ORIGINAL ARTICLE

Characteristics associated with Covid-19 in patients with Rheumatic Disease in Latin America

Characteristics associated with Covid-19 in patients with Rheumatic Disease in Latin America

Características associadas ao Covid-19 em pacientes com doença reumática na América Latina

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Characteristics associated with Covid-19 in patients with Rheumatic Disease in Latin America: data from the Covid-19 Global Rheumatology Alliance physician-reported registry

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Resumen
en Español

Objectivo
Comparar las características de los pacientes con enfermedades reumáticas y COVID-19 reportados en América Latina con aquellos del resto del mundo.

Método
Los pacientes del COVID-19 Global Rheumatology Alliance Physician-Reported Registry fueron incluidos. Se examinaron las características demográficas, características de las enfermedades reumáticas, comorbilidades, diagnóstico de COVID-19 y tratamiento, así como desenlaces. Se usaron pruebas de Chi cuadrado y t de Student fueron usados para comparar los grupos (América Latina vs el resto del mundo). Se usaron regresiones logísticas multivariables fueron usadas para estimar los Odds Ratio (ORs) y los intervalos de confianza (IC) al 95% para hospitalización (sí/no) y soporte ventilatorio (no hospitalizado u oxígeno suplementario solamente vs ventilación no invasiva, invasiva o ECMO); y modelos de Poisson para estimar los ORs y IC95% de mortalidad.

Resultados
Se incluyeron setenta y cuatro pacientes de América Latina y 583 del resto del mundo fueron incluidos. Las enfermedades reumáticas más frecuentes en ambos grupos fueron artritis reumatoide (35% vs 39%, respectivamente) y lupus eritematoso sistémico (22% vs 14%, respectivamente). La mortalidad fue similar en ambos grupos (12% en América Latina vs 11% del resto del mundo, p=0.88). No obstante, los pacientes de América Latina del registro tuvieron mayor probabilidad de necesitar ventilación no invasiva o invasiva, después del ajuste [OR= 2.29, IC95% (1.29, 4.07), p<0.01].

Conclusión
Los pacientes de América Latina con enfermedades reumáticas y COVID-19 reportados a este registro global presentaron una mayor necesidad de soporte ventilatorio, no obstante, tuvieron una mortalidad similar a los pacientes del resto del mundo.

Palabras claves
COVID-19, ENFERMEDADES DEL TEJIDO CONECTIVO, MORTALIDAD

GLOBAL
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Resumen
en Inglés

Objective

To compare the characteristics of patients with rheumatic diseases and COVID-19 reported from Latin American countries with those from the rest of the world.

Methods

Patients from the COVID-19 Global Rheumatology Alliance Physician-Reported Registry were included. Details regarding demographics, rheumatic disease features, comorbidities, COVID-19 diagnosis and treatment, and outcomes were examined. Chi-squared and t-tests were used to compare associations between groups (Latin America vs. rest of the world). Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of hospitalization (yes/no) and ventilatory support (not hospitalized or supplementary oxygen only vs. non-invasive, invasive ventilation, or ECMO); Poisson models were used to estimate ORs and 95% CIs of mortality.

Results

Seventy-four patients from Latin America and 583 patients from the rest of the world were included. The most frequent **rheumatic diseases** in both groups were rheumatoid arthritis (35% and 39%, respectively) and systemic lupus erythematosus (22% and 14% respectively). Mortality was similar between groups (12% Latin America vs 11% rest of the world, p=0.88. However, Latin American patients in the registry had a higher odds of requiring non-invasive or invasive ventilation, after adjustment [OR= 2.29, 95%CI (1.29, 4.07), p<0.01]..

Conclusion

Latin American patients with rheumatic disease and COVID-19 reported to this global registry presented a higher need for ventilatory support, however experienced a similar mortality than patients from the rest of the world.

GLOBAL
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Resumen
en Portugués

Objectivo
Comparar as características clínicas de pacientes com doenças reumáticas e COVID-19 da América Latina com os de outras partes do mundo.

