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CES MEDICINA

INVESTIGATION ARTICLE

Anemia in Colombian patients with systemic lupus erythematosus

Anemia en pacientes colombianos con Lupus Eritematoso Sistémico

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How to cite: Santamaria-Alza, Y; Sánchez-Bautista, J; Alarcón-Gómez, ZM; Coy-Quiroga A. Anemia in Colombian patients with systemic lupus erythematosus. *Rev CES Med*. 2023;37(2). pp. 25-33. https://dx.doi.org/10.21615/cesder.7224

Abstract

Introduction: systemic Lupus Erythematosus (SLE) is an autoimmune disease with multi-organ involvement. Anemia is common in SLE, presenting up to 50% of patients and is associated with activity of the disease. The objective of the study was to discriminate the different causes of anemia in patients with SLE and the associated variables with its presentation in a cohort of patients in Bucaramanga, Colombia. **Methods:** a cross-sectional study of 114 patients that met the classification criteria of SLE determined by the Systemic Lupus International Collaborating Clinics (SLICC) criteria. Descriptive analysis was performed. Quantitative variables were used: means and standard deviations (SDs) were used for those with normal distribution, and median and interquartile ranges were used for those who did not. Bivariate analysis using logistic regression with OR measurement, *p*-value, and confidence intervals was performed. **Results:** the most frequent cause of anemia was anemia of chronic disease/inflammation (60.53 %), followed by iron deficiency anemia (28.95%), autoimmune hemolytic anemia (24.56%) and megaloblastic anemia (2.53%). An association with a significant difference was found between anemia of chronic disease/inflammation and the presence of pericardial disease (OR 2.11, *p*=0.045). Iron deficiency anemia showed association with increase in the mortality rate (OR 2.66, *p*= 0.04), while the use of cyclophosphamide and azathioprine showed a decrease in the probability of presenting iron deficiency anemia (OR 0.14, *p*=0.045; OR 0.32, *p*= 0.048, respectively). Regarding the subjects with hemolytic anemia, a decrease was found a decrease in the probability of having it in the patients using azathioprine (OR 0.25, *p*=0.042). **Conclusion:** this is the first Colombian study that evaluates anemia in patients with SLE. The most frequent anemia was anemia of chronic disease/inflammation. The prevalence of megaloblastic anemia in patients with SLE was determined for the first time. Likewise, the increase in the probability of mortality in patients with iron deficiency anemia was reported, which should be considered in clinical practice.

Keywords: Anemia; Systemic Lupus Erythematosus; Acquired Autoimmune Hemolytic Anemia; Iron Deficiency Anemia.

Resumen

Introducción: el Lupus Eritematoso Sistémico (LES) es una enfermedad autoinmune con afectación multiorgánica. La anemia es frecuente en el LES, presentándose hasta en un 50% de los pacientes y se asocia a la actividad de la enfermedad. El objetivo del estudio fue discriminar las diferentes causas de anemia en pacientes con LES y las variables asociadas a su presentación en una cohorte de pacientes de Bucaramanga, Colombia. **Métodos:** estudio transversal de 114 pacientes que cumplieron con los criterios de clasificación de LES determinados por los criterios Systemic Lupus International Collaborating Clinics (SLICC). Se realizó un análisis descriptivo. Se utilizaron variables cuantitativas: medias y desviaciones estándar (DE) para aquellos con distribución normal, y medianas y rangos intercuartílicos para aquellos que no la tenían. Se realizó un análisis bivariado mediante regresión logística con medición de Odds Ratios (OR), valor de p e intervalos de confianza. **Resultados:** la causa más frecuente de anemia fue la anemia por enfermedad crónica/inflamación (60,53 %), seguida de la

Date of correspondence:
Received: February 26, 2023.
Revised: February 28, 2023.
Accepted: April 26, 2023.

