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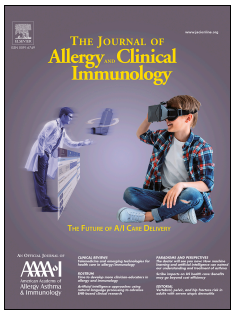

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Phenotype, genotype, treatment, and survival outcomes in patients with X-linked inhibitor of apoptosis deficiency

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Abstract

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 of onset present challenges for patient management.

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

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

Results: 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 (IBD) were the most common. Patients frequently developed multiple features with no clear genotype–phenotype correlation. 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. 9 asymptomatic mutation carriers were identified with a median age of 13.5 years.

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.

Keywords: XIAP deficiency, HLH, IBD, HSCT, conservative treatment, adult

Word Count 247

Capsule Summary

The presentation and evolution of XIAP-deficiency is variable between individuals and associated with substantial morbidity and mortality, highlighting the need for additional studies of disease pathogenesis and therapeutic options.

Keywords:

Primary Immunodeficiency, X-linked inhibitor of apoptosis, phenotype, therapy, survival outcomes

Abbreviations:

AICD	Activation-induced cell death
ARDS	Acute respiratory distress syndrome
BIRC4	Baculoviral inhibitor of apoptosis repeat-containing protein 4
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
GVHD	Graft versus host disease
GI	Gastrointestinal
HG	Hypogammaglobulinemia
HHV-6	Human Herpesvirus 6

HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex viruses
IBD	Inflammatory bowel disease
IVIG	Intravenous immunoglobulin
MAC	Myeloablative conditioning
MAPK	Mitogen-activated protein kinase
MMF	Mycophenolate mofetil
MOF	Multisystem organ failure
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOD2	Nucleotide Binding Oligomerization Domain Containing 2
PID	primary immunodeficiency
RIC	Reduced intensity conditioning
SCIG	Subcutaneous immunoglobulin
SM	Splenomegaly
TNF	Tumor necrosis factor
VOD	Veno-occlusive disease
XLP	X-linked lymphoproliferative disease

135	XLP-2	X-linked lymphoproliferative disease type 2
136	XIAP	X-linked inhibitor of apoptosis
137	5-ASA	5-aminosalicylic acid

138

139

140 **Clinical Implications**

141 XIAP deficiency may present to a range of pediatric and adult specialties making
142 better awareness of this condition a priority. Accurate diagnosis enables specific
143 therapeutic options such as hematopoietic stem cell transplantation.

144

Introduction

X-linked inhibitor of apoptosis (XIAP) deficiency, also called X-linked lymphoproliferative disease Type 2 (XLP2), is a rare, primary immunodeficiency (PID) 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 NOD2-dependent NF-κB and MAPK activation by its ubiquitin ligase activity[2–7]. Reduced or absent XIAP expression has been shown to enhance apoptosis, reduce 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 transplant (HSCT) has been recognized as the only curative treatment for XIAP deficiency and is most often used in pediatric patients presenting with severe HLH and/or IBD. However, due to 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 and so uncertainty remains

around 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 2006-2020 in electronic databases - 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 (XLP). In this study, a total of 167 patients using our searching items were included to summarize clinical features, genetic mutations, treatments, and survival outcomes. All studies were analyzed to identify duplicate patients based on 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, non-abscesses skin symptoms, autoimmune disorders, liver disorders, and other less common features. Partial HLH that fulfilled less 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 to estimate the overall survival probabilities of patients with XIAP deficiency and used the log-rank test to compare survival between groups. Student's t-test was used to compare the frequency of certain phenotypes and age at onset between groups. P-value < 0.05 was considered to be statistically significant.

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 (Table E1)[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%) (Figure 1A). HLH typically occurred earlier than other manifestations, with a median age of onset of 2.5 years (range 0-28 years) (Table E2). HLH was often triggered by EBV infection (37/100, 37%) and in a small number of cases, other herpes viruses were reported (CMV n=4; HHV-6 n=2; HSV-1 n=1). Other features of XIAP deficiency displayed a wide range in age of onset, although skin manifestations (including abscesses and non-infectious presentations) and autoimmune complications typically occurred outside early childhood (Figure 1B and Table E2). For patients with clinical manifestations, 88 patients (52%) were reported to have more than one distinct phenotype throughout their life (Figure 1C). Nine asymptomatic individuals identified because of other symptomatic family members were reported (Figure 1C).

The most common features at first presentation were HLH and IBD (56% and 20% respectively; Figure 1D). 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) (Figure 1E).

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 (Figure 2, Table E1). Mutations distribute throughout the entire gene and all five domains of the encoded protein. Eight mutations including R381X, R238X, R222X, N341YfsX348, K299LfsX307, Q332EfsX347, E349del, and R443H, were frequently detected in more than three 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 (Table E3). There was no significant difference in the number of clinical features seen in patients with residual vs absent XIAP expression (Figure 3A). 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 (Figure 3B). Early age of splenomegaly onset significantly correlated with absent XIAP expression (p=0.01, Figure 3C) 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), overall survival, age of onset, or severity (11/35 underwent HSCT at a median age of 5 years,

range 0.4-15) in the missense group comparing with the patients bearing other types of loss-of-function (LOF) mutations (of whom 39/132 underwent HSCT at a median age of 3.5 years, range 0.4-21) (Supplementary Figure 1).

HSCT outcomes in XIAP deficiency

Out 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 (Figure 4A and 4B, Table E4). Post-transplant follow-up was reported for 43/50 (range 13-1387 days, median 330 days post-HSCT) (Figure 5A). Overall survival was significantly better (p=0.02) for patients with IBD or IBD+HLH recorded as an indication for HSCT than patients transplanted for HLH (Figure 4B, Figure 5B). Overall mortality for patients managed with HSCT was high (15/50, 30%) and negatively impacted by active HLH at the time of HSCT (p=0.03, Figure 5C). Reduced intensity conditioning (RIC) mainly consisting of fludarabine and melphalan significantly improved outcomes (p= 0.04) compared with myeloablative conditioning (MAC) regimens for patients with HLH as the indication for HSCT, as previously described[21] (Figure 5D). Both RIC and MAC achieved good outcomes in patients with IBD as the indication for HSCT, although numbers are small (Figure 5E). There was no significant impact of age of onset or residual XIAP protein on HSCT outcomes (Figures 4C and 4D). Overall survival following HSCT in 22 patients (12 HLH, 6 IBD, 3 HLH+IBD, and 1 aplastic anemia) reported after 2015 was significantly improved compared with 28 patients (18 HLH, 5 IBD, 4 HLH+IBD, and 1 asymptomatic) reported before 2015 (p=0.06, 89% vs 41% at 1350 days post-HSCT, Figure 5F). The majority of transplant survivors were reported to be well at last follow-up (Table E4), with only a few patients developing limited GVHD. Fifteen deaths following HSCT (15/50, 30%) were due to recurrent HLH, GVHD, severe bacterial/fungal infections,

respiratory failure, cardiac toxicity, multisystem organ failure (MOF), veno-occlusive disease (VOD), acute encephalitis, acute respiratory distress syndrome (ARDS), and 'cytokine syndrome' (Table E4). Only one asymptomatic patient (P15, Table E1) underwent MAC-HSCT at 4 years of age but died at +247 days after transplantation due to fungal septic thrombosis of the pulmonary veins and artery[13,21].

Outcomes for conservative management in XIAP deficiency

117/167 (70%) 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 of disease onset was significantly older for conservatively managed patients compared with those undergoing HSCT (4 vs 1.3 years, p=0.01) (Figure 4E).

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 used 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, 49/54 survived (86%) at a median age of 10 years (range 0.2-39 years) and a 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 treated with immunosuppressive drugs or anti-CD20 antibody. Five (9%) patients died due to complications resulting from HLH at a median age of 1 year (range 0.1-20 years) and

all died within one 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-ASA, cyclosporin A, cyclophosphamide, azathioprine, thalidomide, tacrolimus, anti-CD20 antibody, anti-TNF-α antibody, and mycophenolate mofetil (MMF). In addition, 5 patients required surgical treatments including colectomy and ileostomy. With conservative treatment, 16/20 patients were alive (80%) at a median age of 17 years (range 1-39 years) and a median time of 14.5 years after diagnosis (range 0-30 years). However, 14/18 had chronic gastrointestinal symptoms, refractory to treatment. Four patients died due to severe IBD complications (20%), at a median age of 21.5 years (range 4-54 years) and a median time of 18.5 years after diagnosis (range 0-38 years).

10 patients with both HLH and IBD were treated conservatively with drugs (some combinations of steroids, 5-ASA, anti-TNF, and immunosuppressants) with or without bowel surgery. 8/10 (80%) 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 of 7 years and 42 years due to colitis and pulmonary edema, respectively.

Conservative treatment for other phenotypes of XIAP deficiency was reported for 25 patients. Intravenous or subcutaneous immunoglobulin replacement therapies (IVIG or SCIG) were commonly used in patients with primary hypogammaglobulinemia or secondary to immunosuppressive therapies. Infections were managed with intermittent or prophylactic antibiotics. Local steroid treatment for uveitis was reported in one case. Three patients with splenomegaly underwent splenectomy and one had an unsuccessful trial of sirolimus. In addition, one patient with liver failure underwent

liver transplantation. In total, 21/25 (84%) 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). 4/25 (16%) died due to partial HLH (at age 2.5 years), liver failure (29), pneumonia (52), 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 (Figure 4F), but were significantly worse for patients presenting at less than 5 years of age compared with later presentation (Figure 3G, p=0.04). Residual XIAP expression did not affect the outcome for the conservatively managed group (Figure 4H).

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 of onset (Figure 6A, B). There was no significant difference in the frequency of individual features observed in adults compared with pediatric patients (Figure 6A). 34/53 (65%) patients had more than one features over the lifetime (Figure 6C). 23/53 (43%) patients developed one to four new additional features in adulthood (Figure 6D).

Only 5/53 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 aplastic anemia. All five were reported to be alive and well (Table E5).

The majority 48/53 (91%) of adults with XIAP deficiency were conservatively managed (Table E6). Of these, 14/48 (29%) were reported to have had a range of manifestations in childhood (most commonly HLH) but were symptom free in adulthood. All of this group were reported to be alive and well. 9/48 (19%) 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 one patient died from fulminant colitis. 10/48 (21%) patients had disease onset in childhood with new features in adulthood and of this group, 3 patients died from colitis (2 patients at the age of 27 years and 42 years) and liver failure (29 years). Importantly, 12/48 (25%) patients had their first symptoms of XIAP deficiency at or after the age of 16 years of which 3 died from HLH (age 20 years) and pneumonia (2 patients at age 52 years and 54 years). Three asymptomatic individuals were reported to be well and without treatment (age 18, 21, and 46 years). The overall survival proportions for conservatively managed XIAP deficiency in adulthood was 86% at age 30 years and 37% at age 52 years (Figure 6E). Worse overall survival was observed in patients developing new disease features in adulthood (33% at 30 years) in comparison to other adult patients including those with no active symptoms in adulthood (100% during age 16 to 43 years), with recurrent symptoms in adulthood (88% during age 16 to 41 years) or with first symptoms in adulthood (90% during age 20 to 46 years) (Figure 6F). Residual XIAP expression did not impact the overall survival for the conservatively managed adult patients (Figure 6G).

