Original Article

Pulmonary Computed Tomography Screening Frequency in Primary Antibody Deficiency

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What is already known about this topic? Patients with primary antibody deficiency (PAD), in general, frequently suffer from airway disease and interstitial lung disease, associated with severe morbidity and mortality. However, predictive factors to identify the individual patients at risk for these pulmonary complications are lacking.

What does this article add to our knowledge? This study identifies risk factors that can distinguish specific patients with PAD at risk for airway disease and interstitial lung disease presence and progression.

How does this study impact current management guidelines? The current study provides new information about risk factors that can distinguish patients with PAD at risk for airway disease and interstitial lung disease presence and progression. The study results could guide future screening frequency.

BACKGROUND: Patients with primary antibody deficiency (PAD) frequently suffer from pulmonary complications, associated with severe morbidity and mortality. Hence, regular pulmonary screening by computed tomography (CT) scanning is advised. However, predictive risk factors for pulmonary morbidity are lacking.

OBJECTIVE: To identify patients with PAD at risk for pulmonary complications necessitating regular CT screening.

METHODS: A retrospective, longitudinal cohort study of patients with PAD (median follow-up 7.4 [2.3-14.8] years) was performed. CTs were scored using the modified Brody-II scoring system. Clinical and laboratory parameters were retrospectively collected. Potential risk factors were identified by univariate analysis when $P < .2$ and confirmed by multivariable logistic regression when $P < .05$.

RESULTS: The following independent risk factors for progression of airway disease (AD) were identified: (1) diagnosis of X-linked agammaglobulinemia (XLA), (2) recurrent airway infections (2.5/year), and (3) the presence of AD at baseline. Signs of AD progression were detected in 5 of 11 patients with XLA and in 17 of 80 of the other patients with PAD. Of the 22 patients who progressed, 17 had pre-existent AD scores ≥7.0%. Increased AD scores were related to poorer forced expiratory volume in 1 second values and chronic cough. Common variable immunodeficiency and increased CD4 effector/memory cells were risk factors for an interstitial lung disease (ILD) score ≥13.0%. ILD ≥13.0% occurred in 12 of 80 patients. Signs of ILD progression were detected in 8 of 80 patients, and 4 of 8 patients showing progression had pre-existent ILD scores ≥13.0%.

CONCLUSION: We identified risk factors that distinguished patients with PAD at risk for AD and ILD presence and progression, which could guide future screening frequency; however, independent and preferably prospective validation is needed. **(J Allergy Clin Immunol Pract 2024;12:1037-48)**

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This work was supported by the Louise Vehmeijer Stichting and ZonMW. The sponsors had no role in the conception, design, analysis, or publication of this article.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication April 20, 2023; revised December 21, 2023; accepted for publication December 26, 2023.
Received for publication April 20, 2023; revised December 21, 2023; accepted for publication December 26, 2023.
Available online January 3, 2024.
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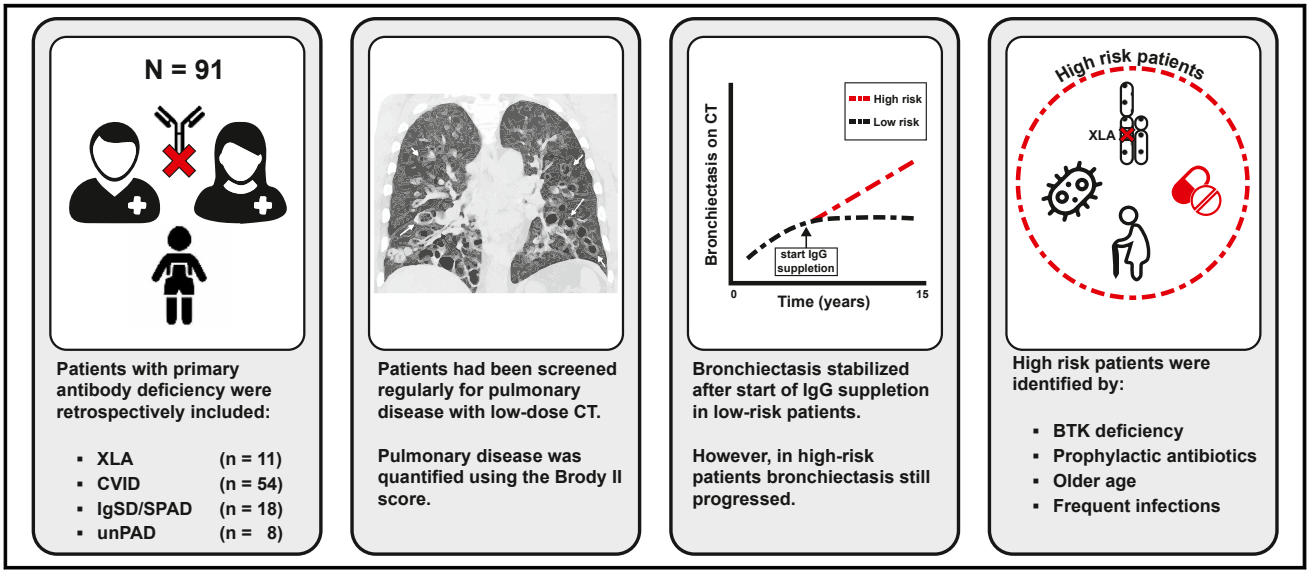
2213-2198

https://doi.org/10.1016/j.jaip.2023.12.047

VISUAL SUMMARY



Key words: *Primary antibody deficiency; CVID; Airway disease; GLILD; Brody II score; Risk factor*

Primary antibody deficiency (PAD) is the most common group of primary immunodeficiencies and can be categorized into immunoglobulin subclass deficiency (IgSD), specific PAD (SPAD), common variable immunodeficiency (CVID), congenital agammaglobulinemia (such as X-linked agammaglobulinemia [XLA]), and unclassifiable PAD (unPAD).[1-3] PAD is frequently complicated by pulmonary disease, which can be categorized into airway disease (AD) and granulomatous lymphocytic interstitial lung disease (GLILD) and may cause high morbidity and mortality.[4] Both entities can be quantified by computed tomography (CT) to score severity and monitor progression.[5]

AD is caused by recurrent lower respiratory tract infections and the subsequent structural damage and is characterized by bronchial wall thickening, bronchiectasis, and signs of mucus plugging on CT.[6-10] Clinical manifestations of AD are chronic (productive) cough with recurrent respiratory exacerbations and dyspnea by exertion, but early disease may go unnoticed.[10,11] Bronchiectasis represents the most severe manifestation in the spectrum of AD.[12]

Abbreviations used
AD- Airway disease
CI- Confidence interval
CT- Computed tomography
CVID- Common variable immunodeficiency
FEV_1- Forced expiratory volume in 1 second
GLILD- Granulomatous lymphocytic interstitial lung disease
IgSD- Immunoglobulin subclass deficiency
ILD- Interstitial lung disease
IRT- Immunoglobulin replacement therapy
PAD- Primary antibody deficiency
SPAD- Specific polysaccharide antibody deficiency
unPAD- Unclassifiable primary antibody deficiency
XLA- X-linked agammaglobulinemia

Bronchiectasis is diagnosed in 34% of patients with CVID and is associated with chronic sinusitis, pneumonia, and decreased pulmonary function.[7,13-15] Thus, the presence of AD and specifically of bronchiectasis can lead to a downward spiral where patients increasingly suffer from pulmonary infections, leading to accumulation of lung tissue damage and chronic local inflammation. In turn, this results in more hospitalizations, decreased quality of life, and end-stage pulmonary failure, and eventually may lead to early death.[4,7,10,14-17]

