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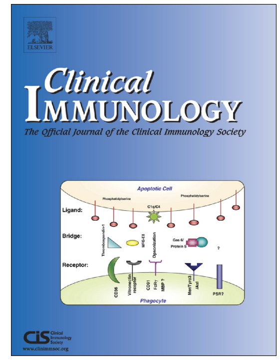

Ataxia-telangiectasia: Immunodeficiency and survival

Nienke J.H. van Os, Anne F.M. Jansen, Marcel van Deuren, Asgeir Haraldsson, Nieke T.M. van Driel, Amos Etzioni, Michiel van der Flier, Charlotte A. Haaxma, Tomohiro Morio, Amit Rawat, Michiel H.D. Schoenaker, Annarosa Soresina, Alexander M.R. Taylor, Bart P.C. van de Warrenburg, Corry M.R. Weemaes, Nel Roeleveld, Michèl A.A.P. Willemsen

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ATAXIA-TELANGIECTASIA: IMMUNODEFICIENCY AND SURVIVAL

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ABSTRACT

Ataxia-telangiectasia (AT) is a neurodegenerative disorder characterized by ataxia, telangiectasia, and immunodeficiency. An increased risk of malignancies and respiratory diseases dramatically reduce life expectancy. To better counsel families, develop individual follow-up programs, and select patients for therapeutic trials, more knowledge is needed on factors influencing survival. This retrospective cohort study of 61 AT patients shows that classical AT patients had a shorter survival than variant patients (HR 5.9, 95%CI 2.0-17.7), especially once a malignancy was diagnosed (HR 2.5, 95%CI 1.1-5.5, compared to classical AT patients without malignancy). Patients with the hyper IgM phenotype with hypogammaglobulinemia (AT-HIGM) and patients with an IgG_2 deficiency showed decreased survival compared to patients with normal IgG (HR 9.2, 95%CI 3.2-26.5) and patients with normal IgG_2 levels (HR 7.8, 95%CI 1.7-36.2), respectively. If high risk treatment trials will become available for AT, those patients with factors indicating the poorest prognosis might be considered for inclusion first.

Highlights:

- More knowledge is needed on factors influencing survival in patients with AT;
- Patients with AT-HIGM have a severely reduced life expectancy compared to patients with normal IgG levels;
- AT-HIGM patients may be candidates for future high risk therapeutic trials.

Key words: ataxia telangiectasia, survival, hyper IGM phenotype, primary immunodeficiency

Abbreviations:

95%CI: 95% Confidence interval

AT: Ataxia-telangiectasia

ATM: Ataxia telangiectasia mutated

AT-HIGM: Hyper IgM phenotype with hypogammaglobulinemia

HR: Hazard ratio

OR: Odds ratio

1. INTRODUCTION

Ataxia-telangiectasia (AT; OMIM 208900) is an autosomal recessive neurodegenerative disease caused by mutations in the ataxia telangiectasia mutated (*ATM*) gene[1]. The *ATM* gene codes for ATM kinase, which plays a role in cell cycle control and DNA repair[2]. Over 400 *ATM* mutations have been described so far[3]. AT is characterized by cerebellar ataxia, oculocutaneous telangiectasia, increased radiosensitivity, growth retardation, predisposition to malignancies and diabetes mellitus type II, and a primary cellular and humoral immunodeficiency causing recurrent sinopulmonary infections[4]. The immunodeficiency is caused by impaired double-strand break repair processes, such as V(D)J recombination[5] and class-switch recombination[6, 7], and features a reduced number of circulating T-cells (in particular CD3+CD4+CD45RA+ naïve T-cells) and B-cells, frequently causing decreased or absent serum IgA and IgG_2[8, 9]. An estimated 10% of AT patients have decreased IgA and IgG levels with normal to increased IgM levels[10], designated as 'hyper IgM phenotype with hypogammaglobulinemia' (AT-HIGM). AT is incurable and patients have a reduced life expectancy due to cancer, pulmonary disease, and infections[11].

The clinical spectrum of AT is variable[12] with residual kinase activity and the related type of *ATM* mutation contributing to the life expectancy[11, 13]. Variant AT patients have a milder clinical phenotype and a longer lifespan compared to classical AT patients[11-13]; their longer life expectancy may be attributed to less severe immunodeficiency[8, 9] and delayed onset of cancer[11].

Much is known about the pathogenesis of AT but knowledge of factors predicting survival is lacking. To further individualize follow-up programs for AT patients, and eventually select eligible patients for future therapeutic trials, better knowledge on factors that contribute to survival is needed.

The aim of this study was to identify such factors in both classical and variant AT.

2. MATERIAL AND METHODS

2.1. Ascertainment of study cohort

Data were retrospectively collected from Dutch and Icelandic cohorts of AT patients. For patients previously described by Verhagen et al.[13], the follow-up period was extended by six years. The clinical diagnosis of AT was confirmed by the identification of pathogenic *ATM* mutations in all subjects. The *ATM* mutation analysis and the measurements of ATM protein and ATM kinase activity in patients with available lymphoblast cell lines were performed using previously described methods [14, 15]. Data on age, gender, nationality, age and cause of death, immunoglobulin levels of IgA, IgG, IgG_2, IgM, and lymphocyte subsets (all pre-treatment, in case of immunoglobulin replacement therapy), and presence of cancer were collected from the cohort database or the medical records of the patient's primary hospital. Immunoglobulin plasma levels and lymphocyte subsets were assessed using methods previously described [16], and compared to age-related reference values [17, 18]. The follow-up period was defined as starting at birth and continuing until death or August 31, 2014, whichever came first. Patients lost to follow-up were excluded from the study. This study was approved by the Regional Committee on Research involving Human Subjects Arnhem-Nijmegen.

2.2. Patient definitions

The patients were classified into four groups, based on the presence of ATM protein and ATM kinase activity*.* The classical AT patients comprised patients without detectable ATM protein (group 1), patients with ATM protein but without ATM kinase activity (group 2), and patients with missing data on ATM protein and ATM kinase activity, but with clinical phenotypes similar to those in groups 1 and 2 *(Supplement 1)* (group 3). Group 4 consisted of variant AT patients with residual kinase activity. Patients with decreased IgG and IgA levels but with normal or elevated IgM levels at the time of diagnosis were classified as AT-HIGM (group 1a), and those with normal total IgG levels as group 1b.

2.3. Literature search

To supplement the data from our cohort, we searched all available literature for reports on patients with AT-HIGM. We searched all available literature until January 2016 through the electronic databases PubMed, EMBASE, the Cochrane Library, and Web of Science. For all patients that were alive at time of publication, the first authors of the papers were contacted for additional information on survival.

2.4. Statistical analysis

Using IBM SPSS statistics 22.0 for Windows (IBM SPSS Inc., Chicago, IL, USA), we performed descriptive statistics and logistic regression analyses to calculate odds ratios (OR) with 95% confidence intervals (95%CI) for associations between immunoglobulin deficiencies and AT phenotypes. Differences in survival between groups were assessed using Cox proportional hazard models to calculate hazard ratios (HR) with 95%CIs, which are more informative than p-values. The OR and HR represents the strength of the association, while the 95%CI shows the imprecision in the estimate. Confidence intervals that do not or only just include the null value (OR/HR=1) are indicative of statistically significant and/or noticeable results. To avoid interpretation problems because of low numbers in multivariable analyses, the HRs were only adjusted for gender. In sensitivity analyses, patients with <10 years of follow-up (n=11, al classical AT) were excluded. GraphPad Prism v5.03 was used to display Kaplan Meier survival probability curves from birth through August 2014, at which point patients were censored if the event (e.g. death or malignancy) had not yet occurred.

3. RESULTS

3.1. Cohort description

The total cohort consisted of 63 patients. Two patients that were lost to follow-up were excluded from the analysis, leading to inclusion of 61 AT patients (29 male and 32 female patients), divided into 48 patients with classical AT (17 in group 1, 19 in group 2, and 12 in group 3) and 13 patients with variant AT (*Table 1 and Figure 1a*). In total, 50 of these patients were previously described by our research group[13] in a genotype-phenotype correlation study, while 27 patients were also described in other reports[8, 19-23].

The ages of the patients ranged from 4 to 56 years. At the end of follow-up, 32 patients were deceased and 29 were alive. In the latter group, 16 patients, all with classical AT, were still under 30 years of age *(Figure 1b).* Among 48 classical AT patients, only six patients (12.5%) survived beyond 30 years of age: two in group 1 and four in group 2. The two patients from group 1 died at ages 40 and 54 from malignancies, whereas the other four patients were 35, 32, 49, and 50 years old and still alive at the end of follow-up. Among the variant AT patients, all but one survived beyond 30 years of age. Fifty different mutations in 33 exons were found in the cohort, while 19 patients had homozygous *ATM* mutations *(Table 1)*.

