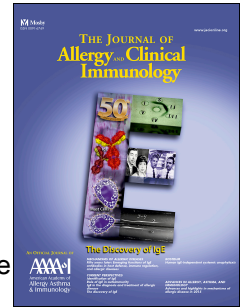


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Autoimmune and inflammatory manifestations occur frequently in primary immunodeficiencies

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ABSTRACT**Background**

Primary immunodeficiencies (PIDs) are inherited diseases associated with a considerably increase in susceptibility to infections. It is known that PIDs can also predispose to cancer and immune diseases including allergy, autoimmunity and inflammation.

Objective

We aimed at determining the incidence of autoimmunity and inflammation in PID patients.

Methods

We have retrospectively screen 2183 consecutive cases of PID in the French CEREDIH registry for the occurrence of autoimmunity and inflammation.

Results

One or more autoimmune and inflammatory complications were noted in 26.2% of patients, with a risk of onset throughout the patient's lifetime. The risk of autoimmune cytopenia was at least 120 times higher than in the general population, the risk of inflammatory bowel disease in children 80 times higher and the risk of other autoimmune manifestations was approximately 10 times higher. Remarkably, all types of PID were associated with a risk of autoimmune and inflammatory complications, although the greatest risk was associated with T cell PIDs and common variable immunodeficiency. The occurrence of autoimmune disease is a negative prognostic factor for survival.

Conclusions

Our results provide the basis for a detailed, prospective evaluation of autoimmunity and inflammation in the context of PID, with a view to accurately assessing these risks and describing the possible impact of medical intervention.

INTRODUCTION

Primary immunodeficiencies (PIDs) are inherited disorders that result in impaired immune responses. On the basis of national or continent-wide registries, the prevalence of PIDs is currently estimated to be around 4 to 10 per 10⁵ live births¹⁻⁶. Many distinct syndromes have been described as a consequence of functional impairment of the innate and/or adaptive arms of the immune system. The development of genomic tools has led to the discovery of up to 300 genes in which mutations cause PIDs⁷. PIDs profoundly modify life expectancy and quality of life - primarily because of increased susceptibility to infections which may be broad or restricted. Furthermore, it has long been known that PID patients can be prone to cancers^{5,8,9} and immune diseases such as allergy¹⁰, inflammation and autoimmune diseases¹¹⁻¹³. Indeed, these manifestations are sometimes even part of the initial description of the disease, as for instance in Wiskott-Aldrich syndrome¹⁴ and chronic granulomatous disease (CGD)¹⁵. Although the occurrence of autoimmunity in various forms of PIDs (primarily common variable immunodeficiency (CVID)^{16,17}) has been widely reported, the incidence and types of autoimmune and inflammatory manifestations in PIDs have never to the best of our knowledge been surveyed. Hence, we decided to retrospectively screen the French national PID registry (CEREDIH)³ for autoimmune and inflammatory disorders encountered in the latest 2183 patients for whom data are available. The survey's main objectives were thus to estimate the overall frequency of these manifestations, identify at least some associated risk factors and assess the manifestations' influence on overall survival. The present retrospective study may serve now as the basis for a detailed prospective analysis of the medical interventions of value in preventing and/or treating the autoimmune and inflammatory complications of PIDs.

METHODS

We systematically screened PID patients living in France for the occurrence of autoimmune or inflammatory complications (Suppl. Table 1). Data were consecutively collected between September 1st, 2013, and February 1st, 2016 on 2183 patients either upon initial registration in the CEREDIH database (hosted by the secured online ESID Registry, see www.esid.org) or during follow-up of previously registered patients³. All of the data were retrospectively collected within the CEREDIH French national registry. Information of new cases and follow up were retrieved on a regular basis by the CEREDIH staff who are visiting the centers and have access to patients records. This is at this occasion, starting from September 1st 2013 up to February 1st 2016 that information on autoimmunity were collected, in addition to the previously established set of data.

The study population did not differ from the overall CEREDIH registry population (n=5952) in terms of age or gender. There were slight differences in the proportions of subjects with innate PIDs and with T-cell PIDs other than severe combined immunodeficiency (SCID) or combined immunodeficiency (CID) (Suppl. Table 2). The types of autoimmune/inflammatory complications and the date or age at onset were recorded, when available. Manifestations occurring after allogeneic hematopoietic stem cell transplantation (HSCT) were not included in the analysis. The database was approved by the French National Data Protection Commission (*Commission Nationale Informatique et Libertés*). The study procedures (analysis of the CEREDIH registry) were approved by the French National Consultative Committee on Data Processing in Healthcare Research (*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé*; reference 06.327, dated September 7th, 2006). Among many variables, the CEREDIH database contained information on the patient's date of birth, place of residence, clinical diagnosis, molecular

diagnosis, allergy status, cancer status, and type of treatment, i.e immunoglobulin replacement therapy or HSCT.

Continuous variables are quoted as the median or mean (range). In survival analyses, we used the Kaplan-Meier non-parametric model to estimate the time to event. The threshold for statistical significance was set to $p < 0.05$ in all analyses. Statistical analyses were performed using the R software (version 3.2.3)¹⁸.

RESULTS

Overall frequency and distribution of autoimmune and inflammatory conditions

Of the 2183 surveyed patients (median age: 20 years; mean age: 25.8 years; range: 0.5-92), 571 (26.2%) had developed at least one autoimmune or inflammatory condition. The wide range of manifestations (n=852) encompassed most of the known autoimmune diseases (Table 1 and Suppl. Table 1), with the notable predominance of autoimmune cytopenia (mostly anemia, n=110 manifestations) and/or thrombocytopenia (n=130 manifestations). When comparing the study population with the general population in Western Europe¹⁹⁻²⁵, we observed a marked increase in relative risk reaching 3- to 14-fold. The increase was particularly marked for autoimmune cytopenia (x 120) (Table 2)²⁶. The relative risks are high in the pediatric population as illustrated by the 830 fold increase risk for autoimmune hemolytic anemia, the 80 fold increased risk of inflammatory bowel disease and the 40 fold increased risk of arthritis among children with PID compared to control French cohorts^{26 27 28 29 30}. As shown in Table 3, 31.6% of the affected patients had experienced more than one autoimmune or inflammatory manifestation. These manifestations occurred throughout the patient's lifetime, since the cumulative incidence plot was almost linear after the first 8 to 10 years of life (Figure 1). Forty percent of the patients had been affected by the age of 50.

The risk of autoimmunity and inflammation as a function of the PID

When considering PID patients with increased susceptibility to infections, i.e. after excluding patients with an isolated hemophagocytic lymphohistiocytic syndrome (n=64, with 2 cases of autoimmunity or a PID characterized by autoimmunity and lymphoproliferation in the absence of significant infections i.e. ALPS, APECED, IPEX, CTLA4 deficiency and gain of function mutations of STAT3 (n=108, 73 cases of autoimmunity), the risk of autoimmunity/inflammation was 24.6% (496 out of 2011) and thus did not differ from the risk

in the overall study population. It is striking to note that all groups of patients classified as having B-cell CVIDs, other B-cell PIDs, T-cell PIDs or innate immune system deficiencies were at risk of autoimmune or inflammatory manifestations (Table 4 and Suppl. Table 3). CVID and combined immunodeficiencies were associated with the highest risk. It is noteworthy that 25% of the patients with innate PIDs had autoimmune or inflammatory manifestations (e.g. in CGD). When considering age at onset, these manifestations occurred earlier in life in patients with T cell and innate immune deficiencies than in patients with B-cell PIDs. The frequencies in these groups tended to converge at a value of above 40% in patients ≥ 50 years of age (Figure 2). As shown in Supplementary Table 4, cytopenia and rheumatologic manifestations were more frequently associated with T cell PIDs than with other PIDs. We performed a univariate analysis of risk factors associated with the occurrence of autoimmunity/inflammation in PID patients. Cancer and allergy (supplementary table 5), but not gender, were apparently associated with autoimmunity (Table 4). Allergy was the only independent risk factor in an adjusted Cox model analysis (Table 5). Early onset of infections as well as treatment modalities, i.e immunoglobulin substitution did not impact on frequency (not shown).

Influence on survival

The overall survival time was found to be significantly shorter in the PID patients with autoimmune/inflammatory manifestations than in those without these manifestations (Figure 3). The difference in survival was also observed when analyzing subgroups with CVIDs, other B-cell PIDs and T cell PIDs but not innate PIDs (Suppl. Figure 2). Since patients with the most severe forms of PID tend to undergo allogeneic HSCT (n=380 in the present study), we looked at whether the occurrence of autoimmune or inflammatory manifestation before

transplantation had an impact on survival post HSCT. As shown in Figure 4, pre- HSCT autoimmunity/inflammation was associated with worse survival.

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DISCUSSION

The present retrospective study is the first to report the frequency and distribution of autoimmune and inflammatory manifestations in a group of PID patients. The study's nature, i.e retrospective and cross-sectional was associated with some obvious limitations despite the fact it is supported by a national registry. Given the importance of providing optimal care for patients with PIDs, our present results should be viewed as an incentive to launch a prospective analysis of autoimmunity in a large group of patients with PID. Despite this caveat, the present study based on the French CEREDIH PID registry produced some important findings: (i) autoimmunity/inflammation was observed in a large minority (26.2%) of PID patients, (ii) a wide range of manifestations were observed, (iii) these manifestations occurred throughout the patient's lifetime, (iv) virtually all PIDs are associated with an elevated risk of autoimmunity/inflammation, and (v) the autoimmune/inflammatory manifestations have prognostic significance.

