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Phenotype, genotype, treatment, and survival outcomes in patients with X-linked inhibitor of apoptosis deficiency

Linlin Yang, MD, PhD,[a,b,c] Claire Booth, MD, PhD,[d,e] Carsten Speckmann, MD,[f,g] Markus G. Seidel, MD,[h] Austen J. J. Worth, MD, PhD,[d] Gerhard Kindle, MD,[f] Arjan C. Lankester, MD, PhD,[i] Bodo Grimbacher, MD,[b,f,j,k,l] the ESID Clinical and Registry Working Parties,* Andrew R. Gennery, MD, PhD,[m] Mikko R. J. Seppanen, MD,[n] Emma C. Morris, MD, PhD,[a,b] and Siobhan O. Burns, MD, PhD[a,b]

London and Newcastle upon Tyne, United Kingdom; Shenzhen, China; Freiburg, Germany; Graz, Austria; Leiden, The Netherlands; and Helsinki, Finland

Background: X-linked inhibitor of apoptosis (XIAP) deficiency is a rare primary immunodeficiency disease caused by *XIAP* gene mutations. A broad range of phenotype, severity, and age at onset present challenges for patient management.

Objective: We sought to characterize the phenotype, treatment, and survival outcomes of XIAP deficiency and to assess parameters influencing prognosis.

Methods: Data published from 2006 to 2020 were retrospectively analyzed.

Results: A total of 167 patients from 117 families with XIAP deficiency were reported with 90 different mutations. A wide spectrum of clinical features were seen, of which hemophagocytic lymphohistiocytosis (HLH) and inflammatory bowel disease were the most common. Patients frequently developed multiple features with no clear genotype–phenotype correlation. A total of 117 patients were managed conservatively and 50 underwent hematopoietic stem-cell transplantation (HSCT), with respective overall survival probabilities of 90% and 53% at age 16 years. The predominant indication for HSCT was early-onset HLH. Active HLH and myeloablative conditioning regimens increased HSCT-related mortality, although HSCT outcome was much better after 2015 than before. For conservatively managed patients reaching adulthood, survival probabilities were 86% at age 30 years and 37% by age 52 years, with worse outcomes for patients developing the disease before the age of 5 years or with new disease features in adulthood. Nine asymptomatic mutation carriers with a median age of 13.5 years were identified.

Conclusions: Our study demonstrates the variable nature of XIAP deficiency, which evolves over life for individual patients. Better therapeutic strategies and prospective studies are required to reduce morbidity and mortality and improve decision making and long-term outcomes for patients with XIAP deficiency. (J Allergy Clin Immunol 2022;150:456-66.)

Key words: *XIAP deficiency, HLH, IBD, HSCT, conservative treatment, adult, primary immunodeficiency, X-linked inhibitor of apoptosis, phenotype, therapy, survival outcomes*

X-linked inhibitor of apoptosis (XIAP) deficiency, also called X-linked lymphoproliferative disease type 2 or XLP-2, is a rare primary immunodeficiency caused by *XIAP* (formerly *BIRC4*) gene mutations.[1] The *BIRC4* gene encodes the XIAP protein that is critical for multiple cell responses, not only preventing cell death by directly inhibiting caspase activities but also regulating nucleotide binding oligomerization domain containing 2 (NOD2)-dependent nuclear factor kappa–light-chain enhancer of activated B cells and mitogen-activated protein kinase activation by its ubiquitin ligase activity.[2-7] Reduced or absent XIAP expression has been shown to enhance apoptosis, reduce

From [a]the Department of Clinical Immunology, Royal Free London NHS Foundation Trust, London; [b]the Institute for Immunity and Transplantation, University College London, London; [c]the Department of Hematology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen; [d]the Department of Immunology and Gene Therapy, Great Ormond Street Hospital for Children NHS Trust, London; [e]Molecular and Cellular Immunology, UCL Great Ormond Street Institute of Child Health, London; [f]the Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center—University of Freiburg, Freiburg; [g]the Center for Pediatrics and Adolescent Medicine, Department of Pediatric Hematology and Oncology, Faculty of Medicine, Medical Center—University of Freiburg, Freiburg; [h]the Research Unit for Pediatric Hematology and Immunology, Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz; [i]the Department of Pediatrics, Stem Cell Transplantation Program, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden; [j]DZIF—German Center for Infection Research, Satellite Center Freiburg, Freiburg; [k]CIBSS—Centre for Integrative Biological Signalling Studies, Albert-Ludwigs University, Freiburg; [l]RESIST—Cluster of Excellence 2155 to Hanover Medical School, Satellite Center Freiburg, Freiburg; [m]the Translational and Clinical Research Institute, Newcastle University and Pediatric Immunology + HSCT, Great North Children's Hospital, Newcastle upon Tyne; and [n]the HUS Rare Disease Center, Children and Adolescents, University of Helsinki and Helsinki University Hospital, Helsinki.

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Corresponding author: Siobhan O. Burns, University College London, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, England, United Kingdom. E-mail: siobhan.burns@ucl.ac.uk.

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Abbreviations used
BIRC4: Baculoviral IAP repeat-containing 4
HLH: Hemophagocytic lymphohistiocytosis
HSCT: Hematopoietic stem-cell transplantation
IBD: Inflammatory bowel disease
MAC: Myeloablative conditioning
NOD2: Nucleotide binding oligomerization domain containing 2
OS: Overall survival
RIC: Reduced-intensity conditioning
XIAP: X-linked inhibitor of apoptosis

autophagy, and interrupt NOD2-mediated inflammatory signaling, with impact on both innate and adaptive immunity.[2,3,8-12] XIAP deficiency in humans was first identified in 2006 as a novel genetic disorder causing immunodeficiency, and since then, more than 100 affected individuals have been reported worldwide, broadening the clinical picture.[1,10,13-61] Earlier reports were dominated by severe phenotypes associated with hemophagocytic lymphohistiocytosis (HLH), splenomegaly, and inflammatory bowel disease (IBD). The variability of the disease condition has become more apparent with increased reporting. The diversity of disease phenotype, breadth of severity (which can be from asymptomatic to fatal), and unpredictable onset between early infancy to adulthood present significant challenges for decision making in patient management.

