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Prevalence of Systemic Lupus Erythematosus and Coexisting Autoimmune Diseases in Puerto Rico in the Context of Hurricane Maria and the COVID-19 Pandemic

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease that tends to coexist with other autoimmune conditions. The prevalence and etiology of the concurrent autoimmune diseases of SLE patients remains unknown. In Puerto Rico (PR) the prevalence of SLE was last reported in 2007 as a striking 159 per 100,000 individuals. The purpose of this investigation is to provide an updated prevalence of SLE and its autoimmune comorbidities in Puerto Rico in the setting of Hurricane Maria and the COVID-19 pandemic.

Methods: Patient record information from the Puerto Rico Health Insurance Administration (PRHIA) was used to identify individuals with SLE between the years 2018 through 2020. Demographic characteristics such as age and sex were recorded. In addition, medications and comorbidities were evaluated. Prevalence was estimated.

Results: A total of 12,918 cases of SLE were analyzed. Prevalence was estimated to be 536 per 100,000 individuals at its peak in 2019. In individuals with SLE, 3.6% had at least 1 additional autoimmune diagnosis. Patients who were female, aged 35 to 54, or with a record of using corticosteroids within the past three years were identified as more likely to be affected by an additional autoimmune disease.

Conclusion: Our findings reveal an increased prevalence of SLE as compared to previous studies in both the United States and Puerto Rico. We also contributed to limited literature on the co-occurence of SLE with other autoimmune diseases and its associated factors.

Key Words: Systemic lupus erythematosus; Autoimmune disease; COVID-19 pandemic; Hurricane maria

INTRODUCTION

A recent meta-analysis of U.S. registries demonstrated that Black populations, followed by Hispanic populations, followed by females had the highest prevalence of Systemic Lupus Erythematosus (SLE).1 Interestingly, the ancestral background of the Puerto Rican population is composed of European, West African, and Native Taíno populations, matching the meta-analysis data [1,2]. The last prevalence of systemic lupus erythematosus (SLE) reported for Puerto Rico was back in 2007 at an astounding 159 per 100,000 individuals [3]. However, this number is outdated and is potentially underestimating the current burden of disease on the island. In 2007, the estimated prevalence of SLE in Puerto Rico was 277 per 100,000 females and 25 per 100,000 males. This marked difference between females and males is consistent with worldwide findings [3,4]. In comparison, the estimated prevalence of SLE in the United States from 2003 to 2008, ranged between 81 to 102.5 per 100,000 individuals, and the sex and age adjusted incidence was 7.2 per 100,000 individuals [5]. As such, previous prevalence estimates

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of SLE suggest higher rates in Puerto Rico than year matched prevalence estimates in the United States [3,5]. This difference has been attributed to the exposure to ultraviolet radiation in regions near the equator, like Puerto Rico [4]. Other factors that may influence the prevalence of SLE include age, socioeconomic status, and comorbidities [3]. Moreover, in the past five years, the Puerto Rican population has been heavily impacted by devastating natural disasters, including Hurricane Maria in 2017 and the ongoing COVID-19 pandemic, which began in earnest in 2020.

Natural disasters and epidemics are well-known to cause substantial shifts in the incidence and prevalence of health outcomes. For example, a recent publication demonstrated that chronic illnesses, such as hypertension, arthritis, and high cholesterol, were more prevalent after Hurricane Maria [6]. Yet, similar post-hurricane health outcomes in the context of autoimmune diseases are nonexistent. Additionally, there is growing evidence of an association between SARS-CoV-2 infection and autoimmunity [7]. However, this data has yet to be extensively studied for SLE and has not been extended to Puerto Rico.

Interestingly, many autoimmune diseases have been reported to coexist with other autoimmune diseases, such as autoimmune thyroid diseases and rheumatoid arthritis [8,9]. In SLE, connective tissue autoimmune diseases, including scleroderma, Sjogren's syndrome, rheumatoid arthritis, Raynaud's disease, and mixed connective tissue disease, are the most commonly reported coexisting autoimmune diseases [10]. Additionally, patients with cutaneous lupus erythematous have increased rates of coexisting autoimmune diseases [11]. Despite this data, there have been limited large scale studies on the frequency of coexisting autoimmune diseases in patients with SLE and its associated risk factors.

To the best of our knowledge, the prevalence of concurrent autoimmune diseases in patients with SLE in Puerto Rico has yet to be studied. There is also a lack of literature regarding the frequency of coexisting autoimmune conditions in SLE patients. With this study, we contribute to growing the literature on autoimmune comorbidities in SLE patients. We also provide an updated prevalence rate of SLE in Puerto Rico in the context of both Hurricane Maria and the COVID-19 pandemic.

