Clinical picture and treatment of 2212 patients with common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) is an antibody deficiency with an equal sex distribution and a high variability in clinical presentation. The main features include respiratory tract infections and their associated complications, enteropathy, autoimmunity, and lymphoproliferative disorders.
Objective: This study analyzes the clinical presentation, association between clinical features, and differences and effects of immunoglobulin treatment in Europe.
Methods: Data on 2212 patients with CVID from 28 medical centers contributing to the European Society for Immunodeficiencies Database were analyzed retrospectively.
Results: Early disease onset (<10 years) was very frequent in our cohort (33.7%), especially in male subjects (39.8%). Male subjects with early-onset CVID were more prone to pneumonia and less prone to other complications suggesting a distinct disease entity. The diagnostic delay of CVID ranges between 4 and 5 years in many countries and is particularly high in subjects with early-onset CVID. Enteropathy, autoimmunity, granulomas, and splenomegaly formed a set of interrelated features, whereas bronchiectasis was not associated with any other clinical feature. Patient survival in this cohort was associated with age at onset and age at diagnosis only. There were different treatment strategies in Europe, with considerable differences in immunoglobulin dosing, ranging from 130 up to 750 mg/kg/mo. Patients with very low trough levels of less than 4 g/L had poor clinical outcomes, whereas higher trough levels were associated with a reduced frequency of serious bacterial infections.
Conclusion: Patients with CVID are being managed differently throughout Europe, affecting various outcome measures. Clinically, CVID is a truly variable antibody deficiency syndrome. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Common variable immunodeficiency, immunoglobulin replacement, patient self-reported outcomes, quality of life, primary antibody deficiency, autoimmunity, enteropathy, granulomas, lymphadenopathy, treatment*

Abbreviations used
CVID: Common variable immunodeficiency
ESID: European Society for Immunodeficiencies
IQR: Interquartile range
IVIG: Intravenous immunoglobulin
PAGID: Pan-American Group for Immunodeficiency
SCIG: Subcutaneous immunoglobulin

Common variable immunodeficiency (CVID) forms a heterogeneous group of disorders characterized by impaired antibody provision. It is the most frequent clinically symptomatic primary antibody disorder, with a prevalence of approximately 1:50,000 to 1:25,000. In most patients with CVID, the genetic cause remains undefined. Several genes causing CVID have been discovered, but these account for only a fraction of diagnosed CVID cases.[1] A hereditary relation between selective IgA deficiency and CVID has been demonstrated in approximately 20% of analyzed selective IgA families.[2]

Since 2004, the European Society for Immunodeficiencies (ESID) has maintained a pan-European registry for primary immunodeficiencies. To date, more than 18,700 patients have been reported from 30 countries (www.esid.org/registry-number-of-patients). A disease-specific subsection for CVID was created in 2004, with the aim of defining clinical phenotypes and studying therapy regimens and their effects, in particular immunoglobulin replacement, which is the main stay medication in the treatment of CVID. This article presents the first evaluation of data collected in the ESID CVID registry from 2004 to 2012.

Results on clinical phenotypes will be placed in perspective with other major cohort studies published earlier. These include results from a cohort of 248 patients with CVID published by Cunningham-Rundles and Bodian[3] in 1999, which has been fundamental in forming the general picture of this disease. An update on this cohort was published recently.[1] Further cohort studies have been published from a European CVID registry,[4] the Italian Primary Immunodeficiencies Network (IPINET) group,[5] the EUROclass group,[6] and the French DEFI group.[7-9] The latter 2 groups analyzed the correlation between B- and T-cell phenotypes and clinical phenotypes, whereas the former focused mainly

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on the prevalence and possible correlations of clinical features within their cohorts.

With our analysis, we set out to verify previous observations and associations and to identify new associations that have not been detected in smaller or single-center cohorts.

The second focus of our analysis was to document differences in treatment protocols between centers and the effect of different immunoglobulin dosing schemes. The effect of increased immunoglobulin dosing or IgG trough levels (ie, the IgG level measured directly before immunoglobulin administration) has been investigated in earlier randomized trials[10-12] and in recent cohort studies.[13,14] Some of these studies showed a significant reduction in infections with higher immunoglobulin doses[12] or trough levels,[13] and a recent meta-analysis of published clinical studies covering a total of 676 patients indicated a reduction in the incidence of pneumonia of 27% with each 100 mg/dL trough level increment.[15] We analyzed the association of different IgG trough levels in our cohort with patient-reported health outcomes and clinical features, adding a further perspective to previous observations.

Product guidelines recommend IgG doses of between 400 and 800 mg/kg body weight per month, but there are also recommendations that patients should reach a certain IgG serum trough level of 7 g/L, for example. Others argue that instead the specific clinical picture of each patient with CVID requires a specific IgG dose that cannot be based on the idea of a "unique general protective trough IgG level."[13] Therefore our analysis also evaluated the differences in dosing of immunoglobulin replacement between centers, and we discuss the existing dosing protocols.

METHODS

We analyzed data on 2212 patients with a confirmed diagnosis of CVID reported in the ESID Database. We chose to use the ESID registry as a resource for this study because it provides us with longitudinal data for a large cohort of patients. The disadvantage of this approach is that the data are not as completely documented and reviewed as in a clinical trial. The primary source for the data is the patient's file. Data are often entered by research assistants and not physicians, which means that some information is lost on the way from the patient visit to data entry. Still, we believe that the registry approach provides valuable insight because of the sheer size of the cohort.

The ESID Database is physically maintained and managed at the Center for Chronic Immunodeficiency, University Medical Center Freiburg, Germany. Modalities for studies, as well as patient consent forms, are available at www.esid.org/registry (see the site's "Studies" section).

The diagnosis of CVID was based on the ESID/Pan-American Group for Immunodeficiency (PAGID) criteria[16]:

- male or female patient with a marked decrease in IgG levels (≥2 SDs less than the mean for age) and a marked decrease in levels of at least 1 of the isotypes IgM or IgA and fulfilling all of the following criteria:
  1. onset of immunodeficiency at greater than 2 years of age;
  2. absent isohemagglutinins, poor response to vaccines, or both; and
  3. exclusion of defined causes of hypogammaglobulinemia.

Our centers did not use criterion 1 (age of onset >2 years) but instead validated the diagnosis after age 4 years to exclude children with only transient hypogammaglobulinemia. This is in line with a revision of CVID criteria that is currently being undertaken by ESID and PAGID (www.esid.org/clinical-summarymeeting-on-how-to-update-diagnostic-criteria-in-pid-368-0). All participating centers explicitly validated the diagnosis for each patient before analysis.

The actual data pertaining to the diagnosis are only partly entered in the database because the designation of the diagnosis was done by the centers. Centers entered all their patients with CVID who provided informed consent for the registry. Centers were also asked to update their data before analysis. The data lock was October 23, 2012. Data were reported by 26 medical centers and 2 national registries from 16 countries between 2004 and 2012 (see Table E1 in this article's Online Repository at www.jacionline.org). These centers were selected because the amount, depth, or both of data they contributed was sufficient for our analyses. The 2 national registries are not separate entities but use the ESID Database as their data collection platform. Therefore everything that applies to the ESID centers in this study also applies to the national registries. It must also be noted that the study mainly represents referral centers that see the patients who are most ill, and therefore there might be a bias in this respect.

Not all patients had complete data in all of the analyses. In each analysis a subset of patients with available data was included based on inclusion criteria. These are defined in the paragraphs below. The number of patients included in each analysis is given in the Results section. For data sets and definitions, see Table E2 in this article's Online Repository at www.jacionline.org.

The following paragraphs describe the central points of the statistical analysis. A detailed description of the statistical methods applied is provided in the Methods section in this article's Online Repository at www.jacionline.org.

If not stated otherwise, the level at which results were defined as being statistically significant was set at a P value of less than .01.

The analysis on the diagnostic delay was restricted to countries with at least 30 patients with information.

In the clinical features analysis we tested a total of 19 variables. We included only those patients with complete data on clinical features (ie, enteropathy, autoimmunity, granulomas, bronchiectasis, splenomegaly, splenectomy, pneumonia, lobectomy, lymphoma, solid tumor, and meningitis/encephalitis). Because of the lack of detail in the original data, we could not differentiate between organ autoimmunity and autoimmune cytopenia, as has been done in other studies.[9]

Further items in this analysis were sex; IgG level at diagnosis, median IgG trough level, and the difference between these 2 values (ie, ΔIgG); median IgA and IgM levels; age at onset and diagnosis; and diagnostic delay. An analysis of B- and T-cell phenotypes in patients with CVID is currently being performed by a different group of centers (the EURO-PADnet consortium). Therefore we were not authorized to include these parameters.

