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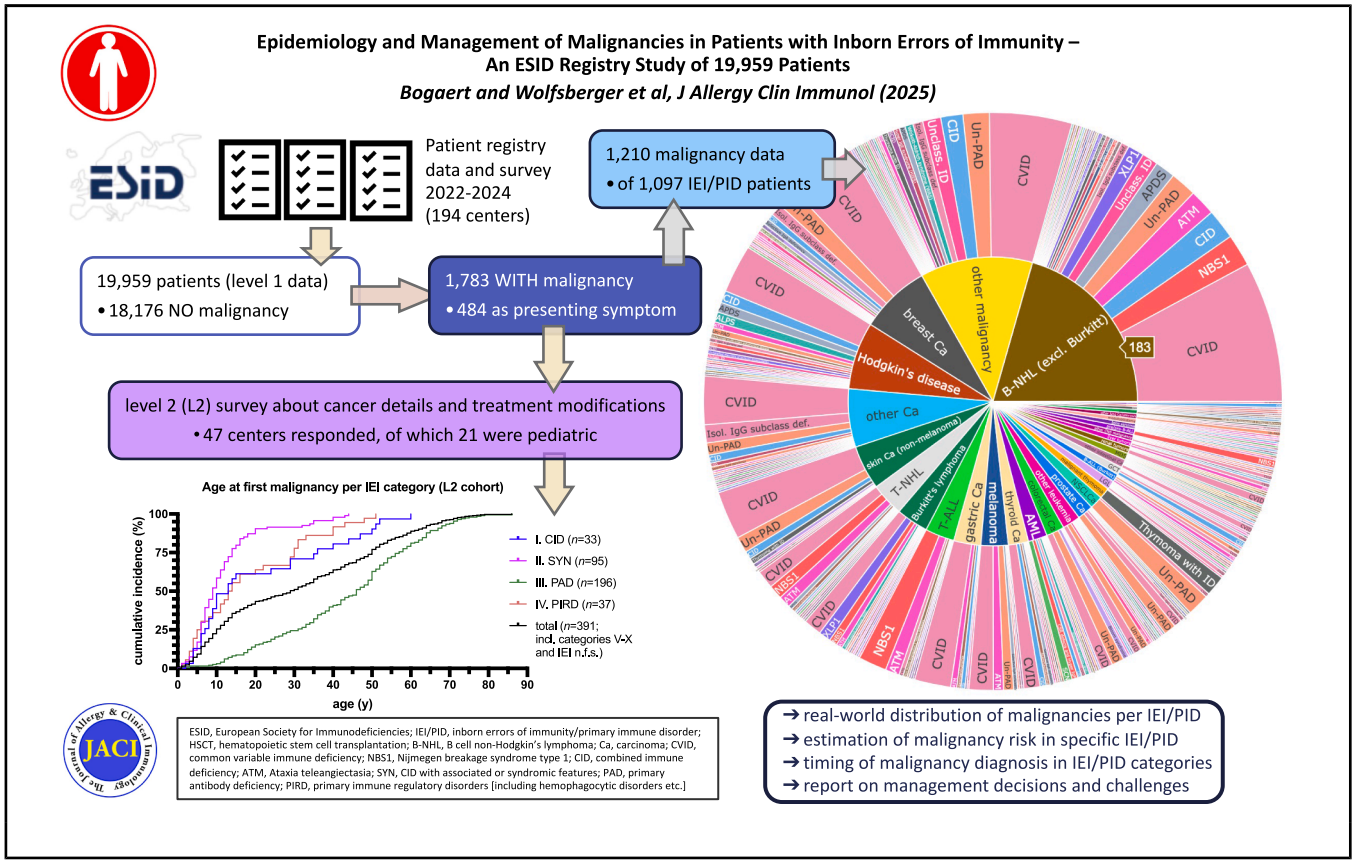
GRAPHICAL ABSTRACT



Capsule summary: This large European Society for Immunodeficiencies Registry study quantifies malignancy burden in inborn errors of immunity/primary immune disorder, identifies disease-specific patterns, and reveals management modifications and challenges, underscoring the urgent need for dedicated oncological surveillance guidelines and tailored treatment strategies in this vulnerable population.

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Epidemiology and management of malignancies in patients with inborn errors of immunity—An ESID registry study of 19,959 patients

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Background: Inborn errors of immunity (IEI), or primary immune disorders (PIDs), predispose individuals to infections, autoimmunity, inflammation, allergy, and malignancy. Malignancies are a major cause of morbidity and mortality in patients with IEI/PIDs, with poorer outcomes compared with the general population.

Objective: We sought to determine the frequency and types of malignancies in patients with IEI/PIDs and to assess clinical management approaches across Europe.

Methods: Descriptive analyses were performed on malignancy data within each IEI category. In addition, a European Society for Immunodeficiencies Registry survey (05/2022-03/2024) collected data on management strategies and challenges.

Results: Of 19,959 patients with IEI/PIDs, 1783 (8.9%) developed malignancies, of whom 27.1% presented malignancy as first manifestation of IEI/PIDs. A total of 1210 malignancies were specified; B-cell non-Hodgkin lymphoma was most common (24.2%). Detailed malignancy-IEI/PID association maps are provided. Predominantly antibody deficiencies accounted for 59.1% of malignancy cases, with a higher median age at first malignancy (43.6 years) compared with other IEI/PID categories, for example, combined immunodeficiencies with syndromic or associated features (11.7 years). Survey findings revealed that oncological treatment was modified because of IEI/PIDs in 21.5% of cases, with assumed negative impacts of IEI/PIDs on complications and outcomes (in 27.4% and 30.7%, respectively). IEI/PIDs influenced transplant decisions in 16.5% of cases. Management practices such as interdisciplinary decision finding and guideline availability were recorded.

Conclusions: This study provides comprehensive epidemiological data on malignancies in IEI/PIDs, highlighting the need for tailored screening and management. Survey results emphasize the real-world challenges and support the development of IEI/PID-specific oncological surveillance guidelines and treatment strategies. (J Allergy Clin Immunol 2026;157:739-53.)

Key words: *Inborn errors of immunity (IEI), primary immunodeficiency (PID), primary immune disorder (PID), malignancy, cancer predisposition syndromes, tumor predisposition, ESID registry*

Inborn errors of immunity (IEI), or primary immune disorders (PIDs), comprise a heterogeneous group of disorders characterized by varying defects in the immune system and are currently associated with mutations in 508 different genes as well as 17 phenocopies.[1] Individual IEI/PID subtypes are usually rare or extremely rare, but, collectively, they represent a relevant global health burden.[2,3] Besides an increased susceptibility to infections, IEI/PIDs may present with autoimmunity, autoinflammation, allergy, and malignancies; they are increasingly recognized as cancer predisposition syndromes.[4,5] Multiple mechanisms are involved in the development of malignancies in patients with IEI/PIDs. Next to the historical concept of impaired immunosurveillance as an important cancer driver, recent work has demonstrated that the same molecular defect causing the IEI/PID can also directly promote oncogenesis.[6-8] These factors intrinsic to the IEI/PID encompass, for example, defects in hematopoietic cell differentiation, lymphocyte signaling, or DNA repair. In addition, extrinsic factors indirectly linked to the IEI/PID can contribute to carcinogenesis, such as chronic inflammation and inadequately controlled infection with transforming pathogens.[6-8]