Earlier research showed that AD/bronchiectasis may be caused by the cumulative effect of recurrent pulmonary infections.[4,8,10,13,18] However, bronchiectasis was also found in patients with CVID who did not experience lower respiratory tract infections.[8] Furthermore, the severity of PAD, expressed as poorer B-cell functionality, was associated with bronchiectasis and more respiratory complications.[14,15,18-21] One study found that AD progression was observed in patients with IgG trough levels <10 g/L during immunoglobulin replacement therapy (IRT).[22] Moreover, bronchiectasis may also be the result of recurrent micro aspiration caused by chronic recurrent sinusitis.[23]

Despite these previous efforts, it remains unclear if 1 single risk factor is responsible for AD progression or if the causes are multifactorial. Moreover, earlier studies mostly investigated risk factors associated with the presence of bronchiectasis without taking the severity into account, which might bias risk factor prediction outcomes. In addition, it is unclear if risk factors for AD progression are similar for all PAD subtypes because associations between bronchiectasis and PAD classification have been shown.[13,15,18]

GLILD is caused by immune dysregulation and can be characterized by nodules, ground-glass opacities, and reticulation on CT.[7,8,10,17] The clinical manifestations of GLILD are chronic (dry) cough and exertional dyspnea. GLILD is diagnosed in 10% to 20% of patients with CVID, and AD and GLILD often co-occur.[24-26] GLILD has been associated with a ≥50% reduction of life expectancy due to evolvement to end-stage pulmonary failure and can be part of a systemic immune dysregulation disorder that may include systemic granulomatous disease,

splenomegaly, diffuse lymphoproliferation, and autoimmune cytopenias.[24,26-29]

Risk factors for GLILD have been studied less, but GLILD has been associated with autoimmune cytopenia and splenomegaly, lower IgG and IgA levels at diagnosis, reduced class switched memory B cells and increased $CD21^{low}$ B cells, and reduced pulmonary function in patients with CVID.[8,20,26,30] Publications about risk factors for GLILD development have been scarce, with a small sample size and relatively short follow-up times.

In this study, we analyze CT scans of patients with PAD during a follow-up time of 7.4 years (2.3-14.8 years) and aim to identify radiologic findings identified by CT scoring as well as clinical and immunologic risk factors that might predict progression of AD and GLILD in patients with PAD.

METHODS

Study population

Patients with PAD, adults and children, in care at the University Medical Center Utrecht between 2008 and 2021 were screened for pulmonary disease at regular intervals using chest CT.

Study design

We conducted a noninterventional, single-center, retrospective cohort study. Retrospective documentation started at the first CT screening event. Secondary clinical and lab parameters recorded 12 months before or after CT screening date were retrospectively collected from the patients' records.

Eligibility

Patients were included if they met the following criteria:

- A diagnosis of XLA, CVID, IgSD, and/or SPAD according to the European Society for Immunodeficiencies criteria or an unclassifiable hypogammaglobulinemia (unPAD).
- Active IRT.
- Availability of at least 2 CT scans with a minimum interval of 2 years.

The follow-up stopped when active GLILD treatment started because initiating treatment interferes with the prognostic factors for GLILD progression.

All CT scans had been performed routinely as part of the standard care screening protocol in our hospital or because of a clinical indication. The standard screening protocol consists of CT scanning every 5 years or every 2 to 3 years in patients with pulmonary complications. Most participants in this study already participated in a broad observational review board–approved study (National PID study, METC: NL40331.078) for which they had provided written consent. The remaining participants provided their consent for the use of medical data and CT images.

CT screening and scoring

We used a previously described routine protocol for CT.[5,7] Scans were acquired during inspiration and expiration. All scans were volumetric and reconstructed with thin slices. Dose was maintained as low as possible by adapting kilovoltage and milliamperes to patient size. The presence of structural pulmonary disease was scored by an independent observer according to the modified Brody-II method, used in previous studies (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).[5,7,8,22] Signs of AD were scored by assessing the presence of bronchiectasis, airway wall thickening, mucus plugging, tree-in-bud, and air trapping. Signs of interstitial lung disease (ILD) were scored by assessing the presence of opacities, ground glass, septal thickening, and lung nodules. Sum scores for AD and ILD were calculated and used as a primary parameter. As previously described, an AD score of $\geq$7.0% was considered clinically significant. A score of 7.0% represents AD in its early stage and is used to prevent calling a scan abnormal that has some bronchial wall thickening, mucus plugging, and air trapping, which can also be seen in the general population.[7,8] In this study, we defined an arbitrary AD score increase of >0.5% points/year as clinically significant, based on a theoretical increase of 7% points during the longest follow-up time.

Secondary parameters

Secondary parameters consisted of clinical, laboratory, and pulmonary parameters recorded during regular outpatient visits and are listed in Table E2, available in this article's Online Repository at www.jaci-inpractice.org. Data recorded 12 months before and up to 12 months after CT screening dates were used. Time until PAD diagnosis was defined as the time (years) between year of onset of disease-related symptoms and year of PAD diagnosis. Cough and dyspnea were defined as clinical symptoms of pulmonary disease. Cough that lasted longer than 8 weeks was defined as chronic cough. Continuous variables were included if they were collected at least once during follow-up.

Statistical analysis

Continuous, non-normally distributed variables were analyzed using the Kruskal-Wallis test or the Mann-Whitney *U* test as appropriate. χ^2 tests and Fisher exact tests were performed for categorical variables as appropriate. Time-dependent data were analyzed with generalized linear models, when assumptions of linearity and distribution were met. First, medians of continuous variables were calculated, and risk factors were analyzed using the previously described univariable methods. Variables with a *P* value of <.2 were selected for multivariable risk factor analysis. Multiple imputation was applied to account for missing data when <40% of the original data were missing. Variables were excluded when >40% of the original data were missing. Because outcome variables were binominal in nature and the dataset contained both continuous and categorical predictors, multivariable logistic regression was used to analyze the remaining risk factors. Significance was reached when $P < .05$. Cutoffs were calculated, requiring a minimum sensitivity of 80%, and the sensitivity and specificity of combined risk factors were calculated. Moreover, a cutoff for AD scores was calculated that could predict the presence of chronic cough using a minimum sensitivity of 80% as prerequisite. R Studio version 4.2.1 was used for data analysis.

RESULTS

Study population

We included 91 patients (11 XLA, 54 CVID, 18 IgSD/SPAD, and 8 unPAD patients), with a median follow-up of 7.4 years (2.3-14.4 years) and 273 CT scans. At inclusion, the median age was 26.5 years (7-71 years), and 32 patients were children (<18 years). The median duration of PAD-related symptoms before first CT scan was 13 years (0-47 years), and the median diagnostic delay was 5.5 years (0-39 years). Patients with XLA tended toward a longer duration of PAD-related symptoms and a shorter diagnostic delay (Table I).

TABLE I. Patients with XLA had a different distribution of potential identifying factors for increased AD scores and AD progression

