The incidence and type of cancer in patients with ataxia-telangiectasia via a retrospective single-centre study

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Summary

Ataxia-telangiectasia (A-T) is a hereditary immune system disorder with neurodegeneration. Its first neurologic symptoms include ataxic gait in early childhood, with slowly progressive cerebellar ataxia, oculomotor apraxia, oculocutaneous telangiectasia, and progressive muscle weakness. Neonatal screening for severe T-cell deficiency was recently found to diagnose A-T patients with a significantly reduced naive T-cell pool. Our study includes 69 A-T patients between 8 January 2002 and 1 December 2019. Nineteen cases of cancer were diagnosed in 17 patients (25%), with a median overall survival [OS; 95% cumulative incidence (CI)] of 26.9 years for the entire cohort. The 15-year OS of 82.5% (72-95%) was significantly decreased among A-T patients with malignancies, who had a median OS of 2.11 years, with a two-year-estimated OS of 50.7% (31-82%). Haematological malignancies were the major causes of death within the initial years of life with a 15 times increased risk for death [HR (95% CI); 6.9 (3.1-15.2), P < 0.001] upon malignancy diagnosis. Male patients with A-T are at a higher cancer risk than their female counterparts. This manuscript highlights the need for cancer surveillance and prevention, as well as optimal treatment in this cohort.

Keywords: Ataxia-telangiectasia, primary immunodeficiency, malignancy, radio sensitivity, cancer surveillance.

Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder with causative mutations in the gene encoding the ATM protein on chromosome 11q22-23.1 ATM protein interacts with a large number of immune, haematopoietic, and endocrine targets, resulting in a broad multisystemic clinical manifestation and genotype-phenotype correlation.2 Affected patients usually show their first neurologic symptoms in early childhood, followed by slowly progressive cerebellar ataxia, oculomotor apraxia, oculocutaneous telangiectasia, dysphagia, progressive muscle weakness, and endocrine disorders.3,4 ATM plays a major role in the double-string (ds)DNA repair mechanism, affecting cell cycle control and apoptosis.5 Thus chromosomal instability, also termed chromothripsis, is a major consequence of ATM dysfunction, leading to increased radiosensitivity.5 Studies are still in progress to investigate whether the lack of immunological surveillance, the disturbed cell regulative capacity of the ATM protein, or both, is responsible for the increased malignancy risk.6 The significantly increased susceptibility to malignancies has already been shown to affect 25% of patients at a median age of 12-5 years. Of particular interest, heterozygous ATM carriers have a reduced life expectancy due to cancer (especially breast and gastrointestinal malignancies) and ischaemic heart disease.7 It is the leading cause of death in patients with A-T.8 Because of chemo sensitivity, there are no unified chemotherapy protocols for optimal cancer treatment in A-T patients, especially in paediatric patients. Two approaches are discussed. Some authors have suggested a treatment according to the protocol with subsequent dose modifications depending on the tolerability of the first treatment block, whereas others prefer a per se chemotherapy treatment with reduced toxicity.

In A-T, there is also a variable extent of immunodeficiency, ranging from severe combined immunodeficiency phenotype to mild alteration of the humoral immunity. Counts of T and B lymphocytes and/or the level of...
immunoglobulins in peripheral blood can correlate with the severity of immunodeficiency in some patients. In addition, the ‘hyper-IgM phenotype’ has an inferior prognosis.9,10 A-T patients can be detected by the recently implemented T-cell receptor excision circles (TREC)-based new-born screening for severe T-cell deficiencies, while these patients are only a few days old and asymptomatic. Detailed knowledge about the risk of malignancy is necessary to prevent malignancy as well as develop optimal therapeutic regimens and parents’ counselling.

In this work, we present the course of the disease and patient outcomes in a single-centre study including 69 A-T patients from whom 16 patients developed a malignancy and one patient developed a benign brain tumour. However, this study did not focus on the comparative analysis of the treatment (due to the low number of cases). A retrospective study by I-BFM is currently gathering data on A-T patients with leukaemia and lymphoma, assessing their detailed treatment modalities and providing insight into the optimal treatment (study start July 2019; ClinicalTrials.gov Identifier: NCT04037189).

