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Prevalence of hospital readmissions and related factors in patients with autoimmune diseases

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ABSTRACT

Objective: Autoimmune diseases generate an impact on the morbidity and mortality of patients and are a burden for the health system through hospital admissions and readmissions. The prevalence of readmission of patients with these diseases has not yet been described as a group, but rather as sub-phenotype. The objective of this study is to determine the prevalence of hospital readmissions in a Colombian population with autoimmunity and the factors related to readmission.

Methods: All patients with autoimmune diseases who were evaluated by the rheumatology service and hospitalized between August 2018 and December 2019 at the Fundación Hospital Infantil Universitario De San José de Bogotá were described. A bivariate analysis was done, and three multivariate logistic regression models were built with the dependent variable being readmission.

Results: Of the total 199 admissions, 131 patients were evaluated and 32% were readmitted. The most frequent sub-phenotype in both groups (readmission and no readmission) was SLE (51% and 59%). The most frequent cause of hospitalization and readmission was disease activity (68.7% and 64.3%). History of hypertension was associated with readmission (adjusted OR: 2.98–95% CI: 1.15–7.72). In a second model adjusted for confounding variables, no factor was associated. In a third model analyzing the history of kidney disease and previous use of immunosuppressants (adjusted for confounding variables), the previous use of immunosuppressants was related to readmission (OR: 2.78–95% CI 1.12–6.89).

Conclusion: Up to a third of patients with autoimmunity were readmitted and arterial hypertension was an associated factor. This suggested a greater systemic compromise and accumulated damage in patients who have these two conditions that may favor readmission. A history of immunosuppressant use may play a role in readmission, possibly by increasing the risk of developing infections.

1. Introduction

Autoimmune diseases (AIDs) are a broad spectrum of complex, heterogeneous, chronic and non-communicable ailments, that can involve a specific organ or affect individuals systemically [1,2]. They have multiple characteristics in common such as signs and symptoms, pathophysiology, genetic factors, ancestry, environmental factors (i.e. autoimmune ecology), female gender [3] predominance, similar treatments, etc. This similarity is called the autoimmune tautology, and it has made it possible to globally unify the characteristics of AIDs as phenotypes from the molecular and genetic level to the clinical aspect in a translational approach [1,2].

The AIDs have a global prevalence of approximately 3% and, in Colombia, one that is close to 5%. Therefore, this group of diseases is

Abbreviation's list: AHT, Arterial Hypertension.; AIDs, Autoimmune Diseases.; APS, Antiphospholipid Syndrome.; RA, Rheumatoid Arthritis.; DMARDs, Disease-modifying antirheumatic drugs.; ICD – 10, International Classification of Diseases 10th edition.; ICU, Intensive Care Unit.; SLE, Systemic Lupus Erythematosus.; SjS, Sjögren Syndrome.; SS, Systemic Sclerosis.

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known to cause a significant hospital and even economic burden [4,5]. A meta-analysis (2013) done in Colombia, found that, of all the patients with an AID admitted to the emergency department, up to 25% required hospitalization and, of these, up to one third required care and support in the ICU [6]. In addition, factors related to hospital readmissions are connected to an increase in morbidity and mortality, the cost of the disease, and effect on the patient's quality of life. Hospitalization is defined as the set of interventions and procedures necessary to provide a health service within the in-hospital setting. Readmissions are admissions to a health entity within a certain period following discharge from a hospital [7].

The frequency of readmission and the description of patients with Systemic Lupus Erythematosus (SLE) in a Spanish population [8] and in North American populations [9,10] have been reported. The main causes of readmission were disease activity, infections, the need for diagnostic or therapeutic procedures, and thrombotic events [8]. Regarding rheumatoid arthritis (RA), the main causes of hospital readmission were cardiovascular disease, musculoskeletal affection, and respiratory disease, based on a study of a North American population [11]. There is data on the prevalence of other AIDs such as Systemic Sclerosis (SS) or Sjögren Syndrome (SjS) [5,12], but data regarding hospitalizations or readmissions of patients with these diseases are scarce. There is no information either on the readmission of patients with polyautoimmunity, a term that refers to the coexistence of more than one autoimmune disease in a single individual, and which is prevalent in 34.4% of patients with AIDs [13].

There are studies in Latin America that include some Colombian patients, but they deal with specific AIDs, and do not analyze them as a group. For example, the Latin American guidelines for the treatment of SLE provide recommendations for interventions based on experience, availability, and accessibility of the different therapeutic alternatives [14], but do not provide epidemiological data on hospitalization or readmissions. There are other studies with local data describing patients in the hospital setting such as one carried out in Medellin, Colombia with 130 hospitalized SLE patients. This one found that the number one cause of hospitalization was disease activity (57%) and the most frequent compromise was kidney disease (74%) although no data on hospital readmission were provided [15].

Therefore, the conclusion was drawn that there is insufficient information from evaluations of the Colombian or Latin-American population regarding the factors related to readmission of patients whether they are patients with a specific autoimmune disease, AIDs patients evaluated as a group, or patients with polyautoimmunity. The hypothesis of autoimmune tautology creates the need to evaluate AID as a group, and it is for this reason that this work aims to take this approach and take into consideration these characteristics, that are part of the spectrum of AID, but that can also be omitted when studying only each sub-phenotype. Given that similar treatment is one of the ten shared characteristics among AIDs according to the autoimmune tautology [1,2], it is important to know the hospitalization features when analyzed as a group and the impact in their outcome. Due to the above, there is a need to describe the prevalence of hospital readmission of patients with these conditions and to know what factors are related to these readmissions.

