Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations

Check for updates

Julian Thalhammer, MD,[a,b]* Gerhard Kindle, MD,[a]* Alexandra Nieters, PhD,[a] Stephan Rusch,[a] Mikko R. J. Seppänen, MD,[c] Alain Fischer, MD,[d,e] Bodo Grimbacher, MD,[a,f,g,h] David Edgar, FRCP, FRCPath,[i,j] Matthew Buckland, MD,[k,l] Nizar Mahlaoui, MD, MPH, PhD,[d,e] and Stephan Ehl, MD,[a,g] for the European Society for Immunodeficiencies Registry Working Party‡

Freiburg, Germany; Helsinki, Finland; Paris, France; Dublin, Ireland; and London, United Kingdom

Background: Inborn errors of immunity (IEI) are rare diseases, which makes diagnosis a challenge. A better description of the initial presenting manifestations should improve awareness and avoid diagnostic delay. Although increased infection susceptibility is a well-known initial IEI manifestation, less is known about the frequency of other presenting manifestations.

Objective: We sought to analyze age-related initial presenting manifestations of IEI including different IEI disease cohorts.

Methods: We analyzed data on 16,486 patients of the European Society for Immunodeficiencies Registry. Patients with autoinflammatory diseases were excluded because of the limited number registered.

Results: Overall, 68% of patients initially presented with infections only, 9% with immune dysregulation only, and 9% with a combination of both. Syndromic features were the presenting feature in 12%, 4% had laboratory abnormalities only, 1.5% were diagnosed because of family history only, and 0.8% presented with malignancy. Two-third of patients with IEI presented before the age of 6 years, but a quarter of patients developed initial symptoms only as adults. Immune dysregulation was most frequently recognized as an initial IEI manifestation between age 6 and 25 years, with male predominance until age 10 years, shifting to female predominance after age 40 years. Infections were most prevalent as a first manifestation in patients presenting after age 30 years.

Conclusions: An exclusive focus on infection-centered warning signs would have missed around 25% of patients with IEI who initially present with other manifestations. (J Allergy Clin Immunol 2021;148:1332-41.)

Key words: *Primary immunodeficiency, inborn error of immunity, presenting symptom, immune dysregulation, autoimmune, inflammatory, syndromic, warning signs, registry*

Inborn errors of immunity (IEI) are rare diseases. The estimated minimum prevalence of IEI based on registry documentation ranges from 2.7 to 5.9 to 11:100,000 in Germany, the United Kingdom, and France, respectively.[1-3] Currently, there are more than 450 different IEI known, most of them with a specific monogenetic cause.[4] The delay from initial manifestations to diagnosis of IEI for index cases is often several years.[2] This diagnostic delay can be critical for patients, because they may not receive appropriate therapy in a timely fashion.[5,6] An important reason for diagnostic delays is the poor specificity of initial presenting symptoms, which are not recognized as indicators of an underlying IEI. Indeed, it would not be rational to diagnose an IEI in all patients presenting with pneumonia or autoimmune thrombocytopenia, but the combination of these 2 manifestations or their occurrence in a child with syndromic features should prompt further investigations.

From [a]the Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Medical Center, University of Freiburg, Faculty of Medicine, and [b]the Center for Pediatrics, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg; [c]the Rare Disease and Pediatric Research Centers, Hospital for Children and Adolescents and Adult Immunodeficiency Unit, Inflammation Center, University of Helsinki and HUS Helsinki, University Hospital, Helsinki; [d]the Pediatric Immuno-Haematology and Rheumatology Unit and [e]the French National Reference Center for Primary Immune Deficiencies (CEREDIH), Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris; [f]DZIF – German Center for Infection Research, Satellite Center Freiburg, [g]CIBSS – Centre for Integrative Biological Signalling Studies, Albert-Ludwigs University, and [h]RESIST – Cluster of Excellence 2155 to Hanover Medical School, Satellite Center Freiburg, Freiburg; [i]St James's Hospital and [j]Trinity College Dublin, Dublin; and [k]the Institute of Immunity and Transplantation, University College London, and [l]the Department of Immunology, Royal Free London NHS Foundation Trust, London.

*These authors contributed equally to this work.

‡For a complete list of European Society for Immunodeficiencies Registry Working Party collaborators, please see the Acknowledgment section at the end of the article.

The European Society for Immunodeficiencies Registry was supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF] grant nos. 01GM0896, 01GM1111B, 01GM1517C, 01EO1303, and 01ZZ1801B), the European Union (grant no. HEALTH-F2-2008-201549 [EUROPADnet]), the pharmaceutical companies Novartis, GlaxoSmithKline, LFB, UCB UK, and Pharming, the Plasma Protein Therapeutics Association, the Care-for-Rare Foundation, PROimmune e.V., ERN RITA, and the European Society for Immunodeficiencies (www.ESID.org).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Data sharing: Deidentified patient data collected for this study are available to others with publication of this article according to the European Society for Immunodeficiencies Registry data access and publication rules (https://esid.org/Education/Call-for-studies/Data-access-and-Publication-rules-Research-Proposal-Form).

Received for publication December 24, 2020; revised March 31, 2021; accepted for publication April 8, 2021.

Available online April 23, 2021.

Corresponding author: Stephan Ehl, MD, Institute for Immunodeficiency, University Medical Center, Breisacher Strasse 115, 79106 Freiburg, Germany. E-mail: stephan.ehl@uniklinik-freiburg.de.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

Crown Copyright © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

https://doi.org/10.1016/j.jaci.2021.04.015

Abbreviations used
ALPS: Autoimmune lymphoproliferative disease
AT: Ataxia telangiectasia
CVID: Common variable immunodeficiency
DGS: Di-George syndrome
ESID: European Society for Immunodeficiencies
HIES: Hyper-IgE syndrome
IEI: Inborn errors of immunity
IUIS: International Union of Immunological Societies
PID: Primary immunodeficiency
SCID: Severe combined immunodeficiency
WAS: Wiskott-Aldrich syndrome

Pediatricians and primary care physicians are in the best position to initiate diagnostic tests to confirm or exclude IEI. Their awareness of these rare conditions is critical to reduce diagnostic delay.[7] In 1993, the Jeffrey Modell Foundation published 10 warning signs of primary immunodeficiency (PID) to increase awareness for PID.[8] The 10 warning signs resulted from an expert consensus. They focus on the nature, number, intensity, and localization of infections, their response to therapy, their impact on growth, and the family history.

In the last 30 years, the understanding of what comprises a PID has significantly expanded. One important step forward was the appreciation that patients with PID frequently suffer from immune dysregulation, that is, autoimmune and autoinflammatory manifestations.[9,10] In a retrospective study of the national French PID registry,[11] 26% of 2183 patients with PID had experienced at least 1 manifestation of immune dysregulation during their lifetime. Autoimmune cytopenias and inflammatory bowel disease emerged as the most frequent manifestations.[12] In some conditions, immune dysregulation can be the only manifestation in the absence of infection.[13] To acknowledge this widening spectrum of PID manifestations, the more comprehensive term inborn error of immunity (IEI) has been introduced to describe these conditions and has replaced the term PID in the latest 2019 classification by the International Union of Immunological Societies.[4] Based on these insights, several studies have suggested additions to the 10 warning signs, but these suggestions were not based on large data sets focusing on initial manifestations.[7,14-16]

Although many large cohort studies have reported on the prevalence of various clinical manifestations in IEI, the question of the initial presenting manifestation has received less attention.[3,11,12] Improved knowledge about presenting features is however critical to early recognition of IEI particularly for nonspecialists who play a key role in recognizing early warning signs of IEI. To address this, the redesign of the European Society for Immunodeficiencies (ESID) Registry in 2013[17] introduced data fields to record the initial disease-related clinical features of patients with IEI. Here, we present an analysis of 16,486 patient data sets with information on the initial clinical presentation. Our results provide a data-based rationale to add immune dysregulation and syndromic features to the PID warning signs, which we hope will improve the early diagnosis of IEI.

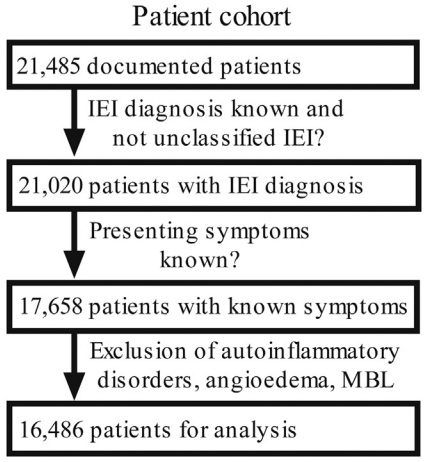


FIG 1. Criteria for selection of patients for study inclusion. *MBL*, Mannose binding lectin.

