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Ataxia Telangiectasia in Latin America: clinical features, immunodeficiency and mortality in a multicenter study

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Research Article

Keywords: Ataxia Telangiectasia, Primary Immunodeficiency Diseases, Immunologic Deficiency Syndromes, Survey, Latin America

Posted Date: October 31st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3481215/v1

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Abstract

Ataxia-telangiectasia (AT) is a rare neurodegenerative genetic disorder leading to neurological defects, telangiectasias and immunodeficiency. We aimed to study the clinical and immunological features of Latin American patients with AT and analyze the factors associated with AT-related mortality. Referral centers (*n* = 46) from 9 Latin American countries participated in this retrospective cohort study. AT was defined with ESID Criteria. Designated physicians in each healthcare center reviewed medical records of 218 patients with AT. Data from 218 patients with AT were analyzed. Mean ± standard deviation ages at symptom onset and diagnosis were 1.6 ± 1.1 and 5.7 ± 3.5 years, respectively. Most (66.9%) patients presented recurrent airway infections, which was significantly associated with IgA deficiency. Humoral deficiencies included IgA deficiency in 60.8% of patients and IgG deficiency in 28.6%. Lymphopenia was present in most cases, mainly affecting T and B cells. Around half of patients used antibiotic prophylaxis (57.7%) and immunoglobulin replacement (49.1%). No complications due to live viral vaccines were reported. Their mean survival was 24.2 years and Kaplan-Meier 20-year-survival rate was 52.6%. Low IgG levels were associated with decreased life expectancy (hazard *ratio* 2.1; 95% CI, 1.11–3.93), whereas male sex was a protecting factor (hazard *ratio* 0.52; 95% CI, 0.27–0.99). There was a high frequency of recurrent infections and immunologic abnormalities in our sample of patients with AT. Higher mortality was associated with female gender and low IgG levels. These findings suggest that immunologic status should be investigated in all patients with AT, thus helping us to improve therapeutic strategies.

INTRODUCTION

Ataxia-telangiectasia (AT; OMIM 208900 [1]) is a rare autosomal recessive inborn error of immunity caused by variants in the ataxia telangiectasia mutated (ATM) gene, which is located at 11q22.3 [2]. ATM protein belongs to the family of phosphatydylinositol 3-kinases and is involved in mitogenic signal transduction, intracellular protein transport and cell cycle control [3]. AT is characterized by progressive neurodegeneration, oculocutaneous telangiectasia, immunodeficiency, pulmonary manifestations, increased radiosensitivity, cancer predisposition, metabolic disorders, and several other features [3,4]. There is a significant clinical and laboratorial variability among patients, and evidence suggest a genotype-phenoptype correlation, influencing the kinase quantity and function [5].

To date, there is no curative treatment for AT. Bone marrow transplant might be considered in some situations, but it is not yet recommended or recognized as a curative option [6]. Efforts are being made to enable gene therapy for these patients, but further studies are needed to pave the way for future trials in humans [7]. Therefore, AT is currently managed with supportive care and symptomatic treatment [8].

Children and adults with AT suffer from increased mortality, with a median age of death of 14 years old, due to several complications such as malignancies, infections, nutritional and other complications [9]. Evaluating survival rates and their predictors in AT patients is essential for clinical practice; however, such evidence is scarce, mainly due to the rareness of the disease. Epidemiologic surveys are also relevant to expand the knowledge of AT natural history and improve patient care.

The Latin American Society for Immunodeficiencies (LASID) registry was established in April 2009 and, until the end of 2016, almost three hundred AT patients were registered [10]. Yet, there is no previous multicenter epidemiological study in the continent. Therefore, we aimed to investigate ataxia-telangiectasia diagnosis, treatment, and clinical outcomes in Latin America, as well as to identify risk factors for mortality in these patients.

METHODS

All referral centers (n = 111) participating in the LASID Registry (https://registrolasid.org/docs/Estatisticas_LASID-2016_Jun.pdf) were formally invited by e-mail to participate. Charts from 9 countries were retrospectively reviewed and data was filled out by the responsible physician in a Google Form semi-structured survey. The following data was analyzed: age, sex, neurological symptoms, infections, malignancy, wheelchair use, lab tests, familial history, and treatment.

We followed ESID criteria [11] to consider AT diagnosis. A definitive diagnosis was defined by the presence of male or female with disabling variants on both alleles of *ATM* gene AND one of the following: increased radiation induced chromosomal breakage in cultured cells OR progressive cerebellar ataxia. A probable diagnosis was settled if they presented with progressive cerebellar ataxia and at least THREE of the following abnormalities: ocular or facial telangiectasia, alpha fetoprotein more than 2 Standard Deviation (SD) above normal for age, serum IgA at least 2 SD below normal for age or increased chromosomal breakage after exposure to irradiation. Possible diagnosis of AT was considered if patient presented with progressive cerebellar ataxia and at least ONE of the same findings described above.