Allogeneic hematopoietic stem-cell transplantation (HSCT) has been recognized as the only curative treatment for XIAP deficiency and is most often used in pediatric patients with severe HLH and/or IBD. However, as a result of the relatively high transplant-related mortality in some described cohorts, conservative treatment has been preferred for patients with milder disease phenotypes, or older age.[21] No systematic studies have been performed to compare the survival outcomes of transplanted and conservatively managed patients in childhood or adulthood, so uncertainty remains around the timing and patient selection for HSCT. Therefore, we conducted this retrospective study of published cases to better understand the disease course of patients with XIAP deficiency and the impact of treatment.

METHODS

We collected retrospective data published from 2006 to 2020 in electronic databases such as PubMed by using the following search terms: X-linked inhibitor of apoptosis protein, XIAP, X-linked inhibitor of apoptosis protein deficiency, XIAP deficiency, BIRC4 deficiency, *XIAP* mutations, *BIRC4* mutations, mutations in *XIAP,* mutations in *BIRC4, XIAP* variant, *BIRC4* variant, and X-linked lymphoproliferative syndrome. In this study, data from a total of 167 patients using our search items were included to summarize clinical features, genetic mutations, treatments, and survival outcomes. All studies were analyzed to identify duplicate patients on the basis of mutation, pedigree, and clinical phenotype details, and duplicate patients were excluded from analysis. Female carriers were excluded.

Clinical presentations were classified into HLH, IBD, HLH-independent splenomegaly, hypogammaglobulinemia, infections, fevers, nonabscess skin symptoms, autoimmune disorders, liver disorders, and other less common features. Partial HLH that fulfilled fewer than 5 of 8 diagnostic criteria of HLH-2004[62] was classified into "others." Splenomegaly was considered to be HLH independent only in patients who were not described to subsequently develop HLH.

We performed Kaplan-Meier analysis using GraphPad Prism 9 software (GraphPad Software, La Jolla, Calif) to estimate the overall survival (OS) probabilities of patients with XIAP deficiency, and we used the log-rank test to compare survival between groups. The Student *t* test was used to compare the frequency of certain phenotypes and age at onset between groups. $P < .05$ was considered to be statistically significant: $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.

RESULTS

Clinical, genetic, and molecular phenotypes in XIAP deficiency

To date, 51 reports describing 167 individuals from 117 families carrying *XIAP* mutations were identified using our search strategy (see Table E1 in this article's Online Repository at www.jacionline.org).[1,10,13-61] While HLH and IBD were most common (60% and 30% of patients respectively), a wide spectrum of other clinical features were reported, including infections (19%), HLH-independent splenomegaly (14%), hypogammaglobulinemia (13%), liver disease (13%), autoimmune disorders (9%), fever (8%), dermatologic symptoms (2%), and other less common features (19%) (Fig 1, *A*). HLH typically occurred earlier than other manifestations, with a median age at onset of 2.5 years (range 0-28 years) (see Table E2 in this article's Online Repository). HLH was often triggered by Epstein-Barr virus infection (37/100, 37%), and in a small number of cases, other herpesviruses were reported (cytomegalovirus n = 4; human herpesvirus 6 n = 2; herpes simplex virus type 1 n = 1). Other features of XIAP deficiency displayed a wide range in age at onset, although skin manifestations (including abscesses and noninfectious presentations) and autoimmune complications typically occurred outside early childhood (Fig 1, *B,* and Table E2). For patients with clinical manifestations, 88 patients (52%) were reported to have more than 1 distinct phenotype throughout their life (Fig 1, *C*). Nine asymptomatic individuals identified via other symptomatic family members were reported (Fig 1, *C*).

The most common features at first presentation were HLH and IBD (56% and 20% respectively; Fig 1, *D*). Other features presented first in a significant minority of patients: splenomegaly (13%), infections (7%), hypogammaglobulinemia (4%), autoimmune disorders (3%), fevers (3%), liver diseases (1%), and other less common phenotypes (5%). For some patients (12/167, 7%), the first presenting symptom was reported to occur in adulthood (≥16 years of age) (Fig 1, *E*).

Ninety different mutations in *XIAP* were described in identified reports, including 34 frameshift mutations, 23 missense mutations, 13 deletions of exons/amino acids, 16 nonsense mutations, and 4 splice-site mutations (Fig 2, Table E1). Mutations distribute throughout the entire gene and all 5 domains of the encoded protein. Eight mutations, comprising R381X, R238X, R222X, N341YfsX348, K299LfsX307, Q332EfsX347, E349del, and R443H, were frequently detected in more than 3 families. Although there was no overall genotype–phenotype correlation, E349del was notable for presentation with primary hypogammaglobulinemia (3/3).

XIAP protein expression was determined in 63 patients, with 59% demonstrating absent protein expression, 17% demonstrating significantly reduced protein expression, 14% demonstrating moderately reduced expression, and 10% patients having slightly reduced or equivalent expression to health controls (see Table E3 in this article's Online