IgG_2 subclass plasma levels were measured in 46 out of the 61 patients (38 with classical AT and 8 with variant AT), of whom 29 had an IgG_2 deficiency. Only one IgG_2 deficiency was observed in a variant AT patient. IgA levels were measured in 53 patients, of whom 25 had an IgA deficiency. None of the variant AT patients had IgA deficiency. IgG and IgM levels were normal in the majority of patients, but 7 classical AT patients without expression of ATM protein had AT-HIGM (group 1a). Among the patients in this group with normal IgG levels (group 1b), 78% were IgG_2 deficient compared to 60% in group 2 (OR 2.3, 95%CI 0.4-15.3), with IgA deficiency in 60% of patients in group 1b versus 41% in group 2 (OR 3.6, 95%CI 0.8-17.0). The lymphocyte subsets of patients from group 1a (AT-HIGM group) are shown in *Supplement 2*.

Table 1: Features of 61 AT patients from the Netherlands and Iceland.

	No	Sex	Ethni-city#	Age or age at death	ATM mutations		Immunoglobulin levels				Cancer type	Cause of death	Immuno-globulin therapy	Antibiotic prophylaxis
					Allele 1	Allele 2	IgG	IgG_2	IgA	IgM				
Group 1a *Classical AT patients, ATM protein absent, AT-HIGM phenotype*	1	M	NL	13†	exon 19-61 c.2467+1551 del 97kb	exon 19-61 c.2467+1551 del 97kb	D	D	D	N	Lymphoma	Malignancy	Yes	Yes
	2a	F	AF	9†	exon 37 c.5188C>T	exon 37 c.5188C>T	D	D	D	N	-	Respiratory failure	Yes	x
	2b	F	AF	12†	exon 37 c.5188C>T	exon 37 c.5188C>T	D	D	D	N	-	Respiratory failure	Yes	Yes
	2c	M	AF	10†	exon 37 c.5188C>T	exon 37 c.5188C>T	D	D	D	N	Hepatocellular carcinoma	Malignancy	Yes	x
	3	F	MO	14†	exon 21 c.2921+5G>A	exon 21 c.2921+5G>A	D	D	D	N	-	Respiratory failure	Yes	Yes
	4*	F	BE	9†	exon 12 c.1563_1564delAG	exon 39 c.5515 C>T	D	D	D	N	Lymphoma	Malignancy	Yes	Yes
	5	F	IC	12†	exon 19 c.2554C>T	exon 19 c.2554C>T	D	D	D	N	-	Respiratory failure	Yes	Yes
Group 1b *Classical AT patients, ATM protein absent*	6	M	NL	20	exon 9 c.790_790delT	exon 12 c.1563_1564delAG	N	D	D	N	-	-	Yes	Yes
	7	F	NL	22†	exon 10 c.1027_1030delGAAA	exon 13 c.1660_1660delA	N	D	D	N	B-cell non-Hodgkin lymphoma	Urinary tract bleeding§	Yes	No
	8	F	TR	9†	exon 12 c.1514_1515delTT	exon 12 c.1514_1515delTT	↑	x	N	↑	Hodgkin lymphoma	Malignancy	Yes	Yes
	9a	F	NL	21†	exon 12 c.1563_1564delAG	exon 39 c.5515 C>T	N	N	N	N	-	Not noted	No	No
	9b	F	NL	10†	exon 12 c.1563_1564delAG	exon 39 c.5515 C>T	N	D	N	N	B-cell lymphoma	Malignancy	No	No
	10	M	TR	12	exon 43 c.6082 C>T	exon 43 c.6082 C>T	N	D	D	N	-	-	No	Yes
	11 µ	M	NL	40†	exon 12 c.1563_ 1564delGA	exon 23 c.3078 G>T	D-N	D	D	N-↑	B-cell non-Hodgkin lymphoma	Malignancy	Tempo-rarily	No
	12	M	AN	22	exon 27 c.3741-1G>C	exon 37 c.5197G>C	N	D	D	N	-	-	Tempo-rarily	No
	13*	M	NL	54†	exon 6 c.331+5G>A	exon 29 c.4040delT	N	N	N	↑	Prostate cancer	Malignancy	No	No
	14*	M	IC	15	exon 6 c.309C>G	exon 12 c.1369C>T	N	D	D	N	-	-	No	No
Group 2 *Classical AT patients,*	15a	F	IR	9†	exon 61 c.8633T>G	Unidentified	x	x	x	x	Hodgkin lymphoma	Malignancy	No	Yes
	15b	M	IR	26†	exon 61 c.8633T>G	Unidentified	N-D	D	N	N	Hodgkin lymphoma	Malignancy	Yes	Yes

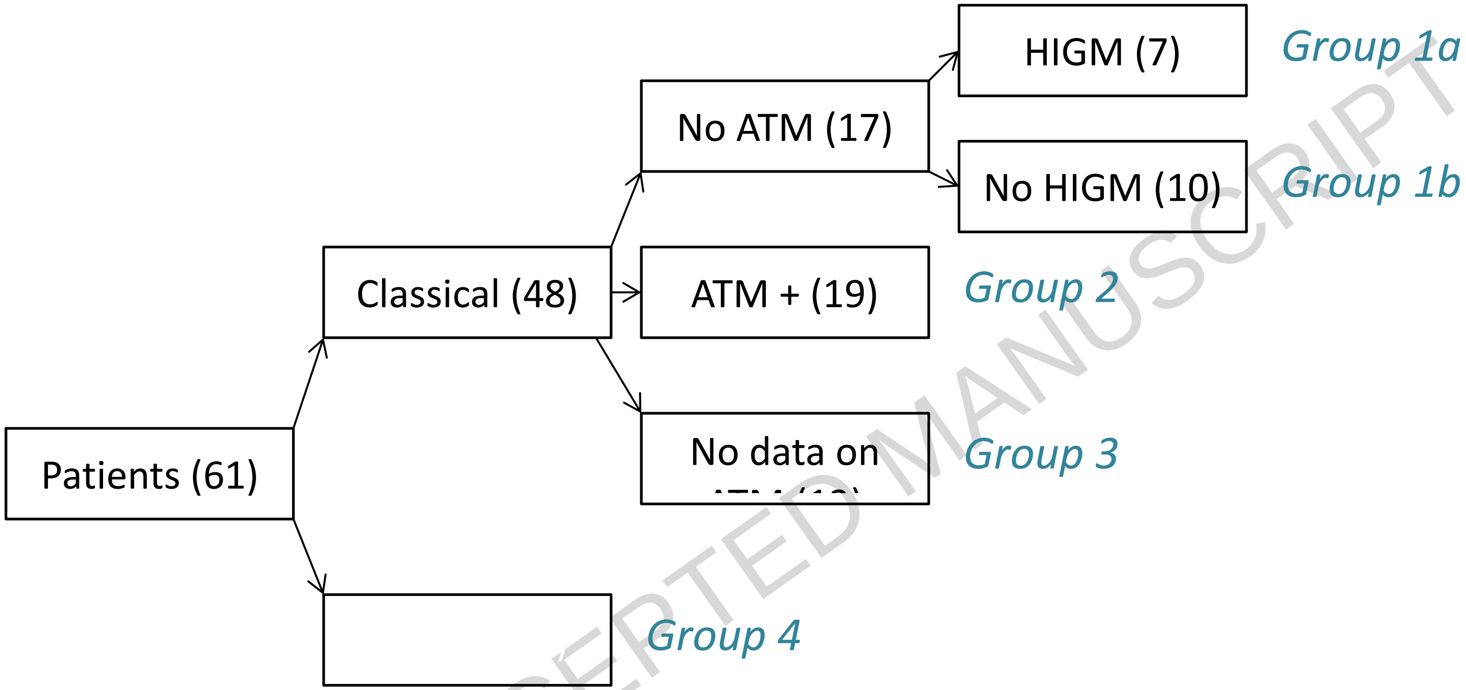
ATM protein present, no kinase activity	16	F	NL	13	exon 48 c.6629delA	exon 60 c.8578_8580delTCT	N	N	D	N	-	-	Yes	Yes
	17a	M	NL	15	exon 55 c.7875_7876delTGinsGC	exon 55 c.7875_7876delTGinsGC	N	D	N	N	-	-	No	Yes
	17b µ	F	NL	4†	exon 55 c.7875_7876delTGinsGC	exon 55 c.7875_7876delTGinsGC	D-N	D	D-N	N	Acute lymphoblastic leukemia	Pulmonary hypertension§	Tempo-rarily	Yes
	18a	F	NL	22†	exon 55 c.7875_7876delTGinsGC	exon 55 c.7875_7876delTGinsGC	N-D	D	N	N	-	Respiratory failure	Yes	Yes
	18b	M	NL	10†	exon 55 c.7875_7876delTGinsGC	exon 55 c.7875_7876delTGinsGC	N	D	D	N	Lymphoma	Respiratory failure/ malignancy	No	No
	19	F	NL	27†	exon 55 c.7875_7876delTGinsGC	exon 60 c.8578_8580delTCT	N-↑	N	D	N	Breast cancer	Respiratory failure/ malignancy	x	x
	20a	M	NL	26†	exon 41 c.5762-2 A>T	Unidentified	N	D	N	N	-	Respiratory failure	No	Yes
	20b	M	NL	14†	exon 41 c.5762-2 A>T	Unidentified	N	x	D	N	-	Respiratory failure	No	Yes
	21	M	NL	21	exon 6 c.331+5G>A	exon 55 c.7875_7876delTGinsGC	N	N	D	N	-	-	No	No
	22	F	TR	22	exon 26 c.3576 G>A	exon 26 c.3576 G>A	N	N	N	N	-	-	No	Yes
	23a	F	TR	24†	exon 26 c.3576G>A	exon 26 c.3576G>A	x	x	x	x	Dermatofibro-sarcoma protuberans	Resuscitation needed for unknown cause	No	No
	23b	M	TR	35	exon 26 c.3576G>A	exon 26 c.3576G>A	N	D	↑	N	Dermatofibro-sarcoma protuberans	-	No	No
	24a*	M	NL	32	exon 29 c.4109+5G>A	exon 55 c.7875_7876delTGinsGC	N	D	D	N	-	-	No	No
	24b*	F	NL	28	exon 29 c.4109+5G>A	exon 55 c.7875_7876delTGinsGC	↑	N	↑	↑	-	-	No	No
	25* ∞	F	NL	9	exon 14. c1898+2T>G	exon 32 c.4477C>G	D	D	N	N	-	-	Yes	No
	26*	M	TR	7	exon 48 c.6679C>T	exon 48 c.6679C>T	N	N	D	N	-	-	No	No
	27*	M	IC	7	exon 12 c.1369	exon 65 c.9139C>T	N	x	N	N	-	-	No	x
Group 3	28	M	TN	17†	exon 14 c.1810 C>T	exon 47 c.6482 G>C	↑	x	N	↑	Non-Hodgkin lymphoma	Not noted	x	x
Classical AT patients, no data on ATM protein and	29	F	NL	25	exon 17 c.2376+1G>A	exon 55 c.7875_7876delTGinsGC	x	x	x	x	-	-	x	x
	30	M	KR / GE	9†	exon 12 c.1563_1564delAG	exon 53 c.7542T>G	N	D	D	↑	T-cell lymphoma	Malignancy	No	No
	31	M	TR	15†	exon 58 c.8264dupA	exon 58 c.8264dupA	N	x	N	N	T-cell acute	Asystole after	No	No

