Long-term follow-up of 168 patients with X-linked agammaglobulinemia reveals increased morbidity and mortality

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Background: X-linked agammaglobulinemia (XLA) is the prototype of primary humoral immunodeficiencies. Long-term follow-up studies regarding disease-related complications and outcome are scarce.

Objective: Our aim was to describe the natural history of XLA.

Methods: A nationwide multicenter study based on the Italian Primary Immunodeficiency Network registry was established in 2000 in Italy. Affected patients were enrolled by documenting centers, and the patients' laboratory, clinical, and imaging data were recorded on an annual base.

Results: Data on the patients (N = 168) were derived from a cumulative follow-up of 1370 patient-years, with a mean follow-up of 8.35 years per patient. The mean age at diagnosis decreased after establishment of the Italian Primary Immunodeficiency Network registry (84 months before vs 23 months after). Respiratory, skin, and gastrointestinal manifestations were the most frequent clinical symptoms at diagnosis and during long-term follow-up. Regular immunoglobulin replacement treatment reduced the incidence of invasive infections. Affected patients developed chronic lung

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disease over time (47% after 40 years of follow-up) in the presence of chronic sinusitis (84%). Malignancies were documented in a minority of cases (3.7%). Overall survival for affected patients was significantly reduced when compared with that for the healthy male Italian population, and it further deteriorated in the presence of chronic lung disease. Conclusions: This is the first detailed long-term follow-up study for patients with XLA, revealing that although immunoglobulin replacement treatment reduces the incidence of invasive infections, it does not appear to influence the development of chronic lung disease. The overall survival of affected patients is reduced. Further studies are warranted to improve patients' clinical management and increase awareness among physicians. (J Allergy Clin Immunol 2020;146:429-37.)

Key words: *X-linked agammaglobulinemia, Bruton tyrosine kinase, chronic lung disease*

X-linked agammaglobulinemia (XLA) (also known as Bruton-type agammaglobulinemia [Online Mendelian Inheritance in Man No. 300755]) is a rare form of primary immunodeficiency with an X-recessive pattern of transmission that affects males and is characterized by severe reduction of peripheral B-cell percentage (less than 2%), severely reduced serum immunoglobulin levels of all classes, and lack of recall humoral response to antigens.[1] Ogden Carr Bruton, a pediatrician, described the first case of XLA in 1952.[2] In 1993, 2 separate groups identified the genetic cause of XLA in monoallelic mutations in Bruton tyrosine kinase (BTK), which encodes for a kinase essential for early B-cell development.[3,4] Since then, more than 500 different mutations in BTK have been identified (http://structure.bmc.lu.se/idbase/).[5] In recent decades, the prevalence of XLA has been estimated to be approximately 1 case per 250,000 live births.[6-10] One-third of cases are familial, whereas the remaining two-thirds of cases are believed to arise from new mutations. Clinical onset in affected patients typically occurs in early childhood, frequently in the first year of life, when maternal antibodies wane and the patients fail to produce their own immunoglobulins.[7,11-18] The spectrum of infectious manifestations is quite wide and may include infections of the upper and lower respiratory tracts, gastrointestinal infections, and invasive infections such as sepsis and meningitis. The pathogens involved are mainly encapsulated bacteria, but viruses and parasites may complicate the clinical course of the disease as well.[7,11-18] Once the diagnosis is made, immunoglobulin replacement treatment has been shown to be effective, at least in part, in reducing the incidence and frequency of the infectious episodes in affected patients.[7,11-19] Nonetheless, 1 of the major complications for patients with XLA is a high risk of development of bronchiectasis and chronic lung disease (CLD).[7,11-13,19]

Although XLA has been known for more than 6 decades, data in the literature regarding long-term follow-up of affected patients are lacking, thus rendering the natural history of this disease still not well characterized. In this study, we collected data on the clinical presentation, treatment, and follow-up of a large cohort of patients with XLA to better define the disease's natural history, real-life overall survival, and long-term associated comorbidities.

Abbreviations used
BTK: Bruton tyrosine kinase
CLD: Chronic lung disease
IPINet: Italian Primary Immunodeficiency Network
PVP: Postvaccination poliomyelitis
SCIG: Subcutaneous immunoglobulin
XLA: X-linked agammaglobulinemia

METHODS

Patient data

Patients' data were collected from the online database of the Italian Primary Immunodeficiency Network (IPINet) registry (https://www.aipeop.org/web/). A total of 60 medical centers that are members of the IPINet documented data for patients with XLA who were followed at their clinic at diagnosis and at least once during every year of follow-up. Enrollment data included the patient's personal data, family pedigree, date of diagnosis, immunologic data, clinical manifestations, and treatment at diagnosis and during follow-up. A questionnaire examining relevant clinical and immunologic features was completed annually on enrollment. This collective effort was initiated in 2000. Data included in this study were collected for the period from 2000 to 2017. Cumulative follow-up data for 1370 patient-years were collected, with a mean follow-up of 8.35 years per patient.