Métodos
Foram avaliados pacientes incluídos no COVID-19 Global Rheumatology Alliance Physician-Reported Registry. Para análise foram utilizados dados demográficos, características da doença reumática, comorbidades, diagnóstico, tratamento e desfechos relacionados à COVID-19; para comparação entre os grupos foram utilizados o teste Chi-quadrado e o teste-t (América Latina vs. outras partes do mundo). Para estimar o odds ratios (ORs) (IC=95%) de hospitalização (sim/não) e assistência ventilatória (não hospitalizado ou apenas oxigênio suplementar vs. ventilação não invasiva, invasiva ou oxigenação por membrana extra-corpórea) foi utilizada análise de regressão múltipla; para estimar risco de morte foi utilizada distribuição de Poisson (IC=95%).

Resultados
No período entre 24 de março e 22 de maio de 2020, foram incluídos 74 pacientes da América Latina e 583 de países de outros continentes. A doença mais frequente em ambos os grupos foi artrite reumatoide (35% e 39%, respectivamente) e lupus eritematoso sistêmico (22% e 14% respectivamente). A mortalidade foi similar entre os grupos (12% na América Latina vs. 11% no resto do mundo, p=0.88. No entanto, pacientes da América Latina apresentaram um risco maior de necessidade de ventilação invasiva, após ajustes [OR= 2.29, IC 95% (1.29, 4.07), p<0.01].

Conclusão
Pacientes com doenças reumáticas e COVID-19 da América Latina incluídos neste registro global apresentam maior necessidade de assistência ventilatória, embora apresentem uma taxa de mortalidade similar a dos pacientes de outras partes do mundo.

Key words
COVID-19, ENFERMEDADES DEL TEJIDO CONECTIVO MORTALIDAD.

Introducción

The coronavirus disease 2019 (COVID-19) pandemic is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). By June 17th, more than 8.3 million individuals have been diagnosed with COVID-19 and more than 440 000 patients have died. This pandemic started in Wuhan, China in late 2019; then the epicenter of the pandemic moved to Europe and after that to the US; the epicenter continues to move and is now in Latin America. Within Latin America, Brazil is the most affected country of the region (and the second in the world) with more than 950 000 cases and more than 46 000 deaths, followed by Peru with more than 240 000 cases and more than 7 200 deaths, Chile with more than 220 000 cases and more than 3 600 deaths, and Mexico with almost 160 000 cases and more than 19 000 deaths (1).

Socioeconomic factors will certainly make the impact of COVID-19 harder in this region than in the developed world. Latin America is one of the world regions with the highest level of healthcare access disparities (2). Latin American countries have a lower human development index, lower clean water access and a higher distrust in public governance than the 15 non-Chinese countries with the highest reported number of COVID-19 cases as of March 8th, 2020 (mainly US and Europe) (3). Additionally, due to the precarious housing conditions in our countries, social distance is practically impossible for a large proportion of the Latin American population. The COVID-19 pandemic has overtaken Latin American health care capacity with inadequate numbers of hospital beds, intensive care facilities and medical personnel (4). In addition, comorbidities associated with bad prognosis of COVID-19, such as obesity, diabetes and hypertension are highly prevalent in the region and may contribute to worse outcomes (5).

The impact of autoimmune diseases as well as immunosuppressive drugs on the risk of infection and the prognosis of COVID-19 has not been defined. However, autoimmune diseases and immunosuppressive drugs increase the risk of serious infections; these patients may have worse prognosis than those from the general population (6, 7). In addition, patients with rheumatic diseases may have cardiovascular, lung and renal diseases that places them at higher risk of COVID-19 related complications (8-11). Individuals with rheumatic diseases in Latin America may have more disadvantages than those in developed countries, particularly related to access to regular health services and adequate treatment before the pandemic; these issues are further exacerbated during the COVID-19 pandemic (12).