TABLE I. Female and male patient distribution

	Female	Male	Female/male ratio
Total living patients	1041	969	1.1
Age 4-11 y	40	89	0.5
Age 12-17 y	56	83	0.7
Age 18-29 y	155	188	0.8
Age ≥30 y	790	609	1.3

RESULTS

We analyzed data on 2212 patients. At the time of analysis (October 23, 2012), 2010 patients were reported to be alive, whereas 124 were deceased, and 78 had been lost to follow-up. One thousand one hundred thirty-one (51.1%) patients were female, and 1081 (48.9%) patients were male. Of the living patients, 129 (6.4%) were younger than age 12 years, 139 (6.9%) were between 12 and 17 years old, and 1742 (86.7%) were 18 years and older. The overall ratio between female and male patients was approximately 1, but when we calculated the ratio for different age groups, there were about twice as many boys than girls in the group of children and considerably more women than men in the group of those age 30 years and older (Table I).

Of the living patients, 1614 (80.3%) were receiving immunoglobulin replacement at their last follow-up. A genetic mutation

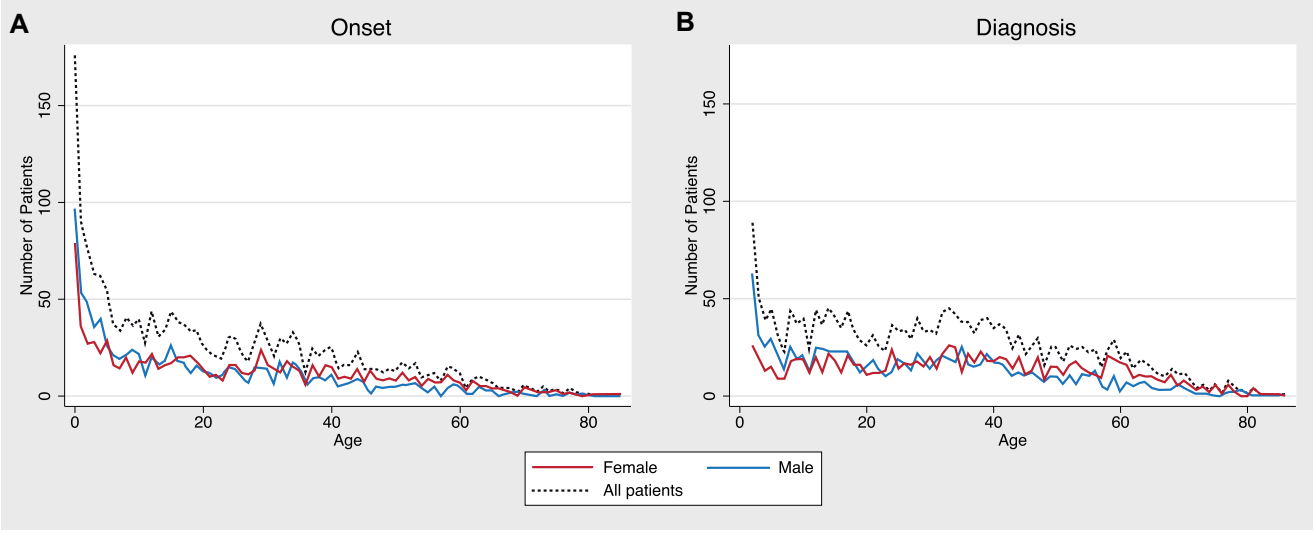

FIG 1. A, Age at onset of symptoms in the total cohort (n = 1914), among female patients (n = 985), and among male patients (n = 929). **B,** Age at diagnosis in the total cohort (n = 2134), among female patients (n = 1094), and among male patients (n = 1040). An age of 0 years means less than 12 months of age.

TABLE II. Comparison of diagnostic delay between patients with early and late disease onset and patients given a diagnosis before and from 2000 onward

Country	No.	Diagnostic delay, median (IQR)	No.	Diagnostic delay, median (IQR)	*P* value
		Year of diagnosis <2000		Year of diagnosis ≥2000	
Czech Republic	31	4.0 (1.7-14.5)	40	2.3 (0.9-5.7)	.05
France	262	4.7 (1.0-12.2)	544	4.5 (1.0-13.0)	.54
Germany	93	5.0 (1.1-11.8)	226	4.8 (1.30-12.0)	.70
The Netherlands	61	1.0 (0.0-7.2)	112	2.7 (0.4-7.3)	.06
Spain	80	9.0 (3.0-20.5)	57	4.6 (0.5-13.4)	**.04**
United Kingdom	126	5.3 (1.4-17.0)	114	4.5 (1.0-11.6)	.26
Complete cohort	653	5.0 (1.0-13.5)	1093	4.2 (1.0-12.0)	.37
		Age at onset <10 y		Age at onset ≥10 y	
Czech Republic	14	8.6 (4.3-18.0)	57	2.0 (1.0-5.7)	**<.001**
France	203	10.0 (3.0-20.0)	603	3.1 (0.6-10.3)	**<.001**
Germany	127	6.0 (1.8-16.3)	192	4.0 (0.8-9.2)	**.003**
The Netherlands	72	3.2 (0.8-7.3)	101	1.2 (0.0-7.2)	.05
Spain	64	7.5 (3.0-23.0)	72	6.0 (0.8-20.0)	.26
United Kingdom	80	8.8 (1.7-28.9)	160	4.0 (1.0-10.3)	**.002**
Complete cohort	560	7.2 (2.0-18.3)	1185	3.1 (0.7-10.0)	**<.001**

P values in boldface indicate statistical significance.

was reported in 60 (2.7%) patients. Forty-six patients had mutations in *TACI*, 6 had mutations in *ICOS*, and 4 had mutations in *CD19* and *BAFFR* each. No other mutations were reported.

Age at onset and diagnosis and diagnostic delay

A total of 1913 patients had available data on the date of onset of symptoms, and 2134 had data for the date of CVID diagnosis. Six hundred forty-four (33.7%) patients had an onset before the age of 10 years, representing a very pronounced peak. The peak is more pronounced in male patients (370 [39.8%]) than in female patients (274 [27.9%]; Fig 1, *A*, and see Fig E1, *A*, in this article's Online Repository at www.jacionline.org). As for the age at onset, we observed that male patients were given diagnoses earlier, which correlates with the earlier age at onset. Fig 1, *B*, might imply 2 peaks of diagnosis, one during childhood and the other between 30 and 40 years of age (see Fig E1, *B*). It must be noted that 36 patients were reported to have an age at diagnosis of 1 year because hypogammaglobulinemia was diagnosed at that age. This diagnosis was then confirmed as CVID following the ESID/PAGID diagnostic criteria at the age of 4 years.

The median diagnostic delay varied considerably between countries. For all patients combined, the median diagnostic delay was 4.1 years (interquartile range [IQR], 1-11.8 years). The delay was highest in Spain (7 years; IQR, 2-20 years) but 4.5 years in the United Kingdom, 4.8 years in Germany, 4.5 years in France, and 3.4 years in the Czech Republic. It was lowest in Poland (1.8 years) and The Netherlands (2.1 years). Interestingly, when we compared the delay between patients given a diagnosis before and since 2000, the delay was shorter for the latter group in all countries except The Netherlands. However, the difference was statistically significant for Spain only ($P = .04$, Table II), where the delay for patients receiving a diagnosis since 2000 was 4.6 years compared with 9 years for those given a diagnosis before

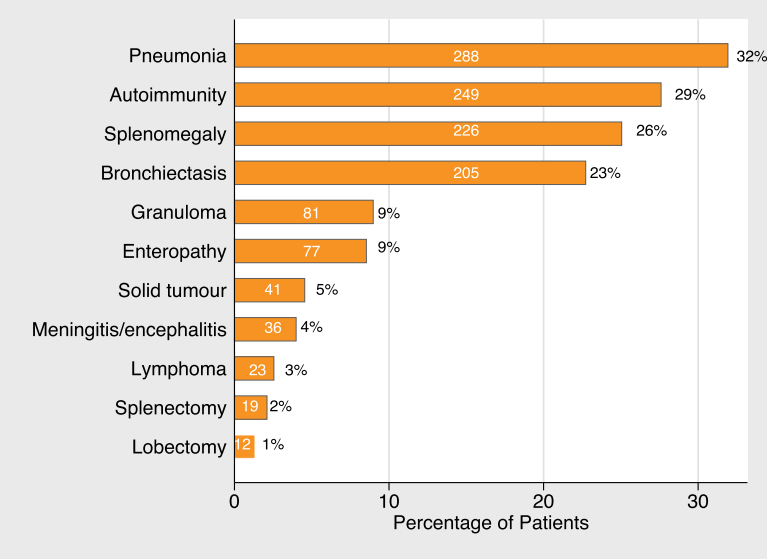

FIG 2. Frequency of clinical features in our cohort (n = 902). *Numbers in bars* represent the absolute number of patients per feature.

