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BRIEF REPORT

Risk Factors for COVID-19 and Rheumatic Disease Flare in a US Cohort of Latino Patients

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Objective. Latino patients are overrepresented among cases of coronavirus disease 2019 (COVID-19) and are at an increased risk of severe disease. Prevalence of COVID-19 in Latinos with rheumatic diseases is poorly reported. This study was undertaken to characterize COVID-19 clinical features and outcomes in Latino patients with rheumatic diseases.

Methods. We conducted a retrospective study of Latino patients with rheumatic diseases from an existing observational cohort in the Washington, DC area. Patients seen between April 1, 2020 and October 15, 2020 were analyzed in this study. We reviewed demographic characteristics, body mass index (BMI), comorbidities, and use of immunomodulatory therapies. An exploratory classification and regression tree (CART) analysis along with logistic regression analyses were performed to identify risk factors for COVID-19 and rheumatic disease flare.

Results. Of 178 Latino patients with rheumatic diseases, 32 (18%) were identified as having COVID-19, and the incidence rate of infection was found to be 3-fold higher than in the general Latino population. No patients required intensive care unit–level care. A CART analysis and multivariable logistic regression analysis identified a BMI of >30.35 as a risk factor for COVID-19 (odds ratio [OR] 3.37 [95% confidence interval (95% CI) 1.5–7.7]; $P = 0.004$). COVID-19 positivity was a risk factor for rheumatic disease flare (OR 4.57 [95% CI 1.2–17.4]; $P = 0.02$).

Conclusion. Our findings indicate that Latino patients with rheumatic diseases have a higher rate of COVID-19 compared with the general Latino population. Obesity is a risk factor for COVID-19, and COVID-19 is a risk factor for rheumatic disease flare. Latino patients with risk factors should be closely followed up, especially post–COVID-19 in anticipation of disease flare.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) is a highly contagious, novel coronavirus with high morbidity and mortality, and its impact has been amplified by social disparities in the US (1–5). Risk factors for higher morbidity and mortality with coronavirus disease 2019 (COVID-19) include age >65 years, obesity, and comorbidities such as hypertension, diabetes mellitus, and lung disease (6,7). Patients with rheumatic diseases could especially be at risk of complications from COVID-19 due to immune system dysfunction and concomitant use of immunomodulatory therapies. However, evidence on outcomes of COVID-19 in patients with rheumatic diseases has been conflicting to date. Initial reports (8) revealed no unique or outstanding risk factors, apart from what has already been noted in the general population. An Italian study indicated a possible increased incidence of COVID-19 in patients with rheumatic diseases (9).

Studies of COVID-19 in patients with rheumatic diseases have focused on risk factors for morbidity and mortality directly attributable to SARS–CoV-2 infection. The potential effects of COVID-19 on the trajectory of the underlying rheumatic disease have not been characterized. Infectious agents have been proposed as an environmental trigger for autoimmunity, and viral infections are a known trigger for rheumatic disease flares. Therefore, it may be anticipated that patients with a rheumatic disease

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and SARS–CoV-2 infection would be at a higher subsequent risk of a flare of the baseline rheumatic disease.

Latinos represent the largest and fastest growing minority population in the US. Latinos living in the US not only have a higher prevalence of obesity, diabetes, and kidney disease, but also have lower rates of insurance coverage than the general population (10,11). Latinos are more likely to work in positions considered to be essential, thus increasing their risk of exposure to infections (12). Such jobs often provide limited or no sick time, further perpetuating the increased risk to Latino workers (13). The combination of these factors has led to a disproportionate impact of COVID-19 on Latino patients, resulting in increased incidence, severity of disease, and mortality (1,3–5).

At the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) rheumatology clinic, we follow up a diverse cohort of patients with rheumatic diseases, the majority of whom are Latina women, 75% of whom were born in Central America or Mexico with the remainder born in South America or the Caribbean. These patients have a representative mix of autoimmune diseases typically seen in outpatient settings, with most patients receiving immunomodulatory therapy. Given the importance of understanding the risk of COVID-19 in Latino patients with rheumatic diseases, we investigated risk factors for SARS–CoV-2 infection and subsequent rheumatic disease flare.