In order to determine the impact of SARS-CoV-2 infection on subjects with rheumatic diseases and to evaluate the impact of immunosuppressive drugs on prognosis, the COVID-19 Global Rheumatology Alliance (C19-GRA) was created; among its activities, this alliance has developed a provider-reported registry which includes adult patients from around the world (13, 14). Latin America countries are actively participating in this international effort. The purpose of this study is to compare the characteristics of C19-GRA physician registry Latin American patients with those from the rest of the world.
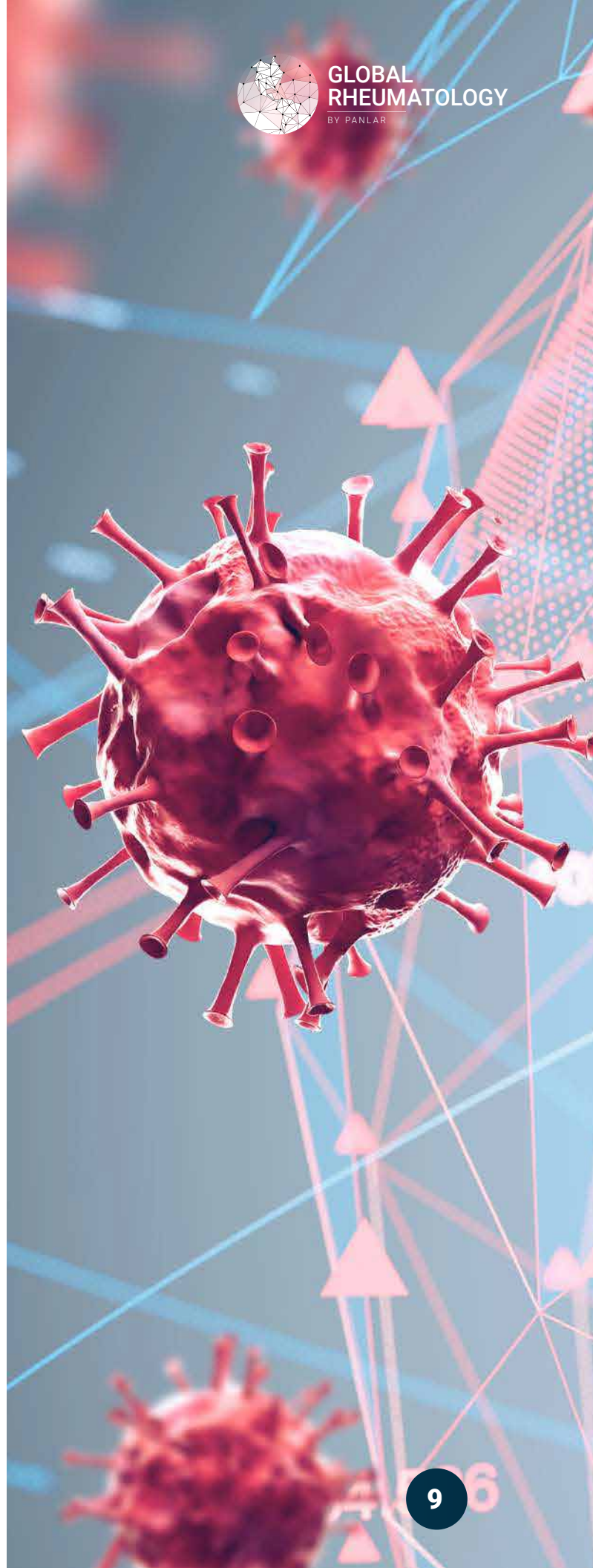
Material y Métodos

The details of this registry have been described (15, 16). Briefly, C19-GRA data of patients with rheumatic disease diagnoses and COVID-19 are captured by rheumatologists and other health care providers in two parallel international data entry portals, one limited to European countries (hosted by the University of Manchester, UK) and the other one for all other sites (hosted by the University of California, San Francisco, California, USA). The database has been reviewed by ethics boards in several countries. Using the UK Health Research Authority decision tool, the EULAR-COVID-19 Database is not classed as a research study and UK National Health Service (NHS) ethics approval is not required. The University of California San Francisco IRB has reviewed the COVID-19 Global Rheumatology Alliance and deemed the registry as not human subjects research since it is intended for surveillance or quality improvement. In Latin America, the protocol has been reviewed and approved according to local regulations. Patients from Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Honduras, Mexico and Peru were included. There is no requirement for patient consent. The data collection form is available in several languages (including English, Spanish, Portuguese, among others).