Study parameters	XLA	CVID	IgSD/SPAD	unPAD
N	11	54	18	8
General parameters				
Age (y) (IQR)	24.5 (16.3)	31.5 (24.8)	20 (20)	13 (28.8)
% Males (n)	100 (11)	50 (27)	50 (9)	50 (4)
% Genetic variant (n)	100 (11)	38 (8)	50 (3)	17 (1)
Years of PAD-related symptoms (IQR)	23.5 (14)	11 (9)	14.5 (12)	10.5 (9)
Diagnostic delay of PAD (IQR)	2 (3.5)	5 (7)	8.5 (9.3)	9 (9)
Years of follow-up (IQR)	5.5 (2.2)	8.3 (3.6)	6.3 (4.8)	6.1 (3.9)
Average number of CTs performed during follow-up	3.1	2.6	3	2.7
Pulmonary status				
% Current smoker (n)	0 (0)	23 (10)	24 (4)	25 (2)
% Asthma (n)	0 (0)	15 (8)	11 (2)	13 (1)
% COPD (n)	0 (0)	2 (1)	0 (0)	25 (2)
% Incidental cough (n)	27 (3)	28 (15)	28 (5)	25 (2)
% Chronic cough (n)	36 (4)	31 (17)	17 (3)	38 (3)
% Dyspnea (n)	0 (0)	13 (7)	6 (1)	13 (1)
Infectious complications				
Patient-reported use of antibiotic courses per year (IQR)	0.97 (0.9)	0.7 (0.7)	0.92 (0.7)	1.64 (1.7)
% Prophylactic antibiotics (n)	45 (5)	46 (25)	33 (6)	75 (6)
Prophylactic antibiotics (mo/y) (IQR)	3.8 (3)	5 (4)	8.5 (2)	8.2 (5)
Infections per year (IQR)	0.95 (0.8)	0.68 (0.7)	0.92 (0.7)	1.21 (1.4)
IRT dose (g/kg/wk) (IQR)	0.11 (0.03)	0.12 (0.04)	0.14 (0.06)	0.17 (0.08)
Noninfectious complications				
% Noninfectious complications (n)	9 (1)	33 (18)	6 (1)	13 (1)
% GLILD (n)	0 (0)	24 (13)	0 (0)	0 (0)
% Autoimmune cytopenia (n)	0 (0)	13 (7)	0 (0)	0 (0)
% Other autoimmune disease (n)	0 (0)	19 (10)	6 (1)	13 (1)
% Enteropathy/IBD (n)	9 (1)	19 (10)	0 (0)	0 (0)
% Lymphoproliferation (n)	0 (0)	17 (9)	0 (0)	0 (0)
% Malignancies (n)	0 (0)	6 (3)	0 (0)	0 (0)
% Treated with immunosuppressants (n)	27 (3)	31 (17)	0 (0)	25 (2)
Length of immunosuppressive therapy (mo/y) (IQR)	2.5 (5)	2.9 (7)	0 (0)	11.8 (2)
Laboratory parameters at baseline				
IgG through levels (g/L) (IQR)	9.4 (3.4)	8.2 (3.3)	10.1 (4.0)	9.1 (4.5)
IgA (g/L) (IQR)	0.3 (0)	0.3 (0.4)	1.2 (0.7)	0.6 (0.4)
IgM (g/L) (IQR)	0.2 (0)	0.3 (0.6)	0.9 (0.4)	0.5 (0.6)
CD3+ cells (10^9/L) (IQR)	1.4 (0)	1.3 (1.1)	1.3 (0.4)	1.5 (0)
CD3+CD4+ cells (10^9/L) (IQR)	0.8 (0)	0.7 (0.6)	0.7 (0.3)	0.9 (0)
CD3+CD8+ cells (10^9/L) (IQR)	0.6 (0)	0.6 (0.4)	0.5 (0.3)	0.5 (0)
CD19+ cells (10^9/L) (IQR)	0 (0)	0.2 (0.3)	0.3 (0.1)	0.3 (0)
CT scores at baseline				
AD score, % (IQR)	7 (11.5)	7 (10.1)	2 (7)	3 (6)
ILD score, % (IQR)	6 (4.5)	4 (7)	2 (4)	2 (7)

We found that male sex and underlying genetic variants were more frequent in XLA. Moreover, there was less diagnostic delay, and there were less noninfectious complications among patients with XLA. Furthermore, immunoglobulin levels were lower in patients with CVID than in patients with IgSD/SPAD and patients with unPAD, whereas IRT dosing was higher in patients with unPAD than in patients with CVID and XLA.

AD, Airway disease; *COPD*, chronic obstructive pulmonary disease; *CT*, computed tomography; *CVID*, common variable immunodeficiency; *GLILD*, granulomatous interstitial lung disease; *IBD*, inflammatory bowel disease; *IgSD*, immunoglobulin subclass deficiency; *ILD*, interstitial lung disease; *IRT*, immunoglobulin replacement therapy; *PAD*, primary antibody deficiency; *SPAD*, specific polysaccharide antibody deficiency; *unPAD*, unclassified primary antibody deficiency; *XLA*, X-linked agammaglobulinemia.

Clinical, pulmonary, and laboratory parameters

Clinical, laboratory, and pulmonary parameters are shown in Table I. We found that IRT dose was higher in patients with unPAD than in patients with CVID and XLA. We found no difference in the proportion of patients who smoked and had asthma or chronic obstructive pulmonary disease, nor in the frequency of pulmonary symptoms between the different PAD groups. We found significantly more noninfectious complications in patients with CVID, specifically more GLILD, which was not reported in the other PAD groups. Despite this difference, we found no difference in immunosuppressant treatment between the different groups. We could not compare baseline immune subsets and carbon monoxide diffusion capacity between the different PAD groups because of missing data.

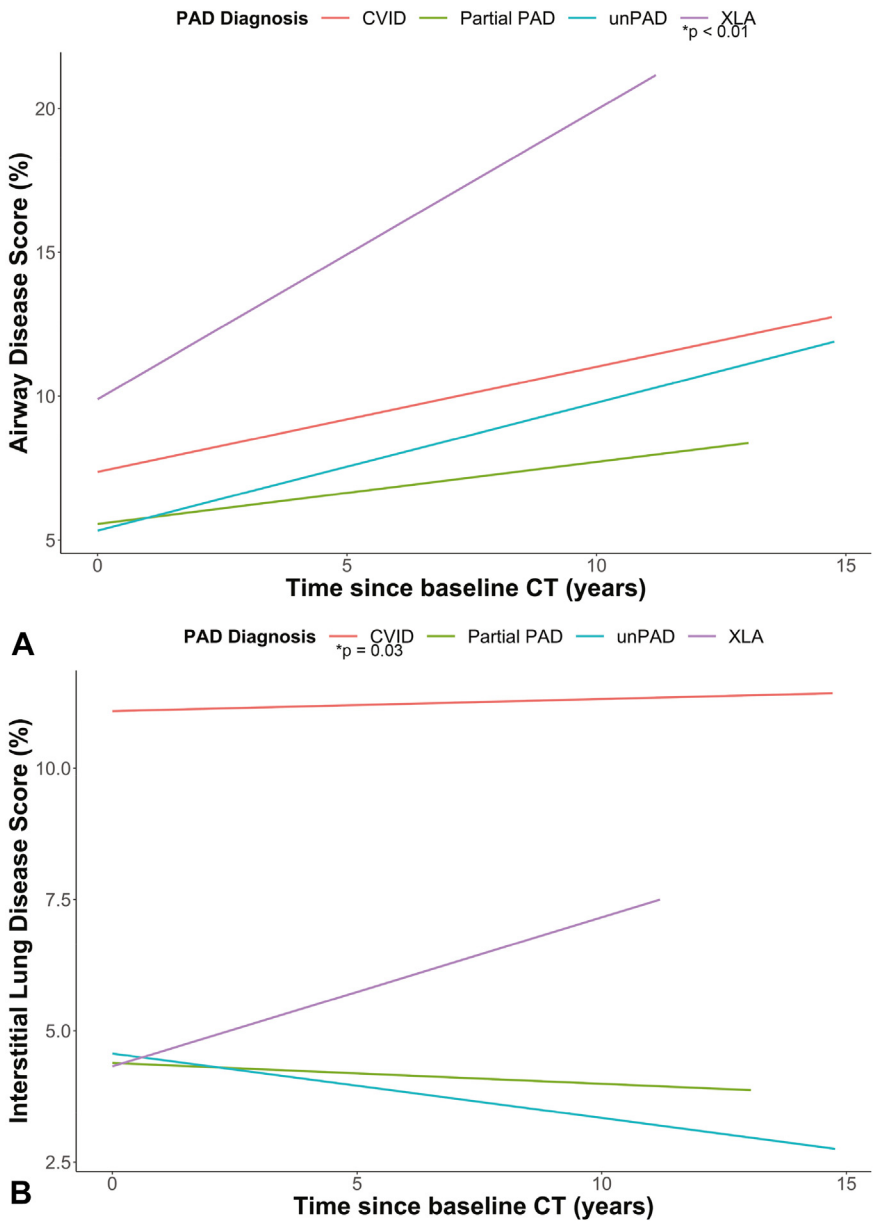


FIGURE 1. Airway disease (AD) scores were increased in patients with XLA, and interstitial lung disease (ILD) scores were increased in patients with CVID compared with other patients with PAD. (**A**) AD scores increased significantly over time on follow-up computed tomography (CT) scans ($P = .005$) and were higher in patients with XLA. (**B**) ILD scores did not increase significantly over time but were significantly higher in patients with CVID. *CVID*, Common variable immunodeficiency; *PAD*, primary antibody deficiency; *unPAD*, unclassifiable PAD; *XLA*, X-linked agammaglobulinemia.

