Identifying Patients with Group 3 Pulmonary Hypertension Associated with COPD or ILD Using an Administrative Claims Database

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Abstract

Background  Group 3 pulmonary hypertension (PH) describes a subpopulation of patients with PH due to chronic lung disease and/or hypoxia, with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) being two large subgroups. Claims database studies provide insights into the real-world treatment patterns and outcomes among these patients. However, claims data do not provide sufficient detail to assign the clinical subtype of PH required for identifying these patients.

Methods  A panel of PH clinical experts and researchers was convened to discuss methodologies to identify patients with Group 3 PH associated with COPD or ILD in retrospective claims databases. To inform the discussion, a literature review was conducted to identify claims-based studies of Group 3 PH associated with COPD or ILD published from 2010 through June 2020.

Results  Targeted title and abstract review identified 11 claims-based studies and two conference abstracts (eight based in the United States [US] and five conducted outside the US) that met search criteria. Based on insights from the panel and literature review, the following components were detailed across studies in the identification of Group 3 PH associated with COPD and ILD: (a) COPD or ILD identification, (b) PH identification, (c) defining the sequence between COPD/ILD and PH, and (d) other PH Group and Group 3 PH exclusions.

Conclusion  This article provides recommended approaches and considerations for identifying and studying patients with Group 3 PH associated with COPD or ILD using administrative claims data that provide the foundation for future validation studies.

Keywords  Pulmonary hypertension · Real-world evidence · Retrospective claims studies · Algorithm

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Background

Pulmonary hypertension (PH) is a condition characterized by elevation in pulmonary artery pressures of varying etiologies, which may result in substantial morbidity. PH is clinically classified into five groups, defined by the World Symposium on PH, according to differing pathological findings between groups, including underlying cause of disease, clinical presentation, and hemodynamic characteristics [1]. PH clinical classifications are also used by healthcare providers for medical management and by the Food and Drug Administration (FDA) for labeling of new drugs approved for the treatment of PH [1, 2].

Group 3 PH describes a subpopulation of patients with PH due to chronic lung disease and/or hypoxia. In particular, chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) are two large subgroups of chronic lung disease patients who often develop PH [2, 3]. In COPD, the prevalence rate ranges from 30 to 70% [4]. Because ILD is composed of multiple lung diseases, its prevalence is difficult to estimate. In idiopathic pulmonary fibrosis (IPF), the most common type of ILD, prevalence rates of PH range from 8 to 15% at initial diagnosis to 46% at evaluation for lung transplant and 86% at the time of transplant [5–10]. Wide ranges in prevalence can be due to heterogeneity in the definitions for PH, diagnostic modalities for PH, differences in patient populations, physiologic characteristics, and severity of underlying lung disease [4, 11].

Administrative claims are generated following healthcare utilization for the purposes of payment. Medical documentation is converted to standardized codes using uniform coding systems. The International Classification of Diseases (ICD), a medical classification system, is the international standard for reporting diseases and health conditions. In the US, the ICD, 9th Revision, Clinical Modification (ICD-9-CM) and ICD, 10th Revision, Clinical Modification (ICD-10-CM) provide a system of diagnostic codes assigned for each encounter.

ICD-9-CM diagnostic codes provide the level of detail to indicate PH but are not specific to groups of PH defined by World Symposium on PH. All groups of PH due to lung disease are generally coded under the same four-digit codes. The newer ICD-10-CM, implemented in October 2017, provides five-digit codes for PH with greater differentiation but was not required for billing and reimbursement until October 2018 [12]. The designated code for Group 3 PH is I27.23, and it remains to be seen how frequently and accurately the utilization of this code will be.

While collected for billing purposes, claims data can provide real-world evidence outside the setting of a clinical trial about the treatment patterns, risk factors, patient outcomes, healthcare resource utilization, and costs for patients covered by health insurance plans. However, using diagnostic codes in claims databases for the identification of patients with Group 3 PH associated with lung disease conditions like COPD and ILD is not sufficient. Additional considerations must be applied to patient identification to reduce misclassification and improve the usefulness of claims data to understand the medical management and health-related outcomes of patients with these conditions.

Recently, a focused review provided recommended algorithms for the identification of patients with pulmonary arterial hypertension (Group 1 PAH) [13]. Others have explored the use of machine-learning approaches to reduce selection bias in patient identification [14]. Our goal is to provide readers with information to determine the most appropriate methodology for claims-based patient selection under different types of research questions about Group 3 PH associated with COPD or ILD.

Methods

A panel of US-based healthcare providers and researchers with expertise in PH was convened to discuss methodologies to identify patients with Group 3 PH associated with COPD or ILD in retrospective claims databases. Panel members included US-based practicing pulmonologists (n = 2), a nurse (n = 1), pharmacists (n = 6) with expertise in PH and backgrounds in public health and/or claims-based analysis, and researchers (n = 2) with expertise in pharmacoeconomics, epidemiology, and claims-based analysis.

We conducted a literature review to identify studies and explore considerations when using claims-based data to identify patients with Group 3 PH associated with COPD or ILD. The recommendations in this article are those of the authors convened for the discussion and are based on group consensus.

The literature review utilized EMBASE and MEDLINE (via EMBASE) to identify English language articles published from 2010 through June 2020, on adult patient population, including both US and international studies. We looked for claims-based studies, retrospective studies, or healthcare management-related studies, focused on both PH and lung diseases causing Group 3 PH, or that specifically mentioned Group 3 PH. The search terms for lung diseases and PH were derived from several sources [3, 15] and decided upon by the panel. Search terms were required in the title or abstract (Supplemental Table 1). We also referred to a similar effort around conceptualization of Group 1 PAH in order to provide further support [13].

