ORIGINAL PAPER

Clinical characteristics and outcomes of patients with inflammatory and autoimmune rheumatological diseases admitted for intensive care in Colombia

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SUMMARY

Objective. Contemporary studies reporting outcomes of critical care in patients with inflammatory and autoimmune rheumatological diseases are scarce. This study describes 15 years of experience from 2005-2019 in a Colombian referral hospital.

Methods. This observational, descriptive, consecutive case series study was performed on adult patients with inflammatory and autoimmune rheumatic diseases who were admitted to the intensive care unit (ICU) of the San Ignacio University Hospital in Bogotá (Colombia), from January 1, 2005, to December 21, 2019. We describe the sociodemographic characteristics, admission causes and criteria, lengths of stay, immunosuppressive treatment, systemic support, and mortality.

Results. The study included 300 patients with a median age of 48 years [interquartile range (IQR) 31-62 years], predominantly female (76%). Disease exacerbations (30%), infections (17.6%), and cardiovascular diseases (15%) were the main causes of admission. Respiratory failure (23%) most commonly caused by septic shock (24%) was the principal indication for intensive care admission. The most frequent infections were community-acquired pneumonia (11.6%) and soft-tissue infections (9%). In 40.3% of patients, inotropic and vasopressor support was required. The median length of stay was 4 days (IQR 2-8), and global mortality was 21.6%.

Conclusions. Rheumatic diseases in the ICU are still associated with high morbidity and mortality. Patients with inflammatory and autoimmune rheumatic diseases require a meticulous clinical approach, strict clinical monitoring, frequent assessment of complications, evaluation of systemic support needs, and specific management.

Key words: *Intensive care unit, rheumatic disease, hospital mortality, hospital stay, infections.*

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INTRODUCTION

Inflammatory and autoimmune rheumatological diseases affect as much as 3% of the general population (1, 2). During the natural course of these diseases, 25% of patients will visit the emergency room, and one third of them will require intensive care unit (ICU) management (3). In the ICU, these patients will have a higher risk of mortality, organic dysfunction, and infectious complications compared to other population groups (4). Descriptive studies in Europe report rheumatic disease exacerbation, followed by infectious complications, as the principal cause of hospitalization (5). The length of hospital stay is highly variable: less than a week on average, with less than three days from emergency room admission to ICU transfer (6). Mortality reported in the ICU for rheumatic-disease patients is as high as 50% (7). Mortality is associated with various etiologies, generally attributed to cardiovascular events, malignancies, and infections (8).

Studies previously published in Latin America (9, 10) are outdated and describe small samples of ICU patients with specific autoimmune diseases. They do not accurately depict the current circumstances of such patients. The goal of the present study is to describe a consecutive case series of patients with inflammatory and autoimmune rheumatological diseases admitted during the past 15 years to the intensive care unit of a referral hospital in Colombia. This study re-

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ports ICU admission causes, length of stay, immunomodulatory treatments, systemic support, and global mortality (along with specific mortality for each rheumatic disease).

MATERIALS AND METHODS

This is an observational descriptive study of a consecutive series of patients with inflammatory and autoimmune rheumatological diseases who were admitted to the ICU of the San Ignacio University Hospital in Bogotá (Colombia). The study included patients over 18 years old with an inflammatory or autoimmune rheumatologic disease diagnosed by a rheumatologist before or during the hospitalization when they were admitted to the ICU, from January 1, 2005, to December 31, 2019. The study excluded patients with ICU stays of less than 24 hours, those without rheumatology assessment, and those who required referral to another institution. The study was endorsed by the Ethics and Research Committee of Pontifical Javeriana University and San Ignacio University Hospital (Act No. 2019/166).

The authors identified patients in a consultation database of the Department of Rheumatology, which includes records of all patients admitted to the ICU with a previous diagnosis of inflammatory and autoimmune rheumatologic disease. An institutional policy guarantees this consultation for all patients in this group. For patients with more than one ICU admission, only the last one was considered. From the clinical histories, the authors collected information on the patient's age, sex, body weight, height, body mass index (BMI), and any immunosuppressive treatment before admission. The cause and indication for critical care were taken from the report of the physician performing the first ICU clinical assessment. The date of discharge was collected to calculate the length of the hospital stay. The authors also collected data on required respiratory and kidney support, days of vasoactive support, infections, antibiotic use, and immunosuppressive therapy. In the case of death, the date was registered.