2000. For the whole cohort, there was also no statistically significant difference ($P = .37$).

Patients with an early onset (<10 years) had a statistically significantly longer diagnostic delay in 4 of 7 countries (Table II). The difference was very high in 2 countries (eg, 10 vs 3.1 years in France; $P < .001$). For the cohort as a whole, there was also a large difference of 7.2 versus 3.1 years ($P < .001$).

Association between clinical features, immunoglobulin levels, date of onset, and diagnostic delay

The total frequency of the clinical features in 902 patients with available data is depicted in Fig 2. The prevalence of each feature varied considerably between centers (see additional material in Table E3 in this article's Online Repository at www.jacionline.org; data from the French cohort had to be excluded because of incompleteness). Notably, 2 of the features were particularly frequent in certain countries. These were bronchiectasis, which was reported much more frequently by British centers in particular (up to 66%), and splenomegaly, which was reported most frequently by centers in Germany and the Czech Republic (up to 62%).

Seventy-one of 203 tumors were lymphomas. Solid tumors were not primarily gastrointestinal tumors but also include 13 cases of breast tumors and 20 cases of skin tumors. Eleven percent of all lymphomas, 49% of autoimmunity cases, and 22% of splenomegaly cases occurred before CVID diagnosis. Further information on this is shown in Table E4 in this article's Online Repository at www.jacionline.org.

Univariate analysis. Table III provides an overview of the statistically significant relationships found in our cohort. The most significant associations are described in the following paragraphs. For ease of reading, the word "significant" is omitted because only statistically significant relationships with P values of less than .01 are described. Numeric values represent the median, unless stated otherwise.

Our analyses suggested positive associations between most of the pairs of autoimmunity, enteropathy, granulomas, and splenomegaly (eg, 39% of patients with autoimmunity had splenomegaly compared with only 20% of patients without autoimmunity). However, enteropathy and granulomas were not associated with each other. Splenectomy was found to be associated with the presence of autoimmunity, granulomas, and lymphoma.

Patients with bronchiectasis were found to have significantly lower IgM values (0.18 g/L) than those without (0.26 g/L). They also had a longer diagnostic delay (6 vs 3.2 years).

Patients with pneumonia were more likely to have meningitis (7% vs 3%). Additionally, patients with pneumonia had lower IgG trough levels (7.4 vs 8.1 g/L) and a younger age at onset (11.6 vs 16 years).

The age at onset was associated with many clinical features. Patients with an older age at onset more often had autoimmunity, splenomegaly, lymphoma, and solid tumors. Conversely, patients with pneumonia had a younger age of onset (12 vs 17 years). IgG levels at diagnosis, IgG trough levels, IgA levels, IgM levels, and diagnostic delay were negatively associated with age of onset. This implies that patients with an older age of onset had lower values of all of these variables.

Patients with pneumonia and splenomegaly had lower IgG trough levels compared with patients without these features. Both low IgA and IgM levels were associated with splenomegaly. For further correlations of the immunoglobulin level, see the Results section in this article's Online Repository at www.jacionline.org.

As mentioned before (Fig 1, *A*), male patients were found to have a younger age of onset than female patients (10.7 vs 18 years). Male patients also had lower IgG trough levels (7.6 vs 8.2 g/L) and a shorter diagnostic delay (3 vs 5 years).

A possible explanation for the statistical difference between male and female patients might be that male patients with an early onset might include undiagnosed X-linked immunodeficiency disorders. Therefore we additionally compared the frequency of symptoms between boys with an age of onset of less than 10 years and the remaining patients.

Enteropathy, autoimmunity, splenomegaly, and granulomas were all less common in boys with an early onset. Enteropathy

TABLE III. Summary of statistically significant relationships (univariate analysis)

	Autoimmunity	Granulomas	Bronchiectasis	Splenomegaly	Splenectomy	Pneumonia	Lobectomy	Lymphoma
Enteropathy	+++			++			+	
Autoimmunity		+++		+++	+++	−		
Granulomas				+++	+++			
Bronchiectasis							+++	
Splenomegaly					+			
Splenectomy								+++
Pneumonia								
Lobectomy								
Lymphoma								
Solid tumor								
Meningitis								
IgG diagnosis								
IgG trough								
IgG change								
IgA								
IgM								
Male sex								
Age at onset								

+, Positive association, $P < .05$; ++, positive association, $P < .01$; +++, positive association, $P < .001$; −, negative association, $P < .05$; − −, negative association, $P < .01$; − − −, negative association, $P < .001$; *empty cells*, $P \geq .05$.

occurred in 3% of boys younger than 10 years compared with 10% of the remaining group (autoimmunity: 19% vs 30%). Conversely, pneumonia was more prevalent in boys with an early onset (43%) compared with the other patients (29%, $P = .001$). Additionally, boys with an early age of onset had higher IgG and IgM levels at diagnosis. Three hundred thirty-four patients with an early age of onset had data on B-cell numbers. Of these, 26 had 1% or fewer B cells. Seventeen of these were male.

Patients with pneumonia and splenomegaly had lower IgG trough levels compared with patients without these features. Both low IgA and IgM levels were associated with splenomegaly.

Multivariate analysis. There were 274 patients with information for all variables that were eligible for the first analysis. The results (see Table E5 in this article's Online Repository at www.jacionline.org) suggested that IgG levels at diagnosis and IgA and IgM levels contributed to the same factor and were positively correlated. IgG trough levels and ΔIgG values were also positively correlated.

Another group of associated variables was splenomegaly, granulomas, and autoimmunity, which were positively associated. This supports the observation we made in the univariate analysis. Finally, we found that the pairs of enteropathy and diagnostic delay, as well as bronchiectasis and lobectomy, were also positively correlated, indicating that patients with enteropathy are more likely to have a long diagnostic delay and patients with bronchiectasis are more likely to undergo lobectomy.

We repeated this analysis, omitting IgG levels at diagnosis and ΔIgG values because these were the variables with many missing data. Doing so, the number of patients increased to 566. The results (see Table E6 in this article's Online Repository at www.jacionline.org) indicated that age at diagnosis, diagnostic delay, and bronchiectasis were positively correlated. Furthermore, IgA and IgM levels were positively associated. The same was found for splenomegaly and granulomas, as well as lymphoma and splenectomy. Solid tumors were negatively associated with the IgG trough level, which implies that patients with a lower IgG trough levels have solid tumors more frequently than those with higher trough levels.

The observation of strong associations among autoimmunity, splenomegaly, enteropathy, and granulomas in the univariate analysis prompted us to perform a multivariate analysis of these four variables. The results (see Table E7 in this article's Online Repository at www.jacionline.org) suggested that splenomegaly and granulomas, as well as enteropathy and autoimmunity, form 2 pairs, which suggests that a patient is likely to have both splenomegaly and granulomas or both enteropathy and autoimmunity.

Patient survival

Data for this analysis were available for 2134 patients (96.5% of the total 2212 patients), of whom 119 were deceased. We found that age at diagnosis and age at onset were both significantly associated with patient survival ($P < .001$). Older age at onset and older age at diagnosis were both associated with an increased risk of death at any time. A 1-year increase in age at diagnosis was associated with the risk of death increasing by 4.5% (for the age at onset, it is 3%). A longer diagnostic delay was also associated with an increased risk of death (1.7% per 1-year increase) and thus reduced survival times. The presence of a lymphoma and solid tumor was also associated with an increased risk of death.

There was no strong evidence that any of the other variables examined were significantly associated with patient survival. Notably, in this data set there was also no difference between the group of patients with noninfectious complications and those without.

In a multivariate analysis on the joint effect of the aforementioned variables, age at diagnosis was the main correlating factor with patient survival. To illustrate this, the survival of patients with early- and late-onset CVID is depicted in a Kaplan-Meier plot (Fig 3).

IgG dosing

The calculation of average immunoglobulin treatment intervals and monthly doses showed a statistically significant difference between centers ($P < .001$).