Our results demonstrate that autoimmune and inflammatory diseases are much more frequent by a factor of at least 10 in PID patients than in the general population. This increase in risk is extremely high (by a factor of 120) for autoimmune cytopenia (including both anemia and thrombocytopenia), inflammatory bowel disease or arthritis in children^{19 26 27 28 29 30}. This finding suggests that patients with autoimmune anemia and/or thrombocytopenia should be screened for PIDs – ideally, but perhaps not exclusively during childhood. For instance, one can estimate that when there is in France 360 pediatric cases of autoimmune anemic ($12 \text{ M} \times 3 \times 10^{-5}$), there will be 50 PID cases ($2000 \text{ children with PID} \times 2.5 \times 10^{-2}$) so 15%. The same holds true for the occurrence of inflammatory bowel disease and perhaps inflammatory arthritis in children. The fact that almost the entire spectrum of autoimmune diseases can be observed in patients with PIDs obviously suggests the operation of many different underlying mechanisms. It is noteworthy that with the exception of autoimmune

cytopenia, organ-specific autoimmunity and systemic autoimmunity, autoantibody-mediated autoimmunity and T-cell-mediated autoimmunity were all occurring in this group of PID patients. It is difficult to understand why autoimmune cytopenia is so predominant notably but not exclusively in the setting of T cell IDs. It remains to be seen whether the abundance and spreading of self-antigens expressed by blood cells and related self-reactive T and B cell clones have a role. It would be interesting to assess the proportions of self-reactive B cells that target red blood cell or platelet self-antigens in patients with PIDs vs. healthy individuals.

Our results confirmed literature reports^{16,17} in which CVID was frequently associated with autoimmunity/inflammation including granulomas. Although the prominence of autoimmunity in T cell IDs had been suspected, it was confirmed by our data. In contrast, we were somewhat surprised to observe that autoimmune/inflammatory manifestations are rather common complications of all types of PIDs - including innate immune deficiencies. In the latter group, inflammatory lesions and notably inflammatory bowel disease were particularly frequent. It is also important to note that the risk of onset of autoimmunity persists throughout the patient's life; however, this should be put in perspective with the fact that a causal factor is continuously present. In contrast to the situation in the general population, no real gender bias was observed in patients with PIDs; this finding suggests that the known gender-associated risk factors (x1.7²²) are not exacerbated by PIDs. Furthermore, the occurrence of other non-infectious complications of PIDs e.g. allergy and cancer is associated with autoimmunity/inflammation. At this time, we cannot say whether allergy and cancer should be considered as risk factors or rather as common consequences of the underlying PID. However, we suspect that pre-existing allergy may have a role based on the adjusted Cox model analysis. The influence of infections on autoimmunity/inflammation has not been characterized and thus warrants specific attention in prospective studies. It is possible that

persistent infection in a patient with a PID may trigger autoimmunity and accentuate inflammation, as suggested by the recent report in which persistent rubella vaccine virus was found in granulomas in several PID patients³¹. Lastly, our results show that autoimmunity worsens the prognosis for patients with a PID. The latter finding highlights the need for careful examination of the efficacy/toxicity balance of both biologic and non-biologic immunosuppressive treatment for autoimmunity in the context of PID.

Many researchers have discussed the various mechanisms by which autoimmunity/inflammation can be triggered in the context of PID^{11-13,31,32}. These mechanisms include (i) the exacerbated production of type I interferon, (ii) IL1 production, (iii) defective negative selection of self-reactive T and B cells with high affinity, (iv) defective editing of the B cell receptor in the periphery, (v) defective peripheral (self)-antigen-induced cell death, (vi) gain of function of B or T cell activation/effector molecules, (vii) defective T regulatory cells, (viii) homeostatic expansion of self-reactive T lymphocytes, (ix) an intrinsic defect in cis regulatory molecules, and (x) defective clearance of immune complexes and apoptotic cell bodies. “A la carte” combinations of these factors in the various PIDs may predispose patients to autoimmunity and inflammation. It is beyond the scope of this study to discuss in detail the involvement of these mechanisms, when recognized, in the many PIDs associated with autoimmunity.

In conclusion, the present study both provides valuable information and raises further questions on the occurrence of autoimmune/inflammatory diseases in PIDs. For scientific and medical reasons, a detailed, international analysis of these complications e.g. a prospective analysis of a large cohort of PID patients should now be organized.

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Disclosure of Conflicts of Interest

None reported.

Table 1a. Categorization of the 852 autoimmune or inflammatory manifestations observed in 571 patients with PID.

	n=	%
Cytopenias	269	31.4
Gastrointestinal disorders	208	24.4
Skin	120	14.1
Rheumatologic disorders	109	12.8
Endocrine disorders	69	8.1
Lung	30	3.5
Eye	14	1.7
Kidney	11	1.3
Vasculitis and other systemic disorders	9	1.0
Neurologic disorders	8	1.0
Urologic disorders	3	0.4
Other	2	0.3
Total	852	

Table 1b. Number of patients with the most common autoimmune and/or inflammatory manifestations, as a function of the type of PID

		Cytopenia n (%*)	Rheumatologic manifestations n (%*)	Gastrointestinal manifestations n (%*)
B-cell CVIDs	n= 408	68 (16.6)	22 (5.4)	39 (9.5)
Other B-cell deficiencies	n= 585	23 (3.9)	25 (4.3)	24 (4.1)
T-cell deficiencies	n= 845	117 (13.8)	37 (4.4)	63 (7.3)
Innate deficiencies	n= 324	9 (2.8)	16 (5.0)	50 (15.5)
Total	2162	217 (10)	100 (4.6)	176 (8.1)

* based on the total number of patients who have at least one autoimmune or inflammatory manifestation (n=571)

NB: some patients had more than one type of autoimmune or inflammatory manifestation and so the total n may exceed the total number of patients. Likewise, the sum of the percentages can exceed 100%.

Table 2. The relative risk of autoimmune disease in patients with PID

	Prevalence per 1x10 ⁵ PID pts	Prevalence per 1x10 ⁵ of the general population	Relative risk
Cytopenia	12000	100	120
Autoimmune hemolytic anemia (children, France)**	2500	3	830
Immune thrombocytopenia (France)***	6000	100	60
Rheumatologic disorders*	5000	860	6
Rhumatoid arthritis (children, France)****	800	20	40
Inflammatory bowel disease (adults, France)*****	7800	180	43
Inflammatory bowel disease (children, France)*****	5500	70	80
Skin*	6000	600	10
Endocrine disorders*	3000	1000	3
Eye*	700	100	7
Kidney*	500	63	8
Vasculitis and other systemic disorders*	250	17.5	13
Neurologic disorders*	400	130	3

() : brackets refer to the control population.

*: references¹⁹⁻²⁵; **: references²⁶; ***: references²⁷; ****: references²⁸

*****: references^{29,30}

Table 3. Frequency of multiple occurrences of autoimmune/inflammatory manifestations in patients with PID

Number of manifestations per patient		Percentage of patients
0	1612	73.8
1	389	17.8
2	113	5.2
3	44	2.0
4	20	.9
5	4	.2
6	1	

Table 4. Univariate analysis of risk factors for the occurrence of autoimmunity and/or inflammation.

	Autoimmunity/ inflammation			
	n=	n=	(%)	
• All patients	2183	571	(26.2)	p value
• Male gender	1255	320	25.5	NS
• PID diagnosis				
B-cell PIDs	993	253	(25.5)	] < 0.001
CVID	408	156	(38.3)	
non-CVID	585	97	(16.6)	
T-cell PIDs	845	232	(27.5)	] p<0.001
SCID	160	11	(6.9)	
CID	424	132	(31.1)	
Others	261	89	(31.7)	
Innate	323	83	(25.6)	NS
Unclassified	21	4	(19.0)	
• Allergy	395	123	(31.1)	0.0009
• Cancer	148	55	(37.2)	0.002

Table 5. Adjusted Cox model of variables associated with autoimmunity/inflammation

Adjusted Cox model of variables associated with autoimmunity *			
	Risk factor	Hazard ratio [95% confidence interval]	p
PID category	CVID	1	-
	Other (non-CVID) B-cell deficiencies	0.80 [0.47-1.38]	0.42
	T-cell deficiencies	3.17 [1.92-5.24]	<0.001
	Innate immunity deficiencies	3.16 [1.61-6.20]	<0.001
	Allergy	7.44 [4.92 - 11.26]	<0.001
Malignancy		0.70 [0.35-1.38]	0.30

* For patients with no missing data for the model's variables

Figure legends

Figure 1. Cumulative incidence of autoimmune/inflammatory manifestations in PID patients as a function of age. The data came from 1678 patients for whom age at onset of the first manifestation was recorded. The dotted lines indicate $\pm 2SD$.

Figure 2. Cumulative incidence of autoimmunity/inflammatory manifestations in PID patients, as a function of the PID disease group.

Figure 3. Probability of survival of PID patients, as a function of the occurrence of autoimmune/inflammatory manifestations

Figure 4. Probability of survival of PID patients after HSCT, according to the presence or absence of pre-existing autoimmunity/inflammation

Supplementary Figure 1. Cumulative incidence of cytopenia, rheumatologic disorders and autoimmune gastrointestinal manifestations, as a function of age.