Patients and methods

Data were collected retrospectively by chart review of A-T patients who were treated in the inpatient and outpatient care units of the Department for Children and Adolescents, University Hospital Frankfurt, Germany. Additional data were received from other centres in cases where treatment was continued at local centres. The study was approved by the local ethics committee of the University Hospital Frankfurt (Application No. 147/18).

Statistical analyses

A detailed description of the statistical analyses is available at Data S1.

Results

Patient and disease characteristics

The study included 69 A-T patients [39 female [(57%)] vs. 30 male (43%)] who were under regular follow-up at the Division for Allergy, Pneumatology and Cystic Fibrosis of the Department for Children and Adolescents, University Hospital Frankfurt, Germany between 1 August 2002 and 1 December 2019. There were five cases of T-cell acute lymphoblastic leukaemia (26% T-ALL), nine cases of non-Hodgkin lymphoma (46% NHL), including four diffuse large B-cell lymphomas (DLBCL), four B-cell lymphomas, and one natural killer cell lymphoma (NK) NHL. Two patients developed Hodgkin disease (1% HD), and one (0.5%) case of meningioma was reported. A second malignancy was observed in one patient with initial B-cell NHL who developed hepatocellular carcinoma (HCC). Another patient had relapsed T-ALL 10 years after the first treatment. Further, non-haematological, malignancies were not observed in this cohort. P2 and P3 as well as P1 and P16 were siblings (Table I).

Underlying genetic mutation

The diagnosis was based on genetic mutation and/or abnormal ATM protein activity. Mutations in ATM were available in 13/17 patients, being mostly homozygous and (compound) heterozygous leading to ATM protein abolishment. For P17 only one heterozygous mutation was found without evidence of a second variant.

Treatment characteristics

One patient with meningioma underwent surgery and achieved complete remission; others were treated with chemotherapy and/or immune therapy. One patient (P5) underwent allogeneic stem cell transplantation (Table I).

Acute lymphoblastic leukaemia (ALL)

Among patients with T-ALL (P1–P5), treatment was performed as per the AEIOP BFM 2009 protocol; except for P3 other patients received up-front dose modifications and no irradiation. P3, previously undiagnosed with A-T, received the full treatment protocol including cranial radiotherapy. This patient achieved long-term remission; however, radiation-related intracranial cavernomas led to severe lethal intracerebral bleeding at the age of 11 years.

Modified treatment was applied to P1, who was under treatment at the last follow-up (LFU). P2 achieved remission for 10 years; however, he relapsed with T-ALL at the age of 16 years and received an individualised protocol at LFU. Treatment modification included dose reduction of daunorubicin, idarubicin and methotrexate (MTX), mostly at 50%. P4 showed a partial response to the treatment, however, he developed a bowel obstruction and pleural effusions leading to respiratory failure. P5 received an early alloHSCT because of non-remission, developing a fulminant relapse a few days after alloHSCT.

Non-Hodgkin lymphoma (NHL)