Rheumatologists designate how the diagnoses of COVID-19 were made, including by PCR, antibody or metagenomic testing, CT scan or other laboratory assays; a presumptive diagnosis based on specific symptoms, signs or imaging was also considered. Sociodemographic information, including age, gender, race/ethnicity (reported by the physician, and in most cases this was derived from the patient's self-report in the medical record), smoking status, rheumatic disease diagnosis, disease activity (as physician global assessment), comorbidities, and medications prior to COVID-19 are being recorded.

Medications prior to COVID-19 were categorized as conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs; antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus); biologic DMARDs [bDMARDs; abatacept, belimumab, CD-20 inhibitors, interleukin (IL)-1 inhibitors, IL-6 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, tumor necrosis factor inhibitors (anti-TNF)]; targeted synthetic DMARDs (tsDMARDs) namely Janus Kinase (JAK) inhibitors and glucocorticoids.

Additionally, whether patients had received any pharmacological treatment for COVID-19, the status of the infection (resolved, unresolved, unknown), the need for ventilatory support [not required, supplemental oxygen, non-invasive ventilation, invasive ventilation/extracorporeal membrane oxygenation (ECMO), required, type unknown] its outcome [death, hospitalization, complications like acute respiratory distress syndrome (ARDS), sepsis, myocarditis/heart failure, secondary infection, cytokine storm] have also been recorded.

Statistical analyses

Data are reported as means and standard deviations (SDs) or numbers and percentages. Characteristics of Latin American patients and patients from other countries were compared using Chi-square test or Student's t test. Additionally, in order to evaluate if being from Latin America was associated with poorer outcomes, multivariable regression models were performed. For death, a Poisson regression model was used, and for hospitalization (yes/no) and need for ventilatory support (non-invasive or invasive ventilation vs. none) logistic regression models were performed. All the models were adjusted by sex, age > 65 years, smoking status (ever/never), rheumatic disease diagnosis [rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)], psoriatic arthritis, spondyloarthritis, other], comorbidities (hypertension/cardiovascular disease, lung disease, diabetes, and chronic renal insufficiency/ESRD), rheumatic disease medications taken prior to infection (csDMARD monotherapy; b/tsDMARD; csDMARD + b/tsDMARD combination therapy), any NSAID use, prednisone-equivalent glucocorticoid use, and disease activity (remission/low vs. moderate/high).

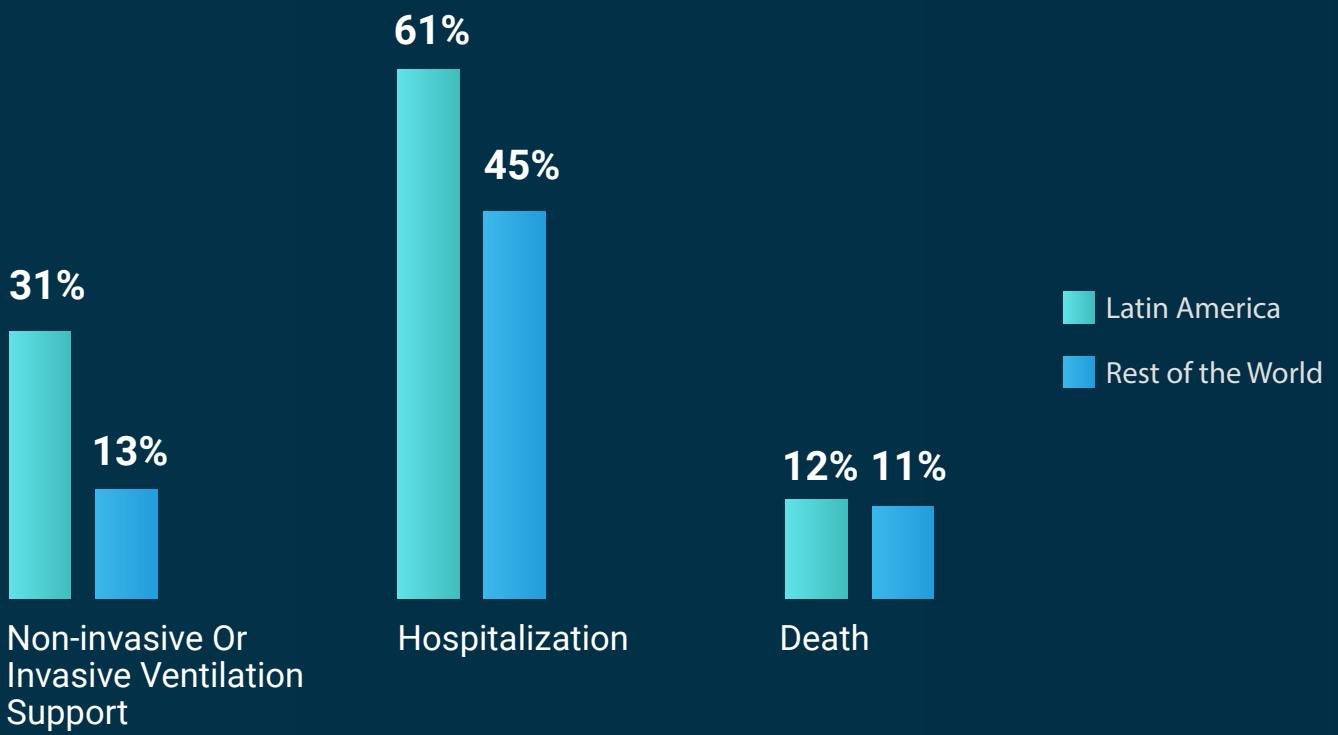All analyses were conducted in Stata V.16.0 (StataCorp, Texas, US).