Additionally, we reviewed abstracts from 2018 through 2020 from the American Thoracic Society, the American College of Chest Physicians, and the Pulmonary Vascular Research Institute to identify relevant studies.
Results

The broad literature search strategy resulted in 2,646 potential observational studies in patients with Group 3 PH associated with COPD or ILD (Supplemental Table 1). The targeted title and abstract review identified 11 studies and 2 conference abstracts for claims-based studies focusing on Group 3 PH associated with COPD or ILD; 8 studies based in the US and 5 non-US (Table 1) (Supplemental Fig. 1).

The focus of these studies varied. Four studies evaluated measures across multiple PH groups or Group 3 PH in general [16–19]. There were 3 studies on patients with COPD [20–22]: 2 studies each in ILD [23, 24] and IPF [25, 26] and 1 study in systemic sclerosis classified as Group 3 PH [27]. One study looked at PH in ILD, COPD, and combined ILD and COPD [28].

Most studies (n=9) claimed to be identifying Group 3 PH and included steps in their methodology to filter for these patients (such as ensuring that PH occurred after COPD/ILD or excluded non-Group 3 PH) [16–22, 24–26, 28]. Other studies took additional steps in their methodology but did not specifically claim to identify Group 3 PH [26] or reported PH as a comorbidity to the lung disease [23–25].

In the following discussion section, we outline key components to consider in the development of an algorithm for Group 3 PH associated with COPD or ILD. For each, we outline the findings from the literature search that relate to the component followed by our summary and recommendations.

Discussion

There are several components to consider when choosing an algorithm. The methods used in the published literature for identifying adult patients with Group 3 PH associated with COPD or ILD relied on the following considerations: (a) identification of COPD or ILD, (b) identification of PH, (c) defining the sequence between COPD/ILD and PH diagnoses, and (d) other PH groups or other Group 3 PH exclusions. We provide a summary of the published literature findings followed by considerations as to the impact of how restricting or relaxing the criteria for each of these components can impact the diagnostic performance of the algorithm. Components of the recommended algorithm are provided in Fig. 1.

Identification of COPD or ILD

Findings in the Literature

The criteria used for the identification of COPD and ILD within the examined studies included (a) diagnosis codes, (b) relevant procedures, and (c) claims for medication. All 13 studies used diagnosis codes to identify patients with COPD or ILD, with 11 studies reporting ICD-9-CM codes [16–22, 24–26, 28] and 5 reporting ICD-10-CM codes [19, 20, 23, 27, 28].

Except for one COPD study conducted in the US that required the COPD diagnosis to be in the primary position [21], the remaining studies allowed the COPD or ILD diagnosis codes to be in either the primary or secondary position. Twelve studies identified patients from either inpatient or outpatient claims [16–23, 25–28] and the one remaining study used inpatient claims only [24]. In addition, 6 of the 12 studies using outpatient claims included a requirement for multiple claims (i.e., ≥ 2 claims) with a specified diagnosis [17, 20–22, 26, 28].

Only two studies utilized procedures specific to COPD or ILD to identify patients (i.e., pulmonary function tests in patients evaluated for ILD). Lautsch et al. excluded patients with prior lung transplant, while Frank et al. required patients to have at least one diagnostic procedure including bronchoscopy, lung computerized tomography (CT), pulmonary function testing, or assessment of autoantibodies [20, 23]. Two additional studies utilized procedures specific to COPD or ILD in sensitivity or subset analyses, including lung biopsy and CT [25, 26]. Requiring a procedure for COPD or ILD identification resulted in a significant drop in case count but did not change the general outcome of the studies.

Summary and Recommendations

After reviewing codes across studies, recommended diagnosis codes for COPD and ILD are provided in Table 2. While the US and non-US studies utilized similar ICD-9-CM codes for COPD and ILD, they differed more frequently when it came to ICD-10-CM. The US studies used codes down to the fifth digit, whereas non-US studies tended to use the higher, more general code down to the fourth digit. Thus, corresponding codes should be verified if international versions of ICD are used.

In addition, we recommend searching for COPD or ILD diagnoses in the primary or secondary position. When PH symptom exacerbations are due to underlying COPD or ILD, PH may be the primary reason for utilization diagnosis. We also recommend using both inpatient and outpatient claims unless doing so would affect study objectives (e.g., a study looking at hospital readmissions). When outpatient codes are used, we recommend using ≥ 2 to reduce the likelihood that a single diagnostic claim is used for patient identification.