DOI: 10.21615/cesmedicina.7224
ISSNe: 2215-9177
ISSN: 0120-8705
https://revistas.ces.edu.co/index.php/medicina

anemia ferropénica (28,95 %), la anemia hemolítica autoinmune (24,56 %) y la anemia megaloblástica (2,53 %). Se encontró asociación con diferencia significativa entre la anemia de enfermedad crónica/inflamación y la presencia de enfermedad pericárdica (OR 2,11, p=0,045). La anemia ferropénica mostró asociación con aumento en la tasa de mortalidad (OR 2,66, p= 0,04), mientras que el uso de ciclofosfamida y azatioprina mostró una disminución en la probabilidad de presentar anemia ferropénica (OR 0,14, p=0,045; OR 0,32, p = 0,048, respectivamente). En cuanto a los sujetos con anemia hemolítica, se encontró una disminución en la probabilidad de tenerla en los pacientes que usaban azatioprina (OR 0,25, p=0,042). **Conclusión:** este es el primer estudio colombiano que evalúa la anemia en pacientes con LES. La anemia más frecuente fue la anemia por enfermedad crónica/inflamación. Se determinó por primera vez la prevalencia de anemia megaloblástica en pacientes con LES. Asimismo, se reportó el aumento de la probabilidad de mortalidad en pacientes con anemia ferropénica, lo que debe ser considerado en la práctica clínica.

Palabras clave: Anemia; Lupus Eritematoso Sistémico; Anemia Hemolítica; Anemia Ferropénica.

Introduction

Systemic lupus erythematosus (SLE) is a complex disease with variable presentations, course and prognosis characterized by remissions and flares caused by the production of autoantibodies, complement activation, and immune complex deposition [1].

The prevalence of lupus ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among African-Americans [2]. Several studies have shown that some sociodemographic characteristics such as ethnicity, gender, age, income, education, and access to health care are important variables associated with the outcome of SLE [3]. The prevalence of SLE in Colombia according to a study was 8.77 per 10,000 persons between 2012 and 2016 [4].

Hematological abnormalities are common in SLE, presenting up to 70% of patients, of which anemia can occur in up to 50% of patients and this may be of autoimmune or non-autoimmune cause [5]. The most common form is the anemia of chronic disease/inflammation, followed by iron deficiency anemia in approximately one third of the patients, autoimmune hemolytic anemia in the 10%, and cyclophosphamide-induced myelotoxicity [6].

Anemia of chronic disease/inflammation is mainly developed due to circulating cytokines that lead to changes in iron homeostasis, alteration of erythroid progenitor cells, the production of erythropoietin, and the lifespan of red cells [7]. Chronic renal disease in SLE may cause a decrease in erythropoietin or antibodies against it, which could contribute to the pathogenesis of this anemia [8]. Iron deficiency anemia is common in patients with SLE, the main mechanisms are abundant blood loss in menses and increased gastrointestinal blood loss in patients taking non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and oral anticoagulants [6].

Autoimmune hemolytic anemia (AIHA) is a frequent cause of anemia in patients with SLE, and it involves anti-red blood cell (RBC) antibodies that damage erythrocytes in either a complement-dependent or independent manner [9]. AIHA may be the first manifestation of SLE and could appear several years before SLE diagnosis is made. Patients with this anemia are more likely to have increased anti-dsDNA antibodies [10].

It is important to recognize the presence of anemia in patients with SLE, which is usually associated with the activity of the disease. Approximately 50% of the patients in a flare of the disease present a hematocrit level down to 30% [11], which seems to reflect the pro-inflammatory effect on the function of the bone marrow and the survival of peripheral blood cells [12]. It has recently been reported that hematological manifestations can predict the course of the disease and mortality; as well as, being associated with early death, in-hospital death, and reduced survival [13]. Therefore, the objective of the present study was to characterize anemia in patients with SLE and to determine the variables associated with the presentation of anemia.

Methods

This study was approved by the ethics committees of the Hospital Universitario de Santander and Universidad

Industrial de Santander, in accordance with the current legislation.

Study design

An observational, cross-sectional study with analytic emphasis, which included patients who met the classification criteria of SLE determined by the Systemic Lupus International Collaborating Clinics (SLICC) criteria and who were presented with anemia to the Hospital Universitario de Santander, between 2012 and 2016.

Population

The population included patients presenting the diagnosis of both anemia (defined as hemoglobin levels <12g/dL in females and <13 g/dL in males) [14] and who met the classification criteria of SLE by the SLICC criteria. Exclusion criteria were lack of information for more than 20% of the analyzed variables, pregnancy, patients with solid tumors, in chemotherapy, in radiotherapy and subjects with hematological disorders other than anemia (leukemia, lymphomas, myelodysplastic syndrome, myelofibrosis, medullar aplasia).

Variables

Dependent variables were evaluated by the presence of anemia of chronic disease/inflammation (defined as microcytic or normocytic, associated with normal or elevated ferritin and low serum iron levels and transferrin levels), iron deficiency anemia (microcytic anemia with a decrease in ferritin levels and the percentage of transferrin saturation), autoimmune hemolytic anemia (defined as anemia with an increase in the rate of reticulocyte production, an increase in lactate dehydrogenase, bilirubin and positive direct Coombs test) and megaloblastic anemia (macrocytic anemia with low levels of folic acid or vitamin B12).