Discussion

Our study characterizes phenotype, genotype, treatment, and the survival outcome of 167 patients identified with XIAP deficiency based on retrospective data published worldwide 2006 -2020. The clinical picture of XIAP deficiency is evolving beyond 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 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 with 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 with 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[13,17,20,22,28,31,35,37,46,52,63,64]. In contrast with other genetic forms of HLH, CD8+T cell cytotoxicity and NK cell function have both been reported to be normal in XIAP deficiency[13,20,63]. The most consistent findings are increased activation-induced cell death (AICD) in T cells reported in most patients in multiple studies[17,22,46,63], impaired NOD2 pathway signaling in more recent publications[43,46,50,64,65], 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[13,22,25,43,46,63]) and measurement of peripheral blood iNKT cell populations (low or normal[13,18,31,63]).

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 transplant, as previously described[21]. Our data demonstrates a significant difference in the probability of survival following HSCT for cases reported after 2015 compared with before (89% vs 41% at 1350 days post-HSCT), highlighting the impact of changing practice to achieve full control of HLH activity before transplantation and the use of RIC conditioning protocols[21,44]. In contrast to HLH, only a limited number of patients who developed IBD-associated features responded well to conservative treatment and the majority were resistant to therapy and suffered from refractory features throughout their life. By contrast, limited data have shown an excellent

response to HSCT with 7/8 transplanted patients surviving without reports of IBD recurrence. This data supports the use of 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 as HSCT has until recently only rarely been offered to adults with PID (including XIAP deficiency) on the basis that patients presenting later may have less severe disease in addition to worse outcomes following HSCT. Of the group of 48 adult patients with conservatively managed XIAP currently described, overall survival 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 including 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 following HSCT for adults with PID in general[63] should encourage clinicians to consider this option for adults with XIAP who are 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 worsening quality of life and 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 is small which is likely to be compounded by both failure to report and failure to diagnose all patients with XIAP, 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 timespan 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 PID in general[63], and in the management of HLH, both of which are likely to impact more recent XIAP 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 (for example anti-IL18 approaches for IL18 mediated inflammation (https://clinicaltrials.gov/ct2/show/NCT03113760). Furthermore, the frequency of asymptomatic XIAP-deficiency may be under-estimated. Our data suggests that asymptomatic carriers of pathogenic mutations identified as relatives of index cases, should be monitored carefully for the development of disease. Based on current information, the risk of pre-emptive curative treatment with HSCT, would rarely be 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 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 transplant, 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 wide 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.

Figure Legends

Figure 1. Clinical presentation and age of onset reported in XIAP deficiency.

(A-B) Clinical features and corresponding age of 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-E) Initial features and corresponding age of 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.

Figure 2. Genetic findings in XIAP deficiency.

The location of mutations causing exon deletions are indicated by *horizontal* lanes. The location of missense mutations, frameshift, nonsense mutations, deletions, and splice-site mutations are indicated by *vertical* lanes. In brackets, the number of patients and main features including HLH and/or IBD presented in those patients carrying same mutations are listed.

Figure 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 of onset. (C) Correlation between the expression level of XIAP protein and age at onset of certain phenotypes.

Figure 4. Overall survival 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 hematopoietic stem cell transplantation (HSCT). (B-D) Association of overall survival (OS) with clinical features, age of 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 of onset, OS with XIAP expression in conservatively managed patients. *P <0.05.

Figure 5. Overall survival 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 transplant time (reported before or after 2015). *P <0.05.

Figure 6. Characterization of adult patients with XIAP deficiency.

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

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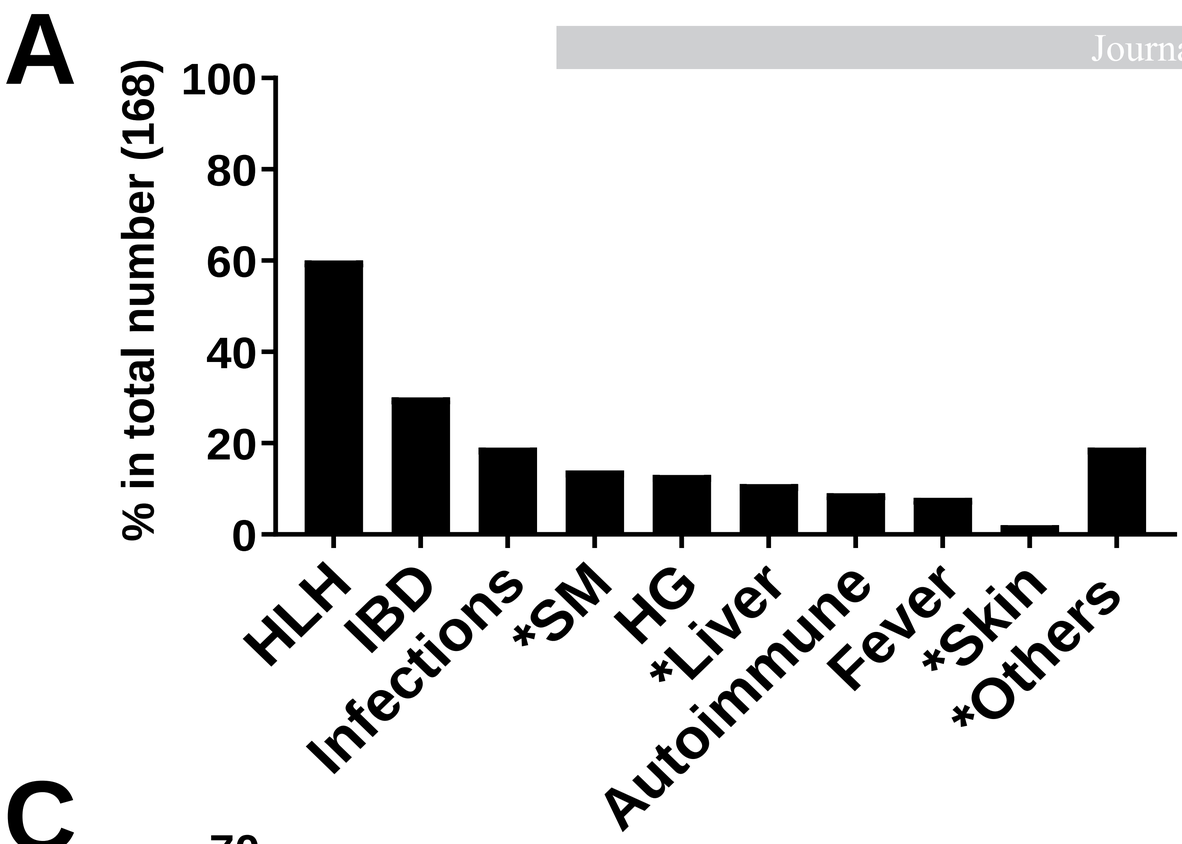