Onset of clinical or laboratory features and age of diagnosis were defined according to information found in medical records. Immunoglobulin plasma levels and lymphocyte subsets were compared to age and population related reference values [12,13].

This study was approved by all referral centers ethical committee and informed consent was obtained from every participant or his/her legal guardian.

Statistical analysis

Variables were compared across groups by using the x^2 or Fisher exact test for categorical variables. Continuous variables were expressed as mean and standard deviation (SD). McNemar and Cochran's Q test were used to compare two or three evaluation's moments, respectively. Life expectancy was estimated from birth to age at the time of survey or until age of death. Kaplan-Meier curves were used to compare survival across groups of categorical variables. Survival function was estimated for each of the variables; later, they were compared using the Log Rank test (Mantel-Cox). Numerical variables were adjusted using the Cox proportion hazel models. To evaluate the simultaneous effect of all the predictive variables in survival probability, the sample was adjusted to the Cox regression. Due to sample size

limitations, variables with $p < 0.1$ in the univariate analysis were included at the multivariate analysis. All the variables that were not statistically significant at 5% were excluded one on one by order of significance (backwards method). The proportional risks assumption was verified using the Schoenfeld test. Statistical analysis was performed using SPSS statistical software (version 20.0; SPSS, Chicago, IL, USA.) and STATA (version 12; STATA Corp., College Station, TX, USA), always considering 5% as the level of significance.

RESULTS

Sample description

Data from 218 patients with AT from 46 healthcare centers located from nine LA countries was collected in this multicenter study between July 2015 and February 2018. These patients had a mean age of 13.7 years at the time of the survey. Table 1 shows the demographic and main clinical features of the study sample. According to ESID Criteria, 90 patients (41.5%) had a probable AT diagnosis, 59 patients (27.2%) had possible diagnosis AT, and 69 patients (31.8%) had definitive AT.

Table 1
Demographic and clinical features of the study sample of patients with AT in Latin America

Characteristic	*n* (%)
Country	**218 (100.0)**
Brazil	123 (56.4)
Mexico	34 (15.6)
Argentina	32 (14.7)
Colombia	13 (6.0)
Chile	5 (2.3)
Peru	4 (1.8)
Uruguay	3 (1.4)
Paraguay	3 (1.4)
Honduras	1 (0.5)
Sex	**218 (100.0)**
Female	111 (51.0)
Male	107 (49.0)
Family History	**218 (100.0)**
Positive	92 (42.2)
Brother	70 (76.1)
Cousin or uncle	20 (21.7)
Not specified	2 (2.2)
Negative	126 (57.8)
Consanguinity	**207 (100.0)**
Yes	53 (25.6)
No	154 (74.4)
Presenting Symptom(s)[a]	**218 (100.0)**
Ataxia	159 (72.9)

[a] 13 patients reported 2 first symptoms

[b] 3 cases presented with excessive salivation and 1 case with dysarthria

Characteristic	*n* (%)
Infections	34 (15.6)
Telangiectasia	29 (13.3)
Ocular apraxia	5 (2.3)
Others[b]	4 (1.8)
[a] 13 patients reported 2 first symptoms	
[b] 3 cases presented with excessive salivation and 1 case with dysarthria	

Clinical features

The mean age at onset of symptoms was 1.6 years (SD 1.57) and the mean age of diagnosis was 5.6 years (SD 3.48); in consequence, the mean diagnostic delay was of 4.1 years (SD 3.07). Ataxia occurred in all patients and was the presenting symptom in 159 patients (72.9%) and occurred on average at 2.1 (SD, 1.9) years of age. At the age of 3 years, 75% of them had ataxia; at the age of 6 years, 95% developed ataxia. Additional clinical features concerning neurologic, gastrointestinal, endocrine, and cutaneous systems and respective ages of onset are shown in Table 2.