kinase activity											lymphoblastic leukemia	extubation§		
	32	F	NL	15†	exon 9 c.738_739delCTinsA	exon 55 c.7875_7876delTGinsGC	N	x	D	N	B-cell lymphoma	Respiratory failure/ malignancy	No	Yes
	33	M	NL	18	exon 7 c.484 C>T	exon 14 c.1898+2 T>G	N	D	N	N	Lymphoma	-	Yes	Yes
	34*	F	NL	10†	exon 65 c.9019 G>T	Unidentified	N	D	D	N	-	Respiratory failure	Yes	Yes
	35a	F	SR	49	exon 20 c.2839-579_2839-576del4	exon 31 c.4396 C>T	↑	N	↑	N	-	-	No	x
	35b	F	SR	50	exon 20 c.2839-579_2839-576del4	exon 31 c.4396 C>T	↑	x	↑	↑	-	-	No	x
	36	M	NL	17†	exon 20 c.2662 G>T	exon 48 c.6679 C>T	N	D	N	N	B-cell non-Hodgkin lymphoma	Malignancy	x	No
	37*	F	SR	9	exon 19 c.2620G>T	exon 31 c.4344_4345delAT	N	D	D	↑	-	-	No	Yes
	38*	M	NL	4	exon 12 c.1564_1565delGA	exon 55 c.7875_7876delTGinsGC	N	N	D	N	-	-	No	x
Group 4	39	F	NL	54	exon 7 c.496+5G>A	exon 55 c.7875_7876delTGinsGC	x	x	x	x	-	-	No	No
Variant AT patients, ATM protein present, residual kinase activity	40	F	NL	47†	exon 57 c.8147T>C	exon 12 c.1391_1395delTGTGT	N	x	N	x	Breast cancer, chronic myeloid leukemia	Malignancy	No	No
	41	F	NL	43	exon 57 c.8147T>C	Unidentified	N	N	N	N	Breast cancer	-	No	No
	42	F	NL	56	exon 9 c.717_720delCCTC	exon 57 c.8147 T>C	x	x	x	x	-	-	No	No
	43	F	NL	40	exon 42 c.5932 G>T	exon 57 c.8147 T>C	N	N	N	N	-	-	No	No
	44a	F	NL	39	exon 21 c. 2909 T>G	exon 49 c.6908dupA	N	N	N	N	-	-	No	No
	44b	M	NL	23†	exon 21 c. 2909 T>G	exon 49 c.6908dupA	x	x	x	x	Ectopic pituitary tumor	Malignancy	No	No
	45a	M	NL	39	exon 6 c.331+5G>A	exon 6 c.331+5G>A	N	N	N	N	-	-	No	No
	45b	F	NL	42	exon 6 c.331+5G>A	exon 6 c.331+5G>A	N	D	N	N	-	-	No	No
	46	F	NL	56	exon 22 c.2922-1G>A	exon 57 c.8147 T>C	N	N	N	N	-	-	No	No
	47a	M	NL	48†	exon 23 c.3136 C>T	exon 53 c.7622 T>G	N	N	N	N	Pancreatic cancer	Malignancy	No	No
	47b	M	NL	51	exon 23 c.3136 C>T	exon 53 c.7622 T>G	N	N	N	N	-	-	No	No
	47c	M	NL	51†	exon 23 c.3136 C>T	exon 53 c.7622 T>G	x	x	x	x	Acute lymphoblastic leukemia	Malignancy	No	No