CT parameters

We compared AD and ILD progression between the different groups over time and found that AD scores were significantly higher in patients with XLA (5.08 [95% confidence interval (CI): 1.07-9.12], Figure 1). In addition, ILD scores were significantly higher in patients with CVID (5.92 [95% CI: 0.62-11.22], Figure 1).

Our previous findings suggest that potential risk factors for AD might be different in XLA, and we therefore studied the patients with XLA as a separate subgroup. Finally, no signs of GLILD were detected on CT scans among patients with XLA. Therefore, we did not perform a subgroup analysis for ILD risk factors in XLA.

Airway disease in XLA

AD scores were stable during follow-up in more than half of the patients with XLA (Figure 2); we thus used median AD scores to investigate identifying factors for increased AD scores (AD score of $\geq$7.0%). Increased AD scores were present in 6 of 11 patients with XLA for which no identifying factors were found in univariate analysis. AD progression occurred in 5 of 11 patients with XLA, which tended to be more frequent than in the

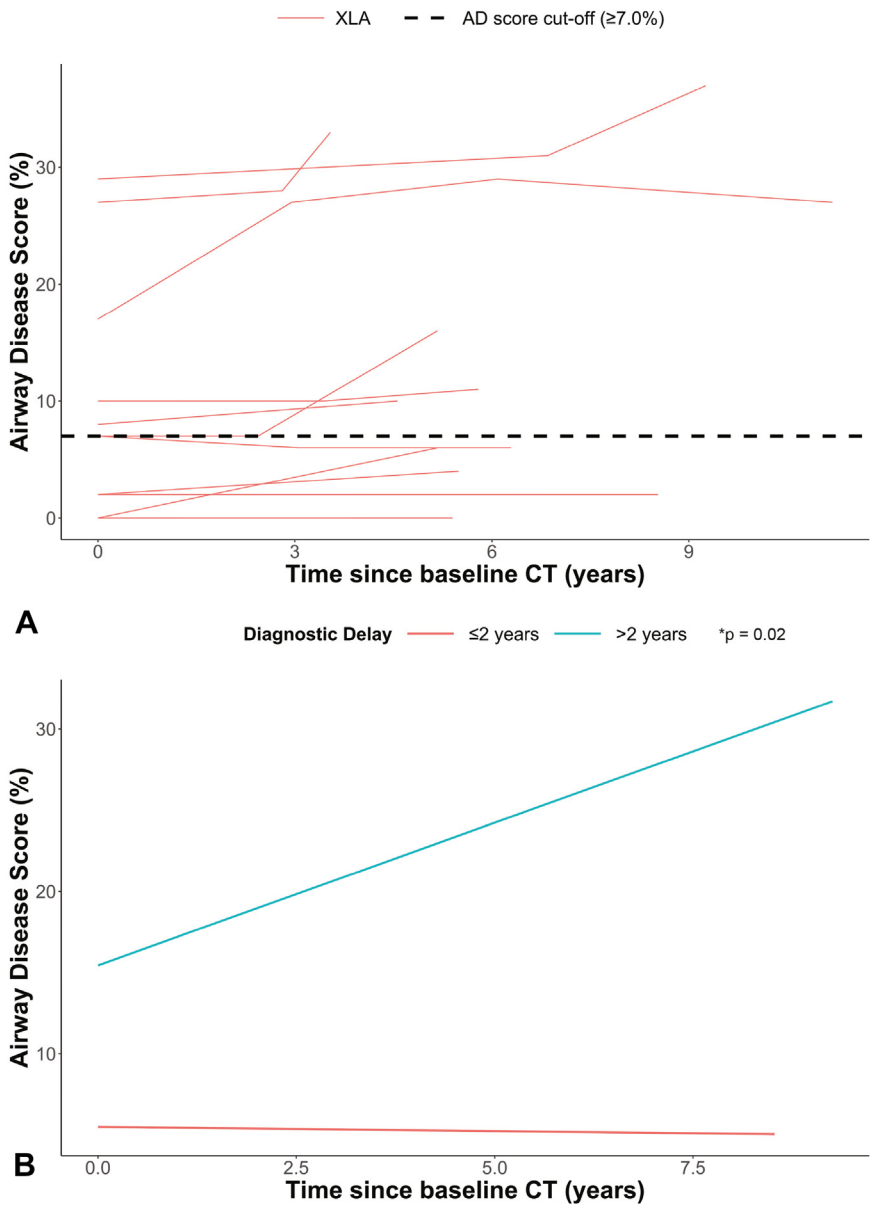


FIGURE 2. Diagnostic delay of the X-linked agammaglobulinemia (XLA) diagnosis (>2 years) was a risk factor for airway disease (AD) progression in patients with XLA. (**A**) A spaghetti plot of AD scores in patients with XLA showed that 5 of 11 patients progressed. Patients who progressed had longer diagnostic delay. (**B**) Patients with a diagnostic delay of >2 years had higher AD scores and potentially progressed faster ($P = .1$) than the remaining patients with XLA. *CT,* Computed tomography.

other patients with PAD ($P = .08$). Diagnostic delay was a univariate predictor for AD progression in patients with XLA (Figure 2). A diagnostic delay of >2 years could identify patients who showed AD progression later on with 80% sensitivity and 100% specificity and resulted in higher AD scores (9.94 points [95% CI: 0.1-18.78]).

Airway disease in CVID, unPAD, and SPAD/IgSD

Increased AD scores were detected in 26 patients with CVID (48.1%), 5 patients with IgSD/SPAD (27.8%), and 3 patients with unPAD (37.5%) during follow-up. We found that higher age at inclusion, lower median B-cell count, and the presence of noninfectious complications in general, and specifically GLILD, were all significant univariate predictors. Moreover, a lower median CD4 count, higher median percentage of CD8 effector/memory cells, lower median percentage of switched memory B cells, lower median IgM levels, and longer diagnostic delay were all potential univariate predictors for increased AD scores. After multivariable analysis (Table E3, available in this article's Online Repository at www.jaci-inpractice.org), age at baseline and median B-cell count were identifying factors for increased AD scores (Figure 3). Cutoffs were calculated, and we found that age ≥40 years at inclusion or median B-cell counts ≤205 could predict AD scores ≥7.0% with 79.4% sensitivity and 76.1% specificity.

