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Primary Ciliary Dyskinesia Registry

Mohammadreza Modaresi[1], Nasrin Jalalimanesh[1], *Shaghayegh Rahmani[2]

1.Pediatric Pulmonary Disease and Sleep Medicine Research Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
2.Clinical Research Development Center, 22 Bahman Hospital, Faculty of Medicine, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran.

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ABSTRACT

Introduction:
Primary ciliary dyskinesia (PCD) is a rare genetic disease that is estimated to occur in about 1 in 15,000 people. A patient registry is a well-known tool for collecting a sufficient number of patients with a rare disease to evaluate and monitor the patient's information in a standard and continuous way, as well as to conduct clinical research on the disease, which can be used for early diagnosis. Standard treatment and follow-up of PCD patients will help us. In this study, we developed a PCD registry for the Iranian population.

Materials and Methods:
In this study, for the first time in Iran, the PCD Registry was presented to record demographic information, clinical diagnostic symptoms, diagnosis method, management, and follow-up of patients called IPOLD (Iranian Pediatric Orphan Lung Disease). This PCD Registry can be used in all provinces of Iran, and a network of PCD treatment centers can be established. Two hundred fifty-six patients diagnosed with PCD, regarding demographic information, diagnostic clinical symptoms, disease diagnosis method, imaging, spirometry, and microbiological findings, were referred to university hospitals and clinics covered by the Tehran University of Medical Sciences from April 1401 to April 1402. We used SPSS to analyze data and performed descriptive tests.

Results:
In this study, the average age of disease diagnosis was 5.7 years. The most common diagnostic symptom of the patients was chronic cough, with the belief of 94.3%. 56.7% of patients with distress were hospitalized and hospitalized in infancy. Bronchiectasis was seen in CXR or Chest CT in 28 patients (11%), and the severity of bronchiectasis was evaluated using the Bronchiectasis Severity Index (BSI); 13 cases have mild bronchiectasis (46%) and 15 moderate cases (53%). Atelectasis was seen in 47% of patients, with the predominance of RML involvement in 35%. Lung infiltration was reported in 15% of patients. PCD diagnosis method in 46 patients was based on PICADAR clinical diagnosis, 173 patients by nasal nitric oxide test, 31 by genetic test, and six by TEM.

Conclusion:
The patients' information was registered in the registration system, IPOLD, Iran, for children's orphan lung disease.

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***Corresponding author:** E-mail: sh79316@yahoo.com*

Introduction

Primary ciliary dyskinesia (PCD) is a rare genetic disorder that affects the structure and function of cilia in the respiratory tract, reproductive system, and other organs. This condition primarily affects children and can lead to a wide range of symptoms and complications. This article will explore the introduction of primary ciliary dyskinesia in children, including its causes, prevalence, clinical presentation, diagnostic methods, and potential treatment options (1-4).

Cilia are tiny hair-like structures found on the surface of cells throughout the body. They play a crucial role in various physiological processes, including the movement of mucus, bacteria, and other foreign particles out of the respiratory tract. These cilia are structurally abnormal or dysfunctional in primary ciliary dyskinesia, impairing ciliary movement (5).

The exact cause of primary ciliary dyskinesia is genetic mutations that affect the proteins responsible for cilia structure and function. These mutations are usually inherited in an autosomal recessive manner, meaning both parents must carry a copy of the mutated gene for their child to develop the condition. However, in some cases, PCD can occur due to spontaneous mutations (6).

Primary ciliary dyskinesia is estimated to affect approximately 1 in 10,000 to 40,000 individuals worldwide, making it a rare disorder. The prevalence may vary among different populations and ethnicities. Although PCD can occur at any age, symptoms typically appear in early childhood (7).

Children with primary ciliary dyskinesia often present with chronic respiratory symptoms due to impaired mucociliary clearance. These symptoms may include persistent cough, recurrent respiratory infections (such as bronchitis or pneumonia), wheezing, nasal congestion, and sinusitis. Additionally, PCD can affect the functioning of other organs, leading to symptoms such as chronic ear infections, hearing loss, infertility, and laterality defects (where organs are positioned abnormally) (8,9). Diagnosing primary ciliary dyskinesia in children can be challenging due to the variability in symptoms and the rarity of the condition. A thorough evaluation is necessary, including a detailed medical history, physical examination, and specialized tests. These tests may include nasal nitric oxide measurement, ciliary biopsy, high-speed video microscopy, genetic testing, and imaging studies (10).