PATIENTS AND METHODS

Study cohort. All patients consented to and were participants in an institutional review board–approved natural history study at the Intramural Research Program of the NIAMS. The patients were part of an observational cohort of 307 active participants with rheumatic diseases who were referred to our clinic primarily from federally qualified health centers in the local area. All participants were contacted from April 1, 2020 to June 1, 2020 by telephone and were made aware of COVID-19 symptoms and informed of the steps to follow in case of exposure to or infection with SARS–CoV-2. Patients were further assessed for COVID-19 symptoms or exposure prior to each in-person contact (i.e., laboratory testing or clinic visit), as well as during each virtual clinic appointment. During the study period from April 1, 2020 to October 15, 2020, we identified 32 patients with COVID-19, and all of them were of self-reported Latino ethnicity. No non-Latino patients (n = 81) reported COVID-19 infection during the study period. Latino patients seen during the study period who were asymptomatic for COVID-19 and denied having any exposure (but were not tested for COVID-19) were selected as a comparator group (n = 146).

SARS–CoV-2 infection. SARS–CoV-2 infection was defined as a confirmed SARS–CoV-2 viral RNA real-time polymerase chain reaction (PCR) test result or the presence of anti–SARS–CoV-2 antibodies. Antibodies to SARS–CoV-2 were detected using the Elecsys anti–SARS–CoV-2 immunoassay (Roche Diagnostics). Given the difficulty in obtaining real-time PCR testing to detect SARS–CoV-2 during the early phases of the pandemic, we also included 1 patient with COVID-19–like symptoms who was not tested but had a close household contact with COVID-19 (Table 1).

Study design and data collection. This was a retrospective study using an existing observational cohort. The following variables were recorded: demographic characteristics, rheumatic disease type, disease flare, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, previous lung disease), current immunomodulatory treatment, changes to immunomodulatory treatment, glucocorticoids (mg) received before and after infection, and mortality. For SARS–CoV-2–positive patients, we also reported COVID-19 manifestations, management, and hospitalization course. Due to the heterogeneous nature of the cohort, rheumatic disease flare was defined as any escalation of immunomodulatory therapy. The COVID-19 incidence rate for Latino residents of the local area was calculated using local health department case counts as the numerator (14) and census data (15) as the denominator, with results reported as a range of cases reported by the counties and municipalities comprising the area.

Statistical analysis. Data on continuous variables are expressed as the mean ± SD, and categorical variables are summarized as the number (%) of patients. Given our small cohort size and multiple variables, we adopted a complementary analytic strategy utilizing a traditional logistic regression approach to identify risk factors for COVID-19, along with an exploratory classification and regression tree (CART) method. CART analysis focuses on identifying a subgroup of patients characterized by a set of interacting risk factors, whereas logistic regression focuses on identifying risk factors that have independent associations with the outcome. A CART analysis was performed to identify COVID-19 risk factors using age and BMI as continuous variables and sex and presence of comorbidities as categorical variables (Minitab 20.1.1). To identify risk factors for rheumatic disease flare, a CART analysis using COVID-19 status and missed immunomodulatory treatments as covariates was performed. CART results were analyzed using a 2-tailed mid-*P* exact test. Multivariate logistic regression analyses were performed to identify risk factors for COVID-19 and rheumatic disease flare (SAS 9.4). Univariate logistic regression analyses using various immunomodulatory treatments were performed to identify risk factors for COVID-19.

RESULTS

Patient population. A total of 178 Latino patients with rheumatic diseases were included in our analysis. The 32 patients who were diagnosed as having COVID-19 were predominantly women (91%) with a mean age of 46 years. Demographic and other (non–COVID-19) clinical characteristics in this group were generally similar to those in the COVID-19–negative group (Table 1). All of the COVID-19 patients were either essential workers themselves

Table 1. Characteristics of the patients with rheumatic diseases by COVID-19 status*