The overall relative cancer risk in individuals with IEI/PIDs is estimated to be 1.42- to 2.3-fold higher than in the general population.[9-12] However, considerable variation exists between IEI/PID subtypes in the extent, type, and at which age they develop malignancies.[1,13] Lymphomas—primarily mature B-cell non-Hodgkin lymphomas (B-NHLs)—are the most common

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Abbreviations used
AT: Ataxia telangiectasia
B-NHL: B-cell non-Hodgkin lymphomas
CID: Combined immunodeficiency
CVID: Common variable immunodeficiency
ESID: European Society for Immunodeficiencies
HSCT: Hematopoietic stem cell transplantation
IEI: Inborn errors of immunity
L1/L2: Level 1/2
NBS: Nijmegen breakage syndrome
PAD: Predominantly antibody deficiency
PID: Primary immune disorder

malignancies in IEI/PIDs. Solid tumors and leukemias also occur but are considerably less frequent. Specifically, B-NHL accounts for approximately 48% to 50% of cancers in IEI cohorts, with diffuse large B-cell lymphoma representing a significant share.[14] Importantly, malignancy may be the first clinical manifestation of an underlying IEI/PID, especially when the disorder has a mild, atypical, or late-onset clinical presentation or its treatment is associated with unusual toxicities.[5,15] Generally, oncological outcomes in patients with IEI/PID are considered to be worse than in immunocompetent patients, and the occurrence of a malignancy in patients with IEI/PID substantially diminishes survival probabilities as compared with those without a malignancy. This is mainly attributed to increased treatment-related toxicities, reduced efficacy of standard oncological regimens, and/or higher risks of relapse and secondary malignancies.[13,16,17] Despite growing awareness of the elevated cancer risk in patients with IEI/PIDs and associated poorer outcomes, management remains highly variable.[13,16-21] Currently, cancer is the second leading cause of death in patients with IEI/PIDs, following infections.[13] Two key strategies may help improve this unfavorable situation: (1) standardizing surveillance screening and preventive care and (2) developing upfront adapted treatment protocols. To support these strategies with robust evidence, especially considering the broad clinical spectrum and rarity of many IEI/PID subtypes, additional data collected on a large scale are required. In this study, we retrospectively analyzed the types, management, and outcomes of malignancies in patients with IEI/PIDs using data from the European Society for Immunodeficiencies (ESID) registry, supplemented by a complementary survey conducted among ESID registry documenting centers. With this dual approach, we aimed to provide a more comprehensive picture of cancer in IEI/PIDs, addressing gaps in epidemiological knowledge and real-world clinical management challenges.

METHODS

Study design

Data on malignancies in patients with IEI/PIDs were retrospectively retrieved from the ESID registry baseline data sets (level 1 [L1]) and through an additional survey (level 2 [L2]). The ESID registry is an international database on patients with IEI/PIDs, collecting their clinical and laboratory features, genetic findings, and treatments.[3] L1 of the ESID registry gathers a standardized core set of data, including demographic information, clinical and genetic diagnoses, and whether a malignancy occurred during the patient's lifetime. Registrants are requested to update L1 data annually. All registered patients provided written informed consent themselves or by their parents or legal representatives at their treating centers, in accordance with the ESID agreement and their local ethics committees (on the basis of latest amendment approval from Institutional Review Board 00002556/24-334ex11/12).[22,23]

ESID registry L1 study population

In L1 of the ESID registry, the malignancy status is recorded either in a field for presenting manifestations or in the current status report, which indicates whether a patient has developed a malignancy in their lifetime (binary "ever in lifetime" field without age at diagnosis), and if so, it asks to specify the type. Therefore, the L1 estimates represent prevalence among registered patients (proportion ever affected) rather than age-specific incidence or lifetime cumulative risk. Direct comparison with incidence-based literature requires caution. In the present study, a subgroup of these patients of whom the malignancy type was sufficiently documented at L1 (1097 of 1783 [61.5%] patients with 1210 malignancies) was further analyzed for the association between IEI/PID subtype/category and type of malignancy (Fig 1). IEI/PID subtypes were categorized on the basis of the latest classification of the International Union of Immunological Societies: *class I*, immunodeficiencies affecting cellular and humoral immunity or combined immunodeficiencies (CIDs); *class II*, CIDs with associated or syndromic features; *class III*, predominantly antibody deficiencies (PADs); *class IV*, diseases of immune dysregulation (sometimes referred to as primary immune regulatory disorders, although including more entities than those, eg, also hemophagocytic lymphohistiocytosis disorders); *class V*, congenital defects of phagocyte number or function; *class VI*, defects in intrinsic and innate immunity; *class VII*, autoinflammatory disorders; *class VIII*, complement deficiencies; *class IX*, bone marrow failure disorders; and *class X*, phenocopies of IEI/PIDs associated with autoantibodies or somatic variants, and unspecified IEI/PID.[1]

Malignancy in IEI/PID management survey

L2 substudies of the ESID registry allow the implementation of research projects that collect additional information to address specific questions in either a selected group of patients or of a single IEI/PID. For this study, additional L2 data were obtained from registered patients who had developed cancer. By means of an electronic survey, details on malignancy type, treatment, outcome, and follow-up were collected. The questionnaire was developed in close collaboration with oncologists to ensure clinical relevance and completeness. A call for participation was emailed directly to all ESID registry centers (n = 194), posted on the ESID website, and announced at relevant conferences. Furthermore, a notification was displayed within the online ESID registry interface. Respondents were asked to complete the survey in consultation with the treating oncologists. The survey was done using REDCap, hosted at University Medical Centre Freiburg.[24,25] The L2 survey was open from May 1, 2022, to