METHODS

A cross-sectional study was conducted utilizing de-identified patient administrative claims from the Puerto Rico Health Insurance Administration (PRHIA), also known as Administracion de Seguros Salud de Puerto Rico (ASES). The database included patient age, sex, medical diagnoses (using ICD-10 coding), and medication utilization. The database did not include any identifying information, such as name, medical record number, date of birth, or address, and could not be linked back to the subjects from whom it was originally collected.

We selected patients with SLE living in Puerto Rico between 2018 and 2020. Inclusion criteria consisted of children and adults aged 0 to 99 years who had a diagnosis of SLE by licensed physicians from 2018 to 2020. Exclusion criteria included incomplete records and records that have been lost to follow-up after diagnosis. Records with information missing from the dataset, such as corticosteroid use, were excluded. We estimated that the sample size needed to achieve a statistical power of 80% should be no less than n=196.

The demographic data, SLE diagnosis, other documented autoimmune diseases, and other non-autoimmune comorbidities of 12,918 SLE records were analyzed. The demographic variables examined included age, subclassified into groups: ≤18, 19 to 34, 35 to 54, and ≥ 55, and sex [3]. A 'coexisting autoimmune disease' or 'autoimmune comorbidity' was defined as an additional autoimmune disease outside of SLE. Autoimmune diseases were included if they were listed in Hayter and Cook's [12]. Consolidated list of autoimmune diseases defined by modified versions of Witebsky's postulates. The autoimmune diseases with ICD-10 codes included in our study are shown in Additional File 1. Other comorbidities that did not meet the criteria defined above are summarized in Additional File 2. Informed consent was not obtained as this study involves the secondary analysis of existing data collected for non-research purposes and does not fall within the regulatory definition of research involving human participants. All research methods were conducted and approved per the Institutional Review Board of San Juan Bautista School of Medicine.

Demographic variables and clinical characteristics of SLE records in our dataset were summarized using descriptive statistical measures, including the mean and standard deviation for continuous variables. We used contingency tables to display frequency data for selected autoimmune and non-autoimmune comorbidities distributed for sex, age (2 x 4), and corticosteroid use (2 x 2). Association between frequencies for each measure was given by $\chi 2$, with a statistical significance set at $P<.05$. Statistical analysis was performed with R studio statistical software.

RESULTS

Table 1 summarizes the demographic characteristics of our study population. Of the 12,918 SLE records analyzed, 85.5% were female and 14.5% were male, with a female to male ratio of approximately 6:1. The mean age of all SLE patients within our dataset was 50.9% ± 16.7. Prevalence trends of SLE in Puerto Rico from 2018 to 2020 were organized by sex and year and are summarized in **Table 2**. At 536 per 100,000 individuals, the highest prevalence demonstrated was in 2019. In 2018 and 2020, the prevalence was 246 per 100,000 individuals and 370 per 100,000 individuals, respectively. The prevalence of SLE patients in the PRHIA database from 2018 to 2020 was highest in females in 2019 at 825 per 100,000 individuals. By comparison, the prevalence was 181 per 100,000 individuals in males in that same year.

Table 1: Demographic characteristics of SLE patients in PRHIA database from 2018 to 2020

Measure	2018 (n=2506)	2019 (n=5981)	2020 (n=4431)	All (n=12918)
Age, Mean (SD)	50.9 (18.5)	51.6 (16.8)	50.1 (15.6)	50.9 (16.7)

Male, No. (%)	425 (17.0)	904 (15.1)	543(12.3)	1,872 (14.5)
Female, No. (%)	2,081 (83.0)	5,077 (84.9)	3,888 (87.7)	11,046 (85.5)
Ages are presented by the mean and standard deviation (SD) for each year and amongst all years. The proportion of male and female patients with SLE is presented as No. (%).				

Table 2: Estimated prevalence of SLE in puerto rico from 2018 to 2020.
Prevalence trends of systemic lupus erythematosus (SLE) in males, females, and all patients in 2018, 2019, and 2020 are shown. Prevalence is estimated per 100,000 individuals.

	2018		2019		2020	
	Individuals with SLE	**Prevalence (per 100,000)**	**Individuals with SLE**	**Prevalence (per 100,000)**	**Individuals with SLE**	**Prevalence (per 100,000)**
All	2,506	246	5,981	536	4,431	370
Females	2,081	372	5,077	825	3,888	595
Males	425	93	904	181	543	100

Selected comorbidities in patients with SLE in Puerto Rico are reported throughout 2018 to 2020 (Additional File 3). Comorbidities with the highest frequencies in patients with SLE included essential hypertension (33.7%), type 2 diabetes mellitus (19.5%), hypothyroidism (18.0%), anemia (14.2%), and major depressive disorder (9.06%) (Additional File 3). These remained relatively consistent throughout the years, except for major depressive disorder, which increased considerably between 2018 (6.3%) to 2020 (11.2%).