	COVID-19–positive patients (n = 32)	COVID-19–negative patients (n = 146)
Demographic characteristics		
Age, mean ± SD years	46 ± 8.1	48.7 ± 9.9
Female sex	29 (90.6)	125 (85.6)
Male sex	3 (9.4)	21 (14.4)
BMI, mean ± SD kg/m^2	32.5 ± 6.1	29.7 ± 5.0
Comorbidities	9 (28.1)	36 (24.7)
Hypertension	7 (21.9)	32 (21.9)
Diabetes mellitus	2 (6.3)	12 (8.2)
Previous lung disease	3 (9.4)	5 (3.4)
Rheumatic disease		
RA	14 (43.8)	73 (50.0)
SLE	8 (25.0)	44 (30.1)
Overlap/MCTD	3 (9.4)	3 (2.1)
Other inflammatory/autoimmune (ANCA-associated vasculitis, PsA, primary SS, AS, SSc)	7 (21.9)	24 (16.4)
Other noninflammatory (FM)	0 (0)	2 (1.4)
Medications		
Glucocorticoids	7 (21.9)	56 (38.4)
Average daily dose, mean ± SD mg	7.4 ± 6.3	5.5 ± 2.4
cDMARDs	26 (81.3)	119 (81.5)
Biologic/small-molecule inhibitor	13 (40.6)	45 (36.0)†
COVID-19		
Symptoms present	32 (100)	–
Known COVID-19 contact‡	24 (82.8)	–
COVID-19 real-time PCR§	25 (96.2)	–
COVID-19 serology¶	23 (85.2)	–
COVID-19 real-time PCR or serology	31 (96.9)	–
COVID-19 real-time PCR or serology or known contact	32 (100)	–

* Except where indicated otherwise, values are the number (%) of patients. COVID-19 = coronavirus disease 2019; BMI = body mass index; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MCTD = mixed connective tissue disease; ANCA = antineutrophil cytoplasmic antibody; PsA = psoriatic arthritis; SS = Sjögren's syndrome; AS = ankylosing spondylitis; SSc = systemic sclerosis; FM = fibromyalgia; cDMARDs = conventional disease-modifying antirheumatic drugs; PCR = polymerase chain reaction.
† Data were available for a total of 125 patients.
‡ Data were available for a total of 29 patients.
§ Data were available for a total of 26 patients.
¶ Data were available for a total of 27 patients.

or lived with an essential worker. The majority were uninsured (25 of 32 [78.1%]). None of the COVID-19 patients were smokers. The mean BMI of the COVID-19 patients was higher than that of the COVID-19–negative patients (32.5 versus 29.7) (Table 1). Prevalence of hypertension, diabetes mellitus, and previous lung disease was similar between the 2 groups. All but 2 patients were receiving immunomodulatory treatment at the time of COVID-19 diagnosis. Immunomodulatory medications were paused during COVID-19 infection in 14 of 30 patients (46.7%). The COVID-19 incidence rate in our cohort was 17,978 per 100,000 persons, which was 3-fold higher than the 4,689–5,809 per 100,000 persons incidence rate observed in the Latino residents and 5- to 11-fold higher than the 1,540–3,431 per 100,000 persons for the general population, both within the local catchment areas, during the study period.

Clinical symptoms and disease management in patients with rheumatic diseases and COVID-19. All patients who presented with COVID-19 developed symptoms, with cough and/or fever present in 66% of patients (Figure 1A). SARS–CoV-2 infection was confirmed by real-time PCR in 25 of 26 patients, and 5 of the remaining 6 patients were found to have antibodies to SARS–CoV-2 (Table 1). One individual could not obtain real-time PCR testing and received a subsequent negative antibody test result 4 months later but had classic COVID-19 symptoms and a COVID-19–positive household contact. Most patients (81%) required only outpatient treatment for COVID-19 (Figure 1B). Two of the 6 hospitalized patients required supplemental oxygen and have since recovered completely. No patients required admission to the intensive care unit, and no deaths were reported in this cohort.

Treatment regimens for patients with rheumatic diseases and COVID-19. The most common rheumatic disease treatment category was conventional disease-modifying antirheumatic drugs (Table 1 and Figures 1C and D). COVID-19–positive patients had lower glucocorticoid usage (21.9%) with a higher mean daily dose (7.4 mg) (Table 1). Of the COVID-19 patients, 75.0% were being treated with hydroxychloroquine,

