

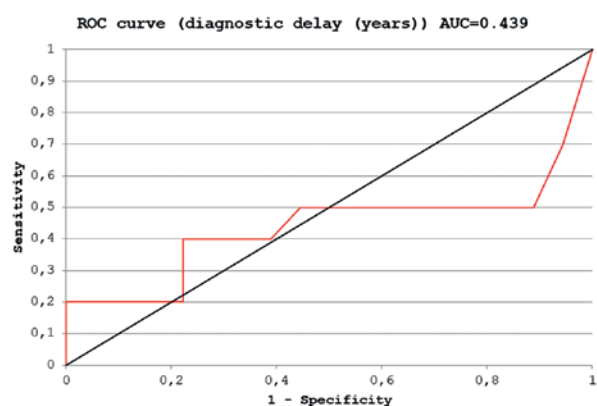
Supplementary material

This supplementary file provides detailed clinical data supporting the main text, including stratification of patients by clinical phenotype, diagnostic delay, immunodeficiency subtype, and outcome.

Supplementary Table 1. Clinical characteristics of patients according to diagnostic delay

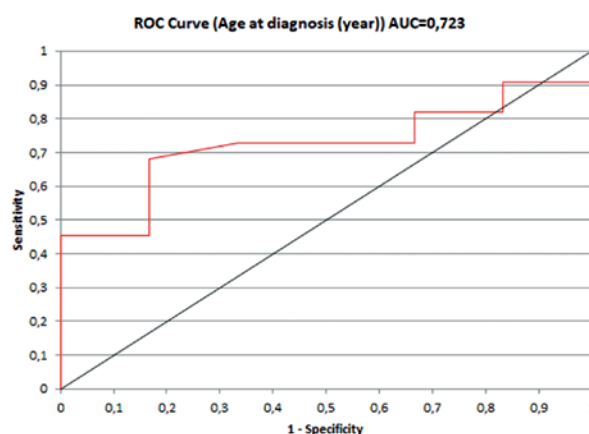
Parameter	Diagnosis within 6 years (<i>n</i> = 13)	Diagnosis over 6 years (<i>n</i> = 15)	<i>p</i> values
Childhood onset, <i>n</i> (%)	3 (23.07)	7 (46.67)	0.2543
Female patients, <i>n</i> (%)	4 (33.77)	10 (66.67)	0.1284
Recurrent infections, <i>n</i> (%)	10 (76.92)	15 (100.0)	0.0873
Morphological lung abnormalities, <i>n</i> (%)	10 (76.92)	9 (60.0)	0.4348
Lymphoproliferation, <i>n</i> (%)	5 (38.46)	6 (40.0)	1
Autoimmunity, <i>n</i> (%)	5 (38.46)	5 (33.33)	1
Granulomatosis, <i>n</i> (%)	0 (0)	4 (26.67)	0.1016
Malignancy, <i>n</i> (%)	3 (23.07)	5 (33.33)	0.6860

[†] *n* – number of patients. **p* > 0.05 indicates no significant difference



Supplementary Fig. 1. ROC analysis of diagnostic delay

Probability distributions is depicted as a red line (–). When all non-infectious manifestations were considered together as features of immune dysregulation, we did not find a diagnostic delay which significantly differed between those with only infectious complications and those with other manifestations (ROC analysis – AUC: 0.4389, *p* = 1.3366)



Supplementary Fig. 2. ROC analysis of age as a discriminator of immune dysregulation manifestations among patients with primary immunodeficiency

Probability distributions is depicted as a red line (–). At the age of 41, the sensitivity was 68.2% and the specificity 83.3%, AUC: 0.723, *p* = 0.0249

Supplementary data about flow cytometry

Flow cytometry data: Although we found higher cell numbers in the unPAD group (for lymphocyte count: 1608.00 vs. 2353.714, for CD3+: 1311.40 vs. 1900.29, for CD4+: 753.50 vs. 911.14, for CD8+: 537.90 vs. 979.71, for CD19+: 111.00 vs. 130.57, $p > 0.05$), this was not statistically significant in any of the examined lymphocyte subgroups (the study is based on data from 21 patients (75%); the others did not have flow cytometry at diagnosis). Among patients with available CD19+CD27+IgD– B cell data, several were diagnosed with CVID due to low cell numbers; however, only a limited number of patients with unPAD had available data, and therefore statistical analysis could not be performed.

