostic and/or procedure codes and potentially include treatment codes and temporal components (e.g., Algorithms 3, 6, and 10) may be considered, while those with exclusionary codes or more complex requirements should be avoided.

We selected six algorithms (that represented a wide range of sensitivities and specificities) and compared the characteristics of the true positives and true negatives identified by these algorithms with those of the total pool of true PAH and other (non-PAH) PH patients, respectively. There was a natural variation in the clinical characteristics of correctly identified PAH and other PH patients across the different algorithms, and the characteristics of these cohorts were broadly consistent with those of their respective total pools of true PAH and true other (non-PAH) PH patients. This correlation demonstrates that the correctly identified patients are representative of the overall population of PAH patients at Stanford. The exceptions to this were the algorithms that only identified a small number of true PAH or true other (non-PAH) PH patients, thus demonstrating the potential for bias when selecting an algorithm.

Strengths and limitations

Limitations of our study include that it represents the experience of a single center, and therefore this study cohort may not represent PH populations in other databases. For example, all patients in our study underwent RHC, whereas this might not be the case in other centers. This study cohort also does not reflect the real-world prevalence of PAH among PH patients, as the majority of patients in the Stanford PH database had PAH. This particularly high prevalence of PAH is part of the reason that PPVs (which are directly proportional to disease prevalence) are uniformly high in our data set. Therefore, we focused on sensitivity and specificity. As our study was performed in a PH database, the performance of the algorithms described herein will likely not be generalizable to other non-PH databases (e.g., a general claims database). A major strength of our study is that we used RHC, the gold standard diagnostic test for PAH,[1] to validate the algorithms for patient identification. Therefore, our findings help to ensure that research in coded healthcare databases is fit for purpose, and demonstrate the importance of validating a new algorithm using the gold standard diagnostic test where possible. Another advantage of our study is the relatively large sample size of the clinical registry for a disease with several rare subgroups (including PAH).

Impact of findings

There is a diverse range of code-based algorithms for PAH in the literature, but few are validated.[22] It is important to improve research based on administrative data since it offers the opportunity to study a large, representative sample of PAH patients, including racial and ethnic groups that have been underrepresented in clinical registries.[6] Moreover, algorithms must be able to distinguish PAH from PH Group 2–5, since PAH is distinct from them in treatment options, prognosis, and epidemiology.[1] Our study helps address the unmet need to identify a range of universally accepted algorithms, so that we can move towards standardization of claims/

TABLE 5 Recommendations for the selection, design, and/or reporting of code-based algorithms used to identify patients in coded healthcare databases.

Recommendations
Researchers should assess the patients' characteristics that are relevant for the research question (e.g., other diagnostic, procedure, and drug codes) before finalizing their code-based algorithm for cohort building
Researchers should tailor algorithm selection/design to the specific research question (i.e., is a highly specific or highly sensitive algorithm required?)
Researchers are encouraged to include minimum and/or maximum time between orders/codes in their algorithms and define these criteria in publications

administrative-based research in PAH. Additional validation work in different databases and healthcare settings is warranted to further improve cohort identification for a given research question, as previous work has shown that the same algorithm can perform differently in different databases.[6]

We have also provided guidance on selecting the most suitable algorithm for a given research question and on interpreting research conducted in claims/administrative databases. Based on our findings, we have made three key recommendations for researchers while selecting/designing and reporting their algorithms (Table 5).

Future work should focus on the application of machine-learning methods to help refine and create algorithms for improved identification of PAH patients.[24,25] The more accurately PAH patients can be identified in coded databases, the more accurately machine-learning models can be developed, trained, and applied. Kogan et al. used machine learning to develop a model to detect undiagnosed PH based on patients' EHR data.[26] Once finalized, this model could be applied to EHRs from a network of hospitals, for example, to identify patients who should be investigated for PH and potentially reduce diagnostic delay in PAH. The success of such a machine learning model heavily relies on the way patients are identified based on administrative codes. Therefore, further code-based characterization of true PAH patients, such as that described here, could help refine these models.