The independent variables were: systemic involvement (nephropathy, pericardial compromise, antiphospholipid syndrome, pneumopathy), disease activity (measured using SLEDAI 2K, ECLAM, and MEX-SLEDAI), laboratory tests at the admission (Erythrocyte sedimentation rate [ESR], C-Reactive protein [CRP], complement C3 and C4, anti-dsDNA antibodies and, anti-nuclear antibodies) and data on the course of the disease (in-hospital death, hospital re-admission, and length of hospital stay).

Statistical analysis

Data imputation for missing information was made using the KNN method. Descriptive analysis was performed. Qualitative variables were expressed in relative and absolute frequencies. Quantitative variables were expressed using means and standard deviations (SDs) for those with a normal distribution, and median and interquartile ranges (IQR) for those who did not.

As an exploratory analysis, we performed a univariate logistic regression between each of the dependent and independent variables. Odds ratios (OR), *p*-value, and 95% confidence intervals were calculated.

Results

Between 2012 and 2016, 239 patients were screened with a diagnosis of SLE. After the exclusion of subjects, 114 patients were included in the study; 78.95% were women, the median age was 34 years (IQR 23 and 47 years), and the median time since SLE diagnosis was 40.5 months (IQR 23 and 53 months).

Regarding comorbidities, 60.53% of the patients had nephropathy, 53.51% had skin disease, 53.51% had pneumopathy and 36.84% pericardial disease. 97% of the patients had been treated with steroids, 44.74% with antimalarial drugs, and 13.3% with azathioprine.

In this population, there was a high grade SLE activity index. The median score of ECLAM was 5 (IQR 3 and 6.5), the SLEDAI 2K median score was 14 (IQR 8 and 23) and the SLEDAI MEX median score was 10 (IQR 6 and 14).

Regarding laboratory analysis, the ESR median was 45.5 mm/hour (IQR 23 and 75.5), CRP median was 15 mg/dL (IQR 5.4 and 32.7), C3 complement median of 68 mg/dL (IQR 44 and 95), C4 complement median of 12 mg/dL (IQR 5 and 20), antinuclear antibodies median was 73.6 IU/mL (IQR 35.7 and 126), and anti-dsDNA median was 395.95 IU (IQR 83.3 and 1123).

Hemoglobin mean value was 8.95 g/dL with a SD of 2.23, mean corpuscular volume (MCV) median was 85.4 fl (IQR 80.2 and 89.3), mean corpuscular hemoglobin (MCH) median was 27.55 pg/cell (IQR 26 and 29.3). When performing the characterization of the anemias, a positive Coombs test was found in 24.56% of the patients, median lactate dehydrogenase (LDH) was 262 U/L (RIQ: 198 - 373), median total bilirubin was 0.39 mg/dL (IQR 0.23 - 0.64), median indirect bilirubin was 0.1 mg/dL (IQR 0.07 - 0.33), median ferritin value of 696 ng/mL (IQR 261 - 1200), median transferrin saturation of 17.4% (IQR 9 - 32.35%), folic acid median of 311.4 ng/mL (IQR 131 - 565) and the median of vitamin B12 was 311.4 pg/mL (IQR 131-565). The description of the population is summarized in Table 1.

Table 1. General characteristics in SLE patients with anemia.

Variable	Value
Age (years)	M: 34 (IQR 23 – 47)
Females	n: 90 (78.95%)
Duration of disease (months)	M: 40.5 (IQR 23 – 53)
Nephropathy	n: 69 (60.53%)
Skin compromise	n: 61 (53.51%)
Pericardial compromise	n: 42 (36.84%)
Respiratory compromise	n: 61 (53.51%)
Antiphospholipid syndrome	n: 28 (24.56%)
Steroid use*	n: 111 (97.37%)
Methotrexate use*	n: 17 (14.91%)
Antimalarial use*	n: 51 (44.74%)
Cyclophosphamide use*	n: 15 (13.16%)
Mycophenolic acid use*	n: 15 (13.16%)
Azathioprine use*	n: 22 (19.3%)
ECLAM score	M: 5 (IQR 3 – 6,5)
SLEDAI 2K score	M: 14 (IQR 8 – 23)
MEX-SLEDAI score	M: 10 (IQR 6 – 14)
Positive VDRL	n: 13 (11.5%)
ESR (mm/hour)	M: 45,5 (IQR 23 – 75,5)
CRP (mg/dL)	M: 15 (5.4 – 32.7)
Complement C3 (mg/dL)	M: 68 (IQR 44 – 95)
Complement C4 (mg/dL)	M: 12 (IQR 5 – 20)
Anti-dsDNA antibodies (UI/mL)	M: 395.9 (IQR 83.3 – 1123)
Antinuclear antiboides (UI/mL)	M: 73.62 (IQR 35.7 – 126)
Creatinine (mg/dL)	M: 0.8 (IQR 0.62 – 1.8)
Blood urea nitrogen (mg/dL)	M: 16.32 (IQR 10.2 – 32 .28)
Hematuria	n: 52 (45.61%)
Proteinuria	n: 50 (43.86%)