Flow cytometric evaluation of peripheral T- and B-lymphocyte percentages was performed at diagnosis by using mAbs (anti-CD3, anti-CD4, anti-CD8, and anti-CD19 or anti-CD20). Patients with a suspected diagnosis of XLA were analyzed for BTK mutations by Sanger sequencing or next-generation sequencing. Evaluation of BTK expression was performed in a limited number of patients.

Statistical analysis

Comparisons between patients and healthy subjects were performed by using the Student *t* test. The significance threshold was set at P less than .05. GraphPad Prism software (version 8) was used for statistical analysis (GraphPad Software Inc, La Jolla, Calif) ($*P < .05$; $**P < .01$; $***P < .001$; $****P < .0001$).

RESULTS

Patient cohort

In all, 168 male patients affected with XLA were included in the study. Their mean age at diagnosis was 66 months (median, 36 months; range, 1-592 months), with an evident descending trend in recent years (Fig 1, *A*). In particular, whereas the mean age at diagnosis for patients born before 2000 (118 of 168) was 84 months, the mean age at diagnosis for patients born after the year 2000 (50 of 168) was significantly lower (ie, 23 months), underlining the role of the IPINet registry and related activities in increasing awareness for XLA among physicians and specialists. A positive family history for XLA was identified in 66 of 168 patients (39.3%), whereas the cases of the remaining 102 of 168 patients (60.7%) were sporadic. No significant difference in mean age at diagnosis (64 months for familial vs 67 months for sporadic cases) was observed between the 2 groups.

Serum immunoglobulin levels at diagnosis

Serum immunoglobulin levels were low for all classes, with the following mean values: IgG, 191.4 mg/dL; IgA, 10.2 mg/dL; and IgM, 15.2 mg/dL (Fig 1, *B-D*, respectively). A small percentage of patients (21.4% [36 of 168]) presented with at least 1

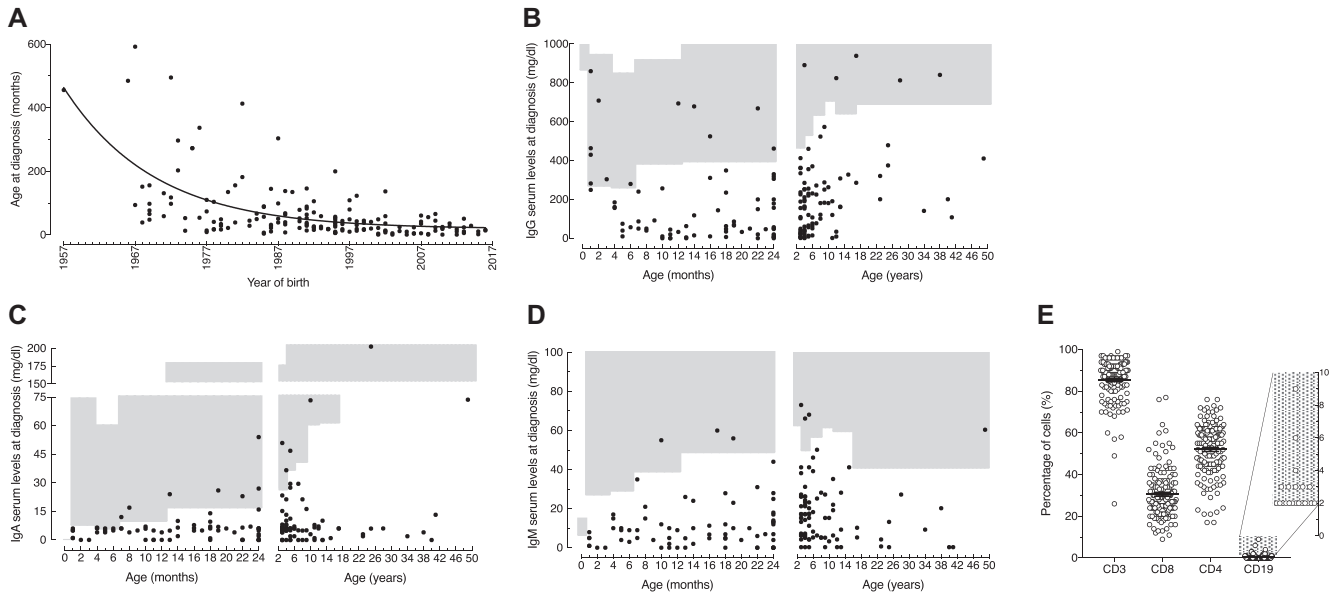

FIG 1. Age and immunologic presentation of 168 patients with XLA at diagnosis. **A**, Age at diagnosis (shown in months) in correlation with the year of birth. **B,** Serum levels of IgG at diagnosis (*gray areas depict normal values for age*). **C,** Serum IgA levels of IgA at diagnosis (*gray areas depict normal values for age).* **D,** Serum IgM levels at diagnosis (*gray areas depict normal values for age*). **E,** Peripheral lymphocyte subsets (CD3, CD8, CD4, and CD19) at diagnosis (*dotted light gray area depicts peripheral B-cell* percentages ≥*2%*).