METHODS

Patients

As of March 2019, 21,485 patients of 68 nationalities were documented by 29 countries participating in the ESID Registry based on informed consent (No. 493/14 of the Ethical Committee Freiburg). From these, the following were excluded: 161 patients without an IEI diagnosis and 304 patients with "unclassified immunodeficiency," because there was concern whether these patients indeed represent patients with IEI, or rather secondary immunodeficiencies or other diseases. Another 3362 patients were excluded because data on presenting symptoms were unavailable. We excluded 127 patients with mannose binding lectin deficiency, because its classification as an IEI is debated.[4,18] Moreover, 611 patients with hereditary or acquired angioedema were not considered because this large group of patients presents in a distinct way that might distort global analysis. The 87 patients with "unclassified complement deficiencies" also mostly presented with angioedema and were thus also excluded. Finally, we excluded 346 patients with autoinflammatory diseases, because these patients are mostly documented in other registries, resulting in an incomplete picture of these disease entities. Overall, 16,486 patients were included (Fig 1). Diseases were grouped on the basis of 2019 International Union of Immunological Societies classification[3] with minor modifications, as detailed in Table I.

Initial presenting manifestations

Registry participants were asked to record the presenting symptom(s) associated with the IEI diagnosis as judged by the treating physician at the time, irrespective of the date of final clinical or genetic diagnosis. Six main categories for presenting symptoms were offered, and for each patient it was possible to select more than 1 category: (1) infection, (2) immune dysregulation, defined as at least 1 of the following: lymphoproliferation (splenomegaly, hepatomegaly, lymphadenopathy), granuloma, autoimmunity (eg, cytopenia, thyroid disease, joint disease, hepatitis, vitiligo, alopecia, diabetes), inflammatory bowel disease, celiac disease, vasculitis, eczema or autoinflammatory manifestation (eg, fevers and rashes), (3) malignancy, (4) syndromic manifestation, defined as dysmorphic features such as short stature, facial abnormalities, microcephaly, skeletal abnormalities, other organ manifestations such as albinism, hair or tooth abnormalities, heart or kidney defects, hearing abnormalities, primary neurodevelopmental delay, seizures, (5) other symptoms, and (6) no symptoms. This last category allowed documentation of patients in whom a diagnosis was established before the onset of clinical manifestations, for example, due to family history or based on laboratory abnormalities.

TABLE I. Analyzed disease groups

This article	IUIS	Disease group*	n	Most relevant diseases (n)
Group 1 including APDS	1	Immunodeficiencies affecting cellular and humoral immunity	1,832	SCID (807), CID w/o genetic diagnosis (454), CD40 and CD40 Ligand def (159), APDS (131), Omenn syndrome (59), HLA class II def (52), selective CD4 def (50), DOCK8 def (47), atypical SCID (46)
Group 2 including bone marrow failure	2	CID with associated or syndromic features	2,463	AT (677), DGS (613), HIES (354), WAS (291), XLT (42), NBS (143), unclassified syndromic PID (75), CHH (48), NEMO and NFKBIA def (36), DC (25), ICF (22), Netherton syndrome (16), Bloom syndrome (14)
Group 3a	3	Predominantly antibody deficiencies	4,228	CVID (4,228): no genetic diagnosis (4,069); genetic diagnosis: TACI (98), NFkB1 (25), NFkB2 (21)
Group 3b without APDS, including thymoma with immunodeficiency	3	Predominantly antibody deficiencies	4,853	Unclassified antibody def (1,325), sel. IgA def (946), agammaglobulinemia (943), isolated IgG subclass def (745), THI (222), SPAD (220), IgA with IgG subclass def (121), thymoma with immunodeficiency (120), CSR and hyper-IgM syndromes (autoinflammatory diseases and no genetic cause) (99), sel. IgM def (86)
Group 4	4	Diseases of immune dysregulation	1,018	ALPS (236), FHL (182), XLP (132), unclassified disorders of immune dysregulation (99), APECED (74), CHS (59), IPEX (39), CTLA4-def (38), GS2 (31), STAT3 GOF (29), LRBA-def (42)
Group 5	5	Congenital defects of phagocyte number or function	1,459	CGD (921), congenital neutropenia (169), unclassified phagocytic disorders (121), SDS (83), cyclic neutropenia (75), GATA2 (43), LAD (25)
Group 6	6	Defects in intrinsic and innate immunity	452	CMC (134), MSMD (111), unclassified defects in innate immunity (63), isolated congenital asplenia (35), IRAK4 and Myd88 def (29), WHIM (24), herpetic encephalitis (15), asplenia syndrome (15)
Excluded	7	Autoinflammatory disorders	—	—
Group 7	8	Complement deficiencies	181	Complement component 2 def (80)
Group 2	9	Bone marrow failure		Classified in group 2 as in IUIS 2017
Excluded	10	Phenocopies of IEI	—	—

APDS, Activated PI3K delta syndrome; *APECED*, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *CID*, combined immunodeficiency; *CHH*, cartilage hair hypoplasia; *CHS*, Chediak-Higashi syndrome; *CMC*, chronic mucocutaneous candidiasis; *CGD*, chronic granulomatous disease; *CSR*, class switch recombination defects; *DC*, dyskeratosis congenita; *Def*, deficiency; *FHL*, familial hemophagocytic lymphohistiocytosis syndromes; *GS2*, Griscelli syndrome type 2; *ICF*, immunodeficiency centromeric instability facial anomalies syndrome; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked; *IUIS*, International Union of Immunological Societies; *LAD*, leucocyte adhesion deficiency; *MonoMAC*, monocytopenia and mycobacterial infection; *MSMD*, defects with susceptibility to mycobacterial infection; *NBS*, Nijmegen breakage syndrome; *SDS*, Shwachman-Diamond syndrome; *sel*, selective; *SPAD*, specific antibody deficiency; *STAT*, signal transducer and activator of transcription; *THI*, transient hypogammaglobulinemia of infancy; *WASP*, Wiskott-Aldrich syndrome protein; *WHIM*, warts hypogammaglobulinemia infections and myelokathexis; *XLP*, X-linked lymphoproliferative syndrome; *XLT*, X-linked thrombocytopenia.
*IUIS 2019 classification of IEI.

Data analysis

Initial presenting manifestations were analyzed by descriptive statistics for all IEI, for IEI disease subgroups as defined above, and for individual IEI conditions. Because almost a quarter of patients presented with various combinations of initial manifestations, we grouped them according to the most frequently observed combinations as follows: (1) infection without dysregulation (including infection only), (2) dysregulation without infection (including dysregulation only), (3) infection and dysregulation (including any other manifestation), and (4) manifestations other than infection and/or dysregulation (including syndromic features and malignancy). The patients without clinical manifestations were grouped in (a) diagnosis based on family history and (b) laboratory abnormalities only.

Age at onset was analyzed according to the pattern of manifestation across all diseases. The ESID Registry allows documentation of the time of initial manifestation as a range of years (within the first year of life, years 1-5, followed by 5-year intervals) or as a precise date with month and year. Age at onset was documented for 14,596 of the 16,486 patients (89%).

Distribution of disease groups, age at onset, and initial manifestation were analyzed by country of residence of the patients. Each analysis considered only those countries contributing at least 1% of total patients to avoid skewing. To assess the impact of immigration, we compared the country of living and the country of birth of patients.

Statistical analysis was performed with IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY), and figures were created with GraphPad Prism version 5 and 8 (GraphPad Software, San Diego, Calif) and Adobe Illustrator version 11 (Adobe Inc, San Jose, Calif).

RESULTS

Infection is the most frequent initial presenting manifestation of IEI

Of 16,486 patients with IEI documented in the ESID Registry and eligible for this study, 12,741 (77%) initially presented with infection, 2,955 (18%) with immune dysregulation, 1,983 (12%) with syndromic features, and 137 (0.8%) with malignancy (Fig 2). A total of 1292 (8%) presented with "other" symptoms (including, eg, aphthae, asthma, alopecia, fatigue, and ataxia), with 254 of them (1.5% of all patients) as the only initial manifestation. Abnormal laboratory test results (eg,

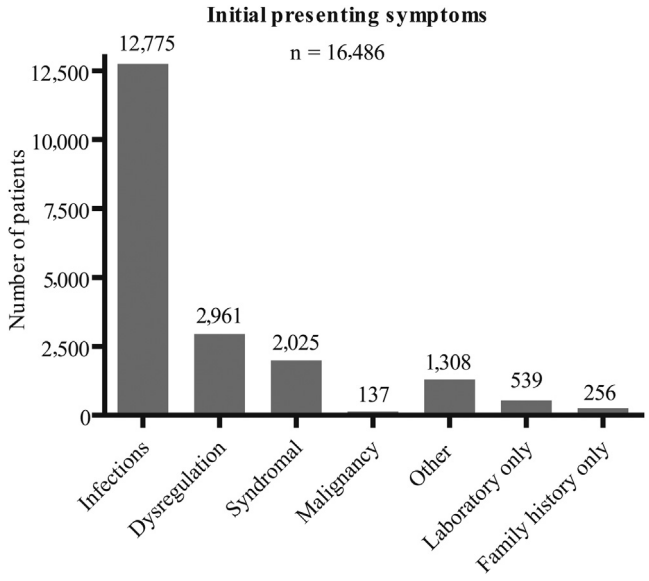


FIG 2. Initial presenting manifestations. For documentation of initial presenting manifestations, multiple categories could be selected for an individual patient (eg, infection and immune dysregulation). Most patients (77%) presented with 1 category of presenting symptoms, 2757 (17%) had 2 categories, and 282 (1.7%) had 3 categories.

hypogammaglobulinemia and thrombocytopenia) alone were documented in 539 patients (3.3%). A positive family history before onset of symptoms was documented in 256 patients (1.5%) (Fig 2). This percentage may be underestimated because some patients with affected family members may have been assigned to "presenting symptoms unknown" instead of "no symptoms at presentation," leading to exclusion from this analysis.