Leucocyturia	n: 45 (39.47%)
Urinary cast	n: 21 (18.42)
Death	n: 19 (16.67%)
Hospital readmission	n: 29 (25.44%)
Haemoglobin (g/dL)	M: 9.25 (IQR 7.82 – 10.6)
Hematocrit (%)	M: 28.5 (IQR 24.6 – 33.1)
Mean corpuscular volume (fl)	M: 85 (IQR 80.2 – 89.3)
Microcytosis	n: 28 (24.6%)
Normocytosis	n: 76 (66.7%)
Macrocytosis	n: 10 (8.7%)
Hypocromía	n: 65 (57%)
Positive Coombs test	n: 28 (24,56%)
Ferritin (ng/mL)	M: 696.4 (IQR 261 – 1200)
Transferrin (mg/dL)	M: 159.7 (IQR 118.9 – 187.8)
Serum iron (ug/mL)	M: 37.9 (IQR 20.7 – 76.7)
Transferrin saturation (%)	M: 17.4 (IQR 9.05 – 32.35)
Folic acid (ng/mL)	M: 8.74 (IQR 8.17 – 15.1)
Vitamin B12 (pg/mL)	M: 311.4 (IQR 131.8 – 565.8)

* Used in the last three months.
M: Median.
IQR: interquartile range.

It was found that the leading cause of anemia in SLE patients was anemia of chronic disease/inflammation (60.53%), followed by iron deficiency anemia (28.95%), hemolytic anemia (24.56%), and megaloblastic anemia (2.53%). In the 17.54% of the patients the cause was unknown. In Figure 1, the cause of anemia in patients with SLE is summarized.

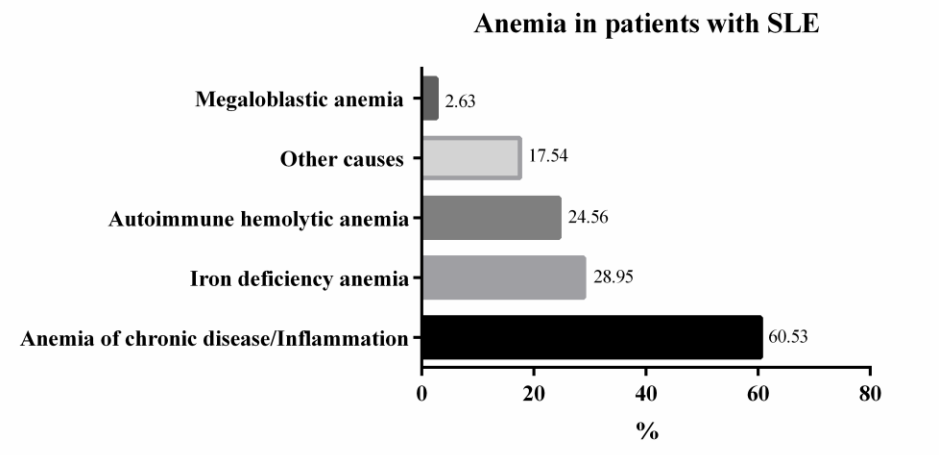

Figure 1. Types of anemia in SLE patients.

The in-hospital death rate among this population was 16.67% and the 25.44% were readmitted for any cause. The mean length of hospital stay was 19.35 days with SD of 22.7.