We also note that PH is a complication of connective tissue disease and can be due to mechanisms other than ILD. Thus, caution should be considered with including connective tissue disease-related codes in the identification of
| Reference    | Data source                                                                 | Study period          | COPD or ILD identification                                                                 | PH identification                                                                 | Timing                                                                 | Non-group 3 exclusions                                                                 |
|--------------|------------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Collard 2012 | MarketScan Thomson Reuters: Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database | Jan 1, 2001–Sept 30, 2008 | ≥2 claims inpatient or outpatient claims on separate days associated with IPF (≥ 2 ICD-9-CM 516.3 OR at least 1 ICD-9-CM 516.3 and a subsequent ICD-9-CM 515 code) Excluded if the patient had ≥ 2 inpatient or outpatient claims with the same diagnosis code for another type of ILD on separate days | ≥1 inpatient or outpatient claim of PH (ICD-9-CM: 416.0) | Incident PH was defined as PH diagnosis after the second lung disease code (PH after lung disease) | N/R                                                                                   |
| Collard 2015 | 5% random and representative sample of the US Medicare beneficiaries, Part A, and B files | 2000–2011            | ≥1 outpatient or inpatient claim of IPF (ICD-9-CM 516.3) Excluded if there were ≥ 1 outpatient or inpatient diagnosis code for other ILD | ≥1 inpatient or outpatient claim of PH (ICD-9-CM 416.0x) | Comorbid PH was determined in the pre-index period before IPF diagnosis (PH before lung disease) | N/R                                                                                   |
| Heresi 2017  | Truven Health Analytics MarketScan Databases: Commercial Claims and Encounters Database and the Medicare Supplemental Database | July 1, 2010–June 30, 2013 | ≥1 claim for a lung disease associated with Group 3 PH | ≥2 inpatient or outpatient claims for PH (ICD-9-CM 416.0 or 416.8) that were separated by at least 1 day but within 12 months of each other AND ≥1 claim for right heart catheterization or echocardiogram during the baseline period | Group 3 PH lung disease claim must have been during the baseline period before PH (PH after lung disease) | Patients with ≥ 1 claim with diagnosis codes or procedures related to Groups 2, 4, or 5 PH were excluded in the study period |
| Medrek 2017  | Veterans Health Administration Corporate Data Warehouse (VISN 16 South Central) | 2000–2012            | ≥1 hospitalization or ≥ 2 outpatient claims where COPD was the primary diagnosis (ICD-9-CM 491, 492, 494, 496) | ≥1 outpatient or inpatient claim of PH (ICD-9-CM 416.0, 416.8) | Incident PH found in the post-index period after COPD (PH after lung disease) | N/R                                                                                   |
| Reference    | Data source                                                                 | Study period          | COPD or ILD identification                                                                 | PH identification                                      | Timing                                                                 | Non-group 3 exclusions |
|--------------|------------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------|------------------------|
| Pedraza-Serrano 2019 | Spanish National Hospital Discharge Database (95% of hospital discharges in Spain) | 2014–2015            | ≥ 1 admission with ILD ICD-9-CM diagnosis codes: IPF (516.31), hypersensitivity pneumonitis (495.9), cryptogenic organizing pneumonia (516.36), lymphangioleiomyomatosis (516.4), pulmonary Langerhans cell histiocytosis (516.5), and sarcoidosis (135) | ≥ 1 admission with a diagnosis code of PH (ICD-9-CM 416.0, 416.8) | COPD and PH diagnoses were found on the same claim (PH at same time with lung disease) | N/R                    |
| Kim 2018     | Veterans Administration National Utilization and Pharmacy Data Systems        | 2005–2012            | ≥ 1 claim for a lung disease associated with Group 3 PH                                   | ≥ 1 inpatient or outpatient claim of PH (ICD-9-CM: 416.x) AND ≥ 1 prescription for daily PDE5i therapy. Daily is defined as pull per month ratio ≥ 30 | Diagnosis code for PH must appear before the first daily PDE5i prescription | Patients were grouped into either Group 1, Group 4/5, or Group 2/3. For patients with diagnoses from multiple groups, an algorithm was used to assign PH groups, preferentially labeling patients as Group 1, 4, and 5 instead of Group 2/3, Patients could belong to multiple PH groups, with the exception of Group 1 |
| Wijeratne 2018 | Institute for Clinical Evaluative Sciences linked databases of universal healthcare coverage for Ontario, Canada residents along with the Ontario Drug Benefit database and the Canada Institute for Health Information databases | 1993–2012            | ≥ 1 hospitalization or emergency department visit for a Group 3-related lung disease diagnosis code | ≥ 1 hospitalization or emergency department visit for PH (ICD-9-CM 416.0, 416.1, 416.8, 416.9; ICD-10-CM I27.0, I27.1, I27.2, I27.8, I27.9) | Assessed for Group 3-related lung disease in the 5 years before the first PH claim (PH after lung disease) | ≥ 1 claim for Groups 2 or 4 PH utilizing diagnosis codes. Patients with no Group 2, 3, or 4 PH diagnosis codes were assigned as Group 1. |
| Butt 2019    | Danish Central Population Registry and the National Prescription Registry     | 1978–2015            | ≥ 1 outpatient or inpatient claim of first-time diagnosis of SSc (ICD-10-CM M34, except for M34.2) | ≥ 1 outpatient or inpatient claim of PH (ICD-8-CM 426 or ICD-10-CM I27) | Incident PH was defined as PH diagnosis after SSc diagnosis (PH after lung disease) | N/R                    |
| Reference | Data source | Study period | COPD or ILD identification | PH identification | Timing | Non-group 3 exclusions |
|-----------|-------------|--------------|----------------------------|-------------------|--------|-----------------------|
| Frank 2019 | Scientific Institute of the Allgemeine Ortskrankenkasse Statutory Health Insurance Funds (WIdO) insurance claims | 2009–2014 | ≥ 1 code for IPF (ICD-10-CM J84.1) or sarcoidosis (ICD-10-CM D86.0–D86.9) from outpatient or inpatient. Excluded any individuals without confirmed outpatient diagnoses from pulmonologist, an internal specialist, and without any inpatient diagnoses for the relevant diseases AND at least 1 relevant diagnostic procedure (bronchoscopy, lung computerized tomography, pulmonary function testing, or assessment of autoantibodies) from a visit with a relevant diagnosis | ≥ 1 code for PH (ICD-10-CM 127.0, 127.8, 127.9) from inpatient or outpatient | Comorbid PH was determined in the same quarter as incident ILD diagnosis, either IPF or sarcoidosis (PH at the same time as lung disease) | N/R |
| Hemnes 2019 | US PharMetrics Plus Commercial data set (pharmacy, medical, hospital claim; nationally representative) | 2012–2016 | ≥ 2 claims from outpatient or inpatient claims ≥ 30 days apart for either COPD or ILD | ≥ 2 claims from outpatient or inpatient claims ≥ 30 days apart for PH (ICD-9-CM 416.0, 416.8; ICD-10-CM I27.0, I27.20, I27.21, I27.23, I27.24, I27.29, I27.89) | COPD and ILD claims were required in the baseline period, prior to the PH claim (PH after lung disease) | Patients with ≥ 1 claim of Group 2, 4, or 5 PH in the pre-index period were excluded. Criteria included ICD-9/10-CM diagnosis, ICD-9/10-CM procedure, and CPT procedure codes |
| Trammell 2019 | Veterans Health Administration Corporate Data Warehouse | Jan 2003–Sept 2015 | ≥ 1 outpatient or inpatient claim for a Group 3 PH-related lung disease diagnosis code | ≥ 2 outpatient claims ≥ 30 days apart or ≥ 1 inpatient claim for PH (ICD-9-CM 416.0, 416.2, 416.8, 416.9) | Assessed for lung disease codes in the baseline period and up to 6 months after PH diagnosis (PH after and same time as lung disease) | ≥ 1 claim of Group 2, 4, or 5 PH codes were assessed in baseline and up to 6 months after PH diagnoses. If a patient did not have any Group 2, 3, 4, or 5 PH codes, they were counted as Group 1. If patients fell under multiple groups, then they were captured in the “multiple groups” cohort |
Table 1 (continued)