Table 2
Clinical features and age of onset of the study sample of patients with AT in Latin America

Characteristic	*n* (%)	Age of onset (years)		Total
		Mean	SD	
Neurological features				
Ataxia	218 (100.0)	2.1	1.9	218
Dysarthria	156 (85.2)	5.2	3.2	183
Postural change	144 (75.4)	4.9	3.6	191
Ocular apraxia	133 (74.7)	5.2	2.8	178
Wheelchair	112 (56.3)	9.3	3.2	199
Other[a]				15
Gastrointestinal features				
Excessive Salivation	98 (55.7)	5.5	3.8	176
Dysphagia	98 (50.0)	8.8	4.4	196
Hepatic Steatosis	24 (14.3)	13.1	6.7	168
Gastrostomy	16 (8.3)	11.5	4.5	193
Other[b]				18
Dermatologic features				
Ocular telangiectasia	207 (97.6)	3.2	2.4	212
Cutaneous telangiectasia	113 (57.1)	4.4	3.2	198
Other				26
Endocrine features				
Diabetes	4 (4.4)	17.4	5.4	90
Hypothyroidism	2 (2.3)	9.8	7.7	87

[a] 6 patients had seizures and 9 patients had choreoatetosis

[b] 10 patiens had chronic diarrhea and 7 patients had reflux

Recurrent airway infections (pneumonia, otitis, and sinusitis) were reported in most cases (n = 140, 66.9%). Over half of patients (*n* = 119, 55.9%) presented two or more episodes of pneumonia, and an isolated pathogen was identified in 16 patients (12.2%). Relevant viral infections were reported in 21

patients (9.6%), including severe varicella, extensive/refractory HPV, systemic CMV and EBV. Opportunistic infections were seen in 4 cases (1.8%); of them, only one patient had lymphopenia (low CD3 + CD4+). Infectious profile of patients is detailed in **Supplementary Table S1**.

A variety of vaccines was administered to patients with AT (**Supplementary Table S2)**. No severe adverse event related to vaccines was reported, including the yellow fever vaccine.

Malignancies were found in 23 patients (10.8%) and the mean age of onset was 11.9 years (SD 5.9). From these, most cases (*n* = 13, 61.9%), were hematologic neoplasms (lymphoma or leukemia), followed by central nervous system tumors in 6 patients (28.6%) and gastrointestinal carcinomas in 2 of them (9.5%). Forty patients (21.5%) reported a positive familial history of cancer.

Immunologic workup

The most common humoral immune abnormality at the first immunological evaluation (defined as a value more than 2 SD above or less than 2 SD below the mean for age) was low IgA in 121 patients (*n* = 121, 60.8%), followed by low IgG in 55 patients (*n* = 55, 28.6%) and low IgM in 4 patients (*n* = 4, 2%). We also assessed the proportion of patients who had IgA levels ≤ 7 mg/dL (*n* = 95, 46.3%). The IgG level was considered only for patients before immunoglobulin treatment. IgM levels were elevated in 109 patients (55,1%). Trends in immunoglobulin levels by age are illustrated in Figs. 1A, 1B and 1C; absolute values are shown in **Supplementary Table S3**. Concerning to vaccine antibody responses, most patients did not respond to pneumococcal (*n* = 58, 79.5%) and B hepatitis (*n* = 23, 60.5%) immunization. Other vaccines, such as tetanus, rubella and measles had a positive antibody response (**Supplementary Table S4**). Among patients with two different measurements of immunoglobulin and who were not receiving immunoglobulin replacement therapy. IgA and IgM levels tend to decrease with age (*p* = 0.001 and 0.047, respectively) (**Supplementary Table S5**).

We also correlated immunoglobulin levels with infections; there was a significant association between serum IgA levels ≤ 7 mg/dL and recurrent airway infections (*p* = 0.038). IgG levels and pneumococcus antibody response after vaccination did not show statistical association with infections (*p* = 0.686 and 0.500, respectively).

Regarding to the cellular compartment, absolute counts of T cells (CD3+, CD3 + CD4 + and CD3 + CD8+), NK cells (CD16 + 56+) and B cells (CD19+) were assessed at the first immunological evaluation and, if possible, at a second period of time. Figures 2A, 2B, 2C, 2D and 2E illustrates the distribution of lymphocyte subset counts according to age, and absolute values are reported in **Supplementary Table S6**. At the first evaluation, most patients presented with low CD3 + cells (*n* = 114, 76.5%), low CD3 + CD4 + cells (*n* = 120, 79.5%), low CD4 + CD8 + cells (*n* = 83, 55.0%) and low CD19 + cells (*n* = 115, 92.0%). We also classified patients according to their lymphocyte absolute count; 22 patients (14.6%) had CD3 + CD4+ < 200 cells/mm^3, 4 patients (4%) had NK cells ≤ 2% and 9 patients (7.9%) had B cells ≤ 2% (**Supplementary Table S7**). Finally, among patients who had two measurements of lymphocyte subsets over time, data showed no strong tendency of variability in T, B or NK cell counts with age.