2. Methods

2.1. Population and sample

A population of patients with a previous or de novo diagnosis of any AID was analyzed, based on the diagnostic criteria of the rheumatology team of experts during the observation period from August 2018 to December 2019. All subjects were taken from a database of hospitalized patients, whether it was their first time or not, at the Fundación Hospital Infantil Universitario De San José – Bogotá, who met the inclusion criteria (>16 years of age and a diagnosis of one of the AIDs based on the ICD-10). Patients whose clinical record had less than 50% of the required data and an initial hospitalization of less than 48 h (e.g., lack of data, transfer of patients to another institution) were excluded.

2.2. Design

An analytical cross-sectional study was done, the prevalence of hospital readmissions was described, and two groups of patients were compared (those who were readmitted and those who were not).

2.3. Process

Data collection was carried out consecutively from the medical records by a trained researcher who filled out two forms using the REDCap [16] tool created by the researchers. Data capture of first hospitalization and hospital readmissions was done. Information on sociodemographics, medical history, clinical characteristics of hospitalization, type of medications used, laboratory reports, and the immunological profile of the patients was included.

2.4. Methodology

A bivariate analysis was done to compare each independent variable with respect to hospital readmission at any time within the observation period. For categorical variables, the Chi2 test or Fisher's test was used in cases of low expected values. For quantitative variables, the Student's t-test was used when presenting a normal distribution, and Mann-Whitney *U* test for independent samples when presenting non-normal distribution.

To identify the factors associated with readmission, a multivariate logistic regression model was developed by calculating the Odds Ratio (OR). The dependent variable was defined as hospital readmission, and independent variables were those that were statistically significant from the bivariate analysis. The limit on variables to be included was subject to the number of cases based on the Freeman equation [17]. The model was adjusted by two confounding variables: sex and duration of the disease. Statistical significance was defined with a 95% confidence interval and a p value of 0.05 in the bivariate and multivariate analysis. Collinearity was evaluated to show possible linear relationships between the independent or predictive variables of the model.

The data were processed using the STATA.15 software.

2.5. Biases

When collecting the data from the medical records, there was a risk of incurring information biases since the criteria by which the patients were diagnosed was not known at the time of the assessment, and these criteria have also changed over time. Therefore, a single database belonging to the same institution was chosen to enable a certain level of concordance and homogeneity among the data.

Another possible source of bias is Neyman bias since AIDs are chronic diseases and when hospitalization is required, there is a greater probability of having outcomes such as death.

Because this is by nature an observational study, it was exposed to confounding biases. These were controlled by defining selection and exclusion criteria, and by using a multivariate association model in the analysis.

2.6. Ethical aspects

According to resolution 8430/1993 (Colombian Law) and chapter I, article 11, this study is category A and is classified as risk-free research because no intervention and/or intentional modification of the variables was carried out.

The study had the approval of the Ethics Committee on research with human beings of the Fundación Hospital Infantil Universitario de San

José (act No. 117) and was approved by the Institutional review board of the Fundación Hospital Infantil Universitario De San José. The group of researchers adhered to the principles of the Declaration of Helsinki.

3. Results

The total population covered consisted of 161 individuals. Excluded patients corresponded to 5 repeated records, 10 patients evaluated at the outpatient service, 13 with no diagnosis of AID, one with a single, less-than-48-h hospitalization, and one under 16 years of age. The final total included patients were 131.

3.1. Sociodemographic characteristics and medical history

Of the 131 patients, 76.3% were female, marital status was predominantly married, a large number came from urban areas, most had a high school level of education, and the majority had a medical provider (24.4% Famisanar, 19% Medimas, 15.2% Servisalud). The main autoimmune diseases were SLE, in first place (51.1%), followed by RA (15.2%) and SS (9.1%). (See Table 1).

Of the total number of patients, 37% had polyautoimmunity (APS - 32.6% and SjS 22.4% were the most frequent conditions involved in polyautoimmunity). Eight patients had more than 2 AIDs. Of these, 3 patients had autoimmune thyroid disease followed by autoimmune cytopenia (n: 1), autoimmune liver disease (n: 1), Evans syndrome (n: 1) and APS (n: 1). Of this group of patients (polyautoimmunity), 93.9% were female, 48.6% were married, and 93.9% were from urban areas. Fourteen patients with polyautoimmunity were readmitted (28.6%). (See Appendix A.1 and A.2).

Of the group, 17.5% had familial autoimmunity (8 of the patients had more than one relative with an AID). The relative most frequently affected was the mother, followed by sister, father, and brother. The most frequent AID shared in the family nucleus was SLE, followed by RA, and multiple autoimmune diseases represented by one case each. (See Table 2).

With respect to comorbidities, 37.4% of the patients had arterial hypertension (AHT), 26.7% hypothyroidism (without registration of antibody analysis to confirm autoimmune etiology), and 15.2% had cardiovascular diseases. In the 8 patients with a history of cancer, thyroid cancer predominated, followed by 6 different types of neoplastic pathologies. Of the 100 women in the study, 62 had no gynecological-obstetric history records and 38 did. Of these, 31% had a history of at least one miscarriage and 9% had pre-eclampsia in one of their pregnancies. (See Table 2).