| Reference | Data source | Study period | COPD or ILD identification | PH identification | Timing | Non-group 3 exclusions |
|-----------|-------------|--------------|----------------------------|-------------------|--------|------------------------|
| Lautsch 2020 | Optum’s Clininformatics Data Mart composed of commercial health plan data and Medicare Advantage members | 2014–2018 | ≥ 2 outpatient or inpatient claims for COPD. Patients were excluded who had previous lung transplant, as determined by procedure codes | ≥ 2 outpatient or inpatient claims for PH | COPD codes must have been prior to PH (PH after lung disease) | Excluded patients with ≥ 1 diagnosis of chronic thromboembolic PH or left heart disease PH and those with utilization of PAH-targeted therapy prior to the PH diagnosis |
| Wu 2020 | Taiwan National Health Insurance plan database (includes hospitals, clinics, and pharmacies) | 2002–2017 | ≥ 3 outpatient or ≥ 2 inpatient diagnosis claims for COPD (ICD-9-CM 490, 491, 492, 496) AND Treated using COPD medications (LABA, LABA/ICS, LAMA, LABA/LAMA, SABA, SAMA, SABA/SAMA, systemic beta-2-adrenergic receptor agonists, ICS, methylxanthines), according to outpatient claims for more than 28 days within 1 year after the primary COPD diagnosis | ≥ 3 outpatient claims or ≥ 2 inpatient claims or > 2 emergency room claims for PH (ICD-9-CM 416.0, 416.8, 416.9; ICD-10-CM I27.0, I27.2, I27.8, I27.9) | Patients with PH claims before COPD were excluded. Incident PH was assessed after COPD (PH after lung disease) | ≥ 1 claim for ICD-9-CM diagnosis codes for select Group 1, 2, or 4 PH diseases |

COPD chronic obstructive pulmonary disease, CPT Current Procedural Terminology, ICD-8-/9-/10-CM International Classification of Diseases, 8th or 9th or 10th Revision, Clinical Modification, ICS inhaled corticosteroid, ILD interstitial lung disease, IPF idiopathic pulmonary fibrosis, LABA long-acting beta agonist, LAMA long-acting muscarinic antagonist, N/R not reported, PAH pulmonary arterial hypertension, PDE5i phosphodiesterase-5 inhibitor, PH pulmonary hypertension, SABA short-acting beta agonist, SAMA short-acting muscarinic antagonist, SSc systemic sclerosis, US United States
ILD. We specifically recommend limiting diagnostic codes to connective tissue disease with respiratory or lung involvement. We also suggest alternative methods for the assessment of patients whose underlying conditions overlap across PH classification, such as analyzing patients meeting criteria for multiple PH groups separately.

Based on the findings from the evaluated studies, we do not recommend using any COPD/ILD-related procedure codes or medication claims for patient identification.

**Identification of PH**

**Findings in the Literature**

The criteria used for the identification of PH within examined studies can be classified into the following: (a) diagnosis codes, (b) relevant procedures, (c) claims for medication, and (d) exclusions. All 13 studies used ICD-9-CM and ICD-10-CM diagnosis codes to identify patients with Group 3 PH associated with COPD or ILD. The majority ($n = 11$) [16–22, 24–26, 28] contained ICD-9-CM codes for patient identification, while six contained ICD-10-CM codes [19, 20, 22, 23, 27, 28]. No studies required the PH diagnosis to be in the primary position. Twelve studies identified patients from either inpatient or outpatient claims [16–23, 25–28] and the remaining one study used inpatient claims only [24]. The use of additional criteria such as a requirement for multiple claims was reported in five studies [16, 18, 20, 22, 28].

Only one study utilized PH-related procedures (i.e., right heart catheterization [RHC] or echocardiogram) in identification of patients with PH [16], and no studies required claims for any PH-related medications except Kim et al., which focused on appropriate use of phosphodiesterase-5 inhibitors (PDE5is) [17].
Table 2  Lung disease diagnosis codes for COPD and ILD