The statistical analysis of continuous variables used central tendency measurements and averages according to data distribution. Qualitative variables are presented as frequency measurements and percentages. The global mortality rate and mortality for the most frequent rheumatic diseases in this population were calculated. All data were analyzed with the statistical software Stata version 14 (StataCorp LLC, College Station, TX, USA).

RESULTS

The study included 300 patients with inflammatory and autoimmune rheumatologi-

Table I - Diagnosis of inflammatory and autoimmune rheumatological disease of patients admitted to intensive care unit.

Rheumatic disease	n=300	%
Systemic lupus erythematosus	118	39.3
Rheumatoid arthritis	49	16.3
Dermatomyositis	21	7
Diffuse systemic sclerosis	15	5
Sjögren's syndrome	14	4.6
Limited systemic sclerosis	13	4.3
Antiphospholipid syndrome	11	3.6
Small-vessel vasculitis	7	2.3
Microscopic polyangiitis	7	2.3
Mixed connective tissue disease	5	1.6
Immune thrombocytopenic purpura	5	1.6
Granulomatosis with polyangiitis	5	1.6
Polymyositis	4	1.3
Pulmonary-renal syndrome	4	1.3
Reactive arthritis	4	1.3
Anti-synthetase syndrome	3	1
Psoriatic arthritis	3	1
Still's disease	2	0.6
Bechet's disease	2	0.6
Gout	2	0.6
Takayasu's arteritis	1	0.3
Spondylarthritis	1	0.3
Autoimmune hemolytic anemia	1	0.3
Cryoglobulinemia	1	0.3
Polyarteritis nodosa	1	0.3
Polymyalgia rheumatica	1	0.3

cal diseases. The most frequent were systemic lupus erythematosus (SLE) (39.3%), rheumatoid arthritis (RA) (16.7%), and dermatomyositis (7%). Table I presents the rheumatic disease diagnoses included in the study. The study population was 76% female with a median age of 48 years [interquartile range (IQR) 31-62 years], with a lower median age for patients with SLE and a more advanced age for RA and dermatomyositis. The median BMI for the study population was in the normal weight range (22.6, IQR 20-25.7) and was similar for each disease. The ambulatory treatment before ICU admission included glucocorticoids (GC) in 53% of patients, most frequently prednisolone and deflazacort. The majority of patients receiving GC (89.3%) had SLE. In 60.3% of patients, the treatment included concomitant anti-rheumatic drugs, among them azathioprine (18.2%), methotrexate (17.1%), and hydroxychloroquine (14.4%). Table II reports the sociodemographic characteristics of the study population.

The cause of ICU admission was different for each disease. A general approach to the causes of intensive care requirements in patients with inflammatory and autoimmune rheumatological disease is presented in Table III. 42.7% of patients with SLE were admitted to the ICU due to increased disease

Table II - Sociodemographic characteristics of the study population by disease.

Variables	Total n=300 (%)	SLE n=116 (%)	RA n=50 (%)	DM n=21 (%)
Sex				
Males, n (%)	72 (24)	21 (18.1)	13 (26)	8 (38.1)
Females, n (%)	228 (76)	95 (81.9)	37 (74)	13 (61.9)
Age, years, median (IQR)	48 (31-62)	34 (26-49)	63 (54-71)	49 (39-70)
BMI (kg/m^2), median (IQR)	22.6 (20-25.7)	22.2 (20.1-24.9)	23.3 (20.8-27.3)	21.9 (19.5-27.7)
Malnutrition (<18)	32 (11)	10 (8.4)	6 (12)	3 (14.3)
Normal weight (18-24.9)	180 (60)	78 (67.7)	29 (58)	11 (52.4)
Overweight (25-29.9)	65 (21)	8 (6.7)	9 (18)	4 (19)
Obesity (≥30)	23 (8)	20 (16.9)	6 (12)	3 (14.3)
Baseline treatment				
Glucocorticoid, n (%)	159 (53)			
Prednisolone	14 (89.3)	69 (59.5)	27 (54)	10 (47.6)
Deflazacort	13 (8.2)	5 (4.3)	3 (6)	0 (0)
Metilprednisolone	2 (1.2)	0 (0)	1 (2)	0 (0)
Others	2 (1.2)	0 (0)	0 (0)	0 (0)
Immunosuppressive, n (%)	181 (60.3)			
Azatihoprine	33 (18.2)	18 (15.5)	0 (0)	3 (14.3)
Methotrexate	31 (17.1)	1 (0.9)	10 (20)	1 (4.8)
Hydroxychloroquine	26 (14.4)	15 (12.9)	0 (0)	0 (0)
Others	90 (49.7)	19 (16.4)	15 (30)	2 (9.5)
Origin, n(%)				
Bogotá D.C.	237 (79)	85 (73.3)	42 (84)	13 (61.9)
Cundinamarca	27 (9)	14 (11.9)	4 (8.16)	3 (14.3)
Boyacá	11 (4)	2 (1.7)	1 (2.04)	3 (14.3)
Other departments	25 (8.3)	15 (12.7)	3 (6.12)	2 (9.5)