TABLE III. *(Continued)*

Solid tumor	Meningitis	IgG diagnosis	IgG trough	IgG change	IgA	IgM	Male sex	Age at onset	Diagnostic delay
						−		+	+
					−			++	
					−			+	
					−	− − −			+++
		− −	− − −		− − −	− − −		+++	
	++		− −		−			− −	
								++	−
			−					+++	+
			+++	− − −	+++	+++		− − −	
				+++	+++	+++	− −	− − −	++
							−	−	
						+++		− − −	
							−	− − −	
								− − −	− − −
									− − −

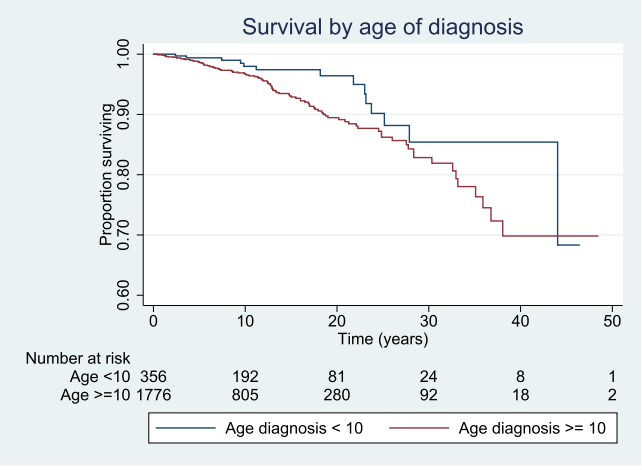

FIG 3. Kaplan-Meier graph depicting patient survival in relation to age at diagnosis.

There was a median intravenous immunoglobulin (IVIG) treatment interval of 30 days when all centers were analyzed together. The same value was obtained from both the patient-level and interval-level analyses. Most centers had exactly 30 days as the mean treatment interval (17/27). In the remaining 10 centers the median treatment interval varied from 21 up to 41 days (see Table E8 in this article's Online Repository at www.jacionline.org).

There was a larger variation between centers in the average monthly dose (IVIG and subcutaneous immunoglobulin [SCIG], Table IV). The median dose for all centers combined was approximately 460 mg/kg/mo. The patient-level analysis indicated that the median dose in the centers ranged from 129 mg/kg/mo (Prague) up to 750 mg/kg/mo (Thessaloniki and Ippokration).

When only considering the IVIG route, there was a median dose of 455 mg/kg/mo. This median dose varied from 130 mg/kg/mo (Prague) to 638 mg/kg/mo (Dresden). The median SCIG dose was 463 mg/kg/mo from the patient-level analyses, with a similar figure for the interval-level analysis. The median doses ranged from 138 mg/kg/mo (Prague) to 1335 mg/kg/mo (Thessaloniki and Ippokration based on 2 patients).

IgG trough levels and health outcomes

Data from 518 patients were analyzed for "days missed," 609 patients for "days in the hospital," 553 patients for "infectious episodes," and 447 patients for "serious bacterial infections." The number of periods varied between 1275 periods covering 1056 patient-years for "serious infections" and 1918 periods covering 1479 patient-years for "days in the hospital."

The differences for the outcomes "days missed" and "infectious episodes" were not statistically significant. The differences between trough level groups were most pronounced for serious infections (Fig 4, *A*). There were significant differences for all categories used ($P < .001$). The overall number of serious infections was low because many patients had no serious infections. However, the upper quartiles of the distribution suggested that there were a decreasing number of serious infections with increasing IgG levels.

The differences for "days in the hospital" showed high statistical significance ($P = .004$) when the cutoff in IgG trough levels was made at 4 g/L. A significant difference was also found by using 7 g/L as the cutoff ($P = .02$). When a significant result was observed, patients with a lower IgG trough level had a higher number of days in the hospital. Patients with a median IgG level of less than 4 g/L had a median of 0.8 days in the hospital per year compared with a median of 0 for those with higher IgG levels. There was also a significant difference when we divided patients into 5 IgG groups (Fig 4, *B*), which is again most pronounced for the less than 4 g/L group.

We found identical trends when we analyzed the data for IVIG treatment only. In contrast, the SCIG data showed only small significant differences with improved outcome at higher IgG trough levels, indicating that patients receiving SCIG with an IgG

TABLE IV. Average IgG doses in milligrams per kilogram of body weight per month

	Interval-level analysis		Patient-level analysis	
Center	**No. of intervals**	**Median (IQR)**	**No. of patients**	**Median (IQR)**
Barcelona	10	576 (400-585)	5	576 (400-576)
Bornova-Izmir	25	508 (383-681)	12	527 (409-679)
Bratislava	9	532 (502-561)	7	531 (466-576)
Brno	50	337 (237-469)	20	327 (223-427)
Cairo	2	400 (400-400)	1	400 (400-400)
Cambridge, Addenbrooke's	50	544 (365-658)	22	547 (410-657)
Dresden	10	579 (522-638)	4	495 (372-587)
Dublin	10	662 (510-784)	9	556 (510-784)
Düsseldorf	2	481 (417-545)	2	481 (417-545)
France, CEREDIH	537	486 (379-654)	398	483 (378-650)
Freiburg, Center for Chronic Immunodeficiency	208	383 (262-495)	97	388 (262-462)
Hannover, Immunology	83	272 (168-495)	46	292 (171-484)
Hannover, Pneumology	34	455 (352-670)	15	469 (353-792)
Jönköping	13	433 (393-594)	7	393 (355-433)
Krakow	143	417 (351-526)	30	400 (385-450)
Leipzig	65	416 (349-582)	33	428 (351-602)
Leuven	28	448 (400-605)	12	471 (409-521)
London, Barts	52	673 (547-836)	19	711 (564-949)
London, UCL ICH/GOS	34	631 (435-794)	15	611 (518-666)
London, UCL Royal Free	182	482 (396-583)	82	481 (412-568)
Manchester	25	535 (440-666)	21	254 (440-657)
Moscow	12	295 (206-405)	5	309 (278-500)
Munich	27	411 (309-495)	16	429 (342-544)
The Netherlands	106	502 (404-714)	72	494 (405-702)
Prague	80	134 (79-197)	24	129 (77-188)
Tallinn	6	373 (318-407)	5	361 (318-385)
Thessaloniki, Ippokration	14	720 (600-1000)	5	750 (620-1000)
Thessaloniki, Papageorgiou	8	543 (506-655)	5	580 (511-606)
All centers combined	1825	454 (339-603)	989	460 (355-610)

The figures reported are the median dose (in milligrams per kilogram per month) and the corresponding IQR. The number of intervals/patients contributing to each figure is also reported.

trough level of greater than 4 g/L had good clinical benefit. This unexpected observation might be a result of a bias to start a special subset of patients with CVID on SCIG and calls for a prospective validation in a controlled setting.

In summary, we found that the differences in days in the hospital and serious bacterial infections between the groups at less than and greater than 4 g/L was higher than the differences using the other cutoffs. This is valid, irrespective of the route of administration.

Of the 11 clinical features used in the previous analysis, only pneumonia showed a correlation with serious infections, and bronchiectasis showed a correlation with missed days. When we further analyzed these, there was a significant difference in outcome between IgG groups for patients without pneumonia, with the number of serious infections slightly decreasing with increased IgG levels. However, there were no differences for patients with pneumonia. In contrast, a decrease in the number of missed days only existed in patients with bronchiectasis but not in those without.

DISCUSSION

First of all, we must caution that our results reflect clinical observations and measures and must be distinguished from a controlled clinical trial. Some of the variables in our analysis represent "soft" data, such as the date of onset, as well as patient-reported health outcomes. In addition, centers apply different methods to diagnose findings, such as enteropathy and bronchiectasis. This might explain, at least in part, the differences in the frequency of single features between centers.

However, it is reassuring to see that the overall frequency of the clinical features in our cohort is almost completely in line with what has been found in other major multicenter cohort studies.[4,5] However, similar to Chapel's European cohort,[4] there is a large variability in the prevalence of features between centers. Possible explanations are differences in awareness, diagnostic protocols, clinical assessment, and populations.

We would also like to point to a possible weakness of the hypothesis-free approach that we used for the multivariable analysis. It might be that the variables that group together do so not because of physiologic interrelatedness but because of 1 or more sampling biases of some type, such as selective reporting.