immunoglobulin class within normal range for age (Fig 1, *B-D* and see Table E1 in this article's Online Repository at www.jacionline.org). Of these 36 patients, 17 showed normal serum IgG values for age. Of the latter 17 patients, 8 had an age at diagnosis less than or equal to 12 months, suggesting that the IgG was most likely of maternal origin. Of these 8 patients, 7 also had a positive family history for XLA. The single patient without a positive family history, who was less than 12 months of age, presented with undetectable IgA, IgM, and peripheral B-cell percentages (0%) (see Table E1). The remaining 9 patients with serum IgG levels within normal range for age showed a positive family history for XLA in 4 of 9 cases (44.4%) and low peripheral B-cell percentages (≤2%) in 7 of 9 cases (77.8%) (see Table E1). Of these 9 patients, 1 had normal IgG and peripheral B-cell percentages (9%), but low serum IgA and IgM levels for age with a positive family history for XLA (see Table E1). The remaining 19 patients showed low IgG levels for age, with either IgA or IgM level within the normal range (see Table E1). All 19 patients showed low peripheral B-cell percentages (≤2%); 7 of 19 patients had a positive family history for XLA (see Table E1).

Lymphocyte subsets at presentation

Peripheral lymphocyte subset evaluation was performed at diagnosis and showed normal $CD3^+$ T-cell percentages in all patients (mean percentage of $CD3^+$ cells, 84.9%), with conserved $CD8^+$ and $CD4^+$ T cell distribution (mean percentage of $CD8^+$ cells, 30.54%; mean percentage of $CD4^+$ cells, 52.1%) (Fig 1, *E*). Peripheral B-cell percentages were below 2% in the majority of cases (147 of 168 cases [87.5%]) (mean percentage of $CD19^+$ B cells, 0.58%). In all, 21 patients presented with of peripheral B-cell percentages of 2% or higher (Fig 1, *E* and see Table E2 in this article's Online Repository at www.jacionline.org). Of these 21 patients, had a positive family history for XLA; 13 of these 21 patients showed a reduction of all 3 immunoglobulin classes, whereas 7 showed a reduction of 1 of 3 immunoglobulin classes; 1 patient with 2 of 3 immunoglobulin classes within the normal range for age displayed a positive family history for XLA (see Table E2). Of the 21 patients, 13 presented with peripheral B-cell percentages of 2%, which is the classical cutoff for suspicion of XLA, with a positive family history for XLA in 6 cases; 8 of 13 patients had levels of all immunoglobulin classes below normal range for age. The remaining 8 patients with a peripheral B-cell percentage higher than 2% exhibited a positive family history in 5 of 8 cases, with only 3 of these 8 patients having 1 of 3 immunoglobulin classes within the normal range for age (see Table E2). Collectively, our data on patients' immunologic presentation at diagnosis suggest that the combination of peripheral B-cell percentages, serum immunoglobulin levels, and family history allow for identification of patients with XLA even in the minority of cases in which 1 of these parameters may not fully satisfy the classical diagnostic criteria for this disease.

BTK mutation analysis

Among the patients, 157 belonging to 125 families were genetically characterized whereas the remaining patients had reduced levels of BTK expression. Mutations were reported by using RefSeq NM_000061 under the Human Genome Variation Society recommendations. BTK sequencing revealed 104 different mutations, among which 20 were recurrent and 18 were novel (Table I and see also Table E3 in this article's Online Repository at www.jacionline.org).

In more detail, the most frequent types of mutations were missense mutations (49%), followed by indels (18%), nonsense mutations (17%), and mutations affecting splice sites (12%), with a minor incidence of large deletions (4%). Among the 18 novel mutations, missense and nonsense mutations were the most

