Activated phosphoinositide 3-kinase δ syndrome: Update from the ESID Registry and comparison with other autoimmune-lymphoproliferative inborn errors of immunity

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Background: Activated phosphoinositide-3-kinase δ syndrome (APDS) is an inborn error of immunity (IEI) with infection susceptibility and immune dysregulation, clinically overlapping with other conditions. Management depends on disease evolution, but predictors of severe disease are lacking.

Objectives: This study sought to report the extended spectrum of disease manifestations in APDS1 versus APDS2; compare these to CTLA4 deficiency, NFKB1 deficiency, and STAT3 gain-of-function (GOF) disease; and identify predictors of severity in APDS.

Methods: Data was collected from the ESID (European Society for Immunodeficiencies)-APDS registry and was compared with published cohorts of the other IEIs.

Results: The analysis of 170 patients with APDS outlines high penetrance and early onset of APDS compared to the other IEIs. The large clinical heterogeneity even in individuals with the same *PIK3CD* variant E1021K illustrates how poorly the genotype predicts the disease phenotype and course. The high clinical overlap between APDS and the other investigated IEIs suggests relevant pathophysiological convergence of the affected pathways. Preferentially affected organ systems indicate specific pathophysiology: bronchiectasis is typical of APDS1; interstitial lung disease and enteropathy are more common in STAT3 GOF and CTLA4 deficiency. Endocrinopathies are most frequent in STAT3 GOF, but growth impairment is also common, particularly in APDS2. Early clinical presentation is a risk factor for severe disease in APDS.

Conclusions: APDS illustrates how a single genetic variant can result in a diverse autoimmune-lymphoproliferative phenotype. Overlap with other IEIs is substantial. Some specific features distinguish APDS1 from APDS2. Early onset is a risk factor for severe disease course calling for specific treatment studies in younger patients. (J Allergy Clin Immunol 2023;152:984-96.)

Key words: *APDS, PIK3CD, PIK3R1, PI3K, STAT3, CTLA4, NFKB1, IEI, ESID, immunodeficiency*

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Abbreviations used

AD: Autosomal dominant
APDS: Activated phosphoinositide 3-kinase δ syndrome
CMV: Cytomegalovirus
ESID: European Society for Immunodeficiencies
GOF: Gain of function
HSCT: Hematopoietic stem cell transplantation
IEI: Inborn error of immunity
ILD: Interstitial lung disease
PI3K: Phosphoinositide 3-kinase

Activated phosphoinositide 3-kinase (PI3K) δ syndrome (APDS), also called PASLI (p110-delta-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency), is an autosomal-dominant (AD) inborn error of immunity (IEI). Heterozygous gain-of-PI3Kδ-activity variants in *PIK3CD* or *PIK3R1* cause APDS1 and APDS2, respectively,[1-5] which show large phenotypic overlap. APDS is characterized by early-onset recurrent respiratory infections, chronic lymphoproliferation (benign and malignant), and other signs of immune dysregulation such as enteropathy and cytopenia.[6-10] While previous cohort studies have illustrated a variety of clinical features of APDS, the identification and standardized documentation of additional patients allows extending the spectrum of disease manifestations that can be reliably associated with the 2 variants of the disease.

Interestingly, many clinical features of APDS are shared with other autoimmune-lymphoproliferative IEIs, including CTLA4 deficiency,[11-13] NFKB1 deficiency,[14,15] and STAT3 gain-of-function (GOF) disease.[16,17] All 4 IEIs present an AD mode of inheritance and can cause increased infection susceptibility, early-onset benign lymphoproliferation, multisystem autoimmunity, and an increased risk of lymphoma. Biomarkers facilitating diagnosis such as soluble Fas ligand and vitamin B_{12} for autoimmune lymphoproliferative syndrome are lacking, rendering the differential diagnosis between these 4 IEIs particularly challenging. However, a comparison of clinical manifestations between these conditions has not been performed. Delineation of entity-specific disease patterns can have diagnostic implications, while overlapping disease features may indicate pathophysiological convergence of affected signalling pathways, potentially offering opportunities for shared targeted interventions.

The clinical course of APDS is highly variable. While it can be life-threatening in childhood, stable disease into late adulthood has also been reported.[6-8] This variability makes it difficult to advise patients about their individual prognosis and best treatment approach. The most promising current therapeutic options include rapamycin, PI3Kδ inhibitors, and hematopoietic stem cell transplantation (HSCT).[8,18-22] Yet, the standard of care and use of these therapies in the long-term management of patients with APDS remains to be defined. These interventions and their potential side effects must be balanced against the risks of the natural disease course. However, information on the natural history of APDS is still limited, and no clear risk factors for severe disease evolution have been identified.

In this study, we used an updated dataset of the ESID (European Society for Immunodeficiencies)-APDS registry of 170 patients with APDS and published datasets[13,15,17] on other autoimmune-lymphoproliferative IEIs to address the following questions: (1) What are the clinical overlaps and characteristic differences among APDS, CTLA4 deficiency, NFKB1 deficiency, and STAT3 GOF disease? (2) Are there differences in the spectrum of disease manifestations between APDS1 and APDS2? (3) Can we identify early predictors of severe disease evolution in patients with APDS?

METHODS

The ESID-APDS registry

ESID is a nonprofit association whose aim is to improve knowledge in the field of IEIs. The APDS subregistry is the first level 3 dataset within the international internet-based ESID registry (https://esid.org/Working-Parties/Registry-Working-Party/ESID-Registry/The-3-levels-datasets-and-driving-questions). Documentation into the ESID registry is organized in 3 levels. Level 1 is open to capture all patients with IEIs and includes a minimal dataset on initial manifestations, age at diagnosis, immunoglobulin replacement, and HSCT with yearly follow-up on survival and changes in therapy.[23] Level 2 makes it possible to set up research projects that include some laboratory values and more details on treatments for a selected group of diseases. Level 3

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allows the implementation of large datasets designed to address specific and extended clinical questions on a single IEI defined by a study protocol, including a statistical evaluation plan. All level 2 and 3 projects include level 1 data. Requirements for patients' registration are positive vote from the local ethics committees, agreement between the treating center and ESID, and signed ESID patient consent. Patient registration in the APDS subregistry also requires approval of evidence supporting the functional relevance of the mutation by a principal investigator. Patient data can be entered by authorized users via a standard web browser through encrypted communication.[24] The first patient was registered in September 2015. The number of new patients documented per year is shown in Fig E1, *A* in this article's Online Repository (available at www.jacionline.org), and the percentages of patients registered by the different countries are shown in Fig E1, *B*.

Patients

Forty-six centers collected data on 170 patients with APDS (data closure for analysis: November 10, 2022). Sixty-eight patients were already reported[8] (Table E1 in this article's Online Repository at www.jacionline.org). The study was carried out in accordance with the recommendations of section 15 of the Code of Conduct of the General Medical Council of Baden-Württemberg, Germany. The protocol was approved by the Ethics Committee of the University of Freiburg, Germany (IRB approval No. ESID registry: 493/14; IRB approval No. APDS registry: 458/15). All subjects or their parents/legal caregivers gave written informed consent in accordance with the Declaration of Helsinki.

To perform the comparison with other AD IEIs, the largest published cohort studies[13,15,17] were taken as reference, and the frequency of reported clinical and immunological features were compared among all 4 IEIs, because there are currently no level 3 ESID registry data on the other IEIs. A study proposal was written, and was approved by the ESID registry steering committee, to collect level 1 data on the initial presentation of the analyzed IEIs from the ESID registry. Subsequently, complete data from patients whose documenting centers agreed to the protocol were included in the analysis.

Statistical analysis

Data were exported and organized using Microsoft Excel (Microsoft, Redmond, Wash). Data visualisation and statistical analysis were performed using R version 4.1.0 (R Foundation, Vienna, Austria). Proportions among all IEIs were compared using Pearson chi-squared test. Analyses with a P value < .05 (*) were considered statistically significant. Only significant comparisons among all IEIs are shown in the figures. We performed a logistic regression to analyze the probability of severity in dependency of following variables: age at onset below the age of 1 year, gender, immunoglobulin replacement treatment, APDS1, both infections and immune dysregulation at presentation, only immune dysregulation at presentation, diagnostic delay, and diagnosis before 2015 (before the discovery of the genetic cause of the disease). For missing value imputation, we used the R package mice with predictive mean matching for numeric data and logistic regression imputation for binary data. To avoid overfitting, we performed bidirectional stepwise model selection by Akaike information criteria.

Weighted Cox regression. Data are doubly truncated because the age at severity onset falls in the time interval between age at disease onset and age at study entry. We used inverse probability weighted Cox regression for doubly truncated data[25] to analyze the cumulative probability of severity in dependency of the binary variable age at onset under/over 1 year.