Supplementary Table 2. Detailed clinical data for all patients in the cohort

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG* (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ IgD- B cells (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immuno-suppressive therapy
1	Male	Adult	1	75	Yes		Basal cell carcinoma Temporal arteritis Pulmonary fibrosis	2.71	118	46	66	13	No data were available	Effective	CID*	Corticosteroid
2	Male	Adult	2	58	No	Malignancy	Recurrent infections: upper respiratory Inclusion body myositis, Antiphospholipid syndrome Mucinous adenocarcinoma of the cecum, Lymphadenopathy Pulmonary fibrosis	4.96	348	298	89	52	No data were available	No data were available	CID	Corticosteroid
3	Female	Adult	25	45	Yes		Recurrent infections: upper and lower respiratory, gastrointestinal infections Autoimmune gastritis Neuroendocrine tumour Bronchiolitis, pulmonary cavity	6.4	630	315	232	41	8.1	Effective	CID	No
4	Male	Adult	1	76	Yes		Recurrent infections: upper and lower respiratory Chronic inflammatory demyelinating polyneuropathy Glioblastoma multiforme Pulmonary fibrosis	2.48	1518	1334	166	147	1.0	Ineffective	CVID*	Corticosteroid

Supplementary Table 2. Cont.

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG ⁺ (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ IgD- B cells (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immuno-suppressive therapy
5	Male	Adult	7	53	Yes		Recurrent infections: upper and lower respiratory Pulmonary Inflammatory sequelae	0.17	1560	526	1034	66	2.7	Effective	CVID	No
6	Male	Childhood	27	32	Yes		Recurrent infections: upper and lower respiratory Genitourinary infections Splenomegaly Eczematous dermatitis Diarrhoea with weight loss	1.39	1414	724	622	208	0.6	Effective	CVID	No
7	Female	Childhood	12	17	Yes		Recurrent infections: upper and lower respiratory, genitourinary, gastrointestinal infections Enteropathy Leukoderma	1.99	No data were available	No data were available	No data were available		0.4	Ineffective	CVID	No
8	Male	Adult	27	55	Yes		Recurrent infections: upper respiratory Gastrointestinal infections Pulmonary sarcoidosis Hepatomegaly, splenomegaly, lymphadenopathy	1.43	819	598	217	7	Not detectable	Ineffective	CVID	Corticosteroid, azathioprine

Supplementary Table 2. Cont.

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG* (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immunosuppressive therapy
9	Female	Childhood	54	59	Yes		Recurrent infections: upper and lower respiratory, gastrointestinal infections, Immune-mediated thrombocytopenia, Autoimmune haemolytic anaemia, Pulmonary inflammatory sequelae	0.23	1103	609	491	31	0.5	Effective	CVID	Corticosteroid, rituximab
10.	Female	Childhood	13	18	Yes		Recurrent infections: upper and lower respiratory Gastrointestinal infections Positive family history Eczematous dermatitis	1.6	1139	541	566	69	0.5	Ineffective	CVID	No
11.	Female	Adult	18	41	Yes		Recurrent infections: upper and lower respiratory Gastrointestinal infections Bronchiectasis, pulmonary fibrosis Diarrhoea with weight loss	1.37	735	446	294	64	1.2	Ineffective	CVID	No

Supplementary Table 2. Cont.

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG ⁺ (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ IgD- B cells (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immunosuppressive therapy
12	Female	Adult	6	34	Yes		Recurrent infections: upper and lower respiratory Gastrointestinal infections	0.07	1885	1076	786	88	6.0	Effective	CVID	No
13	Male	Adult	2	46	Yes		Autoimmune encephalitis Pulmonary fibrosis Cheilitis, dermatitis	0.07	1513	961	552	130	4.6	No data were available	CVID	Corticosteroid
14	Male	Adult	39	59	Yes		Recurrent infections: upper and lower respiratory infections Prostate adenocarcinoma Pulmonary fibrosis and inflammatory sequelae	4.87	1428	720	651	273	5.2	Effective	CVID	No
15	Female	Adult	12	52	No	Malignancy	Recurrent infections: upper and lower respiratory Gastrointestinal infections Autoimmune gastritis Diffuse large B cell lymphoma Lymphadenopathy, hepatomegaly, splenomegaly Enteropathy	0.66	1628	832	722	323	No data were available	No data were available	unPAD*	Corticosteroid, rituximab

Supplementary Table 2. Cont.