| Lung disease subgroup | ICD-9-CM | ICD-10-CM | Description |
|-----------------------|----------|-----------|-------------|
| Chronic obstructive pulmonary disease | 491.0 | J41.0 | Simple chronic bronchitis |
|                      | 491.1 | J41.1 | Mucopurulent chronic bronchitis |
|                      | 491.8 | J41.8 | Other chronic bronchitis |
|                      | 491.9 | J42 | Unspecified chronic bronchitis |
|                      | 491.20 |          | Obstructive chronic bronchitis without exacerbation |
|                      | 492.0 | J43.0 | Unilateral pulmonary emphysema [MacLeod’s syndrome] |
|                      |      | J43.1 | Panlobular emphysema |
|                      |      | J43.2 | Centrilobular emphysema |
|                      | 492.8 | J43.8 | Other emphysema |
|                      |      | J43.9 | Emphysema, unspecified |
|                      | 491.22 | J44.0 | Chronic obstructive pulmonary disease with (acute) lower respiratory infection |
|                      | 491.21 | J44.1 | Chronic obstructive pulmonary disease with (acute) exacerbation |
|                      | 496 | J44.9 | Chronic obstructive pulmonary disease, unspecified |
| Interstitial lung disease | 517.1 | J17 | Rheumatic pneumonia |
|                      | 500 | J60 | Coal worker’s pneumoconiosis |
|                      | 501 | J61 | Pneumoconiosis due to asbestos and other mineral fibers |
|                      |      | J62.0 | Pneumoconiosis due to talc dust |
|                      | 502 | J62.8 | Pneumoconiosis due to other dust containing silica |
|                      | 503 | J63.0 | Aluminosis (of lung) |
|                      |      | J63.1 | Bauxite fibrosis (of lung) |
|                      |      | J63.2 | Berylliosis |
|                      |      | J63.3 | Graphite fibrosis (of lung) |
|                      |      | J63.4 | Siderosis |
|                      |      | J63.5 | Stannosis |
|                      |      | J63.6 | Pneumoconiosis due to other specified inorganic dusts |
|                      | 505 | J64 | Unspecified pneumoconiosis |
|                      |      | J65 | Pneumoconiosis associated with tuberculosis |
|                      | 504 | J66 | Airway disease due to specific organic dust |
|                      | 495 | J67 | Hypersensitivity pneumonitis due to organic dust |
|                      | 495.0 | J67.0 | Farmer’s lung |
|                      | 495.1 | J67.1 | Bagassosis |
|                      | 495.2 | J67.2 | Bird fancier’s lung |
|                      | 495.3 | J67.3 | Suberosis |
|                      | 495.4 | J67.4 | Malt worker’s lung |
|                      | 495.5 | J67.5 | Mushroom worker’s lung |
|                      | 495.6 | J67.6 | Maple-bark-stripper’s lung |
|                      | 495.7 | J67.7 | Air conditioner and humidifier lung |
|                      | 495.8 | J67.8 | Hypersensitivity pneumonitis due to other organic dusts |
|                      | 495.9 | J67.9 | Hypersensitivity pneumonitis due to unspecified organic dust |
|                      | 506 | J68 | Respiratory conditions due to inhalation of chemicals, gases, fumes, and vapors |
|                      | 506.4 | J68.4 | Chronic respiratory conditions due to chemicals, gases, fumes, and vapors |
|                      | 506.9 | J68.9 | Unspecified respiratory conditions due to chemicals, gases, fumes, and vapors |
| Lung disease subgroup | ICD-9-CM | ICD-10-CM | Description |
|----------------------|----------|-----------|-------------|
|                      | J66.0    | J70.1     | Byssinosis |
|                      | J66.1    | J70.3     | Flax-dressers’ disease |
|                      | J66.2    | J70.4     | Cannabinosis |
|                      | J66.8    | J70.8     | Airway disease due to other specific organic dusts |
|                      | J66.8    | J70.8     | Chronic and other pulmonary manifestations due to radiation |
|                      | J70.3    | J70.8     | Chronic drug-induced interstitial lung disorders |
|                      | J70.4    | J70.8     | Drug-induced interstitial lung disorders, unspecified |
|                      | 508.1    | J70.8     | Respiratory conditions due to other specified external agents |
|                      | 518.3    | J82       | Pulmonary eosinophilia |
|                      | 516.2    | J84.02    | Pulmonary alveolar microlithiasis |
|                      | 516.1    | J84.03    | Idiopathic pulmonary hemosiderosis |
|                      | 515      | J84.10    | Pulmonary fibrosis, unspecified |
|                      | 516.8    | J84.11    | Idiopathic interstitial pneumonia |
|                      | 516.30   | J84.111   | Idiopathic interstitial pneumonia, NOS |
|                      | 516.31   | J84.112   | Idiopathic pulmonary fibrosis |
|                      | 516.32   | J84.113   | Idiopathic non-specific interstitial pneumonitis |
|                      | 516.33   | J84.114   | Acute interstitial pneumonitis |
|                      | 516.34   | J84.115   | Respiratory bronchiolitis interstitial lung disease |
|                      | 516.36   | J84.116   | Cryptogenic organizing pneumonia |
|                      | 516.37   | J84.117   | Desquamative interstitial pneumonia |
|                      | 516.35   | J84.17    | Other interstitial pulmonary diseases with fibrosis, in diseases classified elsewhere |
|                      | 516.38   | J84.18    | Lymphoid interstitial pneumonia |
|                      | 516.39   | J84.19    | Other specified interstitial pulmonary disease |
|                      | 516.40   | J84.20    | Interstitial pulmonary disease, unspecified |
|                      | 710.0    | M32.13    | Lung involvement in systemic lupus erythematosus |
|                      | 710.1    | M34.81    | Systemic sclerosis with lung involvement |
|                      | 710.3    | M33.01    | Juvenile dermatomyositis with respiratory involvement |
|                      | 710.4    | M33.11    | Other dermatomyositis with respiratory involvement |
|                      | 710.5    | M33.21    | Polymyositis with respiratory involvement |
|                      | 710.6    | M33.91    | Dermatopolymyositis, unspecified with respiratory involvement |
|                      | 714.81   | M05.1     | Rheumatoid lung disease with rheumatoid arthritis |
|                      |          | M05.10    | Rheumatoid lung disease with rheumatoid arthritis of unspecified site |
|                      |          | M05.11    | Rheumatoid lung disease with rheumatoid arthritis of shoulder |
|                      |          | M05.111   | Rheumatoid lung disease with rheumatoid arthritis of right shoulder |
|                      |          | M05.112   | Rheumatoid lung disease with rheumatoid arthritis of left shoulder |
|                      |          | M05.119   | Rheumatoid lung disease with rheumatoid arthritis of unspecified shoulder |
|                      |          | M05.12    | Rheumatoid lung disease with rheumatoid arthritis of elbow |
|                      |          | M05.121   | Rheumatoid lung disease with rheumatoid arthritis of right elbow |
|                      |          | M05.122   | Rheumatoid lung disease with rheumatoid arthritis of left elbow |
|                      |          | M05.129   | Rheumatoid lung disease with rheumatoid arthritis of unspecified elbow |
|                      |          | M05.13    | Rheumatoid lung disease with rheumatoid arthritis of wrist |
|                      |          | M05.131   | Rheumatoid lung disease with rheumatoid arthritis of right wrist |
|                      |          | M05.132   | Rheumatoid lung disease with rheumatoid arthritis of left wrist |
|                      |          | M05.139   | Rheumatoid lung disease with rheumatoid arthritis of unspecified wrist |
Summary and Recommendations