Thirty distinct autoimmune diagnoses were analyzed. Among the most common comorbidities in patients with SLE were discoid lupus erythematosus (1.98%), rheumatoid arthritis (1.13%), autoimmune thyroiditis (1.11%), and systemic involvement of the connective tissue (1.08%) (Additional File 4). The proportions of coexisting autoimmune diseases within our dataset varied by sex and age group (Additional File 5). In female patients ≤ 18 years old, the most frequently coexisting autoimmune disease was autoimmune thyroiditis, while in males, it was juvenile myositis. In patients ≥ 55 years old, the most common coexisting autoimmune disease was type 1 diabetes mellitus in females and systemic involvement of the connective tissue in males. In our dataset, 3.6% of individuals with SLE had at least one additional coexisting autoimmune condition (**Table 3**).

Table 3: Coexisting autoimmune diseases in patients with SLE from 2018 to 2020. Table shows the frequency of autoimmune diseases coexisting in patients with SLE, where each patient is represented only once. Frequency is displayed as the number of persons with autoimmune comorbidities in all patients with SLE.

Number of additional autoimmune diseases	**0**	**1**	**2**	**3**	**4**	**5**
Frequency of patients	12,448	406	51	10	1	2

Demographics and clinical features, including sex, age, and corticosteroid use in the past three years, were reported in patients with SLE with and without coexisting autoimmune conditions (Tables 4 and 5). Contingency table analyses showed that those with at least one coexisting autoimmune conditions were more likely to be females, in the 35 to 54 age range, and with corticosteroid use in the past three years, as the expected values were less than what we observed (P<.05) (**Table 4 and 5**).

Table 4: Demographic and clinical features of patients with SLE with coexisting autoimmune conditions.

Measure	**No Coexisting Autoimmune Disease (n=7746)**	**≥ 1 Coexisting Autoimmune Disease (n=2213)**	**P Value**
Female	6,653 (6,727.10)	1,996 (1,921.90)	<.00001*
Male	1,093 (1,018.90)	217 (291.10)	
Age			
≤ 18	464 (461.23)	129 (131.77)	.01*
19-34	1,339 (1,344.02)	389 (383.98)	
35-54	3,056 (3,113.49)	947 (889.51)	
≥ 55	2,887 (2,827.26)	748 (807.74)	

Table 5: Demographic and clinical features of patients with SLE without coexisting autoimmune conditions

	Observed Value (Expected Value)		
Measure	**No Coexisting Autoimmune Disease (n=6607)**	**≥ 1 Coexisting Autoimmune Disease (n=2180)**	**P Value**
Corticosteroid Use in past 3 years			
Yes	4626 (4762.57)	1708 (1573.43)	<.001
No	1981 (1844.43)	472 (608.57)	

Table 4 is about Frequency of patients with Systemic Lupus Erythematosus (SLE) versus patients with SLE and ≥ 1 coexisting autoimmune disease distributed by sex and age group from 2018 to 2020 are presented in a 2 x 4 contingency table. Frequencies are displayed as 'observed value (expected value)' where expected values diverging from observed indicate association when P<.05. P value for each measure is determined by $\chi 2$ with significance set at P<.05.

*Statistically significant P<.05.

Table 5 is about Frequency of patients with systemic lupus erythematosus (SLE) versus patients with SLE and ≥ 1 coexisting autoimmune disease distributed by corticosteroid use from 2018 to 2020 is presented in a 2 x 2 contingency table. Frequencies are displayed as 'observed value (expected value)', where expected values diverging from observed indicate association when P<.05. P value for each measure is determined by $\chi 2$ with significance set at P<.05.

With an increasing worldwide SLE prevalence [4] our study, which reports the current prevalence of SLE and coexisting autoimmune disease in Puerto Rico, is particularly relevant. Our data revealed prevalence rates consistent with the increasing trend seen worldwide [13]. Also, similar to previous studies, our data had an expected marked distinction between rates of SLE in males and females, with a female to male ratio of 6:1 [3,4].