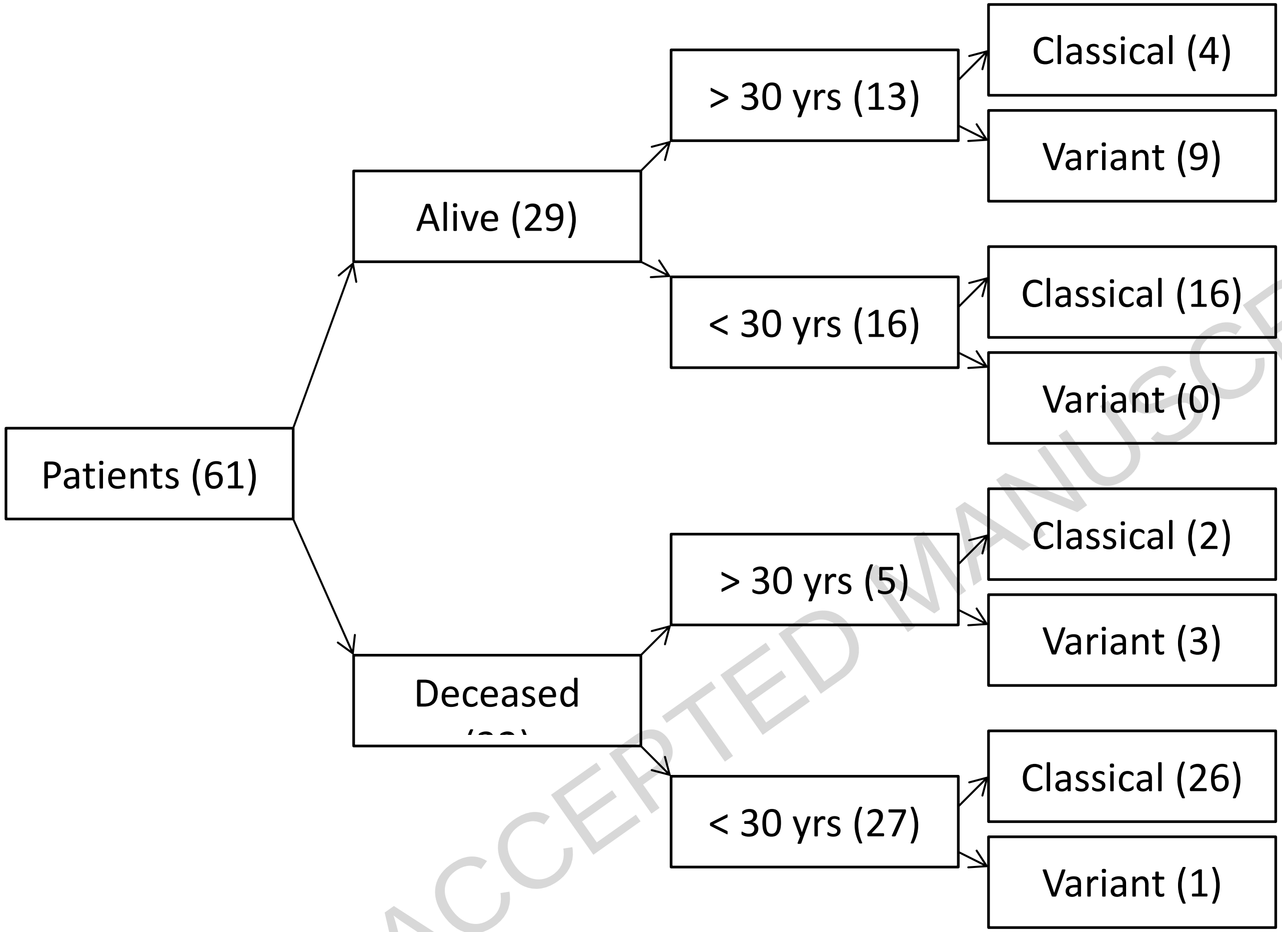
* Patient was not described before by Verhagen et al. (n=11);
a-b-c Patients are siblings;
† Patient is deceased;
# NL = Dutch; AF = Afghan; MO = Moroccan; BE = Belgian; IC = Icelandic; TR = Turkish; AN = Antillean; IR = Iranian; TN = Tunisian; KO = Korean; GE = German; SR = Surinamese;
D= deficient; N= normal; ↓= decreased (compared to age-related reference values [17, 18]); x= not measured or unknown;
§ Cause of death was a complication of malignancy treatment;
µ Patient 17b was excluded from our IgA immunoglobulin analysis since IgA levels were variable during life. Patients 11, 15b, and 18a were excluded from the AT-HIGM group since IgG levels were variable during life.
∞ Patient 25 was excluded from group 1a (AT-HIGM) since she had normal IgA levels and her IgG level increased to normal after only two gifts of immunoglobulin replacement therapy.

Figure 1: Flow charts of the cohort.

1a. Flow chart of groups based on ATM kinase activity, ATM protein detectability, and HIGM status.



1b. Flow chart of cohort based on survival.

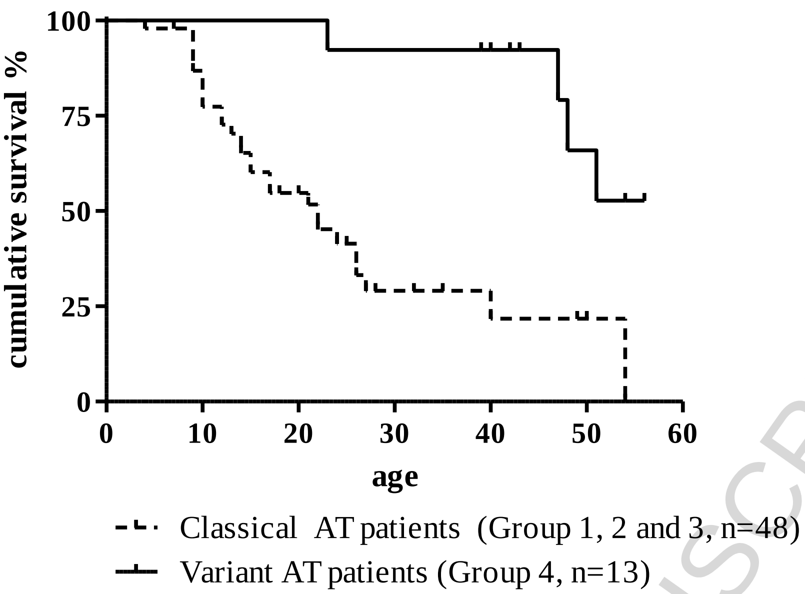

Patients (61)
Alive (29)
Deceased
> 30 yrs (13)
< 30 yrs (16)
> 30 yrs (5)
< 30 yrs (27)
Classical (4)
Variant (9)
Classical (16)
Variant (0)
Classical (2)
Variant (3)
Classical (26)
Variant (1)

3.2. Survival analyses

As shown in *Figure 2,* patients with classical AT generally died at a much younger age than variant AT patients. The corresponding hazard ratio for classical AT compared to variant AT was 5.9 (95% CI 2.0-17.7). Only very slight differences in HR were observed when gender was included as co-variable and after exclusion of AT-HIGM patients or patients with less than 10 years of follow-up *(Supplement 3).*

Classical AT patients without detectable ATM protein (group 1) seemed to have a slightly lower chance of survival compared to patients with ATM protein without kinase activity (group 2) (HR 1.8, 95%CI 0.7-4.4; HR adjusted for gender (HR_{gender} 2.2, 95%CI 0.9-5.7)) *(Supplements 3 and 4)*. When group 1a was excluded from the analysis, patients without detectable ATM protein (group 1b) and patients with ATM protein without kinase activity (group 2) did not differ in survival (HR 0.9, 95% CI 0.3-3.0).

Figure 2: Survival of patients with classical (group 1,2,3) and variant (group 4) AT



	Years	0	10	20	30	40	50
Classical	At risk	48	33	18	6	3	1
	Deceased	0	10	19	26	27	27
	Censored*	0	5	11	16	18	20
Variant	At risk	13	13	13	12	9	5
	Deceased	0	0	0	1	1	3
	Censored *	0	0	0	0	3	5

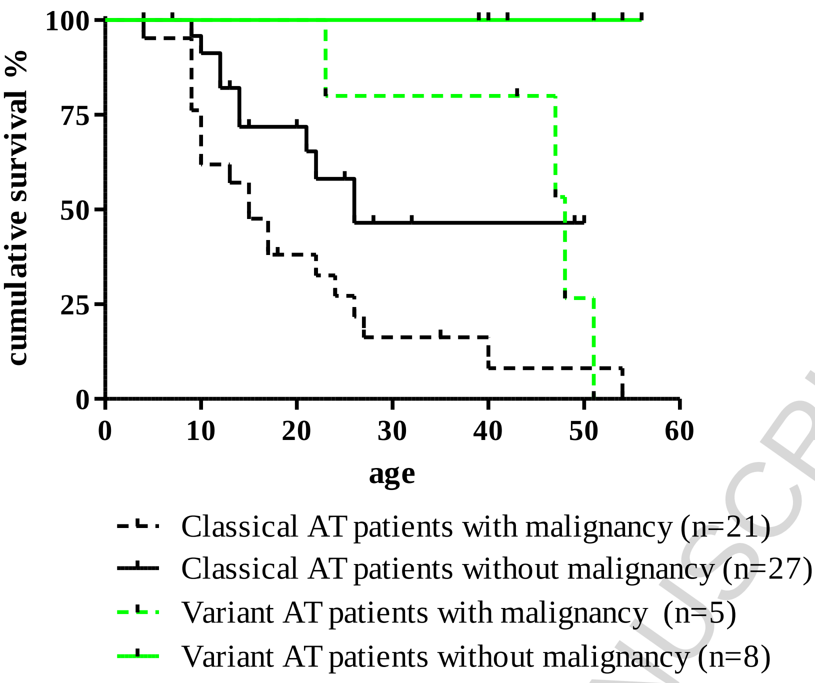
* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.