RESULTS

APDS has low genetic heterogeneity, early onset, and strong penetrance

Among the 170 patients with APDS, 115 had heterozygous disease-causing variants in *PIK3CD* and 55 in *PIK3R1* (Table E1). Eight different disease-causing variants were found spanning p110δ with E1021K accounting for 90% (Fig 1, *A* and *B*). All patients with APDS2 carried deleterious splice site disease-causing variants resulting in "skipping" of exon 11 of p85α (Table E1). In contrast, 45 different *CTLA4* disease-causing variants were found among 133 patients,[13] 56 disease-causing variants were identified in 157 NFKB1-deficient patients,[15] and 72 different variants were reported in 191 patients STAT3 GOF.[17] Thus, genetic heterogeneity of APDS appears to be lower compared to the other 3 IEIs. Median age at first clinical manifestation was 1 year in patients with APDS, with no gender difference and no difference between APDS1 and APDS2. Age at onset was lower than that reported for CTLA4 (median 11 years)[13] and NFKB1 (median 12 years)[15] deficiency, while patients with STAT3 GOF disease also presented early in life (median 2.3 years)[17] (Fig 2, *A*). The initial clinical manifestations experienced by patients with APDS were most frequently infections (54%) and infections combined with immune dysregulation (29%) and less frequently immune dysregulation without infections (8%) (Fig 2, *B*). This was similar to NFKB1 deficiency (Fig 2, *B*), while patients with STAT3 GOF and CTLA4 deficiency more frequently first presented with immune dysregulation without infection (37% and 44%, respectively). Only 4 patients with APDS were reported to be without clinical symptoms at registration (age at registration 1, 1, 3, and 44 years), but 2 of them received immunoglobulin replacement for hypogammaglobulinemia. In the CTLA4 and NFKB1 cohorts, 19.5% and 23% were reported to be clinically healthy, respectively. While unaffected STAT3 GOF carriers were not included in the Leiding et al[17] cohort, a recent review[26] included 18% asymptomatic STAT3 GOF individuals. Hence, compared to these 3 other IEIs with overlapping phenotypes, disease penetrance appears to be higher in APDS.

APDS has an earlier and more severe infection profile

Respiratory infections were frequent in all 4 IEIs with the highest occurrence in APDS (92%) (Fig 3, *A*). Other common infections in APDS included invasive bacterial infections (53%) and infectious lymphadenitis (30%). Only 1 case of cytomegalovirus (CMV)-associated lymphadenitis was reported in the CTLA4 cohort, and no cases were mentioned among the patients with NFKB1 or STAT3 GOF. *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Staphylococcus aureus* were the most frequently reported respiratory pathogens in all diseases, while infections with *Pseudomonas aeruginosa* were reported more frequently in patients with APDS (n = 15 of 169) and those with STAT3 GOF (n = 8 of 191). *Escherichia coli* and *Salmonella*

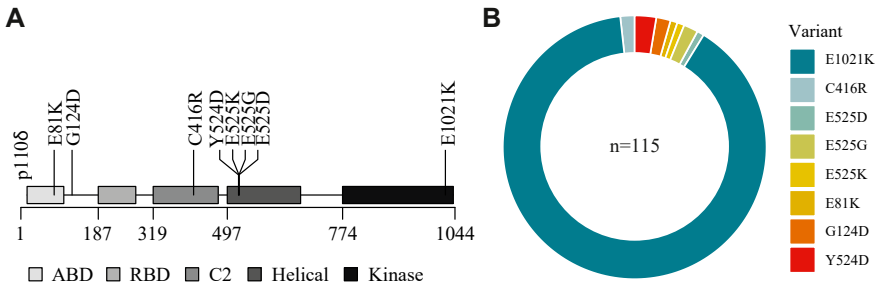

FIG 1. Overview of the *PIK3CD* disease-causing variants in the registry. **A,** Localization of the variants in the *PIK3CD* gene. **B,** Frequency of the different variants. *ABD*, Adaptor-binding domain; *RBD*, Ras-binding domain.

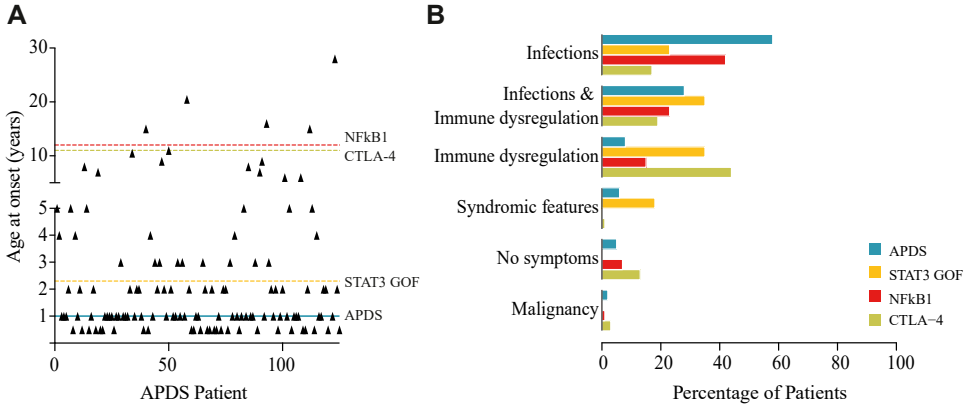

FIG 2. Initial clinical presentation. **A,** Age at disease onset of patients with APDS (median represented by the *blue line;* patients with APDS represented by *triangles*). The median age of patients at onset of NFKB1 deficiency (*red*), CTLA4 deficiency (*green*), and STAT3 GOF (*yellow*) is superimposed as a *dotted line*. **B,** Initial clinical presentation of patients with APDS (n = 170) compared to patients with NFKB1 deficiency (n = 83), CTLA4 deficiency (n = 113), and STAT3 GOF (n = 41). Malignancy refers to both lymphoid and nonlymphoid malignancy. Data on all 4 IEIs were extracted from the ESID registry.

were the most frequently isolated pathogens in bacterial intestinal infections. Chronic EBV (22%, age range 1-37 years, median 5 years) and chronic CMV (14%, age range 1-35 years, median 8.5 years) were present in patients with APDS (Fig 3, *A*). Similarly, in patients who are CTLA4-deficient, EBV and CMV led to clinically relevant infections in 18% and 10%, respectively, while the reported incidence was below 5% in NFKB1 deficiency and STAT3 GOF. Acute viral infections were reported in 47% of patients with APDS. No cases of *Pneumocystis jirovecii* infection were reported in the APDS cohort and mycobacterial infections were rare (4 patients with BCG disease and 1 with pneumonia due to *Mycobacterium xenopi*). Parasitic infections were rare in all conditions; 2 cases of infection with *Cryptosporidium parvum*, 2 with *Giardia lamblia,* and 2 with *Toxoplasma* were reported in the APDS cohort. Opportunistic infections were all prior to HSCT.

Bronchiectasis is more prominent than interstitial lung disease in APDS

A total of 143 patients with APDS had chest imaging (computed tomography scan or magnetic resonance imaging) performed: pathological findings were detected in 73%. Bronchiectasis was most frequent in APDS (50%, age range 1-43 years; median 7 years), but was also reported in the other IEIs (Fig 3, *B*). Small airway disease was noted in 29% of patients with APDS (age range 1-50 years; median 8 years). Interstitial lung disease (ILD) was only reported in 2% of patients who were APDS-deficient and in 7% of those who were NFKB1-deficient. In contrast, patients with CTLA4 deficiency were often (36%) reported to have granulomatous-lymphocytic ILD (Fig 3, *B*). Similarly, ILD occurred in 43% of patients with STAT3 GOF. Lung disease was severe enough to justify lung transplantation in 2 patients with CTLA-4 deficiency and 2 patients with STAT3 GOF. Interestingly, 30 patients with APDS (18%) had asthma as concomitant diagnosis, compared to 6% in the CTLA4 cohort, and no reported cases in the other 2 cohorts. Lung function, assessed in 91 patients with APDS, was abnormal in 47%.

APDS is characterized by chronic benign lymphoproliferation and early malignancy

Chronic benign lymphoproliferation, including both splenomegaly and persistent lymphadenopathy (defined as lymph nodes larger than 1 cm, affecting more than 1 site for longer than 1 month), was most frequent in APDS (86%), followed by CTLA4 deficiency (73%), and STAT3 GOF disease (73%) with a lower incidence of 52% in NFKB1 deficiency (Fig 3, *C*). Conversely, cytopenia was significantly less frequent in APDS (19%, most frequent: autoimmune hemolytic anemia in 12 patients) than in