It should also be noted that the years analyzed in this study coincide with a particularly vulnerable period for the Puerto Rican healthcare system. In 2017, Hurricane Maria devastated the island, leaving millions without access to electric power and safe water sources, contributing to a 62% increase in mortality rate [14]. In 2018, the health infrastructure in Puerto Rico was in the process of being rebuilt. Rodríguez-Madera suggests that the hurricane created even more vulnerabilities in an already damaged healthcare infrastructure [15]. For example, approximately 3,000 deaths can be directly attributed to the prolonged inability to access medical care post-Hurricane Maria. Within our dataset, we observed that the number of individuals insured by government sponsored health insurance was markedly less in 2018 than in 2019 and 2020, consistent with the decreased access to health services post-Hurricane Maria. The peak prevalence observed in 2019 may be partly due to the restoration of essential infrastructures, such as communication systems, electricity, and transportation, which would allow increased access to care. We should also consider stress as a likely contributor to this increase in prevalence in 2019. The etiology of autoimmune diseases, such as SLE, is multifactorial, and both physical and psychological stress has been implicated as a trigger to their development and onset [16]. Although we were not able to include data from years prior to Hurricane Maria, which took place in late 2017, literature has demonstrated that Puerto Ricans experienced higher than typical rates of stress and mental health disorders after this event [17]. Given the synergistic relationship between stress and SLE, it is possible that the stress associated with Hurricane Maria may have contributed to the peak prevalence we observed in 2019. In 2020, we saw a downward trend of cases. Interestingly, this corresponds to the first year of the COVID-19 pandemic, where access to health services decreased due to the imposed restrictions. However, literature that examines the impact of COVID-19 on access to healthcare in Puerto Rico is limited [18]. Therefore, it is essential to follow the data into the coming years to understand the impact of the COVID-19 pandemic on these rates.

We believe that this is the first work to explore the frequency of coexisting autoimmune diseases in patients with SLE in Puerto Rico. In our study, 3.6% of patients with SLE has at least one additional autoimmune comorbidity. This rate closely approximates the rate of developing an autoimmune disease in the general population (4.5%) [12]. We expected that given the high rates of SLE in Puerto Rico, the frequency of coexisting autoimmune diseases would be higher than in other regions. It is, however, much lower than the rate reported by a small retrospective study of patients in a United Kingdom clinic, which determined that up to 30% of their patients with SLE had at least one additional autoimmune condition [19]. Of note, 72 of the 78 Puerto Rican municipalities have been classified as medically underserved areas, in part due to specialty physician shortages [20]. Therefore, future research should also include the specialty of the diagnosing physician as a possible factor that may impact the frequency of coexisting autoimmune diseases. Including this in an analysis may reveal a more subtle effect of patients' socioeconomic status, as access to specialty care is further restricted by the number of physicians on the island that have the training to identify other, possibly rarer autoimmune conditions.

Among the autoimmune comorbidities we studied, the prevalence of autoimmune thyroiditis (1.11%) in SLE patients was similar to previous reports [8,9]. However, the coexistence of SLE and rheumatoid arthritis (1.13%) and SLE and discoid lupus erythematosus (1.74%) was less in our study [8,9]. The most common comorbidities seen in our study were mainly non-autoimmune and included: essential hypertension (33.7%), type 2 diabetes mellitus (19.5%), and hypothyroidism (18%). These were also among the most common comorbidities in the 2007 Puerto Rico SLE prevalence study [3]. Of note, our study demonstrated an uptrend in rates of depressive disorders since 2018, particularly in 2020, the first year of the COVID-19 pandemic.

Studies assessing the risk factors that predispose individuals with autoimmune diseases to the development of other autoimmune diseases are also limited [11]. Here, we report that female patients, patients within the age group of 35 to 54, and patients with corticosteroid use were more likely to have an additional autoimmune disease. Various molecular-genetic studies have demonstrated that spontaneous autoimmune disease occurs secondary to suppression of T regulatory cells (Tregs) [21-23]. Certain classes of immunosuppressive medications, like the corticosteroids often used to manage symptoms of SLE, alter Treg function. Furthermore, recent data shows that the mechanism of action of glucocorticoids, a subclass of corticosteroids, relies on Tregs to reduce autoimmune inflammation [24]. Although this mechanism of action is beneficial to reducing flares in an acute setting, it is unclear what long term effects this modulation may have on Tregs, especially in cases where there is prolonged corticosteroid use. In clinical practice, the European Alliance of Associations for Rheumatology (EULAR) recommends minimizing the medium to long term use of glucocorticoids in SLE patients to <7.5 mg/day for less than six months with an early transition to other maintenance medica-

tions, such as hydroxylchloroquine, to prevent the known adverse effects of long term glucocorticoid use [25]. In our study, we were unable to assess the duration and dosage of corticosteroid use; however, we determined that corticosteroid use was more common in patients with SLE and at least 1 additional autoimmune comorbidity. It is unclear whether the use of corticosteroids in these individuals results from increased SLE flares or is part of the management plan for the other autoimmune disease. Therefore, it would be interesting to analyze whether long term corticosteroid use increases the risk of developing additional autoimmune diseases. We recommend that future studies assess this critical question with varying durations and dosages of corticosteroids. Our findings incentivize screening for coexisting autoimmune diseases in SLE patients and promote an individualized approach to their clinical care.