Regarding their pharmacological history, the use of glucocorticoids predominated, followed by use of antimalarials, immunosuppressants, and then by DMARDs. (See specifications in Table 2).

3.2. General characteristics of the first hospitalization

The main cause of hospitalization was disease activity; secondly, infections; and thirdly, other causes. These included gastrointestinal bleeding, preeclampsia, and drug toxicity in two patients, cervical adenitis, hypertensive emergency, hyperglycemia, and intestinal obstruction in one patient each. (See Table 3 and Fig. 1).

Among the autoimmune clinical manifestations during hospitalization, hematological (37.4%), articular (34.3%), and renal (29.7%) were the most frequent. Regarding the laboratory tests, hematological alterations, elevated C-reactive Protein (CRP), hypoalbuminemia, and alterations in kidney function were the results found the most frequently. Within the autoimmunity markers, hypocomplementemia and a positive profile in the antibodies to extractable nuclear antigens (ENAS) predominated. (See Table 3 and Appendix B).

With the first hospitalization, 94.6% of the patients were discharged while the rest died. Of the total, 47.3% presented infections on admission or during hospitalization. The predominant infection was pneumonia. From the same group, 16.8% required admission to the ICU, of which more than 50% required vasopressor management and about a third, ventilatory support. Of this group, 18% were readmitted to the ICU at some point during this hospitalization. Twelve individuals underwent kidney biopsy and 10 had lupus nephritis (in any of its stages).

Regarding pharmacological treatment, patients received mainly glucocorticoids (80.1%), followed by antimalarials (48.1% of which 75% had been receiving it and continued it during hospitalization), and immunosuppressants (40.4%). (See Table 3).

Table 1
Sociodemographic characteristics and main autoimmune disease.

Variables	n = 131 Median (IQR)		Readmitted n = 42 Median (IQR)	Not Readmitted n = 89 Median (IQR)	P value
Aye (years)	43(30)		43 (31)	43 (29)	0.691
Variables	**n = 131**	**%**	**Readmitted n = 42 (%)**	**Not Readmitted n = 89 (%)**	**P value**
Female	100	76.3	32 (76.19)	68 (76.4)	0.979
Marital status	92				0,097
Married	53	57.6	12(41.38)	41(65.08)	
Single	28	30.4	11(37.93)	17(26.98)	
Divorced/ Separated	6	6.5	3(10.34)	3(4.76)	
Widowed	5	5.4	3(10.34)	2(3.17)	
Place of origin	126				0,426
Urban	119	94.4	79(92.94)	40(97.56)	
Rural	7	5.56	1(2.44)	6(7.06)	
Occupation	111				0,549
White-Collar worker	23	20.7	5(15.63)	18(22.78)	
Houseworker	21	18.9	4(12.50)	17(21.52)	
Retired	21	18.9	9(28.13)	12(15.19)	
Blue-Collar worker	19	17.1	7(21.88)	12(15.19)	
Student	11	9.9	4(12.50)	7(8.86)	
Others	10	9	2(6.25)	8(10.13)	
White-Collar and Blue-Collar workers	6	5.4	1(3.13)	5(6.33)	
Main AID	131				0,577
SLE	67	51.1	25(59.52)	42(47.19)	
RA	20	15.2	4(9.52)	16(17.98)	
SS	12	9.1	4(9.52)	8(8.99)	
Vasculitis	6	4.5	1(2.38)	5(5.62)	
APS	6	4.5	3(7.14)	3(3.37)	
AC	5	3.8	2(4.76)	3(3.37)	
Polymyositis	3	2.2	0	3(3.37)	
ASD	2	1.5			
AS	2	1.5	0	2(2.25)	
Reactive Arthritis	1	0.7	0	1(1.12)	
EnA	1	0.7	1(2.38)	0	
AIH	1	0.7	0	1(1.12)	
MG	1	0.7	1(2.38)	0	
IAP	1	0.7	0	1(1.12)	
SjS	1	0.7	0	1(1.12)	
Evans Syndrome	1	0.7	1(2.38)	0	
MAS	1	0.7	0	1(1.12)	

AC: Autoimmune Cytopenia; AIH: Autoimmune Hepatitis; APS: Antiphospholipid Syndrome; AS: Ankylosing Spondylitis; ASD: Adult-onset Still Disease; EnA: enteropathic arthritis; IAP: Immune Axonal Polyneuropathy; IQR: Interquartile Range; MAS: Macrophage Activation Syndrome; MG: Myasthenia Gravis; RA: Rheumatoid Arthritis; SjS: Sjögren Syndrome; SLE: Systemic Lupus Erythematosus; SS: Systemic Sclerosis.

3.3. Characteristics of readmission

Of the total number of patients, 42 were readmitted, or 32%. Of these, two had four readmissions, 6 had three, and 18 had two readmissions. Two died in the first readmission and one in the second readmission (n = 3; 7.14%). Patients with SLE were the most frequently

Table 2
Medical history and clinical characteristics.