The association of autoimmunity, granulomas, and splenomegaly has been discussed before in the EUROclass trial.[6] An overlap between these and enteropathy has also been shown before in the DEFI cohort.[7] Our results underscore that there is a strong association between these features and that granulomas and splenomegaly are strongly linked, whereas enteropathy is linked to autoimmunity. This is an intriguing observation because it puts CVID enteropathy in close proximity to autoimmunity rather than to postinfectious complications. It is also interesting to see that enteropathy is significantly associated with the lack of IgM, but not IgA, the most prevalent immunoglobulin in the gut. It must be noted that enteropathy was not associated with

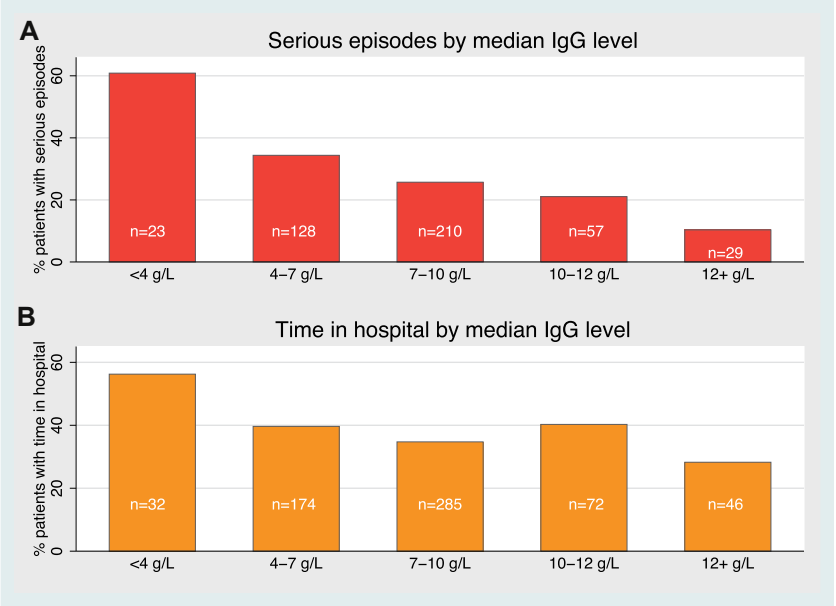

FIG 4. Health outcomes in correlation to IgG trough levels. The "n" within each bar is the total number of subjects having the indicated median IgG level. **A,** Patients with serious bacterial infections. **B,** Patients hospitalized because of immunodeficiency. Because the total number of serious infections and days in the hospital were low, the graph shows the percentage of affected patients.

any extent of respiratory tract infections. However, it is well possible that few of the enteropathy cases in our cohort actually reflect infections with rare or difficult to diagnose organisms, such as cryptosporidium or norovirus. However, it is also worth mentioning that other disorders, such as enteropathy, possibly represent an ineffective or inappropriate gastrointestinal response to subclinical infection, which can occur when infection is not eliminated promptly, because of antibody deficiency or where there is an inappropriately skewed immune response. It is also noteworthy that enteropathy is not strongly associated with granuloma formation, which often occurs in the lungs. Hence these 2 complications in patients with CVID might have a different pathophysiology.

Although Quinti et al[5] found no multivariate association of splenomegaly with any other clinical or laboratory abnormality, our multivariate analysis suggests strong links with granulomas, autoimmunity, and enteropathy.

It is interesting to see that bronchiectasis was not associated with any other secondary complication, except for lobectomy. A possible explanation might be that bronchiectasis is a consequence of infections, whereas other complications are a consequence of immune dysregulation. It is surprising to see that pneumonia was not associated with bronchiectasis, as in other studies.[14] Possibly this is due to a reporting bias. For example, data on episodes of pneumonia before diagnosis of CVID are often difficult to attain and probably underreported. The observation of lower IgM levels in patients with bronchiectasis confirms the results from other studies that have shown the protective effect of IgM antibodies in the lung.[17,18]

Age at onset

It has often been communicated that there are 2 peaks of onset in patients with CVID, one in children aged 1 to 5 years and a second in persons aged 16 to 20 years.[3] However, the second peak was never confirmed in any follow-up study. In light of our results, it seems unlikely that there is a second peak. Thirty-five percent of our patients presented with their first symptoms between 0 and 9 years of age, which is far earlier than in any other published cohort. There was no second peak of onset in our cohort.

This might be due to the fact that 6.4% of the patients in our cohort were less than 12 years of age and another 6.9% were aged 12 to 17 years. Furthermore, we included a comparatively large number of centers that also follow children (21/26 centers). This probably reduces the statistical bias of studies that are based on fewer (and mainly adult) centers and patients, such as the single-center study of 248 patients by Cunningham-Rundles and Bodian,[3] the study with 6 centers and 334 patients by Chapel et al,[4] or the study with 26 centers and 224 patients by Quinti et al.[5]

We found that more boys than girls have an early onset of less than 10 years of age. Cunningham-Rundles and Bodian[3] found a similar significant difference in their cohort (23 years for male patients vs 28 years for female patients, although in general, the age at onset in our cohort was much lower (12 vs 18 years, respectively). Other studies did not compare the onset between male and female patients.[4,5]

Our subanalysis of boys with an onset before the age of 10 years suggests that patients with early-onset CVID are more prone to infections rather than noninfectious complications and possibly represent a distinct clinical entity. Alternatively, in this group we are missing patients with X-linked primary immunodeficiencies, such as X-linked agammaglobulinemia or X-linked lymphoproliferative syndrome.

The high proportion of male patients in our cohort (39.8%) with a disease onset before the age of 10 years raises the question of whether there might be patients with undetected X-linked agammaglobulinemia with mutations in Btk in this subgroup. Therefore we asked our centers for their Btk screening policy. Half of the centers explicitly reported that the main indication to

screen for Btk was very low B-cell numbers (CD19 <1% or 2% of lymphocytes). Some explicitly exclude Btk before they give a child a diagnosis of CVID, whereas the center in Cairo reported it had no access to molecular genetics. In addition, the cohort included patients who received a diagnosis decades ago and therefore have not been tested for Btk if they were not included in recent studies that included Btk screening. Therefore we suggest that early onset of CVID should prompt physicians to perform further molecular diagnostics, such as targeted primary immunodeficiency gene panel sequencing.

Additionally, male patients were found to have significantly lower IgG trough levels on treatment than female patients, whereas there was no significant difference in the IgG level at diagnosis between male and female patients. This might be explained by a better adherence of female patients to immunoglobulin replacement therapy, and there might possibly be an underlying social-educational explanation. On the other hand, it is interesting to note that male patients had a shorter diagnostic delay.

Patient survival

Our observations regarding age at onset and diagnosis, as well as diagnostic delay, are in line with recently published results.[1] Our report confirms the major role of the age at diagnosis for patient survival. This speaks in support of focusing awareness activities to decrease the diagnostic delay.

Resnick et al[1] also found that survival 40 years after diagnosis was reduced in patients with CVID when compared with that in the general population. The corresponding analysis in our cohort was not possible because of the structure of the cohort. Most of our centers only reported their living patients. Therefore if we calculate survival from the time of diagnosis for each patient, our cohort performs exceptionally well.

IgG dosing

The differences in IgG dosing intervals and individual doses (median values from 129 up to 750 mg/kg/mo) prompted us to ask the contributing centers for their general policy on immunoglobulin replacement. In general, centers reported that they start out at a dose of 400 mg/kg/mo. Three centers reported that they start with very high doses of 1000 mg/kg/mo and then reduce to 400 mg/kg/mo. This might explain why some centers have high median doses because the high starting doses are included in the calculation.

The main difference between centers was in the targeted trough level. Nine centers reported that they did not target a specific trough level. Of the remaining centers, 5 reported that they targeted a trough level of greater than 5 g/L, 4 that they targeted a trough level of greater than 6 g/L, 7 that they targeted a trough level of greater than 7 g/L, and 1 that they targeted a trough level of greater than 8 g/L. Interestingly, English centers generally targeted high trough levels of 7 or 8 g/L, and 2 of them explicitly cited the recent studies by Orange et al[15] and Lucas et al[13] as an empiric basis for their dosing decision. The center in Prague (which in the analysis showed an extremely low median immunoglobulin dose of 129 mg/kg/mo) acknowledged that their patients were underdosed because of the lack of financial coverage by health insurance.

In summary, the initial dosing scheme seems to differ between centers, but most centers reported that they later adjust the IgG dosage individually based on each patient's clinical course. Bronchiectasis was mentioned as a major indicator to use a higher IgG dose by 3 centers.

IgG trough levels and health outcomes

The observation of a particularly clear difference in the frequency of serious bacterial infections between patient trough levels of less than 4 g/L and 4 g/L or greater is in line with the observation by Quinti et al[14] that pneumonia was more frequent in patients with a trough level of less than 4 g/L. Therefore we conclude that the risk of pneumonia increases if patients are not maintained at greater than an IgG trough level of 4 g/L. The observation that higher doses of IgG in patients receiving SCIG in our cohort are not associated with a better outcome is unexpected and requires confirmation in prospective controlled trials.