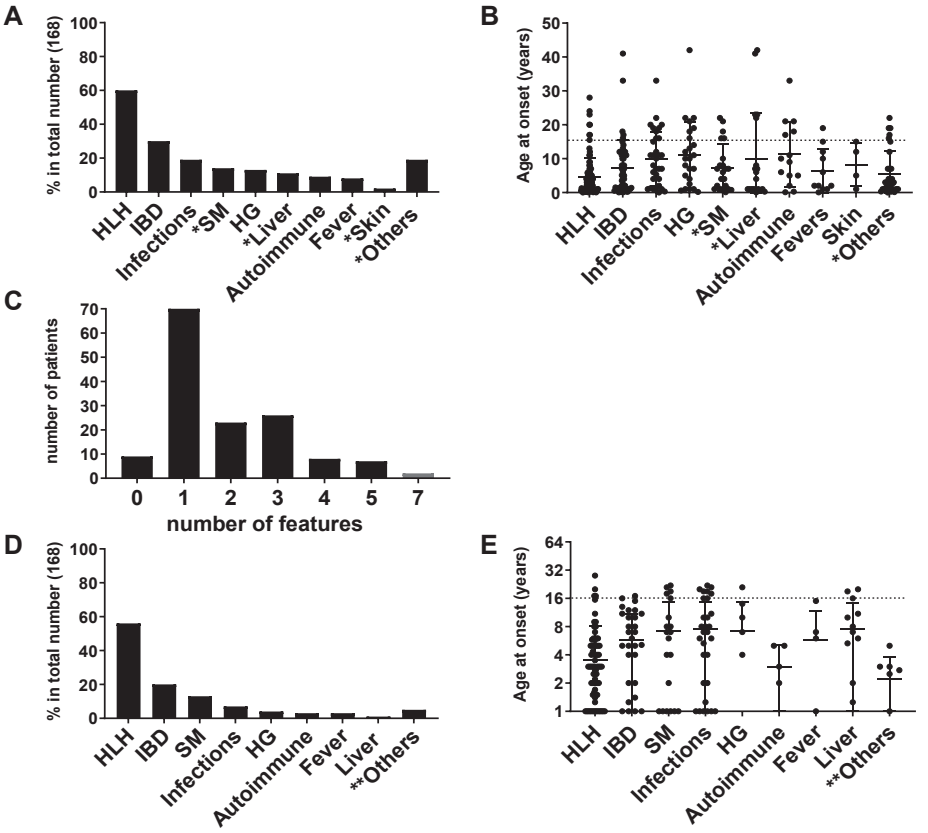

FIG 1. Clinical presentation and age at onset reported in XIAP deficiency. **A** and **B,** Clinical features and corresponding age at onset presented in patients with XIAP deficiency. **SM,* HLH-independent splenomegaly; *HG,* hypogammaglobulinemia; *Liver, liver disorders, including hepatitis, liver dysfunction, and liver failure; *Skin, symptoms without abscesses. **C,** Number of features developed in each individual. **D** and **E,** Initial features and corresponding age at onset presented in patients. *Others, including rare cases of partial HLH, diarrhea, hypersplenism, nodular lung disease, granulomatous and lymphocytic interstitial lung disease, failure to thrive, seizure, ventricular septal defect, facial palsy, encephalitis, IgA vasculitis, organ failure, and malignant tumor. **Others, including partial HLH, skin rash, severe diarrhea, renal failure, leukocytosis and thrombocytopenia, and neutropenia.

Repository at www.jacionline.org). There was no significant difference in the number of clinical features seen in patients with residual versus absent XIAP expression (Fig 3, *A*). Although patients with absent expression presented earlier than those with residual protein (median age 2.5 vs 4.5 years), this did not reach statistical significance in this cohort (Fig 3, *B*). Early age at splenomegaly onset significantly correlated with absent XIAP expression ($P = .01$, Fig 3, *C*), but no other significant correlations were seen for clinical features and XIAP expression.

We specifically examined 35 patients identified with missense mutations, resulting in variable expression of XIAP protein (reported to range from normal to absent). There was no difference in the most common presenting features (HLH and IBD), OS, age at onset, or severity (11/35 underwent HSCT at a median age of 5 years, range 0.4-15 years) in the missense group compared to patients bearing other types of loss-of-function mutations (of whom 39/132 underwent HSCT at a median age of 3.5 years, range 0.4-21 years) (see Fig E1 in this article's Online Repository at www.jacionline.org).

HSCT outcomes in XIAP deficiency

Of 167 patients, 50 (30%) underwent HSCT (age range 0.7-19 years, median 5 years), including 30 with HLH, 11 with IBD, 7 with both HLH and IBD, 1 with aplastic anemia, and 1 asymptomatic individual (Fig 4, *A* and *B,* and see Table E4 in this article's Online Repository at www.jacionline.org). Post-transplantation follow-up was reported for 43 of 50 (range 13-1387 days, median 330 days after HSCT) (Fig 5, *A*). OS was significantly better ($P = .02$) for patients with IBD or IBD + HLH recorded as an indication for HSCT than patients transplanted for HLH (Fig 4, *B,* and Fig 5, *B*). Overall mortality for patients managed with HSCT was high (15/50, 30%) and negatively affected by active HLH at the time of HSCT ($P = .03$, Fig 5, *C*). Reduced-intensity conditioning (RIC), mainly consisting of fludarabine and melphalan, significantly improved outcomes ($P = .04$) compared to myeloablative conditioning (MAC) regimens for patients with HLH as the indication for HSCT, as previously described[21] (Fig 5, *D*). Both RIC and MAC resulted in good outcomes in patients with IBD as the indication for HSCT, although numbers are small (Fig 5, *E*). There was no significant impact of age at onset or residual XIAP protein on HSCT outcomes (Fig 4, *C*