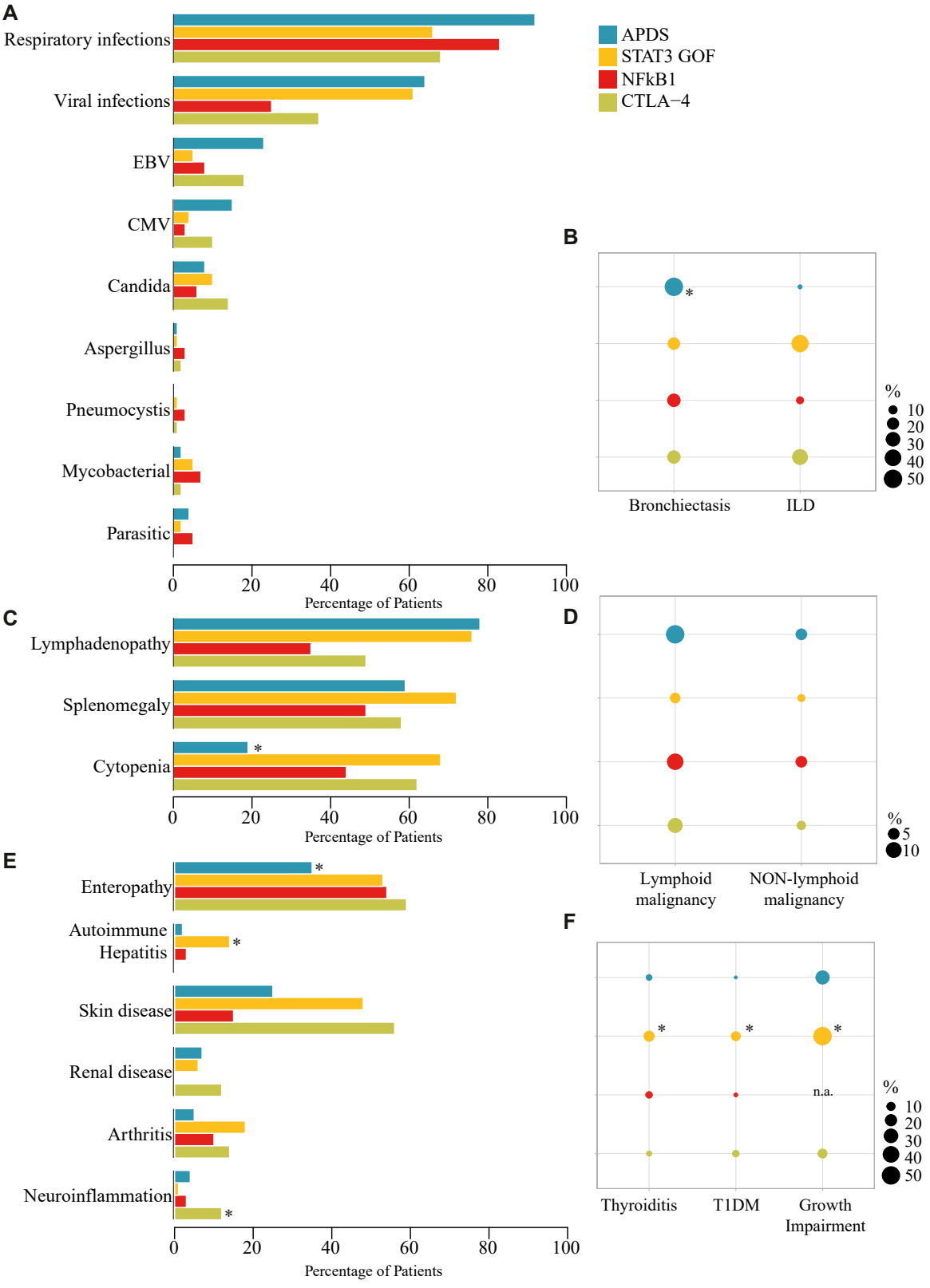

FIG 3. Main clinical manifestations. **A,** Main infectious complications of patients with APDS (n = 170) compared to patients with NFKB1 deficiency (n = 121), CTLA4 deficiency (n = 90), and STAT3 GOF (n = 191). **B,** Lung disease. **C,** Hematological complications. **D,** Malignancy. **E,** Other inflammatory manifestations. **F,** Endocrinological manifestations. *P < .05 in a t-test performed between every IEI. Data on NFKB1 insufficiency, CTLA4 insufficiency, and STAT3 GOF were extracted from published cohort papers.[13,15,17] *NA*, Not available; *T1DM*, type 1 diabetes mellitus.

CTLA4 deficiency (62%), NFKB1 deficiency (43.9%), and STAT3 GOF disease (68%) (Fig 3, *C*). Lymphoma was documented in 14% of patients with APDS, 11% of those with NFKB1, and 9% of those withCTLA4, but only 4% of patients with STAT3 GOF (Fig 3, *D*). Lymphomas in APDS included 7 Hodgkin lymphomas, 10 non-Hodgkin lymphomas, 1 intestinal large B-cell lymphoma with plasmablastic differentiation, 1 follicular lymphoma, 1 large B-cell lymphoma, 1 mature T-cell/natural killer–cell lymphoma, 1 lymphoma without further histological information; 17 of 22 lymphoma cases were preceded by chronic benign lymphoproliferation. Of note, 10 of 20 lymphoma cases in APDS were EBV-associated. Moreover, of the 22 patients with APDS who have lymphoma, 4 suffered also from other malignancies (2 ovary neoplasms; 1 papillary renal cell carcinoma; 1 malignant neoplasm of the submandibular gland). Furthermore, 1 patient with APDS had a B-cell chronic lymphocytic leukaemia, 1 suffered from hepatocellular carcinoma, 1 had a breast ductal carcinoma *in situ*, 1 patient had a papillary thyroid carcinoma, and 1 a rhabdomyosarcoma. The median age at diagnosis of any malignancy was much lower in patients with APDS (19 years) than in those with NFKB1 deficiency (46 years).

Autoimmune and inflammatory diseases are relevant in APDS, but less frequent than in the other diseases

Enteropathy, ranging from protracted diarrhea to inflammatory bowel disease, was reported in 35% of patients with APDS, less frequently than in the other IEIs (Fig 3, *E*). Rare cases of eosinophilic esophagitis and sclerosing cholangitis were also reported.[27] Autoimmune hepatitis was particularly frequent in STAT3 GOF (Fig 3, *E*). Noninfectious skin disease was reported in 25% of patients with APDS and mainly included eczema and granulomas (Fig 3, *E*). This was less prominent than in CTLA4 deficiency (56%, mainly eczema) and STAT3 GOF disease (48% skin lesions including eczema, psoriasis, and alopecia) but more frequent than in the NFKB1 cohort (15%), where patients suffered more frequently from skin infections. Endocrinopathies, including autoimmune thyroiditis and type 1 diabetes mellitus, were reported in all 4 IEIs (Fig 3, *F*) but were most frequent in STAT3 GOF disease. Renal disease affected 6% to 12% of patients in the APDS, CTLA4, and STAT3 GOF cohorts, while it was not reported in NFKB1 deficiency. Moreover, 5 patients with APDS were diagnosed with vasculitis, and 2 different patients had SLE. One patient was diagnosed with chronic kidney disease, and 2 received a kidney transplantation. Arthritis incidence was similar in all IEIs studied (Fig 3, *E*). Less than 5% of patients in the APDS, STAT3 GOF, and NFKB1 cohorts had inflammatory brain disease, while this was significantly more frequent in patients with CTLA4 (12%). In APDS, noninflammatory neurological manifestations including neurodevelopmental delay were observed in 16% of patients. Growth impairment was frequent in APDS (32%) and STAT3 GOF disease (57%), less frequent in CTLA4 deficiency (14%), and not reported in NFKB1 deficiency (Fig 3, *F*).

Increased IgM and reduced naive T cells are characteristic immunological abnormalities of APDS

Hypogammaglobulinemia was common in all 4 IEIs, but most frequent in NFKB1 deficiency. APDS is often characterized by elevated serum IgM (35%), while low IgM, a common feature in the other 3 diseases, was rare in APDS (Fig 4, *A*). While T-cell lymphopenia is common in all 4 IEIs, a low frequency of naive CD4 T cells was most frequently reported in APDS. Reduced switched memory B cells and increased transitional B cells were reported, but they were not particularly characteristic for patients with APDS (Fig 4, *B*).

Distinct features of APDS1 versus APDS2 indicate pathophysiological differences

Among initial presenting manifestations, syndromic features, mainly growth impairment and facial dysmorphism, were more frequent in APDS2 (Fig 5, *A*; details are provided in Table E2 in this article's Online Repository at www.jacionline.org). Infectious complications were equally distributed (Fig E2 in this article's Online Repository at www.jacionline.org), but opportunistic infections were more frequent in APDS1. Significantly, bronchiectasis was more frequent in APDS1 (60%) than in APDS2 (26%) (Fig 5, *B*). The prevalence of asthma was similar (18% vs 16%). Splenomegaly and cytopenia were more frequent in APDS1, but lymphoma was more frequent in APDS2 (Fig 5, *C*). Growth impairment was more frequent in APDS2 and skin disease in APDS1 (Fig 5, *D*). Among immunological abnormalities, low T-cell counts were more frequent in APDS1, while IgA reduction was more frequent in APDS2 (Fig 5, *E*).