1a/ autoimmune cytopenia

1b/ Rheumatologic disorders

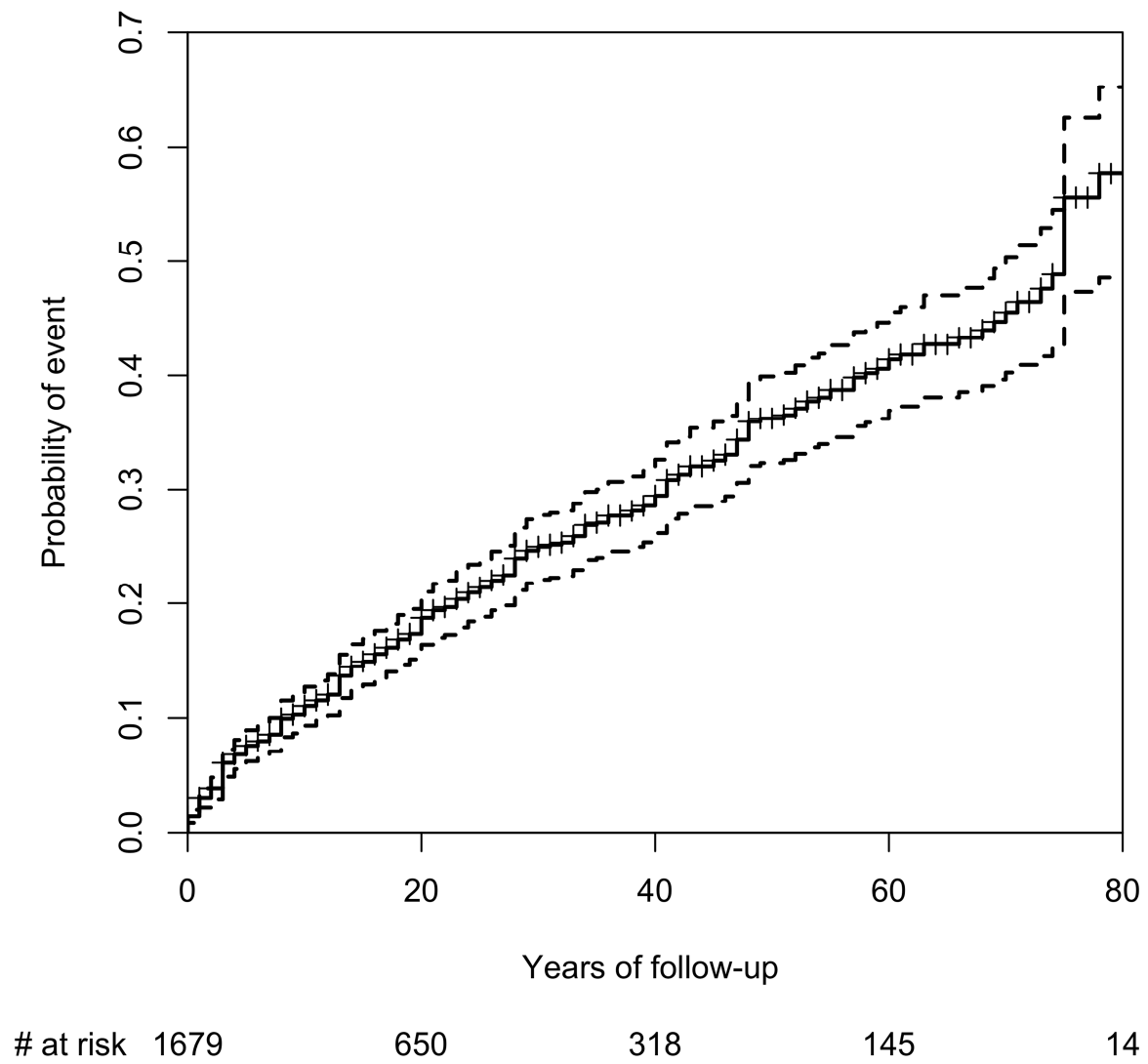
1c/ Gastrointestinal disorders

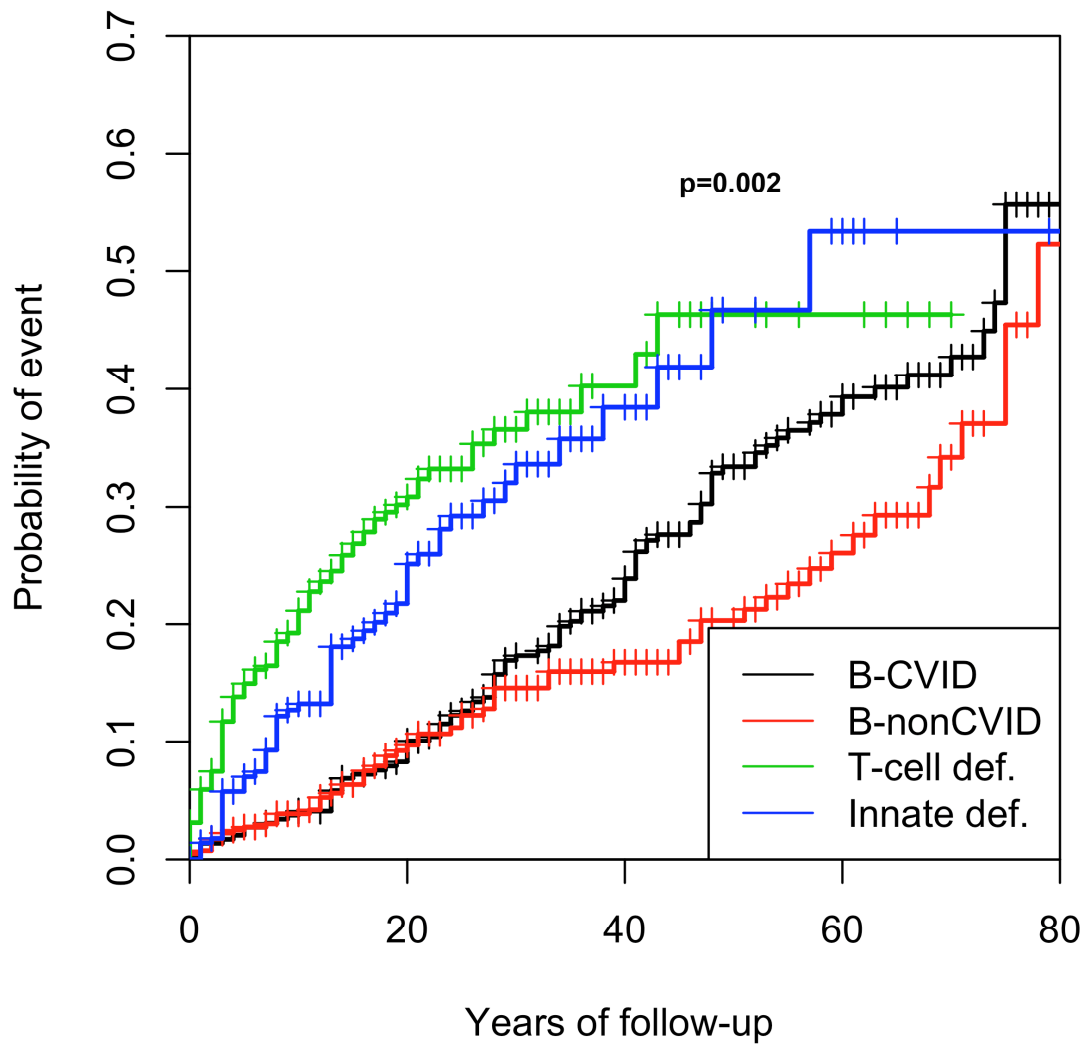
Supplementary Figure 2. Survival of PID patients with CVID (A), other B cell PIDs (B), T cell PIDs (C) and innate PIDs (D), as a function of the occurrence of autoimmunity/inflammation.

