



# Adult patients with idiopathic pulmonary hemosiderosis: a comprehensive review of the literature

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Received: 15 January 2022 / Revised: 1 February 2022 / Accepted: 15 February 2022 / Published online: 18 February 2022  
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## Abstract

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease without a known incidence or prevalence in adults. Our knowledge of this entity is limited as there is no prospective or retrospective study with a reasonable number of patients. The objective is to describe the demographics, clinical manifestations, diagnosis, treatment, and prognosis of adult patients with IPH. The Medline and Embase databases were searched from inception to 2021 with appropriate search formulas to identify relevant articles following strict inclusion and exclusion criteria. Statistical analyses were performed for the entire cohort and prespecified subgroups. A total of 84 patients were identified. The majority of patients were males 54/84 (64.3%). The median age was 27 years. The manifesting symptoms were present in the following frequencies: anemia 76/83 (91.6%), dyspnea 71/83 (85.5%), hemoptysis 70/84 (83.3%), cough 22/84 (26.2%), and chest pain 9/84 (10.7%). The classic triad was present in 61/84 (79%) patients. The mean hemoglobin during the initial presentation was 8.4 gm/dL. A total of 16/57 (19.5%) tested positive for autoantibodies. The median delay in the diagnosis of IPH was 1.02 years. Immunosuppressive therapy was prescribed in 49/79 (62%) patients, and recurrence occurred in more than half of the patients 36/66 (54.5%). A total of 63/79 (79.7%) patients were alive during the final follow-up. IPH is more common in young adults with a male predominance. A high index of suspicion is necessary to attain an early diagnosis and possibly reduce the short-term mortality of nearly 20% and long-term complications.

**Keywords** Adult · Autoantibody · Corticosteroid · Demographics · Idiopathic pulmonary hemosiderosis · Prognosis · Survival

## Introduction

Idiopathic pulmonary hemosiderosis (IPH) is characterized by diffuse alveolar hemorrhage (DAH) by an unknown mechanism. Our knowledge of adult IPH is limited, primarily due to the lack of prospective or retrospective studies with a sizeable number of patients. As a result, clinical information, often inadequate, has been obtained mostly from

case reports and small case series. Given the rarity of IPH, the feasibility of a large prospective study in the future is also questionable.

A recent study published in 2017 attempted to elucidate several aspects of adult IPH by analyzing the cases reported between 2000 and 2015 in Medline and Chinese databases [1]. The authors identified a total of 37 patients and reported their demographics, symptomatology, delay in diagnosis, treatment, and prognosis. However, the study had two critical limitations. First, the number of patients was modest at best, as only patients reported in the past 15 years were included. Second, several patients included in this study were either diagnosed with IPH when they were in the pediatric age group [2] or had provided inadequate information about individual patients [3, 4].

We undertook this project to overcome these challenges and shed light on IPH in the adult population. To do so, we have created an “Adult IPH Database” from all reported adult cases in the Medline and Embase databases since their

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inception. We have followed strict criteria for inclusion of patients into our database. We aim to inform the reader regarding the demographics, clinical manifestations, diagnosis, treatment, and prognosis of adult patients with IPH.

## Materials and methods

### Creation of IPH database

This is a retrospective study of adult IPH cases reported in the literature. We searched the Medline and Embase databases from their inception to December 31, 2021, with the appropriate MeSH terms and formula to identify adult patients with IPH. The following search formula was used: “idiopathic pulmonary hemosiderosis OR IPH OR pulmonary hemosiderosis AND adult”; and “idiopathic pulmonary hemosiderosis OR IPH OR pulmonary hemosiderosis.” The identified citations were then screened to exclude duplicates, abstracts, and pediatric patients. The full texts of the remaining manuscripts were examined by two independent reviewers (BKS and AB). The reviewers also meticulously hand searched the bibliography of the included manuscripts to identify additional papers. An exhaustive effort was implemented to obtain all available manuscripts. However, we could not find some manuscripts that were primarily reported in the 1950s and 1960s.

### Patient population

The patient population consisted of adult patients with IPH reported in the literature. Patients diagnosed with IPH as a child but subsequently reported as adults were excluded from this study. Similarly, if the diagnosis of IPH was made based on clinical presentation and radiologic appearance without demonstration of hemosiderin-laden macrophages (HLM) from respiratory tract samples, they were not considered to have IPH. Patients with pulmonary hemorrhage (without lung biopsy) who had clinical manifestations suggestive of established autoimmune diseases were also excluded. For the purpose of subgroup analysis, the entire cohort was divided into two, patients reported between 1950 and 1990 (cohort A) and from 1990 to 2021 (cohort B). We arbitrarily chose this cut-off as testing for autoantibodies, including antineutrophil cytoplasmic antibody (ANCA), became more common in clinical practice in the early 1990s.

### Study objectives

The primary objectives of the study were as follows: (1) determination of demographics, delay in diagnosis, clinical and radiologic manifestations, the prevalence of autoantibodies, treatment, and prognosis among adult patients with

IPH. The secondary objectives were to assess any potential differences between cohorts A and B.

### Inclusion criteria

Reported manuscripts fulfilling the following criteria were included in the study: (1) adult patients who were diagnosed with IPH at the age of 18 and above, (2) the diagnosis of IPH was made by histopathologic analysis of lung tissue obtained either by biopsy (bronchoscopic or surgical) or on autopsy studies, (3) in the absence of a tissue sample, demonstration of HLM from bronchoalveolar lavage (BAL) and sputum were considered adequate, (4) patients reported from the inception of the databases to December 31, 2021.

### Exclusion criteria

The exclusion criteria were as follows: (1) Patients with adult-onset IPH for whom adequate information could not be obtained from the published manuscript, (2) studies that primarily reported long-term complications of a previously diagnosed case of IPH, (3) adult IPH cases reported as meeting abstracts, (4) manuscripts reported in a non-English language.

### Definitions

“Delay in diagnosis” denoted the duration between the first reported respiratory symptoms and the diagnosis of IPH. “Definite IPH” was defined as patients for whom the diagnosis was secured by histopathologic examination of the lung, either by lung biopsy or on autopsy. “Probable IPH” was characterized by consistent clinical and radiologic findings and demonstration of HLM from a sample obtained from the respiratory tract without a histopathologic proof. “Recurrence of disease” represented any deterioration of the patient’s condition with signs or symptoms consistent with IPH, new or worsening radiologic infiltrate, or requirement of reinitiation of increased immunosuppressive medications. Regarding clinical manifestations, systemic symptoms included any of the following: fever, night sweats, chills, weight loss, loss of appetite, fatigue, and malaise.