With the bivariate analysis, significance difference between anemia of chronic disease/inflammation and the presence of pericardial disease (OR 2.11, *p*=0.045) and leucocyturia (OR 2.12, p=0.041) was found. Iron deficiency

anemia showed an association with an ESR value higher than 20 mm/hour (OR 3.01, *p*= 0,046) and an increase in the mortality rate (OR 2.66, *p*= 0.04), while the use of cyclophosphamide and azathioprine showed a decrease in the probability of presenting iron deficiency anemia (OR 0.14, *p*=0.045; OR 0.32, *p*= 0.048, respectively). Regarding the subjects with hemolytic anemia, a decrease was found in the probability of having it in the patients using azathioprine (OR 0.25, *p*=0.042), with CRP lower than 10 mg/dL (OR 0.27, *p*= 0.007), with anti-dsDNA lower than 300 IU/mL (OR 0.28, *p*=0.009), and with creatinine higher than 2mg/dL (OR 0.32, p= 0.041). It was also shown that patients older than 50 years old have higher risk of developing megaloblastic anemia (OR 8.09, *p*=0.038). The results of the bivariate analysis are shown in Table 2.

Table 2. Associated factors to anemia in patients with SLE.

Variable	OR	CI 95%	*p* value
Anemia of chronic disease/inflammation			
Pericardial compromise	2.11	1.35 – 4.77	0.045
Leucocyturia	2.12	1.48 – 4.73	0.041
Iron deficiency anemia			
ESR > 20 mm/hour	3.01	1.22 10.99	0.046
Cyclophosphamide use	0.14	0.01 – 0.87	0.045
Azathioprine use	0.32	0.08 – 0.88	0.048
Death	2.66	1.28 – 7.32	0.04
Hemolytic anemia			
Azathioprine use	0.25	0.05 – 0.76	0.042
CRP < 10 mg/dL	0.27	0.11 – 0.70	0.007
Anti-dsDNA antibodies < 200 UI/mL	0.28	0.10 – 0.73	0.009
Creatinine > 2 mg/dL	0.32	0.09 – 0.93	0.041
Megaloblastic anemia			
Age > 50 years	8.09	1.46 – 93.72	0.038

Discussion

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown causes that can affect the skin, joints, kidneys, lungs, nervous system, serous membranes, as well as other organs, the hematological system is particularly affected with different manifestations [15]. Hematological manifestations can occur with different frequencies according to factors such as gender, age, immune abnormalities, genetic, hormonal and environmental factors [16,17]. Regardless of their age and gender, Hispanic, African-Americans, and Asian patients with SLE usually have more hematological, serosal, neurological, and renal manifestations compared with other populations [18]. Colombia is country with a Hispanic population where the distribution and characteristics of anemia in patients with SLE have not been described before.

Previous studies have reported prevalence of anemia in patients with SLE similar to each other, with values higher than 50% [2, 6, 19]. We found an average value of hemoglobin of 9.25 g/dL, which is lower compared to the study conducted in India by PK Sasidharan et al with an average value of 9.5 g/dL or in the study conducted in Greece by M. Voulgarelis et al with an average value of 10.1 g/dl [20-21].

After doing the etiological classification of anemia, we found that the main cause of anemia in patients with SLE is the anemia of chronic disease/inflammation representing 60.53% of all causes of anemia. These results are comparable with other cohorts, where the prevalence of this entity has varied between 60 and 80% [8]. Iron

deficiency anemia was found to be 28.95%, a value slightly lower than the one reported in a study carried out in Athens [21], where it was present in 35.6% of the subjects with SLE. This may be due to the fact that iron deficiency anemia can appear due to different conditions, which includes diet and presence of blood loss, which was not measured in either of the two studies [21]. The third cause of anemia in our population was autoimmune hemolytic anemia, which was present in 24.56% of the subjects, a finding that is similar to the one found in a study conducted in India by Sasidharan et al where the prevalence was 27.9% [20]. However, when comparing our results with those presented by Voulgarelis et al, in our population, there was a higher prevalence of autoimmune hemolytic anemia, since in their study the prevalence was 14.4%. These findings can be explained because our population showed higher disease activity, which is related to higher occurrence of autoimmune processes [21].

Megaloblastic anemia is a rare etiology of anemia in patients with SLE and we found a frequency of 2.3% in our population. In the literature review that was made, we could not find the real prevalence of this anemia since it is usually reported under the category of other causes of anemia.

One of the strengths of this study is the fact we measured the protective and risk factors for the appearance of different types of anemia. For the anemia of chronic disease/inflammation, it was identified as risks factors of its appearance the presence of pericardial compromise and leukocyturia. Studies, such as the one carried out by Aleem et al, showed the association of serositis (pericarditis and pleural effusion) as a risk factor for the presentation of anemia of chronic disease/ inflammation [22], which is similar to our population. There have been studies that reported serositis as a risk factor for autoimmune hemolytic anemia [23], findings which differ from our results. Renal alterations have been showed to be markers of anemia of chronic disease/inflammation [24], in our study the association with leukocyturia was determined.