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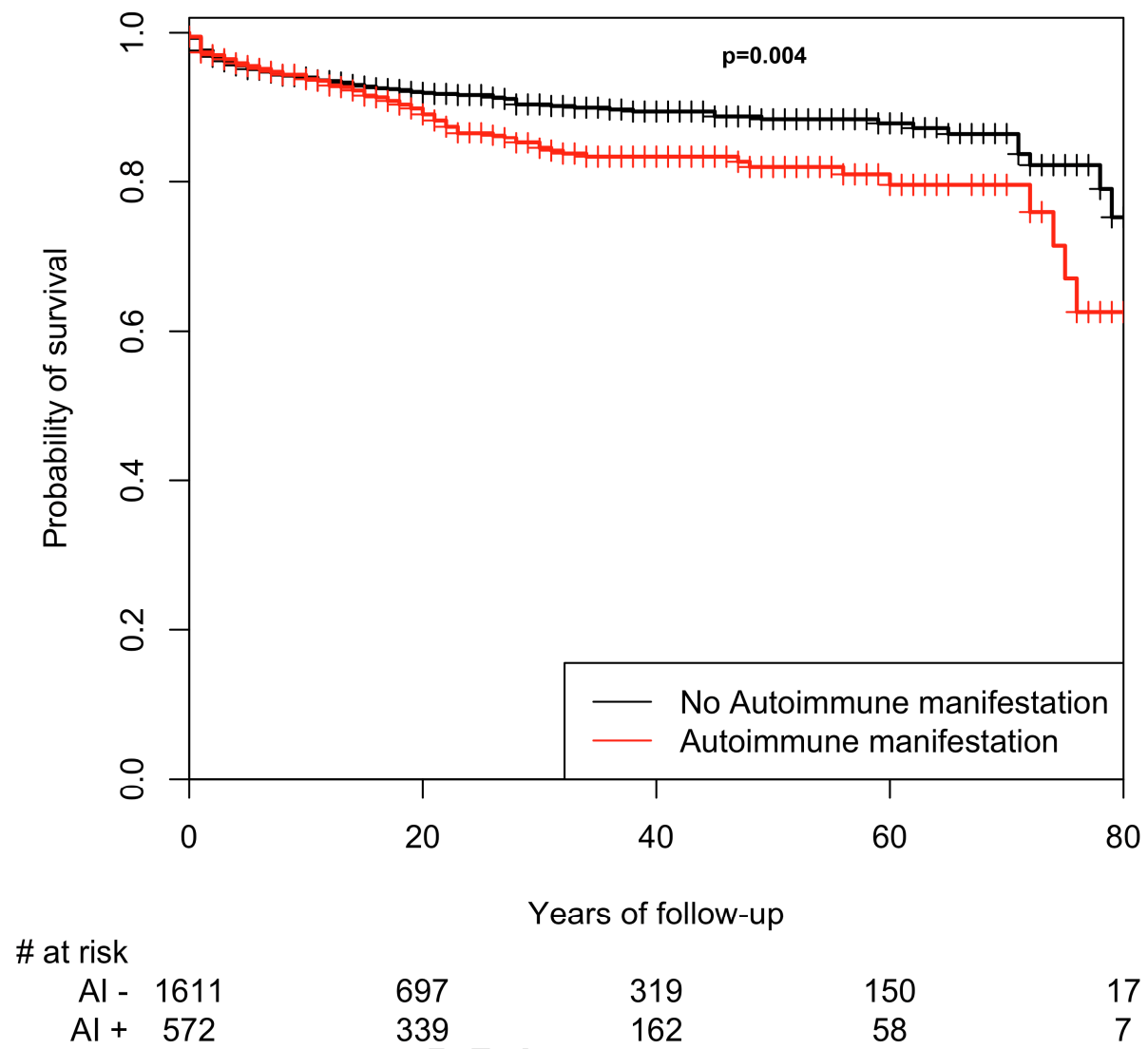
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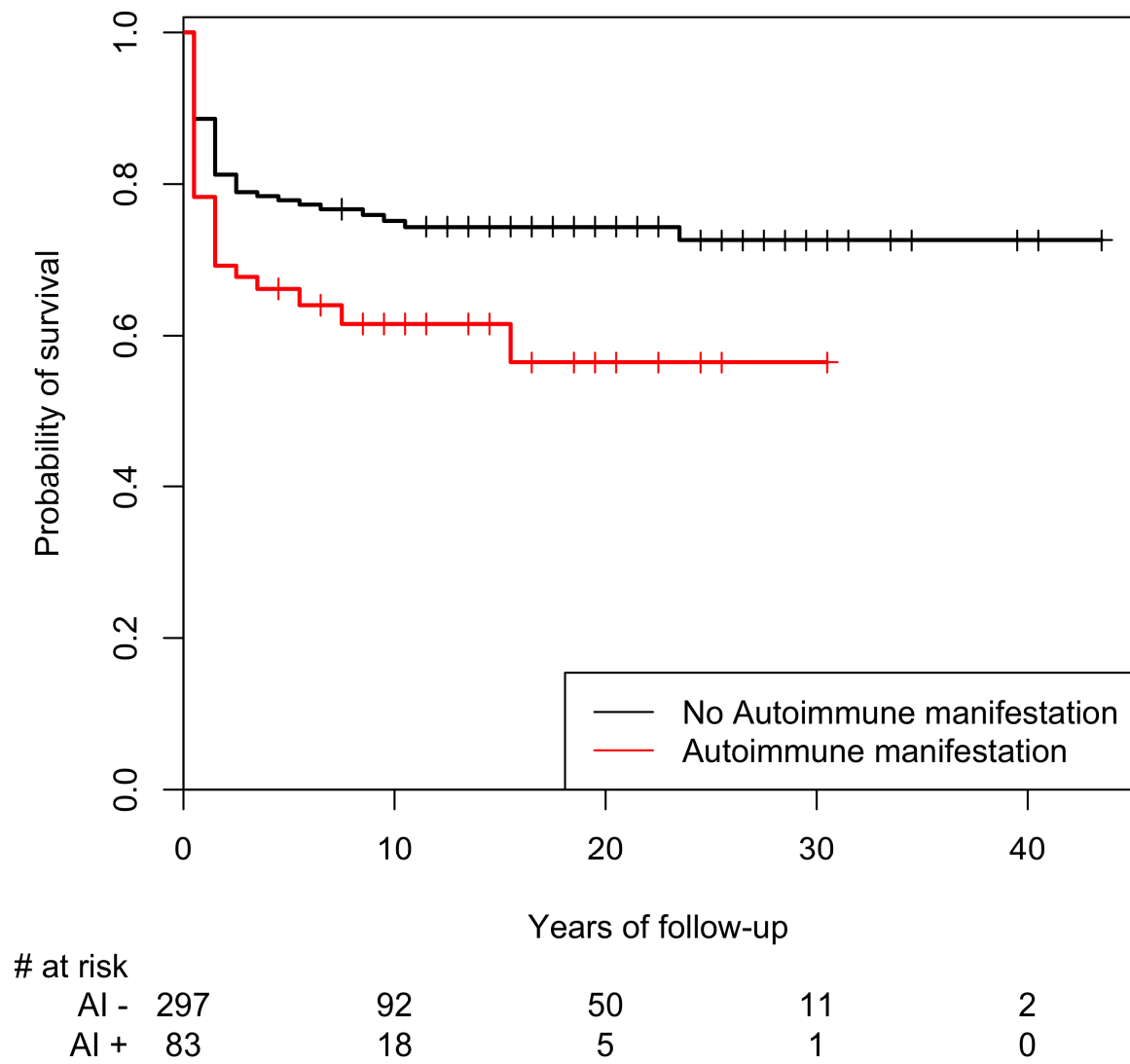
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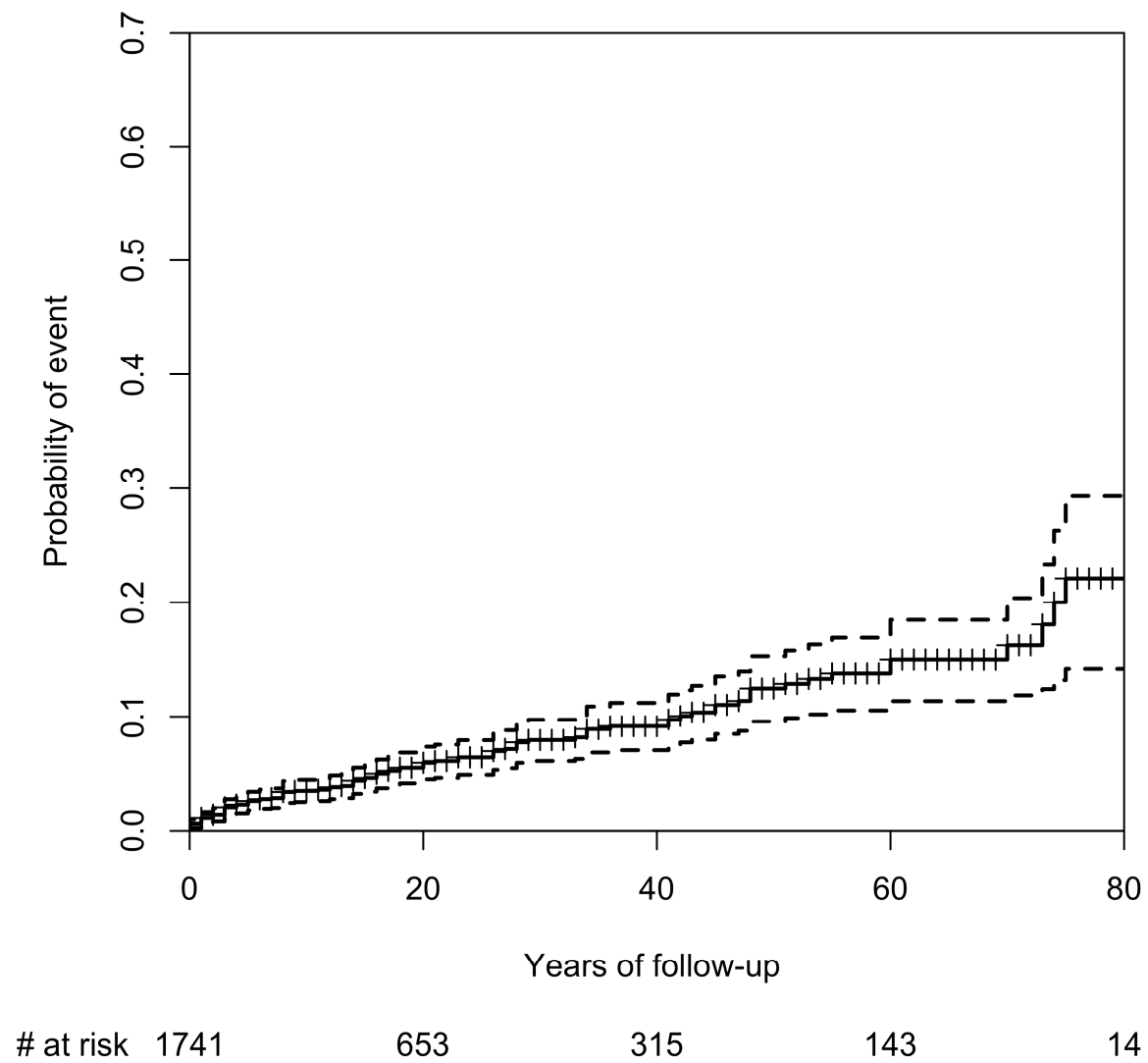