Eijkhout et al[12] observed no differences between low and high immunoglobulin dosage regimens for "days in the hospital" and "days missed." Interestingly, they found a statistically significant reduction in overall infections but not for serious infections in particular. In contrast, our study suggests that the association of higher trough levels with improved outcomes is mainly restricted to the frequency of serious bacterial infections, which supports the results of the meta-analysis performed by Orange et al.[15] This might suggest that higher trough levels are essential to prevent serious bacterial infections, but patients could still have moderate infections and noninfectious complications that affect their quality of life and clinical course, as also shown in Quinti et al.[5,14]

The analysis of correlations between clinical features and health outcomes provides no clear indication that there is a specific subgroup of patients with CVID characterized by a single clinical feature in which the relationship between IgG trough levels and patient-reported health outcomes differed significantly from the remaining patients. We would also like to point out that "days in the hospital" and "days missed" represent outcomes that are much more affected by local standards of medical care and broader cultural differences than more objective measures, such as the total infection rate.

Conclusion

What is CVID? CVID is a collection of different clinical conditions with the common denominator of a profound antibody deficiency. It has been shown that CVID can be caused by intrinsic B-cell defects[19-21] but also by the lack of T-cell costimulation.[22] Hence its pathoetiologic background is diverse. Therefore it is not surprising that the clinical observations in patients with CVID are also diverse, as the name indicates: common *variable* immunodeficiency. By analyzing 2212 patients with CVID, we obtained evidence that (1) the clinical complications of splenomegaly and granulomas on the one hand and autoimmunity and enteropathy on the other hand are interrelated; (2) there are a considerable number of boys with early-onset CVID; (3) immunoglobulin replacement does not serve all complications in patients with CVID; and (4) there is a considerable difference in the management of CVID between centers within Europe. How this affects the ultimate outcomes of quality of life and patient survival should be the target of future trials using the ESID Database.

The direct implications of this work for future action in the management and research of CVID are as follows:

- In male patients with CVID and an early onset of symptoms, known X-linked disorders possibly leading to

hypogammaglobulinemia should be excluded by means of genetic testing.
- The current definition of CVID leads to a very heterogeneous collection of patients with very different clinical problems, and hence analysis in clinical trials, for example, is problematic. This observation challenges the concept of CVID as one disease entity and calls for an improved and more refined definition and grouping of patients with CVID.
- The infection-only type of CVID might result in a superior quality of life than seen in patients with CVID with other complications. Therefore biomarkers and scoring systems identifying patients at risk for the granulomatous form of CVID, CVID enteropathy, autoimmune complications, or lymphoma, for example, are very much needed.
- To study possible differences between IVIG substitution and subcutaneous replacement (eg, the role of the IgG trough level), prospective large controlled clinical trials are necessary.

Furthermore, we have shown that using an electronic patient registry to acquire data on patients with CVID from a large number of medical centers is one possibility to answer disease-specific questions. We have pointed out the drawbacks of this method, which mostly consist of differences in diagnostic protocols, availability of data, and differences in the interpretation of "soft" items, such as the date of onset.

Despite these drawbacks, our cohort has a size that is unprecedented and provides a much larger statistical power than previous studies. Therefore we strongly recommend continuing efforts to build and maintain patient registries in Europe and beyond.

We thank Paul Bassett at Meridian HealthComms for performing the statistical analysis. ICD-10 codes, terms, and text are used by permission of the World Health Organization from the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

Key messages

- **Early-onset CVID is more frequent than previously recognized.**
- **Higher IgG trough levels are associated with fewer serious infections.**
- **Patients given a diagnosis earlier in life have superior survival.**
- **Diagnostics and management of CVID differ throughout Europe.**

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METHODS

If not stated otherwise, the level at which results were defined as being statistically significant was set at a *P* value of less than .01.

Onset, diagnosis, and diagnostic delay

We analyzed the distribution of the age at onset and age at diagnosis. Furthermore, we calculated the diagnostic delay, which is the time between onset of symptoms and diagnosis, for each country. Countries with less than 30 patients with diagnostic delay information were omitted. For the diagnostic delay, we first used all available data and then in a second round restricted the analysis to patients receiving a diagnosis since 2000 to determine whether the delay was shorter for the patients with more recent diagnoses. We also compared the diagnostic delay between early (<10 years of age) and late onset (>10 years of age).

The date of onset was defined as the date of the first severe infection. In contrast to the "date of diagnosis," the "date of onset" of CVID represents "soft" data because it relies on patients' and parents' information and recollection. Although we acknowledge that these data are not precise, we believe that their analysis is still very important because the "date of diagnosis" is confounded by different issues, such as access to health care in respective countries, the skills and knowledge of primary physicians, and, last but not least, the individual health perception of each patient. Moreover, only the "date of onset" analysis allows for the calculation of a diagnostic delay, which represents very important information for health care authorities.

Association between clinical features, immunoglobulin levels, date of onset, and diagnostic delay

In this analysis we tested a total of 19 variables, first in a univariate and then in a multivariate analysis. We included only those patients with complete data on clinical features (ie, enteropathy, autoimmunity, granulomas, bronchiectasis, splenomegaly, splenectomy, pneumonia, lobectomy, lymphoma, solid tumor, and meningitis/encephalitis). These were reported by using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, classification. Details on the means of verification for each feature were not collected.

Because of the variability of details in the original data, all of these items were converted to Boolean (yes/no) variables. This implies that some of the depth of the original data is lost (eg, patients who have "yes" for pneumonia might have 1 or more episodes of pneumonia in the original data). It also means that our results do not take into account any temporal association between variables. Because of the lack of detail in the original data, we could not differentiate between organ autoimmunity and autoimmune cytopenia, as has been done in other studies.[E1]

Further items in this analysis were sex; IgG level at diagnosis, median IgG trough level, and the difference between those 2 values (ie, ΔIgG); median IgA and IgM levels; age at onset; and diagnostic delay. Data were not available in all patient data sets for these variables, except for sex.

Univariate analysis. In a first step we examined the association between each pair of variables. For situations in which there were 2 categorical variables, the χ^2 test was used. Comparisons of continuous variables between groups were performed with the unpaired *t* test for normally distributed variables and the Mann-Whitney test for variables that were not normally distributed. Associations between continuous variables were examined by using Spearman rank correlation.

There were 171 different analyses looking at associations between pairs of variables. With so many comparisons, there is a much increased likelihood of finding a statistically significant result because of chance alone. To guard against this, the level at which results were defined as being statistically significant was set at a *P* value of less than .01.

Multivariate analysis. In a second step we performed a hypothesis-free multivariate analysis. This implies that we did not select 1 or more "outcome" variables based on clinical experience, for example, because we wanted to identify potential associations that might have been overlooked before. Our approach was performed by using factor analysis. This method divides total data variability into key components to explain the largest amount of variability in the data. Factors contributing to the same component are considered to be associated with each other. A scree plot was used to select the appropriate number of components for evaluation. The size of each variable's contribution to each factor can be determined by the factor loading size. A loading of 0.5 or greater indicates that a variable was associated with that component. A varimax rotation was used to enable a clearer interpretation of the results. The distribution of the IgA and IgM levels was found to be highly skewed. As a result, these variables were analyzed on the log scale.

The analysis was performed twice. Initially, all variables were tried in the analysis. This restricts the analysis to only those patients with valid data values for all variables. This resulted in no occurrences of splenectomy, and therefore this variable was omitted from the analysis.

Second, the analysis was repeated, this time omitting the IgG level at diagnosis and ΔIgG because these were the variables with the most missing data. By omitting these variables, the analysis was performed on a larger sample size, allowing the splenectomy variable to be included.

Patient survival

We examined the association between the same set of variables and patient survival. A series of univariate Cox regression analyses was performed to examine the association between each factor and survival times.

The length of patient survival was defined as the time from the date of diagnosis to the date of death. Patients who did not die were censored at the point of last known follow-up. The effect of each variable was quantified by a hazard ratio, indicating the likelihood of death at any time. Patients with no available date of diagnosis were excluded.

IgG dosing

We examined dosing differences of immunoglobulin replacement as reported by each of the contributing centers. First, we analyzed the treatment intervals for IVIG only. In a second analysis we analyzed monthly doses (in milligrams per kilogram of body weight) in total and for IVIG and SCIG separately.

The analysis was restricted to intervals reported in treatments started in the year 2000 or later to ensure the latest information on immunoglobulin dosing. Additionally, the analysis was restricted to centers with IgG dosing data on 6 or more patients. The outcome values were found to have a skewed distribution, and therefore the medians and IQRs were used to summarize the data, and the Kruskal-Wallis test was used to compare between centers.