Early diagnosis of primary ciliary dyskinesia is crucial to prevent complications and initiate appropriate management strategies. Although there is no cure for PCD, treatment aims to alleviate symptoms, reduce the frequency and severity of respiratory infections, and improve overall quality of life. It may involve a multidisciplinary approach, including respiratory therapies (such as airway clearance techniques and inhalation medications), antibiotics for infections, hearing aids for hearing loss, fertility counseling, and surgical interventions when necessary (11-14).

Primary ciliary dyskinesia is a rare genetic disorder that affects the structure and function of cilia in children. It can lead to many symptoms and complications, primarily involving the respiratory tract and other organs. Early diagnosis and appropriate management are crucial in improving outcomes for children with PCD. Further research is needed to understand the underlying genetic mechanisms and develop targeted therapies for this condition. In this study, we developed a PCD registry for the Iranian population.

Materials and Methods

This project has been implemented as a cross-sectional study supervised by the Iranian pediatric and pulmonology centers. All data exchange was undertaken through the Tehran University of Medical Sciences. This study was approved by the ethical committee of the Tehran University of Medical Sciences.

Data analyses were performed with SPSS for Windows (Version 16). In this study, for the first time in Iran, the PCD Registry was developed and recorded patients' demographic characteristics, clinical symptoms, diagnostic methods, management, and follow-up of patients as a pilot called IPOLD (Iranian Pediatric Orphan Lung Disease). This PCD Registry can be used in all provinces of Iran and create a network

of PCD treatment centers to standardize diagnostic algorithms and evaluate the effectiveness of treatments. The patients' files from April 2022 and April 2023 were searched for data on all hospitalizations (admissions and outpatient contacts) in pediatric hospitals where the ICD10 codes Q89.3 (PCD). Data from the PCD Registry comprised information on children registered with at least one case in 2022 or earlier. Information on patients who had died or emigrated before 2022 was excluded from the database. Data entered SPSS, and we performed descriptive tests for data analysis.

Results

Of 256 patients referred to the clinic, 153 were boys (59.7%) and 103 were girls (40.2%). The age range of disease diagnosis was from one month to 18 years old, with an average age of 5.7 years. Seven (2.7%) were born preterm, and 249 (97.2%) were born at term. One hundred fifty-five patients (60.5%) had related parents. There was a history of infertility in first-degree relatives in 62 patients (24%) and two male patients with azoospermia. Twenty-four patients (9.3%) had a history of PCD in first-degree relatives, and 23 of them (8.9%) had a history of PCD in their siblings. The age of disease diagnosis in 111 patients was younger than five years (43%), and in 145 patients, the age was ≥ 5 years. The most common diagnostic symptom was chronic wet cough, with a prevalence of 94.3%. 56.7% of patients had a history of respiratory distress and hospitalization in infancy. A history of chronic otitis media in 38% of patients led to hearing loss in 17% of cases. Chronic rhinitis was reported in 78% of patients, and frequent sinusitis in 34.7% of patients. A history of recurrent pneumonia was reported in 42.4% of patients, and 10% of patients had chronic atelectasis. Dextrocardia and laterality defects were reported in 42.6% of patients (Figure 1).