### Data items

The included studies were coded, and the extracted data were then tabulated in a standardized Excel sheet (Microsoft Corporation). The following data were gathered: author name, year of reporting, country of the study, patient demographics, presenting symptoms, delay between the symptom onset and the diagnosis of IPH, testing for autoantibodies, autoantibody positivity, type of positive autoantibodies, temporal relationship of autoantibody determination with

the diagnosis of IPH, clinical and radiologic manifestations, lung biopsy results when available, treatment and clinical outcome of the disease.

### Statistical analysis

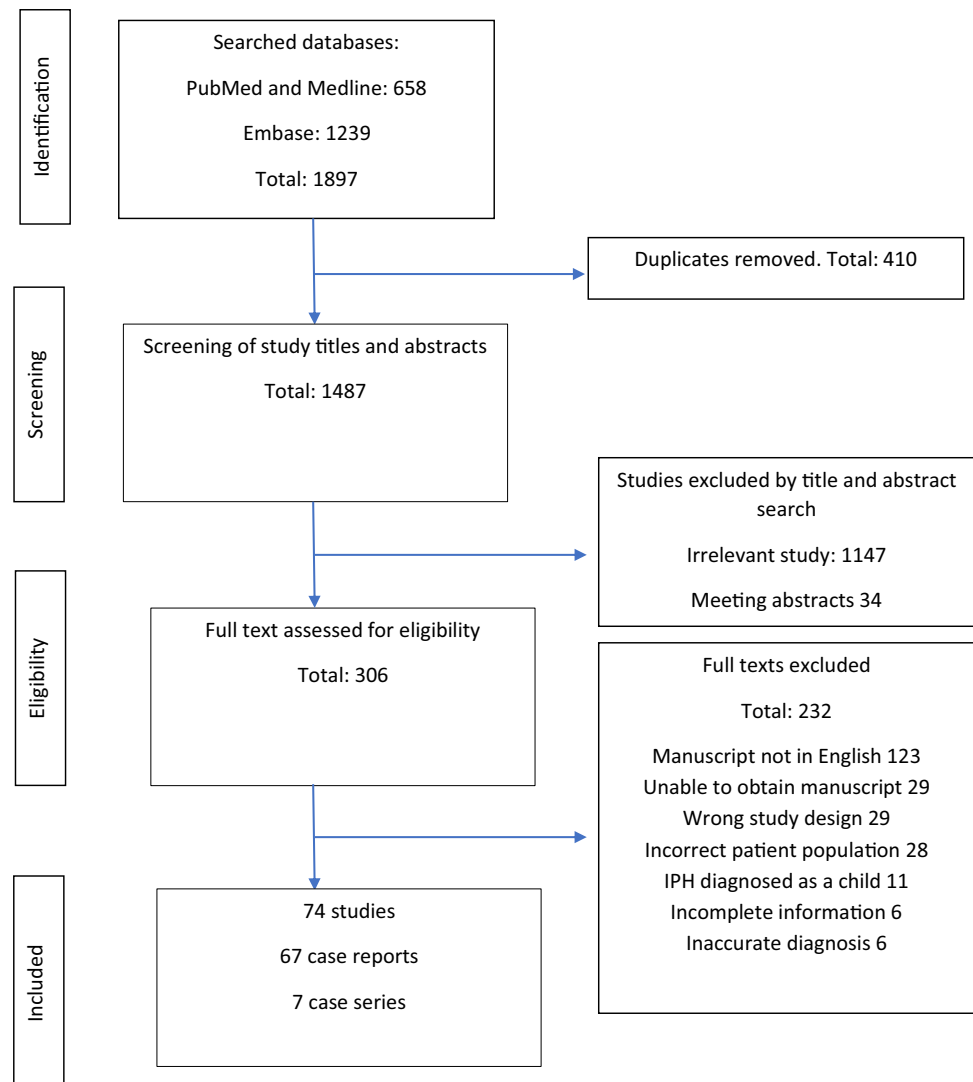
Descriptive and inferential statistical analyses were performed using the IBM SPSS statistics software package 28. Normally and non-normally distributed data were reported as mean (standard deviation, SD) and median (interquartile range, IQR), respectively. In addition, independent *t*-test was used to compare continuous variables, and chi-square test was used to compare categorical variables. Univariate and multivariate analyses of continuous variables were performed to identify risk factors for poor outcomes, namely risks of recurrence and survival.

## Results

### Study characteristics

Seventy-four manuscripts fulfilling the inclusion criteria were included in this study [5–79]. The study selection process is shown in Fig. 1. No prospective studies were identified. A retrospective study by Miwa et al. that included nine patients was not included in this review as the information regarding individual patients was limited [3]. Similarly, patients from 2 additional retrospective studies were excluded due to inadequate information, inaccurate diagnosis, and being previously reported by other authors [80, 81]. Of the 74 studies, 67 papers were a single case report, whereas the other 7 were small case series. The patients were reported from all continents (Table 1).