Treatment

Prophylactic antibiotics were used in 123 patients (57.7%), and, in 81 patients (71.1%), infections were considered controlled with this treatment. Immunoglobulin replacement therapy was being used in 104 patients (49.1%); infections were considered controlled with this treatment in 84 patients (89.4%). Data also showed that the use of immunoglobulin replacement therapy was more frequent among patients with recurrent airway infection compared to patients who did not present recurrent airway infection ($p < 0.001$). All patients received at least one complementary treatment, including respiratory physiotherapy ($n = 140$, 70.7%), motor physiotherapy ($n = 177$, 88.9% respectively), speech therapy ($n = 116$, 62.0%) or occupational therapy ($n = 90$, 48.1%). Other treatments reported included equine therapy ($n = 18$), hydrotherapy ($n = 30$), and psychotherapy ($n = 43$).

Survival analysis

In survival analysis, data from 188 patients were analyzed. The average age of first evaluation was 13.7 years (SD 6.3); minimum age was 0.6 years and maximum age was 38.8 years. Mean time of survival was 24.21 years (95% Confidence Interval (CI) 21.47–26.95) and median time of survival was 23 years (95% CI 17.52–28.48). Kaplan-Meier 10-year and 20-year-survival rates were 95.0% and 52.6%, respectively. A higher survival function was seen in male patients compared to female ($p = 0.036$) and in patients with normal or high IgG levels comparatively to those with low levels of IgG ($p = 0.009$). Other variables did not influence in survival analysis. **Supplementary Figures S1A**, **S1B** and **S1C** illustrate Kaplan-Meyer curves of overall survival rate, survival rate by gender and survival rate by IgG levels, respectively. Initial results of survival analysis by variables are shown in **Supplementary Table S8**.

Simple Cox regression model showed no effect in survival function regarding age of symptoms onset ($p = 0.449$), age of diagnosis ($p = 0.904$) or time of diagnostic delay ($p = 0.733$). After adjusting values by multivariate regression, gender (hazard *ratio* 2.1; 95% CI 1.11–3.93; $p = 0.049$) and IgG level at first immunological evaluation (hazard *ratio* 0.52; 95% CI 0.27–0.99; $p = 0.022$) maintain statistically significance (Fig. 3). From these data, it can be inferred that male patients present death risk 48% less than female patients. It is also possible to assume that patients with low levels of IgG have a 2,1 times greater chance of death than patients with normal IgG. Schoenfeld test was not significant ($p = 0.934$), indicating no violation of the presupposition.

DISCUSSION

This retrospective cohort described 218 patients with AT in Latin America. Cerebellar ataxia was the first manifestation (around 2 years of age), followed by a myriad of symptoms as patients grow older: ocular and cutaneous telangiectasia, postural changes, ocular apraxia, dysarthria, and excessive salivation. After 8 years of age, patients presented with dysphagia, endocrinologic and metabolic disorders, and use of wheelchair. Due to its rareness (estimated prevalence of less than 1–9/100,000 and incidence between 1 in 20,000/100,000 live births [14]) and lack of telangiectasias in initial presentation, it is not uncommon to observe a significant diagnostic delay among AT patients, usually around 4 years after onset of

symptoms [15,16,17,18]. This situation has been changing as access to newborn screening (NBS) is growing worldwide. T-cell receptor excision circles and kappa-receptor excision circles measurements through Guthrie cards at birth can detect AT patients before clinical symptoms occur. Despite a curative treatment is not available, early diagnosis of AT allows to carry out timely in-depth immunological and genetic testing, may prevent the development of severe infections, and improve quality of life [19,20]. Currently, many countries among Latin America are leading efforts to implement NBS for immunodeficiencies and reduce the diagnostic and treatment delay [21].

Infections are frequent among patients with AT, mainly in the upper and lower respiratory tract (pneumonia, bronchitis, otitis, and sinusitis), varying from 40–70% among studies [15,16,17,18,22]. As also shown by our analysis, bacteria are the most frequent pathogens. Some relevant viral infections and opportunistic agents have also been reported [22,23], but much less often (< 10% and < 2% of cases, respectively). In addition, bronchiectasis is commonly described, probably due to recurrent lower respiratory tract infections and chronic inflammation [9,16].

Regarding the immunological profile, we found low IgA and high IgM levels the most frequent humoral defects among AT patients, followed by low IgG in 28% of patients. Although no severe adverse reactions, variable vaccine responses were observed, with higher seroconversion with tetanus, measles and rubella vaccines, and lower titles of specific IgG to pneumococcus and hepatitis B. In the cellular compartment, CD3+, CD4+, CD8 + and CD19 + lymphopenias were present in most cases. These abnormalities of the adaptive immune system were observed by most cohorts [9,15,16,22,24,17,25], some of them even suggesting the “hyper IgM profile” to be included in the diagnostic criteria [18].