TABLE I. The 18 novel mutations of BTK in 157 patients with XLA

Patient no.	BTK_EXON	BTK_MUT	BTK_EFF	Polyphen	Mutationtaster	CADD
1	2	c.40T>C	p.Ser14Pro	1/D	1/D	27.4
2	2	c.40T>C	p.Ser14Pro	1/D	1/D	27.4
3	2	c.A52del	p.Lys18Argfs*6	—	1/D	—
4	3	c.221delC	p.Pro74Leufs*47	—	1/D	—
5*	4	c.307C>T	p.Gln103*	—	1/D	29.3
6*	4	c.307C>T	p.Gln103*	—	1/D	29.3
7	6	c.493T>C	p.Cys165Arg	1/D	1/D	25.9
8	8	c.592_596delinsCTAACTACATA	Lys199Thrfs*3	—	1/D	—
9	IVS10	c.895-2A>G	Splicing defect	—	—	—
10*	12	c.1032T>G	p.Tyr344*	—	1/D	18.73
11*	12	c.1032T>G	p.Tyr344*	—	1/D	18.73
12*	12	c.1032T>G	p.Tyr344*	—	1/D	18.73
13	14	c.1228delA	Thr410Leufs*6	—	1/D	—
14	15	c.1375C>T	p.Gln459*	—	1/D	26
15	15	c.1399C>T	p.Gln467*	—	1/D	38
16	15	c.1507A>T	p.Lys503*	—	1/D	26.9
17*	15	c.1541C>A	p.Ser514*	—	1/D	28.5
18*	15	c.1541C>A	p.Ser514*	—	1/D	28.5
19	IVS15	c.1567-1G>A	Splicing defect	—	—	—
20	16	c.1579T>G	p.Cys527Arg	0.4/B	1/D	32
21	IVS16	c.1632-1G>A	Splicing defect	—	—	—
22	17	c.1691C>A	p.Ser564Tyr	1/D	1/D	22.7
23	17	c.1702_1704delGTC	p.Val568del	—	1/D	—

B, Benign; *CADD*, combined annotation-dependent depletion; *D*, damaging; *MUT*, mutation; *Polyphen*, polymorphism phenotyping.
*Familial cases.

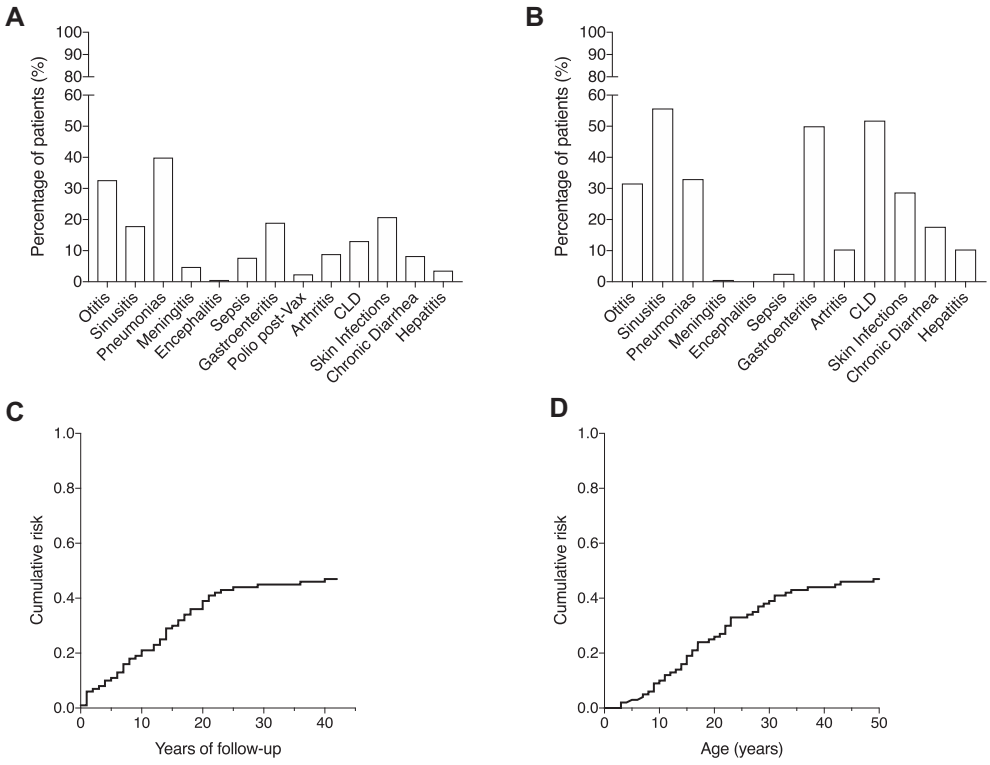

FIG 2. Clinical manifestations of patients with XLA at diagnosis and during follow-up. **A,** Clinical symptoms at diagnosis. **B,** Clinical complications during follow-up. **C,** Cumulative risk for the development of CLD based on years of follow-up for the affected patients. **D,** Cumulative risk for the development of CLD based on age of the affected patients. *post-VAX*, After vaccination.

frequent (8 and 7, respectively), followed by mutations affecting splice sites, indels, and large deletions (1 in each category) (Table I).

Clinical features at diagnosis

The prevalence and type of clinical manifestations before diagnosis are shown in Fig 2, *A*. Respiratory infections were the most frequent clinical features, with pneumonias recorded in 39.9% of patients (67 of 168), otitis media in 32.7% (55 of 168), and sinusitis in 17.9% (30 of 168). Of note, 13.1% of patients (22 of 168) were affected with CLD at diagnosis according to the results of a lung computed tomography scan (presence of bronchiectasis, peribronchial wall thickening, and atelectasias).[11] Besides presenting with respiratory infections, the affected patients frequently (in 35 of 168 cases [20.8%]) presented with skin infections. The gastrointestinal tract was also associated with a positive history for gastroenteritis in 19% of cases (32 of 168), whereas chronic diarrhea was reported in 8.3% of cases (14 of 168). Invasive infections were also reported at diagnosis: sepsis in 7.7% of patients (13 of 168), meningitis in 4.8% (8 of 168), and encephalitis in 0.6% (1 of 168). Postvaccination poliomyelitis (PVP) related to the oral attenuated Sabin vaccine was reported in 2.4% of cases (4 of 168). Finally, other manifestations such as arthritis and hepatitis were documented in 9.5% of affected subjects (16 of 168) and 3.6% of affected subjects (6 of 168), respectively.

