# Long-term outcome in Wiskott-Aldrich syndrome and X-linked thrombocytopenia patients: an observational -prospective multi-center study of the Italian Primary Immune Deficiency Network (IPINET)

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## Summary

**Background** **Wiskott-Aldrich Syndrome (WAS) is characterized by eczema, infections, and severe bleeding, but may also include autoimmunity and malignancy. Subjects with X-linked thrombocytopenia (XLT) can display a mild phenotype, although severe complications may occur at any age. WAS and XLT are caused by mutations of the *WAS* gene. However, retrospective studies have shown conflicting results about their genotype–phenotype correlation and their relative risk of complications.**

**Methods** **To evaluate the outcome of patients with WAS or XLT, since January 2004, patients with identified WAS mutations were enrolled in the WAS/XLT IPINet registry at diagnosis and annually evaluated until December 2018 by participating AIEOP-IPINet centers; data were prospectively collected by each participating center throughout a web-based centralized system and then retrieved from the registry for the analysis. This prospective study enrolled 117**

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patients (according to Zhu criteria, 92 were affected by WAS and 25 by XLT) with appropriate hematological features and documented *WAS* mutation.

**Findings** The median follow-up was 6 years (range 1–30 years), resulting in 1110 patient years. At diagnosis, only the patients with WAS presented invasive infections, such as sepsis, meningitis, cerebral abscesses, herpetic infections, and candida infections, while patients with XLT did not present invasive infections. The most common autoimmune manifestations in patients with WAS were hemolytic anemia (20%) and vasculitis (9.3%), inflammatory bowel disease (5%), arthritis (4%), nephropathy (2%), and coeliac disease (1%). Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) was performed in 71 (61%), autologous hematopoietic stem cell gene therapy (HSC-GT) in 10 (8.5%), splenectomy in 16 (14%) patients, while 26 patients (22%) received none of these therapies. The overall survival at 25-year follow-up was 75% for patients with WAS after HSCT. Considering the cut-off date year 2000, it improved to >80%. Patients with WAS treated by haploidentical HSCT with αβTCRT-/CD19 B-cell depletion or gene therapy showed 100% survival at 5 years. The overall survival rate at the 20-year follow-up of the 25 patients with XLT was 83% but with a cumulative incidence of 100% and 19% of infections and autoimmunity, respectively, at the 15-year follow-up.

**Interpretation** The evidence of the heterogeneity of WAS and XLT outcomes could be instrumental to draw updated recommendations for the management of the patients affected by these rare conditions. It would be desirable to expand the tools to estimate the risk of infectious and autoimmune events in patients with XLT and the impact of their treatment, including HSCT over time.

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**Keywords:** Wiskott-Aldrich syndrome; X-linked thrombocytopenia; Overall survival; Disease-related events; Management

### Research in context

#### Evidence before this study

Although the previous studies have offered important insights into genotype–phenotype correlation and informed on the relative risk of complications associated with WAS/XLT, their retrospective nature makes it difficult to assess the natural history of the disease and the response to treatment. Currently, treatment for patients with XLT remains a matter of debate.

#### Added value of this study

Patients with WAS or XLT were followed up for 30 years. This has provided the opportunity to define the long-term outcome of patients with WAS or XLT. The study has shown that patients with XLT can develop severe infectious episodes comparable to the ones experienced by patients with WAS. Despite patients with XLT present a lower number of infections at diagnosis, some of them show a WAS-like phenotype characterized by severe bleeding, infections, or autoimmunity later in life.

#### Implications of all the available evidence

The evidence of the heterogeneity of WAS and XLT outcomes could be instrumental to draw updated recommendations for the management of the patients affected by these rare conditions. It would be desirable to expand the tools to estimate the risk of infectious and autoimmune events in patients with XLT and the impact of their treatment, including HSCT over time. In particular, additional studies are required to identify the immunological and/or genetic markers that can predict the risk of progression of patients with XLT to severe disease and to standardize the indication to HSCT.

## Introduction

Wiskott-Aldrich syndrome is a rare inborn error of immunity caused by an X-linked mutation in the gene *WAS* encoding the Wiskott-Aldrich syndrome protein (WASp).[1,2] Mutations in the *WAS* gene can determine four distinct phenotypes characterized by variable features and severity: the classical WAS; the milder form termed X-linked thrombocytopenia (XLT); the

intermittent thrombocytopenia; and the congenital X-linked neutropenia that lacks the clinical findings characteristic of WAS/XLT.

More than 400 *WAS* gene mutations have been reported, the majority of which are missense variants mostly located in exons 1–4, or splice-site aberrations, nonsense, deletions, or insertions mutations that generally highly affect WASp expression.[3] Mutations that cause absent or truncated WASp expression are associated with the classical WAS phenotype, whereas mutations that allow expression of reduced amounts of normal molecular weight WASp are often associated with an XLT phenotype. Finally, missense gain-of-function mutations in the Cdc42-binding site are a cause of X-linked neutropenia.[4–6] However, exceptions to this genotype–phenotype correlation have been reported. Furthermore, prediction of the clinical course is particularly difficult in very young infants, making it difficult to provide targeted therapeutic recommendations.

A 5-point severity clinical score has been developed to discriminate patients with milder presentation (score ≤2), characterized by micro-thrombocytopenia and susceptibility to infections or mild eczema, from patients with severe, classical WAS phenotype (score 3 to 5), with serious infections, severe eczema, autoimmune complications and/or malignancy.[7–9]

Most patients with classical WAS phenotype present within the very first months to years of life, and have a poor prognosis without curative treatment. Low counts of circulating small-sized platelets represent a pathognomonic feature of the disorder and may cause spontaneous and/or post-traumatic bleeding episodes that may vary in severity from petechiae to hematomas or life-threatening intracranial or abdominal hemorrhages. Patients with WAS are susceptible to infections sustained by various pathogens (bacteria, viruses, or fungi). Respiratory tract infections are common, but enterocolitis, sepsis, meningitis, impetigo, cellulitis, and abscesses have also been reported. The increased susceptibility of patients with WAS and those with XLT to infections is related to the role of immunoregulatory functions of WAS protein in hematopoietic cells.