BMI, body mass index; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; DM, dermatomyositis; IQR, interquartile range.

activity, and 16.3% were classified as having severe disease. 15% of these patients were admitted for septic shock. 7% were admitted for coronary syndrome, and one had myocarditis secondary to organ involvement. 6% had alveolar hemorrhage, 6.8% had serositis with pleural and pericardial effusion, and 6% had hypertensive crises related to chronic kidney disease due to lupus nephropathy. 5.2% had convulsive status, and 4.3% were diagnosed with neurolupus.

Among patients with RA, 38% had cardiovascular complications such as myocardial infarction and cardiogenic shock, 34% had infectious diseases, and less than 1% were admitted to the intensive care unit as a result of elevated disease activity. 50% of patients with dermatomyositis were admitted for increased disease activity, with respiratory failure being the most common associated complication, 38% for septic shock, and 14% for cardiovascular disease, most commonly myocardial infarction and cerebrovascular disease. Among patients with systemic sclerosis, 28.8% presented with cardiovascular complications, and the same percentage were admitted to the ICU for septic shock and 32.1% for respiratory failure associated with pulmonary involvement and pulmonary hypertension.

Respiratory failure, secondary to pulmonary thromboembolism, was the leading cause of admission in patients with antiphospholipid syndrome (54%).

In general, 41.6% of patients had infectious diseases, with community-acquired pneumonia (11.6%) and skin/soft tissue infections (9%) being the most common etiologies. Table IV summarizes information about infections.

The median ICU stay was 4 days (IQR 2-8), with similar values (4-5 days) for each inflammatory and autoimmune rheumatological disease. The most frequent indications of ICU management were respiratory failure (23%), and the need for vasopressor support for septic (26.6%) and hypovolemic shock (6%). Systemic support most commonly used was vasopressor (40.3 %), respiratory (39.6%), and renal replacement therapy (17.3%) (Figure 1). The median number of days with vasopressor and respiratory support was very similar for different rheumatic diseases, while the need for renal replacement therapy was higher for diseases such as limited systemic sclerosis and Sjögren's syndrome.

Table III - Causes of intensive requirement in patients with inflammatory and autoimmune rheumatological disease.

Indication, n (%)	SLE n=116	RA n=50	DM n=21	DSS n=15	LSS n=13	SJS n=14	APS n=11
Increased disease activity	50 (42.7)	1 (2)	10 (50)	6 (40)	3 (23)	3 (21)	11 (100)
Infection/septic shock	18(15)	17 (34)	8 (38)	4 (26)	3 (26)	3 (21)	0
Cardiovascular disease	8 (7)	19 (38)	3 (14)	4 (26)	3 (26)	0	0

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; DM, dermatomyositis; DSS, diffuse systemic sclerosis; SjS, Sjögren's syndrome; LSS, limited systemic sclerosis; APS, antiphospholipid syndrome.

Table IV - Infections in patients with inflammatory and autoimmune rheumatological disease admitted to intensive care unit.

Infections, n (%)	Total n=300	SLE n=116	RA n=50	DM n=21	DSS n=15	SjS n=14	LSS n=13	APS n=11
Total	125 (41.6)							
CAN	35 (11.6)	16 (13.5)	3 (6.1)	1 (4.7)	1 (6.6)	0 (0)	2 (15.3)	0 (0)
Skin and soft tissue	27 (9)	11 (9.3)	3 (6.1)	4 (19.4)	1 (6.6)	1(7.1)	0 (0)	0 (0)
Nosocomial Pneumonia	22 (7.3)	8 (6.7)	3 (6.1)	2 (9.5)	1 (6.6)	3 (21.4)	0 (0)	0 (0)
Nosocomial UTI	21 (7)	2 (1.6)	3 (6.1)	2 (9.5)	2 (13.3)	0 (0)	0 (0)	0 (0)
UTI	9 (3)	2 (1.6)	2 (6.1)	1 (4.7)	1 (6.6)	1 (7.1)	0 (0)	1 (9)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; DM, dermatomyositis; DSS, diffuse systemic sclerosis; SjS, Sjögren's syndrome; LSS, limited systemic sclerosis; APS, antiphospholipid syndrome; CAN, community-acquired pneumonia; UTI, urinary tract infection.