**Fig. 1** Flow chart showing the selection of studies



**Table 1** Patient demographics, clinical manifestations, diagnostic modalities, treatment, and outcomes

| Author              | Year | Country   | Gender | Age at IPH diagnosis | Symptom onset to diagnosis in weeks | Ab checked (Ab if positive) | Classic triad | Histopathology  | Immunosuppression | Follow-up period in years | Recurrence | Survived |
|---------------------|------|-----------|--------|----------------------|-------------------------------------|-----------------------------|---------------|-----------------|-------------------|---------------------------|------------|----------|
| Tait et al          | 1952 | UK        | M      | 31                   | 45                                  | No                          | No            | Yes (autopsy)   | No                | 2                         | Yes        | No       |
| Manderson et al     | 1954 | UK        | M      | 22                   | 156                                 | No                          | Yes           | No (sputum HLM) | No                | 1                         | Yes        | Yes      |
| Hamer et al         | 1955 | Singapore | M      | 19                   | 312                                 | No                          | Yes           | No (sputum HLM) | No                | 3                         | Yes        | Yes      |
| Browning et al      | 1956 | USA       | M      | 25                   | 52                                  | No                          | Yes           | Yes (autopsy)   | No                | NS                        | Yes        | No       |
| Browning et al      | 1956 | USA       | M      | 22                   | 211                                 | No                          | Yes           | Yes (autopsy)   | No                | NS                        | Yes        | No       |
| Browning et al      | 1956 | USA       | M      | 29                   | 156                                 | No                          | Yes           | No (sputum HLM) | Yes               | 3                         | Yes        | Yes      |
| Wynn-Williams et al | 1956 | UK        | M      | 28                   | NS                                  | No                          | Yes           | Yes (SLB)       | No                | 1                         | Yes        | Yes      |
| Boyd et al          | 1959 | UK        | M      | 37                   | 936                                 | No                          | Yes           | Yes (autopsy)   | No                | NA                        | NS         | No       |
| Boyd et al          | 1959 | UK        | M      | 33                   | 8                                   | No                          | No            | Yes (SLB)       | No                | 4                         | No         | Yes      |
| Boyd et al          | 1959 | UK        | F      | 19                   | 208                                 | No                          | Yes           | No (sputum HLM) | Yes               | 0.25                      | Yes        | Yes      |
| Gurewich et al      | 1959 | USA       | F      | 22                   | 3                                   | No                          | Yes           | Yes (SLB)       | Yes               | 1                         | No         | Yes      |
| Nickol              | 1960 | UK        | F      | 36                   | 260                                 | No                          | Yes           | Yes (SLB)       | Yes               | 1                         | Yes        | Yes      |
| Yettra et al        | 1960 | UK        | M      | 23                   | 208                                 | No                          | Yes           | No (sputum HLM) | No                | 7                         | Yes        | Yes      |
| Spreace et al       | 1963 | Germany   | M      | 20                   | 4                                   | No                          | NS            | Yes (autopsy)   | Yes               | NS                        | NS         | No       |
| Murphy et al        | 1965 | Australia | M      | 25                   | 52                                  | No                          | Yes           | Yes (autopsy)   | Yes               | NS                        | Yes        | No       |
| Samuels et al       | 1965 | USA       | F      | 22                   | 6                                   | No                          | Yes           | Yes (TBLB)      | No                | 4                         | No         | Yes      |
| Sarkar et al        | 1965 | UK        | M      | 42                   | 38                                  | No                          | Yes           | Yes (SLB)       | Yes               | NS                        | No         | Yes      |
| Aledort et al       | 1967 | USA       | M      | 23                   | 55                                  | No                          | No            | No (sputum HLM) | No                | 1                         | NS         | Yes      |
| DeGowin et al       | 1968 | USA       | F      | 44                   | 104                                 | No                          | Yes           | Yes (SLB)       | No                | 0.58                      | Yes        | Yes      |
| Elliot et al        | 1970 | USA       | M      | 21                   | 156                                 | No                          | No            | Yes (SLB)       | NS                | NS                        | NS         | NS       |
| Byrd et al          | 1973 | USA       | M      | 22                   | 156                                 | No                          | Yes           | Yes (SLB)       | Yes               | 4                         | No         | Yes      |
| Irwin et al         | 1974 | USA       | M      | 21                   | 8                                   | Yes                         | Yes           | Yes (SLB)       | No                | 1.58                      | Yes        | Yes      |
| Jiji et al          | 1974 | USA       | M      | 33                   | 312                                 | No                          | No            | Yes (autopsy)   | Yes               | NS                        | NS         | No       |
| Donlan et al        | 1975 | USA       | M      | 37                   | 312                                 | No                          | Yes           | Yes (SLB)       | No                | NS                        | No         | Yes      |
| Donald et al        | 1975 | Australia | F      | 18                   | 2                                   | Yes                         | Yes           | Yes (SLB)       | Yes               | 0.75                      | Yes        | Yes      |
| Donald et al        | 1975 | Australia | M      | 21                   | 12                                  | Yes                         | Yes           | Yes (SLB)       | Yes               | 0.58                      | Yes        | Yes      |
| Rodriguez et al     | 1980 | Spain     | F      | 52                   | 78                                  | Yes                         | Yes           | Yes (TBLB)      | Yes               | 0.5                       | No         | Yes      |
| Moses et al         | 1982 | USA       | F      | 21                   | 208                                 | Yes                         | Yes           | No (sputum HLM) | No                | 9                         | No         | Yes      |
| Ludmerer et al      | 1986 | USA       | M      | 36                   | 8                                   | Yes                         | Yes           | Yes (SLB)       | No                | 0.16                      | No         | Yes      |
| Nomura et al        | 1987 | Japan     | F      | 43                   | 1                                   | Yes                         | Yes           | Yes (TBLB)      | NS                | NS                        | NS         | NS       |
| Bain et al          | 1989 | UK        | M      | 27                   | 104                                 | Yes (antithyroid)           | Yes           | Yes (SLB)       | No                | 12                        | Yes        | Yes      |
| Chaudhry et al      | 1991 | UK        | F      | 53                   | 26                                  | Yes                         | Yes           | Yes (TBLB)      | No                | NS                        | NS         | Yes      |
| Pacheco et al       | 1991 | Spain     | M      | 22                   | 780                                 | Yes (anti-CD)               | Yes           | Yes (TBLB)      | No                | 4                         | No         | Yes      |
| Bouros et al        | 1994 | Greece    | M      | 19                   | 52                                  | Yes (anti-CD)               | Yes           | Yes (TBLB)      | No                | 0.5                       | No         | Yes      |
| Bavry et al         | 2000 | USA       | M      | 39                   | 0.7                                 | Yes                         | Yes           | Yes (TBLB)      | NS                | NS                        | NS         | NS       |
| Godoy et al         | 2000 | Brazil    | M      | 48                   | 78                                  | Yes                         | No            | Yes (SLB)       | Yes               | 0.58                      | Yes        | No       |