In previous publications, radiographically relevant AD has been reported as AD scores ≥7.0%, but its clinical relevance is uncertain.[8] Chronic cough is an important symptom of AD and was reported by 23 patients during follow-up. Patients with a chronic

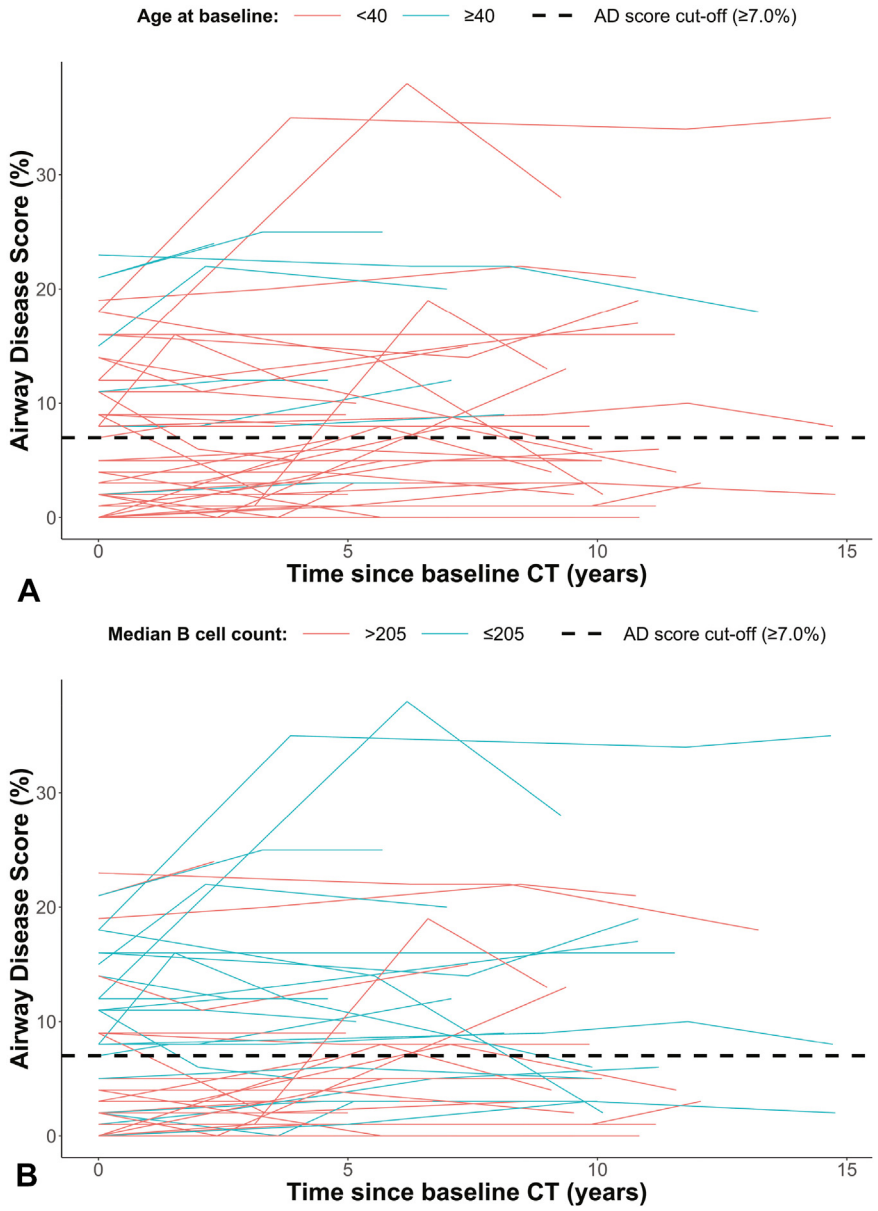


FIGURE 3. Baseline age ≥40 and average B-cell count ≤205 were independent risk factors for increased airway disease (AD) scores. Spaghetti plots of AD scores in the remaining patients with primary antibody deficiency were generated. (**A**) Patients ≥40 years and (**B**) patients with median B-cell counts ≤205 showed AD scores ≥7.0% more frequently. *CT,* Computed tomography.

cough had significantly higher AD scores (12.7% vs 2.7%, $P < .001$), and median AD scores ≥7.0% during follow-up could identify patients with chronic cough with 78.3% sensitivity and 68.4% specificity. Moreover, pulmonary function tests were performed in 48 of 80 patients. In these patients, worse forced expiratory volume in 1 second (FEV_1, % of predicted) correlated with higher AD scores ($r = -0.32$, $P = .007$). Together, these results indicate that AD scores ≥7.0% are clinically relevant.

Airway disease progression in CVID, unPAD, and SPAD/IgSD

AD progression was detected in only 11 of 54 patients with CVID, 4 of 18 patients with IgSD/SPAD, and 2 of 8 patients with unPAD. A higher age at inclusion, an AD score of ≥7.0% at baseline, more infections per year, more courses of antibiotics per year, longer prophylactic antibiotic use, and the presence of noninfectious complications (specifically GLILD) were all significant univariate identifying factors for AD progression. Moreover, we found that a longer time since PAD manifestations commenced, smoking, lower CD8 counts, higher percentage of CD8 effector/memory cells, and higher median IRT dose were potential univariate identifying factors for AD progression. After multivariable analysis (Table E4, available in this article's Online Repository at www.jaci-inpractice.org), the mean number of infections per year and an AD score of ≥7.0% at baseline were predictive factors for AD progression. The total duration of prophylactic antibiotics was a potential identifying factor (Figure 3). We calculated cutoff values to identify patients with

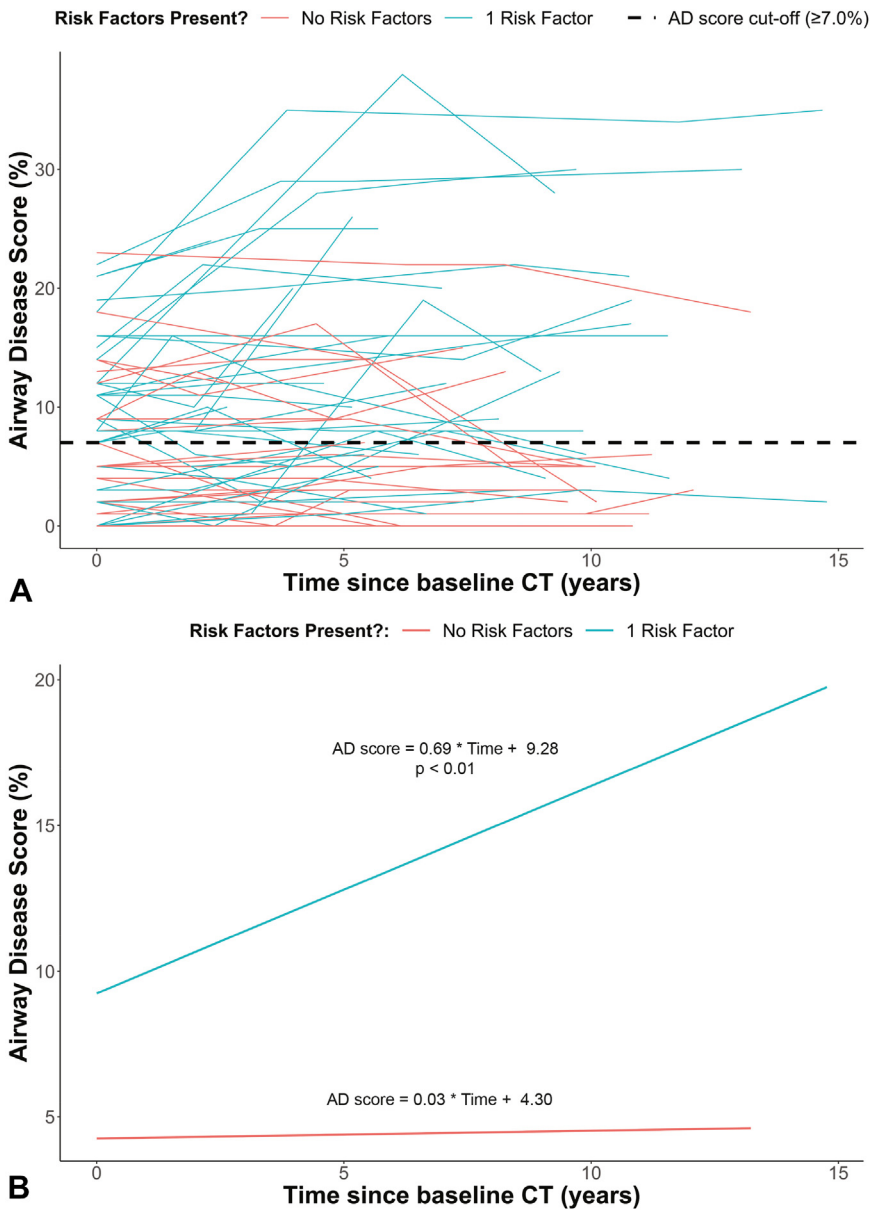


FIGURE 4. Infections ≥2.5/year and airway disease (AD) scores ≥7.0% at baseline were identifying factors for patients with AD progression. (**A**) Individual patients with ≥2.5 infections/year and/or AD scores ≥7.0% at baseline (blue) were at risk for progression of AD scores. (**B**) Patients with ≥2.5 infections/year and/or AD scores ≥7.0% at baseline (blue) progressed, whereas patients without risk factors did not progress. *CT,* Computed tomography.