Sixty-five patients (21.6%) died in the hospital. Specific mortality per disease was 23.7% for systemic lupus erythematosus and 22.4% for RA. For less common rheumatic conditions such as anti-synthetase syndrome, pulmonary-renal syndrome, and cryoglobulinemia, mortality was 100%. For systemic vasculitides, it was 42.85%. Septic shock was the principal cause of death in 52% of cases, followed by multi-organ failure in 10.7%, and alveolar hemorrhage in 9.2% (Figure 1).

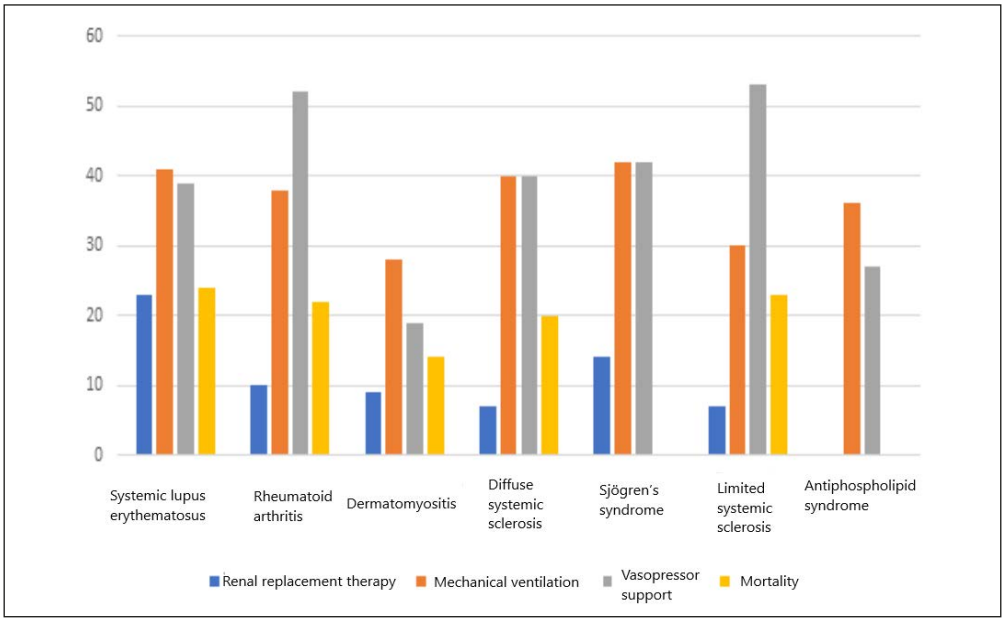

Figure 1 - Mortality and support need for rheumatic patients in intensive care (percentages).

Table V - Immunomodulatory treatments used.

Variables	Total n=300	SLE n=116	RA n=50	DM n=21	DSS n=15	SjS n=14	LSS n=13	APS n=11
Immunomodulator								
Glucocorticoids, n (%)	241 (80.6)	107 (90.6)	37 (73.4)	21 (100)	7 (46.6)	8 (57.1)	6 (46.1)	5 (45.4)
Prednisolone	130 (53.9)	58 (54.2)	26 (70.3)	7 (33.3)	4 (57.1)	2 (25)	3 (50)	2 (40)
Methylprednisolone	82 (34)	44 (41.1)	3 (8.1)	13 (61.9)	1 (14.3)	4 (50)	0 (0)	1 (20)
Hydrocortisone	19 (7.9)	4 (3.7)	5 (13.5)	1 (4.8)	2 (28.6)	2 (25)	2 (33.3)	1 (20)
Dexamethasone	10 (4.1)	1 (0.9)	3 (8.1)	0(0)	1 (14.3)	0 (0)	1 (16.7)	1 (20)
Antirheumatics, n (%)	138 (46)	86 (72.8)	10 (20.4)	11 (52.3)	2 (13.3)	3 (21.4)	4 (30.7)	1 (9.09)
Azathioprine	51 (36.9)	31 (36)	3 (30)	6 (54.5)	1 (50)	3 (100)	1 (25)	0 (0)
Hydroxychloroquine	22 (15.9)	20 (23.2)	1 (10)	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)
Cyclophosphamide	20 (14.5)	11 (12.8)	0 (0)	1 (9.1)	0 (0)	0 (0)	1 (25)	0 (0)
Chloroquine	19 (13.8)	16 (18.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Methotrexate	14 (10.1)	0 (0)	5 (50)	3 (27.3)	1 (50)	0 (0)	2 (50)	0 (0)
Others	12 (8.7)	8 (9.3)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Therapeutic plasma exchange, n (%)	18 (6)	10 (8.6)	0 (0)	0 (0)	1 (6.7)	0 (0)	0 (0)	0 (0)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; DM, dermatomyositis; DSS, diffuse systemic sclerosis; SjS, Sjögren's syndrome; LSS, limited systemic sclerosis; APS, antiphospholipid syndrome.