Table 1 (continued)

| Author             | Year | Country   | Gender | Age at IPH diagnosis | Symptom onset to diagnosis in weeks | Ab checked (Ab if positive) | Classic triad | Histopathology | Immunosuppression | Follow-up period in years | Recurrence | Survived |
|--------------------|------|-----------|--------|----------------------|-------------------------------------|-----------------------------|---------------|----------------|-------------------|---------------------------|------------|----------|
| Tedeschi et al     | 2001 | Italy     | F      | 27                   | 312                                 | NS                          | NS            | Yes (VATS)     | Yes               | 3                         | Yes        | Yes      |
| Helman et al       | 2003 | USA       | F      | 27                   | NS                                  | Yes                         | Yes           | Yes (SLB)      | Yes               | 1.42                      | Yes        | Yes      |
| Helman et al       | 2003 | USA       | F      | 20                   | 52                                  | Yes                         | Yes           | Yes (SLB)      | Yes               | NS                        | Yes        | No       |
| Malhotra et al     | 2004 | India     | M      | 28                   | 208                                 | Yes (anti-CD)               | Yes           | Yes (TBLB)     | No                | 0.5                       | No         | Yes      |
| Turray et al       | 2004 | Turkey    | F      | 27                   | 104                                 | Yes                         | Yes           | Yes (SLB)      | Yes               | 1                         | No         | Yes      |
| Ioachimescu et al  | 2005 | USA       | M      | 77                   | 78                                  | Yes                         | No            | Yes (SLB)      | Yes               | 7                         | Yes        | Yes      |
| Soto et al         | 2005 | USA       | F      | 24                   | 1                                   | No                          | Yes           | No (BAL, HLM)  | Yes               | NS                        | NS         | Yes      |
| Corte et al        | 2006 | Australia | M      | 18                   | 8                                   | Yes                         | Yes           | Yes (TBLB)     | No                | 0.125                     | No         | Yes      |
| Deniz et al        | 2007 | Turkey    | M      | 20                   | 3                                   | Yes                         | Yes           | Yes (SLB)      | Yes               | 0.33                      | No         | Yes      |
| Gencer et al       | 2007 | Turkey    | F      | 23                   | 208                                 | Yes                         | No            | No (BAL)       | No                | 2                         | NS         | No       |
| Gencer et al       | 2007 | Turkey    | F      | 18                   | NS                                  | Yes                         | No            | Yes (SLB)      | Yes               | NS                        | NS         | Yes      |
| Jecko et al        | 2007 | UK        | F      | 20                   | 156                                 | Yes                         | Yes           | No (BAL, HLM)  | No                | 2                         | Yes        | Yes      |
| Bal et al          | 2008 | India     | M      | 32                   | 26                                  | Yes                         | Yes           | Yes (autopsy)  | No                | NS                        | NS         | No       |
| Chen et al         | 2008 | Taiwan    | F      | 50                   | 208                                 | Yes                         | Yes           | Yes (TBLB)     | Yes               | 0.083                     | No         | Yes      |
| Harte et al        | 2008 | Ireland   | F      | 26                   | NS                                  | Yes                         | No            | Yes (VATS)     | Yes               | 7                         | Yes        | Yes      |
| Harte et al        | 2008 | Ireland   | M      | 38                   | NS                                  | Yes                         | Yes           | Yes (SLB)      | Yes               | 3                         | Yes        | No       |
| Mayes et al        | 2008 | USA       | M      | 40                   | 12                                  | Yes (anti-CD)               | Yes           | Yes (VATS)     | Yes               | 0.5                       | Yes        | Yes      |
| Dutkiewicz et al   | 2010 | USA       | M      | 74                   | 104                                 | Yes (anti-RF)               | Yes           | Yes (VATS)     | Yes               | 0.67                      | Yes        | Yes      |
| Fatma et al        | 2010 | Tunisia   | M      | 50                   | 2                                   | Yes                         | Yes           | Yes (SLB)      | Yes               | 0.16                      | Yes        | No       |
| Fuji et al         | 2010 | Japan     | M      | 83                   | 4                                   | Yes (antithyroid)           | No            | No (BAL, HLM)  | Yes               | NS                        | No         | Yes      |
| Man et al          | 2010 | Romania   | M      | 18                   | 20                                  | Yes                         | Yes           | Yes (SLB)      | Yes               | 2.5                       | No         | Yes      |
| Nishino et al      | 2010 | USA       | F      | 50                   | NS                                  | Yes (anti-CD)               | No            | Yes (SLB)      | NS                | NS                        | NS         | NS       |
| Ramirez et al      | 2010 | Mexico    | M      | 18                   | 34                                  | No                          | NS            | Yes (autopsy)  | NS                | NS                        | NS         | No       |
| Schroers et al     | 2010 | Germany   | F      | 19                   | 4                                   | Yes                         | Yes           | Yes (TBLB)     | Yes               | 1.4                       | No         | Yes      |
| De santos et al    | 2012 | Brazil    | M      | 29                   | 20                                  | Yes (anti-CD)               | Yes           | No (BAL, HLM)  | No                | 0.5                       | No         | Yes      |
| Kahraman et al     | 2012 | Turkey    | M      | 23                   | 156                                 | Yes                         | Yes           | Yes (VATS)     | Yes               | 8                         | Yes        | Yes      |
| Tzouveleakis et al | 2012 | Greece    | M      | 27                   | 104                                 | Yes                         | No            | Yes (VATS)     | Yes               | 0.25                      | No         | Yes      |
| Cambuzzi et al     | 2013 | Brazil    | M      | 45                   | 52                                  | Yes                         | No            | Yes (SLB)      | Yes               | 0.17                      | Yes        | Yes      |
| Gerherdy et al     | 2013 | Australia | F      | 29                   | 60                                  | Yes                         | Yes           | Yes (TBLB)     | Yes               | 1.5                       | Yes        | Yes      |
| Patrucco et al     | 2013 | Italy     | M      | 27                   |                                     | Yes                         | Yes           | Yes (TBLB)     | Yes               | 4                         | Yes        | Yes      |
| Singhal et al      | 2013 | India     | M      | 27                   | 8                                   | Yes (anti-CD)               | Yes           | No (BAL, HML)  | No                | 1                         | No         | Yes      |
| Moses et al        | 2014 | India     | F      | 38                   | 12                                  | Yes                         | Yes           | Yes (TBLB)     | Yes               | 0.083                     | No         | Yes      |
| Berger et al       | 2015 | USA       | F      | 26                   | 26                                  | Yes (anti-CD)               | Yes           | Yes (TBLB)     | Yes               | 4                         | No         | Yes      |
| Khilnani et al     | 2015 | India     | M      | 19                   | 156                                 | Yes (anti-CD)               | Yes           | Yes (TBLB)     | No                | 2                         | No         | Yes      |