Age at first clinical presentation predicts disease severity in APDS

The majority of patients with APDS received immunoglobulin replacement treatment (73%), and many patients received immunomodulating therapies (Fig E3, *A* and *B* in this article's Online Repository at www.jacionline.org), ranging from rapamycin (37%) to PI3Kδ inhibitors (5%). Twenty-nine of 168 patients with APDS (17%) underwent allogenic HSCT between the ages of 5 and 51 years (median 13.5 years). Fourteen of 170 patients with APDS (8%) died at a median age of 18.5 years (5-44 years). Five deaths were lymphoma-related, 5 were HSCT-related, and 1 was related to both. Two patients died from severe respiratory infection and 1 from intracranial bleeding secondary to thrombocytopenia. To evaluate prognostic factors for a severe disease course in APDS, we defined severe disease as follows: (1) severe invasive infection and immune dysregulation (excluding chronic benign lymphoproliferation and cytopenia) or chronic lung disease, (2) severe immune dysregulation, (3) malignancy. If a patient had already developed a severe invasive infection or severe immune dysregulation or chronic lung disease before age 13 years, the disease course was also considered severe. Criteria for severe disease were fulfilled by 93 of 169 patients (range 2-50 years; median age at transition to severe disease 9.5 years) (Fig 6, *A*, Tables E3 and E4 in this article's Online Repository at www.jacionline.org). All deceased patients had severe disease with a median time of 6 years (range 1-21 years) between fulfilling these criteria and death. The risk for severe disease increased with patient age (Fig 6, *B*) and with years since the first clinical disease manifestation (Fig 6, *C*). The risk doubled in the age range 10 to 15 years compared to age range 0 to 10 years. Age at onset below 1 year significantly correlated with the probability of developing severe disease (Fig 6, *D*). Other significant risk factors could not be identified through a multivariate logistic regression

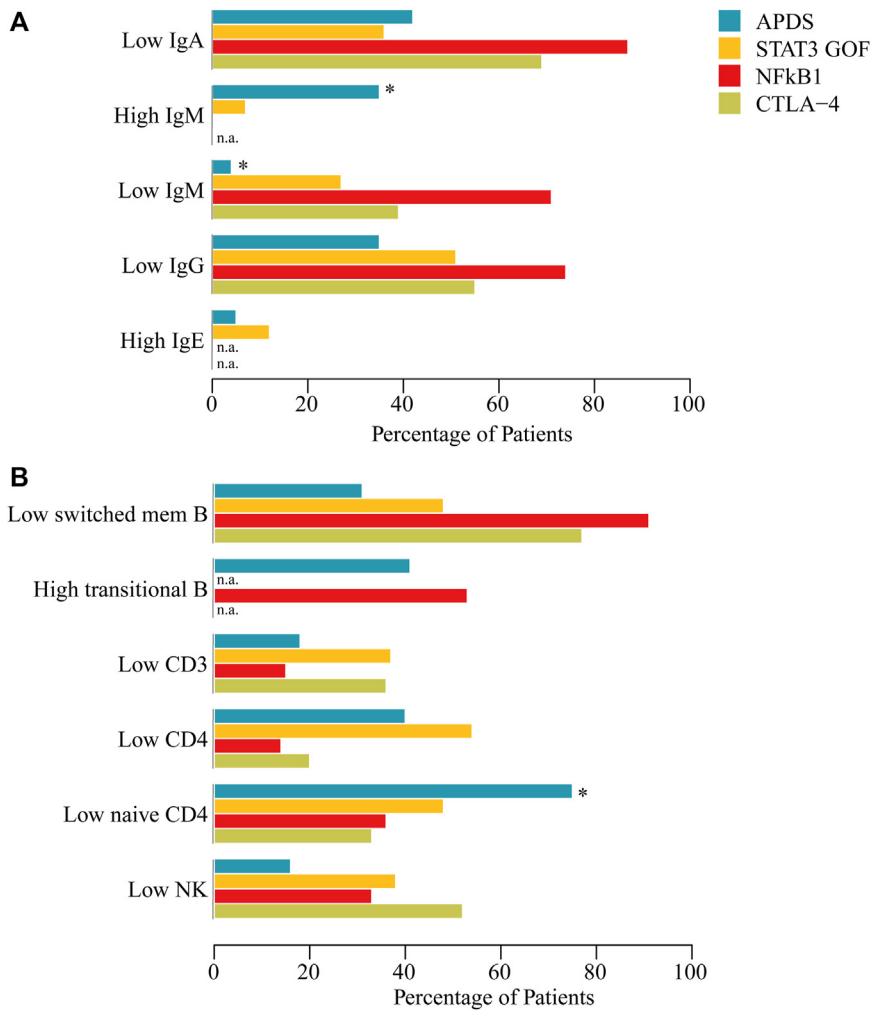

FIG 4. Immunological abnormalities. **A,** Immunoglobulin abnormalities of patients with APDS (IgG, n = 145; IgA, n = 137; IgM, n = 137; IgE, n = 56) compared to patients with NFKB1 insufficiency (n = NA), CTLA4 insufficiency (n = 77), and STAT3 GOF (IgG, n = 169; IgA, n = 161; IgM, n = 161; IgE, n = 52). **B,** Cellular abnormalities of patients with APDS (CD3, n = 152; CD4, n = 151; naive CD4, n = 106; transitional B cells, n = 46; switched memory B cells, n = 83; natural killer [*NK*] cells, n = 116) compared to patients with NFKB1 insufficiency (n = NA), CTLA4 insufficiency (CD3, n = 44; CD4, n = 62; naive CD4, n = 57; switched memory B cells, n = 30; NK cells, n = 61) and STAT3 GOF (CD3, n = 171; CD4, n = 169; naive CD4, n = 31; switched memory B cells, n = 31; NK cells, n = 151). **P* < .05 in a *t*-test performed between every IEI. Data on NFKB1 insufficiency, CTLA4 insufficiency, and STAT3 GOF were extracted from published cohort papers.

analysis (Fig E4 in this article's Online Repository at www.jacionline.org).

DISCUSSION

We report the evaluation of the, so far, largest APDS cohort of 170 patients with functionally validated, germline heterozygous variants in *PIK3CD* or *PIK3R1* documented through a standardized registry.

While highlighting the low genetic heterogeneity among patients with APDS, we show that patients with APDS1, the majority of which carry the *PIK3CD* E1021K mutation, display high phenotypic diversity. This illustrates that identical variants in a disease-causing gene can lead to diverse clinical consequences. This emphasizes the significance of additional genetic, epigenetic, and environmental factors in determining disease manifestations in autoimmune-lymphoproliferative diseases. This clinical variability is associated with a very high penetrance, as there was only 1 patient above the age of 5 years reported to be asymptomatic in the registry. However, systematic segregation studies would be needed in APDS as well as in the other IEI cohorts to better evaluate the true penetrance of these diseases and indirectly estimate the extent of underdiagnosed cases.

We structured the updated analysis of the APDS cohort in the context of a comparison with 3 other AD autoimmune-lymphoproliferative IEIs for which substantial cohorts have been published[13,15,17]: CTLA4 deficiency, NFKB1 deficiency, and STAT3 GOF disease. In general, there was a high clinical overlap between the investigated IEIs, indicating relevant pathophysiological convergence of the different affected pathways. This convergence is supported by experimental observations: for example, a link between mammalian target of rapamycin