Symptoms of immune dysregulation are important initial manifestations of IEI and are relevant in IEI subgroups primarily presenting with infections

Overall, 3063 patients (19%) initially presented with more than 1 manifestation, most frequently a combination of immune dysregulation and infection (48%). We analyzed this combination of presenting symptoms in more detail in disease subgroups. Patients presenting with various combinations of manifestations excluding infections or immune dysregulation were categorized as "other manifestations only." Overall, 68% of patients initially presented with infections without immune dysregulation, 9% presented with immune dysregulation without infections, 9% had infection and immune dysregulation, 9% other manifestations only, 1.6% were diagnosed with positive family history only, and 3.3% had laboratory abnormalities only (Fig 3, *A*).

We then looked at the initial presenting manifestations in disease subgroups and specific disease entities (Fig 3, *B*, and Table I). Sixty-one percent of patients with diseases of immune dysregulation initially presented with immune dysregulation. Importantly, however, infection was not the initial or not the only initial manifestation in up to 25% of patients in a disease category classically linked with infection. Immune dysregulation with infections or without infections was in group 1 "Immunodeficiencies affecting cellular and humoral immunity" 10% and 8%, in group 3a "common variable immunodeficiency (CVID)" 11% and 6%, in group 3b "Antibody deficiencies other than CVID" 9% and 5%, in group 5 "Congenital defects of phagocyte number or function" 6% and 7%, and in group 6 "Defects in intrinsic and innate immunity" 7% and 3% (Fig 3, *B*).

The significance of immune dysregulation as initial manifestation was also evident in a subgroup analysis of 921 patients with chronic granulomatous disease and 920 patients with severe combined immunodeficiency (SCID; including Omenn and "leaky SCID") (Table II). In both groups, 13% initially presented with immune dysregulation, around 5% in the absence of infection. Notably, in this era, before newborn screening for severe T-cell deficiency in Europe, 9% of patients with SCID were diagnosed without clinical symptoms, 5% due to family history and 4% due to laboratory abnormalities only. This asymptomatic initial presentation was also in the range of 5% to 10% in the other patients of groups 1, 3a, 3b, 5, and 6 (Fig 3, *B*).

Syndromic features are frequent initial signs of IEI before or at presentation with other clinical manifestations

In group 2, "Combined immunodeficiencies with associated or syndromic features," 44% of patients initially presented with "symptoms other than infections and/or immune dysregulation" (syndromic features in 89%), followed by "infection without dysregulation" (37%) (Fig 3, *B*). Ataxia telangiectasia (AT), Di-George syndrome (DGS), signal transducer and activator of transcription 3–associated hyper-IgE syndrome (HIES), and Wiskott-Aldrich syndrome (WAS) were analyzed in more detail (Table II). Initial manifestation of a syndrome in the absence of infection or immune dysregulation was documented in 53% of patients with AT, 65% of patients with DGS, 3% of patients with HIES, and 13% of patients with WAS, respectively. Correspondingly, "infection without dysregulation" was much less prominent and represented the single initial presenting manifestation in 32% of patients with AT, 27% of patients with DGS, 67% of patients with HIES, and 25% of patients with WAS. Although "immune dysregulation without infection" as initial presenting manifestation was below 5% in patients with AT and patients with DGS, it was present in 21% of patients with HIES and 29% of patients with WAS. Moreover, 10% of patients with WAS initially presented with "laboratory abnormalities only," that is, thrombocytopenia.

Infection is an important initial presenting symptom in diseases of immune dysregulation

As expected, the most frequent initial manifestation in group 4, "Diseases of immune dysregulation" (n = 1018), was "immune dysregulation without infection" (47%). However, "infection without dysregulation" was also prominent (25%), followed by "immune dysregulation and infection" in another 14%. Initial presentation with "immune dysregulation without infection" reached 65% in the subgroup of 236 patients with autoimmune lymphoproliferative syndrome (ALPS). Unexpectedly, however, 17% of patients with ALPS presented with infection, about half of them in combination with dysregulation. However, 50 of the 236 patients with ALPS were registered without a genetic diagnosis, and ALPS-like diseases with infection susceptibility may have skewed the initial presentation. Positive family history led to diagnosis in 9% of patients with ALPS, which is more than

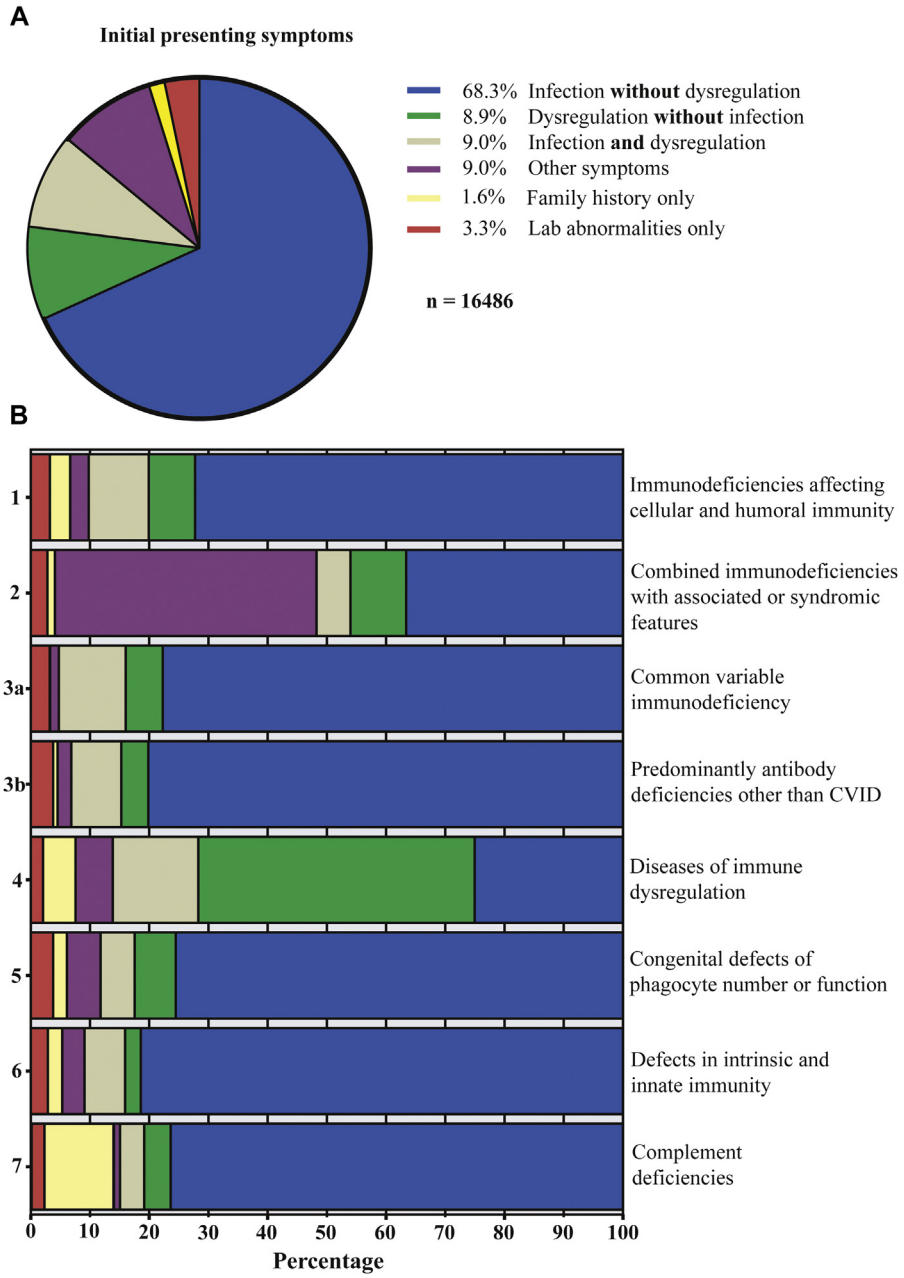


FIG 3. Pattern of initial presenting manifestations. **A,** Patterns of initial presenting manifestations in the complete cohort. "Other" summarizes initial presentation with syndromic features, malignancy, or other symptoms. **B,** Patterns of initial presenting manifestations by IEI disease groups.

for most other IEI. Among 182 patients with familial hemophagocytic lymphohistiocytosis syndromes, 61% initially presented with dysregulation without infection. Interestingly, infection without dysregulation was documented more commonly than infection with dysregulation (19% vs 11%), suggesting that not every infection, considered the presenting manifestation, was immediately associated with hemophagocytic lymphohistiocytosis.