WASp is a cytoplasmic protein and participates in the transduction of signals from the cell surface to the actin cytoskeleton of hematopoietic cells. Therefore, WAS is included in the group of actinopathies. WASp defects affect the chemotactic and phagocytic functions of the innate immune cells and impair the adaptive immune response resulting in defects of cell motility, cytotoxicity, and functions.[10] Low counts of naïve T cells, CD8 T cell lymphopenia, impaired T-cell proliferation and defects of CXCR5+ CD4+ T follicular helper cells (Tfh) in supporting IgG production represent typical features of the T-cell immunodeficiency of WAS. There is a variable degree of B-cell lymphopenia, but the count of memory B cells is often decreased, especially in older patients, and there is frequent expansion of the $CD21^{low}$ B cellsubset.[11,12] These abnormalities of B lymphocyte development and differentiation are associated with dysgammaglobulinemia with low levels of IgM and isohemagglutinins, elevated serum IgA, and inefficient response to vaccinations. Autoimmune manifestations are often observed; autoimmune cytopenia, IgA nephropathy, and Henoch-Schönlein purpura are particularly common, followed by arthritis, vasculitis, and inflammatory bowel disease (presenting either as Crohn's disease or ulcerative colitis). Malignancies may affect up to 20% of patients with classical WAS in the first decade of life, with a higher risk in patients with concurrent autoimmunity.[13,14] However, a retrospective study on 173 patients with XLT also reported the occurrence of autoimmunity and malignancy in 12.1% (median age of 12.2 years) and 5.2% (median age of 34 years) of patients, respectively.[15] Among neoplasms, non-Hodgkin lymphoma, often EBV-triggered, and frequently involving extranodal sites, is especially frequent, followed by other hematological and non-hematological malignancies.

The management of patients with WAS or XLT relies both on supportive and targeted therapies. It is known that splenectomy increases platelet count, but it also increases the risk of serious infections, and its use should be carefully evaluated. Alternatively, Eltrombopag should be considered to control severe thrombocytopenia, particularly as a bridge treatment towards definitive therapy.[16] Hematopoietic stem cell transplantation (HSCT) and lentiviral hematopoietic stem cell gene therapy represent potentially curative treatments for patients affected by Wiskott-Aldrich syndrome.[17]

In recent years, large retrospective series and case reports have documented an improved outcome of HSCT, particularly since the year 2000, with a 3- and 5-year overall survival of ~90%. Age older than 5 years, severity of clinical manifestations at the time of transplant, use of alternative donors, particularly transplants from umbilical cord blood and mismatched related donors, and type of conditioning all remain risk factors for poorer outcomes.[18–28] The most recent analysis of 197 patients conducted by the Centers of the European Society for Blood and Marrow Transplantation recommended the conditioning regimens as indicated by the Inborn Errors Working Party (IEWP) based on either busulfan or treosulfan combined with fludarabine and thiotepa to achieve the best survival and lower the rate of Graft Versus Host Disease (GVHD),[29] but considering age ≥5 years as a risk factor for a worse outcome.[24] For those patients who do not have a suitable HSCT donor available, lentiviral vector-mediated hemopoietic stem/progenitor cell gene therapy may represent a valuable option.[30] Without definitive therapy, retrospective analysis has shown that patients with WAS are at high risk of experiencing life-threatening events as reported by

results of cumulative incidence of severe bleeding, severe infection, autoimmunity or malignancy of 45%, 61%, 46%, and 31% at 15 years, and 61%, 70%, 62% and 45% at 30 years, respectively.[31]

While these studies have offered important insights into genotype–phenotype correlation and informed on the relative risk of complications associated with WAS/XLT, their retrospective nature—often extending to various decades—makes it difficult to assess the natural history of the disease and the response to treatment in the modern era. To address this limitation, we conducted a national multicenter prospective study of a large cohort of Italian patients diagnosed with WAS/XLT from 2004 to 2018 to investigate the natural history of the disease and analyze the different therapeutic options and the long-term outcomes.

## Methods

### Patients

In 2004, the Italian Association of Pediatric Hematology and Oncology (AIEOP)-Italian Network for Primary Immunodeficiencies (IPINet) jointly formulated and adopted updated recommendations for the diagnosis and treatment of WAS/XLT (available at www.aieop.org).

The eligibility criteria to enter the study protocol were: (1) identification of a causative WAS mutation and (2) platelet count <100,000/μL; and/or platelet volume <7.5 fL. All patients who satisfied the eligibility criteria and presented a causative WAS mutation were enrolled. Enrolled patients were classified at diagnosis as WAS or XLT according to Zhu et al.[7]

Since **January** 2004, patients with identified WAS mutations were enrolled in the WAS/XLT IPINet registry at diagnosis and annually evaluated until December 2018 by participating AIEOP-IPINet centers; data were prospectively collected by each participating center throughout a web-based centralized system and then retrieved from the registry for the analysis. The AIEOP-IPINET network includes 59 hematological/immunological clinical centers. For this study, 16 centers have submitted clinical data of 117 patients with WAS or XLT identified in Italy during the study period. The dataset included blood exams (differential blood count, routine biochemistry, immunoglobulin serum levels, lymphocyte subsets, genetic WAS gene analysis), imaging data (chest X-rays, lung and sinus CT scans, abdomen ultrasonography etc.), treatment details (Ig replacement treatment, antibiotic prophylaxis etc.), infectious history data (type of infection, type of pathogen, if isolated, type of treatment, duration of infection, admission or not), cancer data (type of cancer, treatment), and outcome (alive, deceased). The WAS database was locked in December 2018 for data gathering. The registration and diagnosis forms were completed for patients meeting the inclusion criteria. Patient data were recorded every six months based on clinical information gathered from patients. Every referral center has access to the data regarding its center. Once the request has been approved by the IPINet steering group, the central operative office (www.cineca.org) can extract all necessary datasets based on queries submitted by IPINet members.