Comparison of clinical presentation between familial and sporadic cases showed that respiratory, gastrointestinal, and skin infections were slightly more frequent among sporadic cases (see Fig E1, *A* in this article's Online Repository at www.jacionline.org). Encephalitis and sepsis were mostly seen among the sporadic cases (see Fig E1, *A*).

Patients' presentation was particularly different when the year of birth was taken into consideration. When the limit year of birth set at year 2000 (ie, the year of establishment of the IPINet registry for XLA) (see Fig E1, *B*), patients born before 2000 showed a more severe clinical history, with an increased prevalence of recurrent respiratory infections of the upper and lower respiratory tracts when compared with the prevalence in the patients born after 2000 (see Fig E1, *B*). Of note, all patients with CLD at diagnosis (13.1% [22 of 168]) were born before 2000. Invasive infections such as meningitis and sepsis were mainly observed in patients born before 2000, whereas encephalitis and PVP were exclusively reported in patients born before 2000. An increased prevalence of gastrointestinal and skin involvement was also observed in patients born before 2000 (see Fig E1, *B*).

Clinical features during follow-up

During a cumulative follow-up of 1370 patient-years, 164 patients with XLA who were receiving regular immunoglobulin replacement treatment were followed for a mean follow-up period of 8.35 years per patient (range, 1-18 years). The most common clinical manifestations registered during follow-up were respiratory infections (Fig 2, *B*). In more detail, 34.1% of patients (56 of 164) had pneumonias, with a mean number of 0.08 episodes per patient-year (Table II); 33.5% of patients (55 of 164) presented with otitis media, with a mean number of 0.095 episodes per patient-year (Table II); and 56.7% (93 of 164) of subjects experienced sinusitis, with a mean number of 0.28 episodes per patient-year (Table II).

TABLE II. Incidence of infectious episodes among patients with XLA during follow-up

Infection	No. of patients (%)	No. of episodes	Episodes/ patient-year
Pneumonia	56 (34.1%)	107	0.08
Otitis	55 (33.5%)	130	0.095
Sinusitis	93 (56.7%)	382	0.28
Sepsis	4 (2.4%)	4	0.003
Meningitis	1 (0.6%)	1	0.0007
Encephalitis	0 (0%)	0	0
Arthritis	17 (10.4%)	26	0.02
Gastroenteritis	86 (52.4%)	198	0.14
Skin infection	50 (30.5%)	113	0.08

Although CLD was present at diagnosis in 13.1% of patients (22 of 168), during follow-up and during regular immunoglobulin replacement treatment, another 38.4% of patients (63 of 164) developed CLD, reaching a combined 51.8% of patients with XLA (85 of 164) who were affected with CLD. The diagnosis of CLD was made after an overall mean follow-up period of 12.78 years (range, 1-39 years) at an overall mean patient age of 19.67 years (range, 2-43 years). Development of CLD was not associated with the IgG dose administered for immunoglobulin replacement treatment (see Fig E2 in this article's Online Repository at www.jacionline.org). A small percentage of patients with XLA (15.8%) were undergoing antibiotic prophylaxis before the development of CLD; this percentage increased on diagnosis of CLD (40.3%). The long-term follow-up of our cohort of patients with XLA allowed us to calculate the real-life cumulative risk for development of CLD among patients with XLA, which turned out to be 47% after 40 years of follow-up (Fig 2, *C*). The cumulative risk for development of CLD at 50 years of age was 47% (Fig 2, *D*).

Chronic sinusitis based on pathologic computed tomography scans and clinical criteria was present in 56.7% of patients (93 of 164) during the last follow-up. The mean patient age at diagnosis of chronic sinusitis was 16.29 years (range, 4-41 years), with a mean follow-up of 13.56 years (range, 1-30 years). Of note, during the last follow-up, 53 of 164 patients with XLA showed both chronic sinusitis and CLD.

Gastrointestinal involvement was identified in 52.4% of patients (86 of 164), with a mean number of 0.14 episodes per patient-year (Table II). Skin infections were reported in 30.5% of patients (50 of 164), with a mean number of 0.08 episodes per patient-year (Table II). Arthritis was recorded in 10.4% of patients (26 of 164), with a mean number of 0.02 episodes per patient-year (Table II). Finally, invasive infections such as sepsis, meningitis, and encephalitis were registered in 2.4% (4 of 164), 0.6% (1 of 164), and 0% of subjects, respectively (Table II). Although the majority of clinical complications during follow-up showed a similar prevalence between sporadic and familial cases, invasive infections of the central nervous system were reported only in the sporadic cases.