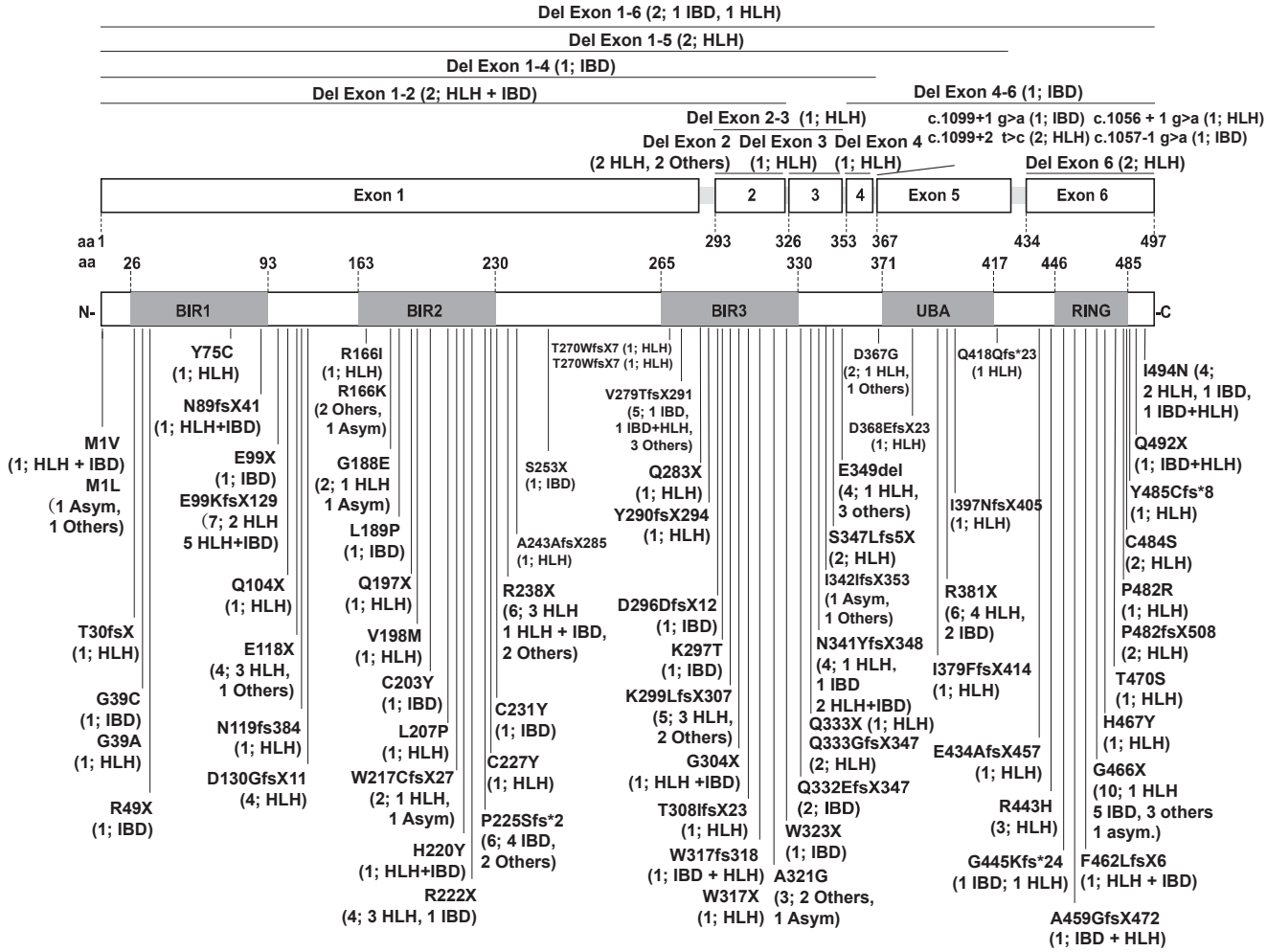

FIG 2. Genetic findings in XIAP deficiency. *Horizontal lanes* indicate the location of mutations causing exon deletions; *vertical lanes*, the location of missense mutations, frameshift, nonsense mutations, deletions, and splice-site mutations. Number of patients and main features including HLH and/or IBD presented in those patients carrying the same mutations is provided in *brackets*.

and *D*). OS after HSCT in 22 patients (12 HLH, 6 IBD, 3 HLH + IBD, and 1 aplastic anemia) reported after 2015 was significantly improved compared to 28 patients (18 HLH, 5 IBD, 4 HLH + IBD, and 1 asymptomatic) reported before 2015 ($P = .06$, 89% vs 41% at 1350 days after HSCT, Fig 5, *F*). The majority of survivors of transplantations were reported to be well at last follow-up (Table E4), with only a few patients developing limited graft-versus-host disease. Fifteen (30%) of 50 deaths after HSCT were due to recurrent HLH, graft-versus-host disease, severe bacterial/fungal infections, respiratory failure, cardiac toxicity, multisystem organ failure, veno-occlusive disease, acute encephalitis, acute respiratory distress syndrome, and "cytokine syndrome" (Table E4). Only 1 asymptomatic patient (P15, Table E1) underwent MAC-HSCT at 4 years of age but died at +247 days after transplantation from fungal septic thrombosis of the pulmonary veins and artery.[13,21]

Outcomes for conservative management in XIAP deficiency

A total of 117 (70%) of 167 patients were managed conservatively without HSCT (age range 0.1-54 years, median 13 years), of whom 105 had long-term outcome data recorded. The clinical features of conservatively managed patients included HLH without IBD (54, 47%), IBD (20, 17%), HLH and IBD (9, 8%), other manifestations in 25 (21%), and 8 without clinical presentations (7%). Age at disease onset was significantly older for conservatively managed patients compared to those undergoing HSCT (4 vs 1.3 years, $P = .01$) (Fig 4, *E*).

Treatment, where recorded, varied considerably both within and between groups with specific clinical phenotypes. For the conservatively managed group of 54 patients presenting with HLH without IBD, steroids (dexamethasone/prednisolone) were provided alone or in combination with other drugs including immunoglobulin, biologics (anti-CD20 antibody, anti-CD52 antibody, and TNF inhibitor), etoposide, and cyclosporin A. Insufficient information was recorded to determine response rates to individual treatments. Overall, 49 (86%) of 54 survived at a median age of 10 years (range 0.2-39 years) and median time of 4 years after diagnosis (range 0-27 years). Among the survivors, 23 were reported to be alive and well, although 6 patients were still being treated with immunosuppressive drugs or anti-CD20 antibody. Five patients (9%) died from complications resulting from HLH at a median age of 1

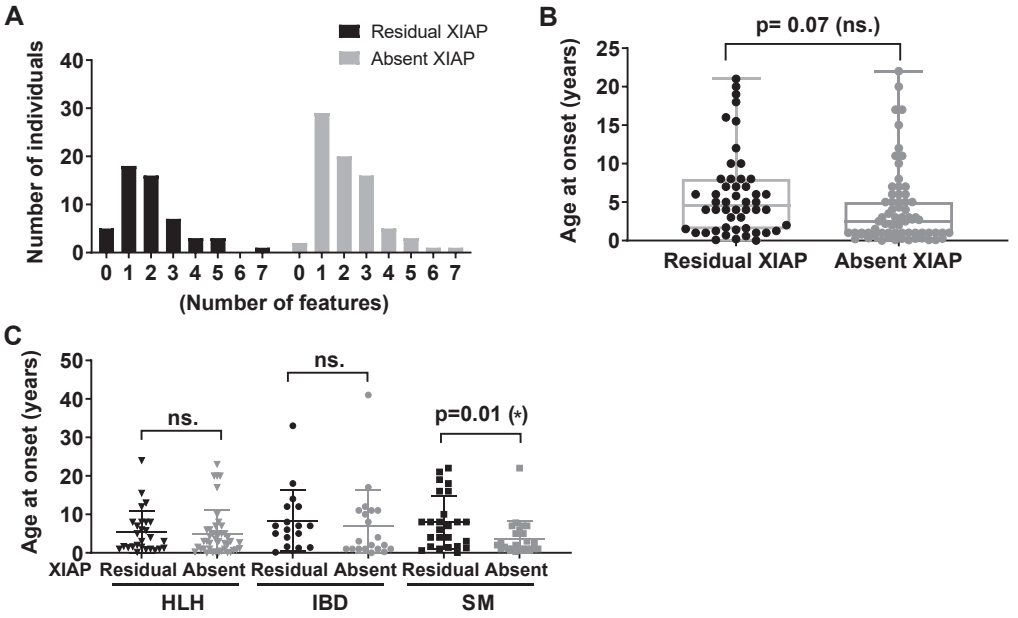

FIG 3. Correlation between clinical features and XIAP expression. **A,** Correlation between the expression level of XIAP protein and number of distinct features developed in patients through their whole life. **B,** Correlation between the expression level of XIAP protein and age at onset. **C,** Correlation between the expression level of XIAP protein and age at onset of certain phenotypes.

year (range 0.1-20 years), and all died within 1 year after diagnosis. Reasons why this group did not undergo HSCT were not recorded.