Variables	n: 131 Median (IQR)		Readmitted n = 42 Median (IQR)	Not Readmitted n = 89 Median (IQR)	P Value
Years of illness	3.6(10.4)		5.83(11.14)	2.86(8.88)	0.158
Number of cigarettes per day	8(12)		6(8)	10(17)	0.496
Years of cigarette exposure	12(13)		16(8)	12(13)	0.608
Variables	n: 131	%	Readmitted n = 42 (%)	Not Readmitted n = 89 (%)	P Value
Polyautoimmunity	49	37.4	14(33.33)	35(39.33)	0.508
APS	16	32.6	4(28.57)	12(34.29)	
SjS	11	22.4	3(21.43)	8(22.86)	
RA	4	8.1	0	4(11.43)	
SLE	4	8.1	2(14.29)	2(5.71)	
Others	14	28.5	5(35.71)	9(25.71)	
Familial Autoimmunity	23	17.5	8(19.05)	15(16.85)	0.758
Comorbidities					
AHT	49	37.4	21(50)	28(31.46)	0.041*
Hypothyroidism	35	26.7	13(30.95)	22(24.72)	0.452
Cardiovascular (not AHT)	20	15.2	9(21.43)	11(12.36)	0.178
Respiratory Disease	11	8.4	3(7.14)	8(8.99)	1.000
Cancer	8	6.1	4(9.52)	4(4.49)	0.268
DM2	8	6.1	4(9.52)	4(4.49)	0.268
Gastrointestinal Disease	7	5.3	0	7(7.97)	0.096
Psychiatric Disorders	7	5.3	2(4.76)	5(5.62)	1.000
Kidney Disease	7	5.3	5(11.90)	2(2.25)	0.034*
Miscarriages:	38				0.457
0	22	57.8	10(71.43)	12(50.0)	
1	12	31.5	3(21.43)	9(37.50)	
2	2	5.2	0	2(8.33)	
3	2	5.2	1(7.14)	1(4.17)	
Toxicological History					
Smoking	20	15.2	4(9.52)	16(17.98)	0.209
Current/14	3	17.6	1(33.33)	2(14.29)	0.465
Previous/16	14	87.5	2(66.67)	12(92.31)	0.350
Alcoholism	7	5.3	2(4.67)	5(5.62)	1.000
Organic Solvents	7	5.3	1(2.38)	6(6.74)	0.429
Previous Treatment					
DMARDS	25				0.256
MTX	16	12.2	4(9.52)	12(13.48)	
LFA	4	3.0	1(2.38)	0	
MTX + LFA	4	3.0	0	4(4.49)	
MTX + LFA + SSZ	1	0.7	0	1(1.12)	
Immunosuppressant Drugs	37				0.038*
AZT	18	13.7	8(19.05)	10(11.24)	0.038*
MMF	13	9.9	5(11.90)	8(8.99)	
CYA	2	1.5	2(4.76)	0	0.038*
AZT + MMF	2	1.5	2(4.76)	0	
Cyclophosphamide	1	0.7	0	1(1.12)	
AZT + MMF + CYA	1	0.7	0	1(1.12)	
Antimalarials	41	31.3	19(45.24)	22(24.72)	0.018*
Chloroquine	22	16.7	11(26.19)	11(12.36)	
Hydroxychloroquine	19	14.6	8(19.05)	11(12.36)	
Glucocorticoids	69				0.292
Prednisone	63	48.0	23(54.76)	40(44.94)	
Deflazacort	6	4.5	3(7.14)	3(3.37)	
Biologics	7				0.906
Rituximab	3	2.2	0	3(3.37)	
Certolizumab	1	0.7	0	1(1.12)	
Golimumab	1	0.7	0	1(1.12)	
Secukinumab	1	0.7	0	1(1.12)	
Tofacitinib	1	0.7	0	1(1.12)	

AHT: Arterial Hypertension; APS: Antiphospholipid Syndrome; AZT: azathioprine; CYA: Cyclosporine; DM2: Type 2 Diabetes Mellitus; DMARDS: Disease-modifying antirheumatic drugs; IQR: Interquartile Range; LFA: Leflunomide; MMF: Mycophenolate Mofetil; MTX: Methotrexate RA: Rheumatoid Arthritis; SjS: Sjögren Syndrome; SLE: Systemic Lupus Erythematosus; SSZ: Sulfasalazine; *$p < 0.05$.

readmitted (n = 25; 59.5%). The main cause of readmission was disease activity (n = 27, 64.3%). Patients who were readmitted were more likely to have a history of AHT compared to those who were not readmitted (50% vs 31.46%, p = 0.041). The most frequent manifestations during readmission were hematological (n = 15.35.7%). Of the patients readmitted, 57% had hospital infections and 21% required treatment in the ICU. Tables 1–3 describe the characteristics of the patients who were readmitted compared to those who were not. The total number of patients who died presented some type of infection. Of these, 5 had SLE (50%), 2 vasculitis, one had Polymyositis, one RA, and one SS.

3.4. Bivariate analysis and multivariate logistic regression model

When the bivariate analysis was done, the history of AHT, kidney disease, previous use of immunosuppressants, previous use of antimalarials, articular manifestation, antiviral and antiparasitic drug use during hospitalization, and low levels of C3 and C4; gave statistically significant differences. When adjusted to a multivariate model, only the

Table 3
Hospitalization characteristics.