As all studies included PH-related diagnosis codes and there was general consensus on these codes across studies, we recommend utilizing a limited list of consensus codes (Table 3). Corresponding codes should be verified if international versions of the ICD are used. We recommend that PH diagnosis be in the primary or secondary position, as COPD or ILD associated with PH symptom exacerbation may be reported in the primary position. We also recommend using both inpatient and outpatient claims unless the study objectives are limited to one or the other. When outpatient codes are used, require at least two to reduce the likelihood that a single diagnostic claim is used for patient identification and specify a minimum time frame of at least 30 days for how far apart the outpatient claims need to be in order to qualify.

We generally do not suggest utilizing PH-related procedures. While the guideline-driven practice is to confirm cases by means of RHC, studies suggest that less than two-fifths of patients with PH have an RHC prior to diagnosis.

Table 2 (continued)

| Lung disease subgroup | ICD-9-CM | ICD-10-CM | Description |
|-----------------------|----------|-----------|-------------|
| M05.14                |          |           | Rheumatoid lung disease with rheumatoid arthritis of hand |
| M05.141               |          |           | Rheumatoid lung disease with rheumatoid arthritis of right hand |
| M05.142               |          |           | Rheumatoid lung disease with rheumatoid arthritis of left hand |
| M05.149               |          |           | Rheumatoid lung disease with rheumatoid arthritis of unspecified hand |
| M05.15                |          |           | Rheumatoid lung disease with rheumatoid arthritis of hip |
| M05.151               |          |           | Rheumatoid lung disease with rheumatoid arthritis of right hip |
| M05.152               |          |           | Rheumatoid lung disease with rheumatoid arthritis of left hip |
| M05.159               |          |           | Rheumatoid lung disease with rheumatoid arthritis of unspecified hip |
| M05.16                |          |           | Rheumatoid lung disease with rheumatoid arthritis of knee |
| M05.161               |          |           | Rheumatoid lung disease with rheumatoid arthritis of right knee |
| M05.162               |          |           | Rheumatoid lung disease with rheumatoid arthritis of left knee |
| M05.169               |          |           | Rheumatoid lung disease with rheumatoid arthritis of unspecified knee |
| M05.17                |          |           | Rheumatoid lung disease with rheumatoid arthritis of ankle and foot |
| M05.171               |          |           | Rheumatoid lung disease with rheumatoid arthritis of right ankle and foot |
| M05.172               |          |           | Rheumatoid lung disease with rheumatoid arthritis of left ankle and foot |
| M05.179               |          |           | Rheumatoid lung disease with rheumatoid arthritis of unspecified ankle and foot |
| M05.19                |          |           | Rheumatoid lung disease with rheumatoid arthritis of multiple sites |

*ICD-9/10-CM* International Classification of Diseases, 9th or 10th Revision, Clinical Modification, ILD interstitial lung disease, NOS not otherwise specified

Table 3 PH diagnosis codes

| ICD-9-CM | ICD-9-CM description | ICD-10-CM | ICD-10-CM description |
|----------|----------------------|-----------|----------------------|
| 416      | Chronic pulmonary heart disease | I27 | Other pulmonary heart diseases |
| 416.0    | Primary pulmonary hypertension | I27.0 | Primary pulmonary hypertension |
| 416.8    | Other chronic pulmonary heart diseases | I27.2 | Other pulmonary heart disease |
|          |                      | I27.20 | Pulmonary hypertension, unspecified |
|          |                      | I27.21 | Secondary pulmonary arterial hypertension |
|          |                      | I27.23 | Pulmonary hypertension due to lung disease and hypoxia |
|          |                      | I27.29 | Other secondary pulmonary hypertension |
|          |                      | I27.89 | Other specified pulmonary heart diseases |
| 416.9    | Chronic pulmonary heart disease, unspecified | I27.81 | Cor pulmonale (chronic) |
|          |                      | I27.9 | Pulmonary heart disease, unspecified |

*ICD-9/10-CM* International Classification of Diseases, 9th or 10th Revision, Clinical Modification, PH pulmonary hypertension
within 3 months before or after medication \[29\] or within 12 months following diagnosis \[30\]. We also note that claims data indicate if a patient received a diagnostic test but do not include test results, thus utilizing echocardiography, which is non-specific to Group 3 PH, would not improve the sensitivity of patient identification. Thus, we recommend limiting the use of procedure codes for sensitivity analysis in patient identification or to limit the study population when a purer cohort is required. Lastly, we do not suggest utilizing PH-related medications for patient identification, as therapies used in Group 1 PAH are often used on- and off-label for Group 3 PH associated with both COPD and ILD.