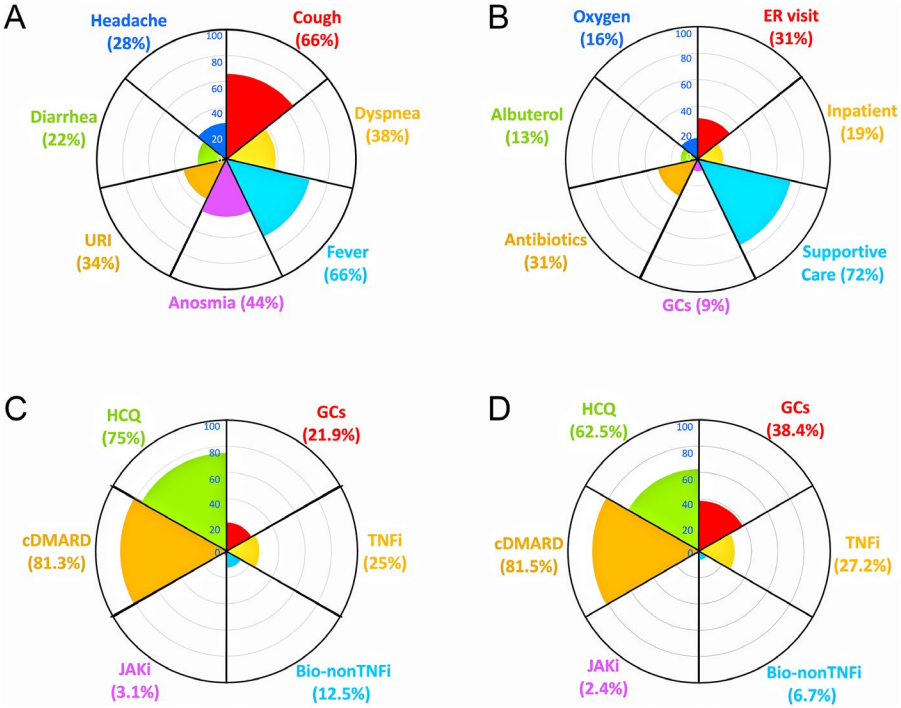

Figure 1. Pie radar charts of clinical characteristics of Latino patients with rheumatic diseases. **A**, Presenting symptoms of coronavirus disease 2019 (COVID-19) in patients with a rheumatic disease. **B**, Management of COVID-19 in patients with a rheumatic disease. **C**, Baseline immunomodulatory treatment profile of COVID-19–positive patients with a rheumatic disease. **D**, Baseline immunomodulatory treatment profile of COVID-19–negative patients with a rheumatic disease. URI = upper respiratory tract infection; ER = emergency room; GCs = glucocorticoids; cDMARDs = conventional disease-modifying antirheumatic drugs; HCQ = hydroxychloroquine; JAKi = JAK inhibitor; TNFi = tumor necrosis factor inhibitor; bio-nonTNFi = non-TNFi biologic agents.

whereas 40.6% were being treated with biologics or small-molecule inhibitors (Table 1 and Figures 1C and D).

Risk factors for COVID-19 infection in patients with rheumatic diseases. Next, we wanted to explore risk factors for COVID-19. CART analysis identified a BMI of >30.35 as the main COVID-19 risk factor, observed in 62.5% of patients (P = 0.004) (Figure 2A). Among the nonobese patients, age >39.5 years was identified as the main risk factor. As an alternative approach, we performed a multivariable logistic regression analysis using all the above variables (age, sex, BMI, diabetes, hypertension, and previous lung disease) and identified BMI as a risk factor for COVID-19 (odds ratio [OR] 3.37 [95% confidence interval (95% CI) 1.5–7.7] for a BMI of >30.35 versus <30.35; P = 0.004) (Figure 2C).

Effect of rheumatic disease treatment on risk of COVID-19 infection. We then examined whether specific therapeutic agents played a role in increasing susceptibility to COVID-19. Univariate logistic regression analysis of each type of immunomodulatory therapy was performed to identify risk factors for COVID-19 (Figure 2E). None of the immunomodulatory therapies demonstrated any statistically significant effect on susceptibility to or protection against COVID-19.

Follow-up of patients with COVID-19 and rheumatic diseases. Twenty-seven patients (84%) were evaluated in clinic after COVID-19, and 8 were experiencing a rheumatic disease flare. The median oral glucocorticoid dose increased from 0 mg to 12.5 mg daily. Persistent symptoms attributable to COVID-19 were seen in 10 patients (31.3%) (anosmia [n = 3], new generalized alopecia [n = 3], new or worsened headaches [n = 2], new peripheral neuropathy [n = 1], and weight loss >10% due to anorexia [n = 1]).