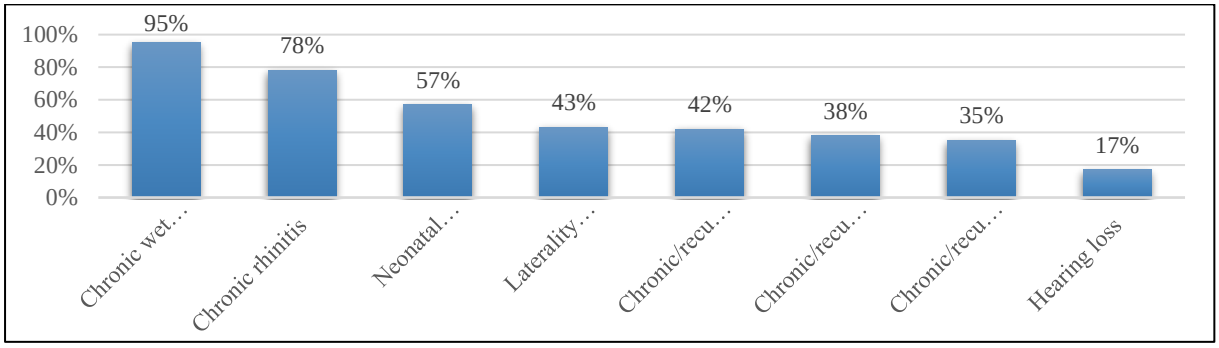

Fig 1: frequency of congenital and chronic diseases

The most common finding was coarse crackles in 92% of patients. Wheezing was reported in 82% of patients, and finger clubbing was detected in 10% of patients. Bronchiectasis was seen in CXR or Chest CT in 28 patients (11%), and the severity of bronchiectasis was checked using (BSI) Bronchiectasis Severity Index; 13 cases had mild bronchiectasis (46%) and 15 cases moderate (53%).

Atelectasis was seen in 47% of patients, with the predominance of RML involvement in 35%. Lung infiltration was reported in 15% of patients (Figure 2).

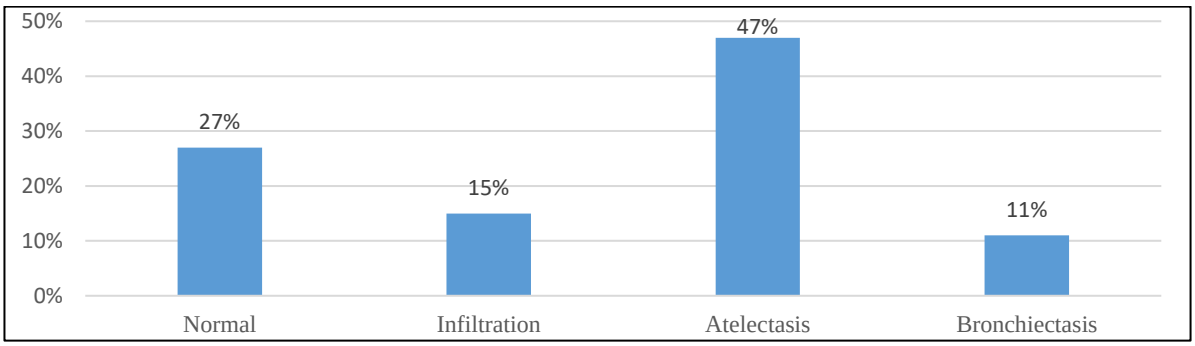

Fig 2: Radiographic findings of patients

Sputum and BAL cultures were positive in 41% of patients with Staphylococcus aureus, 24% had Hemophilus influenza, and 8% had Streptococcus pneumonia. Pseudomonas aeruginosa was positive in 5% of patients, and Pseudomonas colonization was seen in only two patients. PICADAR Score: All studied patients had scores ≥10.

Nasal NO Testing: 173 patients over five years of age had nNO < 77 nL/min with a range of 1 to 55 and an average of 29.8 (Figure 3).