3.3. Malignancy

Among the classical AT patients, 21 (44%) had a malignancy compared to 5 patients (38%) in the variant group, with a median age at first diagnosis of 15 (range 4-52) and 42 (range 23-51), respectively. Of the 21 classical AT patients with a malignancy, 16 had a hematological malignancy, mostly lymphomas (n=14), and 19 patients died: 17 (81%) due to their malignancy and two from unknown causes *(Table 1).* Of these 19 patients, 17 died within one year after diagnosis. In the variant group, all five cancers developed in adulthood and four patients died of their malignancy: two of leukemia at ages 47 and 51 and two of solid tumors at ages 23 and 48 *(Figure 3 and Supplement 5).*

AT patients with a malignancy showed reduced survival compared to patients without a malignancy (HR 3.7, 95%CI 1.7-8.1), especially when patients with the AT-HIGM phenotype, who had an overall poorer survival, were excluded (HR 5.9, 95%CI 2.2-15.7) *(Supplement 3)*. The corresponding HR when having a malignancy was 2.5 (95%CI 1.1-5.5) for the classical group, but could not be calculated for the variant group due to low numbers. Adjustment for gender and exclusion of patients with <10 years of follow-up slightly increased or decreased the HRs, respectively. Classical AT patients without a malignancy and variant AT patients with a malignancy had a similar overall chance of survival (HR 1.1, 95%CI 0.3-3.8).

Figure 3: Survival of AT patients with and without malignancy (in classical and variant patient groups)



		Years	0	10	20	30	40	50
Classical	Malignancy	At risk	21	13	7	3	1	1
		Deceased	0	8	13	17	18	18
		Censored *	0	0	1	1	2	2
	No malignancy	At risk	27	20	11	3	2	0
		Deceased	0	2	6	9	9	9
		Censored *	0	5	10	15	16	18
Variant	Malignancy	At risk	5	5	5	4	4	1
		Deceased	0	0	0	1	1	3
		Censored *	0	0	0	0	0	1
	No malignancy	At risk	8	8	8	8	5	4
		Deceased	0	0	0	0	0	0
		Censored *	0	0	0	0	3	4

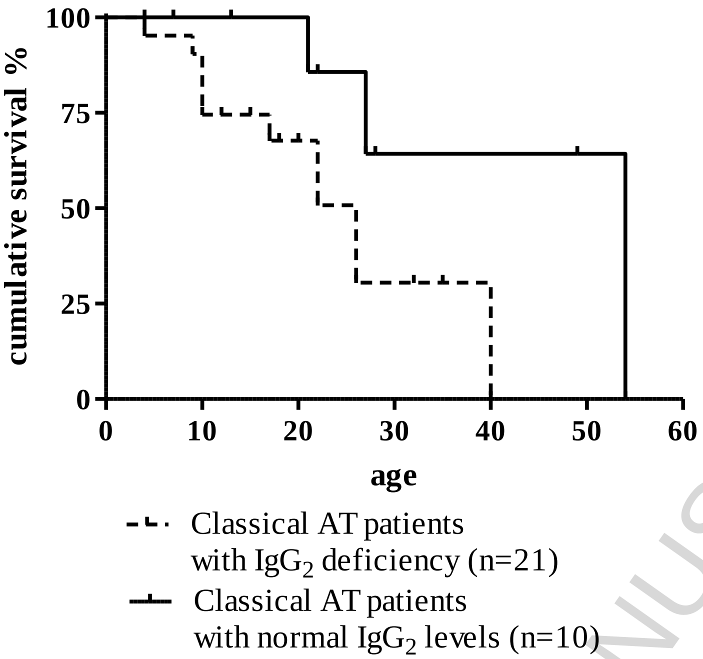
* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.

3.4. Immunology

3.4.1. IgG_2 deficiency

AT patients with an IgG_2 deficiency had greatly reduced survival compared to patients with normal IgG_2 levels (HR 10.2, 95%CI 2.3-45.0), even when the analyses were restricted to classical AT patients (HR 5.3, 95%CI 1.2-23.5). With adjustment for gender, both of these HRs increased to 13, as more female patients with IgG_2 deficiencies died and at a younger age compared to male patients (*Supplement 3*). When the AT-HIGM phenotype was excluded in order to prevent bias, the HRs were 7.8 (95%CI 1.7-36.2) for all IgG_2 deficient patients and 4.0 (95%CI 0.9-18.7) for classical AT patients only (Figure 4), while the HRs adjusted for gender varied between 8.1 and 11.5, respectively. Among the 29 classical AT patients with IgG_2 deficiency, malignancies occurred in 45% compared to 24% among patients with normal IgG_2 levels (OR 2.6, 95%CI 0.7-10.1) and 18 patients were deceased at the end of follow-up: 10 (56%) died from malignancies, seven (39%) from respiratory failure, and one (6%) patient from either a combination or both.

Figure 4: Survival of classical AT patients (AT-HIGM excluded) with IgG_2 deficiency and patients with normal IgG_2 levels



		Years	0	10	20	30	40
Classical without AT-HIGM	IgG_2 deficiency	At risk	21	14	8	3	0
		Deceased	0	5	6	10	11
		Censored *	0	2	7	8	10
	Normal IgG_2	At risk	10	8	7	2	2
		Deceased	0	0	0	2	2
		Censored *	0	2	3	6	6

* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.

3.4.2. IgA deficiency

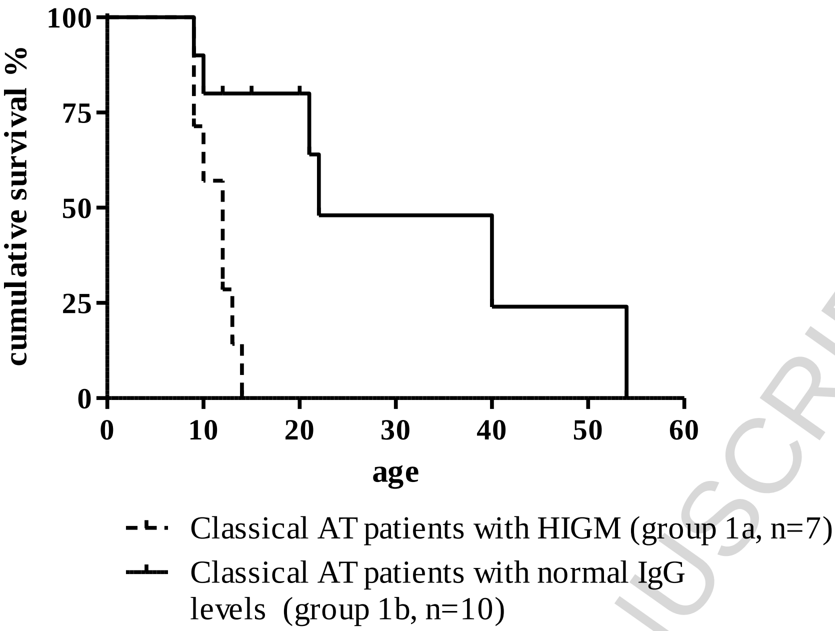
None of the patients with variant AT had an IgA deficiency. The HR for classical AT patients with IgA deficiency was 2.2 (95%CI 0.9-5.1), compared to classical patients with normal IgA levels. When patients with the AT-HIGM phenotype were excluded from the analysis, the HR was 1.4 (95%CI 0.6-3.8), indicating that survival was similar for classical AT patients with and without IgA deficieny *(Supplement 6)*. Malignancies did not occur more frequently among IgA deficient patients compared to patients with normal IgA levels either (36% and 43%, respectively, OR 0.8, 95%CI 0.2-2.3). Both malignancies and respiratory failure were equally often the cause of death among IgA deficient patients. Patient 17b was excluded from the IgA immunoglobulin analysis since IgA levels were variable during life.

3.4.3. Hyper IgM phenotype

The survival of AT patients with AT-HIGM (group 1a) was much worse than that of classical AT patients without ATM protein but with normal IgG levels (group 1b)(HR 8.0, 95%CI 1.6-40.1) (*Figure 5*) or other AT patients with normal IgG levels (*Supplement 3*). All patients with AT-HIGM died before the age of 15, three from a malignancy (two of which were lymphomas), and four from respiratory failure. In group 1b, five patients died from a malignancy (50%) and one from an unknown cause *(Table 1).*

In addition to the seven patients in our cohort, 15 other patients with AT-HIGM were described in the literature *[20, 24-33].* We received additional information on survival for five patients that were alive at the time of publication (patients L2a, L3, L6, L7, and L14*, Table 2)*. Eight of these 15 patients were reported to have died: seven between 2 and 12 years of age and one at age 24. The remaining patients (n=7) were alive at the time of publication, but at least three of them died after publication, at 10, 11, and 15 years of age.

Figure 5: Survival of classical AT patients with AT-HIGM phenotype (group 1a) and patients with normal IgG levels (group 1b)



	Years	0	10	20	30	40
AT-HIGM	At risk	7	4	0		
	Deceased	0	3	7		
	Censored *	0	0	0		
Normal IgM	At risk	10	8	5	2	1
	Deceased	0	2	2	4	5
	Censored *	0	0	3	4	4

* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.