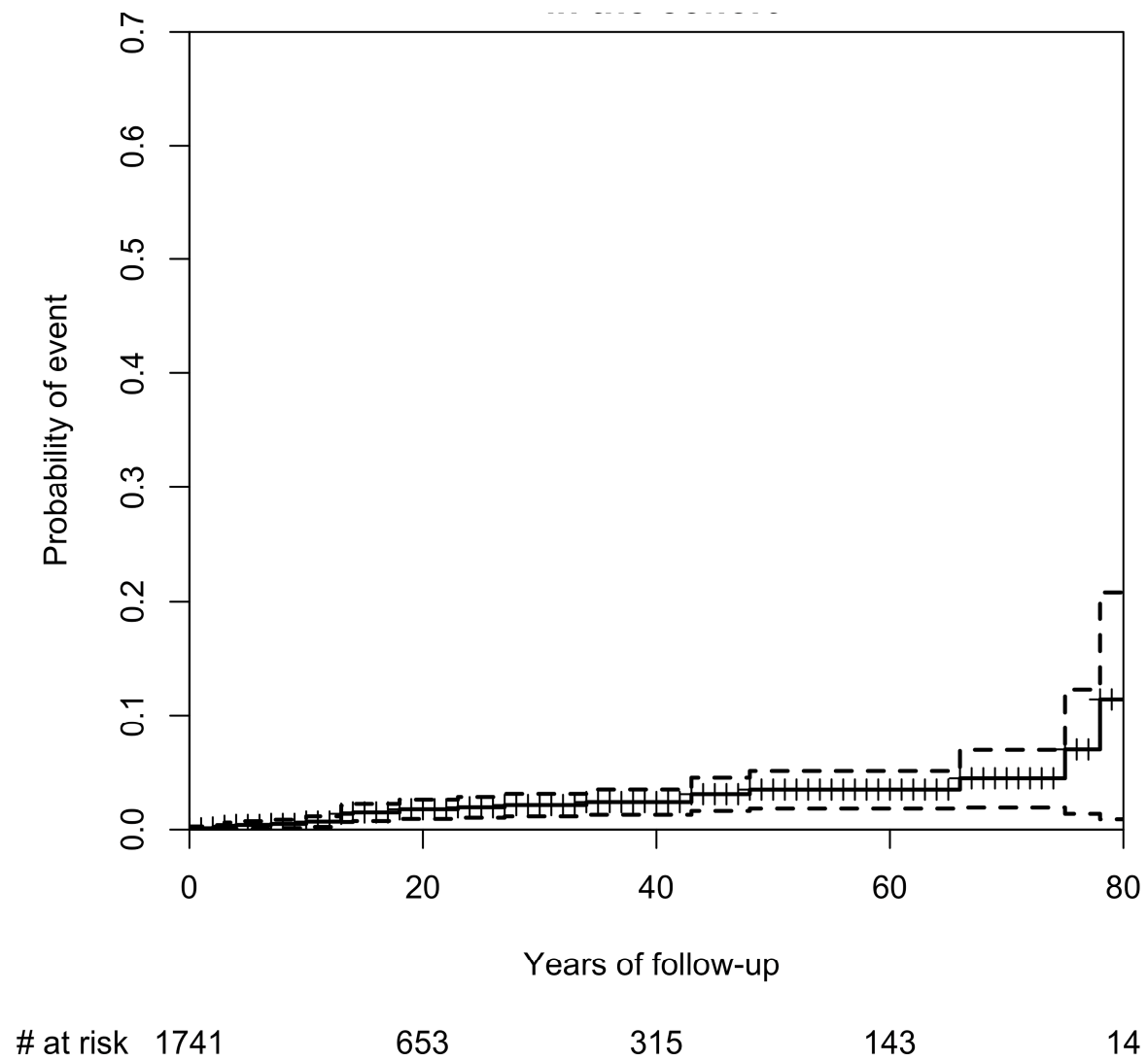


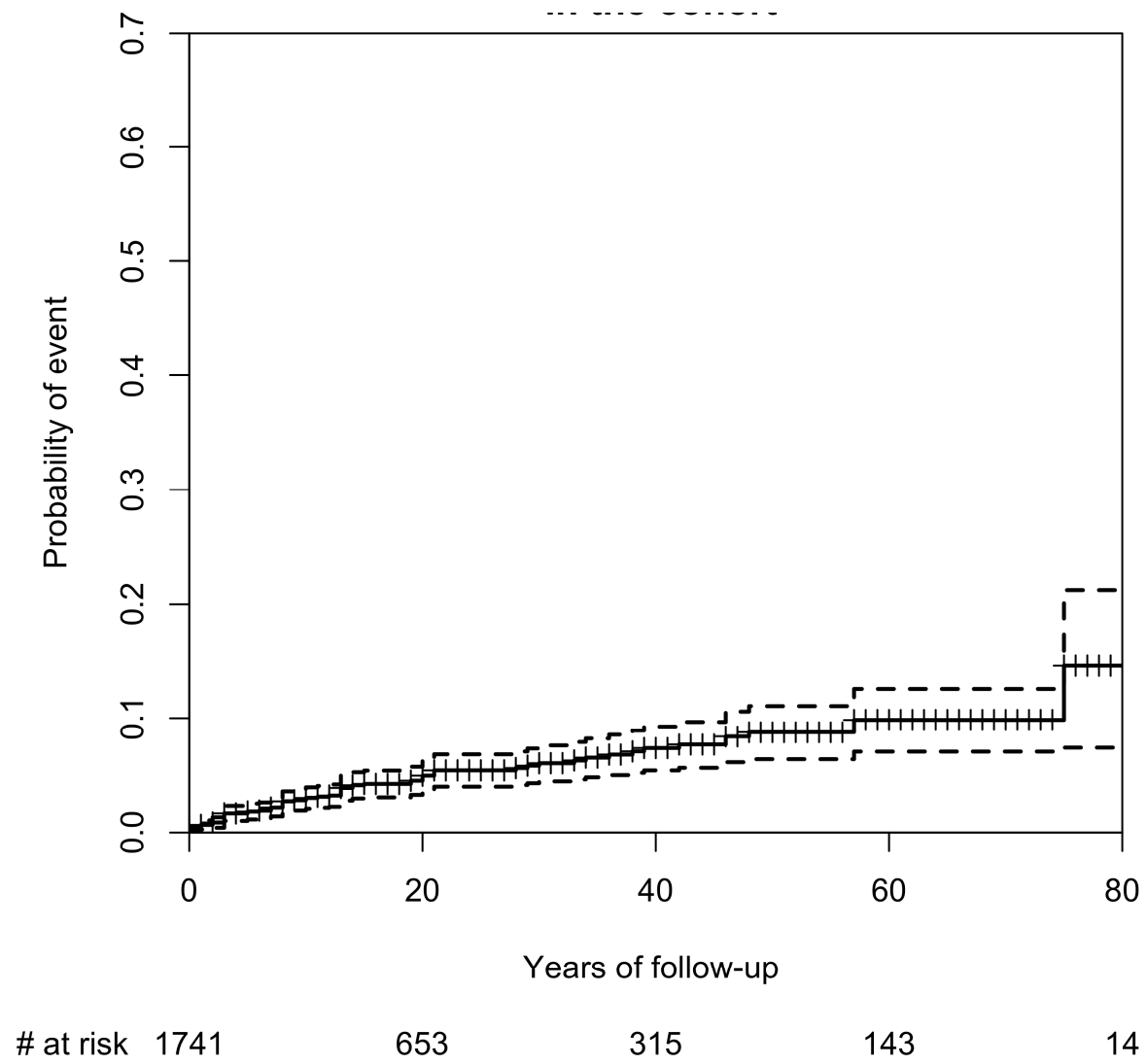
# at risk					
B-CVID	294	256	168	83	6
B-nonCVID	406	192	104	49	7
T-cell def.	675	104	22	5	0
Innate def.	288	93	21	6	1