Nine cases of NHL were reported, including four DLBCL (P6–P9), four B-cell NHL (P10–P13), and one NK NHL (P14). P6–P9 received individual therapies using steroid and bi-weekly rituximab (375 mg/m²) to reduce chemotoxicity, which was tolerated well in all patients. P6–P9 achieved complete remission, and P6 and P7 were in remission as of December 2020 at 22 and 27 months respectively. The follow-up programme included magnetic resonance imaging (MRI) of the site of the previous tumour every six months. Nonetheless, P8 and P9 needed treatment intensification.
| ID  | Sex | ATM mutation                  | Malignancy | Age at malignancy, years | Treatment | Status at LFU                                                                 |
|-----|-----|--------------------------------|------------|--------------------------|-----------|------------------------------------------------------------------------------|
| P1  | M   | 1470dupT; p.(Thr491Tyrfs*8)   | T-ALL      | 10                       | Modified AEIOP BFM 2009 | Alive, 11 years. Pred poor response, ongoing treatment                      |
| P2  | M   | NA                             | T-ALL      | 6                        | Modified AEIOP BFM 2009 | Alive, relapse at 16 years, ongoing treatment                                |
|     |     |                                |            | 16                       | T-ALL relapse           | Died, 11 years. Remission, cavernoma haemorrhage                            |
| P3  | M   | NA                             | T-ALL      | 3                        | Standard AEIOP BFM 2009 + radiation | Died, 25 years. Partial response, treatment toxicity with bowel obstruction and respiratory failure |
| P4  | M   | NA                             | T-ALL      | 24                       | Modified AEIOP BFM 2009 | Died, 2 years. Early fulminant relapse post alloHSCT                         |
| P5  | M   | c.2921+1G>A; p.(?); c.3320T>A; p.(Leu1107*) | NHL/T-ALL  | 2                        | Modified AEIOP BFM 2009 + alloHCST | Died, 38 years. Progressive HCC                                            |
| P6  | F   | c.2064delA; p.(Glu688Aspfs*15) | NHL/DLBCL  | 8                        | Rituximab + steroid     | Alive, 11 years. Remission                                                   |
| P7  | M   | c.7327C>T; p.(Arg2443*)         | NHL/DLBCL  | 5                        | Rituximab + steroid     | Alive, 8 years. Remission                                                    |
| P8  | F   | c.3802delG; p.(Val1268*)        | NHL/DLBCL  | 5                        | Rituximab + steroid and CPM   | Died, 5 years. Non remission                                                 |
| P9  | M   | c.2098C>T; p.(Gln700*) c.6229ins17; p.(Leu2077Phefs*5) | NHL/DLBCL  | 21                       | Rituximab + steroid and CPM   | Died, 22 years. Non Remission                                               |
| P10 | F   | c.5441insT; p.(Leu1814Trpfs*14) | NHL B      | 24                       | MTX, vincristine, cytarabine | Died, 14 years. Sepsis in remission                                        |
|     |     | c.6095G>A; p.(Arg2032Lys)      | HCC Secondary malignancy | 38                       | Nivolumab                  | Died, 13 years. Non remission                                               |
| P11 | M   | c.5932G>T; p.(Glu1978*) c.4227 delG; p.(Ser1411Alafs*40) | NHL B      | 13                       | Modified NHL-BFM            | Died, 18 years. complete remission, progressive interstitial lung disease (high dose steroid → severe BK virus pos macrohaematuria) Death in respiratory failure due to progressive ILD |
| P12 | M   | c.513C>G; p.(Tyr171*)          | NHL B      | 7                        | Modified NHL-BFM           | Died, 19 years. Non remission                                               |
| P13 | M   | c.8385del10; p.(Phe2796Serfs*10) | NHL B      | 18                       | Modified NHL-BFM           | Died, 10 years. Remission, lung infection, progressive ILD, respiratory failure. |
| P14 | M   | c.751delG>T; p.(Val251Cysfs*4) | NHL NK     | 8                        | Modified Euro-LB 02        | Died, 14 years. Sepsis in remission                                        |
| P15 | M   | NA                             | Hodgkin    | 13                       | 8 × brentuximab 3-weekly -> mod. COPP+rituximab   | Died, 11 years. ADV sepsis and toxicity                                     |
| P16 | M   | c.1470dupT; p.(Thr491Tyrfs*8)  | Hodgkin    | 9                        | Brentuximab -> vinorelbine + gemcitabine | Died, 11 years. Pred poor response, ongoing treatment                      |
| P17 | F   | c.5932G>T; p.(Glu1978*)        | Meningeom  | 16                       | Surgery                    | Alive, 24 years                                                            |

ADV, adenovirus; alloHSCT, allogeneic haematopoietic stem cell transplantation; COPP, cyclophosphamide, oncovin, procarbazine and prednisone; CPM, cyclophosphamide; F, female; HCC, hepatocellular carcinoma; het, heterozygous; hom, homozygous; ILD, interstitial lung disease; LFU, last follow-up; M, male; MTX, methotrexate; NA, not available; NHL, non-Hodgkin lymphoma; B, B cell; DLBCL, diffuse large B-cell lymphoma; NK natural killer cell; T-ALL, T-cell acute lymphoblastic leukaemia.
including cyclophosphamide (CPM) and remained with progressive disease despite treatment escalation. Both patients died without remission.

Patients with B-NHL (P10–P13) received modified polychemotherapy based on the Euro-LB and NHL-BFM protocols; among them P10 achieved stable long-term remission, while P11–P13 died in non-remission. Likewise, P14 (NK NHL) died in non-remission. Eventually, P10 developed HCC as a second malignancy more than 10 years later. This patient received nivolumab and died of progressive HCC at 39 years of age.