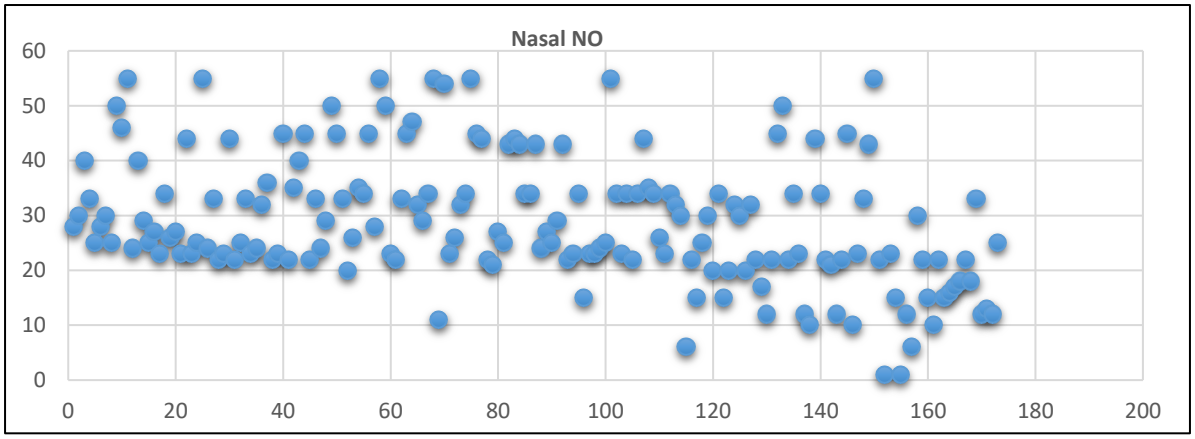

Fig 3: Distribution of Nasal NO Testing

Genetic testing was done on 31 patients. CCDC40 recessive autosomal mutation was reported in 10 patients (32%). The inheritance pattern was X-linked in 30 AR patients and one patient with PIH1D3 mutation. Other mutations included CCDC39, CCDC65, CCNO/5q11.2, COL12A1, DNAAF2, DNAH5, DNAH9, DNAHI2, DNAHN, DNAI2, GAS1 SPAG1. Two patients with CCDC40 and DNAAF2 mutations had a nasal nitric oxide test <77 nL/min.

Six patients were diagnosed with PCD using TEM. The structural defects of the cilia were observed in the examination with an electron microscope. Three patients had defects in the internal dynein arm, two in the internal and external dynein arms, and one in the external dynein arm. Spirometry was performed on 220 patients, of which 68% had obstructive spirometry, most had mild to moderate obstruction (87%), and about 13% had severe obstruction. Only two patients in Restrictive pattern spirometry and one mixed pattern patient were reported. The rest were normal (28%).

The most common drugs used by the patients were bronchodilators and hypertonic saline nebulizers (in 90% of patients), intranasal corticosteroids, and systemic antibiotics (often coamoxiclav and azithromycin). ENT surgeries were performed in 8.5% of patients. A history of lung exacerbation was reported in 83.7% of patients.

Discussion

PCD is a rare genetic heterogeneous disorder characterized by dysfunction of motile cilia that leads to chronic upper and lower respiratory tract infections, fertility problems, and organ orientation disorders (11,12). The inheritance pattern of PCD is often autosomal recessive and rarely autosomal dominant and X-dependent. (13). PCD is more common in societies where consanguineous marriage is common (14), as was also determined in our study. So far, 50 genetic mutations that lead to PCD and motile cilia dysfunction are known (11,14), and in this study, 12 types of PCD gene mutations were mentioned. In this study, the average age of disease diagnosis was 5.7 years.

Ciliated epithelial cells are present in the nasal cavity, paranasal sinuses, middle ear, airways, fallopian tubes, cervix, vas deferens, and ependyma. Dysfunction of respiratory system cilia leads to mucociliary clearance disorder and frequent and chronic infections of the respiratory system. Dysfunction of embryonic cilia leads to organ orientation disorders (dextrocardia, Situs inversus, and heterotaxis), and dysfunction of cilia in sperm flagellum and fallopian tubes leads to infertility (15).

Studies have shown that the clinical manifestations of PCD in children include chronic wet cough (the most common symptom), recurrent pneumonia (≥ 60% of patients), chronic rhinitis/sinusitis (≥ 60% of patients), chronic otitis media (≥ 60% of patients), decreased conductive hearing (20-60% of patients) (7). In addition, most PCD patients have a history of neonatal respiratory distress (about 80% of patients) (6). Situs inversus totalis is prevalent in 55% of patients and heterotaxy in 12% (13). Similarly, in this study, the most common diagnostic symptom of patients was chronic wet cough, with a prevalence of 94.3%. 56.7% of patients had a history of respiratory distress and hospitalization in infancy. A history of chronic otitis media in 38% of patients led to hearing loss in 17% of cases. Chronic rhinitis was reported in 78% of patients, and frequent sinusitis in 34.7% of patients.

A history of recurrent pneumonia was reported in 42.4% of patients, and 10% of patients had chronic atelectasis. Dextrocardia and laterality defects were reported in 42.6% of patients.