Variables	n: 131 Median (IQR)		Readmitted n = 42 Median (IQR)	Not Readmitted n = 89 Median (IQR)	P Value
Length of Hospital Stay (days)	11(14)		11.5(18)	11(11)	0.319
ICU Length of Stay (days)	6(6)		6(6)	7(7)	0.813
SLEDAI (n = 42): mean (SD)	13.54 (8.4)		12.37 (8.4)	14.52 (8.5)	0.416
Variables	n: 131	%	Readmitted n = 42 (%)	Not Readmitted n = 89 (%)	P Value
Cause of Admission	131				0.689
Disease Activity	90	68.7	27(64.29)	63(70.79)	
Infection	27	20.6	10(23.81)	17(19.10)	
Other	10	7.6	4(9.52)	6(6.74)	
Thrombosis	2	1.53	0	2(2.25)	
Cardiovascular	2	1.53	1(2.38)	1(1.12)	
Autoimmune Manifestations					
Hematological	49	37.4	15(35.71)	34(28.20)	0.784
Arthritis or arthralgia	45	34.3	13(30.95)	32(35.96)	0.574
Renal	39	29.7	10(23.81)	29(32.58)	0.305
Cutaneous	30	22.9	6(14.29)	24(26.97)	0.107
Systemic	22	16.7	7(16.67)	15(16.85)	0.979
Neurological	20	15.2	4(9.52)	16(17.98)	0.209
Pulmonary	19	14.5	3(7.14)	16(17.98)	0.100
Cardiovascular	17	12.9	4(9.52)	13(14.61)	0.419
Thrombotic	8	6.1	2(4.76)	6(6.74)	1.000
Ocular	3	2.2	1(2.38)	2(2.25)	1.000
Gastrointestinal	3	2.2	1(2.38)	2(2.25)	1.000
Infections	62	47.3	24(57.14)	38(42.70)	0.122
Pneumonia	18	29	4(16.67)	14(36.84)	0.088
UTI	11	17.7	5(4.3)	6(17.79)	0.736
Soft Tissue Infections	11	17.7	2(8.33)	9(23.68)	0.178
Septic Shock	11	17.7	3(12.50)	8(21.05)	0.505
Sepsis	10	16.1	4(16.67)	6(15.79)	1.000
ICU Hospitalization	22	16.8	9(21.43)	13(14.61)	0.330
Vasopressors	12	54.5	4(44.44)	8(61.54)	0.666
Mechanic Ventilation	7	31.82	2(22.22)	5(38.46)	0.648
ICU Readmission	4	18.2	2(22.22)	2(15.38)	1.000
Pharmacological Therapy					
Glucocorticoids	105	80.1	35(83.33)	70(78.65)	0.531
Antimalarials	63	48.1	23(54.76)	40(44.94)	0.294
Immunosuppressors	53	40.4	21(50.00)	32(35.96)	0.126
DMARDs	10	7.6	3(7.14)	7(7.87)	1.000
Biologics	2	1.53	0	2(2.25)	1.000
Antibiotics	56	42.7	18(42.86)	38(42.70)	1.000
Antifungal medication	6	4.5	2(4.76)	4(4.49)	1.000
Antiparasitic medication	5	3.8	4(9.52)	1(1.12)	0.036*
Antiviral medication	4	3	4(9.52)	0	0.010*
Laboratory Tests					
Hb < 12 g/dl	86/131	65.6	29(69.05)	57(64.04)	0.574
WBC<4000	23/131	17.6	7(16.67)	16(17.98)	0.854
Lymphocytes <1500	87/131	66.4	29(69.05)	58(65.17)	0.661
Thrombocytopenia	26/131	19.8	10(23.81)	17(19.10)	0.534
CRP > 5 mg/L	64/72	88.9	25(96.15)	39(84.78)	0.244
AST >48	18/75	24	6(26.09)	12(23.08)	0.778
ALT >55	13/74	17.6	4(18.18)	9(17.31)	1.000
AF > 130	4/16	25	2(50)	2(16.67)	0.245
Albumin <3.5 g/dl	45/45	100	14(87.50)	23(79.31)	0.691
LDH>160 U/L	50/56	89.3	15(88.24)	35(89.74)	1.000
CPK>300 U/L	3/11	27.3	1(50)	2(22.2)	0.491
Reticulocyte >1.5%	15/27	55.6	4(40)	11(64.71)	0.257
Glycemia >126 mg/dl	18/56	32.1	6(30)	12(33.33)	0.798
TSH> 5 UI/L	6/39	15.4	2(22.22)	4(13.33)	0.607
Creatinine >1.1 mg/dl	36/125	28.8	15(35.71)	21(25.30)	0.225
BUN>20 mg/dl	49/124	39.5	17(40.48)	32(39.02)	0.876
24-Hour Urine Protein >500 mg	27/46	58.7	13(68.42)	14(51.85)	0.261
Proteinuria in random sample	56/96	58.3	23(66.70)	33(52.38)	0.102
ANAS (+)	32/39	82.1	8(88.89)	24(80)	1.000
C3 Consumption	58/99	58.6	23(69.7)	35(53.03)	0.113
C4 Consumption	47/99	47.5	19(57.58)	28(42.42)	0.155
Anti-DNA (+)	34/72	47.2	13(54.17)	21(43.75)	0.404
Anti-SSA (+)	19/42	45.2	5(41.67)	14(46.67)	0.769
Anti-SSB (+)	20/42	47.6	7(58.33)	13(43.33)	0.379
Anti-Smith (+)	16/40	40	5(45.45)	11(37.93)	0.728
Anti RNP (+)	5/40	12.5	2(18.18)	3(10.34)	0.603
Rheumatoid Factor (+)	6/26	23.1	0	6(27.27)	0.542
AcL IgM	4/33	12.1	2(18.18)	2(9.09)	0.586
AcL IgG	6/33	18.2	2(25)	3(13.64)	0.589