In group 7, "Complement deficiencies," infection without immune dysregulation was the most common presentation (78%), whereas 12% presented on the basis of a positive family history only. Immune dysregulation alone was rare as a presenting manifestation (1%), which may in part be explained by limited registration of patients with lupus-like diseases treated in rheumatology centers that do not routinely enter their patients into the ESID registry.

Malignancies can be the initial presenting symptom of various IEI

In 137 patients with IEI, malignancy was documented as the initial manifestation. One-third of presentations with malignancies (45 of 137) occurred in patients with CVID. Thymoma with immunodeficiency (Good syndrome) was the second most

TABLE II. Initial presenting symptoms in specific immunodeficiencies

IEI	Total patients	Infections	Immune dysregulation	Syndromic	Malignancy	Laboratory abnormalities only	Family history only	Other
SCID	920	82	13	7	0.1	4	5	9
APDS	131	88	31	4	2	—	2	4
WAS	291	41	44	24	0.3	10	2	19
AT	677	34	3	74	4	1	0.3	20
DGS	613	31	8	83	—	1	2	8
HIES	354	75	28	15	0.2	0.3	1	28
CVID	4244	89	18	2	1	3	0.1	4
ALPS	236	17	74	7	0.4	5	9	10
FHL	182	30	73	2	—	0.5	6	3
CGD	921	87	13	2	0.2	1	3	4

Percentage of patients presenting with the indicated symptoms in the given subgroups of IEI. Multiple presenting symptoms could be documented for a single patient. For example, a patient presenting with infections and malignancy will be counted in each of these 2 categories This accounts for the fact that the total sum of percentages can exceed 100 in 1 column. SCID includes SCID, atypical/leaky SCID, and Omenn syndrome. HIES contains STAT3-associated HIES only. See Table I for disease abbreviations.

TABLE III. Initial presenting symptoms by age groups

Symptom	<1 y	1-5 y	6-10 y	11-15 y	16-20 y	21-25 y	26-30 y	31-35 y	36-40 y	41-45 y	46-50 y	>50 y	Total
Infections	74	81	82	79	86	84	87	92	89	92	88	93	11,746
Immune dysregulation	18	18	24	28	25	24	21	15	21	22	16	12	2,791
Malignancy	0.3	0.5	1	1.1	1.7	1.3	1.9	1.2	1.9	2.4	4.3	2.2	127
Syndromic	21	15	8	7	2	3	3	1	1	0.3	0	1	1,899

Percentage of patients presenting with the indicated symptoms by age groups for 14,596 patients in the ESID Registry. Multiple categories could be documented (see also comment to Table II).

frequent initial presentation with IEI-associated cancer (18 of 118), followed by Nijmegen breakage syndrome 1 (n = 17; 13% of patients with Nijmegen breakage syndrome 1). Remarkably, 3 of 4 patients with CD27 deficiency and 9 of 45 (20%) patients with X-linked lymphoproliferative disease 1 had a malignancy at initial presentation. IEI-associated malignancies occurred within the first year of life in 14 or 0.3% of all patients. Notably, in adults, 1 of 50 patients with IEI had a malignancy as the initial manifestation (Table III).

Age at initial presenting manifestation

Altogether 89% of our cohort (14,677 patients) was analyzed for the age at symptom onset (Fig 4, *A*). According to the treating physician, one-third of patients (33%) showed a first manifestation retrospectively related to the IEI within the first year of life and another third (30%) between the ages of 1 and 5 years (Table IV). More than 75% of patients had had symptoms before the age of 16 years, whereas 9% presented after the age of 40 years. When looking at the pattern of manifestations, initial presentation in the absence of infection or immune dysregulation was particularly frequent in the first 6 years of life, when 15% presented with other manifestations, mostly syndromic features (Fig 4, *C*). Between age 6 and 25 years, almost a quarter of patients initially manifested with immune dysregulation in the presence or absence of infection (Table III). Beyond the age of 30 years, infection without immune dysregulation was the presenting manifestation in around 80% of patients with IEI (Fig 4, *C*).

Age-related sex differences in presenting manifestations

The ESID Registry contains more registrations of male than of female patients (56% vs 44%), explained by the X-linked inheritance of many IEI such as X-linked agammaglobulinemia, X-linked SCID, X-chronic granulomatous disease, X-linked lymphoproliferative syndrome, and WAS. Their usual presentation before age 6 years leads to a particular male predominance within the first years of life (Fig 4, *D*). This shifts to a female predominance with increasing age, most evident after the age of 50 years (Fig 4, *D*). Notably, we observed a significant change in the sex ratio of patients presenting with immune dysregulation with increasing age. Up to age 10 years, more than 60% of patients with immune dysregulation as only or concomitant presenting manifestation were boys. Male/female ratios were roughly similar between age 10 and 30 years, and only thereafter, females predominated, reaching up to 70% after age 40 years (see Fig E1 in this article's Online Repository at www.jacionline.org).

Differences between countries

We observed a different distribution of the contribution of the various disease groups and of the age at onset between countries (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org). This led to differences in the pattern of initial manifestation between participating countries (see Fig E4 in this article's Online Repository at www.jacionline.org). The impact of immigration could not be estimated because the country of birth and the country of residence was different in only 4.6% of patients. Because the nationality of the parents was not documented, a migration effect is likely underestimated by this number.

DISCUSSION

Here, we report the age-related presenting manifestations of IEI in general and in different IEI disease groups across a cohort of 16,574 patients documented in the ESID Registry. Our results

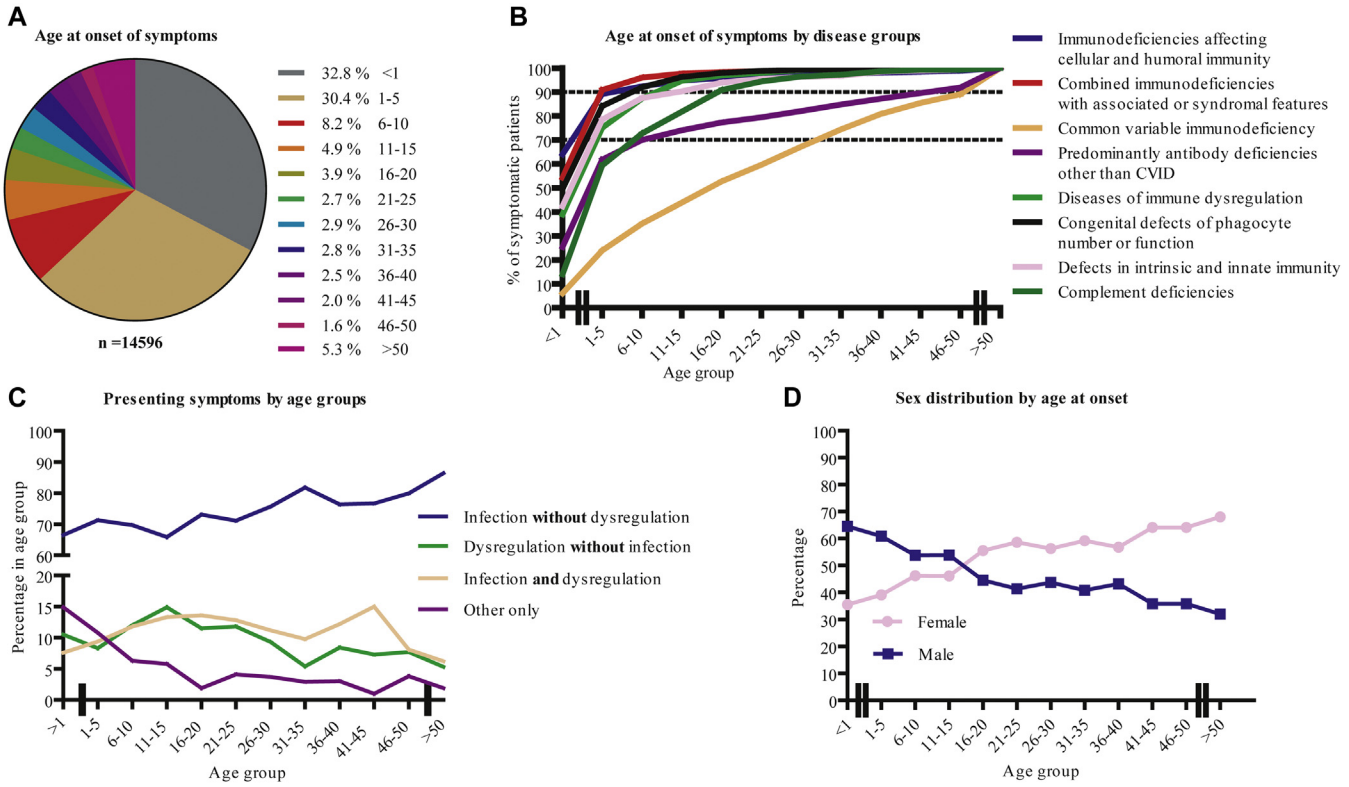


FIG 4. Age and sex dependence of initial presenting manifestations. **A,** Age at initial presenting manifestation in 14,596 patients with known age at onset of symptoms. **B,** The percentage of symptomatic patients is depicted by age at onset of symptoms for the different disease groups. **C,** Percentage of patients presenting with the indicated patterns of initial manifestation by age groups. "Other" summarizes initial presentation with syndromic features, malignancy, or other symptoms. **D,** Sex distribution by age groups of manifestation as percentage of total patients.