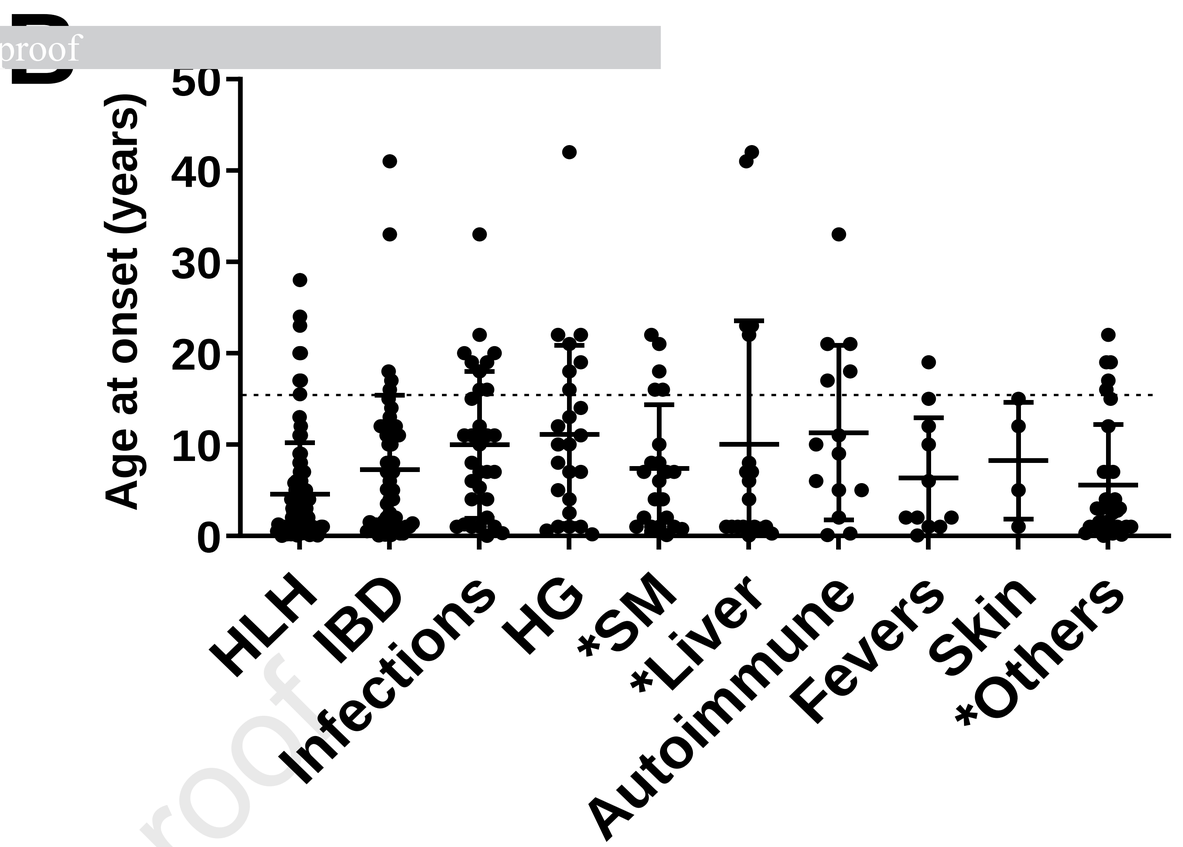

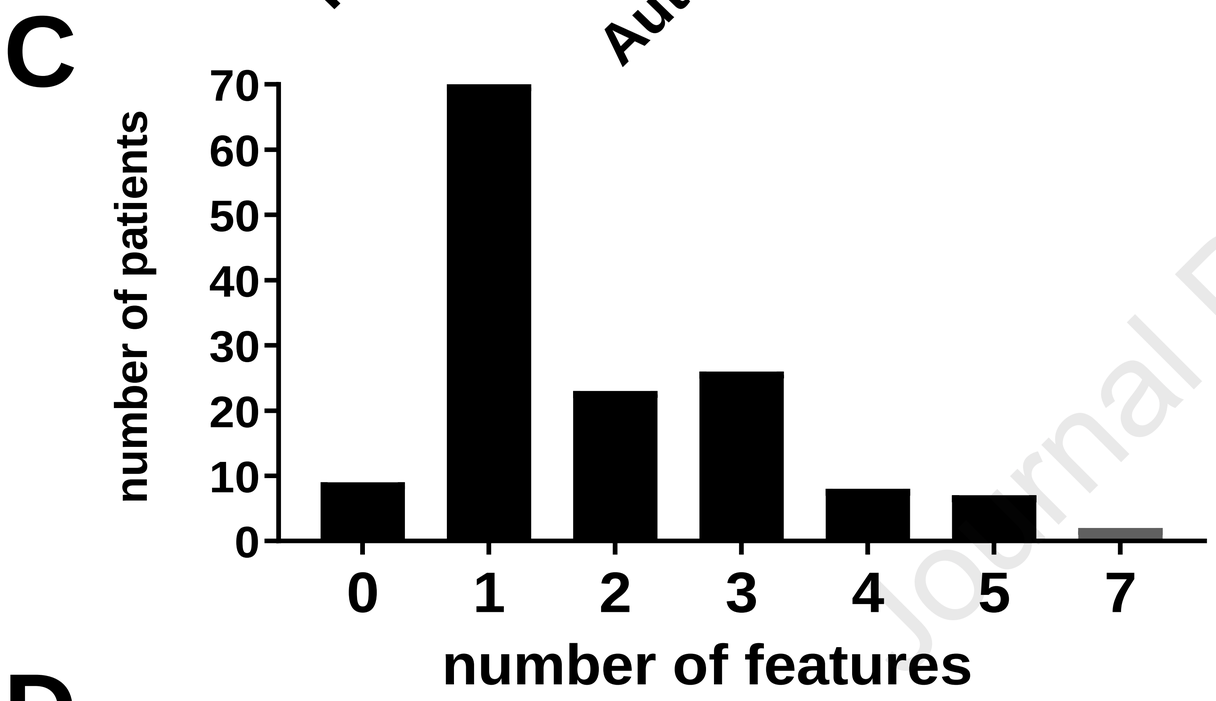

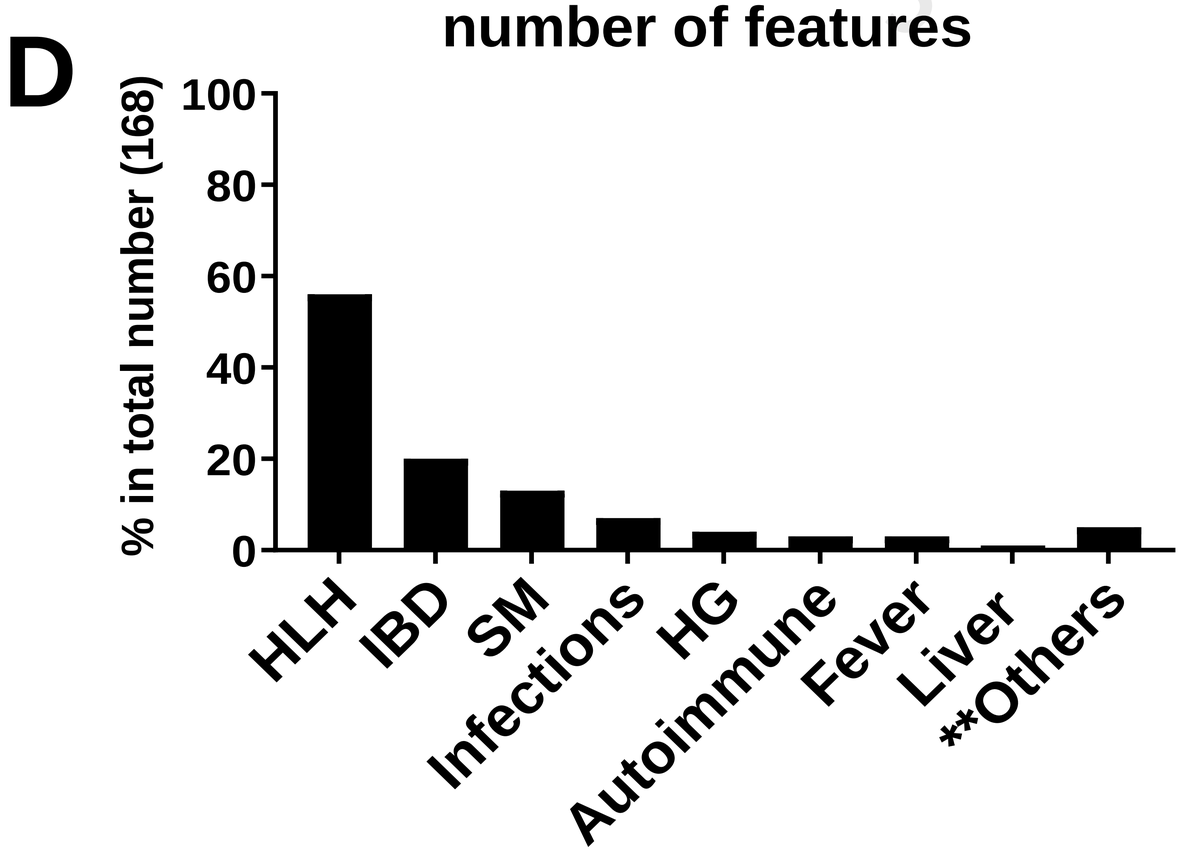

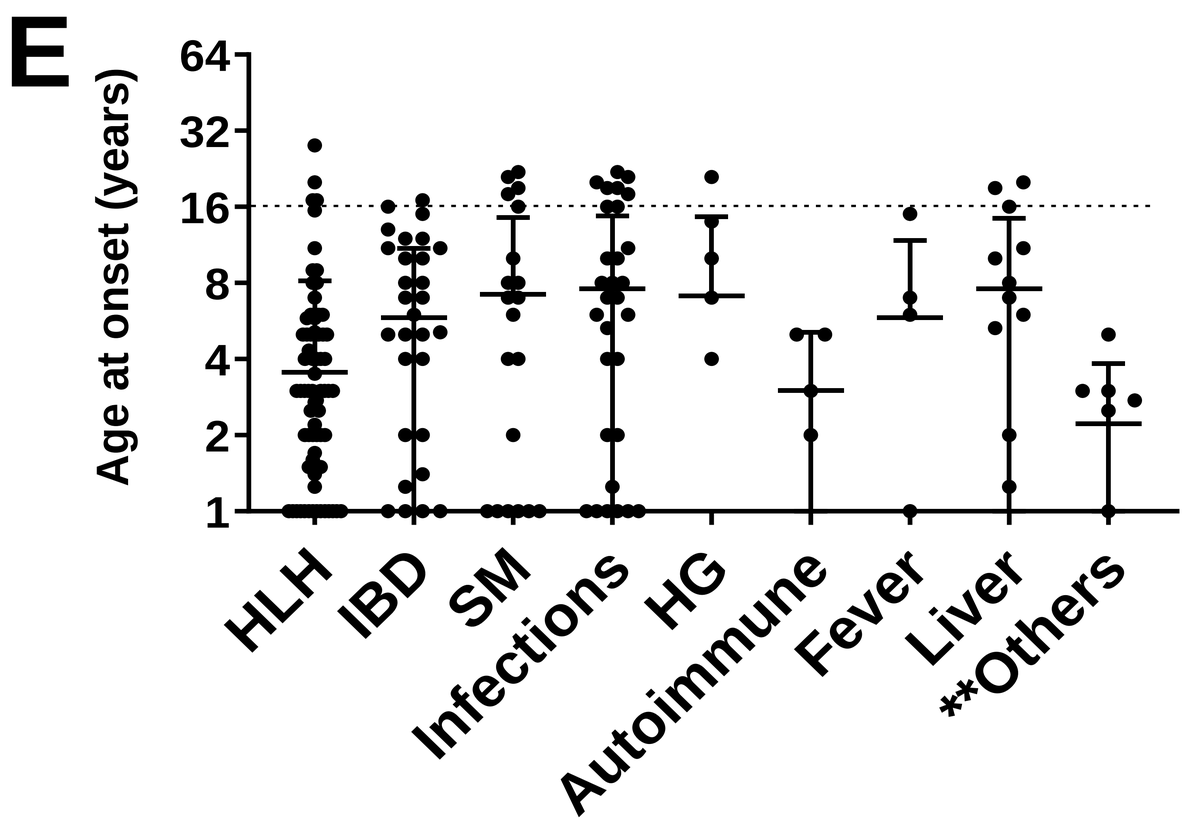

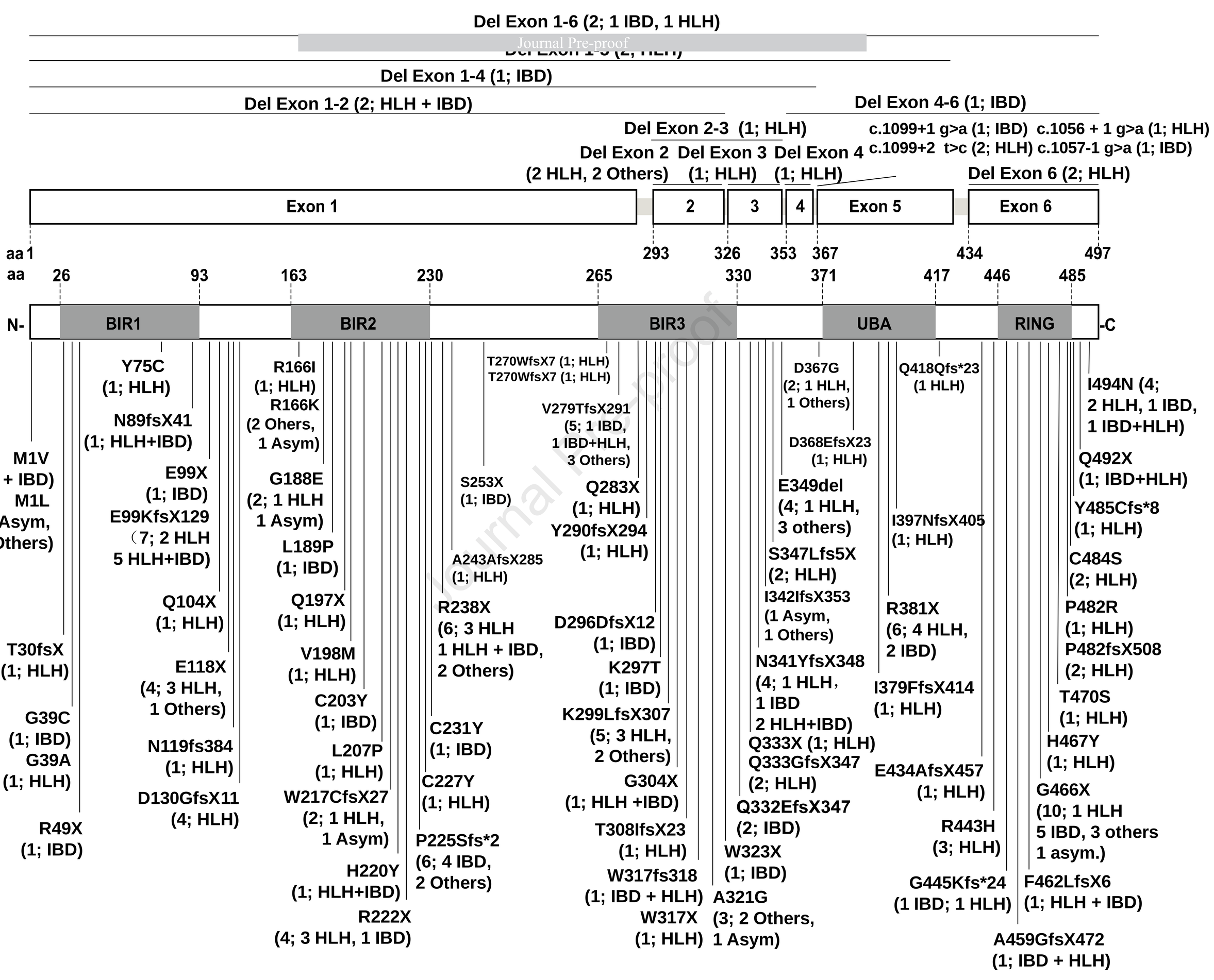

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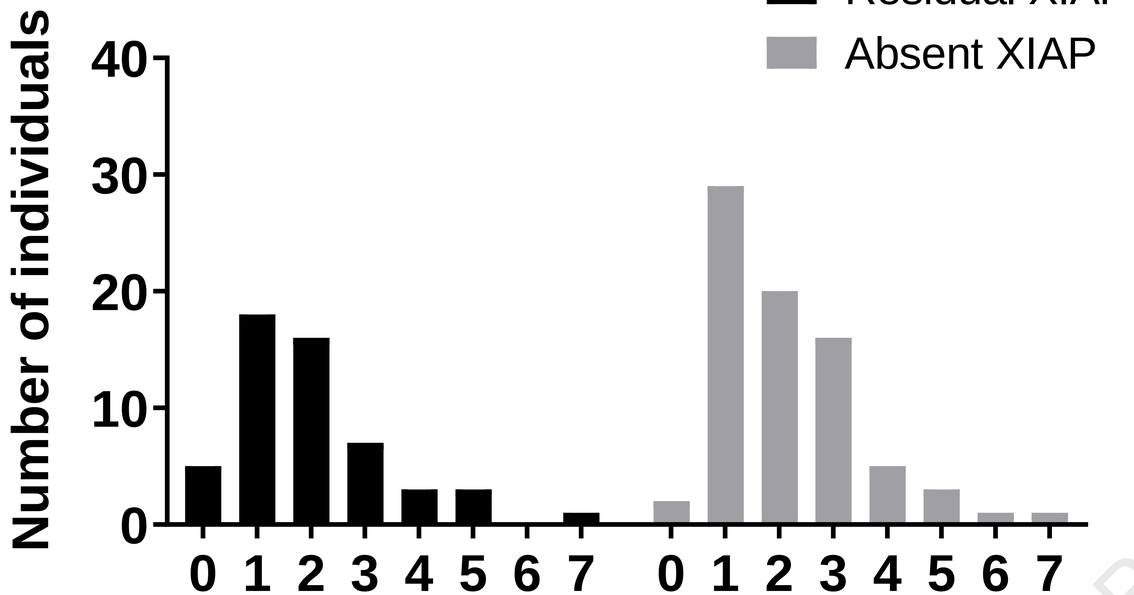