Resultados

From March 24 - May 22, 2020, data for 74 patients from Latin America were collected; data for patients from the rest of the world collected as of April 20, 2020 were used as a comparison (n=583).

The characteristics of both groups are depicted in Table 1. RA (35% and 39%, respectively) and SLE (22% vs 14%, respectively) were the most common diagnosis in both groups. Psoriatic arthritis was less frequent in patients reported by providers in Latin America than other countries (3% vs 13%, p=0.02).

Latin American patients used conventional DMARDs (81% vs 66%, p=0.01), antimalarials (38% vs 21%, p<0.01) and glucocorticoids (51% vs 31%, p<0.01) more frequently than patients from other countries, but biologic DMARDs were less frequently used (16% vs 35%, p<0.01). Pharmacological treatment for COVID-19 (68% vs 43%, p<0.01) as well as for ARDS (30% vs 9%, p<0.01) was more common in patients from Latin America. Mortality was similar among both groups (12% vs 11%, p=0.88), but hospitalization was more frequent among patients from Latin America (61% vs 45%, p=0.02)

In the multivariable analyses, after adjustment for covariates described above, cases reported by providers in Latin America were associated with a higher need for non-invasive or invasive ventilatory support [OR= 2.29 95%CI (1.29, 4.07), p<0.01], but not with the probability of death [OR= 1.34, 95%CI (0.65, 2.78), p=0.43] or hospitalization [OR= 1.79, 95%CI (0.99, 3.20), p=0.05].

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61%

45%

31%

13%

12% 11%

■ Latin America

■ Rest of the World

Non-invasive Or
Invasive Ventilation
Support

Hospitalization

Death

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Demographic and clinical characteristics of patients with rheumatic disease with COVID-19

	Latin America (N=74)	Rest of the World (N=583)	p value
Gender	54 (73%)	412 (71%)	0.78
Age: mean value (SD)	53.51 (15.6)	55.81 (15.57)	0.23
Primary rheumatic diseases*			
RA	26 (35%)	225 (39%)	0.65
SLE	16 (22%)	80 (14%)	0.10
Spondyloarthtitis	7 (9%)	48 (8%)	0.89
Psoriatic arthritis	2 (3%)	75 (13%)	0.02
Vasculitis	6 (8%)	155 (9%)	0.99
Sjögren's síndrome	7 (9%)	24 (4%)	0.08
Inflammatory myopathy	4 (5%)	20 (3%)	0.6
Other inflammatory arthritis	0 (0%)	21 (4%)	0.19
Gout	1 (1%)	19 (3%)	0.59
Systemic sclerosis	2 (3%)	16 (3%)	0.72
Sarcoidosis	1 (1%)	8 (1%)	0.61
Undifferentiated connective tissue disease	2 (3%)	7 (1%)	0.61
Other	11 (15%)	39 (7%)	0.02