Regarding iron deficiency anemia in Colombian patients with SLE, the use of azathioprine and cyclophosphamide was found to decrease the likelihood of its appearance. This could be explained given that these medications have been associated with the presence of anemia secondary to bone marrow involvement [6], which does not necessarily mean that the use of these medications reduces the risk of iron deficiency anemia but is caused by a different mechanism than the iron deficiency. In the reviewed literature, no similar data were found. Interestingly, iron deficiency anemia is associated with an increase in ESR values, as well as an increase in mortality risk, which is consistent with the results of a study conducted in Mexico by Hernández et al, which showed an increase in mortality in patients with hematologic alterations [12]. In our study, iron deficiency anemia was the only type associated with an increase in the probability of death in patients with SLE, which is very important, given that iron deficiency anemia can be caused by nutritional deficiency issues, an easily modified variable that could have a positive impact on the prognosis of the disease in patients with SLE.

In relation to autoimmune hemolytic anemia, high creatinine values have showed a decrease in the likelihood of presenting it, this can be explained given that the alteration in the parameters of renal function were associated with anemia of chronic disease/inflammation, which does not necessarily mean less risk of presenting autoimmune hemolytic anemia but patients with renal impairment have different mechanism to developed anemia. Likewise, the use of azathioprine was associated with a lower probability of developing this type of anemia, which could be explain due to the immunomodulatory effect of the drug, which decreases the immunological impairment of the disease [6]. Low values of CRP were associated with a lower risk of presenting autoimmune hemolytic anemia, which is consistent with the biological plausibility of the disease, in which at lower inflammation, lower activity status of the disease and therefore less likelihood of autoimmune events. Finally, there was less risk of having this type of anemia in patients with low titers of anti-dsDNA antibodies, which is consistent with the results found by Jeffries et al [10].

With regard to megaloblastic anemia, the prevalence of this disease associated with SLE has not been reported yet in the medical literature, probably due to its low presentation, as found in the present study. It is noteworthy that megaloblastic anemia was also related to the presence of advanced age; similar data can be found in the

general population [25]. Table 3 shows comparative data between several similar studies and the present study.

Table 3. Comparison of the characteristics of anemia in patients with SLE.

Characteristic	Study					
	Voulgarelis et al.	**Beyan et al.**	**Shaikh et al.**	**Sasidharan et al.**	**Mittal et al.**	**Santamaria-Alza et al.**
Year	2000	2007	2010	2012	2013	2023
Country	Greece	Turkey	Pakistan	India	India	Colombia
Hemoglobin	10.1 g/dL	-	-	9.5 g/dL	9.8 g/dL	9.25 g/dL
Anemia of chronic disease/inflammation	37.1%	46%	40%	-	68%	60.5%
Iron deficiency anemia	35.6%	-	30%	-	32%	29%
Autoimmune hemolytic anemia	14.4%	-	16.6 %	27.9%	4.7%	24.6%
Other causes	12.9%	-	-	-	-	17%

Despite the great variety of factors affecting the presentation of the disease, we found consistent results with those already described. One of the main advantages of this study is to know the regional statistics to improve the tools to predict prognosis and give a more appropriate management from early stages of SLE. Likewise, the identification of risk factors of the different types of anemia will favor the prevention and early recognition of them. In the same way, hypotheses can be generated for carrying out future studies in which the local consistency of the results and their extrapolation can be determined.

The limitations of this study are its retrospective nature which can present selection, information, and classification bias; however, these were mitigated by the meticulous collection of the information and the trained personnel. It is also important to mention that being a cohort of a tertiary hospital, the patients treated could have more SLE activity than patients in general who suffer from the disease, so extrapolation to outpatients should be done with caution.

In conclusion, anemia is a frequent problem in patients with SLE. The most prevalent cause in Colombian population with SLE is anemia of chronic disease/inflammation, followed by iron deficiency anemia and hemolytic anemia. For the first time in the country, the prevalence of megaloblastic anemia in patients with SLE was determined, which should be considered as clinically important, especially in patients older than 50 years. Iron deficiency anemia was the only type of anemia associated with an increase of in-hospital mortality, which should be contemplated in clinical practice to have positive outcomes in patients with SLE.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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