AD progression for the mean number of infections per year (2.5/year). The duration of prophylactic antibiotic therapy did not improve sensitivity or specificity. The presence of 1 or more identifying factors resulted in higher AD scores (4.98 points [95% CI: 2.12-7.8]) and faster progression (0.69 points/year [95% CI: 0.18-1.2], Figure 4). Together, these risk factors could predict AD progression with 100% sensitivity and 67.4% specificity.

GLILD and GLILD progression in PAD

In previous publications, radiographically relevant ILD has been reported as an ILD score of ≥5.0%; however, it is not known if this is specific for GLILD.[8] The ILD score, used in this study, assessed CT-related changes that can also be signs of other causes of ILD, like smoking and aging. We therefore analyzed the CT scans of patients with PAD (30 scans in 13 patients) with signs of GLILD according to an independent radiologist and who had not received prior GLILD treatment. We compared these with the CT scans of patients with PAD (201 scans in 67 patients) with no signs of GLILD.

Because the ILD scores were stable during follow-up for most patients, we used the median ILD scores to analyze risk factors for relevant ILD. A median ILD score ≥5.0% identified CT scans that had GLILD-related abnormalities with 100% sensitivity and 68.2% specificity, whereas a median ILD score of ≥13.0% identified CT scans that had GLILD-related

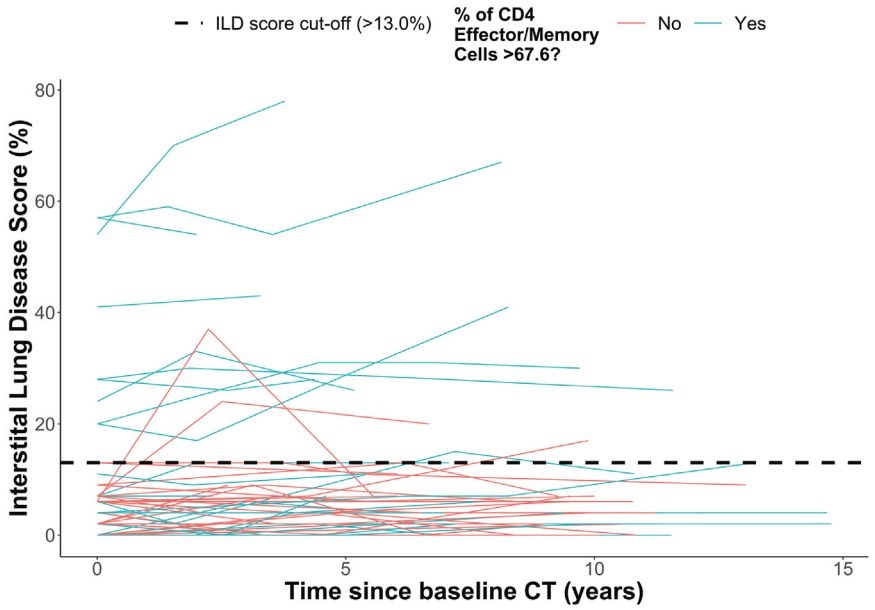


FIGURE 5. High CD4 effector/memory fractions (>67.7%) in peripheral blood are a risk factor for interstitial lung disease (ILD) scores ≥13.0% in patients with primary antibody deficiency (PAD). A spaghetti plot of ILD scores in the remaining patients with PAD showed that patients with CD4+ effector/memory fractions >67.6% had ILD scores ≥13.0% more frequently. *CT,* Computed tomography.

abnormalities with 79% sensitivity and 89% specificity. Among patients diagnosed with GLILD, ILD scores ≥13.0% occurred on at least 1 CT scan in 11 of 13 patients.

Next, we investigated potential identifying factors for an ILD score of ≥13.0%. ILD scores ≥13.0% occurred in 11 patients with CVID and 1 patient with IgSD/SPAD. We found that AD scores ≥7.0% at inclusion, higher percentage of CD4 effector/memory cells, lower percentage of switched memory B cells, higher IRT dose, and the presence of noninfectious complications were all significant univariate risk factors for a median ILD score of ≥13.0%. Moreover, higher age at inclusion, smoking status, PAD diagnosis, higher percentage of CD8 effector/memory cells, lower IgG trough levels, more infections per year, and antibiotic courses per year were potential univariate risk factors. After multivariable analysis (Table E5, available in this article's Online Repository at www.jaci-inpractice.org), we found that the median percentage of CD4 effector/memory cells was a significant risk factor for increased ILD scores (Figure 5, $P = .03$). The median percentage of CD4 effector/memory cells >67.6% could identify patients with ILD scores ≥13.0% with 83.3% sensitivity and 68.2% specificity.

ILD progression was defined as an ILD score increase of ≥1.0% point/year during follow-up. ILD progression was reported in 7 patients with CVID and 1 patient with IgSD/SPAD. Univariable and multivariable risk factor analysis did not identify risk factors for ILD progression.

DISCUSSION

This is our third retrospective, observational study that quantifies AD and ILD development in patients with PAD.[8,22] Previously, we included only patients with CVID and XLA. In the current study, we included all types of patients with PAD who were treated with IRT, with an extended follow-up and a multivariable approach.[8,22] We found that age at baseline ≥40 years and median B-cell counts ≤205 were sensitive and specific predictive factors for increased AD scores. Furthermore, increased AD scores were related to poorer FEV_1 and chronic cough. The presence of ≥2.5 infections per year and increased AD scores at inclusion could identify patients with PAD at risk for AD progression. Finally, we found that an ILD score of ≥13.0% and a percentage of CD4 effector/memory cells >67.6% were sensitive and specific to predict the presence of radiographically diagnosed GLILD, but we did not identify predictors for progression of GLILD.

Median B-cell counts ≤205 were a predictive factor for increased AD scores. This supports that the reduced function of B cells is an important factor associated with AD development in patients with PAD. In accordance with previous research, we also found other predictive markers such as reduced switched memory B cells and IgM levels in the univariate analysis.[14,15,18-21] Age was also associated with increased AD scores; however, we hypothesize that age is not an independent risk factor but merely an intermediate factor. Older patients probably have more diagnostic delay and longer disease duration with possible undertreatment and are thus potentially more at risk for disease complications, as has previously been described.[18] Increased signs of AD were also related to clinical outcomes such as chronic cough and decreased FEV_1 in pulmonary function tests, which further emphasizes the need for clinical measures that will prevent AD and future pulmonary complications in patients with PAD.