Table 1 (continued)

| Author            | Year | Country  | Gender | Age at IPH diagnosis | Symptom onset to diagnosis in weeks | Ab checked (Ab if positive) | Classic triad | Histopathology      | Immunosuppression | Follow-up period in years | Recurrence | Survived |
|-------------------|------|----------|--------|----------------------|-------------------------------------|-----------------------------|---------------|---------------------|-------------------|---------------------------|------------|----------|
| Sherani et al     | 2015 | India    | F      | 48                   | 1                                   | Yes                         | Yes           | Yes (VATS)          | Yes               | 1.5                       | No         | Yes      |
| Karatas et al     | 2016 | Turkey   | M      | 21                   | 1                                   | Yes (anti-CD)               | Yes           | No (BAL HLM)        | No                | 0.5                       | No         | Yes      |
| Popp et al        | 2016 | Romania  | F      | 48                   |                                     | Yes (anti-CD)               | Yes           | No (BAL HLM)        | Yes               | 0.5                       | No         | Yes      |
| Prabhu et al      | 2016 | India    | M      | 69                   | 52                                  | Yes                         | Yes           | No (BAL HLM)        | Yes               | 0.083                     | Yes        | No       |
| Agarwal et al     | 2017 | India    | M      | 27                   | 156                                 | Yes                         | Yes           | Yes (VATS)          | Yes               | NS                        | NS         | Yes      |
| Silva et al       | 2017 | Portugal | F      | 19                   | 468                                 | Yes                         | Yes           | Yes (SLB)           | Yes               | 6                         | Yes        | Yes      |
| Kania et al       | 2019 | Poland   | M      | 54                   | 156                                 | Yes                         | No            | Yes (TBLB)          | Yes               | 0.25                      | No         | Yes      |
| Butt et al        | 2020 | Pakistan | M      | 26                   | 1                                   | Yes                         | Yes           | No (sequential BAL) | Yes               | NS                        | Yes        | Yes      |
| Butt et al        | 2020 | Pakistan | F      | 26                   | 208                                 |                             | Yes           | Yes (SLB)           | Yes               | NS                        | NS         | No       |
| Gocho et al       | 2020 | Japan    | F      | 52                   | 208                                 | Yes                         | No            | Yes (VATS)          | No                | 5                         | Yes        | Yes      |
| Poberezhets et al | 2020 | Ukraine  | M      | 30                   | 1                                   | Yes                         | Yes           | No (BAL HLM)        | Yes               | NS                        | NS         | Yes      |
| Austin et al      | 2021 | USA      | M      | 39                   | 520                                 | Yes (anti-CD)               | Yes           | Yes (VATS)          | Yes               | NS                        | NS         | NS       |
| Iwasaki et al     | 2021 | Japan    | M      | 50                   | 312                                 | Yes                         | Yes           | No (BAL HLM)        | Yes               | 1.5                       | Yes        | Yes      |
| Walsh et al       | 2021 | Ireland  | M      | 50                   | 6                                   | Yes (anti-GM-CSF)           | No            | Yes (VATS)          | Yes               | NS                        | No         | Yes      |

BAL, bronchoalveolar lavage; CD, celiac disease; F, female; HLM, hemosiderin laden macrophages; M, male; NS, not specified; RF, rheumatoid factor; SLB, surgical lung biopsy; TBLB, trans-bronchial lung biopsy; VATS, video-assisted thoracoscopic surgery

## Subject demographics

A total of 84 patients were included in this review. A total of 31/84 (36.9%) patients were reported between 1950 and 1990 and the remaining 53/84 (63.1%) between 1991 and 2021. The median age of the entire cohort at the time of IPH diagnosis was 27 (IQR 22–39.7 years). The majority of patients were males 54/84 (64.3%). The demographic data among the subgroup of patients are detailed in Table 2. The age at diagnosis of IPH did not vary statistically depending on the gender of the patient in the entire cohort,  $t(82) = 0.44$ ,

**Table 2** Patient's demographics and delay in the diagnosis of IPH

| Patient demographics                      | Mean (SD)<br>Median (IQR)         |
|---|-----------------------------------|
| <b>Age at IPH diagnosis in years</b>      |                                   |
| All patients                              | 32.51 (14.46)<br>27 (22–39.7)     |
| Male                                      | 33.03 (15.52)<br>27.5 (IQR 17)    |
| Female                                    | 31.57 (12.53)<br>26.5 (IQR 24.25) |
| Age at IPH diagnosis (1950–1990 cohort)   |                                   |
| All patients                              | 28.19 (8.89)<br>25 (21–36)        |
| Male                                      | 27.13 (6.67)<br>25 (IQR 11.25)    |
| Female                                    | 30.28 (13.00)<br>22 (IQR 23)      |
| Age at IPH diagnosis (1991–2021 cohort)   |                                   |
| All patients                              | 35.03 (16.46)<br>25 (22.5–48)     |
| Male                                      | 37.09 (18.44)<br>29.5 (IQR 27.25) |
| Female                                    | 31.90 (12.64)<br>27 (IQR 26.50)   |
| <b>Delay in diagnosis in weeks</b>        |                                   |
| All patients                              | 53.5 (8–195)                      |
| Male                                      | 52 (148)                          |
| Female                                    | 78 (203)                          |
| Delay in IPH diagnosis (1950–90 cohort)   |                                   |
| Male                                      | 104 (184.5)                       |
| Female                                    | 78 (205)                          |
| Delay in IPH diagnosis (1991–2021 cohort) |                                   |
| Male                                      | 43 (150)                          |
| Female                                    | 82 (192.5)                        |
| <b>Gender</b>                             |                                   |
|   | Percentage                        |
| Male (entire cohort)                      | 54/84 (64.3%)                     |
| Male (1950–1990 cohort)                   | 22/31 (71%)                       |
| Male (1991–2021 cohort)                   | 32/53 (60.4%)                     |

IPH, idiopathic pulmonary hemosiderosis; IQR, interquartile range; SD, standard deviation

$p = 0.329$ . The reported cases with age distribution are shown in Fig. 2.