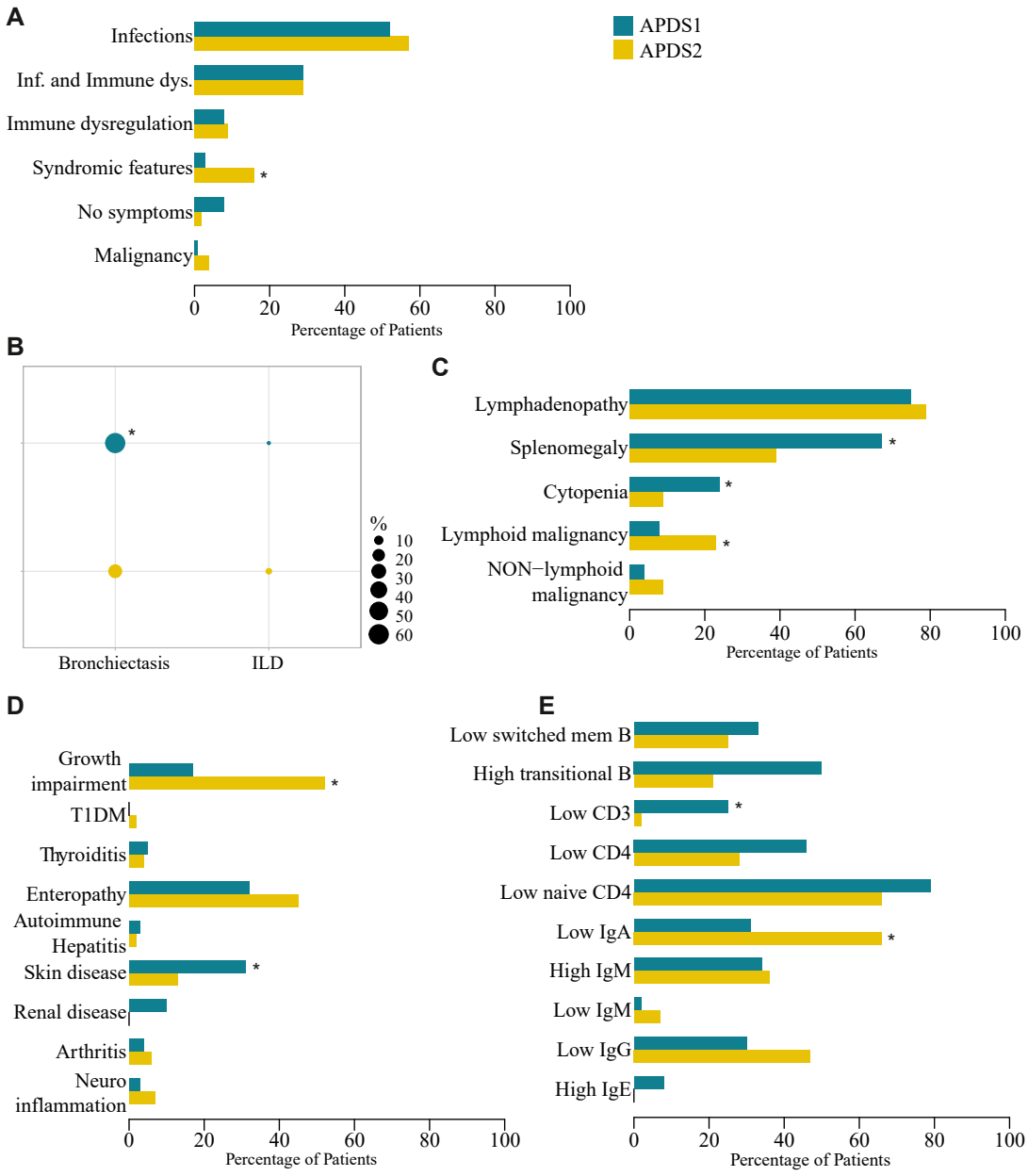

FIG 5. APDS1 versus APDS2. **A,** Initial presentation. Malignancy refers to both lymphoid and nonlymphoid malignancy. **B,** Lung disease. **C,** Hematological complications. **D,** Other inflammatory (*Inf*) and endocrinological manifestations. **E,** Immunological abnormalities. *$P < .05$ in a *t*-test performed between every IEI. *dys*, Dysregulation.

activation and disease pathophysiology is evident not only in APDS,[4] but also in STAT3 GOF[28] and CTLA4 deficiency.[29] This justifies the frequent use of the mammalian target of rapamycin inhibitor rapamycin in these 3 diseases, although variable treatment success indicates involvement of additional pathways. A potential link of mammalian target of rapamycin activation to NFKB1 deficiency is less clear, mirrored by the reported use of rapamycin in only 2% of the patients in the largest published cohort.[15]

Variability and overlap between the IEIs render it difficult to predict the diagnosis prior to genetic evaluation. However, some differences emerge from the comparative analysis. APDS has the earliest onset, mainly with recurrent respiratory infections and this contrasts with the frequent initial presentation with immune dysregulation typical of CTLA4 deficiency and STAT3 GOF disease. Of note, the initial presentation with recurrent infections only rarely leads to the diagnosis of APDS, as recently highlighted by Ahmed et al[30] who could diagnose only 1 patient with APDS among 79 children admitted to the hospital for severe or recurrent respiratory infections. Infections are a crucial aspect in all 4 IEIs throughout the disease course, with highest frequencies observed in APDS and NFKB1 deficiency. These 2 conditions present mechanistically different but equally profound B-cell dysfunction.[14,31-33] Regarding infections, it is important

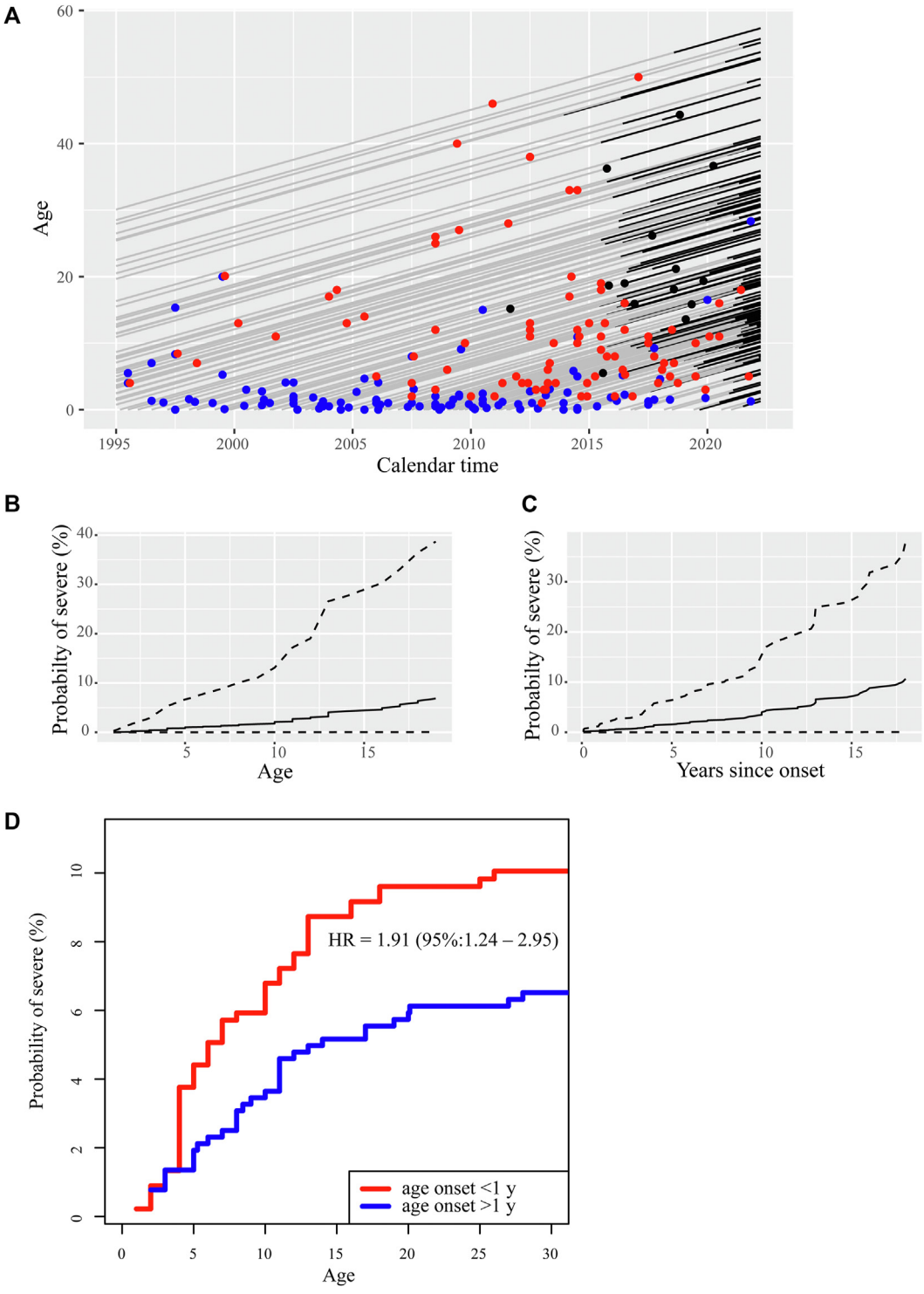

FIG 6. APDS disease evolution. **A,** Lexis diagram displaying all patients as lines from birth to time of last follow-up with the time of onset (*blue dot*), severity (*red dot*), and death (*black dot*). The line changes from *gray* to *black* at the time of entry into the registry (prospective observation). **B,** Cumulative probability of fulfilling criteria for a severe disease course with 95% confidence band; time scale is age in years. **C,** Cumulative probability of severe disease with 95% confidence band; time scale is years since onset. **D,** Weighted Cox regression to analyze the cumulative probability of severe disease depending on the variable age at onset </> 1 year. *HR*, Hazard ratio.

to note that regional exposure to different pathogens can influence the reported frequency of the infections. For example, a recent paper on a Chinese APDS cohort[34] reported a much higher incidence of primary mycobacterial infections than in this APDS series of patients. Chronic viral infections are confirmed to be relevant, especially in APDS and CTLA4 insufficiency. On the other hand, our extended APDS registry cohort analysis reveals that opportunistic infections are rather rare in this disease.

Lung disease is a prominent feature in APDS, and its early identification is crucial in the management of patients with IEIs. Of note, bronchiectasis and small airway disease were characteristic, while ILD was reported infrequently in APDS. It is important to note that small airway disease is likely underestimated in APDS, because specific expiratory imaging is needed for early detection.[35] Importantly, asthma was recently pointed out as a relevant manifestation in an American APDS cohort[36] and had been already reported in some patients of small case series.[37] The ESID-APDS registry does not specifically ask for asthma, but it was repeatedly documented as "further diagnosis," thereby providing additional evidence to consider it an APDS-related manifestation.

Of the IEIs evaluated, APDS had the highest incidence of benign and malignant lymphoproliferation. This implies a diagnostic challenge of differentiating between benign and malignant lymphoproliferation.[38] Imaging and fluorine-18-fluorodeoxyglucose positron emission tomography do not provide a definitive diagnosis, similar to other lymphoproliferative IEIs.[39] For this reason, a thorough evaluation of the clinical course by experienced clinicians and an adequate histological analysis by pathologists trained in analyzing lymphoid tissue of patients with IEIs is paramount to rule out lymphoma in these patients. The high incidence of nonlymphoid malignancies reported in our APDS cohort is noteworthy: while the increased risk of malignancy in patients with IEIs has long been known,[40] increased awareness of APDS as cancer predisposition syndrome[41] calls for improved clinical care and research at the critical interface between immunology and oncology.[42]

The analysis of the large APDS registry cohort also identifies arthritis, renal disease, neuroinflammatory disease, or type 1 diabetes as rare but possible APDS-related complications. Overall, the differences between APDS and clinically overlapping IEIs highlighted by our work are not sufficient to define a specific APDS pattern or clinical diagnostic criteria for the disease. It is possible that including a higher resolution immunological analysis (such as high-dimensional multiomics single-cell data) may help to identify diagnostic biomarkers but, currently, identification of a genetic variant in combination with its functional validation remains the only valid criteria.