Conservative management of 20 patients with IBD (without HLH) consisted of some combination of steroids, 5-aminosalicylic acid, cyclosporin A, cyclophosphamide, azathioprine, thalidomide, tacrolimus, anti-CD20 antibody, anti–TNF-α antibody, and mycophenolate mofetil. In addition, 5 patients required surgical treatments, including colectomy and ileostomy. With conservative treatment, 16 (80%) of 20 patients were alive at a median age of 17 years (range 1-39 years) and at median time of 14.5 years after diagnosis (range 0-30 years). However, 14 of 18 had chronic gastrointestinal symptoms that were refractory to treatment. Four patients died from severe IBD complications (20%) at a median age of 21.5 years (range 4-54 years) and at median time of 18.5 years after diagnosis (range 0-38 years).

Ten patients with both HLH and IBD were treated conservatively with drugs (some combinations of steroids, 5-aminosalicylic acid, anti-TNF, and immunosuppressants) with or without bowel surgery. Eight (80%) of 10 survived at a median age of 10 years (range 3-32 years) and a median time of 6.7 years after diagnosis (range 1.6-22 years); 2 (20%) died at age 7 years and 42 years of colitis and pulmonary edema respectively.

Conservative treatment for other phenotypes of XIAP deficiency was reported for 25 patients. Intravenous or subcutaneous immunoglobulin replacement therapies were commonly provided to patients with primary hypogammaglobulinemia or as a result of immunosuppressive therapies. Infections were managed with intermittent or prophylactic antibiotics. Local steroid treatment for uveitis was reported in 1 case. Three patients with splenomegaly underwent splenectomy, and 1 had an unsuccessful trial of sirolimus. In addition, 1 patient with liver failure underwent liver transplantation. In total, 21 (84%) of 25 of conservatively managed patients with other phenotypes were alive at a median age of 16 years (range 2.3-46 years) and a median time of 14 years after diagnosis (range 1-42 years). Four (16%) of 25 died from partial HLH (at age 2.5 years), liver failure (29 years), pneumonia (52 years), and pneumorrhagia (age unknown) respectively. Eight asymptomatic patients were reported to be alive without any disease symptoms and no treatment at a median age of 14 years (range 9-46 years).

Overall, survival probabilities were not significantly different for conservatively treated patients with HLH, IBD, HLH + IBD, or others (Fig 4, *F*), but they were significantly worse for patients younger than 5 years compared to a later presentation (Fig 3, *G*, $P = .04$). Residual XIAP expression did not affect the outcome for the conservatively managed group (Fig 4, *H*).

XIAP in adulthood

To understand the natural history and survival of patients with XIAP deficiency who reach adulthood (≥16 years of age), we identified 53 patients reported at or after 16 years of age. Clinical features reported in adult patients included HLH (22/53, 42%), IBD (19/53, 36%), HLH-independent splenomegaly (17/53, 32%), infections (17/53, 32%), hypogammaglobulinemia (10/53,19%), liver disease (8/53, 15%), autoimmune disorders (5/53, 9%), fever (5/53, 9%), skin manifestations (1/53, 2%), and other less common phenotypes (8/53, 15%), with a wide range in age at onset (Fig 6, *A* and *B*). There was no significant difference in the frequency of individual features observed in adult compared to pediatric patients (Fig 6, *A*). Thirty-four (65%) of 53 patients had more than 1 feature over their lifetime (Fig 6, *C*). Twenty-three (43%) of 53 patients developed 1 to 4 new additional features in adulthood (Fig 6, *D*).

Only 5 of 53 adult patients with XIAP deficiency were reported to have undergone HSCT in or before adulthood (age range 15.5-19 years) for a range of indications including HLH, IBD, and