(*continued on next page*)

Table 3 (*continued*)

Variables	n: 131 Median (IQR)		Readmitted n = 42 Median (IQR)	Not Readmitted n = 89 Median (IQR)	P Value
Lupus Anticoagulant	9/29	31	5(55.56)	4(20)	0.088
B2GP1 IgG	3/14	21.4	0	3(23.08)	1.000
B2GP1 IgM	2/18	11.1	2(33.33)	0	0.098
Anti ScL 70 (+)	1/9	11.1	0	1(16.67)	1.000

AcL: Anticardiolipin; AF: alkaline phosphatase; ALT: Alanine Aminotransferase; ANAS: Antinuclear Antibodies; AST: Aspartate Aminotransferase; B2GP1: beta-2 glycoprotein 1; BUN: Blood Urea Nitrogen; C3: Complement C3; C4: Complement C4; CPK: Creatine Phosphokinase; CRP: C Reactive Protein; DMARDs: Disease-modifying Antirheumatic Drugs; DNA: Deoxyribonucleic Acid; g/dl: Grams Per Deciliter; Hb: Hemoglobin; ICU: Intensive Care Unit; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IQR: Interquartile range; LDH: lactic Dehydrogenase; Mg: Milligrams; mg/dl: Milligrams per Deciliter; ScL 70: Anti-topoisomerase I; RNP: ribonucleoprotein; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SSA: Sjögren's Syndrome Related Antigen A; SSB: Sjögren's syndrome type B; TSH: Thyroid-stimulating hormone; UTI: Urinary Tract Infection; U/L: Units Per Liter. WBC: White Blood Cells.

history of AHT reflected an association with hospital readmission with an OR of 2.98, (CI 95%: 1.15–7.72) (Model 1 in Table 4). Adjusted for confounding variables (age and years of illness) the best-fitting model did not reflect an association between AHT and readmission (Model 2 in Table 4). A third model was developed including variables that, based on previous literature findings, are clinically relevant (history of kidney diseases and previous use of immunosuppressants). This model was adjusted for confounding variables and showed an association between a history of immunosuppressant use and readmission with an OR of 2.78 (CI: 1.12–6.89) (Model 3 in Table 4).

4. Discussion

AIDs share many characteristics, as indicated by the autoimmune tautology, showing that they have common disease development mechanisms, with hospitalization being one of the most relevant factors for prognosis and outcome [2]. This research describes the clinical characteristics of 131 Latin American patients with AID at the same hospital who had 199 hospital admissions of which 32% were readmissions. The most frequent AID at first admission and at readmissions was SLE. The main cause of admission and readmission was disease activity followed by infection. Of the total population, 7.6% died (in the first hospitalization or in subsequent readmissions). Of these, all presented some type of infection, and SLE was the most frequent disease among patients with this outcome. The history of AHT reflected an association with hospital readmission.

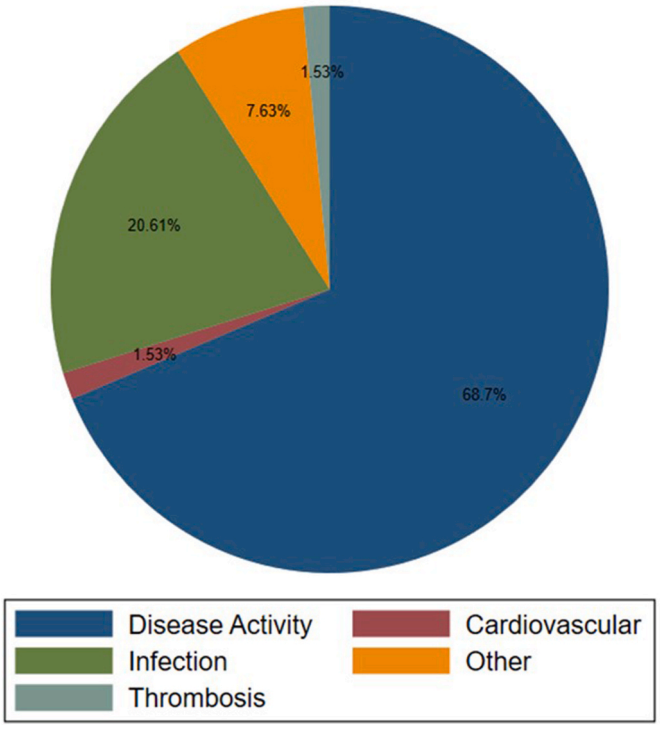

Fig. 1. Disease activity as the main cause of hospitalization in patients with AIDs at the Fundación Hospital Infantil Universitario De San José de Bogotá.