### Statistics

Categorical variables were presented as frequencies or percentages and compared with the use of the Chi–Square test and Fisher's exact test, as appropriate; associations of the crosstabs were verified using standardized adjusted residuals. Continuous variables were presented as means ± SD (in case of a normal distribution), or medians and min/max (in case of a skewed distribution) and compared with the use of Student's T-test, Anova, or the Mann–Whitney and Kruskal–Wallis test and also with Wilcoxon ad Friedman tests.[32] The normality of the variable distributions was assessed using the Kolmogorov–Smirnov test. Non-parametrical comparison tests were used for variables that did not follow normal distribution. The Kaplan–Meier method was used to estimate the probability of overall survival (OS). Death from any cause was considered an event and surviving patients were censored at the last follow-up (until December 2018). Log-rank test was used to compare OS probabilities between different groups of patients.[33,34] All variables having a P value < 0.05 in univariable analysis were included in a multivariable analysis on OS, using the Cox proportional regression model.[35]

The probabilities of severe bleeding, infections, autoimmunity, hematopoietic recovery, and acute or chronic GVHD after HSCT were calculated using the cumulative incidence function estimator with death as a competing risk[36] Gray's test was used to compare probabilities between different groups of patients.[37] The 95% confidence intervals (CI) were estimated using log–log transformation. All *p*-values were two-sided and considered as significantly different when less than 0.05. Analyses were performed using the statistics language R[38] and Stata software version 7.0.[39]

### Ethics

All patients or their legal representatives signed informed consent for data entry into the AIEOP-IPINet registry and their use in the analysis following the Declaration of Helsinki (Ethical Committee approval study NP 6118).

### Role of funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### Clinical and molecular features at diagnosis

One hundred twenty-seven patients were eligible for the study. Data were regularly collected for 117 patients who were included in this analysis, with a median follow-up of 6 years (range 0–30 years), resulting in 1110 patient-years. The WAS scoring system according to Zhu et al., with the subsequent refinements by Ochs et al., was applied at disease diagnosis to classify patients with classical WAS phenotype (n. 92) or XLT phenotype (n. 25) (Supplemental Figure S1).

The median age at diagnosis was 8.2 months (range 0–20 yrs) for patients with WAS and 6.5 years (range 0–54 yrs) for those with XLT ($p = 0.025$). About 79% of the whole cohort were diagnosed between 1 and 4 years of age and 3.4% above 15 years of age, respectively. Statistical analysis has shown that patients with WAS were diagnosed significantly earlier than those with XLT (Table 1).

At inclusion, the median platelet count was 26,000/μL (range 1000–336,000) for patients with WAS and 35,000/μL (range 3000–158,000) for those with XLT; the mean platelet volume had a median value of 4.5 fl (range 3–9) for patients with WAS and 5 fl (range 3–7) for those with XLT. Six out of 90 patients (6.7%) had platelet counts above 100,000/μL. The extent of thrombocytopenia at diagnosis was not significantly different between patients with WAS and those with XLT ($p$ = 0.469).

Genetic diagnosis of *WAS* gene in patients with WAS revealed deletions (29/92, 31%), missense mutations (20/92, 21%), splice-site mutations (17/92, 18%), non-sense mutations (15/92, 16%), insertions (7/92, 7%), other (4/92, 4%). In patients with XLT we identified missense mutations (22/25, 88%) and splice-site mutations (3/25, 12%)

Consistent with previous reports, bleeding episodes were the most common manifestation at presentation: varying degrees of bleeding occurred in both patients with WAS and those with XLT, including petechiae and ecchymoses (WAS 49/92, 53%, XLT 17/25 68%), epistaxis (WAS 8/92, 8%, XLT 6/25, 24%), bloody diarrhea (WAS 20/92, 22%, XLT 2/25, 8%), or intracranial bleeding which was detected in a comparable number of patients with WAS and those with XLT (WAS 2/92, 3%, XLT 1/25, 4%) (Table 1). We observed a higher proportion of patients with WAS to present severe bleeding at diagnosis in comparison to patients with XLT. Still, the difference was not significant ($p = 0.62$), which is consistent with previous observations.[40] The number of infectious episodes between patients with WAS and those with XLT was not significantly different (p = 0.92). Eczema, which was present in 65 patients with WAS (70%), was chronic in 25 patients (38%) and refractory to conventional treatments in 11 patients (17%).

At diagnosis, the most common infections in patients with WAS were: otitis (25%), gastroenteritis (19%), and pneumonia (17%), while patients with XLT showed a low rate of infections (Table 1).

The proportion of patients with WAS experiencing invasive infections was as follows: sepsis (6%), meningitis (2%), and cerebral abscesses (4%), herpetic infections (2%), and candida infections (7%), while patients with XLT did not present invasive infections. Patients with both WAS and XLT developed these complications; however, severe opportunistic infections

| Characteristics[a] | WAS (n. 92) | XLT (n. 25) | P[b] |
|---|---|---|---|
| Age at diagnosis, median | 8.2 months (range: 0–20 yrs) | 6.5 years (range: 0–54 yrs) | 0.021 |
| Ethnicity, n | | | |
| Caucasian | 89 | 25 (100) | 0.573 |
| Arabic | 1 | | |
| Hispanic | 2 | | |
| Mutations, n (%) | | | |
| Deletion | 29 (31) | 0 | |
| Missense | 20 (21) | 22 (88) | |
| Splice-site | 17 (18) | 3 (12) | |
| Non-sense | 15 (16) | 0 | |
| Insertion | 7 (7) | 0 | |
| Other | 4 (4) | 0 | |
| Platelets, median | | | |
| Count (μL/cmm) | 26,000 (range: 1000–336,000) | 35,000 (range: 3000–158,000) | 0.469 |
| Volume (fl) | 4.5 (range: 3–9) | 5 (range: 3–7) | 0.590 |
| Bleeding, (%) | | | |
| Petechiae | 53 | 68 | 0.620 |
| Epistaxis | 8 | 24 | |
| Bloody diarrhea | 22 | 8 | |
| Intracranial bleeding | 3 | 4 | |
| Hematuria | 5 | 0 | |
| Infections, (%)[c] | | | |
| Otitis | 25 | 4 | 0.920 |
| Bronchiolitis | 7 | 2 | |
| Pneumonia | 17 | 2 | |
| Interstitial pneumonia | 5 | 0 | |
| Meningitis | 2 | 0 | |
| Candidiasis | 7 | 0 | |
| Enteritis | 19 | 2 | |
| Sepsis | 6 | 0 | |
| Cerebral abscess | 4 | 0 | |
| Herpetic infection | 2 | 0 | |
| Autoimmune manifestations, (%) | | | |
| AIHA | 20 | 0 | – |
| Vasculitis | 9.3 | 0 | |
| IBD | 5 | 0 | |
| Arthritis | 4 | 0 | |
| Nephropathy | 2 | 0 | |
| Coeliac disease | 1 | 0 | |
| Malignancy, (n. pts) | 2 | 1 | 0.517 |