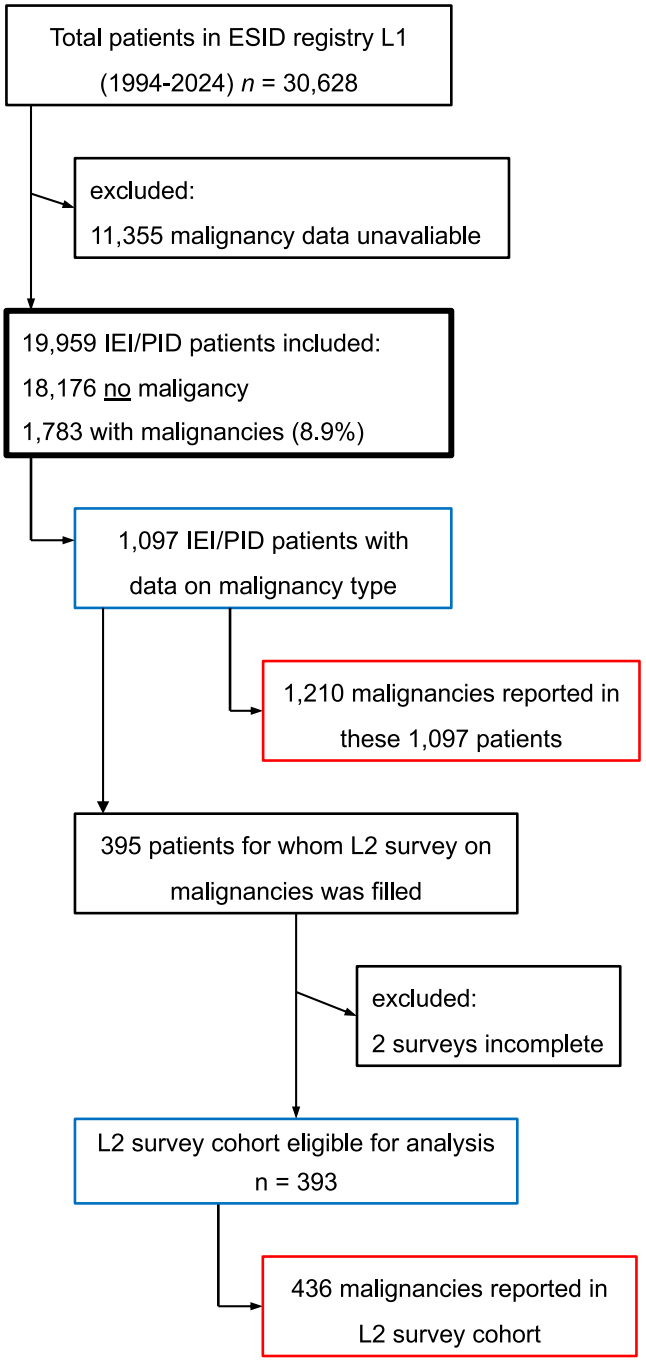

FIG 1. ESID registry L1 (baseline) and L2 (survey) cohort. **A,** Flowchart showing the selection of the ESID registry L1 cohort on patients with IEI/PIDs and malignancy and the selection of the L2 survey cohort.

March 31, 2024. Survey questions are provided in this article's Online Repository at www.jacionline.org.

Statistical analysis

Statistical analysis was done using GraphPad Prism (version 10.4.2; San Diego, Calif) for L1 registry data and IBM SPSS Statistics (version 26.0; Armonk, NY) for L2 survey data. The interactive sunburst charts were designed with Plotly Open Source Graphing Library (Montreal, Quebec, Canada) for Python. In the L2 survey analysis, missing data (nonresponses) were excluded. The answer option "unknown" was considered a valid response and included in the statistical analysis.

RESULTS

Malignancies reported in the ESID registry L1 study population

As recently published in the ESID registry 1994 to 2024 report, information on the malignancy status was available for 19,959 of 30,628 registered patients with IEI/PIDs, and 1,783 of the 19,959 patients (8.9%) had a history of malignancy, 484 (27.1%) of whom as first presenting symptoms.[3] The present study examined the association between IEI/PID categories and subtypes and the types of malignancy in 1097 patients with IEI/PIDs, with a total of 1210 malignancies recorded in L1 of the ESID registry (Figs 1 and 2). Interactive association maps of IEI/PIDs with malignancies show hierarchical sunburst pie charts with zoom-in functionality and provide more details regarding proportions and absolute numbers of which malignancy types occurred in which IEI/PID (see Fig E1, *A-C*, https://esid.org/html-pages/Suppl_figure_ESID_sunburst_malignancy_17.html www.jacionline.org) and *vice versa* (Fig E1, *D-F,* https://esid.org/html-pages/Suppl_figure_ESID_sunburst_malignancy_rev_29.html). Overall, lymphomas were the most frequently reported malignancies, accounting for 36.3% of cases. Among these, B-NHL (excluding Burkitt lymphoma) represented 20.6%, Hodgkin disease 7.5%, T-NHL 3.7%, and Burkitt lymphoma 3.6% (Fig 2). Solid tumors were also highly prevalent, with skin cancer (both melanoma and nonmelanoma [8.0%]) and breast cancer (7.9%) being the most commonly reported types. Leukemias accounted for only 8.0% of malignancies in the ESID registry cohort (Fig 2; see also Fig E1, *D*). Notably, certain IEI/PID subtypes were associated with specific malignancy types. Although B-NHL (excluding Burkitt lymphoma) was the most prevalent malignancy type across many IEI/PID subtypes, myeloid neoplasms were more frequently observed in phagocyte disorders, DNA repair disorders, and bone marrow failure syndromes (Fig E1, *D*). PAD and more specifically common variable immunodeficiency (CVID) were the most frequently recorded IEI/PID category and subtype, respectively, associated with malignancy (Fig E1, *A* and *D*). PAD was reported in 59.1% of all patients with cancer in the ESID registry, and CVID accounted for 33.3% (Fig 2).

Estimation of malignancy risk of selected IEI/PID diagnoses

Replies to the registry L1 question "Did the patient ever suffer from malignancy?" allow an estimation of the minimum risk distribution of malignancies across various IEI/PIDs. Table I provides the minimum (reported) and estimated prevalence of current or past malignancy across selected IEI/PID subtypes within the age range of the ESID registry patient cohort. Of note, this represents a cross-section of all ages and not a long-term followed prospective cohort. It includes CVID (malignancies reported in 404 of 6686 patients; unknown/not reported, 35%; prevalence, 6.0%-9.3%), unclassified PAD (110 of 2474; unknown, 35%; prevalence, 4.4%-6.9%), ataxia telangiectasia (AT; 70 of 792; unknown, 34%; risk, 8.8%-13.4%), CID not further specified (83 of 789; unknown, 33%; prevalence, 10.5%-15.7%), autoimmune