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG* (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ B cells (% of B cells)	Responses against COVID-19* vaccination	PID subgroup based on ESID* criteria	Immunosuppressive therapy
16	Male	Adult	1	64	No	Heart failure	Recurrent infections: upper respiratory Cutaneous vasculitis Atelectasis	5.01	No data were available	No data were available	No data were available	No data were available	No data were available	No data were available	unPAD	Corticosteroid
17	Female	Adult	1	48	No	Cirrhosis	Recurrent infections: upper and lower respiratory Hepatomegaly, splenomegaly Cirrhosis Pulmonary fibrosis and inflammatory sequelae, bronchiectasis	1.99	No data were available	No data were available	No data were available	No data were available	No data were available	No data were available	unPAD	No
18	Female	Childhood	8	23	Yes		Recurrent infections: upper and lower respiratory, Erythema nodosum, Splenomegaly, lymphadenopathy	0.33	No data were available	No data were available	No data were available	No data were available	No data were available	No data were available	unPAD	No
19	Female	Childhood	14	17	No	Unknown	Recurrent infections: upper and lower respiratory Invasive ductal carcinoma Pulmonary fibrosis	2.8	No data were available	No data were available	No data were available	No data were available	No data were available	No data were available	unPAD	No
20.	Female	Childhood	65	70	Yes		Recurrent infections: upper and lower respiratory Chronic motor axonal neuropathy Pulmonary fibrosis	4.55	2332	1565	708	102	16.5	Effective	unPAD	No

Supplementary Table 2. Cont.

Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG ⁺ (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ IgD- B cells (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immuno-suppressive therapy
21.	Female	Adult	5	74	Yes		Recurrent infections: upper and lower respiratory Pulmonary fibrosis, Alveolitis	5.3	No data were available	No data were available	No data were available	No data were available	19.1	Effective	unPAD	Corticosteroid
22.	Male	Adult	53	73	No	Malignancy	Recurrent infections: upper and lower respiratory, gastrointestinal, Hepatocellular carcinoma Cutaneous sarcoidosis, Granulomatous colitis lymphadenopathy, hepatomegaly, splenomegaly Positive family history Enteropathy, cirrhosis Pulmonary inflammatory sequelae, bronchiectasis	0.18	2617	596	1912	43	No data were available	No data were available	unPAD	Corticosteroid

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Patient	Sex	Disease onset	Disease duration	Age at diagnosis	Alive	Cause of death	Clinical manifestations	IgG* (g/l)	CD3+ T count (984-1984/ul)	CD4+ T count (643-1175/ul)	CD8+ T count (336-876/ul)	CD19+ B-cell count (97-399/ul)	CD27+ IgD- B cells (% of B cells)	Responses against COVID-19* vaccination	PID* subgroup based on ESID* criteria	Immuno-suppressive therapy
23	Female	Adult	19	41	Yes		Recurrent infections: upper and lower respiratory, gastrointestinal, Myasthenia gravis Granulomatous lesion on the face Lymphadenopathy Diarrhoea with weight loss	2.72	1253	1044	365	191	16.9	There was no vaccination	unPAD	Corticosteroid Mycophenolate mofetil
24	Female	Childhood	4	9	Yes		Recurrent infections: upper respiratory, gastrointestinal	5.29	1096	642	458	127	No data were available	No data were available	unPAD	No
25	Male	Adult	4	29	Yes		Recurrent infections: upper and lower respiratory Lymphadenopathy Bronchiectasis, bronchiolitis obliterans	1.29	2732	1106	1499	49	No data were available	She was not vaccinated	unPAD	No
26	Male	Adult	3	47	Yes		Low Ig levels detected during investigation of Raynaud's phenomenon humoral immune response did not develop to HBV* vaccination, objective sicca complaints, allergy, diarrhoea/weight loss	3.4	1644	593	1194	79	No data were available	Effective	unPAD	No

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27	Male	Childhood	5	6	Yes		Recurrent infections: upper and lower respiratory, Gastrointestinal, IBD*-like disease Pulmonary fibrosis and inflammatory sequelae, bronchiectasis	2.51	No data were available	No data were available	No data were available	No data were available	No data were available	There was no vaccination	Hyper-IgM syndrome	Corticosteroid
28	Male	Childhood	2	2	Yes		Recurrent infections: upper and lower respiratory, Gastrointestinal Bronchiectasis, chronic bronchitis	1.4	No data were available	No data were available	No data were available	No data were available	No data were available	There was no vaccination	XLA*	No

CID – combined immunodeficiency, COVID-19 – coronavirus disease 2019, CVID – common variable immunodeficiency, ESID – European Society for Immunodeficiencies, HBV – hepatitis B virus, IBD – inflammatory bowel disease, IgG – immunoglobulin G, PID – primary immunodeficiency disorder, unPAD – unclassified primary antibody deficiency, XLA – X-linked agammaglobulinaemia