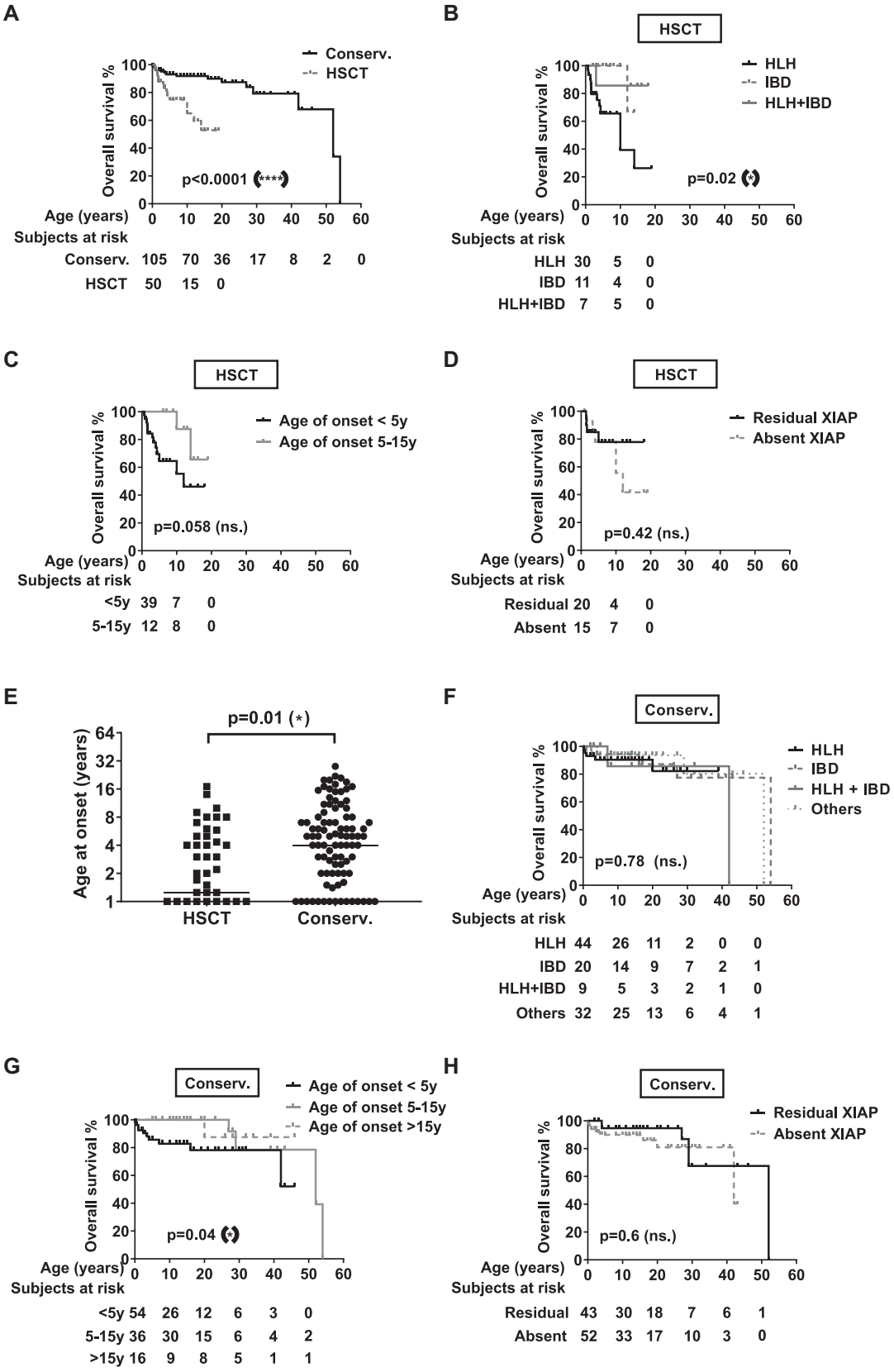

FIG 4. OS in XIAP deficiency and its association with treatment, phenotypes, age at onset, and XIAP expression. **A,** Kaplan-Meier survival analysis of patients managed conservatively or with HSCT. **B-D,** Association of OS with clinical features, age at onset, and XIAP expression in transplanted patients. **E,** Correlation between age at onset and type of treatment. **F-H,** Association of OS with clinical features, OS with age at onset, and OS with XIAP expression in conservatively managed patients. **P* < .05.

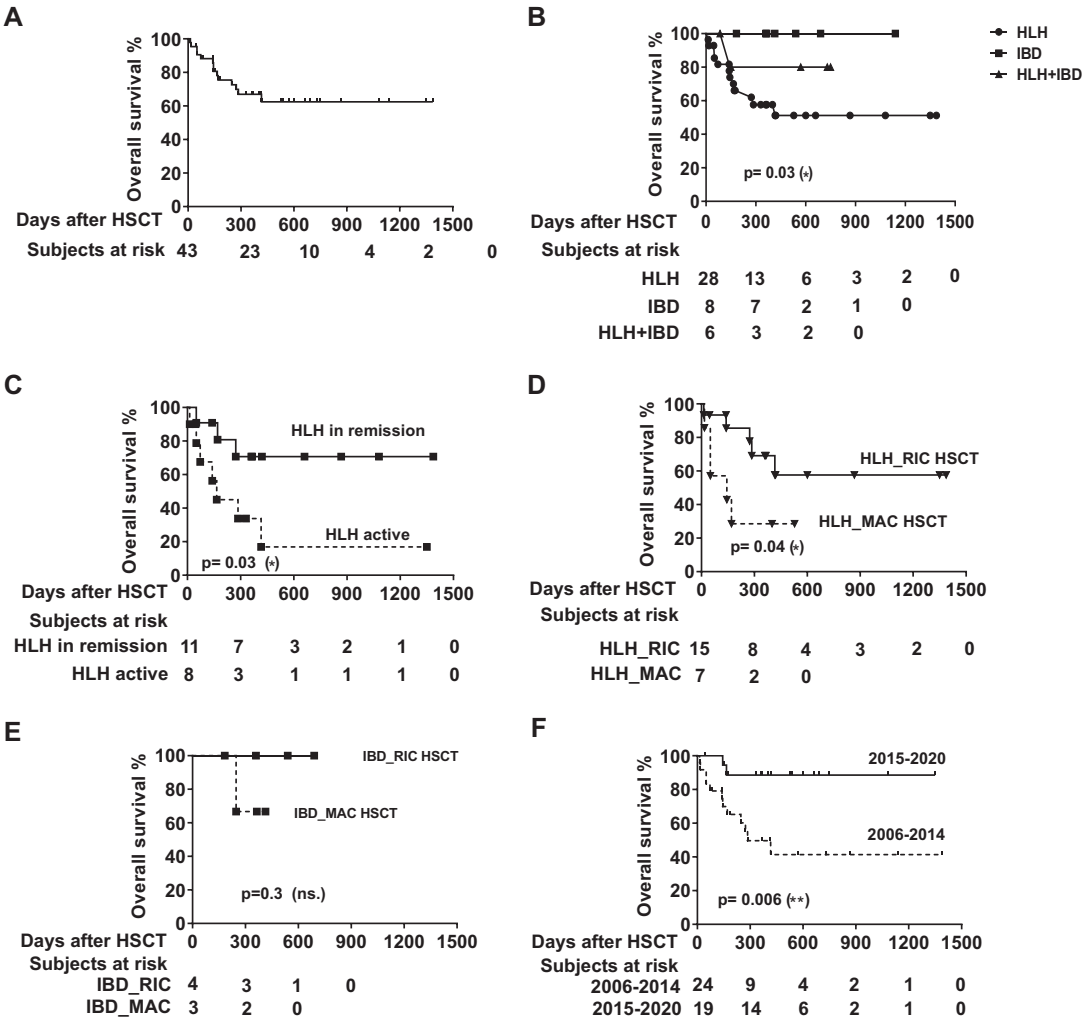

FIG 5. OS of transplanted patients with XIAP deficiency and its association with phenotypes, age at onset, and XIAP expression. **A,** Kaplan-Meier survival analysis of patients with XIAP deficiency who underwent HSCT. **B,** Survival analysis of patients presenting with distinct phenotypes. **C,** Survival comparison of HLH activity before transplantation. **D,** Survival comparison of RIC and MAC regimens used in patients transplanted for HLH. **E,** Survival comparison of RIC and MAC regimens patients transplanted for IBD. **F,** Survival comparison of transplantation time (reported before or after 2015). *$P < .05$. **$P = .006$.

aplastic anemia. All 5 were reported to be alive and well (see Table E5 in this article's Online Repository at www.jacionline.org).