TABLE IV. Age at initial presentation for selected immunodeficiencies

Immunodeficiency	Total patients	<1 y	Age 1-5 y	Age range (y) at which >70% had symptoms	Age range (y) at which >90% had symptoms
All IEI	14,677	33	30	6-10	36-40
SCID	833	87	12	<1	1-5
APDS	122	36	53	1-5	6-10
WAS	254	82	15	<1	1-5
AT	631	12	78	1-5	1-5
DGS	579	81	15	<1	1-5
HIES	333	50	32	1-5	11-15
CVID	3,663	6	18	31-35	> 50
ALPS	195	25	43	6-10	11-15
FHL	169	68	17	1-5	6-10
CGD	844	45	39	1-5	6-10

Table of age at onset of presenting manifestations for specific IEI. Presentations within the first year of life and at age 1-5 y are shown in percent. The age range at which 70% and 90% of patients had their initial presenting manifestations is shown in the right columns. SCID includes SCID, atypical/leaky SCID, and Omenn syndrome. HIES contains STAT3-associated HIES only. See Table I for disease abbreviations.

emphasize the importance of both immune dysregulation and syndromic features (18% and 12% of all patients, respectively) in addition to infections as the initial manifestation of IEI. A third of patients (33%) showed initial manifestation of their IEI within the first year of life and another third (30%) between age 1 and 5 years. Different initial manifestations were prominent in specific age groups: (1) syndromic features (in the absence of infection or immune dysregulation) in the first 6 years of life (10%), (2) immune dysregulation (with or without infection) between age 6 and 25 years (25%) with a male predominance, and (3) infection without immune dysregulation in patients with IEI older than 30 years (80%). These findings provide a data-based rationale to update widely used warning signs for primary immunodeficiencies.

An important goal of this study was to provide information across all types of IEI to better advise primary care physicians

how to identify patients with IEI, enhance referral to immunologists, and reduce diagnostic delay. The ESID Registry with its contributions from 29 countries is a unique resource for such analysis. Nevertheless, registry data have obvious limitations. Not all patients are registered, and rates of registration per country vary.[19] In particular, incomplete registration of certain patient groups can significantly skew the overall distribution of initial presenting manifestations. We therefore decided not to include the 346 patients documented in International Union of Immunological Societies category VII (autoinflammatory diseases). Although for most other IEI, the ESID Registry is the main European documentation platform, it captures only a small fraction of patients with autoinflammatory diseases because many more (>4000) of these patients are documented in the EUROFEVER registry.[20] A similar limitation probably applies to patients presenting with malignancy or isolated immune dysregulation because they may be seen and diagnosed only by specialists not affiliated to the ESID Registry.

It is also important to note that there are potentially subjective and retrospective elements to classifying a clinical problem as the initial presenting symptom of an IEI. This includes, for example, the judgment as to which infection marked the beginning of an abnormal infection susceptibility or, for example, interpreting whether chronic diarrhea was caused by prolonged infection or a different inflammatory etiology. Moreover, infection or immune dysregulation may be more obvious as initial presenting features than syndromic features, which may be mild or evolve over time, as may developmental delay. A more precise analysis of the different aspects of immune dysregulation would have been interesting, but unfortunately these data were not available. In particular, initial presentations with allergy were included as immune dysregulation. Finally, the results of this study represent a snapshot of the diagnostic approaches and possibilities of the last 25 years. The widespread implementation of newborn screening for severe T-cell lymphopenia will increase the number of patients diagnosed before onset of symptoms, to the benefit of these patients.[21]

With these limitations in mind, several important observations emerged from this study. Although previous studies have emphasized the importance of autoimmune and inflammatory manifestations in the course of IEI, this is the first study focusing on the initial presenting manifestations in a large patient cohort. More than 20% of patients across all immunodeficiencies did not initially manifest with an infection. Eighteen percent of patients were documented with initial autoimmune or inflammatory manifestations, and this may be an underestimate because of limited awareness of the association of such manifestations with IEI. Moreover, autoinflammatory diseases, which frequently manifest with fever and other features of immune dysregulation, were excluded from this analysis, but represent an important group of all IEI. Immune dysregulation was most prominently recognized as the initial manifestation in the age group from 6 to 25 years. Notably, among patients presenting with immune dysregulation, boys dominated until age 10 years and only after age 40 years, the female predominance expected from non-IEI cohorts was observed. The fact that immune dysregulation as the initial manifestation was less prominent in patients presenting at a later age may indicate that IEI are still underdiagnosed, particularly in adults presenting with autoimmunity or inflammation. Interestingly, the percentage of patients with IEI recorded as not demonstrating immune dysregulation decreased from 89% in 1991 to 71% in 2019 (see Fig E5 in this article's Online Repository at www.jacionline.org). This may reflect an increasing awareness of immune dysregulation as well as the recent description of several more frequent autosomal-dominant disorders of immune dysregulation such as activated PI3K delta syndrome, signal transducer and activator of transcription 3 gain-of-function disease, and nuclear factor kappa B 1 or CTLA4 deficiency.

Notably, 12% of patients had syndromic features as part of their initial presentation. This was particularly relevant within the first 6 years of life, when around 10% of children initially presented with syndromic features in the absence of infection or immune dysregulation. This observation reflects that many genes relevant for a functional immune system are also involved in pathways relevant for the development of other organs. Although our data cannot answer the question how frequently relevant immune manifestations occur in children with syndromic diseases in general, they support the view to consider the immune system as another organ in the context of "organ screening" in syndromic patients, in particular if presenting with infections, autoimmunity, or inflammatory disease.[22]

Less than 1% of patients presented with malignancy, and only 45 patients (0.3%) presented with malignancy in the absence of other clinical manifestations. These figures have to be taken with caution, because the initial presentation of these patients to oncologists may favor underreporting. On the other hand, however, some malignancies, in particular lymphomas, can be associated with hypogammaglobulinemia, leading to documentation as CVID of some patients with secondary immunodeficiency in the context of lymphoma.

From a global perspective, our mostly European findings deserve some additional comments. A worldwide review of primary immunodeficiency registries pointed out the significant heterogeneity in the distribution among IEI in different regions of the world.[23] Thus, the contribution of combined immunodeficiencies ranged from 5% to 27%, phagocytic disorders from 3% to 18%, and complement disorders from 0.5% to 13% of all documented IEI. Founder mutations and the frequency of consanguinity in a society will influence the distribution of IEI, with a relevant impact on the overall distribution of presenting symptoms.[24] Paucity of diagnostic facilities, limited financial resources, and limited expertise will further skew the documented prevalence of different IEI due to lack of awareness and underdiagnoses.[25] In addition to these overall effects, the presenting manifestations of individual IEI are also influenced by the epidemiological, climate-related, and living conditions in different regions of the world.[26] This includes effects of the prevalence of infectious diseases and of vaccination schedules.[27] Based on these considerations, adaptation of warning signs to different areas of the world may be required.[26]

What are the implications of this study? Making a precise diagnosis is the prerequisite for disease-specific therapies, which are increasingly available for IEI.[28] Diagnostic delay is associated with poorer health outcomes.[29,30] Successful efforts have been made to raise awareness for IEI among the public and the medical community by publication of the 10 warning signs by the Jeffrey Modell Foundation. However, in recent years, several smaller studies have demonstrated insufficient sensitivity and specificity of these warning signs, especially in the infant and pediatric population, and discussed the need for adjustment.[7,14-16,31,32]

Our study provides a rationale based on an exceptionally large data set to add immune dysregulation and syndromic features as an additional element to these warning signs. To stimulate discussion for such a revision, we refer to the German national guideline on the diagnosis of IEI, which was the result of an interdisciplinary expert consensus process in 2010.[33] This guideline proposes 2 acronyms as pillars summarizing the IEI warning signs.[34] ELVIS focuses on pathological susceptibility of infection and is short for **e**xciting pathogen, **l**ocalization, **v**ariation from the usual course of infection, **i**ntensity, and total **s**um of infections.[35] GARFIELD focuses on immune dysregulation and is short for **g**ranuloma, **a**utoimmunity, **r**ecurrent **f**ever, **e**czema, **l**ymphoproliferation, **d**iarrhea.[12] In addition, this guideline mentions syndromic features, family history, growth failure, and laboratory abnormalities—specifically hypogammaglobulinemia, neutropenia, and lymphopenia. The 10 warning signs promoted by the Jeffrey Modell Foundation have greatly contributed to raise awareness of IEI. The ever-increasing number of novel IEI and phenotypes of known IEIs over the last 25 years has changed our view on these diseases and how to diagnose them. This analysis of initial presenting manifestations in the ESID Registry contributes important data allowing improvement of the warning signs, with the goal of a further reduction in the diagnostic delay for our patients.