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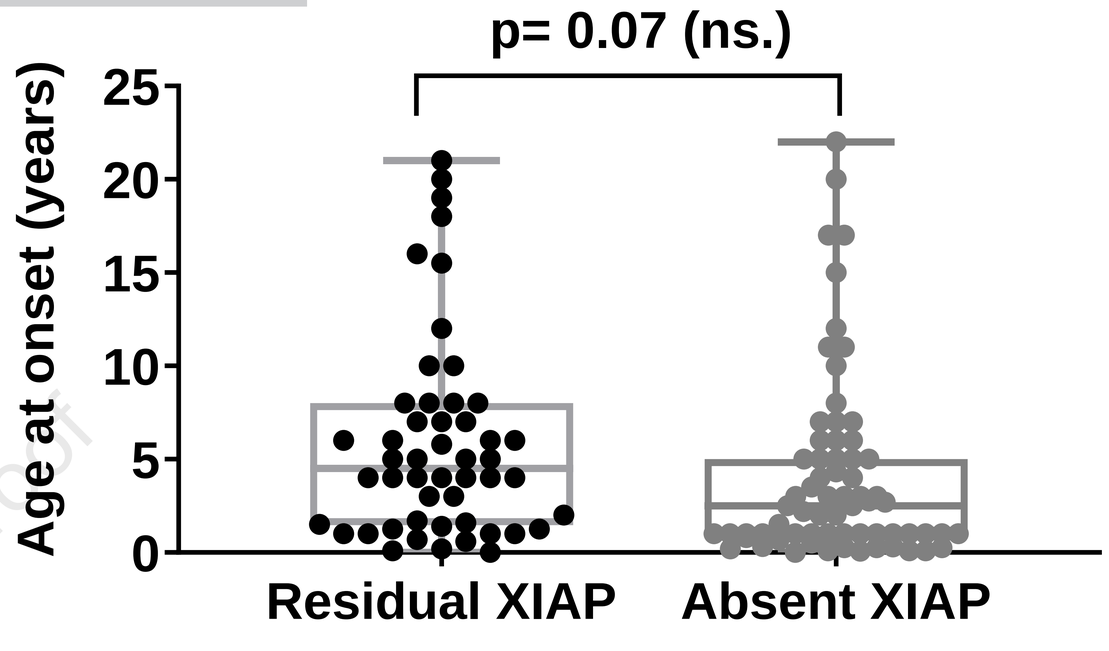

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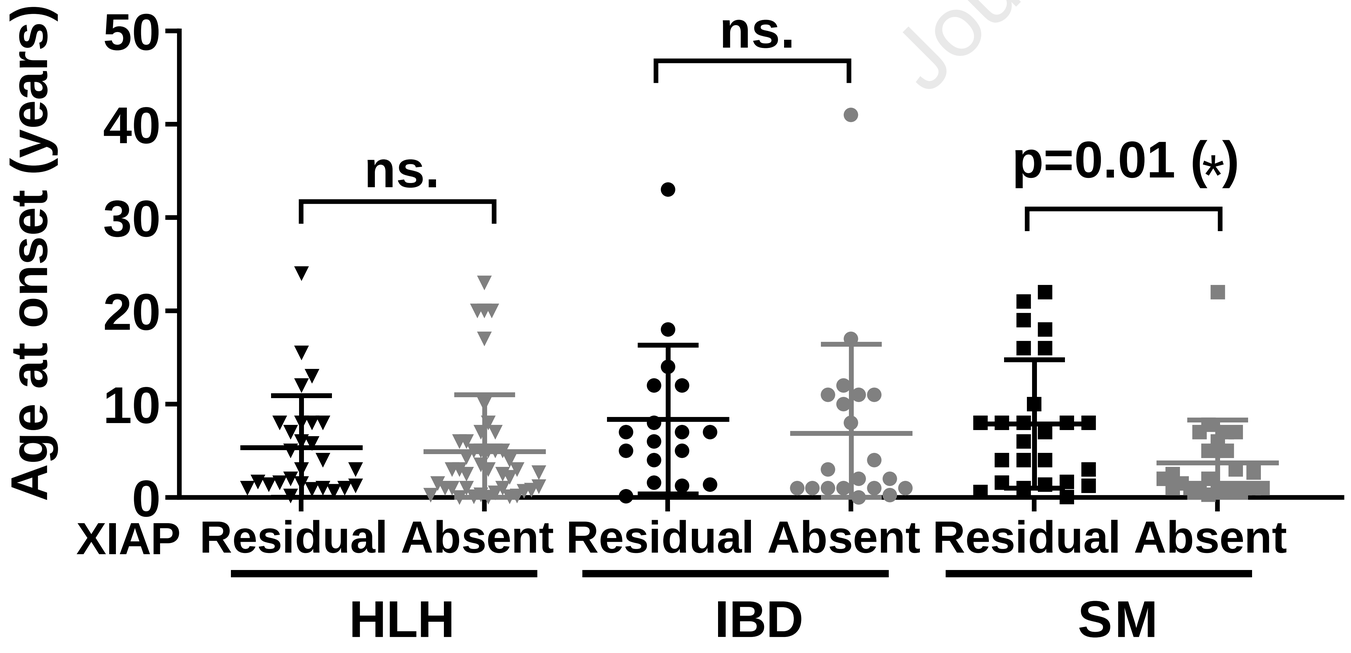

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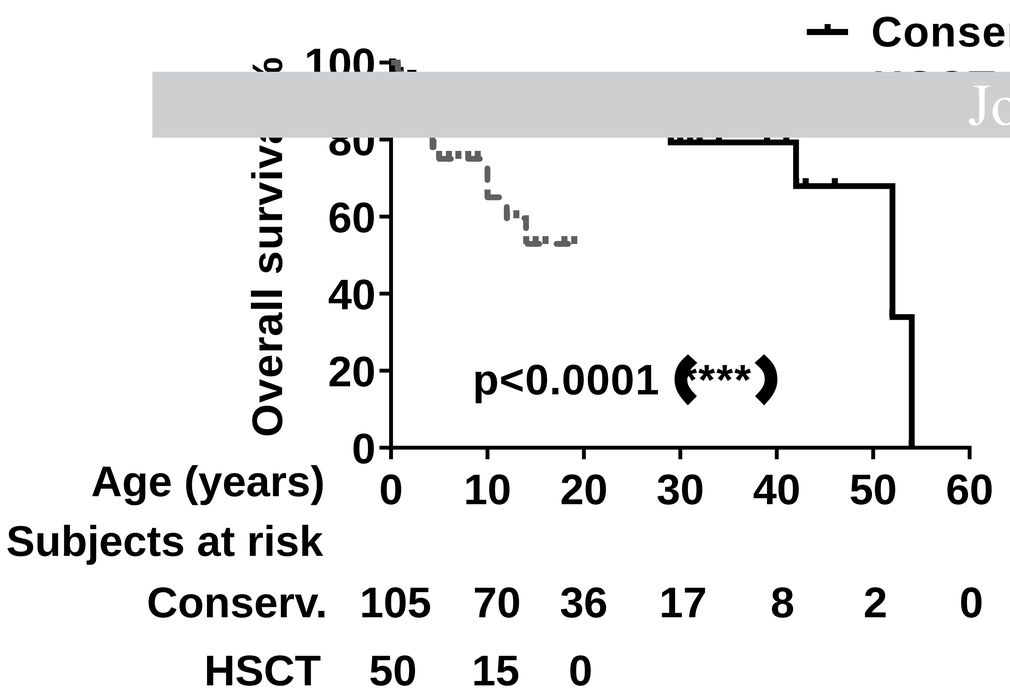