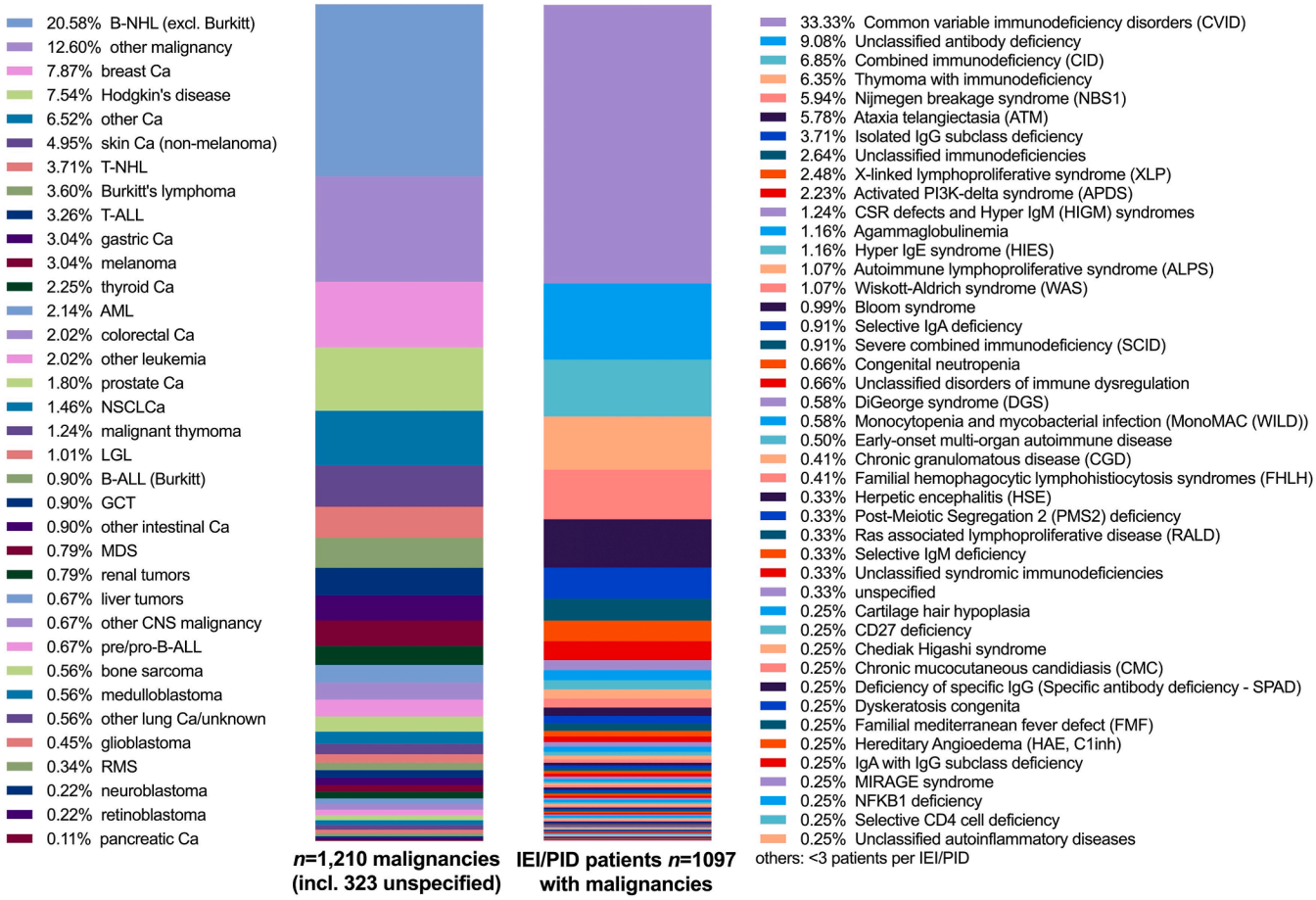

FIG 2. Malignancy subtypes and IEI/PID diagnoses of patients with reported malignancies in the ESID registry L1 cohort. Distribution of malignancies (n = 1210) according to types in patients with IEI/PIDs (*left*) and distribution of IEI/PID subtypes in patients with malignancies (n = 1097; *right*) in the analyzed ESID registry L1 cohort. The association of certain malignancy subtypes with specific IEI/PID categories and diagnoses together with absolute numbers per diagnosis are graphically shown in Fig E1, *A* (IEI/PID-centered view), and Fig E1, *D* (malignancy-centered view). The interactive hierarchical pie charts with mouse-over and click-to-zoom functions are available at https://esid.org/html-pages/Suppl_figure_ESID_sunburst_malignancy_17.html and at https://esid.org/html-pages/Suppl_figure_ESID_sunburst_malignancy_rev_29.html, respectively. *Ca*, Carcinoma.

lymphoproliferative syndrome (13 of 428; unknown, 20%; prevalence, 3%-3.8%), Nijmegen breakage syndrome (NBS; 72 of 256; unknown, 34%; prevalence, 28.1%-42.6%), activated PI3K delta syndrome (27 of 173; unknown, 35%; prevalence, 15.6%-24.1%), Wiskott-Aldrich syndrome (13 of 501; unknown, 34%; prevalence, 2.6%-3.9%), Good syndrome (thymoma with hypogammaglobulinemia; 77 of 189; unknown, 35%; prevalence, 40.7%-63.1%), and RAS-associated leukoproliferative disease (4 of 10; unknown, 27%; prevalence, 40%-55%).

Characteristics of the L2 survey cohort

Overall, colleagues from 47 ESID registry documenting centers responded to the call for the L2 survey study (24.2% response rate). On the basis of the names of the documenting centers, 21 were exclusively pediatric and 3 exclusively adult. For the remaining 23 centers, it was unclear whether they served pediatric patients, adults, or both. The survey was successfully completed for 35.8% (393 of 1097) of the registered patients with IEI/PIDs and cancer of whom data on malignancy type were available (Fig 1). The demographic characteristics of the survey cohort are provided in Table II. Comparable with the IEI/PID distribution of the L1 cohort of patients with malignancies—and thus representative—most of the patients in the L2 survey cohort had PAD as an underlying condition, followed by CIDs with associated or syndromic features and diseases of immune dysregulation (50.1%, 24.3%, and 9.5%, respectively). Of note, no patients with bone marrow failure syndromes were registered in the L2 survey. The median duration of follow-up was 11.5 years (range, 0-54 years). A total of 436 malignancies were reported in the survey cohort, with 39 patients who had developed more than 1 malignancy and with a comparable distribution of malignancy subtypes as in the L1 cohort (Fig 3, *A*). Of the 436 malignancies in the survey cohort, lymphomas (47.7%) and solid tumors (including brain tumors; 43.6%) were most frequently reported. Leukemias accounted for only 8.5%. One patient had multisystemic Langerhans cell histiocytosis (Fig 3, *A*). The risk groups (in case of leukemias) or stages (in case of lymphomas and solid tumors)

TABLE I. Estimated prevalence of current or history of malignancy in selected IEI/PIDs

	CVID	Unclassified PAD	AT	CID nfs	WAS	ALPS	NBS	Good syndrome*	APDS	RALD
Total in ESID registry†	6686	2474	792	789	501	428	256	189	173	10
Malignancy reported	404	110	70	83	13	13	72	77	27	4
Reporting fraction in respective IUIS category‡	0.65	0.65	0.66	0.67	0.66	0.80	0.66	0.65	0.65	0.73
Reported prevalence (%)	6.0	4.4	8.8	10.5	2.6	3.0	28.1	40.7	15.6	40
Estimated prevalence§ (%)	9.3	6.9	13.4	15.7	3.9	3.8	42.6	63.1	24.1	55

ALPS, Autoimmune lymphoproliferative syndrome; *APDS*, activated PI3K delta syndrome; *IUIS*, International Union of Immunological Societies; *nfs*, not further specified; *RALD*, RAS-associated leukoproliferative disease; *WAS*, Wiskott-Aldrich syndrome.

*Good syndrome: thymoma with hypogammaglobulinemia.

†Data from ESID registry 2025 report on 30,628 patients; selected IEI/PID diagnoses listed in descending order, according to Kindle et al.[3]

‡Proportion of patients of whom the question "Did the patient ever suffer from malignancy?" was answered ("Yes" or "No"; total of which combined is 19,959 of 30,628 patients; see Fig 1 for algorithm) in the corresponding IUIS category in the L1 ESID registry, according to Kindle et al.[3]

§Compared with about 5% prevalence of people living with and beyond cancer in the general population of Europe (23.7 million of 478 million people as of 2020; European Cancer Information System).[12] The "reported" and "estimated" values are prevalence ranges derived from the L1 "ever malignancy" field and the disorder-specific reporting fraction; they are not age-adjusted incidence rates. Literature values quoted for some entities (eg, AT and CVID) are often lifetime or age-bounded cumulative incidence in selected cohorts and thus not directly comparable as discussed.

of the malignancies at diagnosis are shown in Fig E2 (in the Online Repository available at www.jacionline.org). The distribution of malignancies across the IEI/PID categories is provided in Table E1 (in the Online Repository available at www.jacionline.org). The median age at diagnosis of the first malignancy was 29 years (range, 0-86 years) and of the second or higher malignancy was 54 years, both ranging from early childhood to late adulthood (Table II). The first malignancy was reported to be the presenting feature of the IEI/PID (malignancy diagnosed before or simultaneously with IEI/PID) in about 30% of the survey cohort. This was more often indicated in children (<18 years) than in adults: in 38.6% of pediatric cases versus 25.6% of adult cases was the malignancy reported as presenting feature of the IEI/PID. The age at diagnosis of the first malignancy differed substantially between the categories of the underlying IEI/PID, with IEI/PID with syndromic features showing the earliest presentation (median, 11.7 years; n = 95), followed by disease of immune dysregulation (17.8 years; n = 37), whereas that of PAD was 43.6 years (n = 196; see Fig E3, *A*, in this article's Online Repository at www.jacionline.org). To visualize the differing age at first manifestation of all recorded malignancies as function of patient age in the largest IEI/PID categories (ie, CID, SYN [syndromic], and PAD) and the total L2 subcohort (including all other categories with fewer than 10 patients; total), cumulative incidence curves are shown in Fig 3, *B*.