PICADAR is an accurate and valid clinical diagnostic tool for PCD, which is used for patients with persistent wet cough from early childhood and includes seven parameters predicting PCD, including gestational age, history of hospitalization in infancy, respiratory symptoms in infancy, stable rhinitis, and chronic symptoms related to ear and hearing, organ orientation disorders and heart defects. According to ERS studies, patients with a PICADAR Score ≥10 have a >90% chance of having a positive PCD diagnostic test. In this study, due to the unavailability of diagnostic tests for PCD and the limitations of diagnostic tests, PICADAR was used as a diagnostic test based on clinical symptoms in all patients studied, and all patients had Score ≥10 (2).

There are four major clinical criteria for the PCD phenotype according to the ATS guideline, including unexplained respiratory distress in term infants, daily cough throughout the year starting before the age of 6 months, daily nasal congestion and congestion all year long, starting before six months, and organ orientation defects. If at least two of these four criteria are positive in the patient, he should be referred for PCD diagnostic tests. Without at least two major criteria, PCD is unlikely for the patient. In this study, all patients had two major PCD criteria.

In the nasal nitric oxide (nNO) diagnostic test, nitric oxide (NO) is a colorless and odorless gas produced in the upper and lower respiratory epithelium. NO affects the respiratory system, including vasodilation, killing bacteria, and modulating inflammation. The paranasal sinuses mainly produce nasal nitric oxide. The ATS guideline has proposed the nasal nitric oxide test as a first-line screening test for PCD, which can be substituted if genetic testing is unavailable (3). The nasal nitric oxide test can be performed in children over five years old, with values less than 77 nL/min with a sensitivity and specificity of 98% and above 99%, respectively, for diagnostic PCD (>300 nl/min in healthy people). The reason for the low nNO is still being determined. Due to its non-specificity, nasal nitric oxide should not be used as the only diagnostic test for PCD. Its low level is seen in CF, diffuse panbronchiolitis, acute viral infection of the upper respiratory tract, and certain types of primary immunodeficiency. Therefore, before testing, CF should be ruled out by sweat testing or CFTR mutation genetic testing, as up to one-third of CF patients have NO less than 77 nL/min.

This test is simple, fast, non-invasive, and inexpensive; it can be performed on children over five years old who can cooperate. Chemiluminescence NO analyzers are expensive, and their availability is limited. This test can be done in three ways (Exhalation against mouth resistor, breath-hold measurement, and tidal breathing nNO measurements). ATS/ERS guidelines recommend exhalation against resistance as the preferred method.

In this method, the technician puts the nasal probe into the patient's nostril and asks the patient to hold it with his hand, then he asks the patient to take a deep breath, and then he puts the mouth resistor in the patient's mouth, and the patient purses his lips. It closes and slightly inflates its cheeks. The patient begins a slow exhalation with a low, long flow until the technician orders to stop or the patient stops breathing. After a successful test, with an interval of about 30

seconds, the next test is performed on the nose of the opposite side (16). In our study, 173 patients underwent a nasal nitric oxide test in the breathing test clinic of the medical center hospital, and in all these patients, the nasal nitric oxide level was less than 77 nL/min.

So far, 50 genes that lead to PCD and cilia dysfunction have been identified. However, genetic tests are expensive, and available genetic panels only contain 32 genes. In addition, not all PCD mutations are known, and existing genetic tests can only detect 65% of cases, so a negative test does not rule out PCD. In our study, genetic testing was performed on 31 patients. CCDC40 recessive autosomal mutation was reported in 10 patients (32%). The inheritance pattern was X-linked in 30 AR patients and one patient with PIH1D3 mutation. Other mutations included CCDC39, CCDC65, CCNO/5q11.2, COL12A1, DNAAF2, DNAH5, DNAH9, DNAHI2, DNAHN, DNAI2, GAS1 SPAG1. Two patients with CCDC40 and DNAAF2 mutations had a nasal nitric oxide test <77 nL/min (3).

Transmission electron microscopy (TEM) was used to analyze the structure of cilia, and PCD was considered the gold standard diagnostic test. The cross-section of a normal cilium shows a 9+2 arrangement pattern, with nine pairs of microtubules arranged around a central pair of microtubules. Inner dynein arms (IDA) and outer dynein arms (ODA) are located along the microtubules and provide the movement force of the cilia. Radial spokes and nexin connections lead to the stability of the ciliary axoneme (3).

This test has many limitations, and its results are influenced by way of sample collection (for example, nasal scraping or endobronchial mucus or pinch tracheal biopsies) and the way the sample is processed (choice of fixators and the skill of the technician in selecting a few ciliary tufts from the sample) and image quality.