Hodgkin lymphoma (HL)

Two patients (P15, P16) suffered from classic Hodgkin disease; P15 received brentuximab, modified COPP (cyclophosphamide, oncovin, procarbazine and prednison), and rituximab. This patient achieved remission; however, he eventually developed an abdominal infection after implantation of a percutaneous endoscopic jejunostomy (PEJ) tube, resulting in fatal septic shock. P16 received individualised treatment including brentuximab (anti-CD30), vinorelbine and gemcitabine. The patient died of toxicity and adenoviral sepsis.

Brain tumours

One patient (P17) developed meningioma. The tumour was removed completely, and the patient remained in remission on long-term follow-up. No other brain tumours were observed in this cohort.

Overall survival and cause of death

The median OS (95% CI) was 26.9 years, and the estimated 15-years OS was 82.5% (72–95%) for the entire cohort, which was significantly decreased among A-T patients suffering from any type of malignancy. Within the malignancy cohort, the median OS was 2.11 years, with a two-year estimated OS of 50.7% (31–82%). Malignancy was the major cause of death in the first few years of life. Once a malignancy was diagnosed, the risk of death increased by up to 15 times [HR (95% CI): 6.9 (3.1–15.2), P < 0.001]. Over time, respiratory failure, mostly in the presence of pulmonary infections, was the leading cause of death in older A-T patients without malignancy. One patient developed an interstitial lung fibrosis (Fig 1A, B and Table II). Within the entire cohort the OS was significantly inferior for male patients (P < 0.001; Figure S1).

Malignancy incidence and outcome

The estimated CI of malignancy was 21.7% (95% CI, 13–36%) by 15 years, 28% by 20 years, and 38% by 30 years. Death without malignancy (being analysed as a competing risk) occurred in 2.7% (95% CI, 0.4–19%) by the age of 15 years and 6% and 25% by the ages of 20 and 30 years respectively (Fig 2).

Malignancy significantly affected male patients (up to four times) more than females (95% CI, 1.1–10.1, HR 3.29; P = 0.041). By the age of 15 years, the estimated rate of malignancy in the male cohort was 33.3% (95% CI, 19–57%) vs 7.8% (95% CI, 2–30%) for the female cohort (Fig 3A). Within the A-T cohort without malignancy, the estimated risk of death at the age of 15 years was 5% (95% CI, 0.1–34%) for male patients and 0% for the female cohort (P = 0.031; Fig 3B).

Immunodeficiency

Immunological parameters were assessed in each patient, including immunoglobulins G, M, and A; alpha-fetoprotein (AFP) and lymphocyte subsets (total T lymphocytes CD3+, T-helper cells CD3+CD4+, cytotoxic T cells CD3+CD8+, B cells CD19+, NK cells CD56+, naïve T-helper cells, and regulatory T-helper cells). Comparing patients with and without malignancies, there were no significant differences in IgG, IgM, IgA, AFP, total T cells, CD4+, CD8+, and NK cells. Nevertheless, there was a tendency towards more malignancies in patients with a lower CD4+/CD8+ ratio (P = 0.13) and lower B cells (P = 0.16; Fig 4).

Discussion

Ataxia-telangiectasia is a hereditary multisystemic chromosomal instability syndrome. The significantly increased cancer risk is a major clinical challenge, especially in early childhood and adolescence. Chromothripsis seems to be the underlying cause of a distinct type of malignancy in A-T. Accordingly, there is a significantly increased risk of malignancy in the presence of immunodeficiency in patients with A-T. The cancer is especially of haematological origin as aggressive non-Hodgkin lymphoma, acute leukaemia, and Hodgkin lymphoma. The most common leukaemia was T-cell lymphoblastic leukaemia (T-ALL). Our observation is in line with the literature that cancer in paediatric A-T patients is indeed primarily of haematological origin with a high incidence of 21.7% by the age of 15 years. Nevertheless, we observed more malignancies of B-cell origin than T-cell lymphoma/leukaemia in our cohort. Furthermore, we observed a high incidence of DLBCL in A-T patients, which might be associated with persistent Epstein–Barr virus (EBV) positivity due to a lack of EBV clearance in A-T lymphocytes. Nevertheless, in our cohort patients were not diagnosed with a chronic EBV infection previously. The high incidence of haematological malignancies raises the question of whether correction to the haematopoietic system would prevent malignancies. There is evidence that the incidence of cancer correlates with mutations in ATM that caused total loss of expression or function of the gene product (null
mutations/classical A-T) compared with that seen in patients with hypomorphic mutations because of earlier onset of haematologic malignancies. There is also a 30-fold increased risk for breast cancer in A-T patients without residual ATM activity. Among patients without any ATM residual activity, cancer seems to correlate with immunodeficiency; profound IgA deficiency and low B cells. In our cohort, we could not find any significant association between IgA deficiency and malignancy, but we observed a tendency toward a higher incidence of malignancy in patients with lower B lymphocytes.