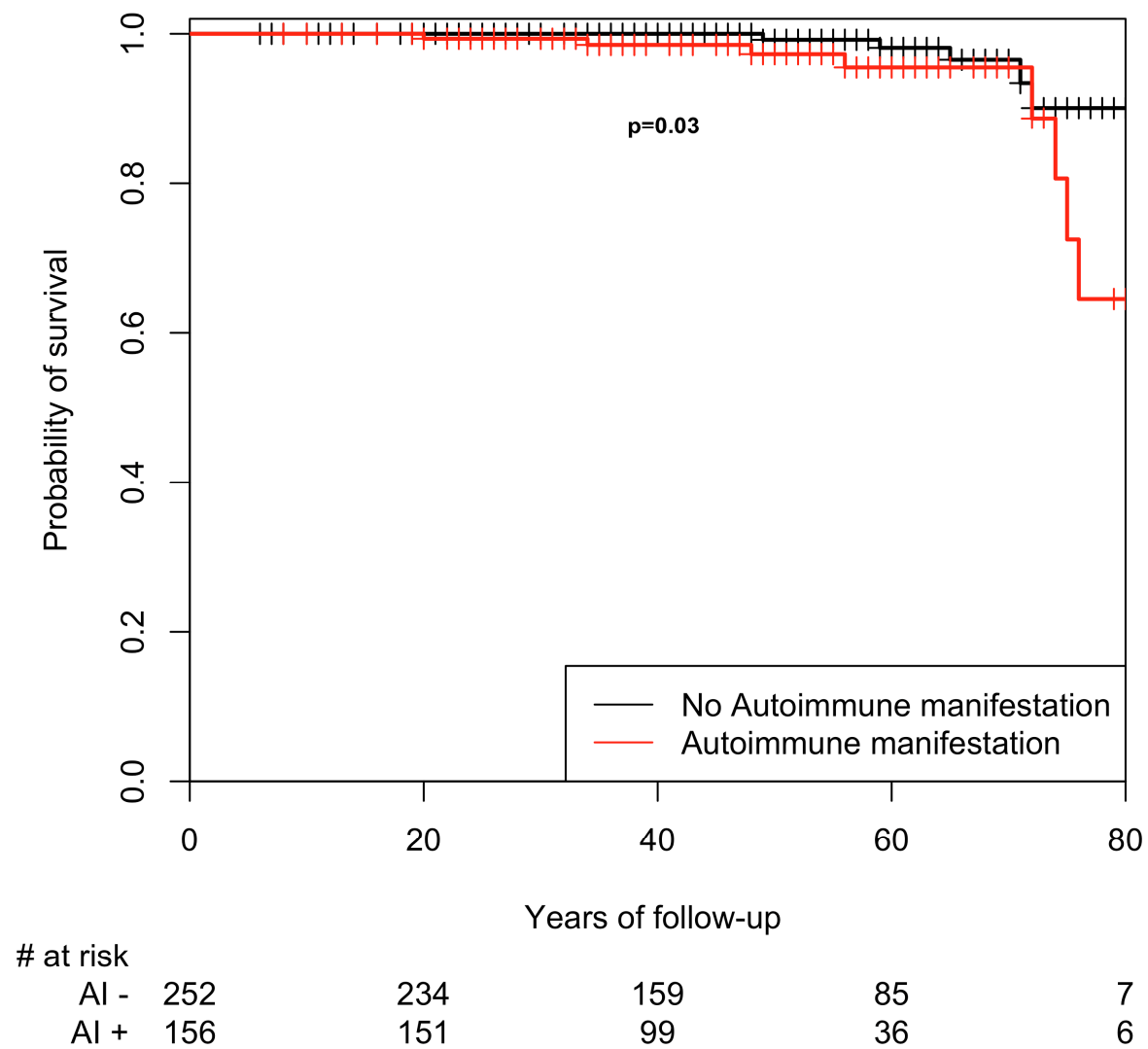


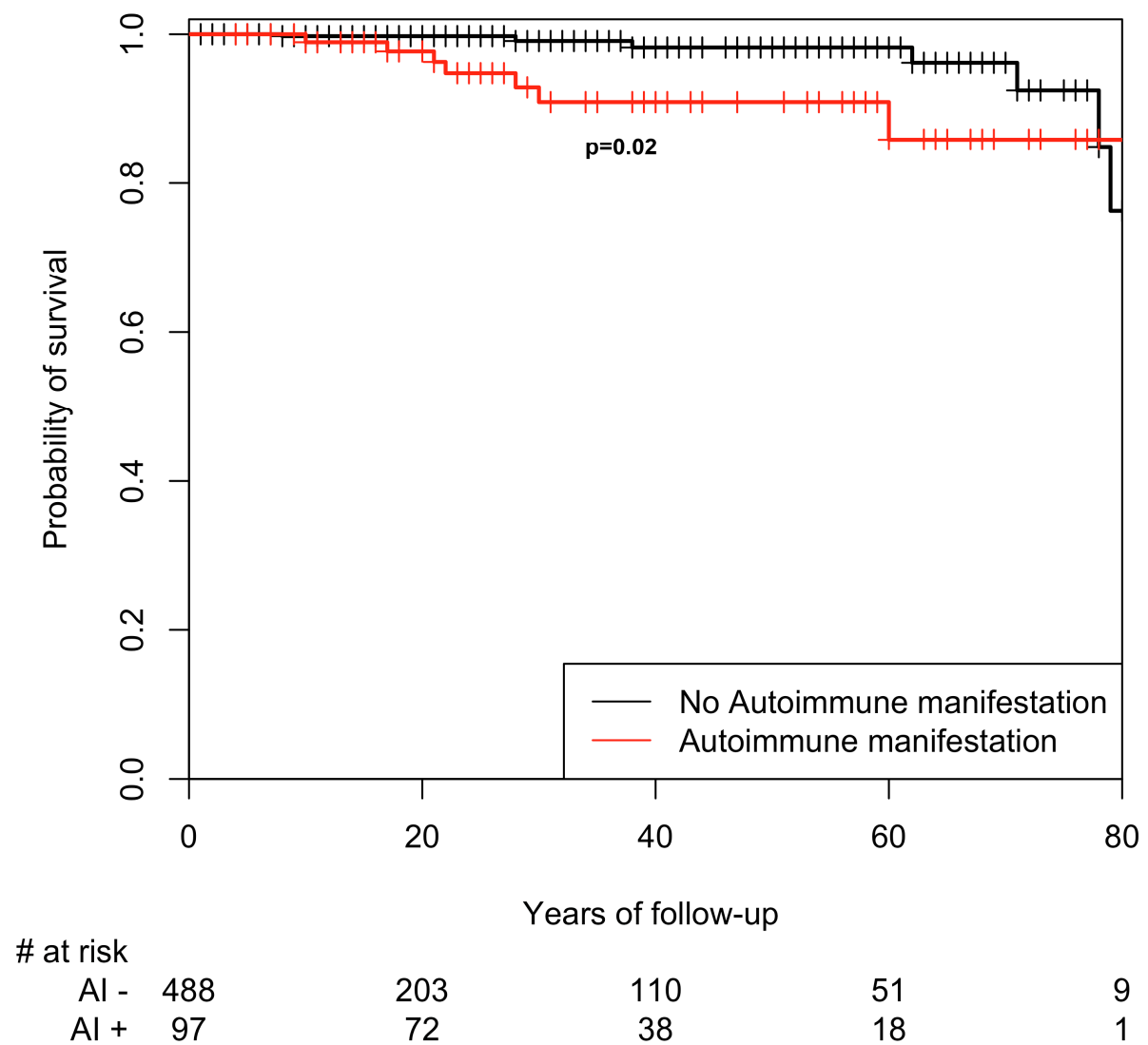


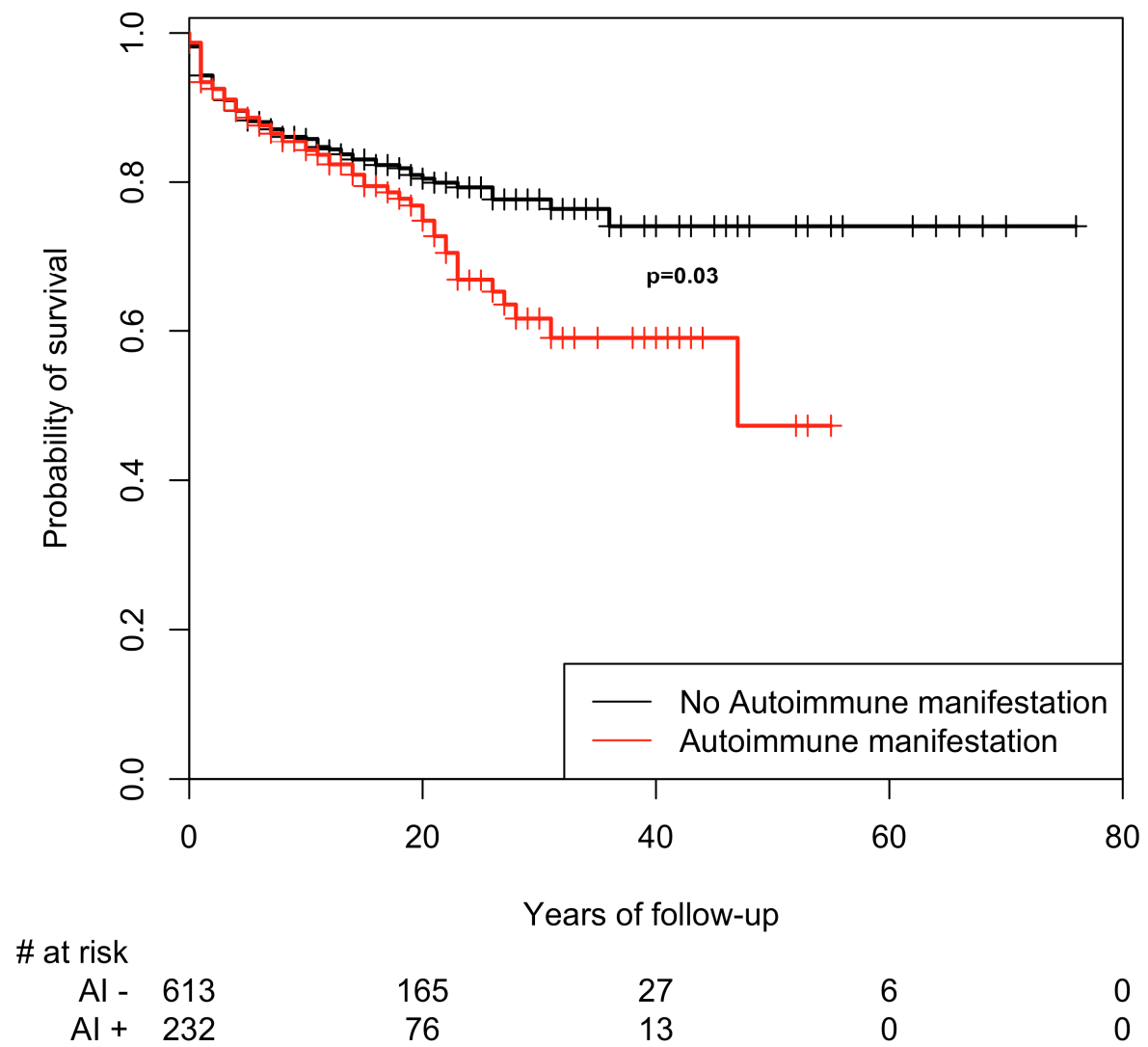


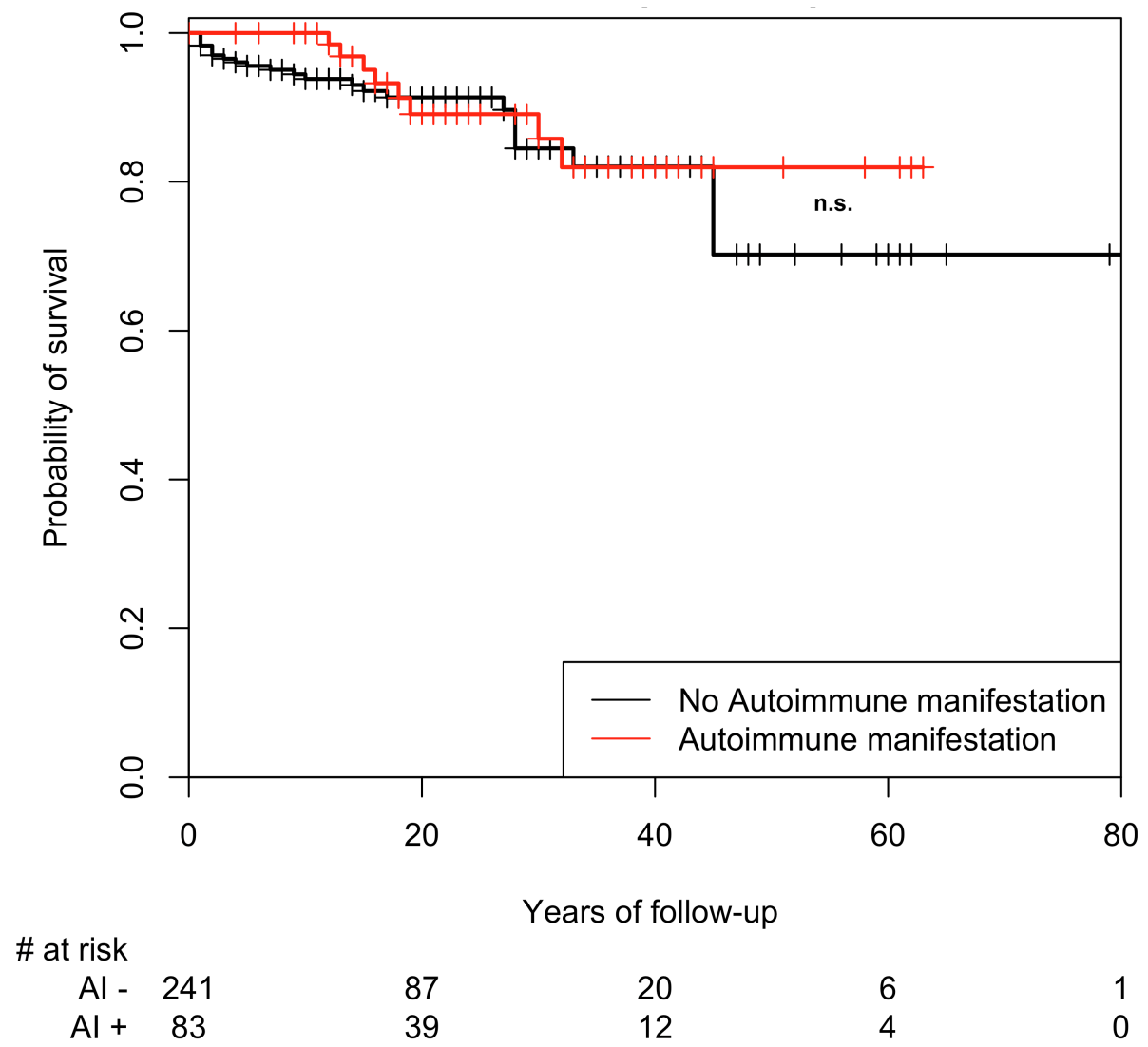












Supplementary Table 1. List of autoimmune and inflammatory manifestations reported in PID patients (ICD-10).

Cytopenia

Idiopathic thrombocytopenic purpura
Other autoimmune haemolytic anaemias
Agranulocytosis
Idiopathic aplastic anaemia
Acquired pure red cell aplasia [erythroblastopenia]

Rheumatologic disorders

Arthritis, unspecified
Polyarthritis, unspecified
Systemic lupus erythematosus, unspecified
Lupus erythematosus
Rheumatoid arthritis, unspecified
Other rheumatoid arthritis
Raynaud syndrome
Ankylosing spondylitis
Pain in joint
Sicca syndrome [Sjogren]

Endocrine disorders

Autoimmune thyroiditis
Insulin-dependent diabetes mellitus
Hypoparathyroidism

Skin

Psoriasis
Vasculitis limited to skin, unspecified
Vitiligo
Alopecia areata
Pemphigus, unspecified
Allergic purpura
Dermatopolymyositis
Granulomatous disorders of skin and subcutaneous tissue
Granuloma annulare
Panniculitis, unspecified

Gastrointestinal disorders

Autoimmune hepatitis
Coeliac disease
Vitamin B12 deficiency anaemia due to intrinsic factor deficiency
Primary biliary cirrhosis
Crohn disease, unspecified
Ulcerative (chronic) pancolitis
Crohn disease [regional enteritis]
Crohn disease of large intestine
Other specified diseases of intestine
Other specified noninfective gastroenteritis and colitis
Gastroenteritis and colitis of unspecified origin
Chronic atrophic gastritis
Other gastritis
Adult hypertrophic pyloric stenosis
Recurrent oral aphthae