In this cohort, AD scores did not progress in most, but not all, patients, probably due to adequate IRT. Patients with AD progression despite adequate IRT either had XLA or could be identified by frequent infections, AD at baseline, and possibly an increased need for prophylactic antibiotics. Frequent infections are the principal pathophysiological mechanism of AD and therefore a risk factor for AD progression.[4,6-10,13,18] An increased

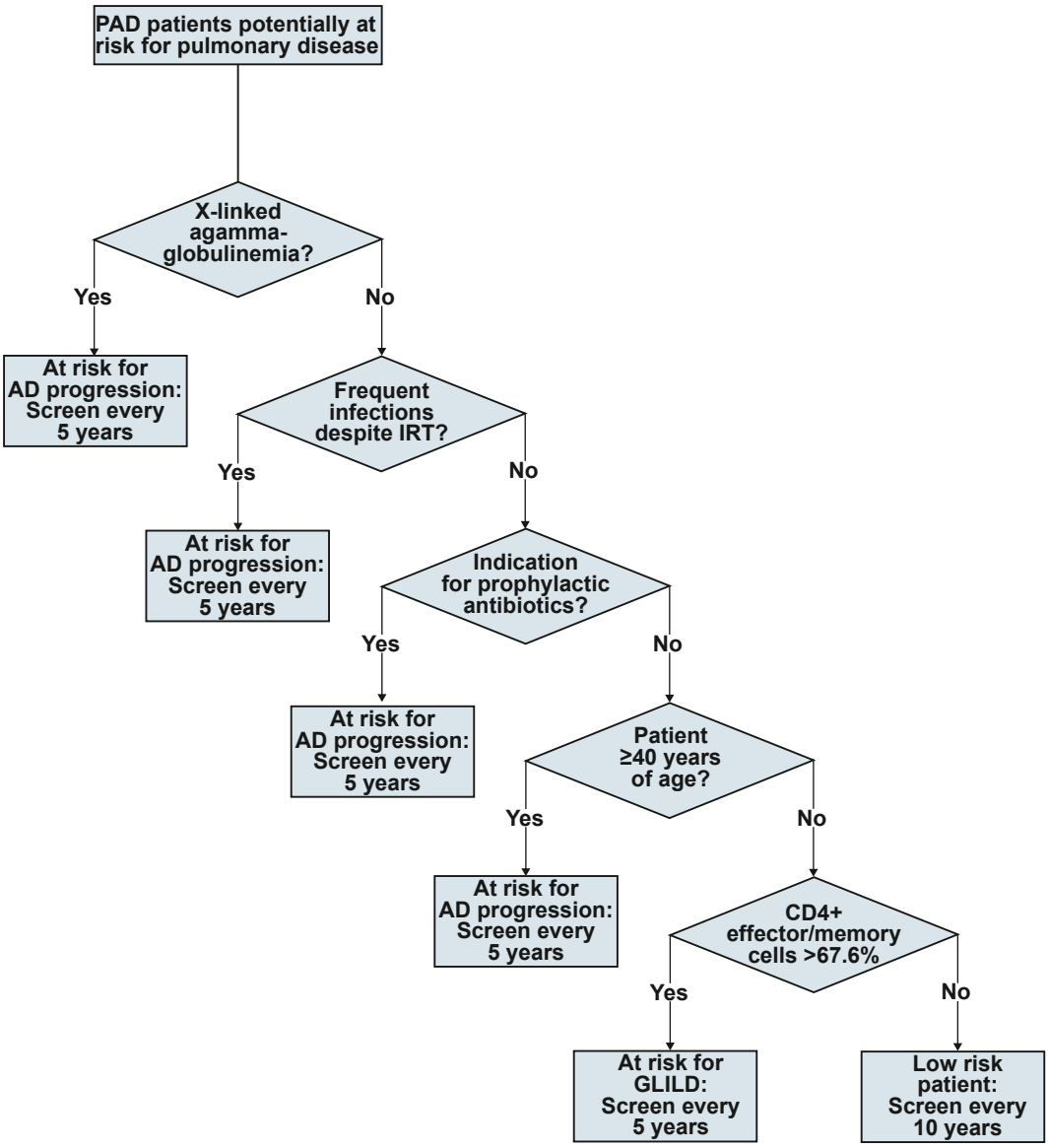


FIGURE 6. Decision tree regarding screening for pulmonary disease in primary antibody deficiency (PAD). *AD*, Airway disease; *GLILD*, granulomatous or lymphocytic interstitial lung disease; *IRT*, immunoglobulin replacement therapy.

need for prophylactic antibiotics is probably an intermediate identifying factor for patients who either potentially encounter more (subclinical) infections or have extensive bronchiectasis with colonization of bacterial pathogens. Still, prophylactic antibiotics are insufficient to halt AD progression in these patients. This raises the question whether additional therapeutic measures should be taken for patients at risk. We did not find a correlation between AD progression and low baseline IgG trough levels.[22] This might be caused by the fact that we studied all forms of PAD and not only CVID. Alternatively, it could be caused by the fact that IRT dosage and advised target IgG trough levels have increased over the years.[31-33]

We found that patients with XLA had higher AD scores and potentially progressed more often. The diagnostic delay of XLA was a risk factor for AD progression similar to the earlier findings of Quinti et al.[18] Although earlier studies found bronchiectasis to be more common in CVID than XLA, we are the first to show quantified results of severity and progression of AD in XLA compared with other PAD subgroups.[18,30,34,35]

To our knowledge, we are the first to report an ILD score cutoff of $\geq$13.0% for the Brody-II scoring system that identifies GLILD in patients with PAD. Moreover, we found that a high percentage of CD4 effector/memory cells is a risk factor for GLILD. Increased CD4 effector/memory cells correlate with decreased naive CD4 cells and has previously been described as a risk factor for GLILD.[8,20] This increase may represent chronic immune activation, and we speculate that this might be part of the underlying pathophysiological mechanism for GLILD.

Given our results, we suggest that CT screening should be performed at least every 5 years in patients with increased risk for pulmonary complications (Figure 6). In addition, screening frequency should be increased in case of (clinical) signs of AD progression, bronchiectasis, or recurrent respiratory tract infections.

Intensive therapy such as increased IRT dosing, antibiotic prophylaxis, antibiotic treatment of exacerbations, and airway clearance techniques taught by chest physiotherapists can be applied to halt AD progression. CT screening frequency could probably be reduced to every 10 years for low-risk patients. The decision tree (Figure 6) saves costs as not all patients with PAD will have to be screened every 5 years. Furthermore, low-risk patients receive less radiation load when CT screening frequency is reduced.

Some limitations of our study should be taken into consideration. First, the retrospective design may have led to selection bias and missing data. Selection bias could have occurred as patients with more severe disease may have undergone more CT scans, pulmonary function tests, and blood tests. As a consequence, pulmonary function testing and immunophenotyping might have only been performed in patients with more advanced disease. Second, we used linear stochastic regression imputation to handle missing data. This method might have resulted in an overidentification of interrelationships because this approach reduces the statistical noise in the dataset. Third, patients with CVID were overrepresented in our PAD cohort. We did not detect large differences nor trends in AD scores between patients with CVID, IgSD/SPAD, and unPAD. Small differences, however, may have gone unnoticed due to the overrepresentation of patients with CVID. Also, the sample size was not large, and we used a data-driven approach to define cutoff values. Our study therefore needs independent replication. Finally, the modified Brody-II scoring system has been validated in pediatric patients only.[5] However, the scoring system has already been successfully used previously in adult patients with CVID.[8,22] Given the complexity and extent of the system, it is not suitable for daily clinical practice and will remain a research tool for now.

CONCLUSION

We have identified sensitive potential risk factors for the presence of AD in patients with PAD. Moreover, we report factors that could identify patients with a greater risk for AD progression despite adequate IRT. We suggest that CT screening frequencies can potentially be reduced for low-risk patients (Figure 6). Patients with XLA should be studied separately because they have a different disease entity with different risk factors that potentially requires a different therapeutical and follow-up approach. To further improve detection and subsequent management of AD in patients with PAD, future research should focus on prospective validation of risk factors in all PAD subgroups.