The European Society for Immunodeficiencies (ESID) Registry is based on contributions by the following national registries: CEREDIH (France), REDIP (Spain), PID-NET (Germany), UKPIN (UK), IPINET (Italy), AGPI (Austria), WID (the Netherlands), Greece, Russia, Iran, and Czech Republic. Additional contributions are received from the following countries: Turkey, Poland, Ireland, Lithuania, Portugal, Belgium, Bulgaria, Bosnia and Herzegovina, Switzerland, Slovakia, Slovenia, Sweden, Croatia, Serbia, Belarus, Hungary, Romania, Ukraine, Estonia, Egypt, and Israel. The ESID Registry is part of the European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA).

Additional members of the ESID Working Group who have contributed as authors to this article are listed here alphabetically by country: **Austria**: Kaan Boztug, Juergen Brunner, Ulrike F. Demel, Elisabeth Förster-Waldl, Lukas M. Gasteiger, Lisa Göschl, Marina Kojić, Andrea Schroll, Markus G. Seidel, Uwe Wintergerst, and Lukas Wisgrill; **Belarus**: Svetlana O. Sharapova; **Belgium**: Jean-Christophe Goffard, Tessa Kerre, Isabelle Meyts, Fien Roosens, Julie Smet, and Filomeen Haerynck; **Bosnia and Herzegovina:** Zelimir Pavle Eric; **Bulgaria**: Veneta Milenova; **Croatia**: Alenka Gagro and Darko Richter; **Czech Republic**: Zita Chovancova, Eva Hlavackova, Pavlina Kralickova, Jiri Litzman, Tomas Milota, and Anna Sediva; **Egypt**: Dalia Abd Elaziz, Radwa Salaheldin Alkady, Rabab El Sayed El Hawary, Alia S. Eldash, Nermeen Galal, Sohilla Lotfy, Safa S. Meshaal, Shereen M. Reda, Ali Sobh, and Aisha Elmarsafy; **Finland**: Mikko R.J. Seppänen; **France**: Pauline Brosselin, Virginie Courteille, Nathalie De Vergnes, Sven Kracker, Martine Pergent, and Philippe Randrianomenjanahary; **Germany**: Gerrit Ahrenstorf, Michael H. Albert, Tobias Ankermann, Faranaz Atschekzei, Ulrich Baumann, Benjamin C. Becker, Uta Behrends, Bernd H. Belohradsky, Anika-Kerstin Biegner, Nadine Binder, Sebastian F.N. Bode, Christoph Boesecke, Benedikt Boetticher, Michael Borte, Stephan Borte, Carl Friedrich Classen, Johannes Dirks, Gregor Dückers, Sabine El-Helou, Diana Ernst, Maria Fasshauer, Gisela Fecker, Kerstin Felgentreff, Dirk Foell, Sujal Ghosh, Hermann J. Girschick, Sigune Goldacker, Norbert Graf, Dagmar Graf, Johann Greil, Leif Gunnar Hanitsch, Fabian Hauck, Maximilian Heeg, Sabine I. Heine, Joerg C. Henes, Manfred Hoenig, Ursula Holzer, Dirk Holzinger, Gerd Horneff, Patrick Hundsdoerfer, Alexandra Jablonka, Donate Jakoby, Oana Joean, Petra Kaiser-Labusch, Christian Klemann, Robin Kobbe, Julia Körholz, Christof M. Kramm, Renate Krüger, Sybille Landwehr-Kenzel, Kai Lehmberg, Johannes G. Liese, Conrad Ferdinand Lippert, Maria Elena Maccari, Katja Masjosthusmann, Andrea Meinhardt, Markus Metzler, Henner Morbach, Ingo Müller, Nora Naumann-Bartsch, Jennifer Neubert, Tim Niehues, Hans-Hartmut Peter, Nikolaus Rieber, Henrike Ritterbusch, Jürgen Kurt Rockstroh, Joachim Roesler, Uwe Schauer, Raphael Scheible, Marc Schmalzing, Reinhold Ernst Schmidt, Dominik T. Schneider, Stefan Schreiber, Catharina Schuetz, Ansgar Schulz, Hendrik Schulze-Koops, Ulf Schulze-Sturm, Volker Schuster, Eva C. Schwaneck, Klaus Schwarz, Carolynne Schwarze-Zander, Mehtap Sirin, Alla Skapenko, Georgios Sogkas, Monika Sparber-Sauer, Carsten Speckmann, Sandra Steinmann, Sophie Stiehler, Klaus Tenbrock, Horst von Bernuth, Klaus Warnatz, Jan-Christian Wasmuth, Michael Weiss, Torsten Witte, Kirsten Wittke, Helmut Wittkowski, and Rainald A. Zeuner; **Greece**: Evangelia Farmaki, Maria N. Hatzistilianou, Ioannis Kakkas, Maria G. Kanariou, Androniki Kapousouzi, Emmanouil Liatsis, Paraskevi Maggina, Efimia Papadopoulou-Alataki, Maria Raptaki, Matthaios Speletas, and Sofia Tantou; **Hungary**: Vera Goda, Gergely Kriván, and Laszlo Marodi; **Iran**: Hassan Abolhassani, Asghar Aghamohammadi, and Nima Rezaei; **Ireland**: Conleth Feighery, Timothy Ronan Leahy, and Paul Ryan; **Israel**: Nurit Assia Batzir, Ben Zion Garty, and Hannah Tamary; **Italy**: Alessandro Aiuti, Donato Amodio, Chiara Azzari, Federica Barzaghi, Lucia A. Baselli, Caterina Cancrini, Maria Carrabba, Marco Cazzaniga, Simone Cesaro, Matteo Chinello, Maria Giovanna Danieli, Rosa Maria Dellepiane, Giovanna Fabio, Eleonora Gambineri, Lorenzo Lodi, Vassilios Lougaris, Carolina Marasco, Baldassarre Martire, Antonio Marzollo, Cinzia Milito, Viviana Moschese, Claudio Pignata, Alessandro Plebani, Fulvio Porta, Isabella Quinti, Silvia Ricci, Annarosa Soresina, Alberto Tommasini, Angelo Vacca, and Clementina Canessa; **Lithuania**: Audra Blažienė and Brigita Sitkauskiene, **Poland**: Ewelina Gowin, Edyta Heropolitańska-Pliszka, Barbara Pietrucha, Anna Szaflarska, Ewa Więsik-Szewczyk, and Beata Wolska-Kuśnierz; **Portugal**: Isabel Esteves, Emilia Faria, Laura Hora Marques, João Farela Neves, Susana L. Silva, Carla Teixeira, and Sara Pereira da Silva; **Romania**: Brindusa Ruxandra Capilna; **Russia**: Marina N. Guseva and Anna Shcherbina, **Slovakia**: Anna Bobcakova, Peter Ciznar, Juliana Gabzdilova, Milos Jesenak, Lenka Kapustova, Jaroslava Orosova, Otilia Petrovicova, and Stefan Raffac; **Slovenia**: Peter Kopač; **Spain**: Luis M. Allende, Arnau Antolí, Gemma Rocamora Blanch, Javier Carbone, Romina Dieli-Crimi, Marina Garcia-Prat, Juana Gil-Herrera, Luis Ignacio Gonzalez-Granado, Pilar Llobet Agulló, Peter Olbrich, Alba Parra-Martínez, Estela Paz-Artal, Daniel E. Pleguezuelo, Nerea Salmón Rodríguez, Silvia Sánchez-Ramón, Juan Luis Santos-Pérez, Xavier Solanich, Pere Soler-Palacin, and Miriam González-Amores; **Sweden**: Olov Ekwall and Anders Fasth; **Switzerland**: Michaela Bitzenhofer-Grüber, Geraldine Blanchard-Rohner, Fabio Candotti, Florentia Dimitriou, Ulrich Heininger, Andreas Holbro, Peter Jandus, Antonios G.A. Kolios, Karin Marschall, Jana Pachlopnik Schmid, Klara M. Posfay-Barbe, Seraina Prader, Janine Reichenbach, Urs C. Steiner, and Johannes Trück; **The Netherlands**: Robbert G. Bredius, Suzanne de Kruijf- Bazen, Esther de Vries, Stefanie S.V. Henriet, Taco W. Kuijpers, Judith Potjewijd, Abraham Rutgers, Kim Stol, Koen J. van Aerde, J. Merlijn Van den Berg, Annick A.J.M. van de Ven, and Jorisvan Montfrans; **Turkey**: Sezin Aydemir, Safa Baris, Figen Dogu, Aydan Ikinciogullari, Elif Karakoc-Aydiner, Sara S. Kilic, Ayca Kiykim, Şefika İlknur Kökçü Karadağ, Necil Kutukculer, Suheyla Ocak, Ekrem UNAL, and Alişan Yıldıran; **Ukraine**: Oksana Boyarchuk, Anna Hilfanova, and Larysa V. Kostyuchenko; **United Kingdom**: Hana Alachkar, Peter D. Arkwright, Helen E. Baxendale, Jolanta Bernatoniene, Tanya I. Coulter, Tomaz Garcez, Sarah Goddard, Mark M. Gompels, Sofia Grigoriadou, Richard Herriot, Archana Herwadkar, Aarnoud Huissoon, Lisa Ibberson, Zoreh Nademi, Sadia Noorani, Shahnaz Parvin, Cathal Laurence Steele, Moira Thomas, Catherine Waruiru, Patrick F.K. Yong, and Helen Bourne.