Stomatitis and related lesions
 Ulcer of anus and rectum
 Anal fistula
 Granulomatous hepatitis, not elsewhere classified
 Liver disorders in other diseases classified elsewhere

Kidney

Glomerular disorders in blood diseases and disorders involving the immune mechanism
 Recurrent and persistent haematuria: Other
 Nephrotic syndrome
 Unspecified nephritic syndrome: Diffuse crescentic glomerulonephritis

Neurologic disorders

Myasthenia gravis
 Intracranial and intraspinal and granuloma in diseases classified elsewhere
 Progressive multifocal leukoencephalopathy
 Encephalitis, myelitis and encephalomyelitis, unspecified

Lung

Other interstitial pulmonary diseases
 Other interstitial pulmonary diseases with fibrosis
 Sarcoidosis, unspecified

Eyes

Focal chorioretinal inflammation
 Other endophthalmitis
 Keratitis
 Episcleritis

Vasculitis

Cerebral arteritis, not elsewhere classified
 Arteritis, unspecified
 Other giant cell arteritis

Systemic

Systemic Inflammatory Response Syndrome of non-infectious origin without organ failure

Urologic disorders

Inflammatory disorders of seminal vesicle

Other

Other osteomyelitis

Assessment of infection – independent skin manifestation among the different PID :

Skin manifestations	Frequency
Psoriasis	26
Vasculitis limited to skin, unspecified	24
Granulomatous disorders of skin and subcutaneous tissue	21
Vitiligo	16
Alopecia areata	13
Pemphigus, unspecified	1
Dermatitis, unspecified	1
Granuloma annulare	1
Panniculitis, unspecified	1

Supplementary Table 2. Comparison of the demographic characteristics of the study population and the overall registry population.