Reported extrinsic cancer risk factors in the survey cohort

The survey explored which factors nonintrinsic to the IEI/PID, such as lifestyle-related factors (ultraviolet exposure, tobacco, and alcohol), pharmacological immunosuppression, chronic inflammation, and infections with transforming viruses or other pathogens, may have contributed to the overall cancer risk. Although multiple answers to this question were possible, chronic inflammation was most often considered a potential additional risk factor (in 30.7% of malignancies) by the survey respondents, and oncogenic/transforming or other pathogens (eg, EBV, hepatitis C virus, hepatitis C virus, or Helicobacter) in 26.4%, lifestyle-related factors in 11.8%, and long-term immunosuppression in 7.3%. The results are summarized in the Results section and in Fig E3, *B*, in this article's Online Repository. Notably, the distribution of these replies over the different types of malignancies showed an expectable pattern, with lifestyle-related factors and immunosuppression considered relatively more relevant in solid cancers but chronic inflammation and chronic infections in all types of malignancies (*not shown*).

Reported oncological treatment in the survey cohort

The survey respondents indicated that in most of the malignancies (77.1%), standard oncological practice was followed, that is, standard treatment with or without adaptations on the basis of toxicities encountered during therapy (Fig 4, *A*). However, in 16.9% of malignancies, oncological treatment was reported to be modified or completely individualized upfront because of concerns related to the underlying IEI/PID (Fig 4, *A*). For those malignancies in which treatment was adapted upfront, it was reported that in 70.2% of cases, immunologists were involved in the decision (Fig 4, *B* [*top*]) and that specific literature or guidelines were available in 62.5% of cases (Fig 4, *B* [*bottom*]). Once cancer treatment was ongoing, the involvement of immunologists was reported to be 46.1%. Allogeneic hematopoietic stem cell transplantation (HSCT) was reported to be performed after or as part of the oncological treatment in 17.3% of lymphomas, in 9.6% of other malignancies, or in 13.3% of all malignancies (total). The IEI/PID was considered to favor the decision of HSCT in 15.1% of patients with malignancies, whereas it was considered an argument against HSCT in 1.4%. Survey results for radiotherapy and immune therapy and for antimicrobial prophylaxis and immunologic therapy during oncological treatment are provided in the Online Repository.

Reported outcome in the survey cohort

At last follow-up, 72.5% of the survey patients were reported to be alive, whereas 25.2% were deceased (2.8% unknown; Table II). The oncological status in patients alive at last follow-up (n = 285) is shown in Fig 4, *C*; more than 85% were reported to be in remission. Of deceased patients (n = 99), the median age at death was 23 years (range, 3-85 years). Of deaths, 61.6%

TABLE II. Demographic characteristics of the ESID registry L2 substudy/survey cohort (n = 393)

Characteristics	n (%)*	Percentage in L1 cohort (n = 1783 patients)†
Sex		
Male	210 (53.4)	
Female	183 (46.6)	
IEI/PID category		
Immunodeficiencies affecting cellular and humoral immunity	33 (8.4)	6.3
CIDs with associated or syndromic features	95 (24.3)	17.5
PADs	196 (50.1)	58
Diseases of immune dysregulation	37 (9.5)	8.4
Congenital defects of phagocyte number or function	2 (0.5)	4.2
Defects in intrinsic and innate immunity	2 (0.5)	1.8
Autoinflammatory disorders	6 (1.5)	0.7
Complement deficiencies	6 (1.5)	0.84
Bone marrow failure disorders	0	0.4
Phenocopies of IEI	6 (1.5)	0.3
Unspecified IEI/PID	8 (2.0)	1.6
Genetic IEI/PID diagnosis		
Yes	188 (47.8)	
No	205 (52.2)	
First malignancy		
Age (y) at diagnosis of first malignancy, median (range)	29.0 (0-86)	
First malignancy diagnosed in childhood (<18 y)	157 (39.9)	
First malignancy diagnosed in adulthood (≥18 y)	236 (60.1)	
Second or higher malignancy, median (range)		
Age (y) at diagnosis of second or higher malignancy	54.0 (5-78)	
Malignancy as presenting feature of IEI/PID		
Yes	120 (30.8)	
No	269 (69.2)	
Primary malignancies per patient		
1	354 (90.1)	
2	35 (8.9)	
3	3 (0.8)	
>3	1 (0.3)	
Overall outcome at last follow-up		
Alive	285 (72.5)	
Dead	99 (25.2)	
Unknown	9 (2.3)	
Follow-up, median (range)		
Duration (y) of follow-up	11.5 (0-54)	
Age (y) at last follow-up	37.0 (3-87)	

*Data are presented as n (%), unless specified otherwise.
†Proportion of patients for whom the question "Did the patient ever suffer from malignancy?" was answered "Yes" between 10 IUIS IEI category of all patients with malignancies reported in the L1 ESID registry, according to Kindle et al.[3]

were indicated to be due to oncological reasons: 41.4% died of a first malignancy, 3.0% of a second or higher malignancy, and 17.2% of oncological treatment toxicities (Fig 4, *C*).

Reported impact of the IEI/PID on oncological outcome in the survey cohort

Respondents judged that the presence of an underlying IEI/PID resulted in prolongation of the oncological treatment in 22.5% of malignancies as compared with oncological patients without IEI/PIDs and negatively affected the oncological outcome in 30.7% of malignancies (Table III; see also Fig E4, *A*, in this article's Online Repository at www.jacionline.org). Most often, the latter was reported to be due to infections or immune dysregulation related to the IEI/PID. Other reported reasons were related to pretreatment and comorbidity in the patients with IEI/PID, or that the maximum oncological treatment could not be given (Table III; see also Fig E4, *B*). Furthermore, in 27.4% of malignancies, complications encountered during oncological treatment were judged to be more severe compared with those in patients without IEI/PIDs and with similar malignancies (Table III; see also Fig E4, *C*, with details of reported complications shown in Fig E4, *D*).

Reported follow-up and surveillance in the survey cohort

After successful treatment of the malignancy (n = 383), follow-up was reported to be mostly done at the hematological/oncological clinic alone (44.9%) or at a combination of both the hematological/oncological and immunologic clinic (43.3%), but rarely at the immunologist alone (5.2%; unknown in 6.5%). In 56.1% of patients, oncological surveillance was reported to be intensified compared with patients without IEI/PIDs after a first primary malignancy had occurred, mostly on the basis of an increased frequency of visits with or without additional laboratory or imaging examinations (Table III; see also Fig E4, *E* and *F*). In addition, in 5 patients, oncological screening was reported to be intensified only after a second (n = 4) or third (n = 1) malignancy had occurred, also by increased frequency and/or increased number of surveillance examinations (Table III). IEI/PID-specific oncological surveillance guidelines were reported to be available in the postmalignancy setting in 43.8% of malignancies. However, in more than half the cases, such guidelines were lacking or unknown to exist (see Fig E5, *A*, in this article's Online Repository at www.jacionline.org). In contrast, IEI/PID-specific oncological surveillance guidelines were available in 76.3% of cases in the setting in which a malignancy had not yet occurred (Fig E5, *B*).