Two sets of analyses were performed. First, an interval-level analysis was performed. This considered each dosing schedule as a separate observation (ie, each interval counts as 1 set of information). A potential drawback of this analysis is that different patients have a different number of intervals, with some patients providing more information than others for the analysis. Therefore a patient-level analysis was performed as well. The median value per patient was calculated, and only a single value per patient was included in the analysis.

IgG levels and patient-reported health outcomes

The aim of this analysis was to examine the association between IgG levels and 4 health outcomes: (1) number of days unable to perform daily duties, (2) days in the hospital caused by the immunodeficiency (excluding visits for immunoglobulin administration and outpatient visits), (3) infectious episodes, and (4) serious bacterial infections (see Table E2). We included only patients with available data for at least 1 of these outcomes who were receiving immunoglobulin replacement and had data on IgG trough levels.

Matching information on IgG levels and health outcomes is not straightforward because IgG levels were measured on specific dates and health outcomes were measured over differing time periods. An additional issue was that sometimes health outcome data were measured over a fairly short period time, which could potentially be misleading if this "picture" was not representative of the patients' outcomes as a whole. The recommended follow-up interval is yearly. The mean interval length in our cohort was 239 days, but the actual intervals vary between a month and up to 3 years,

depending, for example, on how often the patient is actually seen or on the availability of data entry personnel.

Therefore data were analyzed at the patient level such that each patient contributed only 1 measurement to the analysis. This has the advantage that each patient's outcome data were based on all time periods available, thus providing a longer period of time to produce a more reliable estimate of the outcomes. For each patient, the median IgG level was calculated. Only IgG trough values were used. We included only those values that were obtained during the period in which the health outcomes were assessed (defined as within the health outcomes period or within 3 months on either side of this interval).

Outcomes were converted to the number of occurrences of each outcome per year to make comparisons possible. Patients who had their health outcomes assessed for a period of 1 month or less were excluded from the analysis.

Patients were subdivided according to their median IgG level, using 4, 7, 10, and 12 g/L as cutoff values. Four comparison categorizations divided patients into 2 groups: those with median IgG values of greater than or less than specific cutoff values. The final analysis divided patients into one of the 5 intervals.

We analyzed data first irrespective of the route of administration and then separately for intravenous (IVIG) and subcutaneous (SCIG) treatment. Furthermore, we examined whether the relationship between IgG levels and health outcomes varied depending on clinical features.

All 4 outcomes were found to have a positively skewed distribution. Therefore the Mann-Whitney test was used to compare between categorizations in which there were only 2 groups. The Kruskal-Wallis test was used for situations in which there were more than 2 groups.

RESULTS

Immunoglobulin levels

In the univariate analysis the IgG trough level was found to be significantly associated the with the IgG level at diagnosis, with the latter also being associated with the difference in IgG levels before and after immunoglobulin replacement (referred to as ΔIgG), IgA levels, and IgM levels. As expected, higher IgG levels at diagnosis were associated with higher IgG trough levels. Conversely, a higher IgG level at diagnosis was associated with a smaller change in IgG level between diagnosis and treatment. Patients with higher IgG levels at diagnosis also had higher IgA and IgM levels.

Pneumonia, splenomegaly, and sex were all significantly associated with divergent IgG trough levels.

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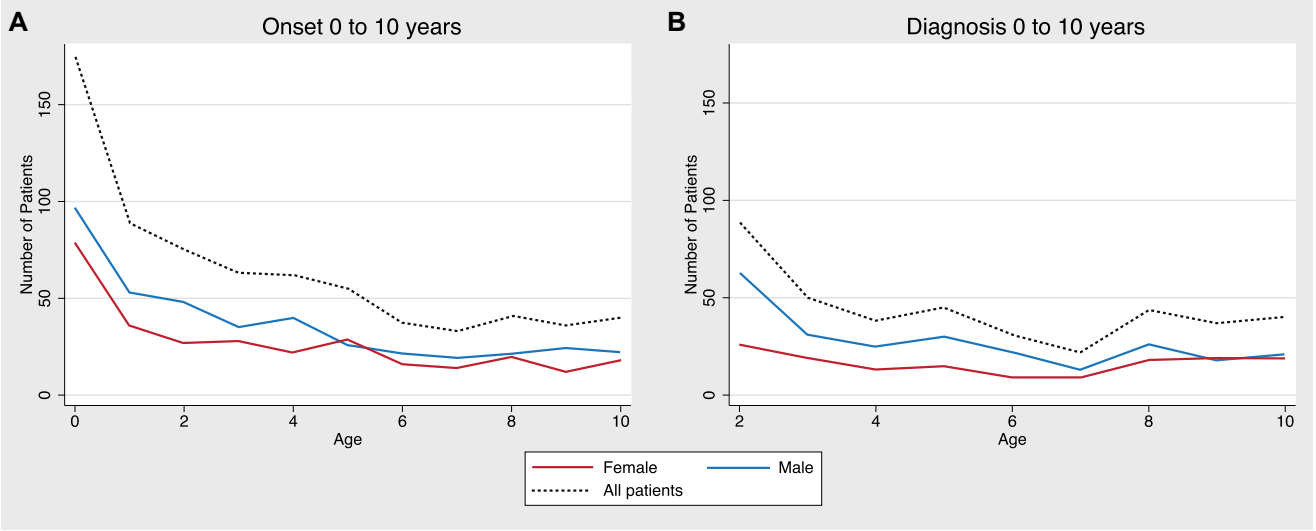

FIG E1. **A,** Age at onset of symptoms for ages 0 to 10 years. **B,** Age at diagnosis for ages 0 to 10 years.

TABLE E1. Contribution of each center to the evaluation

Center name	Children (C)/ adults (A)	Total patients	Patients with data on clinical features	Patients with quality-of-life data	Patients with IgG levels
France, CEREDIH (National registry)	C, A	894	0 (135)	3	841
Freiburg, Center for Chronic Immunodeficiency	C, A	224	187	134	173
The Netherlands, National registry	C, A	190	179	129	180
London, UCL Royal Free	C	144	119	142	143
Barcelona, Vall d'Hebron	C, A	139	18	6	25
Hannover, MHH, Immunology	A	105	51	59	74
Brno, Masaryk University	A	56	54	48	56
Leipzig, St Georg	C, A	54	29	11	36
Cambridge, Addenbrooke's	A	44	41	40	38
Dublin, St James's Hospital	A	38	15	8	38
London, Barts Health	C, A	34	25	30	28
Manchester	C, A	33	2	28	24
Krakow	C	32	24	29	32
Prague, University Hospital Motol	C	31	27	13	31
Munich, Dr von Haunersches	C	28	16	15	23
London, UCL, ICH/GOSH	C, A	26	0	16	27
Hannover, MHH, Pneumology	C	23	18	20	15
UZ Leuven	C	19	18	0	18
Bornova-Izmir	C, A	15	14	10	15
Jönköping	A	14	10	12	9
Cairo University	C	11	9	5	11
Dresden, University Hospital	C	10	8	10	3
Thessaloniki, Ippokration	C, A	10	8	3	10
Moscow, Russian State Children's Hospital	C	9	8	7	8
Bratislava, Medical School	C	8	7	8	8
Thessaloniki, Papageorgiou	C	8	7	8	8
Düsseldorf	C	7	4	2	3
Tallinn	C, A	6	4	6	6
		2212	902 (1037)	802	1883

The children/adult column indicates whether the center cares for children, adults, or both. The national registries in France and The Netherlands centrally gather data from more than 70 centers and include both children and adults. Data on clinical features were available for 135 French patients but not used in the analysis because of incompleteness.