	Overall registry population		Study population		p value
	N patients	%	N patients	%	
Total	5952	100	2183	100	
Male gender	3378	56.8	1264	57.9	0.37
Age, median [Q1;Q3]	20 [10 ; 41]		20 [9 ; 38]		0.053
Main PID categories :					
Adaptive immunodeficiencies					
B-cell CVID	1171	19.7	408	18.7	0.34
Other (non-CVID) B-cell PIDs	1530	25.7	585	26.8	0.33
T-cell SCID	368	6.2	160	7.3	0.07
T-cell CID	931	15.6	334	15.3	0.73
Other T-cell PIDs	781	13.1	351	16.1	<0.01
Innate PIDs	1123	18.9	324	14.8	<0.01
Unclassified PIDs	48	0.8	21	1.0	0.59

Supplementary Table 3

Number of patients with autoimmune or inflammatory manifestations, by PID category								
PID category	Number of manifestations							Total
	0	1	2	3	4	5	6	
Agammaglobulinemia	88	7	3	0	0	0	0	98
Asplenia syndrome (Ivemark syndrome)	1	0	0	0	0	0	0	1
Ataxia telangiectasia (ATM)	55	12	3	0	0	0	0	70
Atypical Severe Combined Immunodeficiency (Atypical SCID)	8	4	1	0	0	0	0	13
Autoimmune lymphoproliferative syndrome (ALPS)	23	25	5	3	0	0	0	56
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	0	4	1	1	1	1	1	9
Barth syndrome	3	0	0	0	0	0	0	3
Bloom syndrome (RECQ2)	1	1	0	0	0	0	0	2
CARD9 deficiency	1	0	0	0	0	0	0	1
Cartilage hair hypoplasia	7	1	1	0	0	0	0	9
CCAAT/enhancer binding protein epsilon deficiency (CEBPE)	1	0	0	0	0	0	0	1
CD8 deficiency	2	1	0	0	0	0	0	3
Chediak-Higashi syndrome	11	0	0	0	0	0	0	11
Chronic granulomatous disease (CGD)	47	32	12	3	2	0	0	96
Chronic mucocutaneous candidiasis (CMC)	14	5	0	0	0	0	0	19
Clericuzio-type poikiloderma with neutropenia syndrome	0	1	0	0	0	0	0	1
COHEN syndrome	0	0	1	0	0	0	0	1
Combined immunodeficiency (CID)	75	20	14	6	0	1	0	116
Common variable immunodeficiency disorders (CVID)	252	110	28	14	4	0	0	408
Complement component 2 deficiency	7	2	0	1	0	0	0	10
Complement component 4 deficiency	1	2	1	1	0	0	0	5
Complement component 5 deficiency	4	0	0	0	0	0	0	4
Complement component 6 deficiency	5	0	0	0	0	0	0	5
Complement component 7 deficiency	1	1	0	0	0	0	0	2
Complement component 9 deficiency	1	0	0	0	0	0	0	1
Congenital neutropenia	42	7	1	0	0	0	0	50
Congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD)	2	0	0	0	0	0	0	2
CSR defects and hyper IgM (HIGM) syndromes	29	6	1	0	0	0	0	36
Cyclic neutropenia	12	1	0	0	1	0	0	14
Defects of TLR/NFkappa-B signaling	2	0	0	0	0	0	0	2
Defects with susceptibility to mycobacterial infection (MSMD)	13	1	1	0	0	0	0	15
Deficiency of specific IgG (Specific antibody deficiency - SPAD)	6	0	0	1	0	0	0	7
DiGeorge syndrome (DGS)	24	9	1	4	0	0	0	38
Dyskeratosis congenita	4	0	0	0	0	0	0	4
Early-onset inflammatory bowel disease	3	1	0	0	0	0	0	4
Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS)	10	0	0	0	0	0	0	10
Factor I deficiency	3	0	0	0	0	0	0	3
Familial hemophagocytic lymphohistiocytosis syndromes (FHLH)	47	0	0	1	0	0	0	48
FOXP3 deficiency (IPEX)	0	9	2	3	3	1	0	18
Glycogen storage disease type 1b (GS1b)	2	0	0	0	0	0	0	2

Griscelli syndrome, type 2	6	1	0	0	0	0	0	7
Herpetic encephalitis (HSE)	6	0	0	0	0	0	0	6
HLA class II deficiency	19	6	0	0	0	0	0	25
Hoyeraal-Hreidarsson syndrome	2	1	0	0	0	0	0	3
Hyper IgE syndrome (HIES)	53	2	0	0	0	0	0	55
IgA with IgG subclass deficiency	4	5	1	1	0	0	0	11
Immunodeficiencies with multiple intestinal atresias	1	0	0	0	0	0	0	1
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	4	1	0	0	1	0	0	6
Infancy onset STING-associated vasculopathy	1	0	1	0	0	0	0	2
Interleukin 2 receptor alpha deficiency (CD25) (IPEX phenotype)	0	0	0	0	1	0	0	1
IPEX-like disease	0	0	1	0	0	0	0	1
Isolated congenital asplenia	25	0	0	0	0	0	0	25
Isolated IgG subclass deficiency	207	22	5	0	0	0	0	234
Leukocyte adhesion deficiency (LAD)	6	0	0	0	0	0	0	6
Monocytopenia and mycobacterial infection (MonoMAC)	1	1	1	0	0	0	0	3
Omenn syndrome	22	2	0	0	0	0	0	24
Other autoinflammatory diseases with known genetic defect	0	3	0	0	0	0	0	3
Properdin P factor complement deficiency (PFC)	2	0	0	0	0	0	0	2
Pulmonary alveolar proteinosis	1	0	0	0	0	0	0	1
Ras associated lymphoproliferative disease (RALD)	0	1	0	0	0	0	0	1
Schimke disease	2	0	0	0	0	0	0	2
Seckel syndrome	0	0	0	0	0	0	0	0
Selective CD4 cell deficiency	5	0	0	0	0	0	0	5
Selective IgA deficiency (symptomatic)	39	8	0	0	0	0	0	47
Selective IgM deficiency	4	0	0	0	0	0	0	4
Severe combined immunodeficiency (SCID)	126	8	1	0	0	0	0	135
Shwachman-Diamond-syndrome	29	2	0	0	0	0	0	31
Steinert-Myotonia Dystrophia	0	2	0	0	0	0	0	2
Thymoma with immunodeficiency	11	5	1	0	0	0	0	17
Trichohepatoenteric syndrome	1	0	0	0	0	0	0	1
Unclassified antibody deficiency	122	20	7	3	3	0	0	155
Unclassified complement deficiencies	1	0	0	0	0	0	0	1
Unclassified defects in innate immunity	4	2	0	0	0	0	0	6
Unclassified disorders of immune dysregulation	2	3	2	1	2	1	0	11
Unclassified immunodeficiencies	17	3	0	0	0	0	0	20
Unclassified phagocytic disorders	2	1	0	0	0	0	0	3
Unclassified syndromic immunodeficiencies	0	0	1	0	0	0	0	1
Warts hypogammaglobulinemia infections and myelokathexis (WHIM)	2	0	0	0	0	0	0	2
Warts, immunodeficiency, lymphedema, dysplasia (WILD) syndrome	1	0	0	0	0	0	0	1
Winged-helix nude deficiency (FOXN1)	1	0	0	0	0	0	0	1
Wiskott Aldrich syndrome (WAS)	50	26	11	1	2	0	0	90
X-linked lymphoproliferative syndrome (XLP)	22	5	5	0	0	0	0	32
Unclassified	1	0	0	0	0	0	0	1

Supplementary table 4. Distribution of major autoimmune/inflammatory manifestations among the main groups of PIDs**a)**

	Overall nb of patients in the study cohort	Cytopenia %	Gastrointestinal manifestations %	Rheumatologic manifestations %
1.Adaptive Immunity B-cell deficiencies CVID	408	16.7	10.0	5.4
2.Adaptive Immunity B-cell deficiencies non-CVID	585	3.9	4.4	4.3
3.Adaptive Immunity T-cell deficiencies SCID	160	3.1	1.3	0.6
4.Adaptive Immunity T-cell deficiencies CID	424	14.6	5.9	6.6
5.Adaptive Immunity Other T-cell deficiencies	261	19.2	14.6	3.1
6.Innate Immunity Deficiencies	324	2.8	15.4	4.9
7.Unclassified PID	21	4.8	9.5	0.0

b) Detailed description**PID**

Agammaglobulinemia	98	2.0	6.1	1.0
ALPS	56	53.6	5.4	1.8
APECED	9	22.0	44.4	11.1
Asplenia	26	0.0	0.0	0.0
Ataxia Telangiectasia and Other DNA-breakage disorders	78	3.8	5.1	2.6
Autoimmune and Immune Dyreg	19	36.8	26.3	5.3
CGD	96	1.0	44.8	2.1
CHS	11	0.0	0.0	0.0
CID	256	13.3	7.8	5.9
Complement	33	3.0	0.0	21.2
CSR defects and HIgM syndromes	10	20.0	0.0	10.0
CVID	408	16.7	9.6	5.4
FHLH	48	2.1	2.1	0.0
GS2	7	14.3	0.0	0.0
HIES	55	0.0	1.8	0.0
HSE	7	0.0	0.0	0.0
Hypogammaglobulinemia	477	4.0	3.8	4.8
IPEX	24	33.3	66.7	4.2
LAD	6	0.0	0.0	0.0
MonoMAC	4	25.0	0.0	0.0
MSMD	15	0.0	0.0	6.7
Other Innate	24	0.0	8.3	0.0
Other Phagocytic and Innate Immunity disorders	9	0.0	11.1	0.0
SCID	160	3.1	1.3	0.6
SCN	104	5.8	3.8	5.8
Unclassified	21	4.8	9.5	0.0
WAS	90	27.8	1.1	12.2
XLP	32	3.1	18.8	12.5

Supplementary Table 5**List of allergies encountered in PID patients**

In bold, the grouping of detailed ALLERGIC manifestations according to the localization, affected organ or system [ICD10 labels].

Allergic respiratory manifestations

Asthma

Respiratory disorder, unspecified

Allergic rhinitis, unspecified

Allergic rhinitis due to pollen

Allergic skin manifestations

Dermatitis, unspecified

Other atopic dermatitis

Allergic digestive manifestations

Allergic and dietetic gastroenteritis and colitis

Allergic urticaria

Malabsorption due to intolerance, not elsewhere classified

Other adverse food reactions, not elsewhere classified

Other allergic manifestations

Allergy, unspecified

Anaphylactic shock, unspecified

Conjunctivitis

Unspecified adverse effect of drug or medicament

Desensitization to allergens