AIHA, autoimmune hemolytic anemia. IBD, inflammatory bowel disease. [a]WAS and XLT patients were negative for comorbidities at diagnosis. [b]Statistical analysis was performed by Wilcoxon rank sum test. [c]Percentage of patients who presented infections at a time between birth and diagnosis.

***Table 1:*** **Characteristics of WAS and XLT patients at diagnosis.**

(including warts, molluscum, and *P. jiroveci* pneumonia) were observed only in those with WAS. The most common autoimmune manifestations in patients with WAS were hemolytic anemia (20%) and vasculitis (9.3%); we also registered inflammatory bowel disease (5%), arthritis (4%), nephropathy (2%), and coeliac disease (1%).

At diagnosis, we registered two patients with WAS who had died of lymphoma and one patient with XLT survived cutaneous lymphoma (2.5% of the entire WAS/XLT cohort) (Table 1).

### Incidence of disease-related events "untreated" patients with XLT or WAS

In a limited number of subjects, 10 patients with WAS and 16 with XLT, who did not receive any potentially curative treatment we have analyzed the incidence of severe bleeding, infections, and autoimmune manifestations At the last follow-up or censored, the overall cumulative incidence of severe bleeding were 0.50 (0.18) and 1.00 at 8–25 years and 28 years of WAS follow-up, respectively, and 0.64 (0.19) at 15 years of XLT follow-up (Fig. 1A). Clinical and genetic features of patients with XLT are shown in Table 2.

Meanwhile, the overall cumulative incidence of infection was 0.75 (0.15) and 0.87 (0.12) at 15 and 25 years of follow-up for patients with WAS, and 1.00 at 15 years for patients with XLT, respectively (Fig. 1B). Considering autoimmune manifestations, the overall cumulative incidence was 0.00 at 15 and 0.71 (0.17) at 25 years of follow-up in patients with WAS, respectively, and 0.19 (0.12) at 15 years of follow-up in patients with XLT (Fig. 1C).

### Therapeutic management: HSCT and HSC-GT

Seventy-one patients with WAS received their first HSCT between July 19, 1988, and August 24, 2018, at a median age of 21 months (range 4.5 months–12 years).

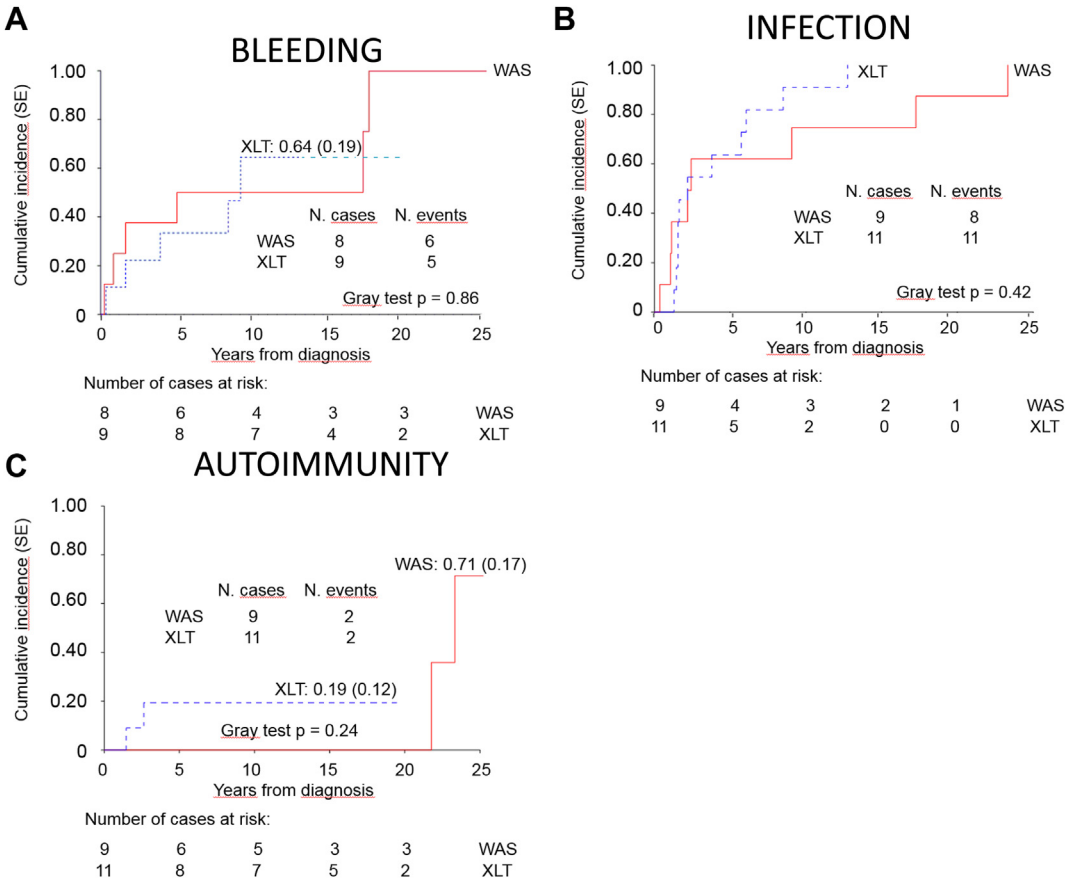


***Fig. 1:*** Cumulative incidence of disease-related events in 11 untreated patients with XLT and 8 untreated patients with WAS. (A) Overall cumulative incidence of severe bleeding (A), infections (B), and autoimmune manifestations (C) in patients with WAS or XLT who did not receive any potentially curative treatment. Cumulative incidence is reported on the *y*-axis; years from diagnosis are shown on the *x-axis*. The standard error is shown in parentheses. Gray's test was used to compare probabilities between XLT and WAS groups. All *p*-values were two-sided and considered significantly different when less than 0.05.