Pathogen isolation

As previously reported,[7,11] identifying the cause of infectious complications in XLA is not always feasible. Considering the long-term follow-up and the size of our XLA cohort, we analyzed the pathogens isolated during the most frequent infectious

TABLE III. Malignancies diagnosed in patients with XLA during follow-up

Patient no.	Year of birth	Age at diagnosis of malignancy, y	Type of malignancy	Status	% of malignancies in XLA	% of malignancies in healthy Italian males*
8	1999	11	Ependymal astrocytoma variant giant cells	Alive	0.61	0.0022
30	1972	33	Colon adenocarcinoma	Alive	1.20	0.0041
74†	1969	38	Liver carcinoma HCV^+	Dead	0.61	0.0033
77	1980	36	Papillary thyroid carcinoma, follicular type	Alive	0.61	0.0109
78	1980	34	Colon adenocarcinoma	Dead	1.20	0.0041
88	1967	37	Gastric carcinoma	Dead	0.61	0.0012

HCV^+, Hepatitis C virus–positive.
*Data from https://gco.iarc.fr.
†Familial case.

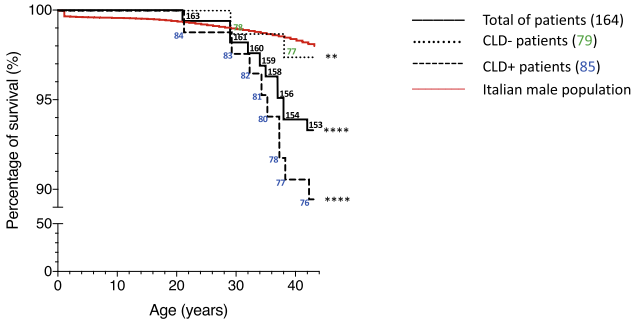

FIG 3. Survival of patients with XLA during long-term follow-up. Survival curve of affected patients (*black line indicates total, dotted line indicates patients without CLD, and dashed line indicates patients with CLD*) compared with the survival of age-matched Italian males (*red line*) (source, www.istat.it). The numbers indicate patients censored at each time point (*black indicates total, green indicates patients without CLD, and blue indicates patients with CLD*). Comparisons between patients and the general population were performed by using the Student *t* test. Significance threshold was set at *P* less than .05. Statistical analysis was performed by using GraphPad Prism software, version 8 (GraphPad Software Inc). $*P < .05$; $**P < .01$; $***P < .001$; $****P < .0001$. *CLD-*, Patients without CLD; *CLD+*, patients with CLD.

complications involving the lungs, gastrointestinal tract, and skin. A total of 107 pneumonia episodes were recorded. Data on pathogen isolation from sputum cultures were available in 25% of cases. *Haemophilus influenzae* and *Streptococcus pneumoniae* were the most frequent pathogens isolated (at rates of 53.58% and 17.86%, respectively), followed by *Pseudomonas spp* (10.71%), *Staphylococcus spp* (7.14%), *Klebsiella pneumoniae* (3.57%), *Branhamella catharralis* (3.57%), and *Pneumocystis jiroveci* (3.57%) (see Fig E3, *A* in this article's Online Repository at www.jacionline.org).

During follow-up, a total of 200 episodes of gastrointestinal manifestations were registered. Pathogens were isolated in only 18.5% of cases. *Giardia lamblia* was the most frequently isolated pathogen (48.65%), followed by *Salmonella* (24.32%), *Campylobacter* (18.92%), *Escherichia coli* (5.41%), and *Blastocistis hominis* (2.70%) (see Fig E3, *B*).

Finally, a total of 115 episodes of skin infections were reported. Pathogens were isolated in 28.7% of cases. The most frequent pathogen was *Staphylococcus aureus* (75.75%), followed by herpesvirus (21.21%) and *Candida spp* (3.03%) (see Fig E3, *C*).

Genotype-phenotype correlation in XLA

Considering the size of our cohort and the long-term follow-up, we investigated whether a genotype-phenotype correlation could be established in XLA, both at diagnosis and during follow-up. Mutations were divided in 5 separate groups (missense mutations, nonsense mutations, indels, splicing mutations, and deletions), and symptoms were evaluated for patients belonging to each group. Our data did not reveal a significant genotype-phenotype correlation in XLA either at diagnosis or during follow-up (see Figs E4 and E5 in this article's Online Repository at www.jacionline.org).

Malignancy

During follow-up, malignancy was diagnosed in a minority of patients with XLA (3.7% [6 of 164]) (Table III). Four of 6 malignancies were localized in the gastrointestinal tract: 2 in the colon, 1 in the stomach, and 1 in the liver. The remaining 2 malignancies involved the thyroid gland and the central nervous system (Table III). Of these 6 patients, 3 (50%) had died due to the malignancy at the last follow-up. No lymphomas were reported in this cohort. The incidence of the aforementioned malignancies in patients with XLA was higher when compared with that reported for healthy male Italians of the same age group (data from www.gco.iarc.fr) (Table III).