## Clinical, laboratory, and radiologic findings

The manifesting symptoms were present in the following frequencies: anemia 76/83 (91.6%), dyspnea 71/83 (85.5%), hemoptysis 70/84 (83.3%), cough 22/84 (26.2%), and chest pain 9/84 (10.7%). Systemic symptoms were present in nearly half, 38/84 (45.2%) patients. The classic triad consisting of hemoptysis, anemia, and radiologic chest abnormalities were present in 61/84 (79%) patients. Respiratory failure during the acute phase of the disease was reported in 13/84 (15.5%).

The mean hemoglobin during initial presentation was 8.4 gm/dL (SD, 2.59) ( $n = 63$ ) and the median serum ferritin concentration was 72.3 ng/mL (IQR, 12.67–130.1) ( $n = 13$ ). A total of 54.2% (45/83) of all patients underwent chest computed tomography (CT), and the rest were imaged by chest radiography. No patient in the older cohort was evaluated by a CT scan, whereas 86.5% (45/52) of patients reported between 1991 and 2021 were. Bilateral alveolar infiltrate on chest imaging was present in 73/81 (90.1%). Other abnormalities included interstitial opacity in 30/81 (37%) and cystic or emphysematous changes in 12/81 (14.8%). Rare radiologic presentations were thoracic lymphadenopathy and pleural effusion.

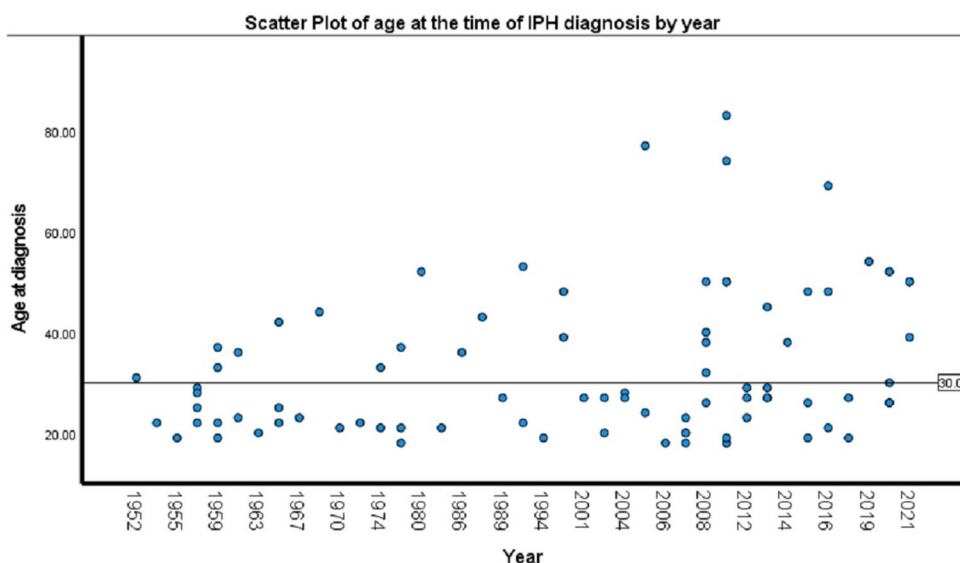
## Autoantibody testing

One or more autoantibodies were tested in 57/82 (69.5%) patients. Among these patients, 16 (19.5%) tested positive. A total of 12/16 (62.5%) of these patients had antibodies suggestive of celiac disease (CD). The other antibodies were antithyroid antibodies (2), rheumatoid factor (1), and anti-GM-CSF (1). Only 8/31 (25.8%) patients underwent antibody testing in cohort A. In contrast, 49/51 (96.1%) patients were tested for autoantibodies in cohort B.

## Diagnosis of IPH

A diagnosis of “definite IPH” by histopathologic analysis was obtained in 65/84 (77.4%) of patients. Lung tissue was obtained by lung biopsy in 56 patients and during autopsy in 9. Among these patients, surgical lung biopsy (SLB) was performed in 29, video-assisted thoracoscopic surgery (VATS) in 11, and bronchoscopic transbronchial lung biopsy (TBLB) in 16. The diagnosis of “probable IPH” was made in the remaining 19 patients by demonstration of HLM from BAL and sputum in 10 and 7 patients, respectively. In the other two patients, sequential BAL demonstrated progressively hemorrhagic fluid return.

**Fig. 2** Scatterplot showing reported cases over the years and age at the time of IPH diagnosis. The majority of patients were less than 30 years old at the time of diagnosis



### Delay in diagnosis

The median delay in the diagnosis of IPH for the entire cohort was 53.5 (*IQR* 8–195) weeks or 1.02 years. Subgroup analysis revealed a longer delay in cohort A compared to cohort B. The detailed data are presented in Table 2. The diagnosis of IPH was also delayed for women compared to men (Table 2). However, the difference in the diagnostic delay between gender was not statistically significant in the entire cohort or previously specified subgroups by one-way independent *t*-test analysis,  $t(74) = 0.213$ ,  $p = 0.416$ .

### Treatment

Following the diagnosis of IPH, immunosuppressive therapy was initiated in 49/79 (62%) patients. A total of 47/49 (95.91%) patients received corticosteroid (CS) as the first-line therapy, and the other two were treated with azathioprine (AZA). A second agent was required in 15/47 (31.91%) of these patients. The most commonly used second-line medications were AZA (9), ACTH (3), antimalarials (2), and cyclophosphamide (CYC) in 1. Among 14 patients simultaneously diagnosed with CD (in 2, the diagnosis was made on small bowel biopsy without any antibody testing), 12 were treated with only gluten-free diet (GFD). The other two patients received immunosuppressive therapy in addition to GFD. Treatment with CS was not associated with a higher survival (chi-square test,  $p = 0.928$ ).

### Follow-up, recurrence, and survival

The median follow-up period for the entire cohort was 1 year (*IQR* 0.5–3) ( $n = 59$ ). Recurrence of the disease was reported in more than half of the patients 36/66 (54.5%). The

recurrence was reported in 16/25 (64%) patients in cohort A compared to that in 20/41 (48.8%) in cohort B. There was no statistical difference in the risk of recurrence between males and females, chi-square test,  $p = 0.777$ . A total of 63/79 (79.7%) patients were alive during the final follow-up. The survival was similar between the two cohorts, 75.9% and 82% in cohorts A and B, respectively. No statistical difference was identified in survival between men and women (chi-square test,  $p = 0.118$ ). Univariate and multivariate analyses of several variables, such as age at diagnosis, delay in diagnosis, and admission hemoglobin, did not predict the risk of future recurrence or survival.