Primary rheumatic diseases*

White	9 (12%)	373 (64%)	<0.01
Black	2 (3%)	78 (13%)	0.01
Latin America	63 (85%)	57 (10%)	<0.01
East Asian	0 (0%)	15 (3%)	0.33
other	0 (0%)	60 (10%)	0.22

	Latin America (N=74)	Rest of the World (N=583)	p value
Smoking status	11 (15%)	127 (22%)	0.22
Comorbidities			
Hypertension	22 (30%)	195 (33%)	0.61
Lung disease	11 (15%)	127 (22%)	0.22
Cardiovascular disease	3 (4%)	63 (11%)	0.11
Diabetes	8 (11%)	69 (12%)	0.95
Morbid obesity	4 (5%)	29 (5%)	0.90
Chronic renal insufficency/ESRD	5 (7%)	40 (7%)	0.83
Cancer	5 (7%)	27 (5%)	0.94
Medications prior to COVID			
Conventional synthetic DMARDs	60 (81%)	382 (66%)	0.01
Biologic DMARDs	12 (16%)	205 (35%)	<0.01
JAK inhibitor	0 (0%)	26 (4%)	0.12
Antimalarials	28 (38%)	123 (21%)	<0.01
NSAID	19 (26%)	106 (18%)	0.16
Glucocorticoids	38 (51%)	182 (31%)	<0.01
COVID-19 diagnosis with PCR (yes/no)	51 (69%)	426 (73%)	0.54
History of travel to area with documented cases of COVID-19? (yes/no)	1 (1%)	97 (6%)	0.09
Country			
Close contact with a confirmed or probable case of COVID-19 infection	25 (34%)	168 (29%)	0.45
Pharmacological treatment for COVID-19 (yes/no)	50 (68%)	249 (43%)	<0.01

	Latin America (N=74)	Rest of the World (N=583)	p value
Outcomes			
Death	9 (12%)	63 (11%)	0.88
Hospitalized	45 (61%)	264 (45%)	0.02
Status			
Resolved	43 (58%)	235 (40%)	<0.01
Unresolved	22 (30%)	232 (40%)	0.12
Unknown	9 (12%)	116 (20%)	0.15
Oxygen			
Not required	8 (11%)	60 (10%)	0.94
Supplemental Oxygen	13 (18%)	118 (20%)	0.69
Non-invasive ventilation	8 (11%)	32 (5%)	0.12
Invasive ventilation/ECMO	15 (20%)	44 (8%)	<0.01
Invasive ventilation/ECMO	1 (1%)	4 (1%)	0.93
Unknown	29 (39%)	325 (56%)	0.01
Complications			
None	46 (62%)	446 (77%)	0.01
ARDS	22 (30%)	51 (9%)	<0.01
Sepsis	5 (7%)	91 (5%)	0.74
Myocarditis/heart failure	0 (0%)	5 (1%)	0.93
Secondary infection	2 (3%)	21 (4%)	0.96
Cytokine storm	2 (3%)	9 (2%)	0.8
Other	3 (4%)	43 (7%)	0.42

*More than one diagnosis are allowed.
SD: Standard deviation. RA: Rheumatoid arthritis. SLE: Systemic lupus erythematosus. DMARDs: Disease-modifying anti-rheumatic drugs. NSAID: Non-steroidal anti-inflammatory drugs .ECMO: Extracorporeal membrane oxygenation.

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Discusión y conclusiones

Despite the fact that Latin American patients with rheumatic diseases reported to the COVID-19 Global Rheumatology Alliance registry had a higher rate of ARDS and used glucocorticoids more frequently and at a higher dose, their mortality rate was similar to that of patients from the rest of the world.