The behavior of some observed variables coincides with previous reports in the literature regarding AIDs as a group (globally and in populations such as the American one). The median age was between 31 and 64 and the highest prevalence was in women [3,18]. In the present study, no differences were found in sociodemographic variables between patients who were readmitted and those who were not. However, when analyzed by AID phenotype, an association was found in various previous studies such as Yazdany et al. who found an inverse association between age and readmission as well as a higher risk of readmission for Black and Hispanic, than for White patients [9].

The prevalence of readmission of patients with AID was 32%. This is the first reported prevalence data for AID as a group since it has previously been described as a sub-phenotype, mainly SLE [8,10]. In spite of the fact that no statistically significant differences were found between the type of AID and readmission, SLE was found in more than 50% of the patients who were readmitted. Other studies have shown that the prevalence of readmission of patients with SLE is 24%, which is very similar to that for patients with heart failure [19].

A mortality of 7.63% was found. This data is important since most mortality studies of patients with AIDs have been done by sub-phenotype (i.e., specific disease analyzed) [11,20]. Other studies exclusively analyzed this outcome in patients admitted to the ICU [21], and others evaluated mortality in AIDs in general and not in hospitalized patients [22]. It should be noted that the most common disease found among patients who died was SLE (50%). This is consistent with global studies [23] and with the study by Herberth L et al. [24], who evaluated the causes of mortality in Latin American patients (Guatemala) who had rheumatological AID in a hospital setting. They showed that those with SLE had the highest mortality (49.7%) and that the majority of deaths were related to an infectious origin similar to what was found in the present study. Although Londoño et al. [5] found that the most prevalent AID in Colombia was RA, here it can be seen that the most frequent disease in the hospital setting is SLE. Taking into account the higher mortality rates in patients with this sub-phenotype [6], it is clear that SLE is the most prevalent when the frequency of AID in the hospital setting is evaluated.

Although AHT was the only factor associated with readmission, in studies of specific AIDs such as SLE in the Colombian population, other related factors have been described such as male sex [25] and the presence of invasive fungal infection [26]. But, as previously explained, there is no evidence of readmissions of patients with AID as a group, and this is important due to the characteristics that AIDs share (autoimmune tautology).

The main cause of hospitalization was disease activity. This was also the cause for SLE patients in Colombia [15]. This highlights how important adequate control of AID activity is. Just as in other studies,

Table 4
Bivariate and multivariate analysis.

Variables	Readmitted n = 42	Not Readmitted n = 89	Crude OR (95%-CI) p value	Model 1 (95%-CI) p value	Model 2 (95% - CI) p value	Model 3 (95% - CI) p value
Female	32 (76.19%)	68 (76.4%)	1.01 (0.38–2.57). p: 0.98		0.98 (0.30–3.22) p: 0.98.	1.35 (0.45–4.08) p: 0.59.
>10 Years of Illness	11 (33.3%)	18 (22.78%)	1.69 (0.62–4.50) p: 0.25		1.89 (0.59–6.07) p: 0.28.	1.60 (0.60–4.23) p: 0.34.
Hypertension	21 (50%)	28 (31.5%)	2.18 (0.96–4.94). p: 0.04*	2.98 (1.15–7.72)*. p: 0.03*	2.60 (0.96–7.07) p: 0.06.	
Kidney Disease	2 (2.25%)	5 (11.9%)	5.88 (0.90–63.39) p: 0.02*			5.61 (0.93–33.79) p: 0.06.
Immunosuppressive therapy	17 (40.5%)	20 (22.5%)	2.35 (0.99–5.56) p: 0.03	2.18 (0.84–5.65). p: 0.11.		2.78 (1.12–6.89) p: 0.03*
Antimalarial therapy	19 (45.2%)	22 (24.7%)	2.52 (1.07–5.86)* p: 0.02*			
Arthritis or arthralgia	9 (21.4%)	36 (40.5%)	0.40 (0.15–0.99)* p: 0.03*	0.48 (0.18–1.25). p: 0.13.		
Antiviral	4 (9.5%)	0 (0%)	NA. p: 0.01 *			
Antiparasitic	4 (9.5%)	1 (1.1%)	9.26 (0.86–461.1). p: 0.02*			
C3 – median (IQR)	63.6 (46)	88 (62.4)	0.99 (0.98–1.00). p: 0.10.			
C4 – median (IQR)	5.1 (13.6)	12.8 (17.9)	0.95 (0.91–0.99)* p: 0.04*	0.96 (0.92–1.01). p: 0.14.	0.96 (0.92–1.00) p: 0.09.	

*$p < 0.05$. Model 1: Adjusted by variables with statistically significant difference form the bivariate analysis. Model 2: Adjusted by gender and years of illness as cofounding variables, best fitted the Akaike information criterion. Model 3: Adjusted by gender and years of illness as cofounding variables, kidney disease and immunosuppressive therapy as clinically relevant variables. U/L: Units Per Liter.

such as that of Bernal-Macías et al. [21], 16.8% of the patients required ICU hospitalization.

Of the 131 patients, most of them received glucocorticoids during hospitalization and almost half of the patients had some type of infection. The foregoing suggests a possible correlation between the use of this type of medication and the presence of infections. Although these factors had no association with readmission, the use of antivirals and antiparasitic drugs was statistically significant in the bivariate analysis, and this is why the suggestion is made to delve into the role of fungal and viral infections on readmission in further studies.