Survival

Long-term follow-up data regarding survival of patients with XLA are limited. Analysis of our cohort's data shows that the overall survival rate at 43 years of age was 92.7%, which is significantly lower than the rate for age-matched healthy controls (98%) (source, www.istat.it) (Fig 3). Subdivision of patients with XLA on the basis of presence or absence of CLD revealed that patients with CLD showed an even lower survival at 43 years of age (90.5%), which is significantly lower than the rate for age-matched healthy controls (Fig 3). Of note, although the absence of CLD in XLA ameliorates survival of patients at 43 years of age (97.4%), their survival still remains significantly lower when compared with that of healthy age-matched controls (Fig 3). The causes of death for 13 patients with XLA are reported in Table IV. All of the deceased patients were born before the year 2000.

Immunoglobulin replacement treatment

During follow-up, all patients were undergoing regular immunoglobulin replacement treatment. At the last follow-up, the endovenous (intravenous immunoglobulin) and subcutaneous routes of administration were almost equally represented: 51% versus 49%, respectively (Fig 4). Regarding the subcutaneous

TABLE IV. Patients with XLA who died during long-term follow-up

Patient no.	Year of birth	Age at diagnosis, y	Age at death, y	Cause of death
10*	1974	5	29	Infectious pneumonia
35	1966	40	42	Septic shock
41*	1979	1	37	Neuroacanthosis
43	1999	3	3	Pseudomonas sepsis
74*	1969	8	38	Cardiac arrest/liver disease
78	1980	11	38	Colon adenocarcinoma
86	1981	12	19	Car accident
88	1967	7	37	Gastric carcinoma
96	1972	6	21	Cardiorespiratory failure
104	1969	13	35	Cardiorespiratory failure
145	1969	4	34	Chronic lung disease/cardiac arrest
146	1986	1	29	Cerebral hemorrhage/thrombocytopenia/liver cirrhosis
149*	1968	12	32	*Pneumocistis jirovecii* infection/cardiac arrest

*Familial case.

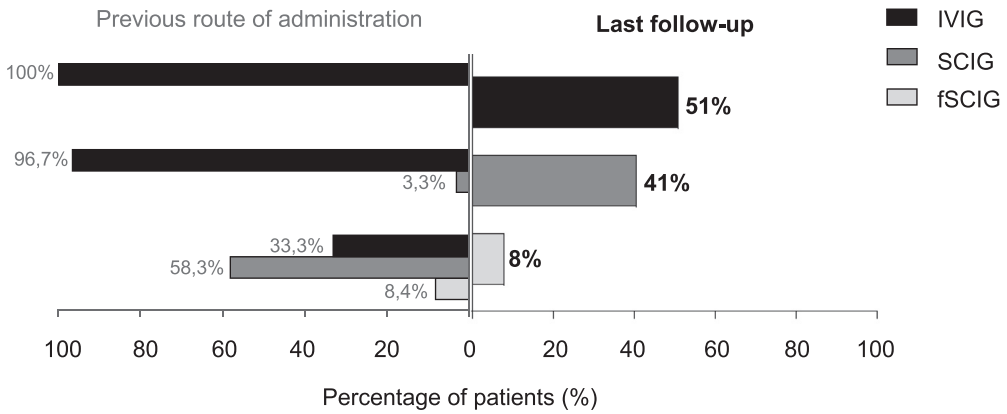

FIG 4. Immunoglobulin replacement treatment in Italian patients with XLA. Immunoglobulin replacement treatment (*black bar indicates intravenous immunoglobulin [IVIG], dark gray bar indicates SCIG, and light gray bar indicates facilitated SCIG [fSCIG]*) at last follow-up (*right panel*), previous route of immunoglobulin administration (*left panel*) for patients undergoing IVIG (*upper left panel*), SCIG (*middle left panel*), and fSCIG (*lower left panel*) replacement treatment.

route, 41% of patients were treated with conventional products (subcutaneous immunoglobulin [SCIG]), whereas 8% were treated with facilitated SCIG products. Almost all of the patients who were undergoing SCIG treatment (96.7%) had been previously treated with intravenous immunoglobulin, and 58.3% of patients undergoing facilitated SCIG treatment had been previously treated mainly with SCIG (Fig 4).

DISCUSSION

In a nationwide longitudinal collaborative effort coordinated by IPINet to better define the natural history of XLA, 168 affected patients with documented XLA were regularly evaluated for a cumulative follow-up for 1370 patient-years, the longest reported to date.