| Patient | Age at last follow-up (years) | WAS gene mutation | Splenectomy | Severe clinical manifestations | Other clinical manifestations | Status |
|---|---|---|---|---|---|---|
| 1 | 57.7 | c.256C > T; p.Arg86Cys | no | / | / | alive |
| 2 | 21.9 | c.230A > G; p.Asp77Gly | yes | | petechiae, cutaneous-mucosal hemorrhages | alive |
| 3 | 18.0 | c.230A > G; p.Asp77Gly | yes | bloody diarrhea | | alive |
| 4 | 41.5 | c.1442T > A; p.Ile481Asn | no | / | / | alive |
| 5 | 27.5 | c.116T > C; p.Leu39Pro | yes | respiratory infections | eczema | alive |
| 6 | 22.7 | c.116T > C; p.Leu39Pro | yes | respiratory infections | petechiae, | alive |
| 7 | 12.8 | c.229G > C; p.Asp77His | yes | | petechiae, eczema | alive |
| 8 | 16.6 | c.538C > A; p.His180Asn | no | viral infection | | alive |
| 9 | 28.3 | c.707C > G; p.Ala236Gly | yes | IgA nephropathy, respiratory infections | | alive |
| 10 | 16.7 | c.777+ 3 insT | no | | cutaneous-mucosal hemorrhages | alive |
| 11 | 2.7 | c.777+ 3 insT | no | intracranial bleeding | otitis, | deceased |
| 12 | 17.8 | c.1442T > A; p.Ile481Asn | no | respiratory infections, chickenpox, | gastroenteritis | alive |
| 13 | 15.1 | c.223G > A; p.Val75Met | no | bloody diarrhea | | alive |
| 14 | 14.6 | c.134C > A; p.Thr45Lys | yes | vasculitis | | alive |
| 15 | 30.6 | c.167C > T; p.Ala56Val | no | | eczema, petechiae | alive |
| 16 | 23.4 | c.218G > A; p.Cys73Tyr | no | | / | alive |
| 17 | 22.5 | c.173C > G; p.Pro58Arg | no | respiratory infections | gastroenteritis, cutaneous-mucosal hemorrhages | alive |
| 18 | 24.5 | c.173C > G; p.Pro58Arg | no | herpes infection, respiratory infections, contagious molluscum | eczema, petechiae | alive |
| 19 | 17.6 | c.91G > A; p.Glu31Lys | yes | sepsis, herpetic encephalitis | | deceased |
| 20 | 57.7 | c.173C > G; p.Pro58Arg | no | / | / | alive |
| 21 | 26.9 | c.167C > T; p.Ala56Val | no | / | / | alive |
| 22 | 8.2 | c.134C > T; p.Thr45Met | no | contagious molluscum, vasculitis | lymphadenitis, | alive |
| 23 | 2.4 | c.559+ 5G > A | no | respiratory infections | otitis, | alive |
| 24 | 16.3 | c.134C > T; p.Thr45Met | no | warts | cutaneous-mucosal hemorrhages, | alive |
| 25 | 16.7 | c.134C > T; p.Thr45Met | no | / | / | alive |

*Table 2:* **Genetic and clinical features of XLT patients.**

Most patients (n = 55) received hematopoietic stem cell grafts (45 allogeneic, 10 autologous), 19 patients received peripheral blood stem cell (PBSC), and 6 patients cord blood (CB) grafts. Data of HLA-matching donors were available for 70 patients: 14 patients received HLA-matched sibling (MSD), 12 patients mismatched related (MMSD), 32 patients matched unrelated (MUD), and 12 patients mismatched unrelated grafts (MMUD), respectively.

The conditioning regimen consisted of busulfan/fludarabine ± thiotepa (BuFlu ± TT) or treosulfan/fludarabine ± thiotepa (TreoFlu ± TT) according to the IEWP HSCT guidelines. The majority of the patients (41–57.7%) received a myeloablative conditioning regimen (MAC) based on/containing busulfan, while 30 (42.3%) received a reduced intensity conditioning (RIC) with fludarabine. Approximately 30% of the recipients of either bone marrow or cord blood transplantation received a RIC.

The median follow-up after HSCT was 8 years (range 4 months–30 years). During follow-up, patients who received allogenic transplants had a median platelet count of 210,000/μL.

Information regarding acute and chronic GVHD was available for 69 and 54 patients, respectively.

The overall cumulative incidence of grade II- IV, III-IV acute GVHD, and chronic GVHD at 1 year were 24.2% (95% CI, 15.6%–37.6%), 9.6% (95% CI, 4.5%–20.6%), and 10.4% (95% CI, 4.5%–23.8%), respectively.

We observed no differences in the cumulative incidence of both acute and chronic GVHD in recipients of HLA-matched sibling, matched unrelated, mismatched related, and mismatched unrelated grafts (data not shown).

After HSCT, 3 patients died of Epstein Barr Virus-related lymphoproliferative disorder, after receiving a MUD (in 2 patients) and a MSD graft. One patient developed thyroid carcinoma following MUD HSCT.

A second HSCT was performed in 6 patients: 3 patients received a second matched unrelated graft, 2 patients received a second matched unrelated transplant following a first mismatched family graft, and 1 patient was transplanted three times from a matched sibling donor.