Polyautoimmunity is one of the several shared characteristics included in the autoimmune tautology [1,2]. The prevalence of polyautoimmunity (34.4%) was similar to that found by Rojas - Villarraga et al. [13] However, in this study, there were no statistically significant differences between polyautoimmunity and readmission. In this group of patients, the female gender was the most prevalent, and the main cause of hospitalization continued to be disease activity. Unlike the findings in all patients with AIDs, AHT was not related to readmission in this patient subgroup.

Patients with AID are known to have a chronic inflammatory state that has an impact on the endothelium and could explain the high and premature cardiovascular morbidity and associated mortality. The risk of cardiovascular events and death in patients with RA and other AIDs has been described as substantially high compared to the general population since it is comparable with that of patients with diabetes mellitus [27]. There is evidence that the pathogenic mechanisms underlying the process of AHT in this group of patients are not only related to endothelial damage, but also other inflammatory processes [28]. In the present study, the history of AHT was found to reflect an association with hospital readmission. Pineda et al. [29] demonstrated that, in hospitalized Colombian patients with RA, a history of AHT significantly increased costs. This probably reflected the impact of the organic damage of RA (with associated AHT) on those costs. In other scenarios, such as patients with SLE [30], there is evidence that AHT is associated with accumulated damage, because SLE patients who had AHT also had a higher damage index, than patients without AHT. Additionally, higher levels of systolic blood pressure have been shown to be predictors of mortality in Brazilian SLE patients [31]. Therefore, it could be said that patients with AIDs who have AHT reflect a greater state of systemic compromise and more accumulated damage that could favor new causes of readmissions.

Although antimalarials have been described as one of the factors associated with a decrease in morbidity in patients with SLE [32,33], they are more frequently used in SLE compared to other AIDs. Therefore, and given that most of the patients who were readmitted had a diagnosis of SLE, the association found in the bivariate analysis could be interpreted as confusion by indication [34] (based on the SLE sub-phenotype). However, when analyzed using the multivariate model, this variable was not associated with readmission.

Although complement C4 was not significant after correlation in the multivariate analysis, it was related to readmission in the bivariate analysis. In their study of patients with SLE, Jüptner et al. [35] suggested that low C4 levels are associated with an earlier onset of SLE and a more severe course of the disease. Considering that this phenotype was the most prevalent in this study, the importance of this marker as an indicator of SLE severity and its possible relationship with greater hospital readmissions in these patients is highlighted.

An increase in hospitalization rates has been found in patients with chronic kidney disease, and the factor most associated with it was high levels of proteinuria [36]. AIDs can affect the kidney directly (antibodies against a renal antigen) or indirectly (with formation of immune complexes or activation of the complement system) [37]. Therefore, a history of kidney disease in patients with AIDs could have an impact on the rate of hospitalizations or readmissions. Additionally, other factors such as infections can also cause readmissions due to sepsis that developed from the acute primary infection [38] and the use of

immunosuppressants increases the risk of developing infections [39]. Thus, due to their clinical relevance, these two variables (adjusted for confounding variables) were included in a third multivariate model and resulted in an association between the use of immunosuppressants and hospital readmission. However, the model that best fit the Akaike information criterion (model 2) and adjusted based on confounding variables did not show an association between any factor and readmission.

Since the study design does not allow causality between the factors associated with readmission to be inferred, the limitations of this study are clear. Despite the adequate design and the multivariate analysis, the results of comparisons may be subject to confounding biases. Since all the patients were drawn from an existing database, there is no guarantee that the sample is representative of the entire hospitalized population with AID, and this may decrease the probability of finding statistically significant differences. This study is at risk of presenting survival bias because patients were evaluated in the hospital setting that, due to their need for hospitalization, already indicated that they had an increased risk of mortality. On the other hand, there was no follow-up to assess readmissions beyond the observed period and, furthermore, many patients were referred to other institutions which made it impossible to know whether they had outcome of interest (readmission) [40].

5. Conclusions

In conclusion, it was found that a third of hospitalized patients with AID were readmitted. Hospitalization and readmission are determining factors in the outcome of patients with AID and are relevant in the context of autoimmune tautology. A history of AHT was the only factor associated with hospital readmission in the first multivariate analysis. This indicated that AIDs and AHT shared pathophysiological mechanisms, and thus caused a significant systemic compromise that could be related to hospital readmission. In the model adjusted for confounding variables, no factor was related to readmission. In a third model that included clinically relevant variables (history of kidney disease and previous use of immunosuppressants), the use of immunosuppressants was associated with readmission. The sociodemographic characteristics of patients who are hospitalized are like those of patients with AIDs in general. The prevalence of polyautoimmunity in this study did not vary with respect to other reports, and the characteristics of patients with polyautoimmunity are not different from either the patients who were readmitted or those that were not. Hospital readmission did not depend on the type of AID and the most prevalent phenotype in both groups (readmission or not) was SLE.

Submission declaration and verification

This study has not been published previously and is not under consideration for publication elsewhere. All authors and responsible authorities approved its publication. If accepted, it will not be published elsewhere in the same form in English or in any other language.

Project financing statement

This project did not receive any type of financial contribution.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2021.100121.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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