Some studies have tried to correlate infection symptoms to immunoglobulin levels in AT patients. Moin and colleagues [17], showed a positive correlation between clinical immunologic symptoms and immunoglobulin deficiencies. On other hand, Nowak-Wegrzyn et al. [22] found no association between frequency of sinopulmonary infections and deficiency of IgG, IgA, or subclasses of IgG. In the present study, although IgG was not correlated with infections, there was a significant association between serum IgA levels ≤ 7 mg/dL and recurrent airway infections. Interestingly, despite frequent T cell lymphopenia in many cases, our patients rarely presented with opportunistic infections.

The discrepancy between the frequent laboratory expression of humoral and cellular abnormalities and the variable clinical expression with infections is still subject of debate; there is evidence of more complex immune defects in these patients. *Kraus et al*. [26] demonstrated abnormal TCR-Vβ repertoires, with different degrees of clonality and reduced expression; no clear clustering of expansions to specific TCR-Vβ genes and abnormal PCR spectratyping analysis of the FR2 IgH BCR gene rearrangements in 50% of the patients. Conversely, *Weitering et al*. [27] recently published a study that shown that AT patients have a fully developed memory T cell compartment despite strongly reduced naïve T cells, which can be explained by the presence of normal numbers of stem cell memory T cells in the naìve T cell compartment, which support the maintenance of the memory T cells. There is also evidence that milder

phenotypes may be influenced not only by residual kinase activity, but abnormal activation of downstream responders to double-strand breakage in the Mre11-Rad50-Nbs1 complex [28,29].

Few studies evaluated longitudinally the immunological markers of these patients. Early evidence suggested immunodeficiency was progressive [30,31]. Despite that, more recent cross-sectional data [22,24] showed that immune abnormalities tend to not deteriorate throughout the time. In fact, *Chopra et al*. [24] even highlight the importance to screen for other factors besides immunodeficiency in patients presenting later with chest symptoms, such as interstitial lung disease, swallowing disorders, poor cough reflex or neurological degeneration. Indeed, in our study, lymphocyte counts did not decay as patients grow older, but there was a significant decrease in IgA and IgM levels with age. This information should be taken into consideration in clinical practice, as periodic immune evaluation is recommended in all patients, especially in those who present with a significant infectious phenotype.

Currently, the management of AT is based on supportive care and symptomatic treatment [32]. Even though some treatments aiming to slow neurodegeneration with antioxidants have risen during the last decades, evidence is still lacking [32,16]. Due to the complexity and severity of AT, patients should receive a multidisciplinary team of health care professionals [33,34,35,36]. Multidisciplinary rehabilitation therapy enables to preserve and improve activity levels, muscle strength and prevent joint contractures [35]. Occupational therapy helps patients to use devices for daily activities and maintain an adequate sitting position [36]. All patients in our cohort were being treated with at least one complementary treatment, including unusual methods like equine therapy and hydrotherapy.

Cancer is the leading cause of death among AT patients [15,22]. Like in other reports [37,38,39,40], our cohort showed hematologic cancers (lymphomas and leukemia) were the most common. It was also observed a high rate of positive familial history of cancer (around 20%). This enhanced cancer susceptibility is well stablished and can be explained by impaired DNA damage responses and radiosensitivity. Besides that, Desimio et al. [41] evidenced reduced NKG2D expression in NK cells of patients with AT, which may contribute to susceptibility to cancer and infections.

Infections are the second major cause of death in patients with AT [9]. Prophylactic antibiotics and immunoglobulin replacement therapy (IgRT) are beneficial in decreasing the severity and frequency of infections [15]. We reported relatively high rates of success with these treatments (57% and 71%, respectively). Traditionally, IgRT is considered in patients with recurrent infections and evidence of low IgG levels and/or poor antibody responses. Further studies are needed to assess the role of prophylactic antibiotics and IgRT in AT-related mortality.

In our study, we found similar mean time of survival than other studies [16,22,34,42], with most patients with AT surviving until the second or third decade of life. Our multiple regression analysis showed that both female gender and low IgG level at first immunological evaluation were significant factors in reducing lifespan of AT. This information is useful in clinical practice, as early interventions in these groups of patients may lead to improved care or a benefit in mortality.

This retrospective cohort study describes the largest cohort of patients with AT in Latin America, providing relevant information of the clinical, immunological profiles, and survival estimates. Despite that, there are some limitations in our study. First, being a retrospective, questionnaire-based study, selection and information biases must be considered. Second, the clinical spectrum of AT is not uniform; different *ATM* mutations, residual protein function and level of kinase activity lead to varied clinical and laboratorial phenotypes [43]. Patients with this “variant” or “atypical” AT may present symptoms at a later age of onset and longer survival rates, in contrast to the “classical” presentation [5]. Third, genotype information and functional assays are still lacking in some countries of LA; by the time of the study, they were rarely available. Due to that fact, we could not gather these data from patients.