Data availability

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

Acknowledgments

All authors contributed to the study conception and design. Data collection and analysis were performed by B. M. Smits, S. L. Boland, and M. E. Hol. The first draft of the manuscript was written by B. M. Smits and S. L. Boland, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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TABLE E1. CT scoring system for CVID and PAD-related pulmonary disease

	Score			
Inspiration (per lobe)	**0**	**1**	**2**	**3**
Size of the largest bronchiectasis	Absent	B<2V	B=2-3V	B>3V
Size of the average bronchiectasis	Absent	B<2V	B=2-3V	B>3V
Extent of bronchiectasis (%)	Absent	<33	33-67	>67
Most severe airway wall thickening	Absent	0.25-0.5V	0.5-1V	>1V
Average severity airway wall thickening	Absent	0.25-0.5V	0.5-1V	>1V
Extent of airway wall thickening (%)	Absent	<33	33-67	>67
Extent of mucus plugging (%)	Absent	<33	33-67	>67
Extent of tree-in-bud (%)	Absent	<33	33-67	>67
Extent of lung nodules	Absent	1	2	>2
Average size of lung nodules				
Extent of consolidations/atelectasis (%)	Absent	<33	33-67	>67
Extent of ground glass (%)	Absent	<33	33-67	>67
Extent of septa thickening	Absent	Few, >3	Marked	Diffuse
Extent of bulla/cysts	Absent	1	2	>2

	Score					
Expiration (per lobe)	**0**	**1**	**2**	**3**	**4**	**5**
Extent of air trapping (%)	Absent	<20	21-40	41-60	61-80	>80
Mediastinum/hilum	Short axis diameter of the largest lymph nodes … mm					

Airway disease (AD) score composites of normalized bronchiectasis score, airway wall thickening score, combined mucus score, and air trapping score. Interstitial lung disease (ILD) score consists of the normalized opacities, ground glass, nodules, and septa thickening scores. Full description of the calculation of AD and ILD scores can be read from Van de Ven et al.[E1]

B, Bronchial lumen diameter; *CT*, computed tomography; *CVID*, common variable immunodeficiency; *PAD*, primary antibody deficiency; *V*, outer diameter of the accompanying pulmonary artery.

TABLE E2. Listing of retrospective gathered variables

	Availability per diagnosis (missing)					
Parameter	**XLA**	**CVID**	**IgSD/SPAD**	**unPAD**	**Imputed?**	**Included in risk factor analysis?**
Demographic characteristics	11 (0)	54 (0)	18 (0)	8 (0)	No	Yes
Genetics	11 (0)	21 (33)	6 (12)	6 (2)	No	Yes
Smoking status	11 (0)	54 (0)	17 (1)	8 (0)	Yes	Yes
IRT	11 (0)	54 (0)	18 (0)	8 (0)	No	Yes
Infections	11 (0)	53 (1)	18 (0)	8 (0)	Yes	Yes
Antibiotic therapy	11 (0)	53 (1)	18 (0)	7 (1)	Yes	Yes
Noninfectious complications	11 (0)	54 (0)	18 (0)	8 (0)	No	Yes
Immunosuppressive therapy	11 (0)	54 (0)	18 (0)	8 (0)	No	Yes
IgG trough levels	11 (0)	54 (0)	18 (0)	8 (0)	Yes	Yes
IgA/IgM	4 (7)	37 (17)	7 (1)	7 (1)	Yes	Yes
FEV_1	8 (3)	32 (22)	6 (12)	5 (3)	No	No
FVC	8 (3)	32 (22)	5 (13)	5 (3)	No	No
Immunophenotyping	3 (8)	39 (15)	9 (7)	6 (2)	Yes	Yes

Continuous variables were counted as available if they were collected at least once during follow-up. For multivariable risk factor analysis, medians of continuous variables were calculated and used. Missing medians were imputed using bootstrapped (n = 100) multiple regression imputation if <40% of the original data were missing.

CVID, Common variable immunodeficiency; *FEV_1*, forced expiratory volume in 1 minute; *FVC*, forced vital capacity; *IgSD*, immunoglobulin subclass deficiency; *IRT*, immunoglobulin replacement therapy; *SPAD*, specific polysaccharide antibody deficiency; *unPAD*, unclassified primary antibody deficiency; *XLA*, X-linked agammaglobulinemia.

TABLE E3. Listing of the multivariable risk factor analysis for AD scores ≥7.0%

	Model 1			Model 2		
Variable	**Estimate**	***P* value**	**VIF**	**Estimate**	***P* value**	**VIF**
Age at baseline	0.04	.15	3.0	0.04	.04	1.3
CD19+ counts	−0.01	.02	2.4	−0.01	.02	2.3
History of noninfectious complications	−0.45	.74	5.7	NA	NA	NA
Active noninfectious complications	0.20	.89	6.2	<0.01	1.0	2.3
GLILD	−0.28	.81	2.3	−0.11	.92	1.9
IgM	0.37	.39	3.2	0.21	.46	1.4
Diagnostic delay	0.02	.60	2.4	0.01	.72	1.4
CD4+ counts	<0.01	.72	2.9	<0.01	.84	1.9
Percentage of CD8 effector/memory cells	<0.01	.72	3.1	NA	NA	NA
Percentage of switched memory B cells	−0.03	.54	5.6	NA	NA	NA

Potential risk factors from the univariable analysis were included, and the variance inflation factor was calculated (model 1). Colinear variables were then removed from the model, and new estimates and *P* values were calculated (model 2).
AD, Airway disease; *GLILD*, granulomatous or interstitial lung disease; *NA*, not applicable; *VIF*, variance influencing factor.

TABLE E4. Listing of the multivariable risk factor analysis for the AD score increase of ≥0.5% points/year

	Model 1			Model 2		
Variable	**Estimate**	***P* value**	**VIF**	**Estimate**	***P* value**	**VIF**
Age at baseline	0.03	.29	1.6	0.03	.23	1.3
History of noninfectious complications	0.93	.69	9.3	NA	NA	NA
AD ≥7.0% at baseline	1.87	.04	1.5	2.74	.03	1.2
Mean infections per year	1.25	.63	22.6	1.42	.01	1.2
Duration of prophylactic antibiotics	2.06	.15	1.9	2.13	.08	1.3
Mean courses of antibiotics per year	0.06	.97	23.2	NA	NA	NA
Active noninfections complications	−0.08	.97	8.7	0.74	.42	1.3
PAD duration	0.05	.29	1.5	0042	.29	1.1
Smoking	0.04	.98	1.4	NA	NA	NA
Percentage CD8 effector/memory cells	−0.01	.87	4.7	NA	NA	NA
CD8 counts	<−0.01	.27	1.5	<−0.01	.19	1.2
Median IRT dose	0.89	.88	1.2	0.17	.98	1.2

Potential risk factors from the univariable analysis were included, and the variance inflation factor was calculated (model 1). Colinear variables were then removed from the model, and new estimates and *P* values were calculated (model 2).
AD, Airway disease; *NA*, not applicable; *PAD*, primary antibody deficiency; *VIF*, variance influencing factor.

TABLE E5. Listing of the multivariable risk factor analysis for ILD scores ≥13.0%

	Model 1: did not converge	Model 2		
Variable	**VIF**	**Estimate**	***P* value**	**VIF**
CD19+ counts	10	<−0.01	.94	1.4
History of noninfectious complications	121	NA	NA	NA
AD ≥7.0% at baseline	59	0.37	.76	1.5
Active noninfectious complications	224	NA	NA	NA
Percentage of CD4 effector/memory cells	77	0.08	.04	1.4
Mean IRT dose	172	NA	NA	NA
Age at baseline	92	<−0.01	.99	1.2
Percentage of switched memory B cells	3133	NA	NA	NA
PAD diagnosis	129	−1.70	.99	1.0
Mean IgG trough levels	12	−0.16	.34	1.1
Mean infections per year	72	0.89	.23	1.2
Percentage of CD8 effector/memory cells	48	NA	NA	NA

Potential risk factors from the univariable analysis were included, and the variance inflation factor was calculated (model 1). Colinear variables were then removed from the model, and new estimates and *P* values were calculated (model 2).

AD, Airway disease; *ILD*, interstitial lung disease; *IRT*, immunoglobulin replacement therapy; *NA*, not applicable; *PAD*, primary antibody deficiency; *VIF*, variance influencing factor.

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