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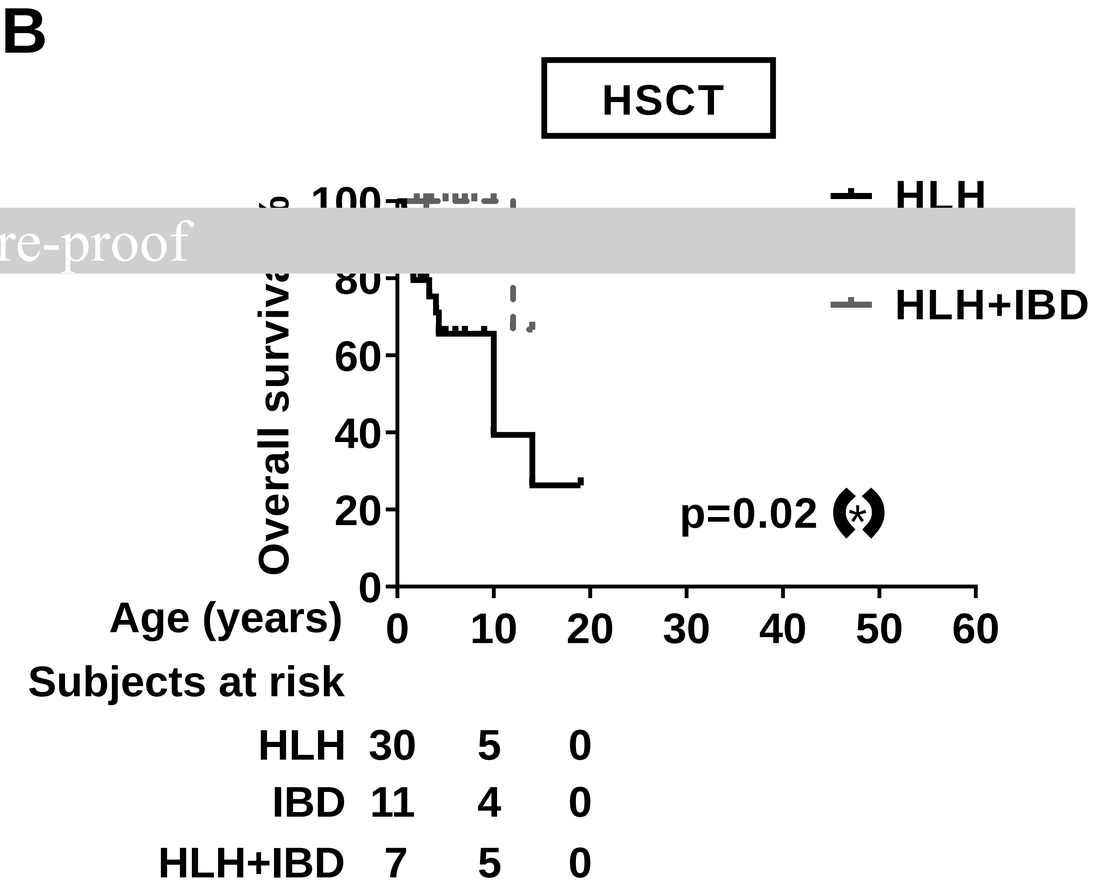

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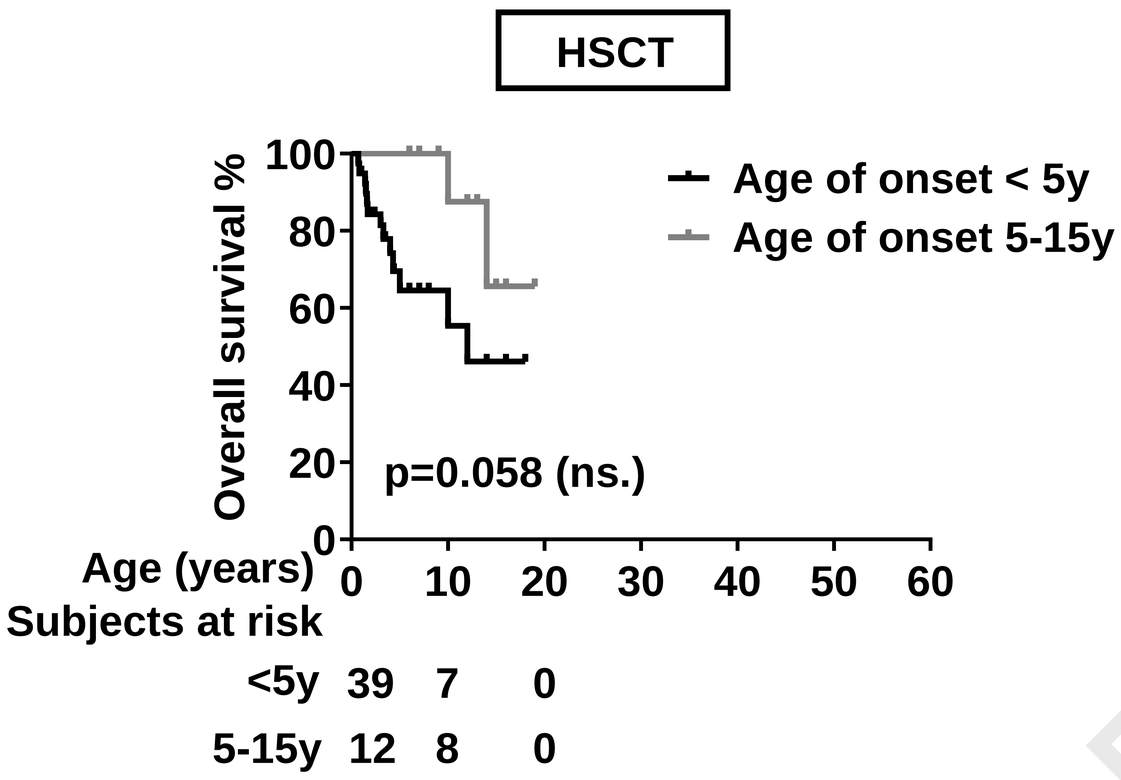

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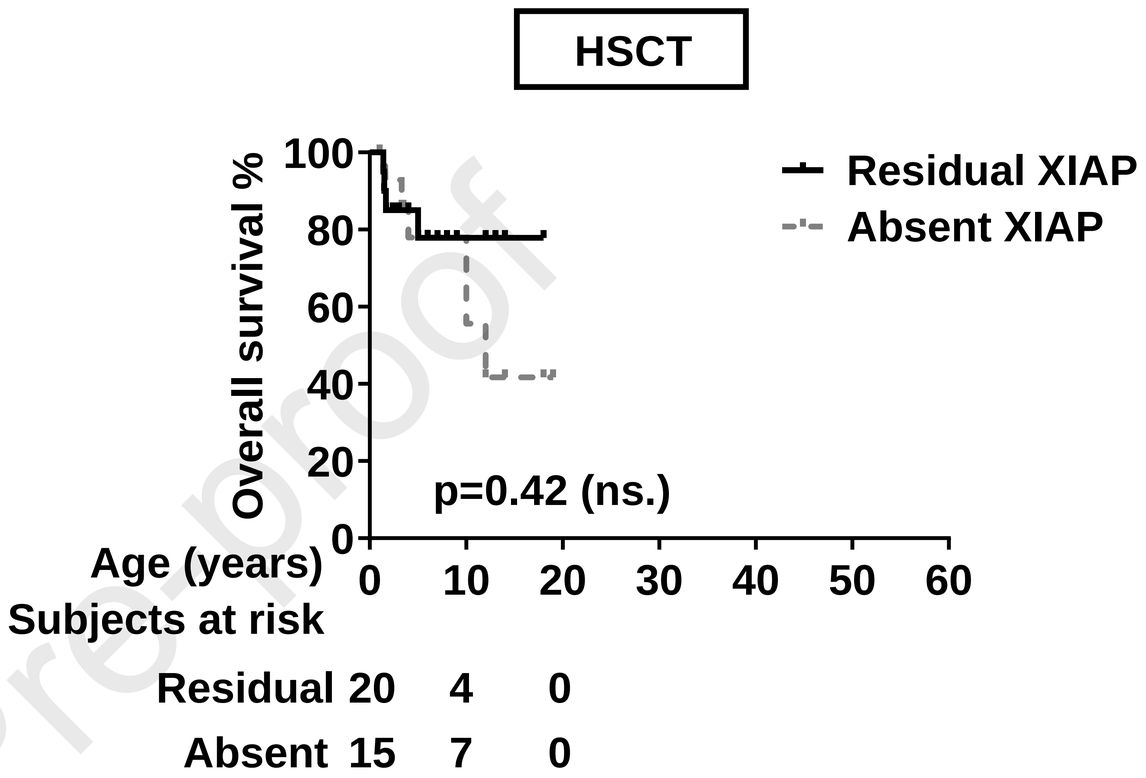