TEM is located. The interpretation of this test is also challenging and requires a pathologist with extensive experience in cilia examination. Non-specific TEM changes due to exposure to environmental pollutants as infections can mimic the appearance of PCD (3). An international guideline is used to reliably diagnose only the PCD hallmark defects to solve these challenges, including Class 1: lack of ODA, lack of ODA+IDA, and lack of IDA with microtubule disorganization.

About 30% of PCD cases proven by genetic testing do not have structural defects in TEM, which is due to the limited sensitivity of this test in detecting small structural changes in the ciliary axoneme. The ATS guideline recommends TEM as a second-line diagnostic test for inconclusive genetic testing (3).

In our study, in 6 patients with clinical symptoms consistent with PCD, the diagnosis of the disease was confirmed with this test. Three patients had defects in the internal dynein arm, two in the internal and external dynein arms, and one in the external dynein arm.

Imaging findings in PCD are usually non-specific and show consolidation, atelectasis, and bronchiectasis. Bronchiectasis happens more commonly in the middle lobe, lingula, and lower lobes (5,7). In this study, bronchiectasis was seen in CXR or Chest CT in 28 patients (11%), and the severity of bronchiectasis was evaluated using the Bronchiectasis Severity Index (BSI). 13 cases had mild bronchiectasis (46%) and 15 moderate cases (53%). Atelectasis was seen in 35% of patients with RML involvement and 47% of those with atelectasis. Lung infiltration was reported in 15% of patients.

ERS/ATS has introduced the Pediatric Bronchiectasis Severity Index (PBSI) as a tool to determine the severity of bronchiectasis in children to determine the severity of treatment and risk of mortality and hospitalization. In our study, the severity of bronchiectasis was checked using BSI; 13 cases had mild (46%), and 15 had moderate (53%) (17). Microbiological cultures of sputum or BAL in PCD usually grow organisms such as Haemophilus influenzae (65% of cases), Staphylococcus aureus, Moraxella catarrhalis, Streptococcus viridens and Streptococcus pneumoniae.

Chronic Pseudomonas infection and NTM are usually seen in adults with progressive disease (12-14). In this study, the most common sputum culture or BAL organism was Staphylococcus aureus (41%), and 24% of patients had Hemophilus influenzae. Pseudomonas aeruginosa was positive in 5% of patients, and Pseudomonas colonization was seen in only two patients.

Pulmonary function tests may be normal in early childhood; however, obstructive airway disease is commonly seen (≥ 60% of patients). Several recent studies have shown that lung function in PCD is disturbed from an early age and is related to the severity of clearance disorder and microtubular structural defects. Similarly, in our study, 68% of patients had an obstructive pattern in spirometry.

PCD treatment is supportive and aims to maintain or improve lung function with early diagnosis and aggressive treatment of disease complications. Studies emphasize the importance of improving airway clearance with chest physiotherapy and exercise. Aggressive antibiotic treatment of infections and prevention of infections with vaccination and avoidance of stimulants and cigarette smoke are recommended. It is recommended to regularly follow up with spirometry, microbiological cultures, examination of airway clearance techniques, and Chest CT.

Monitoring of upper airways, including regular hearing tests, referral to ENT specialists, and sleep tests, are also recommended in these patients (5,13).

Conclusion: In this study, 256 patients diagnosed with PCD were studied regarding demographic findings, clinical symptoms, diagnosis, lung function test results, microbiological cultures, imaging findings, and treatment methods.

We found that a high percentage of patients are diagnosed after the age of 5, which affects the progression of their disease. In this study, PICADAR diagnostic tests, nasal nitric oxide tests, and genetic tests played an important role in PCD diagnosis. Our goal was early diagnosis of PCD, timely initiation of treatment, and regular follow-up of these patients to prevent irreversible lung damage and reduce the hospitalization rate, mortality, and morbidity of these patients.

In this study, for the first time in Iran, the PCD Registry was provided to record demographic information, diagnostic clinical symptoms, diagnosis method, management, and follow-up of patients called IPOLD (Iranian Pediatric Orphan Lung Disease). PCD Registry can be used in all provinces of Iran and create a network of PCD treatment centers to standardize diagnostic algorithms and evaluate the effectiveness of treatments.

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