It has been shown that malignancy treatment in A-T is feasible and should be offered. In a study of 59 cases (53% acute leukaemia, 39% non-Hodgkin lymphomas and 8% Hodgkin lymphomas) the authors concluded that both standard and modified treatment strategies, mostly based on the ALL-BFM protocol, can induce long-term remission. While it is generally accepted that irradiation should be avoided, the question whether an up-front dose modification would be superior to the initiation of standard treatment with optional dose adjustment based on individual toxicity profile was not answered. The authors highlighted the fact that, at least in T-ALL, younger A-T patients showed less toxicity while receiving unmodified treatment than older A-T patients. Furthermore, the authors warned about the cumulative dose of cyclophosphamide exposure because of the risk of haemorrhagic cystitis and sometimes fatal bleeding of bladder telangiectasia. A further study reported three A-T patients (seven-year-old male, Stage IV Hodgkin; nine-year-old male DLBCL and six-year-old female, Burkitt Lymphoma) receiving chemotherapy as per protocol with up-front dose modifications. While their first two patients died of disease progress/relapse, the third patient achieved long-term remission. The authors concluded that a feasible strategy would be to initiate a reduced-dose chemotherapy with the option of dose increase if the first block was tolerated well and/or combining reduced-dose chemotherapy with targeted monoclonal antibody therapy such as rituximab. For A-T patients with acute myeloid leukaemia (AML), the

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**Table II.** Cause of death in patients without a malignancy.

| ID  | Sex | Status at LFU | Cause of death               |
|-----|-----|---------------|------------------------------|
| P18 | M   | Died, 21 years | resp. failure                |
| P19 | M   | Died, 13 years | resp. failure                |
| P20 | M   | Died, 17 years | EBV lymphoproliferation      |
| P21 | M   | Died, 26 years | resp. failure                |
| P22 | M   | Died, 19 years | resp. failure (lung fibrosis) |
| P23 | F   | Died, 38 years | resp. failure                |
| P24 | F   | Died, 30 years | resp. failure                |

EBV, Epstein–Barr virus; F, female; LFU, last follow-up; M, male; resp. respiratory.
challenge is even greater, because dose-intensive treatment is necessary for AML and very limited data are available because AML is rare in A-T.

ATM mutation carriers should receive more screening for breast cancer, and be informed about increased risk of cardiovascular disease.

Most of our patients received a toxicity-reduced chemotherapy protocol (with a poor outcome). We could not conduct a statistical analysis between the two possible approaches of starting a standard treatment versus dose reduction per se. Prospective randomised studies are necessary to compare possible treatment approaches.

A conventional leukaemia treatment, including radiotherapy, could be fatal in A-T; therefore, it is of utmost importance to establish the diagnosis of A-T before initiation of malignancy treatment. General awareness of the disease and disease symptoms among paediatric oncologists is crucial. Cancer prevention and surveillance strategies are available for patients with malignancy predisposition syndromes including preventive colon surgery (APC-associated polyposis) and thyroidectomy (multiple endocrine neoplasia type 2). For haematological malignancies in A-T patients (and other primary immunodeficiency disorders, PID) there is no reasonable surveillance programme. Liver disease and non-alcoholic steatohepatitis (NASH) have been described in the majority of older patients with A-T. The reason for the progressive metabolic imbalance, reduced glucose tolerance, and dyslipidaemia has not been fully elucidated, but the failure of ATM to counteract oxidative stress seems to play a major role in the progression of NASH to cirrhosis or even to HCC. Therefore, older patients with A-T should be monitored for laboratory signs of liver disease and NASH development. Transient elastography seems to be a feasible method for monitoring liver pathologies. HCC preventive care should include at least annual ultrasound and AFP follow-up.