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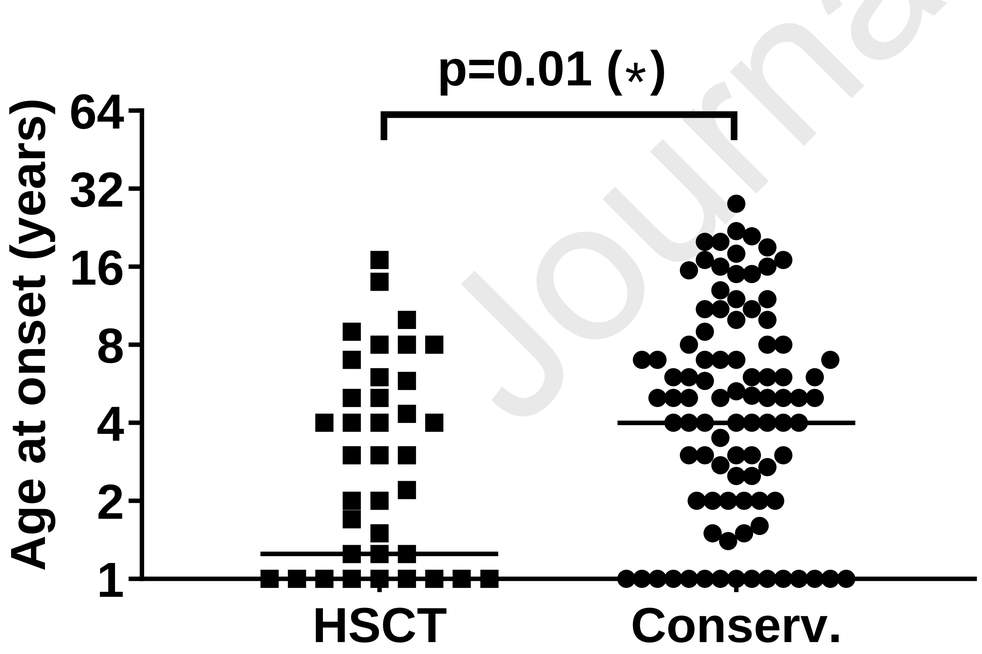

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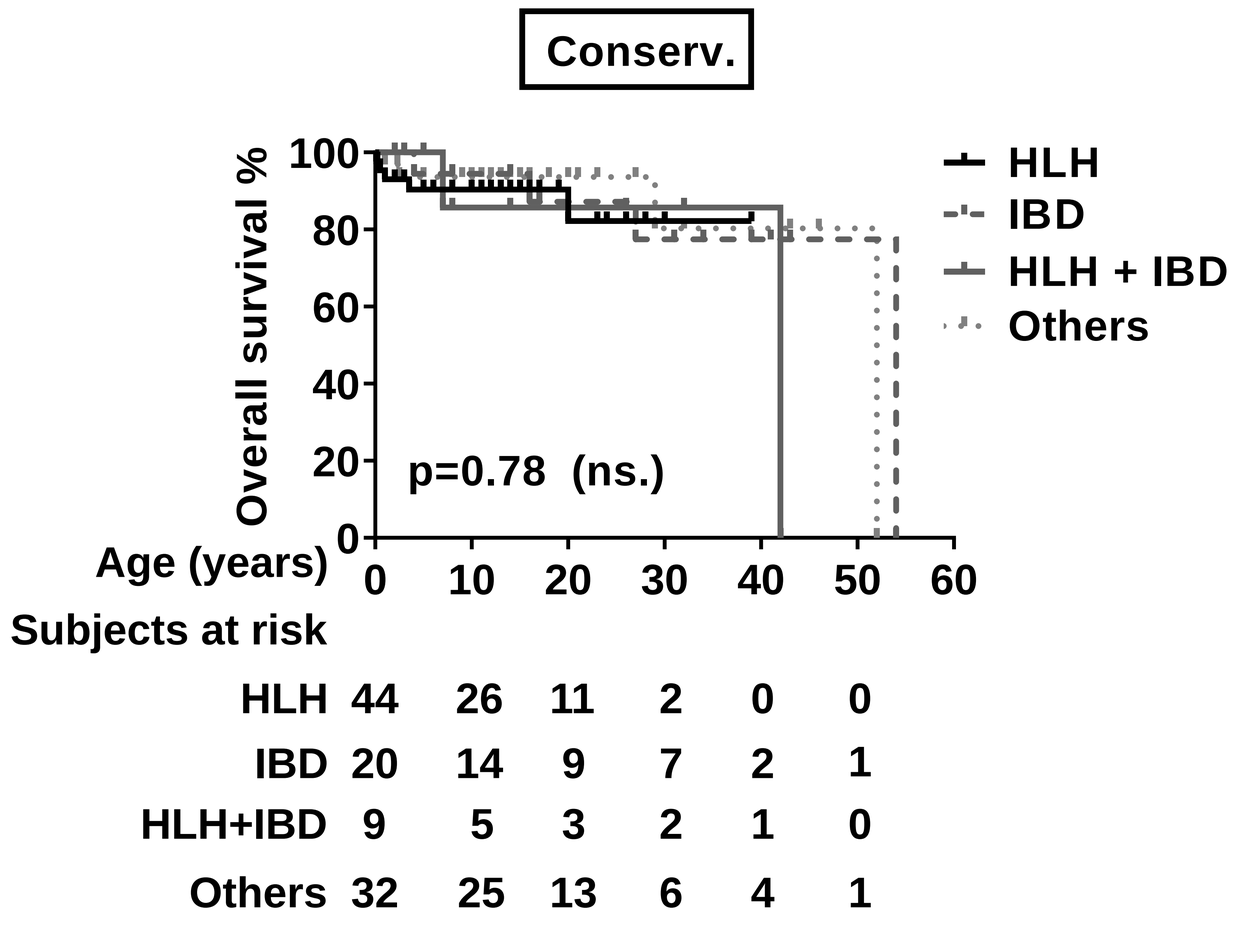

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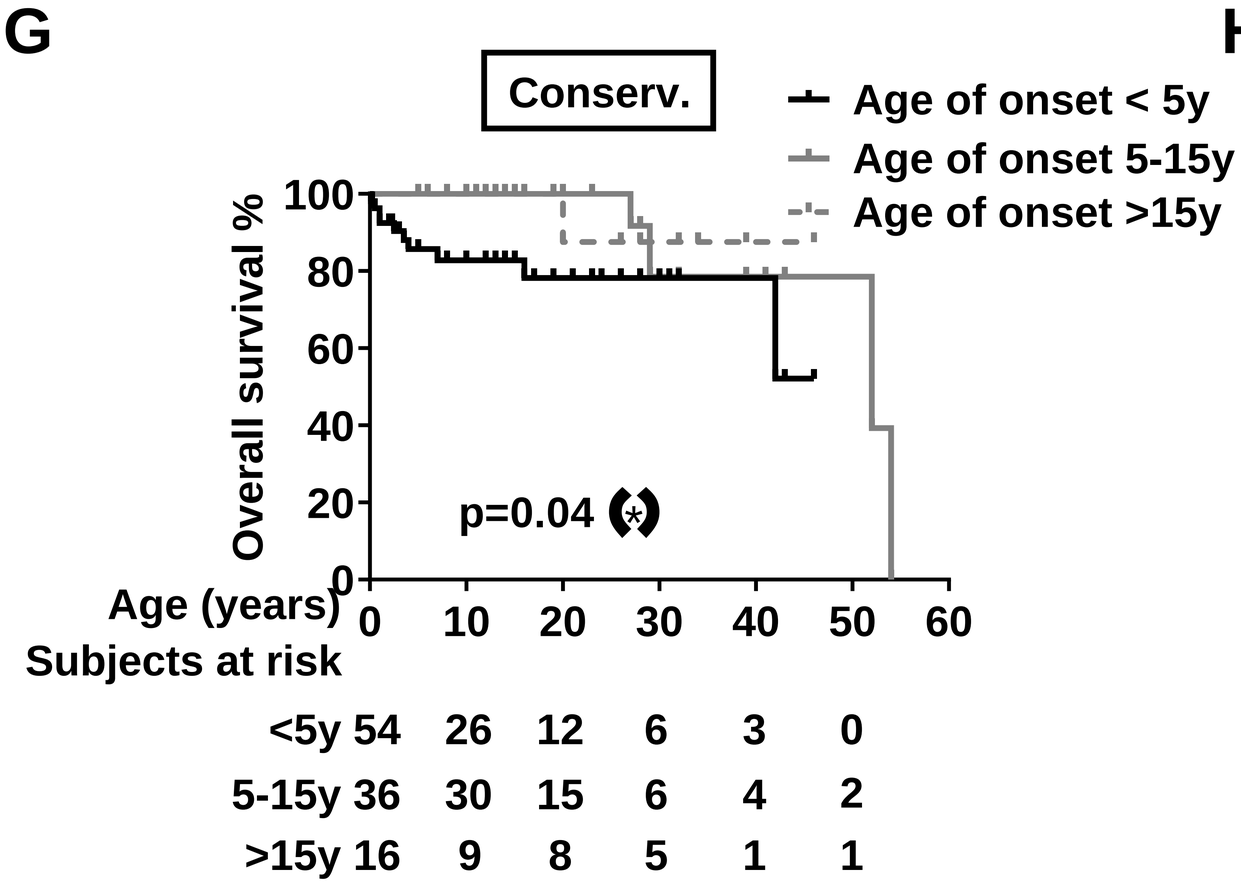

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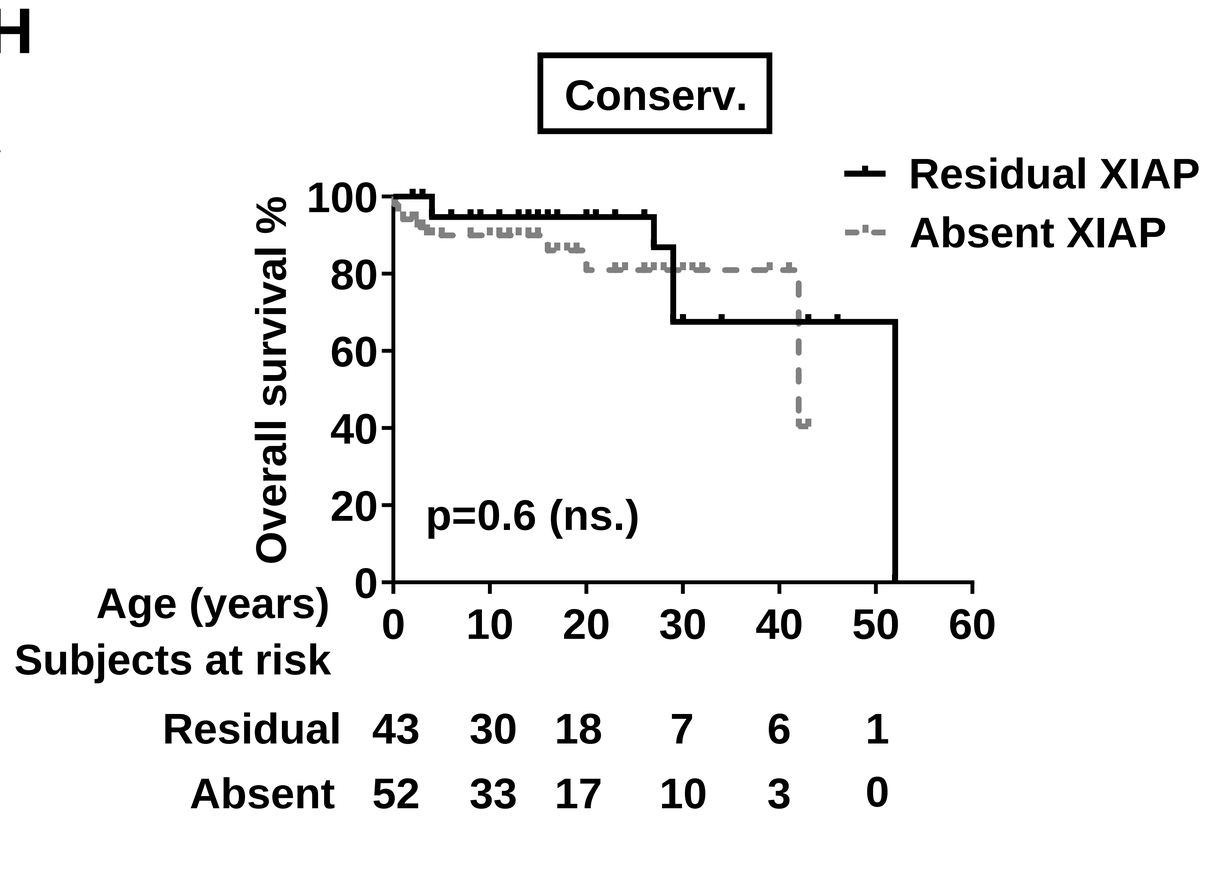