Clinical implications: We provide a data-based rationale to add immune dysregulation and syndromic features to the IEI warning signs, which may significantly improve early IEI diagnosis.

REFERENCES

1. Mahlaoui N, Jais J-P, Brosselin P, Mignot C, Beaurain B, Brito C, et al. Prevalence of primary immunodeficiencies in France is underestimated. J Allergy Clin Immunol 2017;140:1731-3.

2. Shillitoe B, Bangs C, Guzman D, Gennery AR, Longhurst HJ, Slatter M, et al. The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017. Clin Exp Immunol 2018;192:284-91.
3. El-Helou SM, Biegner A-K, Bode S, Ehl SR, Heeg M, Maccari ME, et al. The German National Registry of Primary Immunodeficiencies (2012-2017). Front Immunol 2019;10:1272.
4. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Correction to: Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020;40:65.
5. Joshi AY, Iyer VN, Hagan JB, St Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc 2009;84:16-22.
6. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116-26.
7. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. Ann New York Acad Sci 2011; 1238:7-14.
8. Modell V, Gee B, Lewis DB, Orange JS, Roifman CM, Routes JM, et al. Global study of primary immunodeficiency diseases (PI)–diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol Res 2011;51:61-70.
9. Cunningham-Rundles C. Autoimmunity in primary immune deficiency: taking lessons from our patients. Clin Exp Immunol 2011;164:6-11.
10. Grimbacher B, Warnatz K, Yong PFK, Korganow A-S, Peter H-H. The crossroads of autoimmunity and immunodeficiency: lessons from polygenic traits and monogenic defects. J Allergy Clin Immunol 2016;137:3-17.
11. Fischer A, Provot J, Jais J-P, Alcais A, Mahlaoui N. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol 2017;140:1388-93.e8.
12. Mauracher AA, Gujer E, Bachmann LM, Güsewell S, Pachlopnik Schmid J. Patterns of immune dysregulation in primary immunodeficiencies: a systematic review. J Allergy Clin Immunol Pract 2021;9:792-802.e10.
13. Gambineri E, Torgerson TR. Genetic disorders with immune dysregulation. Cell Mol Life Sci 2012;69:49-58.
14. Lankisch P, Schiffner J, Ghosh S, Babor F, Borkhardt A, Laws H-J. The Duesseldorf warning signs for primary immunodeficiency: is it time to change the rules? J Clin Immunol 2015;35:273-9.
15. Arslan S, Ucar R, Caliskaner AZ, Reisli I, Guner SN, Sayar EH, et al. How effective are the 6 European Society of Immunodeficiency warning signs for primary immunodeficiency disease? Ann Allergy Asthma Immunol 2016;116: 151-5.e1.
16. Bjelac JA, Yonkof JR, Fernandez J. Differing performance of the warning signs for immunodeficiency in the diagnosis of pediatric versus adult patients in a two-center tertiary referral population. J Clin Immunol 2019;39:90-8.
17. Scheible R, Rusch S, Guzman D, Mahlaoui N, Ehl S, Kindle G. The NEW ESID Online Database Network. Bioinformatics 2019;35:5367-9.
18. Heitzeneder S, Seidel M, Förster-Waldl E, Heitger A. Mannan-binding lectin deficiency—good news, bad news, doesn't matter? Clin Immunol 2012; 143:22-38.
19. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova J-L, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol 2013;33:1-7.
20. Toplak N, Frenkel J, Ozen S, Lachmann HJ, Woo P, Koné-Paut I, et al. An international registry on autoinflammatory diseases: the Eurofever experience. Ann Rheum Dis 2012;71:1177-82.
21. Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunol Rev 2019;287:241-52.
22. Schatorjé E, van der Flier M, Seppänen M, Browning M, Morsheimer M, Henriet S, et al. Primary immunodeficiency associated with chromosomal aberration—an ESID survey. Orphanet J Rare Dis 2016;11:110.
23. Abolhassani H, Azizi G, Sharifi L, Yazdani R, Mohsenzadegan M, Delavari S, et al. Global systematic review of primary immunodeficiency registries. Expert Rev Clin Immunol 2020;16:717-32.
24. Al-Herz W, Al-Ahmad M, Al-Khabaz A, Husain A, Sadek A, Othman Y. The Kuwait National Primary Immunodeficiency Registry 2004-2018. Front Immunol 2019;10:1754.
25. Erjaee A, Bagherpour M, van Rooyen C, van den Berg S, Kinnear CJ, Green RJ, et al. Primary immunodeficiency in Africa—a review. South African Med J 2019; 109:3-11.
26. Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014;34:10-22.
27. Pilania RK, Chaudhary H, Jindal AK, Rawat A, Singh S. Current status and prospects of primary immunodeficiency diseases in Asia. Genes Dis 2020;7:3-11.
28. Chellapandian D, Chitty-Lopez M, Leiding JW. Precision therapy for the treatment of primary immunodysregulatory diseases. Immunol Allergy Clin North Am 2020; 40:511-26.
29. Pai S-Y, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med 2014;371:434-46.
30. Elsink K, van Montfrans JM, van Gijn ME, Blom M, van Hagen PM, Kuijpers TW, et al. Cost and impact of early diagnosis in primary immunodeficiency disease: a literature review. Clin Immunol 2020;213:108359.
31. Subbarayan A, Colarusso G, Hughes SM, Gennery AR, Slatter M, Cant AJ, et al. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics 2011;127:810-6.
32. O'Sullivan MD, Cant AJ. The 10 warning signs: a time for a change? Curr Opin Allergy Clin Immunol 2012;12:588-94.
33. Farmand S, Baumann U, Bernuth H von, Borte M, Foerster-Waldl E, Franke K, et al. Interdisciplinary AWMF guideline for the diagnostics of primary immunodeficiency. Klinische Padiatrie 2011;223:378-85.
34. Farmand S, Baumann U, von Bernuth H, Borte M, Borte S, Boztug K, et al. Leitlinie "Diagnostik auf Vorliegen eines primären Immundefekts". Abklärung von Infektionsanfälligkeit, Immundysregulation und weiteren Symptomen von primären Immundefekten: Susan Farmand, Ulrich Baumann, Horst von Bernuth, Michael Borte, Stephan Borte, Kaan Boztug, et al. 2017. Available at: https://www.awmf.org/uploads/tx_szleitlinien/112-001k_S2k_Primaere_Immundefekte_PID_2017-11.pdf. Accessed September 12, 2019.
35. Baumann U, Belohradsky B. Primäre Immundefekte - Warnzeichen und Algorithmen zur Diagnosefindung. Bremen: UNI-MED; 2010.

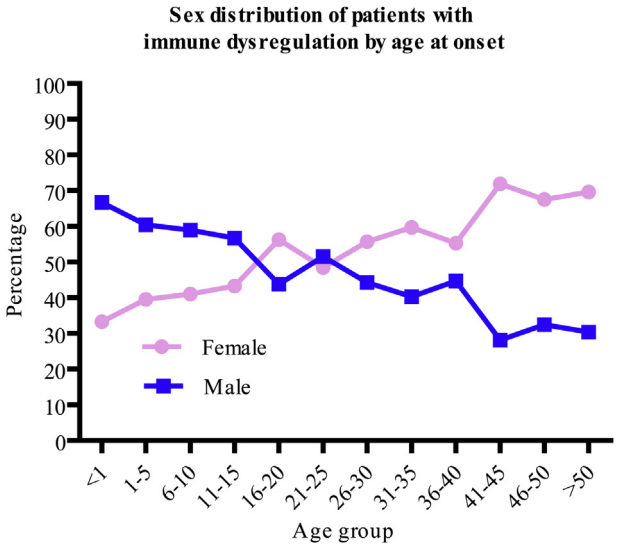


FIG E1. Sex distribution of patients with immune dysregulation by age at onset. The sex distribution of patients presenting with immune dysregulation in the absence or presence of other symptoms by age at onset of symptoms is shown.