Table 2: Review of 22 patients with AT-HIGM in the present cohort and in the literature (L).

No	M / F	Age	Age at death	Cause of death	Phenotype (age)	Diagnosis, chronological (age)	Serum AFP	Mutations	Siblings with AT	Ref-erence
1*	M		13	Lymphoma	Ataxia (1), telangiectasia (4), recurrent infections	AT (2,5)	↑	See table 2	No	-
2a	F		9	Respiratory failure	Ataxia (1), recurrent infections (1), telangiectasia (5)	HIGM (1), AT (1)	↑	See table 2	Patient 2b and 2c	[8, 20] (5-3)
2b	F		12	Respiratory failure	Ataxia (1.5), recurrent infections (1.5), telangiectasia (6)	HIGM (1), AT (1)	↑	See table 2	Patient 2a and 2c	[8, 20] (5-2)
2c	M		10	Hepato-cellular carcinoma	Ataxia (3), telangiectasia (9), recurrent infections	HIGM (9), AT (9)	↑	See table 2	Patient 2a and 2b	[20] (5-1)
3	F		14	Respiratory failure	Ataxia (1), recurrent infections (2), telangiectasia (4)	HIGM (2), AT (2)	↑	See table 2	No	[20] (2)
4	F		9	Lymphoma	Recurrent infections, auto-immune heamolytic anemia, neutropenia, hepatosplenomegaly, lympadenopathy (1), unsteady gait (2), telangiectasia (4)	Not X-linked HIGM (1), AT (2)	↑	See table 2	No	[20] (3), [22]
5	F		12	Respiratory failure	Recurrent infections (0.5), ataxia (1.5)	HIGM (1), AT (2)	↑	See table 2	No	[8, 20] (4)
L1#	F	8			Abnormal gait, lymphadenopathy, hepatosplenomegaly, telangiectasia (2-4), lymphocytic interstitial pneumonitis (5.5)	HIGM (4.5), AT (5)	↑	8822insAACT (codon 2941) 8672 del CT (codon 2945)	Not noted	[33]
L2a	F		11§	Severe pneumonia	Some gait disturbance (5), chronic lung disease	Autosomal recessive HIGM (3), AT (5)	↑	Not noted	Twin sister with HIGM (L2b)	[27]
L2b	F		5	Hodgkin lymphoma	No neurological nor cutaneous features	Autosomal recessive HIGM (3), AT (5)	↑	Not noted	Twin sister with HIGM (L2a)	
L3	F	16§			Mild ocular telangiectasia (6)	Autosomal recessive form of HIGM (6), AT (7)	↑	Exon 48 c.6679 C>T, Exon 34 c.8484delA	Older brother (alive) no HIGM	[25]
L4	M		10	Pneumonia	Not noted	AT (1)	Not tested	Unknown	Younger brother (15, died) no HIGM	[30]
L5	F		24	Severe pneumonia	Not noted	HIGM (4), AT (4)	↑	Unknown	Younger sister (23, alive) no HIGM	
L6	F		10§	Malignant lymphoma	Recurrent infections (1), cerebellar ataxia (2)	HIGM (1), AT (2)	↑	exon 9 c.842delAATT, homozygous	Older sister (5, died) no HIGM	
L7	M		15§	Multi-organ failure due to bladder hemorrhage	Recurrent infections (2), cerebellar ataxia (5)	HIGM (2), AT (5)	↑	exon 10 c.902_1065del164, exon 21 c.2877C>G	Younger brother (9, alive) no HIGM	

L8	F		7	Bleeding as side effect of radiotherapy for Wilms tumor	Recurrent infections (2.5), ataxia (4), no telangiectasia	Autosomal recessive form of HIGM (2.5), AT (5)	↑	Exon 28 3848T>C, Exon 62 8766_8767insT	Not noted	[32]
L9	M		11	Severe pneumonia, AML	Recurrent infections (2), ataxia and ocular telangiectasia (5)	HIGM (2), AT (5)	↑	Exon 15 C 2413→T, Exon 9 del1402-3, AA	Not noted	[28, 29] (K)
L10	F		8	Respiratory failure due to pneumonia	Gait disturbance and ocular telangiectasia (4)	HIGM (2), AT (4)	↑	Exon 53 c.8250C>T, (p.2622Ala>Val) homozygous	Not noted	[24]
L11	M	8			Recurrent infections (0.5), ataxia (3), telangiectasia (6)	HIGM (3), AT (6)	Unknown	Exon 54 c.7788G>A, IV564-2189 del 16.kb (intron 63)	Not noted	[20]
L12	F		12	Respiratory failure	Recurrent infections (1), ataxia (9), telangiectasia (9)	HIGM (1), AT (9)	Unknown	Unknown	Not noted	
L13	M		2	Post-transplant-lymhoproliferative disorder	No clinical features of AT	HIGM phenotype disorder (primary immunodeficiency with unknown cause)(2), AT (post mortem)	↑	Exon 12 c.1316T>C/439 L>P, homozygous	Not noted	[31]
L14	F	8§			Ocular telangiectasia, motor and intellectual impairment (3)	HIGM (2), AT (3)	↑	Exon 44, c.6198+1G>T, homozygous	Healthy brother	[26]

* Patients 1-5: Patients from the present cohort, numbers are in accordance with table 1;
# Patients L1-L14: Patients from the literature search;
§ Age at 1-11-2015, or age of death (not reported in the literature).

4. DISCUSSION

This cohort study confirmed that classical AT patients have reduced survival compared to variant AT patients, although several classical AT patients survived beyond 30 years of age. The presence of a malignancy shortens the life expectancy of classical AT patients. Patients with AT-HIGM phenotype and patients with IgG_2 deficiency had reduced survival compared to classical AT patients with normal IgG and IgG_2 levels, respectively. The presence of ATM protein and IgA deficiency did not influence survival in classical AT patients in the present cohort.

4.1. Variant AT and malignancies

Some have suggested that the survival time of AT patients has not changed in the last 50 years[11]. However, classical AT patients surviving more than 30 years were rarely described in the past, whereas six patients in the present study reached this age. It is well-known that patients with classical AT have a shorter life expectancy of approximately 20 years[13, 34], mainly due to earlier onset of malignancies[35, 36], compared to variant AT patients. The results from the present study are in accordance with this literature, with a difference of 27 years in median age at diagnosis of malignancies. Classical AT patients without malignancies had a 2.5 times higher overall chance of survival compared to classical patients with a malignancy and their main cause of death was respiratory insufficiency, which is also in line with the available literature[11, 34]. We believe that respiratory diseases may contribute to severe complications of cancer treatment and a short survival time after cancer diagnosis in AT patients with malignancies.

The 81% mortality rate due to malignancies among classical AT patients and the death of four out of five variant AT patients with a malignancy are in accordance with the data of Micol et al., who described a mortality rate of 90% for hematological malignancies and 83.3% for carcinomas[11]. The median time of survival after diagnosis was less than one year for classical patients in both our and their cohort[11]. In our variant AT patients, the youngest age at diagnosis of cancer was 23 years. This late occurrence of malignancies is probably due to the residual kinase activity and normal immunoglobulin levels protecting these patients from the development of lymphoid malignancies, especially in childhood[35, 36]. All patients without a malignancy in the variant group were still alive at the end of follow-up. Future studies need longer follow-up times to determine the final course of disease in variant AT patients.

4.2. Immunology

Immunodeficiency in general has been associated with an increased risk of cancer[35]. This study shows that malignancies were not more frequent in AT patients with IgA deficiency compared to those with normal IgA levels. In contrast, malignancies were more common and the major cause of death in IgG_2 deficient patients compared to patients with normal IgG_2 levels. Respiratory failure was not the major cause of death in this group, although low IgG_2 levels have been associated with a decreased polysaccharide antibody response, possibly causing increased susceptibility to respiratory tract infections[37]. This may be explained by the successful administration of antibiotic prophylaxis and immunoglobulin replacement therapy to these patients.

The majority of classical AT patients had reduced levels of IgA but none of the variant AT patients were IgA deficient, which corresponds with the results of Staples et al.[9]. Based on similar percentages of patients with IgG_2 or IgA deficiency in group 1b compared to group 2 and the variability in immunoglobulin levels between siblings (for example IgG_2 levels in families 9 and 24 and 45 and IgA levels in families 18, 20 and 24), it seems that the immune defects in AT do not correlate with detectability of the ATM protein.