The majority (48/53, 91%) of adults with XIAP deficiency were conservatively managed (see Table E6 in this article's Online Repository at www.jacionline.org). Of these, 14 (29%) of 48 were reported to have had a range of manifestations in childhood (most commonly HLH) but were symptom free in adulthood. Everyone in this group was reported to be alive and well. Nine (19%) of 48 patients had developed symptoms in childhood that were persistent/recurrent in adulthood (6 IBD, 1 HLH, 1 partial HLH, and 1 hypogammaglobulinemia), and of this group, 1 patient died from fulminant colitis. Ten (21%) of 48 patients had disease onset in childhood with new features in adulthood, and of this group, 3 patients died from colitis (2 patients at age 27 years and 1 patient at 42 years) and liver failure (29 years). Importantly, 12 (25%) of 48 patients had their first symptoms of XIAP deficiency at or after the age of 16 years, of whom 3 died from HLH (age 20 years) and pneumonia (2 patients aged 52 and 54 years). Three asymptomatic individuals were reported to be well and without treatment (age 18, 21, and 46 years). The OS proportions for conservatively managed XIAP deficiency in adulthood was 86% at age 30 years and 37% at age 52 years (Fig 6, *E*). Worse OS was observed in patients developing new disease features in adulthood (33% at 30 years) compared to other adult patients, including those with no active symptoms in adulthood (100% during age 16 to 43 years), those with recurrent symptoms in adulthood (88% during age 16-41 years), or those with first symptoms in adulthood (90% during age 20-46 years) (Fig 6, *F*). Residual XIAP expression did not affect the OS for the conservatively managed adult patients (Fig 6, *G*).

DISCUSSION

Our study characterizes phenotype, genotype, treatment, and the survival outcome of 167 patients identified with XIAP deficiency on the basis of retrospective data published worldwide from 2006 to 2020. The clinical picture of XIAP deficiency is evolving beyond

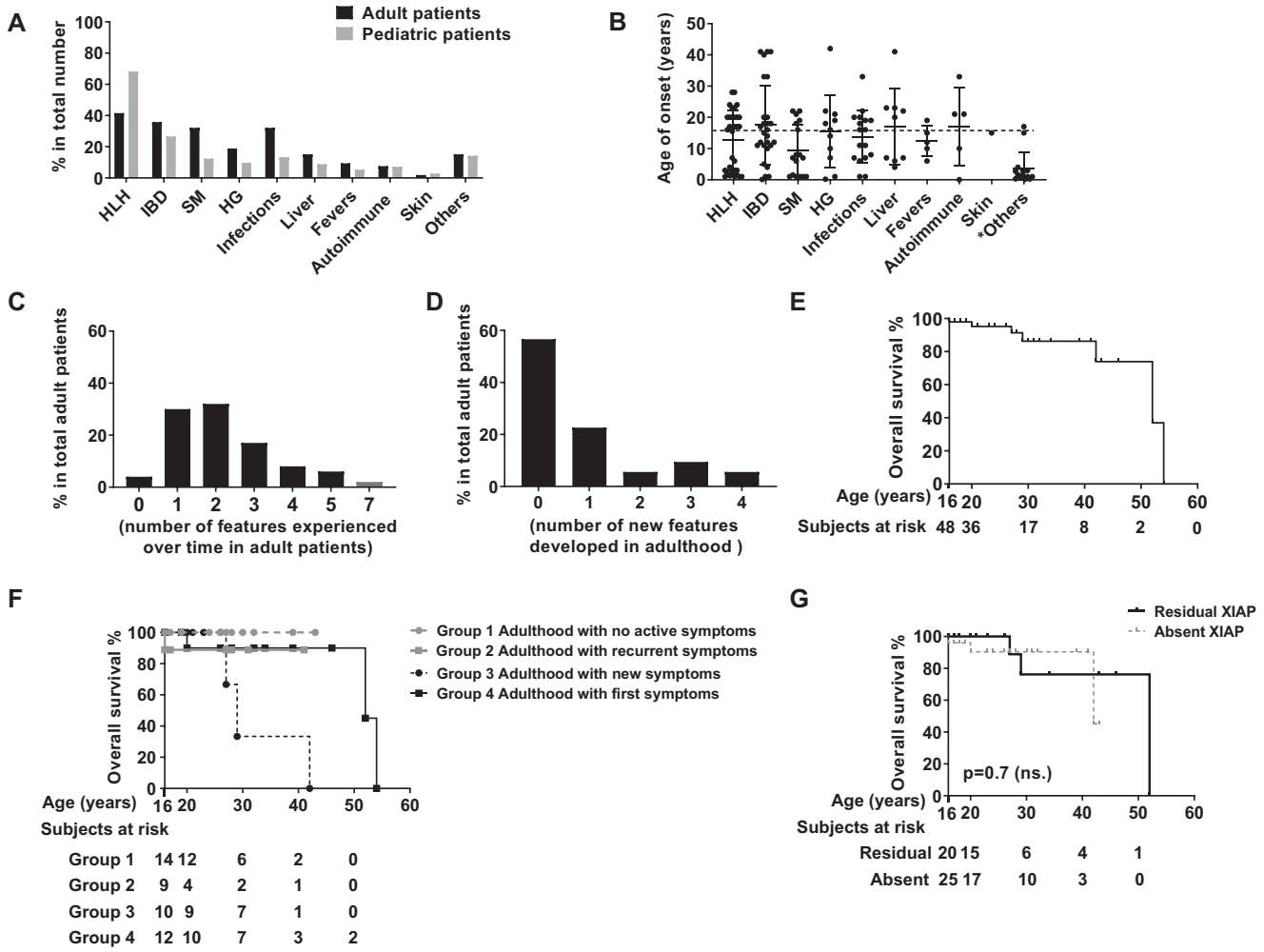

FIG 6. Characterization of adult patients with XIAP deficiency. **A,** Percentage of clinical features presented adult and pediatric patients. **B,** Age at onset for clinical features in adult patients. **C** and **D,** Number of features experienced over time in adult patients. *D,* Number of new manifestations developed in adulthood. **E-G,** OS, association with disease evolution, and XIAP expression for adult patients (not transplanted).

the well-characterized high frequency of HLH and IBD-associated features to include other less common features such as infections, liver disease, hypogammaglobulinemia, fever, HLH-independent splenomegaly, skin manifestations, and autoimmune disorders. Initial presentations vary between patients, and new symptoms may arise over time from birth to adulthood. This emphasizes the importance of awareness of XIAP deficiency across clinical specialties and of genetic screening for *XIAP* mutations in multiple disease cohorts, both in pediatric and adult patients.