CONCLUSIONS

In this cohort of Latin America patients, we found patients with Ataxia Telangiectasia have significant rates of infections (mainly affecting the airway), and low IgA is associated with more frequent sinopulmonary episodes. Although variable vaccine antibody response was seen, there was no reported severe adverse reactions in these patients. Also, immunological abnormalities such as low IgA, high IgM, T- and B-cell lymphopenias were frequent. Treatment regimens used by these patients involved complementary therapies, prophylactic antibiotics, and immunoglobulin replacement therapy. Finally, survival curves showed a mean time of survival of 24.2 years, not affected by age of symptoms onset, age of diagnosis or time of diagnostic delay. Low IgG and male gender were significant risk factors associated with mortality.

Declarations

AKNOWLEDGEMENTS

To Dr Beatriz Costa-Carvalho, our eternal master, friend, and inspiration.

FUNDING

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

CONFLICTS OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHORS’ CONTIBUTIONS

All authors contributed to the study conception and design. Material preparation and analysis were performed by Ellen O Dantas and Jessica Loekmanwidjaja. All authors contributed for data collection. The first draft of the manuscript was written by Ellen O Dantas and Renan A Pereira, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

This study was approved by all referral centers ethical committee.

CONSENT TO PARTICIPATE

Informed consents to participate in the study were obtained from every participant or his/her legal guardian.

CONSENT TO PUBLICATION

Informed consents to publish the results were obtained from every participant or his/her legal guardian, and every author.

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Figures

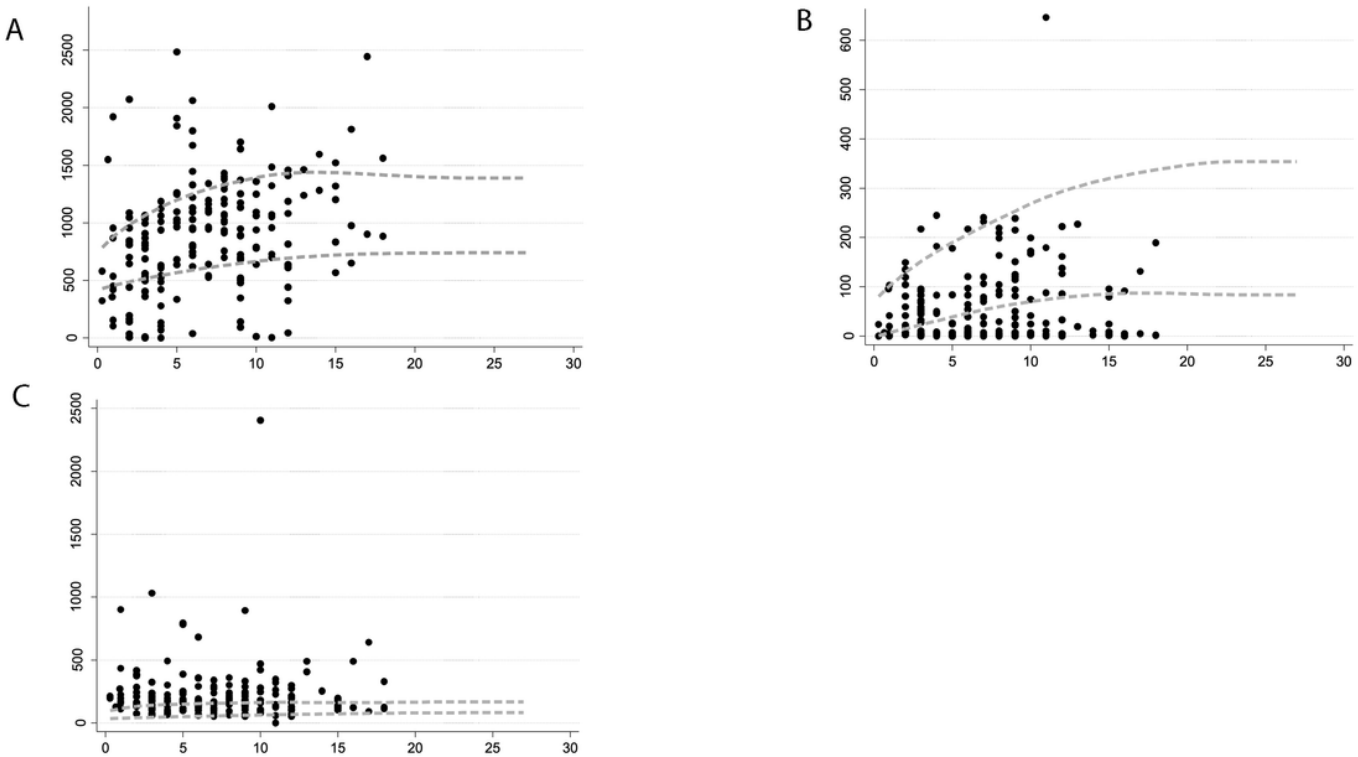

Figure 1

Dispersion graphics of immunoglobulin levels by age (first evaluation). Grey dotted lines indicate 2 SD above and below the mean for age.