The AT-HIGM phenotype is caused by class-switch recombination deficiency and is characterized by decreased levels of serum IgG (and IgG subclasses) and IgA, with normal or increased levels of serum IgM[38]. Since recurrent sinopulmonary infections in patients with AT-HIGM manifest at a very young age, often before ataxia and telangiectasia are present or recognized, patients with HIGM are at risk of being misdiagnosed with ‘HIGM of undetermined cause’ instead of AT-HIGM[8, 20, 24-26].

The present study, as well as all available data from the literature, clearly revealed that HIGM strongly reduces the life expectancy in AT patients, with respiratory failure being a common cause of death. All seven patients in our cohort, and at least 10 out of 15 patients that were described earlier, died before the age of 15. Of all 22 patients with AT and HIGM described so far, no more than 5 (23%) survived beyond adolescence. Despite intravenous immunoglobulin substitution therapy, the AT-HIGM patients in the present cohort developed respiratory insufficiency before the age of 15. This is a major point of interest since lung function is normal in most adolescents with AT [39].

As immunoglobulin levels can vary during life, it may be difficult – especially retrospectively - to determine if a patient truly has or had HIGM. Patient 11 in our cohort was diagnosed with AT-HIGM at the age of 19 and survived with his immune deficiency until death at age 40. He had a low-normal IgG level at age 10 and he did not have recurrent infections during childhood (in contrast to all patients in group 1a). During adulthood, his IgG levels spontaneously increased to normal, although the IgG only consisted of IgG_1. Therefore, we assume that he did not have HIGM during childhood and excluded him from group 1a ('AT-HIGM'). The same holds true for patients 15b and 18a, who developed hypogammaglobulinemia in puberty. In addition, it may be questioned whether the two patients with AT and HIGM who survived beyond 15 years of age (patients L3 and L5, see *Table 2*), indeed had AT-HIGM. Patient L3, described by Soresina et al.[25] had an IgG deficiency with high IgM and normal IgA levels while suffering from proteinuria in early childhood, but normal IgA and IgG levels during immunoglobulin substitution therapy in November 2015. So her hypogammaglobulinemia may have been secondary to proteinuria. Patient L5's immunoglobulin levels at the time of diagnosis were unavailable. Similar to the hypothesis regarding our patient 11 (see above), she may have developed AT-HIGM later in life.

In our cohort, patients with the same *ATM* mutations expressed different phenotypes for AT-HIGM, even some that were siblings. This has also been described previously [25, 27, 30] *(Table 2)* and confirms that no correlation exists between ATM mutations and AT-HIGM phenotypes.

As AT is a severe disease, affecting - among others – the nervous system and the immune system, high-risk therapies targeting the underlying molecular aspects may be considered. This is illustrated by former administration of stem cell transplantation to patients with AT[31, 40, 41] and in patients with other neurodegenerative diseases[42] and primary immunodeficiencies[43]. Due to the poor prognosis of AT patients with HIGM, we believe that these patients are among the first eligible candidates to study the efficacy and safety of such therapies, as this group is expected to profit most from this therapy. Needless to say, no other accountable cause for the IgG deficiency should exist, and HIGM should be present since early childhood and not be a paraneoplastic feature. Since neonatal screening for severe primary immunodeficiency diseases is upcoming in some countries, patients may be diagnosed with AT before the first clinical symptoms emerge [44, 45]. The presence of HIGM in some of these young pre-symptomatic children can be used as a prognostic marker for a poor outcome.

4.3. Strengths and limitations

The strengths of this study are the large number of well-characterized AT patients, the inclusion of patients from different ethnicities, and the extensiveness of the data set. All but the Icelandic patients lived in the Netherlands and benefited from the National Health Care system.

The present cohort contained many young children, but sensitivity analyses excluding patients with <10 years of follow-up did not lead to essential changes in results. As groups 1a and 4 included mainly female patients, adjustments for gender did affect some estimates, but not the interpretation of the results. While studying the Kaplan-Meier curves, for instance in *Figure 2*, one may erroneously assume that over 50% of variant AT patients survived beyond 50 years of age, and that 25% of classical AT patients survived beyond 40 years of age. As listed in *Table 1* and in the table underneath *Figure 2*, however, only 5 out of 13 variant AT patients (38%) and 3 out of 48 classical AT patients (6%) survived beyond 50 and 40 years, respectively. The other 5 variant AT patients and 20 classical AT patients were still alive, but much younger at the time of study and were therefore censored in the analysis. These large numbers of patients with relatively short follow-up times may lead to unrealistically positive cumulative probabilities of survival shown in the Kaplan-Meier curves.

Given the rarity of AT, this study includes a relatively large number of patients. Nevertheless, the main limitations of the study are due to small sample sizes, especially in subgroup analyses. As a result, the data must be interpreted with caution and further investigations with larger cohorts of AT patients are needed to confirm our results. Fortunately, an international effort to register as many patients as possible is now ongoing. Exclusion of patients that were lost to follow-up, missing patients with a mild phenotype that were not diagnosed, publication bias, and unavailability of immunoglobulin levels may have caused selection and/or information bias, but the number of patients with missing data was small. Although this study spanned several decades and management of AT patients might have changed over the years, survival was not influenced by cohort effects of year of birth or diagnosis.

5. CONCLUSION

AT is known as a disease with a highly reduced life expectancy, but we described several patients with classical AT who survived longer than would be expected. On the other hand, this study is the first to show that IgG_2 deficiency and HIGM negatively influence survival in AT patients, and to give an overview of all patients with AT and HIGM described in the literature. We believe that AT patients with HIGM are at extremely high risk of early death, and are therefore most eligible for future therapeutic trials.

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Supplement 1: Clinical features of classical AT patients in group 3

Patient	Ataxia (age)	Telangiec-tasia (age)	Wheelchair bound (age)	Diagnosis AT (age)	Serum AFP *	Malignancy	Died (age)	Additional features
28	2	Not noted	13	5	-	Lymphoma	17	Recurrent infections
29	1	<6	Not noted	6	↑	-	-	-
30	1	<8	7	2	97	Lymphoma	9	Immunodeficiency
31	1	<6	11	7	180	ALL	15	-
32	2	Not noted	11	8	-	Lymphoma	15	-
33	1	<8	8	7	180	-	-	-
34	2	<8	5	Not noted	102	-	10	Recurrent infections
35a	2	<8	10	33	108	-	-	Diabetes, recurrent infections
35b	2	10	Yes, age not noted	33	40	-	-	Diabetes, recurrent infections
36	3	<5	10	6	426	Lymphoma	17	Recurrent infections
37	0.5	7	7	4	310	-	-	-
38	1.5	4 (minimal)	-	3	110	-	-	Recurrent infections

*in ug/l, normal <10

Supplement 2: Immunological parameters of patients from group 1a (AT-HIGM)

Patient	Age of blood test	CD3 ($x10^9/L$)	CD4 ($x10^9/L$)	CD8 ($x10^9/L$)	CD19 ($x10^9/L$)	Naive CD4 ($x10^9/L$)
1	12 years	0.80 (L)	0.60 (N)	0.07 (L)	0.08 (L)	0.03 (L)
2a	8 years	1.50 (N)	0.50 (L)	0.43 (N)	0.07 (L)	0.01 (L)
2b	11 years	0.39 (L)	0.18 (L)	0.16 (L)	0.03 (L)	0.01 (L)
2c	-	-	-	-	-	-
3	2 years	0.35 (L)	0.22 (L)	0.26 (L)	0.08 (L)	0.04 (L)
4	2 years	0.37 (L)	0.31 (L)	0.02 (L)	0.01 (L)	0.15 (L)
5	11 years	0.65 (L)	0.31 (N)	0.31 (N)	0.01 (L)	L

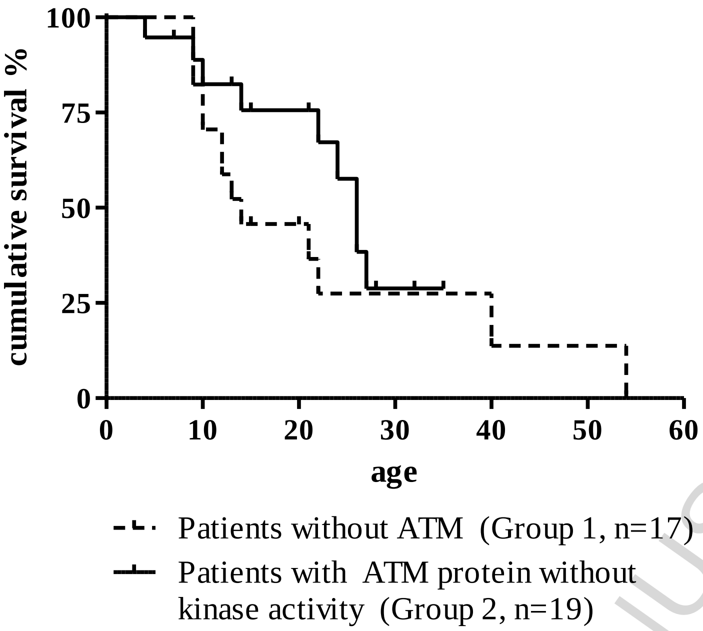
L = below age-related normal value, N= normal age-related value. Reference values are based on the paper by Comans-Bitter et al.[18].