**The Sequence of the COPD/ILD and PH Diagnoses**

**Findings in the Literature**

In order to confirm that COPD or ILD was a contributing factor to the development of PH, patients must have developed lung disease prior to PH. Eight of the 13 evaluated studies required the COPD or ILD diagnosis code to be prior to the PH diagnosis code \[16, 19–22, 26–28\], and one study required an underlying cause of PH (not limited to lung disease) to be documented prior to PDE5i prescription \[17\]. In fact, of the 8 studies that specifically claimed to be studying Group 3 PH, seven of them included this criterion \[16, 19–22, 27, 28\].

**Summary and Recommendations**

We recommend that PH diagnosis occur after the COPD or ILD diagnosis to align with the natural progression of this disease. Patients should be identified and indexed on their first claim with a PH diagnosis code and require a COPD or ILD diagnosis code in the baseline period at least six to 12 months prior to the PH diagnosis.

**Identification of Other PH Group and Other Group 3 PH Conditions**

**Findings in the Literature**

When identifying patients with Group 3 PH, five studies used diagnosis codes to identify and exclude non-Group 3 PH patients \[16, 17, 20, 22, 28\] and two studies used diagnosis codes to separate patients who met criteria for multiple PH groups from those who met only Group 3 PH \[18, 19\]. In addition to diagnosis codes, two studies utilized claims for PAH-induced medications \[20\] and two studies used procedure codes \[16, 28\] to exclude patients from Group 3 PH. One study used PDE5i guidelines to assign patients with multiple diagnoses to an “appropriate use” group \[17\].

Algorithm assignment across PH groups was compared to chart abstraction, resulting in a positive predictive value of 86% for possible inappropriate use across groups of PH.

**Summary and Recommendations**

We recommend methodology to exclude patients with other PH groups prior to their Group 3 PH using diagnosis codes provided in Table 4. We do not recommend excluding patients with other PH conditions that develop after their Group 3 PH diagnosis, as these are relatively uncommon occurrences and may arise from diagnostic workup rather than diagnostic confirmation, as claims data reflect clinical care provided rather than results. We acknowledge that approximately 34% of patients with PH have overlapping diagnoses \[19\] and that excluding these patients may bias results for some research objectives, and the combination of multiple comorbidities may render patients vulnerable to developing PH and contribute to poor prognosis \[19\]. Thus, an alternative method would be to analyze patients meeting criteria for multiple PH groups separately or assign patients to a group based on the objectives of the study \[17\].

Using diagnosis codes in the identification of Group 3 PH does have some limitations. ICD-9-CM codes do not have specificity of classification for secondary PH, and it was not until ICD-10-CM that diagnosis codes provided for greater clinical classification of secondary PH. In addition, diagnosis codes do not reflect severity of the disease, particularly as they relate to distinguishing between multiple underlying causes of disease. So, for a patient with mild heart disease but severe lung disease that contributes significantly to PH, using real-world claims data may inadvertently misclassify this person as Group 2 PH.

In addition, there are some notable considerations. Given the overlap of secondary PH-related conditions in Group 1 PAH and Group 3 PH, we do not recommend using I27.x codes when developing exclusion criteria. Further, when conducting a study to identify Group 3 PH with COPD only, we recommend all patients with diagnosis codes for connective tissue disease be excluded. Lastly, given the high prevalence of sleep disorder breathing in COPD and ILD, we do not recommend excluding patients with this diagnosis.

None of the examined studies utilized PH-related medications to directly identify Group 3 PH, but one study did exclude patients with evidence of PAH-induced medications \[20\].