A IgG levels (mg/dL) by age (years). *n* = 192.

B IgA levels (mg/dL) by age (years). *n* = 199.

C IgM levels (mg/dL) by age (years). *n* = 198.

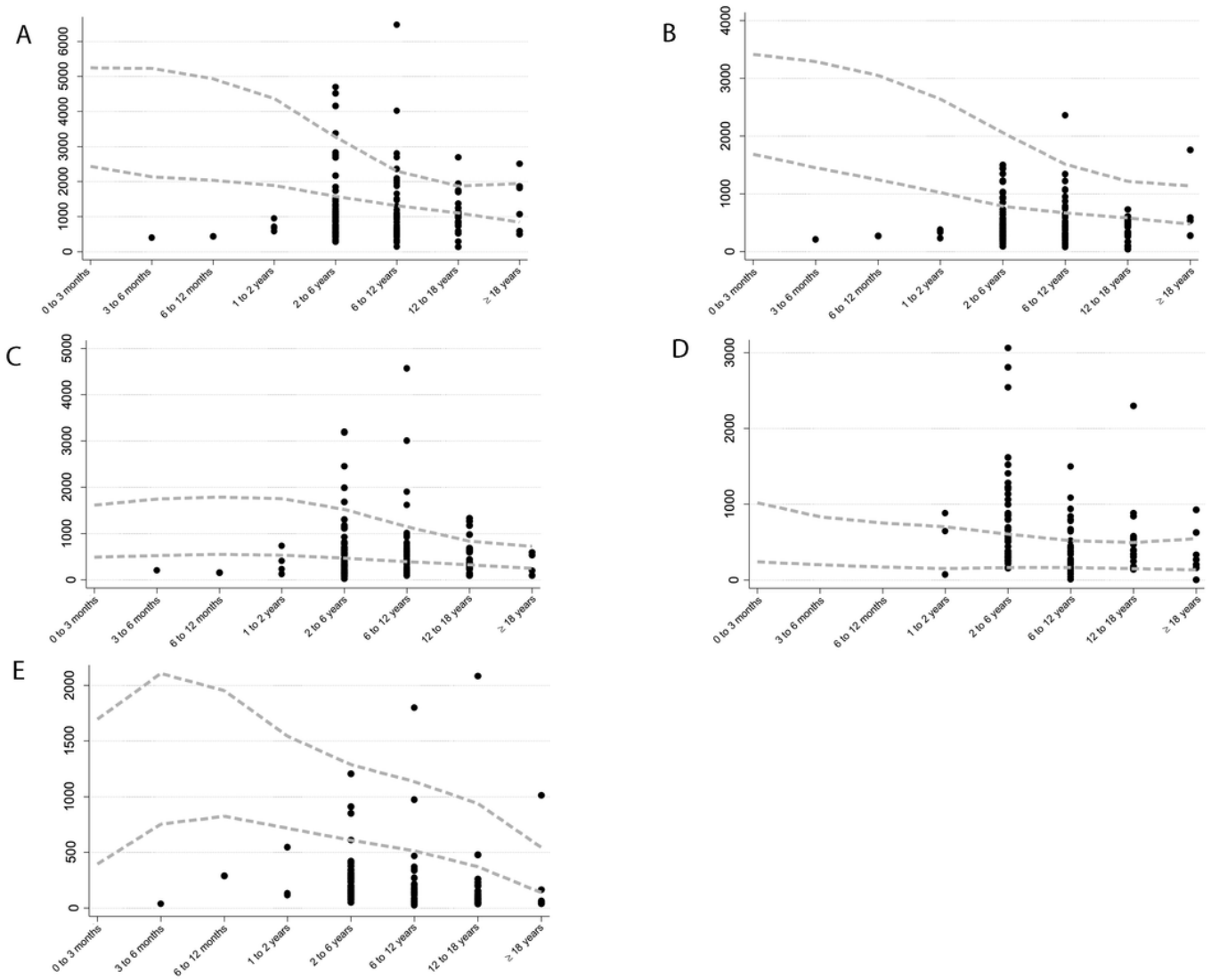

Figure 2

Lymphocyte subsets by age (first evaluation) among a sample of patients with AT in Latin America. Grey dotted lines indicate lymphocyte counts 2 SD above and below the mean for age.