Supplement 3: Hazard ratios (with 95% confidence intervals).

		Classical AT versus variant AT (n=61)	Group 1 versus group 2 (n=36)	Malignancy versus no malignancy (n=61)	IgG_2 deficiency versus normal IgG_2 (n=46)	IgA deficiency versus normal IgA (n=53)	AT-HIGM versus normal IgG
Full cohort							**1a versus 1b**
	HR	5.9 (2.0-17.7)	1.8 (0.7-4.4)	3.7 (1.7-8.1)	10.2 (2.3-45.0)	3.9 (1.7-9.3)	8.0 (1.6-40.1)
	Gender adjusted	6.1 (2.0-18.7)	2.2 (0.9-5.7)	4.4 (1.9-9.9)	13.0 (2.9-58.7)	4.1 (1.7-9.9)	4.9 (0.9-25.4)
	Exclusion < 10 yrs of follow-up	5.4 (1.8-16.4)	1.9 (0.7-5.4)	3.4 (1.5-7.8)	9.0 (2.0-40.5)	4.0 (1.6-10.2)	14.2 (1.6-127.7)
	Gender adjusted and exclusion <10 yrs of follow-up	5.3 (1.7 – 16.3)	2.4 (0.8-7.1)	3.5 (1.4-8.7)	11.1 (2.4-51.6)	4.1 (1.6-10.5	9.3 (1.0-88.5)
HIGM excluded							**1a versus 1b+2**
	HR	5.2 (1.7-16.1)	0.9 (0.3-3.0)	5.9 (2.2-15.7)	7.8 (1.7-36.2)	2.7 (1.0-7.1)	6.7 (2.2-20.7)
	Gender adjusted	5.2 (1.7- 16.2)	1.3 (0.4-4.4)	6.7 (2.4-19.0)	9.2 (1.9-44.2)	2.6 (1.0-7.1)	5.2 (1.7-16.2)
	Exclusion < 10 yrs of follow-up	4.8 (1.5-15.0)	0.9 (0.2-3.6)	4.8 (1.8-13.2)	7.0 (1.5-33.1)	2.8 (1.0-8.0)	12.9 (2.9-57.3)
	Gender adjusted and exclusion <10 yrs of follow-up	4.5 (1.4-14.3)	1.3 (0.3-5.3)	5.0 (1.7-14.7)	8.1 (1.6-40.5)	2.8 (1.0-8.0)	10.7 (2.4-48.9)
Variants excluded							**1a versus 1b+2+3**
	HR	x	x	2.5 (1.1-5.5)	5.3 (1.2-23.5)	2.2 (0.9-5.1)	6.6 (2.3-18.8)
	Gender adjusted	x	x	3.1 (1.3-7.0)	13.1 (2.6-66.8)	2.3 (1.0-5.5)	6.1 (2.1-17.7)
	Exclusion < 10 yrs of follow-up	x	x	2.0 (0.8-4.9)	4.6 (1.0-20.9)	2.2 (0.9-5.4)	12.4 (3.1-48.9)
	Gender adjusted and exclusion <10 yrs of follow-up	x	x	2.3 (0.9-5.9)	12.2 (2.2-66.0)	2.3 (0.9-5.7)	12.3 (3.1-49.4)
AT-HIGM and variants excluded							**1a versus 1b+2+3+4**
	HR	x	x	3.6 (1.3-9.8)	4.0 (0.9-18.7)	1.4 (0.6-3.8)	9.2 (3.2-26.3)
	Gender adjusted	x	x	4.2 (1.5-12.0)	10.9 (1.9-64.1)	1.5 (0.6-4.0)	9.5 (3.3-27.6)
	Exclusion < 10 yrs of follow-up	x	x	2.6 (0.9-7.5)	3.6 (0.7-16.9)	1.5 (0.5-4.2)	17.8 (4.5-70.5)
	Gender adjusted and exclusion <10 yrs of follow-up	x	x	3.0 (1.0-8.9)	11.5 (1.8-75.4)	1.6 (0.5-4.4)	19.9 (4.9-81.1)

Group 1: patients without detectable ATM protein; group 1a: patients with AT-HIGM; group 1b: patients with normal IgG levels; group 2: patients with ATM protein and without ATM kinase activity group 3: patients with missing data on ATM protein and ATM kinase activity, but with clinical phenotypes similar to those in groups 1 and 2; group 4: patients with residual kinase activity (variant AT)

Supplement 4: Survival of AT patients without ATM protein (group 1) and with ATM protein without kinase activity (group 2)



	Years	0	10	20	30	40
Without ATM protein	At risk	17	12	5	2	1
	Deceased	0	5	9	11	12
	Censored *	0	0	3	4	4
With ATM protein without ATM kinase activity	At risk	19	13	10	2	0
	Deceased	0	3	4	9	9
	Censored *	0	3	5	8	10

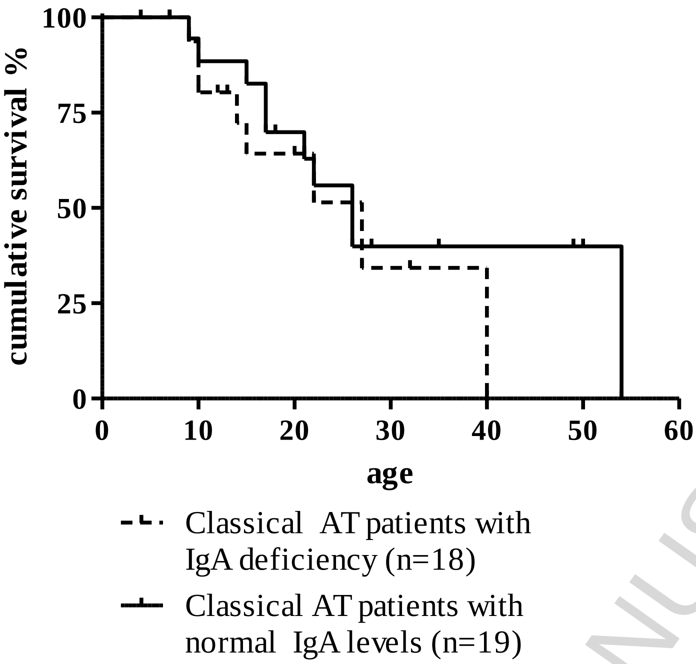
* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.

Supplement 5: Time of survival after cancer diagnosis for classical and variant AT patients

	Patient	Age of diagnosis of cancer (years)	Age of death (years)	Time of survival after cancer diagnosis (years)
Classical	1	12	13	1
	2c	10	10	<1
	4	9	9	<1
	7	17	22	4.5
	8	9	9	<1
	9b	10	10	<1
	11	39	40	1
	13	52	54	2
	15a	8	9	1
	15b	25	26	<1
	17b	4	4	<1
	18b	10	10	<1
	19	27	27	<1
	23a	24	24	<1*
	23b	15	-	-
	28	16	17	1*
	30	8	9	1
	31	15	15	<1
	32	15	15	<1
	33	18	-	-
	36	16	17	1
Variant	40	(42 and) 46	47	(5 and) <1
	41	32	-	-
	44b	23	23	<1
	47a	>45	48	<3
	47c	51	51	<1

* Cause of death was unknown.

Supplement 6: Survival of classical AT patients (AT-HIGM excluded) with IgA deficiency and patients with normal IgA levels



		Years	0	10	20	30	40	50
Classical without AT-HIGM	IgA deficiency	At risk	18	12	6	2	0	
		Deceased	0	3	5	7	8	
		Censored *	0	3	7	9	10	
	Normal IgA	At risk	19	15	10	4	3	1
		Deceased	0	2	5	9	9	9
		Censored *	0	2	4	6	7	9

* Censored patients are patients that were alive in this age category at the end of follow-up. Differences in number of patients at risk can be explained by deaths and censored patients. Deceased and censored numbers are cumulative.