HSC-GT was performed in 10 patients following conditioning with one dose of anti-CD20 and reduced doses of weight-based and pk-adjusted busulfan and fludarabine, lower as compared to the allo-HSCT RIC, and no post-infusion immune suppression. The median age at diagnosis was 7 months (range 1.5 months–12 years) and at the time of therapy was 3 years (range 13 months–14 years).

During follow-up (median 3.9 years, range 0.6–6 years), the median platelet count was 56,000/μL and no GVHD or second intervention occurred.

### Splenectomy

Splenectomy was performed in 17/117 patients (14.5%), 9 patients with WAS (9.8%), and 8 patients with XLT (32%), respectively. Following splenectomy, the platelet count maintained a median of 186,000/μL. In all patients, splenectomy was performed before the year 2000. In patients with WAS, splenectomy was performed at a median of 7 months (range 1–83) after diagnosis, while in 2 patients the diagnosis was done 1 month after splenectomy, and in one patient 4 years after the procedure.

Among patients who received splenectomy, 4 patients (23%) died: 3 were patients with WAS, while one patient with XLT had fatal sepsis and herpetic encephalitis.

### Overall survival

At the last follow-up, 94 patients were alive. For the whole WAS/XLT cohort, the probability of OS (SE) was 0.82 (0.04), 0.80 (0.04), and 0.77 (0.05) at 5, 10–15, 20–25 years from diagnosis, respectively (Fig. 2A). The 20-year probabilities of survival (SE) were 0.83 (0.12) for patients with XLT and 0.75 (0.05) for patients with WAS ($p = 0.12$) (Fig. 2B). The causes of death in 23/117 patients (20%) were infections (n = 15 [65%]), EBV-associated lymphoproliferative disorder (n = 3 [13%]), severe hemorrhage (n = 4, [17%]), and a traumatic event (n = 1 [4%]).

The 15-year probabilities of OS (SE) from HSCT were 0.85 (0.10), 0.79 (0.11), 0.77 (0.08), and 0.59 (0.14) for MFD, partially matched familial donor (PMFD), MUD and partially matched unrelated donor (PMUD), respectively (Fig. 3A).

The 5 to 15-year probabilities of survival (SE) from HSCT were 0.80 (0.06) and 0.50 (0.20) for bone marrow and cord blood as hematopoietic cell sources, respectively, whereas 0.69 (0.13) for peripheral blood stem cells 5 years after HSCT (Fig. 3B). Overall survival was 0.79 when HSCT was performed before 3 years of age, 0.63 when performed after 3 years (Figs. 3C), and 0.76 when performed before 5 years, 0.67 when performed after 5 years (Fig. 3D), respectively.

The analysis of treatment outcomes in patients with WAS using as cut-off data year from 2010, showed that the 5-year survival (SE) from HSCT were 0.75 (0.05), 0.80 (0.18), 0.75 (0.22) and 0.54 (0.20) overall, for MUD, MFD, and PMUD, respectively. While, patients with WAS treated with gene therapy or HSCT from partially matched familial donors (PMFD) after αβTCRT-/CD19 B-cell depletion showed 100% survival (Fig. 4).

The variables present at diagnosis that have been shown to influence the probability of OS in univariable analysis (epistaxis, bloody diarrhea, intracranial bleeding, interstitial pneumonia) were considered for

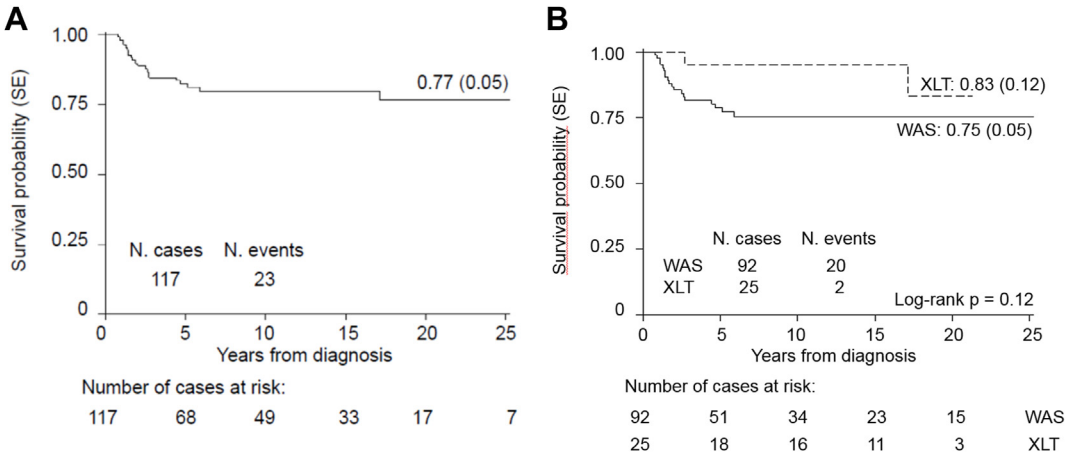


*Fig. 2:* Overall survival of 92 patients with WAS and 25 patients with XLT of the IPINET cohort. Overall survival of patients with WAS and those with XLT (panel A); and the WAS cohort and XLT cohort (B) after 25 years from diagnosis. Survival probability is reported on the *y*-axis; years from diagnosis are shown on the *x*-axis. The standard error is shown in parentheses. The log-rank test was used to examine differences among subgroups.