A wide spectrum of *XIAP* mutations have been reported to date.[1,10,13-61] There is no clear genotype–phenotype correlation, as patients carrying the same mutations presented with variable phenotypes. An exception may be the E349del mutation, which was observed in patients presenting with primary hypogammaglobulinemia and has previously been associated with a lower percentage of memory B cells and IgG production compared to other mutations.[35] Whether other mutations play a pathogenic role in HLH or IBD development requires further investigation. Missense mutations did not appear to confer a less severe phenotype or predict improved outcome, although the number of patients with missense mutations was relatively small (35/167), and future studies with larger cohorts should reassess this. Some mutations preserve partial protein expression, but this was not associated with better survival compared to absent protein. Future studies aimed at correlating protein function with phenotype and survival may be more informative for prognostication than a simple assessment of protein level. A number of different assays to assess protein function have been reported in XIAP deficiency.[1,13,17,20,22,28,31,35,37,46,52] In contrast with other genetic forms of HLH, T-cell cytotoxicity and natural killer cell function have both been reported to be normal in XIAP deficiency.[1,13,20] The most consistent findings are increased activation-induced cell death in T cells reported in most patients in multiple studies,[1,17,22,46] impaired NOD2 pathway signaling in more recent publications,[29,43,46,50,58] and elevation of IL-18 levels in patients with XIAP deficiency–associated HLH.[28] Other tests reported gave variable results, including assessment of T-cell Fas-mediated apoptosis (increased or normal[1,13,22,25,43,46]) and measurement of peripheral blood invariant natural killer cell populations (low or normal[1,13,18,31]).

The majority of patients reported in the literature with XIAP deficiency have been managed conservatively, with a significant

minority (mainly in children with HLH) undergoing HSCT as a potentially curative option. While HLH is typically life threatening, it can also occur in XIAP deficiency as a milder, recurrent form.[15,16,22] This confounds retrospective comparison of HSCT and conservatively managed groups for HLH from published data, as reports frequently lack details of HLH severity. HLH managed with HSCT was associated with high transplant-related mortality, especially in the context of myeloablative conditioning or failure to achieve remission of HLH at the time of transplantation, as previously described.[21] Our data demonstrate a significant difference in the probability of survival after HSCT for cases reported after 2015 compared to before (89% vs 41% at 1350 days after HSCT), thus highlighting the impact of changing practice to achieve full control of HLH activity before transplantation and the use of RIC protocols.[21,44] In contrast to HLH, the disease of only a limited number of patients who developed IBD-associated features responded well to conservative treatment; the majority had disease that was resistant to therapy, and the patients suffered from refractory features throughout their lives. In contrast, limited data have shown an excellent response to HSCT, with 7 of 8 transplanted patients surviving without reports of IBD recurrence. These data support HSCT as a curative option in patients with XIAP-associated IBD.

A key question that initiated this study is whether patients with XIAP deficiency who survive to adulthood have subsequently reduced survival. This is of particular importance because HSCT has until recently only rarely been offered to adults with primary immunodeficiency (including XIAP deficiency) on the basis of the notion that patients seeking care later in the disease course may have less severe disease in addition to worse outcomes after HSCT. Of the group of 48 adult patients with conservatively managed XIAP deficiency currently described, OS probabilities are 86% at age 30 years and 37% at age 52 years. Deaths were more often reported in patients who developed new symptoms in adulthood than in those who developed symptoms in childhood. The causes of death in adulthood were wide ranging and included HLH, IBD, liver failure, and infection. These data demonstrate that XIAP deficiency in adulthood is frequently severe in phenotype, requiring aggressive therapy and careful monitoring. Improved outcomes after HSCT for adults with primary immunodeficiency in general[63] should encourage clinicians to consider this option for adults with XIAP deficiency whose disease is not responding well to conservative management. Although not specifically addressed in this study, the accumulation of different disease features over time in adults living with XIAP deficiency suggests a worsening quality of life; the impact of symptoms and treatment on well-being, education, and employment should be addressed in future prospective studies. The application of a standardized disease activity measure, such as the immune deficiency and dysregulation activity score (https://esid.org/Working-Parties/Registry-Working-Party/Studies/IDDA-Score), would be helpful for comparison of future cohorts.

Our study has a number of weaknesses. The overall number of reported cases of XIAP deficiency is small, which is likely to be compounded by both failure to report and failure to diagnose all patients with XIAP deficiency, thus introducing bias to the analysis. The retrospective nature of data collection from previously published studies means that full and comparable data sets were not recorded for all patients. Times from disease onset to diagnosis or specific events were often not clear, making estimates of diagnostic delay and event-free survival impossible. The long time span over which patients were treated may overestimate poor outcomes from older therapeutic approaches. In particular, substantial improvements over time have been achieved in HSCT outcomes for primary immunodeficiency in general[63] and in the management of HLH, both of which are likely to affect more recent XIAP deficiency cohorts. We were unable to assess the relative benefits of different modes of conservative therapy, which would be an important focus for further studies, particularly as new therapies emerge targeted at pathogenic mechanisms of XIAP deficiency (eg, anti–IL-18 approaches for IL-18–mediated inflammation; NCT03113760). Furthermore, the frequency of asymptomatic XIAP deficiency may be underestimated. Our data suggest that asymptomatic carriers of pathogenic mutations identified as relatives of index cases should be monitored carefully for the development of disease. On the basis of current information, the risk of preemptive curative treatment with HSCT is rarely justified.

In conclusion, our retrospective study demonstrates the variable nature of XIAP deficiency, which evolves over life for individual patients. Reduced survival is seen with both conservatively and HSCT-managed groups, thus highlighting the need for improved therapy for this disease. Early age at onset, development of new features in adulthood, active HLH at the time of transplantation, and MAC regimen for patients with HLH were associated with poorer outcomes. Adults with XIAP deficiency continue to accumulate life-threatening complications, and the paucity of HSCT data for this group complicates decision making for adults with severe manifestations of the disease. Our study is limited by its retrospective nature and long time span of collected data, which may not capture improvements in outcome achieved through better awareness and treatment in more recent years. Further prospective studies capturing detailed information about phenotype, treatment, and quality of life are required for clinicians and patients to make informed decisions, to establish treatment guidelines, and to drive new therapeutic approaches to improve the long-term outcome of patients with XIAP deficiency.

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Clinical implications: XIAP deficiency may present to a range of pediatric and adult specialties, making better awareness of this condition a priority. Accurate diagnosis enables specific therapeutic options such as HSCT.

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