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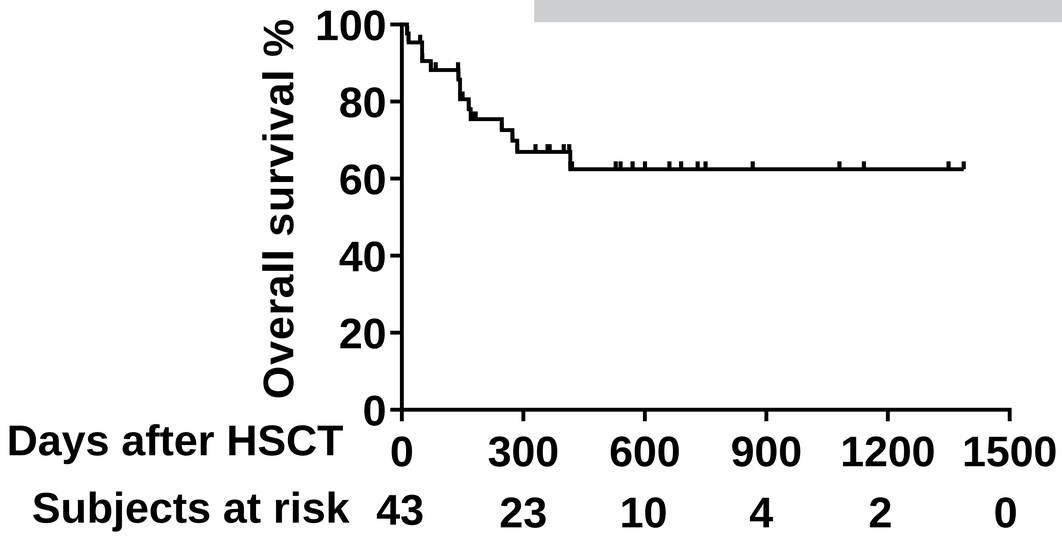

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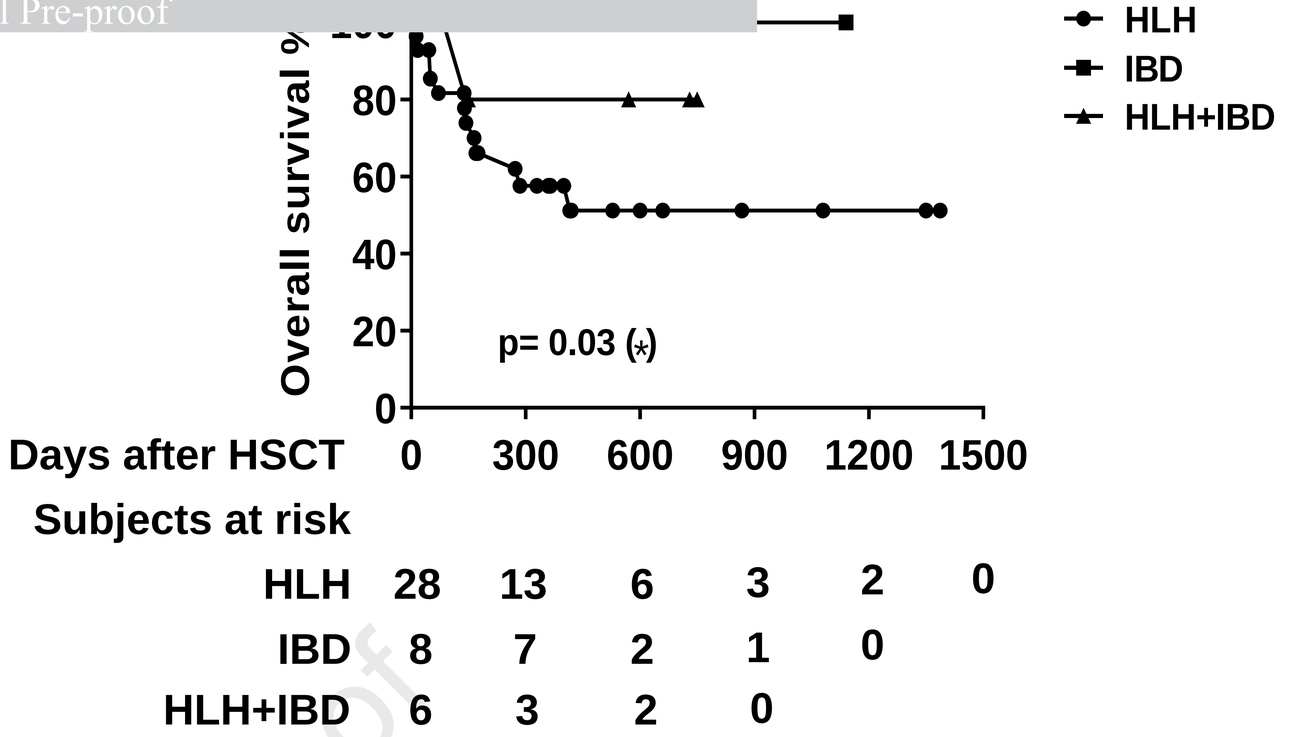

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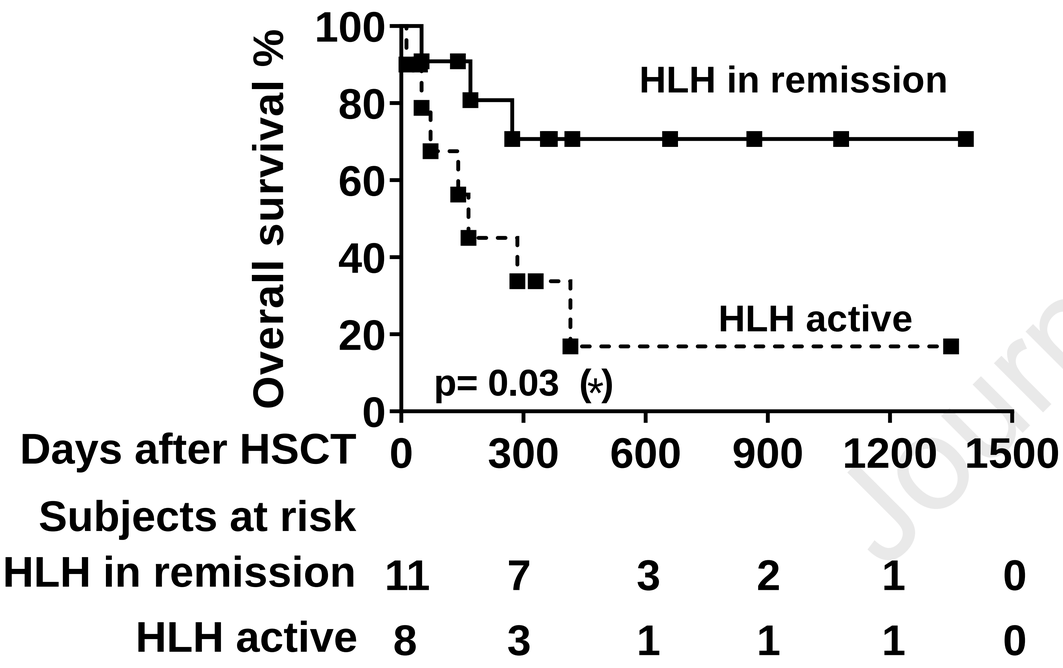

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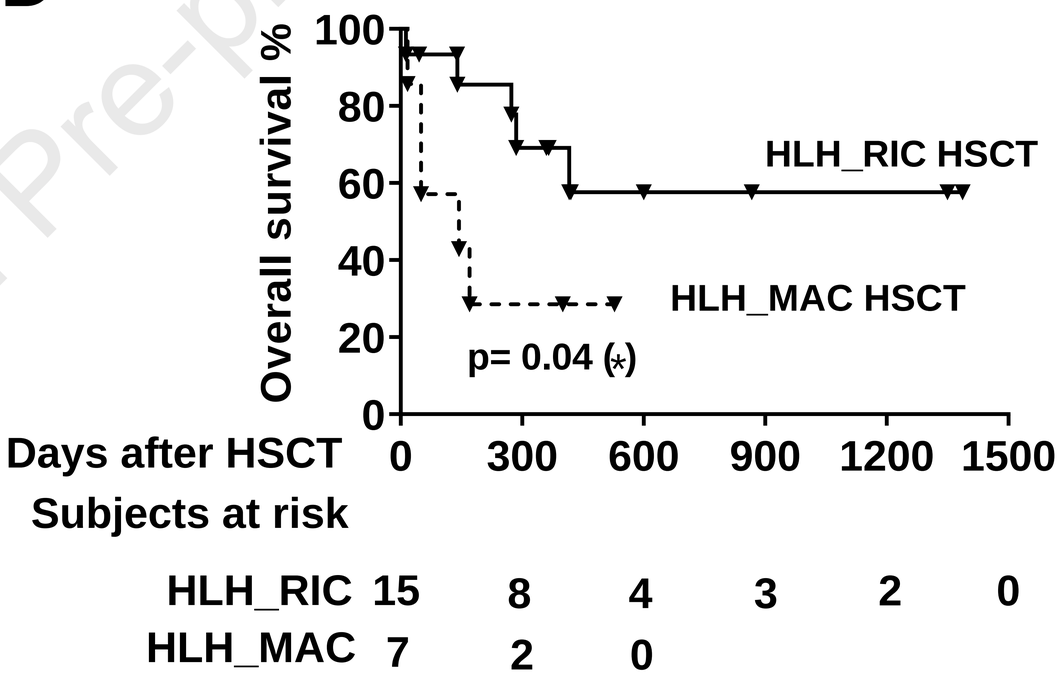