### Discussion

Waldenström reported the first antemortem case of IPH in 1944 [82]. Due to the rarity of IPH in adults, most aspects of this illness have remained somewhat speculative even after seven decades. In this manuscript, we have provided a thorough analysis of adult patients with IPH. To date, this is the most comprehensive review of adult IPH cases. Our paper has confirmed several findings reported earlier by Chen et al. [1] while refuting some previous assumptions and elucidating less well-known aspects of the disease.

IPH is a rare disease that affects both adults and children. The incidence and prevalence of IPH in adults are currently unknown. However, based on the number of reported cases, IPH appears to be more common in children [40]. The incidence ranges between 0.24 and 1.23 cases per million per year in select group of pediatric patients [83, 84]. IPH is also considered more aggressive in children with a higher recurrence rate and poorer prognosis [40]. Most children are diagnosed before ten, and IPH has a distinct female



predominance in this population [85–87]. In contrast, we found that among adult patients, IPH is more common in males. Nearly two-thirds of the patients were males in our study. Similar findings were also reported in previous studies [1, 3, 88, 89]. Although previous studies reported most adult IPH patients to be younger than 30 years [40, 41], this was contradicted by Chen et al., who reported 57% of patients to be older than 30 years in their paper [1]. On the contrary, we have found that most patients are, in fact, younger than 30 years (Fig. 2). This trend persisted even when prespecified subgroups were analyzed (Table 2). Approximately 40% of patients were over 30 years at the time of diagnosis.

Regarding presenting signs and symptoms, our study is in stark contrast with Chen et al. [1]. The proportion of patients with anemia (91.6% vs. 54%), dyspnea (85.5% vs. 62%), hemoptysis (83.3% vs. 81%), productive or non-productive cough without hemoptysis (26.2% vs. 5%), and chest pain (10.7% vs. 5%) were higher in our study. The classic triad, comprising hemoptysis, anemia, and radiologic chest abnormalities, were present in almost 80% of our cohort (not reported by Chen et al.). Systemic symptoms, such as fever, night sweats, chills, weight loss, or loss of appetite, were seen in nearly half of the patients (45%). This is a crucial finding, as the presence of fever and other systemic symptoms may incorrectly dissuade clinicians from strongly considering the diagnosis of IPH and lean toward an infectious etiology for the respiratory symptoms. Due to the nonspecificity of symptoms and variable recognition of IPH among clinicians, a delay and misdiagnosis have often been reported in pediatric and adult patients [1, 87]. Like Chen et al., we also found the mean delay to be 2.3 years from symptom onset to the diagnosis of IPH. It is crucial to emphasize that using an average value could be misleading, as the data was skewed due to outliers. The median delay of 1.02 years is likely more representative of the real-world scenario. Subgroup analysis revealed a trend toward an earlier diagnosis of IPH in the 1991–2021 cohort compared to the older cohort (52 vs. 92 weeks).

The kinetics of iron metabolism in patients with IPH requires special mention. These patients develop functional iron deficiency manifested by the microcytic or normocytic and hypochromic RBCs in peripheral blood smear, low serum iron, normal or high total iron-binding capacity, and bone marrow depletion of iron storage. However, the serum ferritin level may be normal or even elevated, thus mimicking anemia of chronic disease as seen in patients with a systemic inflammatory condition. After an episode of DAH, the RBCs are phagocytosed by alveolar macrophages (AMs). The AMs produce free iron after oxidation of hemoglobin, which subsequently saturates the intracellular apo-ferritin pool and gets stored in the lung storage in the lung as ferritin [90]. Once the ferritin storage reaches maximal capacity, with ongoing hemorrhage, the iron is deposited as

hemosiderin—the unusable form of iron storage—leading to the development of low serum iron and reduced storage in the bone marrow. The ferritin escapes the AMs by an unknown mechanism maintaining or even raising the serum ferritin level [40]. We found an elevated mean serum ferritin level (177.34 ng/mL) despite a mean hemoglobin level of 8.4 gm/dL in our cohort. On the other hand, patients with coexisting CD may have blood work more consistent with iron deficiency anemia [65, 66]. As these patients often suffer from undiagnosed malabsorption for a prolonged duration before medical contact, the elevated ferritin may not be present. In the absence of any systemic inflammatory condition, elevated or normal serum ferritin level in the face of microcytic hypochromic anemia and hemoptysis should prompt the consideration of IPH.

The pathogenesis of IPH is currently unknown. An immunologic mechanism appears to be most likely. We have previously proposed renaming IPH to immune-mediated pulmonary hemosiderosis (ImPH) to signify the immunologic association/causation [91, 92]. The identification of autoantibodies and response to CS therapy have propagated a positive outlook regarding the immune hypothesis among clinicians [85, 86, 93–95]. The other hypotheses proposed by authors in the past are genetic, environmental, and allergic causation of IPH [96, 97]. Identification of autoantibodies has been reported in both pediatric and adult patients with IPH [95]. Approximately one in every five patients in our cohort tested positive for an autoantibody, with antibodies specific for CD being the most common (Table 1). In the 1991–2021 cohort, when antibody testing for CD became more common, 12/47 (25.5%) patients tested positive. The coexistence of IPH and CD has been described in the past and is known as Lane Hamilton syndrome (LHS) [98]. Interestingly, most patients with LHS do not suffer from GI symptoms and should be tested from antibodies for CD when diagnosed with IPH [99]. The other commonly reported autoantibodies in adults include rheumatoid factor and antithyroid antibodies [30, 50, 52]. A more diverse group of antibodies, such as ANA, ANCA, and smooth muscle antibody, have been reported in pediatric patients but not in adults [85, 91]. All patients with IPH who subsequently developed ANCA were diagnosed with IPH as a child [93, 94].