Risk factors for disease flare in patients with COVID-19 and rheumatic diseases. Of the 8 patients with rheumatic disease flare and COVID-19, in 2 the rheumatic disease had been in sustained remission and they were not receiving immunomodulatory therapy, 2 had temporarily discontinued therapy, and the remaining 4 had no interruptions in therapy. We explored the role of COVID-19 positivity and interruptions in immunomodulatory therapy in the risk of disease flares. CART analysis identified COVID-19 positivity as a risk factor for disease flares (P = 0.0007) (Figure 2B). In COVID-19–negative patients, interruptions in immunomodulatory therapy were identified as a risk factor for disease flares (P = 0.00003) (Figure 2B). Multivariate logistic regression analysis also identified COVID-19 positivity as a risk factor for disease flare (OR 4.57 [95% CI 1.2–17.4]; P = 0.02) (Figure 2D).

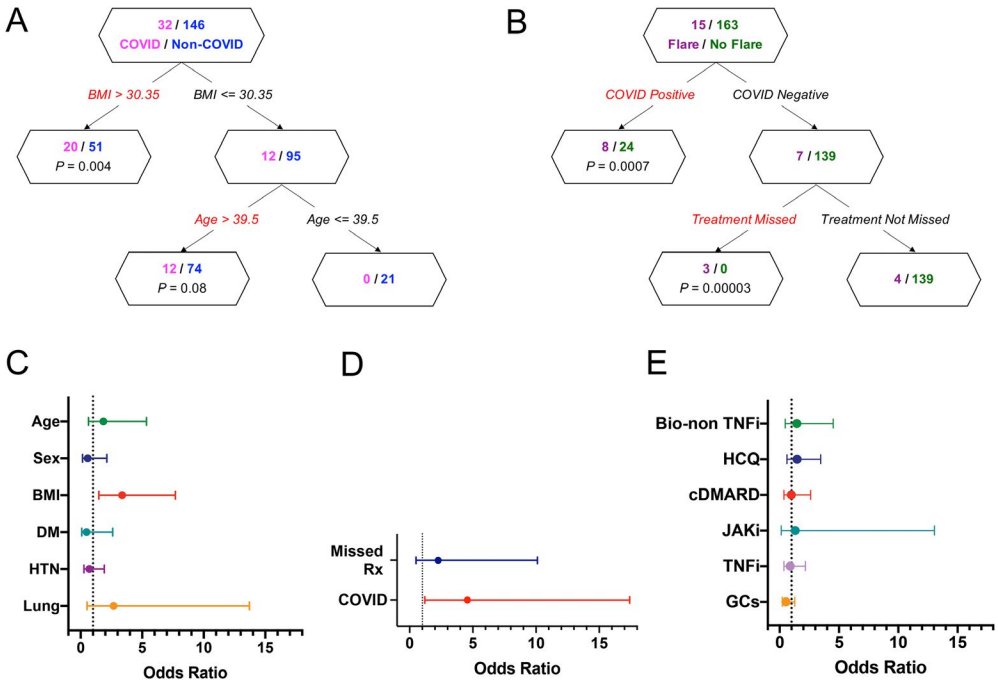

Figure 2. Risk factors for coronavirus disease 2019 (COVID-19) infection and rheumatic disease flare. **A**, Classification and regression tree (CART) analysis predicting risk variables for COVID-19 infection. Body mass index [BMI] and age were included as continuous variables, and sex, hypertension, diabetes mellitus, and previous lung disease were included as categorical variables in the model. **B**, CART analysis predicting risk variables for rheumatic disease flare. COVID-19 status and missing or stopping treatment were included in the model as categorical variables. **C**, Multivariate logistic regression analysis for identification of risk factors for COVID-19. Age >39.5 years, sex, BMI >30.35, diabetes mellitus (DM), hypertension (HTN), and previous lung disease were used as covariates in the model. **D**, Multivariate logistic regression analysis for identification of risk factors for rheumatic disease flare. Missing or stopping treatment and COVID-19 status were used as covariates in the model. **E**, Univariate logistic regression analysis of immunomodulatory treatment for identification of risk factors for COVID-19. Non–tumor necrosis factor inhibitor biologic agents, HCQ, cDMARDs, small-molecule inhibitors (JAKi), TNFi, and GCs were included in the model. Values in **C**–**E** are the odds ratios with 95% confidence intervals. See Figure 1 for other definitions.