Our analysis also highlights some new differences between the 2 forms of APDS, corroborates others already noted through confirmation in a larger cohort, and does not confirm others previously observed[6-8,36,43,44]: thus, we report a significantly higher incidence of cytopenia and skin disease in patients with APDS1 and a significantly higher incidence of reduced IgA in APDS2; we confirmed a higher incidence of bronchiectasis and reduced CD3 T cells in APDS1 and a higher incidence of lymphoma, growth retardation, and syndromic features (detailed in this study) in APDS2. Regarding syndromic features, APDS2 can be differentiated from the SHORT (short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly, and teething delay) syndrome, caused by mutations in the same gene (*PIK3R1*) but affecting another region (C-terminal Src homology 2 domain) resulting in a different effect (impairment of interaction with phosphorylated receptor tyrosine kinases).[45] However, patients with overlapping clinical features have been reported.[46-48] These clinical observations are relevant for the patient management and for research studies that further investigate pathophysiological differences between the catalytic and regulatory kinase components encoded by the mutated genes. Indeed, a recent work could identify relevant differences in B-cell abnormalities between APDS1 and APDS2 and highlight an increased perinatal mortality in APDS2 mice, but not in the APDS1 counterpart.[49] Finally, a recently reported higher incidence of enteropathy in patients with APDS1 and of elevated IgM in patients with APDS2[44] could not be confirmed.

This registry analysis bears some relevant limitations: (1) The compared IEIs were not assessed using the same dataset, which may affect the reported frequency of some symptoms or diagnoses. (2) Some manifestations are *per se* difficult to categorize, for example, enteropathy can be difficult to distinguish from infectious enteritis. Internationally accepted standards of diagnosis and monitoring of these patients could help defining comparable datasets and, already, efforts have been taken in that direction.[50] (3) The registry and the retrospective cohort study structures are inevitably linked to the problem of missing data, leading to incomplete information and the eventual need of statistical corrections. In this study missing values were particularly relevant for laboratory parameters. Data completeness was only sufficient for some basic parameters, revealing that increased IgM and reduced naive T cells are characteristic, but not specific for APDS. It would be of interest to correlate more in-depth immunological parameters to identify possible disease-specific immune signatures and their role as prognostic factors.

One further aim of the current study was to identify predictors for severe disease in APDS, which could be useful for treatment and management choices. The number of variables evaluated as severe disease predictors was limited by the fact that many parameters were used in the definition of severe disease. Moreover, a registry-dependent bias in the identification and registration of younger patients with clinical symptoms of the disease must be taken into consideration, because the disease is not diagnosed through a screening but based on clinical suspicion. The analysis revealed early disease onset as a prognostic factor, with the clinical implication that early-onset cases should be followed closely and evaluated early for treatments such as HSCT. It will be interesting to see in the future how targeted therapy with PI3Kδ inhibitors will impact on the long-term evolution of disease manifestations in APDS. Recent results of a phase 3 trial show promising efficacy, especially regarding the lymphoproliferative disease, with a very good safety profile.[22] The poorer prognosis for patients with early disease onset identified in this study highlights the importance of clinical trials involving younger patients (such as the recently started Pediatric Patients Aged 4 to 11 Years With APDS study; NCT05438407).

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Clinical implications: The largest APDS cohort worldwide is reported. APDS illustrates how a single genetic variant can cause a highly diverse autoimmune-lymphoproliferative phenotype overlapping with similar IEIs. Early disease onset confers more severe disease.

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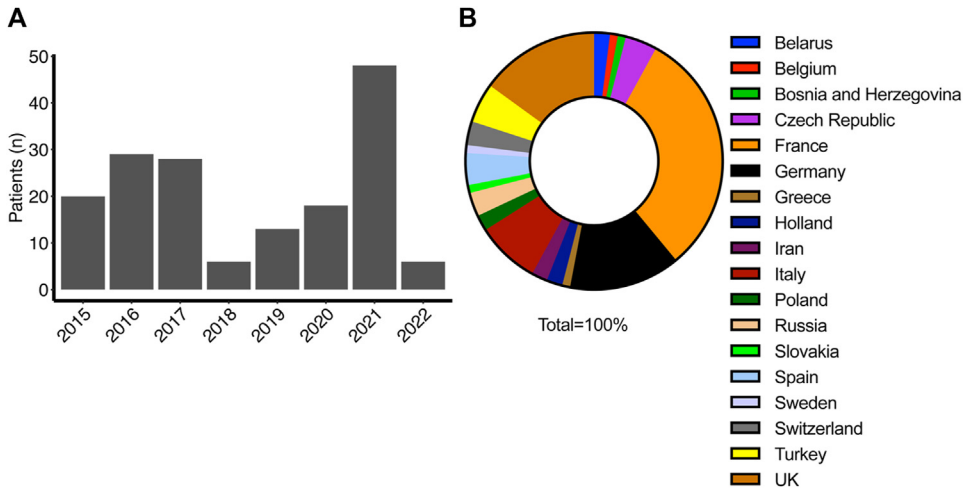

FIG E1. A, Number of new patients documented per year. **B,** Percentage of APDS patients coming from the different countries.

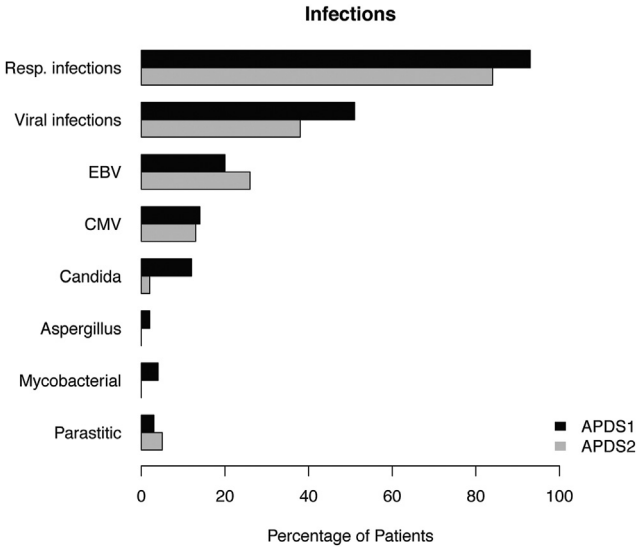

FIG E2. Infectious complications in APDS1 and APDS2.

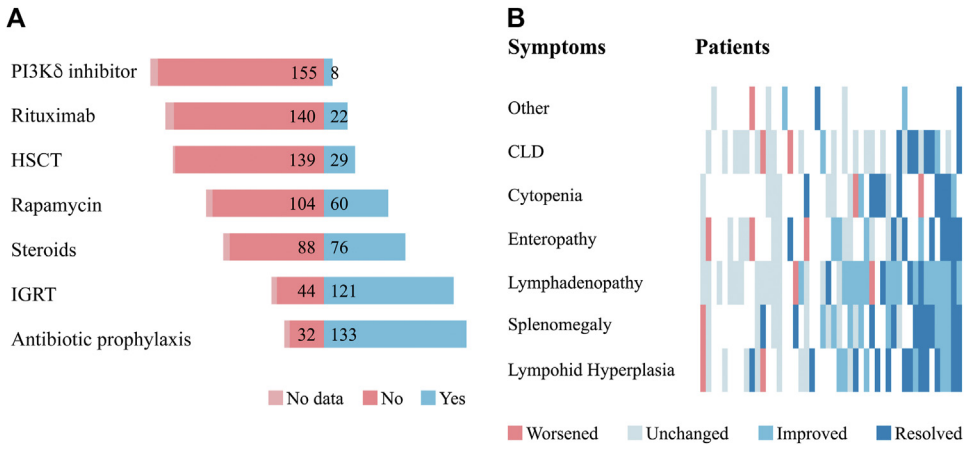

FIG E3. A, Different treatments given to patients with APDS. Number of patients indicated in the graph. **B,** Response to treatment with rapamycin in 48 patients. *White boxes* represent clinical features not present at therapy start. *CLD*, Chronic lung disease; *IGRT*, immunoglobulin replacement treatment.