TABLE E2. Data sets in the ESID Database used for this study

Patient information and diagnosis
Patient ID
Center ID
Center name
Country of center
Date of birth, year
Date of birth, month
Date of death, year
Date of death, month
Date of death, day
Status
Sex
Country
Affected gene
Date of genetic diagnosis, year
Date of genetic diagnosis, month
Date of clinical diagnosis, year
Date of clinical diagnosis, month
Date of onset of symptoms, year
Date of onset of symptoms, month
Patient visits
Date of patient visit
Immunoglobulin replacement therapy
Route of administration
Start date, year
Start date, month
Start date, day
Stop date, year
Stop date, month
Stop date, day
Reason stopped
Dose, value
Dose, unit
Relative dose, value
Relative dose, unit
Dose, frequency
Dose, interval
Autoimmunity, neoplasms, and concomitant diseases
ICD-10 code
ICD-10 text
Treatment
Infection history
ICD-10 code
ICD-10 text
Start, year
Start, month
Start, day
Stop, year
Stop, month
Stop, day
Approximate age at onset
IgG, IgA, and IgM
Date of sample
Laboratory value
Unit
Patient-reported health outcomes
Current visit date
Last visit date
Days in hospital because of the immunodeficiency, excluding outpatient visits and visits for immunoglobulin replacement
Days unable to perform daily duties because of immunodeficiency
Number of infectious episodes
Number of serious bacterial infections defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis or septic arthritis, visceral abscesses, or bacterial meningitis

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

TABLE E3. Prevalence of clinical features in single centers

Center	No.	Enteropathy	Autoimmunity	Granulomas	Bronchiectasis	Splenomegaly
Barcelona	18	0%	6%	0%	6%	6%
Barts and London	25	8%	20%	0%	48%	4%
Bornova-Izmir	14	7%	21%	7%	57%	14%
Bratislava	7	0%	0%	0%	14%	14%
Brno	54	7%	35%	15%	35%	52%
Cairo	9	11%	11%	0%	22%	11%
Cambridge, Addenbrooke's	41	2%	24%	5%	66%	24%
Dresden	8	0%	25%	0%	38%	0%
Dublin	15	0%	27%	7%	33%	13%
Düsseldorf	4	0%	0%	0%	0%	50%
Freiburg, Center for Chronic Immunodeficiency	188	13%	39%	18%	10%	62%
Hannover, Immunology	51	6%	16%	12%	27%	10%
Hannover, Pneumology	18	0%	28%	6%	22%	6%
Jönköping	10	0%	20%	0%	0%	0%
Krakow	24	8%	38%	0%	8%	8%
Leipzig	29	7%	17%	0%	0%	3%
London, UCL Royal Free	119	21%	38%	16%	56%	29%
Manchester	2	0%	50%	0%	0%	0%
Moscow	8	0%	25%	0%	0%	0%
Munich	16	6%	22%	13%	31%	19%
The Netherlands	179	4%	14%	3%	5%	1%
Prague	27	7%	33%	0%	11%	30%
Tallinn	4	0%	50%	0%	0%	25%
Thessaloniki, Ippokration	8	0%	88%	0%	13%	25%
Thessaloniki, Papegeorgiou	7	14%	29%	0%	29%	14%
UZ Leuven	18	6%	28%	11%	6%	11%

Center	No.	Splenectomy	Pneumonia	Lobectomy	Lymphoma	Solid tumor	Meningitis
Barcelona	18	0%	67%	0%	0%	6%	6%
Barts and London	25	4%	16%	0%	0%	4%	0%
Bornova-Izmir	14	0%	29%	0%	7%	0%	0%
Bratislava	7	0%	57%	0%	0%	0%	0%
Brno	54	0%	59%	0%	2%	4%	4%
Cairo	9	0%	78%	0%	0%	0%	0%
Cambridge, Addenbrooke's	41	2%	2%	0%	5%	0%	0%
Dresden	8	0%	50%	13%	0%	0%	13%
Dublin	15	0%	7%	7%	7%	7%	7%
Düsseldorf	4	0%	50%	0%	0%	0%	0%
Freiburg, Center for Chronic Immunodeficiency	188	4%	24%	0%	4%	6%	4%
Hannover, Immunology	51	0%	39%	0%	2%	8%	8%
Hannover, Pneumology	18	6%	33%	11%	0%	0%	6%
Jönköping	10	0%	30%	0%	0%	20%	0%
Krakow	24	0%	63%	0%	0%	8%	13%
Leipzig	29	0%	31%	0%	0%	0%	3%
London, UCL	119	7%	13%	6%	3%	4%	5%
Manchester	2	0%	0%	0%	0%	0%	0%
Moscow	8	0%	38%	0%	0%	0%	0%
Munich	16	0%	75%	0%	0%	6%	6%
The Netherlands	179	0%	38%	1%	3%	6%	4%
Prague	27	0%	22%	0%	0%	0%	0%
Tallinn	4	0%	50%	0%	0%	50%	0%
Thessaloniki, Ippokratio	8	0%	50%	0%	13%	0%	0%
Thessaloniki, Papegeorgiou	7	0%	0%	0%	0%	0%	0%
UZ Leuven	18	6%	50%	0%	0%	0%	0%

TABLE E4. Onset of lymphoma, autoimmunity, and splenomegaly in relation to diagnosis of CVID and initiation of immunoglobulin replacement

Time	Lymphoma (n = 75), no. (%)	Autoimmunity (n = 261), no. (%)	Splenomegaly (n = 226), no. (%)
Before diagnosis	11 (20%)	60 (49%)	4 (22%)
Year of diagnosis	19 (34%)	25 (20%)	5 (28%)
After initiation of immunoglobulin replacement	26 (46%)	38 (31%)	9 (50%)
Missing data	19	138	208

TABLE E5. Factor loadings in multivariate analysis, including IgG level at diagnosis and ΔIgG

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Splenomegaly			0.68		
Enteropathy				0.50	
Autoimmunity			0.68		
Granulomas			0.64		
Bronchiectasis					0.62
Lobectomy					0.68
IgG level at diagnosis	0.80				
IgG trough level		0.82			
ΔIgG		0.91			
IgA (log scale)	0.66				
IgM (log scale)	0.64				
Diagnostic delay				0.77	

Lymphoma, solid tumor, pneumonia, meningitis, age at onset, and sex do not contribute to any factor. Variables with a loading of 0.5 or greater indicate that the variable was associated with that factor component.

TABLE E6. Factor loadings in multivariate analysis, excluding IgG level at diagnosis and ΔIgG

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Splenomegaly			0.554		
Lymphoma					0.822
Solid tumor				−0.662	
Enteropathy					
Autoimmunity			0.547		
Granulomas			0.725		
Bronchiectasis	0.519				
Splenectomy					0.576
IgG trough level				0.556	
IgA (log scale)		0.656			
IgM (log scale)		0.793			
Age at diagnosis	0.748				
Diagnostic delay	0.730				

Pneumonia, meningitis, lobectomy, and sex do not contribute to any factor.

TABLE E7. Factor loadings in multivariate analysis restricted to 4 variables

Variable	Factor 1	Factor 2
Splenomegaly	0.73	
Enteropathy		0.90
Autoimmunity		0.51
Granulomas	0.80	

TABLE E8. Average immunoglobulin dosing frequencies in days

	Interval-level analysis		Patient-level analysis	
Center	**No. of intervals**	**Median (IQR)**	**No. of patients**	**Median (IQR)**
Barcelona	14	21 (21-21)	8	21 (21-26)
Bornova-Izmir	34	46 (31-46)	14	41 (34-46)
Bratislava	9	21 (21-30)	7	21 (21-30)
Brno	42	30 (30-30)	22	30 (26-30)
Cairo	2	30 (30-30)	1	30 (30-30)
Cambridge, Addenbrooke's	30	21 (21-21)	17	21 (21-21)
Dresden	6	30 (30-30)	2	26 (21-30)
Dublin	13	21 (22-22)	12	22 (22-22)
Düsseldorf	0	—	0	—
Freiburg, Center for Chronic Immunodeficiency	98	30 (30-30)	72	30 (30-30)
Hannover, Immunology	58	30 (21-30)	39	30 (21-30)
Hannover, Pneumology	17	30 (30-30)	12	30 (30-30)
Jönköping	8	30 (30-30)	2	30 (30-30)
Krakow	135	30 (30-30)	31	30 (30-30)
Leipzig	37	30 (30-30)	21	30 (30-30)
Leuven	15	30 (30-30)	11	30 (30-30)
London, Barts	20	21 (21-26)	14	21 (21-21)
London, UCL ICH/GOS	30	30 (30-30)	13	30 (30-30)
London, UCL Royal Free	161	22 (22-23)	77	22 (22-22)
Manchester	12	22 (22-22)	11	22 (22-22)
Moscow	14	30 (30-30)	6	30 (30-30)
Munich	18	30 (21-30)	13	30 (26-30)
The Netherlands	135	21 (21-30)	93	21 (21-30)
France, CEREDIH	458	30 (23-30)	388	30 (23-30)
Prague	81	30 (30-30)	22	30 (30-30)
Tallinn	7	30 (30-30)	6	30 (30-30)
Thessaloniki, Ippokration	11	30 (30-30)	5	30 (30-30)
Thessaloniki, Papageorgiou	4	30 (30-46)	4	30 (30-46)
All centers combined	1469	30 (22-30)	923	30 (23-30)