DISCUSSION

This retrospective study, combining data from the ESID registry (L1) with an accompanying survey (L2), constitutes one of the most extensive and detailed analyses to date on the prevalence, clinical features, and management of malignancies in patients with IEI/PIDs. The ESID registry offers valuable epidemiological insights into the types and distribution of malignancies across various IEI/PID categories. Notably,

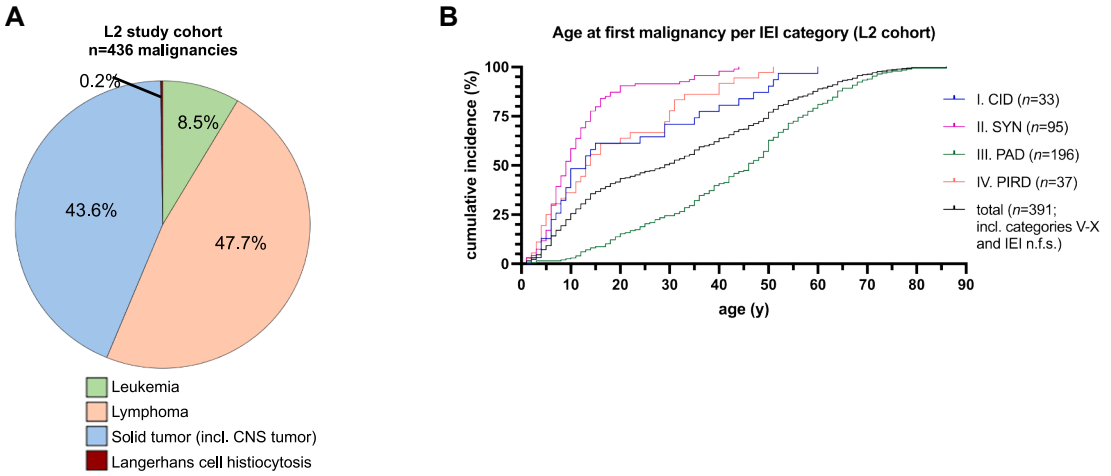

FIG 3. Malignancies in patients with IEI/PIDs: L2 survey cohort. **A,** Overview of malignancies reported in the survey cohort. **B,** Age at diagnosis of the first malignancy across the IEI/PID categories as reported in the L2 survey cohort was plotted as cumulative incidence curves for the IEI/PID categories of CIDs (category I; n = 33), CIDs with associated or syndromic features (category II; n = 95), for PADs (category III; n = 196), and for diseases of immune dysregulation according to the classification of the International Union of Immunological Societies (category IV [PIRD] used for all diseases of immune dysregulation, and not only PIRDs in the strict sense; n = 37) and for the entire L2 cohort in which manifestation ages were available (total; n = 391). Median ages at first malignancy with 95% CI of all reported IEI/PID categories are shown in Fig E3, *A*; numbers at risk of categories V to IX were too low to plot cumulative incidence curves by age. *PIRD,* Primary immune regulatory disorder.

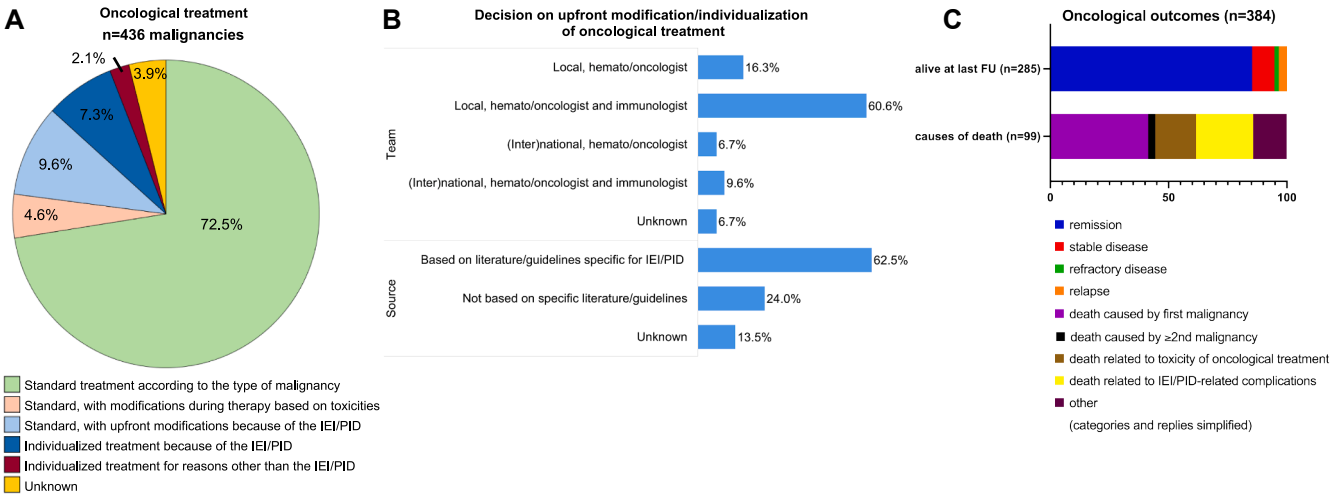

FIG 4. A, Oncological treatment and reported modification decisions. **B,** Basis for the decisions (persons, sources) on upfront treatment modifications. **C,** Oncological outcomes reported in 384 patients of the L2 survey cohort. *CNS,* Central nervous system.

malignancies were reported to have occurred in approximately 8.9% of patients across all ages, and in 27.1% of these cases, cancer was the initial clinical manifestation of an underlying immune disorder.[3] The present in-depth analysis with interactive hierarchical pie charts of IEI/PID categories and diagnoses together with specified malignancy subtypes of 1,210 cases (in 1,097 of 19,959 patients) and *vice versa* provide high-resolution images of the real-world distribution of malignancies in IEI/PIDs, constituting robust evidence as basis for future clinical studies on specific cancer entities in IEI/PIDs. The prevalence estimations and recorded ages at malignancy diagnosis varied significantly depending on the specific IEI/PID subtype, with PAD being the most common category among patients with cancer, as expected because of its overall numerical predominance within the registry cohort and the population, and PAD showing the latest median age at malignancy onset. Among PAD subtypes, activated PI3K delta syndrome had the highest estimated cancer risk (15.6%-24.1%), exceeding that of CVID (6%-9.3%) and, in comparison, that of CID not further specified (10.5%-15.7%), but lower than that of NBS (28.1%-42.6%).

When contrasting these findings with population-based cancer statistics, the markedly increased malignancy risk in patients with

TABLE III. Reported influence of the IEI/PID on the oncological outcome, complications, and surveillance

Survey question (wording simplified)			Responses (multiple reasons possible)	
IEI/PID reported to adversely affect oncological outcome	30.7%	Yes	42.5%	Related to infections associated with the underlying IEI/PID
			41.8%	Related to immune dysregulation due to the underlying IEI/PID
			22.4%	Related to pretreatment and comorbidity
			18.7%	The maximum oncological therapy could not be given
			6%	Other
	57.8%	No		
	11.5%	Unknown		
More severe complications of any kind in comparison with patients without IEI/PIDs but with cancer	27.4%	Yes	79.7%	More severe/frequent infections
			47.5%	Life-threatening infectious complications (intensive care unit)
			44.1%	Grade III-IV inflammatory and/or autoimmune complication
			37.3%	Any other grade III-IV toxicity
	56.6%	No		
	16.0%	Unknown		
Oncological surveillance intensified after first malignancy	56.1%	Yes	32.9%	Increased frequency of routine surveillance examinations
			4%	Additional laboratory/imaging examinations
			32.4%	Both increased frequency and additional examinations
			30.6%	Unknown
	28.4%	No		
	15.5%	Unknown		