	Intensity binary			Intensity_binary		
Predictors	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*
(Intercept)	0.85	0.19 – 3.87	0.832	0.43	0.14 – 1.34	0.149
Age at onset < 1y	3.56	1.50 – 9.09	**0.005**	1.52	0.81 – 2.85	0.192
Gender	1.23	0.54 – 2.82	0.618	1.35	0.71 – 2.59	0.358
IGRT	0.79	0.27 – 2.17	0.651	1.13	0.53 – 2.40	0.744
PIK3CD	1.57	0.67 – 3.72	0.298	1.45	0.73 – 2.87	0.288
Infections & immunedys. at presentation	1.33	0.55 – 3.30	0.530	1.12	0.56 – 2.25	0.750
Only immunedysregulation at presentation	0.27	0.05 – 1.28	0.112	0.64	0.21 – 1.90	0.417
Diagnostic delay	0.98	0.91 – 1.06	0.681	1.02	0.96 – 1.08	0.515
Diagnosis before 2015	0.96	0.38 – 2.39	0.938	1.42	0.70 – 2.92	0.332
Observations	**117**			169		
R^2 Tjur	0.128			0.040		

FIG E4. Logistic regression analysis for predictors of severe disease before (*left column*) and after (*right column*) implementation analysis to fill missing values.

TABLE E1. Demographic and pathogenic variants of patients with APDS

Patient	Sex	Familial case	Gene	Consequence	Living status	Already published in Maccari et al[8]
1	F	Yes	*PIK3CD*	E1021K	Alive	No
2	M	No	*PIK3CD*	E1021K	Alive	No
3	M	Yes	*PIK3CD*	E1021K	Dead	No
4	M	No	*PIK3CD*	E1021K	Alive	Yes
5	M	No	*PIK3CD*	E1021K	Dead	No
6	M	No	*PIK3R1*	ΔAA434-475	Alive	Yes
7	M	No	*PIK3CD*	E1021K	Dead	No
8	F	Unknown	*PIK3CD*	E1021K	Alive	No
9	F	Yes	*PIK3CD*	E1021K	Alive	Yes
10	M	No	*PIK3CD*	E1021K	Alive	No
11	F	No	*PIK3R1*	ΔAA434-475	Alive	No
12	M	No	*PIK3R1*	ΔAA434-475	Alive	Yes
13	M	No	*PIK3R1*	ΔAA434-475	Alive	No
14	F	No	*PIK3CD*	E1021K	Dead	Yes
15	M	Yes	*PIK3R1*	ΔAA434-475	Alive	No
16	M	No	*PIK3R1*	ΔAA434-475	Alive	No
17	F	No	*PIK3R1*	ΔAA434-475	Alive	No
18	F	No	*PIK3R1*	ΔAA434-475	Alive	No
19	F	No	*PIK3CD*	E1021K	Alive	No
20	M	No	*PIK3R1*	ΔAA434-475	Alive	No
21	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
22	F	No	*PIK3CD*	E1021K	Alive	Yes
23	F	No	*PIK3R1*	ΔAA434-475	Alive	No
24	F	No	*PIK3R1*	ΔAA434-475	Alive	No
25	F	Yes	*PIK3CD*	E1021K	Alive	No
26	F	No	*PIK3CD*	E1021K	Alive	Yes
27	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
28	M	No	*PIK3CD*	E1021K	Alive	Yes
29	M	No	*PIK3CD*	E1021K	Alive	No
30	F	No	*PIK3CD*	E1021K	Alive	No
31	M	No	*PIK3CD*	E1021K	Alive	No
32	M	Yes	*PIK3CD*	E1021K	Alive	Yes
33	M	Yes	*PIK3CD*	E1021K	Alive	No
34	F	No	*PIK3CD*	G124D	Alive	No
35	M	Unknown	*PIK3CD*	E1021K	Alive	No
36	M	Yes	*PIK3R1*	ΔAA434-475	Alive	No
37	F	Yes	*PIK3R1*	ΔAA434-475	Alive	Yes
38	F	Yes	*PIK3CD*	E1021K	Alive	No
39	M	Yes	*PIK3CD*	E1021K	Alive	No
40	M	Yes	*PIK3CD*	E1021K	Alive	No
41	M	No	*PIK3CD*	E1021K	Alive	Yes
42	F	No	*PIK3CD*	E1021K	Alive	Yes
43	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
44	M	No	*PIK3R1*	ΔAA434-475	Dead	Yes
45	M	No	*PIK3CD*	E1021K	Alive	Yes
46	M	No	*PIK3CD*	E1021K	Alive	Yes
47	M	Yes	*PIK3CD*	E1021K	Alive	No
48	M	No	*PIK3R1*	ΔAA434-475	Alive	No
49	M	No	*PIK3R1*	ΔAA434-475	Dead	Yes
50	M	No	*PIK3R1*	ΔAA434-475	Alive	Yes
51	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
52	F	Unknown	*PIK3CD*	E1021K	Alive	Yes
53	F	Unknown	*PIK3R1*	ΔAA434-475	Dead	Yes
54	M	No	*PIK3CD*	E1021K	Alive	Yes
55	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
56	F	Yes	*PIK3R1*	ΔAA434-475	Dead	No
57	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
58	F	No	*PIK3CD*	E1021K	Alive	Yes
59	F	No	*PIK3R1*	ΔAA434-475	Dead	Yes
60	M	Unknown	*PIK3R1*	ΔAA434-475	Alive	No
61	F	Unknown	*PIK3R1*	ΔAA434-475	Alive	Yes
62	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes

(Continued)

TABLE E1. *(Continued)*

Patient	Sex	Familial case	Gene	Consequence	Living status	Already published in Maccari et al[8]
63	M	No	*PIK3R1*	ΔAA434-475	Alive	Yes
64	F	No	*PIK3CD*	E1021K	Alive	No
65	M	Yes	*PIK3CD*	E1021K	Alive	Yes
66	F	Yes	*PIK3CD*	E1021K	Alive	No
67	F	Yes	*PIK3R1*	ΔAA434-475	Dead	No
68	M	No	*PIK3CD*	E1021K	Alive	Yes
69	F	Yes	*PIK3CD*	E1021K	Alive	No
70	M	No	*PIK3CD*	E81K	Dead	No
71	M	No	*PIK3CD*	E1021K	Alive	Yes
72	F	No	*PIK3CD*	E1021K	Alive	Yes
73	F	No	*PIK3CD*	E1021K	Alive	No
74	F	No	*PIK3R1*	ΔAA434-475	Alive	No
75	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
76	F	No	*PIK3R1*	ΔAA434-475	Dead	No
77	M	No	*PIK3CD*	E1021K	Alive	Yes
78	F	No	*PIK3R1*	ΔAA434-475	Alive	Yes
79	M	No	*PIK3CD*	E1021K	Dead	Yes
80	F	No	*PIK3CD*	E1021K	Alive	Yes
81	F	No	*PIK3CD*	E525K	Alive	No
82	M	No	*PIK3CD*	E1021K	Alive	Yes
83	F	Yes	*PIK3CD*	E1021K	Alive	Yes
84	M	Yes	*PIK3CD*	E1021K	Alive	Yes
85	M	No	*PIK3CD*	E1021K	Alive	Yes
86	F	Yes	*PIK3CD*	E1021K	Alive	No
87	M	No	*PIK3R1*	ΔAA434-475	Alive	Yes
88	F	No	*PIK3CD*	E1021K	Alive	Yes
89	F	No	*PIK3R1*	ΔAA434-475	Alive	No
90	F	Unknown	*PIK3CD*	E1021K	Alive	No
91	F	No	*PIK3CD*	E1021K	Dead	No
92	M	No	*PIK3CD*	E1021K	Alive	No
93	F	Yes	*PIK3CD*	E1021K	Alive	No
94	F	No	*PIK3CD*	E1021K	Alive	No
95	F	No	*PIK3R1*	ΔAA434-475	Alive	No
96	M	Yes	*PIK3CD*	E1021K	Alive	No
97	F	Yes	*PIK3CD*	E1021K	Alive	No
98	F	No	*PIK3CD*	E525G	Alive	No
99	M	No	*PIK3CD*	E1021K	Alive	No
100	F	Unknown	*PIK3R1*	ΔAA434-475	Alive	No
101	M	No	*PIK3CD*	E1021K	Alive	No
102	F	No	*PIK3CD*	E1021K	Alive	No
103	M	No	*PIK3CD*	E1021K	Alive	No
104	M	No	*PIK3CD*	E1021K	Alive	No
105	F	No	*PIK3R1*	ΔAA434-475	Alive	No
106	M	No	*PIK3CD*	Y524D	Alive	No
107	F	No	*PIK3CD*	E1021K	Alive	No
108	F	No	*PIK3CD*	E1021K	Alive	No
109	M	No	*PIK3CD*	E525D	Alive	No
110	M	Yes	*PIK3CD*	E1021K	Alive	No
111	F	Yes	*PIK3CD*	E1021K	Alive	No
112	F	No	*PIK3CD*	E1021K	Alive	No
113	F	No	*PIK3R1*	ΔAA434-475	Alive	No
114	M	No	*PIK3CD*	E525G	Alive	No
115	F	No	*PIK3CD*	E1021K	Alive	No
116	F	Yes	*PIK3CD*	E1021K	Alive	No
117	F	Yes	*PIK3R1*	ΔAA434-475	Alive	No
118	M	Yes	*PIK3R1*	ΔAA434-475	Alive	No
119	M	Yes	*PIK3R1*	ΔAA434-475	Alive	No
120	M	No	*PIK3CD*	E1021K	Alive	No
121	M	No	*PIK3CD*	E1021K	Alive	No
122	M	No	*PIK3CD*	E1021K	Alive	No
123	F	Yes	*PIK3CD*	E1021K	Alive	No
124	F	No	*PIK3CD*	E1021K	Alive	No