This study helps move us closer to having a range of universally accepted code-based algorithms for identifying PAH patients in coded administrative databases, such as health insurance claims or EHR databases, and demonstrates the importance of aligning the choice of PAH algorithm with the research question. Importantly, this study also demonstrates that addition of defined temporal components (i.e., timing and order of codes) improves algorithm performance, and thus highlights the need to address the lack of this crucial information in published descriptions of PAH algorithms. Ultimately, our findings can help inform guidance on research in code-based databases, which is particularly important for rare diseases such as PAH.

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. EMD and RZ were scientific leaders of the project and manuscript development. DL performed the analysis and HH supervised the analysis. AH was responsible for data (pre-)processing.

ACKNOWLEDGMENTS

We would like to thank Audrey Muller (Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical company of Johnson & Johnson) for her helpful input into initiating the project and reviewing a draft of the manuscript. This analysis was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson. Medical writing support was provided by Victoria Atess and Clare Lowe, of Ashfield MedComms, an Inizio company, and funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson.

CONFLICTS OF INTEREST STATEMENT

EMD and MB are employees of Janssen Pharmaceutical Companies of Johnson & Johnson and own shares of stock/stock options in Johnson & Johnson. RTZ is a consultant to Morphogen-IX, Vivus, GossamerBio, and Merck; his institution has received research grant support from United Therapeutics, Janssen Pharmaceutical, Merck, Tenax, and Celtaxsys. HH, DL, and AH have no conflict of interest to declare.

ETHICS STATEMENT

This analysis was approved as part of the existing relevant IRB approval of the database used in this analysis.

ORCID

Eva-Maria Didden http://orcid.org/0000-0001-7401-8877

Haley Hedlin http://orcid.org/0000-0002-0757-7959

REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-

Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, Schwerzmann M, Dinh-Xuan AT, Bush A, Abdelhamid M, Aboyans V, Arbustini E, Asteggiano R, Barberà JA, Beghetti M, Čelutkienė J, Cikes M, Condliffe R, de Man F, Falk V, Fauchier L, Gaine S, Galié N, Gin-Sing W, Granton J, Grünig E, Hassoun PM, Hellemons M, Jaarsma T, Kjellström B, Klok FA, Konradi A, Koskinas KC, Kotecha D, Lang I, Lewis BS, Linhart A, Lip GYH, Løchen ML, Mathioudakis AG, Mindham R, Moledina S, Naeije R, Nielsen JC, Olschewski H, Opitz I, Petersen SE, Prescott E, Rakisheva A, Reis A, Ristić AD, Roche N, Rodrigues R, Selton-Suty C, Souza R, Swift AJ, Touyz RM, Ulrich S, Wilkins MR, Wort SJ. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618–731.

2. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulm Circ. 2021;11:1–12.
3. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023–30.
4. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. 2017;14:603–14.
5. Anderson JJ, Lau EM. Pulmonary hypertension definition, classification, and epidemiology in Asia. JACC: Asia. 2022;2:538–46.
6. Gillmeyer KR, Nunez ER, Rinne ST, Qian SX, Klings ES, Wiener RS. Development and validation of algorithms to identify pulmonary arterial hypertension in administrative data. Chest. 2021;159:1986–94.
7. Mathai SC, Mathew S. Breathing (and coding?) a bit easier. Chest. 2018;154:207–18.
8. Hoeper MM. Pharmacological therapy for patients with chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015;24:272–82.
9. Singh N, Dorfmüller P, Shlobin OA, Ventetuolo CE. Group 3 pulmonary hypertension: from bench to bedside. Circ Res. 2022;130:1404–22.
10. Chung WJ, Park YB, Jeon CH, Jung JW, Ko KP, Choi SJ, Seo HS, Lee JS, Jung HO. Baseline characteristics of the Korean Registry of Pulmonary Arterial Hypertension. J Korean Med Sci. 2015;30:1429–38.
11. Swerdel JN, Hripcsak G, Ryan PB. PheValuator: development and evaluation of a phenotype algorithm evaluator. J Biomed Inf. 2019;97:103258.
12. Sprecher VP, Didden E-M, Swerdel JN, Muller A. Evaluation of code-based algorithms to identify pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in large administrative databases. Pulm Circ. 2020;10:1–10.
13. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;2015(46):903–75.
14. Anand V, Roy SS, Archer SL, Weir EK, Garg SK, Duval S, Thenappan T. Trends and outcomes of pulmonary arterial hypertension-related hospitalizations in the United States: analysis of the Nationwide Inpatient Sample Database from 2001 through 2012. JAMA Cardiol. 2016;1:1021–9.
15. Choi YM, Famenini S, Wu JJ. Incidence of pulmonary arterial hypertension in patients with psoriasis: a retrospective cohort study. Perm J. 2017;21:16–073.
16. Dufour R, Pruett J, Hu N, Lickert C, Stemkowski S, Tsang Y, Lane D, Drake W. Healthcare resource utilization and costs for patients with pulmonary arterial hypertension: real-world documentation of functional class. J Med Econ. 2017;20:1178–86.
17. Kim D, Lee KM, Freiman MR, Powell WR, Klings ES, Rinne ST, Miller DR, Rose AJ, Wiener RS. Phosphodiesterase-5 inhibitor therapy for pulmonary hypertension in the United States. actual versus recommended use. Ann Am Thorac Soc. 2018;15:693–701.
18. Song S, Lee SE, Oh SK, Jeon SA, Sung JM, Park JH, Chang HJ. Demographics, treatment trends, and survival rate in incident pulmonary artery hypertension in Korea: a nationwide study based on the health insurance review and assessment service database. PLoS One. 2018;13:e0209148.
19. Studer S, Hull M, Pruett J, Koep E, Tsang Y, Drake W. Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database. Pulm Circ. 2019;9:1–12.
20. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2022. Accessed June 2023. https://www.R-project.org/
21. Mathai SC, Hemnes AR, Manaker S, Anguiano RH, Dean BB, Saundankar V, Classi P, Nelsen AC, Gordon K, Ventetuolo CE. Identifying patients with pulmonary arterial hypertension using administrative claims algorithms. Ann Am Thorac Soc. 2019;16:797–806.
22. Gillmeyer KR, Lee MM, Link AP, Klings ES, Rinne ST, Wiener RS. Accuracy of algorithms to identify pulmonary arterial hypertension in administrative data. Chest. 2019;155:680–8.
23. Papani R, Sharma G, Agarwal A, Callahan SJ, Chan WJ, Kuo YF, Shim YM, Mihalek AD, Duarte AG. Validation of claims-based algorithms for pulmonary arterial hypertension. Pulm Circ. 2018;8:1–8.
24. Ong MS, Klann JG, Lin KJ, Maron BA, Murphy SN, Natter MD, Mandl KD. Claims-based algorithms for identifying patients with pulmonary hypertension: a comparison of decision rules and machine-learning approaches. J Am Heart Assoc. 2020;9:e016648.
25. Schuler KP, Hemnes AR, Annis J, Farber-Eger E, Lowery BD, Halliday SJ, Brittain EL. An algorithm to identify cases of pulmonary arterial hypertension from the electronic medical record. Respir Res. 2022;23:138.
26. Kogan E, Didden EM, Lee E, Nnewihe A, Stamatiadis D, Mataraso S, Quinn D, Rosenberg D, Chehoud C, Bridges C. A

machine learning approach to identifying patients with pulmonary hypertension using real-world electronic health records. Int J Cardiol. 2023;374:95–9.

SUPPORTING INFORMATION

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

How to cite this article: Didden E-M, Lu D, Hsi A, Brand M, Hedlin H, Zamanian RT. Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases. Pulm Circ. 2024;14:e12333. https://doi.org/10.1002/pul2.12333