IEI becomes clear: the prevalence of malignancies in the ESID registry cohort (8.9%) was 1.78 times that of the general population in Europe (5%).[12] In addition, according to the NCI SEER (National Cancer Institute - Surveillance, Epidemiology, and End Results [SEER]) database[26] and the EUROCARE-6 study,[12] the median age at diagnosis for many cancers in the general population lies 2 to 3 decades later than in our cohort. For example, NHL in the general population shows a median age at diagnosis of about 67 years, with most cases occurring after the age of 60 years. In contrast, patients with IEI in our registry developed NHL frequently in their thirties and forties. Chronic lymphocytic leukemia typically has a median onset at about 70 years, and more than 90% of cases occur after the age of 50 years in the general population, whereas we documented cases in patients with IEI as young as in their thirties. For colorectal cancer, SEER data indicate that only about 20% of diagnoses occur before age 55 years, with a population-wide median age close to 66 years. In our cohort, however, several patients with IEI developed colorectal cancer in their forties, representing a clear shift toward early-onset disease. Gastric carcinoma shows a similar pattern: less than 5% of cases are diagnosed before age 40 years in the general population, whereas we observed multiple IEI cases occurring well below this age threshold, including patients in their twenties and early thirties. Melanoma, with an average diagnosis age of 63 years in the general population, was also observed at a much younger age among patients with IEI, particularly in those with DNA repair disorders. In terms of relative frequency, the distribution of malignancy types in IEI/PIDs deviates markedly from the general population. Overall, our study confirms that B-NHL is the predominant malignancy in IEI/PIDs (24.2% including Burkitt lymphoma), with solid tumors such as breast cancer (7.9%) and skin cancer (8.0%) also commonly reported—which is in line with previous studies.[13,14,27,28] In addition, we observed relatively high rates of gastric (4.5%) and thyroid (2.0%) cancers in patients with CVID, which is consistent with earlier reports.[9,11,29,30] Leukemias were relatively rare in our cohort (8.0%), reflecting their association with specific leukemia-prone IEI/PID subtypes.[28,31] Although a non-IEI/PID control group would be needed for conclusive evidence, the leukemias and lymphomas reported in patients with IEI/PIDs in our L2 subcohort showed a tendency toward higher risk groups and more advanced stages than in the general population (Fig E2). In the European population, Hodgkin lymphoma accounts for only approximately 0.5% of all cancers,[12] whereas it represented 7.5% of malignancies in our IEI cohort (Fig 2). Likewise, breast cancer is the most common single cancer in the general population (~13% of all incident cancers in women, median diagnosis in the early sixties),[12,26] but in our registry it represented only 7.9% of malignancies, whereas B-NHL was, by far, the leading entity (>24%). Gastric cancer accounts for approximately 3% of cancers in the European population,[12] yet it was reported in 4.5% of our cohort, mainly in patients with CVID. Skin cancers are even more striking: nonmelanoma skin cancer and melanoma together constitute about 5% to 6% of cancers in the general European population,[12] whereas they made up 8% of malignancies in our registry data. Taken together,

these comparisons indicate that although some cancer types (eg, breast) are relatively underrepresented compared with the general population, others (eg, lymphoma, gastric, and skin cancers) are clearly enriched in IEI, and all occur at substantially earlier ages in patients with IEI. The data underline that the oncological risk profile of IEI is distinct from the general population and support the need for IEI-tailored cancer surveillance strategies, with consideration of earlier screening initiation in high-risk subgroups.

Our findings demonstrate the variably increased cancer risks associated with different IEI/PID subtypes. PAD and CVID consistently represented the largest proportion of malignancy cases in IEI/PIDs as reported previously,[9-11,14] which is partly attributable to their higher overall prevalence (PAD: 49.4% of patients in total ESID registry), as suggested by Bayes' theorem, despite the intrinsically higher malignancy risk seen in other, rarer, disorders such as DNA repair defects.[8,29,30,32] Of note, these numbers might still underestimate malignancy risks in CVID, because preexisting lymphoma is still considered an exclusion criterion for making the diagnosis of CVID. In addition, ESID registry L1 data show that patients with PAD are older on average (median, 40 years; Q1-Q3: 23-61 years) than those with other IEI/PID subtypes,[3] which, because of cumulative risks, likely also contributes to the higher cancer burden observed in this category. Patient data included in the L2 survey confirmed that individuals with PAD had the highest median age at diagnosis of a malignancy (43.6 years), whereas CID with syndromic or associated features were the youngest subgroup at their diagnosis of a malignancy (11.7 years vs 20 years median age [Q1-Q3: 12-29 years] of that category in the entire ESID registry), followed by diseases of immune dysregulation and CID. These findings are consistent with the stronger intrinsic risks for oncological transformation in CID with syndromic or associated features and DNA repair defects as well as diseases of immune dysregulation and CID, mostly because of lymphocyte differentiation, maturation, apoptosis, or signaling defects.[6] Although external environmental factors and chronic infections may contribute to malignancy development, our data suggest that intrinsic mechanisms—such as impaired B-cell maturation—play a dominant role in malignancy development in IEI/PIDs.[6] Although "IEI/PID-extrinsic" factors such as chronic infection and inflammation—such as that associated with *Helicobacter pylori* colonization—are well-recognized drivers of tumorigenesis through persistent immune stimulation and impaired immune surveillance, the high prevalence of B-NHL among patients with PAD suggests that lymphocyte-intrinsic mechanisms may play a relevant role also in that category.[6,33] Malignancy in PAD may stem from impaired B-cell development, checkpoint regulation, DNA repair, or altered signaling, rendering B cells intrinsically susceptible to transformation, further fostered by extrinsic cues.[34] The repeated emergence of B-NHL, even in older individuals with long-standing antigenic stimulation and chronic inflammation, points toward underlying defects in B-cell development, maturation, and genomic integrity as key contributors to malignant transformation.

The observation that patients with NBS exhibited a particularly high prevalence of malignancies (minimum 28.1%; estimated 42.6%) is consistent with previous research, indicating an extremely high incidence of malignancies, mostly NHL, in patients with NBS.[35] Similarly, patients with AT showed elevated malignancy prevalence (minimum 8.8%; estimated 13.4%). Although these numbers corroborate findings from the French National Registry of Primary Immune Deficiencies,[36] they may still underestimate the real risk of persons with AT, because they may also be underreported in the ESID registry, depending on their main clinical manifestations. This underestimation is also attributable to the very poor prognosis of early T-lineage leukemias/lymphomas in AT, with many patients dying young and receiving care exclusively in oncology, without systematic feedback to immunology registries.[20,36] Reported lifetime or age-dependent cumulative incidences for AT range from approximately 25% to 40% overall and approximately 10% to 15% by age 20 years in cohort studies, substantially higher than our ESID L1 prevalence estimate (8.8%-13.4%). The discrepancy is expected because (1) L1 provides a point-prevalence of "ever malignancy" among registered patients, whereas the literature typically reports cumulative incidence; (2) early and aggressive T-lineage leukemias/lymphomas in AT carry poor survival, so patients who die early (often treated exclusively in oncology) are less likely to be captured or updated in the immunology center–based registry, causing underascertainment; and (3) DNA repair disorders are underrepresented in ESID overall. Likewise, the prevalence of malignancies in patients with CVID reported in the ESID registry (minimum 6.0%; estimated 9.3%) is an underestimation. In contrast to registry-based prevalence, prospective single-center or referral cohorts frequently report higher cumulative incidences or malignancy risk (~27%-30%), partly because they represent long-surviving, survivor-enriched populations with extended follow-up.[37,38] Moreover, diagnostic conventions can exclude patients with a preexisting lymphoma from being labeled as CVID in the registry, which further biases prevalence downward.[29,30] Studies including an Italian retrospective study have found higher incidences of malignancy in patients with CVID (27%)[37] than observed in our data. This could be due to differences in study design, patient populations and their geographical malignancy risks, diagnostic criteria, or follow-up periods and follow-up institutions, with oncological care centers unlikely to report back to the ESID registry. The Italian study also noted lymphomas as the most frequent malignancy in their CVID cohort,[37] and malignancy was reported to be among possible initial clinical presentations of CVID,[38] both in line with our data.