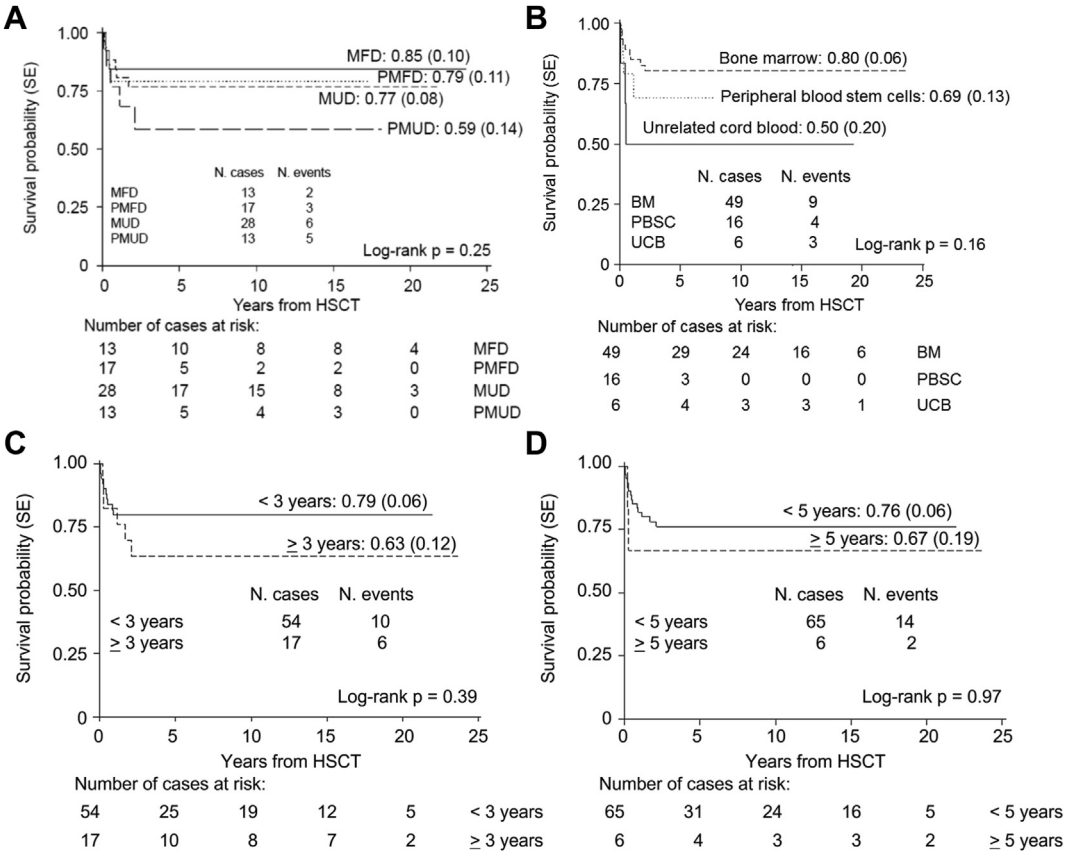


***Fig. 3:*** Survival of patients with WAS after HSCT by donor type, matched familial donor (MFD), partially matched familial donor (PMFD), matched unrelated donor (MUD) and partially matched unrelated donor (PMUD), respectively (A) and by hematopoietic cell source, bone marrow, peripheral blood stem cells and unrelated cord blood (B). Overall survival by age at HSCT: before or after 3 years of age (C) and before or after 5 years (D), respectively. Survival probability is reported on the *y*-axis; years from HSCT are shown in the *x*-axis. The standard error is shown in parentheses. The log-rank test was used to examine differences among subgroups.

multivariate analysis, but none of these proved to be independent factors in influencing OS (Supplemental Table).

## Discussion

Wiskott-Aldrich syndrome exhibits a wide clinical spectrum ranging from mild, isolated thrombocytopenia to full-blown presentation that can be complicated by life-threatening hemorrhages, infections, atopy, autoimmunity, and cancer. Our multicenter national study represents the first prospective evaluation of a large cohort of 117 patients with WAS or XLT. The study aimed at increasing the knowledge of the natural history of the disease and assessing the long-term prognosis of affected patients in terms of both OS after definitive treatments and cumulative incidence of major complications in the absence of any potentially curative procedure.

Children with the severe classical WAS phenotype are candidates for curative allogenic stem cell transplantation or gene therapy via genetically modified autologous stem cell transplantation as the prognosis is poor beyond their second or third decade of life without any definitive treatment. Our results confirmed that most patients with WAS, particularly those with severe disease, experienced the first clinical manifestations of disease in the first months of life, with a significant difference in the time of diagnosis for patients with WAS that are diagnosed at a median age of 8.2 months, compared to 6.5 years for patients with XLT. The diagnosis of WAS/XLT can be delayed well into adulthood, especially in the milder cases. Consistent with current knowledge,[40] severe bleeding (bloody diarrhea, intracranial bleeding) is more common in patients with WAS early in life, while neither the severity of the thrombocytopenia nor the presence and frequency of milder hemorrhagic manifestations (petechiae, ecchymoses) differed between patients with WAS and those with XLT. Invasive infections (sepsis, cerebral abscess, meningitis) occurred only in patients with classical WAS phenotype, as well as opportunistic infection with

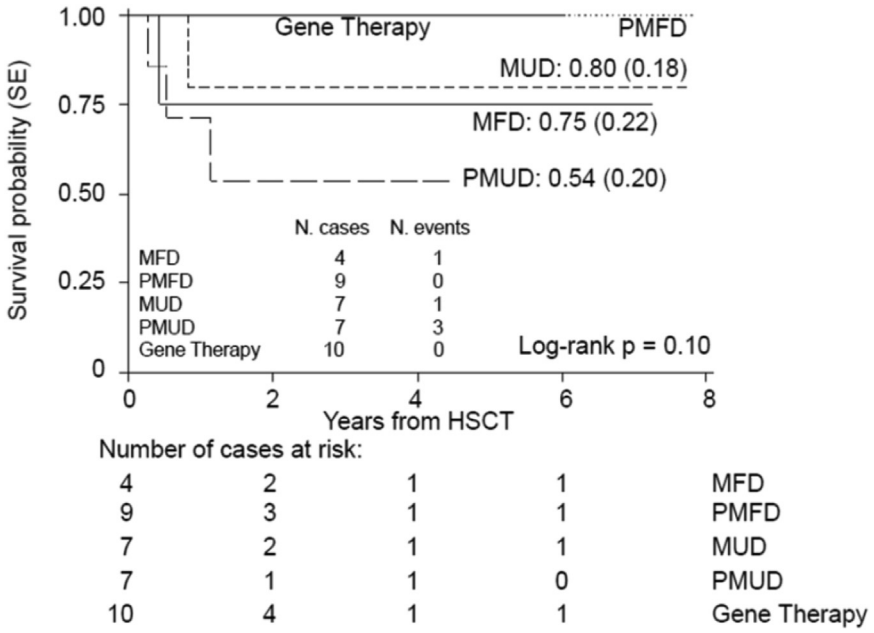


***Fig. 4:*** Overall survival by type of treatment, using as cut-off data year from 2010: matched unrelated donor (MUD), matched familial donor (MFD), and partially matched unrelated donor (PMUD) HSCT, gene therapy, and HSCT from partially matched familial donors (PMFD) after αβTCRT-/CD19 B-cell depletion, respectively. Survival probability is reported on the *y*-axis; years from HSCT are shown in the *x-axis*. The standard error is shown in parentheses. The log-rank test was used to examine differences among subgroups.