A CD3+ (cell/mm^3) by age (years). *n* = 149.

B CD3+CD4+ (cell/mm^3) by age (years). *n* = 151.

C CD3+CD8+ (cell/mm^3) by age (years). *n* = 151.

D CD16+CD56+ (cell/mm^3) by age (years). *n* = 111.

E CD19+ (cell/mm^3) by age (years). *n* = 125.

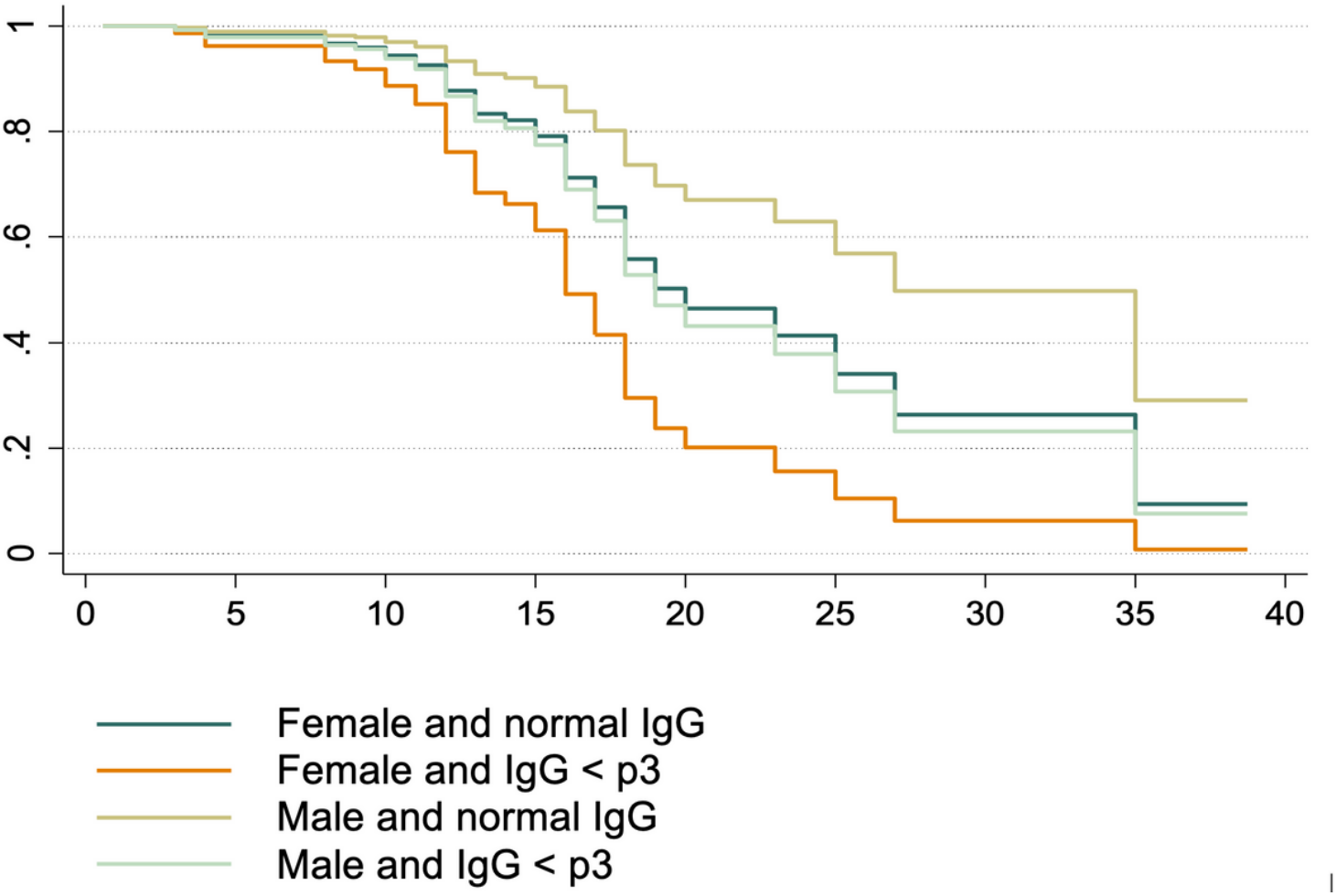

Figure 3

Survival in a sample of patients with AT in Latin America (*n* = 188). Estimate survival function by final Cox model. Gender (hazard *ratio* 2.1; 95% CI 1.11 – 3.93; *p* = 0.049). IgG level at first immunological evaluation (hazard *ratio*0.52; 95% CI 0.27 – 0.99; *p* = 0.022).

Supplementary Files

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- S1C.png
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