GC (80.6%) were the most common type of medication used. More than 90% of patients with lupus and dermatomyositis received GC. Immunosuppressive drugs were administered to 46% of patients, with azathioprine (36.9%), hydroxychloroquine (15.9%), and cyclophosphamide (14.5%) being the most commonly used drugs, primarily in patients with SLE. Table V shows the immunomodulatory therapies used in the ICU for patients with rheumatic diseases.

DISCUSSION

This study describes the characteristics of patients with inflammatory and autoimmune rheumatological diseases who were admitted to an ICU in a referral hospital in Colombia. The study found that in a population mainly composed of adult women with SLE, the main causes of admission were elevated disease activity (28%), infection (17.6%), and cardiovascular diseases (12.3%). The main indication for management in intensive care was respiratory failure, mostly associated with septic shock. The average stay in intensive care was one week. During that time, they required a variety of systemic supports and immunosuppressive therapies, and mortality rates included almost one of every five patients.

This study describes a population with a median age of 48 years, similar to that (46 years) reported in the study by Cavallascas et al. and to local studies like one by Camargo et al. that reported a median age of 43.38±21.44 years (10, 11). However, the present study population's median age was lower than the average age of the patients in their 60s described by Brünnler et al. (12). The explanation for this median age difference may be the higher proportion of younger people in Colombia compared to European countries (13), where other studies took place. The majority of patients in this study were from the central area of Colombia, and they most likely had easy geographic access to the hospital of the study. However, one-fifth of patients were from other areas, a fact that makes extrapolation of findings for the Andean region feasible.

Just as other studies report, women are more affected than men, which relates to a higher prevalence of autoimmune diseases in females (10-12). The BMI was normal in the majority of patients, similar to the findings by Heijnen et al. (4). Surprisingly, 32% of patients had malnutrition, and 29% were overweight or had some degree of obesity, with no comparative data in the critical care setting. However, malnutrition reported in the present study occurred less frequently than that reported in an ambulatory cohort of patients with rheumatic diseases in Poland, at 53% (13). This is probably due to differences in chronic inflammatory processes, diet, physical activity, and comorbidities affecting the muscle-skeletal system and intestine permeability. This difference could also be due to the secondary effects of drugs such as GC (14).

The most frequently seen rheumatic disease in intensive care was SLE, followed by RA and dermatomyositis, similar to reports in case series from Buenos Aires (10), Medellín (11), and Jerusalem (15), and relatively consistent with classic studies such as the ones by Moreels et al. (6) and Pourrat et al. (7). Those studies describe the most frequent disease as RA, followed by SLE and vasculitides.

Glucocorticoid use was 53% lower in the present study than in studies by Cavallasca et al. (11) and Brünnler et al. (12). Those studies reported frequencies of 68% and 70%, respectively (11, 12), with a slightly higher proportion of the use of disease-modifying anti-rheumatic drugs (DMARDs) than in other studies (12). This may reflect the better availability and use of DMARDs in the Cavallasca et al. (11) and Brünnler et al. (12) study locations, as well as the lower prescription of GC in Colombia by the clinical specialties in charge of rheumatic patient management.

The present study population had multiple indications for ICU admission. They were, in order of frequency: respiratory failure, septic shock, and cardiovascular disease. This is similar to the findings by Ranzani et al., where respiratory failure was the principal cause of ICU admission, followed by renal, cardiovascular, and neurological involvement (16). It is also comparable to the

report of Antón et al., in which respiratory failure is the leading cause of ICU admission, followed by infection and exacerbation of the autoimmune disease (17). Septic shock is a condition that affects the need for hemodynamic support, which is consistent with the elevated use of vasoactive agents in more than one third of patients (similar to reports in other studies) (16). The percentage of patients admitted due to exacerbations and complications of their autoimmune disease was 30%, which is less than other series have reported (8). Cardiovascular complications accounted for 15% of admissions to the ICU, above other descriptions from similar groups (18).