*Candida* or herpetic infection. Similarly, at diagnosis autoimmunity and fatal malignancy were present only in patients with WAS. In our cohort, 77% of the patients with WAS were treated with HSCT, 10% with HSC-GT, and 9% underwent splenectomy. Splenectomy was performed before the year 2,000, suggesting how the more recent progress in HSCT procedures made splenectomy an obsolete treatment, but underlying the importance to promote the need of investigating WAS mutations in any male patients before considering splenectomy. The two largest more recent studies to evaluate the outcomes following HSCT that have been conducted by the Primary Immune Deficiency Treatment Consortium[27] and the European Bone Marrow Transplantation/European Society for Immunodeficiency[24] reported an estimated overall survival rates of 91% and 88.7% considering a 5- and 3-year follow-up, respectively. A previous retrospective study by Glasmacher et al. [31] reported a 10-year overall survival of 80% after HSCT which was the definitive treatment in 252/575 patients. In our study, the overall survival rate after HSCT was 75% as evaluated at the longest follow-up time currently reported of 25 years. Consistent with other reports, since the year 2000, we observed a better OS mainly due to the improved HSCT approaches that include the haploidentical-HSCT following αβTCRT-/CD19 B-cell depletion and the possibility to perform autologous HSCT-GT whenever available. [41,42] Other promising options for the treatment of patients with WAS, such as post-HSCT cyclophosphamide were not used in this cohort because they have become available more recently. Similar to what was observed in previous cohort studies, younger age at the time of HSCT, considered as before both 3 and 5 years, of age, correlated with a better outcome.

Currently, treatment for patients with XLT remains a matter of debate. In these patients, the diagnostic delay is often significant, and patients are frequently misdiagnosed as chronic immune thrombocytopenia. Patients with XLT may be candidates for splenectomy for the management of thrombocytopenia and bleeding. Our data confirmed the sustained increase in platelet counts post-procedure. However, splenectomy results in an increased risk of fatal infections and must require life-long antibiotic prophylaxis.[15]

This prospective study of patients with WAS or XLT has shown that patients with XLT can develop after diagnosis multiple infectious episodes at levels comparable to those with WAS. Despite at diagnosis, patients with XLT might have presented a low number of infections, some of them can reveal a WAS phenotype characterized by severe bleeding, infections, or autoimmunity throughout life.

This observation is in accord with a recent retrospective study on 577 patients with WAS showing that even those patients carrying WAS variants that were associated with an XLT phenotype display high morbidity and/or premature mortality.[43] In the present

study, the follow-up of patients with WAS or XLT extends for up to 30 years, the longest reported in a prospective study. This has provided the opportunity to define the long-term outcome of patients with WAS or XLT. Further studies are needed to evaluate the risk of infectious and autoimmune events in individuals with XLT who have not undergone HSCT, as well as the long-term impact of this treatment. Nevertheless, the study has several limitations, including the limited number of patients and incomplete availability of clinical-immunological data during the follow-up and the evaluation of WASP protein expression which has become available more recently. Possible confounding factors are the age at diagnosis which was considerably different between patients with XLT and those with WAS and the broad heterogeneity in the diagnosis tools which have allowed to reduce the diagnostic delay of patients with XLT or WAS. Moreover, the availability of novel methodologies of HSCT, which have improved over time the disease outcome, might influence the generalizability of the study findings.

Our results showed an overall survival rate of 83% for patients with XLT at 20-year follow-up, but with a cumulative incidence of 100% and 19% of infections and autoimmunity, respectively, at 15-year follow-up. These observations highlight how these patients require careful monitoring during regular follow-ups to early diagnose life-threatening infections or chronic complications.

Moreover, young patients with chronic thrombocytopenia should be screened for *WAS* mutations to allow earlier diagnosis of XLT and identify the best therapeutic options before the development of disease-related events that may increase the risks related to the procedure.

Further studies are required to evaluate the immunological features and the risk of progression to severe disease of patients with XLT to standardize the indication to HSCT that remains currently a viable option for patients with WAS especially when a well-matched HLA-identical donor is available. The recent improvement in the outcome of haploidentical -HSCT following αβTCRT-/CD19 B-cell depletion and of post-treatment cyclophosphamide protocols and the possibility offered by gene therapy, when available, constitute valuable therapeutic options for all patients with WAS, especially for those diagnosed early in life.

In conclusion, the results of this prospective study of 92 patients with WAS and 25 patients with XLT showed an overall survival of 75% and 83%, respectively, at 25 years of follow-up. The improvement in the knowledge of the heterogeneity of WAS/XLT disorders together with the application of recommendations elaborated by consensus of experts optimize the current management of the patients. The evaluation of different therapeutic strategies may expand the evidence for the best treatment options that should be recommended at younger ages before the natural progression of the disease with the development of chronic complications.

#### Contributors

Contribution: A.S., R.B, F.P. designed the research, verified and analyzed the underlying data, and wrote the manuscript. RR verified the data and performed statistical analysis. All authors except R.R., S.G., D.M., C.M. contributed data. All authors edited and approved the final manuscript.

#### Data sharing statement

All data will be available through email with publication after getting permission from the corresponding author.

#### Declaration of interests

F.L. declares working with Amgen, Novartis, Sanofi, Vertex. A.A. declares working with Orchard Therapeutics, Fondazione Telethon. The other authors declare no competing financial interests.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103271.

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