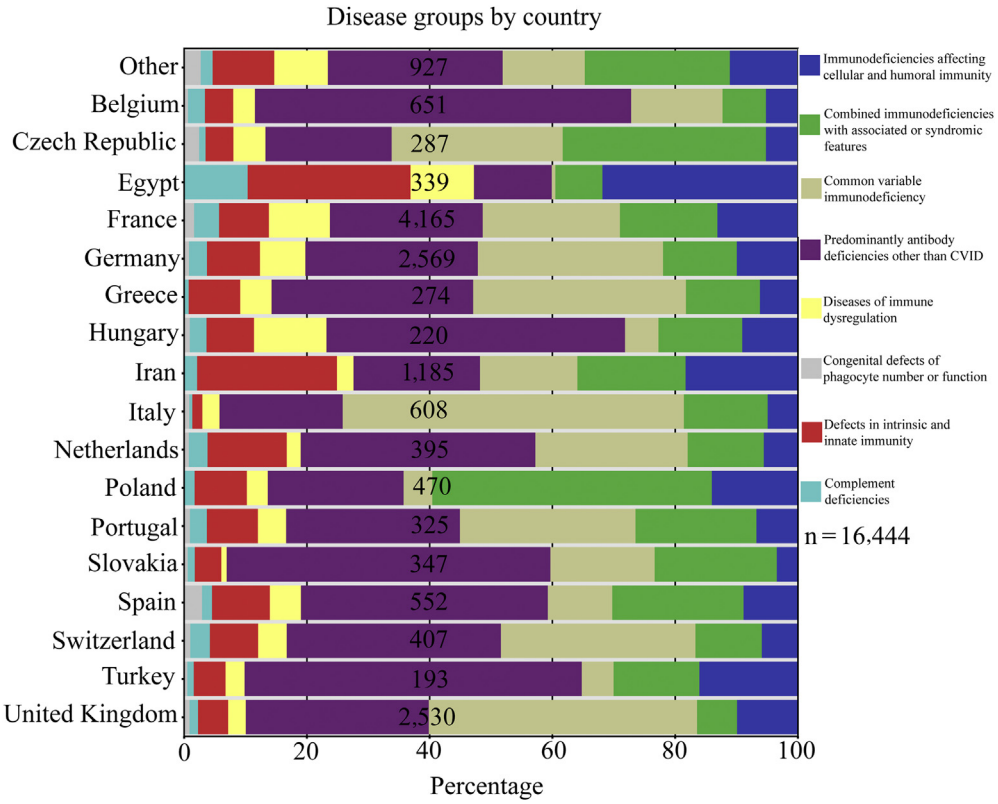


FIG E2. Disease groups by country. The percentage distribution of disease groups is shown for each country contributing more than at least 1% of total 16,444 patients for the respective analysis. The number of patients per country is written in each column. Countries are shown in descending order of registered patients per inhabitants.

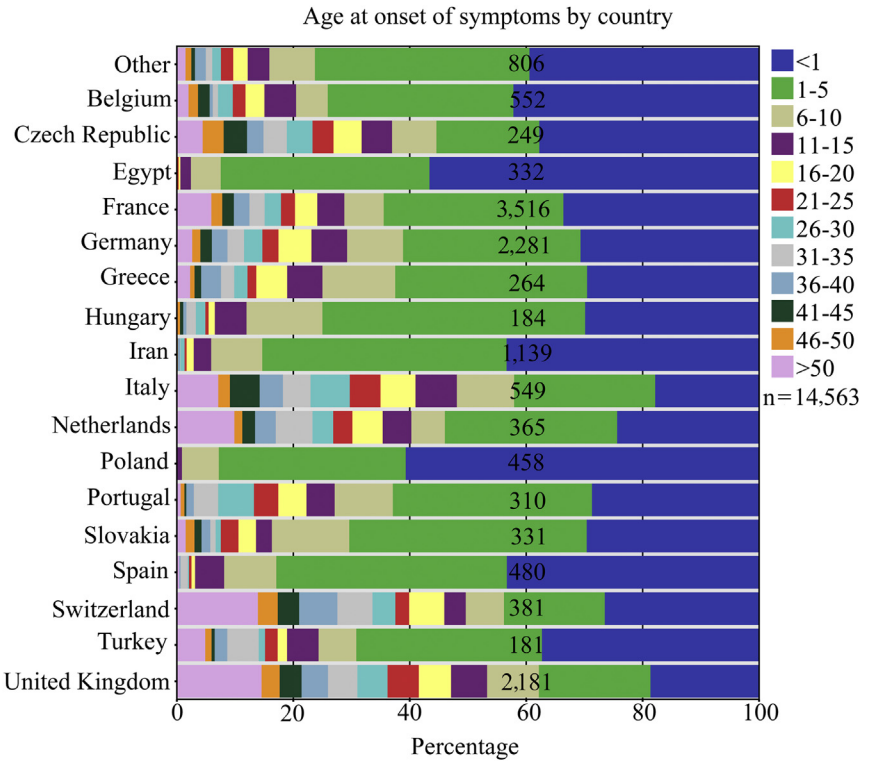


FIG E3. Age at onset of symptoms by country. The percentage distribution of age at onset of symptoms is shown for each country contributing more than at least 1% of total 14,563 patients for the according analysis. The number of patients per country is written in each column. Countries are shown in descending order of registered patients per inhabitants. One explanation for the observed differences is that in some countries, mostly pediatric immunologists contribute to the registry whereas in other countries more adult immunologists contribute. For example, age at onset was less than 6 years in 90% of patients in Egypt, whereas it was less than 6 years in 37% of patients in the United Kingdom.

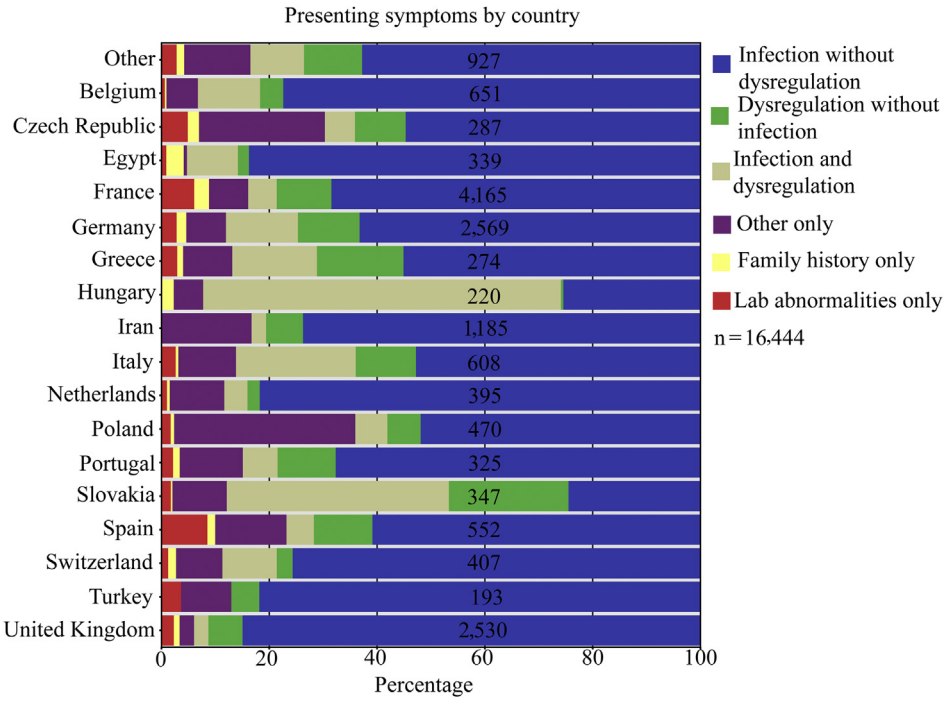


FIG E4. Presenting symptoms by country. The percentage distribution of presenting symptoms is shown for each country contributing more than at least 1% of total 16,444 patients for the according analysis. The number of patients per country is written in each column. Countries are shown in descending order of registered patients per inhabitants. The pattern of initial manifestation was comparable in most participating countries. However, presentation with "infection without dysregulation" varied between maximum 85% in the United Kingdom and 84% in Egypt and minimum 25% in Slovakia and 26% in Hungary.

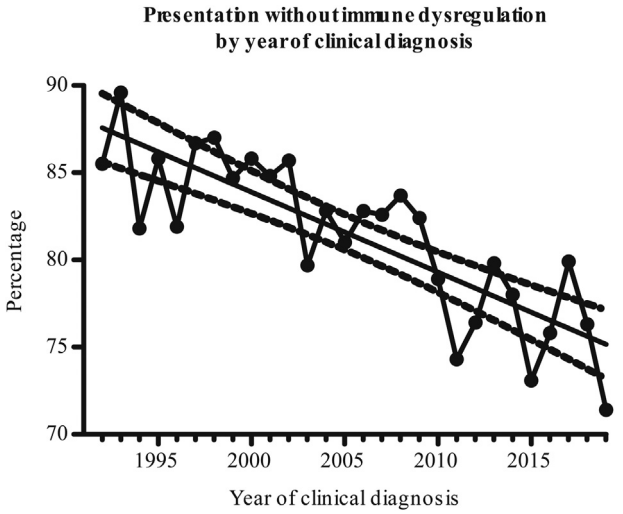


FIG E5. Increasing recognition of immune dysregulation as initial presenting manifestation in recent years. Diagnosis of patients with IEI *without* immune dysregulation at primary manifestation by year of clinical diagnosis. Linear regression with 95% CI is shown.