For respiratory involvement, infectious conditions and alveolar hemorrhage are most frequent at ICU admission (16, 19, 20). In this study, almost half of the patients required mechanical ventilation, which might be due to the prevalence of lung infection and respiratory system involvement in rheumatic disease exacerbations, a finding also consistent with local studies (21).

The frequency of infectious complications was lower than that reported in other series (4, 8). This may relate to the active search for opportunistic infections and the administration of prophylaxis for infections, which are currently standard practices worldwide for patients requiring prolonged immunosuppression and biologic therapy (22). Among infections, respiratory and urinary ones were most commonly reported, which is similar to the findings of other studies (9, 16, 23, 24). Skin and soft tissue infections and infections without apparent focus were also frequently found. Despite a lower frequency of infectious complications in this study, their relevance is not negligible, and they actually represented the main cause of death (septic shock in 50% of cases). This signals an urgent need for early detection and management of infectious complications (20).

This study showed that during the ICU stay, the immunomodulatory therapy was adjusted. Comparison with baseline immunosuppressive therapy evidenced an increase in glucocorticoid use and a reduction in nonsteroid drug use. Studies such as the one by Antón et al. report that the increased glucocorticoid therapy during an ICU stay relates to lower long-term survival, starting from the ICU admission (hazard ratio 22.84, 95% confidence interval 4.33-121.32). Surprisingly, admissions due to rheumatic disease exacerbations were infrequent and did not justify an increased use of GC from 50% at admission to 80% during the ICU stay. This may be because infectious processes and exacerbations of rheumatic disease share clinical characteristics, and clinicians need diagnostic tests to support definitive therapeutic decisions. Empiric use of antibiotics and GC is frequent, even more so when the use of GC, specifically hydrocortisone, impacts the survival of patients with refractory septic shock (25).

In this study, therapeutic plasma exchange was practiced in 6% of the patients, mainly in those with a diagnosis of SLE with alveolar hemorrhage (a percentage similar to the findings of other studies) (16). This present finding, however, is in contrast with the study by Córdoba et al., which reported the main indication of therapeutic plasma exchange as anti-neutrophil cytoplasmic antibody-associated vasculitides with rapidly progressive glomerulonephritis and/or alveolar hemorrhage. The next most common indications in the study by Córdoba et al. were SLE with refractory alveolar hemorrhage, and catastrophic antiphospholipid syndrome (26).

In the study, mortality was 21.6%. This finding is lower than the reported mortality rates of 58% by Heijnen et al. (4) and 53.6% by Thong et al. (23). However, the rate in this study more closely matches recent studies by Bernal et al. and by Camargo et al., with mortality rates of 24% and 16.7%, respectively (9, 10). These findings may relate to the availability of interventions, clinical subspecialties, and resources in the high-complexity center and referral hospital where the patients were treated. A comparison among autoimmune diseases revealed a 38% mortality rate in patients with SLE, which is higher than the 20% mortality rate reported by Ranzani et al. (16).

A great strength of this study is the population size, with the largest reported popula-

tion sample among similar studies in Colombia and Latin America. This represents 15 years of healthcare in a university hospital for patients with rheumatic diseases. Among the weaknesses of this study, the retrospective design might compromise the total availability of information. However, the outcomes are strong, and no major limitations in information collection were found. Conversely, the diversity of included rheumatic diseases may influence the interpretation of the results because when evaluating the less prevalent diseases, the number of patients is reduced. Prospective studies are required to evaluate disease characteristics and specific mortalities.

CONCLUSIONS

Rheumatic diseases in the ICU are associated with high morbidity and mortality. Even though the mortality rate has decreased due to advances in the diagnosis and treatment of complications in rheumatic patients, the mortality rate is still high compared to other diseases requiring intensive care. For this reason, the special population of patients with rheumatic diseases requires a meticulous clinical approach, strict clinical monitoring, frequent assessment of complications, evaluation of systemic support needs, and specific management.

Contributions
All authors contributed equally.

Conflict of interest
The authors declare no potential conflict of interest.

Ethics approval and consent to participate
This study was endorsed by the Ethics and Research Committee of Pontifical Javeriana University and San Ignacio University Hospital (Act No. 2019/166).

Informed consent
Considering the observational nature of the study informed consent was not necessary as approved by Institutional Ethics Committee.

Availability of data and materials
Data and materials are available from the corresponding author upon request.

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