DISCUSSION

We followed up a unique cohort of Latino patients with established rheumatic diseases who are essential workers or living with essential workers and are at the forefront of the COVID-19 pandemic. In our cohort, Latino patients with rheumatic diseases had a higher incidence of COVID-19 as compared to Latino residents within the same geographic region, but none had a poor outcome. We identified obesity and increasing age as risk factors for COVID-19. The presence of COVID-19 along with interruptions in immunomodulatory therapy were found to be risk factors for rheumatic disease flares. None of the specific immunomodulatory therapies increased the risk of COVID-19.

Patients in our cohort and their family members represent essential and frontline workers and thus were already at an increased risk of exposure to COVID-19. Therefore, sociodemographic factors likely greatly contributed to the increased incidence of COVID-19 in our cohort. Previously published studies suggest that Latino patients are more likely to develop severe COVID-19 and have a worse outcome. None of the patients with COVID-19 in the present study required mechanical ventilation or had a poor outcome, although 2 did meet criteria for severe disease. Possible explanations for milder disease in our patient population could include younger age, a greater proportion of female patients, relatively mild preexisting conditions, limited pre-infection glucocorticoid exposure, and perhaps mitigating effects of existing immunomodulatory therapy. It is possible that asymptomatic individuals with COVID-19 were missed because COVID-19–negative patients were not tested by real-time PCR for SARS–CoV-2. Conversely, this would have increased the number of COVID-19–positive cases and increased our incidence rate even further. Given that younger individuals with COVID-19 are more likely to be asymptomatic, the association we found between age >39.5 years and COVID-19 may be explained by a higher prevalence of symptomatic infection in older individuals.

An interesting finding from our study was the identification of a BMI of >30.35 as a risk factor for COVID-19 infection. A BMI of >30 is the definition of obesity, and the finding of a BMI of >30.35 by CART analysis is notable. Obesity has been documented as a risk factor for severe COVID-19 requiring hospitalization, but its role in increased susceptibility to infection has not been evaluated. Obesity affects metabolic and immune functioning, leading to increased COVID-19 risk. Another important observation was that COVID-19 infection increases the risk of

disease flares in patients with rheumatic disease. This risk attributed to COVID-19 was independent of interruptions in immunomodulatory treatments. Rheumatologists should closely follow up patients who report a history of COVID-19, in anticipation of a potential rheumatic disease flare in the postinfection period. Immunomodulatory treatments did not play a role in increasing COVID-19 susceptibility, but our study sample size may have low statistical power to detect associations with individual medications. Potentially, immunomodulatory therapies may play a beneficial role in patients with rheumatic disease who contract COVID-19.

Strengths of our study include a longitudinal, well-established Latino patient cohort, reducing referral bias. Our study allowed for self-reporting of infection, thus reducing the selection bias toward enrollment of sicker patients, as seen in previous reports of COVID-19 in Latino patients. We captured a representative sample of our cohort, with 178 of 226 Latino participants (79%) being assessed during the study period.

Despite these strengths, there are important limitations to this study. It was a retrospective, observational study from a single site, thus limiting the generalizability of the findings. Our cohort of patients and their family members represent essential and frontline workers, who are at an increased risk of exposure to SARS–CoV-2, and this could have led to a selection bias. Surveillance bias due to increased awareness and testing of our patients because of their rheumatic diseases and immunosuppression could have led to increased identification of COVID-19 in our cohort. An Italian study indicated a similar increase in the prevalence of COVID-19 in patients with systemic autoimmune diseases (9). Smoking may be a confounder and was not assessed in this study. None of the COVID-19–positive patients were smokers and thus we could not use this variable in our multivariate analysis. We did include previous lung disease as a covariate that could potentially capture some effects of smoking (both active and passive). Further, we did not assess for community exposure duration or the level of community spread specific to individual patients, and risk of exposure was likely influenced by these factors that we could not capture in our analyses.

In this study of Latino patients with rheumatic diseases, a higher prevalence of COVID-19 was observed, with obesity identified as a risk factor. COVID-19 positivity was identified as a risk factor for rheumatic disease flare. COVID-19 infection–related poor outcomes were not observed, but persistent COVID-19 symptoms were reported. Future studies including marginalized populations, with larger sample sizes from different geographic locations, including younger patients, and with longer follow-up periods, are warranted to confirm these findings.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gourh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fike, Redmond, Ward, Gourh.

Acquisition of data. Fike, Hartman, Redmond, Williams, Ruiz-Perdomo, Chu, Hasni, Katz, Gourh.

Analysis and interpretation of data. Fike, Hartman, Ward, Gourh.

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