As inhaled treprostinil is now FDA approved in both Group 1 PAH and Group 3 PH, and it is likely that medications approved for use in Group 1 PAH are being used off-label in Group 3 PH to improve exercise capacity, we do not recommend relying on medication use to identify or exclude patients.
| Group 1: PAH                                            | ICD-9-CM | ICD-9-CM description                                                                 | ICD-10-CM | ICD-10-CM description                  |
|--------------------------------------------------------|----------|--------------------------------------------------------------------------------------|-----------|----------------------------------------|
| Drug and toxin induced                                  | 995.29   | Unspecified adverse effect of other drug medicinal and biological substance          | T50.5X50  | Adverse effect of appetite depressant  |
| Associated with other systemic diseases                 | 042      | HIV                                                                                 | B20       | HIV                                    |
|                                                        | 572.3    | Portal hypertension                                                                  | K76.6     | Portal hypertension                    |
|                                                        | 745.5    | Atrial septal defect                                                                | Q21.1     | Atrial septal defect                   |
|                                                        | 745.4    | Ventricular septal defect                                                           | Q21.0     | Ventricular septal defect              |
|                                                        | 120.x    | Schistosomiasis                                                                     | B65.x     | Schistosomiasis                        |
| Group 2: PH with left heart disease                    |          |                                                                                      |           |                                        |
| Left ventricular systolic dysfunction                   | 414.10   | Aneurysm of heart (wall)                                                             | I25.3     | Aneurysm of heart                      |
| Left ventricular diastolic dysfunction                  | 425.3    | Endocardial fibroelastosis                                                           | I42.4     | Endocardial fibroelastosis             |
|                                                        | 428.1    | Left heart failure                                                                  | I50.1     | Left ventricular failure               |
|                                                        | 428.2    | Systolic heart failure                                                               | I50.22    | Chronic systolic heart failure         |
|                                                        | 428.3    | Diastolic heart failure                                                              | I50.3     | Diastolic heart failure                |
| Valvular disease                                        | 394, 424.0| Disease/disorders of mitral valve                                                   | I34.0, I34.8| Non-rheumatic mitral valve insufficiency/disorder |
|                                                        | 395, 424.1| Disease/disorders of aortic valve                                                   | I35.x     | Disease/disorders of aortic valve      |
|                                                        | 396      | Disease of mitral and aortic valve                                                  | I08       | Disease of mitral and aortic valve     |
|                                                        | 746.3–746.7, 746.81| Mitrail/aortic valve surgery                                                  | Q23       | Mitrail/aortic valve surgery           |
| Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies | 425.1 | Hypertrophic obstructive cardiomyopathy | I42.1 | Hypertrophic obstructive cardiomyopathy |
|                                                        | 425.8    | Cardiomyopathy in other diseases classified elsewhere                                | I43       | Cardiomyopathy in other diseases classified elsewhere    |
|                                                        | 746.8    | Other specified congenital anomalies of heart                                      | Q24       | Other specified congenital anomalies of heart   |
| Hypertensive heart disease                              | 402.01, 402.11, 402.91| Malignant hypertensive heart disease with heart failure                               | I11.0     | Hypertensive heart disease with heart failure |
|                                                        | 402.11   | Benign hypertensive heart disease with heart failure                                 |          |                                        |
|                                                        | 402.91   | Unspecified hypertensive heart disease with heart failure                             |          |                                        |
| Hypertensive heart and kidney disease                  | 404.01, 404.03, 404.11, 404.91, 404.93| Hypertensive heart and chronic kidney disease with heart failure and chronic kidney disease stage 1–4 or unspecified | I13.0, I13.2| Hypertensive heart and chronic kidney disease with heart failure and stage 1–4 or unspecified |
|                                                        | 404.03, 404.13, 404.93| Hypertensive heart and Chronic kidney disease with heart failure and with chronic kidney disease stage 5 or end-stage renal disease | I13.2     | Hypertensive heart and chronic kidney disease with heart failure and with stage 5 or end-stage renal disease |
| Group 3: Other lung diseases                            |          |                                                                                      |           |                                        |
| Alveolar hypoventilation disorder                      | 327.24   | Idiopathic sleep-related non-obstructive alveolar hypoventilation                    | G47.34    | Idiopathic sleep-related non-obstructive alveolar hypoventilation |
| ICD-9-CM | ICD-9-CM description                                | ICD-10-CM | ICD-10-CM description                                                                 |
|---------|---------------------------------------------------|-----------|---------------------------------------------------------------------------------------|
| 327.25  | Congenital central alveolar hypoventilation syndrome | G47.35    | Congenital central alveolar hypoventilation syndrome                                   |
| E902.0  | Accident due to residence or prolonged visit at high altitude | W94.11XA | Exposure to residence or prolonged visit at high altitude, initial encounter           |
|         |                                                   | W94.11XD | Exposure to residence or prolonged visit at high altitude, subsequent encounter        |
|         |                                                   | W94.11XS | Exposure to residence or prolonged visit at high altitude, sequela                     |
| 993.2   | Other and unspecified effects of high altitude    | J98.15    | Mediastinitis                                                                         |
| 519.2   | Mediastinitis                                     | J98.15    | Mediastinitis                                                                         |
| 756.6   | Anomalies of diaphragm                            | Q79.0     | Congenital diaphragmatic hernia                                                       |
| 770.7   | Chronic respiratory disease arising in the perinatal period | P27.1     | Bronchopulmonary dysplasia originating in the perinatal period                        |
| 516.64  | Alveolar capillary dysplasia with vein misalignment | J84.843   | Alveolar capillary dysplasia with vein misalignment                                    |
| 748.5   | Agenesis, hypoplasia, and dysplasia of lung        | Q33.3     | Agenesis of lung                                                                       |
|         |                                                   | Q33.6     | Congenital hypoplasia and dysplasia of lung                                           |
| 516.63  | Surfactant mutations of the lung                  | J84.83    | Surfactant mutations of the lung                                                      |
| 516.62  | Pulmonary interstitial glycogenosis               | J84.842   | Pulmonary interstitial glycogenosis                                                    |
| 516.0   | Pulmonary alveolar proteinosis                    | J84.01    | Alveolar proteinosis                                                                   |
| 516.69  | Other ILD of childhood                            | J84.848   | Other ILD of childhood                                                                 |
| 415.1   | Pulmonary embolism                                | I26.99    | Other pulmonary embolism                                                              |
|         |                                                   | I26.90    | Septic pulmonary embolism without acute cor pulmonale                                 |
| 416.2   | Chronic pulmonary embolism                        | I27.24    | Chronic thromboembolic pulmonary hypertension                                         |
| V12.51  | History of venous thrombosis and embolism         | Z86.718   | Personal history of other venous thrombosis and embolism                              |
| 282     | Hereditary hemolytic anemias                      | D55       | Anemia due to enzyme disorders                                                        |
| 283     | Acquired hemolytic anemias                        | D56       | Thalassemia                                                                           |
| 283.4   | Polycythemia vera                                 | D57       | Sickle cell disorders                                                                  |
| 238.79  | Other lymphatic and hematopoietic tissues          | D58       | Other hereditary hemolytic anemias                                                    |
| 135     | Sarcoidosis                                       | D86       | Sarcoidosis                                                                           |
| 277.89  | Other specified disorders of metabolism           | E88.89    | Other specified metabolic disorders                                                   |
Conclusion

Correctly identifying adult patients with Group 3 PH associated with COPD or ILD in claims-based studies can improve the value of research findings for application in clinical care and population health, the utility of real-world evidence in support of FDA regulatory approvals, and more accurately inform formulary decision-making. When using the recommendations provided herein, care should be taken to consider policy and regulatory changes, such as FDA approvals and updated guidelines and their impact on how patients are identified. While some studies reported that they used validated codes or algorithms for either COPD/ILD or PH, it is important to note that only one reviewed study provided results on the validation of their patient identification algorithm. Future research should be conducted to validate patient identification algorithms, especially the combination of criteria required for the identification of Group 3 PH associated with COPD or ILD.

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Declarations

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