Limitations of our study included the under prediction or misclassification of specific comorbidities due to inconsistent use of ICD classification by physicians (e.g., autoimmune thyroiditis was included in autoimmune comorbidities while unspecified hypothyroidism was included in other comorbidities). Due to these discrepancies in coding, we decided to report both autoimmune and non-autoimmune comorbidities. In the specific case of the coexistence of SLE and rheumatoid arthritis, it is crucial to observe that they have overlapping symptoms (e.g., joint pain and swelling), which may result in underreporting.

There were limitations with the database used, PRHIA. For example, the database only includes individuals enrolled in government sponsored health insurance. According to the most recent report published by the U.S. Centers for Medicaid and Medicare Services (August 2021), there are 1.5 million adults and children, or approximately half of the island's population (3.5 million in 2020), enrolled [26,27]. We could not access data from private insurances because the Transparency and Open Data Law [28], which requires digitalization and publication of data, only regulates government agencies to access such information, effectively obscuring data for half of the population. Another limitation of PRHIA was the restricted number of searchable categories and data filters, which prevented us from obtaining the patient's ethnicity and education level. Given that autoimmune diseases like SLE are multifactorial in etiology, these demographic variables are vital to understanding the development and progression of the illness. Additionally, we were not granted access to data prior to 2018, meaning we couldn't assess trends before Hurricane Maria and the COVID-19 pandemic.

With all this information in mind, our study highlights the need to have an interconnected repository of healthcare data. Ideally, it should include the medical records of patients serviced by the public and private sectors to foster continuous, sustainable research, and innovation in health care initiatives and policies that could benefit the entire Puerto Rican population.

CONCLUSION

Our study results contribute to the ongoing research of coexisting autoimmune diseases and influencing factors. We also provide an updated prevalence of SLE in Puerto Rico from 2018 to 2020, years in which Hurricane Maria and the COVID-19 pandemic greatly impacted the health care infrastructure. Based on our findings, it may be warranted to screen patients with SLE in Puerto Rico for other autoimmune diseases, especially females, those between the ages of 35 to 54, and those who use corticosteroids. However, as SLE can present in various ways, affect multiple organ systems, and, as demonstrated, often coexist with other autoimmune diseases, the most beneficial management is one that is personalized for each individual.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All research methods were conducted and approved per the Institutional Review Board of San Juan Bautista School of Medicine. All study procedures were carried out in accordance with relevant guidelines and regulations. Our data analysis involves the secondary analysis of existing data collected for non-research purposes and does not fall within the regulatory definition of research involving human participants. The data is not individually identifiable as it was stripped of all identifying information and could not be linked back to the subjects from whom it was originally collected. Therefore, informed consent was not collected in our study. IRB reference number EMS-JBIRB-15-2021.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from Puerto Rico Health Insurance Administration (PRHIA) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of Puerto Rico Health Insurance Administration (PRHIA).

COMPETING INTERESTS

The authors declare that they have no competing interests.

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No funding was received to produce this manuscript.

AUTHORS' CONTRIBUTIONS

CKG analyzed patient data and curated figures for the manuscript. CKG was a major contributor to the original draft preparation and the reviewing and editing process. EPR contributed significantly to the original draft preparation, the acquisition of patient data, and data curation. EPR also assisted in validation of project and data, review and editing manuscript, and arranging the data for formal analysis. AR assisted in preparing the original draft of the manuscript. AR also played a major role in the revision and editing process of the final manuscript for publication. AR also was a major contributor to the formatting process of the final manuscript to submit to journals. MSC assisted in the preparation of the original manuscript as well as subsequent review and editing. MSC assisted in formatting the manuscript for journal submission, final data revision, significant manuscript editing, and general fact checking. JL analyzed

the raw data provided by PRHIA and created summarized categorical tables used for the statistical analysis of this project. JL also reviewed and edited the final manuscript. CC contributed with the organization and sorting of the raw data that was presented. This included analyzing data from each year and arranging them according to comorbidity and medications. CC was also responsible for reviewing and editing the final draft of the manuscript. AM was involved in data curation and reviewing and editing the final manuscript. MS and AC were involved in project oversight and administration, reviewing and editing the final manuscript, and data curation of data from PRHIA. All authors read and approved the final manuscript.

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