(Continued)

TABLE E1. *(Continued)*

Patient	Sex	Familial case	Gene	Consequence	Living status	Already published in Maccari et al[8]
125	F	Yes	*PIK3CD*	E1021K	Alive	No
126	M	No	*PIK3CD*	E1021K	Alive	No
127	M	No	*PIK3CD*	E1021K	Alive	No
128	M	No	*PIK3R1*	ΔAA434-475	Alive	No
129	M	Unknown	*PIK3R1*	ΔAA434-475	Alive	No
130	F	Yes	*PIK3CD*	E1021K	Alive	Yes
131	M	Yes	*PIK3CD*	E1021K	Alive	Yes
132	M	Yes	*PIK3R1*	ΔAA434-475	Alive	Yes
133	M	No	*PIK3R1*	ΔAA434-475	Alive	No
134	F	Unknown	*PIK3R1*	ΔAA434-475	Alive	No
135	F	Yes	*PIK3R1*	ΔAA434-475	Alive	Yes
136	F	Yes	*PIK3CD*	E1021K	Alive	Yes
137	F	Yes	*PIK3CD*	C416R	Alive	Yes
138	M	Yes	*PIK3CD*	C416R	Alive	Yes
139	M	No	*PIK3CD*	E1021K	Alive	Yes
140	F	Yes	*PIK3CD*	E1021K	Alive	Yes
141	M	No	*PIK3CD*	E1021K	Alive	Yes
142	M	No	*PIK3CD*	E1021K	Alive	Yes
143	M	Yes	*PIK3CD*	E1021K	Alive	Yes
144	M	No	*PIK3CD*	E1021K	Alive	Yes
145	M	Yes	*PIK3CD*	E1021K	Alive	Yes
146	M	Yes	*PIK3R1*	ΔAA434-475	Alive	Yes
147	F	Yes	*PIK3CD*	E1021K	Alive	Yes
148	M	No	*PIK3CD*	E1021K	Alive	Yes
149	F	Yes	*PIK3CD*	E1021K	Alive	Yes
150	F	No	*PIK3CD*	E1021K	Alive	Yes
151	F	Yes	*PIK3CD*	E1021K	Alive	Yes
152	M	Yes	*PIK3CD*	E1021K	Alive	Yes
153	M	Yes	*PIK3CD*	E1021K	Alive	Yes
154	M	Yes	*PIK3CD*	E1021K	Alive	No
155	M	Yes	*PIK3CD*	E1021K	Alive	No
156	F	No	*PIK3CD*	E1021K	Alive	No
157	F	Yes	*PIK3R1*	ΔAA434-475	Dead	No
158	F	Yes	*PIK3CD*	Y524D	Alive	No
159	M	Yes	*PIK3CD*	Y524D	Alive	No
160	M	Yes	*PIK3CD*	E1021K	Alive	No
161	M	Yes	*PIK3CD*	E1021K	Alive	No
162	F	No	*PIK3CD*	E1021K	Alive	No
163	F	No	*PIK3R1*	ΔAA434-475	Alive	No
164	F	No	*PIK3CD*	E1021K	Alive	No
165	M	No	*PIK3CD*	G124D	Alive	No
166	M	No	*PIK3CD*	E1021K	Alive	No
167	F	No	*PIK3R1*	ΔAA434-475	Alive	No
168	F	No	*PIK3R1*	ΔAA434-475	Alive	No
169	F	No	*PIK3CD*	E1021K	Alive	No
170	M	Yes	*PIK3CD*	E1021K	Alive	No

F, Female; *M*, male.

TABLE E2. Syndromic features at presentation

Patient	Description of syndromic features at presentation
16	Short stature and macrocrania
48	Short stature and microcephaly, hypertelorism, epicanthus, high forehead, mild intelligence impairment
63	Short stature and hypertelorism, broad nasal root, prominent cupped ears, smooth philtrum
87	Short stature and triangular face with large neurocranium, hypertelorism, downward slanting eyes, broad nasal root, low-set ears
89	Micrognathia, frontal bumps, exotropia, astigmatism
108	Short stature and brachydactyly, mild facial dysmorphism with high forehead
109	Short stature
116	Short stature, mild intelligence impairment
128	Asymmetry of face, hypertelorism, otapostasis, small upper jaw, small tongue
163	Low-bridged and broad nose, prominent ears, small mouth, thin lips, high palate
157	Short stature; dysplastic small face with narrow jaws, gothic palate, and tooth misplacements; deep backward-rotated ears
134	Short stature, deep-set eyes, astigmatism, prominent jaw, unilateral choanal atresia

TABLE E3. Patients with severe disease

Age at registration (y)	Reason for classification as severe disease
40	Pseudomonas pneumonia, arthritis, GN, bronchiectasis
37	Septic shock, sclerosing cholangitis, carcinoma *in situ* stomach, liver cell carcinoma, bronchiectasis
18	*Legionella* pneumonia, aspergillosis, septic shock, bronchiectasis
16	Sepsis, vasculitis, arthritis, GN, bronchiectasis
27	Sepsis, lymphoma, bronchiectasis
18	Cryptosporidiosis, bronchiectasis, interstitial lung disease
19	*Acinetobacter* pneumonia, GN, lymphoma
32	Lymphoma
19	Sepsis, bronchiectasis
28	Cryptosporidiosis, septic shock, sclerosing cholangitis, bronchiectasis
17	Severe polyarthritis and severe renal disease
30	EBV in tissue, IBD, GN, lymphoma, ovary neoplasm, bronchiectasis
54	*Campylobacter* gut, IBD, arthritis, interstitial lung disease
19	*Pseudomonas* pneumonia, EBV in tissue, GN, bronchiectasis
25	Brain infection, arthritis, lymphoma
13	EBV in tissue, lung granuloma, bronchiectasis
12	EBV in tissue, bronchiectasis
11	IBD, EBV
33	Lupus, lymphoma
10	*Pseudomonas* pneumonia, EBV in tissue, small airway disease
34	Lymphoma, bronchiectasis
26	IBD, arthritis, interstitial lung disease
39	Lymphoma
15	Lymphoma
14	EBV in tissue, IBD
17	Brain infection, EBV in tissue, lymphoma
34	Breast carcionoma, bronchiectasis, small airway disease
13	EBV in tissue, encephalitis, IBD, small airway disease
18	Lymphoma
21	IBD, lymphoma
36	EBV PCR >100,000, septic shock, lymphoma
9	Pulmonary candidiasis, IBD, bronchiectasis, small airway disease
16	Pulmonary candidiasis, bronchiectasis, small airway disease
16	Papillary thyroid carcinoma, bronchiectasis
31	IBD, lymphoma
44	Campylobacter gut, small airway disease, bronchiectasis, COPD
8	*Salmonella* sepsis, EBV in tissue, IBD, small airway disease, bronchiectasis
5	Sepsis, encephalitis, IBD, lung fibrosis
15	EBV >100,000, IBD, lymphoma
18	Sepsis, chronic lung disease
21	EBV in tissue, lymphoma
7	Pseudomonas, CLD
5	Brain infection, eosinophilic esophagitis, bronchiectasis
12	Aspergillosis, bronchiectasis
5	IBD, GN, CLD
17	Brain infection, bronchiectasis
39	Toxoplasmosis, lymphoma
12	CLD, SLE
13	Lymphoma
26	Lymphoma
54	Acute CMV, IBD, lymphoma, papillary renal carcinoma, bronchiectasis
47	B-CLL
19	Lymphoma, small airway disease
24	IBD, GN, bronchiectasis
12	EBV in tissue, IBD
30	IBD, lymphoma, bronchiectasis
43	*Pseudomonas*, brain infection, rhabdomyosarcoma, bronchiectasis

Severe disease is defined as severe infection (eg, sepsis, brain infection, *Pseudomonas* pneumonia) + immune-dysregulation (nonlymphoma and noncytopenia)/CLD or severe immune-dysregulation (eg, enteropathy with need of hospitalization and arthritis and GN) or malignancy. According to this definition, severe disease was observed in 57 of 169 patients.

B-CLL, B-cell chronic lymphocytic leukemia; *CLD*, chronic lung disease; *GN,* glomerulonephritis; *IBD*, inflammatory bowel disorder.

TABLE E4. Additional patients considered as severe

Age at registration (y)	Reason
11	CLD
8	CLD
9	CLD
11	CLD
10	CLD
13	CLD
7	CLD
10	CLD
6	IBD
3	CLD
9	Listeria gut
7	CLD
12	CLD
13	CLD
8	CLD
3	CLD
13	CLD
13	CLD
11	CLD
7	CLD
13	CLD
6	CLD
6	CLD
12	CLD
7	CLD
8	Acute CMV
13	IBD
7	CLD
11	CLD
12	CLD
5	CLD
9	CLD
7	CLD
9	CLD
9	CLD
7	CLD

Patients with age at registration ≤13 years and 1 sign of severe disease (eg, IBD, bronchiectasis) were also considered to suffer from severe disease. Adding these 36 patients resulted in overall 93 of 169 patients with severe disease.
CLD, Chronic lung disease.