The overall mean age at diagnosis was 66 months. Introduction of the national XLA registry in 2000 determined a reduction in the diagnostic delay from 84 months (before 2000) to 23 months (after 2000), suggesting that the establishment of a nationwide registry for primary immunodeficiencies increases awareness among physicians and leads to early diagnosis for affected patients. In fact, in a recent cohort study of 174 patients with agammaglobulinemia who did not utilize a nationwide registry,[14] the average age at diagnosis was 7.09 plus or minus 3.98 years, further underlining the potential role of a national registry for primary immunodeficiencies in increasing awareness among physicians and thus leading to earlier diagnosis for affected patients.

The immunologic presentation of affected patients at onset satisfied the classical diagnostic criteria in the majority of cases. For the remaining cases, diagnosis of XLA was achieved by integrating the immunoglobulin class levels of all classes with the percentages of peripheral B cells and family history for XLA, underlining how combined use of these 3 parameters allows for diagnosis of XLA even in the minority of cases without complete satisfaction of the classical diagnostic criteria for this disease.

The mean age at diagnosis was unexpectedly similar between sporadic and familial cases (67 months vs 64 months, respectively). A similar diagnostic delay for familial cases was observed in another cohort study, in which only one-third of patients with a positive family history had their disease diagnosed before becoming symptomatic,[7] further underscoring the idea that physicians should pay attention to positive family history to achieve early diagnosis of XLA.

Infections of the respiratory tract—mainly otitis media, pneumonia, and sinusitis—were the most common clinical presentations at onset, in accordance with previously reported

data.[7,11-19] Of note, 13.1% of affected patients were affected with CLD at diagnosis. The occurrence of this complication already at diagnosis may be partially explained by various factors such as advanced age, delayed diagnosis, and initial treatment with intramuscular immunoglobulin (which is known to be considerably less effective than endovenous immunoglobulin in reducing the incidence of respiratory infections). Gastrointestinal infections were reported in 19% of patients, confirming that this is a frequent comorbidity, as previously reported.[7,11-20] The incidence of PVP due to the oral attenuated Sabin vaccine was 2.4%, which is quite a bit higher than in previous reports (1%).[7] Both PVP and encephalitis were exclusively documented for patients born before establishment of the IPINet registry in 2000. Regarding PVP, this is also related to the fact that after 2002, the national vaccine schedule has included only the inactivated Salk vaccine.

During follow-up and during regular immunoglobulin replacement treatment, infections of the respiratory tract, such as otitis media, pneumonia, and sinusitis, remained among the major clinical burdens for patients with XLA, suggesting that the lack of mucosal IgA cannot be adequately compensated for by polyspecific IgG replacement treatment. A recent meta-analysis[21] demonstrated that increasing the administered dose of IgG in patients affected with primary immune deficiencies may reduce the incidence of pneumonias and thus also reduce the risk of development of CLD. The high prevalence of CLD in our cohort suggests that regular IgG supplementation does not prevent development of this complication. The long-term follow-up of our cohort allowed us to calculate the cumulative risk of CLD, which is equal to 47% after 40 years of follow-up and equal to 47% at 50 years of age, findings that have not been reported before. In our previous study,[11] the prevalence of CLD was higher, but this was dependent on the composition of the cohort, including the mean age at diagnosis and the type of treatment received. In any case, these findings underline the idea that the development of CLD is a real-life complication in XLA and may affect almost half of affected patients by their 40s and 50s. Considering the impact of CLD on everyday life[22] and especially on long-term outcome, physicians should pay more attention to lung morbidity in XLA and consider, as early as possible, a personalized respiratory physiotherapy program and/or an antibiotic prophylaxis[23] regimen for affected patients.

Gastrointestinal and skin infections were recorded in a significant number of patients, consistent with previous XLA case series.[7,11-13] Previous studies have suggested that the gastrointestinal tract is frequently involved in tumor transformation in patients with XLA.[24-38] In our cohort, 4 patients with XLA developed a tumor of the gastrointestinal tract during follow-up (1 gastric adenocarcinoma, 1 liver carcinoma, and 2 colon adenocarcinomas).

Finally, the overall survival rate for patients with XLA was 92.7% at 43 years of age, and CLD was the major factor found to increase the mortality of patients with XLA, which is in agreement with an international survey reporting that CLD was the leading cause of death among patients with XLA.[19] This is the first real-life definition of long-term survival in patients with XLA, because previously published data for patient registries had a limited follow-up period (4.5 years).[7]

In conclusion, our data describe in a detailed and substantial manner the natural history of XLA during the longest follow-up described to date and underline that immunoglobulin replacement treatment is not sufficient to control all comorbidities that arise over the years. Considering that the life expectancy of affected patients is reduced when compared with that of age-matched healthy controls, clinical management should focus on the prevention and prompt treatment of associated complications, mainly CLD, to improve patients' quality of life and overall survival.

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Key messages

- **Patients affected with XLA experience respiratory, cutaneous, and gastrointestinal complications.**
- **Despite regular immunoglobulin replacement treatment, affected patients tend to develop CLD.**
- **The overall survival of affected patients is significantly reduced when compared with that of healthy male subjects.**

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