Poverty and healthcare access impact on the risk of COVID-19, being 1746.84/100 000 for people in poor neighborhoods and 2600.46/100 000 people in the wealthy neighborhoods in New York. The role of social determinants of health is even more impressive in terms of prognosis, given the risk of death is more than two times higher in very high poverty neighborhoods than in low poverty neighborhoods in New York (242.3 vs 104.88/100 000 people) (17). Given trends seen in other countries, we could assume that the pandemic would hit Latin America very hard. In fact, as of May 22nd, Chile had 3012 confirmed cases per million people, Mexico 462/1000 000, Peru 3299/1 000 000 and Brazil 1459/1 000 000, compared to US with 4765/1 000 000, Russia 2176/1 000 000 or France 2209/1 000 000. The

high case counts in Latin American are despite the fact that the epidemic started later in this region (18). Mortality due to COVID-19 in Latin America ranged between 1.02 % (Chile) and 10.9% (Mexico); however, it is important to point out that these rates depend on the number of tests performed which is very different across countries (18).

Latin America has less than 2.5 physicians and nurses per 1 000 people in 10 out of 20 countries; for example, Guatemala has 0.4 physicians per 1 000 people, Nicaragua 1.0/1 000, Peru 1.3/1 000, Paraguay 1.4/1 000, Bolivia, Dominican Republic and El Salvador 1.6/1 000, Ecuador 2.0/1 000, Brazil and Colombia 2.2/1 000; and US and Canada have 2.6/1 000 people. Furthermore, in Latin America, the health workforce is concentrated in large cities and only Costa Rica, Cuba and Uruguay invest more than 6% of their Gross Domestic Product in health (3,4). The lower frequency of use of biologic DMARDs in patients reported to the registry is likely consistent with lower access to healthcare and specialty medications in Latin America. Additionally, in a recent report, including six

systemic autoimmune disease (SLE, systemic sclerosis, idiopatic inflammatory myopathies, Sjögren's syndrome, mixed connective tissue disease and ANCA-associated vasculitis), the age-standardized mortality rate was lower in Europe than in the rest of regions, including Latin America, and the largest difference was present in SLE patients; in this group, Latin American patients had 5 fold higher age-standardized mortality rate than European patients. However, whether the difference is due to the genetic background of these individuals, environmental factors, health care, social determinants of health or a combination of these factors remains to be elucidated (19). Taking together, we should expect that the mortality rate would be higher in this region than in the rest of the world, but, as of now, the limited data presented do not support this assertion.

At the present time, it is difficult to state if the higher frequency of complications (ARDS or need for ventilatory support) in the Latin American population is due to their sociodemographic characteristics or the precarious healthcare systems serving this population, or if it is due to other factors, like the occurrence of adverse events to the treatments given for COVID-19, the severity of the underlying disease (based on the more frequent use of conventional DMARDs) or immunogenetic factors. Another factor that could be higher doses of prednisone, which has been reported as a predictive factor of hospitalization in the C19-GRA registry or the lower use of anti-TNF, reported as a protective factor of hospitalization in the same registry (16) or even to the occurrence of adverse events to the treatments given for COVID-19.

One of the strengths of this study is that it includes the largest registry of patients with rheumatic disease and COVID-19. The C19-GRA registry includes cases from all around the world. Also, this study highlights the importance of examining the impact of COVID-19 on the daily lives of rheumatic disease patients.

However, this study has some limitations. First, as the registry is voluntary, it does not capture all cases of COVID-19 in patients with rheumatic diseases. Second, the relatively small number of cases reported in Latin America and the lack of extensive population testing strategies in most Latin American countries, precludes us from identifying all cases, may lead to selection bias and prevents us from doing more detailed multivariable analyses.As case entry across Latin America grows, we hope to be able to do comparisons across countries in future analyses. Third, as not all the countries have included patients in the registry, it is possible to have some bias in reporting. However, it is important to point out that the countries with the highest number of COVID-19 cases have included patients in the registry. Fourth, as the indication of hospitalizations varies among the countries due to several factors, including their regulations regarding hospital admissions and the numbers of hospital beds and cases, it is likely that not all hospitalizations reflect the same degree of disease severity.

This communication should reinforce the importance of reporting COVID-19 cases in people with rheumatic diseases in Latin America and around the world, in order to have evidence which hopefully will translate into better recommendations and treatment for our patients.

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