Apart from information on prevalences of malignancy types and ages at onset in patients with IEI/PIDs, the L2 survey provided further insight into the clinical management and real-world challenges of treating malignancies in IEI/PIDs. Consistent with the larger ESID registry L1 data, malignancy was reported as the presenting feature of the IEI/PID in 30.8% of the L2 survey patients, underlining the importance of considering an underlying IEI/PID in patients newly diagnosed with malignancy.[13,15,16] Moreover, nearly 10% of the survey patients were reported to have developed more than 1 malignancy, in line with the percentage recently published in a systematic review by Fekrvand et al[14] (10.1%). Approximately 40% of first malignancies reported in the survey were diagnosed in childhood, which is higher than in other studies.[9-11] This may partly be explained by the relatively large representation of pediatric centers in our survey. We noted that the outcomes of malignancies, with more than 72% alive at last follow-up, were substantially higher than those of a recent study of NHL in patients with underlying conditions.[18] This might be an overestimation of survival; the discrepancy might be due to the fact that our L2 patient cohort was more heterogeneous than the NHL study, and our retrospective data collection via a survey,

although corrected for "unknowns," might select for patients who successfully returned to immunologic care after their oncological treatment (see the "Strengths and limitations" section hereafter).

The management of malignancies in patients with IEI/PIDs requires a careful balance between the risk of a poorer response to standard oncological treatment, increased risk of treatment-related toxicity (especially in DNA repair defects), and an elevated risk of relapse and secondary malignancies (such as the risk of recurrent lymphoma in CVID), compared with patients without IEI/PIDs.[16] Moreover, there is considerable variation in this risk balance between the different IEI/PID subtypes.[16] With the survey, we aimed to gain a better understanding of current practices. According to the respondents, IEI/PID-related upfront modifications of oncological treatment were made in only 16.9% of malignancies. Among these, the decision to modify oncological treatment upfront was based on relevant literature or clinical guidelines in 62.5%. In contrast to the small proportion of malignancies for which treatment was modified upfront, the underlying IEI/PID was reported to have adversely affected oncological outcome in roughly 31% and was to be associated with more severe treatment-related complications in about 27%, with further differentiation of these replies being too granular to interpret after splitting into many subgroups on 2 sides (IEI/PIDs and malignancies). These replies suggest that existing literature and clinical guidelines may not sufficiently cover the complexities of managing malignancies in patients with IEI/PIDs. As for oncological surveillance strategies, it was reported in the survey that guidelines were lacking or unknown to exist in more than half the cases. Indeed, current literature includes international consensus guidelines on cancer treatment and/or surveillance for only a limited number of IEI/PID subtypes, particularly those involving DNA repair and chromosomal instability disorders (eg, Fanconi anemia, dyskeratosis congenita, AT, NBS, Bloom syndrome, and Constitutional Mismatch Repair Deficiency [CMMRD]).[20,39-41] For several other IEI/PID subtypes, such as Shwachman-Diamond syndrome, GATA-2 deficiency, and SAMD9/9L syndromes, general recommendations exist, but evidence is insufficient to establish international consensus on, for example, the frequency and extent of surveillance examinations.[42-45] However, for many IEI/PID subtypes, including CVID and lymphoproliferative disorders, no formal recommendations or guidelines are available.[46-48] In these cases, clinical practice relies on case reports, small series, or expert opinion. International efforts are needed to compile existing knowledge and develop at least a minimum set of recommendations for these IEI/PID subtypes. Finally, the survey indicated varying levels of collaboration between hematologists/oncologists and immunologists in the treatment and follow-up of patients with IEI/PIDs and malignancy, suggesting that further steps are needed to strengthen multidisciplinary care.

Strengths and limitations

The main strengths of this study are the use of the large, multicenter data set provided by the ESID registry as well as the addition of a targeted survey to gather real-world data on malignancy management and outcomes in patients with IEI/PID. However, several limitations must be acknowledged. The retrospective registry-based design is inherently subject to reporting bias, missing data, and inconsistencies in detail, which can lead to a loss of information regarding malignancy subtypes, treatment timelines, or disease outcomes. Because L1 lacks age at cancer diagnosis and time-to-event data, we could not compute age-specific rates or cumulative incidence. To address this limitation in future studies, the ESID registry already implemented "date of onset" fields for many additional manifestations such as autoimmunity, inflammation, allergy, and malignancy as of late 2024. Left-truncation and competing-risk/survivorship bias likely reduce observed prevalence in entities with early aggressive disease (eg, AT), especially wherein oncology-center deaths are not fed back to the registry. In line, registry coverage may be incomplete, because some patients with IEI/PIDs might be registered in national databases or in registries of related medical disciplines, such as the European Working Group of Myelodysplastic Syndromes and Severe Aplastic Anemia in Childhood or the European Society for Blood and Marrow Transplantation and not in the ESID registry. The underrepresentation of DNA repair disorders and bone marrow failure syndromes in ESID centers, because many of these patients are primarily seen by hematologists-oncologists depending on their main clinical problem, is an inherent referral issue and further contributes to downward bias. Furthermore, despite the relatively well-balanced distribution of IEI/PID diagnoses within the L2 malignancy survey cohort compared with the larger L1 registry cohort of patients with IEI/PIDs and malignancy, the relatively low response rate to the survey (24.2% of all ESID registry centers) may limit the generalizability of the survey-based findings. Finally, inherent in the nature of a survey, the L2 cohort lacks negative controls, and several questions in the survey explored only the clinicians' perceptions regarding management and outcomes without the need to substantiate their replies by facts and medical reports; as such, parts of the survey analysis reflect subjective clinical judgment and should be interpreted with this limitation in mind.

Conclusions

The presented epidemiological data on the distribution of malignancy types across IEI/PID diagnoses, on the basis of ESID registry L1 data, provide a valuable resource for clinicians and serve as a foundation for developing future clinical research studies and clinical management guidelines, including recommendations for IEI/PID screening at diagnosis of a malignancy, especially in B-NHL. The clinical need for IEI/PID-specific oncological treatment and surveillance protocols is underlined by the survey results, which provide real-world insights into the management challenges encountered in this complex patient population.

Declaration of Generative AI: The authors used ChatGPT for partial text editing to improve readability; they then reviewed and edited the text and take full responsibility for the content.

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Clinical implications: Overall, about 9% of registered patients with IEI/PIDs developed malignancies—often as first presentation and highly varying between IEI/PID categories—most commonly B-cell non-Hodgkin lymphoma. High oncological treatment modification rates highlight the need for IEI/PID-specific cancer surveillance and interdisciplinary management strategies.

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