The radiologic appearance of IPH is nonspecific. During the acute phase of the disease, a chest X-ray may demonstrate bilateral infiltrate primarily in the middle and lower lung zones [100]. As a general rule, computed tomography (CT) is more sensitive than conventional chest radiology. Unsurprisingly, no patient in the older cohort were evaluated by chest CT as the technology only became available in 1970s and was not widely available until the 1990s [101]. As a result, most of the patients in the recent cohort received CT imaging as a part of their evaluation. CT scan of the

chest shows ground glass opacity (GGO) and, sometimes, consolidative changes in the same distribution. If the hemorrhage is severe, all lung lobes could be involved. In the absence of ongoing bleeding, the alveolar opacity morphs into an interstitial opacity after 48–72 h [102]. Reticular and reticulonodular shadow may predominate at this time. Long-standing disease may result in pulmonary fibrosis involving the posterobasilar area [48, 103, 104]. Less common radiologic features are emphysema or cystic changes [4, 23, 35, 46, 48, 49, 77, 78]. There were rare cases of intrathoracic lymphadenopathy and pleural effusion [77].

IPH is a diagnosis of exclusion. All competing diagnoses need to be excluded before a confident diagnosis of IPH can be made [40, 105–107]. In this manuscript, we have specified the diagnosis as “definite” and “probable.” Patients with a definite IPH diagnosis either underwent lung biopsy or autopsy studies, and the histopathologic analysis was consistent with bland pulmonary hemorrhage without any evidence of inflammatory cellular infiltration, necrosis, vasculitis, or granulomatous inflammation. A “probable” diagnosis of IPH is made without histopathologic examination of the lung but with evidence of hemosiderin-laden macrophages from respiratory tract samples. Although we included the cases of “probable IPH” for analysis in this review as IPH, it is important to remember that even with a negative autoantibody screening, patients may still suffer from seronegative ANCA-associated vasculitis (AAV) or isolated pauci-immune pulmonary capillaritis [108, 109]. A biopsy, either transbronchial or surgical, is therefore preferable. The SLB is more invasive but allows for more tissue allowing the pathologist to do a thorough analysis. Transbronchial lung biopsy is less invasive but may not provide an adequate sample. Transbronchial cryobiopsy provides more tissue with a higher risk of bleeding than conventional TBLB [73]. The classic histopathologic findings in IPH include evidence of bland pulmonary hemorrhage (BH) and change associated with recurrent bleeding. BH refers to the occurrence of alveolar hemorrhage without any evidence of vasculitis, necrosis, granulomatous inflammation, and the absence of immunocomplex deposition or inflammatory cellular infiltration of the pulmonary parenchyma [92, 103]. Hemosiderin deposition can take place intracellularly (in the alveolar macrophages), extracellularly and along the inter-alveolar septum. Collagen deposition and emphysematous changes can be present in advanced disease [103].

One of the limitations that we faced during this study was the absence of long-term follow-up in most patients. The median follow-up was 1 year, and more than half of the patients suffered from recurrence during this period. Corticosteroid (CS) represents the first line of therapy for patients with IPH [110]. A multinational survey among pediatricians showed CS to be the most commonly used medication for both induction and maintenance therapy [111]. The use of

corticosteroid (CS) was associated with clinical improvement even in patients with respiratory failure requiring mechanical ventilation. Interestingly, the survival with CS treatment did not reach statistical significance. This is likely due to the very short overall follow-up period. One-third of patients required a second-line agent. Azathioprine appears to be the most commonly used agent in adults, whereas, in pediatric patients, antimalarials are the second most commonly used medication [111]. Experimental treatment includes mesenchymal stem cell transplant and liposteroid therapy [112, 113]. An overwhelming majority of patients with LHS appear to do well on GFD. However, in case of recurrent bleeding, even with GFD, additional immunosuppressants may be necessary.

Since no prospective or retrospective studies are available in adult patients with IPH, we attempted to identify risk factors for poorer prognosis in terms of “recurrence of disease” and “survival.” Unfortunately, univariate and multivariate analysis of variables, such as age at diagnosis of IPH, duration of symptoms before the diagnosis, and admission hemoglobin, failed to identify any such potential risk factor. This is likely due to the modest number of patients in our study and inadequate information and follow-up time.

### Strength and limitations of the study

Our study has several limitations. First, we had excluded manuscripts published in the non-English literature, which would have increased the number of subjects in our cohort. Second, some manuscripts were excluded as we could not obtain the full texts. The lack of availability was primarily the case for older manuscripts, which led to a fewer number of patients in the 1950–1990 cohort. Third, since most manuscripts were retrospective reports of single cases or small case series, the reported variables were not uniform. Similarly, the risk of publication bias was likely high. Fourth, the follow-up period was limited to assess prognosis with confidence as many patients could have suffered from recurrence of their disease later. Despite the limitations, to our knowledge, this is the most complete review of adult patients with IPH ever reported in the literature. Our study has consolidated the knowledge regarding the demographics, clinical manifestations, modalities used for diagnosing IPH, treatment, and prognosis for these patients.

### Conclusion

IPH is a rare cause of DAH in adult patients and is associated with a significant delay in diagnosis. In this manuscript, we have provided a detailed account of all reported cases of IPH in adults. IPH is more common in males, and the majority of patients are diagnosed before the age of

30 years. Anemia, dyspnea, and hemoptysis are the most frequent symptoms. The classic triad is present in nearly 80% of patients. LHS affects 25% of patients with IPH. Therefore, screening for CD should be performed routinely at diagnosis of IPH. Recurrence is common, and nearly half the patients experience recurrence even with short-term follow-up. CS represents the first line of therapy. Treatment with CS appears to be efficacious but was not statistically associated with improved survival. Prospective studies are required to evaluate the long-term efficacy of CS therapy.

**Abbreviations** AAV: ANCA-associated vasculitis; AM: Alveolar macrophage; ANCA: Antineutrophil cytoplasmic antibody; AZA: Azathioprine; BAL: Bronchoalveolar lavage; CD: Celiac disease; CS: Corticosteroid; DAH: Diffuse alveolar hemorrhage; GFD: Gluten-free diet; HLM: Hemosiderin-laden macrophages; IPH: Idiopathic pulmonary hemosiderosis; SLB: Surgical lung biopsy; TBLB: Transbronchial lung biopsy; VATS: Video-assisted thoracoscopic surgery

**Author contribution** BKS, AB, and SS planned the study. BKS, AB, and SS collected the data. BKS, AB, SS, and BS performed data synthesis. BKS, AB, SS, BS, and BNS prepared the initial manuscript. All the authors contributed to the finalization of the manuscript.

**Data availability** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Disclosures** None.

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