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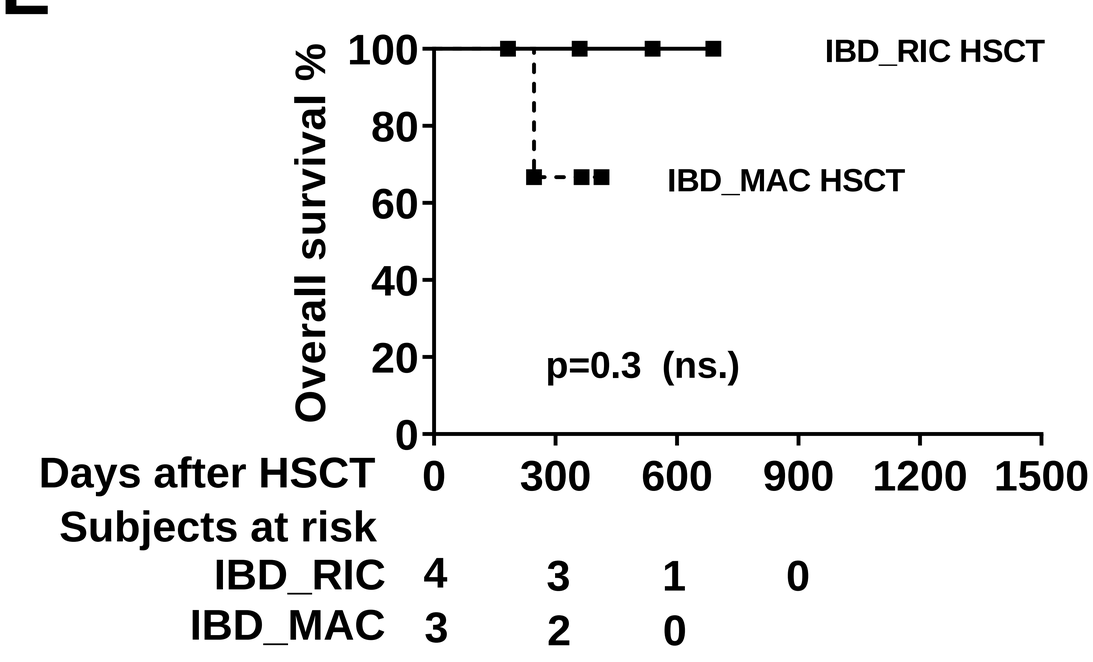

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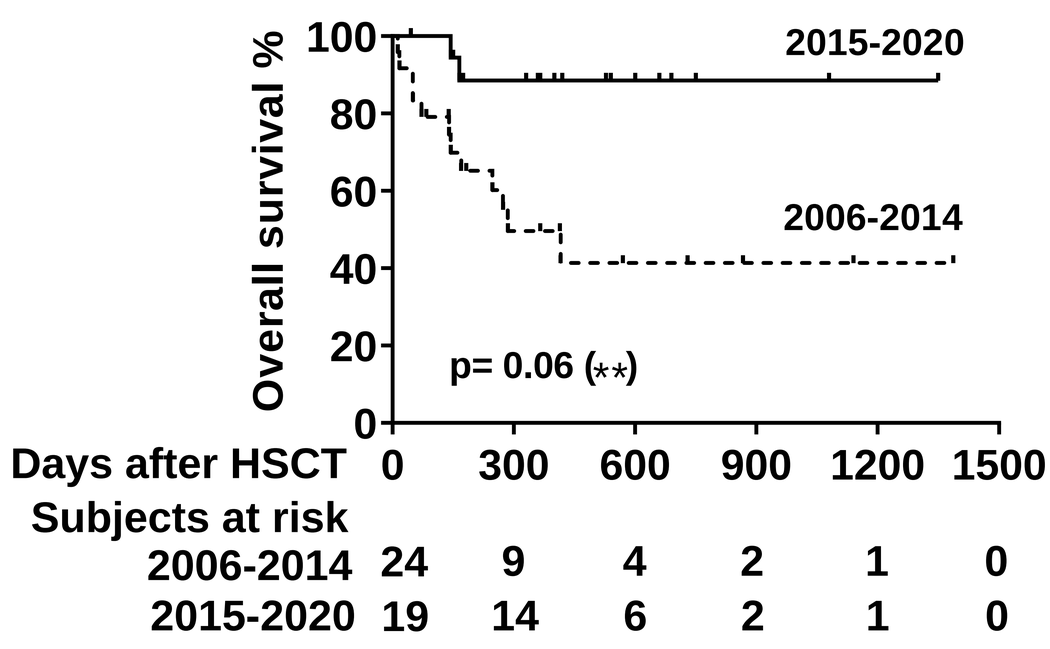

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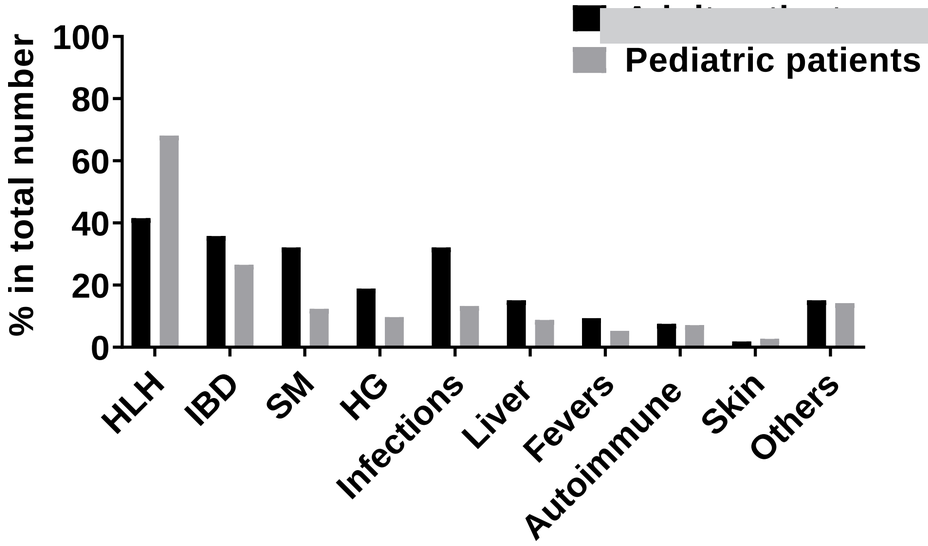

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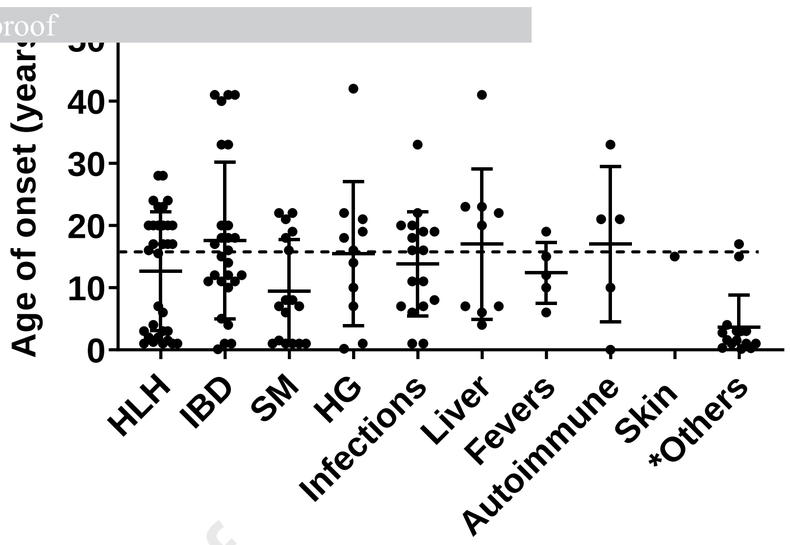

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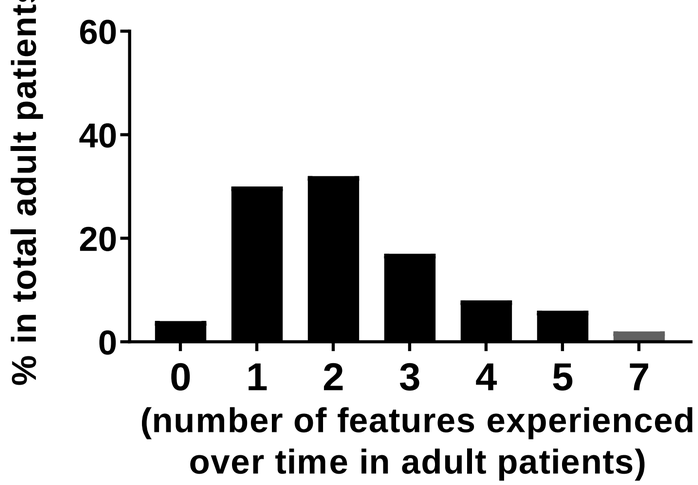

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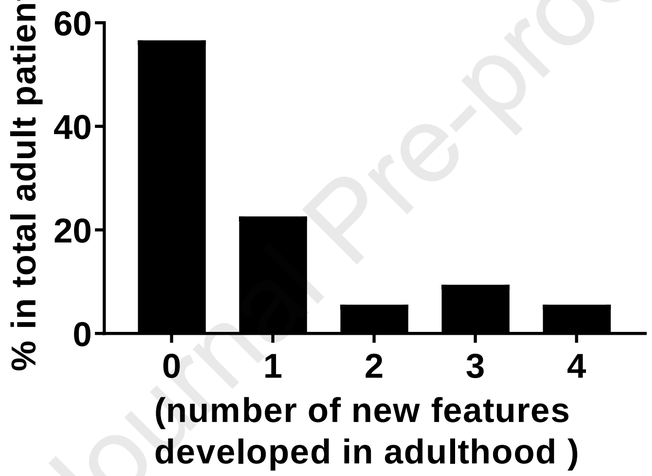

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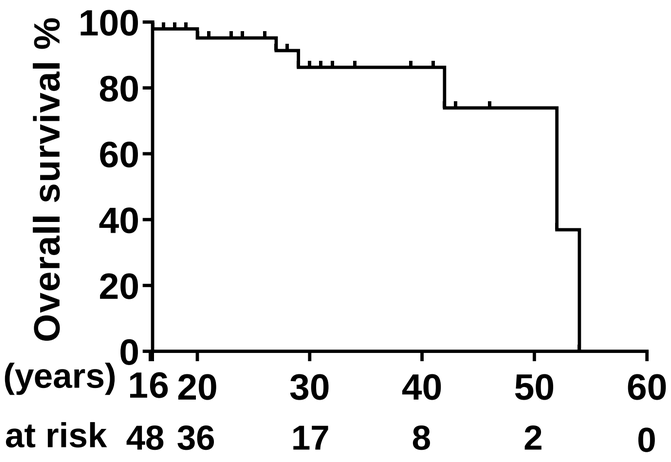

F

G