Known A-T patients with any lymph node enlargement should receive lymph node biopsy and histopathological assessment immediately. For newly diagnosed leukaemia/lymphoma patients functional and genetic diagnostics should be initiated if there are any clinical signs towards A-T (or possibly other PID). However, functional diagnostic (lymphocyte subsets, T-cell proliferation, serum immunoglobulins) might be altered due to acute malignancy. Therefore, serum alpha-fetoprotein (AFP) could be used as a screening tool facilitating the diagnosis of A-T at the time of malignancy treatment. An assessment of ATM activity and ATM sequencing must be added in suspicious cases. Serum AFP is usually high in healthy new-borns, reaching almost undetectable levels by the age of one. AFP levels could be elevated also in liver, ovary, and testicle tumours as well as in (adult) liver cirrhosis and hepatitis. The implementation of TREC-based new-born screening for severe T-cell deficiencies also provides an early detection tool for A-T patients with very low TRECS.

In a murine model, the development of malignancies could be prevented following immune reconstitution by stem cell treatment. AlloHSCT is not routinely performed for A-T, as it is in some cases for Nijmegen Breakage or Fanconi’s anaemia. Nevertheless, pre-emptive alloHSCT might be a treatment option for A-T patients with a severe PID phenotype to correct their immunodeficiency and possibly prevent haematological malignancy. There is growing evidence that minimal-toxicity conditioning regimens, such as cyclophosphamide and fludarabine, enable stable engraftment and proper immune reconstitution in A-T. We are aware of six published and three unpublished (own current data) A-T patients undergoing an alloHSCT, among whom one patient died of liver toxicity post alloHSCT. This patient was initially misdiagnosed as hyper-IgM and had received a full myeloablative treatment.
conditioning. Other patients (including two malignancies and six pre-emptive transplantations for the immunodeficiency) survived the transplant procedure. Since the underlying diagnosis was made early, all of them received a tolerable low-toxicity preparative regimen enabling a stable engraftment and proper immune reconstitution. Another therapeutic approach might be the antisense oligonucleotide (ASO) gene therapy.

Fig 4. Immunological assessment of T cells subpopulations and B cells in peripheral blood of A-T patients with or without malignancy. Total T lymphocytes CD3$^+$ (A), T-helper cells CD3$^+\text{CD}4^+$ (B), cytotoxic T cells CD3$^+\text{CD}8^+$ (C), naive T-helper cells (D), CD4/8 Ratio (E), and B cells CD19$^+$ (F). Jittered dots represent absolute cell counts; horizontal red lines indicate the median and the errors bars show the interquartile range. $P$ values were performed with the Wilcoxon–Mann–Whitney U-test. [Colour figure can be viewed at wileyonlinelibrary.com]
Reliable predictive markers are not available to determine the extent of neurological impairment or to capture the extent of immunodeficiency. Therefore, in the era of new-born screening, in which some A-T patients are detected due to low/absent TREC at birth, physicians face a clinical dilemma.\(^{30}\) Currently, experimental research focuses on a novel treatment involving repetitive transfusion of autologous dexamethasone-included erythrocytes. To date, results and follow-up data are available and have demonstrated a promising positive impact on neurologic outcome.\(^{31}\) However, the impact of steroid treatment on the immunodeficiency and susceptibility to malignancies in A-T patients remains to be evaluated further.

We have delivered a series of cases that underline the high medical burden of this challenging patient collective. The incidence of malignancies, especially for younger patients with A-T, has been underestimated. This is the first study to show the high cancer risk of male patients with A-T. However, this study has some limitations. This study had a retrospective design in a small cohort. In addition, some patients received an individual therapy regime so that the presented cases and their outcomes could not be compared directly. Two patients had not yet completed their five-year follow-up.

**Conclusion**

Haematological malignancies are the leading cause of death among young patients with A-T. In our study male patients are significantly more affected with a high mortality rate; larger studies are needed to verify the findings.

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**Conflicts of interest**

The authors declared they have no conflicts of interest.

**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Fig S1.** Overall survival of entire cohort according to gender. Female Patients showed a significantly higher estimated OS probability than male patients (\(P < 0.001\)). This difference in the estimated survival rates started around the age of 10, reaching 25% at 15 years (women 96.4% vs. men 70.9%).

**Data S1.** Statistical analyses.

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